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Emerging and current management of acute-on-chronic liver failure

Mohsin F. Butt[1,2,3] | Rajiv Jalan[2,4]

[1]Centre for Neuroscience, Trauma and Surgery, Wingate Institute of Neurogastroenterology, The Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK

[2]Liver Failure Group, University College London Medical School, Royal Free Hospital Campus, London, UK

[3]National Institute for Health Research, Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust, University of Nottingham, Nottinghamshire, UK

[4]European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) Consortium, Barcelona, Spain

Correspondence
Rajiv Jalan, Liver Failure Group, University College London Medical School, Royal Free Hospital Campus, Hampstead, London, UK.
Email: r.jalan@ucl.ac.uk

Summary

Background: Acute-on-chronic liver failure (ACLF) is a clinically and pathophysiologically distinct condition from acutely decompensated cirrhosis and is characterised by systemic inflammation, extrahepatic organ failure, and high short-term mortality.

Aims: To provide a narrative review of the diagnostic criteria, prognosis, epidemiology, and general management principles of ACLF. Four specific interventions that are explored in detail are intravenous albumin, extracorporeal liver assist devices, granulocyte-colony stimulating factor, and liver transplantation.

Methods: We searched PubMed and Cochrane databases for articles published up to July 2023.

Results: Approximately 35% of hospital inpatients with decompensated cirrhosis have ACLF. There is significant heterogeneity in the criteria used to diagnose ACLF; different definitions identify different phenotypes with varying mortality. Criteria established by the European Association for the Study of the Liver were developed in prospective patient cohorts and are, to-date, the most well validated internationally. Systemic haemodynamic instability, renal dysfunction, coagulopathy, neurological dysfunction, and respiratory failure are key considerations when managing ACLF in the intensive care unit. Apart from liver transplantation, there are no accepted evidence-based treatments for ACLF, but several different approaches are under investigation.

Conclusion: The recognition of ACLF as a distinct entity from acutely decompensated cirrhosis has allowed for better patient stratification in clinical settings, facilitating earlier engagement with the intensive care unit and liver transplantation teams. Research priorities over the next decade should focus on exploring novel treatment strategies with a particular focus on which, when, and how patients with ACLF should be treated.

1 | INTRODUCTION

The acute-on-chronic liver failure (ACLF) concept as we know it today was introduced in 2002[1] and was based on the observation that relatively young patients with cirrhosis presented to the hospital for the first time with multiorgan failure, entered the intensive care unit (ICU) and died shortly afterwards. The background to this concept was the finding that the insertion of a transjugular intrahepatic portosystemic shunt in a group of patients with uncontrolled variceal bleeding and sepsis could precipitate a syndrome that resembled acute liver failure, including severe intracranial hypertension.[2] Intracranial hypertension is an exceedingly rare complication of decompensated cirrhosis, so the identification of this subgroup of critically unwell patients helped distil two potentially different clinical trajectories for patients with decompensated cirrhosis. The final pieces of the jigsaw were early reports marrying systemic inflammation with organ dysfunction, including portal hypertension, renal dysfunction, and hepatic encephalopathy.[3–5] Contemporary evidence now posits systemic inflammation as a key driver of organ dysfunction in ACLF[6] and a key differentiator from 'mere' decompensation.

Systemic inflammation has been proposed to be the main driver of progression from compensated to decompensated cirrhosis,[7] the recurrence of acute decompensation[8], and the development of organ failure[9] (Figure 1). The European, prospective, observational study (PREDICT) of patients ($n=1071$) with decompensated cirrhosis examined the evolution of systemic inflammation by exploring the inflammatory profiles of patients with stable decompensated cirrhosis (patients without ACLF development or hospital readmissions within the 90-day follow-up period), unstable decompensated cirrhosis (patients with at least one hospital readmission, but without ACLF development within the 90-day follow-up period), and pre-ACLF (patients who developed ACLF within 90 days of study enrolment). There was a significantly higher degree of systemic inflammation at admission in patients with pre-ACLF compared to those with stable/unstable cirrhosis, and the progression of acute decompensation to ACLF in the pre-ACLF group was reflected by a progressive increase in inflammatory markers. As such, this study demonstrates that inflammation is key to the phenotypes of acute decompensation as well as short- and long-term prognoses.

Herein, our overall aim is to provide a narrative review of the diagnostic criteria, prognosis, epidemiology, and general management principles of ACLF. Four specific interventions shall be explored in detail: intravenous albumin, extracorporeal liver assist devices, granulocyte-colony stimulating factor (G-CSF), and liver transplantation. To achieve our aims, the PubMed and Cochrane databases were searched for articles published from inception up to July 2023.

2 | DIAGNOSIS AND PROGNOSIS

Unfortunately, a global effort to identify patients with ACLF and develop unified therapeutic strategies has been hampered by the heterogeneity of the diagnostic criteria for ACLF. The key words of the condition ('acute', 'chronic' and 'failure') have numerous definitions that have been hotly contested since its first description. Some 13 different diagnostic criteria for ACLF have been proposed. The three most popular criteria (Table 1) have been produced by the Asia Pacific Association for the Study of the Liver (APASL), North American Consortium for the Study of End-Stage Liver Disease (NACSELD), and European Association for the Study of the Liver (EASL). Unfortunately, these three diagnostic criteria identify different cohorts of patients with varying mortality (Table 2). Although diagnostic criteria differ globally, there is a consensus that ACLF refers to a subgroup of patients with liver disease who have high short-term mortality due to the development of organ failure(s).

3 | COMPARISON OF APASL, NASCELD AND EASL DIAGNOSTIC CRITERIA

The NACSELD and EASL-CLIF criteria for ACLF identify different cohorts of patients (Table 2). In a Veterans Affair study of 19,082 patients with EASL-CLIF ACLF, 11,955 (62.65%) patients did not meet NACSELD criteria for ACLF who would otherwise have had substantially high 28-day (2,519/11,955, 21.07%) and 90-day (4,244/11,955, 35.27%) mortality rates.[10] More recently, an analysis of the United Network for Organ Sharing database revealed that only 15.3% (1,561/10,198) of patients with EASL-CLIF ACLF met the criteria for having NACSELD-ACLF, and importantly, 29.9% of patients with EASL-CLIF ACLF grade 3 would not be diagnosed as having ACLF by the NACSELD criteria.[11] Moreover, when the group with no organ failure by NACSELD was stratified by the EASL-CLIF classification, the liver transplant mortality rates were 1.5% (grade 0), 10.5% (grade 1), 43.5% (grade 2), and 86% (grade 3), suggesting that the differences in the prevalence of ACLF between both classification systems have important prognostic implications.[11]

The NACSELD-ACLF criteria select patients who are fundamentally sicker, that is patients who require mechanical ventilation support and/or renal replacement therapy. Thus, the criteria fail to identify patients with a milder degree of organ dysfunction who could potentially benefit from early organ failure reversal. Moreover, identifying patients at an earlier stage of organ failure permits a proactive approach to monitor disease progression, as the occurrence of grade 1 EASL-CLIF ACLF confers a higher risk for a subsequent higher grade of ACLF development compared to patients who have never developed ACLF.[13] Furthermore, compared to the EASL classification, since the pre-requisite for diagnosing renal and respiratory failure using the NACSELD classification is the presence of renal replacement therapy and mechanical ventilation, respectively, this reduces the relevance of the NACSELD criteria in the ward-based setting where patients typically start their hospital admission. Importantly, the NACSELD criteria have limited applicability in the developing world where costly renal replacement therapy and respiratory ventilators may not commonly be found.
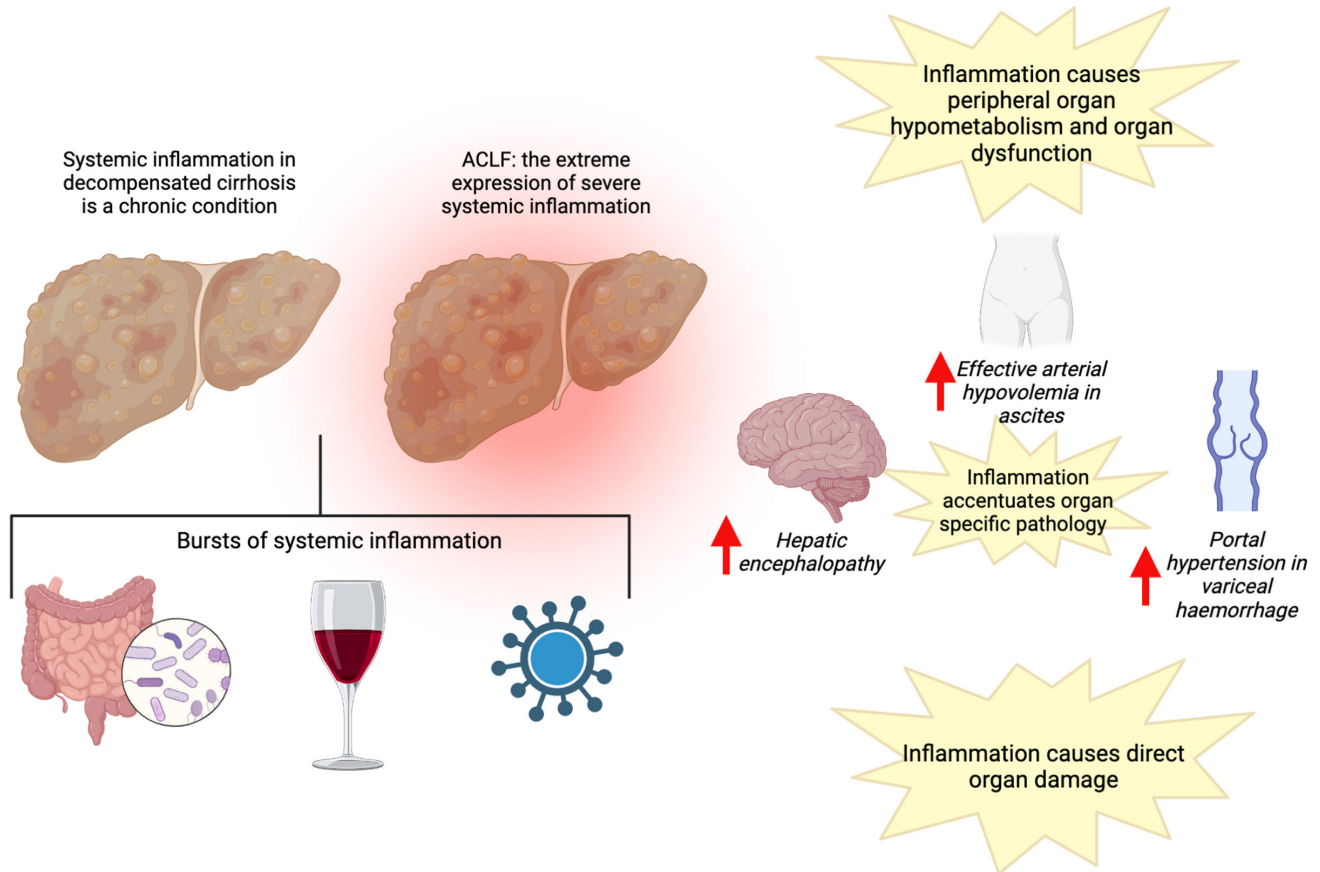
FIGURE 1 The role of systemic inflammation in the development of organ dysfunction in acute-on-chronic liver failure (ACLF). In acutely decompensated cirrhosis, systemic inflammation follows a chronic course, with episodes of hyper-inflammation due to proinflammatory precipitants (e.g., luminal bacterial translocation, alcohol, bacterial infections, or re-activation of hepatitis B). ACLF is the extreme manifestation of systemic inflammation which can cause organ dysfunction and eventual organ failure in three key direct and indirect ways.[159] Firstly, as systemic inflammation is energy intensive, it can cause an energetic trade-off with mechanisms of organ homeostasis. This results in reduced mitochondrial activity in non-immune organs as circulating nutrients (glucose, amino acids, and fatty acids) are shuttled towards enhancing immune hyperactivity, which in turn can cause organ dysfunction.[160–162] Secondly, systemic inflammation can act in synergy with organ-specific mechanisms by enhancing the effect of hyperammonaemia in hepatic encephalopathy,[5,163] aggravating portal hypertension,[164] and increasing effective arterial hypovolaemia in ascites.[6] Thirdly, systemic inflammation can cause direct tissue damage by cytotoxic mediators or the migration of inflammatory cells into tissue.

As for APASL-ACLF, in one analysis using the Veterans Affair administrative dataset, 76.0% (4,296/5,653) patients with EASL-CLIF ACLF did not meet the criteria for APASL-ACLF despite having 28- and 90-day mortality rates of 37.6% and 50.4%, respectively.[14] This suggests that the APASL criteria fail to identify patients with a unique syndrome who have a high short-term mortality and who could potentially be candidates for admission into the ICU or liver transplantation. In another Korean study of patients who met the criteria for APASL and/or EASL-CLIF ACLF ($n = 340$), 58.8% (200/340) met only the criteria for EASL-CLIF ACLF, whereas 19.4% (66/340) met only the criteria for APASL-ACLF, suggesting that the APASL-ACLF criteria would have excluded a significant proportion of patients with 28- and 90-day mortality rates of 32.0% and 48.4%, respectively. There is a level C (low or very low quality) evidence grade for the consensus recommendation to exclude decompensated cirrhosis in the APASL definition of ACLF, and this position has been challenged by the

finding that patients with decompensated APASL-ACLF have a higher mortality rate, especially long-term mortality, compared to patients with non-decompensated APASL-ACLF.[15]

3.1 | Scoring systems

The sequential organ failure assessment (SOFA) score is a well-validated prognostication tool that is used in the ICU but fails to recognise the specific features of cirrhosis.[16] Should patients with ACLF be phenotypically different they deserve different scoring tools to predict prognosis. One such tool, the Chronic Liver Failure-Consortium organ failure (CLIF-C OF) score, was developed using data from the CANONIC study and is used to diagnose organ dysfunction or failure.[17] The CLIF-C ACLF score was developed by combining the CLIF-C OF score with two baseline variables that were identified as the best predictors of mortality: age and white blood

TABLE 1 The definitions of ACLF proposed by different international consortia.

Characteristic	EASL-CLIF	NACSELD	APASL
Basis of definition	The CANONIC prospective observational study.[21]	Analysis of data that were prospectively collected in the NACSELD database.[165]	Consensus document involving international experts from APASL, originally published in 2009[166] and updated in 2014[167] and 2019.[122]
Patient group	Patients with acutely decompensated cirrhosis, with or without prior episode(s) of decompensation.	Patients with acutely decompensated cirrhosis, with or without prior episode(s) of decompensation.	Patients with compensated cirrhosis (diagnosed or undiagnosed) or chronic liver disease who have a first episode of acute liver deterioration due to an acute insult directed to the liver.
Precipitating factor	Intrahepatic (alcoholic hepatitis), extrahepatic (infection, gastrointestinal haemorrhage), or both.	Extrahepatic (infection)	Intrahepatic
Stratification	ACLF is divided into three grades of increasing severity. • ACLF grade 1 includes three subgroups: 1. Patients with single kidney failure. 2. Patients with single liver, coagulation, circulatory or lung failure that is associated with creatinine levels ranging from 1.5 to 1.9 mg/dL or HE grade 1 or grade 2, or both. 3. Patients with single brain failure with creatinine levels ranging from 1.5 to 1.9 mg/dL. • ACLF grade 2 includes patients with two OFs. • ACLF grade 3 includes patients with three OFs or more.	Patients are stratified according to the number of OFs. NACSELD ACLF is defined as two or more OFs of the four described. The four organs include renal (need for dialysis or other forms of RRT), cerebral (HE grade III or IV), shock (MAP <60 mmHg or a reduction of 40 mmHg in systolic blood pressure from baseline, despite adequate fluid resuscitation and cardiac output), pulmonary (need for mechanical ventilation).	Acute hepatic insult manifesting as jaundice (total bilirubin levels of 5 mg/dL or more) and coagulopathy (INR of 1.5 or more or PT of <40%) complicated within 4 weeks by clinical ascites, HE or both. The severity of ACLF is assessed using the AARC score. The grading system defines Grade 1 by scores of 5–7, Grade 2 by scores of 8–10 and Grade 3 by scores of 11–15.
Scoring system	The CLIF-C OF score was developed using data from the CANONIC study and is used to diagnose specific organ dysfunction or failure.[17] The CLIF-C ACLF score was developed by combining the CLIF-C OF score with two baseline variables that were identified as the best predictors of mortality: age and white blood cell count.[17]	The NACSELD-ACLF score is determined by the number of OFs and has been validated in a sample of infected and uninfected patients with cirrhosis.[148]	The AARC-ACLF score was derived from patients enrolled in the AARC study. Five baseline variables (total bilirubin, creatinine, serum lactate, INR and HE) were found to be independent predictors of mortality[168]

Abbreviations: AARC, APASL ACLF Research Consortium; ACLF, acute-on-chronic liver failure; APASL, Asian Pacific Association for the Study of the Liver; CLD, chronic liver disease; CLIF-C ACLF, Chronic Liver Failure Consortium Acute-on-Chronic Liver Failure; CLIF-C OF, Chronic Liver Failure Consortium Organ Failure; EASL-CLIF, European Association for the Study of the Liver - Chronic Liver Failure; HE, hepatic encephalopathy; INR, international normalised ratio; MAP, mean arterial pressure; MELD, Model of End Stage Liver Disease; NACSELD, North American Consortium for the Study of End-stage Liver Disease; OF, organ failure; PT, prothrombin time; RRT, renal replacement therapy.

cell count.[17] The CLIF-C ACLF score has been shown to have higher predictive accuracy (28, 90, 180, and 365 days) and can better predict mortality (28 and 90 days) compared to traditional liver prognostic models, including the Model of End-Stage Liver Disease (MELD), MELD-Na and the Child-Turcotte-Pugh scores.[17]

There are limited data comparing the prognostic power of alcoholic-related liver scoring tools with the CLIF-C scores. In one Indian study of alcohol-related EASL-CLIF ACLF, the CLIF-C ACLF area under the receiver operating characteristic was significantly higher than the Maddrey's discriminant function for predicting

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TABLE 2 Selected studies that have investigated differences in mortality using different ACLF diagnostic criteria.

Reference	Study design	Sample size	Criteria compared	Population	Commonest aetiologies of chronic liver disease	Commonest precipitating factors for ACLF	Key findings
Zhang et al., 2015[169]	Single-centre, retrospective	394	APASL EASL-CLIF	China	• HBV (52.5%) • Alcohol (37.1%)	• Bacterial infection (58.4%) • Superimposed viral hepatitis or reactivation of hepatitis virus (33.5%) • Alcohol (23.4%)	• Among patients with EASL-CLIF ACLF either at enrolment or after enrolment, the 90-day mortality rate was 39.1% for grade 1, 54.1% for grade 2, and 86.7% for grade 3, respectively. • The 90-day mortality rate was 13.1% in patients with APASL-ACLF. • The 90-day mortality rate in patients without EASL-CLIF ACLF both at enrolment and after enrolment was 2.1%.
Kim et al., 2016[170]	Multicentre, retrospective	1470	APASL EASL-CLIF	Korea	• Alcohol (63.1%) • HBV (14.6%)	• Alcohol (40.5%) • GI bleeding (31.2%) • Bacterial infection (9%)	• Patients who only met the EASL-CLIF ACLF definition had significantly lower 28-day (68.0% vs. 93.9%) and 90-day (55.1% vs. 92.4%) survival rates than those who only met the APASL definition. • Patients with previous AD within 1-year had a lower 90-day survival rate (81.0%) than those with AD more than 1 year prior (91.9%) or without previous AD (89.4%). • Patients who had extra-hepatic OF without liver failure had a similar 90-day survival rate (57.0%) to those who had liver failure as a prerequisite (60.6%).
Selva et al., 2017[171]	Single-centre, retrospective	78	APASL EASL-CLIF	Singapore	• HBV (43.6%) • Alcohol (20.5%)	• Infection (59%) • HBV flare (29.5%	• Three-month mortality for ACLF grades 0 to 3 was 0%, 42.9%, 41.7%, and 84.8%, respectively. • Patients who fulfilled the APASL criteria for ACLF exclusively had a 0% mortality rate.
Song et al., 2018[172]	Multi-centre, retrospective study	2017	APASL EASL-CLIF	Korea	• Alcohol (74.6%) • HBV + alcohol (6.3%)	• Alcohol (48.8%) • GI bleeding (26.2%)	• As the ACLF grades increased, the cumulative 28- and 90-day survival rates became significantly lower in patients with ACLF according to the EASL-CLIF definition ($p < 0.05$ and $p < 0.001$). • The 28-day cumulative survival rate of ACLF patients who only satisfied the APASL definition was similar to those of patients without ACLF ($p = 0.177$) • Patients with grade 1 ACLF had a significantly lower cumulative survival rate than those without ACLF (28-day survival rates: $p = 0.003$, 90-day survival rates: $p < 0.001$)
Leão et al., 2019[173]	Single-centre, prospective	146	APASL NACSELD EASL-CLIF	Brazil	• HCV (42.5%) • Alcohol (41.8%)	• Not described	• 29.4% of patients fulfilled EASL-CLIF ACLF criteria, 9.5% of patients fulfilled APASL-ACLF, and 4.1% of patients fulfilled NACSELD-ACLF criteria. • 90-day mortality rate was 78.0% (EASL-CLIF), 64.3% (APASL) and 100% (NACSELD) • When the EASL-CLIF definition was compared to the others (APASL and NACSELD), it proved to be more accurate in predicting death both at 28 and 90 days. On the other hand, there was no significant difference between the performances of NACSELD and AARC definitions.
Mahmud et al., 2019[14]	Veterans Health Administration database, retrospective	80,383	APASL EASL	USA	• HCV (2.2%) • HCV + alcohol (2.2%)	• Not described	• 4,296/80,383 (5.34%) of cirrhotic patients developed EASL-CLIF ACLF whilst 574/80,383 (0.71%) developed APASL-ACLF. • The 28- and 90-day mortalities for APASL ACLF were 41.9% and 56.1%, respectively, and for EASL-CLIF ACLF were 37.6% and 50.4%, respectively. However, patients with APASL ACLF were sicker at baseline (they had a lower MELD score).
Cao et al., 2020[12]	Single-centre, prospective	468	NACSELD EASL-CLIF	China	HBV (57.5%) Alcohol (9.2%)	• HBV flare (27.7%) • HBV flare plus bacterial/fungal infection (19%) • Bacterial/fungal infection (17.5%)	• NACSLED-ACLF criteria outperformed the EASL-CLIF ACLF classification in the prediction of 7-day mortality with significantly higher specificity, positive predictive value and overall accuracy. The NACSELD and EASL-CLIF criteria had comparable sensitivity and negative predictive value for predicting 7-day mortality. • The advantage of the NACSELD-ACLF criteria decreased in predicting 28-day and diminished in predicting 90-day mortality because of the lower sensitivity and negative predictive value compared to the EASL-CLIF ACLF criteria.

TABLE 2 (Continued)

Reference	Study design	Sample size	Criteria compared	Population	Commonest aetiologies of chronic liver disease	Commonest precipitating factors for ACLF	Key findings
Li and Thuluvath, 2021[11]	United Network for Organ Sharing, Retrospective	54,427	NACSELD EASL-CLIF	USA	Alcohol (44%) HCV (13%)	• Not described	• A total of 10,198 (21%) adult patients had EASL-CLIF ACLF grade 1–3, but of these, only 15.3% had NACELD-ACLF. • Of the 2562 with EASL-CLIF ACLF grade 3, only 48.8% had NACSELD-ACLF. • The 30-day transplant-free mortality in those with no OF by NACSELD was 2.7%, but when the same group was stratified by EASL-CLIF grades 0–3, the mortality rates were 1.5%, 10.5%, 43.5%, and 86%, respectively.

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; APASL, Asian Pacific Association for the Study of the Liver; EASL-CLIF, European Association for the Study of the Liver - Chronic Liver Failure; GI, gastrointestinal; HBV, hepatitis B virus; HCV, hepatitis C virus; NACSELD, North American Consortium for the Study of End-stage Liver Disease; OF, organ failure.

in-hospital, 90-day, and 1-year mortality.[18] In a Korean study of 264 patients with alcoholic hepatitis, the performance of the CLIF-C OF score was superior to the Maddrey's discrimination function and Glasgow Alcoholic Hepatitis score.[19] How the CLIF-ACLF score compares with Maddrey's discriminant function, Lille and Glasgow scores requires exploration in future prospective studies.

4 | EPIDEMIOLOGY

The lack of a universally accepted definition makes it challenging to estimate the prevalence and outcomes of ACLF worldwide. In a meta-analysis of 43,206 patients with EASL-CLIF ACLF and 140,835 without EASL-CLIF ACLF, 35% of hospitalised with decompensated cirrhosis had ACLF.[20] ACLF was found to be associated with a 90-day mortality of 58% and extrahepatic triggers, particularly infections, represented the most frequent ACLF triggers. As reflected in the CANONIC study,[21] the meta-analysis identified renal failure as the commonest organ failure in EASL-CLIF ACLF worldwide.

5 | MANAGEMENT

The management of ACLF requires a multidisciplinary collaboration between hepatologists, intensivists, radiologists, microbiologists, anaesthetists, and surgeons. In general, patients with ACLF should be approached using the *PIRO* principles, which addressi the underlying cause of liver disease (*Predisposing factor*), the precipitating event (*Injury*), inflammation or infection (*Response*), and intensive care (*Organ support*).[16,22] Apart from liver transplantation, there are no accepted evidence-based treatments for treating ACLF, but several different approaches are under investigation. This section provides a brief overview of the key management principles of ACLF and a detailed analysis of four specific therapeutic approaches: G-CSF, intravenous albumin, extracorporeal liver support devices, and

liver transplantation. Consensus-based clinical practice guidelines developed by EASL have been published elsewhere.[23]

5.1 | General approach to management

Systemic haemodynamic instability, renal dysfunction, coagulopathy, neurological dysfunction, and respiratory failure are key considerations in the management of ACLF. Organ failure, the criteria for which have been defined by EASL (Figure 2), should be managed in the ICU and the requirement for invasive medical testing and economic burden[24] can often trigger discussions on treatment futility.[25] ICU refusal of patients with ACLF, even if the initial ACLF grade is high, is not supported. Indeed, EASL-CLIF ACLF patients, compared to septic or medical ICU patients who are matched for baseline parameters of illness severity, have a similar ICU course and 90-day mortality.[26] Moreover, the CANONIC study did not identify any subgroup of patients with a mortality rate approaching 100% that could a priori be considered futile for management.[21] With regards to terminating active treatment in the absence of the availability or eligibility for liver transplantation, one study has suggested that patients with a CLIF-C ACLF score >70 after 48–72 h of ICU treatment may reach a threshold of futility for further ongoing ICU support.[27] However, the decision to terminate active treatment must be considered on a case-by-case basis.

5.2 | Management of systemic haemodynamic instability

Distributive and/or non-distributive causes of shock may underlie systemic haemodynamic instability in ACLF, where the former (typically) relates to sepsis and the latter can relate to obstructive shock (e.g., massive pulmonary embolism), hypovolaemic shock (e.g., variceal haemorrhage), and cardiogenic shock.

In ACLF patients with distributive shock, no resuscitation fluid has been shown to produce a predictable and sustained increase in intravascular volume and data on the specific haemodynamic responses
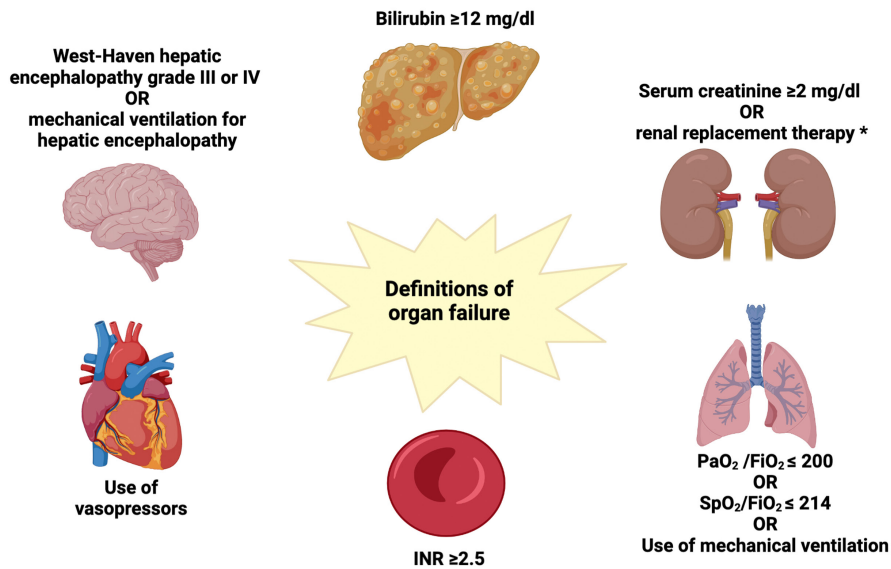
FIGURE 2 The diagnosis of organ failures is based on the Chronic Liver Failure-Consortium Organ Failure (CLIF-C OF) scoring system which assesses six organ systems (liver, kidney, respiration, coagulation, circulation, and brain). These definitions apply to patients non-electively hospitalised for acutely decompensated cirrhosis. Three points are allocated to each of the organ failure described above. *Renal failure is subdivided into different severity: the first stage of renal failure (allocated two points) is where serum creatinine is ≥2 to <3.5 mg/dL; the second stage of renal failure (three points) is where serum creatine is ≥3.5 mg/dL or patients are undergoing renal replacement therapy.

to fluid expansion in cirrhosis are sparce. The goal of resuscitation should be to achieve a mean arterial pressure that ensures organ perfusion, which is generally 60 mm Hg or more. The pivotal Saline versus Albumin Fluid Evaluation (SAFE) study[28] underpins the general recommendation to administer crystalloids (0.9% saline) at an initial dose of 10–20 mL/kg in volume-depleted patients with distributive shock.[29] In this study, investigators reported no difference in 28-day mortality between human albumin solution and crystalloids in 1218 randomised adults with severe sepsis, of whom 36% had septic shock. A subsequent meta-analysis showed that pooled human albumin solution (with or without improvement of baseline hypoalbuminaemia) did not reduce all-cause mortality in adults with sepsis of any severity, including septic shock, in the ICU setting.[30] However, patients with cirrhosis, who could theoretically benefit the most from albumin administration (see section 6.2) were not studied specifically.

Vasoactive drugs, such as norepinephrine or terlipressin, are helpful in situations of persistent hypotension. Although norepinephrine is endorsed as the first-line drug for patients with septic shock who do not respond to adequate fluid resuscitation,[31,32] two meta-analyses have shown no differences in 28-day mortality between patients treated with terlipressin versus norepinephrine.[33,34] In a randomised controlled trial comparing the efficacy of terlipressin and norepinephrine in cirrhotic patients with septic shock, no difference in 28-day mortality was identified between both agents, although terlipressin was significantly more likely to prevent variceal bleeding.[35]

5.3 | Management of renal dysfunction

The International Club of Ascites has recommended that acute renal dysfunction in patients with cirrhosis be classified under the broad heading of acute kidney injury (AKI),[36] which is defined as an acute significant reduction in the glomerular filtration rate. There are several different approaches to grading AKI in patients with cirrhosis and the current definitions depend on absolute or relative changes in serum creatinine and/or urine output. Traditionally, AKI is stratified as pre-renal, renal parenchymal or obstructive in origin. AKI in the context of cirrhosis can also be broadly classified depending on the presence or absence of hepatorenal syndrome (HRS), termed AKI-HRS and AKI-non-HRS, respectively. Causes of pre-renal AKI can include upper gastrointestinal haemorrhage, diuretics, diarrhoea, infection, and HRS. Renal parenchymal AKI may be caused by ischaemic injury, acute interstitial nephritis or glomerulonephritis. Obstructive AKI can be caused by lesions to the ureters or urethra.

The initial approach to the management of AKI in ACLF is the removal of nephrotoxic drugs and the identification of a potential precipitant. The clinical assessment of intravascular volume status is an important first step in correcting hypovolaemia and the type of fluid required for resuscitation should be tailored to the aetiology of AKI. Isotonic crystalloids should be used in cases of intravascular depletion secondary to diarrhoea or overdiuresis, blood in cases of gastrointestinal haemorrhage, and 20%–25% human albumin solution for infections, suspected HRS, or in cases where the case of AKI is unclear.[29]

If renal function does not improve following simple volume expansion, it should be assessed whether the patient fits the criteria for HRS.[36] The goal of treatment in HRS-AKI is the correction of low cardiac output and mean arterial pressure by increasing the effective circulating volume using intravenous human albumin solution combined with systemic vasoconstrictors, such as norepinephrine or terlipressin. ACLF grade is thought to be the

largest determinant of response to terlipressin and albumin.[37] Several meta-analyses have demonstrated that norepinephrine and terlipressin have similar efficacy for HRS reversal with no difference in 30-day survival.[38,39] To date, no head-to-head trial has compared the efficacy of terlipressin versus noradrenaline in the management of HRS in EASL-CLIF ACLF. In one study of patients who fulfilled criteria for APASL-ACLF, terlipressin when used as a continuous infusion led to better rates of HRS reversal (40.0% vs. 16.7%, $p = 0.004$) and to better 28-day survival (48.3% vs. 20.0%, $p = 0.001$) than noradrenaline.[40] As exemplified in the CONFIRM study,[41] caution should be taken if terlipressin and albumin are used together as they may induce pulmonary oedema.

Should medical management not reverse AKI, renal replacement therapy ought to be considered. The indications for renal replacement therapy in ACLF are the same as for the general population: severe and/or refractory electrolyte or acid–base imbalance, severe or refractory volume overload, and/or symptomatic azotaemia.[42] Both continuous renal replacement therapy and haemodialysis have been used in patients with cirrhosis, but continuous renal replacement therapy is perhaps better tolerated as it affords greater cardiovascular stability.[42] Mortality in critically ill cirrhotic patients who require renal replacement therapy is substantially high independent of liver transplantation.[43]

5.4 | Management of coagulopathy

Patients with cirrhosis tend to be in a balanced haemostatic state due to concomitant alterations in pro- and anti-haemostatic pathways.[44] Coagulation changes in ACLF are thought to largely overlap with that of acute decompensation and there is evidence of preserved coagulation capacity in both groups.[45–47] The efficacy of fresh frozen plasma has been found to be similar in patients with compensated/decompensated cirrhosis and ACLF, and the benefits of transfusion in enhancing thrombin generation and reversing coagulopathy are too modest to justify its indiscriminate use.[48]

Despite thrombocytopaenia in cirrhosis,[49] platelet adhesion tends to be preserved in ACLF by increased levels of the platelet adhesive protein von Willebrand Factor (VWF) and decreased levels of the VWF-regulating protease ADAMTS13.[47] Although platelet counts exceeding 50×10^9/L are a practical clinical target in the context of active bleeding,[50] prophylactic fresh frozen plasma and platelet transfusion have a prothrombotic effect in patients with liver disease.[51]

Patients with ACLF have reduced plasma levels of fibrinogen which can be enhanced by fibrinogen concentrate, but not factor XIII or prothrombin complex concentrate (factor II, VII, IX, X), to improve clot quality in vitro.[52] Whether hypofibrinogenemia is independently associated with increased mortality and bleeding events is still hotly contested in the literature.[53,54] A fibrinogen level >120 mg/dL is generally recommended prior to high-risk bleeding procedures or active bleeding, and cryoprecipitate is generally recommended over fresh frozen plasma as it is contained in a smaller volume and will have less overall impact on portal hypertension.[50]

Anaemia has been found to be an independent predictor of ACLF development and can influence mortality in patients with cirrhosis.[55,56] Except in the setting of acute upper gastrointestinal bleeding where a haemoglobin threshold for transfusion of 7 g/dL and a target range after transfusion of 7–9 g/dL is endorsed,[57] an increase in haemoglobin count above a certain threshold is not universally practiced in the management of ACLF.

5.5 | Management of hepatic encephalopathy

The West Haven Criteria are widely used to grade hepatic encephalopathy and determine the progression of disease and impact of treatment, while the Glasgow Coma Scale score guides the need for airway protection. The diagnosis of hepatic encephalopathy should be considered a 'diagnosis of exclusion' as patients with ACLF may suffer from other types of metabolic and non-metabolic encephalopathy, such as psychiatric disorders, cerebrovascular accidents, and drug abuse. As such, laboratory or radiological diagnostics should be considered in ambiguous cases. Following diagnosis, treatment of the precipitating factor for hepatic encephalopathy should occur, e.g., infection control, restoration of electrolyte balance, and/or management of gastrointestinal haemorrhage. Non-absorbable disaccharides, such as lactulose, should be used to achieve two loose stools daily to reduce the quantity of ammonia-producing bacteria,[58] with caution taken to avoid high doses of lactulose which can precipitate hyponatraemia and dehydration. The non-absorbable antibiotic rifaximin is used as secondary prophylaxis and there is currently no robust evidence to support its use in the acute setting of hepatic encephalopathy.[59] In a multi-centre, observational, prospective study of 426 outpatients without previous overt hepatic encephalopathy, researchers developed and validated the AMMON-OHE model, which can be used to identify outpatients at greatest risk for developing a first episode of overt hepatic encephalopathy.[60] The AMMON-OHE model includes sex, diabetes, albumin, creatinine, and ammonia above the upper limit of normal.

5.6 | Management of respiratory failure

Respiratory failure, according to the CLIF-C OF score, is defined by a Horovitz index (PaO_2/FiO_2) < 200 mm Hg. Mechanical ventilation is indicated for respiratory failure and, more broadly, for airway protection in severe hepatic encephalopathy (i.e. West Haven III or IV), gastrointestinal bleeding, and/or upcoming surgery/intervention. There are no studies to suggest that respiratory failure should be managed differently in patients with cirrhosis compared to patients without cirrhosis. However, there are specific cirrhosis-related complications (e.g., hepatic hydrothorax and hepatopulmonary syndrome)

that intensivists should consider as well as tense ascites and chest well oedema that may reduce thoracic compliance and complicated oxygenation.[61]

6 | FOUR KEY THERAPEUTIC APPROACHES UNDER CLINICAL EVALUATION

6.1 | Granulocyte colony-stimulating factor (G-CSF) treatment

Despite overt systemic inflammation, patients with ACLF paradoxically have a degree of immune paralysis (e.g., depletion of memory lymphocytes, CD8$^+$ T cells, and natural killer cells)[62] which may increase a patient's risk of bacterial infection.[63] The aetiology of immune paralysis in ACLF is not clearly elucidated but an overzealous compensatory anti-inflammatory response and immune cell exhaustion from chronic exposure to inflammatory signals (e.g., pathogen-associated molecular patterns) could be responsible.[64]

Bone marrow-derived stem cells have been proposed as a non-invasive approach to rebalance immune perturbation, preserve organ capacity, and foster hepatic regeneration.[65] G-CSF is a glycoprotein that mobilises bone marrow-derived stem cells and is routinely used in haemato-oncology to harvest peripheral blood stem cells for transplantation and hasten neutrophil recovery following chemotherapy.[66] G-CSF is also a powerful immunomodulator and specific, saturable, high-affinity receptors for G-CSF have been found on cells ranging from the myeloblast to the mature neutrophil.[67] For neutrophils, G-CSF can positively augment the maturation process, improve survival and enhance effector function, such as bactericidal activity and phagocytosis.[68] G-CSF therapy may also mobilise IL-19, producing regulatory T cells in peripheral blood[69,70] and plasmacytoid dendritic cells.[71] G-CSF has also been shown to work directly within the liver microenvironment. For instance, oval cells—bipotential stem cells which can differentiate into both hepatocytes and biliary epithelial cells—express G-CSF receptors, and G-CSF has been shown to enhance the endogenous oval cell reaction and increase the migration of bone marrow-derived progenitors to the liver, thus facilitating hepatic regeneration.[72] As such, the putative effect of G-CSF on restoring cell lines, enhancing immune capacity, and driving oval cell reaction may ameliorate inflammation-induced liver injury and promote liver regeneration. Excitingly, in pre-clinical settings, G-CSF has been reported to reduce hepatic injury in models of acute liver injury,[73–76] reduce lipid accumulation in models of non-alcoholic fatty liver disease[77,78], and ameliorate fibrosis in models of chronic liver disease.[79] G-CSF has been evaluated in human subjects with compensated and decompensated cirrhosis,[80–85] and acute alcoholic hepatitis,[86–89] but this review will necessarily restrict its focus on studies that have used one of the diagnostic criteria for ACLF in their methodology (Table S1), followed by a general discussion on the potential advantages and disadvantages of G-CSF in this context.

Clinical trials conducted in Asia have largely supported the use of G-CSF in ACLF,[90,91] whereas studies conducted in Europe have not shown any prognostic benefit of using G-CSF in ACLF.[92] Garg et al[90] conducted one of the earliest randomised controlled trials investigating G-CSF in a group of 47 patients with APASL-ACLF and showed that G-CSF significantly improved survival at day 60 (66% [experimental] vs. 26% [control], $p=0.001$), preserved liver function (MELD and CTP scores), reduced the risk of HRS development (19% [experimental] vs. 71% [control], $p=0.002$), and decreased the risk of sepsis development (14% [experimental] vs. 41% [control], $p=0.04$). In another randomised controlled trial of 55 patients with hepatitis B virus-associated APASL-ACLF,[91] patients treated with G-CSF ($n=27$) were less likely to develop HRS and sepsis compared to a control group ($p=0.027$), had lower CTP and MELD scores at day 30, and had improved 90-day survival rates (48.1% [experimental] vs. 21.4% [control], $p=0.018$). In the only European randomised, multicentre, controlled phase II trial (GRAFT), GCSF failed to demonstrate superiority over standard medical therapy in the treatment of EASL-CLIF ACLF across the different ACLF severity grades and types of organ failures.[92] Indeed, the GRAFT investigators demonstrated that G-CSF did not improve liver function scores, the occurrence of infections, or survival in subgroups of patients without infections, with alcohol-related ACLF, or with ACLF defined by the APASL criteria.

The difference in outcomes between the European and Asian studies is thought to be the result of the fundamentally different diagnostic criteria used to define ACLF. G-CSF administration in the Asian studies occurred prior to the onset of organ failure, which is a phenomenon that characterises EASL-CLIF ACLF, so it is possible that the prognostic benefit of G-CSF may only be seen at the very early stages of hepatic dysfunction. Interestingly, the GRAFT investigators failed to demonstrate the superiority of G-GCF over standard medical therapy even after stratification according to the APASL criteria that were used in the Asian studies. As such, results from the GRAFT study indicate that selection criteria and study design cannot fully explain the differences in efficacy between European and Asian studies.

Clinical studies have largely neglected to model systemic inflammation induced by lipopolysaccharide, which is the bacterial toxin that is widely considered to be the key trigger of the toll-like receptor (TLR)-4 mediated cytokine storm in ACLF. In pre-clinical settings of systemic inflammation, the hepatic expression of lipopolysaccharide-binding protein—an acute phase protein mainly produced by the liver—is upregulated following G-CSF therapy,[93,94] and G-CSF induced lipopolysaccharide-binding protein expression can enhance hepatic inflammation through upregulating expression of lipopolysaccharide receptors, such as TLR-4.[94] G-CSF pre-treatment has also been found to aggravate lipopolysaccharide-induced portal hypertension and microcirculatory disorders, which suggests that G-CSF may induce lipopolysaccharide-sensitisation.[95] As such, the beneficial effects of G-CSF in ACLF may be limited by the fact that G-GCF requires a non-inflammatory environment to exert its protective effects on the liver.[96]

Increased levels of serum G-CSF have been reported in patients with systemic inflammatory response syndrome (SIRS) compared to those without SIRS[9] and it is possible that G-CSF, in the setting of systemic inflammation, is contributing to 'emergency haematopoiesis'. Therefore, additional G-CSF in the setting of pre-existing inflammation may accelerate the cytokine storm. This 'double-edged sword' characteristic of G-CSF, which depends on the inflammatory environment in which it is administered, is supported by the finding that TLR-4 inhibition with TAK-242 can prevent lipopolysaccharide and G-CSF-driven tissue injury and can induce liver regeneration.[97] As such, inhibiting the lipopolysaccharide/TLR-4 pathway prior to G-CSF administration may represent a promising strategy to harness the therapeutic potential of G-CSF, which should be explored in future randomised controlled trials. Further studies combining G-CSF alongside a TLR-4 receptor antagonist are underway (www.a-tango.eu).

Numerous uncertainties remain for using G-GCF in the management of ACLF. There is a lack of global representation in the studies investigating G-CSF in ACLF as studies have principally taken place in Europe and Asia. Moreover, the optimal dosing regimen of G-CSF as well as the time points at which G-CSF should be administered have not yet been investigated in randomised controlled trial settings. Data on the underlying aetiology of liver disease that would best respond to G-CSF therapy are also lacking. Until answers are sought to the above questions, it is not possible to recommend G-CSF as a treatment for ACLF.

6.2 | Albumin

Albumin is a negatively charged, globular, water-soluble 67 kDa protein which is exclusively synthesised in hepatocytes and accounts for approximately 75% of plasma oncotic pressure.[98] Albumin has been studied in the field of hepatology since the early 1950s and 1960s when intravenous albumin was first described for the management of cirrhotic patients with hypoalbuminaemia and ascites.[99] Since its first description, current evidence-based guidance recommends the use of human albumin solution in large-volume paracentesis,[100] HRS,[101] and spontaneous bacterial peritonitis.[102]

In addition to its pro-oncotic property, albumin is a powerful anti-inflammatory and anti-oxidative agent (Figure 3) that circulates in a reduced state with a free thiol group in the cysteine-34 residue, which acts as a free radical scavenger for reactive oxygen species and nitrogen species. Free cysteine-34 accounts for approximately 80% of the antioxidant capacity of human plasma[103] and is vulnerable to reversible and irreversible changes in the presence of systemic oxidative stress. Indeed, in the presence of oxidative stress, cysteine-34 can be converted from its reduced form with cysteine-34

DOMAIN 1: metal binding domain which binds to and removes toxic reactive metal species

DOMAIN 2: binds a variety of substances such as long-chain fatty acids, bilirubin, anions, bile acids, endotoxin, hormones, and eicosanoids

Albumin

DOMAIN 3: contains a free thiol group in the cysteine-34 residue, which is capable of reducing oxidative stress through thiolation, nitrosylation, and oxidation
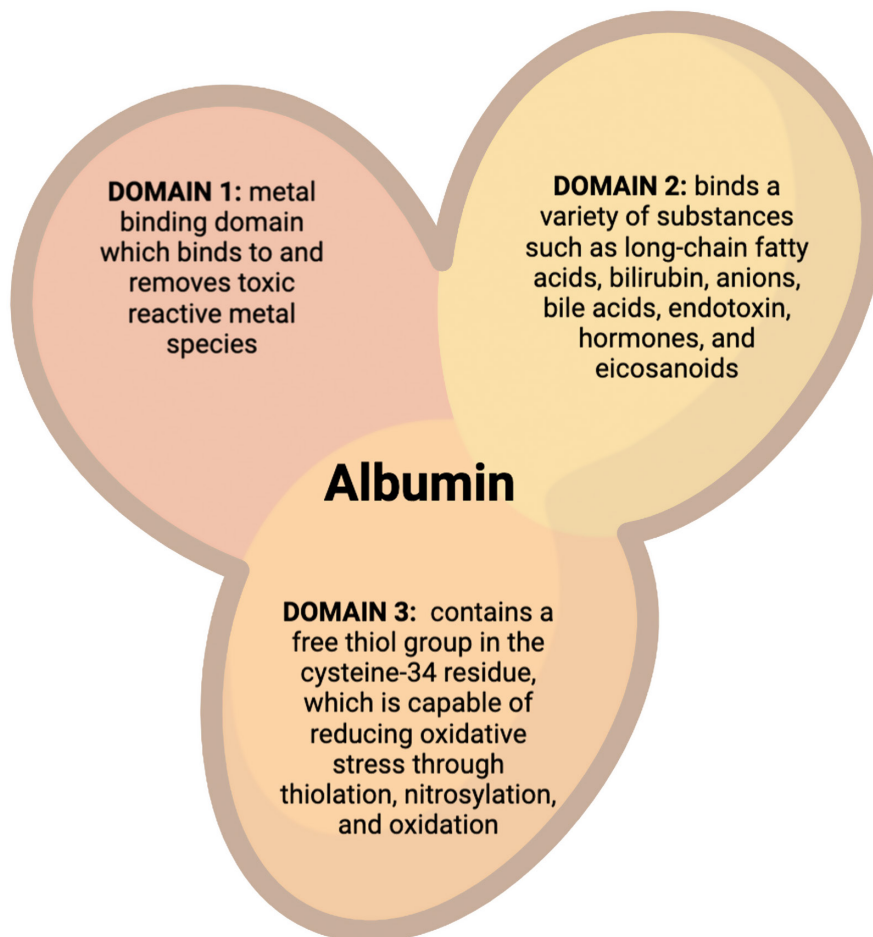
FIGURE 3 The three-domain structure of albumin which helps it serve numerous anti-inflammatory and anti-oxidative activities.

in the free sulphydryl form (human mercaptalbumin) into human non-mercaptalbumin-1 and human non-mercaptalbumin-2: these changes are reversible and irreversible, respectively.[9,104] Oxidative stress of cysteine-34 is associated with the severity of cirrhosis and the extent of systemic inflammation,[9,105] and is strongly associated with the frequency and severity of ACLF.[9] Besides cysteine-34, other pathophysiological post-transcriptional changes to albumin that can occur in the presence of oxidative stress and systemic inflammation include truncation of the N-terminal and C-terminal portions, glycosylation, and dimerization.[106,107] As the concentration of damaged serum albumin increases, the proportion of preserved albumin decreases in parallel, which provides the rationale to administer intravenous albumin in order to increase the 'effective albumin concentration' i.e. albumin that has a preserved functional integrity which can be substantially lower than total albumin concentration routinely measured in clinical practice.[108] At least six seminal trials have assessed the efficacy of albumin infusions in the context of long-term administration (ANSWER, MACHT and pilot-PRECIOSA) and in patients hospitalised for decompensation (INFECIR-2 and ATTIRE), with results that can be extrapolated to the ACLF arena. These trials and their relevance to ACLF are outlined in Table S2.

6.2.1 | Trials of long-term albumin infusion in patients with decompensated cirrhosis

The ANSWER trial elucidated the importance of exogenous albumin infusions during the period leading up to extrahepatic organ dysfunction and ACLF. In this trial, investigators recruited patients with cirrhosis (stable for at least 4 days before enrolment) and persistent uncomplicated ascites despite ongoing diuretic treatment.[109] Patients were randomised to standard medical treatment or standard medical treatment plus human albumin (40 g twice weekly for 2 weeks, and then 40 g weekly) for up to 18 months. The investigators showed that the incidence rate of spontaneous bacterial peritonitis and other bacterial infections, which often precipitate ACLF, were significantly lower in the experimental group compared to the control group. In addition, compared to the control group, the incident rates of extrahepatic organ dysfunction, such as renal dysfunction, HRS type 1, and hepatic encephalopathy were significantly lower in the experimental group. The favourable effects of long-term albumin infusions in improving cognitive function and hepatic encephalopathy in outpatients with cirrhosis have also been demonstrated in the HEAL study.[110]

The MACHT trial threw down the gauntlet in response to the ANSWER trial by demonstrating that long-term administration of midodrine and albumin (40 g every 15 days) showed no improvement in mortality or reduction in complications (AKI, hyponatraemia, infections, hepatic encephalopathy or gastrointestinal bleeding).[111] The MACHT study was a multicentre, randomised, double-blind, placebo-controlled study which recruited decompensated cirrhotic patients on the waiting list for liver transplantation. The discrepancy between both studies may be explained by the fact that patients in the ANSWER trial possibly had a superior baseline liver function (median MELD score 12 vs. mean MELD score 17), suggesting that patients with a greater degree of preserved liver function may be more likely to respond to intravenous human albumin solution. Importantly, the serum albumin level had largely normalised for patients in the experimental arm of the ANSWER trial, which was not the case for the MACHT trial, suggesting that sub-therapeutic albumin infusions may not have any prognostic benefit.

The pilot-PRECIOSA study investigated the effect of administering albumin in non-infected, hypoalbuminaemic patients with decompensated cirrhosis and severe circulatory dysfunction as defined by the presence of ascites, renal dysfunction (serum creatinine ≥1.2 mg/dL or blood urea nitrogen ≥25 mg/dL or dilutional hyponatremia [serum sodium ≤130 mEq/L]), plasma renin activity ≥2 ng/mL/h), and need for diuretic treatment to prevent ascites recurrence (at least 200 mg of spironolactone or 100 mg of spironolactone and 40 mg of furosemide).[112] Two doses of intravenous albumin were evaluated: 1.5 g/kg weekly versus 1 g/kg every 2 weeks over the course of 12 weeks. The high-dose albumin regimen, but not the low-dose albumin regimen, was found to be associated with normalisation of serum albumin, improved stability of the circulation and left ventricular function, and reduced plasma levels of cytokines (interleukin-6, granulocyte colony-stimulating factor, interleukin-1 receptor antagonist, and vascular endothelial growth factor) without significant changes in portal pressure. These promising immune-modulatory effects of albumin observed in the Pilot-PRECIOSA study were confirmed in the INFECIR-2 study.[112]

6.2.2 | Trials of albumin administration in acutely decompensated cirrhosis patients

The INFECIR-2 investigators conducted a multicenter, open-label study to demonstrate that hospitalised patients with cirrhosis and non-spontaneous bacterial peritonitis infections treated with antibiotics and albumin (experimental group) had a higher rate of ACLF resolution and a lower proportion of nosocomial infections compared to antibiotics alone (control group).[113] Patients in the experimental arm had significantly suppressed levels of systemic inflammation reflected by a reduced white blood cell, c-reactive protein, and plasma interleukin-6. However, despite these changes, the in-hospital mortality was not different among both arms, which may possibly reflect a subtherapeutic intravenous albumin regimen, given the fact that only 24.5% (12/49) patients in the experimental arm had increased their serum albumin concentration to within the normal range.

The ATTIRE investigators recruited patients with and without ACLF who had a serum albumin level <30 g/L at enrolment and who were randomly allocated to receive either targeted 20% human albumin solution to increase albumin level to ≥30 g/L for up to 14 days or until discharge, whichever came first, or standard care.[114] From the immune analysis of serum samples collected by the ATTIRE investigators as part of their feasibility trial,[115] China et al. demonstrated

that raising serum albumin above 30 g/L reversed plasma-mediated immune dysfunction by binding and inactivating prostaglandin E_2. Prostaglandin E_2 has been shown to drive cirrhosis-associated immunosuppression[116] and albumin has been reported to bind and catalyse prostaglandin E_2 inactivation.[117] Despite experimental findings in favour of albumin infusion, the ATTIRE phase III randomised controlled trial concluded that albumin infusions to increase the albumin level to a target of 30 g/L or more was not more beneficial than standard medical treatment, and there was no statistically significant difference in the incidence of circulatory dysfunction, respiratory dysfunction, new cerebral dysfunction, or mortality, between both arms.

Although the ATTIRE study should not discourage clinicians from using albumin for recognised indications (large volume paracentesis, HRS and spontaneous bacterial peritonitis), they do not support its targeted use to maintain an arbitrary serum albumin level. A randomised controlled trial that recruits patients with EASL-ACLF and studies the impact of albumin infusion is lacking. Interestingly, a recent meta-analysis has shown that albumin may have the potential to improve hepatic encephalopathy and reduce mortality in patients with cirrhosis,[118] but there is a dearth of evidence in the field and current guidance does not endorse hepatic encephalopathy as an indication for albumin infusion.

6.3 | Extracorporeal liver support

Extracorporeal liver support devices operate outside the body whereby whole blood or plasma passes through a dialysis, adsorption or cellular filter in order to remove circulating toxins and/or provide functional substances to a patient.[119] The 'gold-standard' extracorporeal liver support device should execute three primary hepatic functions: detoxification, stimulation of liver regeneration, and prevention of further hepatic injury.[120] Extracorporeal liver support devices are broadly classified as 'artificial' or 'biological', whereby the former serves a purely detoxifying role, and the latter incorporate hepatocytes into the device to provide functional biological activities. Artificial extracorporeal liver support devices mostly rely on the concept of albumin dialysis and plasma exchange. A summary of the different artificial and biological extracorporeal liver support devices that have been used in the context of ACLF are listed in Table S3.

6.3.1 | Artificial dialysis membranes

Plasma exchange—which operates by using a plasma filter to remove blood plasma and replace it with fresh frozen plasma—has been suggested in one network meta-analysis to be the best currently available extracorporeal liver support device in ACLF regarding 3-month overall survival.[121] The 2019 APASL consensus guidelines also state that 'plasma exchange appears to be a promising and effective bridging therapy in patients with ACLF to liver transplant or spontaneous

regeneration [1, C]'.[122] Although the effect of plasma exchange on survival in ACLF has been studied in several clinical trials,[123–126] most studies relate to cirrhosis caused by viral hepatitis which reduces the generalisability of the studies, especially to European cohorts. A global trial of plasma exchange (APACHE trial) is currently ongoing [NCT03702920].

In the molecular adsorbent recirculating system device, a patient's blood is circulated across an albumin-impermeable membrane against a 20% human albumin solution dialysate, which has been studied in numerous randomised controlled trials for the management of ACLF.[127–129] It was not shown to improve survival in the RELIEF study, which was a large, adequately powered, randomised controlled trial.[127] However, a recent meta-analysis of 165 patients treated with standard medical care and the molecular adsorbent recirculating system demonstrated that high-intensity therapy (≥5 sessions) significantly improved 10- and 30-day mortality compared to standard medical care alone, which was independent of ACLF grade.[130]

The Fractionated Plasma Separation and Adsorption device, also known as Prometheus, is another albumin-based extracorporeal liver support device. Prometheus operates using a primary circuit, in which blood passes through a large pore filter (250–300 kDa cut-off membrane) into a secondary circuit in which albumin-bound toxins are removed via two adsorption columns containing charcoal.[131–136] The HELIOS study—the only randomised controlled trial investigating the influence of Prometheus on survival—showed no difference in 28- or 90-day survival for ACLF patients treated with Prometheus + standard medical therapy compared to Prometheus alone.[135] However, on sub-group analysis, patients with an MELD score of >30 showed a statistically significant 90-day survival benefit with Prometheus therapy compared to standard medical therapy alone.[135]

Evidence suggests that liver failure irreversibly destroys the detoxifying function of albumin[137] and damaged albumin in patients with ACLF can also induce an inflammatory response.[138] DIALIVE is a new extracorporeal liver support device that is used alongside an albumin infusion to achieve the removal and replacement of dysfunctional albumin and physically remove pro-inflammatory cytokines. In a first-in-man randomised controlled trial of patients with alcohol-related ACLF (primary endpoint: safety), there was no significant difference in 28-day mortality or occurrence of serious adverse events between patients treated with DIALIVE (5-day treatment duration) versus the non-DIALIVE (control) group[139] DIALIVE resulted in a significant reduction in the severity of endotoxemia and improvement in albumin function, which translated into a significant reduction in the CLIF-C OF and CLIF-C ACLF scores. Compared to control group participants, patients in the DIALIVE group had a significantly faster resolution of ACLF and a significant reduction in biomarkers of systemic inflammation (e.g., interleukin-8 and ligands for TLR-4). An adequately powered trial is now needed to determine whether DIALIVE leads to improvement in survival.

6.3.2 | Biological dialysis membranes

The Extracorporeal Liver Assist Device (ELAD) is the most widely researched biological extracorporeal liver support device in which human hepatoblastoma (HepG2/C3A) cells mimic in-vivo functions, such as albumin synthesis and cytochrome P450 activity.[119] Several studies have explored the use of ELAD in ACLF.[140–142] In a phase III multicentre, randomised controlled trial setting, the efficacy of standard medical therapy + ELAD was compared to standard medical therapy alone in the treatment of severe alcoholic hepatitis.[142] No difference was observed in the overall survival at any time point (51% vs. 49.5%, log-rank $p=0.90$).

Differences in ACLF definition and differences in the ratio of viral and alcoholic aetiology of cirrhosis have generated a highly heterogeneous cohort of clinical trial patients that have been treated with extracorporeal liver support to-date. The DIALIVE machine is the only extracorporeal liver support device to have been tested in a randomised controlled trial of ACLF patients using EASL-ACLF criteria.[143] Future studies should explore whether specific cohorts of patients, such as those within a certain range of MELD/CLIF-C OF scores, are more likely to respond to extracorporeal liver support[135] and the effect of treatment intensity.[130] Based on the lack of survival benefit studied in randomised controlled trials, EASL does not currently endorse the use of extracorporeal liver support in the management of decompensated cirrhosis.[42]

6.4 | Liver transplantation

There are robust data supporting the role of liver transplantation in the management of ACLF[144–146] and a summary of these studies is listed in Table 3. Patients with ACLF are frequently encountered on the liver transplant waiting list. Indeed, in one European-wide study, 45.6% of patients on the liver transplant waiting list received a transplant for decompensated cirrhosis and, of these, approximately one fifth (19.2%) had ACLF at liver transplant: 4.8% (ACLF-1), 6.4% (ACLF-2) and 8.1% (ACLF-3).[146] In the same study, 1-year survival of patients with ACLF on the liver transplant waiting list was 73% for ACLF-1 or -2 and 50% for ACLF-3, providing strong evidence for the potential need for liver transplantation as a rescue treatment for ACLF,[146] which is supported by a recent meta-analysis.[147]

ACLF-specific scores (e.g., CLIF-C ACLF[17] and NACSELD ACLF[148,149] scores) have greater accuracy in predicting mortality in patients with ACLF compared to the traditionally used organ allocation scores, such as the MELD score, but are not currently used to allocate liver transplants on the waiting list. It has been shown that patients with ACLF-3 are more likely to die or be removed from the waitlist, regardless of MELD-Na score, compared with the other ACLF groups, and the proportion is greatest for patients with an ACLF-3 score and MELD-Na score below 25 (43.8% at 28 days).[145] Clearly the traditional scoring tools disadvantage patients with ACLF as they fail to include factors that impact short- and long-term mortality, for example extrahepatic organ injury, age, and white blood cell count. Given the significance of ACLF in organ allocation, a novel score to predict waitlist mortality has been developed which includes age, MELD score, aetiology, ACLF grade, sex, ethnicity, obesity, and Karnofsky score.[150] This requires further validation to reduce deaths among patients on the transplant waiting list who have ACLF.

Despite the benefits afforded by liver transplantation in ACLF, there is significant heterogeneity in the percentage of liver transplants performed in patients with ACLF between different European countries, ranging from 25% to 40% of all liver transplants in France and Germany to fewer than 6% in the United Kingdom and Spain.[146] This suggests that referral and access to liver transplantation for patients with ACLF across Europe needs to be harmonised to avoid inequities.[151]

There is currently no consensus on the optimal timing of liver transplantation or the patient characteristics which should deny or delay liver transplantation in ACLF. Although patients with ACLF-3 have greater 14-day waitlist mortality than status 1a patients,[152] higher grades of ACLF have anecdotally been considered 'too sick' for liver transplantation. Outcomes from the United Network for Organ Sharing database provide compelling evidence that liver transplantation improves outcomes in ACLF-3 patients.[145] Among patients who receive a liver transplant within 30 days of transplant listing, 1-year survival ranges from 84% with three organ failures to 81% with 5–6 organ failures.[153] In patients with no contraindications to transplantation (e.g., active gastrointestinal bleeding, severe pancreatitis, or suspicion of ongoing infection), there is evidence favouring early (<30 days) transplantation from the onset of ACLF-3. However, data also support delaying transplantation whilst waiting for some improvement in the severity of ACLF, since 1-year post-transplant survival substantially has been shown to be greater in patients listed with ACLF 3 who improved to ACLF grades 0–2 versus those who remained at ACLF 3 at listing and liver transplant.[154] This said, only 25% of patients with ACLF-3 improve to a lower grade of ACLF, so waiting for organ failure recovery may not be practical in most ACLF-3 liver transplant candidates.[154]

Factors associated with relatively poor post-liver transplant outcomes include severe co-morbidities, uncontrolled infection with multidrug-resistant organisms, presence of fungal infection, respiratory failure, requirement for dual inotropes and lactate levels that remain above 9 mmol/L.[155] The transplantation for ACLF-3 model (TAM) score has been proposed as a helpful tool to predict 1-year mortality following transplantation among patients with ACLF-3, which includes the following variables: age, arterial lactate, respiratory failure and white cell count.[156] More recently, the Sundaram ACLF-liver transplant-mortality (SALT-M) score has been developed by USA-based investigators based on data from 521 patients with ACLF grades 2/3, which was subsequently validated using European data.[157] The SALT-M model includes the following variables: age >50 years, use of 1/2+ inotropes, presence of respiratory failure, diabetes mellitus, and body mass index. The c-statistic for the SALT-M score was 0.8 (based on the validation cohort), which presents a compelling argument for the use of this model to predict 1-year

TABLE 3 Studies that have investigated mortality following liver transplantation for ACLF.

References	Country	Illness severity	Number of patients with ACLF who underwent liver transplantation	EASL-CLIF ACLF grade at diagnosis for patients who underwent liver transplantation (number)			Key data related to mortality
				EASL-CLIF ACLF grade 1	EASL-CLIF ACLF grade 2	EASL-CLIF CLIF-ACLF grade 3	
Finkenstedt et al[174]	Australia	APASL	33	–	–	–	Post-LT survival probability for ACLF patients with a mean follow-up of 29 months (range: 52–85 months): 85%
Karvellas et al[175]	Canada	Mean SOFA score at LT: 14.0	198	–	–	–	Post-LT 90-day survival probability: 84% Post-LT 1-year survival probability: 74% Post-LT 3-year survival probability: 62%
Hong et al[176]	Korea	APASL	44	–	–	–	Post-LT 30-day survival probability for ACLF patients: 95.9% Non-LT (control group) 30-day survival probability for ACLF patients: 74.8% Post-LT 1-year survival probability for ACLF patients: 83.5% Non-LT (control group) 1-year survival probability for ACLF patients: 56.2%
Levesque et al[177]	France	EASL-CLIF ACLF	140	68	42	30	Post-LT 90-day survival probability in ACLF grade 1 or grade 2: 84.5% Post-LT 1-year survival probability in ACLF grade 1 or grade 2: 77.2% Post-LT 90-day survival probability in ACLF grade 3: 60% Post-LT 1-year survival probability in ACLF grade 3: 43.3
Huebener et al[178]	Germany	EASL-CLIF ACLF	98	24	45	29	Post-LT 90-day survival probability: 72.4%
Artru et al[144]	France	EASL-CLIF ACLF	337	119	145	73	Post-LT 1-year survival probability for ACLF grade 3 patients: 83.9% Post-LT 1-year survival probability for non-transplanted patients hospitalised in the ICU with multiple organ dysfunction (control group): 7.9% Post-LT survival probability for ACLF-3 was not different from that of matched control patients with no ACLF (90%), ACLF-1 (82.3%) or ACLF-2 (86.2%).
Michard et al[179]	France	EASL-CLIF ACLF	55	–	–	–	Post-LT 1-year survival probability for ACLF patients: 60%
Moon et al[180]	Korea	WCG	190	–	–	–	Post-LT 1-year survival probability for ACLF patients: 79.5% Post-LT 3-year survival probability for ACLF patients: 73.6% Post-LT 5-year survival probability for ACLF patients: 72.1%
Bernal et al[181]	UK	OF or the requirement for organ support, that is the presence of high-grade HE, use of RRT or mechanical ventilation	65	–	–	–	Post-LT 1-year survival probability: 90%
O'Leary et al[182]	USA	NACSELD-ACLF	57	–	–	–	Post-LT 3-month survival probability for ACLF patients: 94% Post-LT 6-month survival probability for ACLF patients: 93%
Thuluvath et al[153]	USA	Three or more OF (defined using CLIF criteria)	3556	–	–	–	Post-LT 1-year survival probability: 83.7%
Bhatti et al[183]	Pakistan	EASL-CLIF ACLF	60	43	15	2	Post-LT 30-day survival probability for ACLF grade 1 patients: 4.6% Non-LT (control group) 30-day survival probability for ACLF grade 1 patients: 60% Post-LT 30-day survival probability for ACLF grade 2 patients: 6.6% Non-LT (control group) 30-day survival probability for ACLF grade 2 patients: 68.4% Post-LT 30-day survival probability for ACLF grade 3 patients: 0% Non-LT (control group) 30-day survival probability for ACLF grade 3 patients: 80% Post-LT 90-day survival probability for ACLF grade 1 patients: 4.6% Non-LT (control group) 90-day survival probability for ACLF grade 1 patients: 80% Post-LT 90-day survival probability for ACLF grade 2 patients: 6.6% Non-LT (control group) 90-day survival probability for ACLF grade 2 patients: 84% Post-LT 90-day survival probability for ACLF grade 3 patients: 0% Non-LT (control group) 90-day survival probability for ACLF grade 3 patients: 92%

TABLE 3 (Continued)

References	Country	Illness severity	Number of patients with ACLF who underwent liver transplantation	EASL-CLIF ACLF grade at diagnosis for patients who underwent liver transplantation (number)			Key data related to mortality
				EASL-CLIF ACLF grade 1	EASL-CLIF ACLF grade 2	EASL-CLIF CLIF-ACLF grade 3	
Sundaram et al[145]	USA	EASL-CLIF ACLF	21,269	7375	7513	6381	Post-LT 1-year survival probability for ACLF grade 1: 89.1% Post-LT 1-year survival probability for ACLF grade 2: 81.1% Post-LT 1-year survival probability for ACLF grade 3: 81.8% Post-LT 1-year survival probability for ACLF grade 3 not requiring mechanical ventilation: 85.4% Post-LT 1-year survival probability for ACLF grade 3 requiring mechanical ventilation: 75.3% Important: There was a high mortality among patients with ACLF-3 on the liver transplant waitlist, even among those with lower MELD-Na scores, so certain patients with ACLF-3 have poor outcomes regardless of MELD-Na score.
Marciano et al[184]	Argentina	EASL-CLIF ACLF	60	34	18	8	Post-LT 1-year survival probability for ACLF patients: 84.9%
Agbim et al[185]	USA	EASL-CLIF ACLF	101	50	32	19	Post-LT 1-year survival probability for ACLF patients: 82%
Artzner et al[156]	France/UK	EASL-CLIF ACLF	152	–	–	152	Post-LT 28-day survival probability for ACLF patients: 85.5% Post-LT 90-day survival probability for ACLF patients: 77% Post-LT 1-year survival probability for ACLF patients: 67.1%
Belli et al[146]	Eight European countries	EASL-CLIF ACLF	234	58	78	98	Post-LT 1-year survival probability for ACLF patients: 81%
Chen et al[186]	China	APASL	29	–	–	–	Post-LT 1-year survival probability for ACLF patients: 87% Non-LT (control group) 1-year survival probability for ACLF: 42.7%
Toshima et al[187]	Japan	Japanese ACLF criteria	31	–	–	–	Post-LT 30-day survival probability for ACLF patients: 90.3% Post-LT 1-year survival probability for ACLF patients: 80.4% Post-LT 5-year survival probability for ACLF patients: 69.4%
Xia et al[188]	China	EASL-CLIF ACLF APASL	EASL-CLIF: 162 APASL: 230	18	97	47	Post-LT 3-year survival for EASL ACLF grade 1 patients: 83.0% Post-LT 3-year survival for EASL ACLF grade 2 patients: 80.3% Post-LT 3-year survival for EASL ACLF grade 3 patients: 69.8% Post-LT 3-year survival for APASL ACLF grade 1 patients: 85.7% Post-LT 3-year survival for APASL ACLF grade 2 patients: 84.5% Post-LT 3-year survival for APASL ACLF grade 3 patients: 75.6%
Artzner et al[189]	Eight European countries	EASL-CLIF ACLF	98	–	–	98	Post-LT 1-year survival probability for ACLF patients: 79%

Abbreviations: ACLF, acute-on-chronic liver failure; APASL, Asian Pacific Association for the Study of the Liver; EASL-CLIF, European Association for the Study of the Liver – Chronic Liver Failure; LT, liver transplant; NACSELD, North American Consortium for the Study of End-stage Liver Disease; SOFA, sequential organ failure assessment.

mortality among patients with severe ACLF who are being considered for liver transplantation. However, both the TAM and SALT-M scores were developed using retrospective data, so further validation of both scores is required.

Although there is strong evidence favouring liver transplantation across all grades of ACLF, several unanswered questions remain, including the best organ allocation system for this population, objective criteria to define when liver transplantation could be futile, the optimal timescale for liver transplantation, and the ideal organ donor characteristics to ensure the best graft and overall survival outcomes. It is hoped that the CHANCE (liver transplantation in patients with CirrHosis and severe ACLF: iNdications and outcome) prospective observational study will answer these questions, which is an ongoing (NCT04613921) collaborative effort between the EASL-CLIF Consortium, International Liver Transplantation Society, and the European Liver and Intestine Transplant Association. The overall aim of this international study is to investigate 1-year graft and patient survival rates after liver transplantation in patients with ACLF-2 or -3 at the time of liver transplantion compared to patients with decompensated cirrhosis and patients with ACLF-2 or -3 who do not receive a transplant (i.e. transplant-free survival rate).

7 | CONCLUSION

Compared to decompensated cirrhosis, ACLF is a clinically and pathophysiologically distinct syndrome that is associated with organ failure and high short-term mortality. The recognition of ACLF as a distinct entity from 'mere' decompensation has allowed for better patient

stratification in clinical settings, facilitating earlier engagement with the ICU and liver transplantation teams. The global prevalence of ACLF in patients admitted with decompensated cirrhosis is as high as 35%,[20] thus distilling an evidence-based management approach for care is essential. Unfortunately, the evidence base is fractured by the heterogeneity of ACLF definitions,[158] so there remains a need to unify a definition to support research studies. In addition to ICU support, liver transplantation is an accepted treatment strategy for this condition, and research priorities over the next decade should focus on which, when, and how patients with ACLF should be treated with emerging therapeutic agents.

AUTHORSHIP

Guarantor of the article: Mohsin Butt.

AUTHOR CONTRIBUTIONS

MFB wrote all versions of the manuscript. RJ reviewed the manuscript for important scientific content. Both MFB and RJ approved the final manuscript. **Mohsin F. Butt:** Conceptualization (equal); data curation (equal); methodology (equal); writing – original draft (lead); writing – review and editing (equal). **Rajiv Jalan:** Conceptualization (equal); methodology (equal); project administration (equal); supervision (lead); writing – review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

RJ has research collaborations with Takeda, and Yaqrit, and consults for Yaqrit. RJ is the founder of Yaqrit Limited, which is developing UCL inventions for treatment of patients with cirrhosis. RJ is an inventor of ornithine phenylacetate, which was licensed by UCL to Mallinckrodt. He is also the inventor of Yaq-001, DIALIVE and Yaq-005, the patents for which have been licensed by his University into a UCL spinout company, Yaqrit Ltd. He is also a co-founder of Hepyx Ltd and Cyberliver Ltd. MFB has no conflicts of interest.

ORCID

Mohsin F. Butt https://orcid.org/0000-0003-0859-6470
Rajiv Jalan https://orcid.org/0000-0002-7747-4015

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.