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OPINION REVIEW

Acute-on-chronic liver failure: Controversies and consensus

Natalie L Y Ngu, Eliza Flanagan, Sally Bell, Suong T Le

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Abstract

Acute-on-chronic liver failure (ACLF) is a poorly defined syndrome characterised by rapid clinical deterioration in patients with chronic liver disease. Consequences include high short-term morbidity, mortality, and healthcare resource utilisation. ACLF encompasses a dysregulated, systemic inflammatory response, which can precipitate extra hepatic organ failures. Common precipitants include infection, alcoholic hepatitis, and reactivation of viral hepatitis although frequently no cause is identified. Heterogenous definitions, diagnostic criteria, and treatment guidelines, have been proposed by international hepatology societies. This can result in delayed or missed diagnoses of ACLF, significant variability in clinical management, and under-estimation of disease burden. Liver transplantation may be considered but the mainstay of treatment is organ support, often in the intensive care unit. This review will provide clarity around where are the controversies and consensus in ACLF including: Epidemiology and resource utilisation, key clinical and diagnostic features, strategies for management, and research gaps.

Key Words: Acute-on-chronic liver failure; Liver cirrhosis; End stage liver disease; Epidemiology; Mortality

Core Tip: Acute-on-chronic liver failure is characterised by rapid clinical deterioration in patients with chronic liver disease. Consequences include high short-term morbidity, mortality, and healthcare resource use. Heterogenous definitions, diagnostic criteria, and treatment guidelines create further challenges to optimal care. This review summarises epidemiology and resource utilisation, key clinical features, strategies for management, and research gaps.

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INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a well-recognised syndrome of rapid clinical deterioration in those with chronic liver disease (CLD). It is associated with high short-term mortality of 22%-74%[1-3]. The prevalence and impact of ACLF is likely underestimated as there is no consensus definition nor diagnostic criteria[4]. The systemic inflammatory response in ACLF often results in extra-hepatic organ failures and frequently necessitates intensive care unit (ICU) level support[5]. The key management principles in the acute phase of ACLF includes the diagnosis and treatment of underlying triggers such as infection, and provision of organ support[1,6,7]. For those surviving to hospital discharge, there is limited guidance for management in the post-admission period and although comparable evidence is scarce, re-admission rates are likely to be 30%-40%[8,9]. In this article, we review the current areas of controversies and consensus with regards to ACLF epidemiology, economic impact, clinical manifestations, diagnostic criteria, and management principles.

EPIDEMIOLOGY

In European populations, the CANONIC study[1] demonstrated 30% prevalence amongst patients admitted with cirrhosis, of which ACLF was the presenting complaint in 20% of hospital admissions using the European Association for the Study of the Liver criteria. In North America, one study demonstrated a 24% prevalence using the North American Consortium for the Study of End Stage Liver Disease criteria, which includes bacterial infection as a criterion[10]. In a study of 565 patients who underwent liver transplantation in Shanghai, China; 41% had ACLF according to Asian Pacific Association for the Study of the Liver (APASL) criteria[11].

The primary aetiology of underlying CLD and the precipitant for ACLF is likewise reflective of local region and definitions. Historically, chronic hepatitis B through vertical transmission has been the most frequent cause of CLD, particularly in Asian populations from which the APASL criteria was derived (49%-59%)[12,13]. Globally, alcohol use disorder has likely overtaken chronic hepatitis B as the most common aetiology for CLD and precipitant of ACLF[13]. The most common precipitating events for ACLF in order of frequency are bacterial infections, alcohol excess, and hepatitis B reactivation[14,15]. The latter remains the most common precipitant for ACLF in Asia[12]. The absence of an identifiable precipitant in up to 40% of patients is a significant contributor to the diagnostic uncertainty and variability in criterion applied[1].

ECONOMIC IMPACT

There is limited data on the total economic burden of ACLF, although this has been explored for cirrhosis and chronic liver disease in Australia[16] and internationally[17-19]. Current cost estimations are extrapolated from cirrhosis populations and mostly reported from the healthcare payer/provider perspective[6]. The indirect costs of ACLF such as lost productivity and disability may be significant, but its value has not been extensively quantified[20]. Whilst hospital-based costs or direct healthcare related costs can be theoretically analysed through application of diagnostic criteria or International Classification of Disease coding to health service records, there is a paucity of data on indirect costs related to disability, impact on carers, and premature mortality.

Direct healthcare costs are related to the number of organ failures, need for ICU support, and total length of stay. Each of these direct cost components are disproportionately higher in ACLF compared to decompensated cirrhosis alone[7]. A population-based cohort study in Thailand demonstrated a 3.5-fold average cost of hospitalization for ACLF compared to hepatic decompensation, using the North

American Consortium for the Study of End-Stage Liver Disease (NACSELD) definition of ACLF of two or more extrahepatic organ failures in patients with cirrhosis[7]. A national inpatient database study from the United States similarly demonstrated increasing annual liver-related hospital expenditure between 2001 and 2011. Inpatient costs increased 2-fold for cirrhosis to $9.8 billion and 5-fold for ACLF to $1.7 billion[6]. The global trend of an increasing prevalence of CLD and incidence of ACLF worldwide[17,21] will further compound the economic burden for healthcare systems.

There are no proven cost-effective interventions for ACLF treatment, which is primarily supportive care in addition to addressing underlying aetiologies and precipitants[19]. Treatments evaluated include intravenous human albumin transfusions which have not demonstrated a mortality benefit in ACLF[22] and variable mortality benefit in hepatic decompensation[23,24]. Indirect ACLF-related costs have been captured in large studies on the global burden of CLD. These suggest a 1.5% contribution to all disability-adjusted life years in 2016, which was more pronounced in countries with a lower socio-demographic index[17,25]. This data may overlook discrepancies in outcomes in countries such as Australia with a higher socio-demographic index as a proxy of development, where Indigenous Australians with cirrhosis have disproportionately higher rates of hospital re-admission and death than non-Indigenous Australians[26]. To reduce healthcare-related costs, interventions for ACLF must achieve the Holy Grail of reduced short-term mortality, length of stay, readmission, and organ failure. Additionally, early use of prognostic scores such as NACSELD-ACLF[10] or chronic liver failure (CLIF)-C ACLF[27] should be routinely applied to accurately predict those who with a poor prognosis and may be better suited to palliative care and thus reduce ineffectual resource allocation.

CLINICAL MANIFESTATIONS AND DIAGNOSTIC CRITERIA

There is no universally accepted set of diagnostic criteria for ACLF, with variable criteria identified by four major international hepatology associations[28,29]. Lack of a consensus remains problematic with the potential for delayed or missed diagnoses, and challenges in applying evidence-based treatment. There is clinical consensus that ACLF is a distinct syndrome to acute hepatic decompensation, however, patients may initially present with clinical features of a decompensating event including worsening of abdominal ascites, jaundice, gastrointestinal bleeding and hepatic encephalopathy (HE)[30]. Features of bacterial infection, such as urinary tract infection, pneumonia, or spontaneous bacterial peritonitis, with may also be present[5]. Organ failure is a hallmark of ACLF and can include renal failure and manifestations of this (such as uremia, acidosis, oliguria), respiratory and circulatory failure[2]. Beyond these non-specific clinical manifestations, the regionally relevant set of diagnostic criteria diverge in the exact thresholds and subtypes of how and what they classify as ACLF.

The *World Gastroenterological Organisation* (WGO) has proposed criteria to identify clinical, prognostic, and pathophysiologic subtypes[3] and define ACLF as an independent syndrome. Five requirements have been stipulated including: (1) Distinction from acute liver failure; (2) distinction from hepatic decompensation; (3) definition of pathophysiology; (4) definition of specific clinical signs and laboratory tests to confirm diagnosis and exclude other disease; and (5) a validated scoring system to assess severity. A system categorising ACLF into three subtypes is shown in Table 1.

The APASL criteria includes a serum bilirubin level ≥ 50 mg/L and International Normalized Ratio (INR) ≥ 1.5 complicated by ascites and/or encephalopathy within 4 wk in a patient with previously diagnosed or undiagnosed chronic liver disease or cirrhosis[31].

The European Association for the Study of the Liver (EASL) and the CLIF consortium definition requires concomitant organ failure and provides prognostication guidance according to the grading of severity[1,27]. ACLF is explicitly excluded in the absence of extra-hepatic organ failure, defined as renal failure with serum creatinine ≥ 2.0 mg/dL or single non-kidney organ failure with HE to meet criteria for low grade ACLF[1]. ACLF severity grading and criteria are summarised in Table 2, with the scoring system and organ system involvement shown in Table 3. The 28-d mortality is graduated from 23.3% in grade 1 to 75.5% in grade 3[1]. Most patients meeting ACLF criteria in the latter cohort required intensive care unit support, highlighting the greater disease severity and associated resource utilisation in this diagnostic system.

The NACSELD criteria was developed as a bedside tool to predict 30-d survival in hospitalised patients with cirrhosis with decompensation in the context of infection[11,32]. The NACSELD-ACLF is defined as two or more of the following organ failures: Brain failure (West-Haven grade 3 or 4 encephalopathy), renal failure (need for renal replacement therapy), respiratory failure (need for bilevel positive airway pressure or mechanical ventilation), and shock (the need for vasopressor support, mean arterial pressure < 60 mmHg, or a reduction of > 40 mmHg in systolic blood pressure from baseline despite adequate fluid resuscitation). Validation studies have demonstrated that the NACSELD-ACLF predicts survival in infected and uninfected hospitalised patients with cirrhosis, and similarly to EASL criteria, demonstrates that the number of organ failures strongly predicts survival[10].

The WGO clinical sub-types were proposed early in the identification of ACLF as a distinct clinical entity and are a useful bedside tool. However, WGO criteria have limited correlation with prognosticating mortality and resource use[3]. The other three definitions (APASL, CLIF-C ACLF and

Table 1 World Gastroenterological Organisation definitions of acute-on-chronic liver failure subtypes[30]

Type A-noncirrhotic	Type B-compensated cirrhosis	Type C-decompensated cirrhosis
Acute flare of noncirrhotic CLD resulting in liver failure including hepatic encephalopathy	Rapid deterioration of previously well-compensated cirrhosis after major insult such as hepatitis (drug, viral, alcoholic), infection, or surgery	Rapid deterioration in those with previous hepatic decompensation

CLD: Chronic liver disease.

Table 2 The European Association for the Study of the Liver and chronic Liver Failure Consortium grading of acute-on-chronic liver failure severity[12,25]

ACLF Grade	Criteria
No ACLF	No organ failure or; one organ failure (liver, coagulation, circulatory, respiratory) with serum creatinine < 1.5 mg/dL and no HE or single cerebral failure and serum creatinine < 1.5 mg/dL
Grade 1	Single kidney failure or single liver, coagulation, circulatory, or respiratory failure + serum creatinine 1.5-1.9 mg/dL and/or HE I-II or single cerebral failure (HE III-IV) + serum creatinine 1.5-1.9 mg/dL
Grade 2	2 organ failures
Grade 3	3 or more organ failures

HE: Hepatic encephalopathy; ACLF: Acute-on-chronic liver failure.

Table 3 Defining organ/system failure using Chronic Liver Failure-Acute-on-Chronic Liver Failure Sequential Organ Failure Assessment scoring[12]

Organ system	Parameter	Score = 1	Score = 2	Score = 3
Liver	Serum bilirubin (mg/dL)	< 6	6-12	> 12
Kidney	Serum creatinine (mg/dL)	< 2	2.0-3.5	≥ 3.5 or renal replacement therapy
Brain	West-Haven grade	0	I-II	III-IV
Coagulation	INR	< 2.0	2.0-2.5	≥ 2.5
Circulation	MAP (mmHg)	≥ 70	< 70	Vasopressors
Respiratory	PaO2/FiO2	> 300	≤ 300 and > 200	≤ 200
	OR SpO2/FiO2	> 357	> 214 and ≤ 357	≤ 214

INR: International Normalized Ratio; MAP: Mean arterial pressure, mmHg millimeters of mercury; PaO2: Partial pressure of arterial oxygen; FiO2: Fraction of inspired oxygen; SpO2: Pulse oximetric saturation.

NACSELD) have better correlation with mortality, primarily due to correlation with objective biochemical parameters, and organ failures with respect to the CLIF-C ACLF criteria. The APASL criteria require the presence of CLD but not necessarily cirrhosis, and that the acute precipitating event must be liver-related[33]. Conversely, CLIF-C ACLF criteria stipulates the presence of underlying cirrhosis, extra-hepatic organ failures and the acute precipitating event can be of non-hepatic origin[32]. Therefore, ACLF populations identified using APASL criteria may include more patients with hepatic decompensation, who may not have the same short-term mortality and economic burden as those with ACLF defined otherwise by EASL. The NACSELD criteria incorporates organ failures but does not specify values for pulse oximetry or arterial blood gases to guide ventilation and therefore is potentially more vulnerable to subjectivity compared to EASL criteria. Recent clinical guidelines published by Bajaj *et al*[34] suggest that none of the current sets of criteria are adequate to inform management. In summary, organ failure appears to be an important marker of mortality in ACLF and is a component of diagnostic criteria for two of the four major definitions described. Standardisation of ACLF definition and management protocols is a critical unmet clinical need. It is the cornerstone to prompt diagnosis, evidence-based management, and reduced population heterogeneity in the research setting.

MANAGEMENT PRINCIPLES

Despite high short-term mortality[35,36], ACLF management is primarily supportive and focuses on reversing organ failure. The key pathophysiologic drivers of systemic inflammation and paradoxical immunoparesis have no specific therapy at present[36], so addressing the precipitating factors, prevention and management of end-organ complications, and targeted organ support constitute the foundations of care[4,31]. However, more than 30% of patients still progress to multiorgan failure and death within 30 d of diagnosis. Model for End-Stage Liver Disease including serum sodium (MELD-Na) and Child-Pugh Scoring systems have limited prognostic integrity as they do not account for the cerebral, respiratory or circulatory dysfunction that accompanies ACLF[5,31].

The APASL ACLF Research Consortium (AARC) ACLF score is a prognostic model constructed from the AARC database. It incorporates five variables, including lactate, grade of HE, INR, bilirubin and serum creatinine levels[37] to stratify patients into grade 1 (score of 5-7), grade 2 (score of 8-10) or grade 3 ACLF (score of 11-15), with 28 day mortality rates of 12.7%, 44.5%, and 85.9% respectively[30]. Grade I ACLF are said to have potential recovery, grade II require intensive monitoring and grade III need immediate intervention and consideration of transplantation[30]. Scores of > 10 should be considered for transplant. This has been predominantly validated in an Asian population. Alternate scoring systems include the CLIF-ACLF SOFA score and the CLIF-Consortium ACLF scores (CLIF-C ACLF). These dynamic scoring systems allow for better prognostication of 28-d mortality rate, hence assisting stratification of ACLF[38-40]. The CLIF-C ACLF score incorporates the CLIF-C Organ Failure score (bilirubin, creatinine, INR, West-Haven grade for encephalopathy, mean arterial pressure and PiO2/FiO2 ratio), along with age and white cell count[5,41]. This has been validated as a prognostic tool in ACLF[2,40], with emerging evidence for its use in guiding treatment options. A CLIF-C ACLF score > 70 represents a subgroup in whom defining limitations of care and futility is important given their very poor predicted outcomes[30,39,41].

Increasingly there appears to be a role for liver transplantation (LT) in a select cohort of these critically ill patients. The percentage of LT performed for ACLF varies significantly between transplant centres and even within regions[4,41,42], which reflects the considerable debate around the concept of liver transplant as a therapeutic strategy. The median transplant-free mortality rate in ACLF is 30%-40% at 28-d[1,40], increasing to 75% for grade 3 ACLF[1], and 40%-60% overall at 6 mo[40,42]. A recent consensus[43,44] developed by 35 international experts from North America and Europe suggested that contraindications to transplant include PaO2/FiO2 < 150 mmHg, noradrenaline dose > 1 μg/kg/min and/or serum lactate > 9[43]. Those who recover from their initial ACLF event are at high risk of recurrent and more severe ACLF in the future[45]. Whilst at this stage transplantation in advanced ACLF is the only curative intervention available, it is associated with higher postoperative complications and longer ICU and hospital stays compared to other indications[30]. Whilst scoring systems are useful in defining timing for LT escalation and features suggesting futility, clinical and ethical challenges remain in the referral and activation of appropriate candidates.

Common precipitating events in ACLF include bacterial infection, alcoholic hepatitis, gastrointestinal bleeding, HE, and reactivation of hepatitis B in endemic regions[41,46]. In European cohorts, bacterial infection is the most common precipitant[30,41], including spontaneous bacterial peritonitis, urinary tract infections and pneumonia[30]. Bacterial infection also predicts the development of organ failure in ACLF[31], hence early detection and treatment of infection are imperative. ACLF patients have higher rates of multi-drug resistant bacteria and demonstrate a lower infection resolution rate[12]. Antimicrobial choice should incorporate local guidelines and involve prompt initiation of empiric broad spectrum antibiotics whilst awaiting sensitivity profiles[4,31,44].

Acute Kidney Injury (AKI) is a frequent feature of ACLF and considered a strong predictor of poor survival in the short and long term[36,47,48]. There is significant overlap between hepatorenal syndrome AKI (HRS AKI) and non-HRS AKI in ACLF. Isolated HRS is believed to only represent a fraction of ACLF renal complications[38]. The management of renal dysfunction in ACLF requires the exclusion of reversible causes, including nephrotoxic contributors, and optimising circulating blood volume to ensure adequate renal perfusion[38,49]. Volume expansion with intravenous albumin and continuous intravenous terlipressin is recommended for those meeting HRS-AKI criteria[49]. Continuous terlipressin infusion is preferable to bolus regimes due to the improved tolerability and reduction in adverse effects[38,49]. Noradrenaline is a possible alternative to terlipressin, with a 2016 meta-analysis of four studies (154 patients) demonstrating no superiority with regards to survival in patients treated with terlipressin *vs* noradrenaline[50]. Renal replacement therapy has historically been restricted to patients with AKI who fail the above methods and have clinical or laboratory indications as per the general AKI guidelines, and this has been translated to the ACLF population given the lack of validated data around this specific cohort[38,49]. There are also unanswered questions regarding the specific benefit of rapid correction of electrolyte abnormalities and hyperammonemia in the ACLF cohort[38].

HE in ACLF is associated with higher mortality, correlating with increasing grades of HE[51]. Management involves identification and treatment of precipitants as well as specific measures for reducing hyperammonaemia and systemic inflammation[31]. Treatment of concomitant infection, drugs and electrolyte abnormalities must always be considered and excluded[38]. Cerebral imaging should be

performed to exclude an alternative cause of altered neurology, especially given the increased risk of bleeding and clotting in this cohort[38]. Ammonia lowering therapies are the cornerstone for managing HE with lactulose as the first line agent (oral, nasogastric or rectal preparations) followed by Rifaximin as second-line therapy[38]. Continuous veno-venous haemofiltration use in acute liver failure has been associated with clinically significant reductions in serum ammonia levels and is a recognised treatment for HE in these patients[52]. There have been no large randomised controlled trials to elucidate the role for haemofiltration or haemodialysis in lowering serum ammonia levels in ACLF[38].

Variceal and other types of bleeding can precipitate ACLF and should be managed similarly to those with decompensated CLD. Non-selective beta-blockers should be continued even in patients with ascites[30,31,53]. Their use is thought to reduce systemic inflammation and have favourable effects beyond their potential haemodynamic benefits[31,53] and should only be ceased in those with haemodynamic instability[44]. Circulatory failure should be managed with volume expansion, and if haemodynamic instability persists, the use of vasopressors, aiming for a mean arterial pressure of ≥ 65 mmHg[44]. Bleeding in the ACLF cohort is predominantly secondary to portal hypertension whilst spontaneous haemorrhage is rare[54]. Historic plasma-based coagulation tests are poor predictors of bleeding in chronic liver disease[55,56]. Newer viscoelastic assays, such as thromboelastography and rotational thromboelastometry assess whole blood, which may be superior and preferential to standard laboratory testing in clinical practice but their role in ACLF management is poorly defined[38,57].

CONCLUSION

ACLF is a distinct and severe clinical entity, separate from hepatic decompensation, with high short-term mortality, healthcare resource utilisation, and poorly defined treatment goals. Clinical diagnosis and management are limited by variable definitions and diagnostic criteria. Future focuses for research should including investigating and defining specific clinical and biomarkers for prognostication and classification of ACLF subtypes, standardisation of prognostic scores for both clinical management and population stratification in clinical trials, and further evidence to support the role for liver transplantation in a well-defined cohort most likely to demonstrate long term benefit.

FOOTNOTES

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