Acute-on-chronic liver failure: Objective admission and support criteria in the intensive care unit

Victor Dong,[1] Constantine J. Karvellas[1,2,*]

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Summary

Cirrhosis is a leading cause of morbidity and mortality throughout the world. Significant complications include variceal bleeding, hepatic encephalopathy, hepatorenal syndrome, and infection. When these complications are severe, admission to the intensive care unit (ICU) is often required for organ support and management. Intensive care therapy can also serve as a bridge to liver transplantation. Along with decompensation of cirrhosis, the concept of acute-on-chronic liver failure (ACLF) has emerged. This involves an acute precipitating event, such as the development of infection in a patient with cirrhosis, which leads to acute deterioration of hepatic function and extrahepatic organ failure. Extrahepatic complications often include renal, cardiovascular, and respiratory failures. Patients with significant extrahepatic and hepatic failures need ICU admission for organ support. Again, in patients who are deemed suitable liver transplant candidates, intensive care management may allow bridging to liver transplantation. However, patients with a Chronic Liver Failure Consortium ACLF score greater than 70 at 48 to 72 hours post-ICU admission do not seem to benefit from ongoing intensive support and a palliative approach may be more appropriate.

Introduction

Liver cirrhosis is a progressive disease characterised histologically by formation of regenerative nodules and bridging fibrous bands.[1] It continues to be a leading cause of morbidity and death throughout the world. The most common aetiologies of cirrhosis in the Western world are non-alcoholic fatty liver disease, alcohol abuse, and chronic hepatitis C infection.[2] Within Asia and sub-Saharan Africa, chronic hepatitis B infection remains the most common aetiology.[2]

Although patients may remain asymptomatic with normal liver function and compensated disease, morbidity and mortality from cirrhosis occur because of decompensation, which is driven by portal hypertension and systemic inflammation and their complications.[3] These complications include development of and bleeding from oesophageal and gastric varices, hepatic encephalopathy (HE), ascites, infection, hepatorenal syndrome (HRS), portopulmonary hypertension, and hepatopulmonary syndrome.[4] Development of decompensated liver disease is significant as it results in a decline in median survival from 12 years to only 2 years in patients with cirrhosis.[5]

In recent years, the concept of acute-on-chronic liver failure (ACLF) has been recognised as a separate clinical presentation from hepatic decompensation in cirrhotic patients. ACLF is characterised by acute and rapid deterioration of hepatic function, after an acute precipitating event, resulting in liver failure and extrahepatic organ failures.[6] It is associated with significant short-term mortality.[7] Although the exact definition lacks standardisation around the world, it is accepted that ACLF leads to the involvement of a variety of extrahepatic organs, including the renal, cardiovascular, and respiratory systems.[8] The 3 most widely used definitions are region specific (Asia, Europe, and North America). The World Gastroenterology Organization has proposed that ACLF be defined as a syndrome in patients with chronic liver disease characterised by an acute hepatic decompensation leading to liver failure in the form of jaundice and elevated international normalized ratio (INR), along with at least one extrahepatic organ failure as a way of unifying the definition of ACLF across regions.[9] Currently, the most widely used definition of ACLF is based on the European Association for the Study of the Liver-Chronic Liver Failure Consortium (EASL-CLIF) Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study.[10]

ACLF is an important syndrome since it is relatively common and often necessitates intensive care unit (ICU) admission for intensive organ support. Its prevalence is about 31% in patients presenting with acute decompensation of cirrhosis.[10] Its incidence in stable outpatients with cirrhosis is 14% after 12 months.[11] It even carries a greater mortality risk than decompensated cirrhosis, as demonstrated by a recent study showing a 90-day mortality rate of 34% in patients with ACLF compared to 1.9% in patients with decompensated cirrhosis.[10] ACLF is divided into 3 grades depending on the number of extrahepatic organ failures

[1]*Division of Gastroenterology, University of Alberta, Edmonton, Canada*
[2]*Department of Critical Care Medicine, University of Alberta, Edmonton, Canada*

* Corresponding author. Address: Department of Critical Care Medicine, Division of Gastroenterology (Liver Unit), University of Alberta, 1-40 Zeidler Ledcor Building, Edmonton, Alberta, Canada T6G 2X8.
E-mail address: dean.karvellas@ualberta.ca (C.J. Karvellas).

present, as defined by the chronic liver failure-sequential organ failure assessment (CLIF-SOFA) score (Table 1). Grade 1 ACLF involves patients with only renal failure, patients with a single organ failure combined with renal dysfunction (creatinine between 1.5 mg/dl to 1.9 mg/dl) and/or mild to moderate HE (West Haven grade 1 or 2 [Table 2]), or patients with HE and renal dysfunction. Grade 2 ACLF involves patients with 2 organ failures and grade 3 ACLF involves at least 3 organ failures (Table 3).[10] The relevance of grading ACLF based on the number of organ failures is based on studies showing that mortality significantly increases as the number of organ failures increase in patients with ACLF, as shown in a study where 28-day mortality based on ACLF grade was 22%, 32%, and 77% for grade 1, grade 2, and grade 3 ACLF, respectively.[10]

Patients with cirrhosis who require hospitalisation are often managed in a non-intensive care setting. However, when complications of decompensated liver disease (variceal bleeding, HE, infection, or HRS) are severe or when ACLF develops with extrahepatic organ failure (renal, cardiac, or pulmonary failure) ICU admission is often required for organ support and attempts at reversal of organ dysfunction, especially as a bridge to liver transplant (LT) in patients who are candidates. However, consideration of ICU admission in cirrhotic patients can be a challenge. This is due to the often irreversible nature of the disease course without LT and the need to balance limited resources, cost, and benefit against futility. Therefore, scores like the Chronic Liver Failure Consortium ACLF (CLIF-C ACLF) score have been proposed and utilised to determine the prognosis of patients with ACLF and to determine when initiating and continuing intensive care treatment in patients with cirrhosis and ACLF is futile.

However, presently, there are no objective criteria for refusal of ICU admission in patients with cirrhosis based solely on initial prognostic scores or severity of illness.[12] Neither the CLIF-C ACLF score nor the severity of ACLF at initial diagnosis demonstrate any absolute cut-off level for which there is complete futility in intensive care management. Thus, careful consideration is required when deciding on ICU admission.

Key points

Acute on chronic liver failure (ACLF, cirrhosis with organ failure) often requires intensive care (ICU) support.

The most common reason for ICU admission in ACLF is infection.

Prognosis in ACLF is dependent on candidacy for liver transplantation and the burden of multiorgan failure.

In patients who are not transplant candidates who have persistent organ failure after a brief period of support (72 hours), a palliative approach may be more appropriate.

Complications indicating intensive care unit admission

As stated, patients with cirrhosis may develop decompensated disease with portal hypertension and functional impairment of the liver, resulting in numerous complications including infection, variceal bleeding, HE, and HRS.[13] Patients with cirrhosis may also develop ACLF, leading to renal, cardiovascular, and respiratory failures. Such complications, when severe, represent indications for management in an intensive care setting (Table 4).

Infection

Bacterial infections are a leading complication in patients with decompensated liver disease. Bacterial infections are present in around one-third of patients with decompensated cirrhosis and account for up to 50% of deaths.[14,15] Patients with cirrhosis have a relative immunodeficiency that puts them at risk of developing infections. A lack of complement and protein C production by the liver impairs the adaptive immune response.[16] Splenomegaly as a consequence of portal hypertension leads to sequestration of immune cells, further reducing the activity of the cellular immune system.[17] Along with a weakened immune system, altered gut microflora and translocation of intestinal bacteria also contribute to the development of infection.[18] Major clinical risk factors for development of infection include recent infection within the past 12 months, malnutrition, and a model for end-stage liver disease (MELD) score of 15 or more.[19] Overall, the most common types of infection encountered by decompensated cirrhotic patients are spontaneous bacterial peritonitis (SBP), urinary tract infections, bacteraemia, pneumonia, and skin infections.[20]

Table 1. Chronic liver failure-sequential organ failure assessment (CLIF-SOFA) score.

System	0 Points	1 Point	2 Points	3 Points	4 Points
Bilirubin (mg/dl)	<1.2	1.2 to <2.0	2.0 to <6.0	6.0 to <12.0	≥12.0
Creatinine (mg/dl)	<1.2	1.2 to <2.0	2.0 to <3.5	3.5 to <5.0	≥5.0 or dialysis
Hepatic encephalopathy grade	0	1	2	3	4
International normalized ratio	<1.1	1.1 to <1.25	1.25 to <1.5	1.5 to <2.5	≥2.5 or platelet count <20 x 10^9/L
Mean arterial pressure (mmHg)	≥70	<70	Dopamine ≤5 or dobutamine or terlipressin	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
PaO_2/FiO_2	>400	>300 to 400	>200 to 300	>100 to 200	≤100

Coloured areas indicate diagnostic criteria for organ failures.
FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen.

Table 2. West Haven Grade for hepatic encephalopathy.

Stage	Clinical features
0	No abnormalities
1	Alterations in behaviour Mild confusion Disordered sleep
2	Lethargy Moderate confusion Asterixis
3	Somnolent but arousable
4	Coma

Bacterial infections are also a major precipitant of ACLF and patients with ACLF not triggered by infection are at high risk of developing bacterial infections. In a study by Fernandez and colleagues, 37% of patients with ACLF had a bacterial infection at the time of ACLF diagnosis.[21] The severity of ACLF, as measured by the prevalence of organ failures and the need for critical care and organ support, was greater when ACLF was caused by infection than if it developed from non-infectious aetiologies.[21] Bacterial infections also conferred increased mortality in patients with ACLF, leading to a 90-day transplant free mortality of 51% compared with 38% in patients who did not have an infectious trigger.[21] Infectious complications developed in 46% of patients with ACLF who did not initially present with an infection and were significantly more frequent in patients with acute decompensation The development of infection also resulted in a significant 90-day transplant free mortality rate of 51%.[21]

Cirrhotic patients have a hyperdynamic circulation with elevated cardiac output, decreased arterial pressure, and reduced systemic vascular resistance. If infection occurs, these patients develop an even more hyperdynamic circulation and become less responsive to alpha-adrenergic agonists.[22] Therefore, cirrhotics are more likely to develop sepsis and progress to septic shock with multiorgan failure from infection, which is a strong indication for ICU admission.[23,24] Currently the use of the Sepsis-3 criteria involving an acute change in the SOFA score (Table 5) of 2 or more points and the simplified quick SOFA (qSOFA) score (Table 6) of at least 2 is advocated for the early identification of cirrhotic patients with sepsis and those who need to be admitted to the ICU.[24,25]

Table 3. Grading of acute-on-chronic liver failure.

Grade of ACLF	Clinical features
0	No organ failure Single non-renal organ failure, creatinine <1.5 mg/dl, no HE
1	Single renal failure Single non-renal organ failure, creatinine 1.5-1.9 mg/dl, and/or grade 1-2 HE
2	Two organ failures
3	Three or more organ failures

ACLF, acute-on-chronic liver failure; HE, hepatic encephalopathy.

Overall these patients have higher mortality rates when compared to septic shock patients without cirrhosis.[22]

One major goal of therapy is the early initiation of appropriate empiric broad spectrum antibiotics.[21] The presence of multidrug-resistant (MDR) bacteria needs to be considered as the global prevalence of MDR bacterial infections in cirrhotics is 34% with variations in prevalence and type of bacteria depending on geographical location.[26] Usage of an empiric antibiotic regimen with appropriate antimicrobial coverage resulted in improved clinical outcomes and mortality.[21,26] Other goals of therapy include attaining euvolemia and maintaining adequate tissue perfusion.[21,27] As such, treatment often requires ICU admission to allow for adequate resuscitation and management of the underlying infection through the use of fluids, vasopressors, and antibiotics.[28] This enables clinicians to target a mean arterial pressure (MAP) of at least 65 mmHg for sufficient organ perfusion.[29]

Variceal bleeding

Oesophageal and gastric varices are portosystemic collaterals that develop as a consequence of portal hypertension and are present in about 50% of cirrhotic patients with the frequency increasing with worsening liver function.[30] Acute variceal bleeding occurs at a rate of up to 15% per year with the greatest risk factor being variceal size.[31] As a varix enlarges, vessel wall tension increases significantly, making it more likely to rupture. Mortality from variceal haemorrhage ranges from 30% to 50% and is a result of exsanguination or progressive hepatic failure.[32] Due to the significant mortality associated with variceal bleeding, intensive care management is often required.

Given the massive amount of haemorrhaging that may occur, airway protection from aspiration through tracheal intubation is often needed.[33] Tracheal intubation may prevent fatal episodes of

Table 4. Objective criteria for ICU admission in patients with cirrhosis.

Type of complication	Criteria for ICU admission
Infection	Septic shock Change in SOFA score ≥2 qSOFA score ≥2
Variceal bleeding	Haemorrhagic shock Tracheal intubation for airway protection Need for balloon tamponade
Hepatic encephalopathy	Grade 4
Renal failure	Development of hepatorenal syndrome not responsive to medical management (withdrawal of nephrotoxic medications and volume replacement with albumin) Acute need for renal replacement therapy
Respiratory failure	PaO_2/FiO_2 <200
Cardiovascular compromise	Refractory hypotension

FiO2, fraction of inspired oxygen; ICU, intensive care unit; PaO2, partial pressure of arterial oxygen; qSOFA, quick SOFA; SOFA, sequential organ failure assessment.

Table 5. Sequential organ failure assessment score.

System	0	1	2	3	4
Respiratory					
PaO_2/FiO_2 (mmHg)	≥400	<400	<300	<200	<100
Coagulation					
Platelets ($x10^9$/L)	≥150	<150	<100	<50	<20
Liver					
Bilirubin (mg/dl)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	≥12.0
Cardiovascular					
Mean arterial pressure (mmHg)	≥70	<70	Dopamine <5 Dobutamine	Dopamine 5.1–15 Epinephrine ≤0.1 Norepinephrine ≤0.1	Dopamine >15 Epinephrine >0.1 Norepinephrine >0.1
Central Nervous System					
Glasgow coma score	15	13–14	10–12	6–9	<6
Renal					
Creatinine (mg/dl)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9	>5.0
Urine output (ml/d)				<500	<200

FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen.

massive aspiration and is an indication for ICU admission.[34] Rapid resuscitation is also required given the potential nature of the bleed with a conservative haemoglobin transfusion threshold of 70 g/L conferring a higher survival rate than that of a more liberal haemoglobin transfusion threshold of 90 g/L.[35] Immediate initiation of vasoactive agents such as somatostatin, terlipressin, or octreotide allows for a decline in portal pressures to help reduce the amount of bleeding. Antibiotic prophylaxis usually with norfloxacin or ceftriaxone is required as it has been shown to reduce the rates of infection, rebleeding, and mortality.[36] Depending on the amount of bleeding that occurs, haemorrhagic shock may arise necessitating ICU transfer and use of vasopressor agents to maintain a MAP of 65 mmHg.[37]

Endoscopic therapy is standard treatment for variceal bleeding and should be undertaken within 12 hours of the bleeding presentation, once adequate resuscitation is achieved.[38] For oesophageal varices, the preferred endoscopic management is variceal band ligation, which has been shown to be superior to sclerotherapy in terms of rates of haemostasis, adverse events, and 6-week survival.[39] Regarding bleeding gastric varices, the preferred endoscopic therapy is cyanoacrylate injection as it results in less rebleeding, treatment-induced ulcer bleeding, and mortality compared to band ligation.[40]

Table 6. Quick sequential organ failure score.

System	Value
Respiratory	
Respiratory rate	≥22/min
Central Nervous System	
Glasgow coma score	≤13
Cardiovascular	
Systolic blood pressure	≤100 mmHg

Despite adequate standard therapy, 20% of patients may have failure of haemostasis and require rescue therapy.[33] Balloon tamponade with either a Sengstaken-Blakemore or Minnesota tube is often utilised as a way of rapidly achieving haemostasis in patients who have massive bleeding or who fail standard endoscopic therapy. Studies have shown that with balloon tamponade, 59% of patients survive to discharge from hospital and 1-year survival is 41%, which makes it an effective rescue therapy.[41] Intensive care admission is mandatory when balloon tamponade is being implemented. Balloon tamponade is often used as a bridge to more definitive therapy in the form of early transjugular intrahepatic portosystemic shunt (TIPS) insertion (within 72 hours post admission). Early TIPS has been shown to reduce 1-year rebleeding and mortality rates compared to pharmacotherapy with endoscopic variceal band ligation and should be strongly considered in cirrhotics admitted to the ICU for variceal bleeding.[42]

Hepatic encephalopathy

HE is a common complication of chronic liver disease in up to 45% of cirrhotic patients and is manifested by impaired cognition, confusion, and a decreased level of consciousness.[43] It occurs as a result of impaired hepatic metabolic function leading to reduced removal of nitrogen-based waste products such as ammonia.[37] Ammonia crosses the blood-brain-barrier and is combined with glutamate to form glutamine, which leads to cerebral oedema.[43] Most instances of HE are precipitated by reversible factors including infection, gastrointestinal bleeding, acute kidney injury (AKI), sedating medications, and constipation.[44] With the onset of HE, mortality at 1 year is greater than 50%.[45] Although the presence of HE in the setting of acute liver failure is often an indication for intensive care admission, occurrence of severe HE in patients with chronic liver disease also calls for ICU management. Grading of HE occurs with the

use of the West Haven grading scale (Table 2). Patients who are grade 4 generally have a Glasgow coma score less than 7 and tend to be comatose.[44] Therefore, the presence of severe HE in cirrhotic patients is an indication for management in the ICU, with patients often requiring tracheal intubation for airway protection. Judicious use of sedation should be carried out with the avoidance of benzodiazepines.[46]

In terms of specific management options for HE, the initial step is to identify and reverse any precipitating causes such as infection or bleeding. Ammonia-lowering therapies are the standard of care and the most frequently utilised agent is lactulose, a nonabsorbable disaccharide that is converted into short-chain fatty acids by the colonic microbiome creating an acidic environment in the colonic lumen. This leads to inactivation of ammonia producing colonic bacteria and conversion of ammonia to nonabsorbable ammonium.[47] Lactulose can be given orally or via nasogastric tube as well as rectally. The antibiotic rifaximin is also a widely used therapy for management of HE, often in combination with lactulose, as its addition to lactulose was found to reduce mortality and length of hospital stay when compared to lactulose alone.[48]

Acute kidney injury

AKI results in renal dysfunction in up to 50% of hospitalised cirrhotic patients.[49] The definition of AKI has been modified in recent years by the International Club of Ascites (ICA) based on ICA-AKI criteria, which split AKI into 3 different stages (Table 7). AKI in cirrhotic patients is now defined as an increase in serum creatinine (sCr) by at least 0.3 mg/dl within 48 hours or an increase in baseline sCr by at least 50% within the last 7 days.[50] Stage 1 AKI involves an increase in baseline sCr by at least 0.3 mg/dl or an increase in sCr by 1.5-fold to 2-fold. Stage 2 AKI results in an increase in sCr by 2-fold to 3-fold from baseline. Stage 3 AKI is defined as an increase in sCr by more than 3-fold from baseline or an increase in sCr to more than 4.0 mg/dl with an acute rise by at least 0.3 mg/dl.[50]

Hepatorenal syndrome (HRS) is a particular form of AKI in patients with cirrhosis. It occurs in up to 40% of patients within the first 5 years of being diagnosed with cirrhosis.[51] In the past, HRS was divided into 2 types. Type 1 HRS was regarded as a rapidly progressing renal failure defined as the doubling of baseline sCr in less than 2 weeks to a value of greater than 2.5 mg/dl.[52] Type 2 HRS was seen as a less progressive renal failure with elevation of sCr to greater than 1.5 mg/dl.[52] More recently, the ICA has defined HRS as meeting the following criteria: i) presence of cirrhosis and ascites; ii) diagnosis of AKI in accordance with the ICA-AKI criteria; iii) absence of shock; iv) no improvement with 2 days of diuretic stoppage and plasma volume expansion with 1 g/kg body weight of albumin; v) absence of nephrotoxic drug use; vi) absence of macroscopic signs of structural renal disease (lack of proteinuria, haematuria, and abnormalities on renal ultrasonography).[50] Risk factors for the development of HRS include gastrointestinal bleeding, bacterial infection, spontaneous bacterial peritonitis, large-volume paracentesis, and alcoholic hepatitis.[53]

Development of HRS is significant as it carries a poor prognosis. Previous studies have indicated median survival in patients with type 1 HRS of 2 weeks while patients with type 2 HRS have a median survival of 6 months.[54] Therefore, it is imperative to identify and treat patients who develop HRS early in the disease course as some reversal of renal dysfunction may be possible. Vasoconstrictors and albumin are the mainstays of medical therapy for HRS and often necessitate ICU admission, especially when HRS occurs in the setting of severe and refractory hypotension. Renal replacement therapy may be considered in the setting of LT candidates.

Terlipressin is a vasopressin analogue that has been studied extensively in HRS. Multiple studies have shown that treatment with terlipressin and albumin leads to significant renal recovery in up to 50% of patients with type 1 HRS.[55] Survival has also been shown to increase with the use of terlipressin and albumin.[56] When utilizing terlipressin, monitoring of central venous pressure is encouraged to help guide albumin use, which requires ICU admission and is not strongly recommended by current international guidelines.[57] Aside from terlipressin, norepinephrine can also be used along with albumin for the treatment of HRS. Norepinephrine has been shown to be as effective and as safe as terlipressin for type 1 HRS and is an alternative when terlipressin is unavailable.[58] Norepinephrine can only be used in an ICU setting. In North America, terlipressin is not available so norepinephrine is the vasopressor of choice for the intensive management of HRS.

Renal failure in the setting of ACLF represents a severe form of AKI and can be precipitated by infection, hypovolemia, or structural renal disease.[8] Based on the CLIF-organ failure (CLIF-OF) scoring system, renal failure is defined as a creatinine greater than 2 mg/dl or need for renal replacement therapy.[59] Occurrence is a result of inflammation and hemodynamic compromise. Renal failure in the ACLF population has been associated with increased mortality with studies showing a 28-day mortality of close to 19%.[10]

Table 7. International Club of Ascites: acute kidney injury definition and staging.

Definition of acute kidney injury	Increase in serum creatinine ≥0.3 mg/dl within 48 hours Increase in serum creatinine ≥50% from baseline within the last 7 days
Staging of acute kidney injury	
Stage 1	Increase in serum creatinine ≥0.3 mg/dl Increase in serum creatinine ≥1.5 to 2-fold from baseline
Stage 2	Increase in serum creatinine >2 to 3-fold from baseline
Stage 3	Increase in serum creatinine >3-fold from baseline Serum creatinine ≥4.0 mg/dl with an acute increase ≥0.3 mg/dl Initiation of renal replacement therapy

Renal failure in patients with ACLF is also more likely to be prolonged and progressive compared to renal failure occurring in cirrhotic patients with acute decompensation. Patients with ACLF who develop AKI and renal failure are also more likely to require renal replacement therapy.[60]

In terms of management of AKI in patients with ACLF, the first step is to address any potential underlying cause. This involves withholding any nephrotoxic drugs, treating potential infections, reducing or withdrawing diuretics, and plasma volume expansion in the presence of hypovolemia.[50] Like AKI in decompensated cirrhotic patients, the mainstay of volume expansion therapy in patients with ACLF and renal dysfunction is the colloid solution albumin.[61] No other colloids such as starch should be used because of the risk of nephrotoxicity.[62,63] However, when these measures do not provide an adequate response and HRS or refractory hypotension develops, ICU admission is often indicated for therapy with vasoactive agents including terlipressin or norepinephrine. Terlipressin may be the vasoactive agent of choice in patients with ACLF who develop HRS, as a recent study by Arora *et al.* demonstrated greater response rates and lower mortality with the use of terlipressin compared to norepinephrine in this patient population.[64] Overall, it appears that the ACLF grade prior to the initiation of treatment for HRS, with terlipressin and albumin, is the greatest predictor of response.[65]

In patients who are awaiting a LT, renal replacement therapy in the ICU may be required as a bridge to LT or combined kidney-liver transplant if renal impairment does not respond to vasopressor and colloid support.[57] In the ICU setting, continuous renal replacement therapy is preferred over haemodialysis as it offers greater haemodynamic stability.[66] Other indications for ICU admission in cirrhotics with renal failure include metabolic derangements such as refractory hyperkalemia, metabolic acidosis, severe uraemia, and fluid overload.

Respiratory failure

Respiratory failure in the context of ACLF often occurs secondary to the inflammatory sequelae of ACLF or because of lung infection. Within this patient population, respiratory failure is defined by the CLIF-OF scoring system as a partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio (P/F ratio) of less than 200 mmHg.[59] Pulmonary infiltrates are also often seen on chest radiography. Overall this demonstrates significant lung injury and a need for ICU admission to facilitate tracheal intubation and use of mechanical ventilation for respiratory support.[67] Management requires ventilation with low tidal volumes that are typical of lung protective ventilation strategies in acute respiratory distress syndrome.[68] Despite such supportive efforts, respiratory failure requiring mechanical ventilation is a poor prognostic sign in patients with ACLF, with 1-year mortality as high as 89%.[69] Nonetheless, ICU management with mechanical ventilation is often used to bridge patients with ACLF to transplant in those who are candidates for LT.

Cardiovascular failure

Patients with chronic liver disease often have baseline hyperdynamic circulation with low systemic vascular resistance.[12] With the development of ACLF, release of proinflammatory cytokines leads to systemic inflammation and peripheral vascular vasodilation, which results in worsening of systemic vascular resistance and mean arterial blood pressure.[70] This leads to reduced end-organ tissue perfusion and a requirement for ICU admission for management with vasoactive agents for haemodynamic support, which defines cardiovascular failure according to the CLIF-OF scoring system.[59] A complicating factor in patients with ACLF is the presence of adrenal insufficiency, which is fairly common in patients with chronic liver disease. Overall this leads to reduced serum cortisol levels and a decreased peripheral response to vasoconstrictor therapy.[71] Also, the existence of cirrhotic cardiomyopathy is present in up to 50% of patients with cirrhosis and can further worsen haemodynamic stability if ACLF develops.[72]

Prognostication in patients with ACLF

ACLF is a dynamic process and patients may require admission and management in an ICU setting as there is potential for improvement. At the same time, patients with ACLF may significantly worsen. Despite the potential for clinical improvement, mortality is high in this patient population, especially in those with multiorgan failure and septic shock.[73] Continued utilisation of intensive care therapies may become futile as the prognosis for patients with ACLF admitted to the ICU remains fairly poor. Overall, it appears that the early clinical course in patients with ACLF helps to determine the prognosis. Different prognostication models including the Acute Physiology and Chronic Health Evaluation (APACHE) II score, the MELD score, and the Child-Turcotte-Pugh (CTP) score have been used to identify patients with ACLF who are at the highest risk of death.[59]

More recently, the CLIF-C ACLF score was developed by the CANONIC study group as a diagnostic and prognostic tool that can be used to determine the risk of mortality in patients with ACLF.[59] Overall, the CLIF-C ACLF score is calculated based on bilirubin, creatinine, HE grade, INR, MAP, and PaO_2, which gives an overview of the number of organ failures present, along with age and white cell count. The CLIF-C ACLF score was found to be more accurate at predicting poor outcomes in all patients with ACLF than the older models such as APACHE II, MELD, and CTP scores, regardless of the care setting.[59] However, it remained unclear how well the CLIF-C ACLF score predicted mortality in patients with ACLF requiring ICU admission.

A recent study by Karvellas *et al.* assessed the performance of the CLIF-C ACLF score in critically ill patients with ACLF who were admitted to the

ICU. CLIF-C ACLF scores and ACLF grades on ICU admission and at day 3 post-ICU admission were evaluated for their ability to differentiate non-survivors and survivors at 28 and 90 days. These scores were also compared directly with APACHE II and CTP scores in terms of their ability to predict survival in patients admitted to the ICU.[74] Patients with a CLIF-C ACLF score of greater than 70 either on ICU admission or at day 3 post-ICU admission were identified as having 90% mortality at 90 days. The CLIC-C ACLF score also had a c-index of 0.75 in terms of separating survivors from non-survivors and performed significantly better than APACHE II and CTP scores.[74] Patients who had an improvement in their ACLF grade at day 3 post-ICU admission had improved survival at 28 and 90 days.[74]

A separate study by Engelmann and colleagues also examined the CLIF-C ACLF score as a way to identify patients admitted to the ICU who were not expected to benefit from continued intensive therapies and compared its prognostic value to other scores of chronic liver disease. CLIF-C ACLF and other chronic liver disease scores were calculated at 48 hours post-ICU admission and mortality at 28 days was observed.[75] All patients with a CLIF-C ACLF score of greater than 70 at 48 hours post-ICU admission died within 28 days.[75]

Regarding the importance of the early clinical course of ACLF in determining prognosis and futility of care, Gustot and colleagues also demonstrated that prognosis correlated better with the clinical course in patients with ACLF (final ACLF grade post diagnosis) than with the ACLF grade at diagnosis.[12] The 28-day mortality rate steadily increased depending on the final ACLF grade with rates of 5.8%, 18.2%, 41.7%, and 91.8% for final ACLF grades of 0, 1, 2, and 3 respectively.[12] This was independent of what the initial ACLF grade was. The authors found that the final ACLF grade was defined between days 3 to 7 post diagnosis in the vast majority of patients (81%) and that the day 3 to 7 ACLF grade could be used to define the early clinical course.[12] Day 3 to 7 ACLF grade had a c-index of 0.85 in predicting 28-day mortality and was significantly better than ACLF grade at diagnosis.[12]

Based on these studies, it could be suggested that limits to further aggressive therapy and organ support may need to be placed on patients with ACLF, who are admitted to the ICU and have poor prognostic scores, especially in patients who do not respond to a trial of short-term therapy and who are not LT candidates. Patients who continue to have a CLIF-C ACLF score of greater than 70 at 48 to 72 hours post-ICU admission should be considered for palliative care instead of ongoing intensive care therapies, especially if deemed to not be transplant candidates. Another algorithm proposed by Gustot and colleagues suggests that for patients not appropriate for LT, withdrawal of care should be considered if the day 3 to 7 ACLF grade is 3, with 4 or more organ failures present, or if the CLIF-C ACLF score is greater than 64 at 3 to 7 days post diagnosis with an ACLF grade of 3 at diagnosis.[12] For patients who have reasonable prognostic scores or who are appropriate transplant candidates, ongoing aggressive therapy could potentially prevent further deterioration and serve as a bridge to LT.

Although patients with ACLF may be too ill to ultimately undergo LT, it remains an important consideration in appropriate candidates. A recent study by Thuluvath and colleagues demonstrated excellent survival post-LT in patients with ACLF, even with a high number of organ failures prior to LT. Patient survival was 90% at 90 days post-LT and 81% at 1-year post-LT for patients with ACLF and 5 to 6 organ failures.[76] Without LT, 30-day survival was only up to 8% in patients with ACLF and 3 or more organ failures.[76] Within this patient population, there may be a narrow window for LT and LT candidacy should be considered early in the clinical course. Continued intensive therapy in the ICU while awaiting LT may allow these patients to survive to LT.

Conclusions

Although the majority of cirrhotic patients can be managed in a non-critical care environment, acute decompensation or the development of ACLF may necessitate transfer to an ICU setting for more intensive support. Complications of variceal bleeding, HE, HRS, and respiratory, renal, and cardiovascular failures, often require critical care management in the ICU. This is especially true in patients who are LT candidates, where intensive management can serve as a bridge to transplantation. However, frequent reassessment and utilisation of prognostic scores such as the CLIF-C ACLF score are required to identify patients who will not benefit from continued intensive care therapies, particularly for patients who are not LT candidates. LT candidacy needs to be evaluated early on. For patients who are not LT candidates, if clinical improvement is not seen within 48 to 72 hours post-ICU admission, serious consideration should be given to palliation as opposed to continued aggressive ICU management. For those patients who are LT candidates continued aggressive therapy may allow bridging to LT.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.
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Authors' contributions

VD and CJK both drafted and significantly revised the final manuscript.

Supplementary data

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