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AASLD Practice Guidance on Acute-on-chronic Liver Failure and the Management of Critically Ill Patients with Cirrhosis

Constantine J. Karvellas[1], Jasmohan S. Bajaj[2], Patrick S. Kamath[3], Lena Napolitano[4], Jacqueline G. O'Leary[5],
Elsa Solà[6], Ram Subramanian[7], Florence Wong[8], Sumeet K. Asrani[9]

[1]Division of Gastroenterology (Liver Unit), Department of Critical Care Medicine, University of Alberta, Edmonton, Canada

[2]Virginia Commonwealth University, Central Virginia Veterans Healthcare System, Richmond, Virginia, USA

[3]Mayo Clinic College of Medicine and Science, Rochester, Minnesota, USA

[4]University of Michigan, Ann Arbor, Michigan, USA

[5]Department of Medicine, Dallas Veterans Medical Center, University of Texas Southwestern Medical Center
Dallas, Texas, USA

[6]Institute for Immunity, Transplantation and Infection, Stanford University School of Medicine, Stanford, California, USA

[7]Emory School of Medicine, Atlanta, Georgia, USA

[8]University of Toronto, Toronto, Canada

[9]Baylor University Medical Center, Dallas, Texas, USA

Correspondence

Sumeet K. Asrani, MD, MSc

Baylor University Medical Center

3410 Worth St, Suite 860,

Dallas, Texas 75246, USA

Email: sumeet.asrani@bswhealth.org

APPENDIX S1 Supporting information

Conflict of Interest:

CJK: Nothing to Disclose

JSB: Research Grants (Paid to Institution) with Valeant, Grifols, Sequana, Mallinckrodt, Cosmo and consulting with Merz

PSK: Nothing to Disclose

LN: Nothing to Disclose

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intensive care unit, global, multiorgan failure, decompensated, mortality

List of abbreviations

AARC Asian Pacific Association for the Study of the Liver Acute-on-Chronic Liver Failure Research Consortium;

AASLD American Association for the Study of Liver Diseases;

ACLF acute-on-chronic liver failure;

ACLF-1 ACLF Grade 1;

AKI acute kidney injury;

ALI acute lung injury;

APASL Asian Pacific Association for the Study of the Liver;

ARDS acute respiratory distress syndrome;

ATN acute tubular necrosis;

CLIF-C Chronic Liver Failure Consortium;

EASL European Association for the Study of the Liver;

EASL-CLIF European Association for the Study of Chronic Liver Failure;

FiO_2 fraction of inspired oxygen;

GI gastrointestinal;

HFNC high-flow nasal cannula;

HRS hepatorenal syndrome;

HRS1 HRS Type 1;

ICU intensive care unit;

INR international normalized ratio;

LT liver transplantation;

MAP mean arterial pressure;

MELD Model for End-Stage Liver Disease;

MELD-LA MELD and lactate;

NACSELD North American Consortium for the Study of End-Stage Liver Disease;

NIV noninvasive ventilation;

PaO_2 partial pressure of arterial oxygen;

PBW predicted body weight;

PEEP positive end-expiratory expiratory pressure;

POPH portopulmonary hypertension;

PRA prerenal azotemia;

q6h every 6 h;

RCT, randomized controlled trial;

RRT renal replacement therapy;

RV right ventricular;

SBP spontaneous bacterial peritonitis;

sCr serum creatinine;

SOFA Sequential Organ Failure Assessment;

TEG thromboelastography;

VTE venous thromboembolism;

WBC white blood cell

PURPOSE AND SCOPE

There are approximately 800,000 hospitalizations a year for cirrhosis complications in the United States, and 7%–8% of these patients require intensive care at an estimated cost of $2 billion[1] but without standardized intensive care protocols. Acute-on-chronic liver failure (ACLF) is a term often applied to patients with chronic liver disease with or without cirrhosis with hepatic and extrahepatic organ failures, most of whom require intensive care. This document from the American Association for the Study of Liver Diseases (AASLD) serves to provide guidance and a data-supported approach for the diagnosis, evaluation, and management of patients with cirrhosis and ACLF as well as cirrhosis and critical illness. It differs from the AASLD Guidelines, which are supported by systematic reviews of the literature, formal rating of the quality of the evidence, and strength of the recommendations. In contrast, this document was developed by consensus of an expert panel and provides guidance statements based on a comprehensive review and analysis of the literature on relevant topics with oversight provided by the AASLD Practice Guidelines Committee. The AASLD Practice Guidelines Committee chose to perform a guidance on this topic because there are an insufficient number of randomized controlled trials (RCTs) available to support meaningful systematic reviews and meta-analyses.

CIRRHOSIS WITH ACLF AND/OR CRITICAL ILLNESS

Introduction

The clinical stages of cirrhosis have traditionally been divided into a compensated phase with no complications and a decompensated phase that manifests with complications of portal hypertension. It has long been recognized, but only relatively recently described, that there is a more rapid phase. In patients with cirrhosis, precipitating events leading to hepatic and extrahepatic organ failures (e.g., neurologic, respiratory, circulatory, renal) may be liver related (e.g., alcohol-associated hepatitis, viral, and drug-induced hepatitis) or non–liver related (e.g., surgery). Often, the precipitant is not identified. Despite intensive care, critically ill patients with cirrhosis are at a high risk of mortality within 1–3 months. Therefore, evaluation of these patients for liver transplantation (LT) and discussion of goals of care with the patient and family are also essential. Although specific criteria to define ACLF vary by region, organ failure is common to all ACLF definitions. This guidance document will primarily focus on the management of patients with cirrhosis and ACLF and/or who require intensive care unit (ICU) level care.[2–5]

Defining ACLF

Currently, there are three major definitions of ACLF depending on geographical location and a fourth by the World Gastroenterology Organization that attempts to combine elements of the three regional definitions of ACLF (see Definitions, Supplementary Materials, http://links.lww.com/HEP/I105).[2–6] These multiple definitions of ACLF have resulted in confusion among clinicians as to how to diagnose and apply management recommendations to specific patients with ACLF. It is very likely that the different societies are characterizing different stages of the same condition (Figure 1). The Asian Pacific Association for the Study of the Liver (APASL) recognizes patients at an early stage of the disease. This definition is likely to be sensitive but not specific for the diagnosis, as most of these patients will not have died by Day 28. The European Association for the Study of Chronic Liver Failure (EASL-CLIF) criteria include patients at an intermediate stage when they are developing extrahepatic organ failure (ACLF Grade 1 [ACLF-1] and ACLF-2) and patients at the late stage (ACLF-3) who are at a higher risk of mortality. However, the inclusion of patients with decompensated cirrhosis means this diagnosis may be made when the condition is more likely than not to be irreversible. The North American Consortium for the Study of End-Stage Liver Disease (NACSELD) criteria include only patients at an often preterminal stage with two or more extrahepatic organ failures. Hence, we propose that any definition of ACLF needs to include the presence of hepatic dysfunction as well as the presence of extrahepatic organ failure. The optimal laboratory cutoffs for defining hepatic failure remain unclear. For example, coagulopathy defined as an international normalized ratio (INR) of 1.5–2.5 or above has been used to define acute liver failure and ACLF. For elevated bilirubin, cutoffs of 5–12 mg/dL have been examined in ACLF (APASL/European Association for the Study of the Liver [EASL] definitions).[2–7] In addition, though ACLF is characterized by an acute onset with rapid deterioration in the clinical condition of patients with chronic liver disease with or without cirrhosis, how rapid the acute episode needs to be also remains unclear. Over the years, there has been considerable debate since this concept of ACLF was first proposed, especially with regard to reversibility (see Historical context, Supplementary Materials, http://links.lww.com/HEP/I105).[8]

Guidance statement

1. We suggest that the presence of all of the following elements are minimum critical components for the definition of ACLF: (1) acute onset with rapid deterioration in clinical condition, (2) the presence of liver failure defined by elevated bilirubin and elevated INR in patients with chronic liver disease with or without cirrhosis, and (3) the presence of at least one extrahepatic (neurologic, circulatory, respiratory, or renal) organ failure.

2. This guidance will focus on the management of patients with ACLF and severe forms of organ failure, who often require ICU management. This guidance is therefore most applicable to patients fulfilling NACSELD ACLF criteria and selected patients with advanced stages of APASL or EASL-CLIF ACLF criteria.

PROGNOSIS AND PREDICTION MODELING

Prediction of ACLF development

Predicting the development of ACLF remains a challenge, especially given the heterogeneous definitions in the literature. The PREDICT study, a large, prospective, European study (n = 1071 patients with decompensated cirrhosis), characterized the clinical course of decompensated cirrhosis and defined predictors of ACLF (EASL-CLIF definition). The study identified a subgroup of patients with decompensated cirrhosis, named "pre-ACLF," who were at higher risk of developing ACLF and of 3-month and 1-year mortality. The patients with "pre-ACLF" were characterized by a higher frequency of complications prior to enrollment and higher levels of systemic inflammatory markers (C-reactive protein and white blood cells [WBCs]) that progressively increased during follow-up together with higher severity scores at admission (Chronic Liver Failure Consortium [CLIF-C] acute decompensation, Model for End-Stage Liver Disease [MELD], and MELD-Na) as compared with patients with decompensated cirrhosis who did not develop ACLF during follow-up. Although these characteristics may help identify patients at higher risk of ACLF development needing closer monitoring, no individual or combination of clinical or analytical variables were identified as accurate biomarkers to predict the development of ACLF.[9]

Prognosis in ACLF

Once it develops, the probability of 28-day mortality in patients with ACLF ranges from 30% to 50% according to different definitions and geographical areas.[2–6, 10, 11]The outcome of patients with ACLF is often driven by the number and severity of organ failures. Severity scores such as MELD and MELD-Na may underestimate mortality among patients with ACLF, as they tend to capture intrinsic liver disease but do not take into account the impact of all extrahepatic organ failures.[10, 11]

Scores combining hepatic and extrahepatic failures

Though several ACLF-specific scores have been proposed, the included components are similar (Table 1). Details regarding development and validation of selected scores are provided in Table 2.

The NACSELD ACLF score includes advanced extrahepatic organ failure in addition to age, MELD, WBC count, and serum albumin measured at the time of hospital admission.[12]

The CLIF-C ACLF score includes both hepatic and extrahepatic organ failures together with age and WBC count and can be calculated at serial time points (previously evaluated on admission and up to Day 7).[4, 6, 13]The APASL ACLF Research Consortium (AARC) score includes five variables evaluated at hospital/ICU admission: serum bilirubin, serum creatinine (sCr), serum lactate, INR, and HE.[14] All scores have been developed and validated in independent data sets and appear to have better diagnostic performance than MELD and MELD-Na as well as ICU-specific scores (e.g., Acute Physiology and Chronic Health Evaluation or Sequential Organ Failure Assessment [SOFA]). Between score comparisons are limited and described further in Table 2.[4, 6, 12–19] Other etiology-specific ACLF scores (e.g., COSSH ~ Chinese Group on the study of severe hepatitis score for HBV-related ACLF) need further study.[20]

Scores incorporating lactate

Serum lactate is associated with the number of organ failures and mortality in critically ill patients with cirrhosis.[21] A model including MELD and lactate (MELD-LA) measured at the time of hospitalization (MELD-LA) was an excellent predictor of in-hospital mortality. Prognostic accuracy of MELD-LA was better than MELD, lactate alone, MELD-Na, or MELD-Na–lactate.[22] MELD-LA levels at the time of admission increased in parallel with the number of organ failures[23] and had similar performance to ICU-specific scores, suggesting that a simpler model may be helpful for prognosis.[24] Lactate added to CLIF-C ACLF outperformed CLIF-C ACLF and MELD scores to predict 28-day, 90-day, and 1-year mortality.[21]

Dynamic evaluation of prognosis in ACLF

As ACLF has a dynamic course, a sequential assessment of prognosis rather than the calculation of a single time point score may be more accurate to predict prognosis. The course of ACLF assessed Days 3–7 after diagnosis was an independent predictor of mortality regardless of initial ACLF grade.[25] Data from a multicenter analysis of critically ill patients with cirrhosis in Europe and North America showed that 90-day mortality in patients with three or more organ failures (ACLF-3) was significantly lower in patients who showed improvement by Day 3 compared with those who did not (40% vs. 79%).[26] Therefore, sequential assessment of CLIF-C ACLF score at Days 3–7 may be used to determine prognosis and accurately predict those patients who may need further support, benefit from early LT, or in whom further treatment may be futile.

Limitations of prognostic models

The potential limitations of prognostic models for ACLF include limited scope of disease severity, subjectivity of individual variables, and reliance on variables at a single time point. The NACSELD ACLF score has the advantage of being an easy-to-apply bedside tool. However, the criteria used represent only advanced organ failure, which may lead to missing earlier stages of ACLF. In contrast, CLIF-C ACLF and AARC scores consider the whole spectrum of severity of the syndrome. All scores include variables with some degree of subjectivity. This includes variable assessment of HE and timing of vasopressor initiation. In addition, the reason for mechanical ventilation is often unclear (airway protection vs. respiratory failure), particularly if retrospective data are used. Furthermore, most scores are static, not dynamic, and thus may not be truly prognostic but simply reflect the clinical course at the time of measurement.

Guidance statements

3. Scores that account for hepatic and extrahepatic organ failures (e.g., NACSELD, CLIF-C, or AARC ACLF scores) are recommended over conventional cirrhosis-related prognostic scores (e.g., MELD or MELD-Na) to assess prognosis in critically ill patients with cirrhosis and/or ACLF.
4. Serial calculation of ACLF-specific scores may be useful for further assessment of prognosis among patients hospitalized with ACLF.

ORGAN-SPECIFIC MANAGEMENT RECOMMENDATIONS IN CIRRHOSIS WITH ACLF AND/OR CRITICAL ILLNESS

Brain failure

Brain failure in all three major ACLF definitions is defined as Grade 3 or 4 HE according to the West Haven criteria, with further refinement using the Glasgow Coma Scale (<8 indicating severe brain injury).[27]

It is important to emphasize that not all alteration in mental status in patients with chronic liver disease is HE. The four principles to manage a patient with cirrhosis with altered mental status, which are consistent with the AASLD/EASL HE guidelines, are as follows: (1) care of the airway to prevent aspiration and transfer to a monitored setting, if necessary; (2) investigation of the cause of altered mental status, including whether this is truly owing to HE or other causes such as alcohol-associated conditions; (3) determination and treatment of precipitating factor(s) of HE; and (4) empiric therapy for suspected HE.[28, 29] All four of

these management strategies should occur concurrently with modifications as the clinical picture becomes clearer over time.

Care of the confused or unconscious patient with cirrhosis

Patients with cirrhosis with altered mental status are prone to delirium, falls, and aspiration pneumonia.[30] Decisions regarding intubation should be individualized, though they are often driven by the following: (1) inability to maintain airway, (2) massive upper gastrointestinal (GI) bleeding, and/or (3) respiratory distress. If possible, a priori discussion of goals of care before intubation should be carried out. For sedation, short-acting medications such as propofol or dexmedetomidine are preferred.[31–33] Although metabolized in the liver, dexmedetomidine (a highly selective alpha-2 adrenergic agonist) can reduce ventilation duration, preserve cognitive function, and reduce the need for benzodiazepines for alcohol withdrawal.[31, 34] Given the synergistic impact of concomitant sedating medications such as benzodiazepines and gabapentin, opioids should be avoided or their use minimized.[35] Pain control, however, is critical to avoid hyperalgesia and to prevent delirium resulting from opioid withdrawal in those on preadmission opioids. Low doses with frequent readjustment and titrations to mental status may be needed.

Investigation of altered mental status

HE is a common cause of altered mental status in patients with cirrhosis, but it is a diagnosis of exclusion. Alcohol intoxication and withdrawal also remain common causes. Other causes are drug related, infections, diabetic ketoacidosis and hyperosmolar hyperketotic state, electrolyte disorders, intracranial bleeding, nonepileptic seizures, and psychiatric disorders. Importantly, several of these can coexist with HE and synergize to worsen the mental status. Routine investigations should include metabolic laboratory assessment; drug, alcohol, and medication history and levels; and other strategies guided by the patient's specific presentation and clinical situation. Routine head CT and MRI in this situation are often not helpful in those with recurrent, nonfocal, and depressive presentations.[36] Brain imaging could be considered in the following circumstances: (1) first episode of altered mental status, (2) seizures or new focal neurological signs, or (3) unsatisfactory response to therapy of precipitating factors and/or HE therapy.[37] Routine measurement of ammonia for diagnosis is also not recommended.[28] Ammonia levels are variable within patients and laboratories and may also be elevated in non-HE conditions. However, a low ammonia level in patients with coma or confusion should point toward etiologies other than HE.[28]

Precipitating factors

Common HE precipitants include infections, GI bleeding, electrolyte disorders, acute kidney injury (AKI), alkalosis, dehydration, constipation, under or overuse of lactulose, and use of central nervous system depressant sedatives. Early empiric antibiotics are reasonable among patients at high risk of infections or in whom infections are likely. GI bleeding should be investigated and treated promptly. Prompt identification and treatment of kidney injury and electrolyte disorders are important.

Empiric HE management

If no obvious alternative cause is immediately apparent, then empiric therapy with lactulose should be started. A nasogastric tube may need to be inserted for lactulose administration, but with due care if the patient recently had variceal band ligation procedure. In the case of ileus, oral lactulose may need to be held.[38] In those with Grade 3 or 4 HE, lactulose enema (300 mL lactulose in 700 mL water for a total of 1 L) may be considered. Regardless of route, the goal is to ensure improved mental status with careful monitoring of electrolytes to prevent dehydration and hypernatremia.[39, 40] The role of rifaximin and i.v. albumin in the acute setting remains unclear.[41–43] Polyethylene glycol has also been studied in trials with success compared with lactulose and maybe an alternative, especially to decrease the risk of ileus/abdominal compartment syndrome in the ICU setting.[44, 45] Ammonia scavengers such as L-ornithine L-aspartate and ornithine phenylacetate have been studied but are not available in the United States and are undergoing further trials.[46, 47]

Guidance statements

5. The West Haven HE criteria and the Glasgow Coma Scale should be used to characterize brain failure in critically ill patients with cirrhosis. Cutoffs of Grade 3 or 4 HE according to the West Haven criteria and Glasgow Coma Scale <8 indicate severe injury.
6. Consider ICU admission for patients with Grades 3 and 4 HE.
7. Investigation and treatment of potential precipitating factors and empirical therapy for suspected HE should be performed.
8. Workup of altered mental status in patients with cirrhosis should include investigation of liver-unrelated causes of altered mental status (e.g., alcohol withdrawal, structural brain injury), especially if this is the first episode of confusion or if a patient does not respond to adequate empirical therapy for HE.

9. Treatment of HE in patients with ACLF/who are critically ill includes lactulose (orally or rectally) or polyethylene glycol if patients are at risk of ileus/abdominal distention. The role of rifaximin as an add-on therapy to lactulose/polyethylene glycol warrants further investigation in ACLF.
10. Medications with short half-lives (e.g., propofol, dexmedetomidine) should be used for sedation and pain control in patients with cirrhosis who require intubation and mechanical ventilation.
11. Routine brain imaging in patients with presentation similar to prior episodes of HE is not warranted.
12. Routine ammonia level testing in patients with cirrhosis and altered mental status is not recommended.

CARDIOVASCULAR FAILURE

Volume status assessment

Baseline assessment of volume status, cardiac function, and fluid responsiveness is essential in all critically ill patients. Overall strategies for volume status assessment are provided in Figure 2. Patients with decompensated cirrhosis demonstrate a hyperdynamic circulation with decreased systemic vascular resistance manifested by low arterial blood pressure and increased cardiac output. This pathophysiology is exacerbated with worsening inflammation in patients with ACLF.[48, 49] In addition to a thorough physical examination, bedside transthoracic echocardiography (TTE) provides additional information regarding the fluid and cardiac status of the patient (cardiac and inferior vena cava preload assessment, evaluation for hypovolemic vs. vasodilatory vs. cardiogenic shock, left ventricular and right ventricular [RV] function) and may help to guide management.[50]

Ongoing accurate monitoring of hemodynamic and circulatory status must be continued during fluid resuscitation in order to guide appropriate therapy and avoid overresuscitation.[31, 51] Monitoring dynamic changes in stroke volume, stroke volume variation, pulse pressure variation, or TTE with fluid boluses or passive leg raise may help guide resuscitation.[52–54] Because of a dearth of ACLF data for cardiovascular complications and shock, it should be acknowledged that a significant amount of data are extrapolated from the general critical care literature.

Resuscitation fluids

Fluid resuscitation i.v. is required for the treatment of hypovolemia and shock states.[55] A meta-analysis of different resuscitation fluids in patients with sepsis and surgical and trauma patients reported that balanced crystalloids (e.g., lactated ringers) and albumin decreased mortality more than hydroxyethyl starch and saline

in patients with sepsis.[56] The largest RCT to date (Plasma-Lyte 148 vs. Saline [PLUS] study) found no difference in mortality or AKI in critically ill adults.[55] An updated meta-analysis including this PLUS study (13 RCTs, n=35,884) concluded that using balanced crystalloids is associated with reduced mortality[57] in the general population of critically ill patients without cirrhosis.

Albumin. Albumin administration is recommended in the management of patients with cirrhosis for select indications (e.g., large-volume paracentesis, paracentesis-induced circulatory dysfunction, spontaneous bacterial peritonitis [SBP], and hepatorenal syndrome [HRS]).[58] Albumin treatment also reduced systemic inflammation and circulatory dysfunction in patients with decompensated cirrhosis.[59] A single-institution, open-label RCT comparing 20% albumin with Plasma-Lyte in 100 patients with cirrhosis and sepsis-induced hypotension reported that albumin had higher rates of shock reversal but no survival benefit and increased pulmonary complications.[60] Another single-institution, open-label RCT (Fluid Resuscitation in Sepsis-Induced Hypotension Among Patients With Cirrhosis study) compared 5% albumin with normal saline in 308 patients with cirrhosis with sepsis-induced hypotension and confirmed that the reversal of hypotension was higher with albumin, with higher 1-week survival (43.5% vs. 38.3%, $p = 0.03$).[61] Unfortunately, there are no large RCT specific to the use of albumin in patients with ACLF. However, recent studies involving albumin in heterogeneous populations may help identify potential adverse events. The Albumin to Prevent Infection in Chronic Liver Failure trial randomized 777 hospitalized patients with decompensated cirrhosis (mostly new or worsening ascites) to daily albumin infusions to maintain serum albumin of 3 g/L throughout the hospitalization or standard care (albumin for large-volume paracentesis, SBP, or HRS).[62] No difference in the composite primary endpoint (infection, renal failure, or death) was identified, and targeting a specific level of albumin may have been associated with significantly higher rates of pulmonary edema and fluid overload. In summary, though albumin has its role in select liver-related indications, its broader use as a resuscitation agent in critically ill patients with cirrhosis and/or ACLF is not well defined.

Vasopressors

Vasopressors may be required for critically ill patients with shock to maintain end-organ perfusion while concurrent fluid resuscitation is ongoing.[63–65] A mean arterial pressure (MAP) target of 65 mm Hg is recommended in septic shock and general ICU patients, but there are no RCTs confirming this approach in patients with cirrhosis or ACLF who generally have lower baseline MAP.[66] A retrospective observational study of 273 critically ill patients with cirrhosis reported that ICU mortality increased below a threshold of 65 mm Hg and suggested maintaining an MAP of >65 mm Hg as an early goal in critically ill patients with

cirrhosis.[67] In contrast, a large RCT of general critical care patients with vasodilatory shock (n = 2600) demonstrated that reducing vasopressors with permissive hypotension (MAP target 60–65 mm Hg) was associated with no difference in 90-day mortality (41.0% vs. 43.8%; adjusted OR, 0.82; 95% CI, 0.68–0.98).[67] The optimal approach is to use an individualized MAP target based on frequent assessment of end-organ perfusion (mental status, capillary refill, urine output, extremity perfusion, lactate, central venous oxygen saturation, and end-organ function). Surviving Sepsis Campaign Guidelines suggest invasive arterial monitoring as soon as practical and suggest starting vasopressors peripherally to restore MAP rather than delaying until central venous access is secured.[68]

Norepinephrine (0.01–0.5 μg/kg/min) is recommended as the first-line vasopressor agent to maintain adequate organ perfusion pressure in patients with septic shock.[68, 69] Vasopressin deficiency has been documented in cirrhosis as well as in many shock states, and the Surviving Sepsis Campaign Guidelines recommends vasopressin as a second-line agent to be added to norepinephrine for septic shock.[68, 70] A meta-analysis confirmed a lower incidence of tachyarrhythmias but a higher rate of digital ischemia with vasopressin versus other vasoactive agents in septic shock.[71] These recommendations are based on literature in the general population without cirrhosis, and trials specifically in cirrhosis and/or ACLF are lacking.

Adrenal insufficiency

Relative adrenal insufficiency (e.g., an increase in serum cortisol of <9 μg/dL after Synacthen administration) is common in patients with cirrhosis and is associated with higher mortality and complications[72] A single-institution prospective study of 160 non–critically ill patients admitted to the hospital for acute decompensation of cirrhosis confirmed relative adrenal insufficiency in 49% of patients, which was associated with significantly higher 90-day mortality (26% vs. 10%, $p = 0.008$). Relative adrenal insufficiency was associated with higher risk of new bacterial infections, sepsis, septic shock, and circulatory dysfunction, but not other complications (HE and AKI). Hydrocortisone (50 mg i.v. every 6 h [q6h] or 200-mg infusion for 7 days or until ICU discharge) is recommended for the treatment of refractory shock requiring high-dose vasopressors based on the results of the ADRENAL[73] and APROCCHSS[74] trials, which documented earlier shock reversal and potential mortality benefit. Specific studies in patients with ACLF regarding steroid efficacy in shock states are small, and some report higher rates of shock reversal with steroid treatment with variable impact on mortality.[75, 76]

Guidance statements

13. Early baseline assessment of volume status, perfusion, and cardiovascular function should be performed in all critically ill patients with cirrhosis.
14. Bedsides echocardiography, it is useful to evaluate volume status and cardiac function in patients with cirrhosis and hypotension or shock.
15. A judicious strategy for intravascular volume resuscitation utilizing hemodynamic monitoring tools should be implemented to optimize volume status in critically ill patients with cirrhosis with shock. Balanced crystalloids (e.g., lactated ringers) and/or albumin (select indications) are recommended for fluid administration if resuscitation is required.
16. Consider a target MAP of 65 mm Hg in patients with cirrhosis and septic shock with ongoing assessment of end-organ perfusion. Invasive hemodynamic monitoring (arterial and central venous catheter) may be needed for adequate assessment of cardiac function and titration of vasopressors and fluid resuscitation.
17. Norepinephrine is recommended as the first vasopressor for patients with hypotension with concurrent appropriate fluid resuscitation. Vasopressin is recommended as a second-line agent when increasing doses of norepinephrine are required.
18. Consider screening for adrenal insufficiency or an empiric trial of hydrocortisone 50 mg i.v. q6h or 200-mg infusion for 7 days or until ICU discharge for treatment of refractory shock requiring high-dose vasopressors in patients with cirrhosis

RESPIRATORY FAILURE

As in general critical care, the etiology of acute diffuse lung injury can be caused by hydrostatic pulmonary edema (e.g., diastolic heart dysfunction) or nonhydrostatic pulmonary edema (e.g., pneumonia). In addition, underlying pulmonary derangements related to portal hypertension (such as hepatic hydrothorax, portopulmonary hypertension [POPH], and hepatopulmonary syndrome) can influence the pulmonary status and management and need to be evaluated. Patients with ACLF are at risk of developing acute lung injury (ALI), defined by hypoxemia and the presence of bilateral infiltrates, and progression to acute respiratory distress syndrome (ARDS).[77]

Complications of cirrhosis that can cause or worsen respiratory failure

Hepatopulmonary syndrome, characterized by the presence of intrapulmonary vascular dilatation/right-to-left shunt, can contribute to hypoxemia in the patients with cirrhosis or ACLF in the ICU.[78] POPH is a subtype of pulmonary arterial hypertension (PAH) that is diagnosed in the setting of pulmonary hypertension without

another clear cause. Patients in the ICU with cirrhosis and POPH should be monitored closely for development of RV dysfunction, especially in conditions that worsen RV afterload (e.g., ALI). Echocardiography can be invaluable in this setting to guide cardiopulmonary management. With respect to mechanical ventilation, low tidal volume and low positive end-expiratory pressure (PEEP) are important to minimize the negative effects of positive pressure ventilation on RV preload and afterload.[79] In select cases, pulmonary vasodilator therapy (e.g., inhaled nitric oxide, epoprostenol) and PAH-targeted therapy can be considered to optimize cardiopulmonary management (reduce mean pulmonary artery pressure [PAP] to <35 mm Hg). At present, most LT centers consider severe POPH (mean PAP of >45 mm Hg) a contraindication for LT.[78, 80] Hepatic hydrothorax can exacerbate derangements in gas exchange in the critically ill patient with cirrhosis. Progressive worsening of pleural effusions can lead to both hypoxemic and ventilatory insufficiency. Intermittent therapeutic thoracentesis is the mainstay of treatment, though rarely, indwelling pleural catheter drainage may be needed for temporary stabilization, especially as a bridge to urgent transplantation.[81] TIPS is often contraindicated because of concern for further hepatic decompensation in the setting of critical illness. Tense ascites may also compromise respiratory function by decreasing chest wall compliance, and serial abdominal assessments should be performed to evaluate the need for a therapeutic paracentesis.[82] In addition, in the patient with ACLF with tense ascites who is mechanically ventilated, timely therapeutic paracentesis may facilitate earlier extubation and decrease the risk of reintubation (see Supplementary Materials, http://links.lww.com/HEP/I105 as well as the 2021 AASLD guidance on ascites, SBP, and HRS).[83]

Noninvasive ventilation

In general critical care, noninvasive ventilation (NIV) has an established role in the management of (1) acute exacerbation of chronic obstructive pulmonary disease and associated hypercapnic respiratory failure[84] and (2) acute cardiogenic pulmonary edema.[85] In the critically ill patient with cirrhosis with these preceding etiologies, the administration of NIV should be considered early in order to mitigate the risk of intubation and mechanical ventilation. Once NIV is initiated, patients must be monitored closely for NIV failure, as delay in intubation is associated with increased mortality. In general critical care, the heart rate, acidosis, state of consciousness, oxygenation, and respiratory rate scale has been shown to accurately predict NIV failure in the first hour.[86] When considering NIV, any critically ill patient with cirrhosis and encephalopathy and/or potentially impaired airway protection should be assessed for the risk of aspiration. In addition,

noninvasive positive pressure ventilation may decrease venous return and preload, thereby negatively impacting the hemodynamic status.

High-flow nasal cannula

In general critical care, high-flow nasal cannula (HFNC) therapy is increasingly utilized in the management of acute hypoxemic respiratory failure and is superior to conventional low flow oxygen delivery systems with respect to oxygenation and need for intubation.[87, 88] Studies comparing HFNC with NIV do not demonstrate a difference with respect to intubation rates or mortality.[89] However, in the context of the critically ill patient, HFNC's favorable characteristics compared with NIV include improved patient comfort, a potentially decreased risk of aspiration in the setting of encephalopathy, and a lesser impairment of venous return caused by a lower PEEP effect. A potential caveat to the use of HFNC is the delay in intubation for progressively worsening hypoxemic respiratory failure.[90] Therefore, during HFNC therapy, the respiratory status of the patient with cirrhosis and/or ACLF should be monitored closely to assess the need for escalation to invasive mechanical ventilation. A model to predict failure of HFNC therapy based on respiratory rate and oxygenation (ratio of oxygen saturation index and oxygen saturation/fraction of inspired oxygen [FiO_2]) has gained increasing application in general critical care and can guide decision-making regarding the need for mechanical ventilation.[91]

Application of mechanical ventilation

Given the dearth of specific ventilation data in patients with ACLF/cirrhosis, mechanical ventilation recommendations are currently derived from the general critical care literature. For patients in the ICU who require mechanical ventilation for reasons other than ARDS, lung protective ventilation with low plateau pressures to prevent ventilator-induced lung injury and spontaneous breathing when possible are advocated. The PREVENT trial compared 6 mL/kg predicted body weight (PBW) with 10 mL/kg PBW in patients without ARDS with goal plateau pressures <25 cm H_2O and reported no significant difference in outcomes.[92]

ARDS

Tidal volume strategy. In the setting of ARDS that necessitates mechanical ventilation, a lung protective strategy with low tidal volume ventilation (defined as 6 mL/kg PBW) and lower plateau pressure (<30 cm H_2O) is recommended because such a strategy has been shown to improve mortality in general critical care.[93–95] In addition to minimizing alveolar barotrauma, this low tidal volume strategy decreases the risk of

systemic cytokine-mediated nonpulmonary organ dysfunction,[95] which may be of particular importance in the patient with ACLF who is at risk of multiorgan failure. Furthermore, a lower tidal volume strategy may have a beneficial effect on hemodynamic status by minimizing the negative effects of positive pressure ventilation on preload in a patient with systemic vasodilation.

Use of PEEP. During mechanical ventilation for mild ARDS (partial pressure of arterial oxygen [PaO_2]/FiO_2, 200–300 mm Hg), a low PEEP strategy (defined as <10 cm H_2O) should be considered. A high PEEP strategy is not recommended, as it can impede venous return and cardiac preload.[95, 96] In the patient with ACLF with a baseline vasodilated state, and with possible superimposed septic vasodilation, a high PEEP strategy can induce or exacerbate hypotension. However, in the setting of moderate to severe ARDS (defined as a PaO_2/FiO_2 < 200 mm Hg), a high PEEP strategy can improve oxygenation[95] with careful monitoring for hemodynamic side effects.

Guidance statements

19. Investigation and treatment of coexisting pulmonary comorbidities related to cirrhosis (hydrothorax, ascites, hepatopulmonary syndrome) should be undertaken in patients with cirrhosis and respiratory failure. In patients with respiratory compromise related to hydrothorax or tense ascites, therapeutic thoracentesis/paracentesis is recommended.
20. HFNC therapy should be considered in the management of acute hypoxemic respiratory failure in patients with ACLF, with close monitoring to assess the need for escalation to invasive mechanical ventilation (e.g., tachypnea, refractory hypoxemia).
21. For patients with cirrhosis and/or ACLF who require mechanical ventilation for reasons other than ALI, lung protective ventilation with low plateau pressures (tidal volume, 6–10 mL/kg PBW) to prevent ventilator-induced lung injury and spontaneous breathing when possible are advocated.
22. In the setting of ACLF with ALI requiring mechanical ventilation, a lung protective strategy with low tidal volume (6 mL/kg PBW) and low plateau pressure (<30 cm H_2O) is recommended.
23. During mechanical ventilation for mild ALI (PaO_2/FiO_2, 200–300 mm Hg) in ACLF, a low PEEP strategy should be considered to minimize the risk of impairing venous return and cardiac preload. A high PEEP strategy may be required in moderate-severe ALI (PaO_2/FiO_2, <200 mm Hg).

KIDNEY FAILURE

Definition and prevalence

Kidney failure is the most common extrahepatic organ failure in ACLF. Kidney failure was observed in between 29% and 75%[6, 97–99] of patients with ACLF when using the EASL-CLIF criteria, and the prevalence was 6%–28% when NACSELD criteria were used.[3, 99–101] Prevalence was higher among patients with infection as a precipitant. In situations of massive hepatic necrosis, such as an HBV flare, kidney failure became less prominent than liver or coagulation failures, occurring in similar proportions of patients (28%–29%) irrespective of whether the EASL-CLIF or the NACSELD criteria were used.[101]

Differential diagnosis

Critically ill patients with cirrhosis can have structural or functional causes of their AKI.[102] Structural causes are mostly related to acute tubular necrosis (ATN), acute glomerulonephritis, and, rarely, acute interstitial nephritis. Functional causes of AKI related to hemodynamic abnormalities are much more common. A more up-to-date definition of HRS-AKI is now being used and is modified from the Kidney Disease Improving Global Outcome's definition of AKI (Table 3).[103] HRS-AKI is now defined as an increase in sCr ≥0.3 mg/dL within 48 h or ≥50% from baseline value without regard for the final sCr level while fulfilling all diagnostic criteria for HRS Type 1 (HRS1) as set out by the International Club of Ascites (ICA).[104] It should be noted that currently published clinical trials used the older 2007 ICA definition of HRS1 (an acute rise in sCr to a threshold of ≥2.5 mg/dL in <14 days without any evidence of structural renal disease or prerenal azotemia [PRA]).[105] Further updates to the HRS-AKI definition are currently underway but not available at the time of this guidance.

When patients in the ICU present with multiorgan failure, the main differential diagnoses of AKI include PRA, ATN, and HRS-AKI. As estimated by the Translational Research Investigating Biomarker Endpoints in AKI Consortium, 50% of AKI episodes in cirrhosis were PRA and 35% related to ATN, whereas the remainder of the cases were related to HRS-AKI; postrenal causes are very uncommon.[106] Differentiating between the different causes of AKI in patients with ACLF is challenging in the context of critical illness, in which there may be several precipitating factors/complications playing a role. Urinalysis and urine examination looking for hematuria, proteinuria, or various casts will differentiate functional versus structural causes of AKI. Biomarkers such as neutrophil gelatinase-associated lipocalin and fractional excretion of sodium or fractional excretion of urea can differentiate ATN from functional causes of AKI.[107] Although a diagnosis of exclusion, HRS-AKI only occurs in patients with cirrhosis and ascites and is often associated with systemic hypotension and hyponatremia; a lack of these clinical features makes the diagnosis of HRS-AKI unlikely.

Management of AKI

The initial management of AKI in patients with cirrhosis follows three broad principles: identify the phenotype of the AKI, remove or treat the precipitating factor, and perform a trial of fluid challenge (Figure 3). As bacterial infection is a common precipitating factor for HRS-AKI, it is imperative that all patients be monitored for evidence of infection. For every hour delay in the start of antibiotics, there is an increase in mortality by 1.86 times from multiorgan failure, including kidney failure. Therefore, in patients suspected of having a bacterial infection, early administration of empiric antibiotics is recommended once all the cultures from appropriate sites have been taken.[108] Antibiotic therapy can be stopped or tailored as culture data become available. In patients who have SBP, the use of albumin in conjunction with antibiotics can prevent the development of kidney dysfunction, especially in patients with high baseline sCr or with liver dysfunction.[109] Consider avoiding radiographic dye, which may worsen the renal ischemia. In patients with ACLF with abnormal hemodynamics, diuretics or nephrotoxic drugs should be withdrawn and fluid challenge given.[110]

The recommended fluid challenge is 25% albumin for both its oncotic and anti-inflammatory properties[111] at a dose of 1 g/kg of body weight to a maximum of 100 g/day for 48 h. Patients should be monitored closely for signs of volume overload/pulmonary edema while receiving albumin. Furthermore, they should also be monitored for progression of kidney dysfunction, emergence of infections or other complications of cirrhosis, or organ failure and treated accordingly.

Pharmacotherapy for HRS-AKI

The mainstay of treatment for HRS-AKI that is not responsive to volume challenge is vasoconstrictor therapy together with albumin (20–40 g/day). The optimal duration of albumin administration is unclear. In the most recent clinical trial using terlipressin for the treatment of HRS1,[112] respiratory failure was observed in 8% of patients who received terlipressin, especially in those with ACLF-3, but not in those who received placebo,[112] and there was a trend toward higher incidence of respiratory failure in those who received a higher volume of albumin in the pretreatment period. Patients should be carefully monitored for pulmonary edema, as some of these patients may have a degree of cirrhotic cardiomyopathy or diastolic dysfunction. In addition, the total amount of albumin administered prior to initiation of terlipressin should also be considered. The published literature so far has only reported on results of vasoconstrictor use in patients with HRS1. There are no studies of vasoconstrictor use in patients with cirrhosis and the newer diagnostic criteria of HRS-AKI. Worldwide, terlipressin is the most widely used vasoconstrictor in cirrhosis for HRS in the

absence of shock, followed by norepinephrine, with a small number of studies reporting on the use of midodrine and octreotide.[113] Terlipressin was recently approved for use in the United States. However, in patients with AKI and shock, norepinephrine is the first drug of choice.

Terlipressin. To date, there are four RCTs on the use of bolus injections of terlipressin versus placebo for the treatment of HRS1 (Table 4).[112, 114–116] The starting dose was 1 mg every 4–6 h, gradually increasing up to 12 mg/day depending on response, for a total of up to 14 days. All the studies showed that terlipressin with albumin was more effective than placebo with albumin in reversing HRS1 in 36%–44% of patients, with three of the studies showing a statistically significant positive response rate.[112, 114, 115] The use of a continuous infusion of terlipressin was able to achieve the same efficacy as bolus dosing with a lower total daily dose and fewer side effects.[28] Common side effects are related to ischemia such as angina, arrhythmia, or digital ischemia, and therefore, terlipressin is not recommended to patients with known ischemic conditions. In the intestinal tract, terlipressin can stimulate intestinal motility, leading to abdominal pain and diarrhea. In the latest North American study of terlipressin for HRS1,[112] more patients who received terlipressin had respiratory compromise, possibly related to multifactorial mechanisms, leading to an increase in afterload from subtle cirrhotic cardiomyopathy such as diastolic dysfunction and/or volume overload from overly aggressive albumin infusions. The fact that this was only observed in patients with ACLF-3 as defined by EASL-CLIF criteria suggests a complex interplay in hemodynamics perturbed by terlipressin and contributing to the respiratory failure.[112] Therefore, clinicians should exercise caution when ordering terlipressin for patients with known cardiac failure or underlying respiratory conditions, especially those with baseline hypoxemia (Food and Drug Administration warning for patients with ACLF-3 and respiratory failure). Predictors of response to terlipressin treatment include markers of better liver function as indicated by a bilirubin of ≤10 mg/dL (170 μmol/L),[117, 119] better kidney function by an sCr of ≤5 mg/dL (440 μmol/L),[117, 119] an increase in the MAP of ≥5 mm Hg with treatment[118, 119], and lower grades of ACLF.[120] In patients with HRS1 and ACLF, ACLF grade (EASL-CLIF) is the major determinant of response to therapy; ACLF-2 and -3 are associated with lower probability of response. Hence, initiation of therapy early on in the course of HRS may be more effective.

None of the studies using terlipressin for HRS1 showed an improvement in overall survival, but in those who responded, the complete reversal of HRS1 was associated with a significantly better survival when compared with nonresponders.[119, 121, 122] In fact, for every 1 mg/dL drop in sCr with vasoconstrictor therapy, there was a 27% reduction in relative risk of mortality.[123]

In the context of ACLF, defined per the AARC, terlipressin was more effective than norepinephrine in reversing HRS1 and in improving 28-day survival.[124] However, further such studies are needed specifically in patients with ACLF.

Norepinephrine. Norepinephrine increases the MAP, and hence the renal perfusion pressure. Studies comparing norepinephrine with terlipressin for the treatment of HRS1 showed noninferiority of norepinephrine in reversing HRS1.[125–129] This finding was also confirmed by meta-analysis.[130–132] However, these trials were small and at high risk of methodologic bias. A recent study reported on the use of low-dose norepinephrine (starting dose: 5 μg/min, maximum dose: 10 μg/min) for the treatment of HRS-AKI in patients who were nonresponders to midodrine and octreotide in a non-ICU setting with cardiac monitoring to reach an MAP >10 mm hg above baseline value.[133] They were able to achieve a complete response in six out of 20 patients and a partial response in three additional patients.

Other agents. Another oral vasoconstrictor, midodrine (dosed 7.5–15 mg orally three times daily), also an alpha agonist, has been used in combination with octreotide, a nonspecific antagonist to splanchnic vasodilators, as a treatment for HRS1. This combination is inferior to a continuous infusion of terlipressin as a treatment for HRS1 but can be safely used in a nonmonitored setting.[121]

Renal replacement therapy

At this time, there is equipoise regarding the optimal timing of renal replacement therapy (RRT) in patients with ACLF, and no clear benefit has been demonstrated for preemptive initiation (e.g., within 12 h of Stage 1 AKI and/or oliguria <6 mL/kg over the preceding 12 h).[104, 134–137] Initiating RRT in patients with decompensated cirrhosis is challenging because of hypotension and coagulopathy.[135] In general, RRT is not recommended as a stand-alone therapy for patients with HRS-AKI unless they are candidates for LT.[104, 134–137] RRT in nontransplant candidates should be considered on a case-by-case basis, especially if not necessarily related to HRS-AKI (e.g., contrast-induced nephropathy). In patients who are LT candidates, the use of RRT can be regarded as a bridge to LT to treat uremia, electrolyte abnormalities, acid–base issues, and fluid overload. Continuous RRT is preferable to intermittent RRT in patients who are hemodynamically unstable.[135] Intraoperative RRT in patients receiving LT has been used, mostly in sicker patients who have required preoperative RRT to deal with intraoperative complications.[138] However, in a recent meta-analysis on the use of intraoperative RRT during LT, there was no difference in the postoperative outcomes, including short-term mortality, the number of days of mechanical ventilation, or the length of hospital stay.[137, 140]

LT is the definitive treatment for patients with HRS-AKI; all patients with HRS-AKI who are potential LT candidates should be referred for transplant evaluation without delay. Patients who have had prolonged course of pretransplant RRT of >6 weeks, or meet recently updated criteria, should be considered for simultaneous liver–kidney transplant. Patients who are nonresponders to pharmacotherapy and who are not LT candidates should be referred for palliative care. Although response to vasoconstrictor therapy has resulted in lowering the MELD score and a potential delay in LT, the posttransplant outcomes of those who received vasoconstrictors were significantly improved, with fewer patients needing RRT and developing chronic kidney disease at 1 year post-LT.[141]

Guidance statements

24. In patients with cirrhosis and AKI, after withdrawing diuretics and treating precipitating factors such as bacterial infection, volume challenge with i.v. albumin at a dose of 1 g albumin/kg of body weight, maximum of 100 gm/day, is recommended for 48 h.
25. Vasoconstrictors and albumin (20–40 g/day) are recommended for patients who fulfill the diagnostic criteria for Stage 2 or greater HRS-AKI and who do not have contraindications. Currently, there is no recommendation for vasoconstrictor use for Stage 1 AKI. The optimal duration of albumin administration in the setting of HRS treated with vasoconstrictors remains unclear.
26. The use of terlipressin (0.5–2.0 mg i.v. q6h or continuous infusion of 2 g/24 h i.v.) is indicated in hospitalized patients with Stage 2 or greater HRS-AKI and without ACLF-3 (EASL-CLIF) or major cardiopulmonary or vascular disease.
27. Norepinephrine can be used as an alternative to terlipressin for patients with HRS-AKI and may be preferred in patients with shock.
28. The use of RRT in patients with cirrhosis and AKI should be individualized. In general, RRT is recommended for patients with HRS-AKI who have failed pharmacotherapy and are listed or being considered for LT.
29. LT is the definitive treatment for HRS-AKI in cirrhosis but needs to be placed in the context of multiorgan failure and overall LT candidacy.

INFECTION

Infection is the most common precipitant of ACLF worldwide, with a prevalence of 48%.[142] Cirrhosis-associated immune-deficiency syndrome predisposes patients to infection and subsequent multiple organ failure (see Supplementary Materials, http://links.lww.com/HEP/I105).[143, 144] High-risk groups include

younger male patients, alcohol-associated cirrhosis, and those with a high MELD score.[142] Invasive procedures and line and catheter placement also increase infection risk. Bacterial features, specifically those causing multidrug-resistant (MDR) organisms, also increase the risk of ACLF and further increase the risk of death.[142, 145] In patients without ACLF who develop infection, risk factors for progression to ACLF include the presence of ascites, HE, higher MELD score, nosocomial infection, inadequate first antibiotic treatment, and type of infection (pneumonia > SBP).[142]

Diagnosing Infection

The most common infections are SBP, urinary tract infection skin/soft-tissue infections, and respiratory infections in descending order.[12, 142] It can be challenging to diagnose sepsis early in patients with cirrhosis because (1) lactate clearance is impaired by liver dysfunction, (2) vasodilator production from portal hypertension lowers MAP, (3) alcohol-associated hepatitis increases WBC count and other markers of systemic inflammation, (4) relative adrenal insufficiency is common in patients with cirrhosis[146], and (5) fever is often absent in patients with cirrhosis who have sepsis.

In contrast, symptoms of new or worsening decompensation, such as worsening mental status, hyponatremia, AKI, relative increase in WBC count, change in hemodynamics, or higher ACLF grade frequently result from infection acquisition. Therefore, a high level of suspicion for sepsis is needed in all patients with cirrhosis who present to the emergency room.

Biomarkers such as C-reactive protein, procalcitonin, lactate, and bacterial DNA are often elevated in patients with cirrhosis both with and without infection, although a persistent elevation of these markers is a poor prognostic indicator.[22, 147–149]

Patients with ACLF and infection have more severe systemic inflammation and a higher probability of death than patients with ACLF without infection.[145] Even if patients survive ACLF, they have an increased risk of subsequent infections; 45% of patients with cirrhosis discharged after successful treatment of one infection acquire another infection within 6 months.[150] A framework for assessment and management of infections is provided in Figure 4. Infection prevention measures are crucial in the hospitalized patient and outlined in Table 5 and Supplementary Materials, http://links.lww.com/HEP/I105.

Nosocomial infections, fungal infections, and MDR organisms

There has been an increase in health care–associated and nosocomial infections in patients with cirrhosis.[151] Nosocomial infections are increasingly caused by MDR organisms and now account for at least 40% of culture-positive infections in cirrhosis/ACLF.[152, 153] The MDR infection rate worldwide in patients with cirrhosis also continues to increase and has now reached 34%, although it is highest in Asia.[154, 155] However, in culture-negative nosocomial infections, the rate of resistance to first-line community acquired antibiotic treatment can be as high as 75%.[160] Nosocomial infections and MDR organisms independently increase the risk of ACLF, and effective antibiotic treatment is essential to improve mortality.[156]

Fungal infections occur in 2%–16% of patients with ACLF and are almost always nosocomial.[157] Antibiotic use results in gut fungal dysbiosis, thereby increasing the risk of fungal infection. Fungal infections more commonly affect patients with high MELD, occur as second infections, and independently increase the risk of ACLF and death.[145, 151, 158] Other risk factors include AKI, diabetes, longer hospitalization, ICU admission, and prior bacterial infection. Overall, the risk of death in patients with cirrhosis and a fungal infection is 30% at 30 days but is higher in patients with fungal peritonitis and fungemia.[157] Patients with ACLF and a suspected infection not responding to antibiotics should be considered to have either an MDR organism or fungal infection. Unfortunately, current diagnostic testing with cultures lacks sensitivity, whereas 1,3-β-D-glucan testing lacks specificity.[159] The combination of PCR testing and 1,3-β-D-glucan testing may improve the sensitivity of testing for invasive aspergillosis. The sensitivity and specificity of antibody and antigen testing for specific fungal infections has not been studied in patients with cirrhosis.

Antibiotic use

When choosing antibiotics, it is essential to consider (1) the etiology of the infection, (2) the severity of the infection, (3) local resistance patterns, and (4) how the infection was acquired (community acquired, health care associated, or nosocomial; Table 6; Table S1, http://links.lww.com/HEP/I105). Once chosen, the pharmacist should be asked to minimize the salt load given with antibiotic administration, and first antibiotic doses for patients with ACLF should be given in the emergency room because each hour delay increases mortality.[160] Differentiating community acquired from health care–associated infection is critical in addition to taking into account recent antibiotic exposure because a lack of response to first antibiotics is associated with an increased risk of AKI and death.[156] Once culture results return, de-escalation of antibiotics is important to decrease the prevalence of MDR organism colonization and subsequent infections. In ICU patients with ACLF, lack of clinical improvement after 48 h should trigger broadening of antibiotic coverage and consideration of fungal coverage.

In LT candidates, reactivation for transplant as soon as clinical improvement and control of infection is achieved may open a "window of opportunity" for transplant[161] in the setting of infection-related ACLF or decompensation. (Table 6)

SBP is the most common infection in patients with ACLF.[12, 142] Delay in starting treatment at hospital admission in patients with SBP almost triples the in-hospital mortality with each hour delay, increasing the absolute risk of in-hospital death by 3.3%.[162] Although a nonneutrocytic bacterascites does not necessarily require therapy in outpatients, bacterascites in inpatients increases the risk of AKI, ACLF, and increased mortality, therefore necessitating early antibiotic therapy.[163]

Guidance statements

30. In patients hospitalized with complications of cirrhosis, especially those with ACLF, a full workup for infection, including a diagnostic paracentesis, blood cultures, urinalysis, urine culture, and chest x-ray is recommended.
31. In patients with a change in clinical status (new or worsening ascites, HE, AKI, organ failure, and/or ACLF) workup for infection should be repeated.
32. Antibiotics should be chosen based on the infection etiology, severity, mode of acquisition, and local resistance patterns.
33. To prevent infections and subsequent ACLF in inpatients with cirrhosis, proton pump inhibitor use and foley catheter should be minimized.
34. Consider broadening antimicrobial coverage to cover MDR organisms and/or fungal infection in patients with nosocomial infections and/or ACLF who are not responding to appropriate antibiotics after 48 h.

COAGULOPATHY

Assessment of bleeding risk

There is a poor correlation between traditional coagulation tests (e.g., INR) and bleeding risk in critically ill patients with cirrhosis.[164] INR is dependent on procoagulant factors I, II, V, VII, and X and does not account for the rebalanced coagulation in patients with ACLF and decompensated cirrhosis from anticoagulant deficiencies. In contrast, viscoelastic testing (e.g., thromboelastography [TEG] and rotational thromboelastometry) provides a functional evaluation of altered pro- and anticoagulant pathways and measures platelet function, hyperfibrinolysis, and premature clot dissolution in real time. However, optimal

cutoffs to guide platelet, cryoprecipitate, or four-factor prothrombin complex concentrate in ACLF have not been studied.[165] ACLF is associated with prolonged initial fibrin formation, clot formation, and reduced clot firmness, which has been associated with higher short-term mortality.[166, 167]

Bleeding rates for paracentesis (0%–3.3%) and thoracentesis (2%) in patients with cirrhosis are low and do not require routine preprocedural coagulation assessment in decompensated cirrhosis or ACLF.[168] Reported bleeding rates for liver biopsy are higher in patients with ≤50 platelets/L.[169, 170] However, transjugular liver biopsy is relatively safe even in patients with decreased platelet counts or prolonged INR.[171] When correction is needed, transfusion of low volume cryoprecipitate or four-factor prothrombin complex concentrate are preferred to high-volume fresh frozen plasma that also contains anticoagulants.[172]

Two recent randomized prospective studies of patients with cirrhosis or ACLF with variceal or nonvariceal bleeding demonstrated that a TEG-guided strategy resulted in fewer blood transfusions compared with the standard of care (SOC) with no difference in failure to control bleeding, rebleeding, or mortality.[173, 174] Similarly, in a randomized trial of 60 patients with cirrhosis undergoing invasive procedures, TEG-guided blood product transfusion (fresh frozen plasma trigger: reaction time > 40 min; platelet trigger: maximum amplitude <30 mm) versus SOC (INR and platelet count) decreased transfusions (16.7% vs. 100%; $p < 0.0001$) with no difference in bleeding or 90-day mortality (Table S2, http://links.lww.com/HEP/I105).[175]

Venous thromboembolism treatment

Patients with cirrhosis demonstrate increased risk of venous thromboembolism (VTE), with rates of PVT estimated at 8% per year in those awaiting LT.[176, 177] Improved outcomes have been reported in patients with cirrhosis with VTE anticoagulated at 1 year, especially those with more extensive mesenteric thrombosis.[178–180] In a systematic review, a significantly higher proportion of anticoagulant treated versus untreated patients experienced PVT recanalization (71% vs. 42%; $p < 0.0001$) with no difference in any type of bleeding but a lower risk of variceal bleeding ($p = .04$).[181] Despite the increased clinical effect observed with decreased anti-thrombin III levels in patients with cirrhosis,[182] low molecular weight heparin (LMWH) is favored. In observational studies, direct-acting anticoagulants (DOACs) have been successfully used in compensated cirrhosis and are superior to coumadin for treatment of PVT.[183, 184] However, DOACs are contraindicated in patients with Child–Turcotte–Pugh Class C cirrhosis because they are metabolized by the liver; therefore, they should be avoided in critically ill patients with cirrhosis.[185]

VTE prophylaxis

Despite having an increased risk of VTE, rates of thromboprophylaxis (mechanical or pharmacologic) are suboptimal.[186, 187] A nonblinded, single-center RCT demonstrated prophylactic LMWH decreased PVT risk (relative risk, 0.05; $p = 0.048$) without increasing mortality or bleeding.[180] A single observational study of pharmacologic versus mechanical VTE prophylaxis reported no difference in mortality or bleeding.[187] Although there are concerns regarding anticoagulation and GI bleeding in patients with cirrhosis/ACLF, the outcome of patients with upper GI bleeding (patients with cirrhosis but not necessarily with ACLF) receiving anticoagulation was significantly associated with the degree of multiorgan failure and comorbidity but not receipt of anticoagulation itself.[188] (For further information, please refer to AASLD 2020 Practice Guidance on Vascular Liver Disorders.[189])

Guidance statements

35. Global tests of hemostasis, such as thrombin generation or whole-blood viscoelastic tests, better capture the general hemostatic status of a patient with cirrhosis but have not been clinically validated.
36. INR should not be used to gauge bleeding risk among patients with cirrhosis/ACLF.
37. Therapeutic anticoagulation in patients with cirrhosis appears to have similar nonportal hypertensive bleeding complication rates compared with the general population. In patients with ACLF and severe thrombocytopenia (platelet count < 50), decisions regarding safety of systemic anticoagulation should be made on a case-by-case basis.

NUTRITION

Nutritional assessment and support are important aspects of management of critically ill patients with cirrhosis because malnutrition is very common and frequently not recognized.[190–192] This is especially relevant given the prevalence of sarcopenia, obesity, frailty, and poor nutritional reserve among these patients.[193] Malnutrition and sarcopenia are independent predictors of adverse clinical outcomes including mortality.[194] Additional insults such as prolonged nil per os (nothing by mouth) status for variceal bleeding, multiple procedures, or presence of HE further reduce the nutritional reserve. Further infections, as well as prolonged ICU stay, can worsen the nutritional status in patients with ACLF.

Nutrition management in malnourished patients with ACLF should be undertaken by a multidisciplinary team to achieve adequate protein and calorie intake for optimal outcomes. A multidisciplinary approach including nutritionists/dietitians and nutrition support teams in inpatients with cirrhosis is associated with improved outcomes and reduced readmissions and promotes synergy between the multiple teams taking care

of these patients.[173, 195–198] An objective assessment of the patient's nutrition status and risk should be performed on all patients at ICU admission. The Society of Critical Care Medicine/American Society for Parenteral and Enteral Nutrition guidelines recommend the use of the Nutrition Risk in the Critically Ill (NUTRIC) score to identify ICU patients who benefit most from early nutrition support.[199, 200] Given that a majority of patients are likely chronically ill, a full nutrition assessment may be needed.

In principle, nutrition support goals for critically ill patients with cirrhosis in the ICU mirror other patients without cirrhosis who may be critically ill. Energy and protein requirements for nutrition support are calculated by predictive equation initially, using dry weight or ideal body weight instead of actual body weight. The recent 2021 AASLD Practice Guidance on Malnutrition, Frailty, and Sarcopenia recently recommended a target caloric goal of 35 kcal/kg for patients without obesity with cirrhosis and 25–35 kcal/kg for patients with obesity with a body mass index of 30–40.[197]However, rather than weight gain, the goal is providing support in the ICU during a catabolic state. In addition, nutrition support goals may change over the hospital course. In alignment with critical care literature, the initial goal of 12–25 kcal/kg may be preferred with evolution toward the higher target goals as the clinical course evolves. There is considerable interindividual variability in patients with ACLF, and indirect calorimetry to measure resting energy expenditure should be used if available for more accurate assessment. Protein restriction is not recommended. Standard ICU protein support is indicated, with higher protein requirements recommended in malnourished patients with ACLF. Administration of micronutrients and vitamins are recommended to treat confirmed or clinically suspected deficiency. Enteral nutrition with a feeding tube may be needed for those requiring invasive ventilation for acute respiratory distress syndrome or other respiratory conditions such as pneumonia. As in most diseases, regardless of ACLF, enteral nutrition is preferred over parenteral nutrition if no contraindications to enteral nutrition are present.[201, 202] This should be started as soon as possible after resuscitation is complete and the patient is not requiring high-dose vasopressors, though the exact vasopressor level is not known. Standard enteral formulas are indicated; there is no benefit of branched-chain amino acid formulas in ICU patients with ACLF.[200] Parenteral nutrition is indicated if contraindications to enteral nutrition (bowel obstruction, ischemic bowel, severe intestinal ileus, and enteral nutrition intolerance) are present.

Because many ICU patients with ACLF are malnourished, it is imperative to monitor for refeeding syndrome after the initiation of nutrition support.[203] Nutrition support is initiated slowly, with 5–10 kcal/kg for the first 24 h, with monitoring serum electrolytes (potassium, magnesium, and phosphorous) both before the

initiation of nutrition and at least every ≥12 h frequently for the first 3 days thereafter and longer if electrolyte abnormalities persist. Aggressive electrolyte repletion and cardiorespiratory monitoring are recommended to avoid cardiac dysrhythmias.[203]

Hyperglycemia is common in ICU patients receiving nutritional support. Guidelines for glycemic control in adult critically ill patients currently recommend a target blood glucose of 140–180 mg/dL (7.8–10 mmol/L) and avoidance of prolonged hypoglycemia. In studies in which tight versus normal glucose control was studied, there was no benefit to a tight (80–110 mg/dL or 4.5–6.0 mmol/L) versus less stringent targets (140–180 mg/dL or 7.8–10 mmol/L).[173, 204–206] Tighter glucose control led to more severe hypoglycemic episodes and higher mortality in some studies; however, these studies were performed in mixed populations and not just those with ACLF.[204, 207, 208]

Guidance statements

38. Early involvement of nutrition support teams is recommended among hospitalized patients with ACLF.
39. An objective assessment of nutrition status and risk (e.g., NUTRIC score) should be performed at ICU admission for patients with cirrhosis and/or ACLF.
40. Energy and protein requirements should be measured by indirect calorimetry if available or, if not available, calculated using predictive equations.
41. Ideal body weight is recommended to be used instead of actual weight for predictive equations to calculate energy and protein requirements in patients with cirrhosis and/or ACLF.
42. Initial caloric target of 12–25 kcal/kg for patients with ACLF should be considered with the upper limit appropriate for patients without obesity and evolution toward higher target goals as clinical course evolves.
43. Protein restriction is not recommended; standard ICU protein support is indicated (1.2–2.0 g/kg ideal body weight/day) for patients with cirrhosis and/or ACLF.
44. Enteral nutrition is recommended over parenteral nutrition in the absence of contraindications.
45. Enteral nutrition should be held in patients requiring high-dose vasopressor support (e.g., >0.15 μg/kg/min of norepinephrine or equivalent).
46. Malnourished patients should be monitored for refeeding syndrome (e.g., hypokalemia, hypophosphatemia, arrhythmias) after the initiation of nutrition support with routine electrolyte/electrocardiogram monitoring.

47. A target blood glucose between 140 and 180 mg/dL (7.8–10 mmol/L) is recommended for patients with cirrhosis and critical illness or ACLF.

LT FOR PATIENTS WITH CIRRHOSIS WITH ACLF AND/OR CRITICAL ILLNESS

Critically ill patients with cirrhosis and MELD scores >40 as well as those with multiorgan failure have higher waitlist mortality than patients with Status 1A.[209, 210] Given the increased risk of premature mortality in patients with cirrhosis and ACLF or critical illness, there is interest in identifying a subset of patients that may benefit from LT.[211]

Outcomes on the waitlist

Among those considered LT candidates, waitlist mortality for critically ill patients with cirrhosis ranges from 20% to 70%, and only a minority make it to transplant. In a single-center study of urgent inpatient LT evaluation over 2 years, 43% were declined for LT, 33% were waitlisted, 18% died, and 6% improved.[212] Overall, 26% of patients underwent LT.

Outcomes after LT

Reported outcomes after LT for patients with ACLF versus without ACLF are heterogeneous and impacted by patient presentation and selection (Table S3, http://links.lww.com/HEP/I105).[213] Studies are often retrospective, use variable definitions of ACLF and critical illness and, therefore, do not clearly identify the subset of patients that are true candidates for LT without contraindications.[214, 215] It is hard to parse out selection bias; further details of patients with ACLF that do not make it to listing are not available.[9, 214, 216] Relevant outcomes of interest such as waitlist mortality and intent-to-treat survival are not uniformly collected.[217, 218]

In a prospective cohort study from the multicenter NACSELD (n = 2793) group, of 265 patients (35%) who underwent LT, survival at 6 months was not different between those with and without ACLF.[219] There is a subset of critically ill patients with cirrhosis who may receive a survival benefit from LT. In carefully selected patients, survival after LT of patients with ACLF-3 was similar to patients with either no ACLF or with ACLF-1 or -2 (CLIF ACLF). However, this came at a cost of higher complications after transplant.[220] Alternatively, in a recent meta-analysis comparing 22,238 patients with ACLF versus 30,791 without ACLF, post-LT survival in those with ACLF was lower as compared with other indications (e.g., 1- and 5-year, 86.0% vs. 91.9% and 66.9% vs. 80.7%; $p < 0.01$) and was associated with increased resource utilization

(ICU and hospital stay) and similar posttransplant complications (74.4% vs. 55.5%, $p = 0.12$).[216] Improvement or stabilization of organ failures, especially pulmonary and circulatory, may be a prerequisite, and improvement in MELD has been associated with improved survival to LT.[219] Data on outcomes after living donor LT in the critically ill are also variable with conflicting data on whether the presence of ACLF is associated with similar or poorer outcomes.[211, 221, 222]

Predictors of transplant outcomes

A singular score or cutoff (either CLIF-C ACLF or AARC) may not be able to predict LT candidacy; rather, a composite of trajectory (stabilization or improvement), end-organ severity, and ACLF scores may be helpful.[26] The question also remains whether an ACLF-specific score is needed or if the MELD-Na score, or its modifications such as MELD 3.0, is adequate.[223]

Table 7 highlights pretransplant predictors of posttransplant outcomes in the critically ill population with cirrhosis. Patients that meet criteria for both EASL and APASL definitions have worse survival as compared with either definition alone.[224] MELD-Na may not completely capture the risk of mortality in the critically ill at low MELD-Na scores but performs well at high MELD scores, which are often seen in ACLF.[11] However, variable performance of MELD-Na is not unique to patients with ACLF. Several scores have been proposed to predict post-LT outcomes, but their performance is inconsistent, requires further validation, or does not capture the granular elements of ACLF (transplantation model for patients with ACLF-3, AARC, MELD, CLIF-C ACLF, the CLIF-OF (organ failure), P-SOFT (preprocurement Survival Outcomes Following Liver Transplant), balance of risk, SOFA, and CLIF-SOFA).[14, 220, 225, 226] Pre-LT factors that likely serve as absolute contraindications to LT include high lactate levels (>9 mmol/L), severe respiratory failure, and increasing vasopressor support.[216, 220, 226, 227] Ventilator support remains a consistent predictor of suboptimal post-LT outcomes, especially in the presence of dialysis, advanced age, and relevant chronic conditions.[210, 228, 229] Rather than the absolute number of organ failures, the severity of organ failure plays a role. Among critically ill patients with cirrhosis in the ICU, severe frailty (clinical frailty scale ≥ 7), infection (ongoing and uncontrolled sepsis, leukopenia, MDR organisms, persistent fevers, and <72 h of antibiotics), FiO_2 ratio <150 mm Hg, high-dose norepinephrine, and a serum lactate level >9 mmol/L were associated with worse posttransplant outcomes.[227, 230] Moderate hypoxemia and respiratory failure ($PaO_2/FiO_2 \geq 150$) may be acceptable for LT, but hemodynamic instability (progressive or sustained vasopressor requirement), severe ARDS (PaO_2/FiO_2 ratio < 150), and uncontrolled sepsis are likely barriers. Other factors considered as contraindications for LT may include HE requiring ventilatory support for >72 h, active GI bleed, and

hemodynamic instability.[3] The impact of age is relative, but in combination with other aspects (e.g., mechanical ventilation or poor functional status) it may be relevant.[231]

Increasing chance of successful transplant outcome

Given the lack of consensus on selection criteria, absolute and relative contraindications and timing of potential transplant candidacy related to the dynamic course among the critically ill make LT decisions difficult (Figure 5). However, there are recent attempts at formulating guidance for LT in the critically ill.[231] Certain features may guide optimal patient selection for LT candidacy.

Lack of progression of organ failure. Stabilization or improvement of organ failure may be key, especially within the first 72 h to 1 week, especially with regard to respiratory failure.[25, 210, 227, 232, 233]

Type and severity of organ failure. Post-LT survival is significantly impacted by respiratory or cardiac failure.[234–236] Progression of severe hypoxemia may be prohibitive for LT.[25, 215, 220, 228, 235, 237] The severity of ALI as assessed by the PaO_2/FiO_2 ratio can guide decision-making regarding a pulmonary contraindication to LT.

Early recognition, stratification, and transplantation. Notwithstanding the limitations of the United Network for Organ Sharing data, select candidates with three or more organ failures have done well but also need early LT.[220, 238] A combination of early transplant after a period of stabilization, or ideally improvement, may be critical for ensuring acceptable outcomes.[216, 232, 239, 240] Early assessment by transplant anesthesiologists is also important to assess cardiopulmonary barriers to successful transplant.

Recognition of need for increased resource utilization and morbidity after LT. There are divergent data whether the rate of complications after LT for critically ill patients/patients with ACLF-3 is similar or higher as compared with other indications. Grade of complications, length of stay, and biliary and vascular complications may be higher.[220, 237, 240] In addition, sepsis and infections are drivers of post-LT mortality.[232, 240–242] Further work on preventive or prophylactic strategies is needed.

Consideration of etiology. Alcohol-associated liver disease and bacterial infection separately are often encountered in the patient with ACLF. Active alcohol use and/or untreated bacterial infection may be prohibitive but potentially reversible.

Futility of care

In patients with ACLF, the decision to withdraw ICU treatment should be based on the likelihood of reversibility and eligibility for LT. In patients not eligible for LT, high ACLF-specific scores at admission may help decisions regarding futility of care and discussing goals of care. In hospitalized patients with cirrhosis, 28-day survival after NACSELD ACLF (≥2 organ failures) assessment has been reported to be as low as 3%.[30] In a multicenter analysis of critically ill patients with cirrhosis in Europe and North America, CLIF-C ACLF score >70 (range, 0–100) at admission or at Day 3 was associated with approximately 90% 90-day mortality.[26] In this scenario, de-escalation of care should be discussed on a case-by-case basis and based on the feasibility of an LT. Data from the Canonic study showed that the 28- and 90-day mortality of patients with four or more organ failures at Days 3–7 after the diagnosis of ACLF-3 was 90% and 100%, respectively, and 100% in patients with CLIF-C ACLF score >64.[25] Data from a retrospective study in an independent cohort of patients confirmed that patients with ACLF and CLIF-C ACLF score ≥70 at 48 h after intensive care had a 100% 28-day mortality rate.[243]

Guidance statements

48. Expedited LT for patients with cirrhosis and ACLF and/or critical illness may be indicated in selected patients, but at present, there is equipoise regarding specific predictors associated with acceptable outcomes.
49. Decisions about futility of care should be based on candidacy for expedited LT available resources and potential reversibility of ACLF.

PALLIATIVE CARE

Palliative care is an essential component of cirrhosis care and has previously been extensively reviewed.[244, 245] Inpatients with ACLF have a high symptom burden, ICU utilization, cost of admission, and risk of death. Therefore, palliative care consultation should be incorporated into the management of critically ill patients with cirrhosis (Table S4, http://links.lww.com/HEP/I105). Although palliative care remains underutilized,[246–251]it is associated with a lower procedure burden and cost saving of ~$10,000 per patient with end-stage liver disease.[247, 252] In the Nationwide Readmissions Database, those who received a palliative care consult had ~50% lower rates of readmission, a shorter length of stay, and inpatient healthcare cost savings.[253] In another study, palliative care consult cut readmissions by two thirds and doubled the chance of hospice discharge.[246] Even when palliative care or hospice are consulted, it most often occurs late.[248–250, 254] In contrast to current practice, a survey found that patients with cirrhosis prefer to undertake advanced care planning before the onset of decompensation.[255] Higher readmission at the end of life and in-

hospital death combined with patient preferences for earlier advanced care planning should serve as a call to action for the hepatology community to engage palliative care sooner but certainly for all patients at ACLF diagnosis or ICU admission.

Quality palliative care

In 2017, an expert panel developed 19 quality indicators for palliative care of patients with end-stage liver disease.[256] Notable quality indicators relevant to patients with ACLF that were infrequently achieved (<20%) included transfer of care, de-escalation orders from one hospital to another, goals of care discussion for patients with end-stage liver disease, being considered for hemodialysis, or requiring mechanical ventilation for >48 h (Table 8).[257] In the future, more work is required to achieve high-quality palliative care, especially in those admitted to the ICU with ACLF.[258]

Palliative care in patients listed for LT

Advanced care planning in patients listed for LT occurs infrequently.[259] LT listing is the single greatest factor impairing palliative care consultation among patients with end-stage liver disease.[260] Although most providers agree that LT listing and palliative care services are not mutually exclusive, attending hepatologists may be the biggest barrier to palliative care referral in listed patients.[261–263] Even after delisting, palliative care referral remains infrequent.[248] Therefore, we need to engage palliative care in all listed patients who develop ACLF (F[264]

Guidance statements

50. In critically ill patients with cirrhosis and/or ACLF, a palliative care consult should be considered to define and explain prognosis and determine goals of care.
51. Any member of a patient's care team can offer primary palliative care with advanced care planning and symptom management. When available, palliative care specialists and hepatologists should work collaboratively to achieve the desired goals of care for each patient.
52. Disease-directed care, such as transplantation evaluation and listing, does not preclude palliative care delivery or specialty palliative care consultation.

FUTURE DIRECTIONS

The immediate priorities are to arrive at a uniform definition of ACLF that can be applicable worldwide, characterize the clinical course, and utilize a standard management protocol for ACLF targeted at early

diagnosis and reversal of precipitating events and organ failure (Table 9). Given the high incidence and mortality of infection in ACLF, early diagnosis and treatment are critical. A key part of the definition of ACLF is identifying the interval after the precipitating event that patients are at increased risk of mortality. ACLF needs to be defined based on a unique set of signs and symptoms, well-defined and distinct pathophysiology, and laboratory tests that can confirm the diagnosis. Most importantly, the diagnosis should inform future specific interventions that have potential to reverse the disease. In addition, objective outcomes (e.g., 1- or 3-month mortality) need to be standardized. Of critical importance is the need for development of hepatic regenerative therapies and artificial/bioartificial liver support devices that will serve as a bridge to LT or even as destination therapy for patients with liver failure.

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FIGURE 1 Conceptual framework for acute-on-chronic liver failure. (1) The presence of liver failure defined by elevated bilirubin and elevated international normalized ratio in patients with chronic liver disease with or without cirrhosis. (2) Acute onset with rapid deterioration in clinical condition. (3) The presence of at least one extrahepatic (neurologic, circulatory, respiratory, or renal) organ failure. Patients with chronic liver disease or cirrhosis undergo an acute insult or injury that is associated with hepatic and extrahepatic organ failure. There is potential for recovery, but if the cascade is irreversible, either palliative care or consideration for liver transplantation may be appropriate in highly selected individuals. Intervention early in the cascade may improve chances of reversibility. For those who recover, some may go back to their original state or decompensation. [1]Insult/injury examples include alcohol-associated hepatitis, drugs, infection, viral hepatitis, and surgery. [2]Inflammatory response may be sterile inflammation or infection related. [3]See section on Increasing chance of successful transplant outcome

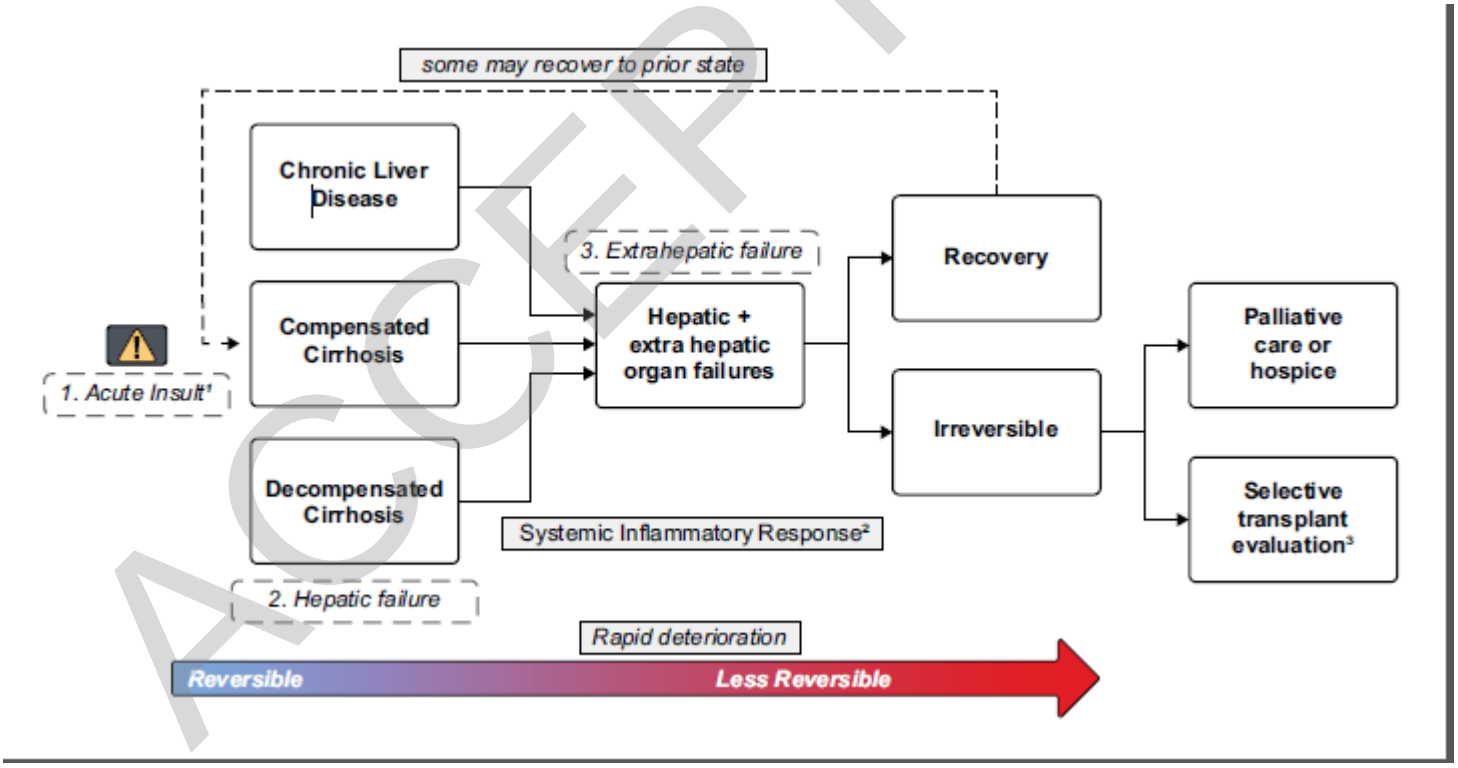

FIGURE 2 Assessment of circulatory function (cardiac and volume status) and management of the critically ill patient with cirrhosis. ACLF, acute-on-chronic liver failure; CVP, central venous pressure; ICU, intensive care unit; LV, left ventricular; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; POCUS, point-of-care ultrasonography; RV, right ventricular; $ScVO_2$, central venous oxygen saturation; UO, urinary output

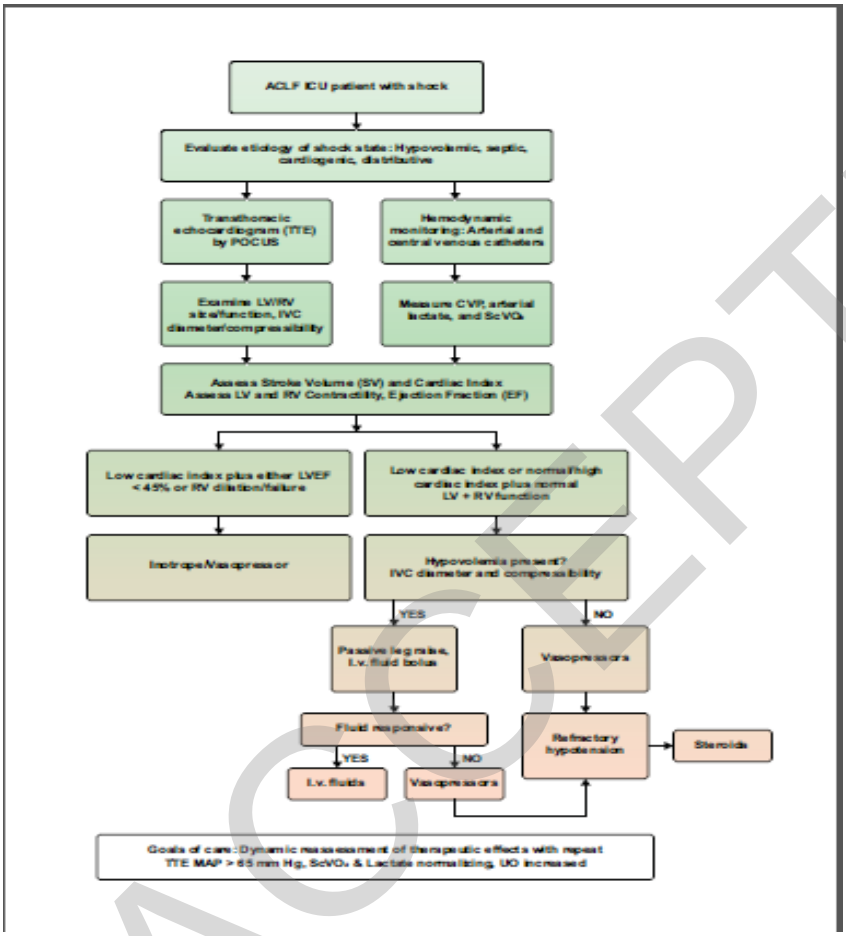

FIGURE 3 Assessment and management of AKI in the patient with acute-on-chronic liver failure/critically ill patient with cirrhosis. AKI, acute kidney injury; GI, gastrointestinal; HRS, hepatorenal syndrome; LT, liver transplantation; sCr, serum creatinine

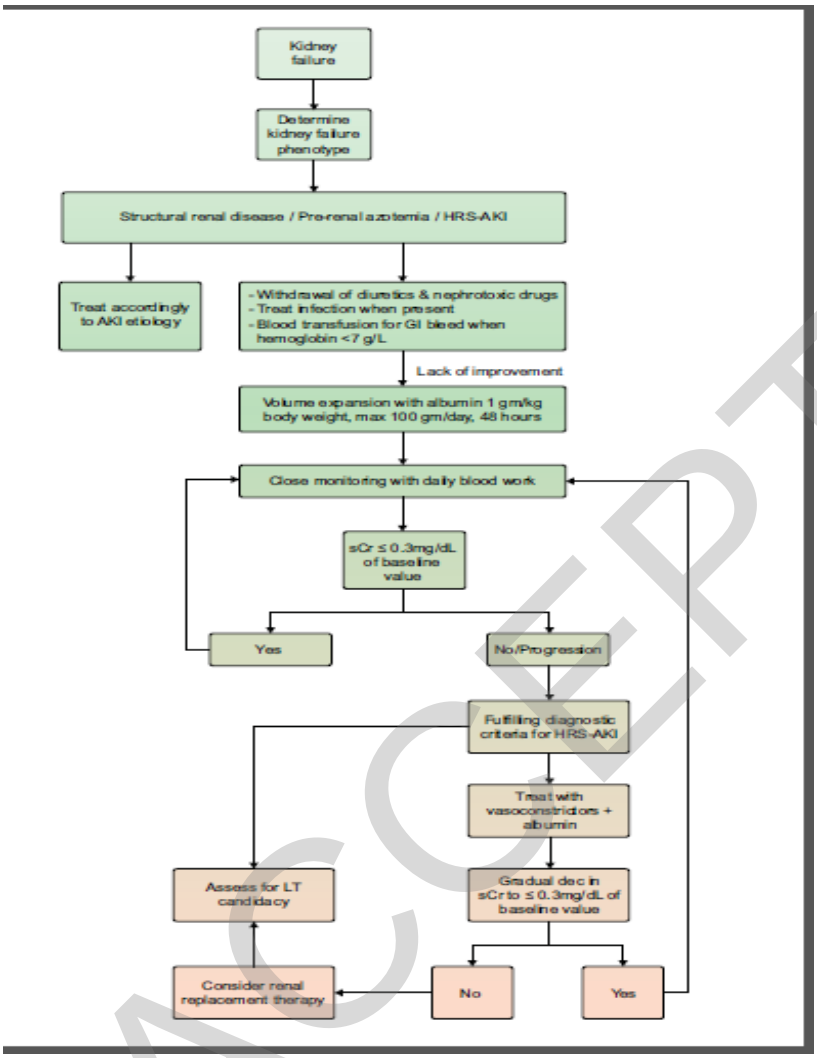

FIGURE 4 Diagnosis and management of infection/sepsis in the critically ill patients with cirrhosis/ACLF. ACLF, acute-on-chronic liver failure; ER, emergency room; PPI, proton pump inhibitor

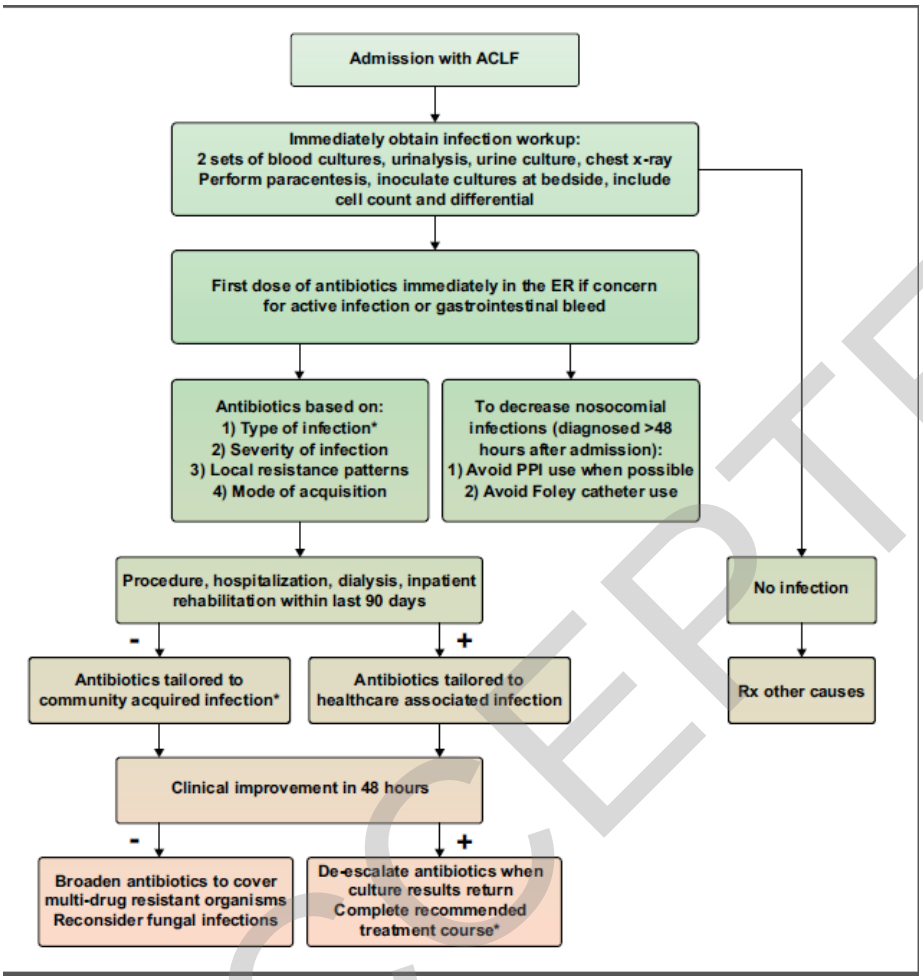

FIGURE 5 Proposed algorithm for assessment of the critically ill patient with cirrhosis/ACLF for LT. AARC, Asian Pacific Association for the Study of the Liver Acute-on-Chronic Liver Failure Research Consortium; ACLF, acute-on-chronic liver failure; CLIF-C, Chronic Liver Failure Consortium; LT, liver transplantation; NACSELD, North American Consortium for the Study of End-Stage Liver Disease

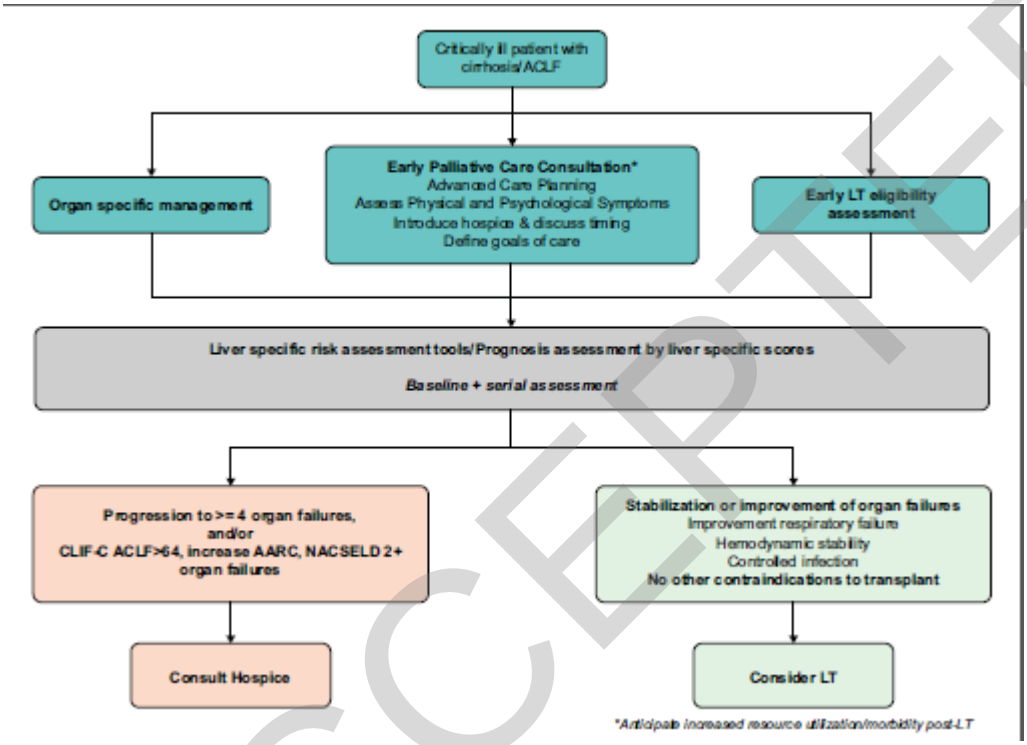

TABLE 1 Comparison of ACLF scoring systems

			Organ failures						Other variables[a]			
Score	**D-Val cohorts**	**MELD or MELD components**	**Organ failure: Liver**	**Organ failure: Kidney**	**Organ failure: Cerebral**	**Organ failure: Respiratory**	**Organ failure: Coagulation**	**Organ failure: CV**	**Age**	**WBC count**	**Albumin**	**Lactate**
NACSELD ACLF [12]	D-US multicenter Val-internal validation	MELD	—	RRT[b]	HE Grade 3 and 4	Mechanical vent	—	Shock	√	√	√	—
CLIF-C ACLF score[4]	D-Eur multicenter Val-Eur single center	TB, sCr, INR	TB ≥ 12 mg/dL[b]	sCr ≥ 2 mg/dL or RRT[b]	HE Grade 3 and 4	PaO_2/FiO_2 ≤ 200 or SpO_2/FiO_2 ≤ 214	Coagulation INR ≥ 2.5[b]	Use of vasopressors	√	√	—	—
AARC ACLF [14]	D-Asia, multicenter Val-internal validation	TB, sCr, INR	TB (mg/dL)[b] <15 15–25 >25	sCr(mg/dL)[b] <0.7 0.7–1.5 >1.5	HE grade 0: 1 point 1 and 2: 2 points 3 and 4: 3 points	—	INR[b] <1.8 1.8–2.5 >2.5	—	—	—	—	√ Points (mmol/L) 1: <1.5 2: 1.5–2.5 3: >2.5
CHOSS ACLF	D-Asia, multicenter,	TB, sCr, INR	TB levels (mg/	sCr levels (mg/d	HE grade	PaO_2/FiO_2 or SpO_2/F	INR[b]	MAP or use of vasopr	√	—	—	—

[20]	HBV etiology Val-Asia, external val		dL)[b]	L)[b]		iO_2		essors				
HBV-ACLF score[265]	D-Asia, multicenter, HBV etiology Val-Asia, HBV etiology	TB, INR	TB levels (mg/dL)[b]	Urea levels	HE grade	—	INR[b]	—	√	Neutrophil	—	—
MELD lactate [22]	D-US, multicenter Val-US, multicenter	MELD	—	—	—	—	—	—	—	—	—	√
CLIF-C ACLF lactate [21]	D-Europe, multicenter Val-internal	TB, sCr, INR	TB ≥ 12 mg/dL[b]	sCr ≥ 2 mg/dL or RRT[b]	HE Grade 3 and 4	PaO_2/FiO_2 ≤ 200 or SpO_2/FiO_2 ≤ 214	Coagulation: INR ≥ 2.5[b]	Use of vasopressors	√	√	—	√

Performance characteristics of tests are provided in Table S1. The diagnostic criteria on the Canonic study were based on the CLIF-SOFA score, which is an adaptation for patients with cirrhosis of the SOFA score used in the intensive care unit setting.[6, 13] However, the CLIF-SOFA score is complex and based on expert opinion. Therefore, the aim of developing a new score was to simplify the CLIF-SOFA and to achieve a

higher prognostic accuracy. The C index of the CLIF-C ACLF score for 28-day, 90-day, 180-day, and 1-year mortality was 0.76, 0.73, 0.72, and 0.71, respectively.

AARC, Asian Pacific Association for the Study of the Liver Acute-on-Chronic Liver Failure Research Consortium; ACLF, acute-on-chronic liver failure; CLIF-C, Chronic Liver Failure Consortium; CV, cardiovascular; D-Val, derivation and validation; FiO_2, fraction of inspired oxygen; INR, international normalized ratio; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; NACSELD, North American Consortium for the Study of End-Stage Liver Disease; PaO_2, partial pressure of oxygen; RRT, renal replacement therapy; sCr, serum creatinine; SOFA, Sequential Organ Failure Assessment; SpO_2, oxygen saturation; TB, total bilirubin; Val-internal, xx; WBC, white blood cell.

[a]Continuous variables, except if indicated.

[b]MELD components: variables used for the definition of specific organ failures that are also components of the MELD score.

TABLE 2 Relevant studies developing and validating ACLF-specific scores

Author, journal (year)	ACLF definition	Population, n	Age (years), sex (male)	Score/variables	Mortality	Outcomes	Comparison with other scores
Prognostic scores in ACLF developed by different societies							
Jalan et al., *J Hep* (2014)[4]	EF CLIF	Europe, multicenter Derivation set: 275 patients from Canonic study with ACLF Validation set: 225 patients with ACLF admitted to ICU (single center, France)	Derivation Age: 54.5 ± 12.1 Male: 176 (64%) Validation Age: 55.1 ± 11.1 Male: 171 (976%)	CLIF-C ACLF score Liver (Bi ≥ 12) Renal (sCr ≥ 2 or RRT) Brain: HE Grades 3 and 4 Coagulation: INR ≥ 2.5 Circulatory: use of vasopressors Respiratory $PaO_2/FiO_2 \leq 200$ or $SpO_2/FiO_2 \leq 214$ Age WBC count	28-day mortality Derivation set: 93 (34%) Validation set: 117 (52%)	28-day mortality (C index) Derivation set: 0.760 Validation set: 0.744	C index Derivation set Child–Pugh: 0.668 MELD: 0.687 MELD-Na: 0.684 Validation set Child–Pugh: 0.653 MELD: 0.645 MELD-Na: 0.648
O'Leary et al., *Hepatol* (2018)[12]	NACSELD	North America, multicenter Training cohort: 1605 Validation cohort (internal validation): 1070	Derivation Age: 57.51 ± 10.68 Male: 991 (63%) Validation Age: 56.78 ± 11.03 Male:	NACSELD ACLF Organ failures: cardiovascular (shock), renal (RRT), respiratory (mechanical ventilation), brain (Grades 3 and 4 HE) Age	30-day survival Training cohort: 1444 (90%) Validation cohort: 950 (89%)	30-day survival (AUC) Training cohort: 0.80 Validation cohort: 0.85	Comparison with APASL for 30-day mortality (AUC) NACSELD: 0.82 APASL: 0.77 Not statistically significant

			668 (62%)	MELD score WBC count admission Albumin admission			
Choudhury et al., *Hepatol Int* (2017)[14]	APASL	Asia, multicenter Derivation cohort: 480 Internal validation cohort: 922	Derivation Age: 45.1 ± 11.8 Male: 434 (90%) Validation Age: 44.8 ± 11.5 Male: 808 (88%)	AARC ACLF Bi sCr INR Lactate HE	28-day mortality Derivation cohort: 210 (44%) Validation cohort: 358 (39%)	28-day mortality (AUC) Derivation cohort: 0.80 Validation cohort: 0.78	AUC 28-day mortality MELD: 0.763 CLIF-SOFA: 0.750 SOFA: 0.728 APACHE II: 0.692 Child–Pugh: 0.657
Wu et al., *Gut* (2018)[20]	ACLF classified according to EF CLIF	China, multicenter Patients with acute decompensation of cirrhosis and patients with severe liver injury for CHB (with or without cirrhosis) (Bi ≥ 5, INR ≥ 1.5) Derivation cohort: 503 External validation cohort: 154	HBV-ACLF (without cirrhosis) Age: 43 ± 11 Male: 79 (86%) HBV-ACLF (cirrhosis) Age: 48 ± 11 Male: 232 (86%) Non–HBV-ACLF (cirrhosis)	CHOSS ACLF HBV-SOFA (modified CLIF-SOFA excluding Bi and INR): -Renal: sCr levels -Brain: HE grade -Cardiovascular: MAP or use of vasopressors -Respiratory: PaO_2/FiO_2 or SpO_2/FiO_2 INR Bi Age	28-day mortality HBV-ACLF (without cirrhosis): 53 (60%) HBV-ACLF (cirrhosis): 122 (52%) Non–HBV-ACLF (cirrhosis): 7 (28%)	28-day mortality (AUC) Derivation cohort:0.829 Validation cohort:0.813	AC 28-day mortality CLIF-C ACLF: 0.796 MELD: 0.736 MELD-Na: 0.736 Child–Pugh: 0.627

			Age: 57 ± 12 Male: 24 (86%)				
Validation or comparison of ACLF prognostic scores							
Rosenblatt et al., *Liver Transpl* (2020)[15]	NACSELD definition	Multicenter, North America Hospitalized patients with cirrhosis (n = 1,523,478) ACLF: 106,634 (7%)	No ACLF Age: 58 ± 0.02 Male: 66% ACLF Age: 56 ± 0.08 Male: 59%	External validation NACSELD ACLF	In-hospital survival: No ACLF: 1,335,394 (94%) ACLF: 50,971 (48%)	In-hospital mortality (AUROC): 0.77	
McPhail et al., *Clin Gastroenterol Hepatol* (2015)[16]	OF defined according to SOFA score	Single center, retrospective, London Patients who were critically ill and with cirrhosis were admitted to a liver ICU 971 patients	Age: 51 (16–90) Male: 615 (63%)	Validation CLIF-SOFA	In-hospital: 506 (52%)	In-hospital mortality (AUC) CLIF-SOFA admission: 0.813 CLIF-SOFA Day 7: 0.842	Admission values (AUC) MELD: 0.786 APACHE: 0.768 SOFA: 0.799 Lactate: 0.699 Day 7 values MELD: 0.764 APACHE: 0.793 SOFA: 0.844 Lactate: 0.712
Lee, *Liver Int* (2015)[17]	ACLF defined by CLIF-SOFA score	Single center, retrospective, Korea Patients with alcoholic cirrhosis	No ACLF Age: 55 (46–65) Male: 116 (55%)	Validation CLIF-SOFA	30-day mortality No ACLF: 3% ACLF-1: 10%	30-day mortality (AUC): 0.943	30-day mortality (AUC): Child–Pugh: 0.705 MELD:

		admitted to tertiary care center 345 patients (ACLF = 125)	ACLF-1 Age: 57 (50–65) Male: 45 (94%) ACLF-2 Age: 61 (53–68) Male: 19 (86%) ACLF-3 Age: 55 (47–62) Male: 46 (84%)		ACLF-2: 37% ACLF-3: 76%		0.804 MELD-Na: 0.804
Engelmann et al., Crit Care 2018[243]	ACLF defined by EF CLIF	Single center, retrospective, London Patients with ACLF admitted to ICU (n=202)	Alive: Age: 50 ± 12 Male: 70 (68%) Dead: Age: 53 ± 11 Male: 66 (67%)	Validation CLIF-C ACLF and define a threshold for futility	28-day mortality: 99 (49%)	28-day mortality according to CLIF-C ACLF thresholds: ≥55: 80% ≥60: 88% ≥65: 94% ≥70: 100%	
Dhiman et al., *World J Gastroenterol* (2014)[18]	ACLF defined by APASL vs. EF CLIF	Single center, prospective, India Patients admitted with acute decompensation of cirrhosis (n = 50) ACLF APASL: 19 (38%) EF CLIF: 38 (76%)	Age: 46 ± 13 Male: 43 (86%)	Comparison CLIF-SOFA vs. APASL criteria and CLIF-SOFA vs. other prognostic scores	28-day mortality: EF CLIF No ACLF: 1 (8%) ACLF: 18(47%) APASL No ACLF: 12 (39%) ACLF: 7(37%)	28-day mortality (AUC) CLIF-SOFA: 0.795	28-day mortality (AUC) APACHE: 0.787 Child–Pugh: 0.739 MELD: 0.710

Cao et al., *Am J Gastroenterol* (2020)[99]	ACLF defined by EF CLIF and NACSELD	Single center, prospective, China Patients admitted with acute decompensation of cirrhosis (n = 468) ACLF EF CLIF: 137 (29%) NACSELD: 35 (7.4%)	No ACLF Age: 55 (47–64) Male: 229 (69%) ACLF Age: 53 (45–63) Male: 116 (985%)	Compare EASL-CLIF vs. NACSELD criteria and scores	28-day transplant free survival EF CLIF: No ACLF: 99% ACLF: 58% NACSELD No ACLF: 92% ACLF: 37%	28-day mortality (accuracy) EF CLIF: 85.3 NPV: 98.47 PPV: 50.41 NACSELD: 92.02 NPV: 91.59 PPV: 97.14	—
Lin et al., *Med Sci Monit* (2020)[266]	AARC criteria	Single center, Israel Patients with cirrhosis admitted to the ICU (n = 786) ACLF = 196	Age: 56 (50–65) Male: 524 (67%)	Validation AARC ACLF score in non-Asian population	28-day mortality 227 (29%)	28-day mortality (AUC) AARC ACLF: 0.754	28-day mortality (AUC) MELD: 0.753 MELD-Na: 0.747 Child–Pugh: 0.688 CLIF-SOFA: 0.743 CLIF-C ACLF lactate: 0.777
Verma et al., *Hepatol Int* (2021)[19]	APASL criteria	Multicenter, prospectively collected data of patients with ACLF from AARC consortium (n = 2864)	Age: 44 (36–53) Male: 2429 (85%)	Comparison of multiple prognostic models: AARC CLIF-C ACLF NACSELD ACLF	30-day survival: 64.9%	C index at enrollment MELD-LA: 0.832 MELD: 0.758 CLIF-C ACLF: 0.820	—

				SOFA APACHE II MELD MELD-LA		NACSELD ACLF: 0.832 AARC: 0.849 C index at day 7 MELD-LA: 0.832 MELD: 0.779 CLIF-C ACLF: 0.808 NACSELD ACLF: 0.856 AARC: 0.872	
Prognostic scores including lactate							
Sarmast et al., *Hepatol* (2020)[22]	No specific data on ACLF, but NACSELD is used to define OF	Multicenter, North America Patients with chronic liver disease admitted to the hospital Derivation cohort: 3588 Validation Cohort 1: 1804 Validation Cohort 2: 726	Derivation cohort Age: 58.1 ± 13.2 Male: 57% Validation Cohort 1 Age: 58.4 ± 13 Male: 57% Validation Cohort 2 Age: 57.5 ± 11.1 Male: 64%	Development MELD lactate score (MELD-LA)	In-hospital mortality Derivation cohort: 705 (20%) Validation Cohort 1: 222 (12%) Validation Cohort 2: 35 (5%)	In-hospital mortality (C index) Derivation cohort: 0.81 Validation Cohort 1: 0.85 Validation Cohort 2: 0.82 Patients admitted to the ICU: 0.74	In-hospital mortality (C index) Derivation cohort MELD: 0.74 MELD-Na: 0.73 Validation Cohort 2 MELD: 0.76
Mahmud et	No	Multicenter,	Age: 58	MELD-LA	In-	In-hospital	In-hospital

al., *Liver Transpl* (2021)[23]	specific data on ACLF	retrospective, North America (VA population) Hospitalized patients with complications of cirrhosis (n = 1306 with lactate at admission)	(53–63) Male: 1009 (97%)		hospital mortality: 59 (6%) 30-day mortality: 125 (12%)	mortality (AUC): 0.789	mortality (AUC) MELD: 0.776
Drolz et al., *Hepatol* (2019)[21]	EF CLIF	Multicenter, Europe Derivation cohort Patients with cirrhosis admitted to the ICU (n = 566) ACLF = 407 External validation cohort: 250 critically ill patients	Age: 58 (51–65) Male: 347 (61%)	Development of CLIF-C ACLF lactate	28-day survival: 332 (59%)	28-day mortality (AUC) Derivation cohort CLIF-C ACLF lactate: 0.79 Validation cohort CLIF-C ACLF lactate: 0.79	28-day mortality (AUC) Derivation cohort: CLIF-C ACLF: 0.75 Validation cohort CLIF-C ACLF: 0.75
Prognostic scores for specific etiologies (HBV)							
Li et al., *J Hep* (2021)[265]	CHOSS ACLF	Multicenter, China Derivation cohort Patients with acute deterioration HBV chronic liver disease (n = 2409). ACLF = 954 (40%). Validation cohort	No ACLF Age: 49 ± 12 Male: 1180 (81%) ACLF Age: 48 ± 12 Male: 837 (88%)	HBV-ACLF score Variables: INR HE grade Bi Neutrophil count Urea Age	28-day mortality Derivation cohort No ACLF: 4% ACLF: 26%	28-day mortality (C index) Derivation cohort: 0.826 Validation cohort: 0.895	28-day mortality (C index) Derivation cohort CHOSS ACLF: 0.793 CLIF-C ACLF: 0.792 MELD: 0.731 MELD-Na: 0.730

		Patients with acute deterioration HBV chronic liver disease (n = 321).					Validation cohort CHOSS ACLF: 0.880 CLIF-C ACLF: 0.857 MELD: 0.767 MELD-Na: 0.785
Other scores or prognostic models							
Abdallah et al., *J Hep* (2021)[226]	EF CLIF	Multicenter, retrospective, North America (UNOS registry) Patients with cirrhosis and ACLF listed for LT (HCV, ALD, and NASH). N = 18,416 ACLF-1 = 8720 ACLF-2 = 5586 ACLF-3 = 4110	Age: 54 ± 9 Male: 69% Caucasian: 63%	MELD-ACLF model Interaction between listing MELD-ACLF grade: ACLF has higher impact on lower MELD scores Other variables include in the model: Age Sex Etiology Obesity Performance status	90-day waitlist mortality (death or too sick for LT): 21.6% ACLF-1: 18% ACLF-2: 20% ACLF-3a: 25% ACLF-3b: 35%	—	—

AARC, Asian Pacific Association for the Study of the Liver Acute-on-Chronic Liver Failure Research Consortium;; ACLF, acute-on-chronic liver failure; ACLF-1, ACLF Grade 1; ALD, alcohol-associated liver disease; APACHE, Acute Physiology and Chronic Health Evaluation; APASL, Asian Pacific Association for the Study of the Liver; AUC, area under the curve; Bi, bilirubin; CHB, Chronic Hepatitis B; CHOSS, Chinese Group on the Study of Severe Hepatitis B; CLIF, chronic liver failure; CLIF-C, CLIF Consortium; CLIF-SOFA, Chronic liver failure- Sequential Organ Failure Assessment ; EASL-CLIF, European

Association for the Study of CLIF; EF, European Foundations; FiO_2, fraction of inspired oxygen; HBV-ACLF, HBV-related ACLF; ICU, intensive care unit; INR, international normalized ratio; LT, liver transplantation; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease;; MELD-LA, MELD lactate; NACSELD, North American Consortium for the Study of End-Stage Liver Disease; NPV, negative predictive value; OF, organ failure; PaO_2, partial pressure of oxygen; PPV, positive predictive value; RRT, renal replacement therapy; sCr, serum creatinine; SOFA, Sequential Organ Failure Assessment; SpO_2, oxygen saturation; UNOS, United Network for Organ Sharing; VA, Veteran Administration; WBC, white blood cell.

TABLE 3 Diagnostic criteria of AKI in cirrhosis[267]

Parameter	Definition
Baseline sCr	Stable sCr in ≤3 months If not available, a stable sCr closest to the current one If no previous sCr at all, use admission sCr
Definition of AKI	Increase in sCr by ≥0.3 mg/dL (26.4 μmol/L) in <48 h or 50% increase in sCr from baseline
Staging	Stage 1: increase in sCr by ≥0.3 mg/dL (26.4 μmol/L) in <48 h or increase in sCr of 1.5 to two times or greater from baseline Stage 2: increase in sCr of more than two to three times from baseline Stage 3: increase in sCr of more than three times from baseline or sCr >4 mg/dL (352 μmol/L) with an acute increase of ≥0.3 mg/dL (26.4 μmol/L) or the initiation of renal replacement therapy
Course of AKI Progression Regression	 Progression of AKI to a higher stage or need for renal replacement therapy Regression of AKI to a lower stage
Response to Rx None Partial Complete	 No regression of AKI Regression of AKI stage with final sCr ≥0.3 mg/dL (26.4 μmol/L) from baseline Regression of AKI stage with final sCr <26.4 μmol/L (0.3 mg/dL) from baseline
Diagnostic criteria for HRS-AKI	• Cirrhosis with ascites • Diagnosis of Stage 2 AKI or higher according to IAC-AKI criteria

	• No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g/kg of body weight to a maximum of 100 g/day • Absence of shock • No current or recent treatment with nephrotoxic drugs • Absence of parenchymal kidney disease as indicated by absence of proteinuria >500 mg/day, microhematuria (>50 red blood cells per high power field) and normal renal ultrasonography

AKI, acute kidney injury; HRS, hepatorenal syndrome; IAC, International Ascites Club; Rx, treatment; sCr, serum creatinine.

TABLE 4 Summary of studies that evaluated vasoconstrictors for the treatment of HRS

Author (year), region	n	Inclusion criteria	Age (years); sex (M/F)	Interventions	Primary endpoints	Outcomes
Martín-Llahí et al. (2008), Spain[114]a	46	• Cirrhosis with either HRS1 or HRS2 • Age: ≥18 years and ≤75 years • No organic nephropathy • No advanced HCC, cardiac disease, or active infection	T+A: 59 ± 10; 16/7 Albumin: 155 ± 11; 3/10	T+A vs. albumin alone	• Improvement of renal function • Survival at 3 months	Responders T+A arm: 10/23 Albumin arm: 2/23 ($p < 0.05$) 3-month survival T+A arm: 6/23 Albumin arm: 4/23 ($p = 0.7$)
Sanyal et al. (2008), United States, Russia, and Germany[115]	112	• Age: ≥18 years • HRS1 per ICA 1996 diagnostic criteria • Absence of cardiovascular disease as	T+A: 51 ± 11; 41/15 P+A: 53 ± 11; 39/17	T+A vs. P+A	Treatment success: sCr <1.5 mg/dL twice in ≤14 days without dialysis, death, or recurrence of HRS	Treatment success T+A arm: 14/56 P+A arm: 7/56 ($p = 0.093$)

		per PI judgement				HRS reversal T+A arm: 19/56 P+A arm: 7/56 (p = 0.008)
Boyer et al. (2016), United States and Canada[116]	196	• Age: ≥18 years • HRS1 per ICA 2007 diagnostic criteria • sCr ≤ 7 mg/dL • MAP ≥ 70 mm Hg • Absence of sepsis, untreated infection, and intrinsic renal disease • >48 h of other vasoconstrictor therapy	T+A: 56 ± 8; 52/45 P+A: 55 ± 9; 67/32 (p = 0.04)	T+A vs. P+A	Confirmed HRS reversal: sCr <1.5 mg/dL twice while on Rx without dialysis or liver transplantation	Incidence of confirmed HRS reversal T+A arm: 19/97 P+A arm: 13/99 (p = 0.22)
Wong et al. (2022) and Wong et al. (2021),	300	• Cirrhosis and ascites • HRS1 per ICA 2007	T+A: 54 ± 11; 120/79 P+A: 54	T+A vs. P+A	Verified HRS reversal: sCr <1.5 mg/dL twice while on	Incidence of verified HRS reversal T+A arm:

United States and Canada[101, 112]		diagnostic criteria • sCr ≤ 7mg/dL • Absence of LVP >4 L in ≤2 days, untreated infection, severe cardiovascular disease • No RRT in <4 weeks	± 12; 59/42		Rx without dialysis and surviving for ≥10 days after Rx completion	63/199 P+A arm: 17/101 (p = 0.006)
Alessandria et al. (2007), Italy[125]b	22	• Cirrhosis and ascites • HRS1 per ICA 1996 diagnostic criteria • Absence of CAD, PVD, or respiratory failure	T+A: 56 ± 3; 9/3 N+A: 55 ± 2; 7/3	T+A vs. N+A[c]	Reversal of HRS: sCr < 1.5 mg/dL	Incidence of HRS reversal T+A arm: 10/12 N+A arm: 7/10 (p > 0.05)
Sharma et al. (2008), India[126]	40	• Cirrhosis and ascites • HRS1 per ICA 1996 diagnostic	T+A: 48 ± 13; 17/3 N+A: 48 ± 10;	T+A vs. N+A	Reversal of HRS: sCr < 1.5 mg/dL	Incidence of HRS reversal T+A arm: 8/20 N+A arm:

		criteria • Absence of CAD, PVD, ventricular arrhythmia, or cardiomyopathy • Absence of bacterial infection in <1 week	17/3			10/20 (p = 0.74)
Singh et al. (2012), India[127]	46	• Cirrhosis and ascites • HRS1 per ICA 1996 diagnostic criteria • Absence of CAD, PVD, ventricular arrhythmia, or cardiomyopathy	T+A: 51 ± 12; 19/4 N+A: 48 ± 12; 19/4	T+A vs. N+A	Reversal of HRS: sCr < 1.5 mg/dL	Incidence of HRS reversal T+A arm: 9/23 N+A arm: 10/23 (p = 0.76)
Goyal et al. (2016), India[128]	41	• Cirrhosis and ascites • 18–70 years • HRS1 per ICA 2007	T+A: 57 ± 6; 17/3 N+A: 55 ± 7; 20/1	T+A vs. N+A	Reversal of HRS: sCr < 1.5 mg/dL	Incidence of HRS reversal T+A arm: 9/20 N+A arm:

		diagnostic criteria • Absence of CAD, PVD, ventricular arrhythmia, or cardiomyopathy • Absence of shock, severe sepsis, or pancreatitis				10/21 (p = 1.00)
Saif et al. (2018), India[129]	60	• Cirrhosis and ascites • Rapid worsening of sCr to >1.5 mg/dL while fulfilling all other diagnostic criteria of HRS • Absence of CAD, PVD, ventricular arrhythmia, or sepsis	T+A: 54 ± 9 N+A: 52 ± 13 No mention of sex of patients	T+A vs. N+A	Reversal of HRS: sCr < 1.5 mg/dL	Incidence of HRS reversal T+A arm: 17/30 N+A arm: 16/30 (p > 0.05)

Kwong et al. (2021), United States[133]	20	• Cirrhosis and ascites • HRS-AKI as per 2015 ICA diagnostic criteria • Absence of other vasoconstrictor use	64 (55–67); 14/6	Norepinephrine for midodrine/octreotide nonresponders	Regression of AKI stage with sCr decreasing to <0.3 mg/dL of baseline	Incidence of full response: 9/20
Cavallin et al. (2015), Italy[121]d	49	• Cirrhosis and ascites • 18–75 years • HRS1 or severe HRS2 per ICA 2007 diagnostic criteria • Absence of CAD, septic shock, cardiac or respiratory failure or stroke • If HCC is present, it needs to be	T+A: 60 ± 12; 21/6 M/O+A: 65 ± 10; 11/10	T+A vs. M/O+A	Reversal of renal failure: sCr < 1.5 mg/dL	Incidence of renal failure reversal T+A arm: 15/27 M/O+A arm: 1/21 ($p < 0.001$)

		within Milan criteria				

CAD, coronary artery disease; F, female; HRS, hepatorenal syndrome; HRS1, HRS Type 1; ICA, International Ascites Club; LVP, large-volume paracentesis; M, male; MAP, mean arterial pressure; M/O+A, midodrine/octreotide and albumin; N+A, norepinephrine and albumin; P+A, placebo and albumin; PI, principal investigator; PVD, peripheral vascular disease; RRT, renal replacement therapy; Rx, treatment; sCr, serum creatinine; T+A, terlipressin and albumin.

[a]Only 17 of 23 patients with T+A in the arm and 18 of 23 patients with albumin alone in the arm had HRS1.

[b]Only nine of the 22 patients had HRS1, and 13 patients had HRS2.

[c]Albumin was only given to 12 of 22 patients.

[d]Only 25 of 27 patients with T+A in the arm and 19 of 21 patients with M/O+A in the arm had HRS1.

TABLE 5 Recommendations to prevent infection-associated ACLF

Intervention	**Rational**
Stop PPIs	Stop PPIs unless the patient has a clear and current indication
Remove Foley catheters	● Limit the use of urinary catheters to eliminate frequent nosocomial UTIs ● Avoid medications that can cause urinary retention, such as anticholinergics, in persons >65 years old
SBP prophylaxis	Antibiotic use for secondary SBP prophylaxis and GI bleeding prophylaxis use
Aspiration prevention measures	● Paracentesis for tense ascites ● Avoid sedating medications: o Benzodiazepines (including zolpidem) o Opiates (including tramadol) ● Avoid vomiting and dehydration from lactulose overuse

	● Careful airway monitoring of patients with a GI bleed and/or HE
Length of stay	Limit length of hospital stay
Ensure vaccines are up to date	● COVID-19 ● HAV and HBV ● Influenza yearly ● Pneumococcus every 5 years when patient is >65 years old, but consider starting in all patients with cirrhosis ● Herpes zoster two doses separated by 2–6 months in adults >50 years old ● Tetanus–diphtheria–acellular pertussis every 10 years

ACLF, acute-on-chronic liver failure; GI, gastrointestinal; PPI, proton pump inhibitor; SBP, spontaneous bacterial peritonitis; UTI, urinary tract infection.

TABLE 6 Peritransplant considerations for infection in patients with cirrhosis and critical illness and/or ACLF

Infection site	Finding	Considerations for peritransplant management
Urinary tract	Asymptomatic bacteriuria	Not a contraindication to LT
Urinary tract	Asymptomatic fungi	Not a contraindication to LT
Urinary tract	UTI without urosepsis	Continue antibiotic therapy pre- and/or posttransplant
Ascites	Spontaneous bacterial peritonitis	Consider reactivation if repeat tap shows >25% decrease in PMN count ≥48 h after therapy initiation
Pulmonary	Spontaneous bacterial empyema	Treat similarly to spontaneous bacterial peritonitis Drainage and/or VATS may be required
Pulmonary	Pneumonia	Consider reactivation after clinical improvement or 7 days of therapy Consider tracheal aspirate in vented patients to guide therapy Consider sampling of associated pleural fluid to rule out empyema
Blood	Bacteremia/culture-negative sepsis	Repeat blood cultures at 2–3 days so that results are available at Day 5 Consider reactivation at ≥5 days of antibiotics if rapid clinical improvement and repeat blood cultures are negative for ≥48 h
Blood	Fungemia	Exclude secondary source and ensure negative blood cultures off therapy prior to reactivation
Skin	—	Consider reactivation after clinical resolution or 5 days of antibiotics
Gastrointestinal	*Clostridium difficile* colitis	Consider reactivation after 7 days with clinical improvement and normalization of WBC count or earlier if flexible sigmoidoscopy documents mucosal healing
Gastrointestinal	History of *C. difficile*	Consider prophylactic treatment in the setting of antibiotics peritransplant

ACLF, acute-on-chronic liver failure; LT, liver transplantation; PMN, polymorphonuclear lymphocyte; UTI, urinary tract infection, VATS, video-assisted thoracoscopic surgery; WBC, white blood cell.

TABLE 7 Pre- and posttransplant factors associated with increased posttransplant mortality in critically ill patients with cirrhosis and/or ACLF

Category	Factors associated with adverse outcomes after LT
Pre-LT factors	• Ventilatory status: on ventilator, respiratory failure, ARDS[212, 215, 216, 225, 226, 228, 236, 268, 269] • Lactate levels > 4 mmol/L[225, 236, 270] • RRT[212, 242, 268] • Sepsis or infections with MDROs[225, 235, 236, 242, 268] • Fungal or nosocomial infection[219] • Longer ICU stay before OLT[268, 271] • ACLF grade and high MELD[9, 212, 213, 238] • Low pre-LT leukocyte count[225] • Advanced age[9, 225, 235, 238, 270] • ACLF progression[272] • HCC[238]
Transplant-related factors	• High donor risk index[215, 225, 238] • Intraoperative blood transfusion[268]
Post-LT factors	• Rejection episodes[273] • Sepsis and multiorgan failure[216]

ACLF, acute-on-chronic liver failure; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; LT, liver transplantation; MDRO, multidrug-resistant organism; MELD, Model for End-Stage Liver Disease; OLT, orthotopic LT; RRT, renal replacement therapy.

TABLE 8 Palliative care quality metrics that should be considered in patients with end-stage liver disease by either the hepatologist or a specialist in palliative care (adapted from Walling et al.)[256]

Outpatients	If a patient has orders to withhold or withdraw life-sustaining treatment, they should be followed. Palliative care or hospice should be offered to patients expected to survive <6 months.
Inpatients	Patients with goals of care for medical therapy documented in one hospital should have them transferred with them to any other hospital. Patients should have a surrogate decision-maker identified within 48 h of hospital admission. Admitted patients who are not transplant candidates with HRS-AKI that does not respond to pharmacotherapy should be offered palliative care or hospice. Patients who are not transplant candidates and required hemodialysis or pacemaker placement should have a goals of care discussion before initiation/insertion. Patients who require mechanical ventilation for >48 h or remain in the ICU for >48 h should have goals of care discussed and documented in the chart. All patients with cirrhosis admitted to the ICU or who had a diagnosis of ACLF should receive a palliative care consult (or hospice consult when appropriate) to define and explain prognosis, determine goals of care, and document medical power of attorney and code status irrespective of transplant listing status.

ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; HRS, hepatorenal syndrome; ICU, intensive care unit.

TABLE 9 Future research directions for the management of critically ill patients with cirrhosis and/or ACLF

Overall	Uniform definition of ACLF that can be applicable worldwide Appropriate duration of onset to define ACLF Standard management protocol for ACLF targeted at early diagnosis and reversal of precipitating events and organ failures Objective outcomes (e.g., 1- or 3-month mortality) that are standardized
Prognosis	Validated clinical scoring systems to assess severity of ACLF early in the clinical presentation Scores that predict future decompensation and not simply reflect current critical illness Establishing interval for serial risk assessment Role of biomarkers such as NGAL or cystatin C[274, 275] in prediction of short-term mortality Role of other inflammatory biomarkers,[276] serum metabolites,[277, 278] and markers of dysbiosis[279, 280] in prediction of short-term mortality
Brain failure	Role of biomarkers for prediction and specific diagnosis of HE-related brain failure Newer therapeutic options that maximize pain control without sedation
Kidney Failure	Role of biomarkers (NGAL, kidney injury molecule 1, cystatin C, IL-18, liver fatty-acid binding protein) to differentiate the causes of AKI[281–283] and assess response to treatment Development of newer classes of drugs such as renal vasodilators in combination with systemic vasoconstrictors[284]
Infection	Novel approaches to identify MDR and fungal organisms earlier in patients with cirrhosis Culture-independent identification of causative organisms using rapid PCR “syndrome

	panels" and metagenomics Studies to assess the optimal antibiotic therapy for SBP prophylaxis after MDR infections Role of microbiome alteration and outcomes after transplantation[285, 286]
Coagulopathy	Utilization of viscoelastic testing (TEG/ROTEM) in larger populations of critically ill patients with cirrhosis
Nutrition	Optimal caloric and protein requirements in critically ill patients with cirrhosis
Cardiovascular	Optimal MAP threshold and vasopressor choice Type, quantity, and target of albumin administration (serum albumin level vs. physiologic measures) Overall resuscitation strategies
Pulmonary	Utility of indices predicting potential failure of noninvasive interventions and the need for escalation to invasive mechanical ventilation Potential benefits of low tidal volume and low PEEP strategies in mechanical ventilation on cardiopulmonary function and survival in patients with ACLF Evidence-based criteria (e.g., PaO_2/FiO_2 < 150 mm Hg) regarding objective respiratory parameters that would preclude transplant[227]
Transplantation	Predictive models for LT candidacy and futility Protocolized assessment, management, and evaluation of potential LT candidates Policies regarding SLKT in critically ill patients with cirrhosis/ACLF
Palliative	Incorporation of palliative care principles into hepatology training Developments of liver-specific hospice to expand its acceptance and use for inpatient and outpatients with cirrhosis

ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; FiO_2, fraction of inspired oxygen; LT, liver transplantation; MAP, mean arterial pressure; MDR, multidrug resistant; NGAL, neutrophil gelatinase-associated lipocalin; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure;

ROTEM, rotational thromboelastometry; SBP, spontaneous bacterial peritonitis; SLKT, simultaneous liver–kidney transplant; TEG, thromboelastography.