Acute on Chronic Liver Failure: Definition and Implications

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KEYWORDS

• Acute on chronic liver failure • Cirrhosis • Dysbiosis • Organ failure • Liver transplant

KEY POINTS

- ACLF is a distinct entity unique from acute decompensation that requires underlying liver disease, occurs secondary to inflammation, and is defined by organ failures.
- Mortality is high in ACLF and increases with severity and number of organ failures.
- Given the increased risk for infection, proton pump inhibitors should be discontinued when clear indication is lacking.
- Identify and treat infections early, as each hour delay of antibiotic administration worsens outcome.
- Refer appropriate patients for liver transplant evaluation early to improve mortality.

INTRODUCTION

As the prevalence of chronic liver disease increases worldwide, more patients with chronic liver disease are hospitalized with complications of cirrhosis. Many complications of liver disease result in decompensation, defined as the development of hepatic encephalopathy, ascites, hepatorenal syndrome, or variceal hemorrhage. However, acute on chronic liver failure (ACLF) has arisen as a separate complication of liver disease, often occurring after a precipitating event, and heralding a high risk of short-term mortality. Although 3 main definitions exist, they all require organ failures with worsening mortality as the number of organ failures increases.

DEFINITIONS

ACLF is a unique condition distinct from acute liver failure (ALF) and acute decompensation (AD). ALF is an infrequent syndrome defined as acute liver injury within 8 weeks (fulminant) or 26 weeks (subfulminant) manifested by hepatic encephalopathy, coagulopathy (international normalized ratio [INR] $\geq$1.5), and jaundice (serum total bilirubin

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≥2 mg/dL) in a patient without preexisting liver disease, with the notable exception of Wilson disease.[1] AD refers to the new development of ascites, hepatic encephalopathy, hepatorenal syndrome, or variceal hemorrhage in a patient with underlying cirrhosis.[2] Although these symptoms are often present in patients with ACLF, AD only requires 1 of the aforementioned events, does not require any organ failure, and may or may not require hospital admission.

Consensus has been reached that ACLF is defined by the number and type of hepatic and extrahepatic organ failures and only occurs in patients with underlying liver disease. Although numerous nuanced definitions with even more prognostic scoring systems have been published worldwide,[3] 3 definitions predominate (**Table 1**).

The Asian Pacific Association for the Study of the Liver (APASL) was the first consensus group to define ACLF using the following criteria[4]:

1. Underlying liver disease, although cirrhosis is not required
2. Hepatic insult resulting in jaundice (defined as a serum bilirubin ≥5 mg/dL) and coagulopathy (INR ≥1.5)
3. Complicated within 4 weeks by ascites and/or hepatic encephalopathy

The APASL definition reflects the patient population most commonly seen in Asia, specifically, acute insults (eg, HBV reactivation), and hepatitis A virus (HAV), hepatitis D virus (HDV), or hepatitis E virus (HEV) superinfection occurring in patients with chronic HBV. Using these criteria, there is an estimated 25% to 37% 30-day mortality.[5]

Second, the European Association for the Study of the Liver (EASL) formed the Chronic Liver Failure (CLIF) consortium, which created the EASL-CLIF definition of ACLF.[6] Cirrhosis is a prerequisite, and the prognosis depends on the number of organ failures that develop (up to 6). Organ failures are defined as:

1. Liver failure if the serum total bilirubin is ≥ 12.0 mg/dL.
2. Kidney failure if the serum creatinine is ≥ 2.0 mg/dL or the patient requires dialysis.
3. Cerebral failure if the West-Haven grade of hepatic encephalopathy is 3 or 4.
4. Coagulation failure if the INR is ≥ 2.5 or platelets are ≤ $20x10^9$/L.
5. Circulatory failure if a vasopressor (dopamine, dobutamine, epinephrine, or norepinephrine) or terlipressin is used.
6. Respiratory failure if the PaO/Fio_2 ratio is ≤ 200 or the SpO_2/Fio_2 ratio is ≤ 214.

The CLIF Consortium-Organ Failure scoring system (CLIF-C OF score) incorporates a grading system contingent on the number of organ failures present (**Fig. 1**):

- ACLF-1 occurs in patients with a single organ kidney failure, a single nonrenal organ failure with kidney dysfunction (serum creatine 1.5-1.9 mg/dL) and/or West Haven grade I-II hepatic encephalopathy, or a single cerebral failure with kidney dysfunction (serum creatine 1.5-1.9 mg/dL).
- ACLF-2 occurs in patients with 2 organ failures.
- ACLF-3 occurs in patients with 3 or more organ failures.

Using a prospective European cohort, hospitalized cirrhotic patients with acute decompensation were further characterized to assist in creation of diagnostic criteria, stages, and natural history. In addition to the characteristics used in their organ failure scoring system, other factors were found to play a significant role in patient prognosis with ACLF development[6]; prognosis declined as white blood cell count (WBC) at presentation increased. This finding was impactful even within the laboratory normal range, since patients with cirrhosis tend to have low WBCs count at baseline.[6] The probability of death was also higher in patients without a prior history of AD compared to those with a history of AD. Although this finding seems counterintuitive, the major

Table 1
Comparison of available definitions for acute on chronic liver failure

	APASL	EASL/CLIF	NACSELD
Definition and severity scoring	Hepatic insult resulting in jaundice (bilirubin $\geq$5 mg/dL) and coagulopathy (INR $\geq$1.5) complicated within 4 weeks by ascites and/or hepatic encephalopathy	Prognosis dependent on the number of organ failures that develop (up to 6 organs – liver, kidney, lung, cerebral, coagulation, circulation) Graded by number of organ failures present: • ACLF-1: kidney failure alone; another organ failure with kidney dysfunction* and/or hepatic encephalopathy;** or cerebral failure with kidney dysfunction.* • ACLF-2: 2 organ failures • ACLF-3: 3 or more organ failures	Prognosis dependent on the number of organ failures present; ACLF requires at least *2* organ failures
Cohort			
Inclusion criteria	• Chronic liver disease or Compensated cirrhosis	• Compensated and decompensated cirrhosis	• Cirrhosis with a complication necessitating hospital admission
Exclusion criteria	• Bacterial infections • History of hepatic decompensation	• Human immunodeficiency virus (HIV) infection • HCC outside Milan criteria • Severe, chronic diseases of extrahepatic origin • Elective/scheduled admissions	• HIV infection • Prior organ transplant • Untreated or widespread malignancies • Elective/scheduled admissions
Study design	Consensus group, observational	Prospective, observational study	Prospective, observational study
Comment	Common precipitants including reactivation HBV as well as superinfections with HAV, HDV, HEV	Unknown trigger in approximately 40% Alcoholic hepatitis and infections common	Infections included

* Kidney dysfunction defined as a serum creatinine 1.5-1.9 mg/dL.
** Hepatic encephalopathy defined here as West Haven grade I and II.

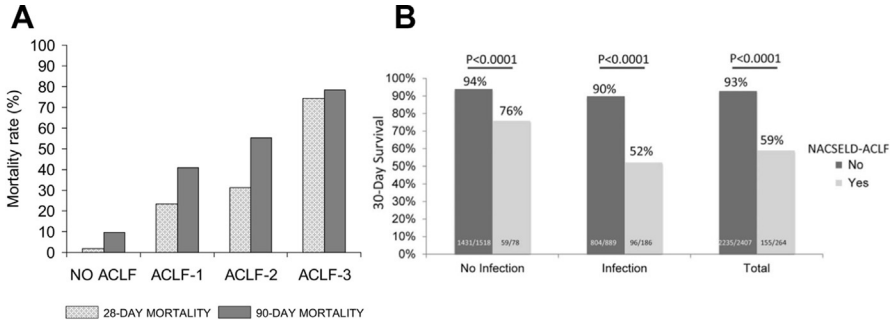

Fig. 1. (*A*) Mortality rate at 28 days and 90 days based on grade of the ACLF. (*B*) 30-day survival for infected and noninfected patients by NACSELD-ACLF. (*From* [*A*] Moreau R, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144(7):1426-37; with permission; and [*B*] O'Leary, J.G., et al., *NACSELD acute-on-chronic liver failure (NACSELD-ACLF) score predicts 30-day survival in hospitalized patients with cirrhosis.* Hepatology, 2018. **67**(6): p. 2367-2374; with permission.)

driver of ACLF is inflammation. As cirrhosis progresses, patients become functionally more immunocompromised. Therefore, the authors hypothesize that patients without a history of AD may have a more vigorous immunologic response to any given insult than patients with a history of prior AD.

To make the diagnosis more user friendly, the North American Consortium for the Study of End-stage Liver Disease (NACSELD) proposed and validated simplified criteria for ACLF based on organ failures (see **Fig. 1**)[7,8]:

1. Kidney failure was defined as requiring dialysis.
2. Brain failure was defined as West Haven grade 3 or 4 hepatic encephalopathy.
3. Respiratory failure was defined as requiring mechanical ventilation or bilevel positive airway pressure.
4. Circulatory failure was defined as the need for pressor support, mean arterial pressure less than 60 mm Hg, or a reduction in systolic blood pressure by 40 mm Hg from baseline despite adequate fluid resuscitation.

ACLF was defined as the development of 2 or more organ failures. This classification was developed using a prospective multicenter Canadian and American cohort of nonelectively admitted patients with cirrhosis who presented with or developed an infection during their index hospitalization.[7] These criteria were validated using a separate prospectively enrolled cohort of 2675 patients with and without infections.[8] As a result of this later analysis, this definition of ACLF was deemed valid in infected and uninfected cirrhotic patients. A separate group independently validated this definition on the nationwide inpatient sample of approximately 1.9 million admitted cirrhotic patients.[9] Although the study was performed using ICD (International Classification of Diseases)-9 codes, 31% of the patients were infected; 5.4% had ACLF, and the c-statistic remained high at 0.75. Of note, nonalcoholic steatohepatitis (NASH) appears to be the most rapidly growing etiology of ACLF in this region of the world.[10]

These 3 groups use definitions largely reflective of the types of underlying liver disease and precipitating events seen in their respective regions.[2] Given the ambiguity and heterogeneity in diagnostic criteria for ACLF between the 3 groups, a consensus conference proposed classifying ACLF into 3 subtypes based on the severity of

underlying liver disease (type A noncirrhotic, type B compensated cirrhosis, and type C decompensated cirrhosis).[3] Consensus was reached on the common precipitants of all subtypes, which are viral infection, superinfection or reactivation, alcohol consumption, drug-induced liver injury, ischemia, surgery, and sepsis. In addition, consensus was also reached on the final common pathway toward ACLF of these subtypes being mediated by inflammation and resulting in organ failure(s), and that the number and type of organ failures determine outcome.

Regardless of how ACLF is defined, the number of hospitalizations for patients that have or develop ACLF is growing nationwide.[11] This rise is occurring on the backbone of an increasing rate of admissions and readmissions for patients with cirrhosis. Of note, half of patients with cirrhosis admitted to the hospital experience readmission within 90 days.[12] Patients at highest risk for readmission in multivariable modeling had higher model for end-stage liver disease (MELD) scores at index admission, diabetes, and hepatic encephalopathy; those taking prophylactic antibiotics and those who had nosocomial infections during index hospitalization also had a high risk of readmission.

Precipitating factors for ACLF are only identified in 50% of cases and often do not predict prognosis even when recognized.[13] Infections are frequent precipitants of hospital admission and readmissions; notably, one-third of hospitalized patients with cirrhosis either present with or develop infections during their admission and on readmission.[14,15] There can be an exaggerated immunologic response to infection, which can lead to organ failure. After successful resolution of infection, the compensatory anti-inflammatory response syndrome (CARS) can create an immune paralysis.[16] This immune dysregulation leaves patients vulnerable to subsequent infections.[17] In fact, 45% of patients discharged from the hospital after successful treatment of an infection develop another infection over the next 3 months. Because three-quarters of these infections occur in a different location from the first infection, it is believed that subsequent infection is caused by an increased susceptibility to infection and not inadequate treatment from the first infection.[18] Risk factors for recurrent infections include older age, proton-pump inhibitor (PPI) use, development of the first infection while on spontaneous bacterial peritonitis (SBP) prophylaxis, and a higher MELD score at admission.

Given the detrimental effects infections have on prognosis, early initiation of primary SBP prophylaxis is tempting. However, as patients with cirrhosis live longer, there has been an increase in multidrug resistant infections in this population.[19] When outcomes of admitted patients on primary versus secondary SBP prophylaxis were compared after propensity score matching for admission MELD and serum albumin, patients on primary prophylaxis had a worse outcome than those on secondary prophylaxis.[20] Specifically, they had a higher risk for acute kidney injury (AKI), death, and liver transplant. Therefore it is essential to strictly adhere to the guidelines for initiation of primary SBP prophylaxis[21]: ascites total protein of no more than 1.5 g/dL and Child-Turcotte-Pugh score of at least 9 and serum total bilirubin of at least 3 mg/dL or serum creatinine of at least 1.2 mg/dL, serum Na no more than 130 meq/L or serum urea nitrogen (BUN) of at least 25 mg/dL. In addition, there is an urgent need to identify agents for use in patients who fail primary or secondary SBP prophylaxis. In the future, it will be essential to develop new ways of preventing infections without the use of antibiotics. Established methods to reduce healthcare-associated infections in these patients should be employed aggressively on admission, including avoidance of urinary catheter placement unless clearly indicated and prompt removal when clinically appropriate, avoidance of long-term indwelling central line catheters, and avoidance of initiation of PPI therapy unless strongly indicated.[22]

RISK FACTORS FOR ACUTE ON CHRONIC LIVER FAILURE

Cirrhotic patients are at risk for ACLF for many reasons. First, cirrhotic patients have gut microbiome dysbiosis, which progressively worsens as liver disease progresses.[23] The cirrhotic dysbiosis ratio (CBR) or the ratio of good bacteria to bad bacteria was developed to evaluate the severity of dysbiosis in this population, and it was demonstrated that this ratio progressively declines from normal outpatients, to compensated outpatients, to decompensated outpatients, and is worst in cirrhotic inpatients.[24] Of note, this ratio is also worse in patients with NASH compared with other types of liver disease. However, although highly correlated with the severity of liver disease, it has never been shown to cause progression of liver disease, nor have alterations been associated with altered outcomes.

Second, not only do patients with cirrhosis have dysbiosis, but they are at risk for small intestinal bacterial overgrowth (SIBO). Risk factors for SIBO include[25] advancing age, antisecretory drugs, altered intestinal motility, and fatty liver. Cirrhotic patients have significant delays in gastric emptying and small bowel transit time at baseline, and this dysmotility worsens with decompensation.[26] Bacterial translocation is seen more commonly in patients with cirrhosis, especially when there is evidence of portal hypertension, which allows the dysbiotic gut microbiota to capitalize on the intestinal permeability as a gateway into the systemic circulation where further damage can be deployed on the poorly armed immune system.[27]

Third, patients with cirrhosis are functionally immunocompromised. The majority of the reticuloendothelial system is located within the liver, where the normal function is to clear endotoxins, bacteria, and cytokines. With portosystemic shunting, blood is directed away from the liver, resulting in disruption of this essential housekeeping function. Furthermore, there are also impairments in intrinsic factors crucial to normal immune function including phagocytosis and chemotaxis.[28]

GUT-HEPATIC ACCESS

The role of intestinal bacteria and their biproducts has garnered increasing attention in the cirrhotic patient population largely because of investigations to better understand the gut-liver access and implications. The intestinal microbiome composition has been shown to be associated with adverse outcomes in patients with cirrhosis. Specifically, increased abundance of the taxa *Proteobacteria (Enterobacteriaceae, Campylobacteriaceae, and Pasteurellaceae)* on admission has been associated with an increased risk of extra-hepatic organ failure, ACLF and death.[29] Intestinal products also influence hepatic lipid metabolism, glucose regulation, and bile acid synthesis, which play contributory roles in influencing microbial composition in the gut.[30] Normal hepatic function serves as the first stop in filtration and detoxification of circulating bacterial biproducts, but this defense mechanism is impaired in cirrhotic patients, allowing for entry into the systemic circulation and resulting in an inflammatory response.[31] With increases in intestinal permeability, this inflammatory cascade can cause or exacerbate decompensation and/or ACLF.

PREVENTION OF ACUTE ON CHRONIC LIVER FAILURE

Because the outcome of ACLF is poor, it is essential to identify mechanisms for prevention. This section highlights suggested ways to mitigate the risk of ACLF development in patients with cirrhosis.

Discontinue Proton Pump Inhibitors

Most patients with cirrhosis are on a PPI for an unknown reason or poor indication. PPIs block the oxidative burst of the neutrophil, thereby causing further immunosuppression in an already immunocompromised host.[32] Many patients are started on a PPI while hospitalized either as prophylaxis or during a gastrointestinal (GI) bleed. As a result, they can and should be discontinued whenever possible. Of note, H2 blockers do not cause immunosuppression, and therefore when acid suppression is required, H2 blockers are a good alternative.[33] PPIs are associated with higher rates of readmission independent of comorbidities, other medications, age, and admission MELD.[34] PPIs also alter the gut microbiome; initiation increases the oral-origin microbiota, which are more pathogenic, and discontinuation decreases these bacteria in overall composition.[34] Discontinuing PPIs in patients without clear indications for them will lower patients' risk for infection and readmissions.[18,33,34]

Use Nonselective Beta-Blockers as Primary Prophylaxis for Variceal Bleeding

Options include: propranolol, nadolol, and carvedilol. Although banding to obliteration and nonselective beta-blocker (NSBB) use are both considered equally efficacious as primary prophylaxis for variceal bleeding, NSBB use is more cost-effective and may improve outcome in patients with ACLF.[35,36] Endoscopic screening for varices is indicated in patients with cirrhosis with platelets less than $150x10^9$/L or with a liver stiffness measurement (LSM) of greater than 20 kPa on ultrasound elastography.[36] Primary prophylaxis should be started in all patients with CTP class A and B cirrhosis with large varices and all patients with CTP class C cirrhosis with small or large varices.[36] However, emerging data have shown patients with compensated cirrhosis and clinically significant portal hypertension (defined by hepatic venous pressure gradient [HVPG]) had a lower risk for decompensation when randomized to an NSBB.[37] This is supported by meta-analysis data showing a lower risk for clinical events (ascites, variceal hemorrhage, or encephalopathy) in patients who have an HVPG response to NSBBs.[38] Although NSBBs have proven efficacy, some patients are not candidates for treatment with them. Patients with ascites with either a systolic blood pressure less than 90 mm Hg or type 2 hepatorenal syndrome are at increased risk for death from NSBB use, and therefore cannot be treated with NSBBs.[39] Especially during admission, NSBB should be discontinued in patients with a low MAP, but reinitiated once the MAP increases.[40]

When selecting an NSBB consider:

a. Propranolol is the least effective and combined with its inconvenient dosing often leads to noncompliance.
b. Nadolol is conveniently dosed once per day, and its lower central nervous system penetration decreases the risk for depression.
c. Carvedilol is the most potent NSBB because of its alpha component; however, this feature can also exacerbate volume overload in CTP B and C patients. Therefore, carvedilol is usually reserved for CTP A patients.[41]

NSBBs have even been found beneficial in patients with ACLF; patients admitted on NSBB had improved 28-mortality.[35] In addition, a trial of 136 patients with ACLF and no or small varices but HVPG of at least 12 showed patients randomized to carvedilol had a lower risk for AKI, SBP, and 28-day mortality but not 90-day mortality.[42]

Although the precise mechanism for improved outcomes in patients with ACLF on NSBBs is unknown, NSBBs have been shown to decrease intestinal permeability

and therefore may decrease the translocation of dysbiotic bacteria into the systemic circulation that may initiate or exacerbate SIRS.[43]

Diagnose and Treat Renal Dysfunction Early

Cirrhotic patients live and die by their kidneys. The new definition of AKI in patients with cirrhosis is an increase in serum creatinine of at least 0.3 mg/dL in 48 hours or an increase in serum creatinine of at least 1.5 fold over baseline.[44,45] Even with complete resolution, a small short-term increase can have a lasting negative impact on prognosis. Similarly, even a peak serum creatinine of less than 1.5 mg/dL can be harmful and worsen prognosis.[46] Although all increases in serum creatinine negatively impact prognosis, some are worse than others.[47] AKI-hepatorenal syndrome (AKI-HRS) and infection-related AKI have the worst prognosis and similar prognostic implications, and parenchymal nephropathy has the least impact on patient survival.[48] However, both have the same impact on the MELD score, which is likely why the MELD score currently has lower predictive power than in the past.[49]

When AKI occurs, it is essential to eliminate all nephrotoxins including nonsteroidal anti-inflammatory drugs (NSAIDS) and aspirin, stop diuretics, and ensure the patient is not intravascularly depleted.[44] A low threshold to initiate intravenous albumin therapy should be utilized even in patients with extravascular hypervolemia, as it is the first-line therapy for AKI, even in patients whose peak creatinine is less than 1.0 mg/dL.[44]

In patients with more advanced AKI with AKI-HRS, vasopressors (terlipressin is first-line treatment in countries where it is available, and norepinephrine is first-line treatment in countries where it is not) in combination with intravenous albumin are indicated.[44,50] This is because vasopressors have been proven superior to midodrine, octreotide and intravenous albumin therapy.[51]

Patients who require dialysis should be considered for liver transplantation. However, in inpatients with decompensated cirrhosis who are not liver transplant candidates, dialysis is most often considered futile, because[52] these patients cannot be adequately dialyzed as an outpatient secondary to low blood pressure limiting fluid removal, and the mortality is approximately 90% at 3 months.

Identify and Treat Infections Early

Most infected cirrhotic patients do not mount a fever, and up to one-third of patients with SBP are asymptomatic. As a result, it is imperative to have a high level of suspicion for an infection when any new symptom of decompensation or organ failure develops. Every hour antibiotics are delayed increases mortality,[53] and therefore, prompt work-up followed by swift antibiotic administration is essential.

Nosocomial infections are frequent (approximately 15%) and increase the risk for death in admitted patients with cirrhosis. Nosocomial infections occur more frequently in patients admitted with an infection, those with an admission MELD greater than 20, those with SIRS, and those taking PPIs, rifaximin, and/or lactulose.[54] Recurrent infections after discharge occur in almost half of admitted cirrhotic patients, but because three-fourths of these infections occur in a different location than the first infection, it simply reflects the host's inability to fight infection rather than a failure of therapy.[18]

Use Intravenous Albumin When Indicated

Intravenous albumin was first used to treat ascites and edema in patients with cirrhosis in 1946 with some success.[55] Patients with cirrhosis not only have inadequate levels but poor quality albumin.[56] Of late, a resurgence of interest in expanding the indication for use of intravenous albumin has occurred. The recent ANSWER trial

documented improved mortality in 440 cirrhotic outpatients with uncomplicated ascites over 18 months with chronic outpatient administration of 40 g of intravenous albumin weekly (hazard ratio [HR] = 0.62; 95% confidence interval [CI] 0.40–0.95).[57] This concept is under further study in the PRECIOSA trial of weight-based (up to 100 g) intravenous albumin treatment every 10 days to patients with uncomplicated ascites and recent hospital admission.[58] Of note, in the published pilot-PRECIOSA study, high-dose intravenous albumin improved circulatory function and left ventricular function and reduced plasma levels of multiple cytokines without increasing portal pressures.

Currently, intravenous albumin is an approved therapy for several indications:

- To prevent paracentesis-induced circulatory dysfunction (PICD) when more than 5 L are removed during a paracentesis
- To prevent AKI in patients with SBP
- To treat AKI

Other unapproved indications include:

- Treatment of hospitalized patients with non-SBP infections to improve survival[59]
- Use in combination with diuretics to improve volume status and prevent renal dysfunction
- Treatment of hyponatremia[60]
- To prevent PICD when less than 5 L are removed during a paracentesis in patients with ACLF[61]

Relative Adrenal Insufficiency

A single prospective clinical trial of admitted cirrhotic patients found almost half had relative adrenal insufficiency. Unfortunately, relative adrenal insufficiency increased the risk for death and doubled the risk for ACLF.[62] Therefore, one should be hypervigilant to ensure this diagnosis is made early in a patient's course.

ACUTE ON CHRONIC LIVER FAILURE AND LIVER TRANSPLANTATION

Given the high mortality and decrease in transplant-free survival once ACLF develops, liver transplantation remains an important rescue therapy for many individuals.[6,8] Some ACLF patients who meet criteria for transplant have higher mortality after transplant compared to those transplanted without ACLF.[63] The severity of ACLF appears to have a negative impact on outcomes after liver transplant, with ACLF grade 3 having the most profound negative impact. In a retrospective study of 72,316 admissions for decompensated cirrhosis in the Veterans Affairs (VA) system spanning over a decade, 26% of admissions met EASL-CLIF criteria for ACLF. Higher mortality was associated with older age, white race, HCC, MELD-Na, and admission to a nontransplant facility. Furthermore, over the 10-year period, ACLF prevalence decreased, while mortality for ACLF-3 increased.[64] Selection of candidates for transplant and post-transplant outcomes are also negatively impacted by the number of organ failures present during an episode of ACLF. Although consistent data show that increasing numbers of organ failures result in increased costs after transplant, most (but not all) data show an increased risk for death after transplant with ACLF grade 3.[63,65–67] In a prospective multinational study performed by NACSELD, 2793 cirrhotic patients were hospitalized, 27.5% were listed for transplant, and 35% of those listed underwent a liver transplant. The patients who were listed were more likely to be younger, have ACLF, AKI, and a higher MELD than the nonlisted patients. ACLF was most prevalent in the dead or delisted patients. In this study, despite the ACLF group having higher preliver

transplant creatinine and perioperative dialysis, the postliver transplant creatinine at 3- and 6-month follow-up was no different than those transplanted patients without ACLF exhibiting excellent renal recovery in both groups.[68] Of note, stabilization with ACLF resolution[67] or sepsis resolution[66] or improvement in MELD may mitigate the increased mortality.[8,69]

SUMMARY

There are significant challenges in appropriately identifying and managing patients with ACLF given rising rates of hospitalizations and high mortality rates. Prevention of ACLF is only possible if clinicians are aware of this clinical entity and its implications. As the outcome can be poor, preventive strategies in patients with cirrhosis are crucial and include:

- Early identification of infections
- Discontinuation of PPI therapy when clear ongoing need is not found and removal of indwelling catheters unless strongly indicated
- Use of intravenous albumin for volume expansion per guidelines
- Early diagnosis and treatment of AKI
- NSBB use for primary prophylaxis of variceal hemorrhage whenever possible

Current available definitions of ACLF allow clinicians to stratify these patients in order to target therapeutic approaches and make more accurate assessments of prognosis. Reassessments throughout the disease course should be implemented in order to select for patients who may benefit from tertiary interventions such as transplant, and those who have reached medical futility. Multiple organ failures can develop rapidly and portend poor outcomes, thus necessitating close monitoring and potentially early transfer to a tertiary care center as transplant has been shown to be a viable option in highly selected patients. Further investigations are needed to elucidate if there is a beneficial response to steroid supplementation in patients with relative adrenal insufficiency, which remains common. Future therapeutic targets may need to address the detrimental effects of intestinal dysbiosis and the impaired systemic inflammatory response in these patients.

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