Acute-On-Chronic Liver Failure

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KEYWORDS

• Acute-on-chronic liver failure • Acute liver failure • Organ failure
• Liver transplantation • Cirrhosis

KEY POINTS

- Acute-on-chronic liver failure (ACLF) is characterized by a precipitating event in patients with underlying chronic liver disease, leading to acute deterioration of liver function and often ending in multiorgan system failure.
- The physiology of ACLF can be divided into a 4-part model: (1) predisposition, (2) injury caused by the precipitating event, (3) response to the injury, and (4) organ failure.
- The definition of ACLF, like the definition of acute liver failure, requires liver dysfunction, and the prognosis depends on the number of extrahepatic organs involved (ie, renal, cerebral, circulatory, and pulmonary). Increasing numbers of organ failures with underlying cirrhosis usually portends progressively worse outcomes.
- Acute renal failure in patients with cirrhosis is associated with an almost 8-fold increased risk of death; smaller increases ($\geq$0.3 mg/dL) in creatinine level, some of which occur lower than the 1.0 mg/dL creatinine cutoff for MELD (Model for End-Stage Liver Disease) point allocation, have significant prognostic implications.
- ACLF carries a high mortality in wait-listed patients, and those who survive require prompt transplantation.

INTRODUCTION

According to the US Centers for Disease Control, chronic liver disease and cirrhosis is the 12th leading cause of death in the United States, and liver disease–related mortality has remained unchanged over the last 3 decades, despite dramatic improvements in general medical care, hepatology care, and post–liver transplant outcomes achieved during that time.[1] Chronic liver disease is not only a significant cause of morbidity and mortality but it accounts for a substantial portion of health care

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expenditure in the United States and worldwide.[2] Therefore, to improve prognostication and outcomes in patients with chronic liver disease, the current terminology that defines liver dysfunction must first be evaluated. Although liver dysfunction was often discussed as compensated versus decompensated cirrhosis, quantitation of liver dysfunction was first reasonably and accurately accomplished by the Child-Turcott-Pugh (CTP) score and is now accomplished in a more granular manner by the Model for End-Stage Liver Disease (MELD) score.[3,4] However, when a cirrhotic patient experiences an acute event, such as an infection, their pre-event MELD score does not accurately predict their mortality risk. The concept of acute-on-chronic liver disease emerged, because cirrhotics often experience a nonlinear progression in their liver disease (**Fig. 1**).[5–7] However, this notion has struggled to achieve universal acceptance as a uniform entity. In an effort to understand the concept and describe its implication peritransplant, it is important to distinguish acute-on-chronic liver failure (ACLF) from decompensation.

ACLF IS NOT DECOMPENSATED CIRRHOSIS

ACLF is a distinct entity from compensated and decompensated liver disease (presence of ascites, hepatorenal syndrome, variceal hemorrhage, hepatic encephalopathy, or synthetic dysfunction). In a population-based study, persons with compensated cirrhosis had a 5-fold, and persons with decompensated cirrhosis had a 10-fold, increased risk of death compared with the general population.[8] Most of the deaths among patients with compensated cirrhosis occurred because of a transition to decompensation and resultant complications. However, unlike the simple features of ascites, encephalopathy, hepatorenal syndrome, variceal hemorrhage, and hepatic synthetic dysfunction that characterize hepatic decompensation, ACLF focuses on the acute events (**Box 1**) that move patients from low-risk to high-risk of organ failure and death.

PHYSIOLOGY OF ACLF

Borrowing from the sepsis literature, Jalan and colleagues[6] parsed the pathophysiologic basis of ACLF into a 4-part model: (1) predisposition, (2) injury caused by

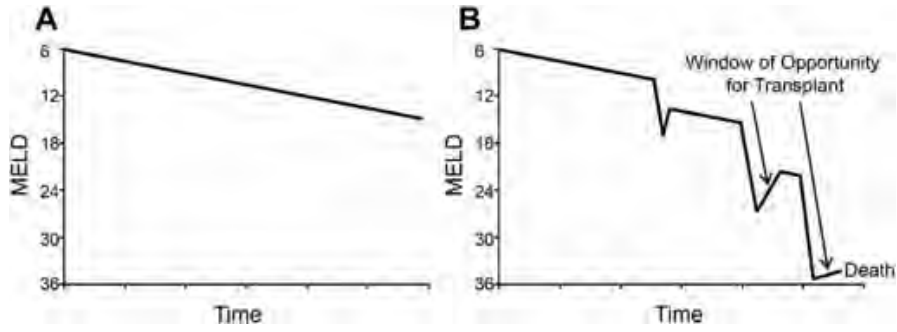

Fig. 1. (*A*) Few patients with cirrhosis experience a smooth and steady increase in MELD score over time. (*B*) Most patients have a background slope of slowly increasing MELD score, which is punctuated by ACLF events, which early on result in recovery, but later on result in longer periods of illness, less recovery potential, and a higher risk of multiorgan system failure. After the acute event has resolved, there is a window of opportunity to transplant patients while their MELD is high enough to receive priority, but they are no longer too sick for transplant.

Box 1
Events known to precipitate ACLF

- Acute alcoholic hepatitis
- Acute hepatotrophic viral infection
  - Acute hepatitis A
  - Reactivation hepatitis B
  - Acute hepatitis D in the presence of hepatitis B
  - Acute hepatitis E
- Drug-induced liver injury
- Gastrointestinal bleeding
- Infection
- Ischemia
  - Hypotension
  - Surgery
  - Trauma
- Portal vein thrombosis

precipitating event, (3) response to injury, and (4) organ failure.[5,7,9,10] In their model, predisposition refers to underlying cirrhosis and concomitant illnesses. Patients with advanced liver dysfunction measured by either MELD or CTP are at greater risk to experience a precipitating event. In patients with a high MELD score, this finding is coupled with an impaired hepatic reserve.

Injury may be caused by one of many insults (see **Box 1**). All causes can cause ACLF; however, there are geographic differences in prevalence: reactivation of hepatitis B and development of acute hepatitis A, D, and E are important causes of ACLF in Asian centers, whereas acute alcoholic hepatitis and infections are more common precipitants of ACLF in Western centers. Despite continent-wide differences, an identifiable precipitating injury remains unknown in many cases.

Because most events that precipitate ACLF, regardless of the continent, are ischemic or infectious in nature, the inflammatory response plays a critical role in the outcome of ACLF. Given that about half of admitted cirrhotics have evidence of infection, and a further 25% develop nosocomial infections with high inpatient mortality, infection plays an overwhelming factor in the natural history of ACLF.[11–13] Overt bacterial infection and possibly covert bacterial translocation with subsequent systemic inflammatory response may be responsible for transition from a compensated to decompensated state.[6] The inflammatory response is important: a robust response is measured by an increased C-reactive protein (CRP) level or an increased leukocyte count and is associated with worse outcomes.[14] It is unclear whether the inflammation is a response to the inciting event or a part of the inciting event. On the other hand, failure of the immune response is also important, given the higher mortality associated with nosocomial or second infections.[12,15]

Organ failure is the last component of ACLF; increasing numbers of organ failures (ie, renal, cerebral, circulatory, and pulmonary) portend progressively worse outcomes in patients with underlying cirrhosis.[14,15] The definition of ACLF, like the definition of acute liver failure (ALF), requires liver disease and dysfunction but is prognostically based on extrahepatic organ failures, which are discussed separately.

Renal

Acute renal failure in patients with cirrhosis is associated with an almost 8-fold increased risk of death,[16] which is reflected by the prominence of serum creatinine in the MELD score.[17] The cause of renal dysfunction, in addition to the serum creatinine level, determines prognosis; hepatorenal syndrome and infection-related renal dysfunction portend a worse prognosis than chronic renal failure.[18] However, the MELD score does not differentiate between causes of renal failure or incorporate differences in baseline creatinine.[19] Recent data have shown that smaller increases (≥0.3 mg/dL) in creatinine level, some of which occur lower than the 1.0 mg/dL creatinine cutoff for MELD point allocation, have significant prognostic implications.[20,21] The chance for recovery is partially related to the absolute change in creatinine, and the risk for death does not completely abate, even if patients experience resolution of their acute renal failure (**Fig. 2**).[20] This situation has resulted in novel categorizations

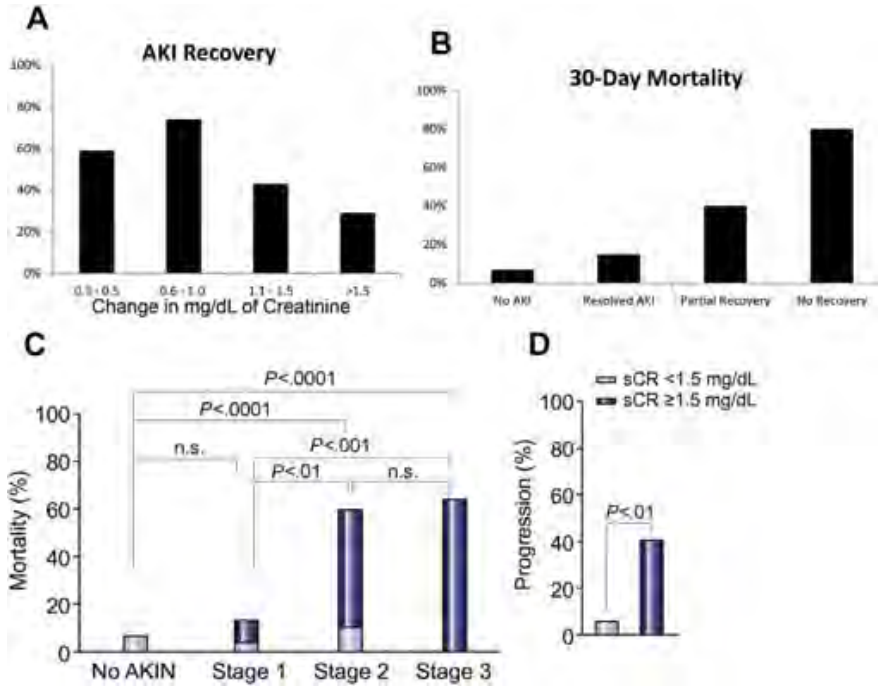

Fig. 2. (*A, B*) Acute kidney injury (AKI) was defined as an absolute increase in serum creatinine (sCR) level 0.3 mg/dL or greater in less than 48 hours or a 50% increase in serum creatinine from baseline. (*A*) The chance for renal recovery was proportional to the absolute change in creatinine, and (*B*) the 30-day mortality was lowest in patients without AKI, and greatest in those without renal recover. (*C, D*) Similar findings were seen with the Acute Kidney Injury Network (AKIN) staging system (see **Table 1**). Progression was less likely in patients whose peak creatinine level was less than 1.5 mg/dL. n.s., not significant. ([*A, B*] *Adapted from* Wong F, O'Leary JG, Reddy KR, et al. North American Consortium for Study of End-Stage Liver Diseases. New consensus definition of acute kidney injury accurately predicts 30-day mortality in patients with cirrhosis and infection. Gastroenterology 2014;145:1280–8, with permission; and [*C, D*] *Reproduced from* Piano S, Rosi S, Maresio G, et al. Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites. J Hepatol 2013;59:486, with permission.)

of renal dysfunction in patients with cirrhosis being proposed and validated beyond just hepatorenal syndrome.[20–22] These scores (Table 1) acknowledge the importance of earlier diagnosis for acute kidney injury and do not require the absence of chronic renal disease. Unlike hepatorenal syndrome, the adoption of these new scoring systems in clinical trials of novel therapeutics will facilitate earlier implementation of therapy and, it is hoped, improve clinical outcomes.

Brain

Akin to ALF, but in contrast to chronic decompensation, patients with ACLF can develop cerebral edema. The resultant increase in intracranial pressure can be reversed with liver transplantation (LT). Brain edema may be caused by the synergy between increased ammonia and the inflammatory response that is often superimposed on an additional hepatic injury.[6] The role of rifaximin as a potential reducer of bacterial translocation, with subsequent diminution of inflammation, is hypothesized to be of benefit but remains untested in persons with ACLF.[6]

Circulatory

ACLF is characterized by a paralysis of immune response similar to changes seen in severe sepsis.[23] Patients with ACLF usually first experience the systemic inflammatory response system (SIRS) and second, the compensatory antiinflammatory response system (CARS). Unlike SIRS, CARS downregulates antigen presentation, causes

Table 1
Definitions of renal dysfunction in patients with cirrhosis

	Hepatorenal Syndrome	Acute Kidney Injury Network	International Ascites Club and Adult Dialysis Quality Initiative
Cirrhosis required	Yes	Yes	Yes
Absence of underlying renal disease	Required	Not required	Not required, Acute-on-chronic kidney disease defined
Minimum serum creatinine level	≥1.5	Stage 2 and 3 yes, serum creatinine ≥1.5	No
Stages/Types	Yes	Yes	No
Criteria	(1) Ascites, (2) no improvement after 2 d of diuretic withdrawal and volume expansion, (3) no shock, (4) no nephrotoxic drugs; type 1: doubling in serum creatinine level to ≥2.5 in <14 d	Stage 1 = ≥0.3 mg/dL in <48 h or increase 1.5–2 × baseline Stage 2 = increase 2–3 × baseline Stage 3 = increase >3 × baseline or >4.0 mg/dL with an acute ≥0.5 mg/dL increase	Acute kidney injury: ≥0.3 mg/dL in <48 h or >50% over baseline Chronic renal disease: estimated glomerular filtration rate <60 mL/min for >3 mo by Modification of Diet in Renal Disease 6 formula

macrophage deactivation, results in antiinflammatory cytokine production, and can result in anergy.[24–26] Therefore, once ACLF occurs, patients are at risk for additional infections.[12] There is a strong correlation between ACLF, previous history of acute decompensation, leukocyte count, and risk of death (**Fig. 3**).[14]

The increased infectious risk is often coupled to cardiac dysfunction; there may be failure to appropriately increase the cardiac output in response to the insult. This finding is in contrast to chronic decompensated cirrhosis, in which cardiac output is appropriately increased. Inotrope support is often needed, similar to persons with ALF. The appropriate inotrope is unknown; however, norepinephrine has been shown in small studies to improve renal function in patients with hepatorenal syndrome and therefore may be beneficial.[27,28]

Pulmonary

The impact of pulmonary compromise on mortality in ACLF is highlighted by its incorporation into the Chronic Liver Failure (CLIF)–Sequential Organ Failure Assessment (SOFA) and the sepsis-related ACLF (S-ACLF) scores.[14,15] Although some patients are intubated for airway protection for severe encephalopathy, several other pulmonary complications can occur. Hepatic hydrothorax can result in pulmonary compromise and, like ascites, can become infected. Transfusion-related acute lung injury likely occurs more often than it is diagnosed[29] and may increase the systemic inflammation present during ACLF. Therefore, minimizing transfusions, when appropriate, is essential.

However, most pulmonary complications that result in ACLF are infectious. Numerous factors increase this risk of aspiration, including diminished airway protection from encephalopathy, increased intra-abdominal pressure from ascites, and endoscopy for gastrointestinal bleeding. In addition, bacterial colonization more commonly occurs with microaspiration or translocation because of overutilization of proton pump inhibitors.[30,31] As a result, respiratory tract infections represent 14% to 48% of infections in cirrhotic patients[32]; however, they disproportionately increase a cirrhotic patient's risk of death.[12,32]

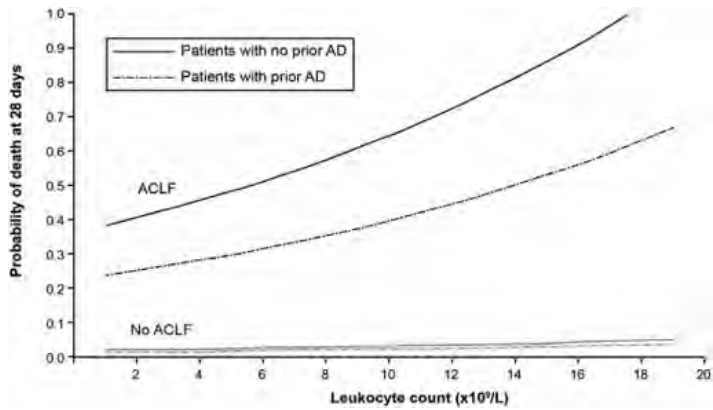

Fig. 3. The probability of death at 28 days is shown based on the presence of ACLF, a previous history of acute decompensation (AD), and leukocyte count. (*Reproduced from* Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1433; with permission.)

DEFINITIONS OF ACLF

The most widely accepted definition of ACLF suggested by an American Association for the study of Liver Diseases (AASLD)/European Association for the Study of the Liver (EASL) consortium is the presence of a precipitating event (identified or surreptitious) in patients with underlying chronic liver disease, leading to acute deterioration of liver function and often ending in multiorgan dysfunction characterized by a high short-term mortality (Table 2).[5–7] However, 3 separate definitions are described derived from multicenter efforts from the Asia Pacific Region (Asia Pacific Association for the Study of the Liver [APASL]),[33] Europe (EASL-CLIF)[14] as well as North America (North American Consortium for the Study of End-Stage Liver Disease [NACSELD])[15] groups.[34]

APASL

APASL, which comprises experts within the Asia Pacific Region, defined ACLF as an "acute hepatic insult manifesting as jaundice (bilirubin level >5 mg/dL) and coagulopathy (international normalized ratio >1.5) complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease."[33] Reactivation of hepatitis B as well as super infection with hepatitis E virus were the predominant causes, and the presence of cirrhosis was not required. The investigators questioned whether sepsis acted as an initial precipitating event or played a role in the progression of ACLF, and debate occurred over whether surgery and variceal bleeding should be included as potential precipitants.

EASL-CLIF

Moreau and colleagues,[14] on behalf of EASL-CLIF, recently reported a novel scoring system for ACLF (Fig. 4). In their study population, 31% of patients had ACLF, most of whom had ACLF in the setting of alcoholic liver disease. Bacterial infections were the number 1 precipitating event, although no precipitant was found in 44% of cases.

The most common cause of death was multiorgan system failure. Cirrhotics with ACLF had a mortality of 34% versus 1.9% for patients with decompensation without ACLF. The type of organ failure (renal failure carried the highest risk) was a risk factor for mortality, and mortality increased as the number of organs with dysfunction increased. ACLF was defined by occurrence of acute decompensation, organ failure, and mortality within 28 days of greater than 15% and characterized into 3 grades (see Fig. 4).[14] The 28-day mortality was 5%, 22%, 32%, and 77% for grades 0, 1, 2, and 3, respectively. Patients with increased leukocyte counts and plasma CRP levels did worse; infection or inflammatory response was one of the most important risk factors for poor outcomes after ACLF.[14,35]

Table 2
Differences in definitions of ACLF

	APASL Definition	AASLD/EASL Consensus
Duration	<4 wk	Not defined
Chronic liver disease	Any fibrosis stage	Cirrhosis only
Most common precipitant	Hepatotrophic viruses	Infections
Other agreed precipitants	Alcohol, drug-induced liver injury, ischemia	
Variceal bleeding	No consensus	Yes
Infection	No	Yes

Adapted from Bajaj JS. Defining acute-on-chronic liver failure: will east and west ever meet? Gastroenterology 2013;144(7):1337; with permission.

A

Organ/system	0	1	2	3	4
Liver (bilirubin, mg/dL)	<1.2	≥1.2 to <2.0	≥2.0 to <6.0	≥6.0 to <12.0	≥12.0
Kidney (creatinine, mg/dL)	<1.2	≥1.2 to <2.0	**≥2.0 to <3.5**	**≥3.5 to <5.0**	**≥5.0**
			or use of renal replacement therapy		
Cerebral (HE grade)	No HE	I	II	III	IV
Coagulation (international normalized ratio)	<1.1	≥1.1 to <1.25	≥1.25 to <1.5	≥1.5 to <2.5	**≥2.5 or platelet count ≤20—10^9/L**
Circulation (mean arterial pressure, mm Hg)	≥70	<70	**Dopamine ≤5 or dobutamine or terlipressin**	**Dopamine >5 or E ≤0.1 or NE ≤0.1**	**Dopamine >15 or E >0.1 or NE >0.1**
Lungs					
PaO_2/FIO_2, or	>400	>300 to ≤400	>200 to ≤300	**>100 to ≤200**	≤100
SpO_2/FIO_2	>512	>357 to ≤512	>214 to ≤357	**>89 to ≤214**	≤89

B

ACLF Grade	Criteria	Additional Criteria
ACLF grade 1	Single renal failure	None
	Single liver, coagulation, circulation or respiratory failure	Creatinine 1.5-1.9 mg/dL and/or mild-moderate encephalopathy
	Single cerebral failure	Creatinine 1.5-1.9 mg/dL
ACLF grade 2	2 organ failures	None
ACLF grade 3	≥3 organ failures	None

C

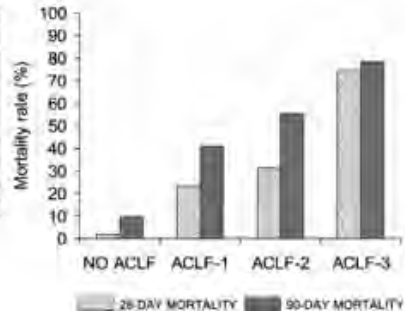

Fig. 4. (*A*) CLIF-SOFA score is used to categorize patients into (*B*) grades of ACLF. (*C*) Patient's risk of mortality is based on their ACLF grade. Bold type in panel (*A*) indicates organ failure. E, epinephrine; HE, hepatic encephalopathy; NE, norepinephrine. (*From* Moreau R, Jalan R, Gines P, et al, CANONIC Study Investigators of the EASL–CLIF Consortium. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144(7):1428.e6; with permission.)

NACSELD

NACSELD recently examined survival in S-ACLF.[15] Overall organ failures were purposefully simply defined: circulatory failure was shock, cerebral failure was West Haven grade 3 or 4 hepatic encephalopathy, renal failure was need for dialysis, and pulmonary failure was need for mechanical ventilation. S-ACLF was defined as 2 or more organ failures, and 30-day mortality increased with the number of extrahepatic organ failures present: 8%, 27%, 49%, 64%, and 77% for 0, 1, 2, 3, and 4, respectively (Fig. 5). Independent predictors of ACLF were nosocomial infections, nonspontaneous bacterial peritonitis as the first infection, low mean arterial pressure, and admission MELD score. In addition to the S-ACLF score, second infections, MELD, and admission white blood cell count were independent predictors of 30-day mortality, whereas a higher admission serum albumin level was protective.

Regional Differences in Defining ACLF

Several differences exist in the definition of ACLF, partly contingent on regional variation in causes of ACLF. First, most patients had reactivation of hepatitis B in the APASL group, alcohol-related cirrhosis in the EASL-CLIF group and hepatitis C in

Fig. 5. NACSELD defined S-ACLF as 2 or more organ failures. (*Adapted from* Bajaj JS, O'Leary JG, Reddy KR, et al, on behalf of NACSELD. Survival in infection-related acute-on-chronic liver failure is defined by extra-hepatic organ failures. Hepatology 2014 Feb 20. http://dx.doi.org/10.1002/hep.27077. [Epub ahead of print]; with permission.)

the NACSELD group. Second, definitions proposed by APASL suggest a duration of the inciting event to be less than 4 weeks, with manifestations of ACLF being characterized by ascites and encephalopathy. However, Western centers place less emphasis on deterioration of liver function and more emphasis on development of extrahepatic organ failure. Third, whereas APASL and NACSELD definitions rely on presenting factors (eg, multiorgan system failure), the EASL-CLIF definition includes the outcome (mortality >15%) in the definition. Fourth, the definition of underlying liver disease also varies across the groups. Chronic liver disease is enough to qualify for the APASL definition, whereas EASL-CLIF and NACSELD require the presence of cirrhosis. Fifth, renal failure and infection play a more prominent role in EASL-CLIF and NACSELD compared with viral hepatitis in APASL definitions.

PREDICTIVE MODELS

Several models may help predict outcomes in patients with ACLF. Certain models were developed to be cause specific. Patients with acute alcoholic hepatitis are at a higher risk for ACLF compared with other hospitalized cirrhotic patients.[14] For this disorder, MELD predicts early mortality but has not been validated in patients with ACLF.[36,37] The Lille model assesses short-term prognosis in patients with alcoholic hepatitis treated with steroids.[38] For cirrhotics undergoing surgery, who are at risk for an ischemic or infectious insult that can result in ACLF, a combination of the MELD score, age, and American Society of Anesthesiologists classification are predictive of short-term mortality.[39]

Other models are not disease specific and capture risk of mortality based on liver function, such as the CTP or MELD score. Given that multiorgan failure is common, models that address end-organ dysfunction such as the SOFA as well as the Acute Physiology Age and Chronic Health Evaluation have been used. Moreau and colleagues[14] examined the sequential SOFA score modified to include factors associated with liver disease (SOFA-CLIF), as discussed earlier (see **Fig. 4**). In contrast to elaborate models, Bajaj and colleagues,[15] using data from the NACSELD data set, showed that extent of multiorgan failure was sufficient to predict short-term mortality in patients with S-ACLF (see **Fig. 5**).

Although laboratory and clinical models may predict outcome, stool analysis may as well. Analysis of the gut microbiome, using the cirrhosis/dysbiosis ratio (CDR), shows

a progressive decrease in the CDR with worsening liver dysfunction, which is predictive of short-term organ failure and death.[40] This finding requires validation in additional studies.

ACLF IN PRETRANSPLANT PATIENTS

Data on ACLF and outcomes among cirrhotics awaiting LT are sparse. Given the high short-term mortality, persons who may be candidates for transplant with ACLF need to be evaluated rapidly. Finkenstedt and colleagues[41] examined ACLF on the waiting list in a single-center European cohort between 2002 and 2010 using the APASL definition (n = 144). Although no precipitant was found in 40%, infection and bleeding were the most common precipitants identified. The mean MELD score was 28, hepatorenal syndrome developed in 53%, wait-list mortality was 54% (median survival was 54 days), and only 10 persons survived without LT over a median follow-up of 1.5 years. Patients with better renal function and lower CRP levels were more likely to receive an LT compared with those with sepsis or those needing mechanical ventilation. Most patients who underwent LT had it occur during their ACLF event. Although it was not explicitly stated, there seemed to be increased short-term mortality; however, there was no difference in long-term (1-year, 3-year, and 5-year) posttransplant mortality between those transplanted with and without ACLF.

Bahirwani and colleagues[42] examined patients at a large American transplant center with ACLF (defined as an increase in MELD score of >5 points within 4 weeks of LT) between 2002 and 2006. There was no significant difference in 3-year renal function, risk of recurrent cirrhosis, graft loss, and death between those transplanted with and without ACLF. However, both studies lacked a comparison with a MELD-matched cohort without ACLF.

MEDICAL THERAPY

There is no ACLF-specific treatment. Appropriate intensive care management of patients with ACLF is the mainstay of treatment, as recently reviewed.[5] Management of ACLF is contingent on first addressing the precipitating event. For example, in the setting of acute alcoholic hepatitis, administration of prednisolone early in the course may play a critical role if warranted by the disease severity and absence of contraindications. Administration of tenofovir for ACLF caused by reactivation of hepatitis B may lead to improved survival.[43] However, a major impact in ACLF risk reduction will be achieved only through novel infection prevention strategies. Although antibiotic-based gastrointestinal bleeding prophylaxis and spontaneous bacterial peritonitis prophylaxis remain essential, ideally the future of ACLF prevention would be with non–antibiotic-related preventative interventions.

Liver Assist Devices

The role of liver assist devices in ACLF management remains unclear.[44] MARS (Gambro, Rostock, Germany), a nonbiological molecular adsorbent recirculating system, was examined in a multicenter study of 180 patients with ACLF complicated with either hepatorenal syndrome, hepatic encephalopathy, or worsening hyperbilirubinemia who were randomized to receive standard medical therapy with or without MARS. Patients assigned to MARS showed significant improvement in bilirubin, creatinine, and hepatic encephalopathy, but at 28 days, a survival benefit was not observed.[45] Similarly, in a study of the nonbiological device Prometheus (Fresenius Medical Care, Bad Homburg, Germany) (which uses fractional plasma separation absorption and dialysis), an overall survival benefit was not observed in patients with

ACLF, but it was seen in subgroup analysis of persons with type I hepatorenal syndrome and MELD scores greater than 30.[44]

ACLF AND OUTCOMES AFTER LT

The decision to proceed with LT in an individual recipient is based on organ availability, recipient disease severity, and the absence of contraindications. It is unclear whether criteria that are applicable to ALF are appropriate for ACLF. There is no specific priority assigned to persons with ACLF above and beyond the inevitable increase in MELD that occurs with ACLF. Recent data suggest that candidates with the highest MELD scores (>36) should be assigned either similar or higher priority than status 1 patients given their significant wait-list mortality.[46] However, the presence of cerebral edema, active infection, and hemodynamic instability, often present in persons with ACLF, remains an obvious contraindication to transplantation. Therefore, timing of transplant is critical. There is a lack of accurate laboratory parameters or biomarkers that signal the earliest safe window of transplant opportunity.

Living donor LT has been used in patients with ACLF caused by hepatitis B reactivation.[47,48] In a single-center analysis in Hong Kong of 32 patients with ACLF between 1996 and 2002,[49] living donor LT was used for patients with ACLF in the intensive care unit with a mean MELD score of 36. Overall operative morbidity was significant (59%), resulting in a 38-day mean length of stay. Patient and graft survival were both 88% at a median follow-up of almost 2 years, and was similar to a reference group who underwent elective living donor with lower MELD scores.

The role of simultaneous liver-kidney transplantation (SLKT) in patients with ACLF and renal dysfunction was recently examined in 133 patients with a mean MELD of 32 undergoing deceased donor transplantation at a single Chinese center between 2001 and 2009.[50] Patients were divided into 3 groups: (1) those with ACLF without renal dysfunction who underwent LT (5-year survival = 72%), (2) those with ACLF with renal dysfunction who underwent LT (5-year survival = 56%), and (3) those with ACLF with renal dysfunction who underwent SLKT (5-year survival = 82%). Many key factors about these patients remain unclear, such as how many patients had acute versus chronic kidney disease and how long the renal dysfunction was present before transplant.[51] Therefore validation is essential.

UNRESOLVED QUESTIONS

Despite the progress in defining ACLF, several questions remain. First, an element of reversibility is proposed among persons with ACLF who are successfully navigated through the acute decompensation. Theoretically, once the acute insult is managed, the long-term prognosis should be similar between MELD-matched patients with and without ACLF. However, this theory has not been well studied, and there is likely a point of no return, which is yet to be defined. Second, definitions from the various groups need to be aligned with the establishment of a common understanding of the underlying substrate (chronic liver disease vs compensated cirrhosis vs decompensated cirrhosis). Third, it is unclear whether all renal dysfunction in patients with ACLF is reversible.[6] Recent investigations have highlighted the importance of the cause, severity, and duration of renal dysfunction as critical determinants of outcome; even persons with normal renal function before ACLF can develop irreversible renal dysfunction after LT.[52–54] Whether this finding is more pronounced in persons with ACLF is unknown. Last, the best way to improve ACLF outcomes is likely through prevention.[55] Because the most common precipitant of ACLF is infection, development of

accurate risk stratification schemes followed by implementation of novel (preferably nonantibiotic) prevention strategies is desperately needed.

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