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REVIEW ARTICLE

Definition of ACLF and inclusion criteria for extra-hepatic organ failure

Xiaojing Wang[1] · Shiv Kumar Sarin[2] · Qin Ning[1]

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Abstract A prominent characteristic of ACLF is rapid hepatic disease progression with subsequent extra-hepatic organ failure, manifesting as either hepatic coma or hepatorenal syndrome, which is associated with a high mortality rate in a short time. The APASL definition mainly emphasizes recognizing patients with hepatic failure. These patients may subsequently develop extra-hepatic multisystem organ failure leading to high mortality. It is therefore worthwhile to identify the short interim period between the development of liver failure and the onset of extra-hepatic organ failure, the potential therapeutic 'golden window.' Interventions during this period may prevent the development of complications and eventually change the course of the illness. Organ failure is suggested to be a central component of ACLF and may behave differently from chronic decompensated liver disease. Clear and practical criteria for the inclusion of organ failure are urgently needed so that patients with these life-threatening complications can be treated in a timely and appropriate manner. Recent studies suggested that the scoring systems evaluating organ failure [acute physiology, age and chronic health evaluation (APACHE) and sequential organ failure assessment (SOFA) scores] work better than those addressing the severity of liver disease [Child-Pugh and model of end-stage liver disease (MELD) scores] in ACLF. However, a key problem remains that the former scoring systems are reflective of organ failure and not predictive, thus limiting their value as an early indication for intervention.

Keywords Acute-on-chronic liver failure · Hepatic coma · Hepatorenal syndrome · Organ failure · Cirrhosis · Liver decompensation

Acute-on-chronic liver failure (ACLF) is a series of deterioration processes leading to jaundice, coagulopathy, hepatic and subsequent multisystem organ failure [1]. HBV-related acute-on-chronic liver failure (HBV-ACLF) accounts for more than 80 % of all ACLF cases in Asia. ACLF has a poor prognosis with an in-hospital mortality ranging from 50 to 66 % [2]. Early identification of the precipitating factors of acute exacerbation and detection of liver decompensation in patients with cirrhosis are essential for adequate early intervention to reverse the deterioration.

Compared to the consensus in 2009, the 2014 APASL consensus recommended that liver failure be classified into different grades to predict outcomes, although it still needs further prospective evaluation. The inclusion criteria for extra-hepatic organ failure were increased. In particular, early identification of cerebral and renal failure was proposed owing to the close relationship between multiorgan failure and high mortality in ACLF. Updated information on prognostic scoring systems is included. Finally, treatment recommendations are more directed toward urgent intervention during the "golden window" [3].

Definition of ACLF

For a long time, there has been a lack of clear definitions of ACLF and uniformity in its diagnostic criteria. Liver failure associated with cirrhosis usually leads to two different

On behalf of the ACLF working party APASL.

✉ Qin Ning
qning@vip.sina.com

[1] Institute and Department of Infectious Disease, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

[2] Department of Gastroenterology, Institute of Liver and Biliary Sciences, G B Pant Hospital, University of Delhi, New Delhi, India

entities: end-stage liver diseases and ACLF [4, 5]. Clinical manifestations such as jaundice and hepatic encephalopathy (HE) are common in these two entities, but the clinical outcomes in terms of the potential for recovery or progress to multiorgan failures are quite different. In other words, ACLF refers to an acute deterioration of liver function and subsequently failure of other organs over several weeks following an acute event, while end-stage liver disease refers to a chronically decompensated liver because of continuous progressive deterioration of the underlying chronic liver disease [6, 7].

The APASL definition mainly emphasizes recognizing patients with hepatic failure. These patients may subsequently develop extra-hepatic multisystem organ failure leading to high mortality. It should also be noted that the possibility for a liver transplant decreases in the presence of extra-hepatic organ failure. It is therefore worthwhile to identify the short interim period between the development of liver failure and the onset of extra-hepatic organ failure, the potential therapeutic 'golden window.' Interventions during this period may prevent the development of complications and eventually change the course of the illness. In 2009, the APASL working party reached a consensus on the definition and diagnostic criteria. ACLF is defined as an acute hepatic insult manifesting jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy, in a patient with previously diagnosed or undiagnosed chronic liver disease [7]. The cutoff levels of jaundice and coagulopathy are defined as serum bilirubin $\geq$5 mg/dl (85 μmol/l) and INR $\geq$1.5 or prothrombin activity <40 %, respectively. Ascites and/or encephalopathies are also taken as criteria to define ACLF [7]. The recently published seminal work from the EASL-CLIF consortium has defined ACLF as an acute decompensation of cirrhosis in the form of development of ascites, HE, gastrointestinal hemorrhage, bacterial infections or a combination of these, associated with at least two organ failures with one being the kidneys identified as a serum creatinine level >1.5 mg/dl, leading to a high 28-day mortality of more than 15 % [8]. The main differences between the two definitions are that the EASL-CLIF definition originates from a population of patients with acute deterioration of cirrhosis, compensated or decompensated. It relies more on the ICU-based criteria of organ failure culminating in death, rather than specifically looking into a group of patients where the insult is predominantly a hepatotropic insult in case of APASL-ACLF. In China, the cutoff levels are serum bilirubin $\geq$10 mg/dl (171 μmol/l) and prothrombin activity <40 % [9]. An EASL-AASLD single-topic symposium [10] also proposed a definition for ACLF: "Acute deterioration of pre-existing chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months due to multisystem organ failure." In this definition, the organ failure is considered a central part of this syndrome.

Clinically, there is a need for classifying liver failure into different grades to predict the outcome of liver failure per se independent of failure of other organs. It is recommended that liver failure can be graded into three grades, which still need to be prospectively evaluated.

Various causal agents, including infectious agents, metabolic abnormalities, and drug or toxin ingestion, may lead to ACLF, and they show wide geographical variation [7]. Alcohol and drugs constitute the majority of acute insults in Western countries. In contrast, infectious agents, particularly HBV, predominate in the Asian countries.

Pathophysiology of ACLF

The pathophysiology of ACLF manifests similarly as septic shock, which is characterized by progressive vasodilatory shock and multiple organ failure. Thus, the predisposition, infection/inflammation, response and organ failure (PIRO) concept employed for sepsis is useful in determining the pathogenesis and prognosis in patients with ACLF. According to this approach, predisposition is indicated by the severity of the underlying disease, injury by the nature/severity of the precipitating event, response by the host response to injury and organs by the extent of organ failure [11].

Activation of the immune coagulation system has been implicated in the pathogenesis of fulminant liver failure. Several studies have shown the importance of Fgl2/fibroleukin prothrombinase in both patients with HBV-ACLF and a fulminant hepatitis mouse model with murine hepatitis virus strain 3 (MHV-3) infection [12–14]. The mouse-fgl2 antisense administration remarkably increased the survival rate of mice with MHV-3-induced fulminant hepatitis [15, 16]. A positive correlation was observed between human-fgl2 expression and the degree of liver injury, as indicated by the bilirubin levels. The hfgl2 expression in peripheral blood mononuclear cells (PBMCs) may be used as a biomarker for monitoring the severity of acute-on-chronic hepatitis B, and hfgl2 could be a potential target for therapeutic intervention [17].

Clinical manifestations and complications of ACLF

The clinical manifestation of ACLF varies according to the severity of liver injury, and it is determined by the chronic and acute insults and the possibility of the syndrome subsequently developing. The injuries involve the entire body, representing a systemic inflammatory response and high

energy expenditure and catabolism. Following the origin of hepatic failure, the subsequent multiorgan failure includes dysfunction of the brain, kidney, lung and other systems. Liver dysfunction represents a loss of metabolic function, decreased gluconeogenesis leading to hypoglycemia, decreased lactate and ammonia clearance leading to lactic acidosis and hyperammonemia, and decreased synthetic capacity leading to coagulopathy. HE is the most severe complication of ACLF; the mortality is higher in patients who progress to grade III and grade IV encephalopathy, where cerebral edema commonly occurs. Renal failure is also common because of either the original insult or hyperdynamic circulation. Another cardinal feature of ACLF is coagulopathy, which results in a prolongation in prothrombin time. And prothrombin time is considered an important index for monitoring the severity of hepatic injury. Infection and sepsis are common in patients with ACLF, and they are associated with high morbidity and mortality [18–20]. Patients with sepsis often present with high fevers, shock and respiratory failure. However, whether sepsis is a cause or consequence of liver failure is still debatable.

Organ failures in ACLF

Liver dysfunction is associated with a decreased detoxification function as manifested by hyperbilirubinemia, encephalopathy and a decrease in prothrombin time, leading to systemic hemodynamic dysfunction, renal failure, cerebral failure and increased susceptibility to infections. A recent cohort study assessed patients with cirrhosis in the ICU from 2005 to 2008; the in-patient mortality amounted to 70 % in the presence of three or four non-hematologic organ failures at day 1 after admission; the presence of three organ failures or more after 3 days of treatment indicated a mortality of 89 % [21–23].

Data from 1343 hospitalized patients with cirrhosis and acute decompensation in 2011 at 29 liver units in eight European countries showed that the 28-day mortality rate among patients who had ACLF when the study began was 33.9 %; among those who developed ACLF, it was 29.7 %, and among those who did not have ACLF, it was 1.9 %; the mortality rate within 28 days after enrollment was 32.0 % in patients with two organ failures and 78.6 % in those with three organ failures or more. It was only 14.6 % in patients with one organ failure [8].

A retrospective study involving 124 patients from China showed that the 1- and 3-month survival rates of HBV-ACLF were 53.23 and 45.97 %, respectively. Having more than two complications (including two) was a significant and independent predictor for mortality [24].

HE is characterized by rapid deterioration of the level of consciousness, increased intracranial pressure (ICP) and reduced cerebral perfusion pressure. The simplest grading of HE is based on changes of consciousness, intellectual function and behavior. The West Haven criteria (Table 1), which are widely used, grade HE from I to IV [25]. According to the 2011 AASLD consensus on ALF, a serum ammonia concentration of 75 mM in patients with ALF was identified as an important threshold for developing intracranial hypertension (ICH), whereas arterial ammonia levels of >100 mM on admission represent an independent risk factor for the development of high-grade HE. A level of >200 mM predicts ICH [26].

Hepatorenal syndrome (HRS) is a unique form of kidney injury in patients with liver failure or end-stage liver diseases. In the diagnostic criteria for HRS proposed by the International Ascites Club (IAC) [27, 28], the rigid cutoff value of SCr ≥1.5 mg/dl has limited the prompt management of patients with milder renal dysfunction. In 2004, the Acute Dialysis Quality Initiative (ADQI) Workgroup developed a consensus known as the risk, injury, failure, loss, end-stage (RIFLE) criteria (Table 2), which stratified acute renal dysfunction into grades of increasing severity based on changes in SCr and/or urine output [29, 30].

Predictive models for organ failures in ACLF

Different predictive models have been established to determine the outcome of patients with ACLF and to facilitate organ allocation for liver transplantation. These prognostic models are divided into two categories: the first

Table 1 West Haven criteria for semiquantitative grading of mental state

Grade 1
Trivial lack of awareness
Euphoria or anxiety
Shortened attention span
Impaired performance of addition
Grade 2
Lethargy or apathy
Minimal disorientation for time or place
Subtle personality change
Inappropriate behavior
Impaired performance of subtraction
Grade 3
Somnolence to semistupor, but responsive to verbal stimuli
Confusion
Gross disorientation
Grade 4
Coma (unresponsive to verbal or noxious stimuli)

Table 2 Acute dialysis quality initiative (ADQI) criteria for the definition and classification of acute kidney injury (modified RIFLE criteria)

AKI stage	Serum creatinine criteria	Urine output criteria
1 (Risk)	Increase of Scr ≥0.3 mg/dl within 48 h or an increase of 150–200 % (1.5-fold–twofold) from baseline	<0.5 ml/kg/h for >6 h
2 (Injury)	Increase in Scr 200–299 % (≥twofold–threefold) from baseline	<0.5 ml/kg/h for >12 h
3 (Failure)	Increase in Scr ≥300 % (≥threefold) from baseline or Scr ≥4.0 mg/dl with an acute increase of ≥0.5 mg/dl or initiation of renal replacement therapy	<0.3 ml/kg/h for 24 h or anuria for 12 h

category used for evaluating the severity of liver disease includes the Child-Pugh and MELD score, and the second category used for evaluating organ failures includes the APACHE and SOFA score. The MELD score has been widely used in CHB and is found to be more objective and efficient in predicting survival of CHB patients with ACLF than the Child-Pugh score. In Europe, the accuracy of the chronic liver failure-sequential organ failure assessment (CLIF-SOFA) score has been validated, as has the MELD score, for predicting short-term mortality in cirrhotics with acute decompensation [12]. Recently, a TPPM scoring system established by Ning's group with reference to and based on MELD, taking complications, number of organ failures and HBV viral load into consideration, was confirmed to have superior predictive value for HBV-ACLF patients when compared with MELD, and it was further validated in another HBV-ACLF cohort [24, 31]. The TPPM scoring system was established based on a population of 531 HBV-ACLF patients from Tongji Hospital (Wuhan). A validation in a larger population in Asian countries will further illustrate its sensitivity and specificity. Recent studies have suggested that, compared to the scoring systems addressing the severity of liver disease (Child-Pugh and MELD), organ failure scores such as APACHE II, SOFA and TPPM may be more reliable for prognosticating ACLF outcomes [21–23, 32–35], because once non-liver organ failure has begun, mortality is mainly determined by the degree of end-organ dysfunction and less by the severity of the liver disease [33–35]. However, a key problem is still that the organ failure scores are mainly reflective of organ failure and not predictive, thus limiting their value as predictors for early intervention. The perfect scoring system for early identification of patients with ACLF has not been well defined yet [10].

Antiviral treatment for HBV-related ACLF

The application of nucleos(t)ide analogs in HBV-related ACLF has become increasingly accepted. Recent studies demonstrated that treatment with nucleoside analogs including entecavir, lamivudine and telbivudine prevented disease progression and increased the survival of patients with HBV-ACLF [24, 31]. Data also showed that the short-term mortality could be reduced if HBV DNA decreases more than 2 logs within 2 weeks [36, 37]. A meta-analysis suggested that nucleos(t)ide analogs could be well-tolerated during therapy, and entecavir and lamivudine provide comparable results [38].

Recommendations

1. Definition of ACLF:
   - Acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease (2a, B).
2. Definition of liver failure in ACLF:
   - Jaundice [serum bilirubin ≥5 mg/dl (85 μmol/l)] and coagulopathy (INR ≥1.5 or prothrombin activity <40 %).
   - Complicated within 4 weeks by ascites and/or encephalopathy (as determined by clinical examination).
3. Grading of ACLF:
   - There is a need for classifying liver failure into different grades to predict the outcome of liver failure per se independent of the failure of other organs; the latter follow the primary hepatic insult.
   - The most predictive variables to accurately predict the outcome of hepatic failure include total bilirubin, INR and HE (2b, C).
   - Classifying liver failure into three classes helps prognosticate the patient outcome at baseline.
   - Intervention studies based on the grade of liver failure may help to improve outcomes (1a, C).
4. Inclusion of organ failure in ACLF:
   - Emergence of changes in behavior as well as a minimal change in the level of consciousness is a sign for early intervention for patients with HE (C1).
   - Serum ammonia concentration of 75 mM is an important threshold for developing ICH (B1).

- Patients with increased Scr $\geq$0.3 mg/dl within 48 h or an increase of 150–200 % (1.5-fold–twofold) from baseline or oliguria (<0.5 ml/kg/h for $\geq$6 h) require prompt management (A1).

5. Early diagnosis for non-liver organ failure is important given the high mortality owing to multiorgan failure (A1).
6. The presence of two or more organ failures is a high risk factor for ACLF short-term mortality (B1).
7. Organ failure scores such as APACHE II, SOFA and TPPM (for HBV-ACLF) are recommended for evaluating the prognosis of short-term mortality in ACLF (B2).
8. Antiviral treatment for HBV-ACLF:
   - Nucleoside analogs could prevent disease progression and increase the survival of patients with HBV-ACLF (C1).
   - Short-term mortality could be reduced if HBV DNA deceases >2 logs within 2 weeks (C1).

Compliance with ethical requirements and Conflict of interest All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study. Xiaojing Wang, Shiv Kumar Sarin and Qin Ning declare that they have no conflict of interest.

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