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REVIEW

Overview on acute-on-chronic liver failure

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Abstract **Liver failure (LF) is defined as severe dysfunction in hepatic synthesis, detoxification, and metabolism induced by various etiologies. Clinical presentation of LF typically includes severe jaundice, coagulation disorder, hepatic encephalopathy, and ascites. LF can be classified into acute LF, acute-on-chronic LF (ACLF), and chronic LF. ACLF has been demonstrated as a distinct syndrome with unique clinical presentation and outcomes. The severity, curability, and reversibility of ACLF have attracted considerable attention. Remarkable developments in ACLF-related conception, diagnostic criteria, pathogenesis, and therapy have been achieved. However, this disease, especially its diagnostic criteria, remains controversial. In this paper, we systemically reviewed the current understanding of ACLF from its definition, etiology, pathophysiology, pathology, and clinical presentation to management by thoroughly comparing important findings between east and west countries, as well as those from other regions. We also discussed the controversies, challenges, and needs for future studies to promote the standardization and optimization of the diagnosis and treatment for ACLF.**

Keywords liver failure; chronic liver failure; acute-on-chronic liver failure; diagnosis; prognosis; treatment

Introduction

Acute-on-chronic liver failure (ACLF) is a syndrome distinct from acute liver failure (ALF) and chronic liver failure (CLIF). ALF is the consequence of rapid deterioration in liver function characterized by abnormal mental status and coagulation in whom without previous liver disease. CLIF is the development of a series of irreversible deterioration in liver function based on underlying decompensation of cirrhosis. However, ACLF is the appearance of acute liver decompensation based on known or unknown underlying liver disease [1–3]. The essential features of ACLF include underlying chronic liver disease (CLD), precipitating factors, reversible and severe liver dysfunction, multi-organ and system failure, and high rate of short-term (i.e., three months) fatality [2]. Thus, ACLF is evidently distinct from CLIF. Patients with ACLF can improve or even fully recover through liver regeneration, although the mortality rate of ACLF is much higher than that of CLIF [4]. By contrast, CLIF cannot be cured except by liver transplantation. The differences among the three types of liver failure are summarized in Table 1.

The incidence of ACLF remains unclear. Bruno *et al.* reported that 59 of 490 (12.0%) cirrhotic patients with complications met the criteria of Asian Pacific Association for the Study of the Liver (APASL) for ACLF [5]. In a prospective study of 1343 patients admitted for acute decompensated cirrhosis, 303 patients (22.6%) met the EASL criteria for ACLF, whereas 112 patients (8.3%) developed ACLF during hospitalization; these results indicated that ACLF accounted for 30.9% of cirrhosis patients with acute deterioration of liver function [2].

The reported mortality rates for ACLF also vary. Moreau *et al.* reported that the 28-day and 90-day non-transplantation mortality rates in 415 patients with EASL-ACLF were 38.3% and 58.3%, respectively [2]. The 30-day mortality rate was as high as 58% in another cohort of 477 EASL-ACLF patients [6]. By contrast, the 90-day mortality rate was 63% in another study using the APASL criteria [7]. However, nearly half of the patients in these studies recovered from ACLF because of liver regeneration, which indicated the reversibility of ACLF. Furthermore, the long-term survival rate of patients who recovered from ACLF

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Table 1 Clinical presentation and diagnostic criteria of three different types of liver failure (LF)

	Acute LF	Acute-on-chronic LF	Chronic LF
Epidemiology	Uncommon	Common	Most common
Underlying liver disease	None	Yes	Yes
Etiology	Various liver injury inducing factors	Intrahepatic or extrahepatic factors	CLD with slow progression
Precipitating factors	None	Yes (some unknown)	None
Time	<26 weeks	<26 weeks	>26 weeks
Duration	Days	Weeks	Months to years
Essential condition of diagnosis	Hepatic encephalopathy (HE), INR	INR, TBIL, and ascites/HE (APASL)	No specific criteria (China, the only factor is PTA<40%)
Pathology	Extensive necrosis	Liver fibrosis in various degrees, acute hepatocyte injury, and necrosis	Diffuse hepatic fibrosis and formation of pseudo-lobules accompanied with distributed hepatocyte necrosis
Clinical presentation	HE, brain edema, coagulation defects	Coagulation defects, hemodynamic dysfunction, immune function failure, SIRS, and multiple organ failure	Multiple organ failure, and SIRS
Therapy	Liver transplantation	Spontaneous recovery, transplantation	Liver transplantation
Prognostic indices	King's college score	Liver specific model (CTP and MELD), general model (SAPS II and APACHE), and organ failure model (OSF, SOFA, and CLIF-SOFA)	MELD
Fatality rate	High	Higher than cirrhosis with same MELD score	

(APASL criteria) was comparable with that of patients with cirrhosis [8], which implied the importance of early and effective treatment.

Controversies in diagnostic criteria for ACLF

Distinction of diagnostic criteria

The principle of ACLF was first introduced in 1995. The ACLF status includes two key elements, namely, acute presentation and simultaneous chronic underlying liver injury [1]. However, no global consensus on specific diagnostic criteria for ACLF has been established despite the well acceptance of this clinical entity, partly because of the great diversity in its underlying etiology, precipitating factors, and clinical presentation. For instance, Wlodzimirow *et al.* summarized 19 research papers on ACLF prognosis, in which 13 diagnostic criteria were used and 73 prognostic indices were identified [9]. Additionally, many terms, such as acute decompensation, acute deterioration, and severe alcoholic hepatitis (SAH), were used to describe the severe conditions. Acute decompensation [2] was defined as the acute development of one major complication of liver disease (i.e., ascites, encephalopathy, gastrointestinal hemorrhage, and bacterial infection) or more. Acute deterioration was similar to acute decompensation. SAH referred to severe liver dysfunction caused by alcoholism with high level of bilirubin, with or without fever, and white blood cell (WBC) elevation, especially those with Maddrey score higher than 32. These concepts were widely used in all kinds of research prior to the publication of the APASL guideline of ACLF in 2009 and the report of the EASL research in 2013. In this paper, the definition is indicated for each reviewed study to show the definition used to enhance the understanding of readers.

Extensive studies have been conducted by several international hepatology societies to standardize the diagnostic criteria for ACLF. For instance, APASL first developed a unified diagnostic criterion for ACLF in 2009. The association pointed out that ACLF was manifested as jaundice and coagulopathy, complicated by ascites and/or encephalopathy within four weeks, in a patient with previously diagnosed or undiagnosed compensated CLD. Serum bilirubin should be higher than 5 mg/dl, accompanied with INR higher than 1.5 or prothrombin activity (PTA) of less than 40% [1]. By contrast, EASL published a completely different diagnostic criteria in 2013 [2]. A diagnostic criterion for ACLF based on organ failure was established because an extensive perspective research showed that multi-organ failure is the main cause of death in these patients [2,6]. The criterion of organ failure was established based on the modified Sequential Organ Failure Assessment (SOFA) score, which was called the CLIF SOFA score. Organ failure was defined according to the following parameters presented: LF, bilirubin $\geqslant$ 12.0 mg/dl; renal failure, creatinine $\geqslant$ 2.0 mg/dl; central nervous system failure, hepatic encephalopathy (HE) $\geqslant$ grade III; and blood coagulation failure, INR $\geqslant$ 2.5 or

platelet (PLT) $\leqslant 20 \times 10^9$/L. The requirement of cardiovascular active drugs (e.g., dopamine) indicates circulatory system failure, and $PaO/FiO_2 \leqslant 200$ or $SpO_2/FiO_2 \leqslant 214$ suggests respiratory failure. ACLF grade 1 (ACLF-1) was defined as cirrhosis patients with renal failure, or a non-renal organ failure with creatinine levels of 1.5–2 mg/dl and/or grade I or II HE. By contrast, ACLF-2 indicated two organ failures, and ACLF-3 involved three or more organ failures. Meanwhile, the North American Consortium for the Study of End-stage Liver Disease also provided a special type of ACLF definition named infection-related ACLF (I-ACLF). They defined extrahepatic organ failure as (1) shock, (2) grade III/IV HE, and (3) need for dialysis and mechanical ventilation. I-ACLF was defined as infectious cirrhotic patients with two or more organ failures [10]. The definition of ACLF provided by the Chinese Society of Hepatology in 2006 stated that severe hepatitis (equivalent to ACLF) can be considered acute or sub-acute deterioration of liver function in patients with CLDs [1]. Chinese ACLF was described as: (1) fatigue with gastrointestinal tract symptoms; (2) rapid progression in jaundice, with serum bilirubin $> 10 \times$ upper limit normal (ULN) or daily increase $\geqslant$ 1 mg/dl; (3) hemorrhagic tendency with INR $\geqslant$ 1.5 or PTA $\leqslant$ 40% and other causes have been excluded; (4) progressive reduction in liver size, and (5) occurrence of HE. Most studies in China adopted this guideline as diagnostic criteria.

The most popular definitions were those of APASL and EASL. However, these two definitions had distinct characteristics. The EASL concept focused on the importance of multi-organ failure, whereas APASL considered LF as the key issue (Table 2). Amarapurkar *et al.* compared the APASL and ESAL diagnostic criteria for ACLF and found that 15/62 (24.2%) patients who met the APASL diagnostic criteria did not meet the ESAL diagnostic criteria [12]. Thus, only 47 cases met both diagnostic criteria. Liu *et al.* found that only 111/274 (40.5%) patients in a hepatitis B virus (HBV)-related APASL ACLF cohort also met the ESAL criteria for ACLF [13]. Patients who met the APASL diagnostic criteria for ACLF showed remarkably less organ failure and mortality than those who met the EASL diagnostic criteria for ACLF. Zhang *et al.* [14] also retrospectively compared the two criteria in 394 Chinese ACLF cases with all kinds of causes. The 90-day mortality-rate for patients who met the APASL definition was 13.1%, whereas that for patients who met the EASL definition was 59.3%. The characteristics of the two ACLF groups defined by EASL and APASL were clearly quite different. Improved controlled studies are needed to determine which of these two criteria is more clinically relevant.

The diagnostic criteria for ACLF were suggested to include the following three key elements to differentiate it from other types of LF: specific clinical and/or laboratory diagnostic criteria; clear difference from ALF and CLIF; and exclusion of other diseases [15]. Thus, patients with similar clinical courses and outcomes can be classified and grouped together. The improved criteria will also be essential for standardizing future studies on natural history and outcomes, as well as for more effective treatment for ACLF.

Controversies on precipitating factors

ACLF can be induced by any precipitating factor similar to those leading to severe liver injury and ALF, such as hepadnavirus and non-hepadnavirus, other liver infection pathogens, liver toxicity drugs, alcohol, autoimmune diseases, Wilson's disease, portal vein thrombosis, and

Table 2 Comparison of ACLF diagnostic criteria by CMA, APASL, and EASL-AASLD

	CMA*	APASL	EASL-AASLD
Definition	Acute (usually within four weeks) liver decompensation in patients with CLDs	Acute hepatic insult manifesting as jaundice and coagulopathy, complicated within four weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed CLD	Acute deterioration of pre-existing CLD, usually related to a precipitating event and associated with increased mortality at three months due to multi-system organ failure
Diagnostic criteria	1. Progressively deepening jaundice (TBil $\geqslant$10 mg/dl or daily increase $\geqslant$1 mg/dl) 2. PTA$\leqslant$40% or INR $\geqslant$1.5 3. with or without HE or other complications 4. divided into 3 grades	1. Previously diagnosed or undiagnosed CLD 2.TBil$>$ 5 mg/dl and INR$>$1.5 or PTA $<$ 40% 3.Ascites and/or encephalopathy in four weeks 4. No grades	ACLF-1: renal failure or a non-renal organ failure associated with creatinine 1.5–2 mg/dl and/or grades I–II encephalopathy ACLF-2: two organ failures ACLF-3: three or more organ failures
Predisposition	Compensated liver disease	Compensated liver disease	Stable compensated or decompensated cirrhosis to date
Precipitating factors	Not mentioned	Infectious and noninfectious causes direct hepatic insult	Infectious and noninfectious causes direct hepatic insult or not (especially infection)

*CMA: Chinese Medical Association [11] .

ischemic hepatitis. Viral hepatitis, especially HBV, is the major cause for ACLF in eastern countries, contrary to the alcoholic liver disease (ALD) in western countries. HBV-related ACLF may occur spontaneously or be induced by various causes of immunosuppression, such as chemotherapy, immunosuppressive agents, CD20 antibody therapy, and immune reconstitution caused by anti-human immunodeficiency virus (HIV) treatment. HCV cirrhosis may also develop to ACLF, although this case was less common than HBV cirrhosis. Other liver infectious pathogens, such as bacteria, parasite, and fungus, can also cause ACLF.

The EASL and APASL criteria both agreed that any cause resulting in direct and severe liver injury could serve as a precipitating factor for ACLF. However, the two criteria have contrasting perceptions on whether extra liver infection is a precipitating factor [1]. Several recent studies indicated that bacterial infection is the major cause of acute liver deterioration [2,16,17]. Thus, the ACLF criteria by EASL-AASLD indicated that extrahepatic infection is the most common precipitating factor. This concept was diametrically opposed to that of APASL. Whether the infection is a trigger or a complication of ACLF in many cases is difficult to determine. In addition, sepsis itself can induce multi-organ failure in cirrhotic patients in the absence of ACLF [1]. Hence, APASL criteria emphasized that extrahepatic infection cannot be considered as a precipitating factor for ACLF. In a retrospective study that used APASL criteria (but included those with infection as the precipitating factor), 102 patients were divided into type I ACLF (non-hepatic injury as precipitating factor) and type II ACLF (hepatic injury as precipitating factor). Type II ACLF was further categorized as follows: IIA, acute viral hepatitis on underlying CLD; IIB, other acute hepatic insults such as drugs/toxins; and IIC, same cause for underlying liver disease that was also responsible for ACLF. The results showed that infection was the most common (47%) precipitating factor in patients with type I ACLF. Six cases with acute viral hepatitis (four with hepatitis E virus and two with hepatitis A virus infection) were found in type IIA ACLF, whereas 30 (29%) patients were considered type IIC ACLF because of alcoholic hepatitis. Thus, non-hepatic infection was considered a very common precipitating event [17].

Most studies concluded that subtypes of precipitating factors do not affect the prognosis of ACLF, although precipitating factors may vary among patients [2,6,7]. Rastogi *et al.* found that histological features induced by different causes of ACLF are similar, except for pericellular fibrosis and Mallory's hyaline, which were observed mainly in those with SAH [18]. However, some researchers believed that the occurrence of ACLF induced by direct liver damage factors (such as drugs and hepatic virus) is different from ACLF induced by extrahepatic factors (such as bleeding and infection) [2,19,20]. In addition, the precipitating factors sometimes could not be identified in certain patients even with detailed medical history and examination [2]. Bacterial translocation or potential infection may serve as the precipitating factors in these patients.

Controversies on ACLF criteria of the underlying CLD

Underlying CLD, which is another main feature for ACLF, can be classified as noncirrhotic liver disease, cirrhosis, and cirrhosis with previous decompensation. However, the kind of CLD that should be considered as the underlying CLD for ACLF requires further clarification. APASL recommendations restricted this condition to compensated liver diseases, such as viral hepatitis, compensated cirrhosis, non-alcoholic steatohepatitis (NASH), cholestasis liver disease, and metabolic liver disease. By contrast, EASL-AASLD defined only compensated and decompensated liver cirrhosis as the underlying CLDs for ACLF [2]. Consequently, published studies do not have uniformed criteria [17]. Some studies included only ACLF cases with cirrhosis [2,8,20] or a mix group of ACLF cases with chronic hepatitis and/or cirrhosis [2,4,18]. Other studies did not even mention the type of underlying CLDs [21,22].

In addition to the confusion caused by the definition of CLD, another issue was the assessment of patients with previous CLD, especially those whose onset of ACLF was the first presentation of their liver diseases. The criteria used for diagnosis widely vary, that is, from laboratory evidence (i.e., WBC and biochemistry), clinical evidence of portal hypertension (i.e., esophageal varices, ascites, and HE), and imaging (i.e., nodular contour of the liver, splenomegaly) to histologic evidence (i.e., liver biopsy with fibrosis stage) [8]. Thus, given the difficulty of liver biopsy and pathological diagnosis for ACLF, further studies are needed to standardize the methods and criteria for CLD or cirrhosis diagnosis.

Jalan *et al.* recently proposed to classify ACLF into three different types according to the three kinds of underlying CLD, namely, types A, B, and C ACLF (Fig. 1) [23]. The clinical significance of the classification should be confirmed in future study, because no solid evidence has been provided in which the underlying CLD showed prognostic importance. Katoonizadeh *et al.* [8] used the APASL criteria in their study, and all seven patients with alcoholic ACLF but no pathologically proved cirrhosis survived. By contrast, the three-month survival rate of cirrhotic patients was only 44.4%. The CNONIC study [2] found that ACLF patients with previous compensated cirrhosis have more severe presentation and higher fatality rate than those with previous decompensated cirrhosis (fatality rate at day 28 was 42.2% vs. 29.6%, $P = 0.03$). Nevertheless, another study reported opposite results. Shi *et al.* found that the 28-day, three-month, and one-year survival of ACLF (EASL criteria) patients with or without

previous decompensated cirrhosis were 58.9% versus 61.4%, 36.2% versus 52.5%, and 29.1% versus 49.6%, respectively [24]. They concluded that previous decompensation mainly decreases the long-term survival chance of ACLF patients. Mookerjee *et al.* showed that in 68 patients with SAH who had pathologic evaluation, 51 (75%) had cirrhosis, 11 were incomplete cirrhosis, and six had suspected cirrhosis [25]. These patients had similar prognoses. Thus, more studies are needed to clarify the clinical significance of underlying CLD.

ACLF-related pathogenesis

Infection, sepsis, and immune responses

Infection, sepsis, systematic inflammation reaction (SIRS), and immune-mediated liver injury were believed to be important accelerating factors and main clinical presentations of ACLF by APASL consensus and EASL study [1,2].

Patients with severe liver disease, such as cirrhosis, ALF, and ACLF, are likely complicated by infection [26,27]. The risk of bacterial infection in cirrhosis is due to multiple factors, such as liver dysfunction, porto-systemic shunting, gut dysbiosis, increased bacterial translocation, cirrhosis-associated immune dysfunction, and genetic factors [28]. The causes of bacterial translocation include intestinal bacterial overgrowth, damage of intestinal mucous membrane barrier, and local and systemic immune dysfunction [20]. These patients might exhibit all kinds of immunity depression, such as reduced level of complement C3 and C4 elements, compromised immunologic surveillance, decreased albumin level and function, downregulated expression of mononuclear WBC DR antigen (decline of antigen presentation ability), NK cell abnormity, declined clearance of bacteria mediated by Fc receptor of giant cells, and inhibition of phagocytic and intracellular lethal function of neutrophil [20,29]. In addition, adaptive immunity is also depressed, such as depletion, decreased proliferation, and increased apoptosis of T cells. The "immune paralysis" status of severe liver diseases can be as serious as that of sepsis [30].

In addition to infection, the host response to infection, namely, SIRS, is crucial. SIRS refers to system inflammation caused by infectious or noninfectious cause. Most SIRSs in ACLF are triggered by infection, which is also called sepsis. No evidence on the direct tissue damage caused by bacteria as a mechanism of organ failure in patients with cirrhosis is available [31]. Infection and SIRS are reciprocal causes. Infection is the most common cause for SIRS in ACLF, and SIRS places such patients at high risk for infection. This characteristic is very similar to the immune response in patients with severe sepsis, that is, SIRS first, followed by a mixed anti-inflammatory response and then compensated anti-inflammatory response [20]. Transformation from pro-inflammatory to anti-inflammatory status leads to increased susceptibility to infection. An increase in multi anti-inflammatory and pro-inflammatory factors, such as TNF-α, sTNF-αR1, sTNF-

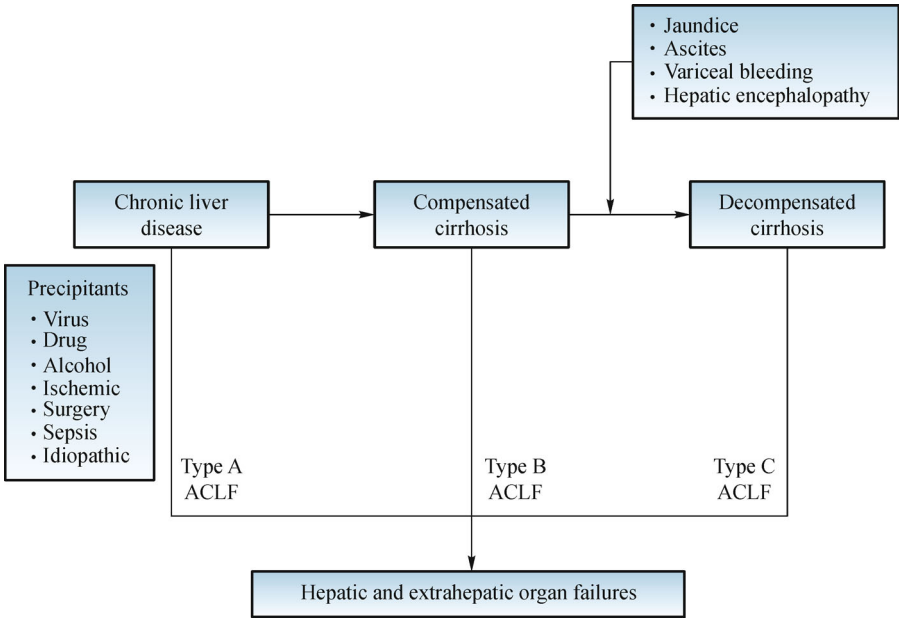

Fig. 1 Pathogenesis for different types of acute-on-chronic liver failure (ACLF) (Adopted from reference [24] with permission from Elsevier). Three types of ACLF are suggested. Type A ACLF is non-cirrhotic ACLF, type B is cirrhotic ACLF, and type C is cirrhotic ACLF with previous hepatic decompensation.

αR2, IL-2, IL-2R, IL-6, IL-8, IL-10, and IFN-γ, has been reported in ACLF patients [32]. This process can change the host's normal anti-infection response into excessive harmful inflammatory reactions that can induce liver function deterioration or failure, and other organ failures, such as activation of coagulation, induction of arterial hyporeactivity to vasoconstrictors and hypotension, and disruption of the endothelial barrier function, particularly in alveolar capillaries [31]. In addition, septicopyemia-induced hyperglycemia, defected arginine vasopressin secretion, adrenocortical insufficiency, and compartment syndrome in these patients lead to systemic and hepatic hemodynamic deterioration, portal hypertension, and hemangiectasis, which promote death in patients with ACLF [20]. SIRS is considered the most important cause of multi-organ failure in ACLF.

Infection and SIRS have attracted much attention, especially in alcoholic ACLF [6]. Karvellas *et al.* showed that in 184 patients with ACLF (non-EASL and non-APASL ACLF definition), 36% had bacteremia, of which 36% were Gram-positive bacterial infection, 58% were Gram-negative bacterial infection, and 6% were fungal infection [33]. The median time of bacteremia onset was 8 days. These patients showed higher MELD score, more severe coma and APACHE score, higher ratio in renal replacement treatment and artificial ventilation, longer ICU stay, and higher mortality rate. In a study on I-ACLF, 28.5% and 22.5% of patients had urinary tract infection and spontaneous bacterial peritonitis (SBP), respectively, which were the most prevalent types of infection. Secondary infections developed in 21.6% of patients. Non-SBP infection was one of the independent factors for predicting the development of I-ACLF, whereas secondary infections were correlated significantly with the 30-day mortality in I-ACLF patients [34].

SIRS has been demonstrated as a common clinical presentation of ACLF and closely related to poor prognosis. Katoonizadeh *et al.* found that the SIRS rate is higher in alcoholic ACLF (APASL definition) group than that in chronically decompensated cirrhosis (69% vs. 23%, $P = 0.0001$), and 60% patients with SIRS in the ACLF group showed negative bacteriology tests [8]. The mortality rate in patients with SIRS was 59%, contrary to the 18% rate in patients without SIRS. SIRS was an independent predictive factor of poor prognosis. Moreau *et al.* found that bacterial infection is much more frequent in EASL-ACLF patients than in non-ACLF patients (32.6% vs. 21.8%) [2]. ACLF patients often had more frequent sepsis and septic shock (11.9% vs. 3.5% and 3.4% vs. 0.1%), higher WBC count [$(10.1 \pm 0.4) \times 10^9$/L vs. $(6.8 \pm 4.1) \times 10^9$/L], and higher level of serum C reactive protein (CRP, 39.4 ± 42.7 mg/L vs. 25.4 ± 31.9 mg/L). WBC count was an independent factor correlated with poor prognosis [2]. A study on 100 patients with cirrhosis and acute renal failure showed that 41% had SIRS and 56% had infection [35]. The in-hospital mortality rate of patients with SIRS was 68% and 33% in those without SIRS ($P = 0.001$). Multivariable analysis indicated that the MELD score and presence of SIRS, other than infection, were independent prognosis factors. In another cohort of patients with pathologically confirmed severe SAH, most patients had ACLF, the AUC of SIRS was 0.76, with a high sensitivity of 0.89, but poor specificity of 0.39 in predicting SIRS-related poor outcome [25]. Jalan *et al.* showed that the mortality rate was 46% in ACLF with SIRS versus 25% in those without SIRS [6]. However, SIRS was not parallel with infection. In addition, CRP variation was also associated with the prognosis of ACLF, i.e., CRP was increased in death cases but decreased in survivors.

Several studies have confirmed that the incidences of infection and SIRS in ACLF patients are significantly higher than those in patients with chronic decompensated cirrhosis, and both factors are significantly associated with poor prognosis [8]. Thus, the EASL definition stated that infection is the most common precipitating factor for ACLF. But APASL recommendations argued that sepsis alone might not directly cause an acute hepatic insult, but it can result in worsening of the overall condition in ACLF patients. Furthermore, sepsis per se can cause organ failure in cirrhotic patients without direct hepatic derangements. Thus, sepsis is not considered a cause of acute insult. In conclusion, the difference in the ACLF definition of EASL and APASL is also reflected in whether infection is considered a precipitating factor.

Hemodynamics in patients with ACLF

Hemodynamics in cirrhotic patients is characterized by portal hypertension, hyperdynamic circulation (cardiac output increase, hemangiectasis, and hypoergia), portal-systemic shunt, and decreased renal blood perfusion. During the progression to cirrhosis, changes in hepatic ultrastructure, such as active inflammation, fibrosis, tuberculation, and thrombogenesis, may lead to reduced and altered hepatic circulation that can contribute to the development of portal hypertension. Another possible mechanism is decreased reactivity to vasoactive substance, such as NO. About 40% of vascular resistance is perceived to originate from dynamic and adjustable mechanism, such as hepatic sinusoidal endothelial cell dysfunction, vascular smooth muscle cell contraction, and activation of hepatic stellate cells [36]. The hemodynamic disturbance of ACLF is different from cirrhosis such that the circulation active substances play a more important pathogenic role. For example, high levels of TNF α and NO in ACLF can accelerate hemangiectasis, and diminished cortisol production can decrease vessel sensitivity to vasoconstrictors [4]. So the hemodynamic disturbance is paralleled with the disease severity.

Kumar *et al.* reported that the hepatic venous pressure gradient (HVPG) level in ACLF was between compensated and decompensated cirrhosis [37]. Severe esophageal varices indicated significantly increased HVPG and poor prognosis in ACLF. Increased intrahepatic bloodstream is positively associated with increased fatality rate in ACLF. Garg *et al.* assessed the baseline HVPG in 57 APASL ACLF patients and follow-up HVPG in 24/31 survival patients [38]. The value of HVPG decreased from the baseline value of 16 mmHg (range, 12–30 mmHg) to the follow-up value of 13 mmHg (range, 6–21 mmHg) ($P < 0.05$). Simultaneously, the mean arterial pressure (MAP), cardiac index, and systemic vascular resistance index significantly improved. Multivariable analysis showed that baseline HVPG and HE are independent prognostic factors for mortality. Mookerjee *et al.* observed histopathological changes and HVPG values in 68 alcoholic cirrhosis patients with acute liver deterioration [25]. The levels of HVPG in ALD patients with severe, mild, and without acute alcoholic hepatitis were 23 ± 2.6, 16 ± 0.8, and 15 ± 0.8 mmHg, respectively, indicating the significant difference ($P < 0.05$) in HVPG, depending on the severity of alcohol-related liver injury. The results also indicated that the severity of portal hypertension in these patients was associated with the degree of hepatic inflammation. The fatality rate in patients with HVPG > 20 mmHg was significantly higher than others. The AUC of HVPG for SAH prognosis was 0.67 (0.60–0.81), and the sensitivity and specificity were 0.6 and 0.69, respectively. In another study, Mehta observed systemic and hepatic hemodynamic changes in 60 patients with alcoholic cirrhosis [39]. Among these cases, 27 were stable cirrhosis, 14 were acute decompensation without ACLF criteria, and 19 cases were ACLF according to EASL definition. ACLF patients had the highest HVPG and lowest MAP than the other two groups. The level of HVPG was correlated with the markers of inflammatory response, norepinephrine levels, creatinine levels, and severity of encephalopathy. The AUROC was 0.87 for the prediction of the three-month mortality of ACLF. Rincon *et al.* compared the features of systemic hemodynamics in 60 patients with SAH, end-stage alcoholic cirrhosis, and viral hepatitis-related cirrhosis [40], and the cardiac outputs were 10.1, 8.1, and 7.5 mmHg ($P < 0.001$), respectively. The values of peripheral vascular resistance were 621, 868, and 833 dyn/cm ($P < 0.001$) [5], and HVPGs were 22.8, 20.5, and 19.8 mmHg ($P < 0.05$). No significant difference in MAP was found among the three groups. In addition, the mean HVPG in non-survivors was significantly higher than that in survivors (26.9 mmHg vs. 19.4 mmHg, $P < 0.001$). Four in 31 patients with HVPG $\leqslant$ 22 mmHg died, whereas 19 of 29 patients with HVPG $>$ 22 mmHg died (66%, $P < 0.001$). The independent prognostic factors for in-hospital mortality were HE, MELD, and HVPG $>$ 22 mmHg. In conclusion, the results indicated that portal hypertension and hyperdynamic circulation were the most prominent factors in those with SAH and correlated with the severity of liver injury and poor prognosis.

Liver and other organs involved in ACLF

Multiple organ failure is the major clinical presentation and cause of death of ACLF patients. However, very few studies on the characteristics of multiple organ failure in ACLF have been conducted. The majority of data were collected from patients with cirrhosis.

LF in ACLF

LF, the essential organ failure in ACLF, is characterized by hyperbilirubinemia and dysfunction of coagulation [20]. However, the diagnostic criteria for LF remarkably vary as previously mentioned. In the APASL ACLF guideline [1], the definition of LF includes serum bilirubin $\geqslant$ 5mg/dl and dysfunction of coagulation (INR $\geqslant$ 1.5 or PTA $<$ 40%) plus confirmation of ascites or HE within four weeks (from onset of symptoms). In this guideline, both jaundice and coagulopathy are mandatory elements for diagnosis. However, in the EASL ACLF definition [2], bilirubin $>$ 12 mg/dl is considered the only diagnostic criteria for LF, and coagulopathy (defined as INR $>$ 2.5) is considered a failure of the hematologic system. Patients with bilirubin lower than 12 mg/dl can also be diagnosed as ACLF, if the serum creatinine level is higher than 2.0 mg/dl. According to the EASL criteria, LF is considered a part of multiple organ failure. Clearly, these two diagnostic criteria are quite different, and further studies are needed to determine which criteria are more practical and reliable.

Brain dysfunction

HE is one of the common complications in ACLF patients. Severe HE was proved to be associated with poor prognosis of ACLF [41–43]. The incidence of HE in ACLF remains unclear. In CANONIC study [2], the incidence of HE in the ACLF group was 57.8% (174/301), which was significantly higher than that in patients with decompensated cirrhosis (27.3%, 286/1047).

HE in ACLF is not similar to that in cirrhosis [41]. First, HE is more likely to develop in ACLF patients who are young and suffer from high-grade alcohol abuse, severe LF and SIRS, bacterial infections, and/or dilutional hyponatremia. By contrast, HE in patients with decompensated cirrhosis tends to occur in older individuals, inactive drinkers, patients with absent severe LF or SIRS, and diuretic users. Second, very few ACLF patients with HE develop cerebral edema. In 81 APASL-ACLF patients with

grades III and IV HE, only three patients developed cerebral edema [44]. Third, the pathology differs. The increase in toxic substance (e.g., NH_3) is the most common cause of HE in cirrhotic patients [45]. However, in addition to NH_3, SIRS, circulatory dysfunction, and other organ failure in ACLF patients can directly lead to brain dysfunction [41]. Several possible pathogeneses have been proposed for ACLF-related encephalopathy. For instance, the degradation of claudin protein in cerebral endothelial cells by inflammatory mediators may result in entry of inflammatory factors into brain tissue via increased permeability of the blood brain barrier [46]. Activation of cerebral microglia and synthesis of pre-inflammatory factors may lead to inflammation of brain tissue [47]. As HE is pathophysiologically, clinically, and prognostically distinct, Jalan suggested that HE in patients with ACLF should be classified as type D HE [42], in addition to the original three types of HE (type A: HE in ALF; type B: HE in portosystemic shunts without intrinsic liver disease; and type C: HE in cirrhosis).

Coagulopathy

Limited studies are available on coagulation dysfunction in ACLF. Most results were obtained from research in patients with cirrhosis or ALF. The common presentation of ACLF-related coagulation dysfunction includes hyperfibrinolysis and platelet dysfunction [2]. High INR levels, caused by the decreased synthesis of coagulation factors, are a typical manifestation of ACLF and are definitely correlated with prognosis. In the past, bleeding tendency was a common concern in patients with severe liver diseases. However, bleeding events are rare with adequate platelet count ($> 5 \times 10^9$/L) because of the rebalance of thromboplastic factors and anticoagulant factors. By contrast, some patients may present with the hypercoagulable state. When acute liver injury occurs, low platelet count is very common because the liver is the organ where thrombopoietin is synthesized [48]. The platelet count is restored with the recovery of liver injury, and it is an independent prognostic factor for patient outcome [49].

Adrenal insufficiency

The incidence of adrenal insufficiency in ACLF was not clear. It was reported that it account for 40%−75% cirrhotic patients with renal failure and infection-related sepsis [50–52]. Adrenal insufficiency was associated with instability of hemodynamics. The related fatality rate was higher in patients with adrenal dysfunction than in those without adrenal dysfunction (80% vs. 37%) [51]. It was recognized that glucocorticoid could improve circulation state in septic patients with adrenal dysfunction [52]. However, it remains to be determined whether routine application of glucocorticoid could improve prognosis in patients with ACLF and sepsis.

Kidney dysfunction

Renal dysfunction in ACLF patients may be caused by infection induced renal injury, hypovolemia, hepatorenal syndrome, underlying renal diseases, and drug-induced renal injury. A retrospective study including 562 patients with cirrhosis and renal dysfunction showed that the distribution of the above mentioned causes were 46%, 32%, 13%, 9%, and 7.5%, respectively. The overall three-month fatality rate in cirrhotic patients with renal diseases was 73%. Among the patients who died from kidney dysfunction, 46% were due to hypovolemia, 31% were due to infection-related kidney failure, and 15% were due to HRS [53].

In multiple prognostic models, creatinine is one of the most important prognostic factors in patients with ACLF. This belief is true even in patients with mild renal dysfunction. However, the diagnosis of kidney injury by serum creatinine is affected by various factors, such as baseline creatinine. The International Ascites Association and Acute Dialysis Quality Initiative proposed that the definition of acute kidney injury (AKI) in cirrhotic patients should be diagnosed as the elevation in serum creatinine of more than 0.3 mg/dl within 48 h, or higher than 50% of baseline in the past six months in patients with relatively stable serum creatinine [54,55]. In a cohort of patients with cirrhosis and infection, at least one incidence of AKI was reported in 49% patients during hospitalization, most of whom showed complete recovery [56]. The thirty-day mortality of those with irreversible AKI was 10-fold higher than those without AKI. The negative predictive value for death was 93% based on the new definition of AKI [53]. Other studies also showed that acute small increases in serum creatinine levels are clinically significant in cirrhotic patients in an intensive care unit (ICU) [57,58] and in cirrhotic patients in an ambulatory setting [59]. Other biomarkers of kidney injury, such as neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and serum cystatin C, are also potential renal damage markers [50].

Pathological alteration

Studies on ACLF pathology are few because of the risk of liver biopsy. However, liver biopsy through the jugular vein has been proven to be safe. Pathology is necessary and important in diagnosis and prognosis prediction.

Significance of pathological detection

Despite the absence of a pathological change specific for

ACLF, most hepatologists agreed that a diagnostic liver biopsy is important to diagnose and identify possible underlying causes, as well as predict prognosis for ACLF [1]. For instance, studies showed that the misdiagnosis rate for alcoholic hepatitis can be as high as 10%–20% [60]. Patients with or without baseline cirrhosis may have identical clinical presentation for ACLF but carry very different prognosis, which can only be differentiated by liver biopsy and pathologic assessment [8]. Pathologic evaluation might also be able to distinguish acute injury with chronic damage of the liver. For instance, the pathologic changes for acute liver injury include hepatocyte ballooning, acidophilic change, cholestasis and necrosis or collapse of parenchymal hepatic cells, bile and duct proliferation, whereas the appearance of fiber stripe or spur indicates CLD. Pathologically, the major differences between ACLF and CLIF are existence of acute hepatitis and necrosis, whereas the difference between ACLF and ALF is fibrosis.

Pathological characteristics and significance of ACLF

Pathological indexes of ACLF include hepatocyte lesions, fibrosis, cholestasis, and liver regeneration. Fibrosis will not be discussed further because it is not different from cirrhosis.

Hepatocyte injury

Necrosis of hepatocytes is a typical presentation for ACLF. To date, a consensus definition of massive hepatic necrosis (MHN) and submassive hepatic necrosis (SMHN) has not yet been agreed upon [61]. For example, MHN was defined by some experts as extensive, diffuse panlobular (panacinar) and multilobular necrosis of $>$ 60%–70% of the entire liver or nearly 100% necrosis. SMHN has been used to describe lesions with global necrosis of fuse panlobular cells between 15% and 90% or 30%–70%. Li *et al.* described the characteristic features of hepatic necrosis of 69 HBV-ACLF (EASL definition) in detail. They found that SMHN, defined as necrosis of 15%–90% of the entire liver, is the typical histological feature of HBV-associated ACLF, which differentiates these patients from end-stage cirrhosis [62]. Compared with ALF, ACLF seldom develops MHN because the septa and remodeling vessels serve as useful "barriers" to prevent necrosis from spreading across the cirrhotic liver [61]. In the 69 cases, approximately 17.4%, 65.2%, and 17.4% of these patients had $<$ 33%, 33%–66%, and 67%–90% of necrotic areas, respectively. Morphological alterations mainly included extensive destroyed parenchymal cells and collapsed sinusoids, which were similar to ALF. Necrotic areas were distributed along terminal hepatic veins and spread to parts or most of the cirrhotic nodules. Some cirrhotic nodules still remained even if extensive necrosis spanned multiple adjacent cirrhotic nodules. Variable amounts of infiltrated lymphocytes and monocytes surrounded the ductuals. All the patients underwent transplantation, so the necrosis area, which ranged from 15% to 90%, was not associated with the patients' outcome. However, Rastogi *et al.* reported contradicting results [18]. They retrospectively investigated liver biopsy of 50 ACLF (APASL definition) patients and found that more than 50% hepatocytic necrosis is an independent factor of poor prognosis. They concluded that the degree of necrosis is of clinical significance.

Hepatocyte injury has also been well studied in ASH, and it is the main cause of ACLF in western countries. The predominant pathological characteristics for ASH include hepatic ballooning, inflammation in hepatic lobule, steatosis, cholestasis in bile canaliculi or bile ducts, cholangiolitis, and fibrosis. Hepatic ballooning is induced by damage of intermediate filament (composed of K8 and K18). The formation of K8/K18 deficiency is due to oxidative and nitrification pressure. Hepatic ballooning only occurs in NASH and ASH, and it is seldom observed in other types of hepatitis [25]. Mookerjee *et al.* explored the pathological characteristics of 68 acute decompensated cases with alcoholic cirrhosis. They developed the ASH grading system (0, 1, and 2) based on the NASH grading system combined with quantification of K8/K18 expression: the proportion of hepatocytes deficient in K8/18 less than 1% was grade 0 (37 cases); 1%–10% was grade 1 (14 cases); and higher than 10% was grade 3 (7 cases) [25]. The pathology grading of ASH was closely correlated with prognosis. The AUC of ASH histologic grading was 0.8, with 73% sensitivity and 70% specificity, better than the AUC for SIRS (0.76), Maddrey score (0.71), and MELD score (0.69). However, no relationship was found between ASH and SIRS (P = 0.3). Only 50% clinically diagnosed SIRS patients had histological ASH, whereas 41% patients without clinically diagnosed SIRS had histological ASH. Cholestasis was more common in patients with SIRS (66% were grade 3 or 4 cholestasis). Similar results were also reported by a five-year ASH study [63].

In summary, the pathological changes in ACLF are distinct from those in ALF and cirrhosis. SMHN is the typical sign of HBV-ACLF, whereas hepatic ballooning is mainly reported in ASH. No agreement has been reached on the prognostic significance of liver pathology, and further studies are needed to clarify this problem.

Cholestasis

Cholestasis was observed in almost all published pathological studies for ACLF. Katoonizadeh *et al.* showed through liver biopsy that cholestasis and cholangitis are more common in alcoholic cirrhosis-based ACLF (APASL

definition) (75% and 64%, respectively) than in decompensated cirrhosis (30% and 24%, respectively) [8]. In HBV-ACLF, most patients with SMHN displayed considerable cholestasis in residual cirrhotic nodules, such as various degrees of bile pigments in hepatocytes, as well as canalicular and newly formed ductular cholestasis. These parameters were detected in 81.2%, 87%, and 92.8% of patients with SMHN, which were significantly higher than those without SMHN (7.8%, 9.1% and 7.8%, $P < 0.001$) [55].

Sakhuja *et al.* suggested that cholestasis can be classified into three groups: type I: fine particles in hepatocytes and bile capillary; type II: thick concentrated cholestasis in bile capillary and a small quality of bile thrombi in bile canaliculi in addition to type I changes; and type III: appearance of significant bile thrombi in bile canaliculi with intrahepatic cholestasis on top of type II changes [64]. Cholestasis in bile canaliculi is the severe form of cholestasis, which often occurs with baseline hepatic and bile capillary cholestasis. However, this classification may not be accepted universally until now.

Cholestasis is closely related to infection. For instance, 72% of alcoholic ACLF patients with infection had cholestasis, whereas 39% of patients without infection had cholestasis. Cholestasis is also a risk factor of infection. Among 18 patients who developed infection during hospitalization, 12 (67%) patients had cholestasis at admission; in 35 patients without infection during hospitalization, only eight (23%) had cholestasis at admission [8]. Although cholestasis and cholangitis have been considered as markers of infection, their causal relationship is still unconfirmed. One speculation is that patients with cholestasis have culture-negative minor infection before admission. After admission, these patients develop obvious infection in a short time period, followed by increased risk for SIRS. The other possibility is the absence of infection at admission in these patients, but cholestasis is a forerunner and risk factor for infection. Studies on septic patients indicated that infection may influence the transportation function of bile canaliculi, leading to cholestasis [65]. Other studies also similarly demonstrated that SIRS is positively related to cholestasis [25].

Liver regeneration

The regenerative response of the liver to injuries involves proliferation of cells in different lineages: (1) matured hepatocytes "committed" cells, contributing to normal cell turnover and responding rapidly to liver injury; and (2) the hepatic progenitor cells (HPCs), located in the canals of Hering, can be activated when loss of hepatocytes is massive or combined with inhibition of the proliferative capacity of hepatocytes [66]. HPCs activation are associated with the degree of hepatocyte loss. When hepatocyte loss is $> 50\%$, the proliferative ability of matured hepatocytes declines, followed by activation of ancestor cells. Therefore, the activation of HPCs can be a sign for poor prognosis in these patients [67]. In transplanted HBV-ACLF patients, much higher amounts of HPCs and ductular reactions were noted than cirrhosis liver. Regenerative cells can mature into intermediate hepatocytes, and CK-7-positive cells were much higher in the ACLF liver than in the cirrhotic liver [62]. Katoonizadeh *et al.* compared biopsy-confirmed hepatocyte regeneration in alcoholic ACLF and chronic liver diseases. They found that the ancestor cells were activated, but few divided into hepatocytes in both groups. These findings indicated that inhibitor(s) may exist for hepatocyte regeneration in cirrhosis and ACLF patients [8]. In patients with ALD, the depression of liver regeneration is associated with oxidative injury induced by alcoholism [8].

Pathological classification of ACLF

The histological changes in ACLF have been classified into two types by APASL based on the study by Sarin *et al.* [1]. The main features of type I include hepatocyte ballooning, rosette formation, hepatic cholestasis, interface inflammation, and fibrosis with various degrees. The main features of type II include significant proliferation of bile ducts, high concentration of bile thrombi, fusion or bridging necrosis, hepatic acidophile retrogression, severe fibrosis, and active inflammation. The prognosis in patients with type II ACLF is worse than that in patients with type I [64].

Prognosis

In theory, the outcomes and reversibility of ACLF depend on the acute precipitating factors, degree of liver injury, and severity of baseline liver disease [1]. The APASL definition states that LF is the core element of ACLF. However, the EASL-AASLD guidelines emphasize multiple organ failure. Accordingly, three types of models have been generated to predict the outcome for ACLF: liver-specific model (i.e., CTP, MELD, and Kings' college criteria), general model (i.e., SAPS II and APACHE), and organ failure model (i.e., OSF, SOFA, and CLIF-SOFA) [68]. The MELD score has been studied extensively and is currently used widely. Studies have indicated that CLIF-SOFA may be superior to other prognostic models in ACLF, severe cirrhosis, ICU patients with underlying liver diseases, and patients after liver transplantation [69–76]. A simplified organ function scoring system (CLIF Consortium Organ Failure score, CLIF-C OFs) combined with two other independent predictors of mortality (age and

WBC) was used to develop a specific prognostic score for ACLF, which was named the CLIF Consortium ACLF (CLIF C) score [77]. The AUROC was 0.79 (0.73–0.85), which was significantly higher than those of MELD, MELD-Na, and CTP. Recently Gustot *et al.* investigated the clinical course of ACLF and found that assessment of ACLF patients at 3–7 days of the syndrome, not assessment at the baseline, is better in defining the emergency of LT and intensive care discontinuation because of futility [78].

Other prognostic indicators, including indocyanine green removal experiment, diethylarginine grading, serum Gc globulin, and HMGB-1, have been reported, but further studies are needed to determine their predictive value. Lin *et al.* established a dynamic prognostic model for nucleoside analog (NA)-treated patients with HBV-related ACLF, which consisted of bilirubin, PTA, PLT, anti-HBe, one-week change in bilirubin and PTA [49]. Thus, the severity of disease and response to treatment were both considered in this model. The AUC was 0.856, which was significantly higher than that of the MELD and MELD-Na scores.

Management for ACLF

The mainstay therapy and complication management for ACLF are similar to those for decompensated cirrhosis. However, the fatality rate of ACLF is still high even with good ICU supportive care. Timely specific and effective treatment for the cause of the disease, such as anti-viral therapy for HBV infection and immunosuppressive therapy for autoimmune hepatitis, is essential.

Drug therapy

Drug therapy can focus on both underlying etiology and pathogenesis of ACLF.

Antiviral therapy in HBV-related ACLF

HBV replication may lead to LF in patients with chronic hepatitis B or HBV cirrhosis. Three meta-analysis papers published recently reported that NA can significantly decrease the fatality rate of HBV-related ACLF.

The first meta-analysis included 11 randomized controlled trials (one from India and 10 from China, APASL definition) [79]. A total of 654 HBV-related ACLF cases were included. Among them, 340 patients were given NA, such as lamivudine (LMV), entecavir (ETV), telbivudine, or tenofovir, and the remaining 314 patients were given placebo or nothing. The general analysis indicated that NA treatment significantly improved the survival rate in one [OR = 2.01, 95% CI (1.29–3.41), $P = 0.003$], three [OR = 2.15, 95% CI (1.26–3.65), $P = 0.005$], and 12 months [OR = 4.62, 95% CI (1.96–10.89), $P = 0.005$]. HBV DNA significantly declined after three months of NA therapy [OR = 54.47, 95% CI (16.37–201.74), $P < 0.00001$]. The incidence of HBeAg seroconversion was significantly higher in the treatment group than that in the control group [OR = 6.57, 95% CI (1.64–26.31), $P = 0.008$]. The second paper included 21 studies (all from China); the survival rate of the LMV group at four, eight, and 12 weeks were significantly higher than those in the control group. However, NA treatment was only effective in patients with early- and medium-stage ACLF [80]. The third meta-analysis involved five studies of ACLF using the APASL criteria [81]. The three-month fatality rate of ACLF patients with NA therapy was lower than that in the control group [44.8% vs. 73.3%, RR = 0.68, 95% CI (0.54–0.84), $P < 0.01$]. The effect of ETV or LMV was similar [36.4 vs. 40.5%, RR = 0.77, 95% CI (0.45–1.32), $P = 0.35$]. No HBV medication-associated adverse events were observed during follow-up.

Granulocyte colony-stimulating factor (GCSF) in ACLF management

GCSF is the most common bone marrow mobilization factor in clinical practice. Mobilized bone marrow stem cells show better engrafting ability and longer lifetime. GCSF has been widely used to treat septic patients to improve immunity, and several studies showed that it is also effective in ACLF. GCSF commonly peaks at 4–7 days after injection in ALF patients [82]. In a small study, 24 cirrhotic patients with acute liver dysfunction patients were randomly assigned into the standard therapy group, low-dose GCSF group (5 $\mu g \cdot kg^{-1} \cdot d^{-1}$), and high-dose GCSF group (15 $\mu g \cdot kg^{-1} \cdot d^{-1}$) for 6 days of therapy [83]. The $CD34^+$ count increased significantly in the two groups that received GCSF since the second day, comparable with the healthy people at the same age. However, at day 5 after GCSF injection, the elevation in $CD34^+$ cells in healthy people was significantly higher than that in ACLF patients, and GCSF was not associated with a significant improvement in liver function in this study. In another study [84], 24 patients with liver biopsy-confirmed ASH were randomly assigned into the GCSF treatment group (10 $\mu g \cdot kg^{-1} \cdot d^{-1}$, $n = 13$) or control group ($n = 11$) for 5 days. At day 7, the circulatory $CD34^+$ cells (747% vs. −6%, $P < 0.003$) and hepatic growth factor (212% vs. −7%, $P < 0.003$) were significantly increased in the treatment group. The second liver biopsy showed that the proliferation of HPCs in the treatment group was 50% higher than that in the control group (11 vs. 2, $P < 0.003$). The increasing extent of Ki67-positive and CK-7-positive cells was correlated with the change in $CD34^+$ cells ($r = 0.65$, $P < 0.03$). The 12-week fatality rate, infection rate, and upper gastrointestinal hemorrhage in the treatment group

were 1, 3, and 1/13, respectively, whereas those in the control group were 0, 4, and 1/11, respectively. Garget *et al.* [85] randomly divided ACLF (EASL criteria) patients into the GCSF 12-dose treatment group (group A, 5 $\mu g \cdot kg^{-1}$, $n = 23$) or placebo group (group B, $n = 24$). After one week of therapy, the mean WBC and neutrophil counts were significantly higher in group A than those in group B ($P < 0.001$). Sixteen cases in the treatment group and seven in the control group survived. The 60-day survival rates in the treatment and control groups were 66% and 26%, respectively ($P = 0.001$). The CTP score, MELD score, and SOFA score in group A were all better than those in group B at day 60. The incidences of hepatorenal syndrome, HE, and sepsis in group A were lower than those in group B [19% vs. 71% ($P = 0.0002$), 19% vs. 66% ($P = 0.001$), and 14% vs. 41% ($P = 0.04$)]. One month after treatment, the amount of intrahepatic $CD34^+$ cells in group A was significantly higher than that in group B. In another randomized study [86] (APASL definition), 27/55 patients in the treatment group were given GCSF (5 $\mu g \cdot kg^{-1}$ for 6 days), whereas 28 patients in the control group received standard therapy only. The results showed that the number of peripheral neutrophil and $CD34^+$ cells elevated from day 3 to day 7 in the GCSF treatment group. On day 15, the cell numbers were still higher in the treatment group than in the control group. The Child-Pugh score in the treatment group was better than that in the control group at day 30. The MELD score was significantly lower than baseline from day 7 to day 30 ($P = 0.004$). The three-month survival rate in the treatment group was significantly higher than that in the control group (48.1% vs. 21.4%, $P = 0.02$). In conclusion, previous studies have indicated that GCSF can improve the survival rate of ACLF patients by promoting liver regeneration and improving immune function [82].

Hormonotherapy

Corticosteroids are often used in ALF treatment because of the importance of immune injury at early-stage ALF [87]. However, its application should be restricted because of the related side effects, particularly secondary infection. The usage of corticosteroids in ACLF remains under great controversy.

Zhang *et al.* studied the effects of dexamethasone at the prophase stage of HBV-related ACLF [88]. The enrollment criteria were bilirubin over 10 mg/dl, ALT $\geqslant$ 5 ULN, and PTA $\geqslant$ 40%. Those patients were speculated to develop ACLF. A total of 170 patients were non-randomly divided into the treatment group and the control group at a 1:2 ratio. Patients in the treatment group were prescribed dexamethasone (10 mg/d) for 5 days. Compared with the control group, the treatment group had significantly lower incidence of ACLF (8.9% vs. 70.2%) and higher survival rate (96.4% vs. 52.6%, both $P < 0.001$). Dexamethasone treatment was revealed as an independent factor influencing the survival rate ($P < 0.001$, OR = 0.055, 95% CI = 0.013–0.225). During four weeks of treatment, serum bilirubin levels in the survived patients were significantly lower in the treatment group than in the control group. In another non-randomized study [89], 30 HBV-ACLF (APASL definition) patients were enrolled in the treatment group (methylprednisolone for 10 days), whereas 26 patients were used as controls. The 28 day mortality rate in the treatment group was much lower than that in the control group (35% vs. 45%). All treated patients exhibited an initial rapid decrease in circulating mDC numbers, and mDC continued to increase in survived patients. They suggested that a higher baseline mDC level and recovered mDC level at the end of treatment may represent a prognostic marker for favorable response to corticosteroid treatment in ACLF patients. Another study from China showed that corticosteroids have no effect on ACLF [90]. Among 134 HBV-ACLF patients, 31 were prescribed with dexamethasone. The 12-week survival rates were 45.7% (16/35) and 48.4% (15/31) in the control and treatment groups, respectively ($P = 0.959$). In addition, no significant difference in MELD score and complications (i.e., infection, gastrointestinal bleeding, encephalopathy, hepatorenal syndrome, and ascites) was determined. As these studies might include different underlying etiologies and was diagnosed according to different criteria, further standardized studies will be needed to assess whether steroid treatment is beneficial to ACLF.

Artificial liver therapy

Artificial liver therapy may be beneficial to ACLF, because of ACLF's reversibility and longer treatment window period than ALF. Research on bioartificial liver technology is currently underway. The non-bioartificial liver system has been widely used in clinical practice, such as molecular adsorbent recirculating system (MARS) and fractionated plasma separation and adsorption (FPSA). Previous studies have indicated that MARS is effective on HE in patients with cirrhosis and hepatorenal syndrome [91–94]. However, a recent study on ACLF reported that MARS does not improve the survival rate of ACLF (non-EASL non-APASL criteria) [95]. The largest randomized controlled study to date on FPSA therapy in ACLF was published in 2012 (non-EASL non-APASL criteria) [96]. A total of 145 cases were involved in this study (77 in the treatment group and 68 in the control group), and 72 patients completed treatment with 585 times of therapy in total. Intent-to-treat analysis showed no difference of the fatality rate at day 28 and day 90 between the two groups. However, FPSA could improve the survival rate in a subgroup with MELD over 30. The 28-day survival rates of the treatment group and

control group were 42% (10/24) and 57% (28/48), respectively, and the 90-day survival rates were 9% (2/24) and 48% (23/48), respectively (P = 0.02). In 45 patients with type I HRS, FPSA showed some effect: the 28-day and 90-day survival rates were 62% vs. 39% and 42% vs. 6% (P = 0.04). However, after adjusting by independent prognostic factor, the difference was no longer significant. A new large-scale clinical research on FPSA treatment in HRS is in progress in Berlin Charite University (LUTHER research) to evaluate the value of FPSA in treating HRS.

Apparently, these studies were all disappointing, but they assessed patients with late-stage ACLF in serious condition (all had extrahepatic organ failure) and had minimal chance for liver regeneration. Thus, future studies should include patients with early-stage ACLF, such as APASL ACLF.

Liver transplantation

In the past, ACLF patients were often excluded from the liver transplantation waiting list because of excessively serious conditions [6]. In recent years, an increasing number of studies indicated that ACLF is one of the suitable indications for liver transplantation. Although the pre-transplantation MELD score in ACLF patients is much higher than that in patient with end-stage cirrhosis, the post-transplantation complications and both short-term and long-term survival rates are similar. The post-liver transplantation five-year survival rate in ACLF patients was 80%–90% [97–101]. However, the mortality rate was high in ACLF patients on the waiting list, as the window period for liver transplantation was usually narrowed in these patients [102]. These findings provided the rationale that ACLF patients should be offered a higher priority when placed on the waiting list for liver transplantation. Given that a MELD score that does not deteriorate by week 2 would predict 93.8% chance of survival for the next 60 days, these patients may not need to be in the waiting list for liver transplantation [103].

All ACLF patients have high risks for bacterial and fungal infections or sepsis, which may result in contra-indication for liver transplantation or make post-transplantation care more complicated [104,105]. The MAP of these recipients should be above 50–60 mmHg. Patients with unstable hemodynamics or in need of high doses of cardioactive drugs are not appropriate for transplantation [1]. In addition, patients with increased intracranial pressure (ICP) and decreased MAP-ICP are also excluded from liver transplantation in some medical centers. Although HRS is controlled by terlipressin, those patients should receive liver transplantation as soon as possible. However, patients with anuria are not appropriate for liver transplantation [1].

At present, the method of predicting the post-transplantation survival rate remains unclear. In some studies, the MELD score was reported to be better than CTP in predicting post-transplantation outcomes (AUC values were 0.84 and 0.747, respectively) [106]. But Duan's research showed that none of the scores, SOFA, MELD, and CTP scores are good enough in predicting the post-liver transplantation survival rate (AUCs were 0.552, 0.547, and 0.547, respectively) [101].

Summary

In summary, ACLF, a serious disease with high short-term fatality rate, has recently gained considerable attention worldwide. However, the definition, diagnosis, pathogenesis, management, and prognosis of this complicated and life-threatening disease remain controversial. Liver transplantation is still the major life-saving modality. To better define the natural history and develop more effective treatment, further studies are urgently needed, specifically prospective controlled multicenter studies, including a large cohort of subjects with different underlying etiologies of ACLF worldwide.

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Compliance with ethics guidelines

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