Acute-on-chronic liver failure: a clinically important new syndrome

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Received 17 February 2018
Accepted 22 February 2018

Journal of Current Medical Research and Practice
January-April 2018, 3:6–21

Acute-on-chronic liver failure is a new syndrome characterized by multiple organ (s) failure and high short-term mortality. This review article focuses on the definitions, diagnosis, and different treatment options for this syndrome. Patient education, anticipation, early identification of the acute insult, and early detection of chronic liver disease would be immensely helpful to prevent the disease.

Keywords:
acute-on-chronic, liver failure, syndrome

J Curr Med Res Pract 3:6–21

2357-0121

Introduction

Acute-on-chronic liver failure (ACLF) is an increasingly known syndrome of acute deterioration of liver function in patients with cirrhosis. This rapid deterioration is rapidly progressive and is associated with multiple organ failures, resulting in high short-term and medium-term mortalities, up to 90% [1].

Development of definition and scoring systems for acute-on-chronic liver failure

To clarify the meaning of ACLF, the Asia-Pacific Association for the Study of the Liver (APASL), a joint conference of the European Association for the Study of the Liver (EASL), and the American Association for the Study of Liver Diseases (AASLD) suggested a definition of this condition. The first definition was developed by APASL in 2009 [2], '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 to have chronic liver disease', and the second one was announced in 2012 at an EASL-AASLD symposium [3], 'Acute deterioration of pre-existing, chronic liver disease, usually related to a precipitating event and associated with increased mortality at 3 months owing to multisystem organ failure.'

The variances between the two definitions have caused confusion rather than clarification. Furthermore, they lack definite clinical signs and laboratory results determining the ACLF. The proper definition for ACLF should meet the following criteria: (i) the condition should be discrete from acute liver failure (ALF), (ii) different from 'decompensated cirrhosis', (iii) pathophysiology should be clear, (iv) specific clinical signs and laboratory or other assessments that settle the diagnosis and dismiss other diseases should be specified, and (v) an authorized clinical scoring system to assess the severity of ACLF should be existing [4]. To obtain these required criteria, it was necessary to have prospective studies, collecting a large number of validated data from patients with chronic liver diseases (with and without cirrhosis) [4].

In 2013, the CANONIC study defined ACLF grades, assessed mortality, and identified differences between ACLF and acute decompensation (AD) using data of 1343 in-hospital patients with liver cirrhosis and AD in 29 European hepatology units. It also established diagnostic criteria for ACLF based on analysis of patients with organ failure [5]. In this study, the authors developed Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) score by modifying the Sequential Organ Failure Assessment score to define the diagnostic criteria for organ failures (Table 1). This score ranges from 0 to 24, and graded into four grades according to the number of organ failures: (i) no ACLF, (ii) ACLF-1, (ii) ACLF-2, and (iv) ACLF-3 [5].

CLIF-SOFA score was updated in 2014 to be Chronic Liver Failure Consortium Organ Failure (CLIF-C OF)

score, as shown in Table 2, by setting two new cutpoints to discriminate three clinical severity classes that were directly related to high-mortality rates at 28 days [6]. The new score ranges from 6 to 18, but it is also graded into four grades like CLIF-SOFA score as follows: ACLF-1 – one organ failure, ACLF-2 – two organ failures, and ACLF-3 – three to six organ failures. The new cutoff values increased the ability to predict 28-day mortality [6].

CLIF-C OF score excluded and included from the diagnosis of ACLF the following:

(1) Excluded:
   (a) No organ failure
   (b) Single nonrenal organ failure with serum creatinine (sCr) less than 1.5 mg/dl and no hepatic encephalopathy (HE).
(2) Included:
   (a) One renal failure
   (b) Single nonrenal organ failure plus renal dysfunction and/or grade 1–2 HE
   (c) Two or more organ failures.

Epidemiology

Data about the epidemiology of ACLF is scarce up till now. The rarity of such data is owing to the lack of a universally accepted definition for ACLF, which hinders conducting epidemiological studies for this entity. The majority of what we know about the prevalence and natural history of ACLF comes from the CANONIC study [7]. ACLF was considerably more prevalent in younger patients and those who had cirrhosis secondary to alcohol or hepatitis B. The most common precipitating factors were infections, active alcoholism, and hepatitis B reactivation. The 28-day mortality was directly proportional to the number of failed organs and varied between 22 and 73%. Mortality was not related to the presence or type of precipitating event, but the early clinical course was the most crucial factor of prognosis. Liver transplantation improves 1-year survival to 80% [8].

Is it important to discriminate between acute-on-chronic liver failure and decompensated cirrhosis?

Patient with chronic decompensation of cirrhosis will develop organ dysfunction at some point during the progression of their liver disease. Usually, this occurs in advanced stages of liver disease where liver transplantation is the only option for treatment, and the chances of reversibility of liver disease are very narrow [9]. This is not the same situation in patients

Table 1 Chronic Liver Failure-Sequential Organ Failure Assessment score

Organ	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	I	II	*III*	*IV*
Coagulation (international normalized ratio)	<1.1	>1.1-1.25	>1.25 to <1.5	>1.5 to <2.5	*>2.5 or platelet count <20 × 109/l*
Circulation (mean arterial pressure) (mmHg)	>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	>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*

The italicized values describes criteria for diagnosing organ failures. E, epinephrine; FiO_2, fraction of inspired oxygen; HE, hepatic encephalopathy; NE, norepinephrine; PaO_2, partial pressure of arterial oxygen; SpO_2, pulse oximetric saturation.

Table 2 Chronic Liver Failure Consortium Organ Failure score

Organ	Subscore=1	Subscore=2	Subscore=3
Liver (bilirubin) (mg/dl)	<6.0	>6.0 to <12.0	*>12.0*
Kidney (creatinine) (mg/dl)	<2	*>2 to <3.5*	*>3.5 or renal replacement therapy*
Cerebral (HE grade)	0	1-2	*3-4*[a]
Coagulation (international normalized ratio)	<2.0	>2.0 to <2.5	*>2.5*
Circulation (mean arterial pressure) (mmHg)	>70	<70	*Use of vasopressors*
Lungs			
PaO_2/FiO_2	>300	<300 and >200	*<200*[b]
SpO_2/FiO_2	>357	<357 and >214	*<214*[b]

The italicized values describes criteria for diagnosing organ failures. Italicized data means organ. HE, hepatic encephalopathy; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; SpO_2, pulse oximetric saturation. [a]Patients submitted to mechanical ventilation due to HE and not due to a respiratory failure were considered as presenting a cerebral failure (cerebral subscore=3). [b]Other patients enrolled in the study with mechanical ventilation were considered as presenting a respiratory failure (respiratory subscore=3).

with ACLF who may often have a good liver reserve and can deteriorate acutely over a short period, usually in association with a precipitating illness that results in organ failure and high risk of death. Some patient may also be in a stable condition despite being in advanced stages of liver disease and deteriorate acutely following a precipitating event progressing to organ failure. By contrast, this patient has a better chance to return to his stable condition, before the acute event [9]. So, it is necessary to differentiate between ACLF and chronic decompensated cirrhosis.

Evolution of a scoring system for patients diagnosed as having acute decompensation but no acute-on-chronic liver failure

A score called the Chronic Liver Failure Consortium Acute Decompensation (CLIF-C AD) was developed for hospitalized patients with cirrhosis without ACLF using the CANONIC data [10]. The reason for developing this score was based on the hypothesis that some patients with AD but no ACLF have a very low risk to develop ACLF, whereas others have a high risk to develop full-blown ACLF and therefore have a high-mortality rates. This score has five independent variables, including age, serum sodium, white cell count, creatinine, and international normalized ratio, and it ranges from 0 to 100. The CLIF-C AD performance is significantly better than the Model for End-Stage Liver Disease (MELD), MELD-sodium, and the Child–Pugh scores in predicting 3- and 12-month mortality. The CLIF-C AD is a better indicator of mortality by 10–20% over these other scoring systems. Moreover, distinct values for CLIF-C AD were developed, for example, a score of less than or equal to 45 was associated with a very low risk of 3-month mortality. The score also identified a high-risk group that has a score 60 or above having a 3-month mortality in ~31% of patients. The intermediate-risk group includes patients with a CLIF-C AD score of more than 45 and less than 60 [10].

Pathogenesis

The PIRO concept (Fig. 1), which is used as a staging system for sepsis, may help in determining pathogenesis and prognosis in patients with ACLF. 'P' is for predisposition, indicating the severity of the underlying illness. 'I' represents injury by a precipitating factor and its severity. 'R' is response by the host to injury, which determines the severity of inflammation, and 'O' is organ failure that occurs as a sequel to previous events. Categorization of patients into these entities helps in defining the pathogenesis, possible interventions, and prognosis at different levels [9].

Figure 1

The PIRO concept of acute-on-chronic liver failure.

(P) Predisposition

No available data support the hypothesis that patients with more severe liver disease (high MELD score or advanced Child–Pugh Score) have a worse outcome than patients with better conditions as in the case of prediction of postoperative mortality. The most valuable predictors of postoperative mortality were the high MELD score, age, and the American Society of Anesthesiologists score [11]. Patients with cerebral edema may die immediately after surgery despite having low MELD score [12].

(I) Injury by precipitating factors

ACLF usually develops after a precipitating factor on top of established cirrhosis. This precipitating factor may be hepatic; alcoholic hepatitis, superimposed viral hepatitis, drug-induced liver injury, portal vein thrombosis, and ischemic hepatitis, or extrahepatic factor such as variceal bleeding, infection, trauma, and surgery. In some patients, no precipitating factors could be identified. The best studied precipitating events for ACLF are superimposed viral hepatitis, surgery, and infection [9].

Hepatitis B virus (HBV)-related ACLF generally develops in two clinical scenarios: first, HBV reactivation on top of chronic HBV infection and chronic liver disease, and second, acute HBV infection on top of chronic liver disease of any etiology [13]. HBV reactivation leads to hepatic decompensation in up to 8% of cases [14]. Hepatic decompensation is more common in patients infected with HBV genotypes B and D, but the frequency is similar in hepatitis Be antigen-positive or hepatitis Be antigen-negative patients. Reactivation of HBV is thought to be owing to alterations in the immunological control of viral replication and reconstitution of host defense. Liver injury is mediated by increased numbers and overactivity of T cells [15]. HBV reactivation leads to increased numbers of HBV-specific $CD8^+$-T-cell numbers with decreased expression of programmed cell death protein 1; resulting in severe liver damage [16,17]. Patients with HBV reactivation and ACLF showed better survival rates when they are treated with tenofovir [18].

Acute hepatitis A viral infection is associated with increased risk of liver failure development and

death [19]. Hepatitis E virus (HEV) is a frequent cause of liver failure in Southern and Central Asia, China, Africa, and the Indian subcontinent [20–22] and leads to rapid hepatic decompensation and death [23]. Large studies from India report high-mortality rates in patients with HEV-related ACLF and ALF [23,24].

The involvement of HEV in precipitating ACLF in the West is not known, as these patients are not routinely tested for HEV, and the prevalence of HEV infection is generally sporadic [25]. HEV infection causes cell-mediated immune injury and hepatocyte damage, with high cytokine levels produced by type 1 and type 2 T-helper cells [26,27]. Moreover, acute hepatitis owing to new HEV infection can contribute up to 20% of acute exacerbations of chronic hepatitis B [28]. Superinfections with hepatitis A virus (HAV) and HEV lead to the development of liver failure. HEV infection is associated with a more severe form of ACLF with higher mortality than those infected with HAV [29,30]. So it is thought that acute HAV and HEV may also lead to the development of ACLF. Further studies are required to evaluate the prevalence of acute HAV and HEV as a precipitating factor for ACLF.

The liver is the main organ for biotransformation of drugs and metabolites; therefore, drugs are one of the most common precipitants of liver failure. Data related to drug-induced ACLF is limited. Devarbhavi *et al.* (2010) [10] reported high mortality (17.1%) in a cohort of patients with cirrhosis with ascites and encephalopathy who developed severe drug-induced liver injury. In a multinational Asian study of 660 patients, drug-induced liver injury contributed as a precipitating factor for ACLF in 9.1% of patients, and the cause in 53.3% of them was attributed to anti-tuberculosis drugs [31]. Antibiotics and antiepileptic drugs account for more than 60% of patients with drug-induced liver injury. Patients with cirrhosis are more susceptible and less likely to recover from drug-induced liver injury owing to reduced hepatic drug clearance, abnormal metabolism, altered excretion, and/or impaired adaptive responses, and high free-circulating drug levels owing to low albumin [32].

Whether to consider acute variceal bleeding as a precipitating factor for ACLF or a form of decompensation of underlying chronic liver disease is debatable [13]. Acute variceal bleeding was considered a precipitating event in 13.8% of patients in the CANONIC study [5] and 28% of cases in another study [33]. If we can say that variceal bleeding leads to hepatic ischemia, then we can consider variceal bleeding a precipitating factor for ACLF [34].

Bacterial infections are more frequent in patients with cirrhosis than in the general population [35–39]. Cirrhosis is associated immune deficiency syndrome, an evolving concept relates to a relative incompetence of the innate and adaptive immune system in patients with cirrhotic. This syndrome is responsible for the decreased ability to immunize against or eradicate infectious agents in comparison with those without cirrhosis [40]. In this context, an acute insult and ongoing hepatocellular injury, as seen in ACLF, would lead to an aberrant host inflammatory response, SIRS, and infection [13].

(R) Response

The response to the precipitating factors that affect patients with cirrhosis occurs in the form of systemic inflammatory response syndrome (SIRS). The definition of SIRS was introduced by the American College of Chest Physicians and the Society of Critical Care Medicine in 1992. The idea behind defining SIRS was to define a clinical response to a nonspecific insult of either infectious or noninfectious origin [41]. SIRS is defined as two or more of the following variables:

(1) Fever of more than 38°C (100.4°F) or less than 36°C (96.8°F)
(2) Heart rate of more than 90 beats/min
(3) Respiratory rate of more than 20 breaths/min or arterial carbon dioxide tension of less than 32 mmHg
(4) Abnormal white blood cell count [>12 000 or <4000/μl or >10% immature (band) forms] [41].

The effect of SIRS on the prognosis of patients with hepatic failure was described for the first time in cases with ALF. In cases with ALF, the presence of SIRS was associated with more severe encephalopathy, associated infection, renal failure, and poor outcome [42–44]. Patients with ACLF showed raised levels of multiple proinflammatory and anti-inflammatory cytokines [45]. More recently, the mortality rates in patients with cirrhosis presenting with renal impairment were significantly higher in the group with SIRS [46,47].

The interaction between the SIRS and infection may lead to immune dysfunction, which may predispose to another infection that would then further aggravate a proinflammatory response resulting in a vicious cycle [48]. This multimodal immunological response was observed in cases with ACLF and severe sepsis, and it is characterized by an initial SIRS response followed by a mixed anti-inflammatory response syndrome) and subsequently compensated anti-inflammatory response syndrome. The underlying mechanism of this phenomenon is not clear up till now, but immune paresis has been suggested as a possible mechanism [49–51].

(O) Organ failures

Organ failures occur as a sequel to the previously mentioned events. It is known from the definition of ACLF that it is associated with multiple organ failures, which is responsible for the high rate of mortality [5]. These organ failures include liver, kidney, brain, cardiac, circulatory, coagulation, and respiratory.

Liver failure

Hyperbilirubinemia and coagulopathy are the hallmarks of the liver failure in cases with ACLF, but the pathophysiological basis is uncertain [1,5,9]. Patients with alcoholic cirrhosis who developed ACLF exhibited hyperbilirubinemia and SIRS in recent studies [52,53]. The investigators observed that the presence of cholestasis was associated with an increased risk of subsequent infection [52]. Another study confirmed that increased bilirubin level is linked to increased risk of infection. The investigators also observed that K8/18 immunostaining was reduced indicating the loss of cellular actin and microtubular structure, which was associated with worse prognosis [54]. At present, there is no clarity on the mechanism of hepatic cell death or regenerative capacity in patients with ACLF. An early biopsy may aid understanding these mechanisms, which in turn will help in the management of patients with ACLF, like new drugs, such as pan-caspase inhibitors or stimulators of hepatic regeneration [55].

Liver inflammation is an important cause for increased portal pressure and subsequently it affects the prognosis of cirrhosis. Patients with ACLF on top of alcoholic hepatitis have increased plasma tumor necrosis factor (TNF)-α level and the higher portal pressures. Anti-TNF-α therapy reduces portal pressure in patients with severe alcoholic hepatitis and cirrhosis [56]. Several studies proved the role of gut-derived endotoxemia in the pathogenesis of portal hypertension [57]. The use of antibiotics such as quinolones and rifaxamin has been associated with a reduction in inflammation and portal pressure by reduction of the portal bacterial load [58,59]. Moreover, neutralization of endotoxins with the administration of high-density lipoproteins has been associated with a reduction in portal pressure [60]. Patients with ACLF showed increased levels of reactive oxidant species, particularly superoxide, leading to increased intrahepatic resistance by reducing the bioavailability of nitric oxide (NO) [61]. In patients with ACLF, defined according to APASL criteria, no differences in the portal hemodynamics between decompensated cirrhosis and ACLF were observed [62], but using the EASL-AASLD definition, the portal pressure was markedly higher [63] in those with ACLF.

Patients with ACLF have reduced activity of hepatic endothelial nitric oxide synthase (NOS) in the presence of cirrhosis with superadded inflammation [64]. NOS activity is regulated by a number of inhibitors such as asymmetric dimethylarginine, which is increased during inflammation, resulting in high asymmetric dimethylarginine levels [65]. This has been suggested as both a prognostic marker and a possible target of therapy [9,65]. Recent studies suggest that there is reduced response to NO in cirrhotic livers, in addition to the decreased production of NO. The dysfunction of the cyclic GMP system in patients with cirrhotic is responsible for the reduced response to NO in patients with liver cirrhosis [66]. Phosphodiesterase-5 inhibitors such as sildenafil, which increase cyclic GMP, have been shown to have a beneficial effect on reduction of intrahepatic resistance [66].

Kidney dysfunction

Acute kidney injury (AKI) is a common feature in patients with ACLF [5]. AKI in cirrhosis is defined as (i) an increase in sCr of more than 0.3 mg/dl (26.5 μmol/l) within 48 h or (ii) raised sCr by more than 50% from the baseline or presumed to have developed within the previous 7 days [67]. Oliguria is not included in the current definition of AKI in patients with cirrhosis, but urine output has been found to be a sensitive and early marker for AKI in ICU patients and to be associated with poor outcomes [68–70]. Thus, worsening of oliguria or development of anuria should be considered as AKI in patients with cirrhosis until proven otherwise, regardless of any increase in sCr [71].

Presence of AKI is associated with increased 7-day mortality [72]. AKI causes in patients with cirrhosis may be classified into (i) prerenal causes [prerenal azotemia and hepatorenal syndrome (HRS), (ii) renal causes (glomerulonephritis, acute tubular necrosis, and acute interstitial nephritis), and (iii) postrenal causes (benign prostatic hypertrophy and abdominal compartment syndrome) [71]. HRS is one of the commonest causes of renal impairment in patients with cirrhosis [73–75]. HRS is thought to be secondary to circulatory dysfunction in which there is splanchnic vasodilatation, resulting in lowering of arterial blood pressure, intense renal vasoconstriction, impaired cardiac function, and marked activation of the sympathetic and neurohormonal systems [75–77].

The characteristics of renal impairment that occurs in association with ACLF is variable. Thus, circulatory changes may be predominant in some patients, whereas in others, there may be an increased synthesis of proinflammatory mediators, or both events may

occur concomitantly. In ~30–40% of patients with cirrhosis and renal dysfunction, spontaneous bacterial peritonitis (SBP) is the precipitating cause [76]. Infection was present in 56% of patients with renal impairment and SIRS, and this was a major independent indicator of mortality in those patients [47]. Administration of terlipressin and albumin remains the current gold standard for treatment of patients with HRS, but it is successful in only 46% of patients [78]. The lack of response to terlipressin and albumin in more than 50% of patients with HRS may be owing to the predominance of other factors than the vascular theory.

Usually, renal impairment has been suggested to be reversible with transplantation unless there is tubular lesion. Recent data suggest that patients who are transplanted with evidence of renal tubular injury on top of cirrhosis usually require renal replacement therapy after transplantation than patients undergoing transplantation with HRS [79].

Improvement of renal impairment with the use of anti-inflammatory agents such as albumin, pentoxifylline, and *N*-acetylcysteine clarifies the important role of inflammation in the pathophysiology of renal dysfunction associated with liver failure [80,81]. The role of albumin in this situation is mainly anti-inflammatory, and it has been shown to protect the kidney during SBP, resulting in better survival rates in patients with renal failure [82,83]. Moreover, using norfloxacin as a prophylaxis for SBP reduces the incidence of renal failure and improves survival [84], by modulating renal nuclear factor-κB and cytokines, possibly mediated through a toll like receptor 4-based mechanism [85].

In a preliminary observation, increased toll like receptor 4 has been shown in renal tubules in patients with ACLF, which was not observed in HRS [85]. Thus, early diagnosis of renal dysfunction in patients with liver cirrhosis may be achieved by the use of urinary biomarkers for renal injury of cirrhosis, and thus allow better detection for the functional and inflammatory causes [9]. These biomarkers include markers of tubular injury such as kidney injury molecule-1, and α glutathione S-transferase markers of inflammation; such as *N*-acetyl-β-D-glucosaminidase, neutrophil gelatinase-associated lipocaline, fatty acid binding protein, and interleukin-18 [86]. It is possible that novel therapeutic approaches may be developed if this hypothesis can be confirmed [9].

Brain dysfunction

HE is one of the main manifestations of liver failure and subsequently ACLF [1,87–89]. Local and systemic changes have been implicated in the pathophysiology of the development of this neurological syndrome. Brain swelling is a principal pathological factor in the development of HE in patients with liver failure [87–90]. Several studies report the presence of a significant increase in intracranial pressure in patients with ACLF [87–89]. Reversibility of brain edema in patients with ALF suggests that brain edema is also reversible is cases with ACLF [91]. Ammonia plays a key role in the development of HE, but the relationship between the severity of hyperammonemia and HE could not be documented [92].

It is hypothesized that inflammatory reactions in patients with ACLF add synergistic effect to hyperammonemia leading to the development of brain edema and HE in those patients. This hypothesis was proved in animal models of cirrhosis, where the administration of endotoxins was associated with the development of acute brain swelling [90]. The mechanism of these increased levels of ammonia may be related to the synthesis of cytokines in the brain, increased inducible NOS expression, oxidative stress, and formation of nitrated protein products [90,93–95]. Conversely, HE could be prevented by reduction of bacterial translocation by the usage of nonabsorbable antibiotic, like rifaximin [96]. Cerebral blood flow is progressively reduced in patients with cirrhosis with HE, but in cases with ACLF, it may be paradoxically increased as seen in patients with ALF [9]. Insertion of a transjugular intrahepatic shunt is known to induce endotoxemia. A recent study demonstrated that TIPSS-induced endotoxemia leads to an increase in the rate of production of NO, resulting in endothelial dysfunction and increased cerebral blood flow. All these data support the hypothesis that HE with ACLF is due to multiple factors [97].

Cardiac and systemic hemodynamics

Hyperdynamic circulation is the main hemodynamic feature in patients with decompensated cirrhosis. Despite the increased cardiac output in patients with decompensated cirrhosis, there is a reduction in the blood flow in some organs, such as kidneys and brain [98]. Unlike decompensated cirrhosis, patients with ACLF have low cardiac output, and both systolic and diastolic functions are affected. This cardiovascular abnormality is associated with increased mortality rates, particularly in patients with renal impairment [99]. Cirrhotic cardiomyopathy was also observed in some patients with decompensated cirrhosis, which may predispose to cardiovascular collapse during any acute inflammatory insult, but no data are present supporting this hypothesis up till now [100].

Cardiovascular collapse in patients with ACLF usually requires large doses of inotropes, like cases with ALF and sepsis [99]. Cardiac dysfunction in ACLF is similar to those in severe sepsis, where there is an increase in the vasodilator factors like TNF and NO and decrease in the cortisol level. Increased vasodilators lead to progressive vascular dilatation, whereas the reduced cortisol levels decrease the sensitivity to vasoconstrictors [101]. Adrenal insufficiency was observed in up to 68% of patients with cirrhosis and severe sepsis, especially those with high Child–Pugh and MELD scores and shock, and it was associated with increased mortality rates [102]. Hydrocortisone administration to patients with septic shock and adrenal insufficiency improves the circulatory failure, but the use of hydrocortisone routinely during sepsis has not been found to improve the outcome [101]. No clear data are available to recommend certain inotropes with specific doses in patients with ACLF, but vasopressin analog in those patients should be used cautiously as it may further reduce cardiac perfusion [102].

Coagulation failure

Coagulation test results are usually abnormal in patients with cirrhosis owing to multiple factors [103]. Production of thrombin is normal in stable patients with cirrhosis, but there is an imbalance between procoagulant and anticoagulant factors (providing the presence of acceptable platelets>50 000 × 10^9/l). Bleeding abnormalities in patients with cirrhosis are far less frequent than it would be expected [104], as hypercoagulable state may be present [105]. When sepsis occurs in patients with liver cirrhosis, endogenous low-molecular-weight heparinoids could be detected; however, they disappear with resolution of infection [106]. This may explain why the usage of antibiotics reduces rates of early variceal rebleeding [107].

The use of prophylactic blood products to correct coagulation abnormalities in an attempt to prevent bleeding is often guided by local protocols and is not evidence based [108]. Moreover, these blood products rarely normalize coagulation abnormalities, and increase circulatory volume, aggravating the risk of transfusion-related reactions, particularly acute lung injury. Despite that recombinant factor VIIa corrects prothrombin time, it does not reduce blood loss during variceal bleeding [109]. Antifibrinolytic agents were proved to reduce blood loss during liver transplantation but have not been evaluated prophylactically during other procedures or for bleeding. Increased fibrinolysis may be associated with defective platelet function in patients with ACLF [109]. Eltrombopag, a thrombopoietin analog, may enhance platelet production in compensated cirrhosis (a trial evaluating this point has been a suspended), probably because of the interaction with the very high levels of Von Willebrand factor in cirrhosis. The use of prothrombin complex concentrates is safer than fresh frozen plasma, as it has 20 times the concentration of factors than fresh frozen plasma without the risks of increased circulatory volumes with transfusions [110]. Despite elevated international normalized ratio, most patients with ALF have normal hemostasis, so prophylactic transfusions of any coagulation products are difficult to justify [111].

Respiratory failure

Approximately 30% of patients with decompensated cirrhosis have reduced arterial oxygen saturation and may have cyanosis [112]. Hypoxemia in liver cirrhosis includes distinctive determinants: (i) ventilation–perfusion mismatch, (ii) occurrence of intrapulmonary right-to-left shunting of blood flow; and (iii) the increased cardiac output associated with liver disease, which further limits oxygenation because it reduces the erythrocyte transit time through lung vasculature and the amount of time available for the oxygenation of hemoglobin. The first two determinants, which are the most important, contribute in varying degrees to the hypoxemia in the individual patients [113].

Other causes of hypoxemia with liver cirrhosis include pleural effusion, raised diaphragms, basal atelectasis, primary pulmonary hypertension, and portopulmonary hypertension [114].

Clinical course of acute-on-chronic liver failure and its importance

ACLF is an extremely dynamic process, and resolution can occur in less than 50% of patients [115,116]. Patients with ACL-1 at diagnosis have significantly better resolution rates in comparison with those who present with ACLF-2 and ACLF-3. Dynamic assessment for patients with ACLF may help in better prediction of the outcome of those patients. It can also improve management for patients with ACLF and minimize futile and expensive care for patients with expected poor prognosis [3,116].

Short-term mortality of patients with ACLF can be accurately predicted by the clinical course of the syndrome according to the evolution between the initial and final ACLF grades independently of the initial grade [116]. The best way to evaluate the clinical course of ACLF is to detect the change that occurred

in the ACLF grade between the third and seventh day after ACLF diagnosis (day3–day7 ACLF). These data signify the importance of intensive care management of patients with ACLF during the first 7 days after diagnosis of ACLF. The reassessment of those patients after this period could help in determining subsequent management: continuation and potential liver transplantation, or discontinuation owing to futility [116].

As patients with ACLF could have a severe early course (final ACLF-2 or ACLF-3) and nonsevere late course (final ACLF-1 or resolution of ACLF), specific therapeutic procedures, such as artificial liver support systems (ALSS), should be evaluated in those patients. These therapeutic modalities can increase rates of ACLF resolution in patients presented with severe early course [117,118].

Management of acute-on-chronic liver failure

First of all, confirmation of the diagnosis of ACLF should be obtained. Application of CLIF-C OFs scores should be done to all patients with cirrhosis presented with complications such as encephalopathy, bleeding, infection, or ascites [9]. After the establishment of ACLF diagnosis, patients should be managed in ICUs. The prognosis of those patients could be determined by using the daily updated CLIF-C ACLFs. This updated score can be used to judge the efficacy or futility of management within 3–7 days [9,116]. In contrast, the absence of ACLF indicates the need to use CLIF-C AD score. Patients with CLIF-C ADs of less than or equal to 45 could be discharged early from the hospital, whereas patients with a score above 60 are at high risk of progressing to ACLF, so it is recommended for them to be managed in intensive care. Patients with a score greater than 45 but less than 60 need to be managed in the hospital [9,10]. Multiple strategies exist in the management of ACLF. These strategies include general measures, specific therapies, bridging and definitive treatments, and emerging therapies [13].

General measures

Nutrition

Although most patients with cirrhosis have moderate to severe malnutrition, many with ACLF have fairly well-preserved nutritional status [119,120]. Despite obesity being one of the risk factors for ACLF, the nutritional reserves for such patients do not last long to support the crisis and regenerating the liver if they became acutely and severely ill [120]. Optimal nutritional support in patients with ACLF has not been well defined [13].

Enteral tube feeding and the use of nutrient-dense formulas (1.5–2.0 kcal/ml) help ill patients who are unable to meet their nutrient needs independently. A target of 1.5–2.0 g protein/kg/day and 39 kcal/kg/day has been shown to improve HE and overall survival [121,122]. Carbohydrate-predominant late evening snack has been shown to be helpful in a few studies [121,123]. Limited data exist on the composition and utility of parenteral nutrition in patients with ACLF and should be used carefully in those with intestinal ileus [119].

Intensive care

Patients with ACLF need close monitoring to detect the development of components of SIRS, hypotension, and shock. Use of prophylactic antibiotics might help in the prevention of infection if given at the onset of SIRS, as it is difficult to differentiate SIRS from early sepsis. However, to date, no prospective or randomized control trial has been conducted on the use of prophylactic antibiotics in ACLF [13]. The choice of antibiotics depends on the type, severity, and origin of infection (community acquired or nosocomial) and local epidemiological data about antibiotic resistance [2]. Patients with ACLF and septic shock are extremely ill with mortality exceeding 80%. Septic shock is fluid responsive in only ~12% and vasopressor responsive in 50% of patients [124]. Terlipressin alone or in combination with noradrenaline helps in reversing septic shock, improving microcirculation, and reducing the risk of variceal bleeding and nosocomial SBP. However, one needs to closely monitor for adverse effects of terlipressin, which can be seen in up to one-third of treated patients [124].

The use of albumin is suggested to improve intravascular volume and prevent and manage AKI and infections. Cyclooxygenase-derived prostaglandin E_2 is one of the main drivers for immunosuppression in patients with AD of cirrhosis, and its level increased in ACLF. Albumin binds to prostaglandin E_2 and reduces its bioavailability, which in turn increases circulating TNF levels, reduces monocyte dysfunction, and reduces the risk of infections [125]. The beneficial effects of albumin could also be owing to its ROS-scavenging activities, protection of endothelial integrity, and binding of toxic molecules. Albumin administration in patients with ACLF could be helpful in managing complications such as SBP, HRS, HE, and non-SBP infections, based on data from those with decompensated cirrhosis [126].

Approximately 40% of patients with ACLF develop HE and require monitoring in the intensive care. Although little evidence exists at present for targeted

ammonia-reduction therapies, such as lactulose and rifaximin, they can be given empirically [34].

Renal impairment occurs in approximately one-quarter of patients with ACLF, and AKI is often preceded by SIRS [72]. Use of terlipressin with albumin is effective at treating AKI in only 35% of patients of ACLF, and the responders do have a survival advantage [72]. Nonresponders to terlipressin treatment might require renal replacement therapy in the form of intermittent hemodialysis, slow low-efficient dialysis, or continuous renal replacement therapy. Besides reducing urea and creatinine levels from the blood, dialysis also reduces ammonia and glutamine levels [127]. Continuous renal replacement therapy might offer several advantages: less fluctuation in the mean arterial pressure, maintenance of stable cerebral perfusion pressure without a rise in intracranial pressure, and a reduction in cerebral edema by preventing rapid osmolar shifts [128]. Continuous renal replacement therapy is preferred over conventional hemodialysis or slow low-efficient dialysis in critical care units in patients with ACLF [129].

Specific therapies

Hepatitis B virus treatments

Early and rapid reduction of HBV DNA levels suppresses hepatocellular necrosis that occurs secondary to cytokine storm [130]. More than 2-log reduction of HBV DNA level from baseline within 2 weeks using tenofovir improved transplant-free survival from 17 to 57% in a randomized controlled trial [18]. Other potent antiviral agents such as entecavir or telbivudine could also be used [13].

Treatments for alcohol-related injuries

Management of a patient with severe alcoholic hepatitis presenting as ACLF includes tailored nutrition, psychosocial rehabilitation, anticraving treatments (e.g. baclofen), and treatments aimed at suppressing inflammation or TNF production (such as corticosteroids or pentoxifylline) [131]. Nutritional intervention is comparable to corticosteroid therapy for survival at 1 month [132]. Nutritional intervention includes intravenous amino acids, with subsequent trials of parenteral and enteral nutrition [132–138]. As limited data exist, it is difficult to recommend one approach over the other; however, in patients who are not eligible for steroid treatment, nutrition therapy could be the obvious choice [132]. Thus, the role of nutrition is emphasized, and steroid-eligible patients should receive both nutrition as well as corticosteroid for maximal benefit [13].

Pentoxifylline, a weak inhibitor of TNF synthesis, has antioxidant properties [81]. In patients with severe alcoholic hepatitis, pentoxifylline improved 6-month survival compared with placebo [139,140], but not in other studies [141,142].

Autoimmune hepatitis

Approximately 20% of patients with autoimmune hepatitis present with severe jaundice, encephalopathy, and coagulopathy, with or without ascites, which resembles ACLF [143]. The use of steroids is beneficial in cases with low MELD score [144] and low UK-MELD score [145], whereas it is not beneficial in patients with higher scores [144]. The lack of large studies to evaluate the use of tacrolimus [146] or mycophenolate [147] leaves limited options for intervention except for early transplantation [13].

Corticosteroids

Steroid therapy is known to suppress inflammatory and immune-mediated hepatocyte injury. The benefit of steroid therapy in patients with alcohol-related ACLF has not been studied. The role of steroids in severe alcoholic hepatitis is somewhat controversial in the presence of ascites owing to the risk of sepsis. Development of sepsis starting after steroid therapy makes patient ineligible for liver transplantation leading to increased risk of mortality [13]. Approximately 60% of patients with severe alcoholic hepatitis showed improved short-term survival with steroids [148]; however, 6-month mortality remained at ~40% [149]. Antibiotic coverage is suggested by most of the studies as infection is seen in 25% patients at admission, and another 25% get infected during corticosteroid treatment [150]. The corticosteroid therapy showed survival benefit only at 28 days, but not at 90 days or 1 year [151].

Experimental therapies

Therapy with *N*-acetyl cysteine, modulation of gut flora [152,153], anti-TNF agents [154], and fecal microbial transplantation [155] are emerging therapeutic options for the treatment of ACLF [13]. Despite their potential, probiotics [156], thalidomide [157], and plasma exchange are only considered as experimental therapies owing to the lack of data at this time [13].

Artificial liver support

The rationale behind artificial liver support is to remove possible toxins and prevent further aggravation of liver failure, stimulate liver regeneration, and support hepatic functions [158]. Patients having liver failure with ACLF experience accumulation of toxic concentrations of bilirubin, bile acids, ammonia,

protein breakdown products (aromatic amino acids, phenol and mercaptans), lactate, glutamine, various mediators of oxidative stress, free fatty acids, endogenous benzodiazepines, iron metabolites, and inflammatory cytokines in both blood and tissues [159]. An ALSS using albumin dialysis leads to removal of these vasoactive substances, improves systemic and splanchnic circulation [160] and liver regeneration [161,162], and serves as a bridge to liver transplantation [158,159].

At present, there are two main devices providing ALSS: the Molecular Adsorbent Recirculating System, Gambro, Sweden, and the fractionated plasma separation and adsorption (the Prometheus System; Fresenius Medical Care, Bad Homburg, Germany). The published RELIEF study using Molecular Adsorbent Recirculating System reported a decrease in sCr and bilirubin levels with improvement of HE on the fourth day of treatment, but without survival benefits [118]. The fractionated plasma separation and adsorption (Prometheus System) device used in the HELIOS study reported a notable reduction in serum bilirubin levels [117]. The survival benefit was limited to patients with type I HRS and a MELD score of more than 30 [117]. A meta-analysis showed a decrease in mortality in those with ACLF when treated with ALSS [163]. Decreasing the MELD score to less than 30 with ALSS before liver transplantation leads to reduced overall mortality [164]. ALSS, therefore, remains a useful tool in a selected group of patients with ACLF to improve their clinical and biochemical status before transplantation [13].

Liver transplantation in acute-on-chronic liver failure

Liver transplantation is a potentially curative treatment for patients with ACLF. Patients with ACLF should have the highest priority for liver transplantation as SIRS and sepsis generally develop within 7 days of hospitalization [165]. Transplantation is only feasible in ~25% of patients with ACLF on the deceased donor liver transplantation waiting list, owing to progressive liver failure and onset of multiorgan failure [116,166]. Disease severity scores such as MELD have been considered to determine organ allocation to those who need the organs, but this may not optimum in cases with ACLF. Disease severity scores do not consider cerebral, circulatory, and respiratory failures, giving no priority for patients with ACLF [116,167].

Pamecha *et al.* [167] proposed serial assessment of disease severity with CLIF-C score for patients with ACLF in the first week of hospitalization for prioritization for liver transplantation. Patients with a MELD score of more than 30, HBV reactivation on top of cirrhosis, serum bilirubin levels of at least 170 μmol/l, prothrombin index more than 40%, a platelet count of less than 1×10^5/l, and presence of encephalopathy should be listed for early transplantation. Although many prediction models of early transplantation listing exist, none reliably predict chances of reversibility of ACLF [167].

In one series from Germany, 91% of patients with ACLF (as defined by APASL) who could not undergo liver transplantation died owing to being too ill, whereas 85% of patients who underwent transplantation survived for a median of 29 months [166]. In a series of 149 patients with ACLF (defined by the APASL criteria) who received either deceased or living donor transplants, a 5-year survival was 90% [168]. In another Chinese series, patients with ACLF (as defined by APASL definition), the 1-, 3- and 5-year survival rates were 76.8, 75.6, and 74.1%, respectively [169].

Liver transplantation for cases with ACLF with acute alcoholic hepatitis is controversial, as the minimum duration of abstinence to prevent recidivism is undecided [13], despite that early liver transplantation for those patients improve survival if they were unresponsive to steroids [170]. The decision becomes even more challenging in a related living donor liver transplantation scenario [171]. Overall, the results of transplantation in patients with ACLF are encouraging [13].

The emergence of regenerative therapy

Liver regeneration in a failing liver

Liver regeneration is a complex process and it depends upon the extent and type of parenchymal injury. In ALF, regeneration occurs by self-replication of normal differentiated hepatocytes and cholangiocytes [172]. In ACLF, it occurs by activation and differentiation of hepatic progenitor cells (HPCs) [172,173]. The TNF ligand superfamily member 12 (TNFSF12, also known as TWEAK) and 12A (TNFRSF12A, also known as FN14) pathways, stimulated by macrophages, T cells and M2 Kupffer cells, are associated with the differentiation of HPCs into hepatocytes in ACLF [173,174]. Dying hepatocytes engulfed by macrophages activate WNT3 signaling, which promotes differentiation of HPC into hepatocytes [175].

Experiments done in various mouse models of liver injury to evaluate liver regeneration from HPC have shown that regeneration from both hepatic and nonhepatic HPCs in adult mouse depends on the extent of hepatic injury [176,177]. Hepatic nonparenchymal cells might also actively participate in liver regeneration. This theory is supported by the increase in the proportion of activated hepatic

stellate cells per 1,000 cells in patients with ACLF in comparison with patients with cirrhosis and healthy individuals [178]. The number of HPCs also positively correlates with patient survival [178,179]. However, whether the expanded number of activated stellate cells dedifferentiate into HPCs [179] or provide paracrine support for liver regeneration needs to be defined [13].

Bone marrow also participates in hepatic regeneration [180]. In response to hepatic injury, stromal cell-derived factor-1 increases in bone marrow and in the regenerating liver, encouraging hepatic regeneration [181]. Bone-marrow-derived epithelial progenitor cells increase after partial hepatectomy as well as in cirrhosis [172,181]. They stimulate liver sinusoidal endothelial cells for tube formation and angiogenesis, which is an essential step in liver regeneration [182,183].

The role of growth factors in hepatic regeneration

Hepatic injury in cases with ACLF is more aggressive than the body's ability to stimulate hepatic regeneration. Moreover, hepatocytes in patients with chronic liver disease are often in a state of replication to replace diseased [184]. Supplementing hepatic regeneration with in-vivo or ex-vivo approaches is, therefore, worthwhile [13]. Di Campli *et al.* [185] showed successful dose-dependent mobilization of bone marrow stem cells in patients with ACLF after 3 days of granulocyte colony-stimulating factor (G-CSF) therapy.

Garg *et al.* [186] found that G-CSF therapy given over 1 month substantially enhanced the mobilization of bone marrow hematopoietic stem cells in comparison with the placebo group and showed homing of these cells in the hepatic parenchyma in follow-up liver biopsy samples. This therapy was associated with a reduction of Child–Pugh, MELD, and Sequential Organ Failure Assessment scores; reduced sepsis; HRS and HE; and improved survival [186]. In very ill patients with a MELD score of more than 30, G-CSF therapy should be considered only if liver transplantation is not feasible and preferably by specialists experienced in this therapy. This approach should not be used in patients with ACLF in the presence of AKI, ongoing sepsis, significant hemolysis, or macrophage activation syndrome. In the latter, it is likely that levels of G-CSF and granulocyte–macrophage colony-stimulating factor levels are already too high [186,187]. G-CSF therapy in human beings has been shown to recruit dendritic cells in the liver and reduce interferon-γ secreting CD8 T cells with improved clinical severity indices [188]. HPC proliferation [189], CXCR4 expression, and neutrophil and macrophage activation are all increased by G-CSF [190].

Developing therapeutic synergism by combining G-CSF with other growth factors is an area of intense research [13]. Erythropoietin has been shown to mobilize endothelial progenitor cells and enhance their in-vivo regenerative role [191]. Darbopoetin-α has higher potency than recombinant human erythropoietin owing to better bioavailability [192]. Kedarisetty *et al.* [187] used the combination of G-CSF and darbopoetin-α, which improved hepatic regeneration compared with placebo. This study showed increased 1-year survival, reduced Child–Pugh score, reduced MELD scores, and lower incidence of septic shock. Other cytokines such as hepatopoietin, hepatocyte growth factor, vascular endothelial growth factor, and bone marrow cell-mobilizing factors, such as plerixafor, are under evaluation [193,194].

Prevention of acute-on-chronic liver failure

Patient education, anticipation, early identification of the acute insult, and early detection of chronic liver disease would be immensely helpful [13]. Universal HBV screening before initiation of immunosuppressive therapy is recommended in hepatitis B surface antigen-positive, and hepatitis B surface antigen-negative but hepatitis B core antigen-positive patients [195]. Nucleotide analogs, such as tenofovir and entecavir, should be pre-emptively used in those with HBV infection [196]. Modulation of gut flora with probiotics ameliorates ethanol-induced liver injury as well as progression of nonalcoholic steatohepatitis to cirrhosis [197], but their role in preventing the development of ACLF is unexplored [13]. The best way for prevention of drug-induced liver injury is to educate patients, monitor alanine aminotransferase levels during drug therapy, and stratify high-risk patients such as the elderly, and those with obesity, diabetes, alcoholism, coinfected with HIV, or using known hepatotoxic drugs [198-201].

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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