

# World Journal of *Hepatology*

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## Acute-on-chronic liver failure in children

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### Abstract

Although various complex definitions of acute-on-chronic liver failure (ACLF) have been suggested in relation to adult patients, there is currently no universal definition of the syndrome in pediatric patients. In simplified terms, ACLF is characterized by the acute deterioration of the liver functions due to the effects of a precipitating factor on the basis of a chronic liver disease. Acute events and underlying liver diseases are very different in children from those seen in adults. Moreover, acute events and underlying chronic liver diseases vary among geographical regions, although it seems that the most common such diseases and acute events are autoimmune hepatitis, Wilson's disease, and their flares. ACLF is associated with a poor prognosis. While no scoring systems have been developed to predict the prognosis for children with ACLF, modified versions of the Asian Pacific Association for the Study of the liver's acute-on-chronic liver failure scoring system and the Chronic Liver Failure-Sequential Organ Failure Assessment criteria can be used in children until specific and validated scoring systems are available. Aside from liver transplantation, there is no proven treatment for ACLF. Thus, the early recognition of ACLF prior to the development of extrahepatic organ failure is important.

**Key Words:** Liver failure; Prognosis; Prevalence; Clinics; Histopathology; Scoring systems; Treatment

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**Core Tip:** Acute-on-chronic liver failure (ACLF) remains poorly defined in pediatric patients. ACLF is associated with acute deterioration in patients with chronic liver disease or cirrhosis due to an underlying precipitating event. In the limited number of pediatric studies conducted to date, the underlying chronic diseases and acute precipitating events have been found to vary among geographical regions, while high rates of short-term mortality have also been reported. This review focuses on ACLF in

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## INTRODUCTION

Acute-on-chronic liver failure (ACLF) remains poorly defined in pediatric patients. Although a few prior pediatric studies have relied on definitions of the syndrome formulated in relation to adult patients[1-9], no study has yet sought to develop a definition of the syndrome in pediatric patients. The simplest definition of ACLF equates it with the development of acute deterioration in patients with chronic liver disease or cirrhosis as a result of an underlying precipitating event[10]. ACLF differs from both acute liver failure (ALF) and acute decompensated cirrhosis. More specifically, ALF is defined as a form of coagulopathy that cannot be corrected with vitamin K when biochemical data indicate the presence of acute liver injury without prior evidence of chronic liver disease[11]. Furthermore, decompensated cirrhosis is defined as the loss of the liver's normal synthetic capacity over time accompanied by the development of jaundice and complications of portal hypertension, including ascites, variceal bleeding, and hepatic encephalopathy (HE)[12].

Many studies have been conducted among adults with ACLF, although such studies have utilized different criteria and etiologies, and they have been conducted in different geographical regions. European, American, and Asian hepatology authorities have devised different definitions of ACLF in light of their specific populations. Despite the use of different definitions and etiologies, the morbidity and mortality rates associated with ACLF have consistently been found to be high in adults[13-15]. In the limited number of pediatric studies conducted to date, the underlying chronic diseases and acute precipitating events in cases of ACLF have been found to vary among geographical regions, while high rates of short-term mortality have also been reported[1-7]. The present review will focus on ACLF in children.

## DEFINING ACLF

Different definitions of ACLF have been suggested in relation to adult patients. For instance, as part of prospective observational studies, the European Association for Liver Studies (EASL)[13], the North American Consortium for End-Stage Liver Disease Studies (NASCELD)[14], and the Asian Pacific Association for the Study of the Liver (APASL)[15] have each suggested different definitions of ACLF in adults, which can sometimes lead to confusion (Table 1). According to both the EASL and the NASCELD, ACLF involves the development of acute hepatic decompensation accompanied by extrahepatic organ failure, which stems from an acute precipitating factor in patients admitted to hospital with cirrhosis. Moreover, the two authorities stress that ACLF is associated with high mortality. With reference to the definition of ACLF suggested by the EASL, in the conducted in the United Kingdom using European (CANONIC) study of cirrhotic patients, acute hepatic decompensation was defined as the development of ascites, HE, gastrointestinal hemorrhage, bacterial infection, or any combination of these disorders. In addition, as a requirement for a diagnosis of ACLF, the NASCELD defines organ failure as shock, HE grade III or IV, renal failure that requires dialysis, and/or respiratory failure that requires mechanical ventilation. Patients with a prior history of decompensated cirrhosis are included within both the EASL and the NASCELD definitions of ACLF. In its definition of ACLF, the APASL includes not only those with cirrhosis, but also those with chronic liver disease. The EASL specifies the time frame for developing ACLF as 4-12 wk, whereas the NASCELD does not specify a time frame[13,14]. The APASL does not include extrahepatic organ failure in its definition of ACLF, although it is recognized as a complication of ACLF. Moreover, patients with decompensated and acutely decompensated cirrhosis are excluded from the APASL definition of ACLF. In fact,

Table 1 Commonly accepted acute-on-chronic liver failure definitions

	APASL	EASL	NASCELD
<b>Definition</b>	An acute hepatic insult manifesting as jaundice (serum bilirubin $\geq 5$ mg/dL) and coagulopathy (INR $\geq 1.5$ ) complicated within 4 wk by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis, and is associated with a high 28-d mortality	An acute deterioration of pre-existing chronic liver disease usually related to a precipitating event and associated with increased mortality at 3 mo due to multisystem organ failure	A syndrome characterized by acute deterioration of cirrhosis with two or more extrahepatic organ failure
<b>Included patients</b>	Acute liver deterioration in patients with previously diagnosed or undiagnosed chronic liver disease including cirrhosis. Acute hepatic triggering factors	Cirrhosis (compensated or decompensated)  Renal failure is mandatory  Patients with an acute decompensation of cirrhosis  Patients with prior decompensation of cirrhosis	Cirrhosis (compensated or decompensated)  Two extrahepatic organ failure  Presentation not necessarily to be liver failure  Can be repeated episodes of ACLF
<b>Excluded patients</b>	Patients with bacterial infections  Patients with cirrhosis who develop acute deterioration of their clinical status are considered to have acute decompensation but not ACLF  Prior decompensation. Non-hepatic acute insults (such as sepsis)	HCC  HIV infection  Receiving immunosuppressive treatments	HIV infection  Disseminated malignancies
<b>Pediatric definition</b>	For children less than 3 years, modified HE assessment scale can be used  Clinical and/or radiological ascites can be used for defining ACLF in children	None	None

ACLF: Acute-on-chronic liver failure; APASL: The Asian Pacific Association for the Study of the Liver; EASL: The European Association for Liver Studies; HCC: Hepatocellular cancer, HIV: Human immunodeficiency virus; INR: International normalized ratio; NASCELD: The North American Consortium for End-Stage Liver Disease Studies.

decompensation preceding jaundice and repeated episodes are said to indicate acute decompensation, not ACLF. Another important difference that sets the APASL definition of ACLF apart from the other definitions is the requirement for the diagnosis of jaundice to be followed by the diagnosis of clinical ascites or HE. More specifically, the APASL definition of ACLF states the following:

ACLF is an acute hepatic insult manifesting as jaundice (serum bilirubin  $\geq 5$  mg/dL (85 micromol/L) and coagulopathy [international normalized ratio (INR)  $\geq 1.5$  or prothrombin activity  $< 40\%$ ] complicated within 4 wk by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis, and is associated with a high 28-d mortality[15].

As mentioned above, there is currently no universal definition of ACLF in pediatric patients. Only the APASL has stated, in its latest guidelines, that, with some minor modifications, its definition of ACLF in adults can be used for children. Due to the difficulty associated with identifying clinical ascites and HE in children, those necessary modifications include recognizing ascites as “clinical and/or radiological ascites” and “diagnosing HE in children younger than 3 years using modified HE assessment scale”[15]. However, there are still several major problems with the APASL definition. First, some instances of ALF in children may not be accompanied by a significant increase in the bilirubin level, such as ALF stemming from metabolic liver disease. Second, the cut-off INR for the diagnosis of ACLF is problematic. Indeed, when defining ALF in children, the INR must be  $\geq 1.5$  with HE or  $\geq 2$  regardless of the HE status[11]. The APASL has referred to these two issues, although it has not made any recommendations. In light of this, in a retrospective study conducted in children, we defined ACLF as follows:

The presence of an acute hepatic insult in previously diagnosed or undiagnosed chronic liver disease causing jaundice (total serum bilirubin  $\geq 5$  mg/dL) and coagulopathy (INR  $\geq 2.0$ ) and clinical and/or radiological ascites and/or HE within 4 wk[16].



Finally, in its consensus report, the World Gastroenterology Organization defined ACLF as follows:

ACLF is a syndrome characterised by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the INR) and one or more extrahepatic organ failures that is associated with increased mortality within a period of 28 d and up to 3 mo from onset[10].

## PREVALENCE

Despite the use of different diagnostic criteria, the prevalence of ACLF has been found to range from 22.6% to 40% in adult patients with cirrhosis[17-19]. Moreover, according to the APASL and EASL criteria, the incidence rate has been determined to be 5.7 and 20.1 cases per 1000 person-years, respectively[20].

We searched the literature published in English and found nine studies concerning ACLF in children[1-9]. Of those nine, six studies were conducted in India. Given that prior studies have relied on different adult definitions and etiologies, and as they have mainly been conducted in a single Asian country, it is difficult to determine the true prevalence of pediatric ACLF. Indeed, the previously reported prevalences are not generalizable. In two centers in India in which the APASL definition of ACLF was used, its prevalence was reported to range from 11.2% to 22.1%[3-5].

## CLINICAL FEATURES OF ACLF

### *Underlying chronic liver disease*

The primary causes of chronic liver disease and cirrhosis in adults are alcohol abuse, hepatitis B (HBV) and C, and non-alcoholic fatty liver disease. While viral hepatitis is the most common cause in Eastern countries, alcohol abuse is the most common cause in Western countries[10,13,14]. In the few studies previously conducted in children, the most common underlying chronic liver diseases were found to be Wilson's disease (WD), autoimmune hepatitis (AIH), and indeterminate chronic liver diseases[4,6]. AIH can present as ACLF, as the exacerbation of a pre-existing chronic liver disease or liver injury caused by an overlapping infectious or toxic agent may lead to ACLF in cases of AIH. There are no definitive data regarding whether or not patients diagnosed with ACLF have a previous history of liver disease. In our prior study, 58.6% of ACLF patients were diagnosed with liver disease for the first time[16].

### *Precipitating acute events*

A precipitating event can trigger the decompensation of liver disease and lead to multiple organ failure. Acute events are known to vary by region in adults. Bacterial infection, sepsis, and alcoholism are the most common acute events in the West, while the reactivation of HBV infection or superinfection, hepatotoxic drugs, and complementary and alternative medicines are the most common acute events in the East[13-15]. The most common acute events in pediatric ACLF were reported in one center in India to be WD (46.5%) and AIH (34.9%) flares[8]. In the other two centers in India, the most common acute events were reported to be hepatitis A virus (HAV) and hepatitis E virus infections[1,2]. In our prior study, the most common acute events were AIH (48.28%) and WD (27.58%) flares. Moreover, the other identified acute events were drug-induced liver injury, Epstein-Barr virus, cytomegalovirus, and HAV infection [16].

## PATHOPHYSIOLOGY

Current knowledge regarding the pathophysiology of ACLF is insufficient. It has been stated that the main trigger of ACLF in adults is increased severe systemic inflammation. Systemic inflammation can cause ACLF through several mechanisms, including: (1) Immune-mediated tissue damage; (2) Mitochondrial dysfunction caused by oxidative stress; and (3) The development of renal hypoperfusion and multiple organ failure due to the effective arteriolar volume decrement caused by vasoactive substances[21,22]. The main causes of systemic inflammation have been reported to be bacterial infection and sepsis originating from the gastrointestinal tract, gastrointestinal bleeding, and severe alcoholic hepatitis[21,23]. It has been suggested



that gastrointestinal hemorrhage causes systemic inflammation through causing ischemia-reperfusion injury secondary to liver ischemia and intestinal bacterial translocation[24]. Excessive alcohol consumption is known to stimulate systemic inflammation by causing both intestinal dysbiosis and bacterial translocation in severe alcoholic hepatitis[23]. The differences in the triggering factors, underlying diseases, and comorbidities seen between children and adults suggest that factors other than those mechanisms also play a role in the pathophysiology of pediatric ACLF.

## LIVER HISTOPATHOLOGY

A diagnosis of chronic liver disease or cirrhosis is typically made on the basis of a physical examination as well as specific laboratory, endoscopic, and/or radiological investigations[12]. A liver biopsy or histopathological examination of the explant liver provides information about necrosis, chronicity, and/or cirrhosis. However, it may not be possible to perform a liver biopsy due to coagulopathy. In such a case, a transjugular liver biopsy or non-invasive modality can be used[11,12,15]. While the histology of ACLF has not yet been thoroughly investigated, it can be predicted that the syndrome has the histopathological features of both ALF and chronic liver disease. Massive necrosis without chronicity is seen in the case of fulminant hepatitis or ALF [11]. Any degree of fibrosis, ductular reaction, or parenchymal collapse in the liver is a sign of ACLF[25]. This issue has not previously been studied in detail in children. In our prior study, massive confluent necrosis and fibrosis with mild to moderate inflammation (neutrophil and eosinophil), as well as evidence of regeneration, were observed in the hepatectomy materials of children who underwent LT. In those who did not undergo LT, the presence of underlying disease (*i.e.*, lymphoplasmacytic cell infiltration in AIH and micro- and macrovesicular steatosis in WD), rare or patchy hepatocellular necrosis, and advanced-stage fibrosis with bridging were all observed[16].

## DIAGNOSIS AND SCORING SYSTEMS

ACLF is associated with a high short-term mortality rate. Data concerning the severity of the syndrome contributes to the selection of an appropriate treatment for it. The validity of a number of scoring models in ACLF has been extensively tested in adults. For instance, the model for end-stage liver disease (MELD), MELD-sodium (MELD-Na), and Child-Pugh-Turcotte scores, which are used in relation to organ allocation, have been found to exhibit low sensitivity because they do not evaluate extrahepatic organ failure, which is important in terms of the prognosis of ACLF[13,14]. Both the Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) (Table 2) and the APASL-ACLF Research Consortium (AARC) (Table 3) scoring systems, which include parameters for evaluating kidney, brain, respiratory, and circulatory functions, have been found to be more reliable with regard to identifying the prognosis of ACLF [13,15]. The APASL has suggested that the AARC system is more sensitive than the CLIF-SOFA when it comes to determining prognoses. ACLF is a dynamic process, which means that the associated scoring systems should be evaluated dynamically. Scoring systems used at the 48<sup>th</sup> hour, after 3–7 d, or after 8–15 d predict the prognosis of ACLF better than a score calculated at the time of admission. An AARC score of < 10, or a score falling below 10 during the first week of admission, indicates a higher likelihood of survival in adults[13–15].

Although there is currently no validated scoring system for pediatric patients with ACLF, a few studies have made use of scoring systems (or their modified versions) designed for use with adults[2,4,8]. The modifications in this regard include the adjustment of the HE assessment, blood pressure, and serum creatinine levels according to the childhood age group[3] (Tables 4 and 5). In one pediatric study[3], the CLIF-SOFA and AARC scores were found to be superior in terms of predicting a poor outcome when compared with the Pediatric End-Stage Liver Disease, Child-Pugh and Pediatric Risk of Mortality-III scores. In the study, AARC and CLIF-SOFA scores of 11 were found to predict a poor prognosis with maximum sensitivity and specificity [area under the receiver operating characteristic curve (AUROC) > 0.9]. In another pediatric study[2] that tested the validity of the CLIF-SOFA system, the maximum sensitivity (100%) and specificity (76%) (AUROC = 0.95) were achieved at a 6.5 cut-off level with regard to predicting mortality. Moreover, in another pediatric study, children with a CLIF-SOFA score ≥ 10 at the time of admission were found to require an urgent referral to an LT center[4]. In our prior study, the AARC and CLIF-SOFA scores were

**Table 2 Chronic liver failure–sequential organ failure assessment score**

Organ/systems	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(or RRT)	≥ 5.0(or RRT)
Cerebral (HE grade)	No HE	I	II	III	IV
Coagulation (INR)	< 1.1	≥ 1.1 to < 1.25	≥ 1.25 to < 1.5	≥ 1.5 to < 2.5	≥ 2.5 or platelet < 20 × 10 <sup>9</sup> /L
Circulation (mean arterial pressure, mm Hg)	≥ 70	< 70	Dopamine ≤ 5 or dobutamine or terlipressin(μg/kg/min)	Dopamine > 5 or E ≤ 0.1 or NE ≤ 0.1(μg/kg/min)	Dopamine > 15 or E > 0.1 or NE > 0.1(μg/kg/min)
Lungs					
PaO <sub>2</sub> /FiO <sub>2</sub>	> 400	> 300 to ≤ 400	> 200 to ≤ 300	> 100 to ≤ 200	≤ 100
or SpO <sub>2</sub> /FiO <sub>2</sub>	> 512	> 357 to ≤ 512	> 214 to ≤ 357	< 89 to ≤ 214	≤ 89

BP: Blood pressure; E: Epinephrine; FiO<sub>2</sub>: Fraction of inspired oxygen; HE: Hepatic encephalopathy; INR: International normalized ratio; NE: Norepinephrine; PaO<sub>2</sub>: Partial pressure of arterial oxygen; RRT: Renal replacement therapy; SpO<sub>2</sub>: Pulse oximetric saturation.

**Table 3 Asian Pacific Association for the Study of the Liver Acute-on-Chronic Liver Failure score**

Points	Total bilirubin (mg/dL)	HE grade	INR	Lactate (mmol/L)	Creatinine (mg/dL)
1	< 15	0	< 1.8	< 1.5	< 0.7
2	15-25	I-II	1.8-2.5	1.5-2.5	0.7-1.5
3	> 25	III-IV	> 2.5	> 2.5	> 1.5

HE: Hepatic encephalopathy; INR: International normalized ratio.

**Table 4 Modified chronic liver failure–sequential organ failure assessment score**

Organ/systems	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, rise from baseline)	< 1.5 ×	1.5 to ≤ 2.0 ×	> 2.0 to ≤ 3 ×	> 3 ×	Need for RRT
Cerebral (HE grade)	0	I	II	III	IV
Coagulation (INR)	< 1.1	≥ 1.1 to ≤ 1.25	> 1.25 to < 1.5	≥ 1.5 to ≤ 2.5	> 2.5
Circulation (systolic BP)	Normal for age	< 5 <sup>th</sup> centile for age	NE < 0.5 μg/kg/min	NE > 0.5 μg/kg/min	NE > 0.5 μg/kg/min and 2 <sup>nd</sup> inotrope
Lungs					
PaO <sub>2</sub> /FiO <sub>2</sub>	> 400	> 300 to ≤ 400	> 200 to ≤ 300	> 100 to ≤ 200	≤ 100

BP: Blood pressure; HE: Hepatic encephalopathy; INR: International normalized ratio; NE: Norepinephrine; PaO<sub>2</sub>: Partial pressure of arterial oxygen; FiO<sub>2</sub>: Fraction of inspired oxygen; RRT: Renal replacement therapy.

found to have high LT-predictive specificity and sensitivity. The CLIF-SOFA system focuses on extrahepatic organ failure, but there were no patients with multiorgan failure in our study. Furthermore, we found that the total bilirubin level ranges were high in the AARC system. Based on these findings, we concluded that the CLIF-SOFA and AARC scoring systems need to be modified for use in children[16].

A previous study found acute kidney injury to occur in 22.6% of children with ACLF and to be associated with a poor prognosis[8]. In a study CANONIC criteria,

**Table 5 Modified Asian Pacific Association for the Study of the Liver Acute-on-Chronic Liver Failure score**

Points	Total bilirubin (mg/dL)	HE grade	INR	Lactate (mmol/L)	Creatinine (rise from baseline)
1	< 15	0	< 1.8	< 1.5	< 1.5 ×
2	15-25	I-II	1.8-2.5	1.5-2.5	1.5 to ≤ 3 ×
3	> 25	III-IV	> 2.5	> 2.5	> 3 × or need RRT

HE: Hepatic encephalopathy; INR: International normalized ratio; RRT: Renal replacement therapy.

20% of 99 patients with biliary atresia were determined to have developed ACLF. Sepsis and gastrointestinal bleeding were identified as the most common precipitants of ACLF. Moreover, the ACLF mortality rate was found to be 20% [9]. In a study conducted among pediatric ACLF patients in the United States, most of the included patients were found to have biliary atresia, while the mortality rate was calculated to be 22% in patients who required hospitalization. In addition, the creatinine and aspartate transaminase levels, the INR, and a positive blood culture on admission were all shown to be associated with the development of ACLF. In this study, the triggers of the underlying decompensation were identified as bleeding, ascites, and an altered mental status in a significant portion of patients [6]. Cholangitis is known to be the most common cause of hepatic decompensation in patients with biliary atresia. Due to it not being a primary parenchymal disease, experts from the APASL study group excluded biliary atresia from among the diseases said to cause ACLF. Additionally, the APASL does not consider extrahepatic causes to be trigger factors in relation to ACLF [15].

## BIOMARKERS

The treatment strategies for ACLF are mainly supportive. Biomarkers have previously been the subject of research concerned with predicting the prognosis of ACLF. These biomarkers aim to predict organ dysfunction at an early stage. Oxidative stress factors (*e.g.*, S100A12 and sRAGE), markers of cell death such as the caspase pathway proteins (which reflect the death of hepatocytes), and immune functions have been investigated in adults patients with ACLF. Unfortunately, the validity of such markers remains unknown [26]. Due to the role of infections in the etiopathogenesis of adult ACLF, the use of certain biomarkers, such as galactomannan or beta-d-glucan for invasive fungal infections and C-reactive protein and procalcitonin for bacterial infections, has been recommended by the APASL in relation to early diagnosis [15]. Renal complications are common in cases of ACLF. While hepatorenal syndrome improves following LT, acute tubular necrosis and structural acute kidney injury, which may cause permanent renal damage, require both LT and kidney transplantation. Thus, the use of new biomarkers of acute tubular necrosis (*e.g.*, N-GAL, Kim-1, IL-18, and 1-FABP) in ACLF may prove beneficial in terms of identifying an appropriate treatment approach [15, 27]. Finally, non-invasive tools and biomarkers developed to measure liver fibrosis may provide useful information when it comes to predicting the prognosis of ACLF.

## PROGNOSIS

Overall, patients with ACLF have a poor prognosis. The APASL emphasizes that ACLF should be recognized during the “golden therapeutic window” prior to the development of extrahepatic organ failure, which is associated with mortality [15]. Studies conducted in adults have reported ACLF mortality rates ranging from 33% to 50% [15, 21]. Pediatric cases of ACLF can be predicted to have better prognoses than adult cases for three main reasons: (1) There are specific treatments for the two most common causes of pediatric ACLF (WD and AIH); (2) Children are likely to have greater liver reserves; and (3) Children exhibit fewer comorbidities [15]. In two studies involving pediatric ACLF cases in two non-transplant centers, the 28-d and three-month mortality rates were reported to be 19.4% and 59%, respectively [1, 2]. In another study, the 28-d mortality and LT rates were reported to be 25% and 8.3%, respectively [3]. In a study conducted in the same center, the three-month mortality and LT rates were reported to be 30.4% and 8.9%, respectively [4]. In a study that used the Pediatric

Acute Liver Failure (PALF) study group's ALF criteria (rather than ACLF criteria), which only included children with the etiologies of AIH, WD, Budd-Chiari syndrome, inborn errors of metabolism affecting the liver, and HBV reactivation, some 59% of patients survived without LT[28]. In a prior study we conducted among 29 pediatric ACLF patients, 24.14% of patients required LT and no patients died[16]. Interestingly, the presence of acute kidney injury increases the likelihood of death or LT by 7.7 times when compared with those who do not develop acute kidney injury[8]. When comparing the mortality rate of ACLF with that of ALF, more than 50% of children with non-acetaminophen-induced ALF died or underwent LT in the PALF study[29].

## TREATMENT OF ACLF

There is no proven treatment for ACLF other than LT. The early recognition of ACLF and its precipitating events during the "golden therapeutic window period" prior to the development of extrahepatic organ failure is important in relation to the success of treatment[15]. ACLF treatments mainly include supportive treatments for hepatic and extrahepatic organ failure (if present). Extracorporeal liver support systems (e.g., the molecular adsorbent recirculating system and plasmapheresis) have long been used as a bridge to LT in both adults and children with liver failure. The purpose behind using such modalities is to improve the clinical situation (especially neurologically) and biochemical parameters. However, the efficacy of extracorporeal liver support systems in adult and childhood liver failure remains unclear[11,15,30]. Optimizing the extracorporeal liver support modalities in children may improve outcomes. A few adult studies have assessed the treatment of ACLF using granulocyte colony-stimulating factor (GCSF)[31,32]. It has been suggested that GCSF may reduce mortality through promoting hepatic regeneration by mobilizing the bone-marrow-derived CD34+ cells and reducing sepsis. In a pediatric study conducted in India, 5 mcg/kg/d GCSF therapy for five days was found to be ineffective in terms of improving survival outcomes[5].

## LT

Although ACLF is associated with high short-term mortality, a significant number of patients recover due to the use of medical and extracorporeal liver support systems[1-4]. The final treatment option is LT in patients who do not otherwise recover. There is no conclusive evidence concerning the efficacy of LT in children, although LT in adults with advanced ACLF has been found to result in good outcomes[13-15]. However, deciding on the timing of LT can be difficult. There are no data available concerning who would benefit from early LT, although the procedure should be performed prior to the development of multiple organ failure and advanced-stage encephalopathy. It may prove useful to use the scoring systems mentioned above when assessing the need for LT.

## CONCLUSION

A definition of ACLF in children has not yet been developed. The etiology of ACLF varies among geographical regions. Moreover, organ dysfunctions are seen less frequently in pediatric ACLF patients than in adult patients. However, the mortality rate associated with ACLF remains high. Although there is no proven scoring system for predicting the prognosis of ACLF, if the AARC system score is > 8-10, a poor prognosis is indicated.

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