

Retrospective Cohort Study

Characteristics and outcomes of chronic liver disease patients with acute deteriorated liver function by severity of underlying liver disease

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Abstract

AIM: To analyze characteristics and outcome of patients with acute-on-chronic liver failure (ACLF) according to the severity of underlying liver disease.

METHODS: One hundred and sixty-seven adult patients with chronic liver disease and acute deteriorated liver function, defined by jaundice and coagulopathy, were analyzed. Predisposition, type of injury, response, organ failure, and survival were analyzed and compared between patients with non-cirrhosis (type A), cirrhosis (type B) and cirrhosis with previous decompensation (type C).

RESULTS: The predisposition was mostly hepatitis B in type A, while it was alcoholic liver disease in types

B and C. Injury was mostly hepatic in type A, but was non-hepatic in type C. Liver failure, defined by CLIF-SOFA, was more frequent in types A and B, and circulatory failure was more frequent in type C. The 30-d overall survival rate (85.3%, 81.1% and 83.7% for types A, B and C, respectively, $P = 0.31$) and the 30-d transplant-free survival rate (55.9%, 65.5% and 62.5% for types A, B and C, respectively $P = 0.33$) were not different by ACLF subtype, but 1-year overall survival rate were different (85.3%, 71.7% and 58.7% for types A, B and C, respectively, $P = 0.02$).

CONCLUSION: There were clear differences in predisposition, type of injury, accompanying organ failure and long-term mortality according to spectrum of chronic liver disease, implying classifying subtype according to the severity of underlying liver disease is useful for defining, clarifying and comparing ACLF.

Key words: Acute-on chronic liver failure; Classification; Injury; Organ failure; Survival

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Core tip: Controversy exists over defining acute on chronic liver failure (ACLF). Recently, multimodal ACLF classification that classifies patients into chronic hepatitis, cirrhosis and cirrhosis with previous decompensation has been suggested. We found that the new ACLF classification has clear differences in predisposition, type of injury, accompanying organ failure and long-term outcome by subtype. ACLF patients showed similar high short-term mortality, especially without liver transplantation, according to the subtype, but showed clear difference in the long-term mortality, indicating that the subtyping of ACLF by severity of underlying liver disease is useful.

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INTRODUCTION

Patients with either diagnosed or undiagnosed chronic liver disease occasionally present with an acute deterioration of liver function caused by direct or indirect insults to the liver. This event, in general, is termed acute-on-chronic liver failure (ACLF)^[1]. However, because of varied etiology and manifestations, there has been a great heterogeneity in defining the disease and, in fact, a recent systematic review has found more than a dozen definitions for ACLF^[2]. Among

these, there are 2 mainstream definitions most widely used in clinical settings and research. The Asian Pacific Association for the Study of the Liver (APASL) consensus introduced an ACLF definition as "an acute hepatic insult manifesting as jaundice (serum bilirubin ≥ 5 mg/dL) and coagulopathy (INR ≥ 1.5), complicated within 4 wk by ascites and/or encephalopathy in patients with previously diagnosed or undiagnosed chronic liver disease/cirrhosis, and is associated with a high 28-d mortality"^[3]. The European Association for the Study of the Liver-chronic liver failure (EASL-CLIF) Consortium defined ACLF as acute decompensation of cirrhosis in the form of one or more major complications of liver disease, including ascites, hepatic encephalopathy, gastrointestinal bleeding, and bacterial infection, associated with at least two organ failures with one being renal failure (serum creatinine ≥ 1.5 mg/dL) and high 28-d mortality of greater than 15%^[4]. They share a common idea that ACLF is a spectrum of disease with varying severity, characterized by multiple organ failure and high mortality^[5-8], with liver transplantation (LT) as the only definitive curative option^[9-11]. However, the discordant details between the 2 definitions results in confusion rather than clarification of the situation. In specific, the 2 groups suggest different explanations for the duration of illness, severity of the underlying liver disease, and the type of precipitating events. However, these factors are what essentially define ACLF, because each factor determines the acuteness of event, chronicity of liver disease, and the type of insult, respectively.

To embrace previously suggested definitions and better clarify this condition, Jalan *et al*^[12] recently proposed a new definition and classification for ACLF. They defined ACLF as "a syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis which is characterized 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"^[12]. In their definition, they included any chronic liver disease, regardless of the presence of cirrhosis, and a wide range of precipitating events that could damage liver function either directly or indirectly. Patients with chronic liver disease but without cirrhotic features were categorized as type A. Type B ACLF was a group with previously well-compensated cirrhosis, while those with a history of jaundice and/or complications of portal hypertension were included in type C. However, they admitted that this is a working definition which is only to identify patients from whom to collect data to ultimately reach a validated definition.

Therefore, the aims of this study were to investigate and compare clinical characteristics, including predisposition (etiologies of chronic liver disease), injury (precipitating events), response (manifestations), short and long-term outcomes according to spectrum

of chronic liver disease (non-cirrhosis, cirrhosis and cirrhosis with previous decompensation), thereby, to determine relevance of subtyping ACLF by severity of underlying disease for future practice and research.

MATERIALS AND METHODS

Study design and study population

This is a retrospective cohort study conducted by using electronic medical records of ACLF patients who visited Samsung Medical Center between January 1, 2011 and June 30, 2014. We included patients 18 years or older and with deteriorated liver function, defined as jaundice (serum bilirubin ≥ 5 mg/dL) and coagulopathy (PT INR ≥ 1.5). A total of 268 patients were identified, and we excluded 101 patients due to the following reason: acute liver failure patients without underlying chronic liver disease ($n = 91$), patients with chronic hepatic decompensation ($n = 9$) (chronic liver failure without acute component), and patients who were on warfarin ($n = 6$). Chronic liver disease was defined when there was evidence of chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection by reviewing serologic markers and history, history of significant alcohol intake, history of chronic abnormality in liver profiles with serologic evidence of autoimmune liver disease, and/or radiological evidence of cirrhosis. The final study sample includes 167 patients. The study was reviewed and approved by the Institutional Review Board of Samsung Medical Center. Because the study is based on the retrospective analysis of existing administrative and clinical data, the requirement of obtaining informed patient consent was waived by the Institutional Review Board of Samsung Medical Center. Patient records/information was anonymized and de-identified prior to analysis.

Measurements

Data on etiologies and severity of underlying liver disease at the time of diagnosis were evaluated. Acute precipitating events, major presenting complications and the presence of organ failure and systemic inflammatory response syndrome (SIRS) were assessed. Additionally, laboratory measurements including complete blood count (CBC), liver function tests, renal function tests, coagulation profile and culture tests were reviewed. Information on LT, mortality and cause of death was collected until a year after the enrollment.

Predisposition and ACLF types

Alcoholic liver disease (ALD), chronic hepatitis B, chronic hepatitis C, autoimmune hepatitis (AIH), Wilson's disease, biliary cirrhosis, Budd-Chiari syndrome, and cryptogenic liver cirrhosis were regarded as chronic liver diseases. Chronic liver disease and cirrhosis were confirmed by a thorough review of available previous medical records: biochemical analysis, ultrasonography, abdomen computed tomography (CT), and

esophagogastroduodenoscopy (EGD). Cirrhosis was considered to be present if thrombocytopenia (platelet $< 150 \times 10^3/\mu\text{L}$), splenomegaly, ascites (by cross sectional images), varices (by EGD, cross-sectional images, or history of variceal bleeding), and cirrhotic features of the liver (nodular surface or caudate lobe hypertrophy) in cross-sectional images were present^[13]. When the findings were compatible with chronic liver disease without any features of liver cirrhosis, patients were designated type A. If patients had a previous history of jaundice and/or complications of portal hypertension such as variceal bleeding, ascites or hepatic encephalopathy, these patients were classified as type C of ACLF. Well-compensated liver cirrhosis patients were included in type B.

Injury, responses and survival

As possible injury, hepatic insults included reactivation of HBV, alcohol ingestion, superinfection by hepatitis A virus (HAV), toxic hepatitis, and AIH flare. Bacterial infection/sepsis, variceal bleeding, and non-variceal bleeding were regarded as extrahepatic insults. Alcohol consumption was considered as the most probable precipitating etiology when active alcohol consumption was documented within the last 4 wk and there was no other apparent cause of the acute event. Positive anti-HAV IgM by ELISA confirmed acute HAV infection. In addition, bacterial infection/sepsis was considered as an acute insult in case of definite evidence of infection, such as positive cultures of blood, ascites, urine and sputum and/or when clinically suspected. If patients had multiple injuries (*e.g.*, HBV reactivation and variceal bleeding) and if it is difficult to differentiate an initial one, both of them were considered. Injury was categorized as unknown when all other possible causes were not matched.

The Model for End-stage Liver Disease (MELD) score, SIRS, and organ failure were investigated^[14]. The presence of each organ failure, as well as the number of organ failures was evaluated at the initial visit (baseline). Type of organ failure was categorized into none, hepatic/coagulation, and extrahepatic \pm hepatic/coagulation. Extrahepatic organ failure was defined for renal, cerebral, circulatory and respiratory organ failure. Organ failure was defined according to the EASL-CLIF score^[4].

The primary end-point was 30-d survival. Secondary end-point was 30-d transplant free survival, 1-year overall survival and 1-year transplant free survival. With transplant free survival, transplant was considered as end point (failure). Patient survival was assessed for 365 d after the initial visit. Patients who were lost to follow-up without reaching the end point were classified as censored cases.

Statistical analysis

Means \pm SD were used for describing continuous outcomes, and analysis of variance was applied to

Table 1 Predisposition, injury and response according to the subtypes *n* (%)

	Type A (<i>n</i> = 34)	Type B (<i>n</i> = 53)	Type C (<i>n</i> = 80)	<i>P</i> value
Age (yr) ^c	51.9 ± 10.3	54.0 ± 10.3	58.0 ± 11.1	0.010
Male	20 (58.8)	32 (60.4)	59 (73.8)	0.159
Predisposition				
HBV ^c	21 (61.8)	19 (35.9)	28 (35.0)	0.020
Alcohol ^{1a,c}	4 (11.8)	25 (47.2)	33 (41.3)	0.001
HCV	0 (0.0)	0 (0.0)	6 (7.5)	0.051
Autoimmune ^c	6 (17.7)	2 (3.8)	2 (2.5)	0.008
Others	3 (8.8)	7 (13.2)	11 (13.8)	0.827
Injury				
Hepatic ^{abc}	30 (88.2)	31 (58.5)	9 (11.3)	< 0.001
Extrahepatic ^{abc}	0 (0.0)	13 (24.5)	44 (55.0)	< 0.001
Unknown ^e	4 (11.8)	4 (7.6)	23 (28.8)	0.005
Both (hepatic + extrahepatic)	0 (0.0)	5 (9.4)	4 (5.0)	0.165
Response				
MELD score	29 ± 8.3	27 ± 5.7	26 ± 6.3	0.137
SIRS	9 (26.5)	19 (35.9)	30 (37.5)	0.516
Organ failures by CLIF-SOFA				
Type of organ failure				
None ^e	8 (23.5)	8 (15.1)	28 (35.0)	0.035
Hepatic/coagulation ^{ce}	19 (55.9)	34 (64.2)	21 (26.3)	0.000
Extrahepatic ^c	7 (20.6)	11 (20.8)	31 (38.8)	0.038
Specific organ type				
Hepatic ^{ce}	26 (76.5)	42 (79.3)	28 (35.0)	< 0.001
Coagulation	10 (29.4)	11 (20.8)	21 (26.3)	0.630
Renal	7 (20.6)	5 (9.4)	17 (21.3)	0.182
Cerebral	2 (5.9)	4 (7.6)	11 (13.8)	0.418
Circulatory ^{ce}	1 (2.9)	4 (7.6)	16 (20.0)	0.021
Respiratory	2 (5.9)	1 (1.9)	4 (5.0)	0.679
Number of organ failure				
None ^e	8 (23.5)	8 (15.1)	28 (35.0)	0.035
One ^e	13 (38.2)	29 (54.7)	26 (32.5)	0.036
≥ 2	13 (38.2)	16 (30.2)	26 (32.5)	0.733

^a*P* < 0.05 Type A vs B using Bonferroni's post hoc test; ^c*P* < 0.05 Type A vs C using Bonferroni's post hoc test; ^e*P* < 0.05 Type B vs C using Bonferroni's post hoc test. HBV: Hepatitis B virus; HCV: Hepatitis C virus; AIH: Autoimmune hepatitis; MELD: Model for end stage liver disease; SIRS: Systemic inflammatory response syndrome; CLIF-SOFA: Chronic liver failure-sequential organ failure assessment.

compare the means of the different ACLF groups. In addition, Bonferroni's method was used as a post-hoc test for group comparison. χ^2 test and Fisher's exact test were employed as needed for categorical variables. The Kaplan-Meier method was applied for estimating the survival rates, and the differences of the survival were compared using a log-rank test. We also obtained Bonferroni adjusted *P*-values to compensate multiple testing procedures. *P*-value of < 0.05 was considered statistically significant.

RESULTS

Predisposition, injury and response according to the ACLF types

Comparison of baseline characteristics is shown in Table 1. The etiology of predisposing liver diseases was significantly different according to the ACLF types. Hepatitis B was the most common etiology in type A, while ALD was more common in type B and type C. AIH was more common in type A. Interestingly, except for unknown cases, all ACLF of type A were caused by injury directed at the liver. HBV flare was the most common precipitating event in type A. On

the other hand, extrahepatic insults such as bacterial infection and bleeding episodes were more responsible for type C. Type B were in-between type A and type C. The specific injuries (precipitating events) are shown in Table 2. MELD score and SIRS at diagnosis were comparable among the types. In terms of organ failure, defined by the CLIF-SOFA system, the extrahepatic failure was more frequent in type C than type A, and hepatic/coagulation failure was more frequent in types A and B than type C.

Outcomes according to the ACLF types

At 30 d, the overall survival rate and the transplant-free survival rate were 83.2% and 61.1%, respectively. At 1 year, the overall survival rate and the transplant-free survival rate were 68.3% and 46.7%, respectively. The most common cause of death was infection (52.8%), followed by bleeding (20.8%). During the follow-up period, 44 patients (12, 16 and 16 in types A, B, and C, respectively) received LT.

According to each ACLF type, the overall 30-d survival rate (85.3%, 81.1% and 83.7% for type A, B and C, respectively, *P* = 0.31; Figure 1A) and transplant-free survival rate at 30 d (55.9%, 65.5%

Table 2 Specific injury according to the acute on chronic liver failure type *n* (%)

	Type A	Type B	Type C	<i>P</i> value
HBV flare ^{abc}	17 (50.0)	11 (20.8)	4 (5.0)	< 0.001
Alcohol ^{ac}	3 (8.8)	19 (35.9)	6 (7.5)	< 0.001
HAV	3 (8.8)	1 (1.9)	1 (1.3)	0.130
Toxin ^e	5 (14.7)	9 (17.0)	3 (3.8)	0.021
AIH flare ^c	7 (20.6)	2 (3.8)	0 (0.0)	< 0.001
Infection ^{ac}	0 (0.0)	13 (24.5)	32 (40.0)	< 0.001
Varix bleeding	0 (0.0)	3 (5.7)	11 (13.8)	0.035
Other bleeding	0 (0.0)	2 (3.8)	6 (7.5)	0.215
Unknown ^e	4 (11.8)	4 (7.6)	23 (28.8)	0.005

^a*P* < 0.05, Type A *vs* B using Bonferroni's post hoc test; ^c*P* < 0.05 Type A *vs* C using Bonferroni's post hoc test; ^e*P* < 0.05 Type B *vs* C using Bonferroni's post hoc test. HBV: Hepatitis B virus; HAV: Hepatitis A virus; AIH: Autoimmune hepatitis.

and 62.5% for type A, B and C, respectively, *P* = 0.33; Figure 1B) were not different among the types. However, the overall 1-year survival was significantly higher in type A (85.3%), as compared to types B (71.7%) and C (58.7%) (*P* = 0.02; Figure 1A). All mortality occurred within 30 d in type A, but mortality continued to occur after 30 d in types B and C. Transplant-free survival rate at 1-year was also lower in type C, as compared to types A and B; but the difference was not statistically significant (52.9%, 51.7% and 34.8% for type A, B and C, respectively, *P* = 0.86; Figure 1B).

Outcome according to the type of organ failure

Among 167 patients, 49 patients (29.3%) had extrahepatic organ failures with or without hepatic/coagulation failure, 74 patients (44.3%) had hepatic/coagulation failure, and 44 patients (26.3%) showed no organ failure defined by EASL-CLIF. The 30-d and 1-year overall survival rate was 55.9% and 51.6% for patients with extrahepatic organ failures, 79.6% and 67.4% for hepatic and/or coagulation organ failure, and 90.0% and 74.5% for patients without organ failure, respectively (Figure 2A). The 30-d and 1-year transplant free survival rate was 48.9% and 19.6% for patients with extrahepatic organ failures, 54.9% and 37.6% for hepatic and/or coagulation organ failure, and 78.7% and 56.7% for patients without organ failure (Figure 2B).

Outcome according to the LT

The 30-d and 1-year overall survival rate was 74.8% and 56.2% for patients without LT, while it was 95.9% and 83.5% for patients with LT. The 30-d survival rate was higher in patients with LT in all ACLF types, although the difference was statistically significant only in type C (Type A: 92.3% *vs* 80.0%, *P* = 0.37; Type B: 93.7% *vs* 76.7%, *P* = 0.14; type C: 100% *vs* 78.7%, *P* = 0.029) and 1-year survival rate (Type A: 92.3% *vs* 80.0%, *P* = 0.37; Type B: 80.2% *vs* 62.4%, *P* = 0.18; Type C: 80.0% *vs* 42.1%, *P* = 0.007).

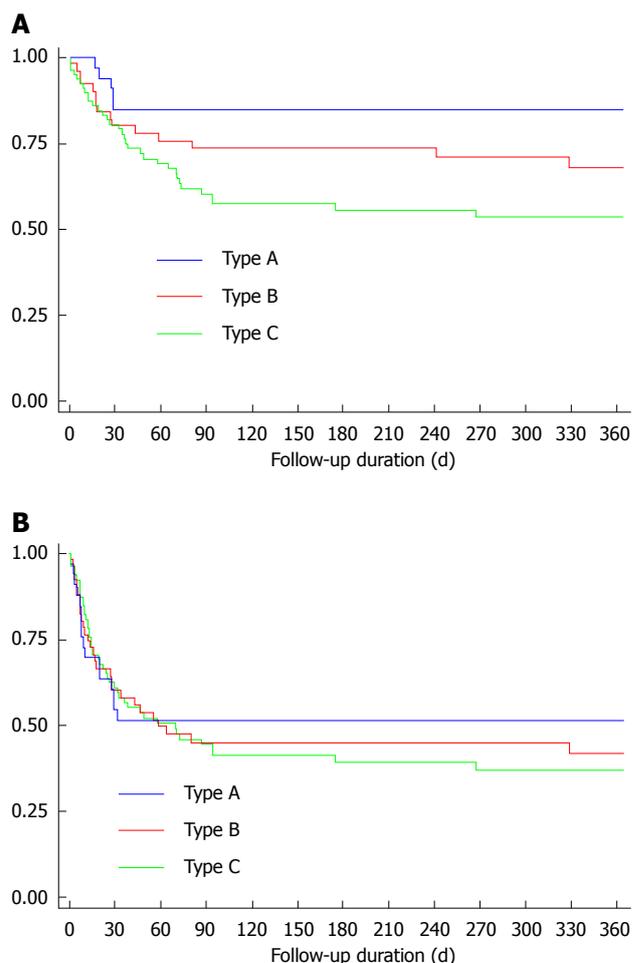


Figure 1 Survival according to newly proposed acute-on-chronic liver failure types. The short-term overall and transplant-free survival was not significantly different according to acute-on-chronic liver failure (ACLF) type, while long-term overall survival was significantly different. A: Overall; B: Transplant-free survival.

DISCUSSION

ACLF, by in the simplest term, is "abrupt hepatic decompensation in patients with chronic liver disease"^[12]. Moreover, ACLF is usually defined as a condition wherein patients are at significantly increased risk for mortality, with improvement in survival with LT^[12]. There is controversy regarding what constitutes a chronic liver disease. APASL includes non-cirrhotic chronic liver disease/cirrhosis, but not decompensated cirrhosis to define chronic liver disease^[3,15] whereas EASL-AASLD includes only cirrhosis, either compensated or decompensated^[4]. The newly proposed ACLF definition includes all spectrum of chronic liver disease and categorizes them as type A (non-cirrhotic), type B (cirrhosis), and type C (decompensated cirrhosis)^[12]. The present study included all stages of chronic liver disease patients with acute deteriorated liver function, defined by jaundice (serum bilirubin \geq 5 mg/dL) and coagulopathy (PT INR \geq 1.5). All types of patients showed comparably high short-term mortality, and improved survival with LT. The overall survival was

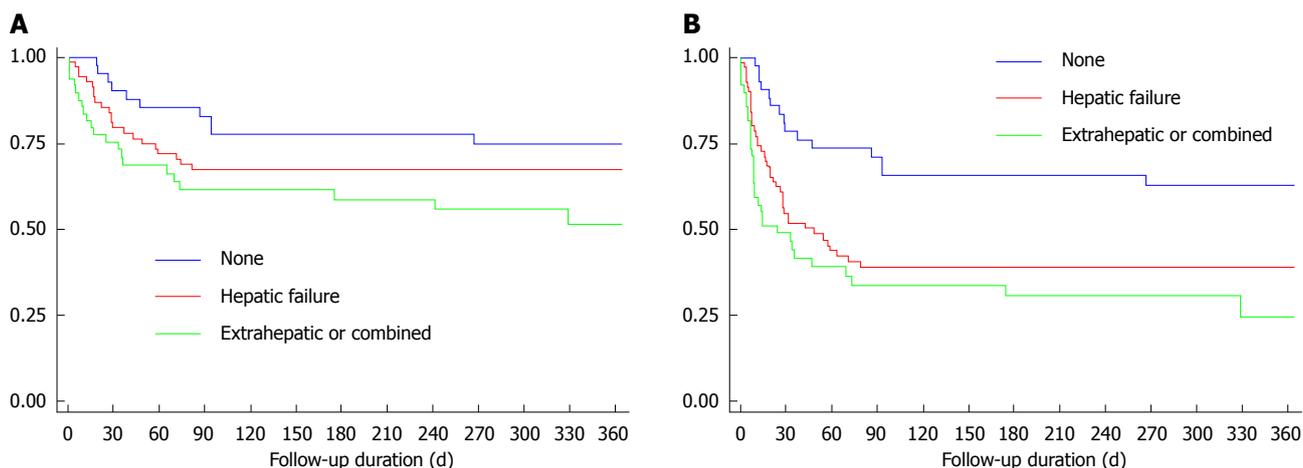


Figure 2 Survival according to the types of organ failure defined by EASL-CLIF. Extrahepatic organ failure showed worst survival, but patients without organ failure also showed low transplant-free survival. A: Overall; B: Transplant-free survival.

significantly better for patients who received LT, and the survival benefit by LT was most prominent in type C (1-year survival rate: 80.0% vs 42.1% for with and without LT, $P = 0.007$). Thus, our finding support that ACLF can be defined for all spectrum of chronic liver disease (*i.e.*, non-cirrhotic to decompensated cirrhosis).

ACLF, by definition, also implies acute insult that leads to acute deterioration of liver function^[3]. For example, superimposed viral hepatitis in chronic liver disease is a well-known injury to put patients at higher risk for acute deterioration of liver function^[16]. Bacterial infection or sepsis is also a major risk factor for adverse event in cirrhosis patients^[17,18]. Acute insults that lead to ACLF can be categorized as hepatotrophic insult (viral hepatitis, alcohol, drug, autoimmune hepatitis, Wilson’s disease, *etc.*) and non-hepatotrophic insults (infection, surgery, bleeding, *etc.*)^[3]. Because ACLF is a potentially reversible disease^[1], it is very important to identify acute insults, and have immediate intervention (*e.g.*, antiviral therapy for hepatitis B, treatment for infection). Importantly, except for few causes where specific injury was uncertain, all type A injuries were hepatotrophic injury (Table 1). In contrast, type C mostly comprised non-hepatotrophic insults, although hepatotrophic insults were observed as well. Type B was in between type A and type C. Organ failure rate was similar in terms of renal, cerebral, coagulation and respiratory failure by ACLF type, but hepatic failure was less frequent and circulatory failure was more frequent in type C (Table 1). Higher rate of circulatory failure in decompensated cirrhosis could be explained by circulatory dysfunction observed in cirrhosis^[19]. Differences in injury (precipitating insult) and response (organ failure rates) by ACLF types provide a rationale to categorize ACLF as type A, B and C, which is also helpful in searching potential injury and planning specific intervention in patients with ACLF. It is also noteworthy that type B and type C were still at risk for mortality after 30 d, leading to a decreased 1-year survival compared to type A. This also provides a

rationale to categorize patients who experienced ACLF, as different long-term prognosis is expected.

The presence of “one or more extrahepatic organ failure” was suggested to define ACLF in the newly proposed ACLF definition^[12]. However, question remains whether “extrahepatic organ failures” are mandatory to define ACLF. ACLF, by its simplest meaning, does not include “extrahepatic organ failures”. The purpose of including “extrahepatic organ failures” in the ACLF definition is to define the population at high risk for mortality. Our data did indeed show extremely poor short-term survival for patients with extrahepatic organ failures defined by CLIF-SOFA (55.9% and 48.9% for overall and transplant free 30-d survival), and good short-term survival for patients without any organ failures defined by CLIF-SOFA (90.0% and 78.7% for overall and transplant free 30-d survival). This is consistent with previous findings that extrahepatic organ failures are an important factor for survival in ACLF^[20]. The association between organ failure and poorer prognosis is supported by numerous studies^[4,11,21-26]. However, patients with only hepatic/coagulation failure also showed high short-term mortality (79.6% and 54.9% for 30-d overall and transplant-free survival). Furthermore, mortality rate exceeding 15% without LT (90.0% and 79.7% for 30-d overall and transplant-free survival) even for patients without any organ failures defined by CLIF-SOFA. Short-term mortality rate of 15% are used to define increased mortality in patients with ACLF^[4]. In this sense, our findings suggest that patients without extrahepatic organ failures could be defined as ACLF as well, when they present with acutely deteriorated liver function, defined by jaundice and coagulopathy. It is likely that presence of “extrahepatic organ failures” may reflect severity of ACLF, however, it may not be a prerequisite for being defined as ACLF. In fact, the APASL definition does not require “extrahepatic organ failures” to define ACLF^[3].

This study had some limitations. First, some of

information on precipitating events could not be obtained regardless of thorough review of medical records because of the retrospective study design. We defined acute deteriorated liver function by jaundice and coagulopathy, as suggested by APASL^[15]. However, in the CANONIC study, acute development of large ascites, hepatic encephalopathy, gastrointestinal hemorrhage, bacterial infection or any combination of above, are used to define acute deteriorated liver function^[4]. Thus, patients who do not fulfill APASL criteria for liver failure, but present with acute deteriorated liver function, defined in the CANONIC study, are beyond the scope of this study. Lastly, sample size was relatively small, requiring larger scale, prospective study.

In conclusion, ACLF is a distinct syndrome that can be defined as acute deteriorated liver function, precipitated by either direct or indirect injury to the liver, resulting in high short-term mortality with LT as a curative option. The study showed that all spectrum of chronic liver patients with acute deteriorated liver function defined by jaundice (serum bilirubin \geq 5 mg/dL) and coagulopathy (PT INR \geq 1.5) can be defined as ACLF. The newly proposed ACLF classification was clinically relevant because different insults and response could be expected, which also suggest different pathophysiology, different management strategy, and different long-term outcome. This suggest that classifying ACLF subtype according to the severity of underlying liver disease is useful for defining, clarifying and comparing ACLF.

COMMENTS

Background

There has been a great heterogeneity in defining the acute-on-chronic liver failure (ACLF). Recently, ACLF subtype according to the severity of underlying liver disease has been proposed.

Research frontiers

Retrospective cohort of chronic liver disease patients with acute deteriorated liver function were analyzed to see whether ACLF subtype is useful.

Innovations and breakthroughs

The study showed that all spectrum of chronic liver patients with acute deteriorated liver function defined by jaundice (serum bilirubin \geq 5 mg/dL) and coagulopathy (PT INR \geq 1.5) can be defined as ACLF. The newly proposed ACLF classification was clinically relevant because different insults and response could be expected, which suggest different pathophysiology, different management strategy, and different long-term outcome.

Applications

Classifying ACLF patients into ACLF subtype will better clarify this condition, and can be used in clinical practice.

Terminology

ACLF is a spectrum of disease with varying severity, characterized by multiple organ failure and high mortality.

Peer-review

This is an interesting and well-written paper addressing an important topic, *i.e.*

the outcome of patients with acute-on-chronic liver disease based on cause of liver disease and precipitating factors of acute disease.

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