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Original Article

Impact of Onset Time, Number, Type, and Sequence of Extrahepatic Organ Failure on Prognosis of Acute-on-chronic Liver Failure

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Abstract

Background and Aims: The impact of the characteristics of extrahepatic organ failure (EHOF) including the onset time, number, type, and sequence on the prognosis of acute-on-chronic liver failure (ACLF) patients remains unknown. This study aimed to identify the association between the characteristics of EHOF and the prognosis of ACLF patients. ***Methods:*** ACLF subjects enrolled at six hospitals in China were included in the analysis. The risk of mortality based on the characteristics of EHOF was evaluated. Survival of study groups was compared by Kaplan–Meier analysis and log-rank tests. ***Results:*** A total of 736 patients with ACLF were included. EHOF was observed in 402 patients (54.6%), of which 295 (73.4%) developed single EHOF (SEHOF) and 107 (26.6%) developed multiple EHOF (MEHOF). The most commonly observed EHOF was coagulation failure (47.0%), followed by renal (13.0%), brain (4.9%), respiratory (4.3%), and circulatory (2.3%) failure. Survival analysis found that MEHOF or SEHOF patients with brain failure had a worse prognosis. However, no significant outcome was found in the analysis of the effect of onset time and sequence of failed organs on prognosis. Patients were further divided into three risk subgroups by the EHOF characteristics. Kaplan–Meier analysis showed that risk stratification resulted in the differentiation of patients with different risks of mortality both in the training and validation cohorts. ***Conclusions:*** The mortality of ACLF patients was determined by the number and type, but not the onset time and sequence of EHOF. Risk stratification applicable to clinical practice was established.

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Keywords: Extrahepatic organ failure; Acute-on-chronic liver failure; Prognosis; Brain failure.

Abbreviations: ACLF, acute-on-chronic liver failure; APASL, Asian Pacific Association for the Study of the Liver; CLIF-C ACLF, chronic liver failure Consortium acute-on-chronic liver failure; CLIF-C OF, chronic liver failure Consortium organ failure score; CLIF-SOFA, chronic liver failure Consortium sequential organ failure assessment; Cr, creatinine; EASL-CLIF, the European Association for the Study of the Liver-Chronic Liver Failure Consortium; EHOF, extrahepatic organ failure; HBV, hepatitis B virus; HE, hepatic encephalopathy; INR, international normalized ratio; MEHOF, multiple extrahepatic organ failure; MELD, Model for End-Stage Liver Disease; NACSELD, North American Consortium for the Study of End-Stage Liver Disease; SEHOF, single extrahepatic organ failure; Simul, simultaneously; TBil, total bilirubin; WGO, World Gastroenterology Organization.

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Introduction

Acute-on-chronic liver failure (ACLF) refers to an entity characterized by acute deterioration on a background of chronic liver disease caused by precipitating events or non-identifiable triggers, which carries high short-term mortality.[1,2] Although it is widely recognized that the prognosis of ACLF is poor, the definitions of ACLF vary worldwide.[3] Three major definitions of ACLF have been proposed. The European Association for the Study of the Liver–Chronic Liver Failure (EASL-CLIF) Consortium and North American Consortium for the Study of End-Stage Liver Disease (NACSELD) defined

ACLF mainly by the existence of extrahepatic organ failure (EHOF).[4,5] The Asian Pacific Association for the Study of the liver (APASL) focused more on the deterioration of liver failure, and EHOF was not essential in the identification of ACLF.[6]

The divergent opinions on East-West definitions of ACLF may be attributed to differences in the etiology of chronic liver disease in Eastern and Western countries.[7] In Eastern patients the main etiology is hepatitis B virus (HBV)-related ACLF. Alcohol-related ACLF is the main etiology in Western patients. Despite the differences of the definitions of ACLF in the East and West, EHOF is always observed in ACLF, and it was reported that EHOF was associated with the prognosis of ACLF patients.[5,8,9] Several studies have reported that the number of failed organs was associated with the mortality of ACLF patients.[5,9,10] However, the effects of EHOF characteristics including onset time, type, and sequence on the prognosis of ACLF remain unknown. Therefore, this study investigated the association between the characteristics of EHOF development and the prognosis of ACLF patients in a large multicenter cohort.

Methods

Patients, study design, and data collection

This retrospective multicenter cohort study was performed in China (ChiCTR1900021539). Patients who were diagnosed as ACLF on admission at the Tianjin Third Central Hospital, Fifth Medical Center of Chinese PLA General Hospital, Beijing You'an Hospital, Shandong Provincial Hospital, First Hospital of Shanxi Medical University, and Third Hospital of Hebei Medical University between November 1, 2012 and October 7, 2019 were included in the analysis. In addition, ACLF patients hospitalized at Tianjin Third Central Hospital between January 1, 2021 and June 30, 2021 were included for validation.

Considering the controversy between the East and West in the definitions of ACLF, the World Gastroenterology Organization (WGO) generalized a globally harmonized consensus definition of ACLF applicable in both the East and West. They stated that ACLF can occur at all stages of the natural history of chronic liver disease, including in the absence of cirrhosis as well as against a background of compensatory cirrhosis and decompensated cirrhosis.[11] Based on the WGO recommendation and the APASL definition, the inclusion criteria of ACLF in this study were: deterioration of liver function within 28 days after an acute insult, manifesting as jaundice (serum total bilirubin [TBil] ≥5 mg/dL) and coagulation dysfunction (international normalized ratio [INR] ≥1.5 or prothrombin activity <40%), on the backdrop of chronic liver disease including noncirrhosis, compensatory cirrhosis, and decompensated cirrhosis. Patients were divided into three WGO categories,[11] namely type A patients without cirrhosis, type B patients with well-compensated cirrhosis, and type C patients with previous hepatic decompensation.

In-hospital and outpatient data were collected from electronic medical records. The exclusion criteria were: (1) liver tumor and other malignant tumors; (2) severe chronic extrahepatic disease, such as severe chronic kidney disease with renal failure, severe chronic obstructive pulmonary disease with respiratory failure, severe coronary heart disease with heart failure, or severe coagulation failure caused by hematological system diseases; (3) post-liver transplantation; (4) patients with incomplete clinical indicator information. The study procedures complied with the principles of the Declaration of Helsinki. Because it was a retrospective study, the Ethics Committees approved it and waived the need for informed consent.

Definitions

The precipitating events were classified into the following categories: non-identifiable, hepatic insult, extrahepatic insult or both. EHOF was diagnosed by the following criteria:[4,12] (1) brain failure West-Haven grade III–IV, (2) renal failure creatinine (Cr) ≥2 mg/dL or use of renal replacement therapy, (3) coagulation failure INR≥2.5, (4) circulation failure use of vasoactive drugs, (5) respiratory failure $PaO_2/FiO_2 \leq 200$ or $SpO_2/FiO_2 \leq 214$ or the need for mechanical ventilation.

Patients who developed EHOF within 24 h from the diagnosis of ACLF were defined as early-onset EHOF, while patients who developed EHOF more than 24 h from the time point when patients met the diagnostic criteria of ACLF were defined as late-onset EHOF. According to the number of EHOF, patients were classified into three groups: none, single extrahepatic organ failure (SEHOF), and multiple extrahepatic organ failure (MEHOF, two or more extrahepatic organs failure). The information on the sequence of failed organs in patients with MEHOF was collected. MEHOF patients were classified according to the type of first failed extrahepatic organ diagnosed, as (1) brain failure, (2) renal failure, (3) respiratory or circulatory failure (RC), or (4) two or more EHOF diagnosed simultaneously (Simul).

Statistical analysis

Continuous data were reported as median and interquartile range or mean±standard deviation. Between-group differences were assessed with Mann-Whitney or *t* tests as appropriate. Categorical variables were reported as frequency and percentage and compared with chi-squared or Fisher's exact tests. The effect of the characteristics of EHOF and risk stratification on the mortality of ACLF patients were analyzed by Cox regression. Risk factors for EHOF were identified by univariate and multivariate logistic regressions. The Kaplan–Meier method and log-rank tests were used to analyze between-group survival. The statistical analysis was performed by R software version 4.1.3. A two-sided *p*-value <0.05 was considered significant.

Results

Clinical characteristics and outcomes of the included patients

The inclusion and exclusion flowchart of ACLF patients is shown in Figure 1. Of the 736 patients who were included, 402 (54.6%) developed EHOF, of which 271 (36.8%) were early-onset and 131 (17.8%) were late-onset (Fig. 1). Table 1 shows the clinical characteristics of the study patients and the comparison between patients with and without EHOF. The mean age was 49 years-old and most (78.7%) were male. HBV infection was the most frequent etiology (58.0%), followed by alcoholic liver disease (19.7%), and 7.7% of the patients had HBV infection combined with alcoholic liver disease while 14.5% had other etiologies. Hepatic insults were observed in 25.8% of patients, while 16.3% of patients had extrahepatic insults, and 6.2% had both hepatic and extrahepatic insults. The overall 28- and 90-day survival rates were 78.3% and 64.6%, respectively. Compared with patients without EHOF, those with EHOF were older (p=0.003). The Child-Pugh, Model for End-Stage Liver Disease (MELD), chronic liver failure Consortium sequential organ failure assessment (CLIF-SOFA), chronic liver failure Consortium organ failure score (CLIF-C OF), and chronic liver failure Consortium acute-on-chronic liver failure (CLIF-C ACLF) scores were higher in patients with EHOF (p<0.001). Extrahepatic insults were more likely to be observed in patients with EHOF

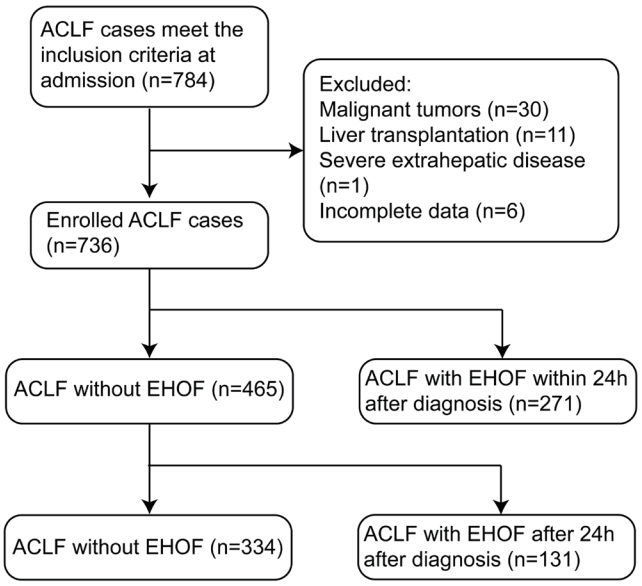

Fig. 1. Inclusion and exclusion flowchart of ACLF patients. ACLF, acute-on-chronic liver failure; EHOF, extrahepatic organ failure.

compared to patients without EHOF. Besides, patients with EHOF were more likely to develop acute variceal bleeding and bacterial infection.

Characteristics of EHOF

Of the 736 patients, 402 (54.6%) developed 527 EHOF events. The numbers, and types of EHOF are shown in Figure 2. Coagulation failure was the most common type of EHOF (346, 47.0%), followed by renal (96, 13.0%), brain (36, 4.9%), respiratory (32, 4.3%), and circulatory (17, 2.3%) failures. Of the patients with EHOF, early-onset EHOF occurred in 67.4% of the patients and late-onset EHOF occurred in 32.5% (Fig. 3A). Of the patients with EHOF, 295 (73.4%) developed SEHOF, 91 (22.6%) developed two EHOF, and 16 (4.0%) patients developed three or more EHOF (Fig. 3B). For patients who had MEHOF (n=107), 5.6% developed brain failure first, 10.3% developed renal failure first, 45.8% developed coagulation failure first, 5.6% developed respiratory or circulatory failure first, and 32.7% of patients had two or more organs failure diagnosed Simul (Fig. 3C).

The characteristics of EHOF according to the etiology and bacterial infection are shown in Table 2. When divided by etiology, alcohol-related ACLF patients were more likely to develop renal failure compared with HBV-related ACLF patients (p=0.001). In addition, patients with infections were more likely to develop renal and coagulation failure (p<0.05). MEHOF was more frequently observed in patients with infection than in patients without infection. Univariate and multivariate logistic regressions identified age and infection as independent risk factors for the development of EHOF (Supplementary Table 1).

Effect of EHOF on the prognosis of ACLF patients

Patients with EHOF had a lower 28- and 90-day survival compared with those without EHOF (no EHOF vs. EHOF 28-day survival was 89.9% vs. 68.6% and 90-day mortality was 79.6% vs. 52.3%; OR 2.95, [95% CI: 2.28–3.82]; p<0.001), as shown in Table 3. Patients with MEHOF were also 2.47 times more likely to not survive than those with SEHOF (p<0.001). We also investigated whether different types of EHOF had the same impact on the prognosis of ACLF patients. Analysis was first conducted in patients with SEHOF. As shown in Table 3, we found that in those with SEHOF, those with single brain failure had a worse prognosis than those with coagulation failure (coagulation vs. brain: OR 0.32, [95% CI: 0.13–0.78], p=0.012), respiratory or circulatory failure (respiratory or circulatory vs. brain: OR 0.15, [95% CI: 0.04–0.57], p=0.005). In ACLF patients with MEHOF, the effects of different types of EHOF on the survival were not significant (Supplementary Table 2).

Impact of the onset time of EHOF on the prognosis of ACLF patients was also investigated. Comparison of the clinical characteristics of early-onset and late-onset ACLF patients is shown in Supplementary Table 3. As shown in Table 3, the onset time was not associated with prognosis (p=0.910). The prognosis of late-onset ACLF patients was similar to that of early-onset ACLF patients (Supplementary Fig. 1, p=0.910). In patients with MEHOF (n=107), the sequence of organ failure was not associated with the prognosis (Table 3).

Risk stratification of ACLF patients based on the number and type of EHOF

We divided the patients into subgroups that differed in risk based on the type and number of EHOF. Patients were first classified into four groups: no EHOF, SEHOF without brain failure, single brain failure, and MEHOF. However, the prognosis of patients with MEHOF was not significantly different from those with single brain failure. For single brain failure vs. MEHOF, 28-day survival was 50.0% vs. 48.2% and 90-day survival was 33.3% vs. 30.6% (p=0.611). Hence, single brain failure and MEHOF were reclassified into one subgroup. Risk stratification based on the EHOF characteristics included three risk subgroups: low-risk (no EHOF), middle-risk (SEHOF without brain failure), and high-risk (single brain failure or MEHOF). According to the risk stratification, 45.4% of the patients were in low-risk, 39.3% were in middle-risk, and 15.4% were in high-risk subgroups (Supplementary Fig. 2).

Twenty-eight-day survival was 89.9% in the low-, 76.7% in the middle-, and 48.4% in the high-risk subgroups and 90-day survival was 79.6% in the low-, 60.6% in the middle-, and 30.8% in the high-risk subgroups. Kaplan–Meier analysis and log-rank tests showed that risk stratification differentiated patients with different risks of mortality (Fig. 4A, low vs. middle, p<0.001; low vs. high, p<0.001; and middle vs. high p<0.001).

Risk stratification also performed well in the differentiation of both HBV-related ACLF (Fig. 4B, p<0.001) and alcohol-related ACLF patients (Fig. 4C, p=0.004) in different risk subgroups. In HBV-related ACLF patients, prognosis of the low-risk subgroup was significantly better than that of the middle- and high-risk subgroups (low vs. middle, p<0.001; low vs. high, p<0.001, log-rank test). The prognosis of the middle-risk subgroup was also significantly better than that of the high-risk subgroup. The 28-day survival was 77.5% vs. 41.9% and the 90-day survival was 61.9% vs. 18.9% (p<0.001) in the middle-, and high-risk subgroup. In alcohol-related ACLF patients, a survival benefit was observed in the low-risk subgroup compared with the middle- and high-risk subgroups (p<0.001). The prognosis of the middle-risk subgroup was better than that of the high-risk subgroup but did not reach significance. The 28-day survival was 79.5% vs. 69.8% and the 90-day survival was 64.9% vs. 56.5% (p=0.305).

The effect of EHOF onset time in different risk subgroups was also investigated. The percentage of high-risk patients was higher in early-onset EHOF patients than in late-onset EHOF patients (Supplementary Fig. 3, p<0.001). In middle-risk subgroups, the prognosis of early-onset EHOF patients

Table 1. Clinical characteristics of ACLF patients with and without EHOF

Variable	All (*n*=736)	Without EHOF (*n*=334)	With EHOF (*n*=402)	*p*-value
Basic characteristics				
Age, years	49±12	47±12	50±12	0.003
Male sex, *n* (%)	579 (78.7)	265 (79.3)	314 (78.1)	0.752
Etiology, *n* (%)				0.678
HBV	427 (58.0)	194 (58.1)	233 (58.0)	
Alcohol	145 (19.7)	63 (18.9)	82 (20.4)	
HBV + alcohol	57 (7.7)	30 (9.0)	27 (6.7)	
Other	107 (14.5)	47 (14.1)	60 (14.9)	
WGO type, *n* (%)				0.707
A	144 (19.6)	66 (19.8)	78 (19.4)	
B	327 (44.4)	153 (45.8)	174 (43.3)	
C	265 (36.0)	115 (34.4)	150 (37.3)	
Insult, *n* (%)				0.043
Not identified	380 (51.6)	181 (54.2)	199 (49.5)	
Hepatic	190 (25.8)	93 (27.8)	97 (24.1)	
Extrahepatic	120 (16.3)	41 (12.3)	79 (19.7)	
Both	46 (6.2)	19 (5.7)	27 (6.7)	
Child-Pugh score	11.00 (10.00–11.00)	10.00 (9.00–11.00)	11.00 (10.00–11.00)	<0.001
MELD score	23.27 (19.38–27.10)	21.13 (17.63–24.43)	25.67 (21.12–28.70)	<0.001
CLIF-SOFA	8.00 (7.00–9.00)	7.00 (7.00–8.00)	8.00 (7.00–10.00)	<0.001
CLIF-C OF	9.00 (8.00–10.00)	8.00 (8.00–9.00)	10.00 (9.00–10.00)	<0.001
CLIF-C ACLF	40.92 (36.12–46.41)	37.75 (33.66–42.05)	43.69 (39.10–49.49)	<0.001
Complications				
W-H classification, *n* (%)				<0.001
0	590 (80.2)	298 (89.2)	292 (72.6)	
I	58 (7.9)	20 (6.0)	38 (9.5)	
II	52 (7.1)	16 (4.8)	36 (9.0)	
III	26 (3.5)	0 (0.0)	26 (6.5)	
IV	10 (1.4)	0 (0.0)	10 (2.5)	
Ascites, *n* (%)	573 (77.9)	263 (78.7)	310 (77.1)	0.660
AVB, *n* (%)	85 (11.5)	26 (7.8)	59 (14.7)	0.005
Bacterial infection, *n* (%)	354 (48.1)	137 (41.0)	217 (54.0)	0.001
Laboratory results at admission				
ALT, U/L	155.00 (54.00–455.00)	141.25 (59.50–445.50)	160.85 (51.25–471.20)	0.793
AST, U/L	177.00 (91.93–414.55)	168.50 (96.00–362.25)	179.90 (86.83–433.50)	0.975
Alb, g/L	29.00 (25.60–32.00)	29.05 (26.30–32.30)	28.30 (25.00–32.00)	0.044
TBil, μmol/L	290.20 (206.15–399.25)	292.60 (211.95–391.85)	285.30 (193.08–404.18)	0.771
PTA, %	34.00 (26.98–41.00)	39.00 (34.50–45.00)	28.00 (23.00–35.00)	<0.001
INR	2.13 (1.81–2.61)	1.87 (1.69–2.09)	2.56 (2.13–3.07)	<0.001
BUN, mmol/L	4.90 (3.42–7.48)	4.70 (3.30–6.55)	5.10 (3.59–9.06)	<0.001
Cr, μmol/L	73.00 (58.00–95.00)	70.00 (56.00–90.00)	76.50 (59.00–101.00)	0.003
Hb, g/L	120.00 (104.00–137.00)	122.00 (107.00–137.00)	119.00 (101.00–137.50)	0.102
WBC, $\times 10^9$/L	6.79 (4.90–9.55)	6.17 (4.63–8.71)	7.36 (5.23–10.13)	<0.001
PLT, $\times 10^9$/L	89.50 (59.75–127.00)	91.70 (62.00–127.00)	87.50 (56.00–126.75)	0.196

ACLF, acute-on-chronic liver failure; Alb, albumin; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; AVB, acute variceal bleeding; BUN, blood urea nitrogen; CLIF-C ACLF, chronic liver failure Consortium acute-on-chronic liver failure; CLIF-C OF, chronic liver failure Consortium organ failure score; CLIF-SOFA, chronic liver failure Consortium sequential organ failure assessment; Cr, creatinine; EHOF, extrahepatic organ failure; HBV, hepatitis B virus; HE, hepatic encephalopathy; Hb, hemoglobin; INR, international normalized ratio; MELD, model for end-stage liver disease; MEHOF, multiple extrahepatic organ failure; PLT, platelet; PTA, prothrombin activity; SEHOF, single extrahepatic organ failure; Simul, simultaneously; TBil, total bilirubin; WBC, white blood cell; W-H, West-Haven; WGO, World Gastroenterology Organization.

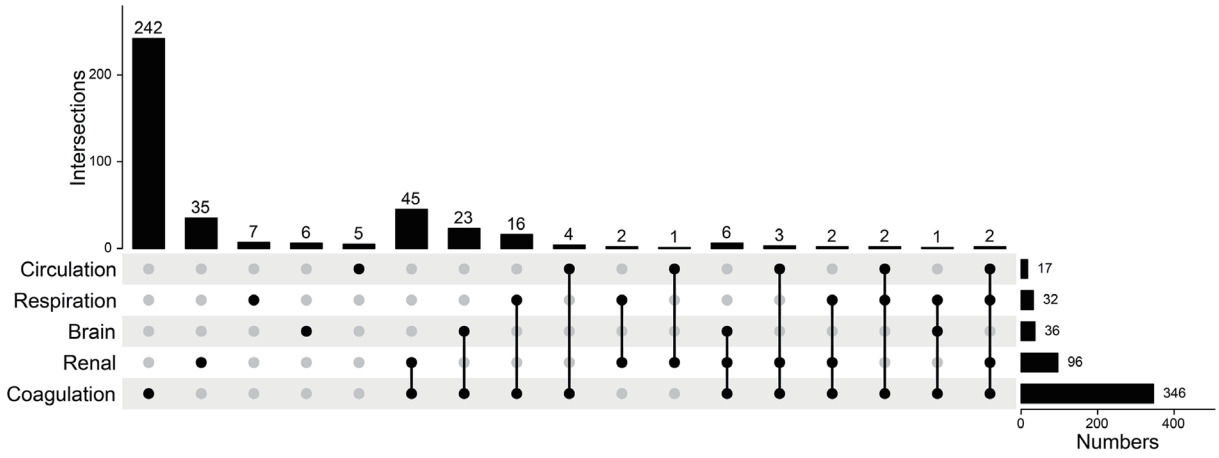

Fig. 2. Type and number of EHOF in ACLF patients. ACLF, acute-on-chronic liver failure; EHOF, extrahepatic organ failure.

was not different from late-onset EHOF patients, with 28-day survival 76.7% vs. 77.0% and 90-day survival 63.7% vs. 56.3% (p=0.160) (Supplementary Fig. 4A). In high-risk subgroups, the prognosis of early-onset EHOF patients was similar to that of late-onset EHOF patients with 28-day survival of 44.6% vs. 63.6% and 90-day survival of 32.9% vs. 23.1% (p=1.000) (Supplementary Fig. 4B). Multivariate Cox regression identified EHOF risk stratification as associated with the prognosis of ACLF patients (Supplementary Table 4), which further demonstrated that EHOF risk stratification was associated with the prognosis of ACLF patients.

Performance of the risk stratification system in the validation cohort

A total of 62 patients were included in the validation cohort. The mean age was 57 years and 61.2% of the patients were male. The etiology included 34 cases (54.8%) with HBV, 12 (19.3%) with alcoholic liver disease, 2 (3.2%) with HBV infection combined with alcohol liver disease, and 14 (22.5%) with other etiologies. Thirty-four patients (54.8%) developed EHOF. The most commonly observed EHOF was coagulation failure (28, 45.1%), followed by renal (12, 19.3%), respiratory (6, 9.6%), brain (4, 6.4%), and circulatory (2, 3.2%) failures. Of the patients with EHOF, 21 (61.7%) developed SEHOF, 10 (29.4%) developed two EHOFs, and 3 (8.8%) developed three or more EHOFs.

According to the risk stratification system, 28 patients (45.2%) were in the low-, 21 (33.9%) were in the middle-, and 13 (21.0%) were in the high-risk subgroups. Risk stratification also performed well in the differentiation of patients at different risks in the validation cohort (Fig. 4D, p<0.001). The 28-day survival was 100% in the low-, 71.4% in the middle- and 15.4% in the high-risk subgroups. The 90-day survival was 89.3% in the low-, 66.7% in the middle- and 15.4% in the high-risk subgroups. Kaplan–Meier analysis and log-rank tests showed that the risk stratification differentiated patients with different mortality risks (Fig. 4D; low vs. middle, p=0.036, low vs. high, p<0.001, and middle vs. high, p=0.002).

Discussion

Using a large, retrospective, and multi-center cohort of ACLF patients, a range of clinical outcomes based on EHOF characteristics was captured. This study underscored that single brain failure and MEHOF were associated with an increased risk of mortality in ACLF patients. In addition, a risk stratification system was established based on the characteristics

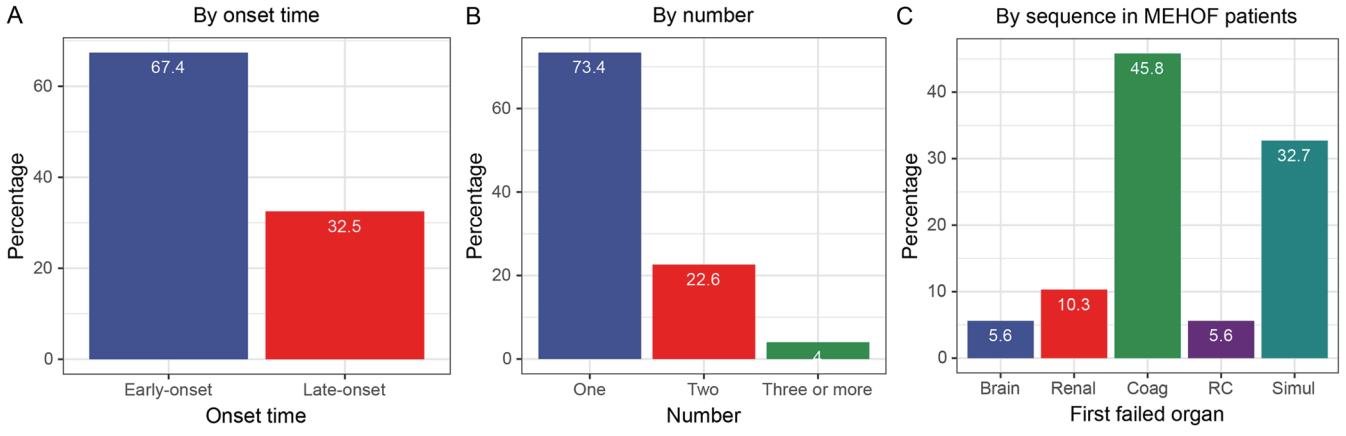

Fig. 3. Distribution of ACLF patients with EHOF. (A–C) Onset (A), number of organs affected (B), and sequence of organ failed (C) in patients with MEHOF (n=107). Simul: Two or more organ failures diagnosed simultaneously. ACLF, acute-on-chronic liver failure; Coag, coagulation; EHOF, extra-hepatic organ failure; MEHOF, multiple extrahepatic organ failures; RC, respiratory or circulatory failure.

Table 2. Characteristics of EHOF according to the etiology and infection

	Etiology			Bacterial infection		
	HBV, *n*=427	**Alcohol, *n*=145**	***p*-value**	**No, *n*=382**	**Yes, *n*=354**	***p*-value**
Brain, *n* (%)	21 (4.9)	7 (4.8)	1.000	18 (4.7)	18 (5.1)	0.865
Renal, *n* (%)	47 (11.0)	32 (22.1)	0.001	30 (7.9)	66 (18.6)	<0.001
Coagulation, *n* (%)	209 (48.9)	64 (44.1)	0.337	161 (42.1)	185 (52.3)	0.006
Respiratory, *n* (%)	20 (4.7)	9 (6.2)	0.511	16 (4.2)	16 (4.5)	0.858
Circulatory, *n* (%)	11 (2.6)	5 (3.4)	0.566	5 (1.3)	12 (3.4)	0.084
Number of EHOF, *n* (%)			0.514			<0.001
None	194 (45.4)	63 (43.4)		197 (51.6)	137 (38.7)	
SEHOF	168 (39.3)	54 (37.2)		144 (37.7)	151 (42.7)	
MEHOF	65 (15.2)	28 (19.3)		41 (10.7)	66 (18.6)	
Onset time of EHOF, *n* (%)	*n*=233	*n*=82	0.585	*n*=185	*n*=217	0.286
Early onset	159 (68.2)	53 (64.6)		130 (70.3)	141 (65.0)	
Late onset	74 (31.8)	29 (35.4)		55 (29.7)	76 (35.0)	
Sequence of EHOF in MEHOF, *n* (%)	*n*=65	*n*=28	0.575	*n*=41	*n*=66	0.006
Brain first	4 (6.2)	2 (7.1)		4 (9.8)	2 (3.0)	
Renal first	6 (9.2)	4 (14.3)		0 (0.0)	11 (16.7)	
Coagulation first	34 (52.3)	10 (35.7)		20 (48.8)	29 (43.9)	
Respiratory or circulatory first	3 (4.6)	3 (10.7)		0 (0.0)	6 (9.1)	
Two or more organs simultaneously	18 (27.7)	9 (32.1)		17 (41.5)	18 (27.3)	

EHOF, extra-hepatic organ failure; HBV, hepatitis B virus; MEHOF, multiple extra-hepatic organs failure; SEHOF, single extra-hepatic organ failure.

Table 3. Survival of ACLF patients based on the characteristics of EHOF

Subgroup	**28-day survival (%)**	**90-day survival (%)**	**OR (95% CI)**	***p*-value**
By existence of EHOF				<0.001
No	89.9	79.6	Ref	
Yes	68.6	52.3	2.95 (2.28–3.82)	
By number of EHOF				<0.001
SEHOF	76.2	60.0	Ref	
MEHOF	48.2	30.6	2.47 (1.87–3.26)	
By onset of EHOF				0.910
Early onset	65.7	53.2	Ref	
Late onset	74.7	51.1	1.02 (0.77–1.34)	
By organ type in SEHOF				
Brain	50.0	33.3	Ref	
Renal	65.7	50.4	0.47 (0.18–1.25)	0.131
Coagulation	77.5	61.2	0.32 (0.13–0.78)	0.012
Respiratory or circulatory	91.7	75.0	0.15 (0.04–0.57)	0.005
By organ sequence in MEHOF				
Brain first	33.3	0.0	Ref	
Renal first	72.7	31.2	0.52 (0.17–1.56)	0.241
Coagulation first	42.3	25.9	0.66 (0.26–1.70)	0.392
Respiratory or circulatory first	66.7	44.4	0.45 (0.12–1.69)	0.236
Two or more organs simultaneously	47.9	42.6	0.58 (0.22–1.53)	0.267

ACLF, acute-on-chronic liver failure; EHOF, extra-hepatic organ failure; MEHOF, multiple extra-hepatic organs failure; SEHOF, single extra-hepatic organ failure.

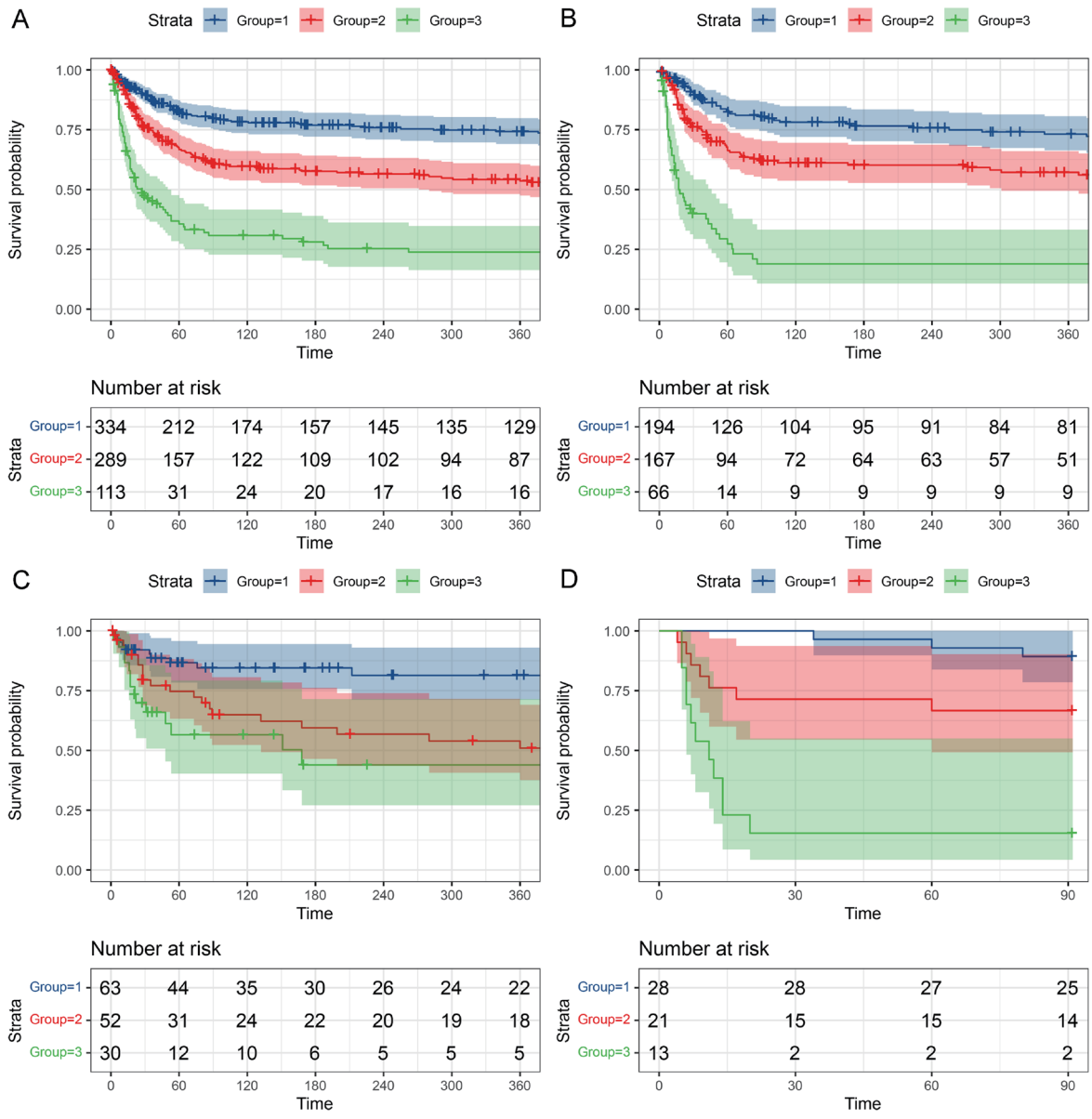

Fig. 4. Kaplan–Meier analysis of ACLF patients. (A–D) Training cohort (A), HBV-related ACLF (B), alcohol-related ACLF patients (C) and validation cohort (D) based on risk stratification. Group 1, low-risk subgroup; Group 2, middle-risk subgroup; Group 3, high-risk subgroup. ACLF, acute-on-chronic liver failure; HBV, hepatitis B virus.

of EHOF, which successfully divided the ACLF patients into different risk subgroups. Our results provide information to guide physicians in identifying the patient subgroups with higher risk of mortality, to help distinguish patients in whom attention should be paid, and to inform discussion with patients and families about disease prognosis.

Coagulation failure was the most frequently observed EHOF, and may have been associated with systemic inflammation response syndrome. Systemic inflammation response syndrome was reported to be the main reason for the progression from acute decompensation to ACLF and may induce coagulation failure.[13,14] A study by Blasi *et al*.[15] in 2018 reported that the hypocoagulable features present in ACLF patients were correlated with systemic inflammation. Our study also found that patients with infection were more likely to develop coagulation failure (no infection 42.1% vs. infection 52.3%, p=0.006; Table 2), indicating the association of inflammation and coagulation failure in ACLF patients.

Previous studies reported that organ failure was associated with the prognosis of ACLF. As the increase on severity grade of ACLF defined by the EASL-CLIF Consortium, patient prognosis worsened.[4] Similar results relating the number of organ failure with survival was found in ACLF patients admitted to an Intensive Care Unit,[9] which was defined by EASL-CLIF. In the NACSELD study, Bajaj *et al*.[5] reported that the survival of ACLF patients was defined by EHOF. Consistent with previous reports, our study found that ACLF patients with EHOF were at significantly greater mortality compared with patients without EHOF. The 28-day survival was 68.6% with EHOF vs. 89.9% without EHOF. The 90-day survival was 52.3% with EHOF vs. 79.6% without EHOF (p<0.001), and the prognosis of ACLF patients got worse as the number of

failed EHOF increased (MEHOF vs. SEHOF: 28-day survival was 48.2% vs. 76.2% and the 90-day survival was 30.6% vs. 60.0%, $p<0.001$).

Studies of the effect of hepatic encephalopathy (HE) on the prognosis of ACLF patients have been performed. As our previous study reported, HE was identified as an independent prognostic factor of ACLF.[16] In a study in China, HE was identified as the strongest predictor of death in ACLF patients precipitated by hepatic insult,[17] indicating a higher risk of brain failure compared with other organs. Long *et al*.[18] investigated the impact of grade 3 HE in subgroups of INR, TBil, and Cr and found that grade 3–4 HE was associated with a higher risk of adverse outcomes independent of other organ failures. Our study demonstrated that in patients with SEHOF, brain failure was associated with a higher risk of mortality than in other types of EHOF. Patients who had single brain failure had a prognosis similar to that of patients who had ≥2 EHOFs. The reason may be related to cerebral edema in patients with ACLF, but further study of the reasons is needed.[19] Our study emphasized the necessity of the prevention, as well as the surveillance, of brain failure in ACLF patients. Attention should be paid to ACLF patients even with just one EHOF when the brain is the involved organ.

The onset time of EHOF was not identified as a factor associated with prognosis. Compared with early-onset EHOF patients, a series of therapies may be applied to late-onset EHOF patients before the development of EHOF and thus may contribute to better survival. However, analysis of the middle-risk subgroup revealed that the prognosis of early-onset EHOF patients was similar to that of late-onset EHOF patients, which may be a result of improvement in the critical care of ACLF but further studies are needed. In the high-risk subgroup, despite the timely therapy of late-onset EHOF, both early-onset and late-onset EHOF patients had poor prognosis with a 90-day survival of <35.0% ($p=1.000$), indicating the poor prognosis of high-risk subgroup patients. Hence, it is of great importance to prevent the development of brain failure or MEHOF, which was considered high risk.

Several models or scores have been established to predict the prognosis of ACLF patients. The EASL-CLIF Consortium, which was an European cohort, diagnosed and graded the ACLF patients by the number and type of EHOFs.[4] The APASL Consortium diagnosed ACLF by liver function (jaundice and coagulopathy), and the severity of ACLF was based on TBil, HE grade, INR, lactate level, and Cr level.[20] In 2018, the Intractable Liver Diseases Study Group of Japan proposed a definition of ACLF for patients in Japan: "patients with cirrhosis and a Child-Pugh score of 5–9 were diagnosed as ACLF when a deterioration of liver function caused by severe liver damage develops within 28 days after an acute insult."[21–23] The severity of the condition in Japanese patients was described by four grades depending on the extent of the deterioration in organ function, following the EASL-CLIF Consortium criteria.[4,23] In this study, the ACLF patients were included mainly according to the deterioration of liver function and we found that the prognosis of ACLF patients was associated with the number and type of EHOF. Our study result was in accordance with the Japanese study and also confirmed that the number and type of EHOF were useful for the stratification of ACLF patients.

Here, we made a risk stratification system based on the number and type of EHOF that performed well in differentiating patients with different mortality risks. Considering the difference of the main etiology in the West and East, we also validated the efficacy of the risk stratification system in subgroups of alcohol-related ACLF and HBV-related ACLF. In addition, the external validation also proved the good performance of the risk stratification system. The risk stratification system is easy to understand and may be practical in the discussion with patients and families about disease prognosis.

Our study has many strengths. First, it was conducted in a large multicenter population of ACLF subjects, allowing for better generalizability. Second, our study not only investigated patients who developed EHOF at admission but also studied subgroups of patients who developed EHOF during hospitalization. Considering the rapid progression nature of ACLF, this would enable more reliable outcomes. Nevertheless, this study was retrospective, and selection bias might have been present. However, its multicenter design, objective inclusion and exclusion criteria, and low data loss helped to mitigate the potential for such bias. Besides, we validated the applicability of the risk stratification system in both the training and the validation cohort, which further confirmed the good performance of the risk stratification system.

In conclusion, our study determined that the survival of ACLF patients depended on the type and number of organ failures. Brain failure was identified as an EHOF with a higher risk of mortality compared with other EHOFs in ACLF patients. In clinical practice, effort should be made to prevent and to perform surveillance of brain failure. In addition, patients with multiple EHOFs had a worse prognosis than patients with a single EHOF. Based on the number and type of EHOFs, a risk stratification system was established, which differentiated patients with different risks of mortality. The risk stratification system is easy to understand, and we consider that it would be applicable in clinical practice.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (SQ, QZ), acquisition of data (YC, FL, ZY), analysis and interpretation of data (SQ, JH, LW), manuscript writing (SQ), critical revision (QZ, TH), statistical analysis (SQ, JH, RC), critical funding (TH), administration (YC, FL), and technical or material support (CZ, LZ, WR, SX, YC, ZD, TH). All authors have made a significant intellectual contribution to this study and have approved the final manuscript.

Ethical statement

All study procedures complied with the ethical principles of the Declaration of Helsinki. The study was approved by the Ethics Committees as a retrospective study (ChiCTR1900021539), and the need for informed consent was waived.

Data sharing statement

All data generated or analyzed in this study are available from the corresponding author upon reasonable request.

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