



OPEN Clinical differences between HBV and alcohol related ACLF in a WGO classification multicenter study

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Acute-on-chronic liver failure (ACLF) exhibits etiological heterogeneity across regions, with hepatitis B virus (HBV)-related ACLF predominant in China and alcohol-related ACLF dominating Western populations. This multicenter retrospective study systematically compared clinical profiles of HBV-related (n = 659) and alcohol-related ACLF (n = 296) stratified by the World Gastroenterology Organization (WGO) A/B/C classification, reflecting underlying chronic liver disease severity. Compared to HBV-related ACLF, alcohol-related ACLF showed higher systemic inflammation (leukocytosis, neutrophilia), bacterial infection ($P < 0.001$), extrahepatic organ failures (single-organ: renal, brain and respiratory, all $P < 0.05$; multi-organ: $P < 0.001$) and higher CLIF-C ACLF/COSHH-ACLF II scores. Conversely, HBV-related ACLF exhibited acute hepatocellular injury (elevated ALT/AST), and higher MELD/MELD-Na scores. These etiological disparities were most pronounced in type C ACLF. Despite these distinct profiles, mortality did not differ between etiologies. Type C ACLF demonstrated poorest profiles and uniformly high 90-day mortality (>45%) regardless of etiology driven by cumulative organ failure burden. Importantly, CLIF-C ACLF and COSHH-ACLF II scores outperformed MELD and MELD-Na scores in predicting outcomes for type C patients. These findings underscore the critical influence of diverse etiologies and severity stages of underlying chronic liver diseases on ACLF profiles and outcomes, thereby necessitating stratified management approaches tailored to underlying chronic liver disease to ultimately improve patient outcomes.

Keywords Acute-on-chronic liver failure, Hepatitis B virus infection, Alcohol-related liver disease, World Gastroenterology Organization, Clinical profiles, Stratified management

Acute-on-chronic liver failure (ACLF) has emerged as a critical global health challenge, characterized by rapid progression and exceptionally high short-term mortality¹. However, the lack of universally accepted diagnostic criteria substantially impedes early identification and timely intervention². This diagnostic ambiguity stems not only from the complex pathophysiology of ACLF but also from apparent regional disparities in underlying etiologies^{1–5}.

In Eastern countries, particularly in HBV-endemic China, HBV remains the leading cause of ACLF, despite a gradual rise in alcohol-related cases in recent years^{6–8}. In contrast, alcohol-related liver disease predominates as the etiology in Western populations^{9–11}. These regional differences in etiology have resulted in divergent diagnostic frameworks. For instance, the Asian Pacific Association for the Study of the Liver (APASL) defines ACLF as acute hepatic insults superimposed on chronic hepatitis or well-compensated cirrhosis, with a primary

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focus on liver failure itself⁶. In contrast, the European Association for the Study of the Liver (EASL) Chronic Liver Failure (CLIF) consortium incorporates both compensated and decompensated cirrhosis in defining chronic liver disease and concentrates much more on the presence of extrahepatic organ failure (EHOF) when defining ACLF⁹. To reconcile the global disparities in ACLF definitions, the World Gastroenterology Organization (WGO) has put forward the A/B/C classification system, aligning with the progressive severity of the underlying chronic liver disease¹². However, the distinct disease trajectories exhibited by HBV-related and alcohol-related ACLF, based on the WGO classification, remain poorly characterized. A deeper understanding of these trajectory differences is crucial for optimizing treatment approaches and improving patient prognosis.

To address this unmet need, our multicenter study systematically characterized HBV-related versus alcohol-related ACLF through a comparative analysis based on the WGO classification. By elucidating the implications of diverse etiologies and chronic liver disease severity on the clinical profiles of ACLF, we aim to lay a foundation for stratified management strategies tailored to underlying chronic liver disease, ultimately improving patient survival and guiding future clinical practice.

Methods

Patients, study design and data collection

The study group selection process is outlined in Fig. 1. This retrospective multicenter study reviewed data from 1193 patients hospitalized for acute deterioration of liver function from January 2008 to October 2019 at Tianjin Third Central Hospital, as well as from November 2012 to June 2019 at 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. The inclusion criteria were occurrence of liver failure, manifesting as jaundice with a TBil ≥ 5 mg/dL and coagulation dysfunction (international normalized ratio [INR] ≥ 1.5 or prothrombin activity $< 40\%$) within 4 weeks after an acute insult. Based on the WGO criteria¹², all eligible patients were further categorized into three types based on the severity of chronic liver disease as follows: type A for patients without cirrhosis, type B for patients with well-compensated cirrhosis, and type C for patients with previous decompensated cirrhosis. The exclusion criteria as follows: (1) non-HBV and non-alcohol etiologies; (2) overlapping HBV and alcohol-related etiologies; (3) hepatocellular carcinoma or other malignant tumors; (4) severe chronic extra-hepatic disease, such as severe chronic kidney disease with renal failure [Estimated Glomerular Filtration Rate (eGFR) < 30 mL/min/1.73 m² for ≥ 3 months], severe chronic obstructive pulmonary disease with respiratory failure [Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage III/IV], severe coronary heart disease with heart failure [New York Heart Association (NYHA) class III/IV] and severe coagulation failure caused by hematological system diseases; (5) post-liver transplantation; (6) concomitant human immunodeficiency virus infection; (7) patients with incomplete clinical indicator information.

All data were retrospectively collected from manual and electronic medical records. For each study patient, we collected baseline data from demographics (e.g., age and sex), etiology of chronic liver disease (e.g., HBV and alcohol), the number and types of acute precipitating events detected before the occurrence of liver failure [e.g., HBV reactivation, active alcoholism, hepatotoxic drugs, bacterial infection, gastrointestinal haemorrhage, others (overwork, surgery and non-HBV hepatotropic viral infection), none and multiple (two or more) precipitating events], acute precipitating events (e.g., no identifiable, hepatic insult, extra-hepatic insult or both),

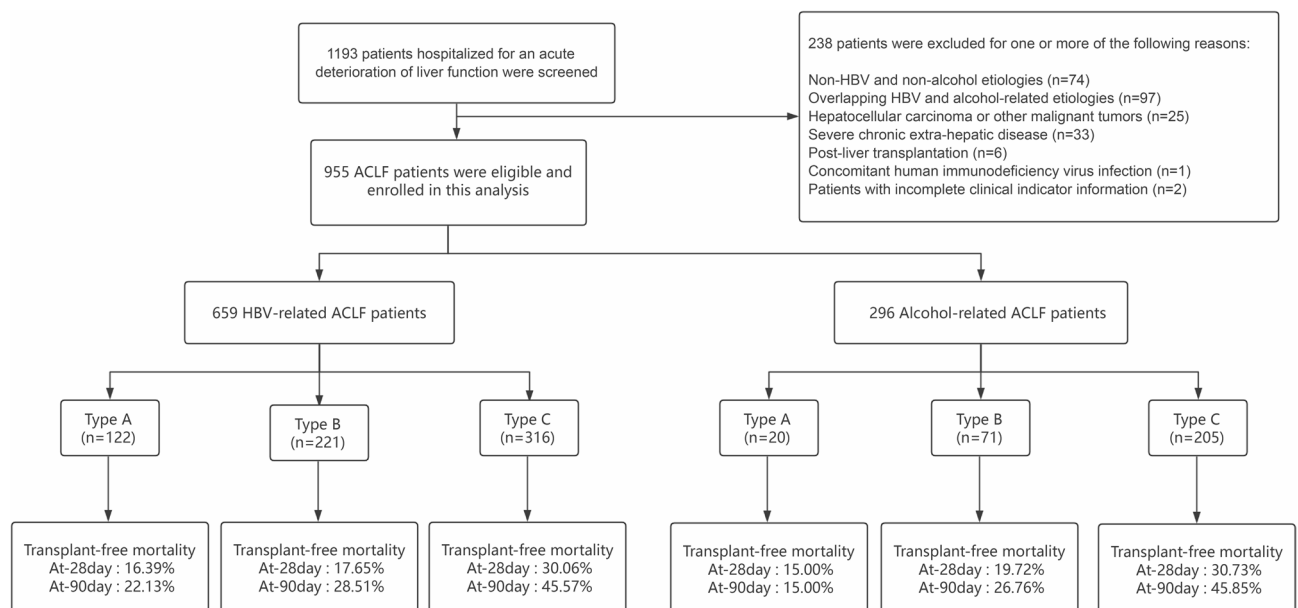


Fig. 1. Flowchart of the study group selection process. ACLF, acute-on-chronic liver failure; HBV, hepatitis B virus.

laboratory parameters [e.g., white blood cell (WBC) count, percentage of neutrophils (N%), hemoglobin (Hb), platelets (PLT), albumin (Alb), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyl transferase (γ -GT), TBil, INR, creatinine (Cr) and serum sodium (Na)], complications during follow-up [e.g., ascites, bacterial infection, gastrointestinal haemorrhage, hepatic encephalopathy (HE)], the number and types of EHO, and prognostic scoring systems scores [Model for End Stage Liver Disease (MELD)¹³, MELD-sodium (MELD-Na)¹⁴, Chronic Liver Failure-Consortium ACLF (CLIF-C ACLF)¹⁵ and Chinese Group on the Study of Severe Hepatitis B-ACLF II (COSSH-ACLF II)]¹⁶. In addition, the outcomes at 28-day and 90-day follow-up were collected for each study patient.

All study procedures complied with the ethical principles of the Declaration of Helsinki. This retrospective study was approved by the Ethics Committees of Tianjin Third Central Hospital, Beijing You'an Hospital, Shandong Provincial Hospital, First Hospital of Shanxi Medical University, Third Hospital of Hebei Medical University, and Fifth Medical Center of Chinese PLA General Hospital. Written informed consent was waived by the Ethics Committees of Tianjin Third Central Hospital, Beijing You'an Hospital, Shandong Provincial Hospital, First Hospital of Shanxi Medical University, Third Hospital of Hebei Medical University, and Fifth Medical Center of Chinese PLA General Hospital due to the retrospective design of the study.

Definitions

EHO was diagnosed by the following criteria^{11,15}: (1) brain failure: West-Haven grade III–IV, (2) renal failure: Cr ≥ 2 mg/dL or use of renal replacement therapy, (3) coagulation failure: INR ≥ 2.5 , (4) circulatory failure: use of vasoactive drugs, (5) respiratory failure: PaO₂/FiO₂ ≤ 200 or SpO₂/FiO₂ ≤ 214 or the need for mechanical ventilation. According to the number of EHO, multiple extrahepatic organ failure (MEHO) was defined as two or more EHO.

Statistical analysis

Continuous variables were described as means $\pm$ standard deviation or median [interquartile range (IQR)] and compared using the t-test, Mann–Whitney U test, one-way ANOVA or Kruskal–Wallis test, as appropriate. Categorical variables were expressed as frequency (%), and properly compared using chi-squared test or Fisher's exact tests. We performed univariate analysis to compare characteristics between survivors and non-survivors. Variables with significant inter-group differences ($P < 0.05$) were entered into multivariable Cox proportional hazards regression models to identify independent predictors of 28- and 90-day mortality. Results are presented as hazard ratios (HR) with 95% confidence intervals. Kaplan–Meier analysis was used to plot 28- and 90-day survival curves, and survival rates were compared using the log-rank test. The areas under the receiver operating characteristic curve (AUROCs) of the various prognostic scoring systems were compared using the Z test with Delong's method.

All the statistical analysis were performed by R software version 4.4.1. A two-sided P value < 0.05 was considered statistical significance.

Results

Description of the study population

As illustrated in Fig. 1, this study enrolled a total of 955 eligible patients who met the inclusion and exclusion criteria. Of these, 69.01% (659/955) had HBV-related ACLF, while 30.99% (296/955) had alcohol-related ACLF. According to the WGO classification, the HBV-related ACLF cohort comprised 122 patients (18.51%) with type A, 221 patients (33.54%) with type B, and 316 patients (47.95%) with type C ACLF. In contrast, the alcohol-related ACLF cohort included 20 patients (6.75%) classified as type A, 71 patients (23.99%) as type B, and 205 patients (69.26%) as type C ACLF.

Within the overall study cohort, 142 patients (14.87%) were classified as type A ACLF, 292 patients (30.57%) as type B ACLF, and 521 patients (54.55%) as type C ACLF. The cohort was predominantly male (83.46%), with a mean age of 48.66 years. In terms of organ failures, coagulation failure (32.25%) was the most common type of EHO, followed by brain failure (8.06%), renal failure (7.75%), respiratory failure (6.49%), and circulatory failure (5.45%). Additionally, 278 (29.11%) patients developed single EHO, 137 (14.35%) patients developed MEHO. The overall 28-day and 90-day mortality rates were 24.50% and 36.65%, respectively (Supplementary Table S1).

Comparison of clinical characteristics between HBV-related and alcohol-related ACLF

As presented in Table 1, ACLF patients with alcohol-related etiology was more frequently precipitated by active alcohol consumption, bacterial infection and multiple precipitants compared to those with HBV-related etiology (all $P \leq 0.001$), whereas HBV reactivation was the most common trigger in patients with HBV-related etiology. Alcohol-related ACLF patients demonstrated significantly elevated WBC, N%, γ -GT and Cr compared to those with HBV etiology (all $P < 0.01$), while HBV-related ACLF patients had significantly higher serum Hb, Alb, ALT, AST and Na levels (all $P < 0.001$). Moreover, alcohol-related ACLF patients had a significantly higher incidence of complications, including ascites ($P = 0.001$), HE ($P = 0.001$), bacterial infection ($P < 0.001$), gastrointestinal hemorrhage ($P < 0.001$). EHO were also more significantly frequent in the alcohol-related cohort. Specifically, alcohol-related ACLF had higher rates of single renal failure ($P < 0.001$), brain failure ($P = 0.003$), and respiratory failure ($P = 0.016$), as well as MEHO ($P < 0.001$).

In addition, alcohol-related ACLF demonstrated higher CLIF-C ACLF and COSSH-ACLF II scores (both $P < 0.001$ vs. HBV). On the other hand, HBV-related ACLF displayed higher MELD and MELD-Na scores (both $P < 0.001$ vs. alcohol). Despite these differences, the 28-day and 90-day mortality rates did not significantly differ between etiologies within the overall cohort or any WGO type (all $P > 0.05$) (Table 1). As illustrated in Supplementary Fig. S1, Kaplan–Meier survival analysis showed no 28- and 90-day survival difference between etiologies (log-rank test: $P = 0.20$ for 28-day; $P = 0.24$ for 90-day).

Characteristics	ALL (n = 955)		
	HBV (n = 659)	Alcohol (n = 296)	P value
Age (years)	48.25 ± 12.04	49.57 ± 9.51	0.090
Male sex, n(%)	511 (77.54%)	286 (96.62%)	< 0.001***
WGO type, n(%)			
A	122 (18.51%)	20 (6.75%)	< 0.001***
B	221 (33.54%)	71 (23.99%)	0.003**
C	316 (47.95%)	205 (69.26%)	< 0.001***
Precipitating events, n (%)			
HBV reactivation	106 (16.08%)	0 (0.00%)	< 0.001***
Active alcohol consumption	1 (0.15%)	28 (9.46%)	< 0.001***
Drugs or Poisons	2 (0.30%)	4 (1.35%)	0.078
Bacterial Infection	96 (14.57%)	71 (23.99%)	0.001**
Gastrointestinal haemorrhage	19 (2.88%)	10 (3.38%)	0.686
Others	143 (21.70%)	22 (7.43%)	< 0.001***
No precipitating events	101 (15.33%)	26 (8.78%)	0.005**
Two or more precipitating events	191 (28.98%)	135 (45.61%)	< 0.001***
Laboratory parameters			
WBC (*10 ⁹ /L)	6.35 (4.49, 8.84)	8.88 (5.87, 13.12)	< 0.001***
N%	71.30 (62.10, 79.05)	78.80 (71.15, 85.95)	< 0.001***
Hb (g/L)	124.30 (111.00, 139.00)	97.00 (81.00, 114.00)	< 0.001***
PLT (*10 ⁹ /L)	85.00 (55.00, 121.50)	82.00 (51.50, 133.00)	0.975
Alb (g/L)	29.60 (26.00, 32.80)	26.55 (23.53, 29.65)	< 0.001***
ALT (U/L)	210.00 (83.00, 636.25)	39.00 (23.00, 62.70)	< 0.001***
AST (U/L)	191.10 (95.00, 441.00)	80.00 (47.50, 145.50)	< 0.001***
r-GT (U/L)	79.00 (47.20, 129.00)	103.10 (42.00, 282.00)	< 0.001***
TBil (mg/dL)	14.83 (9.77, 21.61)	13.69 (8.80, 20.72)	0.080
INR	2.16 (1.83, 2.64)	2.10 (1.80, 2.60)	0.364
Cr (mg/dL)	0.79 (0.62, 1.03)	0.86 (0.62, 1.36)	0.005**
Na (mmol/L)	135.00 (131.70, 137.90)	132.15 (127.40, 135.67)	< 0.001***
Clinical parameters, n (%)			
Ascites	499 (75.72%)	257 (86.82%)	0.001**
Gastrointestinal haemorrhage	35 (5.31%)	74 (25.00%)	< 0.001***
Bacterial infection	370 (56.15%)	217 (73.31%)	< 0.001***
Hepatic encephalopathy	126 (19.12%)	82 (27.70%)	0.004**
Types of extra-hepatic organ failure, n (%)			
Coagulation	219 (33.23%)	89 (30.07%)	0.369
Kidney	28 (4.25%)	46 (15.54%)	< 0.001***
Cerebral	41 (6.22%)	36 (12.16%)	0.003**
Respiratory	34 (5.16%)	28 (9.46%)	0.016*
Circulation	30 (4.55%)	22 (7.43%)	0.089
Number of extra-hepatic organ failure, n (%)			
0	383 (58.12%)	157 (53.04%)	0.158
1	204 (30.96%)	74 (25.00%)	0.065
≥ 2	72 (10.93%)	65 (21.96%)	< 0.001***
Severity scores			
MELD score	23.46 (19.76, 27.06)	17.52 (12.86, 22.31)	< 0.001***
MELD-Na score	25.42 (20.64, 31.94)	23.03 (16.15, 33.64)	< 0.001***
Continued			

Characteristics	ALL (n = 955)		
	HBV (n = 659)	Alcohol (n = 296)	P value
CLIF-C ACLF score	40.56 (35.53, 46.56)	44.33 (39.33, 50.92)	< 0.001***
COSSH-ACLF II score	4.99 (3.84, 6.09)	6.10 (5.10, 6.99)	< 0.001***
Mortality, n (%)			
28-day	154 (23.37%)	80 (27.03%)	0.224
90-day	234 (35.51%)	116 (39.19%)	0.277

Table 1. Comparison of characteristics between ACLF with HBV- and alcohol-related etiology. Categorical variables presented as frequency (%), non-normal continuous variables as median (interquartile range) and normal continuous variables as mean $\pm$ standard deviation. ACLF, acute-on-chronic liver failure; HBV, hepatitis B virus; WBC, white blood cell; N%, percentage of neutrophils; Hb, hemoglobin; PLT, platelets; Alb, serum albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ -GT, γ -glutamyl transferase; TBil, total bilirubin; INR, international normalized ratio; Cr, creatinine; Na, sodium; MELD, Model for End Stage Liver Disease; MELD-Na, MELD-sodium; CLIF-C ACLF, Chronic Liver Failure-Consortium ACLF; COSSH-ACLF II, Chinese Group on the Study of Severe Hepatitis B-ACLF II. *P* value for comparisons between ACLF with HBV- and alcohol-related etiology. **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

	Variables	Multivariable analysis for 28-day mortality		Multivariable analysis for 90-day mortality	
		Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
Total ACLF	N%	1.02 (1.01–1.04)	0.006**	–	–
	TBil (mg/dL)	1.02 (1.00–1.04)	0.018*	–	–
	Complication (Bacterial infection)	–	–	1.48 (1.11–1.98)	0.008**
	Complication (Gastrointestinal haemorrhage)	1.48 (1.02–2.14)	0.038*	1.62 (1.19–2.21)	0.002**
	Complication (Hepatic encephalopathy)	–	–	1.51 (1.17–1.95)	0.002**
	Number of extra-hepatic organ failure: 1	–	–	1.31 (1.00–1.70)	0.047*
	MELD	1.06 (1.03–1.09)	< 0.001***	1.05 (1.03–1.08)	< 0.001***
	CLIF-C ACLF	1.03 (1.00–1.06)	0.045*	1.08 (1.06–1.10)	< 0.001***
HBV-ACLF	WGO type C ACLF	–	–	1.82 (1.17–2.82)	0.008**
	TBil (mg/dL)	1.03 (1.01–1.05)	0.004**	–	–
	Complication (Gastrointestinal haemorrhage)	1.83 (1.09–3.09)	0.023*	1.92 (1.22–3.02)	0.005**
	Cerebral failure	1.68 (1.02–2.76)	0.040*	1.67 (1.04–2.70)	0.035*
	MELD	1.09 (1.05–1.14)	< 0.001***	1.14 (1.06–1.21)	< 0.001***
	CLIF-C ACLF	1.03 (1.00–1.06)	0.045*	1.09 (1.07–1.12)	< 0.001***
Alcohol-ACLF	N%	1.05 (1.01–1.08)	0.004**	–	–
	Alb (g/L)	–	–	0.95 (0.90–1.00)	0.046*
	Complication (Bacterial infection)	–	–	1.83 (1.02–3.30)	0.044*
	Complication (Hepatic encephalopathy)	–	–	2.25 (1.52–3.31)	< 0.001***
	CLIF-C ACLF	1.07 (1.04–1.11)	< 0.001***	–	–

Table 2. Multivariable Cox proportional hazards regression analysis of the independent prognostic factors for 28-day and 90-day mortality in the overall and etiology-stratified ACLF subgroups. ACLF, acute-on-chronic liver failure; CI, confidence interval; HBV, hepatitis B virus; N%, percentage of neutrophils; Alb, serum albumin; TBil, total bilirubin; MELD, Model for End Stage Liver Disease; CLIF-C ACLF, Chronic Liver Failure-Consortium ACLF. **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

In ACLF patients with HBV-related etiology, WGO type C, elevated TBil, gastrointestinal hemorrhage as a complication, cerebral failure, as well as higher MELD and CLIF-C ACLF scores were significantly associated with 28-day and 90-day mortality. In patients with alcohol-related etiology, elevated N% and higher CLIF-C ACLF scores were significantly associated with 28-day mortality, while lower albumin levels, along with complications such as bacterial infection and HE, were significantly associated with 90-day mortality (Table 2). A detailed univariate analysis is provided in Supplementary Table S2.

Comparison of clinical characteristics across WGO ACLF types (A/B/C)

A detailed comparison of clinical profiles and outcomes across WGO ACLF types within the overall cohort, HBV-related subgroup, and alcohol-related subgroup is presented in Supplementary Table S3, Tables 3 and 4, respectively.

Characteristics	Type A (n = 122)	Type B (n = 221)	Type C (n = 316)	<i>P</i> ^a value	<i>P</i> ^b value	<i>P</i> ^c value	<i>P</i> ^d value
Age (years)	41.50 (35.00, 49.00)	47.00 (39.00, 58.00)	51.00 (42.75, 58.00)	< 0.001***	< 0.001***	0.018*	< 0.001***
Male sex, n (%)	99 (81.15%)	167 (75.57%)	245 (77.53%)	0.494	0.280	0.605	0.439
Precipitating events, n (%)							
HBV reactivation	24 (19.67%)	39 (17.65%)	43 (13.61%)	0.212	0.664	0.223	0.138
Active alcohol consumption	0 (0.00%)	0 (0.00%)	1 (0.32%)	1.000	NA	1.000	1.000
Hepatotoxic drugs	0 (0.00%)	1 (0.45%)	1 (0.32%)	1.000	1.000	1.000	1.000
Bacterial Infection	4 (3.28%)	21 (9.50%)	71 (22.47%)	< 0.001***	0.049*	< 0.001***	< 0.001***
Gastrointestinal haemorrhage	0 (0.00%)	0 (0.00%)	19 (6.01%)	< 0.001***	NA	< 0.001***	0.003**
Others	33 (27.05%)	66 (29.86%)	44 (13.92%)	< 0.001***	0.620	< 0.001***	0.002**
No precipitating events	26 (21.31%)	37 (16.74%)	38 (12.03%)	0.041	0.310	0.130	0.016*
≥ 2 precipitating events	35 (28.69%)	57 (25.79%)	99 (31.33%)	0.387	0.611	0.177	0.644
Laboratory parameters							
WBC (*10 ⁹ /L)	6.38 (5.11, 8.58)	5.87 (4.20, 8.39)	6.66 (4.46, 9.17)	0.029*	0.047*	0.014*	0.637
N%	68.45 (60.08, 76.43)	68.30 (60.00, 77.00)	74.60 (65.60, 81.23)	< 0.001***	0.820	< 0.001***	< 0.001***
Hb (g/L)	134.50 (122.00, 144.75)	124.65 (112.25, 140.00)	121.00 (107.00, 133.00)	< 0.001***	< 0.001***	0.008**	< 0.001***
PLT (*10 ⁹ /L)	112.00 (89.25, 144.75)	85.00 (57.00, 115.00)	73.00 (48.00, 113.00)	< 0.001***	< 0.001***	0.010*	< 0.001***
Alb (g/L)	31.50 (28.83, 34.00)	30.50 (26.80, 33.60)	28.15 (25.00, 31.20)	< 0.001***	0.207	< 0.001***	< 0.001***
ALT (U/L)	537.00 (164.00, 1160.80)	210.00 (87.00, 501.00)	157.50 (64.00, 501.75)	< 0.001***	< 0.001***	0.014*	< 0.001***
AST (U/L)	344.50 (137.03, 701.38)	195.50 (107.43, 424.00)	157.50 (82.00, 362.25)	< 0.001***	< 0.001***	0.017*	< 0.001***
γ-GT (U/L)	102.00 (67.00, 137.00)	84.10 (50.80, 137.90)	71.00 (42.50, 121.00)	< 0.001***	0.132	0.014*	< 0.001***
TBil (mg/dL)	14.99 (10.86, 20.39)	15.40 (10.37, 22.59)	13.79 (8.65, 21.18)	0.071	0.574	0.027*	0.196
INR	2.23 (1.84, 2.74)	2.10 (1.78, 2.60)	2.19 (1.89, 2.66)	0.242	0.471	0.086	0.619
Cr (mg/dL)	0.73 (0.58, 0.91)	0.77 (0.62, 0.98)	0.85 (0.66, 1.10)	< 0.001***	0.086	0.002**	< 0.001***
Na (mmol/L)	136.50 (134.50, 138.00)	135.90 (133.00, 138.60)	133.60 (129.00, 137.00)	< 0.001***	0.257	< 0.001***	< 0.001***
Clinical parameters, n (%)							
Ascites	60 (49.18%)	157 (71.36%)	282 (89.52%)	< 0.001***	0.001**	< 0.001***	< 0.001***
Gastrointestinal haemorrhage	0 (0.00%)	7 (3.17%)	28 (8.86%)	0.001**	0.054	0.008**	0.001**
Bacterial infection	9 (7.38%)	137 (61.99%)	224 (70.89%)	< 0.001***	< 0.001***	0.032*	< 0.001***
Hepatic encephalopathy	108 (88.52%)	196 (88.69%)	229 (72.47%)	< 0.001***	1.000	< 0.001***	< 0.001***
Types of extra-hepatic organ failure, n (%)							
Coagulation	46 (37.70%)	67 (30.32%)	106 (33.54%)	0.373	0.187	0.454	0.434
Kidney	3 (2.46%)	6 (2.71%)	19 (6.01%)	0.119	1.000	0.095	0.149
Cerebral	4 (3.28%)	7 (3.17%)	30 (9.49%)	0.004**	1.000	0.005**	0.029*
Respiratory	7 (5.74%)	5 (2.26%)	22 (6.96%)	0.041*	0.124	0.015*	0.831
Circulation	1 (0.82%)	6 (2.71%)	23 (7.28%)	0.033*	0.429	0.031*	0.005**
Number of extra-hepatic organ failure, n (%)							
0	65 (53.28%)	143 (64.71%)	175 (55.38%)	0.047	0.050	0.033*	0.748
1	53 (43.44%)	65 (29.41%)	86 (27.22%)	0.005**	0.013*	0.626	0.001**
≥ 2	4 (3.28%)	13 (5.88%)	55 (17.41%)	< 0.001***	0.436	0.001**	< 0.001***
Severity scores							
MELD score	22.69 (19.19, 26.63)	23.00 (19.43, 26.00)	24.05 (20.29, 27.42)	0.011*	0.422	0.026*	0.009**
MELD-Na score	23.19 (19.90, 27.69)	24.33 (20.19, 29.08)	27.34 (22.28, 36.63)	< 0.001***	0.094	< 0.001***	< 0.001***
CLIF-C ACLF score	37.96 (34.52, 42.76)	39.21 (35.33, 44.84)	42.75 (37.12, 49.59)	< 0.001***	0.158	< 0.001***	< 0.001***
COSSH-ACLF II score	4.51 (3.49, 5.32)	4.67 (3.71, 5.62)	5.40 (4.22, 6.66)	< 0.001***	0.111	< 0.001***	< 0.001***
Mortality, n (%)							
28-day	20 (16.39%)	39 (17.65%)	95 (30.06%)	< 0.001***	0.881	0.001**	0.004**
90-day	27 (22.13%)	63 (28.51%)	144 (45.57%)	< 0.001***	0.249	< 0.001***	< 0.001***

Table 3. Comparison of clinical characteristics across WGO ACLF types in HBV-ACLF cohort (n = 659). Categorical variables presented as frequency (%), non-normal continuous variables as median (interquartile range) and normal continuous variables as mean ± standard deviation. ACLF, acute-on-chronic liver failure; HBV, hepatitis B virus; WBC, white blood cell; N%, percentage of neutrophils; Hb, hemoglobin; PLT, platelets; Alb, serum albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, γ-glutamyl transferase; TBil, total bilirubin; INR, international normalized ratio; Cr, creatinine; Na, sodium; MELD, Model for End Stage Liver Disease; MELD-Na, MELD-sodium; CLIF-C ACLF, Chronic Liver Failure-Consortium ACLF; COSSH-ACLF II, Chinese Group on the Study of Severe Hepatitis B-ACLF II. *P*^a value for comparisons between all the three types of ACLF patients; *P*^b value for comparisons between patients with type A and B ACLF; *P*^c value for comparisons between patients with type B and C ACLF; *P*^d value for comparisons between patients with type A and C ACLF. **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

Characteristics	Type A (n = 20)	Type B (n = 71)	Type C (n = 205)	<i>P</i> ^a value	<i>P</i> ^b value	<i>P</i> ^c value	<i>P</i> ^d value
Age (years)	52.50 (40.00, 57.25)	47.00 (43.00, 54.00)	50.00 (44.00, 55.00)	0.357	0.698	0.296	0.918
Male sex, n (%)	20 (100.00%)	68 (95.77%)	198 (96.59%)	0.863	1.000	0.721	1.000
Precipitating events, n (%)							
HBV reactivation	0	0	0	NA	NA	NA	NA
Active alcohol consumption	3 (15.00%)	8 (11.27%)	17 (8.29%)	0.438	0.701	0.475	0.398
Hepatotoxic drugs	1 (5.00%)	2 (2.82%)	1 (0.49%)	0.063	0.530	0.164	0.170
Bacterial Infection	7 (35.00%)	16 (22.54%)	48 (23.41%)	0.488	0.260	1.000	0.278
Gastrointestinal haemorrhage	0 (0.00%)	0 (0.00%)	10 (4.88%)	0.101	NA	0.069	0.606
Others	2 (10.00%)	3 (4.23%)	17 (8.29%)	0.451	0.302	0.302	0.680
No precipitating events	4 (20.00%)	8 (11.27%)	14 (6.83%)	0.087	0.453	0.307	0.062
≥ 2 precipitating events	3 (15.00%)	34 (47.89%)	98 (47.80%)	0.015*	0.010*	1.000	0.005**
Laboratory parameters							
WBC (*10 ⁹ /L)	9.95 (6.96, 17.18)	8.84 (5.59, 14.30)	8.88 (5.64, 12.75)	0.431	0.449	0.535	0.220
N%	73.40 (66.05, 82.33)	79.75 (74.48, 86.35)	78.80 (71.30, 86.00)	0.271	0.113	0.824	0.125
Hb (g/L)	121.50 (112.75, 133.00)	100.00 (82.50, 120.25)	94.00 (77.00, 109.00)	< 0.001***	0.007**	0.037*	< 0.001***
PLT (*10 ⁹ /L)	138.50 (99.75, 166.75)	101.00 (62.50, 153.00)	72.00 (45.00, 108.00)	< 0.001***	0.030*	< 0.001***	< 0.001***
Alb (g/L)	30.00 (26.15, 32.98)	27.75 (24.43, 29.78)	26.00 (23.35, 29.10)	0.002**	0.068	0.032*	0.002**
ALT (U/L)	127.80 (61.00, 961.50)	40.00 (25.00, 62.00)	36.00 (22.00, 57.00)	< 0.001***	< 0.001***	0.487	< 0.001***
AST (U/L)	137.90 (93.25, 605.00)	102.50 (63.75, 142.95)	70.00 (45.00, 136.00)	0.002**	0.012*	0.090	0.001**
r-GT (U/L)	229.00 (93.58, 394.08)	154.00 (53.50, 323.50)	91.00 (37.25, 227.75)	0.007**	0.235	0.034*	0.008**
TBil (mg/dL)	18.88 (14.90, 23.87)	16.64 (10.56, 23.92)	12.28 (7.97, 18.87)	< 0.001***	0.324	0.002**	< 0.001***
INR	1.99 (1.87, 2.22)	2.00 (1.71, 2.32)	2.19 (1.83, 2.77)	0.033*	0.712	0.014*	0.212
Cr (mg/dL)	0.72 (0.59, 1.02)	0.83 (0.61, 1.07)	0.89 (0.65, 1.54)	0.147	0.466	0.158	0.122
Na (mmol/L)	136.25 (131.38, 137.63)	132.70 (130.45, 136.20)	131.10 (126.05, 135.00)	0.004**	0.141	0.016*	0.012*
Clinical parameters, n (%)							
Ascites	12 (60.00%)	55 (77.46%)	190 (92.68%)	< 0.001***	0.152	0.002**	< 0.001***
Gastrointestinal haemorrhage	1 (5.00%)	13 (18.31%)	60 (29.27%)	0.017*	0.290	0.086	0.017*
Bacterial infection	7 (35.00%)	49 (69.01%)	161 (78.54%)	< 0.001***	0.009**	0.110	< 0.001***
Hepatic encephalopathy	19 (95.00%)	61 (85.92%)	134 (65.37%)	< 0.001***	0.445	0.001**	0.005**
Types of extra-hepatic organ failure, n (%)							
Coagulation	3 (15.00%)	15 (21.13%)	71 (34.63%)	0.032*	0.716	0.034*	0.048*
Kidney	1 (5.00%)	6 (8.45%)	39 (19.02)	0.043*	1.000	0.041*	0.212
Cerebral	1 (5.00%)	3 (4.23%)	32 (15.61%)	0.021*	1.000	0.012*	0.322
Respiratory	0 (0.00%)	1 (1.41%)	27 (13.17%)	0.003**	1.000	0.003**	0.142
Circulation	0 (0.00%)	1 (1.41%)	21 (10.24%)	0.022*	1.000	0.020*	0.229
Number of extra-hepatic organ failure, n (%)							
0	16 (80.00%)	50 (70.42%)	91 (44.39%)	< 0.001***	0.572	< 0.001***	0.004**
1	3 (15.00%)	17 (23.94%)	54 (26.34%)	0.588	0.546	0.754	0.419
≥ 2	1 (5.00%)	4 (5.63%)	60 (29.27%)	< 0.001***	1.000	< 0.001***	0.017*
Severity scores							
MELD score	16.15 (13.44, 19.76)	16.85 (12.38, 20.71)	18.20 (12.86, 23.50)	0.233	0.924	0.111	0.397
MELD-Na score	16.15 (15.33, 23.02)	20.11 (14.76, 25.77)	25.14 (17.60, 36.06)	0.003**	0.380	0.005**	0.028*
CLIF-C ACLF score	45.09 (38.30, 46.41)	42.54 (37.41, 46.84)	45.20 (40.36, 52.25)	0.009**	0.573	0.003**	0.250
COSSH-ACLF II score	4.86 (3.86, 6.19)	5.33 (4.08, 6.35)	6.35 (5.53, 7.21)	< 0.001***	0.346	< 0.001***	< 0.001***
Mortality, n (%)							
28-day	3 (15.00%)	14 (19.72%)	63 (30.73%)	< 0.001***	0.755	0.091	0.199
90-day	3 (15.00%)	19 (26.76%)	94 (45.85%)	0.001**	0.381	0.005**	0.009**

Table 4. Comparison of clinical characteristics across WGO ACLF types in Alcohol-ACLF cohort (n = 296). Categorical variables presented as frequency(%), non-normal continuous variables as median (interquartile range) and normal continuous variables as mean ± standard deviation. ACLF, acute-on-chronic liver failure; HBV, hepatitis B virus; WBC, white blood cell; N%, percentage of neutrophils; Hb, hemoglobin; PLT, platelets; Alb, serum albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, γ-glutamyl transferase; TBil, total bilirubin; INR, international normalized ratio; Cr, creatinine; Na, sodium; MELD, Model for End Stage Liver Disease; MELD-Na, MELD-sodium; CLIF-C ACLF, Chronic Liver Failure-Consortium ACLF; COSSH-ACLF II, Chinese Group on the Study of Severe Hepatitis B-ACLF II. *P*^a value for comparisons between all the three types of ACLF patients; *P*^b value for comparisons between patients with type A and B ACLF; *P*^c value for comparisons between patients with type B and C ACLF; *P*^d value for comparisons between patients with type A and C ACLF. **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

Within the overall cohort, type C ACLF exhibited distinct clinical profiles compared to types A and B. Type C ACLF were more frequently precipitated by bacterial infection, gastrointestinal hemorrhage and multiple precipitants (all $P < 0.05$ vs. types A/B). In addition, laboratory parameters including Hb, Alb, PLT, ALT, AST, γ -GT, TBil and Na were significantly lower in type C (all $P < 0.001$), whereas WBC, N%, and Cr levels were elevated (all $P < 0.05$). Type C also demonstrated higher incidences of ascites, bacterial infection, HE, gastrointestinal hemorrhage, and EHOF (all $P < 0.001$). Specifically, renal (11.13%), brain (11.90%), respiratory (9.40%), circulatory (8.45%) failures, and multi-organ failure (MEHOF, 22.07%) were most prevalent in type C (all $P < 0.001$ vs. types A/B) (Supplementary Table S3).

Within each etiology (HBV and alcohol), as compared to types A and B, type C ACLF consistently exhibited lower serum levels of Hb, Alb, ALT, AST, γ -GT, and Na (all $P < 0.01$) and had a higher incidence of complications, including ascites, infections, HE, and hemorrhage (all $P < 0.05$). Single brain, respiratory, and circulatory failures were more frequent in type C regardless of etiology (all $P < 0.05$ vs. types A/B). MEHOF incidence was highest in type C ($P < 0.001$ vs. types A/B) (Tables 3 and 4).

Furthermore, type C ACLF scored highest across all severity scores: MELD-Na, CLIF-C ACLF, and COSSH-ACLF II (all $P < 0.01$ vs. types A/B).

Mortality rates escalated with disease severity. In the overall cohort, type C had the highest 28-day (type C vs. types A/B: 30.33% vs. 16.20%/18.15%, $P < 0.001$) and 90-day mortality (type C vs. types A/B: 45.68% vs. 21.13%/28.08%; $P < 0.001$) (Supplementary Table S3). This trend persisted in etiology-stratified analyses: HBV-related type C showed the highest 28-day mortality (type C vs. types A/B: 30.06% vs. 16.39%/17.65%; $P < 0.001$) and 90-day mortality (type C vs. types A/B: 45.57% vs. 22.13%/28.51%; $P < 0.001$) (Table 3), while alcohol-related type C exhibited the worst 28-day (type C vs. types A/B: 30.73% vs. 15.00%/19.72%, $P < 0.001$) and 90-day outcomes (type C vs. types A/B: 45.85% vs. 15.00%/26.76%; $P = 0.001$) (Table 4). As illustrated in Fig. 2, Kaplan–Meier analysis confirmed significantly reduced 28-/90-day survival for type C in the overall and HBV cohorts (log-rank test: $P < 0.001$). Alcohol-related type C showed no significant 28-day survival difference but significantly worse 90-day survival (log-rank test: $P = 0.10$ for 28-day; $P = 0.0031$ for 90-day).

Multivariate Cox regression analysis identified independent prognostic factors for 28-day mortality in total ACLF patients as N%, Tbil, gastrointestinal hemorrhage as a complication, and higher MELD and CLIF-C ACLF scores. For 90-day mortality, independent predictors included single EHOF, higher MELD and CLIF-C ACLF scores, and complications such as bacterial infection, gastrointestinal hemorrhage, and HE (Table 2). We subsequently performed multivariable analysis to identify independent predictors of 28-day and 90-day mortality within each WGO ACLF type. In type A, higher MELD and CLIF-C ACLF scores were independent prognostic factors. In type B, age, Tbil, coagulopathy failure, circulatory failure, and higher MELD and CLIF-C ACLF scores were independent prognostic factors. In type C, higher N%, cerebral failure, complications including gastrointestinal hemorrhage and HE, as well as higher MELD and CLIF-C ACLF scores were independent prognostic factors (Table 5). Univariate analysis of factors associated with ACLF prognosis in the overall cohort and across WGO types are presented in Supplementary Tables S2 and S4, respectively.

Performance of the prognostic scoring systems for predicting 28-day and 90-day mortality of patients with type A, B and C ACLF

Figure 3 illustrate the predictive performance of prognostic scoring systems for 28-day and 90-day mortality in patients with three ACLF types.

Through receiver operating characteristic (ROC) curve analysis, in the types A and B ACLF cohorts, the CLIF-C ACLF score did not exhibit significant discriminative ability over the MELD and MELD-Na scores. However, in the type C ACLF cohort with a history of decompensated cirrhosis, the CLIF-C ACLF score demonstrated comparable prognostic performance to the COSSH-ACLF II score but was significantly superior to the MELD and MELD-Na scores for predicting 28-day and 90-day mortality (AUROC: 28-day: CLIF-C ACLF vs. MELD, 0.758 vs. 0.690, $P = 0.021$; CLIF-C ACLF vs. MELD-Na, 0.758 vs. 0.678, $P = 0.004$; 90-day: CLIF-C ACLF vs. MELD, 0.734 vs. 0.669, $P = 0.016$; CLIF-C ACLF score vs. MELD-Na score, 0.734 vs. 0.656, $P = 0.001$).

Discussion

Through a systematic comparison of HBV-related and alcohol-related ACLF across disease severity stages (types A/B/C), this multicenter study provides a comprehensive characterization of distinct ACLF phenotypes differentiated by underlying chronic liver disease for the first time. It underscores ACLF as a heterogeneous syndrome shaped by etiology-specific pathophysiological mechanisms and underlying chronic liver disease severity. These insights highlight the necessity for stratified therapeutic paradigms tailored to underlying chronic liver disease.

The divergence between HBV-related and alcohol-related ACLF reflects fundamentally distinct pathophysiological mechanisms^{4,7,8,16–20}. HBV-related ACLF, often precipitated by viral reactivation, manifests as acute hepatocellular injury evidenced by elevated transaminases (ALT/AST) and higher MELD/MELD-Na scores, reflecting severe hepatic dysfunction²¹. In contrast, our study found that ACLF patients with alcohol-related etiology was more frequently triggered by bacterial infection than by active alcohol consumption. These patients also had a higher susceptibility to bacterial infections during follow-up, as indicated by leukocytosis and neutrophilia, a consequence of systemic inflammation, immune dysregulation, and gut barrier dysfunction^{17,18,20,22,23}. Our study further demonstrated that a high N% and bacterial infection were independent predictors of 28-day and 90-day mortality in this alcohol-related ACLF cohort. The systemic inflammatory milieu in these patients promotes the development of EHOF^{17,18,24}, including renal failure (15.54% vs. 4.25%), brain failure (12.16% vs. 6.22%), respiratory failure (9.46% vs. 5.16%), and multi-organ failure (MEHOF: 21.96% vs. 10.93%). These observations are consistent with the CANONIC study, which showed that alcohol ACLF patients were characterized by high prevalence of bacterial infection and EHOF¹¹. Critically, our data underscores the

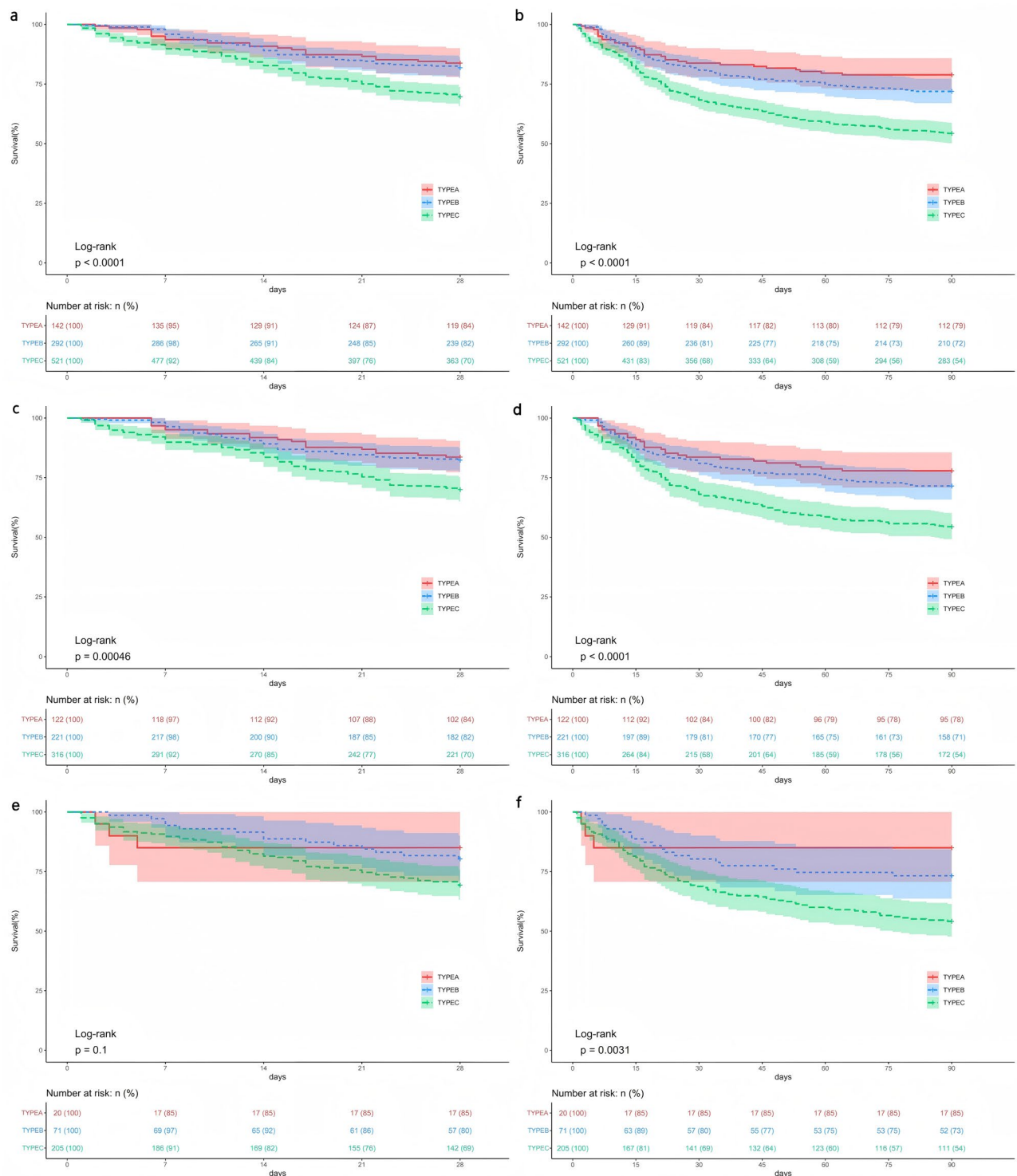


Fig. 2. Kaplan–Meier analysis of three ACLF types. **(a)** Comparison of 28-day survival of type A/B/C ACLF in overall ACLF cohort (log-rank test: overall: A vs. B vs. C, $P < 0.0001$; A vs. C, $P = 0.0011$; B vs. C, $P = 0.00016$). **(b)** Comparison of 90-day survival of type A/B/C ACLF in overall ACLF cohort (log-rank test: A vs. B vs. C, $P < 0.0001$; A vs. C, $P < 0.0001$; B vs. C, $P < 0.0001$). **(c)** Comparison of 28-day survival of type A/B/C ACLF in HBV-related ACLF cohort (log-rank test: overall: A vs. B vs. C, $P = 0.00046$; A vs. C, $P = 0.0038$; B vs. C, $P = 0.0012$). **(d)** Comparison of 90-day survival of type A/B/C ACLF in HBV-related ACLF cohort (log-rank test: A vs. B vs. C, $P < 0.0001$; A vs. C, $P < 0.0001$; B vs. C, $P < 0.0001$). **(e)** Comparison of 28-day survival of type A/B/C ACLF in alcohol-related ACLF cohort (log-rank test: A vs. B vs. C, $P = 0.10$; A vs. C, $P = 0.19$; B vs. C, $P = 0.07$). **(f)** Comparison of 90-day survival of type A/B/C ACLF in alcohol-related ACLF cohort (log-rank test: A vs. B vs. C, $P = 0.0031$, A vs. C, $P = 0.022$, B vs. C, $P < 0.0071$). ACLF, acute-on-chronic liver failure; HBV, hepatitis B virus

	Variables	Multivariable analysis for 28-day mortality		Multivariable analysis for 90-day mortality	
		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Type A ACLF	MELD	1.31 (1.05–1.62)	0.016*	1.20 (1.02–1.42)	0.030*
	CLIF-C ACLF	1.10 (1.03–1.17)	0.003**	1.07 (1.00–1.14)	0.049*
Type B ACLF	Age (years)	–	–	1.05 (1.03–1.07)	<0.001***
	TBI (mg/dL)	1.05 (1.03–1.08)	<0.001***	1.03 (1.01–1.05)	0.007**
	Circulatory failure	–	–	6.63 (2.59–16.97)	<0.001***
	Coagulatory failure	4.11 (2.11–7.99)	0.001**		
	MELD	–	–	1.06 (1.01–1.10)	0.010*
	CLIF-C ACLF	1.05 (1.01–1.10)	0.022*	–	–
Type C ACLF	N%	1.03 (1.01–1.05)	0.001**	–	–
	Complication (Gastrointestinal haemorrhage)	–	–	1.67 (1.21–2.31)	0.002**
	Complication (Hepatic encephalopathy)	–	–	1.63 (1.17–2.26)	0.004**
	Cerebral failure	1.65 (1.04–2.64)	0.035*	–	–
	MELD	1.09 (1.05–1.14)	<0.001***	1.14 (1.06–1.21)	<0.001***
	CLIF-C ACLF	1.05 (1.02–1.08)	<0.001***	1.06 (1.04–1.08)	<0.001***

Table 5. Multivariable Cox proportional hazards regression analysis of the independent prognostic factors for 28-day and 90-day mortality in WGO type A/B/C ACLF subgroups. ACLF, acute-on-chronic liver failure; WGO, World Gastroenterology Organization; CI, confidence interval; MELD, Model for End Stage Liver Disease; CLIF-C ACLF, Chronic Liver Failure-Consortium ACLF; TBI, total bilirubin; N%, percentage of neutrophils. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

imperative for etiology-specific interventions: HBV-related ACLF demands urgent antiviral therapy and robust hepatic support, while alcohol-related cases require intensive infection control and systemic organ protection.

The WGO classification stratifies risk based on the severity of underlying chronic liver disease¹². Patients with type C ACLF, who have previously decompensated cirrhosis and severely compromised hepatic reserve, emerge as the most severe phenotype across both etiologies, with a 90-day mortality rate exceeding 45%. This group of patients exhibits particularly rapid progression to EHOF following acute precipitants, likely due to the cumulative effects of portal hypertension, severely diminished hepatic reserve, systemic inflammation, and immunosuppression^{1,4,11,24–26}. Additionally, the occurrence of cerebral failure, as well as higher MELD and CLIF-C ACLF scores were identified as independent risk factors for adverse outcome in this cohort. These findings indicate that patients with type C ACLF require aggressive surveillance for multiple organ failures, rather than monitoring for isolated liver failure.

Furthermore, this study, utilizing ROC curve analysis, demonstrates that the CLIF-C ACLF and COSSH-ACLF II scores significantly outperform the MELD and MELD-Na scores in predicting the prognosis of type C ACLF patients at high risk of developing EHOF. These findings align with emerging evidence suggesting that MELD and MELD-Na, which primarily assess liver function, may underestimate mortality in ACLF cases complicated by EHOF^{13,14,27}. In contrast, the CLIF-C ACLF and COSSH-ACLF II scores^{15,16}, by incorporating extrahepatic organ failure/dysfunction and WBC count, exhibit superior prognostic accuracy over the MELD/MELD-Na scores, particularly in subgroups with a high likelihood of developing EHOF, such as type C patients, as reported by Shi et al.²⁸. Moreover, alcohol-related cases in our study demonstrated significantly higher CLIF-C ACLF scores (44.33 vs. 40.56 for HBV-related cases, $P < 0.001$) and COSSH-ACLF II scores (6.10 vs. 4.99 for HBV-related cases, $P < 0.001$), consistent with their predisposition to EHOF. Considering COSSH-ACLF II score was originally developed for HBV-related ACLF¹⁶, its potential applicability to non-HBV-related ACLF remains to be confirmed in further studies specifically designed to address this question.

Notably, despite distinct clinical profiles, there was no significant difference in 28- and 90-day mortality between etiologies. Multivariable analysis further confirmed that mortality risk was independently associated with MELD and CLIF-C ACLF scores, as well as the presence of EHOF and specific complications, but not with the underlying etiology (HBV or alcohol). These findings underscore that survival in ACLF is primarily determined by the cumulative organ failure burden rather than the specific etiology of chronic liver disease. The hypothesis is further supported by the observation that patients with type C ACLF, characterized by a high incidence of organ failures, demonstrate uniformly high mortality rates (>45% at 90 days) regardless of the underlying etiology, advocating for standardized protocols for multi-organ support.

This study is limited by incomplete emerging etiologies [e.g., metabolic dysfunction-associated steatotic liver disease (MASLD)], the lack of liver transplantation data, potential exclusion of ACLF grade 1 patients based on CLIF-C ACLF criteria, and the retrospective design. However, the strength of multicenter recruitment, the use of standardized criteria for diagnosis and classification, and minimal data loss helped to mitigate these potential limitations.

In conclusion, this multicenter study successfully provides the first granular characterization of the heterogeneity in clinical profiles between HBV-related and alcohol-related ACLF across diverse severity stages, underscoring the critical importance of stratified treatment strategies tailored to underlying chronic liver disease. Our findings bridge the gap between regionally dominant etiologies and globally harmonized

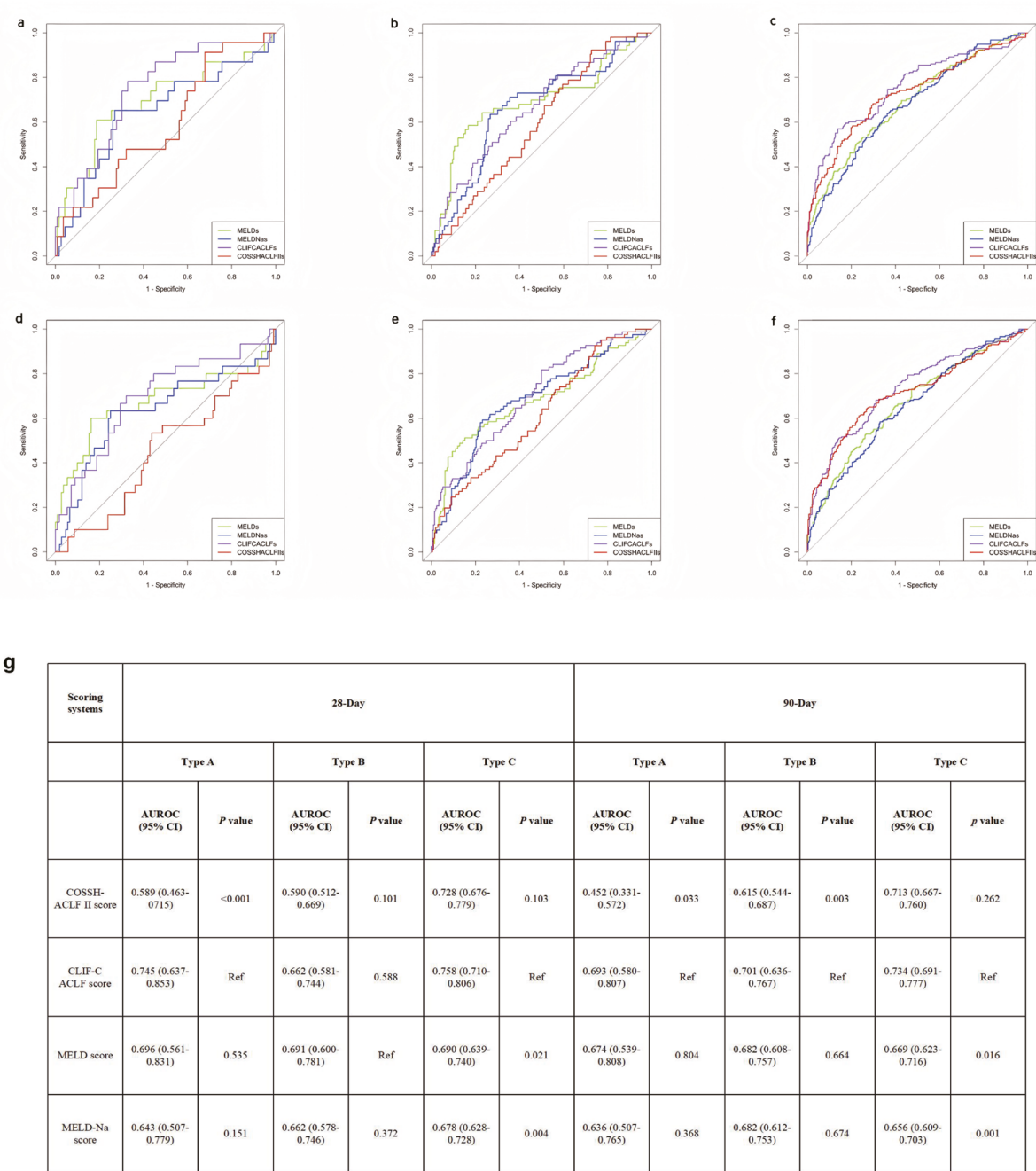


Fig. 3. Performance of prognostic scoring systems for predicting 28-day and 90-day mortality rates across WGO ACLF types. (a–f) Receiver operating characteristic curves for the abilities of prognostic scoring systems to predict the 28-day mortality of patients with type A (a), type B (b) and type C (c) ACLF, as well as the 90-day mortality of patients with type A (d), type B (e) and type C (f) ACLF. (g) Prognostic performance of scoring systems for 28-day and 90-day mortality in type A/B/C ACLF. ACLF, acute-on-chronic liver failure; MELDs, Model for End Stage Liver Disease score; MELD-Nas, MELD-sodium score; CLIF-C ACLFs, Chronic Liver Failure-Consortium ACLF score; COSSH-ACLF IIs, Chinese Group on the Study of Severe Hepatitis B-ACLF II score; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; Ref, accuracy of this model as compared to the other models in predicting mortality.

therapeutic standards, thereby paving the critical way for precision treatment approaches to ultimately enhance patient survival.

Data availability

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

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Author contributions

QZ and JXH collected data, performed statistical analysis, and drafted the final manuscript. STQ, JLB and AMG helped to collect data. FL, CYZ, LYZ, WHR, SJX, YC and ZPD helped to collect data and drafted the final manuscript. TH conceived and designed this study, collected data, and contributed to the critical revision of the

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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