# Predictive value of the Chinese group on the study of severe hepatitis B-acute-on-chronic liver failure score in the short-term prognosis of patients with hepatitis B virus-related acute-on-chronic liver failure

**Jing-Jing Tong[1], Wei Zhao[2], Xiu-Ying Mu[3], Xiang Xu[1], Hai-Bin Su[1], Xiao-Yan Liu[1], Jing Chen[1,4], Xing-Ran Zhai[3], Yu Wang[4], Jin-Hua Hu[1,3,4]**

[1]Liver Failure Treatment and Research Center, The Fifth Medical Center of Chinese PLA General Hospital, Beijing 100039, China;
[2]Department of Clinical Laboratory, China-Japan Friendship Hospital, Beijing 100029, China;
[3]Peking University 302 Clinical Medical School, Beijing 100039, China;
[4]Medical School of Chinese PLA, Beijing 100853, China.

## Abstract

**Background:** As a large, prospective, multicenter study-based prognostic score for hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF), the Chinese group on the study of severe hepatitis B-acute-on-chronic liver failure score (COSSH-ACLFs), has been approved by some foreign scholars; however, its predictive value needs to be verified. This study investigated the predictive value of COSSH-ACLFs for short-term prognosis in Chinese patients with HBV-ACLF.

**Methods:** This retrospective cohort study included 751 patients with HBV-ACLF admitted to the Fifth Medical Center of Chinese PLA General Hospital between January 2011 and December 2014. Spearman method was used to assess the correlation of COSSH-ACLFs with classical scores. Different COX multivariate regression models were used to confirm the relationship between COSSH-ACLFs and short-term prognosis in patients with HBV-ACLF, and stratified analysis was used to further verify the stability of this relationship. We compared the predictive powers of COSSH-ACLFs and other classical scores using area under the receiver operating characteristic curve (AUROC) and *Z*-test.

**Results:** A total of 975 patients with HBV-ACLF were screened, and 751 were analyzed (623 male and 128 female). COSSH-ACLFs was the highest in patients with end-stage ACLF, followed by those with middle- and early-stage ACLF ($H = 211.8$, $P < 0.001$). In the fully adjusted model, COX multivariate regression analysis revealed that COSSH-ACLFs (as a continuous variable) was independently and positively correlated with mortality risk in patients with HBV-ACLF at 28 days (hazard ratio [HR]: 1.37 [1.22, 1.53], $P < 0.001$) and 90 days (HR: 1.43 [1.29, 1.58], $P < 0.001$). The same trend could be observed in the crude model and minimally adjusted model. The AUROCs of COSSH-ACLFs for 28-day and 90-day prognoses in patients with HBV-ACLF were 0.807 and 0.792, respectively, indicating a stronger predictive accuracy than those of classic models.

**Conclusions:** COSSH-ACLFs, with a superior predictive accuracy compared with other classical scores, can strongly predict short-term prognosis in Chinese patients with HBV-ACLF.

**Keywords:** Hepatitis B virus-related acute-on-chronic liver failure; COSSH-ACLF score; Predictive value; Prognosis

## Introduction

Acute-on-chronic liver failure (ACLF), a clinical syndrome characterized by liver failure due to an acute injury on underlying chronic liver disease, is often accompanied by various complications.[1-3] ACLF is characterized by a critical disease condition, rapid progression, and a high short-term mortality rate. Besides liver transplantation, there is still a dearth of specific treatment options.[1,4-6] Therefore, early and accurate assessment of the disease condition and prediction of patient survival are crucial for timely selection of appropriate treatment methods and a better prognosis.

At present, various models are used in clinical practice to evaluate the prognosis of ACLF, all of which have been proven to have different degrees of predictive values.[7-12]

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Jing-Jing Tong and Wei Zhao contributed equally to this work.

**Correspondence to:** Prof. Jin-Hua Hu, Liver Failure Treatment and Research Center, The Fifth Medical Center of Chinese PLA General Hospital, No. 100 Xisihuan Road, Fengtai District, Beijing 100039, China
E-Mail: 13910020608@163.com



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However, most of these models were validated in foreign patients. Because of the difference in etiologies between eastern and western countries as well as the divergence of opinions on the definition of ACLF,[13-16] the application of these models is limited in China. HBV-ACLF is the most important type of ACLF in China, accounting for 87% to 91% of cases.[17,18] The Child-Turcotte-Pugh score (CTPs), model for end-stage liver disease score (MELDs), and MELD-sodium score (MELD-Nas), primarily based on alcoholic liver disease, were initially developed to evaluate the progression of cirrhosis. The chronic liver failure (CLIF)-sequential organ failure assessment score (CLIF-SOFAs) and CLIF-consortium organ failure score (CLIF-C OFs) pay more attention to extra-hepatic organ failure, which is less frequent in patients with HBV-ACLF. Thus, all of these scores have limited accuracy in predicting the prognosis of Chinese patients with HBV-ACLF. Recently, Wu *et al*[19] conducted the first prospective multi-center study of Chinese patients with HBV and established the Chinese group on the study of severe hepatitis B-acute-on-chronic liver failure score (COSSH-ACLFs). However, whether the COSSH-ACLFs is suitable for Chinese patients with HBV-ACLF needs further verification. Therefore, this study aimed to evaluate the predictive value of COSSH-ACLFs for the short-term prognosis (28 days and 90 days) of Chinese patients with HBV-ACLF and to provide new medical evidences for its clinical application.

## Methods

### Ethical approval

This study was approved by the Ethics Committee of the Fifth Medical Center of Chinese PLA General Hospital (No. 2019016D). The data were anonymous, so informed consent was waived. The protocol conforms to the ethical guidelines of the 1975 *Declaration of Helsinki*.

### Study subjects

In this retrospective cohort study, patients with HBV-ACLF from January 2011 to December 2014 in the Fifth Medical Center of Chinese PLA General Hospital were consecutively included. HBV-ACLF was diagnosed according to the guidelines recommended by the Chinese Medical Association.[3,20] The inclusion criteria were as follows: (1) serum hepatitis B surface antigen and/or HBVDNA positivity for at least 6 months; (2) progressive jaundice with total bilirubin (TBil) ten times greater than the upper limit of normality or a daily increase of ≥17.1 μmol/L; (3) prothrombin activity (PTA) ≤40% or international normalized ratio (INR) ≥1.50. The exclusion criteria for the study were: (1) patients aged <18 years; (2) patients with serious underlying diseases of the heart, brain, lungs, kidneys, and other organs; (3) patients with malignant tumors of the liver or other organs; (4) pregnant women; (5) patients with incomplete clinical data because of hospitalization for less than 24 h.

A total of 975 patients were screened, among whom 155 were excluded. During the 90-day follow-up period, 15 patients underwent transplantation and 54 were lost to follow-up and the rate of loss to follow-up was 6.6%. After further exclusion of patients who underwent transplantation and were lost to follow-up, a total of 751 patients were included in the final analysis [Figure 1].

### Type and stage of ACLF

According to the existing liver disease, ACLF could be divided into three types: chronic liver disease with no cirrhosis (type A ACLF), with compensated cirrhosis (type B ACLF), and with decompensated cirrhosis (type C ACLF).[3]

On the basis of the severity of disease, ACLF could be divided into early, middle, and end stages, defined as follows: (1) early stage: 30%< PTA ≤40% (or 1.5≤ INR <1.9), with no complications or extra-hepatic organ failure; (2) middle stage: 20%< PTA ≤30% (or 1.9≤ INR <2.6), with one complication and/or one extra-hepatic organ failure; (3) end-stage: PTA ≤20% (or INR ≥2.6), with two complications and/or two extra-hepatic organ failures.[3]

### Data collection, follow-up, and endpoints

The following data were collected when the patients were enrolled: (1) general information (age, sex, and the type of ACLF); (2) laboratory data: white blood cell, hemoglobin, platelet, albumin, TBil, alanine aminotransferase, aspartate aminotransaminase, alkaline phosphatase, gamma-glutamyltransferase, serum creatinine, total cholesterol, triglyceride, blood sodium, alpha-fetoprotein, blood ammonia, and PTA; (3) data on complications: ascites, infection, acute kidney injury (AKI), hepatic encephalopathy (HE), and gastrointestinal bleeding.

The following prognostic scores were also calculated at baseline: CTPs,[7] MELDs,[8,21] MELD-Nas,[9] CLIF-SOFAs,[10] CLIF-C OFs,[11] and COSSH-ACLFs.[19]

The patients were followed up for 90 days. We considered death as the primary endpoint. Patients who underwent liver transplantation or were lost to follow-up were not included in the final analysis. Information on prognosis was verified through medical records and telephone contact.

### Statistical analysis

SPSS version 24.0 (IBM Corporation, Armonk, NY, USA), GraphPad Prism version 7.00 (GraphPad Software Inc., La Jolla, CA, USA), statistical packages R version 3.4.3 (The R Foundation, Vienna, Austria), and EmpowerStats (X&Y Solutions, Inc., Boston, MA, USA) were used to perform statistical analysis and plot data. Depending on whether the data distribution was normal, measurement data were expressed as mean ± standard deviation or as median and interquartile range. Comparisons among multiple groups were performed using analysis of variance or the Kruskal-Wallis test. Enumeration data were expressed as number of cases (%), and comparisons between groups were performed using the chi-square test. The Spearman method was used for correlation analysis. According to the

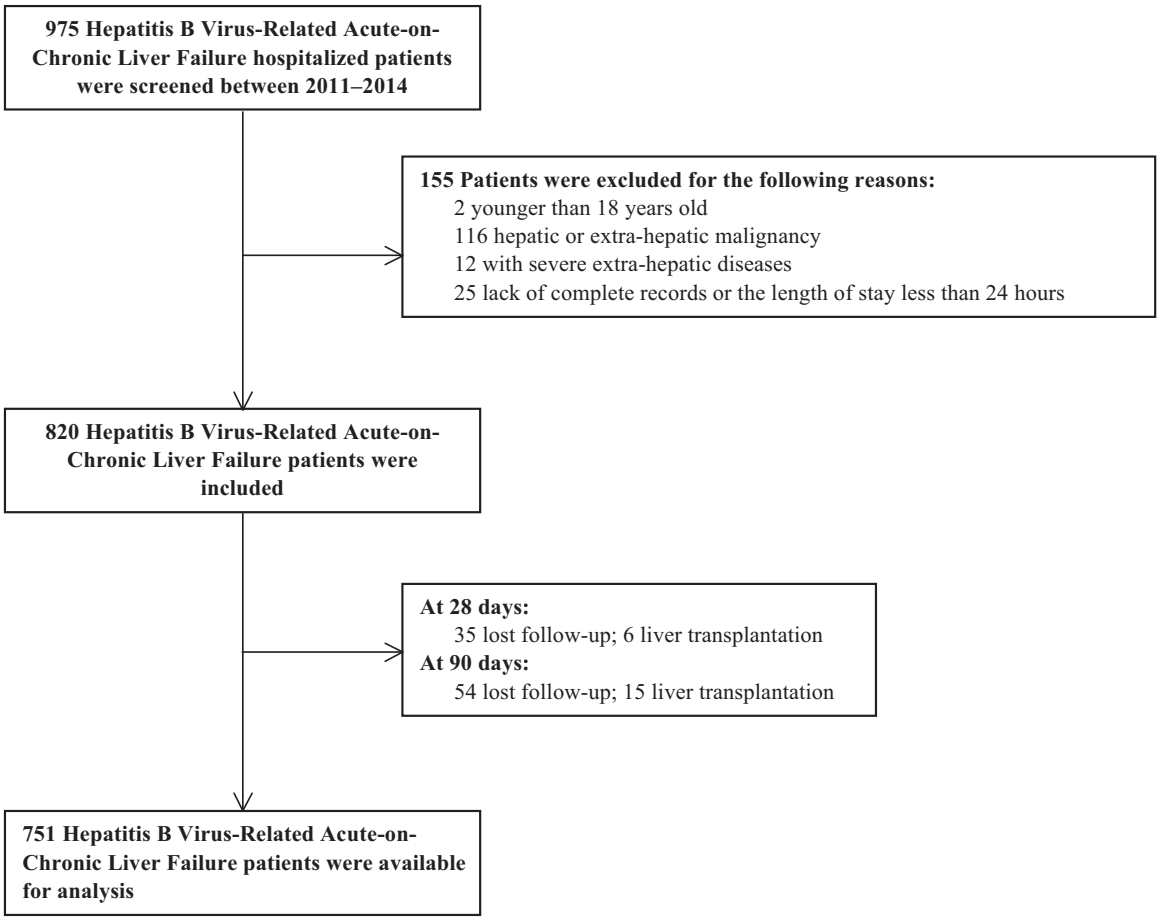



**Figure 1:** Flowchart of screening, recruitment of patients with HBV-ACLF. HBV-ACLF: Hepatitis B virus-related acute-on-chronic liver failure.

COSSH-ACLFs, we divided all subjects into four levels (<3 points; ≥3 points and <4 points; ≥4 points and <5 points; and ≥5 points) from low to high. The COX multivariate regression risk model was used to analyze the relationship between the COSSH-ACLFs (as a whole continuous variable and classified variable) and the short-term prognosis. The log-rank test was used to compare the survival rates of patients with different COSSH-ACLFs segments. The receiver operating characteristic curve was used to evaluate the predictive value of various models for the short-term prognosis of patients with HBV-ACLF. $P < 0.05$ was considered to be statistically significantly different.

## Results

### Baseline characteristics of patients with HBV-ACLF

A total of 751 patients with HBV-ACLF were analyzed. The median age was 44 (37–52) years, with male patients accounting for 83.0% of all subjects. There were 229, 398, and 124 cases of type A, B, and C ACLF, respectively, accounting for 30.5%, 53.0%, and 16.5% of all cases. TBil was 283.4 (206.7–383.9) μmol/L and PTA (%) was 33.1 (25.9–40.0); 261 patients (34.7%) suffered from infections, 156 (20.8%) had AKI, and 129 patients (17.2%) presented HE. There were 376, 265, 110 cases of early-stage, middle-stage, and end-stage ACLF, respectively, accounting for 50.1%, 35.3%, and 14.6% of all cases. The COSSH-ACLFs was 3.7 (3.3–4.4), and the 28-day and 90-day transplantation-free survival rates were 31.7% and 45.4%, respectively [Table 1].

### Correlation between COSSH-ACLFs and severity of HBV-ACLF

The COSSH-ACLFs was the lowest in patients with early-stage ACLF, followed by patients with middle-stage and end-stage ACLF, with significant differences among the three groups ($H = 211.8$, $P < 0.001$). Differences between every two groups being compared were statistically significant (all $P$ values $< 0.001$). The results of Spearman correlation analysis showed that COSSH-ACLFs was positively correlated with CTPs ($r = 0.489$, $P < 0.001$), MELDs ($r = 0.756$, $P < 0.001$), MELD-Nas ($r = 0.636$, $P < 0.001$), CLIF-SOFAs ($r = 0.825$, $P < 0.001$), and CLIF-C OFs ($r = 0.750$, $P < 0.001$) [Figure 2].

### COX multivariate analysis of the correlation between COSSH-ACLFs and short-term prognosis in patients with HBV-ACLF

Non-adjusted and adjusted models are shown in Table 2. As a continuous variable, baseline COSSH-ACLFs correlated with the short-term prognosis of patients with HBV-ACLF in the crude model and minimally adjusted model

**Table 1: Baseline characteristics of patients with HBV-ACLF.**

| Characteristics | Patients ($n = 751$) |
|---|---|
| Age (years) | 44.0 (37.0–52.0) |
| Gender, *n* (%) | |
| Male | 623 (83.0) |
| Female | 128 (17.0) |
| Type of ACLF, *n* (%) | |
| A | 229 (30.5) |
| B | 398 (53.0) |
| C | 124 (16.5) |
| Laboratory parameters | |
| White blood cells ($\times 10^9$/L) | 6.7 (5.0–9.2) |
| Hemoglobin (g/L) | 121.4 (104.0–138.0) |
| Platelets ($\times 10^9$/L) | 84.0 (56.0–117.0) |
| Albumin (g/L) | 29.0 (26.0–32.0) |
| Total bilirubin (μmol/L) | 283.4 (206.7–383.9) |
| Alanine aminotransferase (U/L) | 146.0 (68.0–428.0) |
| Aspartate aminotransferase (U/L) | 170.0 (99.0–365.0) |
| Creatinine (μmol/L) | 89.0 (79.0–105.0) |
| Total cholesterol (mmol/L) | 1.43 (0.92–1.99) |
| Triglyceride (mmol/L) | 0.98 (0.67–1.42) |
| Sodium (mmol/L) | 136.0 (132.0–139.0) |
| Alpha fetoprotein (ng/mL) | 46.8 (16.0–154.8) |
| Blood ammonia (μmol/L) | 64.0 (46.0–87.0) |
| Prothrombin activity (%) | 33.1 (25.9–40.0) |
| Complications, *n* (%) | |
| Ascites | 655 (87.0) |
| Infection | 261 (34.7) |
| Acute kidney injury | 156 (20.8) |
| Hepatic encephalopathy | 129 (17.2) |
| Gastrointestinal bleeding | 25 (3.4) |
| Stage of ACLF, *n* (%) | |
| Early stage | 376 (50.1) |
| Middle stage | 265 (35.3) |
| End stage | 110 (14.6) |
| Severity score | |
| COSSH-ACLFs | 3.7 (3.3–4.4) |
| CTPs | 11.0 (10.0–12.0) |
| MELDs | 24.5 (22.1–27.6) |
| MELD-Nas | 26.4 (23.3–31.6) |
| CLIF-SOFAs | 7.0 (7.0–8.0) |
| CLIF-C OFs | 8.0 (8.0–9.0) |
| Transplant-free mortality, *n* (%) | |
| 28 days | 238 (31.7) |
| 90 days | 341 (45.4) |

Continuous variables were presented as median (interquartile range), categorical variables were presented as number (percentage). CLIF-C OFs: CLIF-consortium organ failure score; CLIF-SOFAs: Chronic liver failure-sequential organ failure assessment score; COSSH-ACLFs: Chinese group on the study of severe hepatitis B-acute-on-chronic liver failure score; CTPs: Child-Turcotte-Pugh score; HBV-ACLF: Hepatitis B virus-related acute-on-chronic liver failure; MELD-Nas: MELD-sodium score; MELDs: Model for end-stage liver disease score.

(Model 1). In the fully adjusted model (Model 3), the baseline COSSH-ACLFs was still independently and positively correlated with the 28-day (hazard ratio [HR]: 1.37 [1.22, 1.53], $P < 0.001$) and 90-day (HR: 1.43 [1.29, 1.58], $P < 0.001$) mortality risk of patients with HBV-ACLF, after adjusting for other confounding factors. For sensitivity analysis, the COSSH-ACLFs was considered a classified variable (grouped as follows: <3 points; ≥3 points and <4 points; ≥4 points and <5 points; and ≥5 points), and the same trend was observed. Compared to the short-term mortality risk of patients in the <3 point group, those of patients in the ≥3 points and <4 points; ≥4 points and <5 points; and ≥5 points groups increased gradually, with HRs and 95% confidence intervals of 3.02 (1.08, 8.43), 4.59 (1.58, 13.31), and 9.31 (2.99, 29.03), respectively, at 28 days and 2.09 (1.07, 4.09), 3.19 (1.55, 6.56), and 6.11 (2.73, 13.68), respectively, at 90 days.

### Survival analysis of patients with HBV-ACLF with different COSSH-ACLFs

During follow-up, 238 and 341 deaths were recorded within 28 and 90 days, respectively. Kaplan-Meier curves showed that the cumulative survival rate was the highest in patients in the lowest COSSH-ACLFs segment (<3 point), followed by patients in the 3-4-point, 4-5-point, and more than 5 point segments (96.0% *vs.* 79.6% *vs.* 59.6% *vs.* 21.0%, $\chi^2 = 230.0$, $P < 0.001$ at 28 days; 89.1% *vs.* 64.4% *vs.* 38.5% *vs.* 12.6%, $\chi^2 = 245.3$, $P < 0.001$ at 90 days). Differences between every two groups being compared were statistically significant (all $P < 0.05$) [Figure 3].

### Stratified analysis and Forest plot

Figure 4 shows the sub-group analysis for the correlation between COSSH-ACLFs and short-term mortality risk in the COX multivariate regression model. The patients were divided into several sub-groups according to sex, age, type of ACLF, and presence of various complications. The results showed that the 28-day and 90-day mortality risk of patients with HBV-ACLF in each sub-group increased with every 1-point increase in the COSSH-ACLFs, and the differences were statistically significant (all $P < 0.05$) except in females ($P = 0.742$ and 0.560 for the 28 days and 90 days death risk, respectively). Further, the association between COSSH-ACLFs and prognosis in the stratified analysis was consistent with the results of the total multivariable COX regression analysis showed in Table 2.

### Short-term prognostic value of COSSH-ACLFs for patients with HBV-ACLF

COSSH-ACLFs was compared with the existing classical prognostic scores, including CTPs, MELDs, MELD-Nas, CLIF-SOFAs, and CLIF-C OFs. COSSH-ACLFs showed excellent predictive power for the 28-day (area under the receiver operating characteristic curve [AUROC] = 0.807) and 90-day (AUROC = 0.792) mortality of patients with HBV-ACLF, with sensitivities of 66.0% (28 days) and 73.0% (90 days); specificities of 79.1% (28 days) and 71.2% (90 days); positive predictive values of 59.5% (28 days) and 67.9% (90 days); negative predictive values of 83.4% (28 days) and 76.0% (90 days); and cut-off values of 4.1 (28 days) and 3.7 (90 days), respectively. COSSH-ACLFs was superior to CTPs ($Z = 1.912$, $P = 0.056$ for 28 days; $Z = 2.000$, $P = 0.046$ for 90 days), MELDs

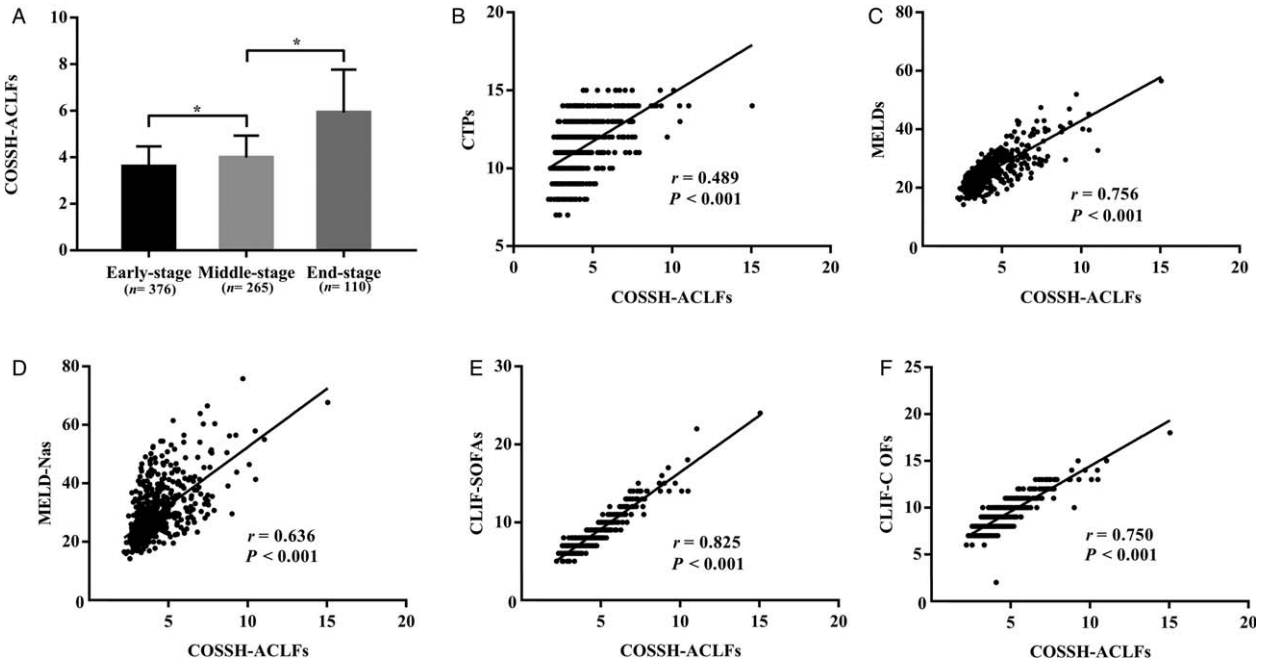



**Figure 2:** Relationship between COSSH-ACLFs and severity of HBV-ACLF ($n = 751$). (A) Comparison of COSSH-ACLFs in patients with different stages of HBV-ACLF. (B) Correlation between COSSH-ACLFs and CTPs. (C) Correlation between COSSH-ACLFs and MELDs. (D) Correlation between COSSH-ACLFs and MELD-Nas. (E) Correlation between COSSH-ACLFs and CLIF-SOFAs. (F) Correlation between COSSH-ACLFs and CLIF-C OFs. * $P < 0.001$. CLIF-C OFs: CLIF-consortium organ failure score; CLIF-SOFAs: Chronic liver failure-sequential organ failure assessment score; COSSH-ACLFs: Chinese group on the study of severe hepatitis B-acute-on-chronic liver failure score; CTPs: Child-Turcotte-Pugh score; HBV-ACLF: Hepatitis B virus-related acute-on-chronic liver failure; MELD-Nas: MELD-sodium score; MELDs: Model for end-stage liver disease score.

**Table 2: Association between COSSH-ACLFs and short-term mortality in patients with HBV-ACLF.**

| | | Crude model | | Model 1 | | Model 2 | |
|---|---|---|---|---|---|---|---|
| **Items** | **Deaths/total, *n*** | **HR (95% CI)** | ***P*** | **HR (95% CI)** | ***P*** | **HR (95% CI)** | ***P*** |
| 28 days mortality | | | | | | | |
| COSSH-ACLFs (continuous) | 238/751 | 1.69 (1.60, 1.79) | <0.001 | 1.69 (1.59, 1.79) | <0.001 | 1.37 (1.22, 1.53) | <0.001 |
| COSSH-ACLFs (classified) | | | | | | | |
| <3 | 4/101 | 1 | | 1 | | 1 | |
| ≥3 <4 | 74/368 | 5.45 (1.99, 14.92) | 0.001 | 4.93 (1.79, 13.57) | 0.002 | 3.02 (1.08, 8.43) | 0.035 |
| ≥4, <5 | 66/162 | 12.60 (4.59, 34.59) | <0.001 | 10.73 (3.86, 29.86) | <0.001 | 4.59 (1.58, 13.31) | 0.005 |
| ≥5 | 94/120 | 40.88 (15.01, 111.35) | <0.001 | 36.15 (13.16, 99.35) | <0.001 | 9.31 (2.99, 29.03) | 0.001 |
| 90 days mortality | | | | | | | |
| COSSH-ACLFs (continuous) | 341/751 | 1.70 (1.62, 1.80) | <0.001 | 1.67 (1.59, 1.77) | <0.001 | 1.43 (1.29, 1.58) | <0.001 |
| COSSH-ACLFs (classified) | | | | | | | |
| <3 | 10/101 | 1 | | 1 | | 1 | |
| ≥3, <4 | 128/368 | 4.08 (2.14, 7.76) | <0.001 | 3.61 (1.88, 6.93) | <0.001 | 2.09 (1.07, 4.09) | 0.031 |
| ≥4, <5 | 100/162 | 8.95 (4.67, 17.15) | <0.001 | 7.57 (3.89, 14.74) | <0.001 | 3.19 (1.55, 6.56) | 0.002 |
| ≥5 | 103/120 | 23.72 (12.36, 45.53) | <0.001 | 20.36 (10.51, 39.45) | <0.001 | 6.11 (2.73, 13.68) | <0.001 |

Model 1 was adjusted for age, gender, type of ACLF; Model 2 was adjusted for Model 1 + total bilirubin, prothrombin activity, ascites, acute kidney injury, hepatic encephalopathy, infection. ACLF: Acute-on-chronic liver failure; CI: Confidence interval; COSSH-ACLFs: Chinese group on the study of severe hepatitis B-acute-on-chronic liver failure score; HR: Hazard ratio.

($Z = 4.823$, $P < 0.001$ for 28 days; $Z = 6.126$, $P < 0.001$ for 90 days), MELD-Nas ($Z = 3.775$, $P < 0.001$ for 28 days; $Z = 4.652$, $P < 0.001$ for 90 days), CLIF-SOFAs ($Z = 6.125$, $P < 0.001$ for 28 days; $Z = 7.122$, $P < 0.001$ for 90 days), and CLIF-C OFs ($Z = 5.093$, $P < 0.001$ for 28 days; $Z = 6.232$, $P < 0.001$ for 90 days) in predicting the short-term prognosis of patients with HBV-ACLF [Figure 5].

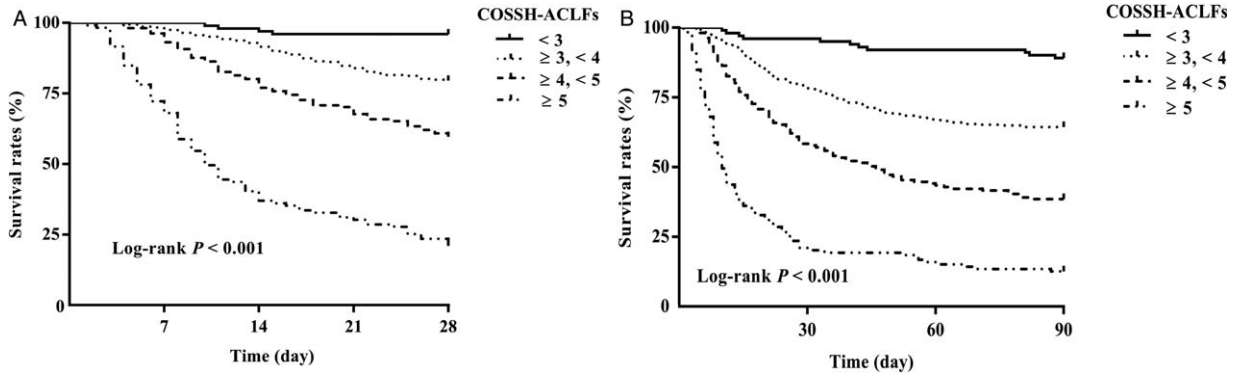



**Figure 3:** Survival curves of patients with HBV-ACLF with different COSSH-ACLFs ($n = 751$). (A) 28-day survival curves of patients with HBV-ACLF. (B) 90-day survival curves of patients with HBV-ACLF. COSSH-ACLFs: Chinese group on the study of severe hepatitis B-acute-on-chronic liver failure score; HBV-ACLF: Hepatitis B virus-related acute-on-chronic liver failure.

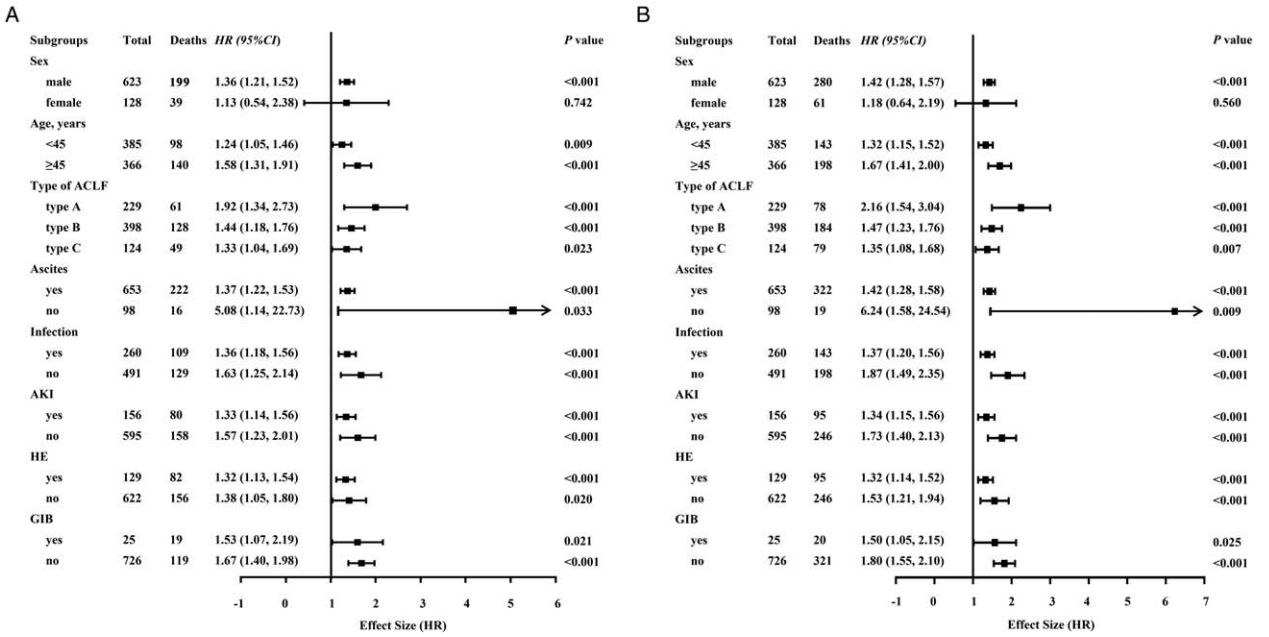
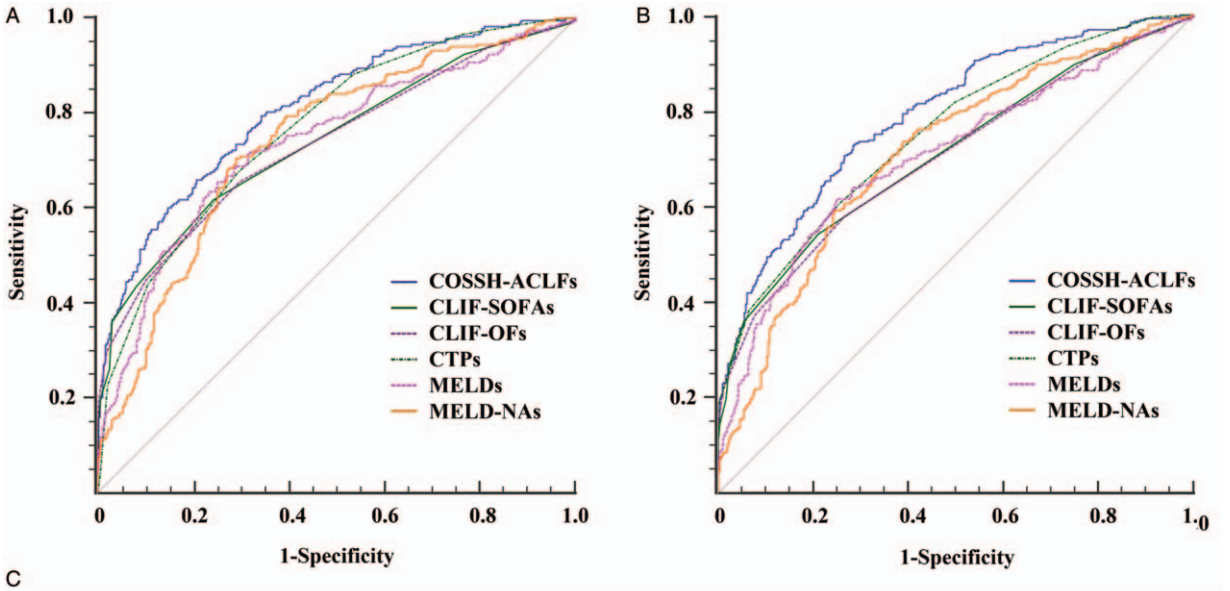



**Figure 4:** Hierarchical analysis and forest maps of the relationship between COSSH-ACLFs and 28 days (A) and 90 days (B) prognosis (multivariate HR and 95% CI were shown for each 1-point increase in COSSH-ACLFs). Each stratification adjusted for all the factors (age, gender, type of ACLF, total bilirubin, prothrombin activity, ascites, acute kidney injury, hepatic encephalopathy, and infection) except the stratification factor itself. ACLF: Acute-on-chronic liver failure; AKI: Acute kidney injury; CI: Confidence intervals; COSSH-ACLFs: Chinese group on the study of severe hepatitis B-ACLF score; GIB: Gastrointestinal bleeding; HE: Hepatic encephalopathy; HR: Hazard ratios.

## Discussion

COSSH-ACLFs, which was derived from a high-quality clinical study in Chinese patients with HBV-ACLF, has been approved by international hepatologists. This study systematically evaluated the predictive capacity of COSSH-ACLFs in patients with ACLF. Encouragingly, in our study, COSSH-ACLFs showed excellent predictive power for short-term prognosis in patients with HBV-ACLF, which was superior to that of other classical prognostic models. COSSH-ACLFs had a significant positive correlation with the severity and short-term prognosis of patients with HBV-ACLF.

Our research shows that the COSSH-ACLFs of patients with end-stage HBV-ACLF is higher than that of patients with middle-stage and early-stage HBV-ACLF, and COSSH-ACLFs has a good positive correlation with CTPs, MELDs, MELD-Nas, CLIF-SOFAs, and CLIF-C OFs. These classical prognosis models have shown positive correlations with the short-term mortality risk of patients with ACLF in previous studies, and CTPs, MELDs, and MELD-Nas have been used in liver transplantation evaluation of patients with end-stage liver diseases.[7,8,10,11,22,23] All of these aspects suggest that COSSH-ACLFs is closely correlated with the severity of ACLF. Among these scores, COSSH-ACLFs has a slightly weaker correlation with CTPs, whereas its correlation with CLIF-SOFAs is the strongest. CTPs lacks effective indicators to evaluate renal function and has a narrow grading system; hence, patients with the same score may have a different prognoses, making it unable to effectively

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| | Severity score | AUROC | Cut-off value | Sensitivity | Specificity | Positive predictive value | Negative predictive value |
|---|---|---|---|---|---|---|---|
| **28d prognosis** | | | | | | | |
| | COSSH-ACLFs | 0.807 | 4.1 | 0.660 | 0.791 | 0.595 | 0.834 |
| | CTPs | 0.768 | 12.0 | 0.677 | 0.706 | 0.516 | 0.825 |
| | MELDs | 0.737 | 25.6 | 0.656 | 0.747 | 0.546 | 0.824 |
| | MELD-NAs | 0.739 | 27.6 | 0.706 | 0.710 | 0.530 | 0.839 |
| | CLIF-SOFAs | 0.740 | 8.0 | 0.618 | 0.754 | 0.539 | 0.810 |
| | CLIF-OFs | 0.735 | 9.0 | 0.656 | 0.702 | 0.505 | 0.815 |
| **90d prognosis** | | | | | | | |
| | COSSH-ACLFs | 0.792 | 3.7 | 0.730 | 0.712 | 0.679 | 0.760 |
| | CTPs | 0.752 | 12.0 | 0.607 | 0.744 | 0.664 | 0.695 |
| | MELDs | 0.706 | 25.2 | 0.616 | 0.746 | 0.669 | 0.700 |
| | MELD-NAs | 0.712 | 25.6 | 0.736 | 0.612 | 0.612 | 0.736 |
| | CLIF-SOFAs | 0.711 | 8.0 | 0.543 | 0.785 | 0.678 | 0.674 |
| | CLIF-OFs | 0.705 | 9.0 | 0.581 | 0.729 | 0.640 | 0.677 |

**Figure 5:** Discrimination ability of COSSH-ACLFs and other classic models to predict the prognosis of patients with HBV-ACLF at 28 days (A) and 90 days (B). (C) Indicators of predictive ability of prognostic models. AUROC: Area under the receiver operating characteristic curve; CLIF-C OFs: CLIF-consortium organ failure score; CLIF-SOFAs: Chronic liver failure-sequential organ failure assessment score; COSSH-ACLFs: Chinese group on the study of severe hepatitis B-acute-on-chronic liver failure score; CTPs: Child-Turcotte-Pugh score; MELD-Nas: MELD-sodium score; MELDs: Model for end-stage liver disease score.

distinguish the severity of the disease.[24] CLIF-SOFAs, developed by the European Association for the Study of the CLIF consortium based on an European multi-center large-scale prospective cohort study (CANONIC study), is the most widely used ACLF prognosis score at present, and it is believed to be able to accurately predict the short-term prognosis of patients.[25-27]

In this study, the correlation between COSSH-ACLFs and the short-term prognosis of patients with HBV-ACLF was investigated from various perspectives. First, COSSH-ACLFs was found to be positively correlated with patients' short-term mortality risk, whether as a continuous variable or as a segmented score. After adjusting for the potential confounding factors, including age, sex, type, TBil, PTA, ascites, AKI, HE, and infection, the other two models were established to further verify this positive correlation, and the increase in mortality risk was greater for higher score segments. The results of the sub-group analysis and Forest plot suggest that the positive correlation between COSSH-ACLFs and the short-term mortality risk of patients with HBV-ACLF was stable in all cases, that is, COSSH-ACLFs was suitable for various patients with HBV-ACLF of different sexes, age ranges, types, and complications.

Our study shows that COSSH-ACLFs has a higher predictive ability for 28-/90-day prognosis in patients with HBV-ACLF than do CTPs, MELDs, MELD-Nas, CLIF-SOFAs, and CLIF-C OFs. This is in accordance with previous results.[19,28,29] Although widely used to predict the prognosis of ACLF, these classical models also have certain limitations. CTPs has a "ceiling effect" that may affect its predictive ability.[24] MELDs and MELD-Nas do not consider the effects of creatinine and hepatic encephalopathy, thus affecting their predictive ability. CLIF-SOFAs and CLIF-C OFs are based on patients with alcoholic and hepatitis C cirrhosis[10] and are not applicable to patients with HBV-ACLF. In non-HBV-ACLF, renal failure and

brain failure are more common,[10,30] whereas in HBV-ACLF, liver failure and coagulation failure are the most common organ failure types.[31,32] Therefore, although COSSH-ACLFs is derived from CLIF-SOFAs, it re-calibrates the risk coefficients of bilirubin and the international standardization ratio and adds influencing factors, such as age, which significantly improves its predictive power.

Our study also has some limitations. We only verified the predictive value of COSSH-ACLFs in patients with HBV-ACLF. Because of the lack of lactic acid and other indicators, COSSH-ACLFs cannot be compared with the Asian-Pacific Association for the study of the liver ACLF research consortium score. In the future, the results of this study must be verified in large-scale multi-center prospective cohort studies including patients with non-HBV-ACLF.

In conclusion, COSSH-ACLFs showed excellent predictive power, which was superior to those of other classical models, for short-term prognosis of Chinese patients with HBV-ACLF. It can accurately predict the severity of HBV-ACLF, which would prove useful in customizing medical treatment and allowing reasonable organ allocation, thus improving the survival rate of patients.

## Conflicts of interest

None.

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