Research Article
Cirrhosis and Liver Failure

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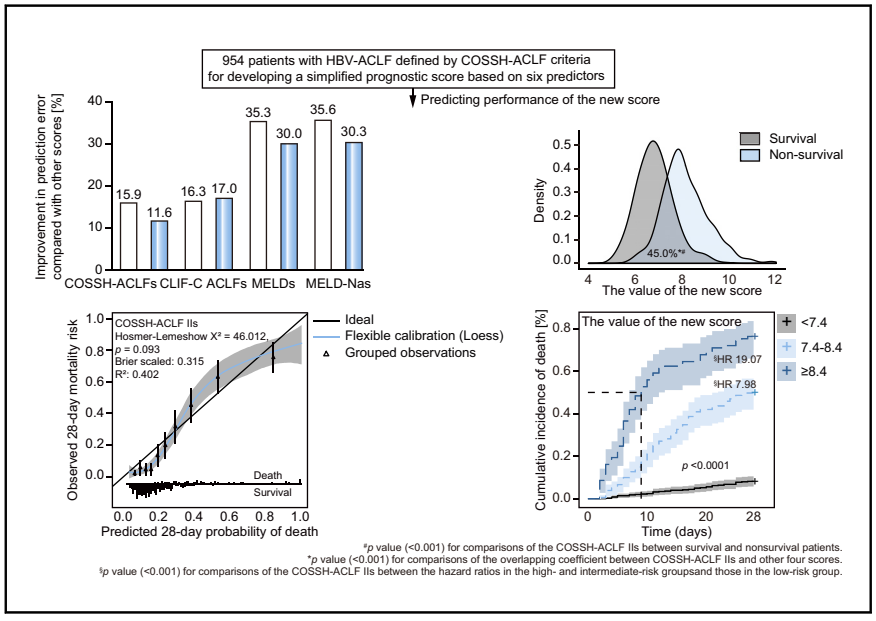
Development and validation of a new prognostic score for hepatitis B virus-related acute-on-chronic liver failure

Graphical abstract



Highlights

- We developed a new prognostic COSSH-ACLF II score based on 6 predictors from a large cohort.
- This score simplifies triage and can be used to stratify patients with HBV-ACLF based on their short-term mortality risk.
- The new score has improved prognostic accuracy and sensitivity for patients with HBV-ACLF.
- This score could be used to guide clinical management and reduce the currently unacceptable mortality rate.

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Lay summary

Hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) is a complex syndrome that is associated with a high short-term mortality rate. We developed a simplified prognostic score for patients suffering from this condition based on a prospective multicentre cohort. This new score had better predictive ability than 4 other commonly used scores.

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Research Article
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Development and validation of a new prognostic score for hepatitis B virus-related acute-on-chronic liver failure

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Background & Aims: Early determination of the prognosis of patients with hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) is important to guide clinical management and decrease mortality. The aim of this study was to develop a new simplified prognostic score to accurately predict outcomes in patients with HBV-ACLF.

Methods: Prospective clinical data from 2,409 hospitalized patients with acute deterioration of HBV-related chronic liver disease were used to develop a new prognostic score that was validated in an external group.

Results: A total of 954 enrolled patients with HBV-ACLF were diagnosed based on the Chinese Group on the Study of Severe Hepatitis B-ACLF (COSSH-ACLF) criteria. Six predictive factors were significantly related to 28-day mortality and constituted a new prognostic score (=1.649×ln(international normalized ratio)+0.457 ×hepatic encephalopathy score+0.425×ln(neutrophil)+0.396 ×ln(total bilirubin)+0.576×ln(serum urea)+0.033×age). The C-indices of the new score for 28-/90-day mortality (0.826/0.809) were significantly higher than those of 4 other scores (COSSH-ACLF, 0.793/0.784; CLIF-C ACLF, 0.792/0.770; MELD, 0.731/0.727; MELD-Na, 0.730/0.726; all p <0.05). The prediction error rates of the new score for 28-day mortality were significantly lower than those of the 4 other scores: COSSH-ACLF (15.9%), CLIF-C ACLF (16.3%), MELD (35.3%) and MELD-Na (35.6%). The probability density function evaluation and risk stratification of the new score also showed the highest predictive values for mortality. These results were then validated in an external cohort.

Conclusion: A new prognostic score based on 6 predictors, without an assessment of organ failure, can accurately predict short-term mortality in patients with HBV-ACLF and might be used to guide clinical management.

Lay summary: Hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) is a complex syndrome that is associated with a high short-term mortality rate. We developed a simplified prognostic score for patients suffering from this condition based on a prospective multicentre cohort. This new score had better predictive ability than 4 other commonly used scores.

Keywords: ACLF; HBV; prognostic score; probability density function; risk stratification.
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Introduction

Acute-on-chronic liver failure (ACLF) has been recognized as a complex syndrome that is associated with a high short-term mortality rate.[1–3] Early diagnosis and prognosis for the effective treatment of ACLF is very important to decrease the high-mortality rate.[4] The model for end-stage liver disease (MELD) and the MELD-sodium (MELD-Na) scores have been widely used to predict the outcome of end-stage liver disease or for organ

allocation in the liver transplant setting.[5–8] Recently, 2 large prospective multicentre cohorts of ACLF, the CANONIC study and the Chinese Group on the Study of Severe Hepatitis B (COSSH) study, indicated that ACLF has regional phenotypic specificities due to the disease aetiology and precipitants.[1] The CANONIC study proposed a definition for ACLF based on patients with acutely decompensated cirrhosis with organ failure(s) in populations mainly impacted by alcohol-related liver disease (ALD) or hepatitis C virus.[2] We recently proposed a definition for hepatitis B virus-related ACLF (HBV-ACLF) based on the COSSH study, which showed that patients with HBV-ACLF had significantly worse clinical characteristics, such as total bilirubin (TB) and international normalized ratio (INR), than non-HBV-ACLF populations, with liver failure being the most frequent organ failure and HBV relapse the most frequent precipitant.[3,4] These 2 well-accepted definitions have been used to develop prognostic scores, the Chronic Liver Failure-Consortium (CLIF-C) ACLF (CLIF-C ACLF) and the COSSH-ACLF scores, for the early prognostication and identification of patients who are likely to have poor outcomes from ACLF and for whom early intensive treatments including prior organ allocation from limited liver donors should be considered.[3,9,10] However, based on the complicated assessment of organ failure, the CLIF-C ACLF and COSSH-ACLF scores should be further simplified and more accurate. This study aims to develop a new simplified prognostic score to accurately predict outcomes in patients with HBV-ACLF.

Patients and methods

Study design

In this study, a 2-step method was used to establish a new prognostic score for patients with HBV-ACLF. First, patients with acute deterioration of HBV-related chronic liver disease were enrolled from the prospective open cohort of the COSSH study (January 2017 to December 2018). The relevant clinical data of these patients were used to identify predictive factor(s) associated with 28-day mortality and develop a new prognostic score. Second, an external group from January 2019 to May 2020 was used to validate the prognostic ability of the new score. The clinical and follow-up data were collected from the electronic data capture system and case report forms. The study protocol was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine. All patients were well informed of the study, and written consent was obtained from the study participants or their legal surrogates before enrolment.

Patients

Patients who were hospitalized for at least 1 day with acute deterioration of HBV-related chronic liver disease were initially screened and enrolled from the prospective open cohort of the COSSH study. The condition of acute deterioration of HBV-related chronic liver disease contains 2 subtypes: i) patients with severe liver injury (TB ≥5 mg/dl) with previously diagnosed chronic hepatitis B; and ii) patients with previously diagnosed cirrhosis presenting with 1 of 5 of the following precipitating events: ascites, upper gastrointestinal bleeding, hepatic encephalopathy (HE),[11] bacterial infection or a high level of jaundice (TB ≥5 mg/dl). All patients received integrative treatment, including antiviral agents for HBV DNA-positive patients, treatment administration for ascites, HE, and bacterial infections, and renal replacement for hepatorenal syndrome as described previously.[3] Clinical data were collected at admission, including demographic data, cirrhosis complications, history of episodes and precipitating events associated with acute deterioration of HBV-related chronic liver disease and ACLF, and laboratory indicators. Information regarding liver transplantation and survival time was also collected. The exclusion criteria are summarized in Fig. 1.

Definition of COSSH-ACLF criteria

HBV-ACLF was diagnosed based on the COSSH-ACLF criteria. The definition identified HBV-ACLF as a complicated syndrome, with a high short-term mortality rate, that develops in patients with HBV-related chronic liver disease, regardless of the presence of cirrhosis, and it is characterized by the acute deterioration of liver function and hepatic and/or extrahepatic organ failure. HBV-ACLF comprises 3 grades based on the frequency of organ failure(s), namely, ACLF-1, ACLF-2 and ACLF-3, as described previously.[3]

Scoring systems

The COSSH-ACLF score was calculated using the formula: 0.741 × INR + 0.523 × HBV-sequential organ failure assessment score + 0.026 × age + 0.003 × TB (μmol/L).[3] The CLIF-C ACLF score was calculated using the formula: 10 × [0.33 × CLIF-organ failure score + 0.04 × age + 0.63 × ln (white blood cells) −2].[9] The MELD score was calculated using the formula: 3.78 × ln [TB (mg/dl)] + 11.2 × ln (INR) + 9.57 × ln [serum creatinine (mg/dl)] + 6.43.[7] The MELD-Na score was calculated based on the MELD score using the formula: MELD − Na − (0.025 × MELD × (140 − Na)) + 140; the serum sodium concentration was between 125 and 140 mmol/L.[8]

Development and validation of a new prognostic score

Based on the clinical data and outcomes of patients with HBV-ACLF, univariate competing risk regression analysis was performed to estimate the effects of death over time using Fine and Gray competing risks regression with the cumulative incidence function, considering liver transplantation as a competing event.[12,13] Gray's test was used for comparisons between cumulative incidence functions. A p value <0.05 was considered significant. The variance inflation factors (VIFs) were calculated to test for collinearity, and variables with a VIF greater than 10 were dropped. Penalized variable selection for the proportional subdistribution hazards (PSH) model was used, and the least absolute shrinkage and selection operator (LASSO) was applied to the model. This method penalizes the sum of the absolute values of the regression coefficients, leading to some coefficients shrinking to zero, thus simultaneously performing feature selection.[14] The Bayesian information criterion was used to select the optimal tuning parameter. Multivariate competing risk regression was used to construct a predictor for patient survival based on the variables selected for the PSH-LASSO model.

The performance of the new prognostic model in predicting outcomes was compared with that of 4 other generic scores: COSSH-ACLF, CLIF-C ACLF, MELD and MELD-Na. The performance of the model was assessed by examining the discrimination, calibration and overall performance. The discrimination is the ability of the model to distinguish patients who died from patients who did not die. Two analysis methods were used for discrimination: the C-index was reported to assess the discriminative performance of the new model; and the probability density function (PDF) was used to define an integral of the density of survival and non-survival over a given range, and the overlapping coefficient was calculated to measure the similarity between the probability distributions of survival and non-

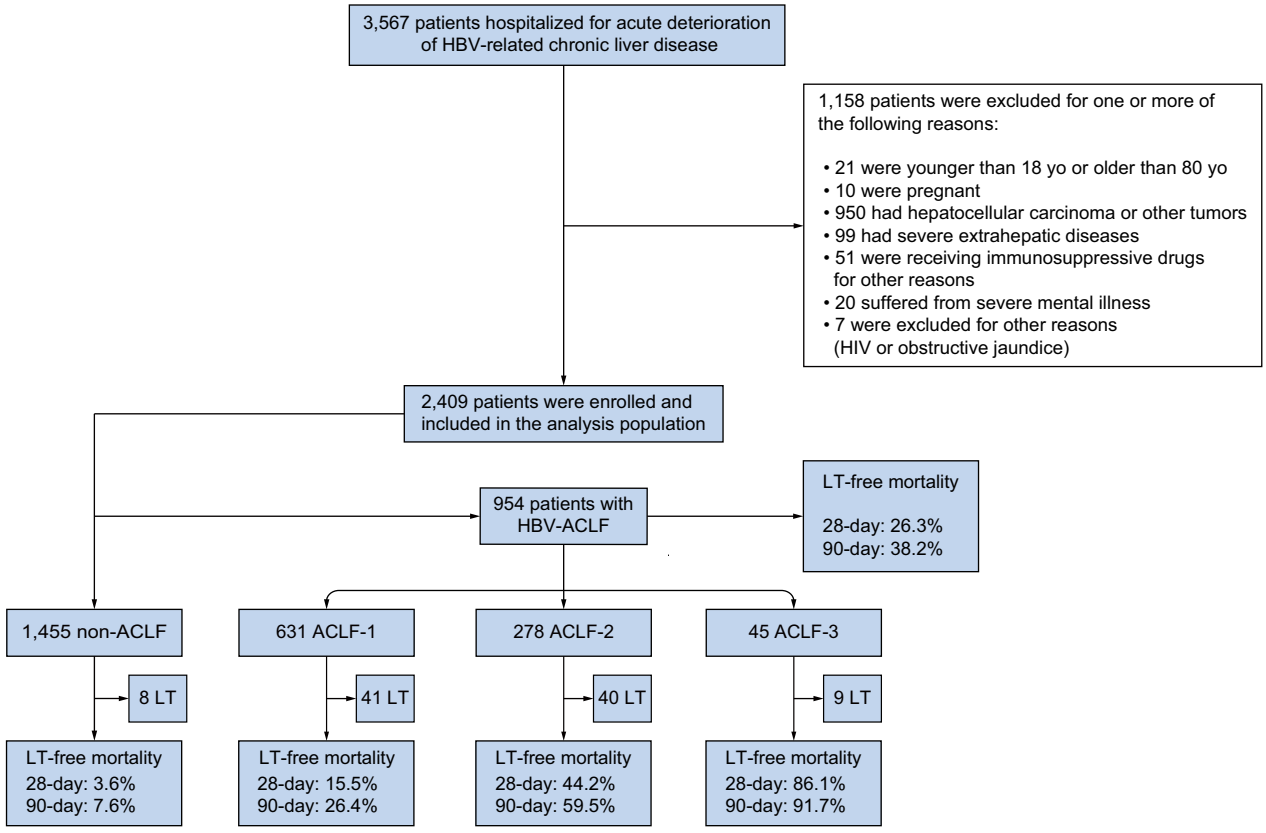

Fig. 1. Screening, enrolment and classification of patients according to the COSSH-ACLF criteria. ACLF, acute-on-chronic liver failure; COSSH, Chinese Group on the Study of Severe Hepatitis B; HBV-ACLF, HBV-related ACLF; LT, liver transplantation.

survival.[15] The overlapping coefficient was compared between the new model and 4 other generic scores by bootstrapping with 1,000 replications. Calibration refers to the predicted risk of the model being equal to the incidence of events. The calibration performance was assessed with a predicted and observed mortalities plot and summarized across the full range of risk scores using the Hosmer-Lemeshow statistic. The overall performance was tested using the R^2 and Brier scaled.[16]

Risk stratification

The optimal cut-off value of the new prognostic score was identified based on selecting the largest $\chi 2$ value using X-tile software (version 3.6.1; Yale University, New Haven, CT, USA) to separate patients into groups with a low-risk, an intermediate-risk and a high-risk of death.[17]

Statistical analysis

The measurements were presented as median (IQR) or mean ± (SD) or numbers (%), unless otherwise noted. Student's *t* test or the Mann-Whitney *U* test was used to compare 2 continuous variables, and the $\chi 2$ test was used to compare categorical variables. The normality assumption was validated using the Shapiro-Wilk test. Significance was defined as p <0.05. The non-normal data were transformed to their natural logarithms. A U-statistics-based C estimator that is asymptotically normal was calculated, and the z-score test was used to compare 2 C-indices (the R 'compareC' Package).[18] The smoothing kernel of each PDF plot was Gaussian. The derivation group was bootstrapped to generate a statistic between the overlap area of the new prognostic score PDF plot with each other scoring model. The goodness-of-fit of the new prognostic score was assessed using the Hosmer-Lemeshow test. An external group of patients was used to validate the performance of the new prognostic scoring system. The scores were assessed and compared using the same methods applied to the derivation data. SPSS software V.25 (SPSS, Chicago, Illinois, USA) was used to compare baseline characteristics; other analyses were conducted in R software, version 3.6 (https://www.r-project.org).

Results

Patients and clinical characteristics

Among 2,409 patients with acute deterioration of HBV-related chronic liver disease enrolled from the prospective open cohort of the COSSH study, 954 (39.6%) were diagnosed with ACLF, and 1,455 (60.4%) were diagnosed with non-ACLF based on the COSSH-ACLF criteria (Fig. 1). The liver transplant-free mortality (28/90 days) rates were significantly higher in the ACLF group than in the non-ACLF group (26.3%/38.2% *vs.* 3.6%/7.6%, p <0.001). The clinical characteristics of all enrolled patients are summarized in Table 1. The most frequent organ failures in patients with HBV-ACLF were liver failure (97.7%) and coagulation failure (30.3%), followed by renal failure (6.0%) and brain failure (3.1%). Laboratory indicators, including TB, INR, serum urea, serum potassium and neutrophils, were significantly worse in the ACLF

Table 1. Patient characteristics at enrolment.

Characteristic	Non-ACLF (n = 1,455)	ACLF (n = 954)	p^a value	ACLF-1 (n = 631)	ACLF-2 (n = 278)	ACLF-3 (n = 45)	p^b value
Male	1,180 (81.1%)	837 (87.7%)	<0.001	566 (89.7%)	233 (83.8%)	38 (84.4%)	0.035
Age (years)	49 ± 12	48 ± 12	0.098	48 ± 12	49 ± 12	49 ± 10	0.528
MAP (mmHg)	89 ± 88	89 ± 89	0.360	88 ± 88	91 ± 90	86 ± 86	0.070
Complications							
GIH	184 (12.6%)	54 (5.7%)	<0.001	31 (4.9%)	16 (5.8%)	7 (15.6%)	0.012
Ascites	795 (54.6%)	543 (56.9%)	0.271	342 (54.2%)	177 (63.7%)	24 (53.3%)	0.026
HE	52 (3.6%)	128 (13.4%)	<0.001	49 (7.8%)	50 (18.0%)	29 (64.4%)	<0.001
BI	332 (22.8%)	357 (37.4%)	<0.001	211 (33.4%)	127 (45.7%)	19 (42.2%)	0.002
HBV DNA level (IU/ml)			<0.001				0.386
$\leq 2\times10^2$	405 (27.8%)	145 (15.2%)		92 (14.6%)	41 (14.7%)	12 (26.7%)	
2×10^2 –2×10^6	761 (52.3%)	559 (58.6%)		376 (59.6%)	161 (57.9%)	22 (48.9%)	
$>2\times10^6$	289 (19.9%)	250 (26.2%)		163 (25.8%)	76 (27.3%)	11 (24.4%)	
Laboratory data							
Alb (g/L)	31.0 (27.0–35.3)	31.0 (28.2–33.9)	0.262	31.0 (28.3–33.8)	30.9 (27.8–34.0)	31.0 (28.6–34.1)	0.968
ALT (U/L)	68.0 (28.8–284.0)	263.0 (97.0–651.0)	<0.001	237.0 (89.0–544.0)	391.0 (121.8–873.0)	200.5 (88.3–719.8)	<0.001
AST (U/L)	85.0 (43.0–204.0)	200.0 (98.0–404.5)	<0.001	177.0 (92.0–351.0)	279.0 (122.0–538.5)	210.0 (112.5–399.0)	<0.001
ALP (U/L)	119.0 (86.0–159.0)	142.0 (116.0–177.0)	<0.001	140.0 (114.0–175.0)	149.0 (121.5–185.5)	132.0 (103.5–154.5)	0.013
TBA (μmol/L)	74.6 (23.2–171.0)	194.0 (145.4–240.8)	<0.001	190.0 (144.0–237.0)	199.2 (143.9–247.3)	205.0 (164.5–247.2)	0.186
TB (μmol/L)	89.0 (24.0–152.0)	341.0 (262.2–415.1)	<0.001	326.8 (251.2–403.9)	355.1 (278.0–429.7)	408.7 (321.0–503.6)	<0.001
GGT (U/L)	85.0 (38.0–154.0)	84.0 (58.0–128.0)	0.036	87.0 (59.0–130.0)	84.0 (54.0–125.0)	62.0 (40.0–93.5)	0.004
Cr (μmol/L)	69.0 (60.0–80.0)	68.0 (58.0–84.0)	0.596	68.0 (58.0–81.0)	67.1 (56.7–86.9)	150.0 (72.0–244.5)	<0.001
Serum urea (mmol/L)	4.7 (3.5–6.5)	4.1 (3.0–6.3)	<0.001	4.0 (3.1–5.8)	3.9 (2.7–6.9)	9.2 (3.7–16.7)	<0.001
TG (mmol/L)	1.1 (0.7–1.8)	1.2 (1.0–1.6)	<0.001	1.4 (1.1–1.8)	1.1 (0.8–1.3)	1.0 (0.8–1.1)	<0.001
Tch (mmol/L)	2.9 (2.3–3.6)	2.1 (1.6–2.7)	<0.001	2.3 (1.8–2.8)	1.9 (1.4–2.4)	1.5 (1.0–1.9)	<0.001
HDL-C (mmol/L)	0.6 (0.3–0.9)	0.2 (0.1–0.3)	<0.001	0.2 (0.1–0.3)	0.2 (0.1–0.3)	0.2 (0.1–0.3)	0.001
LDL-C (mmol/L)	1.6 (1.1–2.3)	1.1 (0.6–1.6)	<0.001	1.1 (0.5–1.7)	1.1 (0.6–1.5)	0.9 (0.4–1.3)	0.297
Glu (mmol/L)	4.9 (4.3–6.0)	4.5 (3.5–5.8)	<0.001	4.5 (3.7–5.8)	4.2 (3.2–5.9)	5.5 (3.5–7.2)	0.033
K (mmol/L)	4.0 (3.6–4.2)	4.1 (3.7–4.5)	<0.001	4.1 (3.7–4.4)	4.1 (3.7–4.5)	4.6 (4.1–5.0)	<0.001
Na (mmol/L)	138.0 (136.0–140.0)	137.0 (134.0–139.0)	<0.001	137.0 (134.9–139.0)	137.0 (134.0–139.0)	135.0 (133.0–139.5)	0.141
WBC (10^9/L)	4.6 (3.3–6.3)	6.7 (5.1–9.3)	<0.001	6.3 (4.8–8.6)	7.5 (5.7–10.0)	10.3 (7.3–13.4)	<0.001
Neutrophil (10^9/L)	2.8 (1.8–4.0)	4.5 (3.3–6.8)	<0.001	4.2 (3.1–5.9)	5.2 (3.7–7.9)	7.8 (5.4–11.4)	<0.001
Lymphocyte (10^9/L)	1.1 (0.7–1.6)	1.2 (0.8–1.6)	0.156	1.2 (0.8–1.6)	1.1 (0.8–1.5)	1.1 (0.7–1.6)	0.457
NLR	2.4 (1.6–3.9)	4.0 (2.6–6.6)	<0.001	3.6 (2.4–5.6)	5.0 (2.9–8.1)	7.6 (4.6–13.2)	<0.001
Hs-CRP (mg/L)	8.3 (4.0–14.8)	11.6 (8.0–17.2)	<0.001	11.8 (8.1–17.4)	11.0 (7.6–16.6)	10.7 (6.9–14.2)	0.351
Haemoglobin (g/L)	122.0 (101.0–138.0)	126.0 (112.0–139.0)	<0.001	127.0 (114.0–138.0)	126.0 (110.8–140.3)	115.0 (102.5–136.5)	0.087
Haematocrit (%)	35.8 (29.7–40.5)	36.2 (32.0–40.1)	0.026	36.2 (32.5–39.8)	36.5 (31.4–40.8)	32.0 (29.7–39.1)	0.053
PLT (10^9/L)	90.0 (58.0–142.0)	99.5 (68.8–139.3)	0.011	100.0 (66.0–137.0)	100.0 (70.0–153.5)	98.0 (67.0–152.0)	0.471
INR	1.3 (1.2–1.5)	2.0 (1.7–2.6)	<0.001	1.8 (1.6–2.1)	2.8 (2.6–3.2)	3.2 (2.8–4.1)	<0.001
Fib (g/L)	1.8 (1.3–2.4)	1.4 (1.1–1.7)	<0.001	1.5 (1.2–1.8)	1.2 (0.9–1.5)	0.9 (0.6–1.2)	<0.001
PT (s)	15.3 (13.7–17.3)	23.1 (19.2–28.8)	<0.001	20.5 (18.3–23.5)	31.1 (28.5–35.1)	35.6 (32.1–43.1)	<0.001
D dimer (ug/L)	503 (3–2042)	1,076 (5–3018)	<0.001	923 (5–2540)	1,336 (4–3624)	4,173 (1,639–6807)	<0.001
AFP (ng/ml)	21 (4–131)	79 (23–230)	<0.001	109 (34–270)	43 (15–151)	40 (9–78)	<0.001
Ferritin (ng/ml)	504 (106–1532)	2,537 (1,316–4198)	<0.001	2,169 (1,193–3635)	3,219 (1,694–5517)	3,548 (1,794–4749)	<0.001
Organ failures							
Liver	212 (14.6%)	932 (97.7%)	<0.001	613 (97.1%)	274 (98.6%)	45 (100.0%)	0.243
Kidney	0	57 (6.0%)	<0.001	15 (3.4%)	21 (7.6%)	21 (46.7%)	<0.001
Coagulation	28 (1.9%)	289 (30.3%)	<0.001	2 (0.3%)	244 (87.8%)	43 (95.6%)	<0.001
Cerebral	12 (0.8%)	30 (3.1%)	<0.001	0	5 (1.8%)	25 (55.6%)	<0.001
Lungs	6 (0.4%)	13 (1.4%)	0.010	0	10 (3.6%)	3 (6.7%)	<0.001

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Table 1. (*continued*)

Characteristic	Non-ACLF (n = 1,455)	ACLF (n = 954)	p^a value	ACLF-1 (n = 631)	ACLF-2 (n = 278)	ACLF-3 (n = 45)	p^b value
Circulation	24 (1.6%)	7 (0.7%)	0.051	1 (0.2%)	2 (0.7%)	4 (8.9%)	<0.001
HE grade I or II	40 (2.7%)	98 (10.3%)	<0.001	49 (7.8%)	45 (16.2%)	4 (8.9%)	0.001
Renal dysfunction	15 (1.0%)	32 (3.4%)	<0.001	16 (2.5%)	14 (5.0%)	2 (4.4%)	0.143
1.5≤INR<2.5	433 (29.8%)	645 (67.6%)	<0.001	612 (97.0%)	31 (11.2%)	2 (4.4%)	<0.001
Severity scores							
COSSH-ACLFs	4.7 (4.4–5.1)	6.1 (5.6–6.8)	<0.001	5.8 (5.4–6.2)	6.9 (6.4–7.4)	8.3 (7.8–9.1)	<0.001
CLIF-C ACLFs	31.4 (27.2–36.0)	41.3 (36.9–46.2)	<0.001	38.9 (34.7–42.8)	45.3 (41.7–50.5)	53.4 (51.3–60.1)	<0.001
MELDs	13.1 (8.7–16.6)	23.4 (20.6–27.2)	<0.001	21.7 (19.9–23.7)	27.5 (25.1–30.6)	37.1 (29.6–41.9)	<0.001
MELD-Nas	14.7 (10.0–18.5)	24.8 (22.1–28.5)	<0.001	23.1 (21.1–25.4)	28.8 (26.1–32.2)	37.6 (30.0–41.8)	<0.001
LT-free mortality							
28-day	52 (3.6%)	232 (26.3%)	<0.001	94 (15.5%)	107 (44.2%)	31 (86.1%)	<0.001
90-day	110 (7.6%)	330 (38.2%)	<0.001	156 (26.4%)	141 (59.5%)	33 (91.7%)	<0.001

The data are expressed as medians (IQR), mean ± (SD) or number of patients (%).
p^a value of comparisons between patients with ACLF and non-ACLF; p^b value of comparisons across ACLF grades (ACLF-1, ACLF-2, and ACLF-3) (Student's *t* test or Mann-Whitney *U* test or χ^2 test).
ACLF, acute-on-chronic liver failure; Alb, albumin; AFP, alpha fetoprotein; AUT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BI, bacterial infection; CLIF-C ACLFs, Chronic Liver Failure-Consortium ACLF score; COSSH-ACLFs, Chinese Group on the Study of Severe Hepatitis B-ACLF score; Cr, creatinine; Fib, fibrinogen; GGT, glutamyl transferase; GIH, gastrointestinal haemorrhage; Glu, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HE, hepatic encephalopathy; INR, international normalized ratio; K, serum potassium; LDL-C, low-density lipoprotein cholesterol; LT, liver transplantation; MAP, mean arterial pressure; MELDs, model for end-stage liver disease score; MELD-Nas, MELD-sodium score; Na, serum sodium; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet count; PT, prothrombin time; TBA, total bile acid; TB, total bilirubin; TG, triglycerides; Tch, total cholesterol; WBC, white blood cell count.

group than in the non-ACLF group. The values of the COSSH-ACLF, CLIF-C ACLF, MELD and MELD-Na scores for patients with HBV-ACLF were 6.1 (5.6–6.8), 41.3 (36.9–46.2), 23.4 (20.6–27.2) and 24.8 (22.1–28.5), respectively, and were significantly higher than those for patients without ACLF.

Development of a new prognostic score

Clinical data and laboratory indicators collected at admission were used to select the most significant risk factors associated with 28-day mortality and to design an accurate prognostic score for patients with HBV-ACLF. Univariate competing risk regression analysis indicated that age, TB, serum urea, triglycerides, serum potassium, neutrophils, INR, and HE were significantly associated with the 28-day mortality (Table S1). Penalized variable selection for the PSH model with LASSO analysis selected 6 independent risk factors (INR, HE, TB, neutrophils, serum urea and age) that were significantly associated with 28-day mortality in patients with HBV-ACLF (Table S2). Discriminant analysis by multivariate competing risk regression indicated that the following 6 independent risk factors could be used for the final prognostic score: ln(INR) (subhazard ratio [sHR] 5.20; 95% CI 3.51–7.71; p <0.001), HE score (sHR 1.58; 95% CI 1.19–2.09; p = 0.002), ln(neutrophil) (sHR 1.53; 95% CI 1.11–2.11; p = 0.009), ln(TB) (sHR 1.49; 95% CI 1.03–2.15; p = 0.036), ln(serum urea) (sHR 1.78; 95% CI 1.37–2.31; p <0.001), and age (sHR 1.03; 95% CI 1.02–1.05; p <0.001) (Table S3). The new prognostic score for patients with HBV-ACLF (COSSH-ACLF II score, COSSH-ACLF IIs) fitted by multivariate competing risk regression was calculated using the following formula: 1.649 × ln(INR) + 0.457 × HE score (HE grade: 0/1, 1-2/2 and 3-4/3) + 0.425 × ln(neutrophil) (10^9/L) + 0.396 × ln(TB) (umol/L) + 0.576 × ln(serum urea) (mmol/L) + 0.033 × age. The probability of death at time "t" can be estimated as $p = 1\text{-}e^{[-CI(t) \times \exp(\beta(t) \times COSSH-ACLF\ IIs]}$. CI(t) and β(t) are the cumulative baseline hazard and the score coefficient estimated by the model fitted for time "t". At the main time, they are as follows: CI (28) = 0.0001705272, β (28) = 1.022168; CI (90) = 0.0002945163, β (90) = 1.019304.

Discrimination of the new score

The discrimination of the new score was measured by the C-index and PDF analysis. The C-indices of the new score for 28-day and 90-day mortality (0.826 and 0.809, respectively) were significantly higher than those of the 4 other scores (COSSH-ACLF: 0.793, p <0.001 and 0.784, p = 0.003; CLIF-C ACLF: 0.792, p <0.001 and 0.770, p <0.001; MELD: 0.731, p <0.001 and 0.727, p <0.001; and MELD-Na: 0.730, p <0.001 and 0.726, p <0.001). The absolute improvements in the C-index values with respect to the 4 other scores were consistently significant in both the derivation group and the validation group (Fig. 2A). Fig. 2B shows the corresponding percent improvement in the prediction error rate obtained with the new score with respect to the 4 other scores. The prediction error rates of the new score for 28-day mortality were significantly decreased compared with those of the COSSH-ACLF (15.9%), CLIF-C ACLF (16.3%), MELD (35.3%) and MELD-Na (35.6%) scores, showing that it had the highest prognostic accuracy.

The results of PDF analysis revealed that the proportion of patients with poor outcomes increased with increasing scores, and there was an obvious distinction between the peaks of the surviving and non-surviving patients (Fig. 3). PDF analysis showed that the overlapping coefficients of the new score for 28-/90-day mortality (45.0%/47.7%) were significantly decreased

A

The C-index of 5 scores for predicting 28-/90-day mortality

Model	COSSH-ACLF IIs C-index (95% CI)	COSSH-ACLFs C-index (95% CI)	CLIF-C ACLFs C-index (95% CI)	MELDs C-index (95% CI)	MELD-Nas C-index (95% CI)
Derivation group					
28-day mortality	0.826 (0.800-0.852)	0.793 (0.765-0.822)	0.792 (0.764-0.821)	0.731 (0.697-0.765)	0.730 (0.694-0.767)
*p value		<0.001	<0.001	<0.001	<0.001
90-day mortality	0.809 (0.786-0.833)	0.784 (0.759-0.809)	0.770 (0.745-0.796)	0.727 (0.698-0.757)	0.726 (0.695-0.757)
*p value		0.003	<0.001	<0.001	<0.001
Validation group					
28-day mortality	0.895 (0.860-0.931)	0.880 (0.829-0.931)	0.857 (0.803-0.910)	0.767 (0.683-0.851)	0.785 (0.686-0.885)
*p value		0.474	0.063	<0.001	0.004
90-day mortality	0.835 (0.788-0.884)	0.828 (0.775-0.881)	0.800 (0.745-0.856)	0.738 (0.665-0.810)	0.730 (0.645-0.815)
*p value		0.757	0.063	0.001	0.005

B

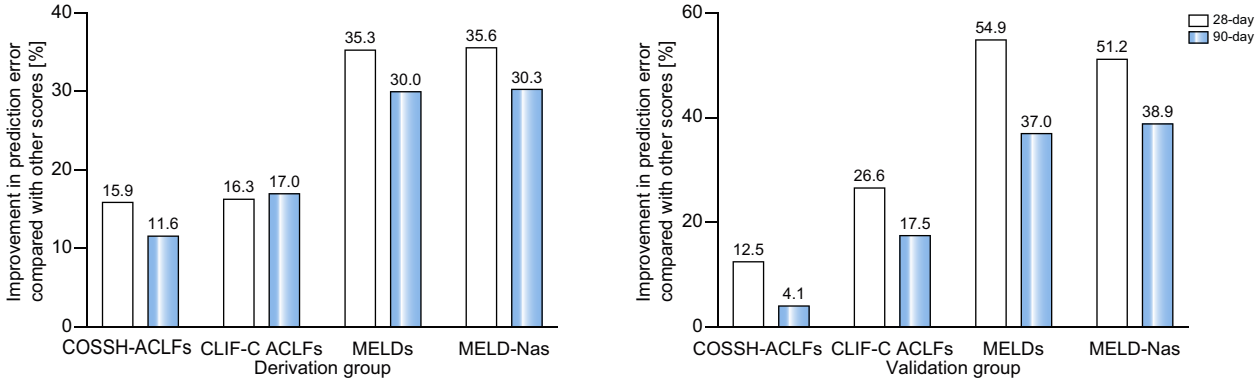


Fig. 2. Predictive discrimination ability of 5 scores. (A) The C-index of 5 scores for predicting 28-/90-day mortality (Z-score test). *p value for comparisons between COSSH ACLF IIs and the 4 other scores in patients with HBV-ACLF. (B) Percent reduction in the prediction error rates of the COSSH-ACLF IIs compared to those of 4 other scores. ACLF, acute-on-chronic liver failure; COSSH-ACLF IIs, Chinese Group on the Study of Severe Hepatitis B-ACLF II score; COSSH-ACLFs, COSSH-ACLF score; CLIF-C ACLFs, Chronic Liver Failure-Consortium ACLF score; MELDs, model for end-stage liver disease score; MELD-Nas, MELD-sodium score.

compared with those of the COSSH-ACLF (53.6%/54.0%) and CLIF-C ACLF (53.9%/57.2%) scores (all p <0.001), indicating that the similarity between the probability distributions of the new score for surviving and non-surviving patients was lower than those of the 2 other scores, showing that it had a more accurate prognostic ability.

Calibration of the new score

The calibration performance across the full range of the new score showed the observed mortality and predicted probability of death at 28 days (Fig. 4). In the derivation group, the observed mortality and predicted probabilities of death were similar across the deciles of the new score at 28 days (Fig. 4A) (overall observed 0.26 *vs.* overall predicted 0.29; R^2 = 0.402; Brier scaled = 0.315; Hosmer-Lemeshow $\chi2$ = 46.012, p = 0.093). The predicted probabilities of the COSSH-ACLF score were significantly higher than the observed risk (Fig. 4B) (R^2 = 0.201; Brier scaled = 0.177; Hosmer-Lemeshow $\chi2$ = 76.767, p <0.001). The predicted probabilities of the CLIF-C ACLF score were significantly lower than the observed risk (Fig. 4C) (R^2 = 0.351; Brier scaled = 0.159; Hosmer-Lemeshow $\chi2$ = 89.035, p <0.001). These results indicated that the new score had the best overall performance. Based on the optimal cut-off point of each score, the new score exhibited the best predictive accuracy for death at 28 days (Fig. 4, blue broken line).

Risk stratification of the new score

The risk stratification of the COSSH-ACLF IIs with an X-tile plot showed that patients with HBV-ACLF were separated into 3 risk strata of death at 28 days based on 2 optimal cut-off values (7.4 and 8.4): low-risk (<7.4), intermediate-risk (7.4–8.4) and high-risk (≥8.4). The 28-/90-day mortality rates of each group were significantly different (low-risk, 8.2%/18.7%; intermediate-risk, 49.7%/65.8%; high-risk, 76.3%/87.7%) (Fig. 6). Compared with the low-risk group, the hazard ratios of death at 28/90 days in the intermediate- and high-risk groups reached 7.98/5.94 (p <0.001) and 19.07/13.54 (p <0.001), respectively. These results indicated that the different risk stratifications of the new score for predicting disease severity were simpler and more accurate than the organ failure-based grade classification of the previous COSSH-ACLF and CLIF-C ACLF scores.

Validation of the new score

An external group of 321 patients with HBV-ACLF was used to validate the performance of the new score (Table S4). The C-indices of the new score for 28-/90-day mortality (0.895/0.835)

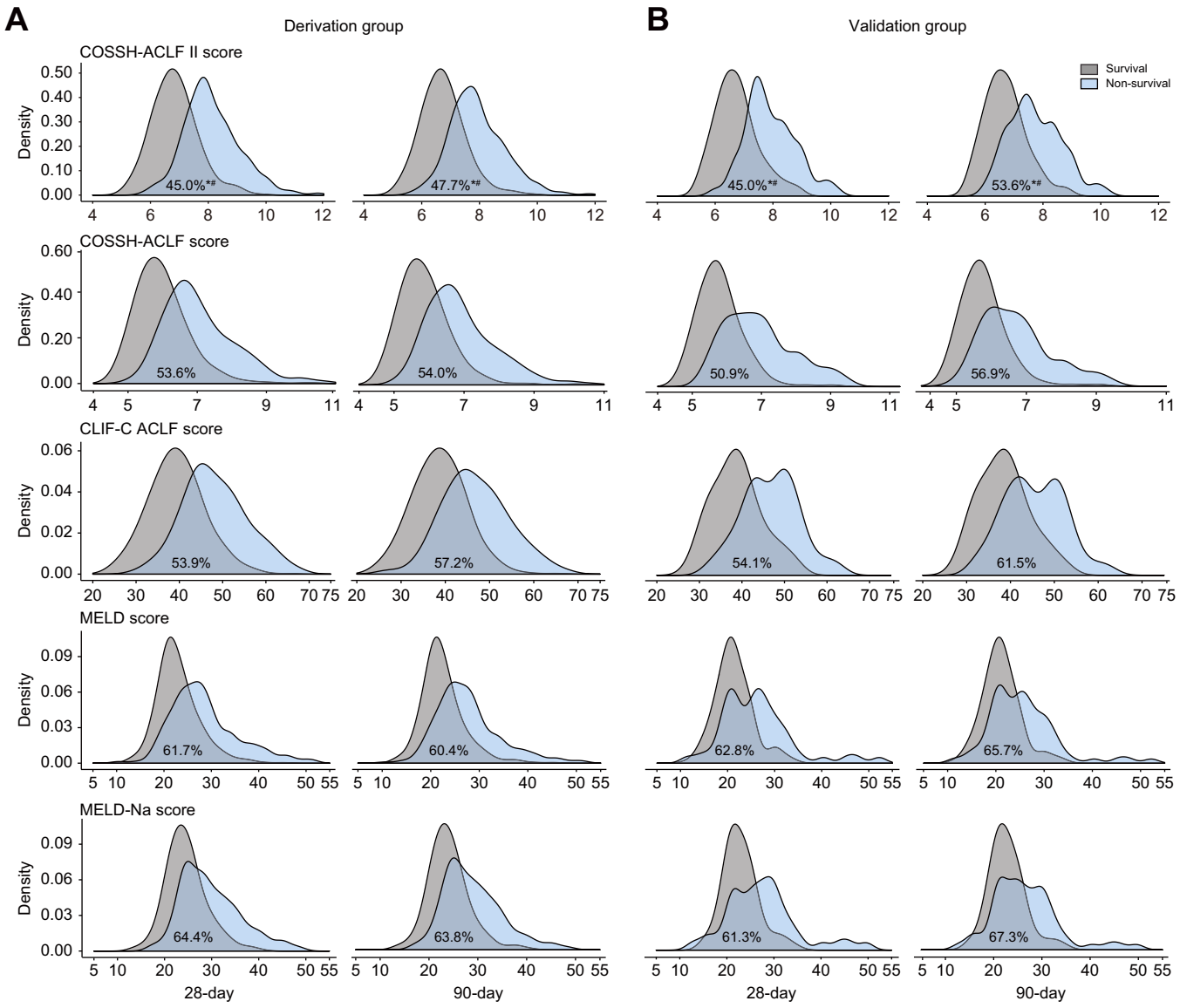


Fig. 3. Probability density function of the COSSH-ACLF IIs for the 28-/90-day prognosis of surviving and non-surviving patients. (A) The derivation group. (B) The validation group. *p <0.001 (Student's t test) for comparisons of the overlapping coefficient between COSSH-ACLF IIs and the other scores. #p <0.001 (Mann-Whitney U test) for comparisons of the COSSH-ACLF IIs between surviving and non-surviving patients. ACLF, acute-on-chronic liver failure; COSSH-ACLF IIs, Chinese Group on the Study of Severe Hepatitis B-ACLF II score; COSSH-ACLFs, COSSH-ACLF score; CLIF-C ACLFs, Chronic Liver Failure-Consortium ACLF score; MELDs, model for end-stage liver disease score; MELD-Nas, MELD-sodium score.

showed no statistical significance compared with the COSSH-ACLF score (0.880/0.828, p = 0.474/p = 0.757) and the CLIF-C ACLF score (0.857/0.800, p = 0.063/p = 0.063), and were significantly higher than those of the MELD score (0.767/0.738, p <0.001/p = 0.001) and the MELD-Na score (0.785/0.730, p = 0.004/p = 0.005) (Fig. 2A). The new score showed a slight improvement compared with the COSSH-ACLF score (12.5%/4.1%) and a significant improvement in the prediction errors for 28-/90-day mortality compared to the CLIF-C ACLF (26.6%/17.5%), MELD (54.9%/37.0%) and MELD-Na (51.2%/38.9%) scores (Fig. 2B).

The PDF analysis also showed a decreased overlapping coefficient of the new score between the surviving patients and non-surviving patients in the validation group (COSSH-ACLF IIs: 45.0%/53.6%; COSSH-ACLFs: 50.9%/56.9%; CLIF-C ACLFs: 54.1%/61.5%, all p <0.001, Fig. 3B). The calibration analysis of the new score validated the similar value of the predicted and observed probabilities of death at 28 days (0.18 *vs.* 0.26), and no significant difference was observed in the lack of fit ($\chi 2$ = 11.722, p = 0.164, Fig. 5) with the Hosmer-Lemeshow test for predicting the 28-day mortality rate in the external validation group. The hazard ratios of death at 28/90 days in the intermediate- (6.21/4.41, p <0.001) and high-risk groups (14.94/11.01, p <0.001) were similar to those in the derivation group compared with the low-risk group and showed a similar separation efficiency in the derivation group (Fig. 6B). These results indicated the improved predictive ability of the new score for short-term mortality compared with the 4 other generic scores.

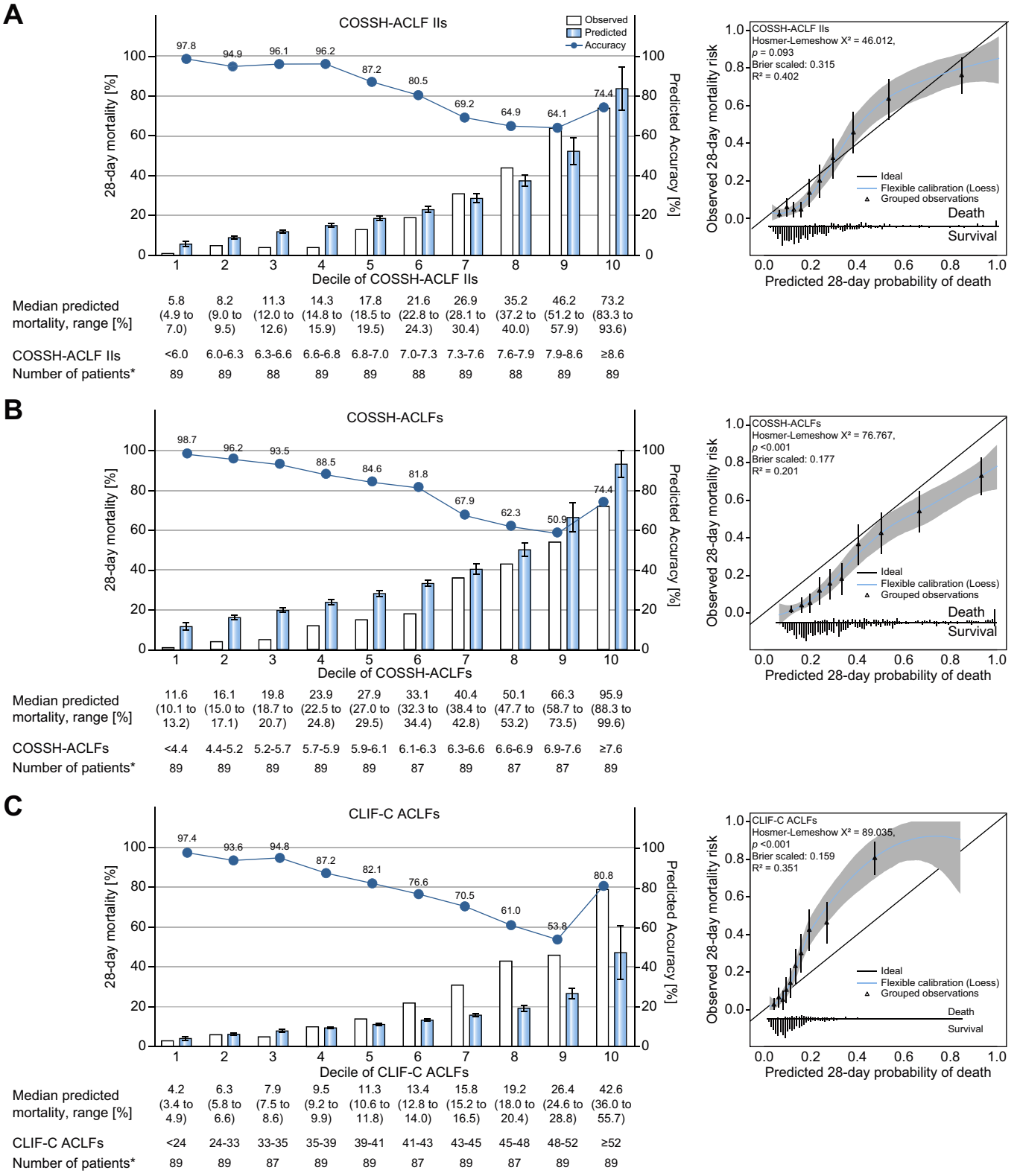
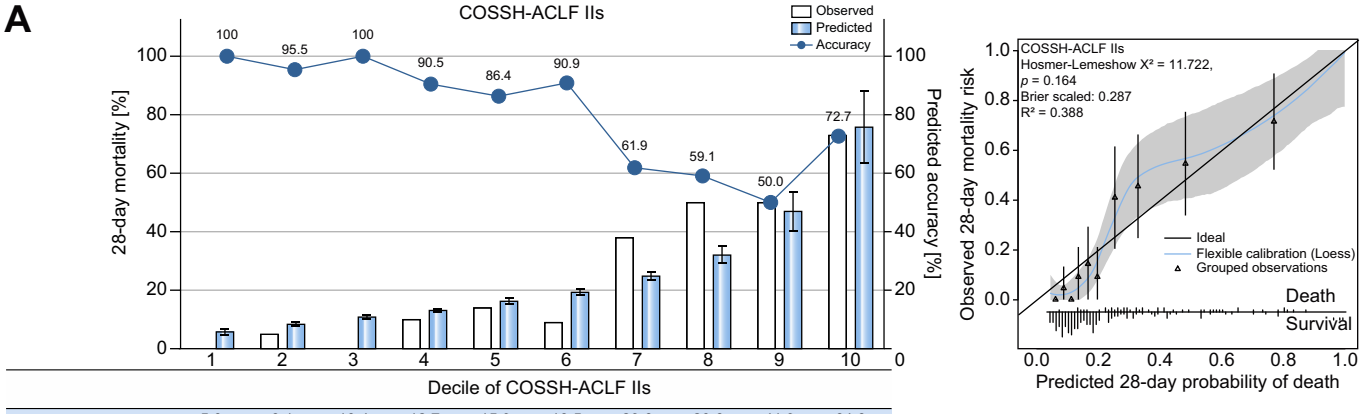
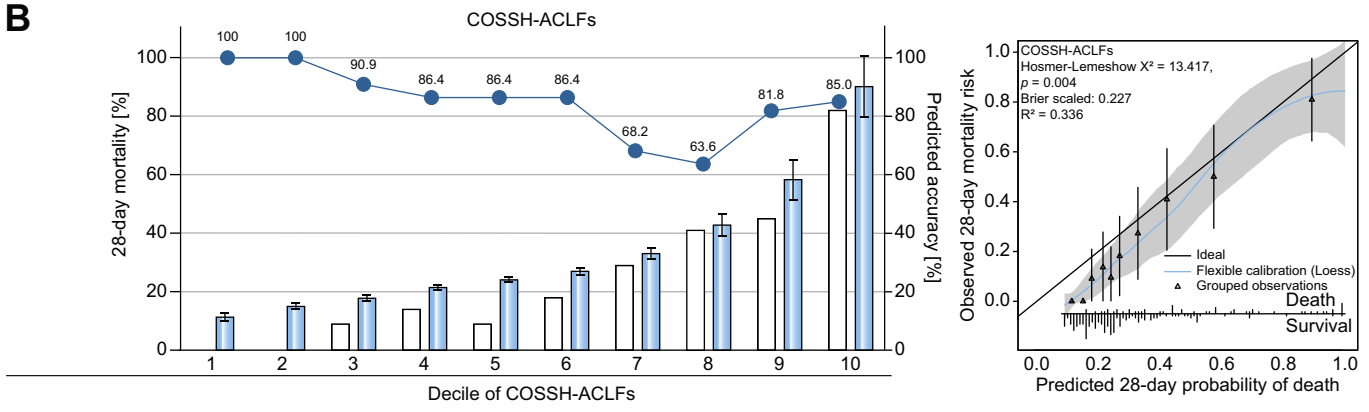


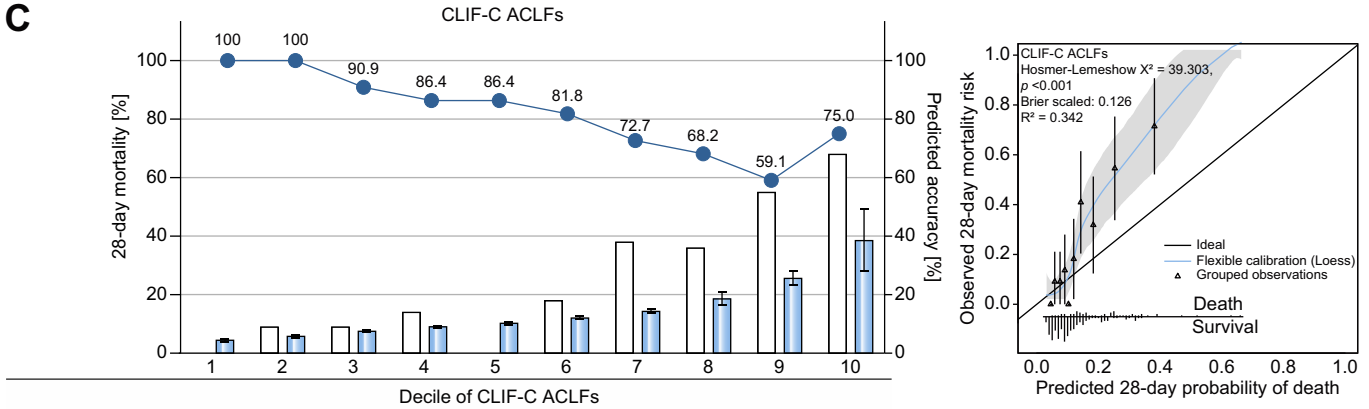
Fig. 4. The calibration of 3 scores for predicting 28-day mortality in the derivation group. (A) COSSH-ACLF IIs. (B) COSSH-ACLFs. (C) CLIF-C ACLFs. Observed *vs.* predicted mortality rates: according to the approximate deciles of the scores. The blue broken line represents the predictive accuracy within the interval (left of all panels). Calibration plot for predicting 28-day mortality with the scores (right of all panels). *Number of liver transplant-free patients. ACLF, acute-on-chronic liver failure; COSSH-ACLF IIs, Chinese Group on the Study of Severe Hepatitis B-ACLF II score; COSSH-ACLFs, COSSH-ACLF score; CLIF-C ACLFs, Chronic Liver Failure-Consortium ACLF score.



Median predicted mortality, range [%]	5.0 (6.0 to 6.6)	8.1 (8.4 to 8.8)	10.4 (10.9 to 11.4)	12.7 (13.0 to 13.6)	15.3 (16.1 to 17.3)	18.5 (19.3 to 20.1)	23.6 (24.8 to 26.3)	29.6 (31.8 to 34.5)	41.3 (44.9 to 53.7)	64.6 (76.3 to 82.2)
COSSH-ACLF IIs	<6.0	6.0-6.2	6.2-6.5	6.5-6.7	6.7-6.9	6.9-7.1	7.1-7.4	7.4-7.8	7.8-8.3	≥8.3
Number of patients*	27	27	27	26	27	27	26	27	27	27



Median predicted mortality, range [%]	11.5 (9.8 to 12.8)	15.0 (14.0 to 16.1)	17.4 (16.7 to 18.8)	21.7 (20.6 to 22.3)	24.0 (23.4 to 24.9)	27.1 (25.9 to 28.0)	33.4 (31.5 to 34.8)	43.3 (39.5 to 45.8)	57.2 (52.1 to 64.3)	94.2 (82.6 to 99.6)
COSSH-ACLFs	<5.1	5.1-5.4	5.4-5.6	5.6-5.7	5.7-5.9	5.9-6.0	6.0-6.3	6.3-6.7	6.7-7.3	≥7.3
Number of patients*	27	27	27	26	27	27	26	27	27	27



Median predicted mortality, range [%]	4.5 (4.2 to 5.0)	5.8 (5.4 to 6.1)	7.6 (7.2 to 7.9)	9.2 (8.7 to 9.4)	10.4 (9.8 to 10.7)	12.0 (11.8 to 12.5)	14.5 (13.7 to 15.0)	18.0 (16.5 to 21.1)	25.6 (23.8 to 27.2)	34.2 (32.5 to 39.7)
CLIF-C ACLFs	<32	32-35	35-37	37-38	38-40	40-42	42-44	44-48	48-51	≥51
Number of patients*	27	27	27	26	27	27	26	27	27	27

Fig. 5. The calibration of 3 scores for predicting 28-day mortality in the validation group. (A) COSSH-ACLF IIs. (B) COSSH-ACLFs. (C) CLIF-C ACLFs. Observed *vs.* predicted mortality rates: according to the approximate deciles of the scores. The blue broken line represents the prediction accuracy within the interval (left of all panels). Calibration plot for predicting 28-day mortality with the scores (right of all panels). *Number of liver transplant-free patients. ACLF, acute-on-chronic liver failure; COSSH-ACLF IIs, Chinese Group on the Study of Severe Hepatitis B-ACLF II score; COSSH-ACLFs, COSSH-ACLF score; CLIF-C ACLFs, Chronic Liver Failure-Consortium ACLF score.

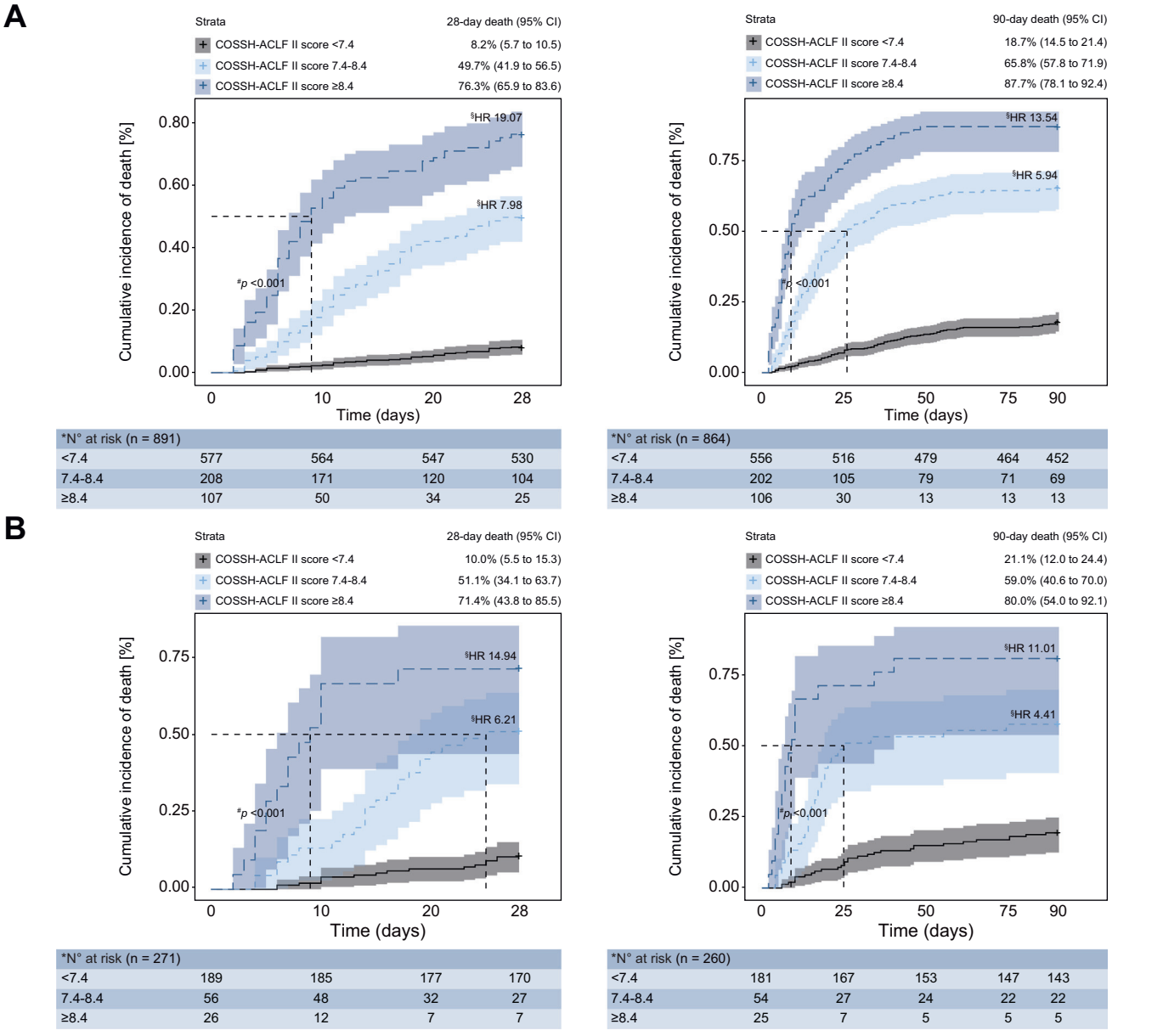


Fig. 6. Risk stratification of the COSSH-ACLF IIs. (A) The derivation group. (B) The validation group. Cumulative incidence of death at 28/90 days stratified according to the COSSH-ACLF IIs classification rule (low-/intermediate-/high-risk: COSSH-ACLF IIs <7.4/7.4-8.4/≥8.4). $^{\#}p$ <0.001 (Log-rank test) for comparisons of the cumulative incidence of death among 3 different risk strata; $^{\S}p$ <0.001 (Likelihood ratio test) for hazard ratios of death in the intermediate- and high-risk groups compared with those in the low-risk group. *Number of liver transplant-free patients. ACLF, acute-on-chronic liver failure; COSSH-ACLF IIs, Chinese Group on the Study of Severe Hepatitis B-ACLF II score.

Discussion

Early determination of prognosis is very important in patients with HBV-ACLF, as it can be used to guide clinical management and to decrease the high short-term mortality rate.[3,4] Any prognostic score should use objective and accessible clinical indicators to simply and accurately predict the disease outcome for clinical application.[19] In this study, the clinical data and laboratory indicators from the multicentre and prospective open cohort of the COSSH study were used to identify the clinical characteristics of patients with HBV-ACLF and develop a new simplified score, the COSSH-ACLF IIs, which can be used to accurately predict the 28-day and 90-day mortality of these patients.

A simplified prognostic score is important for the early prediction of poor outcomes in patients with ACLF. The MELD and MELD-Na scores have been widely used to predict the mortality of patients with end-stage liver disease or for organ allocation.[7,8] However, many studies have demonstrated their limits in accurately predicting short-term mortality in patients with ACLF.[20–22] Recently, the CLIF-ACLF score – based on the CANONIC study – has been developed and is generally used to predict short-term mortality in patients with ALD-related ACLF.[9] Another

COSSH-ACLF score – based on the COSSH study – has been developed and is generally used to predict short-term outcomes in patients with HBV-ACLF.[3] These 2 widely accepted scores are based on complicated scales of 6 organ failures with 11 predictive factors (liver: TB; kidney: creatinine and renal replacement therapy; brain: HE; coagulation: INR; circulation: mean arterial pressure and vasopressor use; respiration: PaO_2, SpO_2, FiO_2, mechanical ventilation use) and mainly focus on indicators related to organ failure regardless of other relevant factors. Therefore, a systemic assessment of clinical data and laboratory indicators will help to develop a simplified prognostic score for patients with HBV-ACLF. In the present study, 6 independent risk factors (TB, INR, age, neutrophil, HE and urea) were selected and we developed a simplified COSSH-ACLF II score for the population with HBV-ACLF. Among these factors, TB, INR and creatinine are associated with liver, coagulation and kidney failure, respectively, and have been commonly used in previous scores. Additionally, age was significantly associated with the severity of ACLF in both the CANONIC and COSSH studies. As an inflammatory factor, neutrophils were used in the COSSH-ACLF II score, corresponding to white blood cells in the CLIF-C ACLF score. HE, indicating brain failure, is used in both our score and previous scores. In the present study, serum urea is used to reflect kidney function, replacing creatinine from the previous COSSH-ACLF score, because of its higher subhazard ratio. Thus, these 6 independent risk factors reflect HBV-ACLF pathophysiology.

The accuracy and sensitivity of prognostic scores are also important to make decisions regarding intensive treatment strategies and predict outcomes in patients with ACLF. The AUROC and C-index are normally used to assess the predictive ability (accuracy and sensitivity) of any new prognostic score. The CLIF-C ACLF score has been shown to have a superior predictive ability compared with the MELD and MELD-Na scores for predicting short-term mortality in patients with ALD-related ACLF according to the AUROC and C-index.[9] The COSSH-ACLF score exhibited the highest predictive value for short-term mortality in patients with HBV-ACLF according to the AUROC value.[3] However, the above 2 scores were mainly focused on sensitivity and specificity, and the similarity between the probability distributions of surviving patients and non-surviving patients was ignored in predicting short-term mortality. In this study, the C-index showed that the new score was significantly more accurate than the 4 other scores for predicting short-term mortality in patients with HBV-ACLF. Furthermore, we used PDF analysis to validate the accuracy of our new score, and the results showed that the new score had the lowest overlapping coefficient, which indicated that it performed better than the COSSH-ACLF and CLIF-C ACLF scores. The PDF could represent the probability distribution of prognostic scores obtained by surviving patients and non-surviving patients, and the overlapping coefficient of the PDF represents a measure of the similarity between 2 distributions.[15] The decreased overlapping coefficient of the COSSH-ACLF II score between the surviving patients and non-surviving patients indicated the distinction of the 2 distributions, illustrating the improved prognostic discrimination of the COSSH-ACLF II score. The calibration performance of the new score, with higher R^2 and scaled Brier values, further indicated that it was more accurate and more sensitive than the COSSH-ACLF and CLIF-C ACLF scores.

Our new score with X-tile plot analysis could also divide patients with HBV-ACLF into low-, intermediate-, and high-mortality strata with a significantly different risk of death at 28 days. These results also indicated that our newly developed prognostic score was simpler and more accurate in predicting the disease severity of patients with HBV-ACLF than the organ failure-based grade classification of the COSSH-ACLF and CLIF-C ACLF scores.

In summary, integrated with PDF and X-tile plot analyses, our newly developed COSSH-ACLF II score – based on 6 predictor factors – can accurately predict and easily stratify the short-term mortality of patients with HBV-ACLF; thus, it may be used to guide patient management. We observed no statistically significant difference in the prognostic performance of the new score and the COSSH-ACLF score in the validation group, which may be associated with the limited number of patients in the validation group. The new score also requires further validation in larger cohorts, and the clinical usefulness of the new COSSH-ACLF II score in prioritizing candidates for liver transplantation must be formally assessed.

Abbreviations

ACLF, acute-on-chronic liver failure; ALD, alcohol-related liver disease; CLIF-C, Chronic Liver Failure Consortium; COSSH, Chinese Group on the Study of Severe Hepatitis B; HBV-ACLF, hepatitis B virus-related acute-on-chronic liver failure; HE, hepatic encephalopathy; INR, international normalized ratio; LASSO, least absolute shrinkage and selection operator; MELD, model for end-stage liver disease; MELD-Na, MELD-sodium; PDF, probability density function; PSH, proportional subdistribution hazards; sHR, subhazard ratio; TB, total bilirubin; VIF, variance inflation factor.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

JL, XL, SY, TF, XZ and BZ contributed equally. The study was designed by JL and supervised by JL, SX, XC and BW. The manuscript was written by JL, XL, JL and XC. The data collection, analysis and interpretation were performed by JL, XL, SY, TF, XZ, BZ, JL, JX, JJ, DS, YL, KR, TW, LY, JL, TL, QC, SS, BG, XZ, JC, LH, PL, HY, WH, ZA, XJ, JT, BW, XC, SX and JL. All authors were involved in the critical revision of the manuscript.

Data availability statement

All the data associated with this study are included in the paper or supplementary materials.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.05.026.

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Author names in bold designate shared co-first authorship

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