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Predicting the Onset of Hepatitis B Virus–Related Acute-on-Chronic Liver Failure

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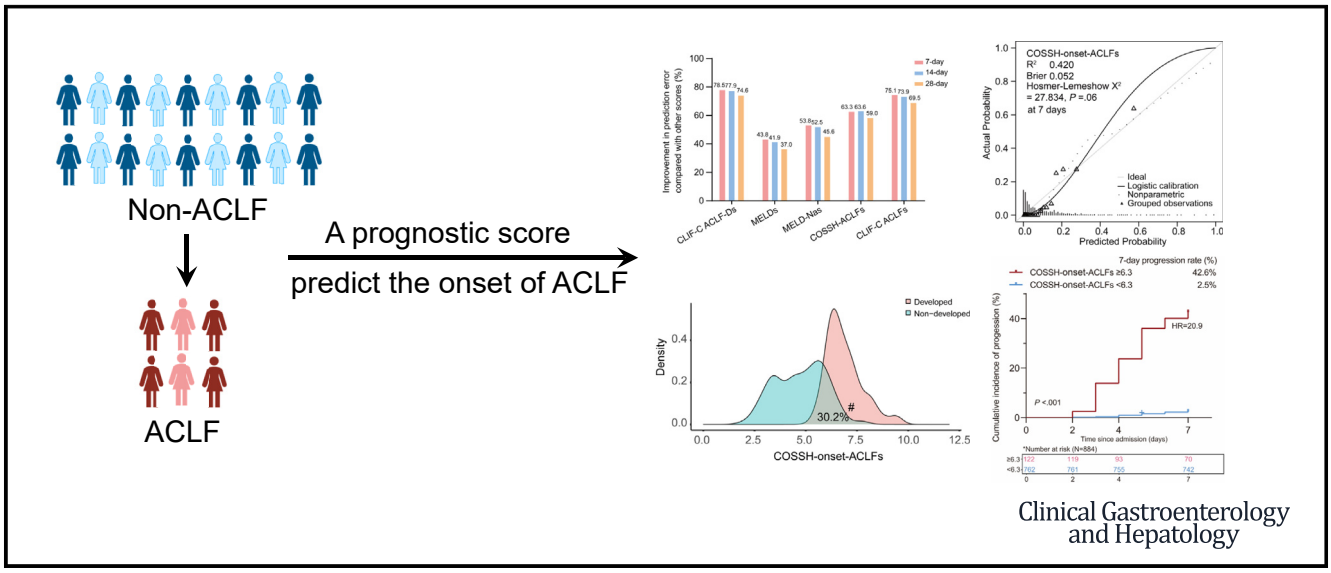

BACKGROUND & AIMS: **Acute-on-chronic liver failure (ACLF) is a life-threatening syndrome with rapid progression. This study aimed to develop and validate a prognostic score to predict the onset of ACLF in hepatitis B virus (HBV) etiology.**

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Abbreviations used in this paper: ACLF, acute-on-chronic liver failure; ADC, acute decompensation of cirrhosis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; C-index, concordance index; CLIF, chronic liver failure; CLIF-C, Chronic Liver Failure Consortium; CLIF-C ACLF-Ds, Chronic Liver Failure Consortium acute-on-chronic liver failure development score; CLIF-C ACLFs, Chronic Liver Failure Consortium acute-on-chronic liver failur score; COSSH, Chinese Group on the Study of Severe Hepatitis B; COSSH-ACLFs, Chinese Group on the Study of Severe Hepatitis B acute-on-chronic liver failure score; COSSH-onset-ACLFs, Chinese Group on the Study of Severe Hepatitis B onset acute-on-chronic liver failure score; HBV, hepatitis B virus; INR, international normalized ratio; LASSO, least absolute shrinkage and selection operator; MELDs, Model for End-stage Liver Disease score; MELD-Nas, Model for End-stage Liver Disease-sodium score; OPLS-DA, orthogonal partial least squares discriminant analysis; PDF, probability density function; PREDICT, PREDICTing Acute-on-Chronic Liver Failure; ROC, receiver operating characteristic; TB, total bilirubin; WBC, white blood cell.

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METHODS: **The prospective clinical data of 1373 patients with acute deterioration of HBV-related chronic liver disease were used to identify clinical characteristics and develop a prognostic score for the onset of ACLF.**

RESULTS: **Of the patients assessed using the Chinese Group on the Study of Severe Hepatitis B (COSSH)–ACLF criteria, 903 patients with non-ACLF at admission (1 received transplantation at 5 days) were stratified: 71 with progression to ACLF and 831 without progression to ACLF at 7 days. Four predictors (total bilirubin, international normalized ratio, alanine aminotransferase, and ferritin) were associated significantly with ACLF onset at 7 days. The COSSH-onset-ACLF score was constituted as follows: (0.101 × ln [alanine aminotransferase] + 0.819 × ln [total bilirubin] + 2.820 × ln [international normalized ratio] + 0.016 × ln [ferritin]). The C-indexes of the new score for 7-/14-/28-day onset (0.928/0.925/0.913) were significantly higher than those of 5 other scores (Chronic Liver Failure Consortium ACLF development score/Model for End-stage Liver Disease score/Model for End-stage Liver Disease sodium score/COSSH-ACLF score/Chronic liver failure Consortium ACLF score; all $P < .001$). The improvement in predictive errors, time-dependent receiver operating characteristic, probability density function evaluation, and calibration curves of the new score showed the highest predictive value for ACLF onset at 7/14/28 days. Risk stratification of the new score showed 2 strata with high and low risk (≥6.3/<6.3) of ACLF onset. The external validation group further confirmed the earlier results.**

CONCLUSIONS: **A new prognostic score based on 4 predictors can accurately predict the 7-/14-/28-day onset of ACLF in patients with acute deterioration of HBV-related chronic liver disease and might be used to guide clinical management.**

Keywords: Prognostic Score; HBV; ACLF; C-Index.

Acute-on-chronic liver failure (ACLF) is a severe syndrome with a complicated pathogenesis.[1,2] The Chronic Liver Failure (CLIF) Consortium Acute-On-Chronic Liver Failure in Cirrhosis study first proposed definition and diagnostic criteria for ACLF based on patients with mainly acutely decompensated alcoholic cirrhosis or hepatitis C virus–related cirrhosis.[3] Whether the definition of chronic liver disease should include cirrhosis and noncirrhosis is controversial.[4,5] Our recent Chinese Group on the Study of Severe Hepatitis B (COSSH) study documented that hepatitis B virus–related ACLF (HBV-ACLF) showed clinical characteristics different from alcoholic liver disease–related ACLF in western populations: liver and coagulation failures were the most common types of organ failure; the 28-/90-day mortality of patients with noncirrhotic HBV-ACLF was significantly higher than that of patients with non–HBV-ACLF; regardless of the presence of cirrhosis, total bilirubin (TB) of 12 mg/dL or greater, and an international normalized ratio (INR) of 1.5 or higher have a higher short-term mortality; HBV exacerbation was frequent precipitating events that may be related to the high mortality in patients with HBV-ACLF.[6] Based on the earlier-described clinical characteristics, our developed COSSH-ACLF criteria for the diagnosis of ACLF in HBV etiology show higher diagnostic sensitivity and prognostic accuracy and bridge a gap in the CLIF-ACLF criteria for HBV-ACLF diagnosis. However, the unacceptably high mortality of ACLF patients still has not decreased significantly because the comparatively late diagnosis would not provide sufficient time for intensive treatments. The strategic indication for intervention should be moved to earlier onset of ACLF.[7,8]

The Chronic Liver Failure Consortium Acute-On-Chronic Liver Failure in Cirrhosis and COSSH studies have shown that some patients with acute deterioration of HBV-related chronic liver disease have a high risk of progression to ACLF.[3,6] Early diagnosis and prognosis of ACLF onset for such patients are important to decrease the high mortality of ACLF patients. However, no appropriate prognostic scores have been developed to identify and predict such patients. A recent PREDICT study (PREDICTing Acute-on-Chronic Liver Failure) initially focused on pre-ACLF and showed that patients who progressed to ACLF from cirrhosis of non-HBV etiology showed a higher mortality rate than patients with ACLF-1 (90-day: 53.7% vs 40.7%).[3,9] Patients identified with pre-ACLF obviously cannot prevent progression, reverse failure, or improve survival through early intervention. Our COSSH study also found that patients with a TB level of 5 mg/dL or higher and an INR of 1.5 or higher who did not fulfill the diagnostic criteria for ACLF had a higher risk of progression to ACLF.[6]

This study aimed to identify the clinical characteristics of patients with a high risk of ACLF onset and develop a new prognostic score to predict the onset of ACLF based on the COSSH study with an open cohort, which may help to develop new management strategies for preventing progression and improving survival.

Patients and Methods

Study Design

To clarify patients with a high risk of progression to ACLF, patients with cirrhosis or severe liver injury resulting from chronic hepatitis B (CHB) were enrolled from the prospective open cohort of the COSSH study (January 2017 to December 2018).[6] Detailed clinical data were collected at admission and during the 28-day observation period from the electronic data capture system and case report forms. The clinical data were used to identify the clinical characteristics associated with the 7-day progression to ACLF. A prognostic score to predict the onset of ACLF was developed by least absolute shrinkage and selection operator (LASSO) penalized Cox regression analysis and orthogonal partial least squares discriminant analysis (OPLS-DA). An external group enrolled from January 2019 to December 2019 was used to validate the predictive ability of the new score. The study protocol was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine. Written informed consent was obtained from patients or their legal surrogates before enrollment.

Patients

Patients hospitalized for at least 1 day with acute deterioration of HBV-related chronic liver disease were enrolled in the present study if they met the following criteria: acute decompensation of cirrhosis (ADC) (ascites, hepatic encephalopathy, upper gastrointestinal hemorrhage, bacterial infection, or any combination of these); and severe liver injury (TB level, $\geq$5 mg/dL) based on CHB.[10] Patients were divided into 2 groups: the ACLF group: patients diagnosed with ACLF at admission; and the non-ACLF group: patients who did not fulfill the diagnostic criteria for ACLF at admission. Patients with non-ACLF who progressed to ACLF at 7 days after admission were further defined as the developed ACLF group, while patients who did not progress to ACLF at 7 days after admission were defined as the nondeveloped ACLF group. All patients received integrative treatment, including antiviral agents for HBV DNA–positive patients; treatment administration for ascites, hepatic encephalopathy, and bacterial infections; and renal replacement therapy for hepatorenal syndrome. HBV-ACLF was diagnosed based on the COSSH-ACLF criteria.[6] CHB was diagnosed according to the 2016 American Association for the Study of Liver Diseases guidelines.[11] Detailed information about the criteria of ACLF and CHB is provided in the Supplementary Methods section. The diagnosis of cirrhosis was based on liver biopsy, imaging, endoscopy, laboratory tests, or clinical symptoms.

What You Need to Know

Background

Acute-on-chronic liver failure (ACLF) is a life-threatening syndrome with rapid progression, and preventing its onset is of the utmost importance.

Findings

This prospective study of 903 hospitalized patients with acute deterioration of hepatitis B virus–related chronic liver disease found that total bilirubin, international normalized ratio, alanine aminotransferase, and ferritin were predictors to construct a prognostic score for predicting 7-/14-/28-day onset of ACLF. This score was validated successfully in an external group of 391 patients.

Implications for patient care

Our newly developed score can help to identify patients with a high risk of progression to ACLF early and may help to reduce the mortality of ACLF.

Development and Validation of a New Prognostic Score for Acute-on-Chronic Liver Failure Onset

The methods of identifying the clinical characteristics of enrolled patients and discovering predictors associated with the onset of ACLF are described in the Supplementary Methods section. The predictors were used to develop the prognostic score model for predicting the onset of ACLF by LASSO–Cox regression. The performance of the new score was compared with 5 other scoring systems (Chronic Liver Failure Consortium [CLIF-C] ACLF development score [CLIF-C ACLF-Ds],[9] Model for End-stage Liver Disease score [MELDs],[12] Model for End-stage Liver Disease-sodium score [MELD-Nas],[13] COSSH-ACLF score [COSSH-ACLFs],[6] and CLIF-C ACLF score [CLIF-C ACLFs][14]) in predicting the onset of ACLF, including model discrimination, calibration, and overall performance.[15,16] Discrimination was assessed by the concordance index (C-index), time-dependent receiver operating characteristic (ROC) and probability density function (PDF)[10,17]; calibration was assessed by calibration curves and goodness-of-fit with the Hosmer–Lemeshow statistic test[10,15]; and overall performance was tested using the R^2 and Brier scales.[16] Better performance is indicated by a higher R^2 and a lower Brier scale score. Detailed methods of discrimination with the C-index and PDF and calibration are shown in the Supplementary Methods section.

Statistical Analysis

The results of the measurements are presented as the means $\pm$ SD, median (interquartile range), or number

(%), unless otherwise noted. The Student t test and the Mann–Whitney U test were used to analyze continuous variables, and the chi-square test and the Fisher exact test were used for categoric variables. A paired t test and McNemar test were used to compare repeated measurements of continuous and categoric variables, respectively. The normality assumption was assessed by the Kolmogorov–Smirnov test. Non-normal data were transformed by natural logarithms. The missing data for the variables are provided in the Supplementary Methods section. The score was developed using the complete case. In all statistical analyses, significance was set at $P < .05$. X-tile software (version 3.6.1; Yale University, New Haven, CT) for risk stratification of a new score was used to identify the optimal cut-off value at all time points, which is a tool for the cut-off point selection by time-dependent assessment of outcome.[18] SPSS software V.25 (SPSS, Chicago, IL) and R V.4.0.2 (https://www.r-project.org) were used to perform the statistical analyses.

Results

Patients

A total of 2073 patients with acute deterioration of HBV-related chronic liver diseases were initially screened in this study, and, of these, 1373 patients were enrolled and included in the analysis population. Based on the COSSH-ACLF criteria, 470 patients were diagnosed with ACLF, and 903 patients were diagnosed with non-ACLF at admission. The ACLF group had higher laboratory indicators (TB, INR, and ferritin) and short-term mortality (28/90/365 days: 31.9%/42.9%/45.8%) than the non-ACLF group (Supplementary Table 1). Among the 903 patients with non-ACLF, 3 received liver transplantation 5/15/26 days after admission before the onset of ACLF, and 71 and 89 progressed to ACLF at 7 days and 28 days, respectively (Figure 1, Supplementary Figure 1*A*). Compared with the nondeveloped ACLF group, the developed ACLF group showed significantly higher 28-day, 90-day and 365-day mortality rates (15.3% vs 2.8%, 17.5% vs 5.9%, and 23.8% vs 7.8%, respectively; $P < .001$) (Figure 1).

Clinical Characteristics of Patients at Admission

The clinical characteristics of the non-ACLF, developed ACLF, and nondeveloped ACLF groups at admission are provided in Table 1. The proportion of patients with cirrhosis and a decompensation history in the developed ACLF group was significantly lower than that in the nondeveloped ACLF group (47.9% vs 73.3%, 7.0% vs 30.1%, respectively). The main complications were significantly different between the 2 groups. In the developed ACLF group, the main complications were ascites (43.7%) and bacterial infection (21.1%), but gastrointestinal hemorrhage occurred in only 1.4% of patients. In the nondeveloped ACLF group, the main complications were ascites (51.3%), gastrointestinal hemorrhage (24.2%), and bacterial infection (24.1%). There were fewer patients who used antiviral drugs within the 6 months before admission in the developed ACLF group than in the nondeveloped ACLF group (22.5%/38.6%, respectively). A total of 47.9% of patients in the developed ACLF group had HBV DNA levels of 2,000,000 IU/mL or greater, compared with 17.8% in the nondeveloped ACLF group. In addition, 7.0% of patients had HBV DNA levels of 200 IU/mL or less in the developed ACLF group, compared with 43.0% in the nondeveloped ACLF group.

Taken together, compared with the nondeveloped ACLF group, the developed ACLF group had a lower proportion of cirrhosis and antiviral drug use, a higher proportion of high HBV DNA levels, and worse laboratory indicators.

The Clinical Characteristics of Patients at Onset of Acute-on-Chronic Liver Failure

The clinical characteristics of the developed ACLF group at admission and at the onset of ACLF are shown in Supplementary Table 2. Among the 71 patients, 70.4% (50 of 71) progressed to ACLF-1, 26.8% (19 of 71) progressed to ACLF-2, and 2.8% (2 of 71) progressed to ACLF-3 at 7 days. The median time from non-ACLF progression to ACLF was 4 days (interquartile range, 3–5 d). Laboratory indicators, including TB, white blood cells (WBCs), and INR, increased significantly during disease progression, and alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase decreased gradually, which indicated severe progression with bilirubin–enzyme separation. The prevalence of liver failure increased significantly from 22.5% to 95.8%. The prevalence of kidney failure, cerebral failure, lung failure, and circulation failure also increased.

Optimum Predictive Factors Associated With the Onset of Acute-on-Chronic Liver Failure

Univariate Cox analysis showed that 30 of 43 factors were identified as statistically significant (Supplementary Table 3). The results of the correlation analysis showed that the 4 sets of factors (ALT and AST, WBCs and neutrophils, INR and prothrombin time, and hemoglobin and hematocrit) were highly correlated ($r > 0.9$), indicating severe collinearity (Supplementary Table 4). ALT level, WBC count, INR, and hemoglobin level were selected for the multivariate regression analysis as a result of hazard ratios ($P < .001$) and more general clinical applications. LASSO–Cox regression analysis showed that ALT, TB, INR, and ferritin were the factors that were most closely related to the progression

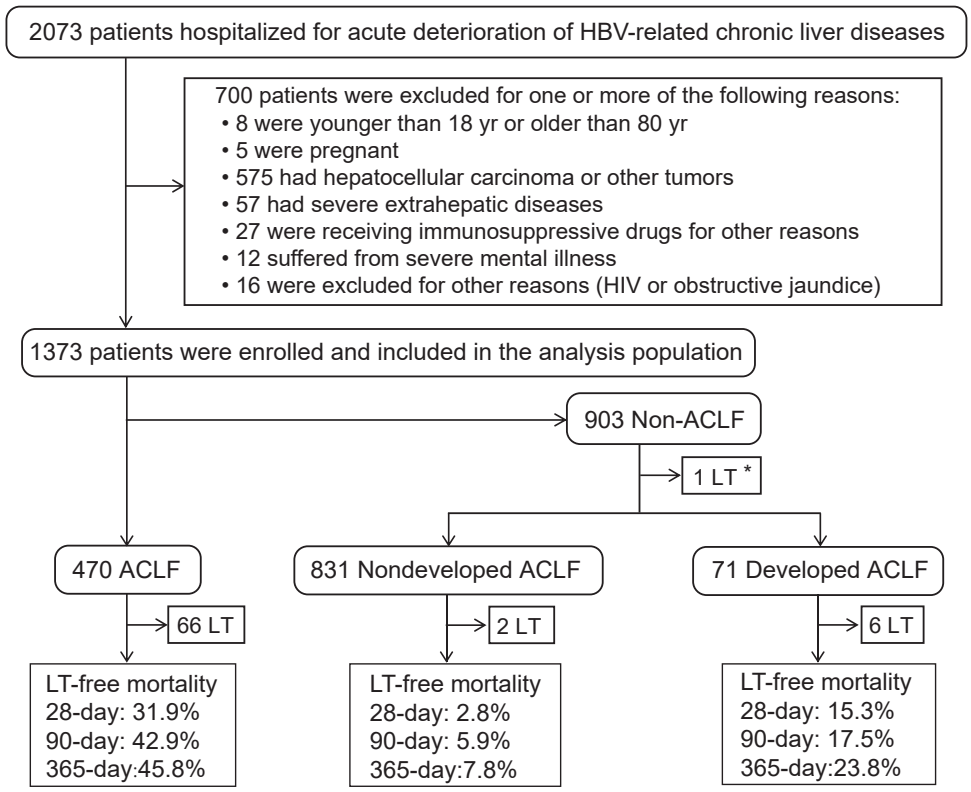

Figure 1. Screening, enrollment and classification of patients. *Liver transplantation 5 days after admission before the onset of ACLF. ACLF, acute-on-chronic liver failure; HBV, hepatitis B virus; HIV, human immunodeficiency virus; LT, liver transplantation.

to ACLF of 26 factors (Supplementary Figure 1*C* and Supplementary Table 5). OPLS-DA analysis with 39 factors (excluding 4 factors: AST, neutrophils, prothrombin time, and hematocrit) showed that developed ACLF patients could be clearly distinguished from nondeveloped ACLF patients. INR, ALT, TB, ferritin, and total bile acid were the top 5 factors that made the greatest contributions to distinguishing developed ACLF patients and nondeveloped ACLF patients with a VIPpred (predictive variable importance of projection) value greater than 1.5 (Supplementary Figure 1*D*). The analysis results combined with LASSO–Cox regression and OPLS-DA showed that ALT, TB, INR, and ferritin were the best predictive factors and were associated significantly with the onset of ACLF at 7 days. Collinearity diagnosis analysis showed no collinearity problem between the 4 predictive factors (Supplementary Table 6).

Development of the New Score to Predict the Onset of Acute-on-Chronic Liver Failure

Four optimum indicators (ALT, TB, INR, and ferritin) associated with the onset of ACLF were used to design an accurate prognostic score for predicting the onset of ACLF at 7 days. The new prognostic score for predicting the onset of ACLF (COSSH-onset-ACLFs) fitted by LASSO–Cox regression was as follows: (0.101 × ln [ALT, U/L] + 0.819 × ln [TB, μmol/L] + 2.820 × ln [INR] + 0.016 × ln [ferritin, μg/L]) (Supplementary Table 5). The probability of ACLF onset can be estimated by the equation $P = 1\text{-}e^{(\text{-CI[t]} \times \exp[\beta(t) \times \text{COSSH-onset-ACLFs}])}$. CI(t) and β(t) are the cumulative baseline hazard and the score coefficient estimated by the model fitted for time t. CI(7) = 0.0003070309, β(7) = 1.040968; CI(14) = 0.0003, β(14) = 1.080117; CI(28) = 0.0004082585, and β(28) = 1.038015.

Performance of the New Prognostic Score

Compared with the 5 other scores, the COSSH-onset-ACLFs had the highest C-indexes (0.928/0.925/0.913) for predicting the onset of ACLF at 7/14/28 days (CLIF-C ACLF-Ds, 0.665/0.661/0.658; MELDs, 0.872/0.871/0.862; MELD-Nas, 0.844/0.842/0.840; COSSH-ACLFs, 0.804/0.794/0.788; and CLIF-C ACLFs, 0.711/0.713/0.715, all $P < .001$) (Table 2). The prediction error rates of the new score were decreased significantly compared with those of the 5 scores (CLIF-C ACLF-Ds, 78.5%/77.9%/74.6%; MELDs, 43.8%/41.9%/37.0%; MELD-Nas, 53.8%/52.5%/45.6%; COSSH-ACLFs, 63.3%/63.6%/59.0%; and CLIF-C ACLFs, 75.1%/73.9%/69.5%) (Supplementary Figure 1*E*). The time-dependent ROC analysis showed that the COSSH-onset-ACLFs had the highest area under the ROC curves (0.939/0.939/0.926) compared with the 5 other scores at 7/14/28 days (Supplementary Figure 2).

The results of PDF analysis showed that the number of developed patients increased with increasing scores, and an obvious distinction was observed between the peaks of the developed ACLF and nondeveloped ACLF patients. The overlapping coefficients of the new score

Table 1. The Characteristics at Admission of Patients With Non-ACLF Related to HBV Infection Including Nondeveloped ACLF and Developed ACLF

Characteristic	Non-ACLF (n = 903)	Nondeveloped ACLF (n = 831)	Developed ACLF (n = 71)	*P* value
Age, *y*	50 [40–59]	50 [41–58]	47 [33–61]	.54
Male, n	80.1% (723)	80.4% (668)	76.1% (54)	.38
MAP, *mm Hg*	80.7 [73.0–88.7]	80.7 [73.0–88.3]	82.7 [76.7–91.0]	.08
Cirrhosis, n	71.3% (644)	73.3% (609)	47.9% (34)	<.001
Complication				
Hepatic encephalopathy	2.9% (26)	2.9% (24)	2.8% (2)	.99
Gastrointestinal hemorrhage	22.4% (202)	24.2% (201)	1.4% (1)	<.001
Ascites	50.7% (458)	51.3% (426)	43.7% (31)	.22
Bacterial infection	23.8% (215)	24.1% (200)	21.1% (15)	.58
Decompensation history	28.4% (256)	30.1% (250)	7.0% (5)	<.001
Antiviral drug use history	37.4% (338)	38.6% (321)	22.5% (16)	.007
HBV-DNA level, *IU/mL*				<.001
≤200	40.2% (363)	43.0% (357)	7.0% (5)	
200-2×10^4	17.2% (155)	18.3% (152)	18.3% (13)	
2×10^4-2×10^6	21.4% (193)	20.9% (174)	26.8% (19)	
≥2×10^6	20.2% (182)	17.8% (148)	47.9% (34)	
Laboratory data				
Alanine aminotransferase, *U/L*	53 [23–281]	44 [22–203]	479 [144–904]	<.001
Aspartate aminotransferase, *U/L*	65 [32–179]	58 [31–147]	340 [162–532]	<.001
Alkaline phosphatase, *U/L*	106 [75–140]	103 [72–137]	131 [113–170]	<.001
Total protein, *g/L*	59.9 [54.9–64.3]	60.0 [54.8–64.4]	58.4 [54.9–62.9]	.41
Albumin, *g/L*	31.7 [27.5–35.5]	31.6 [27.4–35.7]	31.7 [28.5–34.3]	.93
Globin, *g/L*	27.4 [23.3–32.1]	27.4 [23.3–32.2]	27.3 [22.4–31.4]	.45
Total bile acid, *μmol/L*	66 [16–160]	55 [14–149]	185 [137–209]	<.001
Total bilirubin, *μmol/L*	71 [22–155]	55 [21–136]	186 [155–203]	<.001
γ-Glutamyl transferase, *U/L*	67 [27–132]	59 [26–130]	103 [80–148]	<.001
Creatinine, *μmol/L*	69 [60–80]	69 [60–80]	65 [54–72]	<.001
Serum urea, *mmol/L*	4.9 [3.7–6.9]	5.0 [3.7–7.1]	3.8 [2.8–5.4]	<.001
Triglyceride, *mmol/L*	1.0 [0.7–1.9]	1.0 [0.7–1.9]	1.3 [1.0–2.0]	.002
Total cholesterol, *mmol/L*	2.8 [2.3–3.4]	2.8 [2.3–3.4]	2.5 [2.1–3.0]	.009
Glucose, *mmol/L*	4.7 [4.1–5.8]	4.7 [4.1–5.8]	4.3 [3.3–5.5]	.002
Potassium, *mmol/L*	4.0 [3.7–4.3]	4.0 [3.7–4.3]	4.1 [3.8–4.5]	<.001
Sodium, *mmol/L*	139 [137–141]	139 [137–141]	138 [136–140]	.17
C-reactive protein, *mg/L*	7.5 [3.8–14.0]	7.4 [3.6–13.5]	10.6 [6.9–18.7]	.25
White blood cell count, 10^9/L	4.5 [3.0–6.3]	4.4 [3.0–6.2]	6.2 [4.5–7.7]	<.001
Neutrophil count, 10^9/L	2.8 [1.8–4.0]	2.7 [1.7–3.9]	3.8 [2.9–5.3]	<.001
Lymphocyte count, 10^9/L	1.00 [0.60–1.49]	0.99 [0.59–1.48]	1.27 [0.96–1.55]	.001
NLR	2.66 [1.82–4.29]	2.64 [1.79–4.22]	2.89 [2.18–4.89]	.09
Hemoglobin, *g/L*	116 [91–136]	113 [90–134]	133 [121–143]	<.001
Hematocrit, %	34 [28–40]	34 [27–40]	39 [34–43]	<.001
Platelet count, 10^9/L	83 [51–146]	81 [50–144]	116 [79–159]	.003
INR	1.4 [1.2–1.6]	1.4 [1.2–1.6]	1.9 [1.4–2.4]	<.001
Ferritin, *μg/L*	412 [82–1530]	345 [69–1273]	2277 [827–3966]	<.001
α-fetoprotein, *μg/L*	9.4 [2.5–87.0]	7.7 [2.3–80.7]	49.1 [11.8–167.6]	<.001
Organ failure, n				
Liver	12.7% (115)	11.9% (99)	22.5% (16)	.010
Coagulation	3.2% (29)	1.8% (15)	19.7% (14)	<.001
Kidney	0	0	0	N/A
Cerebral	0.8% (7)	0.7% (6)	1.4% (1)	.44
Lungs	0	0	0	N/A
Circulation	3.2% (29)	3.5% (29)	0	.16

Table 1. Continued

Characteristic	Non-ACLF (n = 903)	Nondeveloped ACLF (n = 831)	Developed ACLF (n = 71)	*P* value
Transplant-free mortality, n				
28 days	3.8% (34)	2.8% (24)	15.3% (10)	<.001
90 days	6.7% (60)	5.9% (49)	17.5% (11)	<.001
365 days	8.9% (79)	7.8% (64)	23.8% (15)	<.001

NOTE. One patient underwent liver transplantation 5 days after admission before the onset of ACLF. Categoric variables are expressed as % (n); continuous variables are expressed as either the means ± SD or median [interquartile range]. *P* values are comparisons between nondeveloped ACLF and developed ACLF (Student *t* test, Mann–Whitney *U* test, chi-squared test, or Fisher exact test).
ACLF, acute-on-chronic liver failure; HBV, hepatitis B virus; INR, international normalized ratio; MAP, mean arterial pressure; N/A, not available; NLR, neutrophil-to-lymphocyte ratio.

for predicting 7-/14-/28-day onset of ACLF (30.2%/30.3%/33.4%) were decreased significantly compared with those of the 5 other scores (CLIF-C ACLF-Ds, 75.6%/78.0%/78.0%; MELDs, 36.4%/36.7%/38.5%; MELD-Nas, 40.0%/41.0%/42.2%; COSSH-ACLFs, 60.8%/61.3%/62.8%; and CLIF-C ACLFs, 62.1%/61.8%/62.1%, all $P < .05$) (Figure 2). The calibration curves of the COSSH-onset-ACLFs showed good accordance between the predicted and actual probability of the onset of ACLF at 7/14/28 days (Hosmer–Lemeshow $\chi^2 = 27.834/28.499/26.884$, all $P > .05$) (Figure 3*A*). Taken together, the new score showed the best performance in predicting the onset of ACLF.

Risk Stratification of the New Score

X-tile plot analysis of the COSSH-onset-ACLFs all showed 2 strata with high risk (≥6.3) and low risk (<6.3) of ACLF onset at 7/14/28 days. The onset of ACLF at 7/14/28 days was significantly different between the earlier-described 2 groups (high-risk, 42.6%/49.2%/50.0%; and low-risk, 2.5%/3.2%/3.7%, $P < .001$) (Figure 4*A*). Compared with the low-risk group, the hazard ratios of the onset of ACLF at 7/14/28 days in the high-risk group reached 20.9/20.1/17.8 ($P < .001$). The prognostic scores were significantly higher in patients who progressed to ACLF-2/3 than in patients who progressed to ACLF-1 (Supplementary Figure 3*A*). Moreover, in the patients who progressed to ACLF, the new score (≥7.3 at 7 days, ≥8.0 at 14/28 days) could stratify the cumulative incidence of progression to ACLF-2/3 (Supplementary Figure 3*C*). These results indicated that the different risk stratifications of the new score for predicting ACLF onset were simple and accurate.

Validation of the New Score

An external validation group with 565 patients included 174 with ACLF and 391 with non-ACLF (Supplementary Table 7). Non-ACLF patients (3 received liver transplantation 9/18/25 days after admission before the onset of ACLF, and 34 and 48 progressed to ACLF at 7 days and 28 days) were used to confirm the performance of the new score (Supplementary Figure 1*B*). The clinical and laboratory indicators of the derivation and validation groups were similar (Supplementary Table 8). The C-indexes of the COSSH-onset-ACLFs for predicting the onset of ACLF at 7/14/28 days (0.926/0.893/0.896) were significantly higher than those of 5 other scores (CLIF-C ACLF-Ds, 0.700/0.711/0.714, $P < .001$; MELDs, 0.900/0.861/0.863, $P = .009/<.001/.002$; MELD-Nas, 0.869/0.840/0.842, $P < .001$; COSSH-ACLFs, 0.771/0.793/0.798, $P < .001$; and CLIF-C ACLFs, 0.683/0.730/0.734, $P < .001$) (Table 2). The prediction error rates of the new score for 7-/14-/28-day ACLF onset were significantly lower than those of the 5 other scores (CLIF-C ACLF-Ds, 75.3%/63.0%/63.6%; MELDs, 26.0%/23.0%/24.1%; MELD-Nas, 43.5%/33.1%/34.2%; COSSH-ACLFs, 67.7%/48.3%/48.5%; CLIF-C ACLFs, 76.7%/60.4%/60.9%) (Supplementary Figure 1*F*). The time-dependent ROC analysis showed that the COSSH-onset-ACLFs had the highest area under the ROC curves (0.942/0.909/0.915) compared with the 5 other scores at 7/14/28 days (Supplementary Figure 4). The PDF analysis also showed decreased overlapping coefficients of the new score between the developed patients and nondeveloped patients in the validation group (COSSH-onset-ACLFs, 35.7%/34.9%/34.2%; CLIF-C ACLF-Ds, 71.2%/70.9%/69.1%; MELDs, 36.9%/40.1%/41.1%; MELD-Nas, 41.3%/43.8%/41.9%; COSSH-ACLFs, 56.7%/58.5%/55.8%; CLIF-C ACLFs, 55.6%/56.1%/53.8%, all $P < .05$) (Supplementary Figure 5). The calibration curve analysis showed similar results between the derivation and validation groups (Figure 3*B*). The hazard ratios of ACLF onset at 7/14/28 days in the high-risk group (15.8/13.6/12.6, $P < .001$) also were similar to those in the derivation group compared with the low-risk group, and showed a similar separation efficiency in the validation group (Figure 4*B*). The prognostic scores were higher in patients who progressed to ACLF-2/3 than in patients who progressed to ACLF-1, and the new score also could stratify the cumulative incidence of progression to ACLF-2/3 (Supplementary Figure 3*B* and *D*). These results indicated that the improved predictive ability of the new score for predicting the onset of ACLF was confirmed in the external validation group.

Table 2. The C-Indexes of Six Scores for Predicting the Onset of ACLF at 7/14/28 Days

	COSSH-onset-ACLFs C-index (95% CI)	CLIF-C ACLF-Ds C-index (95% CI)	MELDs C-index (95% CI)	MELD-Nas C-index (95% CI)	COSSH-ACLFs C-index (95% CI)	CLIF-C ACLFs C-index (95% CI)
Derivation group						
7-day progression rate	0.928 (0.910–0.947)	0.665 (0.599–0.731)	0.872 (0.838–0.906)	0.844 (0.807–0.881)	0.804 (0.758–0.851)	0.711 (0.649–0.774)
P value	<.001	<.001	<.001	<.001	<.001	<.001
14-day progression rate	0.925 (0.908–0.943)	0.661 (0.602–0.719)	0.871 (0.841–0.901)	0.842 (0.810–0.876)	0.794 (0.751–0.837)	0.713 (0.658–0.769)
P value	<.001	<.001	<.001	<.001	<.001	<.001
28-day progression rate	0.913 (0.892–0.934)	0.658 (0.602–0.715)	0.862 (0.831–0.892)	0.840 (0.809–0.872)	0.788 (0.746–0.830)	0.715 (0.662–0.768)
P value	<.001	<.001	<.001	<.001	<.001	<.001
Validation group						
7-day progression rate	0.926 (0.898–0.954)	0.700 (0.616–0.785)	0.900 (0.859–0.941)	0.869 (0.821–0.918)	0.771 (0.694–0.847)	0.683 (0.597–0.769)
P value	<.001	<.001	.009	<.001	<.001	<.001
14-day progression rate	0.893 (0.850–0.936)	0.711 (0.642–0.779)	0.861 (0.814–0.907)	0.840 (0.793–0.888)	0.793 (0.734–0.852)	0.730 (0.662–0.797)
P value	<.001	<.001	<.001	<.001	<.001	<.001
28-day progression rate	0.896 (0.854–0.937)	0.714 (0.647–0.781)	0.863 (0.819–0.908)	0.842 (0.796–0.888)	0.798 (0.741–0.855)	0.734 (0.669–0.799)
P value	<.001	<.001	.002	<.001	<.001	<.001

NOTE. *P* value of comparisons between COSSH-onset-ACLFs and the other scores (*z*-score test).
ACLF, acute-on-chronic liver failure; CI, confidence interval; CLIF-C ACLF-Ds, Chronic Liver Failure Consortium acute-on-chronic liver failure development score; CLIF-C ACLFs, Chronic Liver Failure Consortium acute-on-chronic liver failure score; COSSH-ACLFs, Chinese Group on the Study of Severe Hepatitis B acute-on-chronic liver failure score; COSSH-onset-ACLFs, Chinese Group on the Study of Severe Hepatitis B onset acute-on-chronic liver failure score; MELDs, Model for End-Stage Liver Disease score; MELD-Nas, Model for End-Stage Liver Disease-sodium score.

Discussion

Two well-accepted definitions, the CLIF-C and COSSH criteria, can distinguish patients with ACLF from patients with non-ACLF.[3,6] However, some patients with non-ACLF still have a high risk of progression to ACLF within 28 days. A recent PREDICT study identified that pre-ACLF patients could develop ACLF within 90 days and had a similarly high mortality rate as ACLF patients.[9] However, identifying such patients is not helpful to develop early treatment strategies for preventing the onset of ACLF. In this study, we observed that 89 patients with non-ACLF progressed to ACLF within 28 days, and 79.8% (71) of patients progressed within 7 days using COSSH-ACLF criteria. This result indicated the importance of predicting the 7-day onset of ACLF and may help to make early interventions for preventing progression. The patients who progressed to ACLF had a low proportion of cirrhosis but showed higher HBV DNA levels and worse liver and coagulation function. Although the multivariate analysis results showed that antiviral use was not the optimum predictive factor associated with the onset of ACLF, these results still may be associated with lower and inappropriate antiviral use. These results also are consistent with our previous results that some patients with CHB without cirrhosis can develop ACLF, and an HBV exacerbation-triggered excessive immune response can drive CHB or cirrhosis to progress into ACLF.[6,19]

A simple and accurate prognostic score for predicting the onset of ACLF is important in preventing the progression from non-ACLF to ACLF. Four scores (MELDs, MELD-Nas, CLIF-C ACLFs, and COSSH-ACLFs) have been used to predict the mortality of patients with various severe liver diseases.[6,12–14] MELDs and MELD-Nas (including TB, INR, creatinine, or sodium) have been used for organ allocation for transplantation in end-stage liver disease.[12,13] However, they showed lower sensitivity and accuracy in ACLF patients because they cannot reflect extrahepatic organ failure.[10,14] CLIF-C ACLFs and COSSH-ACLFs, mainly based on organ failure, have been developed and are widely used to predict short-term mortality in patients with ACLF.[6,14] Recently, the CLIF-C ACLF-Ds was developed to predict ACLF development in the ADC population based on the PREDICT study and showed no more accuracy than traditional clinical scores.[9] In this study, we found that 4 risk factors (TB, INR, ALT, and ferritin) were strongly associated with progression from non-ACLF to ACLF. TB and INR, as well-known predictors of liver and coagulation function, have been widely used in various diagnostic criteria and prognostic scores for patients with ACLF.[3,6,14] ALT is related to hepatocyte

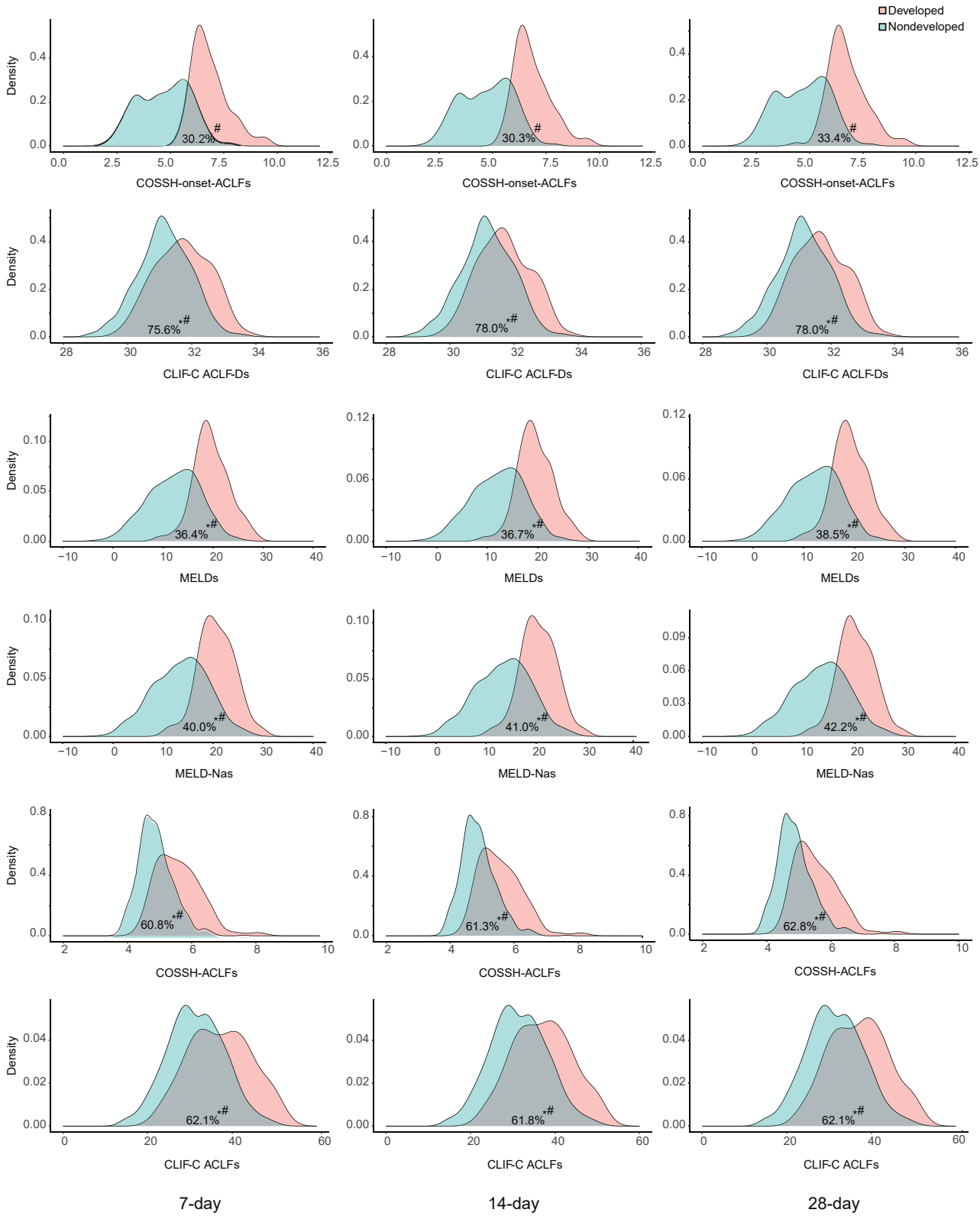

Figure 2. Probability density function of COSSH-onset-ACLFs for predicting 7-/14-/28-day ACLF onset in the derivation group. $^{*}P < .05$ (Student t test) for comparisons of the overlapping coefficient between the COSSH-onset ACLFs and the other scores. $^{\#}P < .001$ (Mann–Whitney *U* test) for comparisons of scores between developed ACLF and nondeveloped ACLF patients. ACLF, acute-on-chronic liver failure; CLIF-C ACLF-Ds, Chronic Liver Failure Consortium acute-on-chronic liver failure development score; CLIF-C ACLFs, Chronic Liver Failure Consortium acute-on-chronic liver failure score; COSSH-ACLFs, Chinese Group on the Study of Severe Hepatitis B acute-on-chronic liver failure score; COSSH-onset-ACLFs, Chinese Group on the Study of Severe Hepatitis B onset acute-on-chronic liver failure score; MELDs, Model for End-Stage Liver Disease score; MELD-Nas, Model for End-Stage Liver Disease-sodium score.

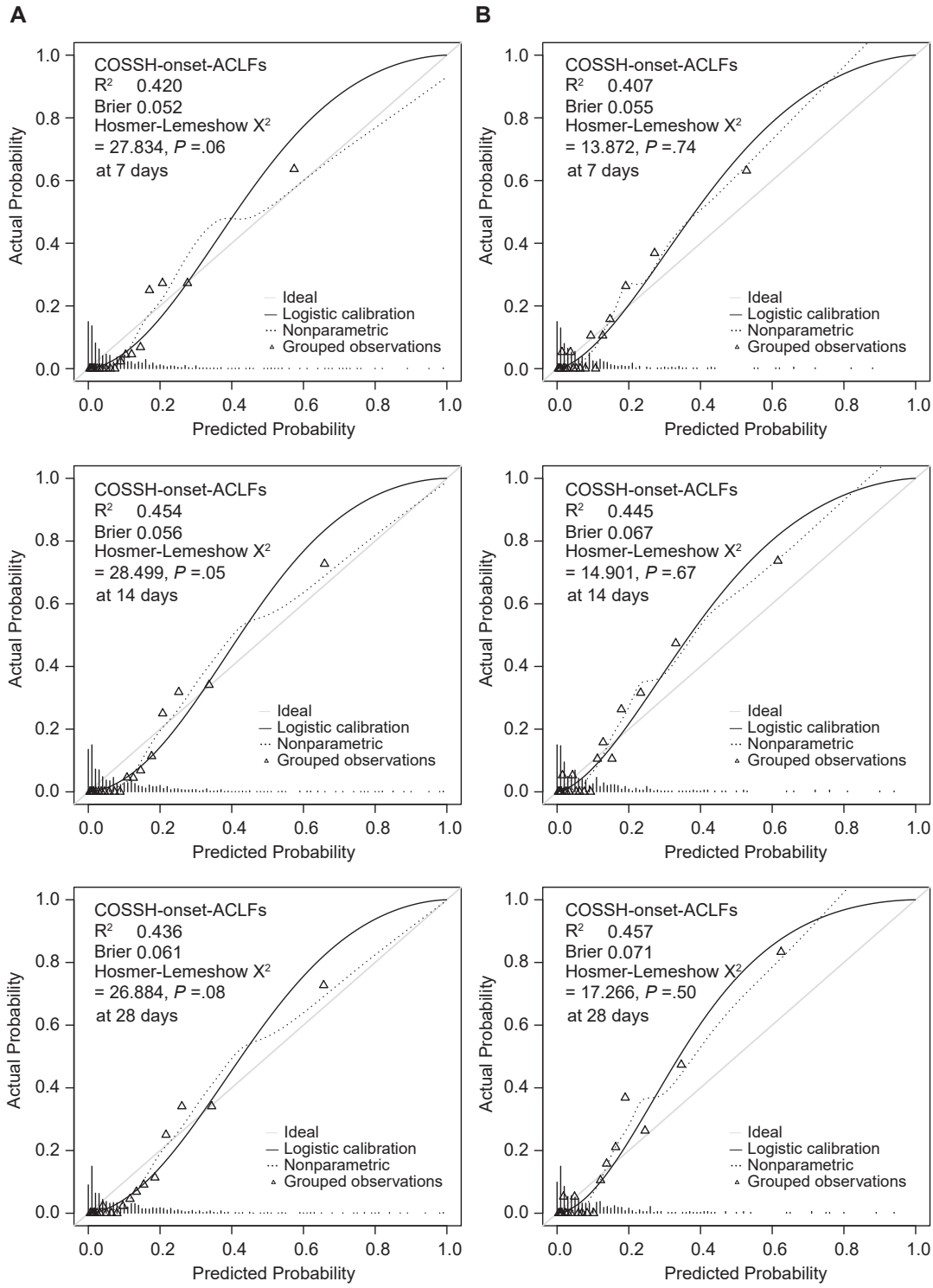

Figure 3. Calibration curves of the Chinese Group on the Study of Severe Hepatitis B onset acute-on-chronic liver failure score (COSSH-onset-ACLFs). (*A*) The derivation group. (*B*) The validation group. R^2 and the Brier score: a higher R^2 value and a lower Brier score indicated better performance.

necrosis.[20] Increased serum ferritin levels are correlated with various diseases including inflammation and malignancy.[21,22] Recent studies also indicated that ferritin could be used to predict early mortality in patients with ADC and may be an important disease marker in alcoholic, viral hepatitis, and ACLF.[23,24] These 4 risk factors can reflect the pathophysiology of patients with progression to ACLF. Our newly developed score with the earlier-described 4 simple clinical factors (TB, INR, ALT, and ferritin) without complicated assessment of organ failure showed the highest predictive value for predicting 7-/14-/28-day onset of ACLF compared with the earlier-described 5 scores based on the C-index, PDF and calibration curve analysis.

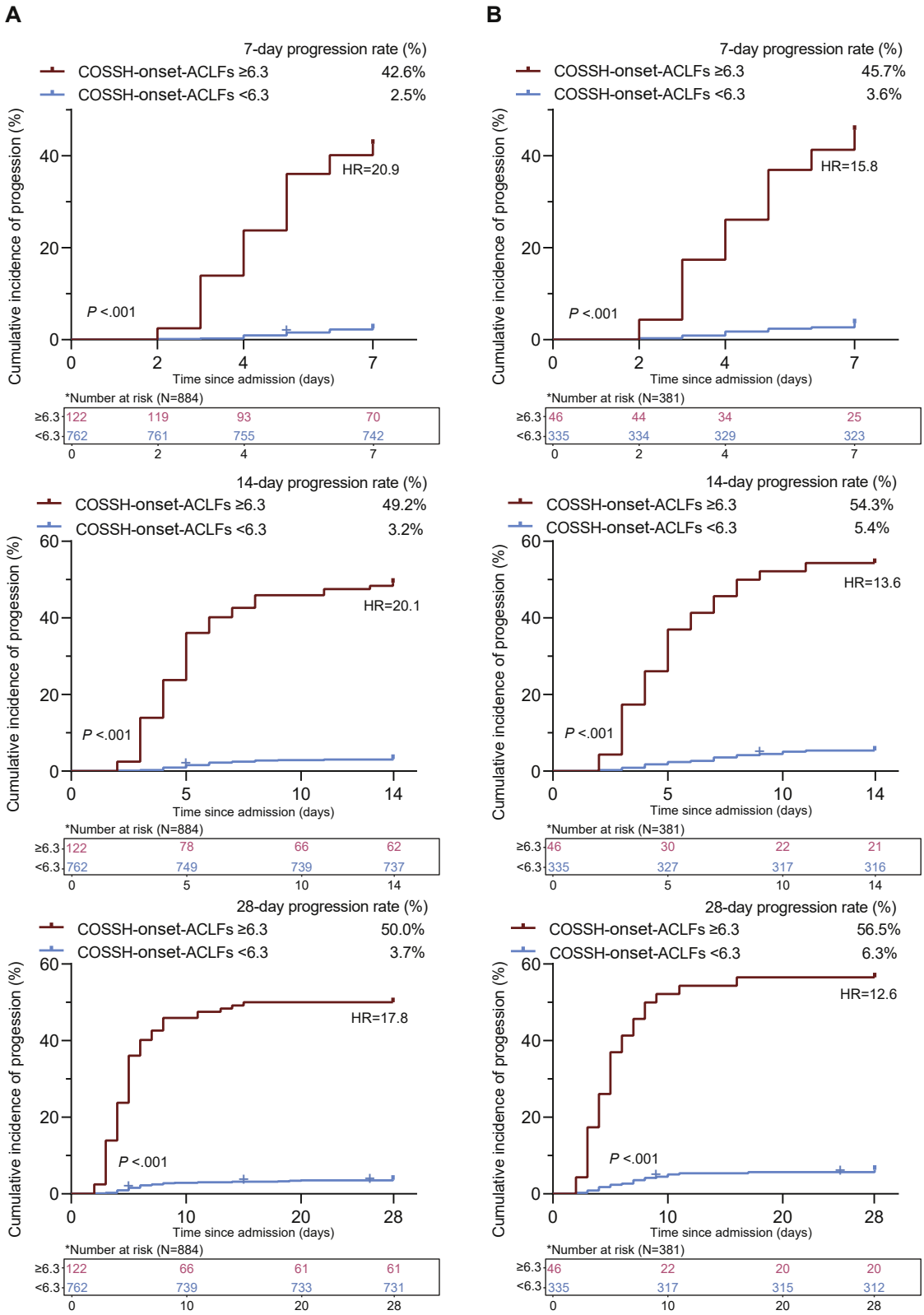

Figure 4. Risk stratification of Chinese Group on the Study of Severe Hepatitis B onset acute-on-chronic liver failure score (COSSH-onset-ACLFs). (*A*) Cumulative incidence of progression to ACLF at 7/14/28 days stratified according to the COSSH-onset-ACLFs classification rule (high/low risk: COSSH-onset-ACLFs $\geq$6.3/$<$6.3) in the derivation group. $P < .001$ (log-rank test) for comparison of the cumulative incidence. (*B*) Cumulative incidence of progression in the validation group. *Number of samples without missing values for alanine aminotransferase, total bilirubin, international normalized ratio, or ferritin. $^{+}$Liver transplantation before the onset of ACLF. HR, hazard ratio.

Our study had some limitations. Only HBV-related patients were enrolled in this study, which may limit the generalization to other etiologies such as alcoholic liver disease. This study included a relatively large sample size, but the number of events was limited. The new score requires further validation in other larger cohorts with different regions/countries and different etiologies.

In summary, early identification of patients with a high risk of progression to ACLF is the most important to reduce the onset and mortality of ACLF. Our newly developed score consisting of 4 simple clinical factors showed the highest performance for predicting the onset of ACLF, which may help to reduce the mortality of ACLF and change the clinical guidelines.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2022.03.016.

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