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Novel prognostic scoring models for hepatitis B virus-related acute-on-chronic liver failure: A comparison with classical models

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ABSTRACT

Early diagnosis and accurate prognostic evaluation are important for guiding clinical treatment and reducing mortality in patients with hepatitis B virus (HBV)-related acute-on-chronic liver failure (ACLF). The present study established novel prognostic scoring models to guide the clinical treatment of patients with HBV-ACLF. We performed a retrospective analysis of clinical data from two cohorts of patients diagnosed with HBV-ACLF. By comparing differences in baseline characteristics and clinical indicators between the survival ($n = 102$) and dead ($n = 64$) groups in the derivation cohort($n = 166$), four laboratory indicators (age, INR, TBIL, and HBeAg status) and three clinical signs (extrahepatic infection, ascites, and hepatic encephalopathy) were identified as independent risk factors. Logistic regression and nomogram models were used to construct three novel predictive models. By comparing the death and survival groups, we found that the three new models had higher predictions for AUROC (average of 0.856) than the three old models (average of 0.773). Model 1 had the strongest predictive power for the short-term survival rate of HBV-ACLF patients. Finally, we verified the predictive value of the new models for HBV-ACLF in a validation cohort ($n = 42$), and the Model 2 demonstrated good predictive accuracy for the 30-day survival rate of patients. The novel model based on seven predictors could accurately predict short-term mortality in patients with HBV-ACLF, which is promising for guiding clinical management and addressing the aetiological differences in Asian populations.

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Introduction

Acute-on-chronic liver failure (ACLF) is a distinct clinical condition characterized by a high short-term mortality risk [1]. Clinically, ACLF manifests as severe systemic inflammation, decompensated cirrhosis, single or multiple organ failure, and elevated 28-day mortality [2]. Currently, liver transplantation is the most advantageous and feasible therapy for patients with ACLF, but its applicability is limited by several factors, such as a shortage of donor liver and poor surgical tolerance in some patients [3]. Therefore, early diagnosis and accurate prognostic assessment are crucial for guiding clinical treatment, optimizing healthcare resource allocation, improving patient outcomes, and reducing mortality in patients with ACLF.

The aetiology of ACLF is multifactorial and its pathogenesis is complex. In Western countries, alcohol consumption or bacterial infections are the primary causes of ACLF. However, in Asian countries, approximately 70% of ACLF cases are caused by HBV, resulting in 120,000 deaths annually [4,5]. The HBV-related ACLF (HBV-ACLF) has been defined 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 [6]. Several studies have reported that HBV genotypes and subtypes have a distinct geographical distribution worldwide, and HBV genotype B and genotype C are the predominant genotypes in Asia [7–9]. HBV genetic variations, e.g. genotype and subtype, and mutations in some regions have been associated with different clinical manifestations, for example, the genotype C is

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significantly more closely associated with severe liver disease than genotype B, and subgenotype C2 infection is a risk factor of liver cirrhosis and HCC with cirrhosis development in the patients with CHB in Southeast China [10–12]. This suggests the specificity of the pathogenesis of HBV-ACLF in Asian populations. However, there was a lack of risk prediction models for HBV-ACLF in Asian population.

At present, risk assessment methods for patients with ACLF in clinical settings, such as the Child-Turcotte-Pugh (CTP) score [13], Model for End-Stage Liver Disease (MELD) score [14] and MELD-sodium (MELD-Na) score [15], are widely used and are constructed based on clinical data from Western populations. Owing to aetiological differences, these models, as mentioned above, exhibit limitations in the prognostic assessment of HBV-ACLF in Asian populations. The CTP score is the first prognostic model implemented in clinical practice. Assessment indicators for CTP included albumin (ALB), total bilirubin (TBIL), prothrombin time (PT), hepatic encephalopathy (HE), and ascites. Each indicator was quantified on a scale of 1 to 3 based on severity, with a total score of up to 15 points. The CTP score is straightforward to calculate and readily accessible; however, it exhibits some subjectivity and ignores the influence of renal function on prognosis. Moreover, the CTP score is primarily used to assess hepatic reserve function in patients with cirrhosis; however, its predictive value for ACLF prognosis is limited. The MELD score assesses liver function based on serum creatinine, bilirubin, international normalized ratio, and the absence or presence of cirrhosis. Compared with the CTP score, the MELD score exhibited greater objectivity and continuity in its indicators, with results demonstrating high repeatability. In addition, by incorporating serum creatinine and aetiology, the MELD score provides a more accurate prediction of prognosis in patients with liver failure [16–18]. However, the MELD score was limited by a lack of indicators of clinical events, such as ascites, hyponatraemia, hepatorenal syndrome and other complications, which were significantly related to the natural history of viral hepatitis and the outcome inpatient long-term follow-up observational studies [19].

Recently, several prognostic models for HBV-ACLF have been developed, such as the Chinese Group on the Study of Severe Hepatitis B-ACLF score (COSSH-ACLF) score [6] and COSSH-ACLF II score [20]. The COSSH-ACLF score was calculated by age, TBIL, HBV-sequential organ failure assessment score and international normalized ratio (INR), and the score has generally used to predict short-term outcomes in patients with HBV-ACLF [6]. However, the COSSH-ACLF score was based on complicated scales of 6 organ failures and mainly focus on indicators related to organ failure regardless of other relevant factors. Therefore, the COSSH-ACLF II score, an improved version of the COSSH-ACLF score was been developed. The COSSH-ACLF II score was established based on TBIL, INR, age, neutrophil, HE and urea [20]. These six quantitative indicators are objective and easy to measure, but the ability to reflect organ function through a single indicator is limited, especially in ACLF, a complex clinical syndrome involving multiple organs. And the COSSH-ACLF II score has been reported to show no significant difference in prognostic performance compared with the COSSH-ACLF score in the validation group [20]. Therefore, further validation is required to assess the predictive value of these new HBV-ACLF scoring models. In addition, it is necessary to develop and optimize HBV-ACLF prognostic models based on different Asian patient cohorts. Therefore, we aim to produce a model that can incorporate more clinical and laboratory indicators than previous models.

This study aimed to establish the novel HBV-ACLF prognostic scoring models based on both laboratory indicators and clinical signs for Asian HBV-ACLF patients, then evaluate whether the model developed in this study outperformed the CTP, MELD, and COSSH-ACLF II scores. The findings of this study will provide supplementary data for epidemiological research on the HBV-ACLF population in Asia and help guide clinical treatment decisions.

Methods

Patients

Two cohorts of subjects were enrolled at different times to develop and validate the new prognostic scores for HBV-ACLF. First, a cohort of 166 patients who were diagnosed with HBV-ACLF and were hospitalized for at least one day at the First Affiliated Hospital of Fujian Medical University from 2015 to 2019 were selected, and their relevant clinical data were used to identify predictive factors associated with 30-day and 60-day mortality and to develop new prognostic scores. An external group of 42 subjects, who were hospitalized from January 2023 to September 2024, was used to validate the prognostic ability of the new models constructed in this study.

The inclusion criteria for the present study were based on those proposed by Wu et al. [6] and Wang et al.. [21] and the consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL 2019) [22]. The inclusion criteria were as

follows: (a) patients who were at least 18 years old; (b) Hepatitis B surface antigen (HBsAg) or HBV DNA positivity for at least 6 months before hospitalization [23]; (c) TBIL > 5×ULN(85 μmol/L) and coagulopathy [prothrombin activity(PTA) < 40% or INR ≥ 1.5] [21]; and (d) acute hepatic insults complicated with ascites and/or HE within 4 weeks. HE was defined and graded according to the West Haven criteria [24]. The Chronic Liver Failure Sequential Organ Failure Assessment (CLIF-SOFA) score was used to diagnose organ failures [25]. The exclusion criteria were as follows: (a) pregnant or lactating patients; (b) co-infection with human immunodeficiency virus; (c) severe comorbidities, such as previous heart, lung, carcinoma, or renal disease; (d) other causes of liver damage, such as hepatitis A, C, or E, autoimmune hepatitis, alcohol consumption, or hereditary liver disease; and (e) liver transplantation.

Our study was approved by the Ethics Committee of the First Affiliated Hospital of Fujian Medical University (Approval No. [2015]084–2) and was designed and performed according to the principles of the Helsinki Declaration. Written informed consents were obtained from all participants before sample collection.

Score calculation for CTPs, MELDs, MELD-Nas and COSSH-ACLF IIs

CTPs was measured using ALB, TBIL, PT, HE, and ascites. According to the scores, patients were classified into grades A (5–6 points), B (7–9 points), and C (10–15 points) [13]. The MELDs was calculated using the formula: $3.78 \times \ln$ [TBIL (mg/dl)] + $11.2 \times \ln$ (INR) + $9.57 \times \ln$ [serum creatinine (mg/dl)] + 6.43 [14]. The MELD-Nas was calculated based on the MELD score using the formula: $\text{MELD} - \text{Na} - (0.025 \times \text{MELD} \times (140 - \text{Na})) + 140$ [15]. The COSSH-ACLF IIs was calculated using the formula: $1.649 \times \ln$ (INR) + $0.457 \times$ hE score (HE grade: 0/1, 1–2/2, and 3–4/3) + $0.425 \times \ln$(neutrophil) (10^9/L) + $0.396 \times \ln$ (TBIL) (μmol/L) + $0.576 \times \ln$ (serum urea) (mmol/L) + $0.033 \times$ age [20].

Development and validation of a new prognostic score

Based on the clinical data and outcomes of patients with HBV-ACLF, univariate and multivariate logistic regression analyses were conducted to identify key risk factors and develop precise prognostic scores. A p value < 0.05 was considered significant. Nomogram visualizations were generated to translate regression coefficients into clinically actionable risk scores. Model performance was evaluated using the area under the receiver operating characteristic curve (AUROC), sensitivity and specificity. For comparison, established scoring systems (MELD, MELD-Na, CLIF-C ACLF) were recalculated using the same cohort data. Predictive accuracy was assessed by applying the models to another validation cohort and comparing AUROC values. Statistical analyses were performed using R software (version 3.6) with the "rms" and "pROC" packages, and internal validation was conducted via 1,000 bootstrap resamples to correct for overfitting.

Clinical and laboratory indicators

A total of 47 parameters were retrospectively collected from the patients' initial venous blood test results at admission. The clinical phenotypes assessed in this study included diabetes, hypertension, fatty liver, hepatorenal syndrome (HRS), acute upper gastrointestinal bleeding (AUGRB), spontaneous bacterial peritonitis (SBP), extrahepatic infection, extrahepatic organ failure, ascites severity, severity grading, and organ failure frequency. Laboratory indicators assessed in this study included gender, age, body mass index (BMI), mean arterial pressure, white blood cell count (WBC), neutrophil count (NEUT), red blood cell count (RBC), haemoglobin (Hb), platelet (PLT), prothrombin time (PT), INR, TBIL, gamma-glutamyl transpeptidase (GGT), blood urea nitrogen (BUN), creatinine (Cr), glucose (GLU), cholesterol (Chol), triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), serum potassium (K), serum sodium (Na), albumin (Alb), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bile acid (TBA), cholinesterase (CHE), apolipoprotein A1 (APOA1), apolipoprotein B (APOB), c-reactive protein (CRP), alpha fetoprotein (AFP), ammonia (AMM), lactate (LAC), which were determined using an automated biochemical system (Siemens Healthcare Diagnostics, USA). The hepatitis B virus DNA (HBV DNA) was quantified using the TaqMan polymerase chain reaction (PCR) assay (Sansure Biotech, China) in a Roche LightCycler 480 Real-Time PCR System (Roche, Switzerland), the primers and probes were provided by the manufacturer, and reaction conditions consisted of initial denaturation at 95°C for 2 minutes, followed by 45 cycles of denaturation at 95°C for 15 seconds and annealing/extension at 58°C for 30 seconds. HBsAg and hepatitis B e antigen (HBeAg) levels were measured using the automatic immune fluorescence analyser Abbott Type

i4000 (Abbott Laboratories, USA), following the manufacturer's instructions.

Statistical analysis

The measurement data were expressed as mean ± standard deviation(SD), and differences were analysed by Mann-Whitney U test or Student's t-test after normality test. The Categorical data are presented as numbers and were compared using the Chi-squared test. Both the p value and the effect sizes measured the statistical results. Statistics on all indicators are shown in Supplementary Table S1-S3. Logistic regression analyses were used to identify independent factors associated with HBV-ACLF. Variables with $p < 0.1$ in the univariate analysis were then included in the multivariable model using the iterative process of forward selection. For multivariate analysis, p value < 0.1 was considered significant. The AUROC was calculated, and the Z test (Delong's method) was used to compare the predictive value of different prognostic scoring systems. Decision curve analysis (DCA) was used to assess the clinical utility of the predictive models. Based on the results of the logistic regression analysis, the 95% confidence interval (CI) and odds ratio (OR) were calculated. SPSS software version 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

Clinical characteristics of HBV-ACLF patients at admission

The clinical characteristics of 166 patients with HBV-ACLF from the derivation cohort are summarized in Table 1. Follow-up was conducted from the first admission until the outcome (death or end of follow-up). According to the clinical outcomes after hospitalization, the enrolled patients were categorized into survival (61%) and dead (39%) groups. Laboratory indicators and clinical signs were compared between the two groups. First, the mean age of the deceased group was significantly higher than that of the survivor group ($p = 0.6614$, effect size = –0.5662). Among the 36 laboratory markers, PT, INR, TBIL and Cr were significantly higher in the dead group than in the survival group, indicating hepatic dysfunction. In addition, the RBC, PLT, LDL, CHE, APOB, and HBeAg positivity rates were significantly lower in the dead group than in the survival group. As anticipated, the deceased group experienced significantly more severe complications, including SBP, ascites, HE, extrahepatic infection, and organ failure (Table 1 and Supplementary Table S1-S3). In addition, the severity scores calculated by CTPs, COSSH-ACLF IIs, MELDs, and MELD-Nas in the dead group were significantly higher ($p < 0.0001$, effect size > 0.5) than those in the survival group (Table 1 and Supplementary Table S1-S3).

Establishment of novel predictive models for mortality risk

Univariate and multivariate logistic regression analyses were conducted using clinical and laboratory data to identify key risk factors and develop precise prognostic scores for HBV-ACLF patients. Univariate logistic regression analysis for laboratory markers indicated that age, RBC count, PLT, PT, INR, TBIL, Cr, LDL, CHE, APOB, LAC and HBeAg status were associated with HBV-ACLF mortality ($p < 0.05$). Multivariate logistic regression analysis further showed that age, INR, TBIL, and HBeAg status could be used as final prognostic scores (Table 2). For clinical signs, SBP, extrahepatic infection, extrahepatic organ failure, severity of ascites, severity grading of HE, and number of organ failures were significantly associated with mortality based on univariate logistic regression analysis ($p < 0.05$). Among the six potential risk factors, extrahepatic infection, ascites severity, and severity grading of HE were independent predictors of HBV-ACLF ($p < 0.001$) (Table 3).

Based on the independent predictors obtained by multivariable logistic regression, we constructed nomogram models for predicting the mortality risk of HBV-ACLF. Model 1 integrated the above independent predictive laboratory indicators and clinical signs of HBV-ACLF (Figure 1(a)). Model 2 was established based on laboratory indicators (Figure 1(b)), whereas Model 3 was established based on clinical signs (Figure 1(c)). The calibration curve revealed a high consistency between the observed and predicted outcomes (Figure 1(d–f)). Model performance was assessed based on sensitivity, specificity, and the AUROC. ROC analysis revealed that the AUROC values of the nomogram models reached 0.898 (Model 1), 0.816 (Model 2), and 0.853 (Model 3), indicating that the models had an excellent ability to differentiate between the dead and surviving groups (Figure 1(g)). The detection efficiency comparison of the models showed that Model 2 had the highest specificity (0.859) and Model 3 had the highest sensitivity (0.912), but the positive predictive value (PPV) of Model 1 was highest (0.833) (Table 4). Then we used DeLong's statistical test, which evaluates the

Table 1. Comparison of indexes at baseline between survived and deceased patients with HBV-ACLF in the derivation cohort.

Characteristics	Survival ($n = 102$)	Dead ($n = 64$)	$t/Z/\chi^2$	P value
Gender (male/female)	80/22	52/12	0.1918	0.6614
Age (year, mean ± SD)	46.03 ± 14.43	53.80 ± 12.19	−3.5777	**0.0005**
Diabetes (Yes/No)	16/86	16/48	2.1922	0.1387
Hypertension (Yes/No)	15/87	13/51	0.8816	0.3478
Fatty liver (Yes/No)	32/70	15/49	1.0935	0.2957
HRS (Yes/No)	7/95	9/55	2.3405	0.1260
AUGIB (Yes/No)	6/96	8/56	2.2301	0.1353
SBP (Yes/No)	7/95	12/52	5.4825	**0.0192**
Extrahepatic infection (Yes/No)	33/69	47/17	26.5862	**<0.0001**
Extrahepatic organ failure (Yes/No)	14/88	20/44	7.4153	**0.0065**
Severity of ascites	0.89 ± 0.76	1.50 ± 0.91	−4.3611	**<0.0001**
Severity grading of HE	0.11 ± 0.34	1.00 ± 1.31	−5.3064	**<0.0001**
Number of organ failures (mean ± SD)	1.14 ± 0.35	1.52 ± 0.94	−3.1413	**0.0017**
BMI (mean ± SD)[a]	23.17 ± 3.20	23.44 ± 3.45	−0.4119	0.6811
Mean arterial pressure (mmHg, mean ± SD)[a]	89.33 ± 11.53	92.12 ± 8.10	1.3690	0.1732
WBC (10^9 cells/L, mean ± SD)	6.58 ± 3.04	7.10 ± 3.41	−0.8759	0.3811
NEUT (10^9 cells/L, mean ± SD)	4.55 ± 2.74	5.10 ± 3.13	−1.2093	0.2265
RBC (10^{12} cells/L, mean ± SD)	4.21 ± 0.84	3.85 ± 0.84	−2.4419	**0.0146**
Hb (g/L, mean ± SD)	127.78 ± 20.75	121.88 ± 24.27	1.6715	0.0965
PLT (10^9 cells/L, mean ± SD)	116.92 ± 57.45	93.05 ± 49.12	−2.8386	**0.0045**
PT (s, mean ± SD)	21.42 ± 5.19	27.82 ± 11.79	−4.8409	**<0.0001**
INR (mean ± SD)	1.88 ± 0.47	2.42 ± 0.75	−5.0980	**<0.0001**
TBIL (μmol/L, mean ± SD)	252.26 ± 127.74	316.24 ± 139.12	−3.2995	**0.0010**
GGT (U/L, mean ± SD)	153.30 ± 116.50	120.98 ± 99.99	−1.8350	0.0683
BUN (mmol/L, mean ± SD)	4.31 ± 3.01	5.12 ± 4.45	−0.5607	0.5750
Cr (μmol/L, mean ± SD)	61.28 ± 19.56	76.00 ± 46.49	2.4019	**0.0187**
GLU (mmol/L, mean ± SD)	5.36 ± 3.82	5.41 ± 2.30	−1.6158	0.1061
Chol (mmol/L, mean ± SD)	3.04 ± 1.15	2.77 ± 0.92	−1.4930	0.1354
TG (mmol/L, mean ± SD)	1.51 ± 0.75	1.30 ± 0.67	−1.7718	0.0764
HDL (mmol/L, mean ± SD)	0.21 ± 0.22	0.30 ± 0.40	−0.3867	0.6990
LDL (mmol/L, mean ± SD)	1.50 ± 0.82	1.23 ± 0.69	−2.2280	**0.0259**
K (mmol/L, mean ± SD)	4.03 ± 0.51	4.06 ± 0.60	−0.3708	0.7113
Na (mmol/L, mean ± SD)	137.53 ± 3.51	136.97 ± 4.16	−1.2361	0.2164
Alb (g/L, mean ± SD)	30.39 ± 5.65	30.06 ± 3.91	−0.8046	0.4210
ALT (U/L, mean ± SD)	667.33 ± 646.27	697.53 ± 703.47	−0.0265	0.9788
AST (U/L, mean ± SD)	474.41 ± 484.23	582.11 ± 633.49	−0.8858	0.3757
TBA (μmol/L, mean ± SD)	219.88 ± 103.96	230.85 ± 98.38	−0.6904	0.4899
CHE (U/L, mean ± SD)[a]	3643.95 ± 1558.98	3136.21 ± 1739.98	−2.0930	**0.0364**
APOA1 (g/L, mean ± SD)	0.41 ± 0.21	0.36 ± 0.21	−1.8171	0.0692
APOB (g/L, mean ± SD)	0.88 ± 0.37	0.71 ± 0.26	−2.9999	**0.0027**
CRP (mg/L, mean ± SD)	16.79 ± 10.70	17.79 ± 11.02	−0.4779	0.6327
AFP (ng/mL, mean ± SD)	189.86 ± 267.19	139.01 ± 230.35	−1.7343	0.0829
AMM (μmol/L, mean ± SD)	62.51 ± 28.37	72.04 ± 52.52	−1.3352	0.1853
LAC (mmol/L, mean ± SD)[a]	2.65 ± 0.89	3.13 ± 1.30	−2.1849	**0.0289**
HBV DNA ($\log_{10}$IU/mL, mean ± SD)	5.08 ± 1.79	4.96 ± 2.02	0.3980	0.6912
HBsAg ($\log_{10}$IU/mL, mean ± SD)[a]	3.41 ± 0.91	3.10 ± 1.33	−1.2938	0.1957
HBeAg (Positve/Negative)	51/51	14/50	13.0569	**0.0003**
CTP score (mean ± SD)	10.33 ± 1.60	11.76 ± 1.43	−5.5498	**<0.0001**
MELD score (mean ± SD)	18.96 ± 4.82	25.74 ± 7.72	−6.3000	**<0.0001**
MELD-Na score (mean ± SD)	19.70 ± 5.09	26.44 ± 7.59	−6.2749	**<0.0001**
COSSH-ACLF II score (mean ± SD)	6.51 ± 0.87	7.56 ± 1.04	−7.0474	**<0.0001**

[a]partial data missing.

significance of differences in the AUROC between the three novel prognostic models. The results showed that the AUROC of Model 1 was significantly different with Model 2 and Model 3 (Table 5).

Performance of survival analysis based on novel model scores

To highlight the clinical significance of the novel models in forecasting mortality risk among HBV-ACLF patients, we conducted a survival analysis to compare the predictive performance of the new models for 30- and 60-day survival with that of the classical models (CTPs, MELDs, and COSSH-ACLF IIs). The Kaplan-Meier (K-M) survival analysis for the three novel models, CTPs, MELDs and COSSH-ACLF IIs showed significant differences in 30- and 60-day survival rates between the high- and low-score groups ($p < 0.001$). Moreover, the 30-day and 60-day K-M curve Hazard Ratios (HR) of Model 1 were highest. (30-/60- day K-M curve HR: Model 1, 9.26/8.07; Model 2, 5.06/4.10; Model 3, 4.84/5.00; CTPs, 4.03/3.87; MELDs, 4.64/3.85; COSSH-ACLF IIs, 4.03/4.01) (Figure 2). Altogether, the results of the K-M analyses suggested that Model 1 could more effectively differentiate between short-term (30-/60-day) mortality and survival in HBV-ACLF patients than classical models.

Table 2. Logistic regression analysis for comparison of laboratory makers at baseline between survival and dead patients with HBV-ACLF.

	Univariate analysis		Multivariate analysis	
Characteristics	Crude *P*	OR (95%CI)	Adjusted *P*	OR (95%CI)
Age	**0.0008**	**1.0424 (1.0174–1.0679)**	**0.0003**	**1.0538 (1.0245–1.0839)**
RBC	0.0097	0.5887 (0.3940–0.8796)	0.8756	–
PLT	0.0087	0.9909 (0.9841–0.9977)	0.1024	–
PT	<0.0001	1.4430 (1.0789–1.2137)	0.3422	–
INR	**0.0005**	**3.7529 (1.7751–7.9345)**	**<0.0001**	**4.6479 (2.3595–9.1555)**
TBIL	**0.0041**	**1.0034 (1.0011–1.0061)**	**0.0245**	**1.0032 (1.0004–1.0060)**
Cr	0.0135	1.0146 (1.0030–1.0263)	0.6656	–
LDL	0.0132	0.4700 (0.2587–0.8541)	0.9961	–
CHE	0.0392	0.9997 (0.9995–0.9999)	0.8851	–
APOB	0.0025	0.1752 (0.0568–0.5411)	0.8636	–
LAC	0.0079	1.5043 (1.1131–2.0330)	0.2723	–
HBeAg status	**0.0004**	**0.2800 (0.1379–0.5686)**	**0.0619**	–

Dead versus survival. Multivariate analysis was performed by forward (LR).

Table 3. Logistic regression analysis for comparison of clinical signs at baseline between survival and dead patients with ACLF.

	Univariate analysis		Multivariate analysis	
Characteristics	Crude *P*	OR (95%CI)	Adjusted *P*	OR (95%CI)
SBP	0.0240	3.1319 (1.1619–8.4418)	0.4141	–
Extrahepatic infection	**<0.0001**	**5.7807 (2.8918–11.5559)**	**<0.0001**	**5.3070 (2.3079–12.2036)**
Extrahepatic organ failure	0.0078	4.0994 (1.7331–9.6963)	0.6449	–
Severity of ascites	**<0.0001**	**2.3956 (1.5857–3.6192)**	**<0.0001**	**2.7833 (1.6785–4.6155)**
Severity grading of HE	**<0.0001**	**3.7298 (2.1269–6.5406)**	**<0.0001**	**3.9292 (2.1391–7.2174)**
Number of organ failures	0.0014	2.9035 (1.5072–5.5934)	0.9082	–

Dead versus survival. Multivariate analysis was performed by forward (LR).

Comparison of novel models established in this study with classical models

To assess the test efficiency of the novel models established in this study, ROC curves were constructed, and the AUROC values were compared with those of classical models. Model 1 had the highest AUROC (0.898), with a sensitivity of 0.781 and a specificity of 0.902. The AUROCs of Models 2 and 3 were 0.816 and 0.853, respectively, which were higher than those of the classical models (CTPs, 0.752; MELDs, 0.784; COSSH-ACLF IIs, 0.784) (Figure 3(a)). Comparing the performance metrics of three novel prognostic models and classical models, we found that Model 1 demonstrated balanced performance, with high specificity (0.902), PPV (0.833), and NPV (0.868), though its sensitivity (0.781) was slightly lower than Model 2 (0.859) and CTP (0.844). Model 2 achieved the highest sensitivity (0.859) but exhibited relatively low specificity (0.686) and PPV (0.632), suggesting a trade-off between detecting true positives and minimizing false positives. Model 3 prioritized specificity (0.912, the highest among all models) at the expense of sensitivity (0.625). While the CTP score had competitive sensitivity (0.844), its specificity (0.559) and PPV (0.545) were markedly inferior to all novel models. The MELD score displayed moderate specificity (0.892) but poor sensitivity (0.594), whereas the COSSH-ACLF II score achieved moderate sensitivity (0.797) but suboptimal specificity (0.667) and PPV (0.600) (Table 6). Using DeLong's test, we found that the AUC of Model 1 was significantly superior to that of CTPs, MELDs, and COSSH-ACLF II. In addition, the AUROC of Model 3 was also better than that of CTPs (Table 7). DCA is an appropriate method for assessing predictive models based on the net benefit and the range of threshold probabilities. In the present study, the clinical utility of Models 1, 2, and 3 was assessed by DCA and compared with the CTP score, MELDs, and COSSH-ACLF IIs. DCA results indicated that Model 1 presented a greater net benefit with a wider range of threshold probabilities for predicting mortality in the derivation cohort (Figure 3(b)).

To further verify the predictive ability of the new models for HBV-ACLF, we established another retrospective cohort as the validation cohort. The baseline clinical characteristics of the seven independent predictors for building Model 1 in the validation cohort are summarized in Supplementary Table S4. The survival analysis of the three novel models showed

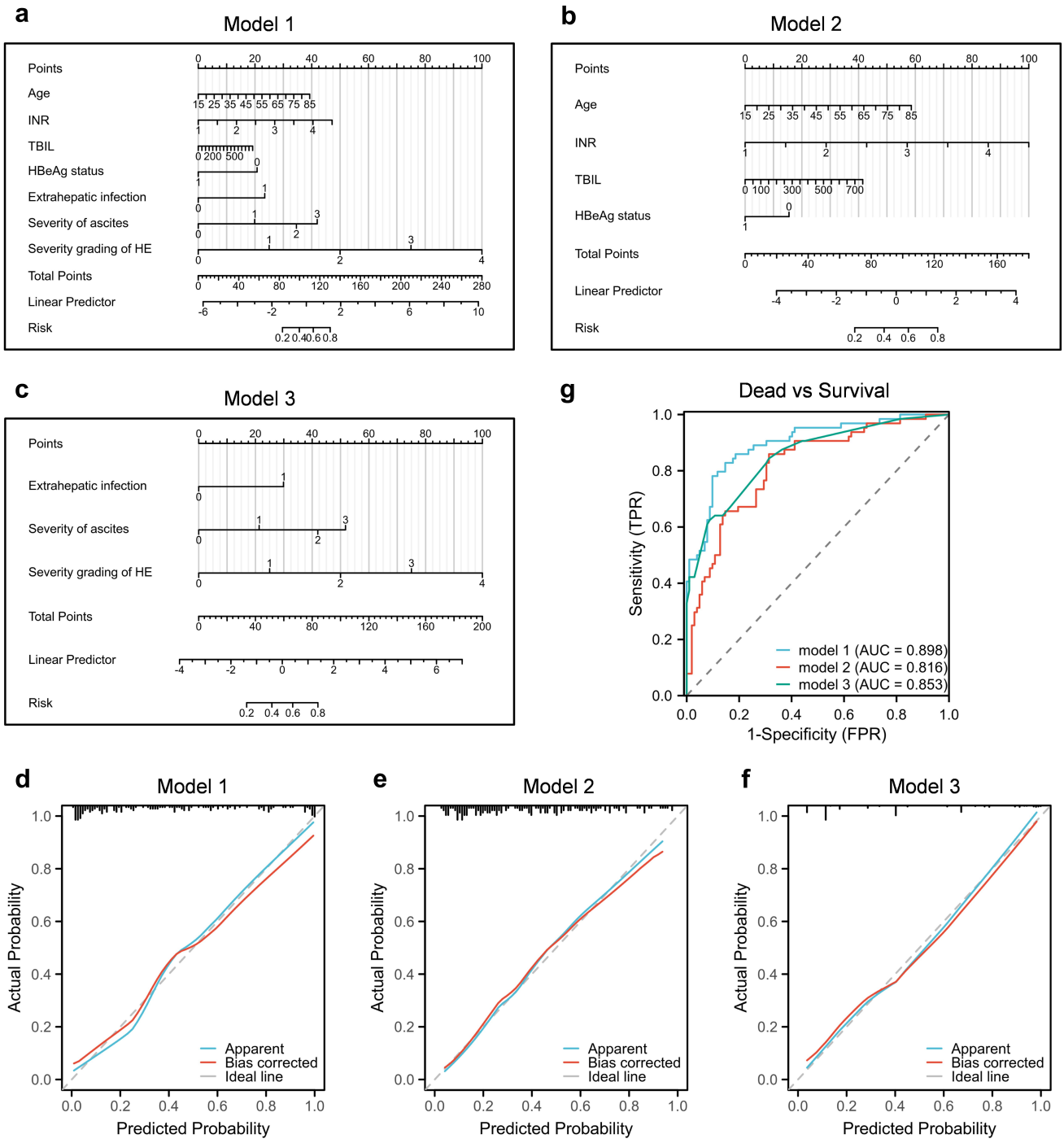

Figure 1. Models for mortality risk prediction were constructed based on nomogram.

(a–c) Nomogram of Model 1(a), Model 2(b) and Model 3(c) development in the derivation cohort. (d-f) Calibration plot for the diagnostic nomogram of Model 1(d), Model 2(e) and Model 3(f). (g) The area under ROC curve of the risk prediction nomogram models.

that Model 2 has effective prediction efficiency of 30-day survival in HBV-ACLF patients from the validation cohort (Figure 3(c)). Although models 1 and 3 were not statistically significant in predicting the survival of the included subjects, which may be due to the small sample size of this validation cohort, suggesting that in the future, cohorts with larger sample sizes are needed to further verify the risk prediction ability of the three new models for HBV-ACLF.

Table 4. Detection efficiency comparison of three novel prognostic models for HBV-ACLF.

Model	Sensitivity	Specificity	PPV	NPV
Model 1	0.78	0.90	0.83	0.87
Model 2	0.86	0.69	0.63	0.87
Model 3	0.63	0.91	0.82	0.79

PPV, positive predictive value; NPV, negative predictive value.

Table 5. Pairwise comparison of prognostic models' performance using DeLong's test for ROC differences.

Model a	Model b	*Z*	*P* value
model 1	model 2	2.9691	**0.0030**
model 1	model 3	2.6922	**0.0071**
model 2	model 3	−0.9445	0.3449

Discussion

HBV-ACLF is the most common type of liver failure in China and is characterized by rapid progression and life-threatening complications, such as hepatic encephalopathy and hepatorenal syndrome, leading to a high short-term mortality rate [6,26,27]. Due to the rapid progression and challenging outcome assessment, an accurate prognostic scoring system is crucial for optimizing therapeutic strategies for patients with HBV-ACLF. However, given the numerous factors influencing ACLF, accurate assessment of disease severity using a single indicator is challenging. Multivariate prognostic scoring models consider factors such as aetiology, laboratory indicators, clinical symptoms, and imaging findings, providing a more accurate and comprehensive evaluation of patient prognosis. CTP and MELD scores have been widely used to predict mortality in patients with liver cirrhosis or end-stage liver disease [13,14]. However, many studies have demonstrated their limits in accurately predicting short-term mortality in patients with ACLF [20,27]. Recently, the COSSH study, a large prospective multicenter cohort of ACLF patients in China, proposed a definition and developed two prognostic scores (COSSH-ACLF and COSSH-ACLF II) for HBV-ACLF [6,20]. However, new scores should be verified based on the complicated assessment of organ failure. Therefore, in the present study, we developed three novel models that integrate laboratory markers (age, INR, TBIL, HBeAg) and clinical signs (extrahepatic infection, ascites, HE) to predict 30-day mortality. The superior performance of these models, particularly Model 1, compared to classical scores including CTPs, MELDs and COSSH-ACLF IIs, highlights their clinical relevance.

The enhanced predictive accuracy of Model 1 likely stems from its comprehensive integration of both hepatic dysfunction markers (e.g. INR, TBIL) and systemic clinical indicators (e.g. HE, ascites). Traditional models like COSSH-ACLF IIs focus primarily on liver-specific parameters, whereas our models capture the multiorgan failure dynamics characteristic of ACLF [2]. For instance, ascites severity correlates with portal hypertension and systemic inflammation, which exacerbate hepatic decompensation and mortality risk [5]. Model 1's dominance may arise from its optimal weighting of HBeAg status, a marker of viral replication linked to immune tolerance [28], and extrahepatic infections, which amplify systemic inflammatory responses and accelerate liver failure [29]. Studies have shown that persistence of HBeAg with high viral load during chronic HBV infection is associated with an increased risk of liver cirrhosis and hepatocellular carcinoma [28,30], which partially validates the reliability of HBeAg as a risk predictor for HBV-ACLF patients. This aligns with recent studies showing that combining virological, biochemical, and clinical variables improves prognostic granularity in HBV-ACLF. Given that Model 1 demonstrates robust predictive accuracy for HBV-ACLF mortality risk and incorporates objectively measurable parameters, its clinical implementation should be prioritized to enhance risk stratification in real-world settings. To operationalize this model, we propose integrating it into electronic health record (EHR) systems for automated risk scoring during patient triage, coupled with the development of clinician-facing decision-support tools that provide real-time mortality probability estimates.

The predisposition, injury, response, and organ failure (PIRO) concept has been introduced to describe the pathological course of ACLF [31–33]. In this study, we enrolled two retrospective cohorts of patients with HBV-ACLF from two liver centres to develop and

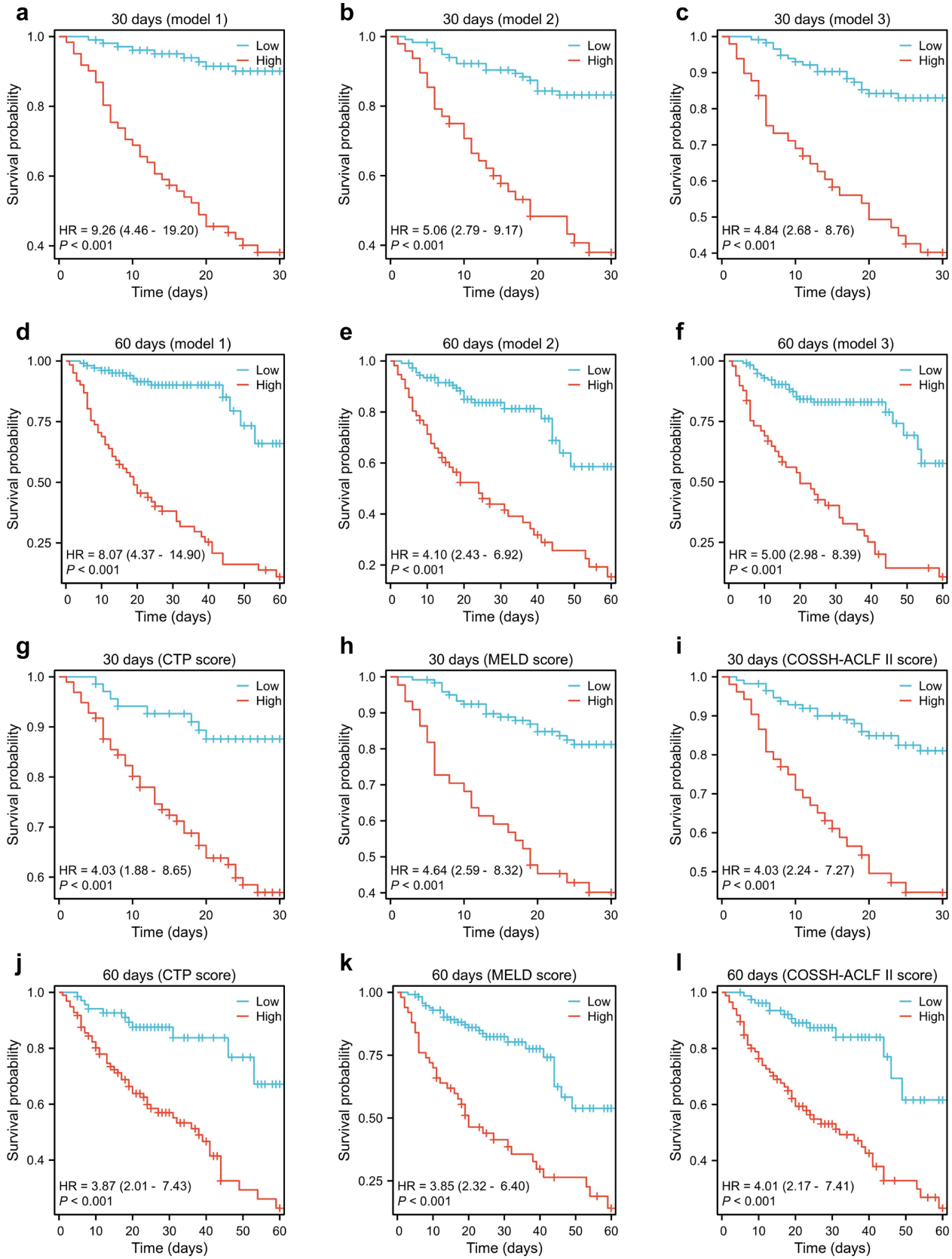

Figure 2. Construction of survival curved based on models in this study.

(a–c) 30-day survival curve of patients with HBV-ACLF diagnosed using Model 1(a), Model 2(b) and Model 3(c). (d–f) 60-day survival curve of patients with HBV-ACLF diagnosed using Model 1(d), Model 2(e) and Model 3(f). (g–i) 30-day survival curve of patients with HBV-ACLF diagnosed using CTPs(g), MELDs (h) and COSSH-ACLF IIs (i). (j–l) 60-day survival curve of patients with HBV-ACLF diagnosed using CTPs(j), MELDs(k) and COSSH-ACLF IIs (l).

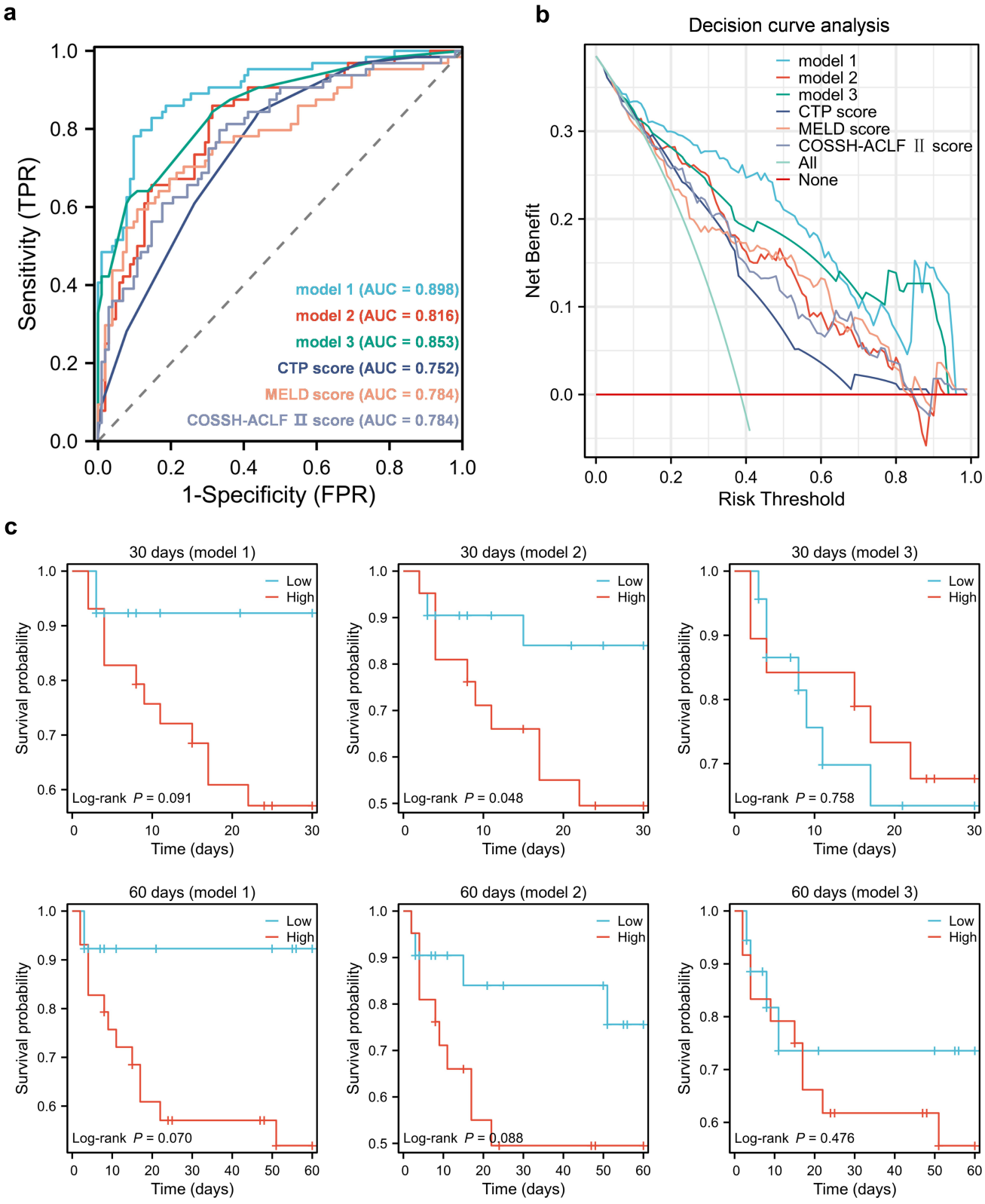

Figure 3. Comparison between models constructed in this study and the known models.

(a) Comparison between Model 1, Model 2, Model 3, CTPs, MELDs and COSSH-ACLF IIs by AUROC. (b) Decision curve analysis (DCA) for the predictive models in the derivation cohort. the line of "None" represents the assumption that no patients developed HBV-ACLF received no intervention, and the line of "All" represents the assumption that all patients developed HBV-ACLF and received interventions. (c) 30/60-day survival curve of patients with HBV-ACLF diagnosed using Model 1, Model 2 and Model 3 in the validation cohort.

Table 6. Detection efficiency comparison of three novel prognostic models and classical models.

Model	Sensitivity	Specificity	PPV	NPV
Model 1	0.78	0.90	0.83	0.87
Model 2	0.86	0.69	0.63	0.89
Model 3	0.63	0.91	0.82	0.79
CTP score	0.84	0.56	0.55	0.85
MELD score	0.59	0.89	0.78	0.78
COSSH-ACLF II score	0.80	0.67	0.60	0.84

Table 7. Pairwise comparison of prognostic models' performance using DeLong's test for ROC differences.

Model a	Model b	*Z*	*P* value
Model 1	CTP score	4.6055	**<0.0001**
Model 1	MELD score	3.4354	**0.0006**
Model 1	COSSH-ACLF II score	3.8077	**0.0001**
Model 2	CTP score	1.7214	0.0852
Model 2	MELD score	1.1293	0.2588
Model 2	COSSH-ACLF II score	1.2058	0.2279
Model 3	CTP score	2.9627	**0.0030**
Model 3	MELD score	1.8525	0.0640
Model 3	COSSH-ACLF II score	1.8456	0.0649

validate new prognostic scores. Based on the multivariate logistic regression analysis in the derivation cohort, seven independent risk factors (age, INR, TBIL, HBeAg, extrahepatic infection, ascites, and HE) were selected, and three simplified scoring models were developed for patients with HBV-ACLF. Among the seven factors, age indicates a predisposition to PIRO, while HBeAg and extrahepatic infection are common precipitating events for ACLF. TBIL, INR, ascites, and HE are associated with liver, coagulation, kidney, and brain failures, which are common fatal organ failures in patients with HBV-ACLF. Hence, the novel scores included three of the four components of PIRO, providing a good indication of HBV-ACLF pathophysiology.

In Asia, 70% of ACLF cases are caused by chronic HBV infection [4], and HBV genotypes have significant regional characteristics, suggesting that the aetiology of HBV-ACLF in Asian population has its own specificity, and it is necessary to establish a prediction model for HBV-ACLF based on Asian population. HBV genotypes B and C, prevalent in Asia, exhibit distinct virological behaviours (e.g. higher rates of HBeAg seropositivity and drug resistance) [9]. Our models explicitly address these aetiological nuances by incorporating HBeAg status, which reflects viral load and host immune response variability [28]. Previous studies have reported that HBeAg-negative patients in Asia often harbour pre-core mutations associated with aggressive disease progression [10]. Additionally, the high prevalence of HBV- ACLF in Asia necessitates region-specific prognostic tools, as Western models (e.g. CLIF-C ACLF and MELDs) are calibrated to alcohol- or HCV-driven cohorts [34]. Our validation across two Chinese centres supports regional applicability, though further studies in diverse Asian cohorts are needed to confirm generalizability.

In summary, our models represent a significant advance in HBV-ACLF prognostication, particularly for Asian populations. By harmonizing virological, biochemical, and clinical data, Model 1 provides a pragmatic tool for guiding resource allocation and therapeutic decisions. While our models demonstrate robustness, several limitations warrant mention. First, socioeconomic factors (e.g. healthcare access, nutrition) were not assessed, though these may influence outcomes. Second, the validation cohort, though independent, was geographically limited; prospective multicentric trials across diverse Asian regions are essential. Therefore, future work should focus on prospective validation, and socioeconomic variable integration, thereby adding the new model to EHR systems to automate triage risk scoring and creating clinician tools that display real-time mortality estimates.

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Authors' contributions

Conceptualization, Ya Fu; Data curation, Tianbin Chen, Ruimin Lai, and Qishui Ou; Formal analysis, Hongyan Guo, Fengling Fang, and Lin Lin; Funding acquisition, Qishui Ou and Ya Fu; Investigation, Hongyan Guo,

Fengling Fang, and Lin Lin; Methodology, Ya Fu; Visualization, Zhaopei Guo, Lu Lai, and Yue Shi; Writing – original draft, Hongyan Guo; Writing – review & editing, Tianbin Chen, Ruimin Lai, Qishui Ou, and Ya Fu. All authors have read and approved the final work.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability statement

The data that support the findings of this study are openly available figshare at https://doi.org/10.6084/m9.figshare.27281490.v2

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