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Research article

Development of novel prognostic models based on dynamic changes in risk factors for hepatitis B associated acute-on-chronic liver failure:a 10-year retrospective study

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ABSTRACT

Background/Aims: Acute-on-chronic liver failure (ACLF) is associated with high short-term mortality, and early prediction is critical to reduce the deaths of ACLF patients. To date, however, the prognostic accuracy of current models for ACLF is unsatisfactory, particularly, in patients with hepatitis B virus (HBV) infection. This study aims to develop novel prognostic models based on the dynamic changes in variables to predict the short-term mortality of HBV-associated ACLF (HBV-ACLF).

Methods: A retrospective cohort study was conducted, with the population comprised in whom ACLF was confirmed.319 patients were enrolled and their clinical data were collected on Days 1 and 7 following hospital admission. Univariate and multivariate analyses were performed to identify risk factors for 28 and 90-day mortality. The dynamic alterations in the risk factors were further analyzed, and Days 1 and 7 prognostic models were constructed. Receiver operating characteristic (ROC) analysis were used to identify and compared the predictors of prognosis among our model.

Results: Univariate and multivariate analyses revealed significant risk factors at Days 1 and 7, which when combined with the clinically important parameters, were used to establish the Days 1 and 7 prognostic models. For 28-day mortality, the predictive accuracy of the Day 1 prognostic model was significantly higher than that of the albumin-bilirubin (ALBI) model. For 90-day mortality, the predictive accuracy of the Days 1 and 7 prognostic models was significantly higher than that of the Model of End-Stage Liver Disease (MELD), MELD-sodium (MELD-Na), and ALBI prognostic models.

Conclusions: The prognostic models established in this study were superior to the existing prognostic scoring systems to accurately predict short-term mortality, and therefore, could be potential novel prognostic tools for HBV-ACLF.

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1. Introduction

Acute-on-chronic liver failure (ACLF) is a syndrome that is characterized by decompensation of liver cirrhosis and liver failure that is associated with short-term mortality. It has been noted that the majority of ACLF patients have preexisting chronic liver disease, including viral hepatitis. According to the World Health Organization, up to 257 million people live with a chronic hepatitis B virus (HBV) infection worldwide, of which 93 million cases were diagnosed in China [1]. In agreement with the high prevalence of HBV infection in China, HBV-related ACLF is the dominant form, which accounts for >80% of all ACLF cases [2]. Due to differences in preexisting liver disease and other clinical characteristics among ACLF patients worldwide, ACLF has a different definition in various major guidelines for the diagnosis and treatment of ACLF. For example, the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver (EASL) define ACLF according to the characteristics identified among the Western population where ACLF is an acute syndrome with a preexisting chronic liver disease, which is accompanied by liver and multiple organ failure. This is associated with a high risk of short-term mortality within 3 months [3]. In 2013, the EASL Chronic Liver Failure Coalition (EASL-CLIF) conducted a prospective observational study on 1434 hospitalized patients with acute decompensation across 29 liver disease centers in 8 countries. Based on the significant risk factors that were identified they established the chronic liver failure-sequential organ failure assessment score (CLIF-SOFA) [4]. The Asian-Pacific Association for the Study of Liver Diseases (APASL) initially reached a consensus on ACLF in 2009 [5] and then updated the definition of ACLF in 2019, which highlighted the high mortality of ACLF patients within 28 days of hospital admission [6].

It has been recognized that early prediction and intervention are key to reduce the deaths of ACLF patients regardless of the causative factors. During the last 20 years several prognostic models, such as the Model for End-Stage Liver Disease (MELD), MELD-sodium (MELD-Na), and albumin-bilirubin (ALBI) prognostic scoring systems were proposed as prognostic tools for ACLF to assist physicians in the early prediction of patients with liver dysfunction or failure that required prompt medical treatment or liver transplantation. However, their prognostic accuracy is unsatisfactory in ACLF patients, in particular, in those patients with HBV infection, or HBV-ACLF [7]. Therefore, new and improved prognostic tools need to be developed for different ACLF populations [8].

This study assesses the clinical characteristics of patients with HBV-related ACLF and their dynamic changes and aims to develop novel and improved prognostic models that predict the short-term mortality of HBV-ACLF.

The prediction through the new prognostic model allows doctors to conduct early assessment and intensive treatment intervention for patients with chronic hepatitis B to reduce the risk of death and mortality from ACLF.

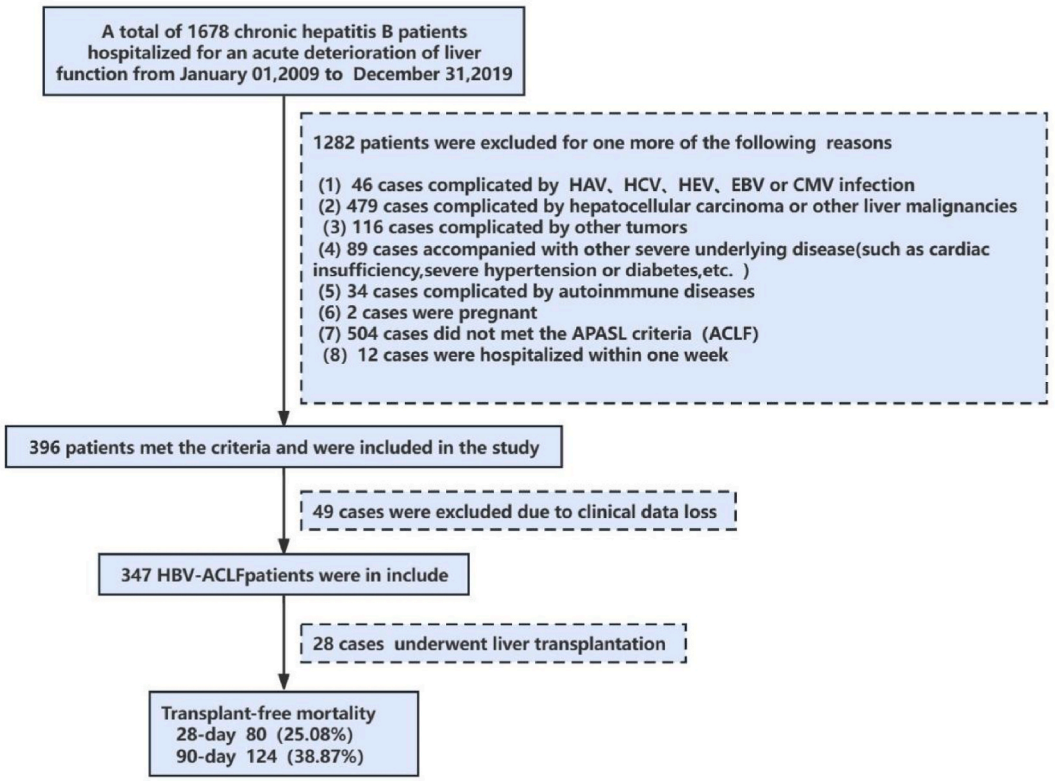

Fig. 1. Flow chart of patient enrolment in this study. ACLF = acute-on-chronic liver failure; CMV = cytomegalovirus; HAV = hepatitis A virus; HBV = hepatitis B virus; HDV = hepatitis D virus; HEV = hepatitis E virus; APASL = Asia-Pacific Association for the Study of the Liver.

2. Methods

2.1. Patient enrolment and data collection

In this cohort study, 319 patients with HBV-related ACLF were retrospectively enrolled for 10 years from July 2009 to June 2019 at the Infectious Department, Changhai Hospital, First Affiliated Hospital of the Naval Medical University (Shanghai, China). During patient enrolment, data for 1678 patients with chronic Hepatitis B (CHB) who were admitted to hospital for acute deterioration of liver function and the schematic diagram of patient enrolment is shown in Fig. 1. The diagnosis of CHB was made based on the criteria in the guidelines for the prevention and treatment of CHB as issued in 2019 [9]. In addition, the criteria for ACLF agreed with those issued by APASL in 2014 [10].

2.2. Inclusion criteria and exclusion criteria

During patient enrolment, the following inclusion criteria were used: (1) all patients had a history of CHB infection with positive hepatitis B surface antigen (HBsAg) or HBV DNA for >6 months; (2) jaundice with total bilirubin (Tbil) ≥5 mg/dL or 85 μmol/L and coagulation dysfunction [international normalized ratio (INR) ≥1.5 or plasma thromboplastin antecedent (PTA) ≤40%] were presented as the main manifestations of their acute liver injury; and (3) ascites, or hepatic encephalopathy (HE), or both occurred within 4 weeks. The patients that had the following clinical conditions were excluded from this study: (1) malignancies; (2) other viral infections [e.g., hepatitis A virus (HAV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV)]; (3) autoimmune hepatitis, alcoholic liver injury, drug-induced liver injury; (4) pregnancy; (5) the length of hospital stay was <7 days; and (6) incomplete clinical data.

The patients received standard clinical treatment, which included liver protection, nutritional support, intravenous infusion of 20% human albumin, correction of their acid-base balance and electrolyte disorders, and antiviral therapy with entecavir or tenofovir fumarate. Patients were followed up for 90 days or until death, during which the relevant examinations were performed regularly, and the test data were recorded.

The data for 319 enrolled patients, such as demographic characteristics, laboratory indexes, and complications (e.g., hyponatremia, hypokalemia, cirrhosis, ascites, hepatic encephalopathy, and abdominal infection) on Days 1 and 7 following hospital admission were collected and analyzed. The study protocol complied with the ethical guidelines of the Declaration of Helsinki, and was approved by the Ethics Committee of Shanghai Changhai Hospital **(CHEC2009–139)**.

2.3. Diagnosis

Cirrhosis was diagnosed based on previous liver biopsy examinations or the following parameters: (1) ultrasonography; (2) computed tomography (CT); and (3) magnetic resonance imaging (MRI) characteristics of a small liver with or without splenomegaly or ascites. In addition, ascites were diagnosed based on ultrasonography, CT, or MRI. HE was diagnosed based on clinical manifestations and ammonia levels in the blood. Hyponatremia was diagnosed based on serum sodium concentration <130 mmol/L, and it was classified as severe if < 125 mmol/L. Hypoproteinemia was defined as a serum albumin level <35 g/L, and hypokalemia was defined as a serum potassium concentration <3.5 mmol/L. For the stratification of other indicators, based on the clinical experience, the cut-off value was 20% of the basic value within 1 week of hospital admission.

2.4. Prognostic scoring systems used for performance comparison

Three existing prognostic scoring systems, including MELD, MELD-Na, and ALBI scores, were assessed in the patients based on data from Days 1 and 7. Although the Child-Turcotte-Pugh (CTP) scoring system is widely utilized as a tool to estimate prognosis and prediction of life expectancy in patients with liver cirrhosis [11], CTP was not used as a reference for comparative study after the following considerations. Between the five clinical measures (Tbil, serum albumin, prothrombin time, ascites, and HE), the item points of ascites and HE were affected by the treatment for the enrolled patients (e.g., diuretics, albumin, lactulose). In addition, the CTP score has inherent limitations (e.g., subjectivity), because it includes subjective factors. It is noted that the CTP score does not include renal function indicators; therefore, affecting the predictive value of the model for patients with renal injury.

The MELD score formula used was: $3.78 \times \text{Ln}$ [serum bilirubin (mg/dL)] $+ 11.2 \times \text{Ln}$ (INR) $+ 9.57 \times \text{Ln}$ [serum creatinine (mg/dL)] $+ 6.43$ (cause: biliary or alcoholic $= 0$, other $= 1$).

The MELD-Na formula used was: MELD $+1.59 \times (135 - \text{Na})$. Patients with serum sodium >135 mmol/L were calculated as 135 mol/L; <120 mmol/L were calculated as 120 mol/L; and 120–135 mmol/L were calculated as specific values.

The ABLI score formula used was: $0.66 \times \log 10$ Tbil (mg/dL) $- 0.085 \times$ albumin (ALB) (g/L).

2.5. Statistical analysis

Statistical analyses were conducted using R 3.5.1 for Mac OS. The Kolmogorov-Smirnov test was used to evaluate whether the data were distributed normally.

For continuous variables, data were presented as mean ± standard deviation (SD) or median with interquartile range and this data was analyzed using the Student's t-test or the Mann–Whitney *U* test. For categorical variables, data were presented as frequencies or

percentages, and this data was compared between groups using Pearson's chi-squared test (χ^2) or Fisher's exact test. In addition, univariate Cox proportional-hazards regression analyses were carried out to determine the association of clinical and laboratory parameters with the prognosis. The variables, including the clinically important but not statistically significant, were included as candidate variables in the multivariate Cox regression analysis to identify the independent predictors for disease progression. The conditional probabilities for stepwise entry and the removal of a factor were 0.05 and 0.10, respectively. The survival of a patient was estimated using the Kaplan–Meier analysis and was subsequently compared using the logrank test.

The prediction performances of the four models were then assessed using the receiver operating characteristic curve (ROC) analysis, where the area under the ROC curve (AUC) was applied to compare the prediction performance of the proposed developed Days 1 and 7 prognostic models with the three existing scoring systems (MELD, MELD-Na, and ALBI) where $p < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline demographic and clinical characteristics, laboratory tests results, and mortality of enrolled patients

319 individuals were retrospectively enrolled in this study. The demographic and clinical characteristics, laboratory test results, and the mortality rate of the enrolled patients during the follow-up period are summarized in Table 1. The median age was 46.5 years (SD ± 12.6), and most patients (87.5 %) were male. Cirrhosis and ascites were present in 190 (59.6%) and 176 (55.2%), respectively (**Table 1**). Among 207 deaths during the follow-up period, 82 patients died within 28 days of follow-up with a mortality rate of 25.7%, and 125 patients died within 90 days of follow-up with a mortality rate of 39.2%.

Table 1
Baseline characteristics, laboratory test results, and outcome of the patients with HBV-ACLF.

Patients characteristics	Patients (n = 319)
Age (years)	46.5 ± 12.6
Gender	
Male	279 (87.5%)
Female	40 (12.5%)
Complications at hospital admission	
Ascites	176 (55.2%)
HE	63 (19.7%)
SPB	42 (13.2%)
Cirrhosis	190 (59.6%)
Laboratory tests	
ALT (IU/L)	237 (97, 603)
AST (IU/L)	180 (104, 383)
ALP(IU/L)	160 ± 62.3
γ-GT (U/L)	104 (68,170)
Tbil (μmol/L)	270.9 ± 155.5
TBA (μmol/L)	192.7 (133.3, 246.2)
INR	2.1 ± 0.9
Serum sodium (mmol/L)	137.1 ± 5.3
Serum potassium (mmol/L)	4.1 ± 0.5
White blood cell ($\times 10^9$/L)	6.14 (4.7, 8.8)
Neutrophil count ($\times 10^9$/L)	3.94 (2.74, 5.85)
Platelet count ($\times 10^9$/L)	117.9 ± 64.4
Prealbumin (mg/L)	64.48 ± 34.33
Albumin (g/L)	31.7 ± 5.1
Serum creatinine (mg/dL)	68 (58, 81)
Scoring systems	
MELD	20.1 ± 7.2
MELD-Na	22.8 ± 10.2
ALBI	−0.79 ± 0.11
Mortality	
28-Day mortality	82 (25.7%)
90-Day mortality	125 (39.2%)

Abbreviations: Note: SBP = Spontaneous bacterial peritonitis; HE = hepatic encephalopathy; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Tbil = total bilirubin; TBA = total bile acids; GGT = gamma-glutamyl transpeptidase; ALP = alkaline phosphatase; INR = international normalized ratio; MELD = Model of End-Stage Liver Disease; MELD-Na = MELD integrating sodium; ALBI = albumin-bilirubin score.

3.2. Univariate and multivariate analysis of factors associated with 28- and 90-day mortality of HBV-ACLF

Univariate analysis revealed that age, HE, alanine aminotransferase (ALT), Tbil, INR, serum sodium, neutrophil, platelet count (PLT), ALB, and serum creatinine levels on Day 1 following hospital admission and HE, Tbil, INR, serum sodium, neutrophil absolute value, PLT, and ALB on Day 7 following hospital admission significantly associated with the 28-day mortality of HBV-ACLF (Table 2). In addition, univariate analysis revealed that age, ALT, Tbil, total bile acids (TBA), INR, serum sodium, neutrophil absolute value, PLT, ALB, serum creatinine levels, and HE at Day 1, and Tbil, INR, and serum sodium levels at Day 7 were significantly associated with the 90-day mortality of HBV-ACLF (Table 3).

The factors identified in the univariate analysis were subsequently used for multivariate Cox proportional-hazards regression analyses to identify independent predictors for the 28- and 90-day mortality of HBV-ACLF. As given in Table 2, age、 HE、Tbil 、INR、neutrophil count and PLT at Day 1 were independently related to the 28-day mortality. In addition, the multivariate revealed that age、Tbil、serum sodium、PLT、ALB and serum creatinine at Day 7 were independently correlated with the 28-day mortality of HBV-ACLF (Table 2). In addition, the multivariate Cox proportional-hazards regression analysis identified the following independent predictors for the 90-day mortality of HBV-ACLF: age、Tbil、serum sodium、PLT、ALB and serum creatinine at Day 1; HE 、Tbil、INR、serum sodium、neutrophil count 、PLT and ALB at Day 7 **(Table 3).**

3.3. Kaplan–Meier survival analysis of HBV-ACLF patients stratified into different categories

Kaplan–Meier survival analysis was performed in HBV-ACLF patients that were stratified into different groups according to serum sodium, ALB, age, Tbil, neutrophil count, and PLT to examine the dynamic changes from Days 1–7 following hospital admission, and the 90-day mortality rates of different groups are shown in Fig. 2. As shown in Fig. 2a the differences in the 90-day mortality were

Table 2
Univariate and multivariate analysis of factors associated with 28-day mortality.

Characteristics	Univariate analysis			Multivariate analysis		
	β	HR (95% CI)	*p*-value	β	HR (95% CI)	*p*-value
Day 1						
Age (years)	0.036	1.036 (1.018, 1.055)	<0.001	0.037	1.036 (1.018, 1.055)	<0.001
Gender (male)	−1.31	0.877 (0.463, 1.659)	0.686			
Complications						
Ascites	0.15	1.162 (0.74, 1.825)	0.514			
HE	1.135	4.434 (2.209, 9.242)	0.025	1.241	2.087 (1.784, 4.186)	0.026
SBP	0.796	2.309 (1.305, 3.996)	0.191			
Cirrhosis	−0.148	0.862 (0.551, 1.349)	0.517			
Laboratory tests						
ALT (IU/L)	−0.001	0.999 (0.998, 1.100)	0.016			
AST (IU/L)	0.000	1.000 (0.999, 1.001)	0.527			
ALP(IU/L)	0.001	1.001 (0.998, 1.004)	0.560			
GGT (U/L)	−0.001	0.999 (0.997, 1.001)	0.175			
Tbil (μmol/L)	0.004	1.004 (1.002, 1.005)	<0.001	0.003	1.003 (1.001, 1.004)	<0.001
TBA (μmol/l)	0.001	1.001 (0.999, 1.003)	0.316			
INR	0.601	1.825 (1.569, 2.122)	<0.001	0.391	1.478 (1.232, 1.774)	<0.001
Serum sodium (mmol/L)	−0.607	0.935 (0.905, 0.967)	<0.001			
Serum potassium (mmol/L)	−0.225	0.798 (0.516, 1.234)	0.311			
White blood cell ($\times 10^9$/L)	0.049	1.051 (0.997, 1.107)	0.066			
Neutrophil count ($\times 10^9$/L)	0.091	1.095 (1.038, 1.157)	<0.001	0.062	1.064 (1.009, 1.123)	0.023
Platelet count ($\times 10^9$/L)	−0.008	0.992 (0.988, 0.996)	<0.001	−0.007	0.993 (0.990, 0.997)	<0.001
Prealbumin (mg/L)	−0.009	0.991 (0.984, 0.999)	0.024			
Albumin (g/L)	−0.070	0.932 (0.889, 0.977)	0.003			
Serum creatinine (mg/dL)	0.008	1.008 (1.005, 1.011)	<0.001			
HBV DNA (log_{10}copies/mL)	0.027	1.022 (0.912, 1.166)	0.545			
Day 7						
HE	0.583	1.792 (1.131, 2.838)	0.013	0.680	1.975 (1.240, 3.144)	0.004
ALT (IU/L)	0.000	1.000 (0.999, 1.001)	0.759			
TBIL (μmol/L)	0.001	1.001 (1.000, 1.001)	<0.001	0.001	1.001 (1.000, 1.001)	0.003
INR	0.454	1.575 (1.421, 1.745)	<0.001	0.504	1.655 (1.459,1.877)	<0.001
Serum sodium (mmol/L)	−0.066	0.936 (0.912, 0.961)	<0.001	−0.061	0.941 (0.915, 0.968)	<0.001
White blood cell ($\times 10^9$/L)	−0.001	0.999 (0.993, 1.005)	0.745			
Neutrophil count ($\times 10^9$/L)	0.063	1.065 (1.031, 1.100)	<0.001			
Platelet count ($\times 10^9$/L)	−0.009	0.991 (0.987, 0.995)	<0.001			
Prealbumin (mg/L)	−0.008	0.992 (0.985, 0.998)	0.015			
Albumin (g/L)	−0.068	0.934 (0.891, 0.979)	0.005			
Serum creatinine (mg/dL)	0.005	1.005 (1.002, 1.007)	<0.001	0.009	1.003 (1.001, 1.006)	0.009

Abbreviations: Note: HR = Hazard ratio; 95% CI = 95% confidence interval; HE = hepatic encephalopathy; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Tbil = total bilirubin; TBA = total bile acids; GGT = gamma-glutamyl transpeptidase; ALP = alkaline phosphatase; INR = international normalized ratio; MELD = Model of End-Stage Liver Disease; MELD-Na = MELD integrating sodium; ALBI = albumin-bilirubin score.

Table 3
Univariate and multivariate analysis of 90-day mortality of patients.

Characteristics	Univariate analysis			Multivariate analysis		
	β	HR (95% CI)	*p*-value	β	HR (95% CI)	*p*-value
Day 1						
Age (years)	0.029	1.029 (1.014, 1.044)	<0.001	0.023	1.023 (1.007, 1.039)	<0.005
Gender (male)	−0.019	0.981 (0.580, 1.659)	0.943			
Complications						
Ascites	0.354	1.425 (0.990, 2.052)	0.057			
HE	0.453	1.573 (0.929, 2.664)	0.092			
SBP	0.678	1.205 (0.655, 2.597)	0.191			
Cirrhosis	0.056	1.057 (0.737, 1.518)	0.762			
Laboratory tests						
ALT (IU/L)	−0.001	0.999 (0.998, 1.000)	<0.001			
AST (IU/L)	0.000	1.000 (0.999, 1.000)	0.252			
ALP(IU/L)	0.001	1.001 (0.998, 1.003)	0.625			
GGT (U/L)	−0.001	0.999 (0.998, 1.001)	0.371			
Tbil (μmol/L)	0.004	1.004 (1.003, 1.005)	<0.001	0.003	1.004 (1.002, 1.005)	<0.001
TBA (μmol/L	0.002	1.002 (1.000, 1.003)	0.025			
INR	0.601	1.825 (1.569, 2.122)	<0.001			
Serum sodium (mmol/L)	−0.070	0.932 (0.908,0.957)	<0.001	−0.043	0.957 (0.929, 0.986)	0.004
Serum potassium (mmol/l)	−0.256	0.774 (0.545, 1.099)	0.153			
White blood cell ($\times 10^9$/L)	0.065	1.068 (1.025, 1.112)	0.066			
Neutrophil count ($\times 10^9$/L)	0.103	1.109 (1.062, 1.158)	<0.001	0.068	1.070 (1.022, 1120)	0.004
Platelet count ($\times 10^9$/L)	−0.009	0.991 (0.988, 0.995)	<0.001	−0.008	0.992 (0.988, 0.996)	<0.001
Prealbumin (mg/L)	−0.007	0.993 (0.987, 0.998)	0.014			
Albumin (g/L)	−0.077	0.926 (0.892, 0.961)	<0.001	−0.053	0.949 (0.911, 0.988)	0.011
Serum creatinine (mg/dL)	0.007	1.007 (1.004, 1.010)	<0.001	0.005	1.005 (1.001, 1.008)	0.011
HBV DNA (log_{10}copies/mL)	−0.462	0.682 (0.458, 0.876)	0.545			
Day 7						
HE	0.529	1.697 (1.148, 2.507)	0.008	0.580	1.787 (1.182, 2.701)	0.006
ALT (IU/L)	0.000	1.000 (0.999, 1.001)	0.431			
TBIL (μmol/L)	0.001	1.001 (1.001,1.001)	<0.001	0.001	1.001 (1.000, 1.001)	<0.001
TBA (μmol/L)	0.001	1.001 (1.000, 1.003)	0.067			
INR	0.495	1.641 (1.501, 1.794)	<0.001	0.463	1.589 (1.415, 1.784)	<0.001
Serum sodium (mmol/L)	−0.063	0.939 (0.918, 0.960)	<0.001	−0.045	0.956 (0.932 , 0.983)	<0.001
Neutrophil count ($\times 10^9$/L)	0.079	1.082 (1.055, 1.110)	<0.001	0.036	1.037 (1.006, 1.069)	0.019
Platelet count ($\times 10^9$/L)	−0.010	0.990 (0.987, 0.993)	<0.001	−0.005	0.995 (0.991, 0.998)	0.002
Prealbumin (mg/L)	−0.010	0.990 (0.984,0.995)	<0.001			
Albumin (g/L)	−0.083	0.920 (0.884, 0.957)	<0.001	−0.071	0.932 (0.895, 0.971)	<0.001
Serum creatinine (mg/L	0.005	1.005 (1.003, 1.007)	<0.001			

Abbreviations:Note: HR = Hazard ratio; 95% CI = 95% confidence interval; HE = hepatic encephalopathy; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Tbil = total bilirubin; TBA = total bile acids; GGT = gamma-glutamyl transpeptidase; ALP = alkaline phosphatase; INR = international normalized ratio; MELD = Model of End-Stage Liver Disease; MELD-Na = MELD integrating sodium; ALBI = albumin-bilirubin score.

statistically significant in the four groups of HBV-ACLF patients following stratification by serum sodium ($\chi^2 = 17.9$, $p < 0.001$). In particular, the 90-day mortality in the Na-1 group (hyponatremia at Days 1 and 7) was 73%, significantly higher than those in the remaining groups ($p < 0.05$). There was no significant difference in the 90-day mortality between the Na-2 and Na-3 groups.

When the HBV-ACLF patients had been stratified based on albumin levels, the differences in the 90-day mortality were statistically significant in the four groups ($\chi^2 = 18.2$, $p < 0.001$) [Fig. 2b]. The 90-day mortality was 59.4% in the ALB-1 group (hypoproteinemia at Days 1 and 7 following hospital admission), significantly increased compared with those in the remaining groups ($p < 0.05$), and there was no significant difference in the 90-day mortality observed between the ALB-2 and ALB-3 groups.

As shown in Fig. 2d, the HBV-ACLF patients were divided into four groups according to their Tbil levels, and the difference in the 90-day mortality between the four groups was statistically significant ($\chi^2 = 50.3$, $p < 0.001$). Of note, the 90-day mortality in the Tbil-1 group (Day 7 following hospital admission, Tbil levels increased by >20% compared with the levels at Day 1), was 49.1%, significantly higher than in the remaining groups ($p < 0.05$). The 90-mortality in the Tbil-4 group (Day 7 following hospital admission, Tbil levels increased by >20% compared with the levels at Day 1) was 2.4%, significantly lower than in the remaining groups ($p < 0.05$). The mortality in the Tbil-2 group was significantly higher than in the Tbil-3 group (decreased by 20% within 7 days of hospital admission, $p < 0.05$).

As shown in Fig. 2 (c, e, and f), the differences in the 90-day mortality were not statistically significant in the groups of the HBV-ACLF patients when they had been stratified into categories according to age, neutrophil count, and PLT ($p > 0.05$).

3.4. Construction and validation of days 1 and 7 prediction models for 28- and 90-day morality of HBV-ACLF

After extensive model fitting and variable selection, the predictors that included age, HE, Tbil, serum sodium, neutrophil, PLT, ALB, and creatinine were used to construct the Day 1 prediction model for 28- and 90-day mortality of HBV-ACLF. Due to the additional

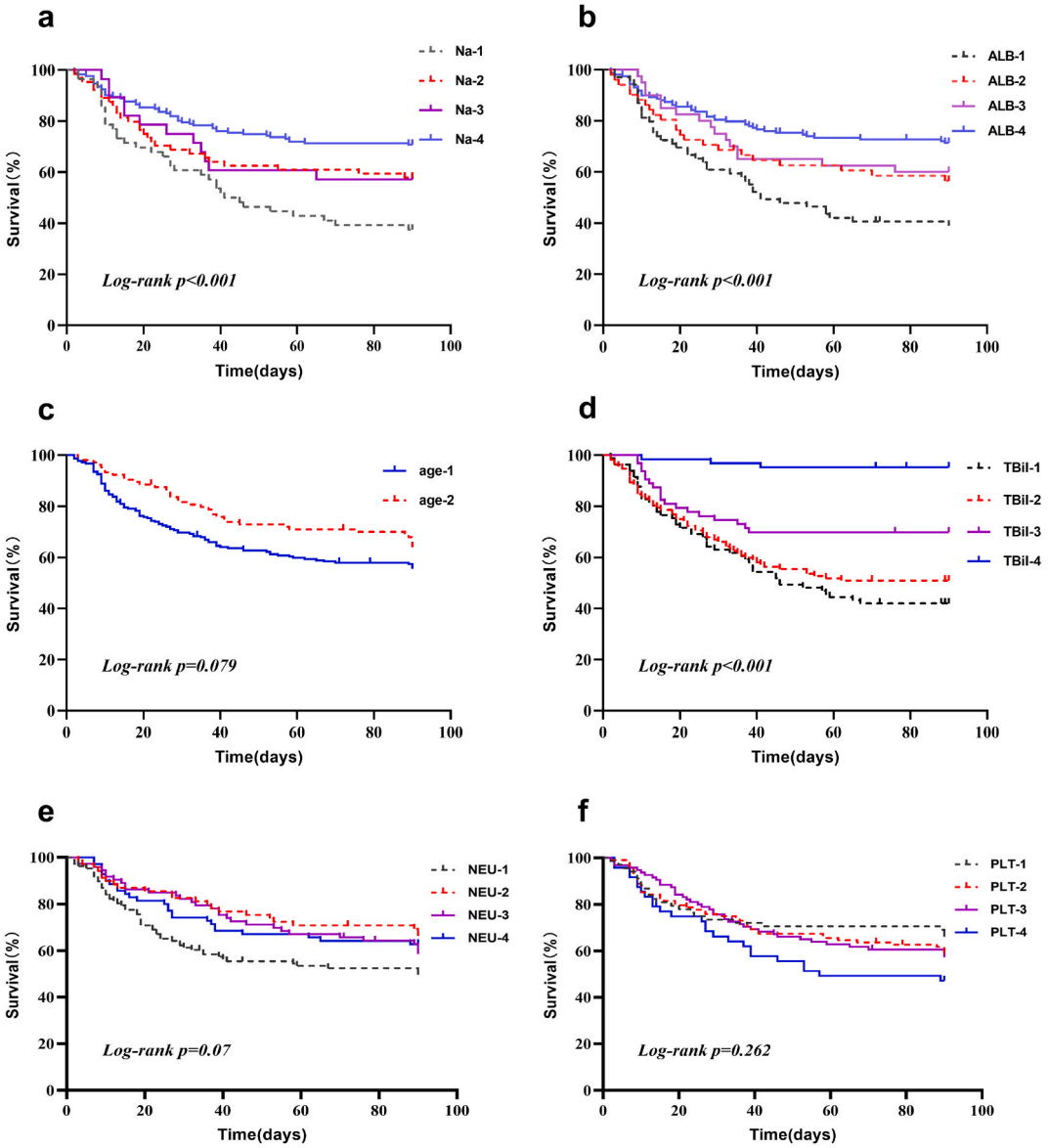

Fig. 2. Kaplan–Meier survival analysis of HBV-ACLF patients stratified into different groups. Laboratory tests data were assessed on Days 1 and 7 following hospital admission. The patients were stratified into different groups according to the following definitions: **(a)** Na-1, hyponatremia present at Days 1 and 7, Na-2 present at Day 1 but not Day 7, Na-3 absent at Day 1 but present at Day 7, Na-4 absent at Days 1 and 7; **(b)** ALB-1, hypoproteinemia present at Days 1 and 7; **(c)** age one ≥40 years, age two < 40 years; **(d)** Tbil-1 increased >20% within 7 days; Tbil-2, increased <20% within 7 days; Tbil-3, decreased <20% within 7 days; Tbil-4 decreased >20% within 7 days; **(e)** HBV-ACLF patients were stratified into four categories: NEU-1, NEU-2, NEU-3, and NEU-4; **(f)** HBV-ACLF patients were stratified into four categories: PLT-1, PLET-2, PLT-3, and PLT-4. APASL = Asia-Pacific Association for the Study of the Liver; Na = serum sodium; NEU = Neutrophil count; ALB = albumin; PLT = platelet count; Hyponatremia was defined by a Na <130 mmol/L; Hypoproteinemia was defined by a ALB <30 g/L).

changes across all the variables between Days 1 and 7, and following a backward stepwise variable selection, the changes in age, HE, Tbil, serum sodium, neutrophil, and PLT were identified as significantly associated with survival of the patients. Based on the variables identified at Day 1 and the five variables that significantly altered between Days 1 and 7 following hospital admission, a dynamic Day 7 prediction model was further developed.

The performance of the Days 1 and 7 prediction models was evaluated using ROC curves. As shown in Fig. 3, the AUC predicted the 28-day and 90-day mortality risk for HBV-ACLF patients. The Day 1 model's predictive accuracy for 28-day and 90-day mortality was (AUC 0.787，95% CI：0.703–0.845) and (AUC 0.836，95% CI：0.791–0.880), respectively. The Day 7 model's predictive accuracy for 28-day and 90-day mortality was (AUC 0.895，95% CI：0.858–0.932) and (AUC 0.871，95% CI：0.834–0.909). The AUC of both models were >0.7, which suggested a good potential to predict HBV-ACLF.

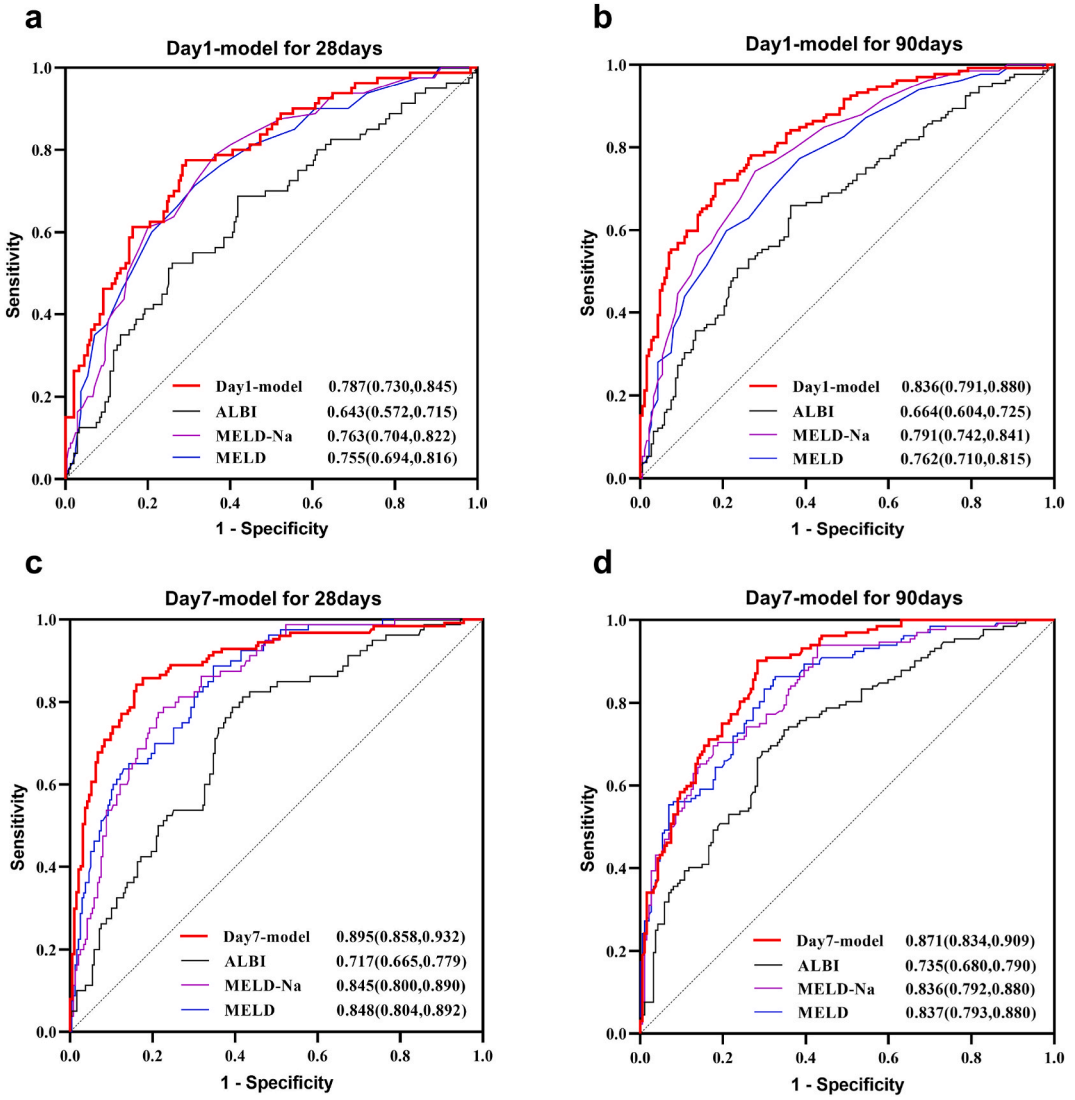

Fig. 3. ROC curves for novel prognostic models compared with MELD, MELD-Na, and ALBI
(a-b) was ROC curves for Days 1 prognostic models compared with MELD, MELD-Na, and ALBI to predict 28-and 90-day mortality of patients with HBV-ACLF. **(c-d)** was ROC curves for Days 7 prognostic models compared with MELD, MELD-Na, and ALBI to predict 28-and 90-day mortality of patients with HBV-ACLF. The AUC was used to estimate the predictive performance of different models.

Table 4
Discrimination ability of Days 1 and 7 predictive models compared with MELD, MELD-Na, and MELD-ALBI scoring systems.

	28-day mortality		90-day mortality	
	z-value	*p*-value versus Day 1 model	*z*-value	*p*-value versus Day 1 model
Day 1 model				
MELD	0.975	0.329	2.762	0.006
MELD-Na	0.813	0.416	2.007	0.039
ALBI	3.315	<0.001	5.289	<0.001
Day 7-model				
MELD	2.356	0.018	1.968	0.043
MELD-Na	2.389	0.008	1.963	0.045
ALBI	4.823	<0.001	4.201	<0.001

Note: Days 1 l and 7 models showed a significantly higher predictive ability compared with the other scoring systems when predicting 90-day mortality.

3.5. The performance of days 1 and 7 prognostic models for 28- and 90-day morality of HBV-ACLF

Delong's test was used to compare the predictive performance of the new Days 1 and 7 prognostic models with the existing MELD, MELD-Na, and ALBI scoring systems. For 28-day mortality, the predictive accuracy of the Day 1 prognostic model (AUC, 0.787) was significantly higher than that of the ALBI model ($p < 0.001$), and compared with the MELD and MELD-Na models, the difference was not statistically significant (Fig. 3a–Table 4). The predictive accuracy of the Day 7 prognostic model (AUC, 0.895) was significantly greater than that of the MELD, MELD-Na, and ALBI scoring systems ($p < 0.05$) (Fig. 3c–Table 4). Of note, the Days 1 and 7 prognostic models had AUCs of 0.836 and 0.871, respectively, which were significantly higher than those of the MELD, MELD-Na and ALBI models to predict 90-day mortality (both models $p < 0.05$) (Fig. 3b and d, Table 4).

4. Discussion

The major findings of this study were summarized as follows: (1) univariate and multivariate analyses revealed significant risk factors at Days 1 and 7 that were associated with the mortality of HBV-ALCF patients; (2) the Days 1 and 7 prognostic models for HBV-ACLF were established based on the dynamic changes of significant and clinical important factors; (3) the Day 1 prognostic model exhibited significantly higher performance than that of the existing ALBI scoring system to predict 28-day mortality of HBV-ACLF patients; and (4) the predictive accuracy of the Day 1 prognostic model and Day 7 prognostic model was significantly greater than that of MELD, MELD-Na, and ALBI prognostic scoring systems to predict 90-day mortality of HBV-ACLF patients. These findings suggested that the Days 1 and 7 prognostic models performed better when predicting the short-term mortality of patients with HBV-ACLF.

The last two decades have witnessed the development of prognostic models for the evaluation of the prognosis and treatment options of patients with liver failure or hepatic insufficiency. The CTP, MELD, and MELD-Na scoring systems are mainly used to evaluate the liver function in patients with liver cirrhosis [12–14]. However, it was noted that the predictive performance of these existing models was limited in patients with ACLF. The ALBI scoring system, which is based on serum albumin and bilirubin in combination, was first used to evaluate the survival of patients with liver cancer [15,16]. Recently, it has been applied to ACLF. Previous research has suggested that the ALBI scoring system is more accurate than the Child-Pugh or MELD scoring system to predict the long-term survival of patients with HBV-related liver cirrhosis [17]. The CLIF-C ACLF score is an internationally recognized prognostic model and the predictive accuracy has been verified in several studies [18]. It can be used to evaluate patients with ACLF who meet the EASL-CLIF criteria for alcoholic liver disease, Hepatitis C, and Hepatitis B, among other causes. HBV reactivation is the most common cause of ACLF in the Asia-Pacific region [19]. However, whether the prognosis model based on the Western diagnostic criteria is suitable for patients with ACLF based on Eastern criteria needs to be verified, because there are differences in the causes of ACLF between the regions, as well as different definitions and diagnostic criteria.

To date, some prognostic models for HBV-ACLF have been proposed. For example [20], combined the neutrophil to lymphocyte ratio, INR, age, and Tbil to construct a predictive model for the 90-day mortality of HBV-ACLF, which showed better predictive values than the MELD, MELD-Na, and CTP models. In addition, in a multicenter large sample prospective clinical study carried out in China [21]. analyzed the clinical data from 1322 hospitalized patients with acutely decompensated cirrhosis and CHB-related liver injury in 13 different liver disease centers and combined this information with INR, SOFA score, age, Tbil, and other factors, to construct a new prognostic model known as the COSSH-ACLFs model.

In this study, the period between Days 1 and 7 following hospital admission was considered the most serious time for HBV-ACLF patient's condition, and the dynamic changes in the clinical characteristics and indicators at Days 1 and 7 were collected and analyzed. Through the dynamic changes observed in each index within the first 7 days of hospital admission, the single dynamic factors that influenced the short-term mortality of the patients were determined. Then, the variables that demonstrated a statistically significant difference were used in the model directly. The dynamic changes in serum sodium, albumin, and Tbil during the first week of hospital admission were significantly correlated with 90-day mortality. In addition, previous research has suggested that independent of the MELD score, hyponatremia was a good predictor for survival for end-stage liver disease and that the improvement of hyponatremia might improve the survival rate of ACLF patients [22–24]. The conclusions of this study are basically consistent with above study.

It is noted in this study that the predictive performance of the Day 1 prognostic model was significantly higher than that of the ALBI model, but there was no significant difference with the MELD and MELD-Na prognostic scoring systems. The prediction performance of the Day 7 prognostic model was significantly higher than that of the ALBI, MELD, and MELD-Na scoring systems. When predicting 90-day mortality, the Days 1 and 7 prognostic models were significantly better than the MELD, MELD-Na, and ALBI models. The above study reinforces the importance of early changes in indicators for long-term disease prediction.

This study has some limitations including: (1) the retrospective nature of this study, including potential bias in patient enrolment, and incomplete clinical information; (2) some indicators, such as HBsAg and hepatitis B e-antigen (HBeAg), were not included in this study due to the high deletion rate; (3) the patients in this study were recruited from a single centre, which might have an impact on the accuracy of the scoring system. Therefore, a multicenter, prospective study, which involves more patients for a longer follow-up period is required to verify these results in this study. (4) in addition, differences in diagnosis and possible laboratory errors are also inevitable.

5. Conclusions

Days 1 and 7 prognostic models were established to predict 28- and 90-day mortality in HBV-ACLF patients. Both models performed

better when predicting short-term mortality compared with traditional scoring systems. The new prognostic models could be improved tools to help in the early and rapid prognostic prediction of HBV-ACLF patients; therefore, clinical interventions or liver transplantation could be carried out to reduce mortality and improve clinical outcomes.

Ethics approval and consent to participate

The study protocol complied with the ethical guidelines of the Declaration of Helsinki, and was approved by the Ethics Committee of Shanghai Changhai Hospital (CHEC2009-139).

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

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CRediT authorship contribution statement

Wenhan Fan: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Wei Liao:** Validation, Data curation. **Shengjun Jiang:** Validation, Data curation. **Yi Chen:** Investigation, Data curation. **Chengzhong Li:** Writing – review & editing, Validation. **Xuesong Liang:** Writing – review & editing, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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