scientific reports

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Nomograms for predicting short-term mortality in acute-on-chronic liver disease caused by the combination of hepatitis B virus and alcohol

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This study aimed to identify predictive factors for the prognosis of acute-on-chronic liver disease (AoCLD) due to both hepatitis B virus (HBV) and alcohol and to develop prognostic models to improve treatment management. AoCLD patients with HBV and alcohol as etiological factors were selected from two multicenter prospective cohorts (NCT02457637,NCT03641872) and included in separate training and validation cohorts ($n=180$ and $n=148$). In the training cohort, the CATCH-LIFE A nomogram (based on age, bilirubin, international normalized ratio, serum sodium, and hepatic encephalopathy score) and CATCH-LIFE B nomogram (based on age, bilirubin, international normalized ratio, serum albumin, white blood cell, platelet count, and hepatic encephalopathy score) had discriminatory ability for predicting 28-day (c-indexes of 0.910 and 0.899) and 90-day mortality (c-indexes of 0.878 and 0.887, respectively). The area under the curve values for 28-day and 90-day mortality prediction by the CATCH-LIFE A nomogram were 0.922 (95% CI : 0.874, 0.971) and 0.905 (0.856, 0.956), respectively, while those for the CATCH-LIFE B nomogram were 0.916(0.861,0.972) and 0.915 (0.866,0.964), respectively. Similar performance results were observed in the validation cohort. Optimal cut-off scores for each nomogram could be used for patient stratification in high- and low-risk groups, and the high-risk groups showed shorter survival times than the low-risk groups in both the training and validation cohorts. Two nomograms constructed from the first short-term follow-up data from patients with AoCLD due to combined HBV infection and alcohol exposure showed good predictive performance for 28-day and 90-day mortality and might be used to guide clinical management.

Keywords HBV infection, Alcohol-related liver disease, Nomogram, Prospective cohort, Transplant free survival

Abbreviations

AoCLD	Acute-on-chronic liver disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
ACLF	Acute-on-chronic liver failure
AD	Acute decompensation
EASL	European Association for the Study of the Liver
HDV	Hepatitis D virus
HEV	Hepatitis E virus
ALT	Alanine aminotransferase

AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
HGB	Hemoglobin
WBC	White blood cell count
NLR	Neutrophil lymphocyte ratio
TB	Total bilirubin
INR	International normalized ratio
Cr	Creatinine
HE	Hepatic encephalopathy
FIB4	Fibrosis index based on four factors
K	Kalium
Na	Serum sodium
NPV	Negative predictive value
PPV	Positive predictive value
LT	Liver transplant
LASSO	Least absolute shrinkage and selection operator

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Hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and alcohol-related liver impairment are the three main causes of chronic liver disease worldwide. China has the world's largest burden of HBV infection[1,2]. Although the incidence of acute HBV infection and has decreased significantly, that of HBV-related chronic diseases has remained stable in recent years[3]. Approximately 80% of cirrhosis cases in China are caused by HBV infection[4]. During more than 20 years from 2005 to 2016, China exhibits a significant increase in alcohol consumption, from annual 4.5 L per capita in 2005 to annual 7.2 L per capita in 2016. In 2016, about 68.6% of men and 42.6% of women reported drinking alcohol and 22.7% of Chinese (aged 15 + years) had engaged in heavy episodic drinking in 2016[5,6]. Although the decline in alcohol-attributable disease burden in China is linked to a reduction in alcohol-related harm in recent years[7]. However, a large number of early drinkers have already developed alcoholic liver disease, and quitting remains challenging for this population. The large number of HBV-infected individuals in China, combined with the prevalence of alcoholic liver disease implies that a notable percentage of chronic liver disease cases among Chinese patients could be related to the combination of HBV infection and alcohol intake. A previous study reported that 7.2% of liver cirrhosis cases in China are caused by a combination of HBV and alcohol, which is close to the proportion due to alcoholic cirrhosis (7.4%) and much higher than the proportion caused by hepatitis C alone (3.1%). The same study also observed exacerbation of liver impairment and an increase in the frequency of liver cirrhosis complications among patients with both alcohol-related liver disease (ALD) and viral hepatitis[4]. This situation may be due to synergistic effects of alcohol consumption and viral hepatitis on the progression of chronic liver disease[8,9].

Despite being a major health concern in China, chronic liver disease caused by the combination of HBV infection and alcohol intake has received little attention in both clinical research as well as basic medical research. To date, the mechanisms underlying the interaction of alcohol with hepatitis B remain incompletely understood. In addition, the clinical characteristics and outcomes of such cases with complex etiologies have not been accurately described. Specifically, research related to the prediction of disease progression and adverse prognosis is particularly lacking for acute-on-chronic liver disease (AoCLD) caused by a combination of HBV infection and alcohol exposure. Therefore, there is an urgent need to understand the prognostic factors for AoCLD caused by the combination of HBV infection and alcohol intake. At present, some scores, such as the Model for End-stage Liver Disease (MELD)[10], MELD-sodium score (MELD-Na)[11] and MELD 3.0[12] scores, have

been used for prognosis prediction in patients with end-stage liver disease caused by either hepatitis B or ALD. However, no research has been conducted to verify the effectiveness of these scores for end-stage liver disease with complex causes such as the combination of hepatitis B and alcohol, and no scoring system specifically tailored for these patients has been developed.

To investigate the clinical features of AoCLD due to both HBV infection and alcohol exposure and to generate an effective prognostic model for end-stage liver disease resulting from this combination, we performed a prospective cohort study among patients with AoCLD who participated in the CATCH-LIFE study established by the Chinese Chronic Liver Failure Consortium from January 2015 to December 2016 ($n=2,600$)[13] and from July 2018 to January 2019 ($n=1,370$)[14]. The objectives of this study were to identify factors that predict a poor prognosis of AoCLD caused by a combination of hepatitis B virus infection and alcohol consumption and to develop a simple prognostic nomogram for the accurate prediction of outcomes in these patients.

Patients and methods

Study design

The study population was sourced from two large multicenter, prospective Chinese cohorts (the CATCH-LIFE training and validation study cohorts). The detailed characteristics of the cohort have been reported previously[13, 14]. Briefly, 2,600 and 1,370 patients with cirrhosis or other chronic liver diseases hospitalized for acute decompensation (AD) and/or acute liver injury were consecutively included in the training and validation cohorts, respectively. The CATCH-LIFE cohort population was enrolled from 15 centers across 13 different provinces (Shanghai, Beijing, Tianjin, Chongqing, Hunan, Hubei, Guangdong, Zhejiang, Shandong, Jilin, Henan, Fujian, and Xinjiang). The distribution of the centers closely reflects the population distribution in China. All participating hospitals used uniform methods and standards to select cases. The study protocol and informed consent form were approved by the Ethics Committee of Renji Hospital (lead center of the CATCH-LIFE study), Shanghai Jiaotong University School of Medicine [Approval No. (2014) 148 k and (2016) 142 k]. The CATCH-LIFE study is registered at www.clinicaltrials.org (NCT02457637, NCT03641872). Written informed consent for participation in the trial was obtained from all enrolled patients. All work involving patient data was carried out in accordance with the Declaration of Helsinki. All enrolled patients received reasonable and sufficient treatment during their hospitalization at third-level grade-A hospitals; these are the highest-level hospitals in China and can ensure that patients receive homogeneous and reasonable treatment.

The AoCLD patients included in the study had chronic liver disease due to various etiologies, including cirrhotic and non-cirrhotic chronic liver disease, and experienced an exacerbation requiring hospitalization. The inclusion criteria for the CATCH-LIFE cohorts were: (1) chronic liver disease with or without cirrhosis, including chronic viral hepatitis, ALD, nonalcoholic fatty liver disease, autoimmune liver disease, metabolic liver disease, and chronic drug-induced liver disease, with a duration of underlying non-cirrhotic chronic liver disease lasing > 6 months; (2) acute liver injury, as indicated by a serum alanine aminotransferase (ALT) or aspartate transaminase (AST) level exceeding 3× the upper limit of normal (ULN) or a total bilirubin (TB) concentration > 2 mg/dL within 1 week before recruitment, or AD, as indicated by hepatic encephalopathy, ascites, gastrointestinal bleeding, or bacterial infection within 1 month before recruitment; and (3) hospitalization or admission under emergency observation for > 24 h. Patients who met any of the following criteria were excluded: (i) age > 80 years; (ii) pregnancy; (iii) malignancy of liver or another organ (including leukemia); (iv) chronic obstructive pulmonary disease of level IV severity; (v) New York Heart Association (NYHA) Functional Class of ≥ 3; (vi) myocardial infarction within 3 months before admission; (vii) diabetes with severe complications; (viii) chronic kidney disease with end-stage renal failure; (ix) treatment with immunosuppressive agents for non-hepatic diseases; or (x) the following causes of liver disease: concomitant HCV infection, hepatitis D virus infection, hepatitis E virus infection, primary biliary cirrhosis, autoimmune hepatitis, schistosomiasis, nonalcoholic fatty disease, chronic drug-induced liver disease, metabolic liver disease, or cryptogenic liver disease. Outcomes, including the main outcome of transplant-free (LT free) mortality, were assessed at 28 and 90 days after diagnosis. Patients who underwent liver transplantation (LT) and those who were lost to follow-up were considered censored. All patients were followed longer than 12 months.

Patients

For the present study, we selected patients from the CATCH-LIFE cohorts with AoCLD clearly caused by a combination of HBV infection and alcohol intake. The etiological diagnosis was based on the diagnostic criteria used for chronic HBV infection and ALD. Chronic HBV infection was defined by positive serum HBsAg test results for > 6 months or a positive HBsAg test result and chronic liver disease proven by biopsy. ALD was diagnosed based on a chronic drinking habit (males > 40 g/day, females > 20 g/day, drinking period > 5 years) or history of heavy drinking within 2 weeks (> 80 g/day) and meeting the requirements for imaging and laboratory evidence of alcohol-related liver disease (e.g., ALT/AST levels > 2×ULN, elevated gamma-glutamyl transferase [GGT] level, and elevated mean corpuscular volume [MCV]). AoCLD cases that met the diagnostic criteria for chronic HBV infection and ALD simultaneously were considered as having a combined causation of HBV and alcohol.

Definitions of related conditions and events

The diagnosis of cirrhosis was based on relevant computed tomography/magnetic resonance imaging findings, laboratory test results, clinical symptoms, and a history of liver disease. The diagnosis of decompensated cirrhosis was made if a patient had a history of at least one decompensation event, such as gastrointestinal hemorrhage, hepatic encephalopathy, overt ascites, and bacterial infection (e.g., spontaneous peritonitis and pneumonia), before enrollment or at baseline. Organ failure was assessed according to the European Association for the Study of Liver-Chronic Liver Failure-Sequential Organ Failure Assessment (EASL-CLIF-SOFA) classification

system[15]. Kidney failure was defined by a serum creatinine level ≥ 2.0 mg/dL or use of renal replacement therapy. Cerebral failure was defined by grade III or IV hepatic encephalopathy according to the West Haven classification. Coagulation failure was defined by an international normalized ratio (INR) > 2.5 and/or platelet count ≤ 20×10^9/L. Circulatory failure was defined by the use of vasoactive agents (dopamine, dobutamine, etc.). Respiratory failure was defined by partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio ≤ 200 (analogous to a SOFA score of 10) or an oxygen saturation (SpO_2) to FiO_2 ratio ≤ 200.

Statistical analyses

The normality of the distribution of continuous variables was assessed using the Shapiro test. Normally distributed and non-normally distributed continuous data are presented as mean ± standard deviation and median (inter quartile range), respectively. Categorical data are presented as frequency (percentage). Comparisons between two groups were performed using the Student *t* test, Mann–Whitney U test, Chi-squared test, or Fisher exact test. Univariate Cox regression analysis was performed to estimate the effects of factors on death. Factors potentially influencing 28-day or 90-day mortality were identified through Least Absolute Shrinkage and Selection Operator (LASSO) regression and multivariate backward step-wise Cox regression. We used two approaches to build nomograms. With the first method, only the variables selected by LASSO regression (lambda. 1se) and variables identified and considered by physicians as relevant indicators were included to construct the CATCH-LIFE A nomogram via Cox regression. With the second method, independent factors related to 90-day mortality on both LASSO regression (lambda.min) and multivariate stepwise Cox regression were used to construct the CATCH-LIFE B nomogram.

Nomogram performance was assessed and validated by time-dependent receiver operating characteristic (ROC) curve, C-index value, and calibration curve analyses in both the training and validation cohorts. The calibration curves were generated using a 500 bootstrapped sample. Patients were divided into high-risk and low-risk groups according to the optimal cutoff value determined by the "surv_cutpoint" function. A Kaplan–Meier plot was constructed to illustrate the time to survival change for patients in different risk categories. Comparisons between survival curves were made using the log-rank test. For all statistical analyses, two-tailed *P* values < 0.05 were considered indicative of statistical significance. Data handling and analysis were performed with R 4.3 (http://www.r-project.org/).

Results

Patients and clinical characteristics

The flow chart of the patient selection process for this study is presented in Fig. 1. For the training and validation cohorts, respectively, totals of 2,600 and 1,370 patients with cirrhosis or other chronic liver diseases hospitalized for AD and/or acute liver injury were screened. According to the inclusion criteria of AoCLD caused by a combination of HBV and alcohol exposure, rather than either condition alone with any other cause, 184 patients were enrolled in the training cohort, and 150 patients were enrolled in the validation cohort. After exclusion due to laboratory test results, the final totals were the training and validation cohorts were 180 and 148 patients, respectively.

The baseline characteristics of the patients enrolled in the training and validation cohorts are compared in Table 1. Compared with the training cohort, the validation cohort included a lower proportion of patients with ascites ($P < 0.001$), infection ($P = 0.002$) and had a higher mean CLIF-SOFA score ($P = 0.013$). No other characteristics differed significantly between the two cohorts.With respect to outcomes, of the 180 patients in training cohort, 19 patients died and 5 patients underwent LT within 28 days, and by 90 days, 35 patients had died and 6 patients had undergone LT. Of the 148 patients in the validation cohort, 13 patients died and 2 patients underwent LT within 28 days, and by 90 days, these totals had increased to 17 patient deaths and 6 cases treated with LT. The LT-free mortality rates at 28, 90, and 365 days were similar between the training and validation cohorts (28/90/365 days: 10.9%/20.1%/24.2% in the training cohort vs. 8.9%/12.0%/14.8% in the validation cohort, all $P > 0.05$; Fig. 1). All references to 28-day and 90-day mortality below represent LT-free mortality at the respective time points.

Prognostic factors associated with AoCLD-related short-term mortality in patients with AoCLD caused by the combination of HBV and alcohol

On univariate analysis, the following factors were significantly higher for patients who died within 28 days after diagnosis than in those who survived beyond 28 days after diagnosis: age, white blood cell (WBC) count, neutrophil to lymphocyte ratio (NLR), total bilirubin (TB) concentration, INR, creatinine (Cr) level, blood urea nitrogen (BUN) level, hepatic encephalopathy (HE) score, and the proportions of patients with infection, renal failure, liver failure, or coagulation failure. However, the serum albumin (ALB) and serum sodium (Na) levels were significantly lower in patients who died within 28 days from diagnosis than in those who survived beyond 28 days. Seven factors (age, INR, TB, BUN, WBC count, Na and HE score) were selected by LASSO regression (lambda.min). After multivariate correction with Cox step-wise regression, the following factors were found to be independently associated with 28-day mortality: age (hazard ratio [HR] = 1.071 [95% confidence interval (CI) 1.025,1.118], $P = 0.002$), TB concentration (HR = 1.046 [1.002, 1.093], $P = 0.039$), INR (HR = 1.810 [1.303, 2.515], $P < 0.001$), WBC count (HR = 1.166 [1.058, 1.284], $P = 0.002$), and HE score (HR = 1.791 [1.033, 3.103], $P = 0.038$) (Supp Table 1).

Two approaches were used to identify prognostic factors associated with 90-day mortality in AoCLD patients caused by a combination of HBV infection and alcohol exposure. First, LASSO regression was applied to reduce the data dimensionality in order to avoid potential collinearity and overfitting among variables. The best lambda value was selected from LASSO regression using 10-fold cross-validation. Under the lambda compression (lambda.1se), four variables (INR, TB concentration, HE score, and serum sodium level) were

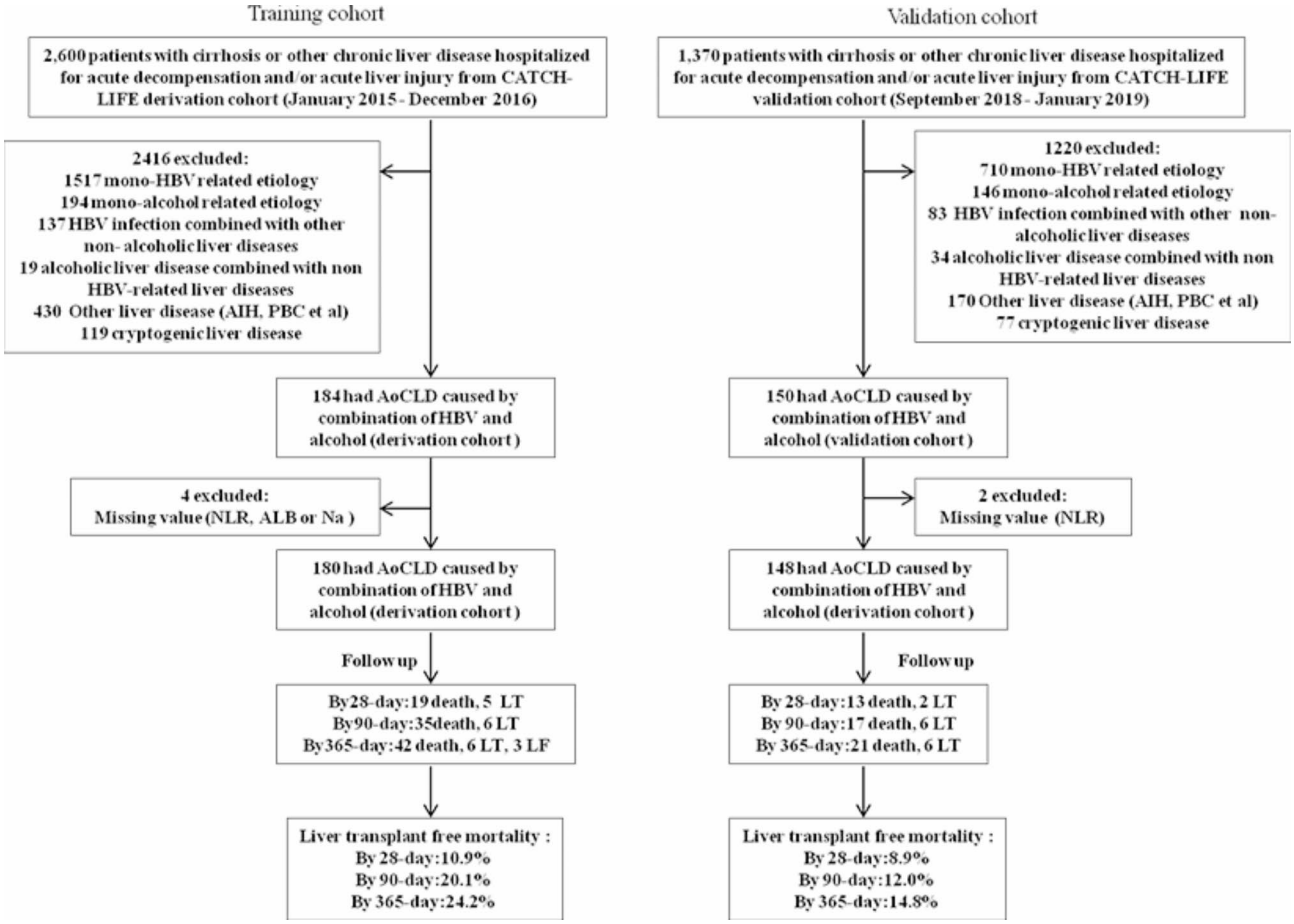

Fig. 1. Flow chart of the inclusion process and clinical outcomes among patients with AoCLD patients caused by a combination of HBV and alcohol were enrolled in the training and validation cohorts. AoCLD, acute-on-chronic liver disease; AIH, autoimmune hepatitis; PBC, primary biliary cholangitis; HBV, Hepatitis B virus; NLR, neutrophil lymphocyte ratio; ALB, albumin; Na, Serum sodium; LT, liver transplantation; LF, lost to follow-up.

found to be independently associated with 90-day mortality. Considering the close relationship between age and liver regeneration and related diseases, age was added to the four selected factors above, and the following data regarding the relationships between these five factors and 90-day mortality were obtained through multiple factor Cox regression and included in model A: age (HR = 1.051 [1.015, 1.088], $P = 0.005$), TB concentration (HR = 1.059 [1.028, 1.091], $P < 0.001$), INR (HR] = 1.698 [1.294, 2.228], $P < 0.001$), serum sodium level (HR = 0.925 [0.882, 0.969], $P = 0.001$), and HE score (HR = 1.877 [1.260, 2.797], $P = 0.002$).

In the second approach employing univariate analysis and LASSO regression (lambda.min) identified 10 factors (age, ALB level, Platelet count, INR, TB concentration, BUN level, HE score, serum sodium level, WBC count, and decompensated cirrhosis) associated with 90-day mortality in patients with AoCLD caused by a combination of HBV and alcohol. After multivariate correction using Cox step-wise regression for these variables, the following factors were found to be independently associated with 90-day mortality and included in model B: age (HR = 1.048 [1.013, 1.084], $P = 0.007$), ALB level (HR = 0.884 [0.802, 0.974], $P = 0.013$), platelet count (HR = 0.990 [0.980,1.00], $P = 0.049$),TB concentration (HR = 1.075 [1.041, 1.110], $P < 0.001$), INR (HR = 1.658 [1.233, 2.229], $P < 0.001$), WBC count (HR = 1.099 [1.021, 1.18], $P = 0.012$), and HE score (HR = 1.903 [1.299, 2.789], $P < 0.001$) (Table 2).

Construction of prediction nomograms

The CATCH-LIFE A nomogram was constructed from the five factors in model A (age, TB, INR, Na and HE score) (Fig. 2). From the independent prognostic factors for 90-day mortality identified by multivariate backward step-wise Cox regression analysis, the CATCH-LIFE B nomogram was constructed from the seven factors in model B (age, ALB, TB, INR, platelet count, WBC count and HE score) (Fig. 2). In each nomogram, the corresponding point for a variable on the "point axis" is its point value. The points for all variables are summed to obtain the point total, and a vertical line is drawn from the "total points axis" to the corresponding "survival axes" to estimate the probability of patient survival. Using the nomograms, a higher score is associated with a worse prognosis.

Characteristic	Training Cohort ($N=180$)	Validation Cohort ($N=148$)	P
Age (years, Mean ± SD)	47.7 ± 9.3	48.6 ± 11.1	0.424
Sex (Male, n,%)	175(97.2)	143(96.6)	0.759
Liboratory tests			
ALB (g/dL, Median(Quartile))	30.8(27.3,34.0)	31.4(27.5,35.5)	0.489
ALT (U/L, Median(Quartile))	124.4(37.7,458.5)	157.5(43.8,639.7)	0.455
AST (U/L, Median(Quartile))	139.0(58.9,290.2)	152.7(65.0,385.9)	0.58
WBC (10^9/L, Median(Quartile))	5.26(3.83,7.16)	5.55(4.20,7.54)	0.441
NLR (Median(Quartile))	2.56(3.83,7.16)	3.13(2.13,5.68)	0.008
PLT(10^9 /L, Median(Quartile))	87.0(58.0,134.0)	88.5(64.5,143.0)	0.676
TB (mg/dL, Median(Quartile))	9.18(2.27,19.77)	8.86(2.37,16.83)	0.41
INR (Median(Quartile))	1.47(1.20,2.07)	1.56(1.29,1.88)	0.277
Creatinine (mg/dl, Median(Quartile)))	0.78(0.68,1.02)	0.82(0.68,1.00)	0.229
BUN (mmol/L, Median(Quartile))	4.60(3.30,6.19)	4.89(3.71,6.90)	0.106
HGB (g/L, Median(Quartile)	123(108,142)	123(103,138)	0.669
Na (mmol/L, Median(Quartile))	137.0(133.9,140.0)	137.9(134.7,140.0)	0.351
K (mmol/L, Median(Quartile))	3.86(3.55,4.22)	3.93(3.58,4.29)	0.732
Scores			
MELD (Median(Quartile))	19.6(12.6 26.3)	20.1(13.7, 23.8)	0.611
MELD-Na (Median(Quartile))	21.2(13.4, 28.4)	20.9(14.2, 25.2)	0.435
MELD 3.0 (Median(Quartile))	18.4(9.9, 26.6)	18.1(10.4, 23.7)	0.412
CLIF-SOFA score(Median(Quartile)))	6.0(3.0, 7.0)	7.0(5.0, 8.0)	0.013
CLIF-SOFA score <7 (n,%)	107(60.5)	73(48.3)	0.028
CLIF-SOFA score ≥ 7 (n,%)	70(39.5)	78(51.7)	
Complications			
Non cirrhosis (n,%)	52(28.9)	45(30.4)	0.188
Compensated cirrhosis (n,%)	16(8.9)	22(14.9)	
Decompensated cirrhosis (n,%)	112(62.2)	81(54.7)	
Ascites (n,%)	103(57.2)	55(37.2)	<0.001
Hepatic Encephalopathy (n,%)	16(8.9)	11(7.4)	0.633
Gastrointestinal bleeding (n,%)	15(8.3)	21(14.2)	0.091
Infection (n,%)	64(35.6)	30(20.3)	0.002
Organ failures			
Renal failure (n,%)	9(5.0)	7(4.7)	0.91
Liver failure (n,%)	79(43.9)	59(39.9)	0.463
Central nervous system failure (n,%)	3(1.7)	1(0.7)	0.63
Coagulation failure (n,%)	25(13.9)	11(7.4)	0.063
Respiratory failure (n,%)	0(0.0)	0(0.0)	-
Circulatory failure (n,%)	0(0.0)	0(0.0)	-

Table 1. Baseline characteristics of patients in training set and validation set. ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell count; NLR, neutrophil lymphocyte ratio; PLT, platelet count; TB, total bilirubin; INR, international normalized ratio; BUN, blood urea nitrogen; HGB, hemoglobin; Na, serum sodium level; K, serum potassium level; MELD, model for end-stage liver disease; MELD-Na, MELD-sodium; CLIF-SOFA: Chronic liver failure-sequential organ failure assessment.

Performance and validation of CATCH-LIFE nomograms

In the training cohort, the CATCH-LIFE A and B nomograms performed very well for both 28-day mortality prediction (AUC: 0.922 [95% CI: 0.874, 0.971]; 0.916 [0.861, 0.972]) and 90-day mortality prediction (AUC: 0.905 [95% CI: 0.855, 0.956]; 0.915 [0.866, 0.964]) respectively. There were no significant differences between the AUCs for the CATCH-LIFE A and B nomograms and those for other scoring systems, such as the MELD 3.0, MELD-Na, MELD or CLIF-SOFA scores. The C-indices for the CATCH-LIFE A and B nomograms for 28-day mortality (0.910 ± 0.023, 0.899 ± 0.027) showed no significant difference from that for the MELD-Na score (0.890 ± 0.026, $P=0.233$/$P=0.596$), MELD score (0.865 ± 0.036, $P=0.096$/$P=0.097$). The C-index for the CATCH-LIFE A (0.910 ± 0.023) was significantly higher than those for the MELD 3.0 score (0.811 ± 0.051, $P=0.026$) and CLIF-SOFA score (0.860 ± 0.032, $P=0.011$). The C-index for the CATCH-LIFE B nomogram for 28-day mortality (0.899 ± 0.027) was significantly higher than those for the MELD 3.0 score (0.811 ± 0.051, $P=0.032$). The C-index for the CATCH-LIFE A for 90-day mortality (0.878 ± 0.022) was significantly higher

Variable	Univariate analysis		Model A		Model B	
	Hazard Ratio(95%CI)	*P* value	Hazard Ratio(95%CI)	*P* value	Hazard Ratio(95%CI)	*P* value
Sex	0.048(0.000,559.146)	0.526	-	-	-	-
Age(years)	1.031(0.996,1.068)	0.088	1.051(1.015,1.088)	0.005	1.048(1.013, 1.084)	0.007
ALB(g/dL)	0.897(0.846,0.951)	<0.001			0.884(0.802, 0.974)	0.013
ALT(U/L)	0.999(0.998, 1.000)	0.267	-	-	-	-
AST(U/L)	1.000(0.999, 1.001)	0.768	-	-	-	-
WBC(10^9 /L)	1.131(1.065,1.201)	<0.001	-	-	1.099(1.021,1.182)	0.012
NLR	1.141(1.048, 1.243)	0.003	-	-	-	-
PLT (10^9 /L)	0.991(0.984,0.999)	0.024	-	-	0.990(0.980,1.000)	0.049
TB(mg/dL)	1.089(1.061, 1.118)	<0.001	1.059(1.028, 1.091)	<0.001	1.075(1.041, 1.110)	<0.001
INR	2.125(1.694, 2.667)	<0.001	1.698(1.294, 2.228)	<0.001	1.658(1.233, 2.229)	<0.001
Cr(mg/dL)	1.355(1.145, 1.604)	<0.001	-	-	-	-
BUN(mmol/L)	1.076(1.043, 1.109)	<0.001	-	-	-	-
HGB(g/L)	0.987(0.975, 1.000)	0.048	-	-	-	-
Na(mmol/L)	0.891(0.855, 0.929)	<0.001	0.925(0.882,0.969)	0.001	-	-
K(mmol/L)	0.969(0.559, 1.680)	0.91	-	-	-	-
Complications						
Non cirrhosis	Ref	Ref	Ref	Ref	Ref	Ref
Compensated cirrhosis	2.131(0.356,12.76)	0.407	-	-	-	-
Decompensated cirrhosis	5.323(1.624,17.44)	0.006	-	-	-	-
HE score	2.259(1.592,3.206)	0.001	1.877(1.260, 2.797)	0.002	1.903(1.299, 2.789)	<0.001
Ascites	2.434(1.140,5.195)	0.022	-	-	-	-
Infection	2.781(1.423, 5.432)	0.003	-	-	-	-
Gastrointestinal bleeding	0.324(0.044,2.364)	0.266	-	-	-	-
Organ failures						
Renal failure	4.081(1.582,10.530)	0.004	-	-	-	-
Liver failure	5.324(2.416,11.729)	<0.001	-	-	-	-
Central nervous system failure	8.386(2.005,35.075)	0.004	-	-	-	-
Coagulation failure	3.769(1.842,7.712)	<0.001	-	-	-	-
Respiratory failure	-	-	-	-	-	-
Circulatory failure	-	-	-	-	-	-

Table 2. Prognostic factors associated with 90-day death caused by combination of HBV and alcohol. ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell count; NLR, neutrophil lymphocyte ratio; PLT, platelet count; TB, total bilirubin; INR, international normalized ratio; Cr, creatinine; BUN, blood urea nitrogen; HGB, hemoglobin; Na, serum sodium level; K, serum potassium level; HE, hepatic encephalopathy; HE score was the same as HE score in CLIF-SOFA, where 0 points were given for no HE, 1 point for grade I, 2 points for grade II, 3 points for grade III, and 4 points for grade IV.

than that for the CLIF-SOFA score (0.830 ± 0.028), but not significantly different from those for the MELD 3.0 score (0.821 ± 0.032), MELD-Na score (0.858 ± 0.026, $P = 0.291$), and MELD score (0.840 ± 0.030, $P = 0.099$). The C-index for the CATCH-LIFE B for 90-day mortality (0.887 ± 0.024) was significantly higher than those for the MELD 3.0 score (0.821 ± 0.032, $P = 0.017$), MELD score (0.840 ± 0.030, $P = 0.023$), and CLIF-SOFA score (0.830 ± 0.028, $P = 0.002$). No significant differences were observed in the C-indices for the CATCH-LIFE B nomogram (0.887 ± 0.024) and MELD-Na (0.858 ± 0.026, $P = 0.153$) for 90-day mortality.

In the validation cohort, the AUCs for 28-day and 90-day mortality prediction by the CATCH-LIFE A nomogram were 0.897(0.823, 0.971) and 0.897 (0.837, 0.961), respectively, while those for the CATCH-LIFE B nomogram were 0.904 (0.839, 0.969) and 0.905 (0.843, 0.967), respectively. The C-indices for the CATCH-LIFE nomogram A for 28-day and 90-day mortality were 0.888 ± 0.037 and 0.884 ± 0.032, respectively, while those for the CATCH-LIFE B nomogram were 0.891 ± 0.034 and 0.888 ± 0.032, respectively. No significant differences were observed among the performance metrics for the CATCH-LIFE A and B nomograms and the MELD, MELD-Na, MELD-3.0, and CLIF-SOFA scores in the validation cohort (Table 3). The predictive performance of the CATCH-LIFE nomograms also were compared with the actual 28-day and 90-day survival among the patients in the training and validation sets. The predictions by both nomograms seemed to be well calibrated with the actual survival (Fig. 3 and Supp Fig. 1).

Risk classification system based on predictive nomograms

Risk classification systems for 28-day and 90-day survival also were developed based on the CATCH-LIFE nomograms for stratification of patients into two distinct prognostic groups. Patients were divided into high-

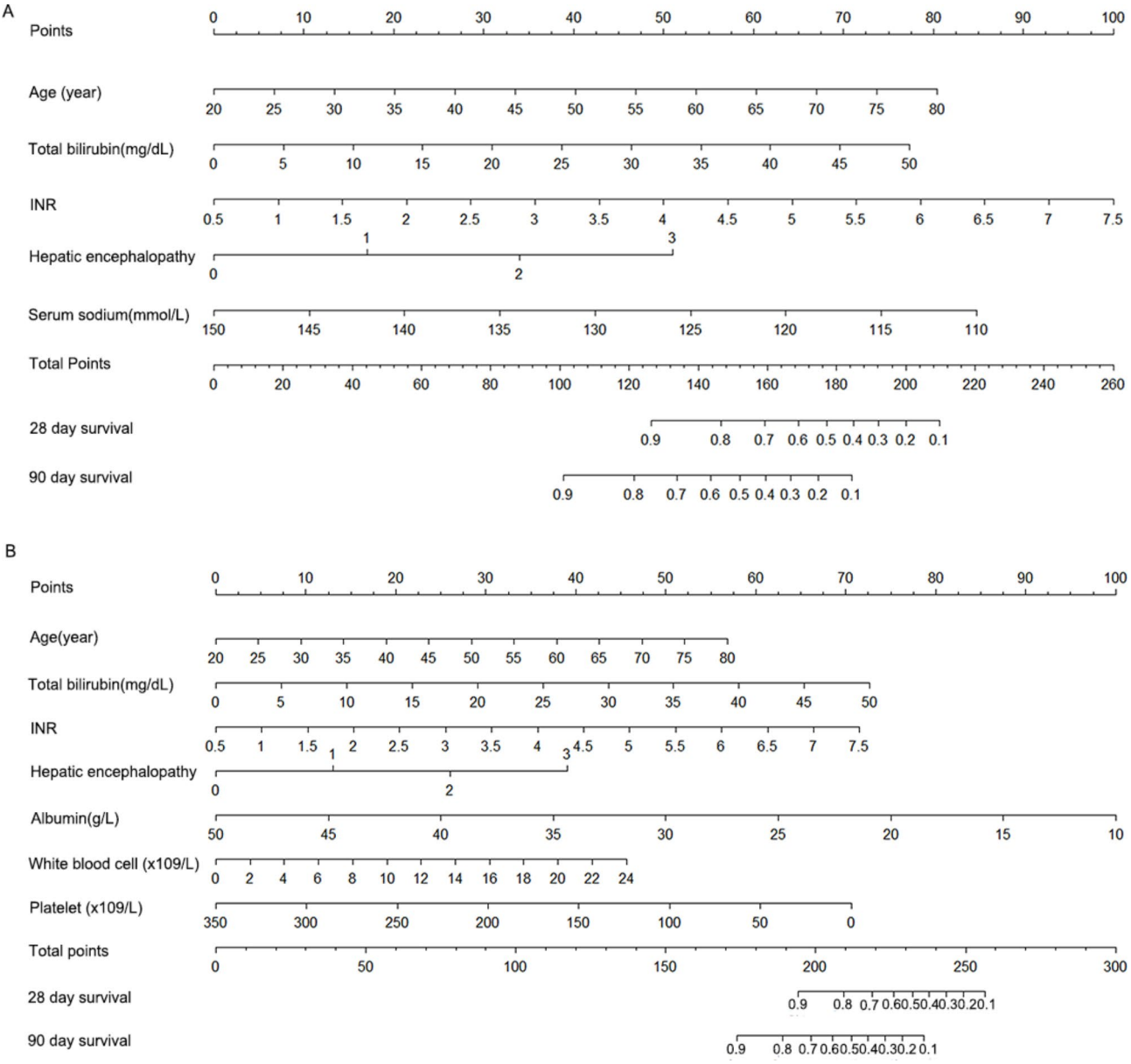

Fig. 2. Nomograms for predicting 28-day or 90-day survival rate (**A**) CATCH-LIFE A nomogram and (**B**) CATCH-LIFE B nomogram. INR, international normalized ratio; Hepatic encephalopathy, hepatic encephalopathy of grade 3 or above is calculated as grade 3.

risk and low-risk groups according to the optimal cutoff value determined by the "surv_cutpoint" function. The optimal cutoff for the CATCH-LIFE A nomogram was 130.5 for predicting both 28-day and 90-day survival. The optimal cutoff values for the CATCH-LIFE B nomogram for predicting 28-day and 90-day survival were 203.6 and 186.8, respectively. For the convenience of application, we rounded the optimal cut-off values to the nearest integer. Therefore, the optimal cutoff points for predicting 28-day and 90-day survival with the CATCH-LIFE A nomogram were both set at 130, while the optimal cutoff points for predicting 28-day and 90-day survival with the CATCH-LIFE B nomogram were set at 200 and 185, respectively.

With both nomograms, the high-risk categories (point total greater than cutoff) were associated with a shorter survival time than the low-risk categories in both the training and validation cohorts ($P < 0.001$; Fig. 4 and Supp Fig. 2). Consistently, significant survival differences were observed between the low- and high-risk groups in the training cohort as well as the validation cohort ($P < 0.001$), indicating that the CATCH-LIFE nomograms offer outstanding predictive ability for identifying those patients with AoCLD caused by combination of HBV and alcohol who are at greatest risk for short-term adverse outcomes (Fig. 4 and Supp Fig. 2).

Predictive factor or model	Training cohort					Validation cohort				
	AUC (95%CI)	C-index	*P*-value	P1	P2	AUC (95%CI)	C-index	*P*-value	P1	P2
28-day death										
CACTH-LIFE A	0.922(0.874, 0.971)	0.910 ± 0.023	<0.001	ref	0.600	0.897(0.823, 0.971)	0.888 ± 0.037	<0.001	ref	0.894
CACTH-LIFE B	0.916(0.861,0.972)	0.899 ± 0.027	<0.001	0.600	ref	0.904(0.839, 0.969)	0.891 ± 0.034	<0.001	0.894	ref
MELD 3.0	0.819(0.704,0.934)	0.811 ± 0.051	<0.001	0.026	0.032	0.859(0.776,0.942)	0.849 ± 0.040	<0.001	0.292	0.279
MELD-Na	0.905(0.846, 0.964)	0.890 ± 0.026	<0.001	0.233	0.596	0.862(0.780, 0.944)	0.855 ± 0.038	<0.001	0.306	0.376
MELD	0.881(0.801,0.960)	0.865 ± 0.036	<0.001	0.096	0.097	0.854(0.767, 0.940)	0.847 ± 0.041	<0.001	0.287	0.282
CLIF-SOFA score	0.879(0.810,0.947)	0.860 ± 0.032	<0.001	0.011	0.055	0.870(0.791, 0.948)	0.861 ± 0.037	<0.001	0.426	0.373
90-day death										
CACTH-LIFE A	0.905(0.855, 0.956)	0.878 ± 0.022	<0.001	ref	0.547	0.897(0.837, 0.961)	0.884 ± 0.032	<0.001	ref	0.837
CACTH-LIFE B	0.915(0.866,0.964)	0.887 ± 0.024	<0.001	0.547	ref	0.905(0.843, 0.967)	0.888 ± 0.032	<0.001	0.837	ref
MELD 3.0	0.853(0.781,0.925)	0.821 ± 0.032	<0.001	0.059	0.017	0.892(0.829,0.955)	0.871 ± 0.032	<0.001	0.706	0.628
MELD-Na	0.886(0.829, 0.943)	0.858 ± 0.026	<0.001	0.291	0.153	0.886(0.826, 0.948)	0.868 ± 0.031	<0.001	0.590	0.578
MELD	0.866(0.802,0.929)	0.840 ± 0.030	<0.001	0.099	0.023	0.876(0.809, 0.943)	0.860 ± 0.033	<0.001	0.482	0.447
CLIF-SOFA score	0.855(0.794,0.917)	0.830 ± 0.028	<0.001	0.011	0.002	0.869(0.802, 0.940)	0.855 ± 0.033	<0.001	0.347	0.308

Table 3. Univariate and multivariate analysis of factors associated with 90-day death caused by combination of HBV and alcohol. MELD, model for end-stage liver disease; MELD-Na, MELD-sodium; CLIF-SOFA, Chronic liver failure-sequential organ failure assessment; *P*-value, significance test for C-index values; P1, Comparison of C-index values differences between various model and CACTH-LIFE A; P2, Comparison of C-index values differences between various model and CACTH-LIFE B.

Discussion

In this multicenter, retrospective cohort study, we developed and validated two nomograms, the CATCH-LIFE A and CATCH-LIFE B nomograms, using different screening variables for the prediction of 28-day and 90-day mortality among patients with AoCLD specifically caused by a combination of HBV infection and alcohol exposure. The CATCH-LIFE A nomogram, based on age, TB, INR, Na and HE score, and the CATCH-LIFE B nomogram, based on age, TB, INR, ALB, WBC, platelet count and HE score, showed good discriminatory ability for predicting 28-day and 90-day mortality is this patient population. Both developed nomograms could be used for patient stratification into high- and low-risk groups that showed significant differences in LT-free survival at 28 and 90 days after diagnosis.

The independent prognostic factors associated with 28-day mortality included age, WBC count, TB concentration, INR, and HE score, which suggested that 28-day mortality due to AoCLD caused by a combination of HBV and alcohol is mainly attributable to acute liver damage, coagulation system failure, and infection. WBCs are associated with the response to infection and inflammation, which is consistent with previously reported findings showing that AoCLD patients who died with 28 days primarily had ACLF, for which the main characteristic is systemic inflammation[16,17]. The independent risk factors associated with 90-day mortality included all of those associated with 28-day mortality (Table 3). In addition to age, TB concentration, INR, WBC and HE score, the factors of ALB level, platelet count and serum sodium level also were associated with the probability of 90-day mortality. Platelet count responsiveness decreases with increasing severity of liver cirrhosis[18]. A low serum ALB level is thought to reflect advanced liver disease, including enhanced liver carcinogenesis and liver failure[19,20]. Another alternative to ALB as a predictive indicator is Na, which is closely related to the prognosis of end-stage liver disease. Other studies also reported that a low serum Na concentration is an independent predictor of mortality in patients with cirrhosis, and the underlying mechanism is related to hemodynamic changes in patients with end-stage liver disease[21–23]. Furthermore, other research also showed that hyponatremia is an independent prognostic factor for a poor 90-day prognosis in patients with AoCLD, and failure to correct hyponatremia within 1 week after admission is often associated with increased mortality[24]. The relationship between serum ALB and Na levels is complex, and some collinearity may be present between these two factors. Accordingly, we did not include them simultaneously in the same model.

Both the CATCH-LIFE A and CATCH-LIFE B nomograms performed well for 28-day and 90-day mortality prediction, with C-indexes > 0.80 and AUCs from time-ROC curve analysis larger than those for the MELD, MELD-Na and CLIF-SOFA scores. These results indicate that the nomograms developed in the present study may have superior predictive ability compared with other scores in the study population. Although some differences were not statistically significant, significant results may arise upon validation in larger patient samples.

The MELD and MELD-Na scores have been widely used to predict the mortality of patients with end-stage liver disease and for donor organ allocation[24–27], but they have not yet been validated in AoCLD caused by a combination of HBV and alcohol. In the present study, we also conducted a prospective cohort validation of the MELD and MELD-Na scores for the first time in liver disease patients with HBV combined with alcohol exposure, and the results showed that these two indicators also offered good short-term mortality prediction efficacy for AoCLD caused by HBV plus alcohol. The present study also included some patients who met the diagnostic criteria for ACLF, and thus, we validated the ability of the CLIF-SOFA score to predict short-term mortality. Hence, we conducted a prospective cohort validation of the CLIF-SOFA score for the first time in liver

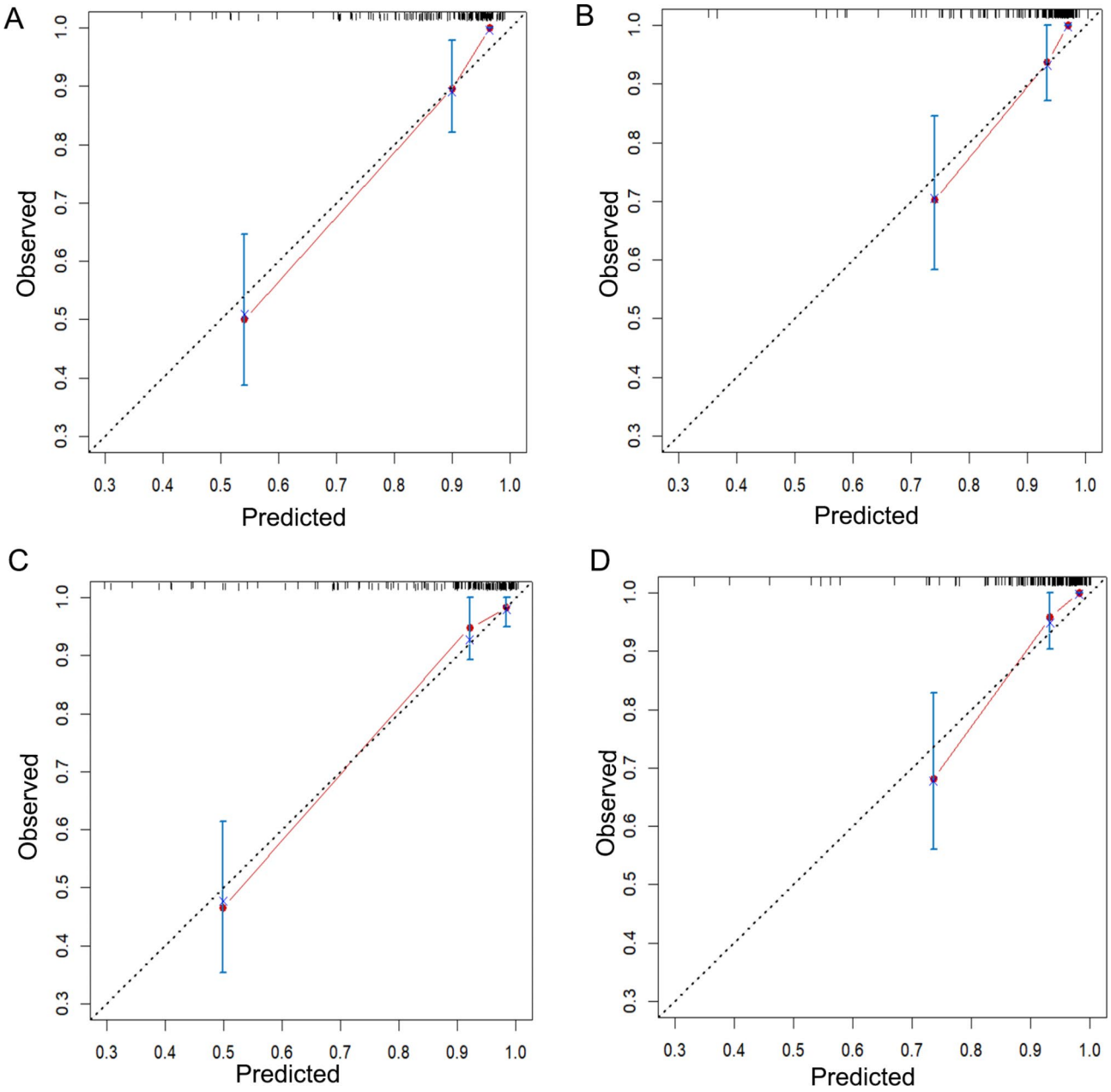

Fig. 3. Calibration curve for the CATCH-LIFE A and B nomograms for the prediction of 90-day mortality among patients with AoCLD caused by a combination of HBV and alcohol in the training and validation cohorts. (**A**) 90-day mortality in the training cohort of CATCH-LIFE A nomogram; (**B**) 90-day mortality in the validation cohort of CATCH-LIFE A nomogram cohort; (**C**) 90-day mortality in the training cohort of CATCH-LIFE B nomogram; (**D**) 90-day mortality in the validation cohort of CATCH-LIFE B nomogram cohort.

disease patients with HBV infection combined with alcohol exposure, and the results showed that the CLIF-SOFA score also had some degree of efficacy for short-term mortality prediction in AoCLD caused by HBV plus alcohol, although it was inferior to the CATCH-LIFE A and B nomograms as well as the MELD and MELD-Na scores.

Our results showed that for patients with AoCLD caused by HBV plus alcohol, a CATCH-LIFE nomogram A score at admission of 130 or higher indicated a significantly increased risk of 28-day and 90-day mortality than a score less than 130. This suggests that patients with these scores require close monitoring to detect changes in their condition and to ensure timely inclusion of these patients on the liver transplant candidate list. CATCH-LIFE nomogram B scores of 185 and higher indicated a high risk of poor prognosis at 90 days, and scores of 200 and higher predicted a poor prognosis at 28 days. Use of this nomogram can further remind the managing doctors to closely monitor the condition of these patients and inform their decision-making.

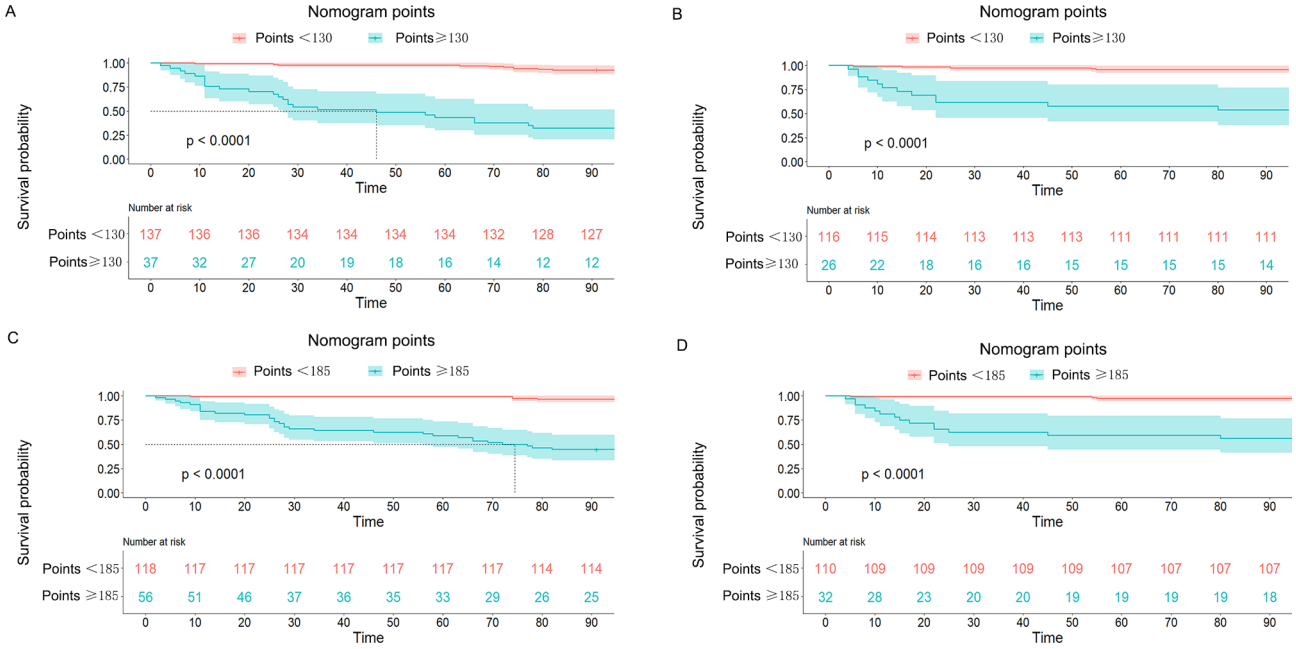

Fig. 4. Survival curves for AoCLD caused by HBV plus alcohol among patients in different risk categories. (**A**) 90-day survival curves for high-and low-risk groups in the training cohort based on the CATCH-LIFE A nomogram; (**B**) 90-day survival curves for high- and low-risk groups in validation cohort based on the CATCH-LIFE A nomogram; (**C**) 90-day survival curves for high- and low-risk groups in the training cohort based on the CATCH-LIFE B nomogram; (**D**) 90-day survival curves for high- and low-risk groups in the validation cohort based on the CATCH-LIFE B nomogram.

The present study has several limitations. The first one is potential flaws in the models, such as fluctuation of the serum Na concentration (CATCH-LIFE A nomogram) with the use of diuretics or supplementation with free water and the effect of intravenous administration of exogenous ALB on the serum ALB level (CATCH-LIFE B nomogram). We aimed to develop two nomograms to suit different sets of patients. For example, for patients who have already received ALB infusion, we recommend use of the CATCH-LIFE A nomogram, while for patients who have already used diuretics and other medications, we recommend use of the CATCH-LIFE B nomogram. Secondly, with the developed nomograms, prognosis is predicted using only indicators collected at the time of admission, excluding relevant factors at later time points, such as the patient's post-discharge alcohol consumption. In addition, the sample sizes in our training and validation cohorts were somewhat small. The reason for this situation is that for chronic liver disease patients with known HBV infection, the combined presence of high alcohol consumption is often ignored. Therefore, many chronic hepatitis B patients, especially men, also have ALD.

In summary, our study results represent the first analysis of short-term follow-up data from patients with AoCLD due to combined HBV infection and alcohol exposure. Our newly developed CATCH-LIFE A and B nomograms can accurately predict short-term mortality and easily stratify these patients into high- and low-risk groups; thus, the developed nomograms may be used to guide patient management. These new scoring systems require further validation in larger cohorts, and their clinical usefulness for prioritizing candidates for liver transplantation must be formally assessed.

Data availability

The data used to support the findings of this study are available from the corresponding author at [yanhang@mail.jlu.edu.cn] upon request.

Received: 18 June 2024; Accepted: 14 October 2024
Published online: 19 October 2024

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Acknowledgements

We are thankful to the participants of this study for their time and participation.

Author contributions

HX, HL, WT, XW, XZ and YH contributed equally and share first authorship. YG obtained the funding. HL and YG designed the study. HX, HL, WT, XW, XZ, YH, JC, ZM, ZQ, FL, XL, YS, YZ, HY, WZ, XW, YF, LQ, WG, YZ, GD, YZ, SS, YH, QZ, YX, JL, RC, MZ, BL, XJ, GZ, HW, YC, SL, JL, JL, TL, RZ, XZ, HR, YG collected the data. HX directed statistical analysis. TL has verified the underlying data. HX and YG drafted the manuscript. YG contributed to the critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. All authors have read and approved the final manuscript.

Funding

This work was sponsored by the National Science and Technology Major Project (2018ZX10723203 and 2018ZX100302), the National Natural Science Foundation of China (grants No. 82170602,81900579), the Project for Middle-aged and Young Excellent Technological Innovation Talents of Jilin Province (20220508079RC), the Natural Science Foundation for self-exploration research of Jilin Province (YDZJ202401427ZYTS), and the Chongqing Natural Science Foundation (CSTC2019jcyj-zdxmX0004).

Declarations

Competing interests

The authors declare no competing interests.

Consent for publication

All authors agreed on the publication of the current version of manuscript.

Ethics approval

The ethics committee of the Ren Ji Hospital, School of Medicine, Shanghai Jiaotong University (China) approved the study and registered it at www.Clinicaltrials.gov. (NCT02457637, NCT03641872).

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-76473-z.

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