BMC Infectious Diseases

RESEARCH Open Access

Low platelet to high-density lipoprotein ratio predicts poor short-term prognosis in hepatitis B-related acute-on-chronic liver failure

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Abstract

Background Acute-on-chronic liver failure (ACLF) is characterized by a systemic inflammatory response, predominantly associated with hepatitis B virus in the Asia-Pacific region, with a high short-term mortality rate. The platelet to high-density lipoprotein ratio (PHR) has been used to predict the prognosis of patients with various inflammatory diseases. We aim to is to use the PHR to predict the short-term prognosis of patients with HBV-ACLF.

Method In this study, we retrospectively analyzed clinical data from 270 HBV-ACLF patients. Using logistic regression, we identified independent risk factors for short-term mortality and developed a prognostic model. This model was then validated, compared, and its clinical utility assessed via decision curve analysis (DCA).

Results Among the 270 HBV-ACLF patients, 98 patients died within 28 days. The deceased group exhibited a higher proportion of severe hepatic encephalopathy and ascites. Additionally, there was a statistically significant difference ($P=0.046$) in the novel inflammation scoring system, PHR, between the two groups. Following stringent variable selection, PHR was identified as a predictive factor for short-term mortality in HBV-ACLF patients using logistic regression analysis (OR: 0.835 (0.756–0.999), $P=0.009$), and it exhibited a synergistic effect with certain traditional scores. The prognostic model constructed based on PHR demonstrated a superior ability to predict short-term mortality compared to traditional scores such as Child-Turcotte-Pugh (AUC: 0.889). Evaluation using calibration curves and decision curve analysis (DCA) suggested its practical utility.

Conclusion PHR can predict short-term mortality in patients, with a low PHR upon admission being associated with an increased risk of death.

Keywords Acute-on-chronic liver failure, Hepatitis B virus, Platelet to high-density lipoprotein ratio, Inflammation score, Risk stratification

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Introduction

Acute-on-chronic liver failure (ACLF) is characterized by an acute deterioration of liver function, manifesting as jaundice, coagulation dysfunction, and the occurrence of ascites, with a high 28-day mortality rate [1]. More than a quarter of patients with cirrhosis present with this condition upon admission [1, 2]. In the Asia-Pacific region, including China, chronic hepatitis B virus (HBV) infection is the primary cause of ACLF, accounting for over 60% of ACLF cases [3]. Currently, there is a lack of specific treatment for ACLF, and the main approaches involve managing precipitating events, organ support, and liver transplantation. Nonetheless, under specific monitoring conditions, the 28-day and 90-day mortality rates for ACLF patients are 37.6% and 50.4%, respectively [4]. Therefore, early diagnosis and understanding of prognosis are crucial means to improve patient survival.

Systemic inflammation is a characteristic pathophysiological feature of ACLF [1]. In fact, Alberto and his colleagues reported that the severity of inflammation, rather than coagulation dysfunction, is the most important predictor of ACLF [5]. The inflammation score based on simple laboratory test indicators, such as monocyte-to-lymphocyte ratio (MLR) [6], neutrophil-lymphocyte ratio (NLR) [7], and lymphocyte-to-white blood cell ratio (LWR) [8], is used to predict the prognosis of patients with liver failure or cirrhosis. However, the need to explore further the potential of inflammatory scoring for predicting the prognosis of patients with ACLF caused by specific etiologies has not been met yet.

The platelet to high-density lipoprotein cholesterol ratio (PHR) is a newly developed systemic inflammation marker, reported as a biomarker for patient prognosis in metabolic syndrome [9] and non-alcoholic fatty liver disease [10]. Interestingly, platelets serve as predictive factors in patients with cirrhosis [11, 12], while high-density lipoprotein (HDL) is associated with immunity [13] and has also been reported as a predictive factor in decompensated cirrhotic patients [14]. However, there is currently a lack of practical data on the association between PHR and the prognosis of ACLF patients, especially hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) patients.

In this study, we employed data from HBV-ACLF patients at our center to explore the potential association between PHR and their prognosis. Additionally, we developed a new prognostic model based on PHR to predict the prognosis of patients within 28 days.

Method

Study design and population

This retrospective study included 270 HBV-ACLF patients who were hospitalized at the First Affiliated Hospital of Nanchang University from April 2021 to March 2023. By analyzing the clinical data of this cohort, we aim to explore the correlation between systemic inflammation-related biomarkers and the 28-day mortality among patients. Patients with HBV-ACLF were recruited according to Asia Pacific Association for study of Liver (APASL) criteria [15], which required HBsAg positivity for at least 6 months, a serum total bilirubin (TBIL) level of 5 mg/dL or higher, an INR level of 1.5 or higher, or a prothrombin activity level of less than 40%, and the development of ascites and/or hepatic encephalopathy within 4 weeks. In general, patients were included when they met following criteria: (1) ≥ 18 years old, (2) diagnosed with HBV-ACLF, (3) no previous use of anti-lipid drugs and (4) clinical information is available. Exclusion criteria included (1) hepatocellular carcinoma, (2) combined with other chronic liver disease, (3) previous liver transplantation, (4) complications with other severe chronic extrahepatic diseases, (5) infection was known to have occurred before admission, and (6) infection with HIV or receiving immune-suppressive medication. Figure 1 depicts the flowchart of the study. Our study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University (IIT [2021] 09). Informed consents of the patients were waived by the Ethics Committee of the First Affiliated Hospital of Nanchang University because of the retrospective and anonymous nature of the study. All relevant statements involving human subjects comply with the Declaration of Helsinki.

Clinical data

A retrospective review of history, physical examinations, and laboratory measurements will be extracted from the inpatient information management system. Necessary laboratory measurements must be measured within 24 h of admission to meet the requirements. Clinical indicators include blood routine examination, liver function tests, renal function tests, coagulation function tests, blood lipid levels, and serum hepatitis B virus DNA (HBV-DNA). Finally, the survival status of the patients at 28 days will be meticulously documented.

Management and treatment

The management of patients with HBV-ACLF is based on established guidelines [2, 15], primarily the Acute-on-chronic liver failure: consensus recommendations of APASL (2019 edition) and the Chinese Guidelines for the Diagnosis and Management of Liver Failure (2018 edition). All patients with HBV-ACLF receive standardized medical treatment during hospitalization, including rest, fluid balance, nutritional support, and the use of nucleotide analogs. The intake of hepatotoxic substances or alcohol is required to be immediately discontinued. Patients are restricted in sodium and water intake and are treated with diuretics. Paracentesis is performed

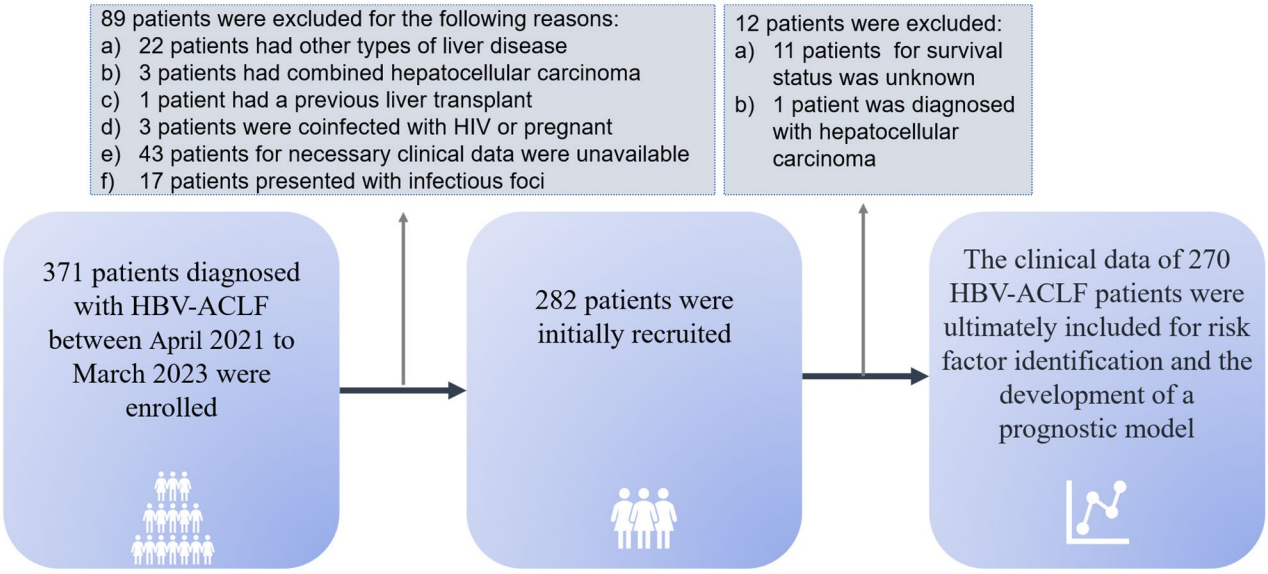

Fig. 1 Design diagram of this study

according to the severity of ascites and other specific patient conditions. For patients with bacterial infections, empirical antibiotic treatment is initiated, and subsequently adjusted based on culture and antibiotic sensitivity test results. In cases of hepatic encephalopathy (HE), precipitating factors are addressed simultaneously with medication, primarily consisting of lactulose, branched-chain amino acids, and ornithine aspartate.

Statistical analysis

Continuous variables were presented using means and standard deviations (SD) or medians and interquartile ranges (IQR), while categorical variables were represented using frequencies (%). We examined whether there were interactions between explanatory variables, such as variance inflation factors (VIF) and variable correlations, and found no significant interactions among the variables considered. Group comparisons were conducted using Student's t-test or Mann-Whitney U test. The diagnostic accuracy of different models was evaluated through Receiver Operating Characteristic (ROC) analysis. ROC curve area under the curve (AUC) was compared following the method described by DeLong et al. All statistical tests were two-tailed with a significance level set at 5%. All analyses were performed using R 4.1.0 (R Project for Statistical Computing, Vienna, Austria). R packages used for model building and statistical analysis included gtsummary, tidyverse, performance, ggcorrplot, pROC, rms, and compareGroups. The source file "stdca.r" obtained from www.mskcc.org was used to generate Decision Curve Analysis (DCA) plots.

Result

Clinical characteristics

This study retrospective analysis a total of 270 HBV-ACLF patients who met the criteria for the APASL, among whom 98 (36.3%) patients died within 28 days. Those patients had a mean age of 49.2±12.4 years and exhibited significant abnormalities in both coagulation function and liver function. Most patients did not present with hepatic encephalopathy at the time of admission, while nearly half of the patients had a small amount of ascites upon admission. Liver function scores for these patients were assessed at admission, including Child-Turcotte-Pugh (CTP) score, Model for end-stage liver disease (MELD) score, MELD sodium (MELD-Na) score, and Chinese Group on the Study of Severe Hepatitis B-ACLF II score (COSSHACLF IIs), which were 11.0 (10.0–12.0), 21.0 (17.4–24.8), 21.2 (17.5–26.9), and 6.81 (6.22–7.70), respectively. Additionally, we calculated a biomarker reflecting systemic inflammation, the PHR, which had a median value of 439 (258–789) in this cohort. Other baseline characteristics are described in Table 1.

Differences in characteristics between the survival and the death groups

Figure 2 provides a visual comparison of liver function scores and PHR scores between the survival and death groups, which indicates that the non-survival group had higher liver function scores and lower PHR scores. Specifically, the death group exhibited a higher proportion of male patients, along with elevated levels of PT, INR, MAP, WBC, TBIL, AST, HBV-DNA, and a higher incidence of severe HE. However, these patients had lower

Table 1 Baseline characteristics of patients with HBV-ACLF

	Cohort (*n* = 270)	Survival (*n* = 172)	Death (*n* = 98)	*P*-value
28-day mortality:				
Survival	172 (63.7%)			
Death	98 (36.3%)			
Male (%)	225 (83.3%)	137 (79.7%)	88 (89.8%)	0.048
Age (years)	49.2 ± 12.4	47.4 ± 11.7	52.3 ± 12.9	0.002
INR	1.85 [1.61–2.34]	1.71 [1.58–1.97]	2.27 [1.89–2.98]	<0.001
PT (s)	20.6 [18.1–25.2]	19.0 [17.4–22.2]	24.8 [20.4–32.2]	<0.001
D-dimer (mg/L)	2.02 [0.93–3.95]	1.53 [0.77–2.92]	3.45 [1.36–5.04]	<0.001
MAP (mmHg)	87.0 ± 12.3	85.6 ± 11.7	89.5 ± 12.8	0.014
White blood cell count (10^9/L)	6.72 ± 3.27	6.16 ± 2.86	7.71 ± 3.70	<0.001
Hemoglobin (g/L)	120 ± 24.6	121 ± 21.7	118 ± 28.9	0.419
Platelet count (10^9/L)	113 ± 57.1	115 ± 51.6	109 ± 65.9	0.458
TBIL (μmol/L)	268 [167–363]	232 [122–330]	338[234–427]	<0.001
Albumin (g/L)	31.6 ± 4.48	31.7 ± 4.82	31.4 ± 3.85	0.587
ALT (U/L)	403 [91.8–1162]	351[84.2–878]	544 [133–1198]	0.06
AST (U/L)	272 [123–665]	219 [99.3–538]	394 [176–964]	0.001
ALP (U/L)	152 [122–196]	152[122–199]	151 [122–193]	0.672
GGT (U/L)	106 [67.0-158]	111[61.8–163]	97.0[68.2–144]	0.504
sCr (μmol/L)	77.8 ± 75.4	75.6 ± 80.1	81.7 ± 66.7	0.508
BUN (mmol/)	3.85 [2.90–5.40]	3.70 [2.90-5.00]	4.10 [2.80–6.40]	0.159
Cholesterol (mmol/L)	2.66 [2.04–3.19]	2.73 [2.16–3.34]	2.37[1.90–2.94]	0.002
Triglyceride (mmol/L)	1.10 [0.71–1.61]	1.24[0.78–1.65]	1.00[0.62–1.48]	0.01
HDL (mmol/L)	0.21[0.12–0.36]	0.23 [0.16–0.36]	0.19 [0.11–0.31]	0.04
LDL (mmol/L)	1.00 [0.54–1.49]	1.02 [0.63–1.55]	0.82 [0.42–1.44]	0.09
sNa (mmol/L)	137 ± 4.29	137 ± 3.88	136 ± 4.86	0.039
HBV-DNA (log_{10} IU/mL)	4.54 [2.75–6.17]	4.25[2.70–5.51]	5.38 [3.27–6.76]	0.001
HE Score:				<0.001
Grade 0	204 (75.6%)	158 (91.9%)	46 (46.9%)	
Grade 1–2	21 (7.78%)	9 (5.23%)	12 (12.2%)	
Grade 3–4	45 (16.7%)	5 (2.91%)	40 (40.8%)	
Ascites:				0.112
Minimal ascites	121 (44.8%)	83 (48.3%)	38 (38.8%)	
Moderate ascites	97 (35.9%)	62 (36.0%)	35 (35.7%)	
Large ascites	52 (19.3%)	27 (15.7%)	25 (25.5%)	
HBeAg-positive (%)				0.057
Negetive	192 (71.1%)	115 (66.9%)	77 (78.6%)	
Positive	78 (28.9%)	57 (33.1%)	21 (21.4%)	
CTP	11.0 [10.0–12.0]	10.0 [9.00–11.0]	12.0[11.0-12.8]	<0.001
MELD	21.0[17.4–24.8]	18.8 [15.8–21.9]	24.4[21.5–27.6]	<0.001
MELD-Na	21.2[17.5–26.9]	18.9 [16.2–22.7]	25.5[22.0-30.3]	<0.001
COSSH-ACLF IIs	6.81 [6.22–7.70]	6.40[5.88–6.88]	7.79[7.21–8.46]	<0.001
PHR	439[258–789]	498 [273–849]	412[231–673]	0.046

Abbreviations INR, international normalized ratio; PT, prothrombin time; MAP, mean artery pressure; TBIL, total bilirubin; ALT, Alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, glutamyl transpeptidase; sCr, serum creatinine; BUN, blood urea nitrogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein; sNa, Serum sodium; HBeAg, hepatitis B virus e antigen; CTP, Child-Turcotte-Pugh; MELD, Model for end-stage liver disease; MELD-Na, MELD sodium; COSSH-ACLF IIs, Chinese Group on the Study of Severe Hepatitis B-ACLF II score; PHR, Platelet /HDL ratio

levels of cholesterol and triglycerides, as well as lower serum sodium levels. The comparison of baseline characteristics and corresponding p-values are presented in Table 1.

Development of prognostic model for prediction of survival

Univariate regression analysis and multivariable regression analysis were used to identify independent risk factors for 28-day mortality rate in patients. Firstly, Gender, Age, INR, PT, MAP, TBIL, AST, BUN, Cholesterol, sNa, HBV-DNA, HBeAg, and PHR were identified as

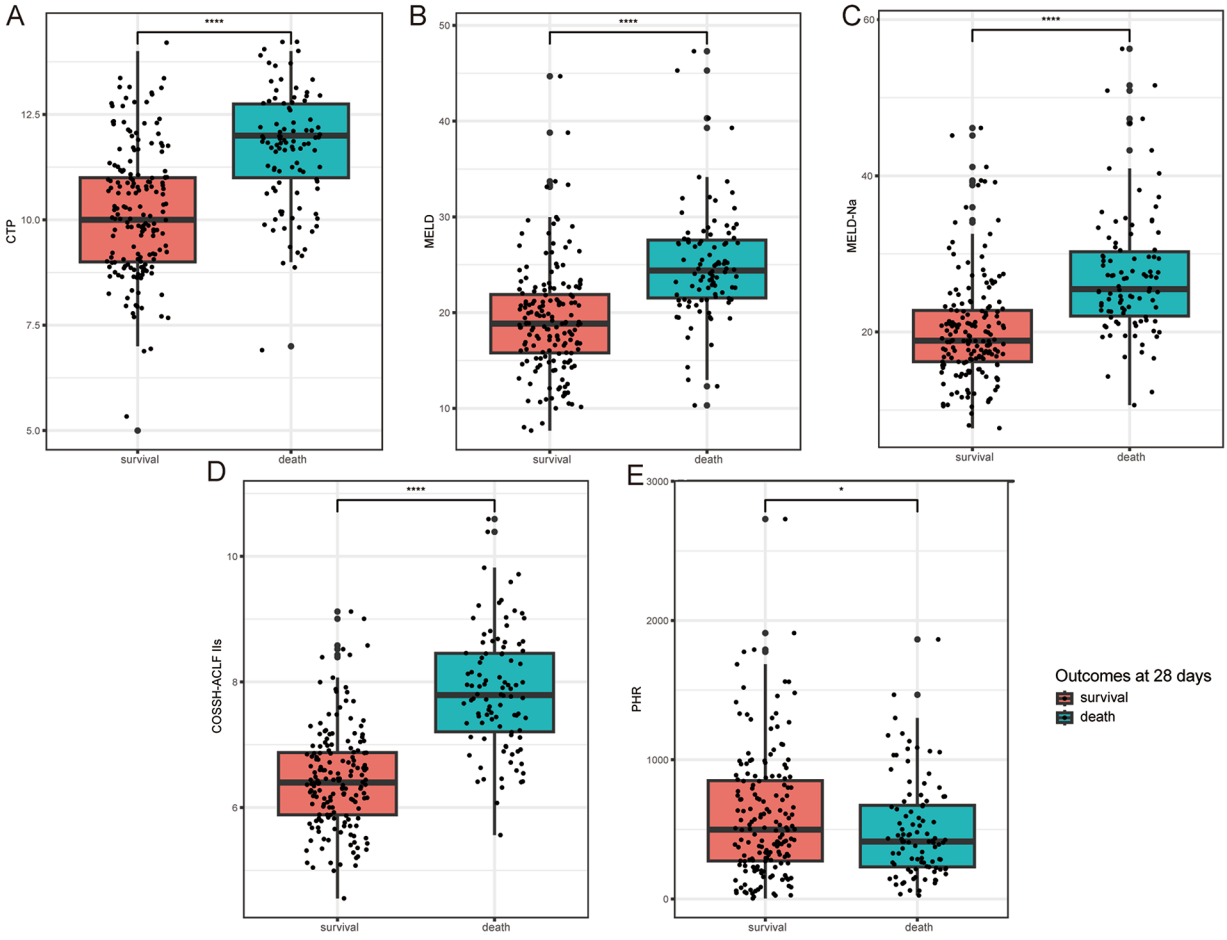

Fig. 2 Box plots of various indicators for the survival and death groups. **A**: Comparison of CTP in the survival and death group at 28 days. **B**: Comparison of MELD in the survival and death group at 28 days. **C**: Comparison of MELD-Na in the survival and death group at 28 days. **D**: Comparison of COSSH-ACLF IIs in the survival and death group at 28 days. **E**: Comparison of PHR in the survival and death group at 28 days

independent predictive factors. To avoid multicollinearity among variables, a correlation test between the variables was conducted to exclude variables that showed strong correlations from the multivariable regression analysis (Supplementary Fig. 1). VIF were also used to assess the multicollinearity among variables in the model. As shown in Supplementary Fig. 2, the VIF values of the variables included in the multivariable regression analysis were within a reasonable range. Finally, we identified Gender (OR: 0.16, 95% CI: 0.05–0.51, $P=0.003$), Age (OR: 1.07, 95% CI: 1.04–1.12, $P<0.001$), PT (OR: 1.1, 95% CI: 1.05–1.16, $P<0.001$), MAP (OR: 1.04, 95% CI: 1.01–1.07, $P=0.018$), WBC (OR: 1.23, 95% CI: 1.08–1.40, $P=0.001$), TBIL (OR:1.01, 95% CI: 1.00-1.01, $P<0.001$), $\log_{10}$DNA (OR:1.61, 95% CI: 1.28–2.06, $P<0.001$), and PHR (OR: 0.835, 95% CI: 0.756–0.999, $P=0.009$) as independent predictive factors (Table 2).

Validation and comparison of predictive model

Based on the above results, the specific formula for the predictive model is as follows: Predictive Model = -1.914 * Gender+0.086 * Age+0.093 * PT+0.035 * MAP+0.218 * WBC+0.006 * TBIL+0.5115 * $\log_{10}$DNA −0.001 * PHR −14.775. In the first step, we constructed the confusion matrix which used to evaluate the performance of our prediction model. The detailed parameters are as follows: Accuracy of 0.8370, Precision of 0.8855, Specificity of 0.8698, Recall of 0.8547, and F1 Score of 0.867 (refer to Fig. 3). Then we validated the model with calibration curve and discrimination analysis. The calibration curve indicated that the model had good predictive accuracy, while the probability curve suggested that the model could effectively differentiate between patients in the survival and death groups (refer to Fig. 4).

We further compared the predictive performance of the developed model with that of commonly used models by conducting a comparison of the area under the receiver operating characteristic curve (AUC) and performing the

Table 2 Univariate and multivariate analysis for 28-day mortality in HBV-ACLF patients

Variables	OR(95%CI)	*p*-value	OR(95%CI)	*P*-value
Gender (female)	0.445 [0.2-0.913]	0.035	0.16 [0.05–0.51]	0.003
Age	1.033 [1.012–1.056]	0.002	1.07 [1.04–1.12]	< 0.001
INR	7.153 [4.124–13.234]	< 0.001		
PT	1.141 [1.091–1.198]	< 0.001	1.1 [1.05–1.16]	< 0.001
Ddimer	1.02 [0.992–1.063]	0.225		
MAP	1.027 [1.006–1.049]	0.013	1.04 [1.01–1.07]	0.018
WBC	1.158 [1.071–1.259]	< 0.001	1.23 [1.08–1.40]	0.001
HB	0.996 [0.986–1.006]	0.381		
PLT	0.998 [0.993–1.003]	0.428		
TBIL	1.005 [1.003–1.008]	< 0.001	1.01 [1.00-1.01]	< 0.001
ALB	0.985 [0.93–1.042]	0.608		
ALT	1[1–1]	0.802		
AST	1.001 [1-1.001]	0.003	1 [1.00–1.00]	0.051
ALP	0.999 [0.995–1.001]	0.472		
GGT	1 [0.998–1.003]	0.724		
sCr	1.001 [0.998–1.005]	0.535		
BUN	1.105 [1.02–1.208]	0.019	1.09 [0.97–1.22]	0.144
Cholesterol	0.729 [0.536–0.958]	0.034	1 [0.72–1.34]	0.995
Triglyceride	0.766 [0.532–1.079]	0.139		
HDL	0.898 [0.403–1.084]	0.195		
LDL	0.79 [0.54–1.134]	0.211		
sNa	0.938 [0.883–0.993]	0.03	0.99 [0.90–1.08]	0.767
HBV-DNA*	1.272 [1.108–1.465]	< 0.001	1.61 [1.28–2.06]	< 0.001
HBeAg (positive)	0.55 [0.304–0.969]	0.043	0.55 [0.22–1.33]	0.188
PHR	0.879 [0.792–0.999]	0.064	0.835 [0.756–0.999]	0.009

*Data will be log10 normalised

Abbreviations INR, international normalised ratio; PT, prothrombin time; MAP, mean artery pressure; WBC, White blood cell count; TBIL, total bilirubin; ALT, Alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, glutamyl transpeptidase; sCr, serum creatinine; BUN, blood urea nitrogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein; sNa, Serum sodium; HBeAg, hepatitis B virus e antigen; PHR, Platelet high-density lipoprotein ratio

DeLong test. In summary, the newly developed model exhibits significantly higher predictive capability compared to the traditional CTP classification, MELD score, and MELD-Na score. However, when compared to the COSSH ACLF II score developed specifically for HBV-ACLF patients, there is no statistically significant difference (refer to Fig. 5; Table 3).

Clinical utility analysis

Decision curve analysis (DCA) is a suitable approach for evaluating predictive models by assessing net benefits across a range of threshold probabilities. It can identify risk models and assist us in making better clinical decisions. As shown in Fig. 6, the prognostic model based on PHR demonstrates superior clinical decision-making performance compared to traditional CTP score, MELD score, and MELD-Na score.

The correlation between biomarkers and existing prognostic scores not only demonstrates the accuracy of biomarker prediction capabilities but also indicates the redundancy or overlap with existing models. If biomarkers can identify individuals who are classified as low-risk by traditional prognostic scoring but are actually at high risk, they would further demonstrate their predictive value and complement the existing prognostic scoring systems. Therefore, we correlated PHR with four widely recognized prognostic scores. As shown in Supplementary Fig. 3, the correlation between PHR and CTP grading is statistically significant with a *P*-value of 0.003, indicating the predictive consistency of PHR for liver classification in patients. However, there was no significant correlation between PHR and MELD score, MELD-Na score, and COSSH-ACLF II score. This suggests that under the same MELD score, MELD-Na score, or COSSH-ACLF II score, prognosis stratification based on PHR levels can provide additional predictive value for patient outcomes.

Discussion

One of the means to alleviate the burden on public health is the early assessment of patients' prognosis, guiding clinical management, and providing personalized care. Systemic inflammation is a major driving factor of ACLF and a significant pathophysiological characteristic of ACLF [1, 2, 4]. In this explorative study, we conducted the first evaluation of the association between the systemic inflammation score PHR and the prognosis of HBV-ACLF. We found a negative correlation between PHR levels and liver function in patients, with lower PHR levels observed in patients with poorer prognosis. Further regression analysis revealed that PHR was an independent risk factor for the 28-day mortality rate of patients. The prognostic performance of the score constructed based on PHR levels was significantly higher than that of

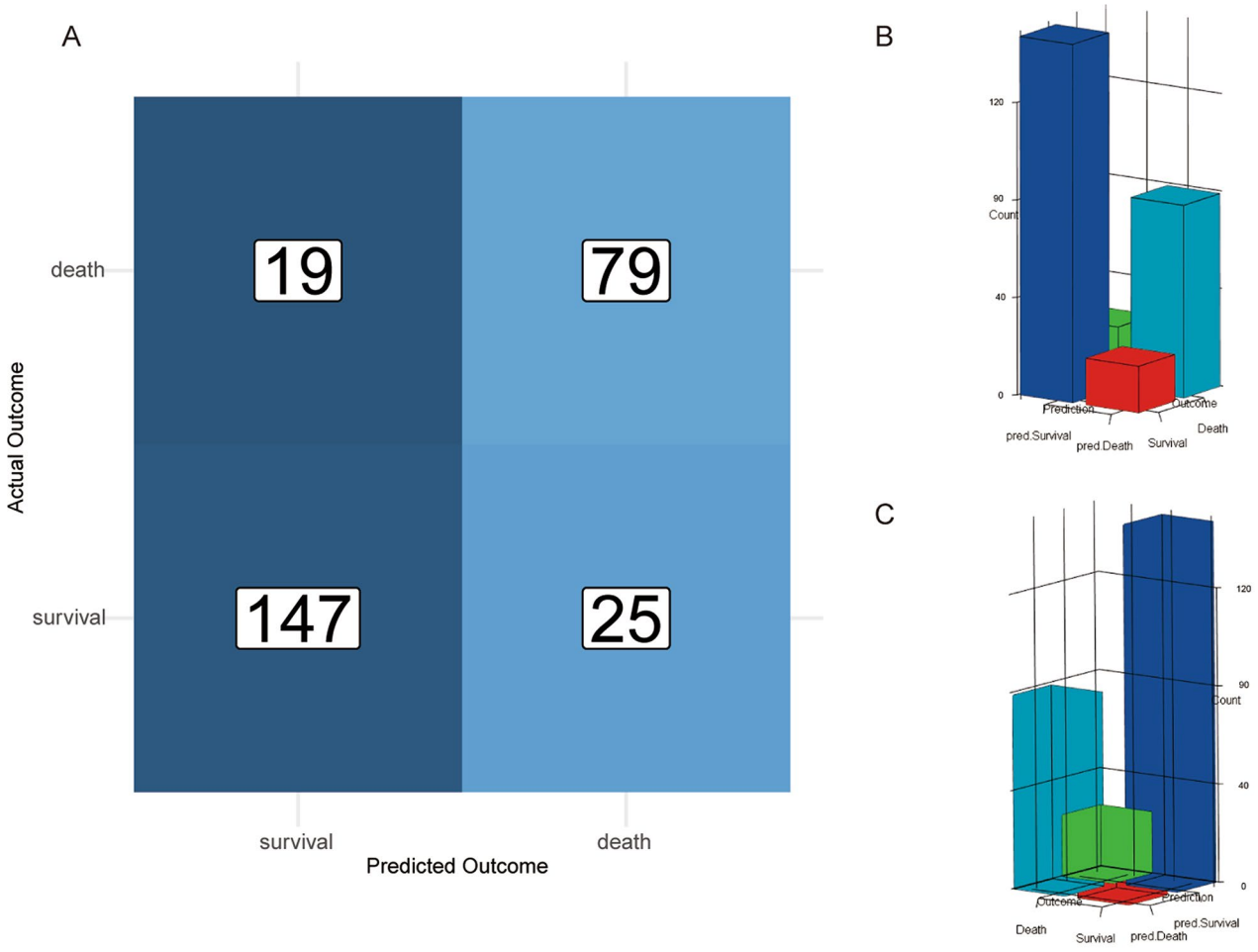

Fig. 3 Parameters of the prognostic model. **A**, **B** and **C**: Confusion matrix of the prognostic mode

CTP score, MELD score, and MELD-Na score. DCA also indicated that the newly developed prognostic score had higher clinical utility than traditional scores.

Several simple, accurate, and objective inflammatory scores have been used for predicting specific inflammatory-related disease spectra, with the most common being NLR. It exhibits excellent predictive abilities in sepsis [16], organ transplantation [17], stroke [18], cancer [19], and liver failure [7, 20] by accurately forecasting disease progression and identifying patient prognosis. The promising clinical utility of these user-friendly systemic inflammatory scores is demonstrated, highlighting their potential value in clinical practice. In fact, the inflammatory score, PHR, also originates from common laboratory indicators and was initially identified to be associated with metabolic syndrome [9]. It is a syndrome characterized by endothelial dysfunction, inflammation, and the release of procoagulant mediators. Chun Feng et al. further investigated the relationship between PHR and liver fibrosis using a large sample cohort, and suggested that PHR could serve as a marker for liver fibrosis [10]. The close association of PHR with inflammation and fibrosis makes it a potential novel biomarker for identifying the prognosis of HBV-ACLF patients in the context of cirrhosis.

Thrombocytopenia is a prominent feature of chronic liver disease and cirrhosis [21]. It has been traditionally believed that excessive platelet clearance is due to splenic hyperfunction caused by portal hypertension. Recent studies, however, have shown a decrease in platelet production and functional defects in platelets [21, 22]. The study by Wang et al. has reported that platelet count is an independent predictor of survival in patients with HBV-ACLF [23]. In patients with liver cirrhosis, platelet count is also one of the predictors of decompensation [24]. In patients with liver cirrhosis, platelet count is also one of the predictors of decompensation [24]. In our cohort, the platelet count of patients in the deceased group was slightly lower than that of the survival group, although not statistically significant. However, in terms of white blood cell count, the level in the deceased group was significantly higher than that in the survival group.

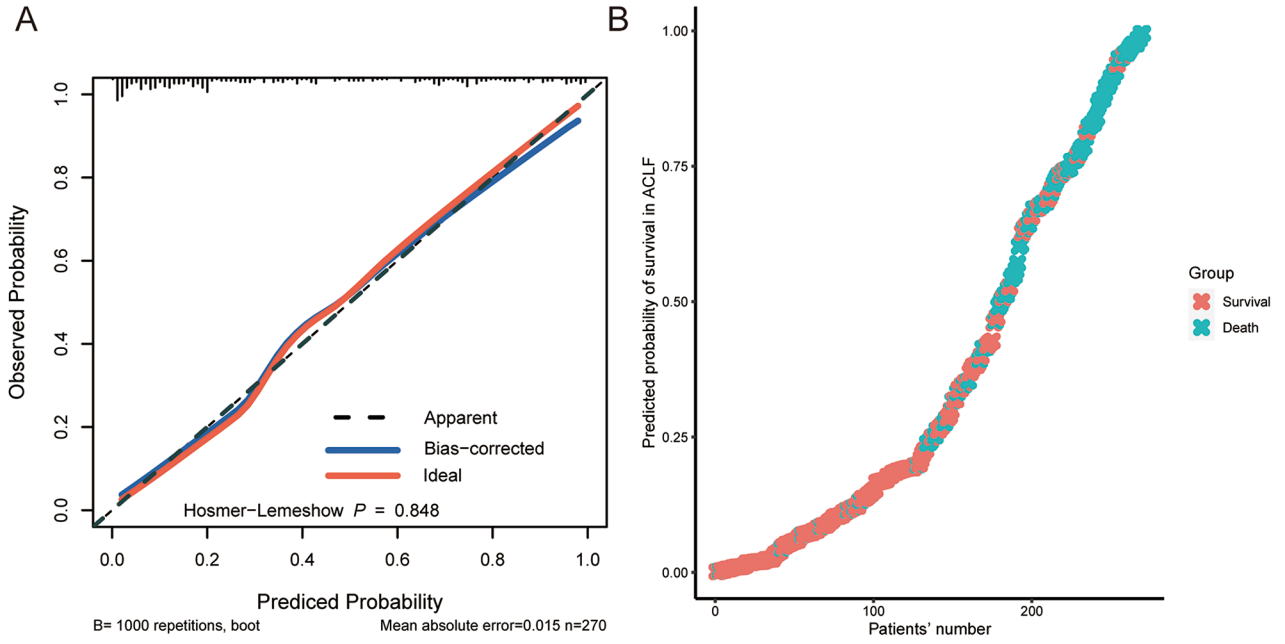

Fig. 4 Validation of the prognostic model. **A**: Calibration curve of the prognostic model. **B**: Probability-Actual Outcome Curve

The potential mechanism may involve an increased degree of platelet-leukocyte aggregation in HBV-ACLF patients, promoting immune dysregulation in the body [25]. This is because platelet-induced leukocyte activation is enhanced, and ongoing platelet activation may also contribute to an increased formation of platelet-leukocyte complexes [25, 26]. Unfortunately, this study did not measure markers of platelet activation, and further research is needed to confirm this hypothesis.

Another parameter in PHR is high-density lipoprotein cholesterol. HDL-C is not only involved in lipid metabolism but also serves as an indicator of immune function in inflammatory diseases. HDL-C possesses various protective functions such as anti-infection, anti-inflammatory, antioxidant, anti-thrombotic, and immune-regulatory properties [13, 27]. Indeed, Markus and his colleagues have found that HDL-C is a reliable predictor of survival in patients with chronic liver failure [28]. Our team has also discovered that low levels of HDL-C can predict poor prognosis in patients with HBV-ACLF [29]. In our cohort, we also confirmed the above results. When comparing between groups, the levels of HDL-C in the deceased group were lower than those in the survival group. Mechanistically, HDL-C can bind to LPS in the blood, reducing inflammatory responses [30]. On the other hand, it regulates inflammasome function to decrease the maturation of pro-inflammatory cytokines [13]. Platelet count and HDL-C alone are not independent risk factors for HBV-ACLF patients. In fact, the PHR is considered a systemic inflammation score and has some correlation with liver fibrosis. It is explainable that the prognosis of ACLF patients with a cirrhotic background, characterized by a systemic inflammatory response, can be represented by this score.

In addition, in our cohort, the COSSH-ACLF II score [31] developed by a Chinese research team demonstrates comparable predictive capability to our developed prognostic model (AUC: 0.874 vs. 0.889, $P=0.459$), suggesting that our prognostic model is non-inferior to COSSH-ACLF IIs. Furthermore, through a correlated analysis between patients' PHR levels and COSSH-ACLFIIs, we found no significant correlation between the two. This implies that at the same COSSH-ACLFIIs, calculating the PHR can further stratify patients for their 28-day prognosis, as PHR also serves as an independent predictor of short-term mortality.

This study has the following limitations. Firstly, it is a single-center retrospective clinical data analysis, inevitably leading to potential biases. However, we have mitigated its impact on the results by employing diverse statistical analyses. Secondly, this study lacks external validation using independent datasets. We only conducted calibration curve analysis through 1000 resamplings and actual probability-prediction probability curve analysis to collectively assess the predictive model's accuracy. Finally, we excluded patients who had been consistently using lipid-lowering drugs, and caution should be exercised in applying the obtained results to this subgroup.

In conclusion, our study indicates that PHR is an independent risk factor for short-term mortality in HBV-ACLF patients. The clinical prediction model built based on PHR exhibits significantly improved accuracy

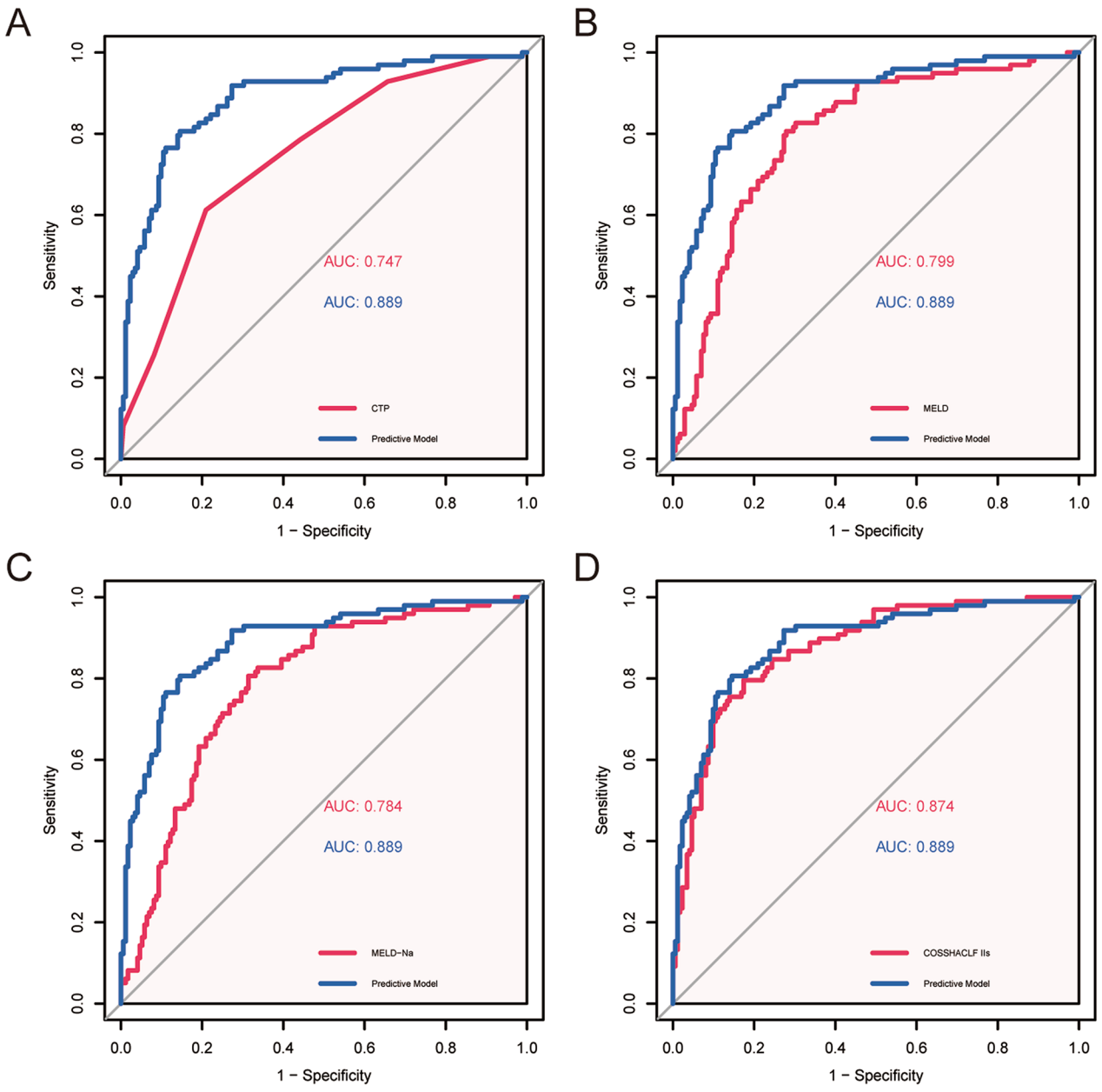

Fig. 5 AUROC analysis of the prognostic model. The AUROC of (**A**) CTP, (**B**) MELD, (**C**) MELD-Na and (**D**) COASS-ACLF IIs comparison with the prognostic model, statistical comparison using the DeLong method

Table 3 Model predictive ability comparison

	AUCs	*P*-Value
CTP vs. Predictive Model	0.747 vs. 0.889	<0.001
MELD vs. Predictive Model	0.799 vs. 0.889	<0.001
MELD-Na vs. Predictive Model	0.784 vs. 0.889	<0.001
COSSH ACLF IIs vs. Predictive Model	0.874 vs. 0.889	0.459

Abbreviations CTP, Child-Turcotte-Pugh; MELD, Model for end-stage liver disease; MELD-Na, MELD sodium; COSSH-ACLF IIs, Chinese Group on the Study of Severe Hepatitis B-ACLF II score

in predicting 28-day mortality compared to traditional prognostic scores. PHR may serve as a simple and accurate biomarker for short-term mortality in HBV-ACLF patients.

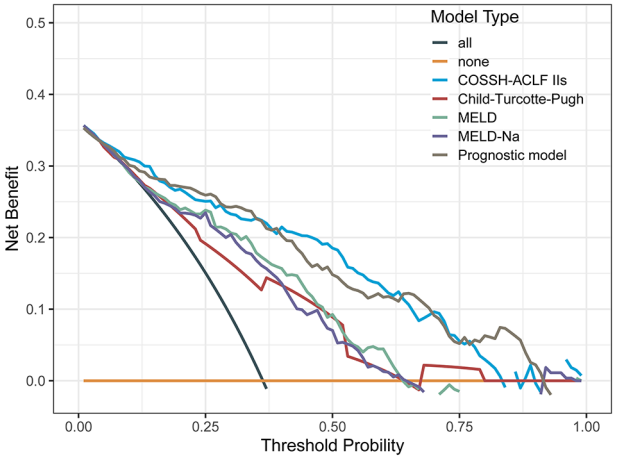

Fig. 6 Clinical utility analysis. DCA curves of different prognostic models

Abbreviations

INR	International Normalized Ratio
PT	Prothrombin Time
MAP	Mean Artery Pressure
TBIL	Total Bilirubin
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ALP	Alkaline Phosphatase
GGT	Glutamyl Transpeptidase
sCr	Serum Creatinine
BUN	Blood Urea Nitrogen
HDL	High-Density Lipoprotein
LDL	Low-Density Lipoprotein
sNa	Serum Sodium
HBeAg	Hepatitis B virus e Antigen
CTP	Child-Turcotte-Pugh
MELD	Model for End-stage Liver Disease
MELD-Na	MELD Sodium
COSSH-ACLF IIs	Chinese Group on the Study of Severe Hepatitis B-ACLF II score
PHR	Platelet /HDL ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-09769-0.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Acknowledgements

We would like to thank the National Natural Science Foundation of China (Grant number: 82360131 and 81960120) and the Postgraduate Innovation Special Foundation of Jiangxi Province (Grant number: YC2023-B058) for financial support. And this work was supported by the Key Laboratory Project of Digestive Diseases in Jiangxi Province (2024SSY06101), and Jiangxi Clinical Research Center for Gastroenterology (20223BCG74011).

Author contributions

Linxiang Liu and ChenKai Huang contributed equally to this study. Linxiang Liu designed and wrote the original draft, Chenkai Huang analyzed the data and provide interpretations of the results. Yuan Nie analyzed the data, Yue Zhang collected the data and created some of the figures. Juanjuan Zhou and Xuan Zhu critically revised the manuscript.

Funding

This study was supported by the National Natural Science Foundation of China (grant number: 82360131 and 81960120) and the Postgraduate Innovation Special Foundation of Jiangxi Province (Grant number: YC2023-B058).

Data availability

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University (Approval IIT-2021-09). Informed consents of the patients were waived by the Ethics Committee of the First Affiliated Hospital of Nanchang University because of the retrospective and anonymous nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 7 July 2024 / Accepted: 20 August 2024
Published online: 29 August 2024

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