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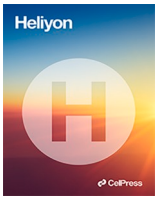

Research article

Lymphocyte to high density lipoprotein ratio can predict the short-term prognosis of hepatitis B virus-related acute-on-chronic liver failure patients

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ABSTRACT

Background: Acute-on-chronic liver failure (ACLF) is a syndrome characterized by systemic inflammation, leading to high short-term mortality. The lymphocyte to high-density lipoprotein ratio (LHR) has been introduced as a novel marker of inflammation. However, its role as a prognostic inflammatory biomarker in the context of hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) has received limited attention.

Methods: We retrospectively included 272 patients with HBV-ACLF who met the definition of APALC. Data on clinical features and laboratory tests were collected from medical records within 24 h. Logistic regression was used to identify risk factors for poor short-term prognosis, and LHR-based prediction (*LHRB*) models were constructed based on risk factors. Furthermore, the accuracy of the LHRB model was validated through rigorous testing.

Results: In the survival and death groups, there were statistical differences in their CTP, MELD, MELD-Na, COSSH-ACLF II scores, and LHR. Multivariate logistic regression identified seven predictors significantly associated with 28-day mortality. Furthermore, statistically significant differences in short-term mortality and certain clinical laboratory tests for poor prognosis were observed between the high and low LHR groups. To assess the predictive performance of various models in terms of short-term mortality, the area under the receiver operating characteristic curve (AUROC) was calculated. The AUROC values for the CTP, MELD, MELD-Na, COSSH-ACLF II, and *LHRB* models were found to be 0.725, 0.788, 0.772, 0.871, and 0.877, respectively. The results in the validation group were similar to those in the training group, and the validation results suggested excellent performance of the *LHRB* model.

Conclusion: LHR levels have the potential to serve as indicators for the prognosis of HBV-ACLF. Additionally, the recently developed *LHRB* model offers an accessible risk assessment tool.

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1. Introduction

Chronic hepatitis B virus (HBV) infection continues to be a significant global health challenge, affecting around 296 million people worldwide, including approximately 86 million chronic cases in China [1]. As a result of HBV infection, there is a subsequent complication of a series of chronic liver diseases, such as acute-on-chronic liver failure (ACLF), which is considered a unique syndrome with high short-term mortality [2]. Therefore, early identification of patients at high risk of poor prognosis is vital to clinical practice.

The existing traditional prognostic scores, such as the Child-Turoctte-Pugh (CTP) score, have subjectively defined variables and the Model for End-Stage Liver Disease (MELD) score is cumbersome to calculate and complex to use. Moreover, they cannot fully meet clinical needs in terms of predictive accuracy [3]. Therefore, it is important to further develop prediction tools with good prediction performance and ease of use.

The immune-mediated systemic inflammatory response is a key component in the development of ACLF [4], and immune dysregulation of pro- and anti-inflammatory processes increases the risk of extrahepatic complications [5]. In addition, inflammatory responses activate various cell death pathways in the liver, contributing to multi-organ dysfunction and high mortality rates. Consequently, assessing inflammatory biomarkers is crucial for predicting the prognosis of ACLF. Many inflammatory biomarkers such as CXCL10 [6], CD163 [7], and NLR [8] are known to be associated with the prognosis of ACLF patients.

High-density lipoprotein cholesterol (HDL-C) serves as a biomarker for numerous diseases. Studies have shown that plasma HDL-C levels can act as a predictor for liver cirrhosis in patients with chronic hepatitis B (CHB) [9]. For patients with liver cirrhosis, HDL-C is also an independent predictor of poor outcomes for such patients [10,11]. The lymphocyte/high-density lipoprotein ratio (LHR), which is the ratio of the number of lymphocytes divided by the level of high-density lipoprotein, is a new inflammatory parameter. LHR has been reported to respond to systemic inflammation in the body of COVID-19 [12] and metabolic syndrome (MetS) [13]. However, for patients with HBV-ACLF, there is a lack of data on LHR as a comprehensive indicator to assess patient outcomes. Building on prior research, we hypothesized that LHR could be a predictor of short-term mortality in HBV-ACLF. This study aims to investigate the association between LHR and 28-day mortality in patients with hepatitis B-associated acute-on-chronic liver failure (HBV-ACLF) and to develop a practical predictive model utilizing LHR.

2. Methods

2.1. Study design and patients

This was a single-center retrospective study that included a total of 272 patients. The cohort was divided into a training group and a validation group in an 8:2 ratio according to the time sequence of patient admission, in order to ensure sufficient data for the establishment of predictive models. The training group was employed to identify independent prognostic factors for short-term mortality and to develop a new prognostic score. The validation group was then used to evaluate and confirm the effectiveness of this score.

Patients with HBV-ACLF were recruited based on APASL criteria, which include 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 below 40 %, along with the development of ascites and/or hepatic encephalopathy within the past 4 weeks. Inclusion criteria were: (1) age $\geq$18 years, (2) diagnosis of HBV-ACLF, and (3) availability of clinical information. Exclusion criteria included: (1) hepatocellular carcinoma, (2) presence of other chronic liver diseases, (3) prior liver transplantation, (4) severe chronic extrahepatic conditions, and (5) HIV infection or use of immune-suppressive medications. Our study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University (IIT [2021] 09), and conducted in accordance with the Declaration of Helsinki. Informed consents of the patients were waived by the Ethics Committee of the First Affiliated Hospital of Nanchang University.

2.2. Clinical data

Demographic and clinical data were retrospectively extracted from records in the inpatient information management system, and laboratory variables for all subjects were measured within 24 h of admission. Demographic variables included gender and age. Clinical variables included international normalized ratio (INR), prothrombin time (PT), D-dimer, mean arterial pressure (MAP), white blood cell count, lymphocyte count, hemoglobin, platelet count, albumin, total bilirubin (TBIL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), blood urea nitrogen (BUN), creatinine, serum hepatitis B virus DNA (HBV-DNA), hepatitis Be Antigen (HBeAg), serum sodium and lipid levels. The presence of hepatic encephalopathy and ascites were also recorded. Finally, the patient's survival status during the 28 days is also recorded in complete detail.

2.3. Definitions

The diagnostic criteria for ACLF, as outlined in the 2019 Asia-Pacific Association for the Study of the Liver (APASL) consensus, are defined as follows: patients must exhibit acute liver injury, indicated by jaundice (serum bilirubin $\geq$5 mg/dL) and coagulation dysfunction [international normalized ratio (INR) $\geq$1.5 or prothrombin activity $<$40 %], along with complications such as clinical ascites and/or encephalopathy within 4 weeks, in the context of either previously diagnosed or undiagnosed chronic liver disease/cirrhosis [14]. Child-Turcotte-Pugh score [15] was computed based on albumin, ascites, serum bilirubin, HE and PT. The MELD

formula [16] was: 3.8 × log (bilirubin [mg/dL]) + 11.2 × log (INR) + 9.6 × log (creatinine [mg/dL]) + 6.43. MELD-Na formula [17] was: (0.025 × MELD × (140–Na)) + 140. COSSH-ACLF II score [18] = 1.649 × ln(INR)+ 0.457 × HE score (HE grade: 0/1, 1–2/2 and 3–4/3) + 0.425 × ln(neutrophil [10^9/L]) +0.396 × ln(TB [umol/L]) + 0.576 × ln(serum urea [mmol/L]) + 0.033 × age. LHR = lymphocyte (10^9/L)/HDL (mmol/L) ratio.

2.4. Statistical analysis

Continuous variables are presented as means with standard deviations (SD) or medians with interquartile ranges (IQR), while categorical variables are represented by frequencies and percentages (%). We examined whether there was an interaction among the explanatory variables and found no significant interactions within the variables considered. Group comparisons were conducted using Student's t-tests or Mann–Whitney *U* test. The diagnostic accuracy of different models was evaluated through receiver operating characteristic (ROC) analysis. The areas under the ROC curves (AUCs) were compared following the methodology described by DeLong et al. All statistical tests were two-sided and set at a significance level of 5 %. All analyses were conducted using R 4.1.0 (R Project for Statistical Computing, Vienna, Austria). The R packages used for model construction and statistical analysis included gtsummary, tidyverse, performance, pROC, rms, and compareGroups. The Decision Curve Analysis (DCA) plots were generated using the source file "stdca.r," which was downloaded from www.mskcc.org.

3. Result

3.1. Study population

A total of 272 patients were enrolled in this retrospective study and were divided into the training group and the validation group according to the chronological order of admission (Fig. 1). As shown in Table 1, there is almost no difference between the baseline characteristics of the training and validation groups, including LHR. In the training group, the mean age was 49.5 years, and poor coagulation and liver function were present in these patients. The majority of these patients did not have concomitant hepatic encephalopathy on admission and their 28-day mortality rate was approximately 36.1 %.

3.2. Baseline comparison of the survival and death groups

Table 2 shows the baseline characteristics of patients with different prognostic outcomes within 28 days. Patients in the death group had higher age, INR, PT, D-dimer, white blood cell count, total bilirubin, AST and HBV-DNA copy number. However, their lymphocyte counts, cholesterol, triglycerides, serum sodium and LHR were lower. Fig. 2 visualizes the differences in liver function scores and LHR between the two groups.

3.3. Identification of independent prognostic factors for 28-day mortality in HBV-ACLF

Univariate analysis first identified age, INR, PT, MAP, white blood cell count, lymphocyte count, total bilirubin, AST, BUN, serum sodium, HBV-DNA copy number, whether e antigen was positive and LHR as candidates. To avoid overfitting of the model due to multicollinearity, we first calculated the variance inflation factor. Next, the highly correlated variables were removed (Supplementary Figure). Finally, Age, INR, MAP, white blood cell count, TBIL, AST, BUN, serum sodium, HBV-DNA copy number, whether HBeAg

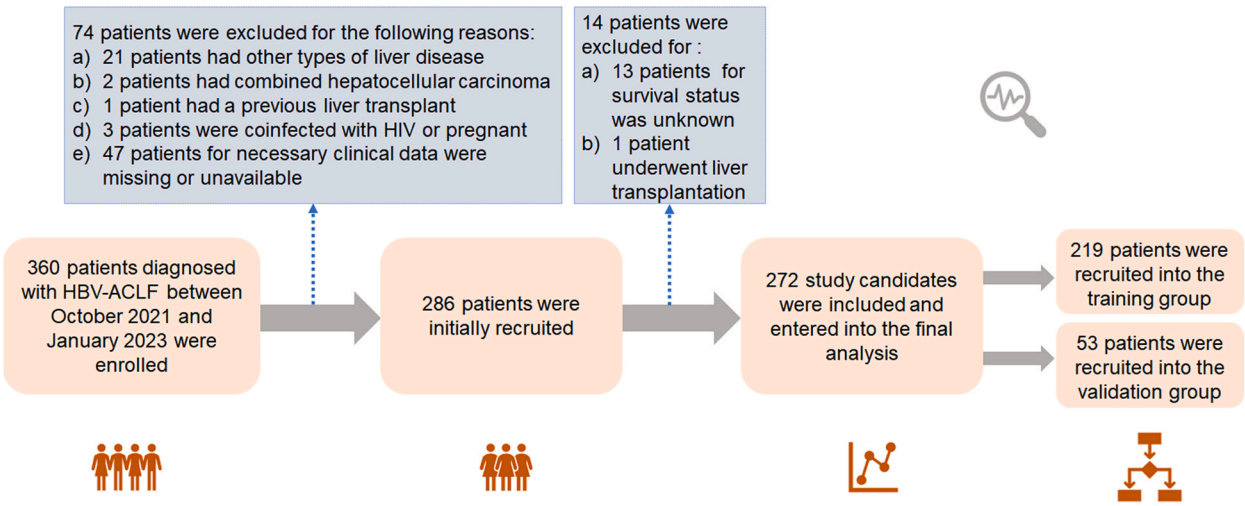

Fig. 1. Design diagram of this study.

Table 1
Baseline characteristics of the training and validation groups.

	Training Group (n = 219)	Validation Group (n = 53)	P-value
male (%)	183 (83.6 %)	43 (81.1 %)	0.826
Age (years)	49.5 ± 12.2	48.3 ± 12.9	0.557
INR	1.89 [1.62–2.40]	1.73 [1.59–2.31]	0.116
PT (s)	21.0 [18.3–25.6]	19.1 [17.5–24.9]	0.098
D-dimer (mg/L)	2.04 [0.94–3.83]	1.99 [0.89–4.28]	0.896
MAP (mmHg)	86.6 ± 12.4	88.0 ± 12.6	0.464
White blood cell count (10^9/L)	6.80 ± 3.38	6.47 ± 2.74	0.462
Lymphocyte count (10^9/L)	1.25 ± 0.64	1.07 ± 0.47	0.026
Hemoglobin (g/L)	120 ± 25.6	118 ± 21.1	0.597
Platelet count (10^9/L)	113 ± 56.9	109 ± 58.6	0.682
TBIL (μmol/L)	271 [169–363]	261 [154–364]	0.846
Albumin (g/L)	31.7 ± 4.63	31.2 ± 3.76	0.386
ALT (U/L)	438 [95.5–1201]	253 [85.0–667]	0.130
AST (U/L)	280 [123–704]	224 [123–495]	0.146
ALP (U/L)	154 [124–203]	149 [115–187]	0.090
GGT (U/L)	106 [69.0–157]	95.0 [59.0–155]	0.398
sCr (μmol/L)	77.5 ± 75.1	77.9 ± 76.3	0.972
BUN (mmol/)	3.90 [2.90–5.40]	3.60 [2.80–5.50]	0.781
Cholesterol (mmol/L)	2.68 [2.04–3.13]	2.63 [2.03–3.33]	0.933
Triglyceride (mmol/L)	1.12 [0.72–1.61]	1.04 [0.67–1.61]	0.743
HDL (mmol/L)	0.22 [0.15–0.36]	0.22 [0.17–0.32]	0.922
LDL (mmol/L)	1.00 [0.56–1.48]	0.99 [0.47–1.56]	0.764
sNa (mmol/L)	137 ± 4.30	137 ± 4.43	0.351
HBV-DNA ($\log_{10}$ IU/mL)	4.60 [2.91–6.33]	3.50 [2.70–5.60]	0.024
HBeAg-positive (%)			0.361
negetive	153 (69.9 %)	41 (77.4 %)	
positive	66 (30.1 %)	12 (22.6 %)	
HEscore:			0.207
Grade 0	162 (74.0 %)	43 (81.1 %)	
Grade 1-2	20 (9.13 %)	1 (1.89 %)	
Grade 3-4	37 (16.9 %)	9 (17.0 %)	
Ascites:			0.917
Minimal ascites	98 (44.7 %)	24 (45.3 %)	
Moderate ascites	80 (36.5 %)	18 (34.0 %)	
Large ascites	41 (18.7 %)	11 (20.8 %)	
28-day mortality:			0.976
survival	140 (63.9 %)	34 (64.2 %)	
death	79 (36.1 %)	19 (35.8 %)	
CTP	11.0 [10.0–12.0]	11.0 [9.00–12.0]	0.682
MELD	21.1 [17.7–25.0]	21.0 [15.0–24.3]	0.278
MELD-Na	21.3 [17.7–27.2]	21.1 [16.6–25.0]	0.319
COSSHACLF	6.87 [6.24–7.70]	6.59 [5.88–7.80]	0.262
LHR	5.97 ± 4.42	5.25 ± 3.15	0.173

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; LHR, lymphocyte/HDL ratio.

positive or not, and LHR were included in the multivariate analysis. We identified age (OR:1.06 CI:1.02–1.10), INR (OR: 4.41 CI: 2.35–9.19), MAP (OR: 1.03 CI: 1.00–1.07), TBIL (OR: 1.01 CI:1.00–1.01), AST (OR: 1.00 CI: 1.00–1.00), HBV-DNA (OR: 1.43 CI: 1.11–1.85) and LHR (OR:0.89 CI:0.80–0.98) as independent risk factors for 28-day mortality in patients with HBV-ACLF (Table 3).

3.4. Baseline comparison of patients in the high LHR and low LHR groups

Patients were divided into high LHR group and low LHR group based on the Youden index of LHR predicting 28-day mortality. In the low LHR group, patients showed higher mortality (45.5 % vs. 21.2 %), and they also had relatively higher liver prognosis scores. In addition, patients in the low LHR group had worse coagulation, lower lymphocyte counts, hemoglobin and platelet counts, and a higher incidence of hepatic encephalopathy (Table 4).

3.5. Development and validation of a predictive model based on LHR

Considering the independent risk factors identified above, we developed an **LHR-b**ased prediction model, which we refer to as the *LHRB* model. *LHRB* model = −0.1098 × LHR+0.0579 × Age(years)+1.6205 × INR+0.0235 × MAP(mmHg)+0.0054 × TBIL(μmol/

Table 2
Comparison of baseline characteristics between the survival and death groups.

	Survival Group (n = 140)	Death Group (n = 79)	P-value
male (%)	113 (80.7 %)	70 (88.6 %)	0.186
Age (years)	47.7 ± 1.9	52.6 ± 2.2	0.004
INR	1.74 [1.59–2.00]	2.39 [1.87–3.06]	<0.001
PT (s)	19.4 [17.8–22.7]	25.3 [20.3–32.4]	<0.001
D-dimer (mg/L)	1.60 [0.85–2.88]	3.17 [1.34–4.92]	<0.001
MAP (mmHg)	85.5 ± 11.7)	88.5 ± 3.4	0.100
White blood cell count (10^9/L)	6.22 ± 2.90	7.82 ± 3.92	0.002
Lymphocyte count (10^9/L)	1.31 ± 0.63	1.13 ± 0.65	0.043
Hemoglobin (g/L)	121 ± 22.1	118 ± 30.9	0.429
Platelet count (10^9/L)	113 ± v48.8	113 ± 69.2	0.953
TBIL (μmol/L)	241 [145–329]	338 [228–427]	<0.001
Albumin (g/L)	31.8 ± 5.01	31.4 ± 3.87	0.492
ALT (U/L)	378 [87.3–1142]	567 [118–1246]	0.130
AST (U/L)	235 [97.6–582]	422 [174–967]	0.004
ALP (U/L)	153 [122–204]	155 [124–201]	0.984
GGT (U/L)	110 [70.8–163]	98.0 [68.0–152]	0.716
sCr (μmol/L)	76.9 ± 88.1	78.6 ± 44.1	0.849
BUN (mmol/)	3.80 [3.00–5.00]	4.00 [2.80–6.70]	0.251
Cholesterol (mmol/L)	2.75 [2.14–3.31]	2.40 [1.92–2.94]	0.008
Triglyceride (mmol/L)	1.25 [0.79–1.63]	0.99 [0.60–1.50]	0.025
HDL (mmol/L)	0.20 [0.15–0.34]	0.23 [0.16–0.36]	0.415
LDL (mmol/L)	1.02 [0.63–1.52]	0.89 [0.44–1.42]	0.342
sNa (mmol/L)	137 ± 3.86	136 ± 4.90	0.032
HBV-DNA (log_{10} IU/mL)	4.34 [2.74–5.68]	5.40 [3.47–6.83]	0.003
HBeAg-positive (%)			0.104
negetive	92 (65.7 %)	61 (77.2 %)	
positive	48 (34.3 %)	18 (22.8 %)	
HEscore:			<0.001
Grade 0	127 (90.7 %)	35 (44.3 %)	
Grade 1-2	8 (5.71 %)	12 (15.2 %)	
Grade 3-4	5 (3.57 %)	32 (40.5 %)	
Ascites:			0.153
Minimal ascites	64 (45.7 %)	34 (43.0 %)	
Moderate ascites	55 (39.3 %)	25 (31.6 %)	
Large ascites	21 (15.0 %)	20 (25.3 %)	
CTP	10.0 [9.00–11.0]	12.0 [11.0–13.0]	<0.001
MELD	19.0 [16.6–22.5]	24.5 [21.4–27.7]	<0.001
MELD-Na	19.3 [16.7–23.3]	26.9 [21.9–30.7]	<0.001
COSSHACLF	6.44 [6.01–6.92]	7.77 [7.29–8.48]	<0.001
LHR	6.68 ± 4.89	4.70 ± 3.09	<0.001

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; LHR, lymphocyte/HDL ratio.

L)+0.0007 × AST(U/L)+ 0.2508 × log_{10}DNA-11.5709. This model has Accuracy of 0.831, Precision of 0.876, Recall of 0.857, and F1 Score of 0.867. The confusion matrix of the *LHRB* model is shown in Fig. 3A and 3B shows the prediction probability curves, both demonstrating the *LHRB* model prediction reliability. The calibration curve internally validates the accuracy of the model, and the decision curve analysis (DCA) suggests the clinical utility of the *LHRB* model from a clinical practice perspective (Fig. 3C–D). Fig. 4 compares the ROC of common liver-related prediction models with the LHRB model. Subsequently, the area under the receiver operating characteristic curve (AUROC) of the liver-related prediction model and the *LHRB* model were conducted in the training and validation groups, respectively, and the statistical tests between them are shown in Table 5.

4. Discussion

Hepatitis B virus-associated acute chronic liver failure is considered the leading cause of ACLF in China, a unique life-threatening syndrome that places a heavy burden on patients and the health care system. Therefore, a simple and effective biomarker and prognostic scoring system is urgently needed to classify patients early and determine individualized treatment strategies. In recent years, LHR has proven to be a novel biomarker of inflammation and has important clinical value due to its easy availability. However, there is no evidence of a relationship between this inflammatory parameter and HBV-ACLF. In this study, we first identified LHR as an independent risk factor for short-term mortality in patients with HBV-ACLF and constructed a new predictive score based on this, which was also initially validated in the validation group.

Lymphocyte to High-Density Lipoprotein Ratio was first developed as a novel inflammatory biomarker in the metabolic syndrome

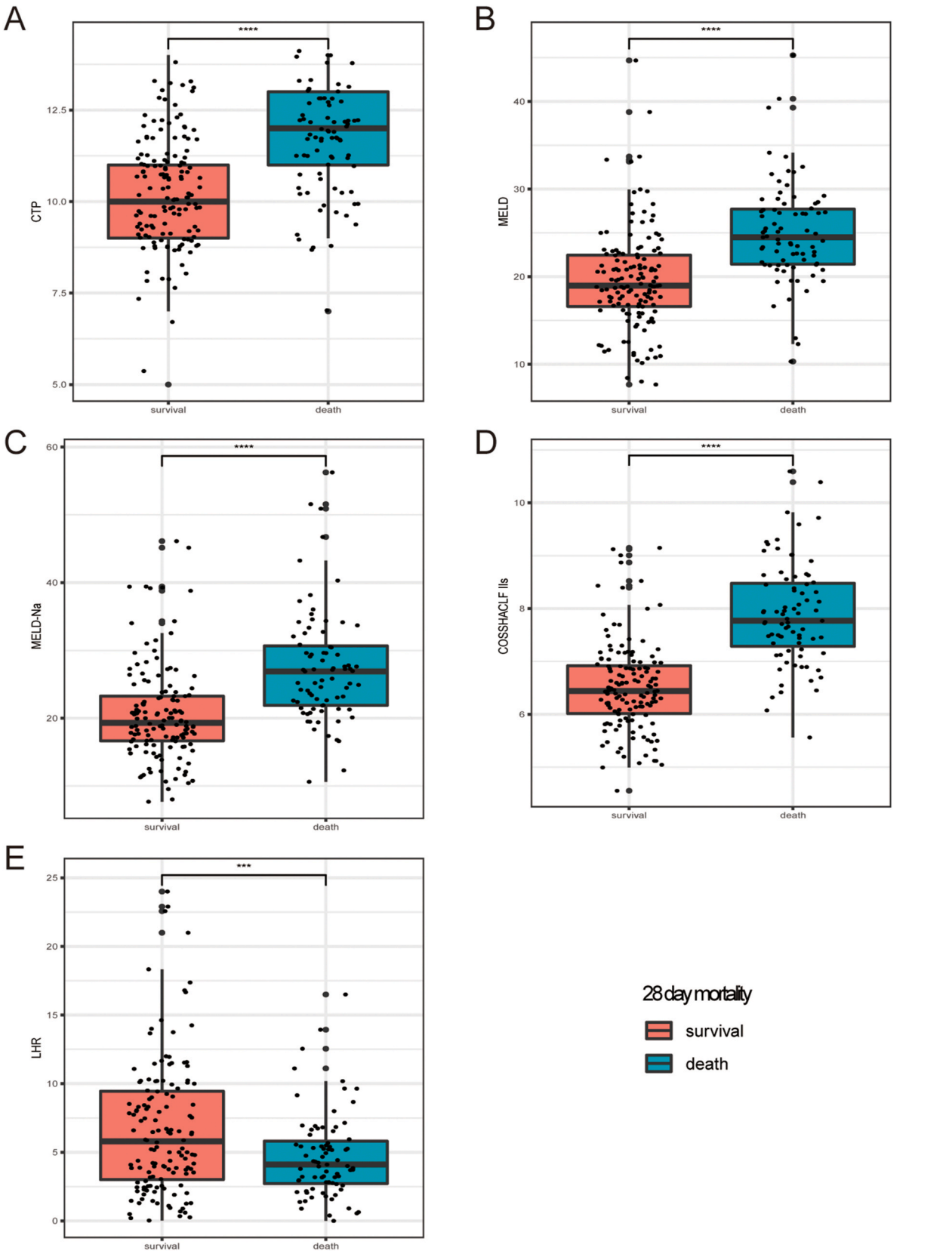

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Fig. 2. Box plots of prognostic scores and LHR for the survival and death groups. A: Comparison of CTP scores between the survival and death groups at 28 days.B: Comparison of MELD scores between the survival and death groups at 28 days.C: Comparison of MELD-Na scores between the survival and death groups at 28 days.D: Comparison of COSSH-ACLF IIs scores between the survival and death groups at 28 days.E: Comparison of LHR between the survival and death groups at 28 days.

(MetS) reflecting the level of systemic inflammation [13]. It was later also used to respond to in vivo inflammation levels in psychiatric-related diseases [19], heart-related diseases [20], and COVID-19 [12]. However, this novel inflammatory biomarker has not been sufficiently appreciated and evaluated in patients with liver disease, especially ACLF characterized by systemic inflammation.

Most studies have concluded that the innate immune system plays a key role in the pathogenesis and prognosis of HBV-ACLF [21,22]. In vivo, HDL mainly performs cholesterol efflux, anti-inflammatory and antioxidant functions, which may be impaired under pathological conditions, in addition to its role as an anti-inflammatory molecule in the immune system [23]. Inflammation is a concern in chronic liver disease, and studies have reported that low levels of HDL are strongly associated with the severity of liver failure, complications, and survival [24]. Another study conducted on patients with CHB yielded an interesting finding: HDL-C levels were associated with liver function, and plasma HDL-C was identified as an independent predictor of progression to cirrhosis [9]. The initial etiology in the above study aligns with our data, suggesting that HDL-C is a reliable predictor of long-term prognosis in patients with chronic HBV infection. This is because HDL-C not only predicts the risk of cirrhosis development but also the risk of adverse events, such as the progression of cirrhosis to hepatocellular carcinoma [23]. In a similar study, HDL was also used as an independent predictor for patients on the HBV-ACLF disease spectrum [25]. On the other hand, there is a profound role of lymphocytes in the development of ACLF, but the immune profile of viral hepatitis-induced ACLF may be more complicated [26]. Li et al. found significantly lower circulating lymphocyte counts and lymphocyte percentages in patients with HBV-ACLF [27] novel biomarker scores based on lymphocyte counts have also been used to provide an understanding of the prognosis of patients with chronic liver disease, such as the neutrophil-to-lymphocyte ratio (NLR) [28,29] and the Platelet-to-lymphocyte ratio (PLR) [28]. Based on the above, we speculate that the lymphocyte to HDL ratio may reflect the immune status in vivo and thus predict the short-term prognosis of ACLF patients.

A single lymphocyte count or HDL level has been suggested as a biomarker for predicting short-term prognosis in patients with ACLF, based on a comparison of this biomarker level in a population of patients with ACLF [25,27]. Since our study did not record data on patient mortality within 90 days, we were unable to assess the prognostic value of the LHR and *LHRB* models in predicting 90-day mortality. However, existing data indicate that HDL-C has a high diagnostic accuracy for 90-day mortality in patients with acute decompensation of cirrhosis, with an AUC of 0.79 [25]. In addition, Wen et al. found that the AUROC for HDL to predict 90-day and 1-year survival in patients with HBV-ACLF was 0.568 and 0.687, respectively, along with a lack of short-term prognostic data [25].

Table 3
Univariate and multivariate predictors of mortality in the training group.

Characteristic	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Sex (female)	0.54 (0.23–1.17)	0.134		
Age	1.03 (1.01–1.06)	0.005	1.06 (1.02–1.10)	0.006
INR	5.5 (3.18–10.16)	<0.001	4.41 (2.35–9.19)	<0.001
PT	1.11 (1.07–1.17)	<0.001		
Ddimer	1.02 (0.99–1.06)	0.264		
MAP	1.02 (1–1.04)	0.089	1.03 (1.00–1.07)	0.048
WBC	1.15 (1.06–1.26)	0.001	1.13 (1.0–1.29)	0.061
Lym	0.61 (0.37–0.97)	0.043		
Hemoglobin	1 (0.98–1.01)	0.385		
Platelet count	1 (0.99–1)	0.949		
TBIL	1.01 (1.00–1.01)	<0.001	1.01 (1.00–1.01)	<0.001
Albumin	0.98 (0.92–1.04)	0.521		
ALT	1 (1.00–1.00)	0.251		
AST	1 (1.00–1.00)	0.009	1.00 (1.00–1.00)	0.033
ALP	1 (1–1)	0.589		
GGT	1 (1–1)	0.72		
sCr	1 (1–1)	0.872		
BUN	1.13 (1.03–1.25)	0.015	1.12 (1.00–1.28)	0.053
Cholesterol	0.78 (0.56–1.04)	0.12		
Triglyceride	0.74 (0.48–1.12)	0.167		
HDL	0.88 (0.33–1.09)	0.628		
LDL	0.86 (0.56–1.28)	0.463		
sNa	0.93 (0.87–0.99)	0.025	0.98 (0.89–1.08)	0.679
HBV-DNA*	1.26 (1.08–1.48)	0.003	1.43 (1.11–1.85)	0.006
HBeAg (positive)	0.57 (0.3–1.05)	0.077	0.79 (0.29–2.10)	0.637
LHR	0.88 (0.81–0.95)	0.002	0.89 (0.80–0.98)	0.028

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; LHR, lymphocyte/HDL ratio.

Table 4
Comparison of baseline characteristics between the high LHR and low LHR group.

	High LHR Group (n = 85)	Low LHR Group (n = 134)	P-value
male	75 (88.2 %)	108 (80.6 %)	0.194
Age (years)	46.9 (12.0)	51.1 (12.1)	**0.012**
INR	1.77 [1.61; 2.10]	1.96 [1.63; 2.63]	**0.016**
PT (s)	20.0 [18.1; 23.7]	21.7 [18.6; 28.3]	**0.018**
D-dimer (mg/L)	1.27 [0.77; 2.73]	2.65 [1.12; 4.70]	**<0.001**
MAP (mmHg)	86.0 (11.4)	87.0 (13.0)	0.538
White blood cell count (10^9/L)	7.22 (2.62)	6.53 (3.77)	0.109
Lymphocyte count (10^9/L)	1.59 (0.60)	1.03 (0.57)	**<0.001**
Hemoglobin (g/L)	126 (22.7)	117 (26.7)	**0.006**
Platelet count (10^9/L)	127 (45.5)	104 (61.6)	**0.002**
TBIL (μmol/L)	253 [188; 350]	280 [147; 384]	0.766
Albumin (g/L)	31.9 (5.25)	31.6 (4.19)	0.601
ALT (U/L)	527 [135; 1272]	360 [76.9; 1190]	0.093
AST (U/L)	391 [132; 876]	264 [113; 668]	0.231
ALP (U/L)	159 [127; 210]	152 [122; 201]	0.323
GGT (U/L)	106 [75.0; 153]	106 [65.2; 158]	0.477
sCr (μmol/L)	78.1 (97.4)	77.1 (57.1)	0.938
BUN (mmol/)	3.80 [2.90; 5.10]	3.90 [3.00; 5.60]	0.520
Cholesterol (mmol/L)	2.68 [2.11; 3.06]	2.66 [1.99; 3.27]	0.791
Triglyceride (mmol/L)	1.49 [1.07; 1.79]	0.94 [0.54; 1.41]	**<0.001**
HDL (mmol/L)	0.15 [0.13; 0.18]	0.30 [0.21; 0.46]	**<0.001**
LDL (mmol/L)	0.78 [0.49; 1.27]	1.08 [0.66; 1.72]	**0.003**
sNa (mmol/L)	138 (3.71)	136 (4.59)	**0.036**
HBV-DNA ($\log_{10}$ IU/mL)	4.58 [3.34; 6.14]	4.63 [2.70; 6.40]	0.906
HBeAg-positive (%)			0.569
negetive	57 (67.1 %)	96 (71.6 %)	
positive	28 (32.9 %)	38 (28.4 %)	
HEscore:			**0.002**
Grade 0	72 (84.7 %)	90 (67.2 %)	
Grade 1-2	8 (9.41 %)	12 (8.96 %)	
Grade 3-4	5 (5.88 %)	32 (23.9 %)	
Ascites:			0.581
Minimal ascites	40 (47.1 %)	58 (43.3 %)	
Moderate ascites	32 (37.6 %)	48 (35.8 %)	
Large ascites	13 (15.3 %)	28 (20.9 %)	
28-day mortality:			**<0.001**
survival	67 (78.8 %)	73 (54.5 %)	
death	18 (21.2 %)	61 (45.5 %)	
CTP	10.0 [9.00; 12.0]	11.0 [10.0; 12.0]	**0.023**
MELD	20.6 [18.3; 22.7]	21.9 [17.2; 25.5]	0.200
MELD-Na	20.8 [18.4; 24.4]	22.7 [17.2; 29.3]	0.159
COSSHACLF	6.58 [6.22; 7.18]	7.12 [6.32; 7.95]	**0.005**
LHR	10.3 (3.95)	3.22 (1.60)	**<0.001**

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; LHR, lymphocyte/HDL ratio.

However, in the LHR-based prediction model we developed, the AUROC for predicting short-term mortality in HBV-ACLF patients reached 0.877. Therefore, we reasonably speculate that the LHR and *LHRB* models may have prognostic value in predicting 90-day mortality. Another fact of interest is that in the poor prognosis group, they had lower LHR levels. This means that the poor prognosis patient population had more reduced levels of circulating lymph counts than reduced levels of HDL. Disturbances in the physiological function and number of immune cells are the initiating link in this syndrome of ACLF [4,21]. Further, in patients with HBV-ACLF, alterations in immune cells, represented by circulating lymphocytes, as a marker of immune disorders, are more likely to advance poor outcomes in these patients compared to HDL.

In the *LHRB* model we developed, the variables of the model are easily accessible in clinical practice, and also include indicators of liver injury, coagulation function, age, and degree of HBV infection, avoiding variables that contain subjectivity, such as CTP scores. The predictive performance in the *LHRB* model was higher than traditional scores such as the CTP score and the MELD score, but comparable to the performance of the recently developed COSSH-ACLF IIs (AUROC: 0.871 vs. 0.877), and the performance of the model in the validation group was also consistent with that of the training group.

This study has some potential limitations. Firstly, as a retrospective single-center study, some bias is unavoidable. The above limitations can be attributed to the relatively small sample size. However, we employed rigorous statistical methods to minimize the impact of bias on the results. Furthermore, we tried to include as many people as possible in the training group in order to construct a

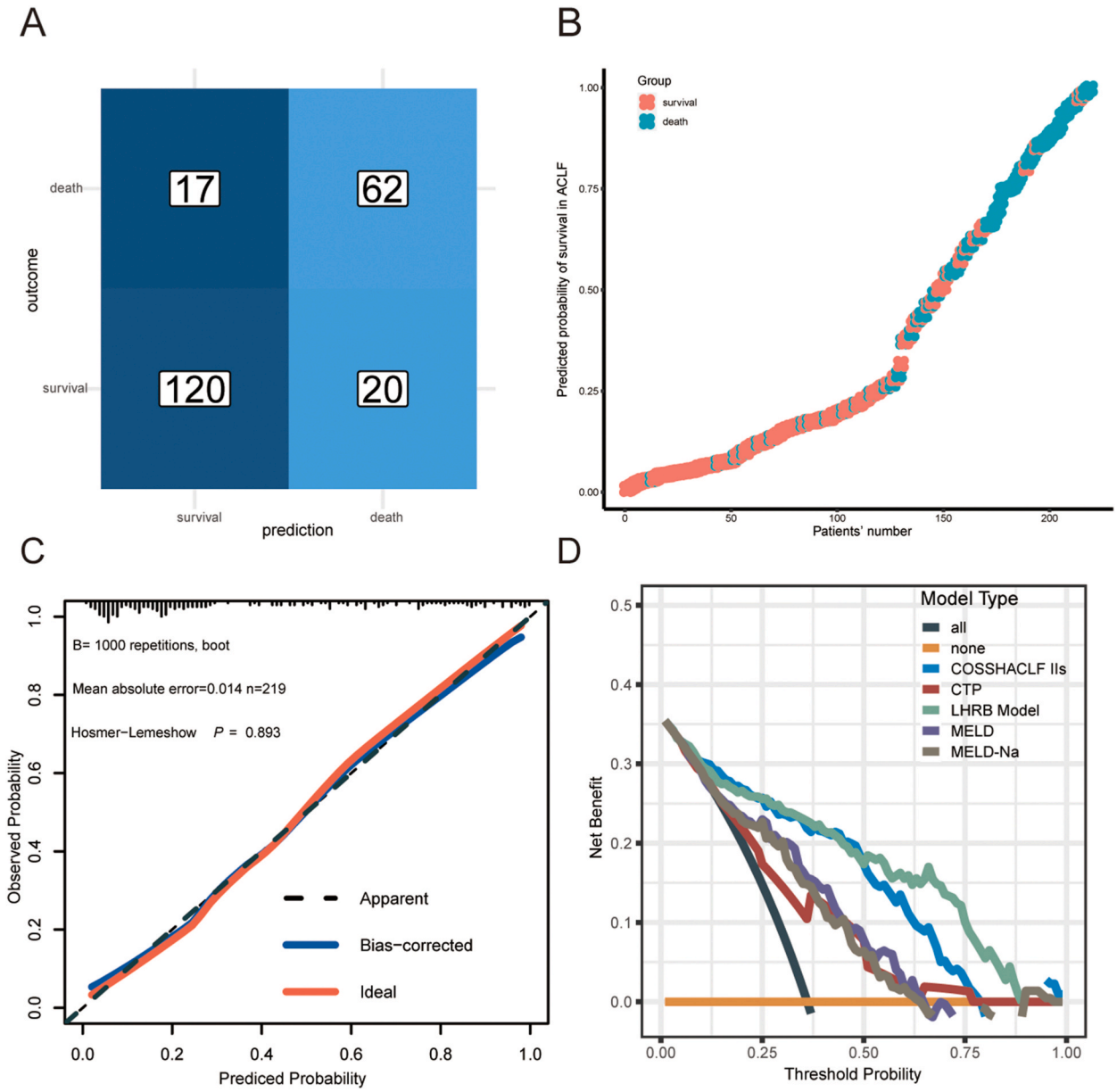

Fig. 3. Validation of the LHRB model. A: Confusion matrix of LHBR model. B: Patient predicted probability of death & actual survival status plot. C: Calibration curve of the *LHRB* model. D: DCA curves of different prognostic models.

robust model to reduce confounding bias. Second, we did not record dynamic changes in blood lymphocyte counts and HDL levels, and changes in immune status in vivo are potential factors influencing patient prognosis. Finally, we lacked data from other medical centers for validation of the *LHRB* model, although a validation group and internal validation were set up in our study.

In conclusion, we found that LHR within 24 h of patient admission was an independent predictor of patient mortality at 28 days, and a prediction model developed based on LHR could more accurately predict the short-term survival status of patients with HBV-ACLF.

Declaration of funding

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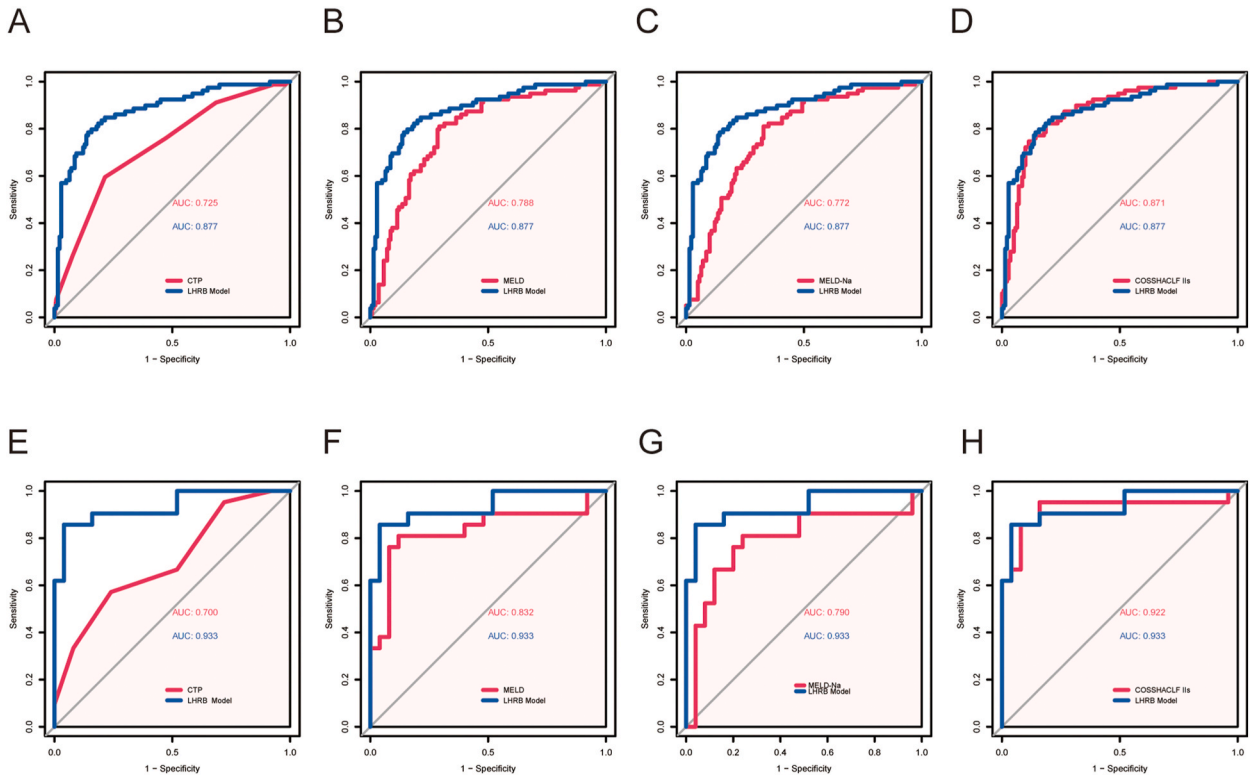

Fig. 4. Area under the receiver operating characteristic curves analysis The AUROC of (A) CTP, (B) MELD, (C) MELD-Na and (D) COASS-ACLF IIs in the training group compared with AUROC of the *LHRB* model, respectively.The AUROC of (E) CTP, (H) MELD, (G) MELD-Na and (H) COASS-ACLF IIs in the validation group compared with AUROC of the *LHRB* model, respectively.

Table 5
Comparison of predictive performance among different models.

	Training group		Validated Group	
	AUCs	P-Value	AUCs	P-Value
CTP *vs LHRB* Model	0.725 vs 0.877	< 0.001	0.700 vs 0.933	0.006
MELD *vs LHRB* Model	0.788 vs 0.877	0.003	0.832 vs 0.933	0.069
MELD-Na *vs LHRB* Model	0.772 vs 0.877	0.001	0.790 vs 0.933	0.021
COSSH ACLF IIs *vs LHRB* Model	0.871 vs 0.877	0.781	0.921 vs 0.933	0.845
LHR *vs LHRB* Model	0.614 vs 0.877	< 0.001	0.645 vs 0.933	< 0.001
LHRB Model (training) *vs LHRB* Model (validation): 0.877 vs 0.933, P-value: 0.224				

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; LHR, lymphocyte/HDL ratio; *LHRB* Model, **LHR-b**ased prediction model.

Data availability

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

CRediT authorship contribution statement

Linxiang Liu: Writing – original draft, Formal analysis. **Chenkai Huang:** Formal analysis, Data curation. **Yue Zhang:** Data curation. **Xuan Zhu:** Writing – review & editing.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37983.

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