ORIGINAL RESEARCH

Derivation and Validation of a Prognostic Model for Acute Decompensated Cirrhosis Patients

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Background: Acute decompensated cirrhosis (AD) is related to high medical costs and high mortality. We recently proposed a new score model to predict the outcome of AD patients and compared it with the common score model (CTP, MELD and CLIF-C AD score) in the training and validation sets.

Materials and Methods: A total of 703 patients with AD were enrolled from The First Affiliated Hospital of Nanchang University between December 2018 and May 2021. These patients were randomly assigned to the training set (n=528) and validation set (n=175). Risk factors affecting prognosis were identified by Cox regression analysis and then used to establish a new score model. The prognostic value was determined by the area under the receiver operating characteristic curve (AUROC).

Results: A total of 192 (36.3%) patients in the training cohort and 51 (29.1%) patients in the validation cohort died over the course of 6 months. A new score model was developed with predictors including age, bilirubin, INR, WBC, albumin, ALT and BUN. The new prognostic score (0.022×Age + 0.003×TBil + 0.397×INR + 0.023×WBC- 0.07×albumin + 0.001×ALT + 0.038×BUN) for long-term mortality was superior to three other scores based on both training and internal validation studies.

Conclusion: This new score model appears to be a valid tool for assessing the long-term survival of AD patients, improving the prognostic value compared with the CTP, MELD and CLIF-C AD scores.

Keywords: new score, prognosis, CTP score, MELD score, CLIF-C AD score

Introduction

Liver cirrhosis is an end-stage liver disease caused by various etiologies, such as viral hepatitis, alcoholic hepatitis, and nonalcoholic steatohepatitis.[1] Liver cirrhosis is divided into compensated cirrhosis and decompensated cirrhosis. The development of complications such as variceal bleeding, hepatic encephalopathy, jaundice and ascites formation herald the onset of acute decompensated cirrhosis (AD).[2] The precipitant factor of AD may be derived from the major clinical event. Bacterial infection is thought to be a major cause of AD in patients; it is the inducer of systemic inflammation through the release of pathogen-associated molecular patterns (PAMPs), which has been confirmed as a trigger for developing acute on chronic liver failure (ACLF).[3,4] ACLF is characterized by the failure of one or more organs, has high short-term mortality, and always occurs in the setting of an episode of AD.[5] The survival date of AD patients drops to 2–4 years.[6] Therefore, it is essential to develop a prognostic model to predict outcomes in AD patients.

Currently, many scoring models for liver cirrhosis are available, including the Child–Pugh score, Model for End-Stage Liver Disease (MELD) and Chronic Liver Failure-Consortium AD score (CLIF-C AD).[7–9] The CTP score is established according to albumin, prothrombin time, serum bilirubin, ascites and hepatic encephalopathy.[7] The accuracy of the CTP score is influenced by subjective criteria such as ascites and HE.[10] The MELD score was developed based on the following laboratory test results: international normalized ratio (INR), creatinine and bilirubin.[8] However, the MELD score does not include inflammatory biomarkers such as white blood cells. The

CLIF-C AD score is proposed to be capable of predicting prognosis in patients with decompensated cirrhosis without ACLF.[9] A previous study confirmed that the CLIF-C AD score was not superior to other well-established prognostic scores in predicting mortality among AD patients.[11] Therefore, the aim of our study was to establish a new prognostic model for AD patients.

Materials and Methods
Patients and Study Design
This study included a total of 703 acute decompensated cirrhosis patients at the Department of Gastroenterology, The First Affiliated Hospital of Nanchang University, between December 2018 and May 2021. Inclusion criteria included the following: (1) age ≥18; (2) diagnosed with cirrhosis (based on histology and/or compatible laboratory and radiologic findings); and (3) acute decompensated events, including gastroesophageal variceal hemorrhage, development of large ascites, hepatic encephalopathy (HE), hepatorenal syndrome (HRS), spontaneous bacterial peritonitis (SBP) or any combination of these. (4) developed a first episode of AD at the time of hospital admission or within 2 weeks before admission. Patients were excluded if they (1) had hepatocellular carcinoma; (2) had evidence of chronic renal disease or other severe chronic extrahepatic diseases; (3) had evidence of infection with human immunodeficiency virus; or (4) had a history of liver transplantation. A total of 703 AD patients were enrolled in the study and randomly assigned to the training set (n=528) or validation set (n=175). Informed consent for participation in this study was obtained from each patient or his or her legal surrogate. This study was approved by the Ethics Committee of The First Affiliated Hospital of Nanchang University.

Data Collection and Treatment
Clinical information, laboratory results, demographic data and acute decompensation events were recorded from medical records. We collected all laboratory results within 24 h after admission. The primary endpoint of this study was 6-month mortality. The CTP score was calculated based on prothrombin time (PT), ascites, albumin, serum bilirubin, and HE.[7] The MELD score was computed according to the formula: MELD=11.2×ln[prothrombin time (international normalized ratio (INR))] + 9.6×ln [serum creatinine (Scr) (mg/dl)] +3.8×ln[total bilirubin (mg/dl)] + 6.43×(etiology: 0 if cholestatic or alcoholic, 1 otherwise).[8] The CLIF-C AD score was calculated as follows: CLIF-C AD= 10×0.03×age (years) + 0.66×ln [serum creatinine (Scr) (mg/dl)] + 1.71×ln (INR) + 0.88×ln [WBC (10^9 cells/L)]-0.05×sodium (mmol/L) +8.[9] For AD patients, standard medical therapies were used, including antiviral treatment, anti-infective therapy, endoscopic hemostatic therapy and other treatments to prevent complications.

Statistical Analysis
Statistical analysis was performed using SPSS 24.0 (SPSS Inc., Chicago, IL, USA) and R 4.2.0 (http://www.r-project.org/). Continuous data are expressed as the mean ± standard deviation, which was compared by using t-tests or the Mann–Whitney test. The chi-squared test or Fisher's exact test was used to analyze the differences in proportions of clinical variables. Independent prognostic indicators of mortality were identified through univariate and multivariate Cox regression analyses. The training set was applied to develop the new score according to the β coefficients from the multivariable Cox analysis. Patients were separated into low-risk and high-risk groups based on the median value of the new score.

Continuous variables are expressed as the mean (SD) and were compared using an unpaired, 2-tailed t-test or the Mann–Whitney test. Categorical variables were compared using the chi-squared test or Fisher's exact test. Univariate risk factors that reached $p<0.2$ were subjected to Cox regression analysis. The Kaplan–Meier survival curves of the high- and low-risk groups were plotted using the R packages "survival" and "survminer" to demonstrate the survival probability of the patients. The ROC curves were calculated using the "survminer", "survival", "timeROC", and "pROC" packages in R software. The heatmap was computed by using the "pheatmap" package. A P value < 0.05 in a two-tailed test was considered statistically significant.

Results

Baseline Characteristics of Acute Decompensated Cirrhosis Patients

A total of 703 AD patients were included in this study, of whom 528 patients were randomly assigned to the training set, and 175 patients were assigned to the validation set (Figure 1). The clinical characteristics of AD patients in the training and validation sets are shown in Table 1. The median age was 54.5±11.8 years, with 77.1% of the patients being male. The main etiology of cirrhosis was hepatitis B virus infection in both the training (364/528, 68.9%) and validation sets (125/175, 71.4%). Variceal bleeding was the most common acute decompensation event in the training (348/528, 65.9%) and validation sets (103/175, 58.9%). There were no significant differences in clinical indicators between the two sets.

Clinical Characteristics of the Nonsurviving and Surviving Patients

We compared the clinical characteristics between survivors and nonsurvivors in the training set. Comparative data showed that bilirubin, creatinine, international normalized ratio (INR), prothrombin time (PT), white blood cell count (WBC), albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), serum urea (BUN), sodium, CTP, MELD and CLIF-C AD were significantly different between survivors and nonsurvivors (all P values<0.05). No significant difference was found in the platelet count (P value>0.05). The clinical characteristics of the training set patients are presented in Table 2.

Construction of the New Score

Furthermore, we confirmed independent prognostic factors for AD patients. As shown in Table 3, in univariate Cox regression analysis, age, bilirubin, creatinine, INR, PT, WBC, albumin, ALT, AST, ALP and BUN were correlated with the mortality of AD patients. In multivariate Cox regression analysis, age, bilirubin, INR, WBC, ALT and BUN were associated with worse prognosis, and elevated albumin predicted a better survival rate. Then, the new score model was established based on multivariate Cox regression analysis. Finally, the formula was as follows: 0.022×Age + 0.003×TBil + 0.397×INR + 0.023×WBC- 0.07×Albumin + 0.001×ALT + 0.038×BUN.

Predictive Performance of the New Score in the Training Set

In the training set, by using the median cutoff value (0.68) to divide the low- and high-risk AD patients, low-risk and high-risk groups were obtained (Figure 2a). Kaplan–Meier survival plots were generated to compare the survival probability between the low- and high-risk groups (Figure 2b), and the patients in the high-risk group had a lower survival probability than those in the low-risk group (P<0.001). The area under the ROC curve (AUCROC) was calculated to compare the prognostic value between the new score and the other three common scores. The AUROC of the new score was 0.814 (95% CI: 0.778–0.847), which was significantly higher than that of the MELD, CTP and
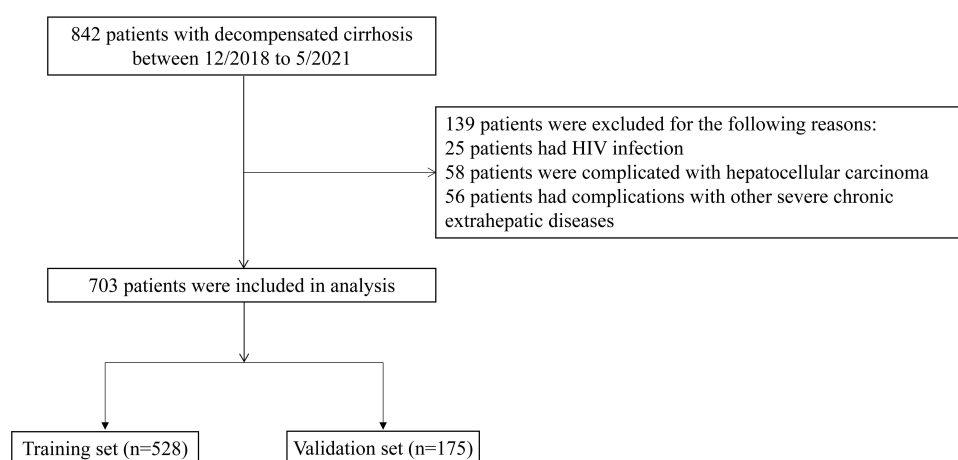

Figure 1 Study flow chart for the training and validation cohorts.

Table 1 Clinical Characteristics of Cirrhosis Patients with AD

	All Patients (n=703)	Training Set (n=528)	Validation Set (n=175)	*P* value
Age (years)	54.5 (±11.8)	54.5 (±11.9)	54.4 (±11.5)	0.873
Male (%)	542 (77.1)	397 (75.2)	145 (82.9)	0.038
Hospitalization days	10 (6–14)	10 (6–14)	10 (6–13)	0.915
Etiology of cirrhosis, n (%)				
HBV infection	488 (69.4)	364 (68.9)	125 (71.4)	0.638
HCV infection	20 (2.8)	17 (3.2)	3 (1.7)	0.433
Alcohol use	96 (12.7)	65 (12.3)	31 (17.8)	0.076
Schistosoma	22 (3.1)	22 (4.2)	0 (0)	0.002
Autoimmune	13 (1.8)	11 (2.1)	2 (1.1)	0.535
Cryptogenic	63 (9.0)	49 (9.3)	14 (8.0)	0.651
Acute decompensation, n (%)				
Variceal bleeding	451 (64.2)	348 (65.9)	103 (58.9)	0.051
Ascites	65 (9.2)	42 (8)	23 (13.1)	0.102
Infection	48 (6.8)	33 (6.3)	15 (8.6)	0.999
Hepatic encephalopathy	41 (5.8)	31 (5.9)	10 (5.7)	0.291
Hepatorenal syndrome	7 (1.0)	5 (0.9)	2 (1.1)	0.687
Clinical parameters				
Bilirubin (μmol/L)	35.6 (19.3–126.3)	33.3 (19.1–121.8)	39.9 (20.1–150.2)	0.294
Creatinine (μmol/L)	74.1 (60.4–97.9)	74.6 (60.3–98.5)	72.8 (60.9–96.2)	0.727
INR	1.4 (1.2–1.7)	1.4 (1.2–1.8)	1.4 (1.2–1.7)	0.736
MAP (mmHg)	83.6 (±11.9)	83.2 (±11.5)	84.8 (±13.0)	0.112
PT (s)	16.0 (14.0–19.5)	16.0 (13.9–19.9)	16.0 (14.1–19.2)	0.754
WBC (10^9/L)	6.4 (4.0–9.8)	6.5 (4.0–10.1)	6.1 (3.9–8.7)	0.245
Platelet (10^9/L)	70.0 (44.0–107.0)	70.0 (43.0–108.0)	70.0 (47.0–100.0)	0.624
Albumin (g/L)	28.6 (25.1–31.8)	28.6 (25.2–31.9)	28.6 (25.0–31.6)	0.888
ALT (IU/L)	35.0 (21.0–87.4)	34.0 (20.0–93.0)	36.0 (21.0–76.3)	0.662
AST (IU/L)	55.0 (33.0–158.0)	54.0 (33.0–161.0)	58.0 (33.0–157.8)	0.978
GGT (IU/L)	40.0 (17.0–107.3)	39.0 (16.0–107.0)	43.3 (19.0–112.0)	0.248
ALP (IU/L)	94.8 (63.0–149.0)	94.0 (60.0–149.0)	97.0 (66.0–150.0)	0.651
BUN (mmol/L)	8.0 (5.2–11.4)	8.0 (5.3–11.4)	8.0 (4.9–11.2)	0.418
Sodium (mmol/L)	138.0 (134.6–141.0)	138.0 (134.0–141.0)	137.8 (134.4–140.9)	0.401

Abbreviations: HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; INR, international normalized ratio; MAP, mean arterial pressure; PT, prothrombin time; WBC, white blood cell count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; BUN, serum urea.

CLIF-C AD scores (0.777 (95% CI: 0.739–0.812); 0.764 (95% CI: 0.726–0.800) and 0.637 (95% CI: 0.594–0.678), respectively) (Table 4 and Figure 2c).

Internal Validation of the New Score

In the validation set, the low-risk and high-risk groups were divided according to the median cutoff value (0.68) (Figure 3a). The survival analysis indicated that the patients in the low-risk group had a higher survival probability than those in the high-risk group (P<0.001) (Figure 3b). The new score had the highest AUROC (0.837, 95% CI: 0.774–0.889), followed by the MELD score (0.805, 95% CI: 0.738–0.861), CTP score (0.763, 95% CI: 0.693–0.824) and CLIF-C AD score (0.694, 95% CI: 0.620–0.762) (Table 5 and Figure 3c).

Relationship Between the New Score and the Three Scores

To further evaluate the correlation between the new score model and the three score models, a heatmap was generated in the training and validation sets. In the training set, the heatmap revealed that patients with high risk scores exhibited

Table 2 Comparing the Clinical Variables Between Non-Surviving and Surviving Patients in Training Set

Variables	No-Survivors (n=192)	Survivors (n=336)	P value
Bilirubin (μmol/L)	86.4 (27.3–271.2)	26.9 (16.7–64.5)	<0.001
Creatinine (μmol/L)	84.5 (64.4–135.9)	70.5 (59.1–86.3)	<0.001
INR	1.7 (1.4–2.1)	1.3 (1.2–1.6)	<0.001
PT (s)	19.2 (15.6–23.6)	15.0 (13.6–17.6)	<0.001
WBC (10^9/L)	8.0 (4.9–12.9)	5.8 (3.7–8.4)	<0.001
Platelet (10^9/L)	72.0 (45.0–114.0)	69.0 (44.0–103.0)	0.386
Albumin (g/L)	26.8 (23.5–31.3)	29.3 (26.0–32.1)	<0.001
ALT (IU/L)	51.5 (26.0–188.0)	28.0 (19.0–63.0)	<0.001
AST (IU/L)	105.0 (48.0–266.0)	43.0 (29.0–87.5)	<0.001
ALP (IU/L)	124.0 (77.0–183.0)	84.5 (58.0–128.0)	<0.001
BUN (mmol/L)	9.2 (5.6–15.0)	7.5 (4.9–10.1)	<0.001
Sodium (mmol/L)	136.9 (133.0–140.8)	138.3 (136.0–141.0)	<0.001
CTP	11.0 (9.0–12.0)	8.0 (7.0–10.0)	<0.001
MELD	19.0 (12.0–25.0)	10.0 (7.0–14.0)	<0.001
CLIF-C AD	20.9 (18.5–23.7)	18.9 (16.7–21.6)	<0.001

Abbreviations: INR, international normalized ratio; PT, prothrombin time; WBC, white blood cell count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BUN, serum urea; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; CLIF-C AD, Chronic Liver Failure Consortium Acute Decompensation score.

Table 3 Univariate and Multivariate Cox Regression Analyses of Factors Associated with Mortality in Training Set

	Univariate Analysis		Multivariate Analysis		
	HR (95% CI)	*p* value	Coef	HR (95% CI)	*p* value
Age (years)	1.017 (1.005–1.030)	**0.005**	0.022	1.023 (1.010–1.036)	**0.001**
Sex, male	1.122 (0.801–1.572)	0.502			
Bilirubin (μmol/L)	1.004 (1.003–1.005)	**<0.001**	0.003	1.003 (1.002–1.004)	**<0.001**
Creatinine (μmol/L)	1.002 (1.001–1.003)	**<0.001**			
INR	2.140 (1.892–2.420)	**<0.001**	0.397	1.488 (1.137–1.946)	**0.004**
PT (s)	1.036 (1.027–1.044)	**<0.001**			
WBC (10^9/L)	1.042 (1.029–1.056)	**<0.001**	0.023	1.023 (1.001–1.045)	**0.041**
Platelet (10^9/L)	1.001 (0.999–1.003)	0.302			
Albumin (g/L)	0.925 (0.899–0.953)	**<0.001**	−0.070	0.933 (0.902–0.964)	**<0.001**
ALT (IU/L)	1.003 (1.001–1.004)	**<0.001**	0.001	1.002 (1.001–1.003)	**0.025**
AST (IU/L)	1.001 (1.000–1.002)	**<0.001**			
ALP (IU/L)	1.002 (1.001–1.003)	**<0.001**			
BUN (mmol/L)	1.039 (1.026–1.052)	**<0.001**	0.038	1.038 (1.013–1.065)	**<0.001**
Sodium (mmol/L)	1.000 (0.986–1.013)	0.972			

Notes: In univariate analysis, *P* value <0.05 were subjected to multivariate analysis and was indicated in bold; In multivariate analysis, *P* value <0.05 was considered significant and was indicated in bold.
Abbreviations: INR, international normalized ratio; PT, prothrombin time; WBC, white blood cell count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BUN, serum urea.

higher CTP, MELD and CLIF-C AD scores (Figure 4a). Additionally, the correlations between the risk score and the three scores were also calculated, and the results showed that the CTP, MELD and CLIF-C AD scores were elevated in the high-risk group (Figure 4b) (all P<0.001). Similar results were also confirmed in the validation set (Figure 5a and b).
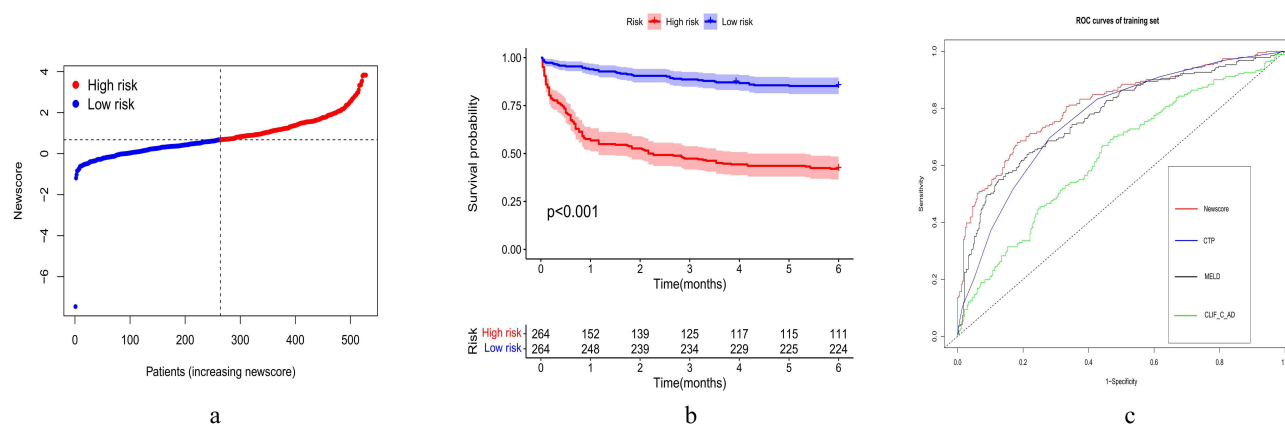
Figure 2 (**a**) According to the median cutoff value, the training set was divided into high- and low-risk groups. (**b**) Kaplan–Meier survival analysis for patients between the high- and low-risk groups in the training set. (**c**) ROC curves were used to compare the prognostic power between the new score model and CTP, MELD and CLIF-C AD scores in the training set.

Abbreviations: CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; CLIF-C AD, Chronic Liver Failure Consortium Acute Decompensation score.

Discussion

In the present study, a new score model was established to assess the individual long-term prognosis of AD patients. This new score model presented superior predictive performance relative to the current prognostic score models, including the CTP, MELD and CLIF-C AD scores.

In the training and validation sets, the leading etiology of AD patients was HBV, which is highly endemic in China.[12] A total of 348 (65.9%) and 103 (58.9%) patients were admitted with variceal bleeding in the training and validation sets, respectively, and variceal hemorrhage is one of the most relevant causes of death in AD patients and clinically significant portal hypertension.[13] According to the results of multivariate Cox regression analysis, we developed the new score model. This new score had better prognostic value than the CTP, MELD and CLIF-C AD scores; moreover, we adopted the internal validation cohort to confirm the prognostic performance of the new score model.

The CTP score is generally applied to evaluate the prognosis of patients with cirrhosis, and the 2 subjective indicators reduce the accuracy of mortality prediction.[14] The MELD score was established to evaluate liver function and confirmed as an independent risk predictor for the prognosis of AD patients, but the calculation of the score was complicated and inconvenient for clinical practice.[15] A previous study confirmed that the CLIF-C AD score had a lower prognostic value than the CTP or MELD score for HBV-AD patients.[16] The new score model was developed based on age, bilirubin, INR, WBC, albumin, ALT and BUN, which had better prognostic value in both the training and validation sets. Numerous studies have revealed that older age is an important factor in predicting poor prognosis for cirrhosis patients.[17,18] Bilirubin is an important blood index for assessing liver function and is also the primary element of the CTP and MELD scores. As an indicator of severe liver injury, INR was included in the MELD and CLIF-C AD scores. WBC

Table 4 The Predictive Value Comparison of New Score and Other Score Systems in Training Set

Prognostic Score	Difference Between Areas (95% CI)	P-value
New score vs CTP	0.050 (0.0129–0.0871)	**0.0082**
New score vs MELD	0.0374 (0.0029–0.0719)	**0.0330**
New score vs CLIF-C AD	0.1780 (0.1310–0.2240)	**<0.0001**

Note: *P* value < 0.05 was considered significant and was indicated in bold.
Abbreviations: CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; CLIF-C AD, Chronic Liver Failure Consortium Acute Decompensation score.
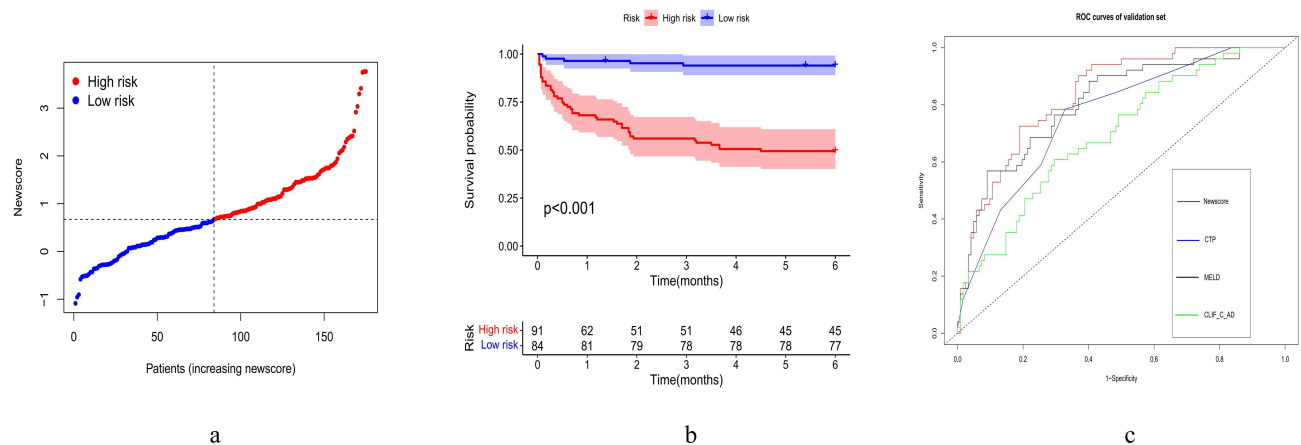
Figure 3 (**a**) According to the median cutoff value, the validation set was divided into high- and low-risk groups. (**b**) Kaplan–Meier survival analysis for patients between the high- and low-risk groups in the validation set. (**c**) ROC curves were used to compare the prognostic power between the new score model and CTP, MELD and CLIF-C AD scores in the validation set.

Abbreviations: CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; CLIF-C AD, Chronic Liver Failure Consortium Acute Decompensation score.

count is an inflammatory biomarker, and systemic inflammation is related to the development of one or more organ failures in AD patients.[19,20] Albumin was confirmed as a biomarker of malnutrition–inflammation syndrome, and decreased albumin had a negative impact on the prognosis of AD patients.[21,22] ALT (alanine aminotransferase) is a significant enzyme in the liver, and a previous study confirmed that elevated ALT levels were associated with an increased risk of hepatic complications, which may influence the prognosis of cirrhosis patients.[23] BUN was the surrogate biomarker for increased severity of renal or systemic illness, and a recent study showed that BUN was a predictive factor for poor prognosis in advanced liver diseases by using machine learning.[24] The new score incorporated these indicators and exhibited better prognostic value in predicting the outcome for AD patients. Moreover, the excellent prognostic performance of the new score was confirmed in the validation set. The new score was significantly correlated with the CTP, MELD and CLIF-C AD scores. These results showed better prognostic value for predicting the outcome in AD patients.

Certainly, our study has some limitations. First, this is a single-center and retrospective study, which may lead to selection bias. Second, our findings may be limited in China, with cohorts of predominantly HBV-related cirrhosis patients. Third, our study lacks external validation, so a prospective, large sample size and multicenter study need to be designed in the future.

In conclusion, this new score model has better prognostic value than the CTP, MELD and CLIF-C AD scores in predicting long-term mortality for AD patients, which may facilitate risk stratification and clinical decision-making for AD patients.

Table 5 The Predictive Value Comparison of New Score and Other Score Systems in Validation Cohort

Prognostic Score	Difference Between Areas (95% CI)	P-value
New score vs CTP	0.0742 (0.0052–0.1490)	**0.035**
New score vs MELD	0.0327 (0.0002–0.0928)	**0.048**
New score vs CLIF-C AD	0.1430 (0.0562–0.2300)	**0.001**

Note: *P* value < 0.05 was considered significant and was indicated in bold.
Abbreviations: CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; CLIF-C AD, Chronic Liver Failure Consortium Acute Decompensation score.
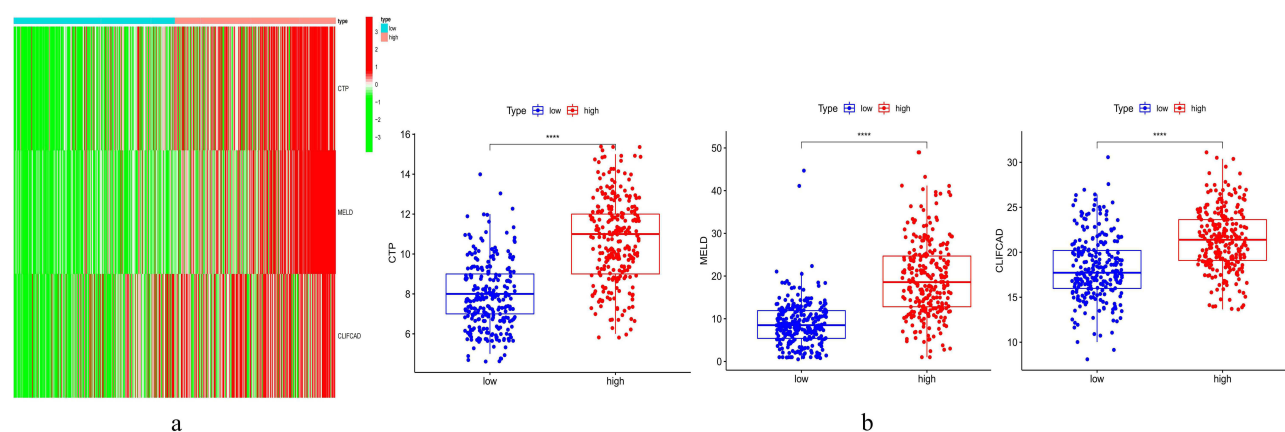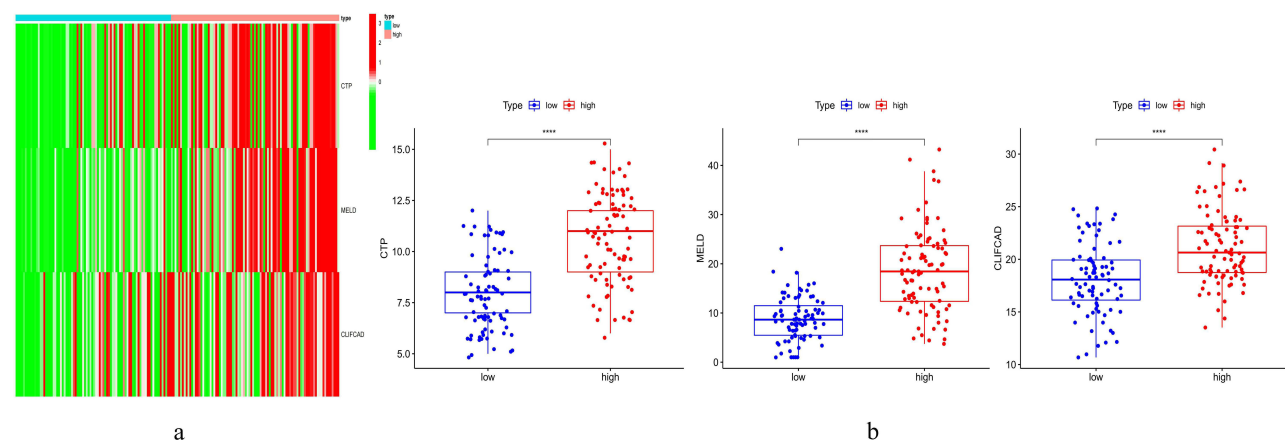
Figure 4 (**a**) The expression of CTP, MELD and CLIF-C AD score in high- and low-risk groups are shown as a heatmap in the training set. (**b**) Correlations between the risk score and CTP, MELD and CLIF-C AD scores in the training set. ****P<0.0001.
Abbreviations: CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; CLIF-C AD, Chronic Liver Failure Consortium Acute Decompensation score.

Figure 5 (**a**) The CTP, MELD and CLIF-C AD scores in the high- and low-risk groups are shown as a heatmap in the validation set. (**b**) Correlations between the risk score and CTP, MELD and CLIF-C AD scores in the validation set. ****P<0.0001.
Abbreviations: CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; CLIF-C AD, Chronic Liver Failure Consortium Acute Decompensation score.

Data Sharing Statement

The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study was performed according to the principles of the Declaration of Helsinki. The study was approved by the ethics committee of the First Affiliated Hospital of Nanchang University. Only subjects who signed the informed consent form were included in the data collection and interviews.

Acknowledgments

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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