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Original Article

Development and Validation of a New Prognostic Model for Predicting Survival Outcomes in Patients with Acute-on-chronic Liver Failure

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Abstract

Background and Aims: Early determination of prognosis in patients with acute-on-chronic liver failure (ACLF) is crucial for optimizing treatment options and liver allocation. This study aimed to identify risk factors associated with ACLF and to develop new prognostic models that accurately predict patient outcomes. ***Methods:*** We retrospectively selected 1,952 hospitalized patients diagnosed with ACLF between January 2010 and June 2018. This cohort was used to develop new prognostic scores, which were subsequently validated in external groups. ***Results:*** The study included 1,386 ACLF patients and identified six independent predictors of 28-day mortality through multivariate analysis (all $p < 0.05$). The new score, based on a multivariate regression model, demonstrated superior predictive accuracy for both 28-day and 90-day mortalities, with Areas under the ROC curves of 0.863 and 0.853, respectively (all $p < 0.05$). This score can be used to stratify the risk of mortality among ACLF patients with ACLF, showing a significant difference in survival between patients categorized by the cut-off value (log-rank (Mantel–Cox) $\chi^2 = 487.574$ and 606.441, $p = 0.000$). Additionally, the new model exhibited good robustness in two external cohorts. ***Conclusions:*** This study presents a refined prognostic model, the Model for end-stage liver disease-complication score, which accurately predicts short-term mortality in ACLF patients. This model offers a new perspective and tool for improved clinical decision-making and short-term prognostic assessment in ACLF patients.

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Keywords: Acute-on-chronic liver failure; ACLF; Outcome prediction; Mortality; Prognosis; Model.

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Introduction

Acute-on-chronic liver failure (ACLF) is a complex clinical syndrome with a high short-term mortality rate of 50–90%.[1,2] It is characterized by clinical complications such as ascites, hepatic encephalopathy, infection, and portal hypertensive hemorrhage.[3] Research has revealed that most patients with ACLF have clinically apparent triggers of systemic inflammation, including proven bacterial infection and gastrointestinal hemorrhage with shock.[4] Despite intensive care and extracorporeal artificial liver support systems, some ACLF patients at high risk of rapid clinical deterioration may require emergency liver transplantation (LT) to improve their chances of survival.[5,6] Due to the rapid progression of ACLF, LT faces practical challenges such as liver shortages and high costs. Therefore, accurate early prognosis of ACLF patients is critical for optimizing treatment options and liver allocation.

Several models have been proposed to predict outcomes for these patients. For example, the Chronic Liver Failure Consortium (hereinafter referred to as CLIF-C) ACLF model and the North American Consortium for the Study of End-stage Liver Disease model, validated by European and American consortia on ACLF, respectively, reflect terminal events in ACLF. These models are primarily suitable for high-risk ACLF patients in the intensive care unit, but their sensitivity to specific complications (such as infection) is inadequate.[7,8] The Asian-Pacific Association for the Study of the Liver (hereinafter referred to as APASL)-ACLF Research Consortium model is

effective for predicting short-term mortality in ACLF patients[9] and is superior to scales such as the Sequential Organ Failure Assessment (hereinafter referred to as SOFA), CLIF-C-SOFA, and Acute Physiology and Chronic Health Evaluation scores in assessing ACLF severity.[10] However, its specificity for predicting 30-day mortality in ACLF patients is only 57%.[11] Given these limitations, there is no consensus on which model is best suited for different populations.

The model for end-stage liver disease (MELD) is a well-recognized scale used for liver transplant allocation. The MELD model is based on serum creatinine, total serum bilirubin, and the international normalized ratio (INR). However, it does not account for all complications related to portal hypertension, such as esophageal variceal bleeding, spontaneous bacterial peritonitis, ascites, and hepatic encephalopathy.[12] Additionally, the MELD-sodium score lacks specificity in predicting outcomes for ACLF patients.[13] A team from Stanford University School of Medicine and Mayo Clinic further optimized the MELD model to create MELD 3.0, which includes albumin.[14] However, this model does not yet address the impact of ACLF-related complications on prognosis. The albumin-bilirubin (ALBI) score is a new model for assessing liver dysfunction severity, based on albumin and bilirubin levels. Although the ALBI score has prognostic value in various contexts, it may be limited in predicting complications related to factors such as multiple organ failure.[15] Few large cohort studies have compared the prognostic efficacy of these new scores in ACLF patients.

Common complications affecting ACLF prognosis include spontaneous bacterial peritonitis (SBP), acute kidney injury (AKI), hepatic encephalopathy (HE), variceal bleeding, pneumonia, and hepatic hydrothorax.[16–20] Understanding these and other risk factors could help identify ACLF patients with a poor prognosis due to complications. However, there is limited information about the impact of various complications on ACLF in large cohorts. This study aimed to identify the risk factors associated with ACLF and develop new prognostic models to accurately predict patient outcomes.

Methods

Study population

We retrospectively collected data from patients admitted to the Fifth Medical Center of the Chinese PLA General Hospital between January 2010 and June 2018. As this was a retrospective study, we could not obtain direct consent from the participants. To maximize privacy protection, we ensured that data were anonymized throughout the study. This study was approved by the Ethics Committee of the 302 Hospital of PLA, the predecessor of the Fifth Medical Center of the Chinese PLA General Hospital.

Patient inclusion criteria

We selected patients who were diagnosed with ACLF and admitted to the Fifth Medical Center of the Chinese PLA General Hospital between January 2010 and June 2018. According to the standards proposed by the Asia–Pacific Association for the Study of the Liver in 2019, patients diagnosed with ACLF met the following conditions: (1) serum total bilirubin ≥5 mg/dL; (2) INR ≥1.5; (3) preexisting chronic liver disease; and (4) complications, including ascites or HE. The exclusion criteria were as follows: (1) preexisting cancer at diagnosis; (2) age younger than 13 years; (3) scheduled liver transplantation; (4) missing data or hospital stay < three days; and (5) diabetes mellitus, chronic kidney disease, or chronic thyroid disease. Although diabetes mellitus is relatively common in the ACLF population, its presence may obscure the relationship between interventional measures and the natural history of liver failure. To minimize the confounding effects of diabetes on study outcomes and to enhance the precision of clinical management and prognostic accuracy within the ACLF cohort, patients with diabetes mellitus were excluded from this investigation.

All patients were followed up for at least three months after discharge or until death. Data on patient outcome events, such as liver transplantation or death, were collected through outpatient medical records or telephone follow-up.

Diagnostic criteria for complications

HE was confirmed according to the West Haven criteria. The presence of ascites was confirmed via ultrasonography and assessed by the need for treatment with diuretics or paracentesis. Variceal bleeding was defined as bleeding requiring endoscopic intervention. AKI was defined according to internationally accepted criteria as an increase in serum creatinine ≥0.3 mg/dL from baseline.[21,22]

Data collection and score calculation

Information on sex, age, albumin, total bilirubin, creatinine, total cholesterol, leukocyte count, hemoglobin, platelet count, INR, and ammonia on admission, as well as treatment data after admission, were collected from medical records. These data were used to calculate the MELD, MELD 3.0, and ALBI scores as follows:

- MELD score = $3.78 \times \log_e$ (bilirubin)+ $11.2 \times \log_e$ (INR) + $9.57 \times \log_e$ (creatinine) + 6.43.[12]
- MELD 3.0 score = 1.33 (if female) + $4.56 \times \log_e$ (bilirubin) + $0.82 \times (137-\text{Na}) - 0.24 \times (137-\text{Na}) \times \log_e$ (bilirubin) + $9.09 \times \log_e$ (INR) + $11.14 \times \log_e$ (creatinine) + $1.85 \times (3.5-\text{albumin}) - 1.83 \times (3.5-\text{albumin}) \times \log_e$(creatinine) + 6.[14]
- ALBI score = $0.66 \times \log_{10}$(bilirubin) - 0.085 × (albumin).
- The ALBI score was subsequently classified into three grades: Grade 1: ≤−2.6; Grade 2: >−2.6, ≤−1.39; and Grade 3: >−1.39.[23]

Outcome measures

The primary outcome was mortality at 28 days, and the secondary outcome was mortality at 90 days. Patient survival status was confirmed after discharge through telephone interviews and/or by analyzing medical records. Each patient was followed for three months or until their date of death.

Development and validation of a new prognostic score model

All patients with ACLF were assigned to a training set for the development of a new prognostic model. Initially, univariate analysis was conducted to examine how each factor of interest influenced short-term mortality (28-day). Subsequently, multivariate logistic regression analysis was used to identify independent factors associated with 28-day LT-free mortality (Table 1). We integrated all the parameters identified through multivariate logistic regression into a new ACLF scoring model. We then evaluated and compared the performance of this new ACLF model, referred to as the MELD-complication score for simplicity in the following text. An external test set containing data from The First Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou set) and Beijing Youan Hospital, Capital Medical University (Youan set) was used for validation. All data required to calculate the ACLF score were measured and are presented in Table 1 (test set). To assess

Table 1. Logistic regression analysis of factors associated with the risk of 28-day mortality

Parameters	Univariable Analysis OR (95% CI)	*p*-value	Multivariable Analysis OR (95% CI)	*p*-value
Age	1.432 (1.131–1.812)	0.003	1.420 (1.050–1.922)	0.023
Aetiology of the disease	1.299 (0.949–1.779)	0.103		
ACLF subtype	1.976 (1.379–2.830)	0.000	1.976 (1.396–2.797)	0.000
Variceal bleeding	2.605 (1.871–3.628)	0.000		
Hepatic encephalopathy	5.220 (4.066–6.703)	0.000	2.281 (1.689–3.080)	0.000
Hydrothorax	1.271 (0.997–1.620)	0.053		
Pulmonary infection	3.394 (2.579–4.466)	0.000	1.413 (1.002–1.994)	0.049
SBP	0.660 (0.477–0.913)	0.012	0.646 (0.473–0.883)	0.006
AKI	3.869 (3.031–4.938)	0.000		
Albumin	1.383 (1.096–1.745)	0.006		
Total bilirubin	1.636 (1.297–2.063)	0.000		
INR	3.709 (2.899–4.744)	0.000	2.806 (2.072–3.800)	0.000
Platelets	1.094 (0.868–1.379)	0.445		
Creatinine	5.305 (4.133–6.809)	0.000		
Urea	3.382 (2.629–4.352)	0.000		
Sodium	1.652 (1.266–2.155)	0.000		
Total cholesterol	1.955 (1.546–2.473)	0.000		
Ammonia	3.219 (2.528–4.099)	0.000		
Haemoglobin	1.195 (0.864–1.653)	0.282		
WBC	2.086 (1.607–2.708)	0.000		
Neutrophil count	7.832 (6.054–10.131)	0.000	2.923 (2.119–4.034)	0.000
MELD score	11.939 (8.927–15.969)	0.000	4.270 (3.026–6.025)	0.000
MELD-3.0 score	3.640 (2.851–4.649)	0.000		
ALBI score	3.000 (2.364–3.808)	0.000		

ACLF, acute-on-chronic liver failure; SBP, spontaneous bacterial peritonitis; AKI, acute kidney injury; INR, international normalized ratio; WBC, white blood cell; MELD, Model for End-stage Liver Disease; ALBI, albumin-bilirubin.

the generalizability of the new model, we collected patient data from the aforementioned hospitals in Hangzhou and Beijing, namely, The First Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou set) and Beijing Youan Hospital, Capital Medical University (Youan set), as external test sets to verify the predictive performance of the new model in different populations. Both hospitals, being of the same level in first-tier cities, ensured homogeneity in treatment across the external test sets.

Statistical analysis

All statistical analyses were performed using SPSS software version 22.0 (IBM Corp, Armonk, NY, USA). For continuous variables, the Kolmogorov–Smirnov test assessed the normality of the data. Continuous variables are expressed as means ± standard deviations or medians (interquartile ranges) depending on normality and were compared between groups using a t test or the Mann–Whitney U test, respectively. Categorical variables are expressed as percentages and were compared between groups using the chi-square test or Fisher's exact test. Survival curves for 28-day and 90-day mortality were plotted based on the number of complications at baseline, and survival differences between groups with different numbers of complications were assessed using the log-rank test. Logistic regression models identified independent risk factors for mortality, with results presented as odds ratios (ORs) and 95% confidence intervals (CIs). The Hosmer–Lemeshow goodness-of-fit test assessed the calibration ability of the prediction model. The predictive ability of each score was valuated via receiver operating characteristic (ROC) analysis. Areas under the ROC curves (AUROCs) and their 95% CIs for the MELD, MELD 3.0, ALBI scores, and the MELD complication score in predicting 28-day and 90-day survival rates of ACLF patients were calculated and compared using the DeLong test. Critical values were determined by maximizing the Youden index, and sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Cumulative survival at 28 and 90 days was analyzed using the Kaplan–Meier method to compare survival times between groups above and below the cut-off value. The predictive performance of the new model was validated using an external test set, and ROC curves compared the predictive power of different prognostic models for 28-day and 90-day mortality in ACLF patients. Finally, AUROCs for the different models were calculated and compared using the DeLong test. A two-tailed p-value ≤ 0.05 was considered statistically significant.

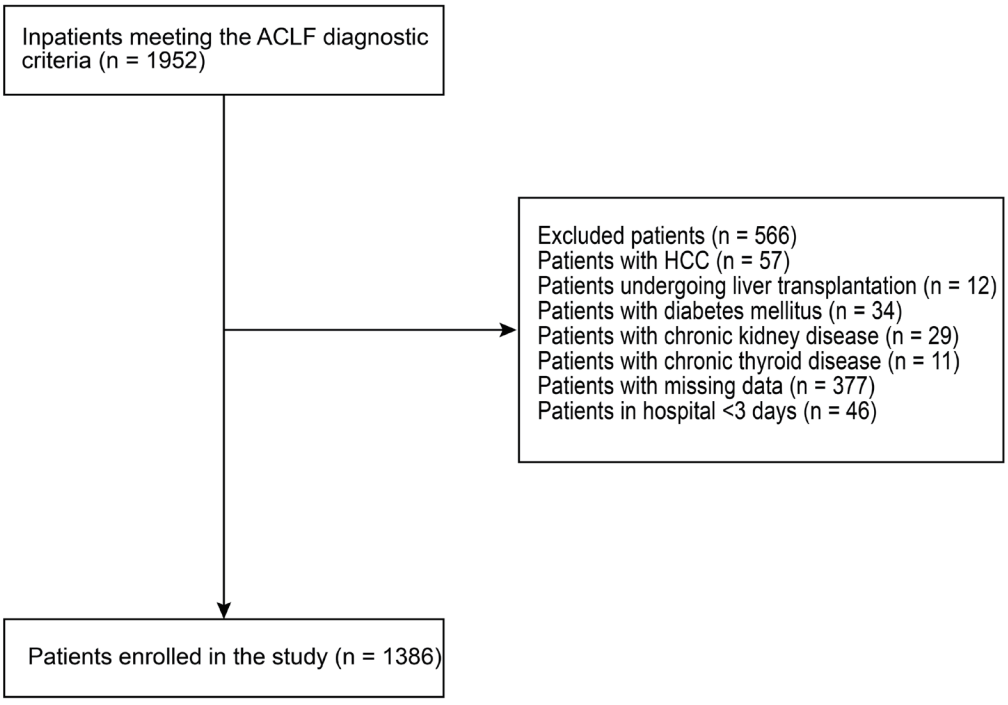


Fig. 1. Flow chart of patient enrollment. ACLF, acute-on-chronic liver failure; HCC, hepatocellular carcinoma.

Result

Study subjects

Of the 1,952 patients initially identified for inclusion in this study, the majority were excluded for various reasons. Ultimately, 1,386 patients were enrolled in the study (detailed information is presented in Fig. 1). Patients who underwent LT within 90 days of hospital admission were also excluded. Clinical characteristics of the enrolled patients: The mean age of the entire cohort was 46.68 ± 9.95 years, and the majority of patients were male. All included patients were followed up for at least three months or until death. The patients were divided into survival and nonsurvival groups based on 90-day follow-up outcomes. The baseline clinical characteristics and laboratory test results of the patients were compared between the survival and nonsurvival groups, as summarized in Table 2. Viral hepatitis B was the most common etiology in both groups, followed by alcohol-related liver disease and other etiologies, including autoimmune hepatitis, drug-induced chronic liver disease, and nonalcoholic steatohepatitis.

We aimed to identify parameters that could differentiate survivors from nonsurvivors to develop a new prognostic score model for patients with ACLF. The nonsurvival group exhibited notable increases in several parameters, including INR, total serum bilirubin, ammonia, white blood cell count, serum blood urea nitrogen, serum creatinine, MELD score, MELD 3.0 score, and ALBI score, compared to the survival group. Specifically, the mean ALBI scores of the survival and nonsurvival groups were −1.12 (−1.42, −0.79) and −0.76 (−1.04, −0.51), respectively (Z = 13.918, p = 0.000). The survival group had higher serum albumin and total cholesterol levels than the nonsurvival group. Additionally, the incidence of hepatic complications in the nonsurvival group was greater than in the survival group (all p < 0.005). These complications included ascites, HE, AKI, variceal bleeding, SBP, pulmonary infection, and hepatic hydrothorax.

Survival analysis was conducted for 28-day and 90-day mortality according to the number of complications at baseline (Fig. 2). The survival curve showed that as the number of complications increased, the survival rate of patients decreased significantly. The proportion of patients with three or more complications in the nonsurvival group was significantly greater than in the survival group for both 28-day and 90-day mortality rates [log-rank (Mantel–Cox) χ^2 = 143.265 and 211.153, respectively, p = 0.000]. Thus, we can conclude that the number of complications is a critical predictor of short-term prognosis for patients with ACLF, with an increase in complications significantly raising the risk of death.

Univariate and multivariate analyses of factors associated with 28-day mortality in ACLF patients

Clinical data and laboratory indicators collected at admission were used to select the most significant risk factors. We conducted univariate and multivariate analyses to identify the risk factors associated with 28-day mortality. Univariate analysis revealed that age, INR, serum creatinine, the MELD score, the ALBI score, HE, variceal bleeding, SBP, and pulmonary infection were associated with 28-day mortality in patients with ACLF. These characteristics were then included in multivariate logistic regression (Table 1); however, we excluded the ammonia level to avoid collinearity. The results of the multivariate analysis revealed that HE, pulmonary infection, and SBP were independent risk factors for short-term mortality and were indeed the most important complications for short-term mortality (ORs = 2.281, 1.413, and 0.646, respectively; all p < 0.05). Other well-known risk factors, including age, the ACLF subtype, INR, neutrophil count, and MELD score, were also found to be independent risk factors for short-term mortality (ORs = 1.420, 1.976, 2.806, 2.923, and 4.270, respectively; all p < 0.05).

Table 2. Comparison of clinical characteristics between the survival and nonsurvival groups

	Survival group (n = 797)	Nonsurvival group (n = 589)		*p*-value
Age (years), mean (SD)	45.77 ± 9.66	47.92 ± 9.49	4.117	0.000[a]
Male, n (%)	682 (85.57)	488 (81.61)	1.903	0.168[c]
Aetiology of the disease			9.461	0.009[c]
HBV, n (%)	672 (84.31)	471 (79.96)		
Alcohol, n (%)	76 (9.54)	55 (9.34)		
Others, n (%)	49 (6.15)	63 (10.70)		
ACLF subtype			84.217	0.000[c]
Subtype A, n (%)	353 (44.29)	122 (20.71)		
Subtype B, n (%)	369 (46.30)	397 (67.40)		
Subtype C, n (%)	75 (9.41)	70 (11.88)		
Complications				
Ascites, n (%)	596 (74.78)	479 (81.32)	14.981	0.002[c]
Variceal bleeding, n (%)	69 (8.66)	95 (16.13)	18.124	0.000[c]
Hepatic encephalopathy			138.246	0.000[c]
No, n (%)	564 (70.76)	234 (39.73)		
Grade I, n (%)	190 (23.85)	262 (44.48)		
Grade II, n (%)	33 (4.14)	70 (11.88)		
Grade III-IV, n (%)	10 (1.25)	23 (3.90)		
Hydrothorax, n (%)	233 (29.23)	211 (35.82)	11.946	0.001[c]
Pulmonary infection, n (%)	104 (13.05)	168 (28.52)	51.659	0.000[c]
SBP, n (%)	237 (29.74)	212 (35.99)	11.447	0.001[c]
AKI, n (%)	248 (31.12)	366 (62.14)	132.101	0.000[c]
Number of complications				
0, n (%)	51 (6.40)	6 (1.02)	127.158	0.000[c]
1, n (%)	344 (43.16)	126 (21.39)		
2, n (%)	280 (35.13)	259 (43.97)		
≥3, n (%)	122 (15.31)	198 (33.62)		
Laboratory data				
Albumin (g/L), mean (SD)	29.78 ± 5.32	28.67 ± 5.76	3.693	0.000[a]
Total bilirubin (μmol/L), mean (SD)	202.25 ± 172.42	383.21 ± 162,69	19.782	0.000[a]
INR, mean (SD)	1.95 ± 0.42	2.18 ± 0.65	10.344	0.000[a]
Sodium (mmol/L), mean (SD)	133.87 ± 5.63	132.17 ± 6.14	5.348	0.000[a]
Total cholesterol (mmol/L), mean (SD)	1.72 ± 0.95	1.46 ± 1.12	4.628	0.000[a]
Ammonia (μmol/L), mean (SD)	94.51 ± 43.07	121.61 ± 59.65	5.582	0.000[a]
Haemoglobin (g/L), mean (SD)	120.47 ± 24.25	117.39 ± 27.38	2.211	0.027[a]
WBC (10^9/L), median (IQR)	6.37 (4.59, 8.82)	7.88 (5.51, 11.26)	6.878	0.000[b]
Neutrophil count (10^9/L), median (IQR)	4.15 (1.52,4.77)	5.71 (3.56,8.94)	7.240	0.000[b]
Platelets (10^9/L), mean (SD)	94.30 ± 55.15	89.95 ± 57.96	1.419	0.156[a]
Neutrophil/PLT ratio, median (IQR)	0.04 (0.02–0.08)	0.15 (0.08–0.30)	18.211	0.000[b]
Creatinine (μmol/L), median (IQR)	87.00 (77.00,110.00)	93.00 (80.00,120.00)	5.642	0.000[b]
Urea (mmol/L), median (IQR)	6.05 (4.50, 9.42)	10.20 (6.10, 16.50)	11.085	0.000[b]
MELD score, median (IQR)	18.32 (14.05,25.21)	32.60 (26.06,41.29)	21.068	0.000[b]
MELD 3.0 score, median (IQR)	26.80 (24.70,29.30)	30.10 (27.20,33.32)	11.662	0.000[b]
ALBI score, median (IQR)	−1.12 (−1.42, −0.79)	−0.76 (−1.04, −0.51)	13.918	0.000[b]
ALBI grade			81.495	0.000[b]
Grade 1	1 (0.13)	0 (0.00)		
Grade 2	224 (28.11)	51 (8.66)		
Grade 3	572 (71.76)	538 (91.34)		

Data are presented as mean ± SD, n (%), or median (interquartile range). [a]t test; [b]Mann–Whitney U test; [c]$\chi 2$ test or Fisher's exact test. ACLF, acute-on-chronic liver failure; SBP, spontaneous bacterial peritonitis; AKI, acute kidney injury; INR, international normalized ratio; WBC, white blood cells; MELD, Model for end-stage liver disease.

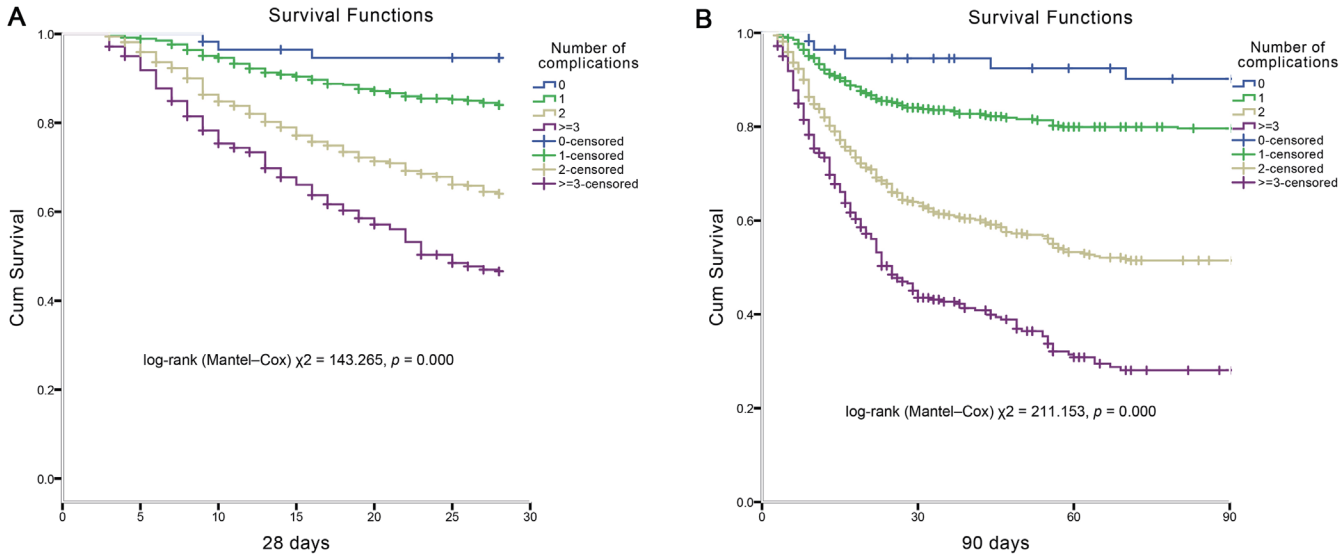


Fig. 2. Survival curves for mortality. Survival curves for 28-day (A) and 90-day (B) mortality according to the number of complications at baseline.

Development of the MELD-complication score

The MELD score is currently recognized as the scoring model for liver transplant allocation. However, because it does not sufficiently consider the impact of clinical complications on prognosis, independent predictors of short-term mortality were determined through multivariate analysis, and a multivariate regression model incorporating the MELD score was developed. As shown by the results of the multivariate analysis, age, the ACLF subtype, INR, MELD score, HE grade, SBP, and pulmonary infection (PI) were found to be independent predictors of 28-day mortality. The formula for this new score, named the MELD-complication score, is as follows: MELD-complication score = −3.585 + 1.452 × ($\log_{10}$(MELD score)) + 0.825 × HE grade + 1.073 × $\log_{10}$(neutrophil count (10^9/L)) + 1.032 × INR + 0.681 × ACLF subtype (liver cirrhosis = 1; non- liver cirrhosis = 0) + 0.346 × age(≥45, y = 1; <45, y = 0) + 0.346 × PI (PI = 1; non-PI = 0) - 0.437 × SBP (SBP = 1; non-SBP = 0). The results of the Hosmer–Lemeshow goodness-of-fit test (chi-square = 9.215, p = 0.324) indicated that the predicted values of the model and the actual observed values were not significantly different and that the prediction model had good calibration ability.

Assessment of the performance of the ALBI score, MELD score, MELD 3.0 score, and MELD-complication score in predicting 28-day mortality

The AUROCs of the three existing prognostic scores (ALBI, MELD, and MELD 3.0) and the novel MELD-complication score were compared to predict the primary outcome. For predicting 28-day mortality, the AUROCs (95% CIs) were as follows: ALBI score, 0.675 (0.645–0.705); MELD score, 0.694 (0.662–0.725); MELD 3.0 score, 0.697 (0.666–0.728); and MELD-complication score, 0.863 (0.843–0.882) (Fig. 3A, C). These results indicate that the MELD-complication score exhibited the highest predictive strength for 28-day mortality, outperforming the ALBI score and the two other MELD scores.

We also assessed the performance of the ALBI score, MELD score, MELD 3.0 score, and MELD-complication score in predicting 90-day mortality via ROC analysis. The AUROCs (95% CIs) of the four scores were 0.678 (0.650–0.707) for ALBI, 0.648 (0.617–0.678) for MELD, 0.662 (0.633–0.692) for MELD 3.0, and 0.853 (0.832–0.873) for MELD-complication, (Fig. 3B, C). These results indicate that the MELD-complication score also has predictive ability for 90-day mortality compared to the ALBI score and the other two MELD scores.

Cut-off values, sensitivity, and specificity of the prognostic scores in predicting ACLF patient mortality

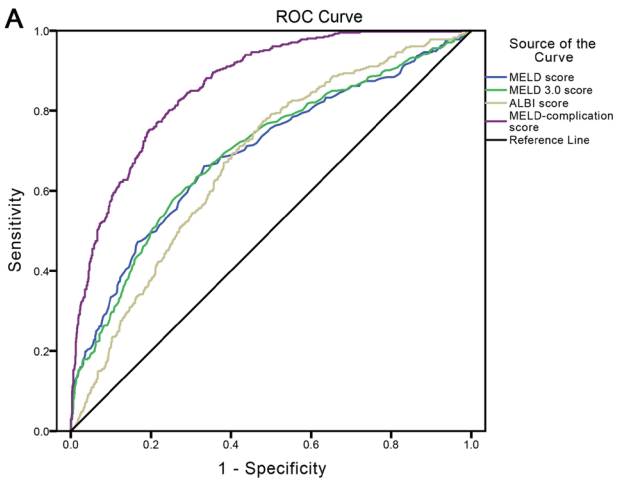
In addition to the AUROC, additional accuracy metrics were calculated for the scores, as shown in Figure 3C. The ALBI score, MELD score, and MELD 3.0 score demonstrated sensitivities of 62.90%, 62.08%, and 64.01%, respectively, while the MELD-complication score exhibited a sensitivity of 77.89% and a specificity of 77.81%. The critical value of 2.58 for the MELD-complication score, determined using the maximum Youden index method, showed that above this threshold, the 28-day mortality rate was 60.42%, whereas below this threshold, the mortality rate was 11.07%. Survival rates for 28-day and 90-day periods were also analyzed using the Kaplan–Meier method according to this cut-off value. The results revealed a significant difference in survival between patients dichotomized by this threshold (log-rank (Mantel–Cox) χ^2 = 487.574 and 606.441, p = 0.000) (Fig. 3D–E).

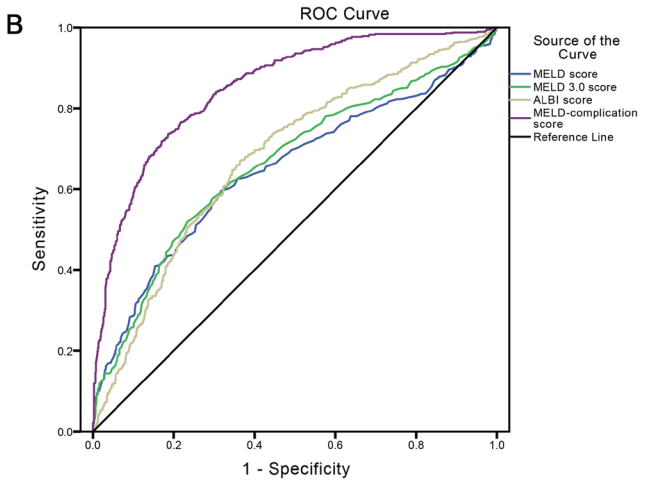
Model performance and validation

The new model was validated in two independent external cohorts: 292 patients from Beijing Youan Hospital, Capital Medical University (Youan cohort), and 242 patients from The First Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou cohort).

Statistical analysis revealed significant differences between the training set and external test set in terms of age, sex, etiology, ACLF subtype, incidence of complications, and multiple laboratory indicators (all p-values < 0.05) (Table 3). These differences highlight the heterogeneity in the ACLF patient population across different medical institutions, and further validate the universality and stability of the new model.

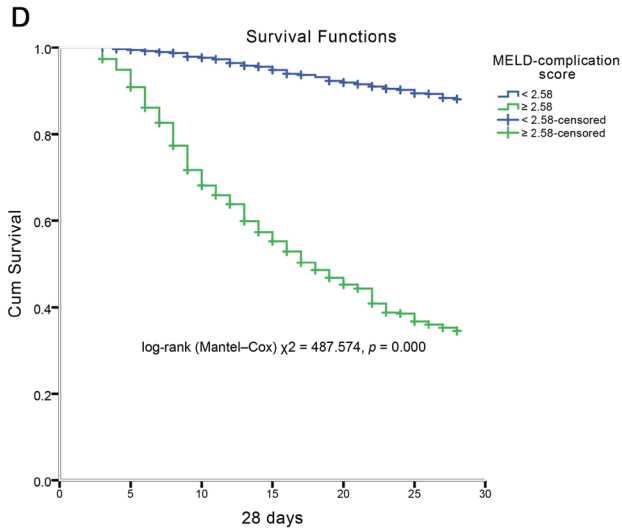
Using ROC analysis, the MELD-complication score outperformed other models in predicting 28-day and 90-day mortality rates in both external test cohorts (Fig. 4). The DeLong test confirmed statistical superiority with p < 0.05 (Table 4).





C

	Cut-off Value	Sensitivity	Specificity	PPV	NPV	AUROC (95% CI)	*p*-value
ALBI score	-0.88	0.63	0.64	62.31	69.51	0.675(0.645–0.705)	0.000
MELD score	26.35	0.62	0.69	70.95	70.73	0.694(0.662–0.725)	0.000
MELD 3.0 score	28.55	0.64	0.68	62.65	65.37	0.697(0.666–0.728)	0.000
MELD - complication score	2.58	0.78	0.78	72.73	76.11	0.863(0.843-0.882)	0.000



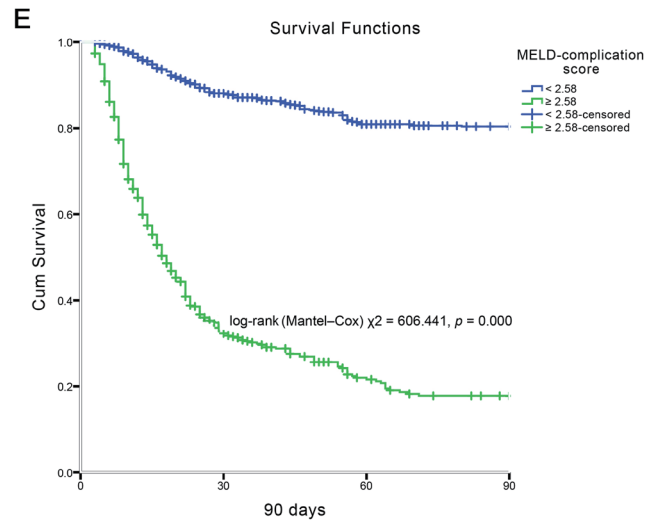


Fig. 3. ROC curves and survival analysis for ACLF mortality prediction in the training cohort. Survival curves for 28-day (A) and 90-day (B) mortality according to the number of complications at baseline. (C) Cut-off values, sensitivity, and specificity of the prognostic scores according to ROC analysis. Cumulative survival at 28 days (D) and 90 days (E) according to the Kaplan–Meier method. ALBI, albumin-bilirubin; ACLF, acute-on-chronic liver failure; MELD, Model for end-stage liver disease; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic.

In the Youan cohort, the AUROCs for 28-day mortality were 0.696 for ALBI, 0.770 for MELD, 0.757 for MELD 3.0, and 0.820 for MELD-complication. For 90-day mortality, AUROCs were 0.693, 0.771, 0.759, and 0.800, respectively. In the Hangzhou cohort, the corresponding 28-day AUROCs were 0.602 for ALBI, 0.662 for MELD, 0.646 for MELD 3.0, and 0.774 for MELD-complication (Fig. 4A–B, Table 4). The 90-day AUROCs were 0.595, 0.661, 0.619, and 0.724, respectively, all indicating the MELD-complication score's predictive advantage (Fig. 4C–D, Table 4).

Discussion

This retrospective study aimed to identify mortality risk factors in patients with ACLF and to develop a prognostic model, termed the MELD-complication score. By analyzing extensive

Table 3. Comparison of clinical characteristics between the training and test sets

	Training set (n = 1,386)	Youan set (n = 292)	Hangzhou set (n = 242)		*p*-value
Age (years), mean (SD)	46.68 ± 9.65	48.12 ± 11.01	54.32 ± 12.65	56.940	0.000[a]
Male, n (%)	1,170 (85.57)	239 (81.61)	179	15.905	0.000[b]
Aetiology of disease				7.497	0.023[c]
HBV, n (%)	1,143 (82.47)	202 (69.18)	165 (68.18)		
Alcohol, n (%)	131 (9.45)	70 (23.97)	39 (16.12)		
Other, n (%)	112 (8.08)	20 (6.85)	38 (15.70)		
ACLF subtype				8.532	0.031[c]
Subtype A, n (%)	475 (34.27)	71 (24.32)	79 (32.64)		
Subtype B, n (%)	766 (55.27)	140 (47.94)	115 (47.52)		
Subtype C, n (%)	145 (10.46)	81 (27.74)	48 (19.83)		
Complications					
Ascites, n (%)	1,055 (76.12)	230 (78.77)	134 (55.37)	286.812	0.000[c]
Variceal bleeding, n (%)	164 (11.83)	31 (10.62)	21 (8.68)	2.192	0.334[c]
Hepatic encephalopathy				123.475	0.000[c]
No, n (%)	798 (57.58)	186 (63.70)	197 (81.40)		
Grade I, n (%)	492 (35.51)	80 (27.40)	13 (5.37)		
Grade II, n (%)	103 (7.43)	20 (6.85)	13 (5.37)		
Grade III-IV, n (%)	33 (2.38)	6 (2.05)	19 (7.85)		
SBP, n (%)	449 (32.40)	181 (61.99)	68 (28.10)	99.429	0.000[c]
Pulmonary infection, n (%)	272 (19.62)	54 (18.49)	22 (9.09)	15.605	0.000[c]
AKI, n (%)	614 (44.30)	36 (12.33)	55 (22.73)	129.429	0.000[c]
Laboratory data					
Albumin (g/L), mean (SD)	29.31 ± 5.53	29.80 ± 5.31	29.91 ± 4.56	1.929	0.146[a]
Total bilirubin (μmol/L), Median (IQR)	235.40 (107.98,433.20)	333.30 (204.40,473.83)	308.45 (235.68,411.60)	42.092	0.000[b]
INR, mean (SD)	2.08 ± 0.60	2.23 ± 0.77	2.10 ± 0.64	6.867	0.001[a]
ALT, median (IQR)	192.00 (78.00,338.00)	118.00 (45.00,456.50)	132.50 (54.25,423.75)	148.696	0.000[b]
AST, median (IQR)	100.00 (169.00,352.50)	151.00 (84.00,321.50)	147.50 (80.00,322.25)	4.603	0.100[b]
Sodium (mmol/L), mean (SD)	133.16 ± 5.91	135.95 ± 7.61	134.21 ± 6.33	82.877	0.000
Ammonia (μmol/L), mean (SD)	106.18 ± 52.60	85.17 ± 49.30	/	36.484	0.000[a]
WBC (10^9/L), median (IQR)	5.59 (3.57, 9.82)	7.12 (5.21, 10.14)	7.00 (5.00,10.00)	16.613	0.000[b]
Neutrophil count (10^9/L), median (IQR)	5.15 (1.70,7.30)	5.34 (3.91,7.61)	5.00 (3.00,7.75)	68.332	0.000[b]
Platelets (10^9/L), median (IQR)	81.00 (52.00,120.00)	101.00 (58.50,145.00)	89.50 (55.00,137.50)	21.521	0.000[b]
Creatinine (μmol/L), median (IQR)	87.00 (72.00,123.00)	63.00 (53.00,77.50)	66.00 (56.00,93.75)	179.745	0.000[b]
MELD score, median (IQR)	25.46 ± 5.55	36.92 ± 2.77	22.41 ± 5.99	654.568	0.000[a]
MELD 3.0 score, median (IQR)	28.10 ± 5.41	35.22 ± 3.55	40.14 ± 3.00	753.985	0.000[a]
ALBIs, median (IQR)	−0.99 (−1.34, −0.69)	−0.85 (−1.18, −0.58)	−0.91 (−1.17, −0.66)	8.995	0.011[b]
28-day mortality (%)	414 (29.87)	67 (22.95)	76 (31.40)	6.387	0.041[c]

Data are presented as mean ± SD, n (%), or median (interquartile range). [a]t test; [b]Mann–Whitney U test; [c]χ2 test or Fisher's exact test. ACLF, acute-on-chronic liver failure; SBP, spontaneous bacterial peritonitis; AKI, acute kidney injury; INR, international normalized ratio; WBC, white blood cells; MELD, Model for end-stage liver disease.

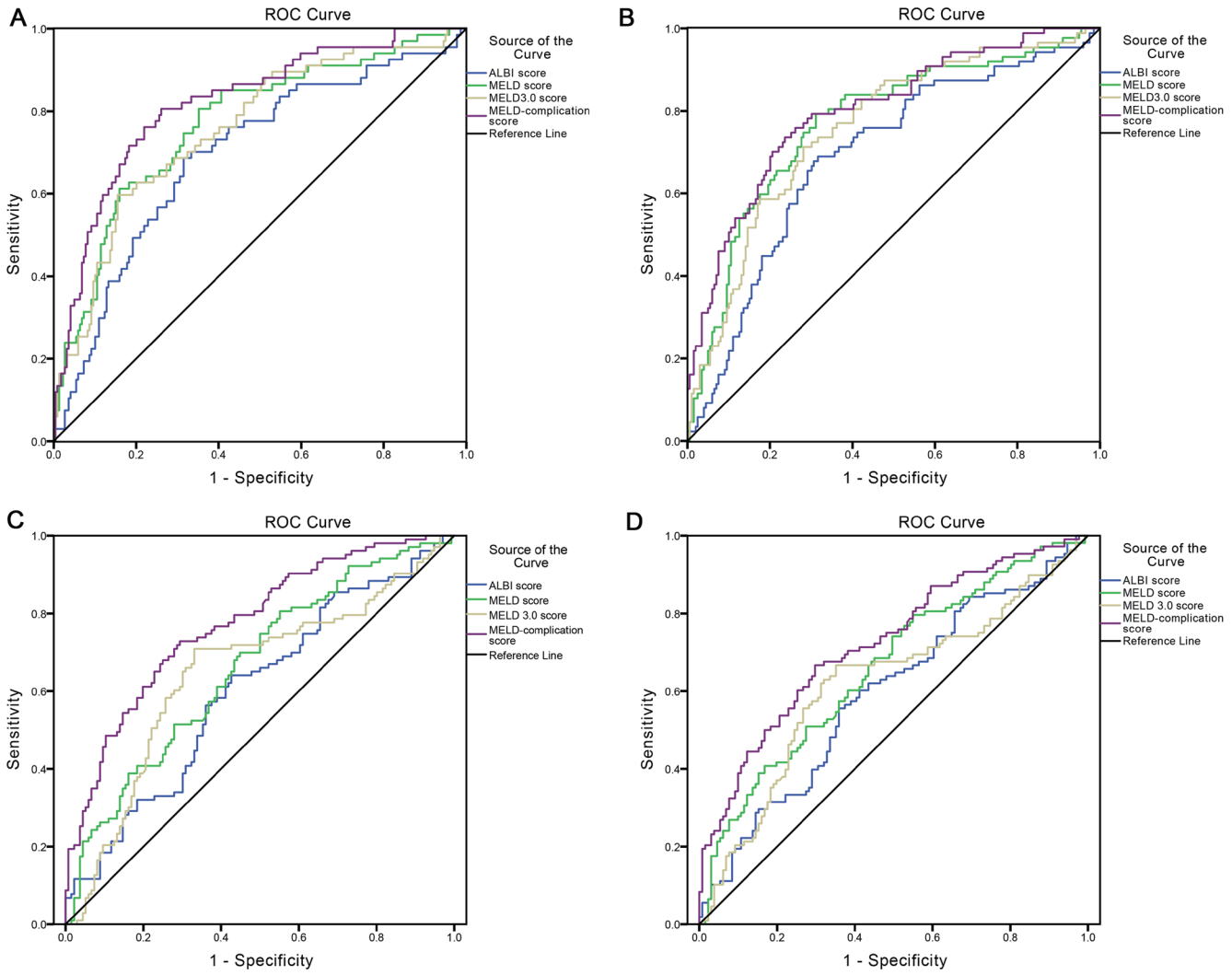


Fig. 4. ROC curves of different prognostic models in predicting 28-day and 90-day mortality in patients with ACLF. (A–B) ROC curves for the prediction of (A) 28-day and (B) 90-day mortality in the Youan cohort. (C–D) ROC curves for the prediction of (C) 28-day and (D) 90-day mortality in the Hangzhou cohort. ALBI, albumin-bilirubin; ACLF, acute-on-chronic liver failure; MELD, Model for end-stage liver disease; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic.

Table 4. AUROCs of the prognostic scores in predicting 28-day and 90-day mortality of patients with ACLF in the external test sets

	28-day mortality		90-day mortality	
	AUROC (95% CI)	***p*-value**	**AUROC (95% CI)**	***p*-value**
Youan				
ALBI score	0.696 (0.623–0.770)	0.000	0.693 (0.626–0.759)	0.000
MELD score	0.770 (0.704–0.836)	0.000	0.771 (0.710–0.832)	0.000
MELD 3.0 score	0.757 (0.690–0.824)	0.000	0.759 (0.699–0.819)	0.000
MELD-complication score	0.820 (0.762–0.879)	0.000	0.800 (0.744–0.857)	0.000
Hangzhou				
ALBI score	0.602 (0.530–0.674)	0.007	0.595 (0.522–0.667)	0.012
MELD score	0.662 (0.593–0.731)	0.000	0.661 (0.592–0.730)	0.000
MELD 3.0 score	0.646 (0.574–0.719)	0.000	0.619 (0.546–0.693)	0.002
MELD-complication score	0.774 (0.714–0.833)	0.000	0.724 (0.659–0.788)	0.000

ALBI, albumin-bilirubin; ACLF, acute-on-chronic liver failure; MELD, Model for end-stage liver disease; AUROC, Receiver Operating Characteristic Area Under the Curve.

clinical data, we identified age, ACLF subtype, INR, MELD score, HE grade, SBP, and white blood cell count as independent predictors of 28-day mortality. Our survival analysis showed that higher numbers of complications were significantly associated with lower survival rates. The non-survivor group had a notably greater proportion of patients with three or more complications [log-rank (Mantel–Cox) $\chi 2$ = 143.265 and 211.153, respectively, p = 0.000], highlighting the critical relationship between complications and prognosis.

The MELD-complication score integrates laboratory values and essential clinical complications, thereby enhancing the prediction of short-term outcomes for ACLF patients. It serves as a valuable decision-support tool for clinicians managing these patients and prioritizing liver transplants.

We compared the prognostic value of the new MELD-complication score with the ALBI, MELD, and MELD 3.0 scores in ACLF patients. The ALBI score, recently developed to assess the prognosis of hepatocellular carcinoma, detects small liver function changes more objectively than the Child–Pugh or MELD scores and predicts survival in non-malignant liver disease.[15] In an HBV-ACLF study, the ACLF group had a significantly higher ALBI score compared to healthy controls and CHB groups, correlating positively with MELD and Child–Pugh scores.[24] However, another study found the ALBI score ineffective in predicting in-hospital mortality in cirrhotic ACLF patients (AUROC: 0.53, 95% CI: 0.42–0.63, p = 0.69).[25] Sun *et al*. found no association between ALBI or ALBI grade and rehospitalization in ACLF patients.[26] Our multivariate analysis revealed that the ALBI score was not an independent risk factor for 28-day mortality; its AUROC values for predicting 28-day mortality and 90-day mortality were 0.675 (0.645–0.705) and 0.678 (0.650–0.707), respectively. In this cohort of ACLF patients, the majority were classified as ALBI grade 3 (80.09%) or ALBI grade 2 (19.84%), with only a minority having grade 1 (0.07%), which is consistent with the results of a previous study.[26] In summary, while the ALBI score has certain advantages in evaluating liver function, its efficacy in predicting the prognosis of ACLF patients remains insufficient. The MELD 3.0 score, though achieving better accuracy in predicting mortality in liver diseases, was not superior to the MELD score in predicting short-term survival in ACLF patients (AUROCs: 0.697 and 0.662 for 28-day and 90-day mortality, respectively). This suggests the need for more accurate and effective tools to evaluate ACLF prognosis.

Through comparative analysis, we expanded our understanding of ACLF's clinical characteristics and developed the MELD-complication score for short-term prognosis. Key risk factors include HE, pulmonary infection, SBP, INR, and neutrophil count.[27–30] Additionally, infections are now considered a major trigger for encephalopathy.[31] This information suggests that bacterial infection is a crucial component of ACLF and that systemic inflammatory response syndrome is the most important factor for assessing the severity of liver failure.[32,33] Some propose that intense systemic inflammation may lead to organ failure through various mechanisms, including neutrophil activation and tissue damage.[34] Despite the lack of a universal ACLF definition for ACLF, HE is recognized as a significant form of organ failure and a key marker of ACLF. Acute systemic inflammation stimulates intense amino acid catabolism, potentially contributing to HE, which in turn predicts ACLF patient mortality.[35] By analyzing the pathophysiological characteristics of ACLF, we developed a new scoring system that integrates the MELD score with important ACLF complications (HE, SBP, and pulmonary infection), INR, and neutrophil count. This system reflects the impact of systemic inflammation on the prognosis of ACLF patients. Regarding clinical application, a prognostic model should be evaluated for its utility in a homogeneous patient cohort in terms of discrimination, calibration ability, and predictive/diagnostic power.[11]

The results of the Hosmer–Lemeshow goodness-of-fit test suggested that the prediction model had good calibration ability. The clinical features selected for inclusion indicate that the new scoring model, which incorporates ACLF complications and the MELD score, is effective for accurately assessing the prognosis of patients with ACLF according to the APASL criteria. The AUROCs revealed that the MELD-complication score, is more accurate in assessing LT-free short-term mortality compared to generic scoring models, including the MELD score, MELD 3.0 score, and ALBI score. The MELD-complication score can be used to stratify mortality risk among ACLF patients, effectively identify high-risk individuals, and demonstrate robustness in two external cohorts, with distinct ACLF etiologies.

Finally, we validated the MELD-complication score in two independent external cohorts from Beijing Youan Hospital, Capital Medical University, and the First Affiliated Hospital of Zhejiang University. All three hospitals are of the same level, and homogeneous in medical standards. By comparing the clinical characteristics of the test set and the training set, we found some differences in patient age, etiology distribution, and incidence of complications. However, despite these differences, the MELD-complication score accurately predicted patient prognosis. The AUROCs for predicting 28-day mortality were 0.820 and 0.774 (all $p < 0.05$), and for predicting 90-day mortality were 0.800 and 0.724 (all $p < 0.05$). This finding indicates that the new model maintains accuracy and stability across various patient groups and medical environments.

This study has certain limitations. The retrospective design may introduce biases, highlighting the need for future prospective studies for validation. Additionally, the relatively small sample size in external cohorts suggests a need for enhanced model robustness. Future research should focus on larger cohorts and long-term prognostic assessments to adapt the model as ACLF treatment strategies evolve.

Conclusions

This retrospective study has identified key risk factors associated with the prognosis of patients with ACLF and developed a novel prognostic scoring model, the MELD-complication score. This new model, which integrates the MELD score with significant complications and indicators of systemic inflammatory response, demonstrated superior predictive accuracy for short-term mortality compared to traditional scores such as MELD, MELD 3.0, and ALBI. The MELD-complication score offers improved predictions of short-term prognosis for ACLF patients, potentially aiding in patient management and liver transplant prioritization. Future validation across diverse patient populations is warranted to ensure the model's generalizability and reliability.

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None to declare.

Conflict of interest

JL has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2020. The other authors have no conflict of interests related to this publication.

Author contributions

Collecting data, performing the statistical analysis, drafting the final manuscript (WL, WL, YR), helping to collect data and perform statistical analysis (DL, BZ, SY, SS), conceptualizing and designing the study, collecting data, and revisinge the final manuscript (SY, YC, JL). All authors were involved in the critical revision and approved the final version of the manuscript.

Ethical statement

This study was approved by the Ethics Committee of the 302 Hospital of PLA, the predecessor of the Fifth Medical Center of the Chinese PLA General Hospital, in accordance with the Declaration of Helsinki (2013005D).

Data sharing statement

All data associated with this study are included in the paper.

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