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DATABASE ANALYSIS

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Prognostic Value of Acute-On-Chronic Liver Failure (ACLF) Score in Critically Ill Patients with Cirrhosis and ACLF

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: In the intensive care unit (ICU), critically ill patients with cirrhosis and acute-on-chronic liver failure (ACLF) continue to have high mortality rates. The AARC ACLF score is a simple, newly-developed score based on Asian ACLF patients, which performs well in prognosis. The present study attempted to verify the prognostic ability of AARC ACLF in non-Asian critically ill patients with cirrhosis and ACLF.

Material/Methods: We enrolled 786 patients. Relevant clinical data were collected within 24 h after admission to compare the differences between survivors and non-survivors, and all the patients were followed up for at least 180 days.

Results: The 28-day, 90-day, and 180-day mortality rates were 28.9% (227/786), 36.4% (286/786), and 40.3% (317/786), respectively. Multivariate Cox regression analysis showed that AARC ACLF score (HR: 1.375, 95% CI: 1.247–1.516, P<0.001) was an independent predictive factor of 28-day mortality, and the AUROC of the predictive ability in 28-day mortality of the AARC ACLF score was 0.754. In addition, the AARC ACLF score was regraded into 3 classes (low risk: AARC ACLF <9, intermediate risk: 9≤ AARC ACLF <12, and high risk: AARC ACLF ≥12). The AARC ACLF score can be used for dynamic assessment by retest at days 4–7.

Conclusions: The AARC ACLF score has a good predictive value for 28-day, 90-day, and 180-day mortality in non-Asian critically ill patients with cirrhosis and ACLF, which is not inferior to CLIF-C ACLFs$_{Lact}$ and other models. It is easy to use at bedside, and it is dynamic and reliable.

MeSH Keywords: End Stage Liver Disease • Liver Cirrhosis • Liver Failure • Proportional Hazards Models

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Background

Liver cirrhosis is the final stage of chronic liver disease [1]. Critically ill patients with cirrhosis have high mortality rates and long hospitalizations in the intensive care unit (ICU) [2–4]. Acute-on-chronic liver failure (ACLF) is a unique form of chronic liver disease, with rapid patient deterioration and poor outcome. The definition of ACLF is heterogeneous [5]. In the present study we used the Asian Pacific Association for the Study of the Liver (APASL) standard, which is more focused on liver damage, in order to include a more homogenous group [6].

Some studies have found that lactate levels have good predictive value in critically ill patients with cirrhosis [7–9], and several traditional models were improved by adding lactate, such as CLIF-C ACLFs$_{Lact}$ [8]. However, most of the models are too complex to use at bedside.

The APASL ACLF Research Consortium (AARC) ACLF score is constructed from the AARC database, in which data were collected prospectively from multiple centers [10]. It has proved to have good prognostic value among Asian people with ACLF. It is a simple prognostic model that is easy to use, relying on a combination of lactate, hepatic encephalopathy grade, INR, bilirubin, and serum creatine levels. Several studies have verified the value of AARC ACLF score in predicting the outcome of children with cirrhosis [11,12]. However, the AARC ACLF score has not been applied in non-Asian people until now and no study has validated the prognostic ability of this score in critically ill patients with cirrhosis compared to CLIF-C ACLFs$_{Lact}$.

The goals of this study were to verify the prognostic value of AARC ACLF score among non-Asian critically ill patients with cirrhosis and ACLF, as well as to study the predictive ability this score compared with Child-Pugh, MELD, MELD-Na, SOFA, CLIF-SOFA, and CLIF-C ACLFs$_{Lact}$.

Material and Methods

Study design

Patient data were obtained from the Medical Information Mart for Intensive Care III (MIMIC-III) database [13], which is a large, single-center, open database currently consisting of more than 40 000 ICU patients who stayed at the ICU of Beth Israel Deaconess Medical Center (BIDMC) between 2001 and 2012. We completed the training course "Protection of Human Research Participants" of the National Institutes of Health (Certificate Number: 25557915) and were thus allowed access to the database. For this retrospective study, formal consent was not required.

Definitions and exclusion criteria

Liver cirrhosis was diagnosed based on computed tomography or ultrasonography, as well as clinical evidence of liver dysfunction, or portal hypertension. ACLF was defined using the AARC criteria updated in 2019 [6].

Patients who met the criteria for liver cirrhosis diagnosis were included in the present study. The exclusion criteria were as follows: (i) younger than 18 years old; (ii) non-first admission; (iii) Asian people; (iv) associated with malignancy, HIV, or liver transplantation; and (v) missing lactate, bilirubin, creatinine, or INR data at admission.

Patients and data collection

The Transact-SQL was used to extract patient information. Indicators were as follows: patients characteristics such as sex, age, etiology of cirrhosis, diabetes, hypertension, ethnicity, survival time, vital signs such as temperature, respiratory rate, heart rate, and blood pressure, and laboratory parameters such as plasma glucose, platelet count, red blood cell distribution width (RDW), serum creatinine, serum sodium concentration, potassium, international standardization ratio (INR), total bilirubin, albumin, prothrombin time (PT), white blood cell (WBC) count, blood urea nitrogen (BUN), and lactate in the first 24 h after admission. To evaluate the dynamic prognostic value, we also recollected data on INR, bilirubin, creatinine, lactate, and INR at days 4–7. Prognostic models including MELD, MELD-Na, Child-Pugh, CLIF-SOFA, SOFA, CLIF-C ACLFs$_{Lact}$, and AARC ACLF were also evaluated. All the participants were followed up for at least 180 days. The primary outcome was 28-day all-cause mortality after ICU admission.

CLIF-SOFA [14], Child-Pugh, CLIF-C ACLFs$_{Lact}$ [8], and SOFA [15] were calculated according to published formulas. MELD: R=9.57×log [creatinine (mg/dl)]+3.78×log [bilirubin (mg/dl)]+11.2×log (INR)+6.4 (etiology: 0 if cholestatic or alcoholic, 1 otherwise) [16]; MELD-Na: R=MELD+1.59×[135-Na (mmol/l)] [17].

Statistical analyses

Continuous variables were assessed by the Kolgomorov-Smirnov test for distribution, with normally distributed data shown as mean±SD, and were compared using the *t* test. Otherwise, results were compared by Mann-Whitney U test and shown as median with interquartile range (IQR). Categorical variables were expressed as numbers (%) and compared using the chi-square test or Fisher's exact test. The association between study factors and the mortality risk were determined by univariate and multivariate Cox proportional hazard models, and expressed as hazard ratio (HR) with a 95% confidence interval (CI). The area under the receiver operating characteristic

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(AUROC) curve combined with DeLong test was used to compare the performance of each scoring system. The best cutoff point of the models was found and compared. The predicted probability of incidence and the actual incidence was compared by calibration curves. The DCA curve [18] was used to compare the net benefit rate of each indicator, Kaplan-Meier analysis was used to identify the cumulative survival, and the log-rank test was used to compare results among groups. Multiple imputations were used to account for the missing PO2/FiO2 and albumin data. All tests were double-sided, and P values less than 0.05 were considered statistically significant. Statistical software SPSS 22, MedCalc (version 19.0.4; Ostend, Belgium), and R package (version 3.6.1; R Foundation) were used for statistical analyses.

Results

General information of study populations

We analyzed data from 786 cirrhotic patients (Figure 1), including 196 patients diagnosed as having ACLF according to the AARC definition (167 ACLF patients were diagnosed at ICU admission and 29 patients developed ACLF after ICU admission). In the study population, there were 524 (66.7%) males and 262 (33.3%) females and the mean age was 56 years (range, 22-89). Most patients were white (74.3%). A total of 227 (28.9%) patients were diabetic and 294 (37.4%) patients had hypertension. In terms of etiology, alcoholism (52.3%) was the most common cause of liver cirrhosis, and 122 patients had more than 1 etiology of cirrhosis. Regarding causes of ICU admissions, acute renal failure was the most common cause (54.1%), followed by acute respiratory failure (35.4%) and severe sepsis (25.1%). The 28-day, 90-day, and 180-day mortality rates were 28.9%, 36.3%, and 40.3%, respectively. With the primary endpoint of 28-day death, the non-survivors had significantly higher scores in MELD (17 *vs.* 15), MELD-Na (21 *vs.* 17), Child-Pugh (10 *vs.* 8), SOFA (11 *vs.* 7), CLIF-SOFA (11 *vs.* 8) scores, and CLIF-C ACLFs$_{Lact}$ (62 *vs.* 48). Non-survivors had higher proportions of patients with use of vasopressor (54.6% *vs.* 27.9%), renal replacement therapy (14.5% *vs.* 6.3%), ventilator support (63.9% *vs.* 55.1%), ascites (33.5% *vs.* 24.9%), spontaneous bacterial peritonitis (12.8% *vs.* 7.0%), hepatorenal syndrome (26.4% *vs.* 11.3%), and ACLF (38.8% *vs.* 19.3%). There were no significant differences in age, sex, height, weight, hepatic encephalopathy, and variceal bleeding (P≥0.05). However, hepatic encephalopathy and age were found to be significantly different in 90-day and 180-day mortality rates. More details are listed in Tables 1 and 2.

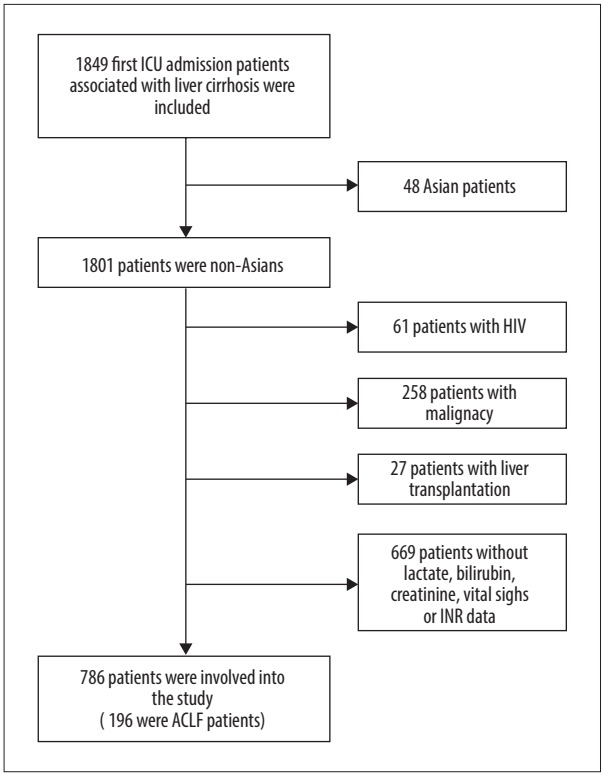

Figure 1. The study flow chart.

Association of the clinical parameters with 28-day mortality

Univariate analysis identified 25 indicators that differed significantly between the survivors group and the non-survivors group (p <0.05, Table 2). All the models we evaluated were also significantly different from the non-survivors. Multivariate Cox regression analysis revealed that AARC ACLF (HR: 1.375, 95% CI: 1.247–1.516, P<0.001), MAP, PaO2/FiO2, vasopressin used, AST, albumin, spontaneous bacterial peritonitis, platelet, and WBC were the independent risk parameters for 28-day mortality. For the factors in AARC ACLF score, bilirubin (HR: 1.030, 95% CI: 1.017, 1.043, p <0.001), creatinine (HR: 1.092, 95% CI: 1.027, 1.161, p=0.005), and INR (HR: 1.375, 95% CI: 1.234, 1.532, p<0.001) remained independent risk factors for 28-day mortality (Table 3). All the statistical results are presented in Tables 2 and 3.

Performance of AARC ACLF and compared with other prognostic models

AARC ACLF score had moderate prognostic ability for cirrhotic patients in 28-day mortality (AUC: 0.754, 95% CI: 0.717–0.791), 90-day mortality (AUC: 0.747, 95% CI: 0.711–0.783), and 180-day mortality (AUC: 0.728, 95% CI: 0.693–0.764). The calibration curve of the AARC ACLF is shown in Supplementary Figure 1. In the ACLF group, the AUC was 0.723 (95% CI: 0.665–0.781) and showed medium prognostic value.

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Table 1. Characteristics of cirrhotic patients in this study, stratified by mortality (n=786, day=28).

Variables	All patients (n=786) [n (%)]	Survivors (n=559) [n (%)]	Nonsurvivors (n=227) [n (%)]	P value*
Demographic parameters				
Age (years)	56 (50–65)	56 (49–64)	58 (50–67)	0.093
Sex (male) [n (%)]	524 (66.7)	374 (66.9)	150 (66.1)	0.050
Height (cm)	172.7 (165.1–178.0)	172.7 (165.1–177.8)	173.0 (163.0–179.1)	0.647
Weight (kg)	84.6 (71.3–99.8)	84.2 (71.1–100.0)	85.0 (72.0–99.0)	0.935
Ethnicity[n (%)]				<0.001
White	584 (74.3)	427 (76.4)	157 (69.2)	
Black	61 (7.8)	50 (8.9)	11 (4.8)	
Other	141 (17.9)	82 (14.7)	59 (26)	
Vital signs and treatment				
Heart rate	89.2±16.8	87.9±16.3	92.4 ±17.6	0.001
Respiratory rate (bpm)	18 (16–21)	18 (15–21)	20 (17–23)	<0.001
Temperature (°C)	36.7 (36.3–37.1)	36.7 (36.4–37.2)	36.4 (36.0–36.9)	<0.001
MAP (mmHg)	73.7 (67.1–82.2)	75.7 (69.5–84.5)	69.4 (64.3–75.6)	<0.001
PaO2/FiO2	218 (133–367)	241 (149–376)	174 (99–329)	<0.001
SpO2/FiO2	194 (101–250)	196 (137–250)	162 (99–245)	<0.001
24-h urine output (ml)	1182.5 (582.0–1940.0)	1360.0 (786.5–2118.5)	656.5 (206.0–1338.5)	<0.001
Vasopressin used [n (%)]	280 (35.6)	156 (27.9)	124 (54.6)	<0.001
Ventilator[n (%)]	453 (57.6)	308 (55.1)	145 (63.9)	0.024
RRT [n (%)]	68 (8.7)	35 (6.3)	33 (14.5)	<0.001
Cirrhosis complication [n (%)]				
Hepatic encephalopathy	214 (27.2)	142 (25.4)	72 (31.7)	0.071
Ascites	215 (27.4)	139 (24.9)	76 (33.5)	0.014
Variceal bleeding	105 (13.4)	69 (12.3)	36 (15.9)	0.189
Spontaneous bacterial peritonitis	68 (8.7)	39 (7.0)	29 (12.8)	0.009
Hepatorenal syndrome	123 (15.6)	63 (11.3)	60 (26.4)	<0.001
Causes of cirrhosis [n (%)]				
Alcoholic	411 (52.3)	276 (49.4)	135 (59.5)	0.010
Biliary	17 (2.2)	13 (2.3)	4 (1.8)	0.790
Hepatitis B	27 (3.4)	15 (2.7)	12 (5.3)	0.069
Hepatitis C	259 (33)	183 (32.7)	76 (33.5)	0.841
Autoimmune	12 (1.5)	9 (1.6)	3 (1.3)	1.000
Other	189 (24)	132 (23.6)	57 (25.1)	0.656

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Table 1 continued. Characteristics of cirrhotic patients in this study, stratified by mortality (n=786, day=28).

Variables	All patients (n=786) [n (%)]	Survivors (n=559) [n (%)]	Nonsurvivors (n=227) [n (%)]	P value*
ACLF [n (%)]	196 (24.9)	108 (19.3)	88 (38.8)	<0.001
Diabetes	227 (28.9)	164 (29.3)	63 (27.8)	0.657
Hypertension	294 (37.4)	216 (38.6)	78 (34.4)	0.261
Diagnosis at ICU admission				
Acute respiratory failure	278 (35.4)	152 (27.2)	126 (55.5)	<0.001
Acute renal failure	425 (54.1)	252 (45.1)	173 (76.2)	<0.001
Cardiorespiratory arrest	19 (2.4)	5 (0.9)	14 (6.2)	<0.001
Congestive heart failure	138 (17.6)	96 (17.2)	42 (18.5)	0.657
Neurological failure	95 (12.1)	70 (12.5)	25 (11.0)	0.556
Severe sepsis	197 (25.1)	86 (15.4)	111 (48.9)	<0.001
Variceal bleeding	105 (13.4)	69 (12.3)	36 (15.9)	0.189
Length of ICU stay	3.48 (1.90–7.02)	3.24 (1.89–7.02)	3.83 (1.90–7.08)	0.600

* Student's t-test or Mann-Whitney U-test was used for continuous variables, and χ^2-test or Fisher's exact test was used for categorical variables. MAP – mean arterial pressure; RRT – renal replacement therapy.

Compared with other models, the predictive value of AARC ACLF was better than Child-Pugh score (p<0.001, Table 4). CLIF-C ACLFs$_{Lact}$ gave the highest AUC (AUC: 0.777, 95% CI: 0.746-0.806), but there were no significant differences in SOFA, MELD, CLIF-SOFA, CLIF-C ACLFs$_{Lact}$ score, and MELD-Na, (p>0.05) from the AARC ACLF score. The AUROC curve of the predictive ability of scoring models are presented in Figure 2. For ACLF patients, AARC ACLF score had medium ability in predicting 28-day mortality and there was no significant statistical difference in among predict models except for Child-Pugh score (Supplementary Table 1). While using a cutoff point of 9.5 for AARC ACLF to predict 28-day mortality, the Youden index was 0.39, sensitivity was 0.67, specificity was 0.72, the positive likelihood ratio (PLR) was 2.41, the negative likelihood ratio (NLR) was 0.46, the positive predictive value (PPV) was 0.50, and negative predictive value (NPV) was 0.84. The predictability and accuracy of other models are listed in Table 5.

Considering both the benefits and the costs of the risk model, we used the DCA curve to assess the potential clinical impact of AARC ACLF score. As shown in Figure 3, it was obvious that the AARC ACLF score has clinical utility for use with cirrhotic patients, and is better than Child-Pugh score (p<0.001).

Regrading AARC ACLF and exploring the relationship with 28-day mortality

When using AARC ACLF, the median score was 10 in the non-surviving group and 9 in the surviving group (p<0.001). To make the model more intuitive, the AARC ACLF was regraded into 3 grades (low risk: AARC ACLF <9, intermediate risk: 9≤ AARC ACLF <12, and high risk: AARC ACLF ≥12) using X-TILE software; and the 28-day mortality rates were 11.2% (35/312), 34.7% (135/389), and 67.1% (57/85), respectively. In Figure 4, the Kaplan-Meier curves show cumulative all-cause survival among each grade of AARC ACLF. The survival probability was clearly different in each grade (Supplementary Figure 2).

Multivariate Cox regression analysis showed that AARC ACLF score was an independent prognostic predictor of 28-day mortality in critical ill patients with cirrhosis. After adjusting for clinical factors, the HR of AARC ACLF remained 1.375 (95% CI: 1.247–1.516), and HR only changed by 4% (Table 6).

Evaluation of AARC ACLF score as a dynamic predictor of mortality

There were 212 patients who had repeated laboratory examinations in 4–7 days, and we used AARC ACLF grade in this subgroup for dynamic assessment. In this subgroup, the 28-day mortality was 21.7% (10/46), 41.2% (56/136), and 50% (15/30), respectively. As shown in Figure 5A, a change from

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Table 2. Laboratory parameters and clinical model scores of cirrhotic patients in this study, stratified by mortality (n=786, day=28).

Variables	All patients (n=786) [n (%)]	Survivors (n=559) [n (%)]	Nonsurvivors (n=227) [n (%)]	P value*
Laboratory parameters				
ALT (IU/l)	39.5 (23.0–81.3)	37.0 (22.0–76.3)	52.0 (28.3–95.3)	0.001
AST (IU/l)	79.0 (44.0–178.5)	73.0 (42.0–147.0)	109.5 (55.0–209.5)	<0.001
Albumin (g/dl)	2.8 (2.4–3.2)	2.8 (2.4–3.3)	2.6 (2.2–3.1)	<0.001
Bilirubin (mg/dl)	3.3 (1.4–8.0)	2.7 (1.3–5.4)	7.0 (2.7–17.5)	<0.001
BUN (mg/dl)	31 (19–51)	27 (17–44)	42 (27–64)	<0.001
Creatinine (mg/dl)	1.4 (0.9–2.6)	1.2 (0.8–2.1)	2.0 (1.3–3.4)	<0.001
Glucose (mg/dl)	101 (83–125)	103 (87–128)	94 (75–118)	<0.001
Hematocrit	26.9 (23.7–30.7)	27.0 (24.0–30.7)	26.2 (23.0–30.7)	0.213
Hemoglobin (mg/dl)	9.1 (8.0–10.5)	9.2 (8.1–10.6)	9.1 (7.6–10.4)	0.156
Platelet (10^9/l)	85 (55–137)	92 (59–148)	72 (51–113)	<0.001
WBC (10^9/l)	11.9 (8–17.9)	11.2 (7.7–16.6)	13.8 (8.4–20.9)	<0.001
RDW	17.2 (15.5–18.9)	16.7 (15.2–18.4)	18.0 (16.4–20.0)	<0.001
INR	1.8 (1.5–2.4)	1.7 (1.4–2.1)	2.4 (1.8–3.1)	<0.001
PT	18.7 (16–23.4)	17.5 (15.4–21.1)	22.4 (18.6–29.4)	<0.001
Lactate (mg/dl)	2.8 (1.9–4.8)	2.5 (1.8–4.2)	3.7 (2.3–7.4)	<0.001
Potassium (mEq/l)	4.6 (4.0–5.2)	4.5 (4.0–5.1)	4.7 (4.1–5.5)	0.046
Sodium (mEq/l)	136 (131–139)	136 (132–139)	135 (129–139)	0.017
Clinical model scores				
Child-Pugh score	9 (7–10)	8 (7–10)	10 (9–11)	<0.001
MELD	16 (9–24)	15 (9–23)	17 (10–26)	<0.001
MELD-Na	18 (11–29)	17 (11–28)	21 (11–30)	<0.001
SOFA	8 (5–11)	7 (5–10)	11 (9–14)	<0.001
CLIF-SOFA	9 (7–11)	8 (6–10)	11 (9–13)	<0.001
AARC ACLF	9 (8–10)	9 (7–10)	10 (9–12)	<0.001
CLIF-C $ACLFs_{Lact}$	52 (43–61)	48 (40–57)	62 (53–72)	<0.001

* Student's t-test or Mann-Whitney U-test was used for continuous variables, and χ^2-test or Fisher's exact test was used for categorical variables. ALT – alanine aminotransferase; AST – aspartate aminotransferase; BUN – blood urea nitrogen; WBC – white blood cell; RDW – red blood cell volume distribution width; INR – international normalized ratio; PT – prothrombin time; MELD – model for end-stage liver disease; SOFA – Sequential Organ Failure Assessment; CLIF-SOFA – Chronic Liver Failure-Sequential Organ Failure Assessment Score.

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Table 3. Univariate and multivariate Cox proportional hazards model of association between clinical parameters and 28-day mortality.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (years)	0.995	0.984, 1.005	0.332			
Sex	0.981	0.744, 1.294	0.893			
Ethnicity						
White	Reference	Reference	Reference			
Black	0.528	0.279, 1.002	0.051			
Other	1.706	1.259, 2.312	0.001			
MAP (mmHg)	0.959	0.945, 0.972	<0.001	0.977	0.958, 0.997	0.025
PaO2/FiO2	0.999	0.998, 1.000	0.005	0.998	0.997, 0.999	0.004
24-h urine output (ml)	0.999	0.999, 1.000	<0.001			
Vasopressin used	2.120	1.629, 2.761	<0.001	1.582	1.097, 2.281	0.014
Ventilator	1.491	1.135, 1.957	0.004			
RRT	1.908	1.317, 2.763	0.001			
ALT (IU/l)	1.000	1.000, 1.001	0.009			
AST (IU/l)	1.000	1.000, 1.000	<0.001	1.000	1.000, 1.000	0.006
Albumin (g/dl)	0.823	0.644, 1.050	0.118	0.761	0.595, 0.975	0.031
BUN (mg/dl)	1.009	1.006, 1.013	<0.001			
Glucose (mg/dl)	0.993	0.990, 0.997	0.001			
Platelet (10^9/l)	0.996	0.994, 0.998	<0.001	0.997	0.995, 1.000	0.037
WBC (10^9/l)	1.025	1.012, 1.039	<0.001	1.020	1.003, 1.038	0.019
RDW	1.111	1.062, 1.162	<0.001			
Potassium (mEq/l)	1.034	0.906, 1.180	0.619			
Sodium (mEq/l)	0.977	0.959, 0.996	0.016			
AARC ACLF	1.434	1.335, 1.539	<0.001	1.375	1.247, 1.516	<0.001
Ascites	1.357	1.027, 1.791	0.035			
Variceal bleeding	1.138	0.790, 1.640	0.487			
SBP	1.894	1.282, 2.799	0.003	1.850	1.129, 3.034	0.015
HRS	1.813	1.347, 2.440	<0.001			

HRs and P values were estimated using Cox proportional hazard model. CI – confidence interval; HR – hazard ratio; MAP – mean arterial pressure; RRT – renal replacement therapy; ALT – alanine aminotransferase; AST – aspartate aminotransferase; BUN – blood urea nitrogen; WBC – white blood cell; RDW – red blood cell volume distribution width; SBP – spontaneous bacterial peritonitis; HRS – hepatorenal syndrome.

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Table 4. Diagnostic accuracy of scoring systems at cutoff points and at different time periods.

Prognostic models	28-day AUROC	P value*	90-day AUROC	P value*	180-day AUROC	P value*
AARC ACLF	0.754	–	0.747	–	0.728	–
Child-Pugh score	0.688	<0.001	0.692	<0.001	0.673	<0.001
MELD	0.753	0.970	0.749	0.904	0.727	0.909
MELD-Na	0.747	0.637	0.738	0.517	0.723	0.715
SOFA	0.766	0.486	0.753	0.723	0.739	0.504
CLIF-SOFA	0.743	0.459	0.745	0.878	0.727	0.888
CLIF-C ACLFs$_{Lact}$	0.777	0.144	0.762	0.310	0.745	0.272

AUROC – area under the receiver operating characteristic curve; MELD – model for end-stage liver disease; SOFA – Sequential Organ Failure Assessment; CLIF-SOFA – Chronic Liver Failure-Sequential Organ Failure Assessment Score. * DeLong test was used to compare the performance of each scoring systems with AARC ACLF.

Grade 1 to Grade 2 at days 4–7 increased the mortality, and this was also true for patients with Grade 2 to Grade 3. When Grade 2 changed to Grade 1, the mortality rate was decreased. The scores reevaluated at days 4–7 as Grade 2 were significantly different from Grade 1, even in the same baseline at Grade 1 (p=0.0012, Figure 5B). For baseline at Grade 2, the survival probability in reevaluated Grade 2/3 (n=75/n=19) was higher than that in reevaluated Grade 1 (n=42, p=0.002, Figure 5C). Additionally, there was no significant difference from baseline at Grade 3 (p=0.739).

Outcome events

The 28-day, 90-day, and 180-day mortality rates were 28.9% (227/786), 36.4% (286/786), and 40.3% (317/786), respectively. In ACLF patients, these mortality rates were 48.6% (137/282), 56.7% (160/282), and 58.9% (166/282), respectively. When using AARC ACLF score, for low-risk patients the 28-day, 90-day, and 180-day mortality rates were 11.2% (35/312), 16.0% (50/312), and 20.8% (65/312), respectively; for moderate-risk patients they were 34.7% (135/389), 44.5% (173/389), and 48.1% (187/389), respectively; and for high-risk patients they were 67.1% (57/85), 74.1% (63/85), and 76.5% (65/85), respectively. Additionally, for ACLF patients, in patients with low risk the predicted 28-day, 90-day, and 180-day mortality rates were 12.2% (5/41), 19.5% (8/41), and 19.5% (8/41), respectively; in patients with moderate risk they were 46.7% (79/169), 55.6% (94/169), and 58.0% (98/169), respectively; and in patients with high risk they were 73.6% (53/72), 80.6% (58/72), and 83.3% (60/72), respectively.

Discussion

AARC ACLF score is constructed by the APASL [10], which is based on Asian ACLF patients. The present study is the first to validate this score in critically ill non-Asian patients with cirrhosis and ACLF, and it is also the first to compare it with other traditional/newly-constructed models. We also evaluated the prognostic value of AARC ACLF score in middle-term (180-day) mortality, which has not been verified before.

Critical ill patients with cirrhosis always have a poor outcome. In this study, the 28-day, 90-day, and 180-day mortality rates were 28.9% (227/786), 36.4% (286/786), and 40.3% (317/786), respectively, which is comparable to the rates reported in previous studies [2,19]. In our study group, ACLF was present in 35.9% (282/786) of patients and the mortality rate was 48.6% (137/282), consistent with other studies [10]. Therefore, a simple bedside prognostic model is needed for critically ill patients. The AARC ACLF model includes 5 readily available parameters: bilirubin, creatinine, INR, lactate, and HE. Bilirubin, creatinine, INR, and HE are the important factors in the prognostic model for cirrhotic patients, as with CLIF-SOFA [14,19]. In this study, we proved that bilirubin, creatinine, and INR were independent predictors of 28-day mortality, consistent with previous studies [17,19,20]. However, we found no statistically significant difference in 28-day mortality between patients with and without HE (p=0.071). In 90-day and 180-day mortality, it has good prognostic value (p<0.001,p=0.001) and is considered an independent risk factor (HR: 1.416, 95% CI: 1.102,1.818, p=0.007; HR: 1.328, 95% CI: 1.046,1.686, p=0.020), consistent with previous studies [21,22]. Monitoring of lactate levels is important in ICU patients with sepsis [23,24]. The liver accounts for 70% of lactate clearance in the human body [25], and several studies have focused on the importance of lactate and lactate clearance in critically ill patients with cirrhosis and in ACLF patients [7,8,26,27]. Some studies proved that using lactate level could improve the accuracy of the traditional model, and constructed improved models like CLIF-C ACLFs$_{Lact}$ [8] and MELD-LA [9]. Lactate level (HR: 1.111, 95% CI: 1.081,1.142, p<0.001) was also verified as an independent risk factor for 28-day mortality

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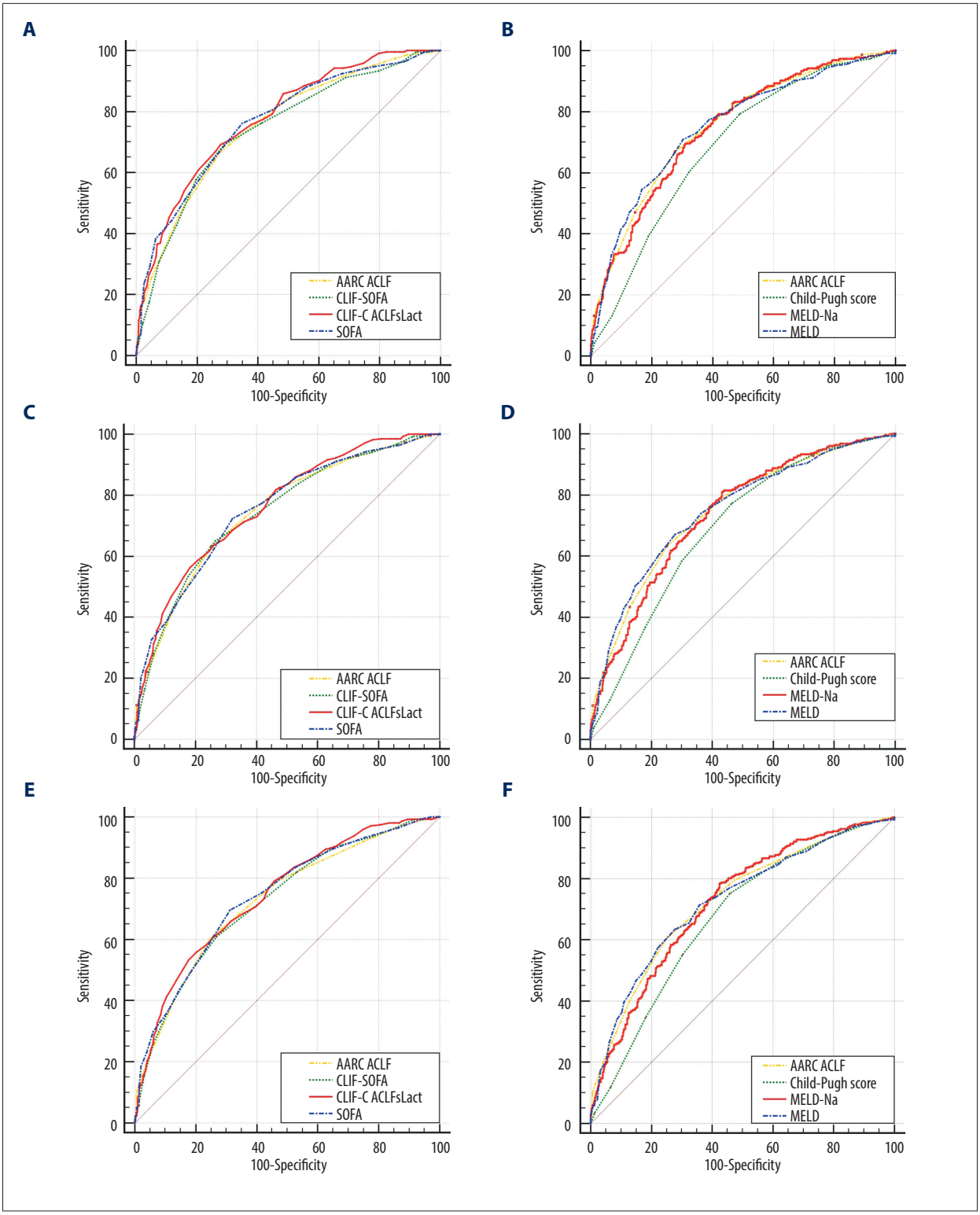

Figure 2. Area under the receiver operating characteristic curve of the predictive ability of AARC ACLF and other scoring models to predict mortality in critically ill patients with cirrhosis. (**A, B**) 28-day mortality; (**C, D**). 90-day mortality; (**E, F**). 180-day mortality.

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Table 5. Diagnostic accuracy of different scoring systems in predicting 28-day mortality at the optimal cutoff point.

Prognostic models	Cut-off point	Sensitivity	Specificity	Youden index	PLR	NLR	PPV	NPV
AARC ACLF	9.5	0.67	0.72	0.39	2.41	0.46	0.50	0.84
Child-Pugh score	8	0.79	0.51	0.31	1.62	0.40	0.40	0.86
MELD	17	0.72	0.68	0.39	2.22	0.42	0.47	0.86
MELD-Na	19	0.75	0.64	0.39	1.17	0.39	0.46	0.86
SOFA	8	0.76	0.65	0.41	2.18	0.37	0.47	0.87
CLIF-SOFA	9	0.69	0.71	0.40	2.39	0.43	0.49	0.85
CLIF-C $ACLFs_{Lact}$	56	0.69	0.73	0.42	2.56	0.43	0.51	0.85

NLR – negative likelihood ratio; NPV – negative predictive value; PLR – positive likelihood ratio; PPV – positive predictive value.

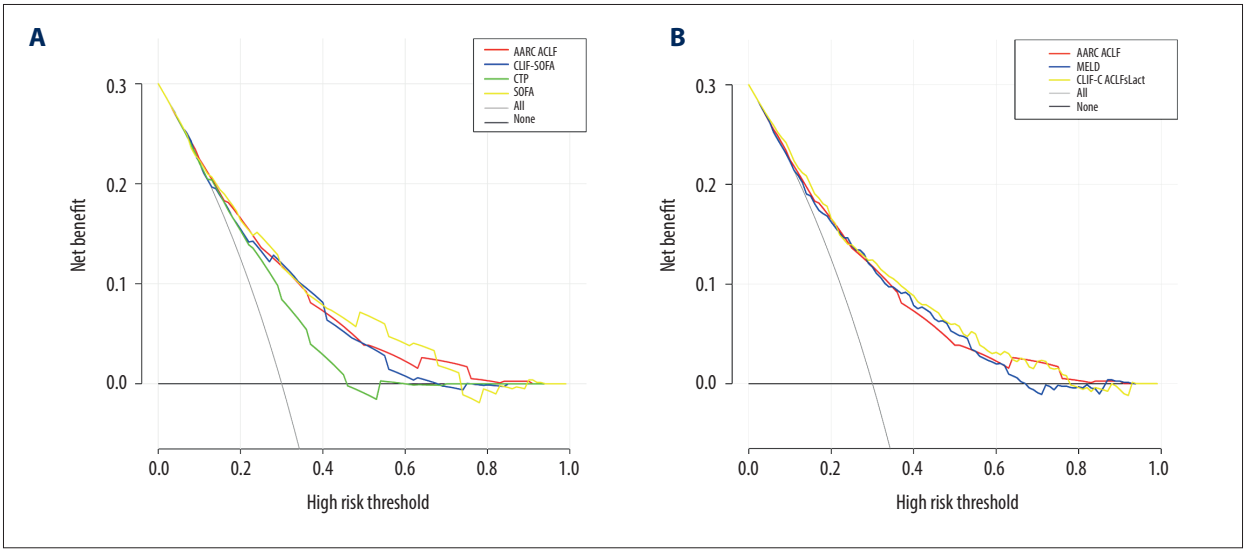

Figure 3. Decision curves for AARC ACLF and other scores to predict the 28-day mortality of critically ill patients with cirrhosis. (**A**) With CLIF-SOFA, Child-Pugh score, and SOFA; (**B**) with MELD, CLIF-C $ACLFs_{Lact}$.

in our study. A previous study demonstrated that lactate and MAP were independent risk factors for patients with sepsis and shock, and lactate was the strongest prognostic parameter [28]. We also found that lactate level performed better than MAP in critically ill patients with cirrhosis (lactate Wald: 55.7, higher than MAP Wald 34.9).

During the study, we adjusted other clinical variables through multivariate analysis to further prove that AARC ACLF score was an independent and significant prognostic factor. Compared with MELD, MELD-Na, SOFA, CLIF-SOFA, and CLIF-C $ACLFs_{Lact}$, AARC ACLF had a comparable prognostic value in non-Asian critical ill patients with cirrhosis and ACLF ($p>0.05$). Among the models, we found that CLIF-C $ACLFs_{Lact}$ was the best, but AARC ACLF is one of the simplest models for use in clinical practice. However, AARC ACLF has previously been proven to be superior to MELD, MELD Na, CLIF-SOFA, and SOFA scores for use in patients with ACLF [10], which differs from the present results.

We suggest several explanations for the above results. First, in our study, the population was non-Asian patients, the same as in the CLIF-C $ACLFs_{Lact}$-based study population, but different from the APASL study. The causes of cirrhosis differ significantly between the East and the West, and different ethnicities may also have different disease progress. Second, in the APASL study [10], the cause of liver diseases in ACLF patients was not just cirrhosis, but, due to the retrospective nature of the present study, we only enrolled the cirrhotic patients, and this may have contributed to the differences.

In addition, the AARC ACLF score is dynamic, and the change in AARC ACLF grade was retested after 4–7 days, showing the risk of death also changed. However, no obvious change was found in grade 3, which differs from the result of a previous study [10]. This disagreement may be due to the insufficient sample size in our study (n=30).

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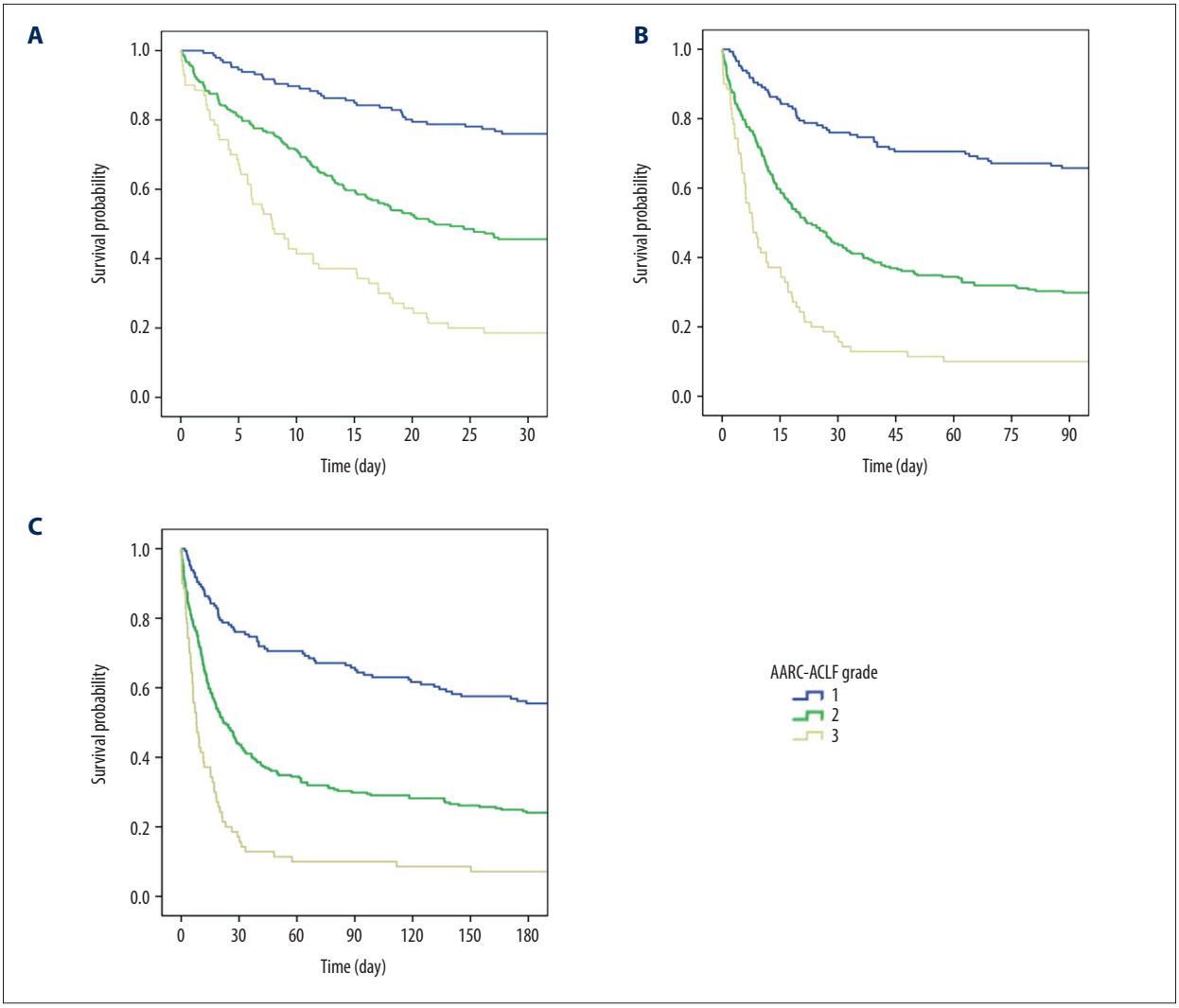

Figure 4. Cumulative 28-day (**A**), 90-day (**B**), and 180-day (**C**) risk of critically ill patients with cirrhosis stratified by different grades of AARC ACLF.

Table 6. Multivariate Cox regression analysis of the effect of AARC ACLF on 90-day mortality.

Variables	Unadjusted			Adjusted model I			Adjusted model II		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
AARC ACLF	1.434	1.335, 1.539	<0.001	1.433	1.332, 1.542	<0.001	1.375	1.247, 1.516	<0.001
AARC ACLF grade									
1	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
2	2.922	2.012, 4.245	<0.001	2.940	2.013, 4.293	<0.001	1.949	1.201.3.163	0.002
3	6.295	4.119, 9.621	<0.001	6.070	3.931, 9.373	<0.001	4.432	2.591, 7.583	<0.001

Adjust I model was adjusted for: age, sex, and ethnicity; adjust II model was adjusted for: age, sex, ethnicity, MAP, PaO2/FiO2, 24 h urine output, blood urea nitrogen, albumin, sodium, potassium, ventilator, white blood cell, vasopressor used, renal replacement therapy, variceal bleeding, ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome. CI – confidence interval; HR – hazard ratio.

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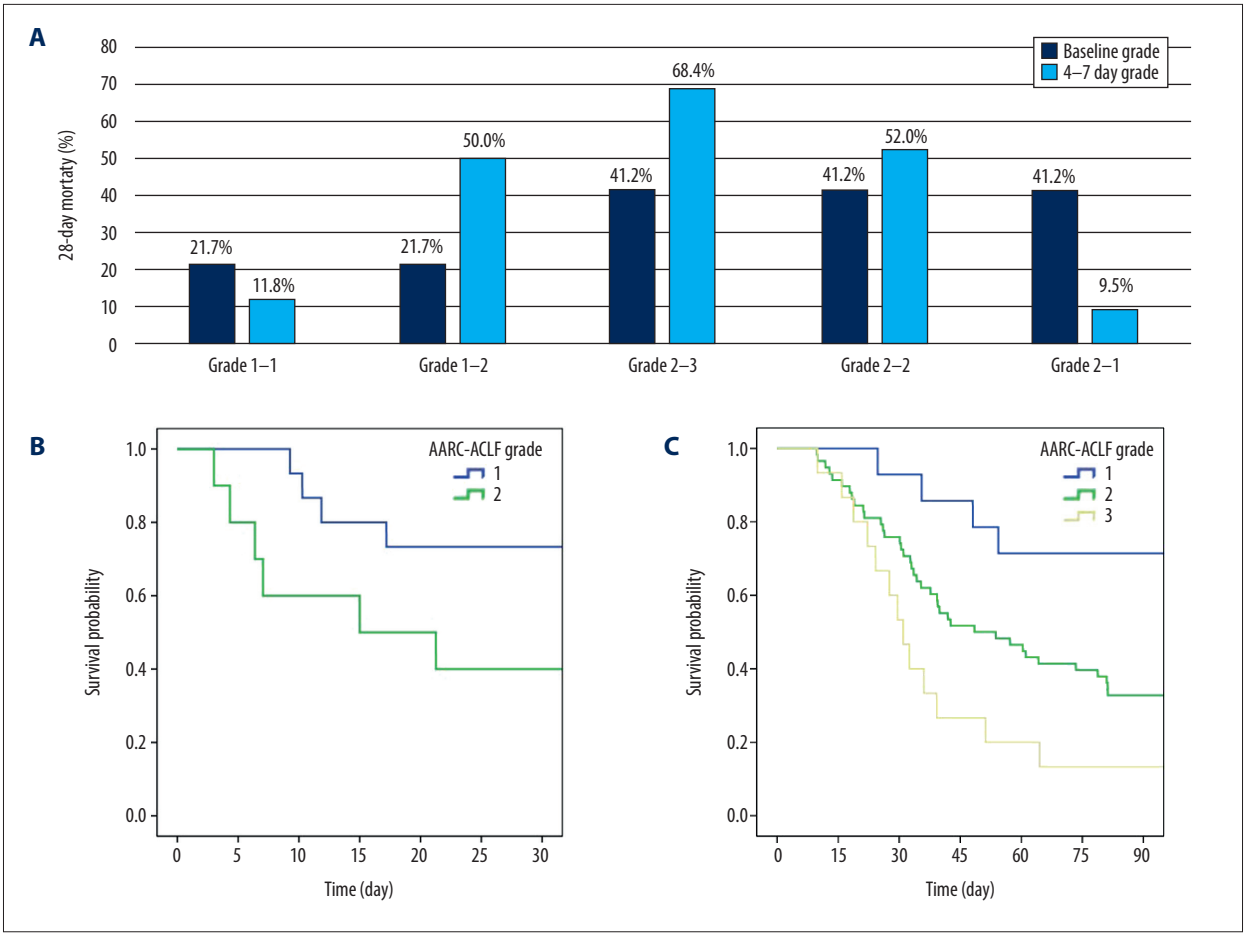

Figure 5. Dynamicity of AARC ACLF grade. (**A**). The dynamic change in AARC ACLF grade. (**B**). Cumulative risk stratified by different grades of reevaluated AARC ACLF grade at days 4–7 while grade 1 at admission. (**C**). Cumulative risk stratified by different grades of reevaluated AARC ACLF grade at days 4–7 while in grade 2 at admission.

The present study has certain limitations. First, it was a single-center retrospective study, and 669 patients were excluded due to the absence of laboratory parameters. There was no significant difference between the missing data group and study group in characteristics (age, height, weight, sex, and ethnicity), but the 28-day, 90-day, and 180-day mortality rates of the study group (28.9%, 36.4%, and 40.3%, respectively) were higher than those of the missing data group (18.4%, 26.9%, and 30.2%, respectively). Our conclusions may not be applicable to all the patients. Second, due to limitations of the database, we only collected 282 ACLF patients and all of them were associated with cirrhosis, but the definition of ACLF [6] consists of other liver diseases that we missed. Third, the endpoint in our study was all-cause mortality, not cause-specific mortality, which may have led to an under- or overestimation of the overall mortality. Fourth, only 212 patients had retested laboratory parameters, which may have caused selection bias, and we found the baseline of the patients were different and might not apply to all critically ill patients with cirrhosis. Finally, we did not evaluate the performance of long-term survival in AARC ACLF. We plan to collect more patients and address these limitations in future research.

Conclusions

The AARC ACLF score was the independent factor of non-Asian critically ill patients with cirrhosis, showing medium prognostic ability in critically ill patients with cirrhosis and ACLF. It also can be used for dynamic assessment in critically ill patients with cirrhosis. For clinicians, it may be a useful tool to quickly recognize patients with high risk of death and predict the need for intervention in a timely manner. Large-scale, prospective, multi-center studies are needed to further verify its applicability.

Conflicts of interest

None.

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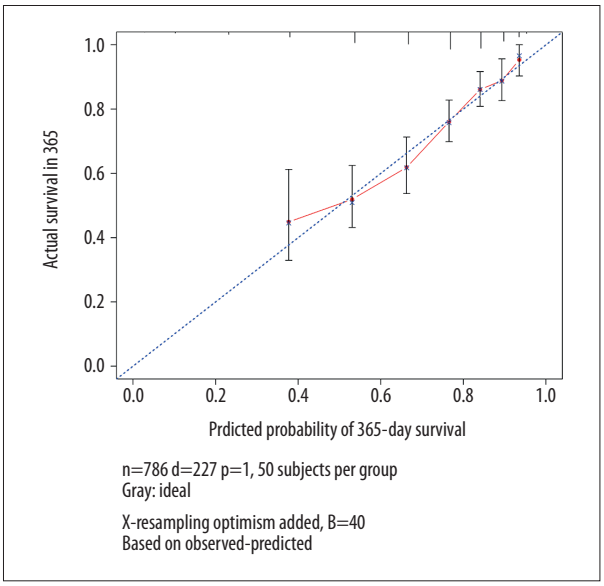
Supplementary Data

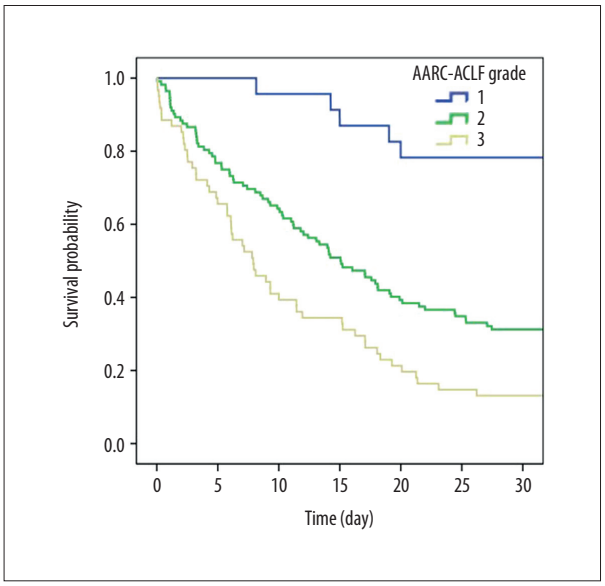
Supplementary Table 1. Diagnostic accuracy of scoring systems at cutoff points and at different time periods in ACLF patients.

Prognostic models	28-day AUROC	P value*	90-day AUROC	P value*	180-day AUROC	P value*
AARC ACLF	0.704	–	0.679	–	0.690	–
Child-Pugh score	0.549	<0.001	0.526	<0.001	0.524	<0.001
MELD	0.666	0.297	0.660	0.589	0.690	0.535
MELD-Na	0.656	0.247	0.645	0.417	0.643	0.264
SOFA	0.688	0.703	0.679	0.998	0.668	0.984
CLIF-SOFA	0.651	0.089	0.640	0.180	0.649	0.167
CLIF-C ACLFs$_{Lact}$	0.719	0.670	0.694	0.665	0.699	0.792

AUROC – area under the receiver operating characteristic curve; MELD – model for end-stage liver disease; SOFA – Sequential Organ Failure Assessment; CLIF-SOFA – Chronic Liver Failure-Sequential Organ Failure Assessment Score. * DeLong test was used to compare the performance of each scoring systems with AARC ACLF.



Supplementary Figure 1. The calibration curve of the AARC ACLF score.



Supplementary Figure 2. ACLF 28-day cumulative risk stratified by different grades of AARC ACLF.

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