

Establishment of prognostic scoring models for different etiologies of acute decompensation in hospitalized patients with cirrhosis

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Abstract

Objective: Acute decompensation (AD) in liver cirrhosis has high mortality. We assessed prognostic scoring models and established prediction models for different etiologies of AD.

Methods: This retrospective analysis included 732 patients hospitalized with acute decompensated cirrhosis without acute-on-chronic liver failure. We performed logistic regression analysis of risk factors for mortality associated with different etiologies, to establish predictive models.

Results: Patients with different etiologies, scored using different scoring systems and various impact factors, exhibited differences with respect to mortality. MELD, CLIF-C-AD, MELD-Na, and AARC-ACLF scores exhibited adequate predictive ability for mortality. Area under the receiver operating characteristic curve for 28-day mortality for MELD, CLIF-C-AD, MELD-Na, AARC-ACLF, and the newly developed AD scores was 0.663, 0.673, 0.657, 0.662, and 0.773, respectively, in the hepatitis B virus group (HBV-AD score = $-5.51 + 0.07 \times \text{WBC count (10}^9/\text{L)} + 0.7 \times \text{AD sum} + 0.4 \times \text{AARC-ACLF score}$); 0.731, 0.737, 0.735, 0.689, and 0.778, respectively, in the alcoholic liver disease group (ALD-AD score = $-4.55 + 0.08 \times \text{WBC count (10}^9/\text{L)} + 1.34 \times \text{AD sum}$); and 0.765, 0.767, 0.814, 0.720, and 0.814, respectively, in the Others group (OTHERS-AD score = $-2.14 + 1.24 \times \text{MELD-Na score} + 4.49 \times \text{AD sum}$).

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Conclusions: The newly developed scoring models for short-term mortality were superior to the other scoring systems in predicting prognosis of acute decompensated cirrhosis in hospitalized patients.

Keywords

Cirrhosis, liver-specific scoring models, mortality, prognosis, acute decompensation, prediction model

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Introduction

Acute decompensation (AD) is the primary cause of hospitalization in patients with cirrhosis. After an AD event, patients are prone to acute-on-chronic liver failure (ACLF).^{1,2} Once ACLF occurs, the patient's condition can deteriorate rapidly, leading to multiple organ dysfunction or failure, accompanied by a high risk of mortality (33% and 51% at 28 and 90 days, respectively).³ Approximately 30% of patients with AD progress to ACLF during admission or hospitalization, and those who do not progress to ACLF also have high mid-term mortality rates (12.6% at 60 days and 27.6% at 1 year).⁴ Therefore, early diagnosis and treatment are needed to improve the survival rate of patients with AD.

Currently, many scoring systems for liver disease are available, including the Model for End-Stage Liver Disease (MELD), Model for End-stage Liver Disease-Sodium (MELD-Na), and the Asian Pacific Association for the Study of Liver (APASL) Acute-on-Chronic Liver Failure Research Consortium (AARC) score.⁵⁻⁸ However, only one scoring system exists for patients with acute decompensated cirrhosis without ACLF, the Chronic Liver Failure-Consortium AD score (CLIF-C AD), which is based on parameters including age, white blood cell (WBC) count, serum sodium, serum creatinine, and the international normalized ratio (INR).⁴

Most hospital admissions and deaths among patients with cirrhosis are associated with AD.⁹ Alcoholic liver disease (ALD) was the main etiology in the CANONIC study¹ and hepatitis B virus (HBV) was the main pathogen in the APASL study.¹⁰ The CANONIC study represents the authority in forecasting prognostic scores for patients with AD, but this score model was derived using data of European populations. To better predict outcome of patients with AD, a comparable scoring system is needed that is based on different etiologies and populations from different geographic regions. Therefore, the aim of our study was to establish new prognostic scoring models for different etiologies of AD in hospitalized patients with cirrhosis and to compare these with currently used scoring models (MELD, MELD-Na, AARC-ACLF, and CLIF-C-AD), to find the optimal scoring models.

Materials and methods

Study population

We retrospectively enrolled patients with cirrhosis who visited the Department of Infectious Diseases of the First Affiliated Hospital of Zhejiang University from May 2016 to February 2017. All patients received an explanation of the study at the time of admission; this was a retrospective study in which no specimens were collected

from the patient. All patients provided their informed consent to participate in the study. After receiving approval from the ethics committee, data collection and the analyses began. This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine (meeting number 9, 20 September 2018). A total of 1600 patients with cirrhosis were screened, and the following were excluded: patients aged <18 years (n=3); those without AD (n=603); and those with hepatitis C virus (HCV, n=13), hepatitis E virus (HEV, n=8), HBV with HCV/HEV (n=40), or ACLF (n=190). Finally, consecutively admitted patients with AD and without ACLF were included based on the criteria of AD in the CANONIC study, including development of overt ascites, hemorrhage, hepatic encephalopathy, and bacterial infection. In the HBV group, patients with positive HBV DNA were immediately treated with nucleoside analogs. The treatment regimens were as follows: a) lamivudine alone, 100 mg daily, b) telbivudine alone, 600 mg daily, c) entecavir alone, 0.5 mg daily, and d) lamivudine (100 mg) plus adefovir (10 mg) daily. Clinical characteristics and laboratory measurements were collected within 24 hours of admission.

Definitions

Cirrhosis was diagnosed using liver biopsy, endoscopic signs of portal hypertension, radiological evidence of liver nodules, or clinical evidence of previous liver decompensation including ascites, hepatic encephalopathy, and upper gastrointestinal bleeding.^{11,12} Bacterial infection was diagnosed based on clinical, biochemical, and imaging evidence. Acute decompensation (AD) of cirrhosis was defined according to the CANONIC study as the presence of one or more of the following complications: overt ascites, hepatic encephalopathy, or

upper gastrointestinal and bacterial infection.¹³ AD sum refers to the number of AD complications; for example, a patient with only one AD complication is denoted AD sum=1, a patient with two AD complications such as upper gastrointestinal combined with bacterial infection is denoted AD sum=2, and so on. In our study, we divided patients into three groups according to etiology: HBV, ALD, and Others. The Others group included patients with autoimmune cirrhosis, schistosomiasis cirrhosis, drug-induced cirrhosis, and unexplained cirrhosis. ACLF was defined according to the APASL¹⁰ study and includes all of the following conditions: a) chronic liver with/without cirrhosis; b) serum bilirubin ≥ 5 mg/dL and INR ≥ 1.5 , complicated within 4 weeks by ascites and/or hepatic encephalopathy, and c) high 28-day mortality.

Statistical analysis and model establishment

Quantitative variables are expressed as mean \pm standard deviation (SD) or median with interquartile range, and comparisons between groups were performed using the Student *t*-test or Mann–Whitney U test for parametric and nonparametric variables, respectively. Categorical parameters are expressed as counts and percentages and were compared using the χ^2 test or Fisher's exact test, as appropriate. The impact of predictors on survival for different etiologies was determined using a *t*-test, and the significant predictors were selected in logistic regression analysis using a stepwise method, to establish the optimal prediction model. The sensitivity (Se), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) were compared at an optimal cut-off value, to evaluate the scoring models in the different groups. An optimal cut-off value was selected by maximizing the sum of the Se and Sp.

The prediction accuracy for mortality at 28 days of the MELD, MELD-Na, CLIF-C-AD, AARC-ACLF, and the new AD scores was assessed in the different groups using the area under the receiver operating characteristic curve (AUC). P values <0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS 24.0 (IBM Corp., Armonk, NY, USA).

Results

Patients

We analyzed 732 patients with cirrhosis who had AD and did not have ACLF. Patients were divided into three groups based on the etiological characteristics. The HBV group included 426 patients, the ALD group included 164 patients, and the

Others group included 142 patients (Figure 1). In the HBV and Others groups, the most common decompensation event was infection, and the incidence of hepatic cell carcinoma was 20% and 13%, respectively. In the ALD group, the most common decompensation event was gastrointestinal bleeding, and the incidence of hepatic cell carcinoma was 5%. Nine patients in each group received liver transplantation, and 21 patients were lost to follow-up. In the HBV, ALD, and Others groups, the proportion of patients who developed ACLF was 22%, 22%, and 15% and the proportion with previous decompensation was 16%, 17% and 47%, respectively. Short- and mid-term mortality rates, 28-day (90-day) mortality, were 18% (26%), 15% (19%), and 18% (38%), respectively.

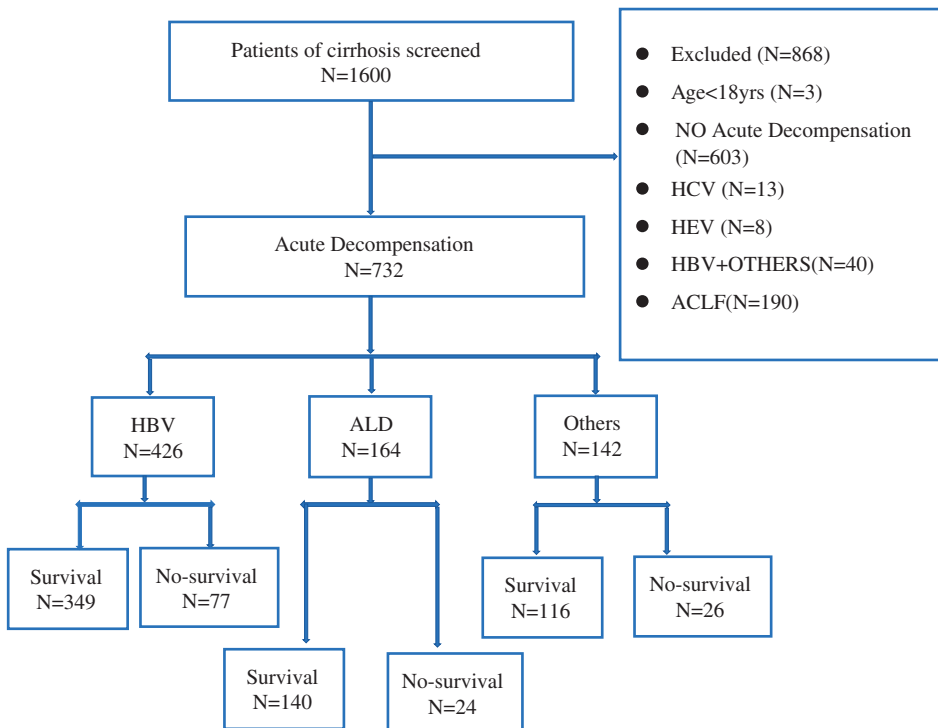


Figure 1. Flow chart of selection of patients included in the study
AD: Acute decompensation, HCV: hepatitis C virus, HEV: hepatitis E virus, HBV: hepatitis B virus, ACLF: acute-on-chronic liver failure, ALD: alcoholic liver disease, Others: autoimmune cirrhosis, schistosomiasis cirrhosis, drug-induced cirrhosis, and unexplained cirrhosis.

Baseline characteristics

Tables 1 and 2 present baseline characteristics of the 732 patients in the three groups, according to etiology. Among the groups, large differences were observed with respect to age, sex, serum sodium, serum creatinine, alpha fetoprotein, hemoglobin, WBC count, and scores of the MELD, MELD-Na, AARC-ACLF, and CLIF-C-AD (all $P < 0.05$). In the HBV and ALD groups, male patients predominated, with 73.3% and 94.5%, respectively. Serum sodium levels were much lower in the ALD group

than levels in the other two groups (137.2 vs. 138.2, HBV group and 138.5, Others group; $P = 0.04$); similar findings were observed for the MELD score (9.2 vs. 15 and 12.1; respectively, $P < 0.001$) and MELD-Na score (10.8 vs. 16.1 and 13.1; respectively, $P < 0.001$). Patients in the Others group were more likely to be anemic than those in the HBV and ALD groups (95 vs. 98 and 104; respectively, $P = 0.005$); WBC counts were also higher than those in the other groups (5.8 vs. 5.6 and 4.6; respectively, $P = 0.008$). Some

Table 1. Baseline characteristics of patients included in the study

Variables	HBV (N = 426)	ALD (N = 164)	Others (N = 142)	P
Age (years)	53 (25–86)	56 (28–86)	64 (18–88)	<0.001
Sex (male)	314 (73.7%)	155 (94.5%)	68 (47.9%)	<0.001
Mortality (28 days)	77 (18.1%)	24 (14.6%)	26 (18.3%)	0.304
HE	0 (0–4)	0 (0–4)	0 (0–4)	0.096
AD sum	1 (1–3)	1 (1–3)	1 (1–3)	0.129
Laboratory data				
Serum albumin (g/L)	30.2 ± 5.6	30.2 ± 4.9	30.1 ± 5.3	0.98
Serum bilirubin (mol/L)	119.8 ± 144.3	131.5 ± 168.6	92.7 ± 134.7	0.06
Aspartate aminotransferase (μ/L)	122.6 ± 219.4	111.0 ± 389.3	74.3 ± 113.6	0.15
Alanine aminotransferase (μ/L)	95.8 ± 192.1	71.4 ± 142.8	60.6 ± 113.5	0.06
International normalized ratio	1.66 ± 0.65	1.59 ± 0.54	1.51 ± 0.72	0.05
Serum sodium (mmol/L)	138.2 ± 4.9	137.2 ± 4.6	138.5 ± 4.9	0.04
Serum creatinine (μmol/L)	73 (28–579)	79 (38–1177)	69 (33–573)	0.02
C-reactive protein (mg/L)	16 (0.2–177)	15.5 (0.3–166.3)	16.3 (0.5–186)	0.89
Alpha fetoprotein (ng/mL)	5.9 (0.3–80000)	3.6 (0.8–80000)	2.3 (0.5–15978)	<0.001
Cancer antigen 125 (μ/mL)	171 (4.59–6837)	162.6 (6.3–3393)	117 (0.9–2744)	0.09
Hemoglobin (g/L)	104 (40–177)	98 (44–182)	95 (40–159)	0.005
WBC count (10 ⁹ /L)	4.6 (0.8–30.1)	5.6 (1–35.1)	5.8 (1.1–35.2)	0.008
Alkaline phosphatase (μ/L)	114 (25–849)	102 (32–1141)	104 (34–935)	0.13
Platelet count (10 ⁹ /L)	94.1 ± 69	104.5 ± 81.2	107.1 ± 73	0.10
Mean arterial pressure (mmHg)	86.3 ± 12.7	65.4 ± 13.2	83.8 ± 13.9	0.14
MELD score	15 ± 7.0	9.2 ± 8.8	12.1 ± 8.4	<0.001
MELD -Na score	16.1 ± 8.9	10.8 ± 10.2	13.1 ± 9.2	<0.001
CLIF-C-AD score	47.5 ± 10.0	50.4 ± 11.6	49.3 ± 11.4	0.007
AARC-ACLF score	6.5 ± 1.3	6.6 ± 1.3	6.2 ± 1.3	0.05

Data are expressed as number (%), mean ± standard deviation or median (interquartile range). HBV: hepatitis B virus; ALD: alcoholic liver disease; AD sum: sum of acute decompensation complications; HE: hepatic encephalopathy; MELD: model for end-stage liver disease; MELD-Na: model for end-stage liver disease-sodium; CLIF-C-AD: Chronic Liver Failure Consortium AD score; AARC: APASL ACLF Research Consortium; ACLF: acute-on-chronic liver failure; WBC: white blood cell.

Table 2. Prognostic scoring models for different etiologies

Variables	HBV (N = 426)	ALD (N = 164)	Others (N = 142)	P
MELD score	15 ± 7.0	9.2 ± 8.8	12.1 ± 8.4	<0.001
MELD -Na score	16.1 ± 8.9	10.8 ± 10.2	13.1 ± 9.2	<0.001
CLIF-C-AD score	47.5 ± 10.0	50.4 ± 11.6	49.3 ± 11.4	0.007
AARC-ACLF score	6.5 ± 1.3	6.6 ± 1.3	6.2 ± 1.3	0.05

MELD: model for end-stage liver disease; MELD-Na: model for end-stage liver disease-sodium; CLIF-C-AD: Chronic Liver Failure-Consortium AD score; AARC: APASL ACLF Research Consortium; ACLF: acute-on-chronic liver failure.

prognostic scoring models showed higher scores in the ALD group than in the HBV and Others groups, as follows: CLIF-C-AD score (50.4 vs. 47.5 and 49.3; respectively, $P < 0.01$) and AARC-ACLF score (6.6 vs. 6.5 and 6.2; respectively, $P = 0.05$). The total number of patients with AD was not significantly different among the groups.

Clinical characteristics of patients with different etiologies and risk factors for death

We found significant differences for AD sum, serum bilirubin, serum creatinine, serum sodium, and WBC count between the survival and non-survival groups for the different etiologies. Among the groups, the parameters of survival and non-survival followed the same trend and exhibited similar characteristics. Parameter values in the non-survival group were significantly higher than those in the survival group, except for serum sodium (all $P \leq 0.05$). In logistic regression analysis, risk factors for death at admission were as follows: in the HBV-group, AD sum (odds ratio [OR]: 2.0; 95% confidence interval (CI): 1.2–3.4; $P = 0.008$), AARC-ACLF score (OR: 1.5; 95% CI: 1.2–1.8; $P < 0.001$), and WBC count (OR: 1.1; 95% CI: 1.0–1.1; $P = 0.028$); in the ALD group, AD sum (OR: 3.7; 95% CI: 1.6–8.4; $P = 0.002$), and WBC count (OR: 1.1; 95% CI: 1.1–1.2; $P = 0.025$); and in the

Others group, AD sum (OR: 89.76; 95% CI: 1.6–5002.4; $P = 0.028$) and MELD-Na score (OR: 3.4; 95% CI: 1.2–10.1; $P = 0.025$) (Table 3). Finally, we established the new prognostic scores using these parameters, as follows:

HBV-AD score = $-5.51 + 0.07 * \text{WBC count} (10^9/\text{L}) + 0.7 * \text{AD sum} + 0.4 * \text{AARC-ACLF score}$;

ALD-AD score = $-4.55 + 0.08 * \text{WBC count} (10^9/\text{L}) + 1.34 * \text{AD sum}$;

OTHERS-AD score = $-2.14 + 1.24 * \text{MELD-Na score} + 4.49 * \text{AD sum}$.

Comparison of the new prognostic scores with known scoring models

The ability of each method to predict mortality was determined using ROC curve analysis; the AUC values were 0.663 (MELD), 0.673 (CLIF-C-AD), 0.657 (MELD-Na), 0.662 (AARC-ACLF), and 0.773 (HBV-AD: 95% CI: 0.669–0.769) in the HBV group; the HBV-AD score was superior to the other scores. Using the same method, we determined the maximum AUC of the ALD group (ALD-AD: 0.778, 95% CI: 0.680–0.876) and Others group (MELD-Na: 0.814, 95% CI: 0.705–0.923; OTHERS-AD: 0.814, 95% CI: 0.705–0.923) (Table 4 and Figure 2). We further compared the Se, Sp, PPV, and NPV, to select the optimal predictive models. In the HBV group, based on the maximum

Table 3. Selected predictive variables to assess risk factors of mortality with different etiologies

Variables	Survival	Non-survival	P	Multivariate analysis OR (95% CI)	P		
HBV							
AD sum	1.2 ± 0.4	1.5 ± 0.6	***	2.0 (1.2–3.4)	***		
AST (μ/L)	109 ± 198	185 ± 292	*				
INR	1.6 ± 0.5	2.0 ± 1.1	**	1.1 (1.0–1.1)	*		
Serum bilirubin (μmol/L)	103 ± 31	195 ± 176	***				
Serum creatinine (μmol/L)	80.6 ± 42.3	96.9 ± 67.7	*				
Alkaline phosphatase (u/L)	129 ± 88	165 ± 142	*				
WBC count (10 ⁹ /L)	5.5 ± 3.8	7.3 ± 4.4	***				
MELD score	14.0 ± 6.8	19.7 ± 10.5	***				
MELD-Na score	15.0 ± 7.8	21.2 ± 11.7	***				
CLIF-C-AD score	46.3 ± 9.2	52.9 ± 11.5	***				
AARC-ACLF score	6.3 ± 1.0	7.4 ± 2.0	***				
ALD							
AD sum	1.2 ± 0.4	1.6 ± 0.6	**	3.7 (1.6–8.4)	**		
WBC count (10 ⁹ /L)	6.5 ± 5.3	10.4 ± 6.6	**				
Serum sodium (mmol/L)	138 ± 4.5	135 ± 5.1	*	1.1 (1.0–1.2)	*		
Serum bilirubin (μmol/L)	118 ± 159	210 ± 204	*				
MELD score	8.3 ± 8.3	14.7 ± 10.0	**				
MELD-Na score	9.7 ± 9.6	17.0 ± 11.3	**				
CLIF-C-AD score	49.0 ± 11.1	58.3 ± 11.4	***				
AARC-ACLF score	6.5 ± 1.2	7.3 ± 1.4	***				
Others							
AD sum	1.1 ± 0.3	1.5 ± 0.8	*			89.8 (1.6–5002.4)	*
INR	1.4 ± 0.5	2.0 ± 1.2	*				
WBC count (10 ⁹ /L)	6.2 ± 4.7	8.7 ± 5.5	*	3.4 (1.2–10.1)	**		
Serum sodium (mmol/L)	139 ± 4.2	135 ± 6.3	*				
Serum bilirubin (μmol/L)	70.9 ± 106	190 ± 197	**				
MELD score	10.6 ± 7.3	19.0 ± 10.0	***				
MELD-Na score	11.2 ± 8.1	21.6 ± 9.5	***				
CLIF-C-AD score	47.1 ± 9.5	58.8 ± 14.1	***				
AARC ACLF score	6.1 ± 1.0	7.3 ± 1.9	**				

AST: aspartate aminotransferase; INR: international normalized ratio; HBV: hepatitis B virus; ALD: alcoholic liver disease; Others: autoimmune cirrhosis, schistosomiasis cirrhosis, drug-induced cirrhosis, and unexplained cirrhosis; AD sum: sum of acute decompensation complications; MELD: model for end-stage liver disease; MELD-Na: model for end-stage liver disease-sodium; CLIF-C-AD: Chronic Liver Failure Consortium AD score; AARC: APASL ACLF Research Consortium; ACLF: acute-on-chronic liver failure; OR: odds ratio; CI: confidence interval.

*P<0.05, **P<0.01, and ***P<0.001.

AUC, 48.6 was selected as the node value of the CLIF-C-AD score, with Se, Sp, NPV, and PPV of 65%, 90%, 65%, and 29%, respectively; -1.18 was selected as the node value of the HBV-AD score and its Se, Sp, NPV and PPV was 49%, 89%, 87%, and 45%, respectively; the difference

between the two scoring systems was statistically significant (P<0.001). In the ALD-group, 53 was selected as the node value of the CLIF-C-AD score, with Se, Sp, NPV and PPV of 67%, 92%, 73% and 30%, respectively; -2.58 was selected as the node value of the new ALD-AD score

Table 4. Predictive value of prognostic scores with different etiologies

Variables	Mortality					
	HBV		ALD		Others	
	AUC	95% CI	AUC	95% CI	AUC	95% CI
MELD	0.663	0.589–0.737	0.732	0.624–0.841	0.765	0.645–0.886
CLIF-C-AD	0.673	0.604–0.741	0.737	0.635–0.839	0.767	0.651–0.884
MELD-Na	0.657	0.584–0.729	0.735	0.623–0.848	0.814	0.705–0.932
AARC-ACLF	0.662	0.589–0.735	0.689	0.570–0.807	0.720	0.604–0.923
HBV-AD	0.733	0.669–0.769				
ALD-AD			0.778	0.68–0.876		
OTHERS-AD					0.814	0.705–0.890

Bold font indicates the best choice for the score; the higher the score, the higher the accuracy. HBV: hepatitis B virus; ALD: alcoholic liver disease; AD: acute decompensation; MELD: model for end-stage liver disease; CLIF-C-AD: Chronic Liver Failure- Consortium AD score; MELD-Na: model for end-stage liver disease-sodium; AARC: APASL ACLF Research Consortium; ACLF: acute-on-chronic liver failure; AUC: area under the receiver operating characteristic curve; CI: confidence interval.

and its Se, Sp, NPV, and PPV was 79%, 95%, 66%, and 29%, respectively; the difference between the two scoring systems was significant ($P < 0.001$). In the Others group, the MELD-Na score node value of 12 yielded the same Se, Sp, NPV, and PPV as the new OTHERS-AD score with node value of -1.65 ; there was no difference between the two scoring systems. (Figure 3).

Discussion

Given the high prevalence and mortality of patients with cirrhosis and AD, it is important to develop tools that can better predict the prognosis of these patients. Arroyo and Li et al.^{14,15} reported that when patients with alcoholic cirrhosis were excluded, the consistency index indicated that the CLIF-C-AD score would exhibit better performance. This means that predictive models for AD in liver cirrhosis without ACLF should be established based on disease etiology. Our study demonstrated significant differences in parameters among the different etiologies. Patients with HBV predominated in our study, consistent with the fact

that China is an HBV-endemic country.⁸ Previous research has shown that the 28-day mortality rate is approximately 5% in patients with cirrhosis and traditional AD;¹ however, our findings showed a higher mortality rate at 28 days (approximately 17%). This is likely because in our study, nearly all patients received a cirrhosis AD score on admission whereas in the CANONIC cohort, score assessment was performed at 48 hours, 1 day, or 3 days. Patients with cirrhosis and AD have unstable conditions and may experience substantial improvement or deterioration within a few days after admission. In addition, owing to their worsening condition, patients with ACLF were excluded, thereby reducing the mortality rate at 28 days among our included patients. Another reason for the higher 28-day mortality in our study as compared with other reports may be the difference in etiologies. The main cause of cirrhosis in our study was HBV but it was ALD in the CANONIC study.

The three groups exhibited differences in values for INR, serum sodium, serum creatinine, alpha fetoprotein, hemoglobin, and WBC count. In the ALD group, serum

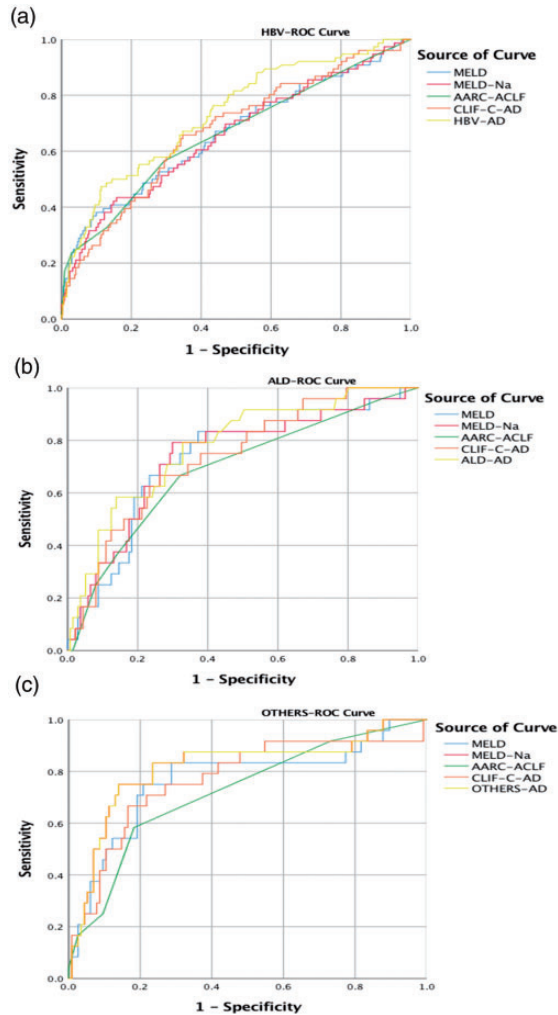


Figure 2. Area under the receiver operating characteristic curve for prediction of mortality in patients with different etiologies

HBV: hepatitis B virus; ALD: alcoholic liver disease; Others: autoimmune cirrhosis, schistosomiasis cirrhosis, drug-induced cirrhosis and unexplained cirrhosis; MELD: model for end-stage liver disease; MELD-Na: model for end-stage liver disease-sodium; CLIF-C-AD: Chronic Liver Failure-Consortium AD score; AARC: APASL ACLF Research Consortium; ACLF: acute-on-chronic liver failure.

creatinine values were substantially increased and serum sodium levels decreased. Kidney injury often occurs in patients with ALD and is increasingly recognized as a predictor of greater morbidity¹⁶. Long-term drinking increases kidney damage, which affects creatinine and

sodium metabolism.¹⁷ WBC counts were significantly higher in the ALD group than in the other two groups and were independently associated with adverse outcomes. It has been suggested that non-surviving patients have a more pronounced systemic inflammatory response, which may

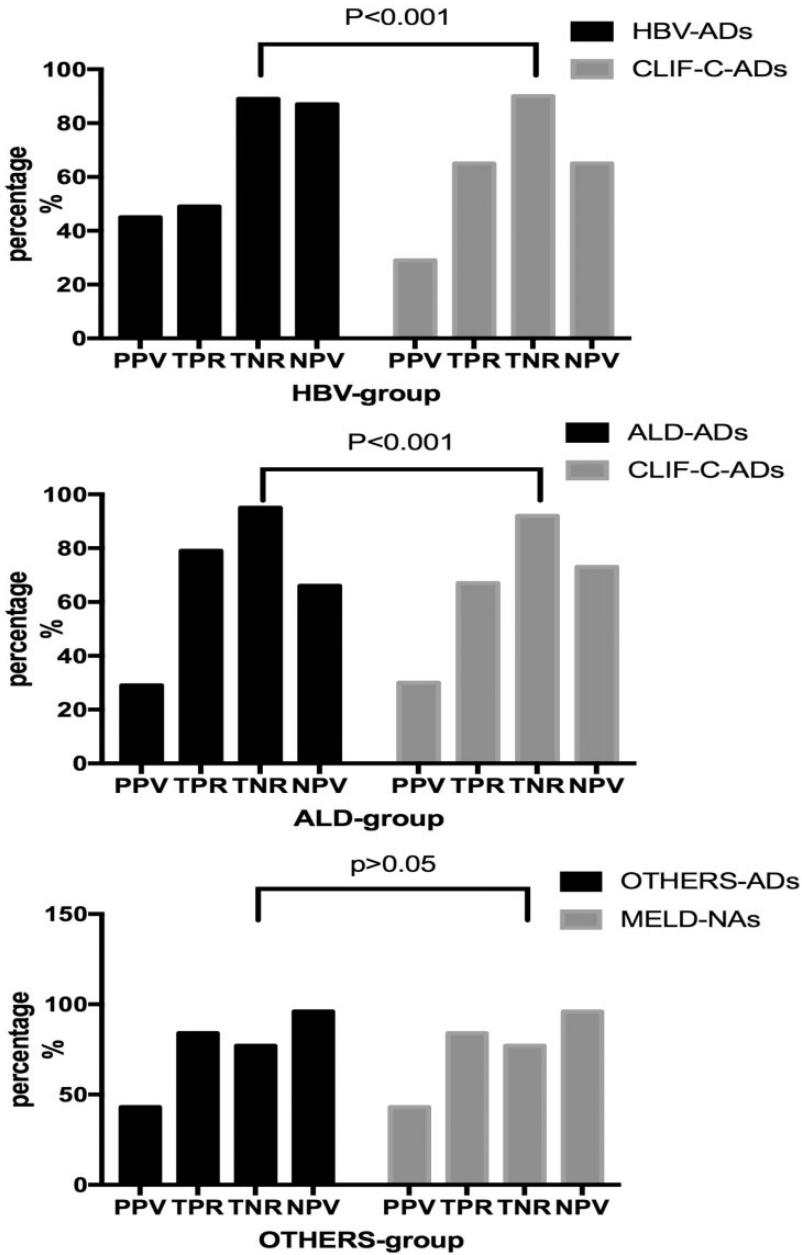


Figure 3. Comparison of sensitivity, specificity, positive predictive value, and negative predictive value, to determine optimal predicting scoring models

provide insight into potential future therapeutic targets. The WBC count is an established biomarker for systemic inflammation,¹⁸ and infections often occur in

patients with ALD.^{19,20} Another interesting finding of our study is that some accepted scoring models exhibited significant differences among the different groups,

highlighting the need to select the appropriate scoring system for different etiologies.

The general principle behind development of a new scoring model is to ensure that it is easy for clinicians to use and can provide prognostic information when a patient is admitted to the hospital. Via analysis of the AUC, we compared the scoring models that we established with the current gold standards for the three different etiologies, the CLIF-C-AD score for the HBV and ALD groups and the MELD-Na score for the Others group. We found that the newly established scoring models were much more precise for predicting mortality at 28 days than the CLIF-C-AD, MELD, MELD-Na, and AARC-ACLF scores in the HBV and ALD groups; however, in the Others group, the MELD-Na and new scoring model exhibited the same predictive value.

In the HBV group, the AUC for the HBV-AD score was 0.733, which was higher than that of the CLIF-C-AD. Further analysis revealed 65% Se and 90% Sp for the CLIF-AD score and 49% Se and 89% Sp for the HBV-AD score; thus, we chose the CLIF-C-AD as the best prognostic scoring model for the HBV group. In the ALD group, we observed 67% Se and 92% Sp for the CLIF-C-AD score and 79% Se and 95% Sp for ALD-AD score; therefore, our developed ALD-AD score was identified as the best prognostic model for the ALD group. Finally, the same Se, Sp, PPV, and PNV were observed for the MELD-Na and OTHERS-AD scores. As the MELD-Na is simple to use and generally widely recognized, we chose the MELD-Na as the most appropriate prognostic scoring model for the Others group. The 95% CIs for the AARC-ACLF, MELD, and MELD-Na scores were consistent with those reported by other investigators.^{21,22} However, the CLIF-C-AD score cut-off value was higher than those in other studies; this difference is likely owing to differences

with respect to the time of score assessment in patients. In our study, all data collection was completed within 12 hours of admission whereas scores in other studies were assessed within 3 days or more; as mentioned, patients with cirrhosis and AD are unstable and may improve or deteriorated quickly after being hospitalized.

In summary, the characteristics of liver cirrhosis with AD vary according to different etiologies of the disease, especially between the two most common types of ACLF, alcoholic and HBV-related. Our study findings showed that the pathogenesis of disease caused by different etiologies varies greatly and requires different prognostic scoring models. We found that the CLIF-C-AD is the best prognostic scoring model for patients with HBV, our newly developed ALD-AD scoring mode is best for patients with ALD, and the MELD-Na is the best prognostic scoring model for patients with other types of cirrhosis. International, multicenter, multi-disease studies are needed to further clarify differences among patients with cirrhosis and AD, to improve patient survival. The newly developed prognostic scoring models showed accurate prognosis; however, these scoring systems require further validation.

Our study has some limitations. First, this study was conducted at a single medical center, which may lead to statistical bias. However, the study institution is one of the largest hospitals in China, and our hospital has a liver transplantation program. Therefore, the included patients were highly representative of Chinese patients with cirrhosis who have AD. Another limitation is that we did not perform continuous assessment of patients' scores during hospitalization.

Authors' contributions

Jifang Sheng and Qun Cai wrote the manuscript. Jifang Sheng made important contributions to the design and final editing of this article.

Jinnan Duan and Hao Wang edited the paper for grammatical and stylistic correctness.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics approval

This study conforms to the Helsinki Declaration and has been approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine

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