Original Paper

Predictive Value of Age-Bilirubin-International Normalized Ratio-Creatinine Score in Short-Term Survival of Acute-on-Chronic Hepatitis B Liver Failure

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Key Words

Liver failure • Predictor • Prognosis • Hepatitis B virus • ABIC score

Abstract

Background/Aims: The age-bilirubin-international normalized ratio-creatinine (ABIC) score, which is a predictive model commonly used for alcoholic hepatitis, has not yet been studied in acute-on-chronic hepatitis B liver failure (HBV-ACLF). We aimed to investigate the predictive value of the ABIC score in patients with HBV-ACLF. **Methods:** This retrospective study involved 398 patients diagnosed with HBV-ACLF, who were divided into a training cohort of 305 patients and a validation cohort of 93 patients. Univariate and multivariate Cox regression models were used to determine risk factors for mortality. Area under the receiver operating characteristic curve (AUC) was calculated to estimate and compare the predictive values of different prognostic scores. **Results:** The ABIC score was significantly higher in the death group of the training cohort than in its survival group. Independent risk factors for mortality identified by multivariate Cox analysis included blood urea nitrogen, ABIC score, and Chronic Liver Failure Consortium Organ Failure (CLIF-C OF) score. For predicting 1- and 3-month

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mortality, AUC was higher for the ABIC score than for the Model for End-stage Liver Diseases (MELD) score (0.732 vs. 0.653, $P < 0.05$, 0.695 vs. 0.619, $P < 0.05$, respectively), CLIF-C OF score (0.693, $P=0.353$, 0.656, $P=0.341$, respectively), and Child-Pugh score (0.675, $P=0.189$, 0.656, $P=0.300$, respectively). Patients with ABIC score > 9.44 had reduced 1- and 3-month survival rates. **Conclusion:** ABIC score is superior to MELD score in predicting short-term survival in HBV-ACLF patients. ABIC score > 9.44 predicts high short-term mortality risk in HBV-ACLF patients.

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Introduction

Acute-on-chronic liver failure (ACLF) is a syndrome characterized by severe acute hepatic abnormalities triggered by factors in patients with chronic liver disease and has high short-term mortality [1, 2]. It is estimated that the 28-day mortality rate of ACLF ranges from 14.6% to 78.6%, depending on the number of organ failures [3]. Hepatitis B virus-related ACLF (HBV-ACLF) constitutes approximately 70% of patients with ACLF in China [4]. A significantly higher 28-day mortality rate is observed in patients with HBV-ACLF than in patients with non-HBV-ACLF [5]. The current primary treatment for ACLF is supportive care rather than targeted therapies. Liver transplantation is the only effective therapeutic intervention for ACLF patients who do not recover spontaneously from intensive care. However, the use of transplantation is restricted by the limited supply of liver donors [6]. Therefore, the management of HBV-ACLF represents a huge economic burden globally [7, 8].

Several models have been developed to predict the prognosis of ACLF. The Model for End-stage Liver Diseases (MELD) score has been extensively used for predicting prognosis in end-stage liver disease as well as determining the priority of patients for liver transplantation [9]. The accuracy of conventional scoring systems such as the MELD and Child-Pugh (CP) scores is limited due to their disregard of extrahepatic organ function [10]. The Chronic Liver Failure Sequential Organ Failure Assessment (CLIF-SOFA) score developed in the European Association for the Study of the Liver (EASL)-CLIF Acute-on-Chronic Liver Failure in Cirrhosis study took parameters of extrahepatic organ functions into consideration and but did not demonstrate prognostic ability superior to that of the MELD score [11]. Modified from CLIF-SOFA, the CLIF Consortium Organ Function (CLIF-C OF) score and CLIF-C ACLF score showed improved prognostic value in patients with ACLF [11]. However, the calculations in these new models are rather complex, limiting their applicability in clinical practice. Early and accurate identification of HBV-ACLF patients with high mortality risk is crucial for determining whether the patients need intensive care or emergency liver transplantation [12].

Currently, there are no specific prognostic systems to predict the short-term outcome of HBV-ACLF. The age-bilirubin-international normalized ratio (INR)-creatinine (ABIC) score was originally proposed as a tool to assess survival in alcoholic hepatitis and to identify patients responding to corticosteroid therapy [13]. The ABIC model is based on age and parameters indicating hepatic function, coagulation, and renal function. It offers a simple and practical method for identifying patients with alcoholic hepatitis at high risk of mortality [14]. However, its predictive value in HBV-ACLF patients has yet to be confirmed. Given that age, INR, total bilirubin (TBIL), and creatinine are reported to be independent risk factors for predicting outcome in patients with liver failure [5, 9, 15], it is possible that ABIC score might be a potential prognostic model for patients with HBV-ACLF.

We therefore designed this retrospective study with the aim of investigating the value of the ABIC score for predicting the short-term prognosis of HBV-ACLF patients based on data collected from training and validation cohorts.

Materials and Methods

Study design and study population

This retrospective study involved 398 newly diagnosed HBV-ACLF patients admitted to the Third Affiliated Hospital of Sun Yat-sen University from April 2013 to December 2016. All patients satisfied the criteria for ACLF according to the consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL), which included jaundice with serum TBIL ≥ 5 mg/dL, coagulopathy with an INR of ≥ 1.5 or prothrombin activity of $< 40\%$ and the development of ascites and/or encephalopathy as determined by physical examination within 4 weeks [1]. Patients who were coinfecting with human immunodeficiency virus (HIV), or hepatitis virus A, C, D, or E, or had alcoholic hepatitis, drug-induced hepatitis, autoimmune hepatitis, or liver cancer were excluded.

The patients were divided into a training cohort and a validation cohort. The training cohort consisted of 305 patients who were admitted from April 2013 to September 2015. The validation cohort consisted of 93 patients admitted from September 2015 to December 2016. All patients or a relative gave written informed consent. The ethics committee of the Third Affiliated Hospital of Sun Yat-sen University approved this study, in accordance with the guidelines of the 1975 Declaration of Helsinki [16].

All patients received standard treatment including bed rest, intravenous albumin, nutritional support, prevention and treatment for complications, and antiviral therapy according to the APASL consensus recommendations [1, 17]. No patients received liver transplantation in this study.

Data collection

Data of both the training and validation cohorts before treatment were collected from electronic medical records and included age, sex, hemoglobin (HGB), white blood cell (WBC) count, platelet (PLT) count, INR, serum alanine transaminase (ALT), aspartate transaminase (AST), albumin (ALB), γ -glutamyl transpeptidase (GGT), creatinine, and blood urea nitrogen (BUN). All laboratory measurements were performed at the Department of Laboratory Medicine of the Third Affiliated Hospital of Sun Yat-sen University.

The CP score was calculated using TBIL, albumin, INR, and severity of ascites and hepatic encephalopathy. The CLIF-C OF score, a simplified version of the CLIF-SOFA score, was calculated as previously described [10]. The Albumin-Bilirubin (ALBI) score was calculated using the following formula: $\text{ALBI score} = (\log_{10} \text{bilirubin} \times 0.66) + (\text{albumin} \times -0.085)$, where bilirubin is in $\mu\text{mol/L}$ and albumin in g/L [18]. The MELD score was calculated according to the formula: $\text{MELD} = 9.57 \times \ln [\text{Creatinine (mg/dL)}] + 3.78 \times \ln [\text{Bilirubin (mg/dL)}] + 11.2 \times \ln(\text{INR}) + 6.43$ [9]. The ABIC score was calculated using the formula: $\text{ABIC} = (\text{age} \times 0.1) + (\text{serum bilirubin} \times 0.08) + (\text{serum creatine} \times 0.3) + (\text{INR} \times 0.8)$ [13]. The laboratory parameters were measured at admission or within 24 h of admission. Patients in each cohort were further divided into survival and death groups based on survival outcome within 1 month and 3 months.

Statistical analysis

Statistical analysis was performed using SPSS version 23.0 for Windows (SPSS, Inc., Chicago, IL), with the exception that ROC curves were compared and survival analysis was performed using the MedCalc version 17.9.7 (MedCalc Software, Ostend, Belgium). Categorical data were expressed as frequency (percentage) and continuous data as mean $\pm$ standard deviation. The Chi-square test and Student's t-test were used to compare the categorical data and continuous data, respectively. A Cox proportional hazards regression model was used to identify the independent risk factors for mortality in HBV-ACLF patients. After univariate Cox regression analysis, variables with $P < 0.05$ in the univariate Cox regression analysis were entered into a multivariate analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated accordingly.

Diagnostic accuracy for ABIC score, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), was assessed by constructing receiver operating characteristic (ROC) curves. To compare the predictive value of ALBI, MELD, CP, CLIF-C OF, and ABIC scores for estimating the outcomes of patients with HBV-ACLF, areas under the ROC curve (AUCs) were calculated for these parameters. The Youden index was used to determine the optimal cut-off point with the best sensitivity and

specificity of the ABIC score. The Kaplan-Meier method was used to perform survival analysis for groups with different cut-off values, and their differences were tested with a log-rank test. A two-tailed *P* value of < 0.05 was considered statistically significant.

Results

Baseline characteristics in HBV-ACLF patients

Baseline characteristics of patients in the training and validation cohorts are listed in Table 1. A total of 398 patients were selected for the study including 335 men (84.17%) and 63 women (15.83%). Age (mean $\pm$ standard deviation) was 45.06 ± 12.70 years. The 1- and 3-month mortality rates of HBV-ACLF patients were 21.86% (87/398) and 31.42% (125/398), respectively. All demographic and laboratory parameters were comparable between the training and validation cohorts. MELD score was 26.93 ± 5.73 in the training cohort and 26.69 ± 5.32 in the validation cohort (*P*=0.716). The CLIF-OF score was 10.05 ± 1.61 in the training cohort and 10.13 ± 1.7 in the validation cohort (*P*=0.676). ABIC scores were comparable between the training and validation cohorts (8.79 ± 1.82 vs. 8.86 ± 1.71 , *P*=0.719). CP scores and ALBI scores were also comparable between the two groups.

ABIC score was an independent risk factor for mortality in HBV-ACLF patients in the training cohort

Univariate analysis was performed to investigate whether the ABIC score is associated with the clinical outcomes of patients with HBV-ACLF in the training cohort. We found that age, HGB, INR, TBIL, BUN, creatinine, MELD score, ALB score, CP score, CLIF-OF score, and ABIC score were significantly different between the two groups (Table 2). There were no significant differences in sex, WBC count, PLT count, ALT, AST, ALB, and GGT between the survival and death groups.

Table 1. Baseline characteristics and outcomes of patients with HBV-ACLF. CI, confidence index; HGB, hemoglobin; WBC, white blood cell; PLT, platelet; INR, international normalized ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin; GGT, gamma-glutamyl transpeptidase; Cr, creatinine; BUN, blood urea nitrogen; MELD, model for end-stage liver diseases; ABIC, age-bilirubin-INR-creatinine; ALBI, albumin-bilirubin score; CLIF-C OFs, chronic liver failure Consortium Organ Failure score; Data were expressed as numbers of patients (%) or mean $\pm$ standard deviation

Variables	All patients (n=398)	Training Cohort (n=305)	Validation Cohort (n=93)	95% CI	P Value
Age (year)	45.06 $\pm$ 12.70	44.88 $\pm$ 12.90	45.62 $\pm$ 12.09	-3.70 to 2.22	0.623
Male	335 (84.17)	260 (85.25)	75 (80.65)		0.287
HGB (g/L)	119.16 $\pm$ 23.69	121.02 $\pm$ 24.12	116.32 $\pm$ 22.09	-1.81 to 9.21	0.188
WBC (10 ⁹ /L)	8.53 $\pm$ 4.14	8.68 $\pm$ 4.31	8.01 $\pm$ 3.49	-0.30 to 1.63	0.177
PLT (10 ⁹ /L)	117.24 $\pm$ 65.46	119.35 $\pm$ 67.33	110.31 $\pm$ 58.73	-6.20 to 24.28	0.244
INR	2.83 $\pm$ 1.08	2.82 $\pm$ 1.08	2.86 $\pm$ 1.11	-0.29 to 0.21	0.749
ALT (IU/L)	649.24 $\pm$ 812.59	667.78 $\pm$ 846.88	588.47 $\pm$ 688.88	-110.00 to 268.61	0.824
AST (IU/L)	461.45 $\pm$ 676.95	483.39 $\pm$ 725.94	389.50 $\pm$ 478.84	-63.68 to 251.46	0.242
ALB (g/L)	31.50 $\pm$ 4.68	31.54 $\pm$ 4.59	31.34 $\pm$ 4.99	-0.89 to 1.30	0.716
TBIL (μ mol/L)	375.05 $\pm$ 169.41	376.09 $\pm$ 172.58	371.64 $\pm$ 159.40	-35.05 to 43.95	0.825
GGT (IU/L)	96.54 $\pm$ 92.64	98.58 $\pm$ 99.26	89.86 $\pm$ 66.47	-12.87 to 30.30	0.428
Cr (μ mol/L)	81.58 $\pm$ 53.03	82.23 $\pm$ 50.86	89.86 $\pm$ 66.47	-9.60 to 15.12	0.661
BUN (mg/dL)	4.96 $\pm$ 4.97	5.09 $\pm$ 5.12	4.56 $\pm$ 4.47	-0.63 to 1.69	0.371
MELD	26.88 $\pm$ 5.63	26.93 $\pm$ 5.73	26.69 $\pm$ 5.32	-1.07 to 1.56	0.716
ABIC score	8.80 $\pm$ 1.80	8.79 $\pm$ 1.82	8.86 $\pm$ 1.71	-0.49 to 0.34	0.719
ALBI score	-1.07 $\pm$ 1.21	-1.02 $\pm$ 0.38	-1.26 $\pm$ 2.42	-0.04 to 0.52	0.099
Child-Pugh	11.31 $\pm$ 1.48	11.25 $\pm$ 1.48	11.49 $\pm$ 1.49	-0.58 to 0.11	0.179
CLIF-C OFs	10.07 $\pm$ 1.63	10.05 $\pm$ 1.61	10.13 $\pm$ 1.71	-0.46 to 0.30	0.559
Survival (days)	67.42 $\pm$ 32.25	66.45 $\pm$ 32.62	70.60 $\pm$ 30.94	-11.66 to 3.35	0.277

We next used univariate and multivariate Cox proportional hazards regression model analyses to identify independent risk factors for mortality in HBV-ACLF patients. Univariate analysis of 18 parameters demonstrated that 11 were significantly associated with mortality (Table 3). We then selected the variables above and performed multivariate analysis using a Cox proportional hazards regression model. Of note, when assessing age, TBIL, INR, creatinine, and ABIC score in this model, only ABIC score was included due to multicollinearity. It was revealed that BUN (HR = 1.048, 95% CI 1.011-1.086, $P < 0.05$), ABIC score (HR = 1.317, 95% CI 1.143-1.518, $P < 0.001$), and CLIF-OF score (HR = 1.380, 95% CI 1.166-1.634, $P < 0.001$) were independent risk factors for mortality in HBV-ACLF patients.

Table 2. Univariate analysis of survival and death group in training cohort. CI, confidence index; HGB, hemoglobin; WBC, white blood cell; PLT, platelet; INR, international normalized ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin; GGT, gamma glutamyl transpeptidase; Cr, creatinine; BUN, blood urea nitrogen; MELD, model for end-stage liver diseases; ABIC, age-bilirubin-INR-creatinine; ALBI, albumin-bilirubin score; CLIF-C OFs, chronic liver failure Consortium Organ Failure score. Data were expressed as numbers of patients (%) or mean $\pm$ standard deviation

Variables	Survival Group (n = 202)	Death Group (n = 102)	95% CI	P value
Age (year)	42.87 $\pm$ 12.32	48.80 $\pm$ 13.21	-8.94 to -2.91	<0.001
Male	174 (86.14)	85 (83.33)		0.609
HGB (g/L)	123.07 $\pm$ 21.74	114.45 $\pm$ 27.19	2.42 to 14.21	0.003
WBC (10^9 /L)	8.78 $\pm$ 4.39	8.56 $\pm$ 4.15	-0.82 to 1.24	0.688
PLT (10^9 /L)	121.68 $\pm$ 61.68	115.56 $\pm$ 77.34	-9.97 to 22.21	0.455
INR	2.68 $\pm$ 0.78	3.11 $\pm$ 1.47	-0.74 to -0.12	0.006
ALT (IU/L)	692.02 $\pm$ 835.32	626.10 $\pm$ 873.52	-136.84 to 268.69	0.523
AST (IU/L)	483.94 $\pm$ 627.44	484.64 $\pm$ 894.85	-176.68 to 171.29	0.976
ALB (g/L)	31.81 $\pm$ 4.71	30.97 $\pm$ 4.29	-0.07 to 2.04	0.067
TBIL (μ mol/L)	352.82 $\pm$ 155.25	424.44 $\pm$ 194.19	-115.27 to -27.96	0.001
GGT (IU/L)	99.82 $\pm$ 101.60	96.90 $\pm$ 95.07	-20.86 to 26.70	0.809
Cr (μ mol/L)	75.55 $\pm$ 37.45	95.52 $\pm$ 68.75	-34.41 to -5.53	0.007
BUN (mg/dL)	4.29 $\pm$ 3.32	6.67 $\pm$ 7.27	-3.88 to -0.88	0.002
MELD	25.95 $\pm$ 4.40	28.91 $\pm$ 7.37	-4.53 to -1.39	<0.001
ABIC score	8.34 $\pm$ 1.50	9.68 $\pm$ 2.09	-1.80 to -0.88	<0.001
ALBI score	-1.06 $\pm$ 0.38	-0.93 $\pm$ 0.35	-0.21 to -0.03	0.007
Child-Pugh	10.98 $\pm$ 1.43	11.81 $\pm$ 1.41	-1.17 to -0.49	<0.001
CLIF-C OFs	9.7 $\pm$ 1.29	10.75 $\pm$ 1.95	-1.46 to -0.62	<0.001

Predictive value of the ABIC score for 1-month mortality in HBV-ACLF patients

Patients in the death group showed significantly higher ABIC scores (9.95 ± 2.01) than those in survival group (8.45 ± 1.63 , $P < 0.001$) within 1 month (Fig. 1a). Dot plots for individual ABIC scores and survival times are also presented (Fig. 1c). AUCs were then used to compare the predictive value of the MELD, CP, CLIF-C OF, and ABIC scores. At 1 month, the AUC of the ABIC score was 0.732 [standard error [S.E.] 0.037, 95% CI 0.678-0.781], which was significantly higher than that of the MELD score (0.653, S.E. 0.044, 95% CI 0.596-0.706; $P < 0.05$) and the ALBI score (0.586, S.E. 0.040, 95% CI 0.528-0.642; $P < 0.01$) (Fig. 2a). The AUCs of the CP score (0.675, S.E. 0.037, 95% CI 0.619-0.727) and the CLIF-C OF score (0.693, S.E. 0.040, 95% CI 0.638-0.744) were also lower than the AUC of the ABIC score, though not significantly. Therefore, the ABIC score may be a better predictor than the MELD and ALBI scores for 1-month mortality in HBV-ACLF patients. We next investigated the cut-off value, sensitivity, specificity, PPV and NPV of the ABIC score for evaluating prognosis in patients with HBV-ACLF. An optimal cut-off value of 9.44 was identified to stratify the patients into two groups in the training cohort, with a sensitivity of 63.2%, specificity of 78.9%, PPV of 46.2% and NPV of 88.2% in predicting 1-month mortality. To compare 1-month mortality between groups with an ABIC score ≤ 9.44 and > 9.44 , Kaplan-Meier survival analysis was performed. HBV-ACLF patients with ABIC score > 9.44 had significantly shorter mean survival times than those with ABIC score ≤ 9.44 (21.03 ± 9.34 vs. 26.53 ± 4.70 days, $P < 0.001$). Meanwhile, patients with a high ABIC score > 9.44 had a significantly lower short-term survival rate than those ABIC score ≤ 9.44 (log-rank $P < 0.001$) (Fig. 2b). A MELD score of 27.88 was identified as the optimal cut-off value with sensitivity of 60.3%, specificity of 72.6%, PPV of 38.7%

and NPV of 86.4% for predicting 1-month mortality (Table 4). Moreover, a CLIF-C OF score of 10.50 was identified as the optimal cut-off value with sensitivity of 58.8%, specificity of 75.5%, PPV of 40.8% and NPV of 86.5% of for predicting 1-month mortality. For CP score, the optimal cut-off value was 12.5 for predicting 1-month mortality with sensitivity of 42.6%, specificity of 84.0%, PPV of 43.3%, and NPV of 83.6%.

Predictive value of the ABIC score for 3-month mortality in HBV-ACLF patients

Patients in the death group showed significantly higher ABIC score (9.67 ± 2.09) than those in the survival group (8.34 ± 1.50 , $P < 0.001$) within 3 months (Fig. 1b). At 3 months, the AUC of the ABIC score was 0.695 (S.E. 0.033, 95% CI 0.640-0.746), which was significantly higher than that of the MELD score (0.619, S.E. 0.038, 95% CI 0.562-0.674; $P < 0.01$) and that of the ALBI score (0.583, S.E. 0.0347, 95% CI 0.526-0.639). The AUC of the ABIC score was higher than that of the CP score (0.656, S.E. 0.033, 95% CI 0.599-0.709) and that of the CLIF-C OF

Table 3. Independent prognostic factors for mortality by the univariate and multivariate Cox proportional hazards regression model. HR, hazard ratio; CI, confidence index; HGB, hemoglobin; WBC, white blood cell; PLT, platelet; INR, international normalized ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin; GGT, gamma glutamyl transpeptidase; Cr, creatinine; BUN, blood urea nitrogen; MELD, model for end-stage liver diseases; ABIC, age-bilirubin-INR-creatinine; ALBI, albumin-bilirubin score; CLIF-C OFs, chronic liver failure Consortium Organ Failure score

Variables	HR	Univariate 95% CI	P	HR	Multivariate 95% CI	P
Age (year)	1.029	1.015-1.044	0.000			
Male	1.336	0.800-2.229	0.268			
HGB (g/L)	0.988	0.980-0.996	0.002	0.996	0.987-1.005	0.413
WBC ($10^9/L$)	0.993	0.949-1.040	0.779			
PLT ($10^9/L$)	0.999	0.996-1.002	0.478			
INR	1.421	1.209-1.671	0.000			
ALT (IU/L)	1.000	1.000-1.000	0.634			
AST (IU/L)	1.000	1.000-1.000	0.777			
ALB (g/L)	0.969	0.929-1.010	0.969			
TBIL ($\mu\text{mol/L}$)	1.002	1.001-1.003	0.000			
GGT (IU/L)	0.828	0.998-1.002	0.828			
Cr ($\mu\text{mol/L}$)	1.006	1.003-1.008	0.000			
BUN (mg/dL)	1.075	1.047-1.104	0.000	1.048	1.011-1.086	0.010
MELD	1.094	1.058-1.131	0.000	0.026	0.905-1.163	0.690
ABIC score	1.388	1.262-1.526	0.000	1.317	1.143-1.518	0.000
ALBI score	2.334	1.197-4.551	0.013	1.383	0.699-2.735	0.352
Child-Pugh	1.446	1.248-1.676	0.000	1.057	0.857-1.302	0.606
CLIF-C OFs	1.509	1.337-1.702	0.000	1.380	1.166-1.634	0.000

Fig. 1. Comparison of ABIC score in survival and death group at the end of 1-month (a) and 3-month (b) follow-up. Blue bars indicate mean and standard deviation of ABIC score. Dot plots (c) for ABIC scores in different survival time have been created. The vertical blue dot line indicated 1-month survival. The horizontal blue dot line indicates the cut-off value of 9.44 for ABIC score for predicting 3-month mortality. The grey area between the two horizontal red lines indicates 25% and 75% percentile (7.47 – 9.88) of ABIC score in 3-month survivors while the green dot line indicates the mean (8.79). ABIC score, age-bilirubin-international-normalized ratio-creatinine score.

Fig. 2. Sensitivities and specificities for ABIC score, CLIF-C OF score, Child-Pugh score and MELD score in predicting 1-month (a) and 3-month (c) mortality of patients in the training cohort. Kaplan-Meier survival curves of patients in training cohort stratified by the optimal cut-off values of ABIC score within 1 month (b) and 3 months (d). ABIC score, age-bilirubin-international-normalized ratio-creatinine score; CLIF-C OFs chronic liver failure Consortium Organ Failure; MELD, model for end-stage liver diseases.

score (0.660, S.E. 0.035, 95% CI 0.604-0.713), though not significantly. Thus, the ABIC score may be superior to the MELD and ALBI scores in predicting 3-month mortality in HBV-ACLF patients. Patients at the end of 3-month follow-up were stratified based on an optimal cut-off value of 9.44, with a sensitivity of 54.4%, specificity of 81.7%, PPV of 60.2%, and NPV of 77.8% (Table 4).

HBV-ACLF patients with ABIC score > 9.44 had significantly shorter mean survival times than those with ABIC score ≤ 9.44 (47.23 ± 36.30 vs. 74.88 ± 26.91 days, $P < 0.001$). Meanwhile, patients with a high ABIC score > 9.44 had a significantly lower short-term survival rate than those with ABIC score ≤ 9.44 (log-rank $P < 0.001$) (Fig. 2d). A MELD score of 29.47 was identified as the optimal cut-off value with sensitivity of 43.7%, specificity of 83.2%, PPV of 57.0% and NPV of 74.3% for predicting 3-month mortality. Moreover, a CLIF-C OF score of 10.50 was determined as the optimal cut-off value with sensitivity of 53.9%, specificity of 78.8%, PPV of 56.1%, and NPV of 76.8% for predicting 3-month mortality.

Table 4. Diagnostic value and cut-off values of ABIC score, CLIF-C OF score, Child-Pugh score and MELD score for predicting mortality of HBV-ACLF patients in training cohort. MELD, model for end-stage liver diseases; ABIC, age-bilirubin-INR-creatinine; ALBI, albumin-bilirubin score; CLIF-C OFs, chronic liver failure Consortium Organ Failure score; PPV, positive predictive value; NPV, negative predictive value

	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1-month mortality					
ABIC score	9.44	63.2	78.9	46.2	88.2
MELD	27.88	60.3	72.6	38.7	86.4
Child-Pugh	12.50	42.6	84.0	43.3	83.6
CLIF-C OFs	10.50	58.8	75.5	40.8	86.5
3-month mortality					
ABIC score	9.44	54.4	81.7	60.2	77.8
MELD	29.47	43.7	83.2	57.0	74.3
Child-Pugh	11.50	63.7	62.4	46.1	76.8
CLIF-C OFs	10.50	53.9	78.8	56.1	76.8

Validation of the ABIC score as a prognostic predictor for 1- and 3-month mortality in HBV-ACLF patients

To further validate the predictive value of the ABIC score, a validation cohort of 93 patients with HBV-ACLF was used. Most of the baseline parameters showed no significant difference between the training and validation cohorts (Table 1). The AUCs of the ABIC score

for 1- and 3-month mortality in the validation cohort were 0.728 (S.E. 0.072, 95% CI, 0.625-0.816) and 0.732 (S.E. 0.070, 95% CI 0.630-0.819), respectively (Fig. 3a & c). The AUCs of the ABIC score for 1- and 3-month mortality were higher than those of the MELD score (0.683, S.E. 0.083, 95% CI 0.578-0.777, $P = 0.524$; 0.714, S.E. 0.0722, 95% CI 0.610-0.803, $P = 0.769$, respectively) and the ALBI score (0.568, S.E. 0.074, 95% CI 0.461-0.671; 0.657, S.E. 0.067, 95% CI 0.551-0.753, respectively), though not significantly. The AUCs of the CLIF-C OF score and the CP score were 0.664 (S.E. 0.071, 95% CI 0.558-0.760, $P = 0.310$) and 0.642 (S.E. 0.069, 95% CI 0.535-0.739, $P = 0.294$) for 1-month mortality, respectively. The AUCs of the CLIF-C OF score and the CP score were 0.656 (S.E. 0.067, 95% CI 0.550-0.752, $P = 0.258$) and 0.684 (S.E. 0.062, 95% CI 0.579-0.777, $P = 0.502$) for 3-month mortality, which were similar to the AUC of the ABIC score.

Patients in the validation cohort were then divided into two groups based on the cut-off values. In the validation cohort, HBV-ACLF patients with ABIC score > 9.44 also experienced significantly reduced survival times than those with ABIC score ≤ 9.44 (49.77 ± 38.35 vs. 81.87 ± 22.36 days, $P < 0.001$). Additionally, patients with ABIC scores > 9.44 had significantly lower 1-month survival rates compared with those with ABIC score ≤ 9.44 (log-rank $P < 0.05$) (Fig. 3b). Compared with patients with ABIC score ≤ 9.44 , those with ABIC score > 9.44 had a decreased survival rate (log-rank $P < 0.001$) at the end of the 3-month follow-up (Fig. 3d).

Predictive value of the ABIC score in HBV-ACLF patients satisfying EASL criteria

The predictive value of the ABIC score in HBV-ACLF patients satisfying the EASL criteria [3] was explored to evaluate its applicability. Among the patients in this study, 225 met the EASL criteria for ACLF. A comparison of ROC curves of different prognostic scores was performed among these patients (Supplemental Fig. 1 - for all supplemental material see www.karger.com/10.1159/000495904/). The ABIC score had the highest AUC (0.742) for predicting 1-month mortality. The AUC of ALBI score was significantly lower than that of the ABIC score (0.565, $P = 0.001$). The CLIF-C OF, MELD, and CP scores each had AUC comparable to that of the ABIC score (0.679, $P = 0.233$; 0.685, $P = 0.114$; 0.653, $P = 0.067$). The AUCs indicated that the CLIF-C OF, MELD, and CP scores were worse than the ABIC

Fig. 3. Sensitivities and specificities for ABIC score, CLIF-C OF score, Child-Pugh score and MELD score in predicting 1-month (a) and 3-month (c) mortality of patients in the validation cohort.

Kaplan-Meier survival curves of patients in validation cohort stratified by the optimal cut-off values of ABIC score within 1 month (b) and 3 months (d). ABIC score, age-bilirubin-international-normalized-ratio-creatinine score; CLIF-C OF score, chronic liver failure Consortium Organ Failure score; MELD, model for end-stage liver diseases.

score in predicting 3-month mortality, although not significantly (0.665, 0.674, and 0.650, respectively; $P = 0.152$, 0.107 , and 0.138 , respectively) (Fig. S1c). The AUC of the ALBI score was the lowest among the prognostic scores tested (0.593 , $P = 0.004$).

Patients were further divided into another two groups according to the cut-off value of the ABIC score. Patients with ABIC scores > 9.44 had significantly shorter mean survival time than those with ABIC score ≤ 9.44 (log-rank $P < 0.001$) in 1 month (Fig. S1b). Patients with ABIC score > 9.44 also had significantly lower survival rates than those with ABIC score ≤ 9.44 in 3 months (log-rank $P < 0.001$) (Fig. S1d). Therefore, ABIC score also showed good predictive value among patients satisfying EASL ACLF criteria.

Discussion

In this study, we demonstrated that the ABIC score was superior to the MELD and ALBI score in predicting 1- and 3-month mortality. An optimal cut-off value of 9.44 was determined for the ABIC score to identify HBV-ACLF patients with poor prognosis. The ROC level was significantly higher for the ABIC score than for the MELD and ALBI scores in HBV-ACLF at the end of 1- and 3-month follow-ups. The predictive value of the ABIC score was comparable to that of the CLIF-C OF score and the CP score. In the validation cohort, ABIC score also had the highest ROC level among these models, though the difference was not statistically significant—this could be attributable to an inadequate sample size.

Originally, the ABIC score was found to be a useful tool for prognostic stratification of patients with alcoholic hepatitis, which has helped to identify patients who might benefit from prednisolone treatment [14, 19]. However, it was not clear whether the ABIC score could be used to predict the outcomes in patients with HBV-ACLF. To our knowledge, this was the first study to demonstrate that the ABIC score also exhibited good performance in estimating the short-term prognosis in HBV-ACLF patients. The parameters needed to calculate the ABIC score reflect functions of organ systems defining the ACLF syndrome, and they are convenient and inexpensive to measure during hospitalization. The ABIC score includes the same variables as the MELD score, but with the addition of age. The high ABIC in non-survivors could be attributed to increased age, TBIL, creatinine, and INR because the ABIC score was generated from the sum of natural logarithms of HR multiplied by these variables.

The role of age as an independent risk factor for mortality in patients with ACLF has been reported previously [3, 20, 21]. Survival in older patients may be affected by increased vulnerability to liver injury due to decreased liver regeneration ability and loss of reserve functions among other organs [22, 23]. Our study also found that BUN was an independent risk factor for short-term mortality of HBV-ACLF patients. BUN is commonly accepted as an indicator for renal dysfunction, which plays an important role in predicting prognosis in cirrhotic patients with spontaneous bacterial peritonitis [24]. A recent study also found that BUN was an independent risk factor for long-term survival in HBV-ACLF patients [25]. In our study, the ABIC score showed good NPV contrasted with low PPV, suggesting that the ABIC score is more useful for excluding low-risk patients, rather than for identifying those at high risk of mortality. Thus, ABIC score may assist clinicians in deciding when to proceed with liver transplantation in patients with ACLF.

Liver failure remains a major challenge for physicians in liver centers and represents a marked health and economic burden in China and the United States [26, 27]. The indications for artificial organ support and emergency liver transplantation in ACLF patients are poorly defined [28]. Several prognostic models and biomarkers have been proposed for predicting the outcomes of these patients; these could assist in guiding management and intervention strategies. Though MELD is treated as the gold standard for the prediction of outcome in patients with end-stage liver disease, the survival rate of approximately 15%-20% cannot be accurately predicted [9, 29]. In addition, CP and MELD scores also have heterogeneous benefits in specific applications [30]. The ALBI score was developed to assess liver function

in patients with hepatocellular carcinoma [18]. However, the ALBI score did not perform satisfactorily in terms of predictive ability in patients with ACLF in a previous study [31]. In the present study, we also analyzed the prognostic value of ALBI score in ACLF and found that it was inferior to that of the ABIC score and that of the MELD score. In addition, the CLIF-C ACLF score has been demonstrated to provide superior prognostic accuracy for ACLF compared with the MELD and CP scores [32, 33]. However, these models are mostly based on data from patients with alcoholic hepatitis or hepatitis C virus infection, which are the leading underlying causes of liver failure in Western countries. Due to the difference in the etiologies of ACLF between Eastern and Western countries, further investigation into whether these models exhibit ideal predictive value in patients with HBV-ACLF is needed. Moreover, the complexity of these models would be somewhat inconvenient in clinical practice.

Various types of biomarkers like plasma interleukin 10, macrophage activation marker soluble cluster of differentiation 163 (sCD163), cell death marker caspase-cleaved keratin 18 (ck18), and neutrophil gelatinase-associated lipocalin have been shown to enhance the prognostic ability of conventional scoring models like MELD in predicting short-term mortality [34-37]. Yet, the detection of certain biomarkers may be restricted because of the requirement for extra techniques and devices. Thus, an effective and practical model that predicts survival in HBV-ACLF patients is urgently needed. ABIC score can be easily calculated during hospitalization, and this enables rapid prediction of the prognosis for HBV-ACLF patients. Through this easy-to-use scoring model, physicians can identify patients with different risk of mortality, which might assist in selecting patients who require additional management or intensive care.

There are some limitations to this study. Firstly, this was a retrospective study in a single center, which could have led to increased selection bias. Thus, a prospective multi-center study with a large data set is needed for future research. Secondly, the inclusion criteria were limited to HBV-ACLF disease; whether the predictive value of the ABIC score could be applied to ACLF from other causes remains to be clarified. In addition, this study focused on the short-term survival of patients with HBV-ACLF; thus, ABIC score and whether it has a predictive value for long-term survival needs to be followed up with longer studies.

In conclusion, our study demonstrated that ABIC score was an inexpensive and a potential indicator that could predict short-term prognosis in HBV-ACLF patients. ABIC score > 9.44 predicts high 1- and 3-month mortality risk in HBV-ACLF.

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Disclosure Statement

All authors declare that no conflicts of interest exist.

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