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A new multiparameter integrated MELD model for prognosis of HBV-related acute-on-chronic liver failure

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Abstract

Hepatitis B virus related acute-on-chronic liver failure (HBV-ACLF) is one of the most deadly diseases. Many models have been proposed to evaluate the prognosis of it. However, these models are still controversial. In this study, we aimed to incorporate some characters into model for end-stage liver disease (MELD) to establish a new reliable and feasible model for the prognosis of HBV-ACLF.

A total of 530 HBV-ACLF patients who had received antiviral therapy were enrolled into a retrospective study and divided into the training cohort (300) and validation cohort (230). Logistic regression analysis was used to establish a model to predict the 3-month mortality from the patients in the training cohort, and then, the new model was evaluated in the validation cohort.

Except for MELD score, 4 other independent factors, namely degree of hepatic encephalopathy (HE), alpha-fetoprotein (AFP), white blood cell (WBC) count, and age, were important for the new model called HBV-ACLF MELD (HAM) model: $R = 0.174 \times MELD + 1.106 \times HE - (0.003 \times AFP) + (0.237 \times WBC) + (0.103 \times Age) - 11.388$. The areas under receiver-operating characteristic curve of HAM in the training and validation cohort were 0.894 and 0.868, respectively, which were significantly higher than those of other 7 models. With the best cut-off value of −1.191, HAM achieved higher sensitivity and negative predictive value.

We developed a new model that has a great prognostic value of the 3-month mortality of patients with HBV-ACLF.

Abbreviations: AARC = APASL ACLF research consortium, ACLF = acute-on-chronic liver failure, ALSS = artificial liver support system, APACHE = Acute Physiology And Chronic Health Evaluation, APASL = Asian Pacific Association for the Study of the Liver, AUROC = area under ROC curve, CHB = chronic hepatitis B, HAM = HBV-ACLF MELD, HBeAg = hepatitis B e antigen, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HE = hepatic encephalopathy, HRS = hepatorenal syndrome, LRA = logistic regression analysis, MELD = model for end-stage liver disease, NAs = nucleos(t)ide analogs, NLR = negative likelihood ratio, NPV = negative predictive value, PLR = positive likelihood ratio, PPV = positive predictive value, ROC = receiver-operating characteristic, SOFA = Sequential Organ Failure Assessment, TB = total bilirubin.

Keywords: prognostic model, risk factors, short-term mortality

1. Introduction

Acute-on-chronic liver failure (ACLF) is a common clinical entity, which may result in life-threatening complications, such as hepatic encephalopathy (HE), hepatorenal syndrome (HRS), infection and bleeding. Accordingly, patients with ACLF run a high risk of short-term mortality.[1,2] The number of individuals infected with hepatitis B virus (HBV) in China accounts for about a third of all global cases, with 130 million HBV carriers and 30 million HBV-related chronic liver diseases.[3,4] Patients with chronic HBV infection or cirrhosis caused by HBV are the main population at risk of ACLF.[5] Regarding the treatment of HBV-ACLF, antiviral therapy and other conservative therapies may save the lives of about 50% to 70% of the patients, while liver transplantation may be the ultimate option for the rest patients. It is well known that several problems exist in liver transplantation, such as the expenditure, the scarcity of donors, and many risks associated with the process of execution.[6] Accordingly, who is suitable for conservative treatment and who will benefit from transplantation in the end is a choice which has to be balanced by every clinician. Furthermore, the sooner the decision is made the more benefit patients might gain. Therefore, a good model which can accurately predict the prognosis of these patients is required to give good advice.

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Some elegant studies have revealed that the model for end-stage liver disease (MELD) assesses well the short-term mortality risk in patients with cirrhosis.[7–9] In recent years, a number of improved models based on MELD, like serum sodium (Na) and model for MELD (MELD-Na), incorporating Na and age MELD model (iMELD), MELD to Na ratio (MESO),[10–12] etc., with the addition of Acute Physiology and Chronic Health Evaluation (APACHE), Sequential Organ Failure Assessment (SOFA), and some regression models[13,14] have been gradually developed to predict the severity of patients with ACLF. However, the predictive accuracy remains unsatisfactory, especially when they are used for Asian patients. This maybe partly attributed to the incongruent definition of ACLF between the East and the West.[15]

In this study, we aim to further improve the MELD scoring system to predict the 3-month mortality of HBV-ACLF patients and test its performance. It may then be turned into a formula for use by clinicians.

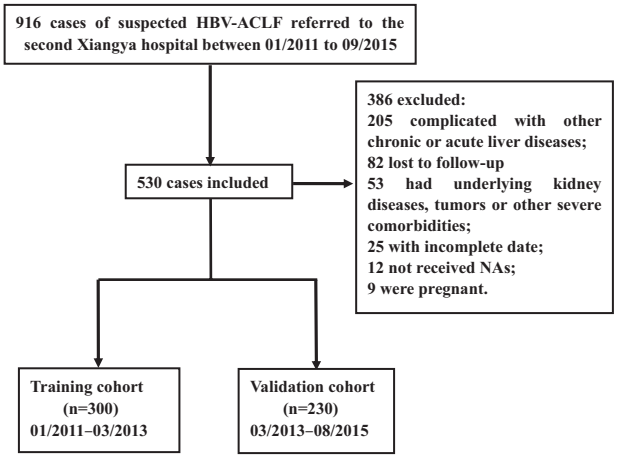

Figure 1. Flow chart of patients selection. CHB = chronic hepatitis B, HBV-ACLF = hepatitis B virus associated acute-on-chronic liver failure, NAs = nucleoside/nucleotide analogs.

2. Methods

2.1. Study design and patients enrollment

Nine hundred sixteen patients with chronic hepatitis B (CHB) or HBV-related cirrhosis, who were diagnosed as ACLF and admitted to the Second Xiangya Hospital of Central South University from January 1, 2011 to September 1, 2015 were screened. ACLF was defined in accordance with the Asian Pacific Association for the Study of the Liver (APASL) ACLF Research Consortium (AARC) as "acute hepatic insult manifesting as jaundice (serum bilirubin $\geq$5 mg/dL (85 mmol/L)) and coagulopathy (international normalized ratio (INR) $\geq$1.5 or prothrombin activity $<$40%) complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis, and is associated with a high 28-day mortality."[1] The patients with coinfection of human immunodeficiency virus (HIV) or other hepatotropic viruses, tumors, toxic liver injury, biliary tract obstruction, intrinsic renal diseases, pregnancy, severe cardiopulmonary comorbidity, other causes of chronic liver diseases (e.g., alcoholic liver disease, schistosomiasis, autoimmune diseases, Wilson disease, etc.) and those who had received a liver transplant were excluded. As an overwhelming majority of patients were treated with nucleos(t)ide analogs (NAs) drugs, those who did not received NAs were also excluded. After the process of selection, a total of 530 patients were eventually enrolled in the following analysis.

The final 530 patients (489 men, 41 women, median age 41 years) were divided into a training cohort and a validation cohort. Patients who were admitted to the hospital from January 1, 2011 to March 5, 2013 entered in the training cohort (n = 300). Those who were admitted from March 5, 2013 to September 1, 2015 were enrolled in the validation cohort (n = 230). The flow chart of the study group selection process is presented in Fig. 1.

The start date of the follow-up was the date of diagnosis of HBV-ACLF. All screened patients were followed up for at least 3 months and had obvious clinical endpoints, namely survival or death. The research protocol was approved by the Human Ethics Committee of the Second Xiangya Hospital of Central South University, China. The study procedure conformed to the Helsinki Declaration and Standards for the Reporting of Diagnostic Accuracy Studies.[16]

2.2. Definitions and therapeutic interventions

The diagnosis of cirrhosis was established on the basis of previous liver-biopsy findings or a comprehensive evaluation of physical examination and evidence obtained by laboratory tests, endoscopy, ultrasonic test, and radiologic imaging.[17] Coinfection with bacteria or fungi was diagnosed based on clinical findings and/or infection-positive cultures of blood, ascites, urine, or sputum. Ascites were detected by physical examination and confirmed by ultrasonic test. HRS was defined according to an increase in serum creatinine of more than 1.5 mg/dL in the absence of intrinsic kidney diseases.[18] The severity of HE was graded with the West Haven criteria.[19]

Standard conservative therapy was the same for every patient, including absolute resting, intravenous infusion of albumin and plasma, and nutritional and energy supplements.[1] All patients who were positive for serum HBV-DNA were given NAs, namely lamivudine, adefovir, entecavir or telbivudine, monotherapy or combination therapy. Antibiotics or antimycotics were used to treat infection. Patients with HE were given lactulose, ornithine aspartate, and dehydrant if needed. Hematodialysis or artificial liver support system (ALSS) may also proceed if needed.

2.3. Observation parameters and popular scoring systems

Medical history was recorded on file on admission. Retrospectively collected data included patient demographics, clinical, laboratory variables, and imaging information. Laboratory parameters, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TB), albumin (ALB), globulin (GLO), alpha-fetoprotein (AFP), platelet count, hemoglobin (Hb), white blood cell (WBC) count, serum creatinine (Cr), international normalized ratio (INR), and Na concentration, were obtained within the first 24 hours after the diagnosis of HBV-ACLF by 3 clinician of our team who did not participate in the subsequent data analysis. Clinical complications, like ascites, HE, infection, gastrointestinal hemorrhage, etc., were detected within the first 72 hours. Additionally, serological tests for hepatitis B surface antigen (HBsAg), anti-HBs, hepatitis B e antigen (HBeAg), immunoglobulin M anti-HBc, immunoglobulin G anti-HBc, and anti-HBe were performed by chemiluminescence immunoassay (MAGLUMI). Serum HBV-DNA was measured by quantitative PCR fluorescence probes (Sansure Biotech, Changsha, Hunan Province, P.R. China; limit of detectability of 10 IU/mL) on admission. Hepatitis C virus antibody was detected by commercially available enzyme-linked immunoassays and HIV antibody

was detected using colloidal gold rapid test (BlueCROSS, Beiqijia Industry Zone, Changping, Beijing, China).

Every patient was assessed using the MELD scoring when diagnosed. MELD scores were calculated according to the Malinchoc formula: $R = 9.57 \times \text{Ln (Cr [mg/dL])} + 3.78 \times \text{Ln (bilirubin [mg/dL])} + 11.2 \times \text{Ln (INR)} + 6.43$.[20] Several MELD-based scores, such as MELD-Na score ($R = \text{MELD} + 1.59 \times (135 - \text{Na [mmol/L]})$, with maximum and minimum Na values of 135 and 120 mmol/L, respectively),[10] iMELD score ($R = \text{MELD} + (\text{age [year]} \times 0.3) - (0.7 \times \text{Na [mmol/L]}) + 100$),[11] MESO score ($R = (\text{MELD/Na [mmol/L]}) \times 100$),[12] MELDNa score ($R = \text{MELD} - \text{Na [mmol/L]} - (0.025 \times \text{MELD} \times (140 - \text{Na [mmol/L]})) + 140$, where Na concentration was between 125 and 140 mmol/L),[21] had also been described to well predict the mortality of end-stage liver diseases. Two popular logistic regression models were referred to be applied to ACLF patients by the AARC consensus: one was established by Sun et al, namely $R = 1.4053 + 3.6017 \times \text{HRS} + 1.2069 \times \text{liver cirrhosis (LC)} - 1.1555 \times \text{HBeAg} - 0.1003 \times \text{ALB} - 0.042 \times \text{prothrombin time activity (PTA)}$[13]; the other was established by Zheng et al,[14] namely $\text{LRM} = -1.343 + 0.772 \times \text{HE} + 2.279 \times \text{HRS} + 0.85 \times \text{LC} + 1.026 \times \text{HBeAg} - 2.117 \times \text{PTA/age}$. All the 7 models above were assessed for comparison.

2.4. Statistical analysis

Continuous variables were expressed by mean ± standard deviation or the median (interquartile range). Binary or nominal variables were described as a number (%). The Kolmogorov–Smirnov test was applied to determine whether the sample data were likely to be derived from a normally distributed population. Comparisons between 2 groups were performed by Student *t* test, the Mann–Whitney *U* test or a χ^2 test.

For the training cohort, we initially evaluated univariate associations by univariate logistic regression analysis (LRA) to identify significant predictors of the prognosis of patients with HBV-ACLF when considered alone. Candidate variables ($P < 0.1$) were entered into a multivariate LRA following a forward stepwise approach. The conditional probabilities for stepwise entry and removal of a factor were 0.05 and 0.10, respectively. Maximum likelihood method was considered in the estimation of the coefficients of the models. Based on the results from multivariate LRA, a new model was developed.

The performance of the new model and other 7 models were compared in the training sample and validation sample by using the receiver-operating characteristic (ROC) curves. Then comparing the areas under ROC curve (AUROC). In addition, the respective sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) of all the models were calculated at the best cut-off points for comparison in the training cohort, and tested in the validation cohort. The Youden index (YI, YI = sensitivity + specificity − 1) was used to identify the optimal cut-off point for each model. For all the analyses, confidence intervals (CIs) were given for the 95% level; a *P*-value of <0.05 was considered statistically significant. All computations were carried out using the SPSS19.0 software (IBM, Armonk, NY).

3. Results

3.1. Establishment of HBV-ACLF MELD (HAM) model

Among the training cohort, median age of the 300 patients is 41 years (276 men, 24 women) and 106 patients died during the 3-month follow-up (35.3%). Details can be seen in the Supplementary Tables 1 and 2, http://links.lww.com/MD/B229. The most common complication was ascites (157 patients; 52.3%), followed by infection (111 patients; 37.0%), HE (52 patients; 17.3%), and HRS (13 patients; 4.3%). The baseline characteristics are shown in Table 1. The following parameters: age (odds ratio (OR) = 1.069, 95% CI: 1.043–1.096, $P < 0.001$), WBC (OR = 1.187, 95% CI: 1.099–1.281, $P < 0.001$), AFP (OR = 0.997, 95% CI: 0.995–0.998, $P < 0.001$), ALB (OR = 0.907, 95% CI: 0.854–0.963, $P = 0.001$), Na concentration (OR = 0.906, 95% CI: 0.858–0.956, $P < 0.001$), HE (OR = 3.234, 95% CI: 2.189–4.780, $P < 0.001$), MELD scores (OR = 1.234, 95% CI: 1.164–1.309, $P < 0.001$), sites of infection (OR = 3.071, 95% CI: 1.902–4.958, $P < 0.001$), ascites (OR = 1.868, 95% CI: 1.152–3.029, $P = 0.011$) were significantly associated with the 3-month mortality considered alone, see Supplementary Table 2, http://links.lww.com/MD/B229.

After the multivariate LRA, independent factors were calculated as shown in Table 2: MELD score (OR = 1.190, 95% CI: 1.108–1.279), AFP (OR = 0.997, 95% CI: 0.995–0.009), WBC (OR = 1.268, 95% CI: 1.122–1.433), age (OR = 1.109, 95% CI: 1.068–1.150), degree of HE (OR = 3.022, 95% CI: 1.710–5.340). Based on these factors, a new model named HAM was established. The new model could be described by formula: $R = 0.174 \times \text{MELD} + 1.106 \times \text{HE} - (0.003 \times \text{AFP [ng/mL]}) + (0.237 \times \text{WBC } [10^9/\text{L}]) + (0.103 \times \text{Age [year]}) - 11.388$. With the optimal cut-off point of −1.191, HAM achieved 91.5% sensitivity and 70.9% specificity.

3.2. Predictive value of HAM compared with other 7 models

In the training cohort, the applicability of HAM in predicting the 3-month mortality was significantly better (AUROC = 0.894, 95% CI: 0.857–0.932), compared with that of other 7 scoring systems: MELD scoring (AUROC = 0.764, 95% CI: 0.703–0.824, $P < 0.001$), MELD-Na scoring (AUROC = 0.754, 95% CI: 0.694–0.814, $P < 0.001$), iMELD scoring (AUROC = 0.812, 95% CI: 0.759–0.865, $P = 0.013$), MESO scoring (AUROC = 0.770, 95% CI: 0.711–0.830, $P < 0.001$), MELDNa scoring (AUROC = 0.774, 95% CI: 0.714–0.833, $P < 0.001$), model by Sun (AUROC = 0.667, 95% CI: 0.598–0.736, $P < 0.001$), model by Zheng (LRM, AUROC = 0.799, 95% CI: 0.743–0.854, $P = 0.005$), respectively (Table 3, Fig. 2A). With the cut-off value of −1.191, HAM achieved a higher sensitivity (91.5%) and NPV (89.3%) than those of other 7 models as shown in Table 4, other diagnostic values and the best cut-off value of each model are also shown.

3.3. Validation of HAM in another cohort

When HAM was finally evaluated in the validation cohort, the AUROC of 0.868 (95% CI: 0.819–0.918) also performed better than that of other 7 scoring systems: MELD scoring (AUROC = 0.746, 95% CI: 0.677–0.815, $P = 0.005$), MELD-Na scoring (AUROC = 0.746, 95% CI: 0.677–0.814, $P = 0.005$), iMELD scoring (AUROC = 0.764, 95% CI: 0.699–0.830, $P = 0.012$), MESO scoring (AUROC = 0.750, 95% CI: 0.681–0.819, $P = 0.005$), MELDNa scoring (AUROC = 0.749, 95% CI: 0.680–0.818, $P = 0.005$), model by Sun (AUROC = 0.647, 95% CI: 0.572–0.721, $P < 0.001$), model by Zheng (AUROC = 0.747, 95% CI: 0.679–0.816, $P = 0.005$) respectively (Table 3, Fig. 2B). With the cut-off value of −1.191, HAM had a sensitivity

Table 1

Baseline characteristics of the training cohort and the validation cohort.

Variable	Training cohort (n = 300)	Validation cohort (n = 230)	$t/u/\chi^2$	P
Death, %	106 (35.33%)	84 (36.52%)	0.080	0.777
Liver cirrhosis, %	141 (47.00%)	105 (45.65%)	0.095	0.758
Male gender, %	276 (92.00%)	213 (92.61%)	0.068	0.795
Age, y	41 (34, 49)	40 (33, 48)	33,782	0.681
HE, %	52 (17.33%)	43 (18.70%)	0.164	0.685
Ascites, %	157 (52.33%)	107 (46.52%)	1.759	0.185
ALT, U/L	514.1 (196.0, 983.5)	476.3 (196.5, 961.7)	33,509	0.629
AST, U/L	278.2 (149.3, 616.4)	261.2 (115.5, 570.7)	30,791	0.142
TB, μmol/L	358.7 ± 123.5	357.8 ± 128.9	−0.080	0.936
Albumin, g/L	31.2 ± 4.3	30.6 ± 3.9	−1.696	0.090
Globulin, g/L	31.5 (25.6, 36.4)	29.6 (24.9, 34.0)	26547	0.039
Cr, μmol/L	66.2 (63.1, 82.4)	68.8 (58.5, 81.6)	33,531	0.579
HRS, %	13 (4.33%)	16 (6.96%)	1.732	0.188
WBC count, 10^9/L	6.9 (5.2, 9.0)	7.2 (5.5, 9.8)	31,911	0.138
Infection (including SBP), %	111 (37.00%)	93 (40.43%)	0.649	0.421
Hemoglobin, g/L	130.9 ± 18.1	131.5 ± 17.1	0.387	0.699
Platelet, 10^9/L	102 (82, 136)	111 (77, 143)	32,875	0.352
AFP, ng/mL	93.0 (15.8, 263.9)	91.4 (34.7, 221.1)	29,510	0.307
HBV-DNA, $\log_{10}$, IU/mL	4.92 (3.57, 6.60)	5.53 (3.91, 7.13)	28,376	0.009
INR	2.51 (2.10, 3.68)	2.32 (1.94, 2.98)	27,571	<0.001
MELD score	26 (23, 31)	25 (22, 29)	28,977	0.002
HBeAg (positivity rate), %	79 (26.33%)	62 (26.96%)	0.012	0.912
Na concentration, mmol/L	136 (132, 138)	136 (134, 138)	31881	0.174
Gastrointestinal hemorrhage, %	4 (1.33%)	5 (2.17%)	0.551	0.458
Treated with LAM	104 (34.67%)	32 (13.91%)	29.395	0.000
Treated with LAM + ADV	48 (16.00%)	11 (4.78%)	16.559	0.000
Treated with ADV	17 (5.67%)	5 (2.17%)	3.992	0.046
Treated with ETV	124 (41.33%)	180 (78.26%)	72.584	0.000
Treated with LDT	7 (2.33%)	2 (0.87%)	1.671	0.196

Continuous values were expressed by mean ± SD or median and interquartile range, and categorical values were described by count and proportions.

ADV = adefovir dipivoxil, AFP = alpha-fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, Cr = creatinine, ETV = entecavir, HBeAg = hepatitis B e antigen, HE = hepatic encephalopathy, HRS = hepatorenal syndrome, INR = international normalized ratio, LAM = lamivudine, LDT = telbivudine., MELD = model for end-stage liver disease, Na = serum sodium, SBP = spontaneous bacterial peritonitis, TB = total bilirubin, WBC = white blood cell.

of 84.9% and NPV of 83.2%, which were also higher, as demonstrated in Table 4. Other diagnostic values were also validated.

4. Discussion

In this study, we demonstrated that patients with HBV-ACLF had a high short-term mortality. Accordingly, the notion that a stratified management of these patients can improve survival emphasizes the importance of having accurate prognostic tools in HBV-ACLF.

MELD scoring was initially established by Malinchoc and confirmed to predict the short-term prognosis of patients with cirrhosis undergoing the transjugular intrahepatic portosystemic shunt procedure.[7] Since 2002, MELD has been found to be useful in determining the priority in the transplant waiting list for patients with end-stage liver disease and the prognosis of decompensated cirrhosis patients.[8,9] Additionally, it has gradually become widely used in severe liver diseases, including HBV-ACLF and has been proven to be helpful for clinicians.[1] Furthermore, the MELD scoring system relies entirely on objective and reliable parameters, such as INR, which can be trusted regardless of the different laboratories, instruments, and reagents.[22] The result of the present study also lent support to the notion. However, MELD does not account for any complication of HBV-ACLF. In clinic, like HE or bleeding

Table 2

Multivariate logistic regression analysis of independent factors for 3-month mortality in patients with hepatitis B virus associated acute-on-chronic liver failure in the training cohort.

Variable	Coefficient	OR	95% CI	P
MELD score	0.174	1.190	1.108–1.279	<0.001
AFP, ng/mL	−0.003	0.997	0.995–0.999	0.002
WBC count, 10^9/L	0.237	1.268	1.122–1.433	<0.001
Age, y	0.103	1.109	1.068–1.150	<0.001
HE degree	1.106	3.022	1.710–5.340	<0.001
Constant	−11.388	<0.001		<0.001

AFP = alpha-fetoprotein, CI = confidence interval, HE = hepatic encephalopathy, MELD = model for end-stage liver disease, OR = odds ratio, WBC = white blood cell count.

Table 3

Comparison of the performance of all models both in the training cohort and the validation cohort by AUROC.

Models	Training cohort (n = 300)				Validation cohort (n = 230)			
	AUROC	*P*	95% CI		AUROC	*P*	95% CI	
HAM	0.894		0.857	0.932	0.868		0.819	0.918
MELD	0.764	<0.001	0.703	0.824	0.746	0.005	0.677	0.815
MELD-Na	0.754	<0.001	0.694	0.814	0.746	0.005	0.677	0.814
iMELD	0.812	0.013	0.759	0.865	0.764	0.012	0.699	0.830
MESO	0.770	<0.001	0.711	0.830	0.750	0.005	0.681	0.819
MELDNa	0.774	<0.001	0.714	0.833	0.749	0.005	0.680	0.818
Sun	0.667	<0.001	0.598	0.736	0.647	<0.001	0.572	0.721
LRM	0.799	0.005	0.743	0.854	0.747	0.005	0.679	0.816

Comparison between the AUROC of each model and that of HAM via *z* test, *P*-value less than 0.05 means there was a significant difference.
AUROC = area under receiver–operator characteristic curve, CI = confidence interval, HAM = HBV-ACLF MELD, iMELD = incorporating serum sodium and age MELD model, LRM = logistic regression model (established by Zheng et al), MELD = model for end-stage liver disease, MESO = MELD to serum sodium ratio, Na = serum sodium, Sun = model established by Sun et al.

characters a high mortality. Accordingly, rather than trying to develop a completely new prognostic model, we modified the MELD scoring for developing a more stable and generalizable model.

This is a large cohort studying in terms of prognosis of HBV-ACLF. Using the LRA, we first developed a model from the training cohort (n = 300) to predict the 3-month mortality risk of HBV-ACLF, then validated it in another independent cohort (n = 230). By drawing the ROC curve and calculating the diagnostic values, we validated that the new model (HAM) is feasible and reliable for predicting the short-term mortality of patients with HBV-ACLF. The classification of the training cohort and validation cohort was dependent on the date of admission, which might partly compensate for the retrospective nature of this study. In the new model, besides the MELD score, HAM is composed of 2 clinical parameters and 2 laboratory parameters. During the process of data collection, we detected that HE in ACLF progressed more quickly than in decompensated cirrhosis (data not shown). HE, as a distinctive characteristic of acute liver failure (ALF),[23] can significantly exacerbate the outcome and be speculated do so in ACLF. The finding of age as another independent risk factor was not surprising, as older patients usually had a longer duration of underlying disease, might have poor hepatocyte regeneration ability in response to acute insults and other organs might be more vulnerable to be involved. This finding was consistent with some other studies.[24,25] AFP is generally regarded as a biomarker of hepatocellular carcinoma and embryonal cell cancer, while it also rises transiently in benign acute or chronic liver injury. Some studies have found the highest concentration of cellular AFP in hepatocytes in front of the necroses.[26] In addition, most recovering ALF patients always exhibit maximum plasma AFP that exceeded 100 ng/mL, which is in agreement with our results.[27] Thus it is not difficult to speculate that AFP elevation might be a biomarker of hepatocyte regeneration after injury and a protective factor of outcome. As infection is one of agents responsible for precipitating ACLF, it goes without saying that WBC as a biomarker reflecting infection is a predictive index for prognosis.

After working out the new model, we evaluated its performance by comparing it with most of the familiar prognostic models of ACLF. Other models, like APACHE or SOFA, evaluate the condition of patients depending on organ failure subgroups.[17] Obviously, they do not apply to the ACLF defined according to the AARC. Moreover, getting the PaO_2 of patient is not a routine for patients not managed in intensive care units (ICU), as all these patients were not admitted to ICU. Therefore,

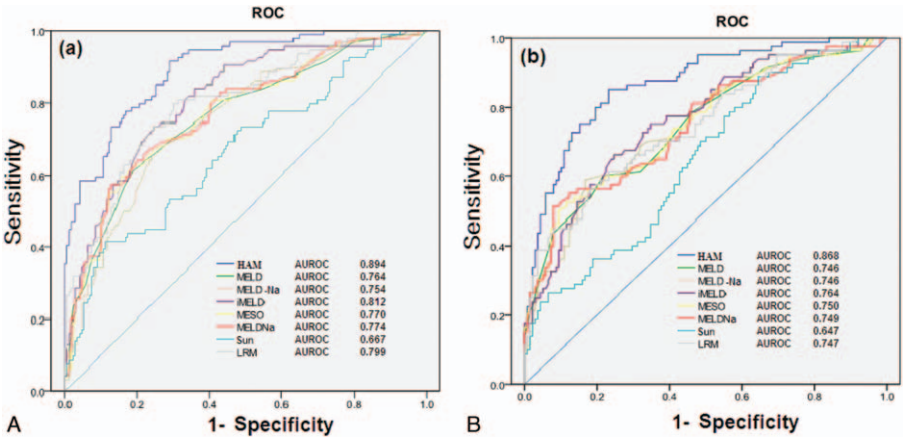

Figure 2. ROC analysis of the predictive accuracy of all the models to predict 3-month mortality of hepatitis B virus associated acute-on-chronic liver failure patients in the training cohort (A) and the validation cohort (B). AUROC = area under ROC, HAM = HBV-ACLF MELD, iMELD = incorporating serum sodium and age MELD model, LRM = logistic regression model (established by Zheng et al), MELD = model for end-stage liver disease, MESO = MELD to serum sodium ratio, Na = serum sodium, ROC = receiver–operator characteristic curve, Sun = model established by Sun et al.

Table 4

Diagnostic values of all the models for predicting 3-month mortality of patients with HBV-ACLF at each cut-off point in the training cohort and validated in the validation cohort.

		Training cohort (n = 300)						Validation cohort (n = 230)					
Models	**Cut-off**	**Sensitivity**	**Specificity**	**PLR**	**NLR**	**PPV**	**NPV**	**Sensitivity**	**Specificity**	**PLR**	**NLR**	**PPV**	**NPV**
HAM	−1.191	0.915	0.709	3.144	0.120	0.759	0.893	0.849	0.750	3.395	0.202	0.772	0.832
MELD	28.50	0.606	0.816	3.289	0.483	0.767	0.674	0.500	0.868	3.789	0.576	0.791	0.635
MELD-Na	30.18	0.649	0.760	2.701	0.462	0.730	0.684	0.500	0.847	3.273	0.590	0.766	0.629
iMELD	45.25	0.734	0.754	2.986	0.353	0.749	0.739	0.547	0.813	2.915	0.558	0.745	0.642
MESO	21.61	0.596	0.844	3.809	0.479	0.792	0.676	0.477	0.917	5.721	0.571	0.851	0.637
MELDNa	31.10	0.574	0.872	4.471	0.488	0.817	0.672	0.419	0.917	5.023	0.634	0.834	0.612
Sun	−2.554	0.723	0.525	1.523	0.527	0.604	0.655	0.686	0.521	1.432	0.603	0.589	0.624
LRM	−1.595	0.798	0.698	2.645	0.289	0.726	0.776	0.640	0.694	2.093	0.519	0.677	0.658

HAM = HBV-ACLF MELD, iMELD = incorporating serum sodium and age MELD model, LRM = logistic regression model (established by Zheng et al), MELD = model for end-stage liver disease, MESO = MELD to serum sodium ratio, Na = serum sodium, NLR = negative likelihood ratio, NPV = negative predictive value, PLR = positive likelihood ratio, PPV = positive predictive value, Sun = model established by Sun et al.

these models have not been compared with. By comparing with the AUROCs of other 7 scoring systems, HAM achieved the highest AUROC of 0.894, which indicates HAM has a good applicability for HBV-ACLF. In light of that the best cut-off point need achieve both the best sensitivity and specificity, HAM acquired the best cut-off point of −1.191. At this point, HAM has the sensitivity of 0.915 and specificity of 0.709. Compared with the diagnostic values of other models, HAM has the higher sensitivity and NPV, which shows that the predictive accuracy of HAM was significantly superior to the previous models. Finally, all these results were tested in the validation cohort and got the consistent conclusions.

Several studies have revealed that NAs can improve the survival of HBV-ACLF by reducing the serum HBV-DNA level, which can result in the suppression of hepatocellular necrosis and cytokine release. It must be emphasized that since all patients of this study received NAs at the beginning, like lamivudine, adefovir, entecavir, or telbivudine, which might be the reason why HBV-DNA level was not significantly associated with the 3-month mortality. It is well known that ACLF is a complex clinical syndrome, which can be accompanied by various complications and involve multiple organs. According to the above data, HAM scoring is the model that takes all these factors into consideration, so as to evaluate prognosis comprehensively.

There were some limitations in this study. First, the number of patients with gastrointestinal hemorrhage both in the training cohort and validation cohort are very small (4 and 5, respectively), making the result insignificant. Second, the diagnosis of cirrhosis was largely dependent on clinical judgment, especially on imaging tests, while pathological diagnosis was rare. The incidence of cirrhosis therefore might have been underestimated. WBC count as one of reliable indexes for infection can reflect the severity of bacterial infection, but peripheral leucocytes in patients with cirrhosis complicated by infection may not increase as high as in whom not with. The influence of cirrhosis on the outcome might be offset or weakened by this reason. In the end, it is still a retrospective study, we are planning to further perform this new model in prospective studies in the future.

In summary, we developed and validated a new prognostic model which is of better value in predicting the 3-month outcome of HBV-ACLF. Accordingly, it may be helpful to allow optimal therapeutic measures to be rapidly undertaken.

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