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Prediction model of the progression of patients with acute deterioration of hepatitis B virus-related chronic liver disease to acute-on-chronic liver failure

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Abstract

This study aimed to establish a new model for predicting acute-on-chronic liver failure (ACLF) (defined by the Chinese Medical Association), which potentially occurs among patients with acute deterioration (AD) of hepatitis B virus (HBV)-related chronic liver disease (CLD).

A total of 754 patients with AD of HBV-related CLD (total bilirubin (TBIL) $>$ 51.3 μmol/L and prothrombin activity (PTA) $<$ 60%, 40% $<$ PTA $<$ 60% when TBIL $\geq$ 171.1 μmol/L) were retrospectively analyzed and divided into a training cohort (580 patients) and a validation cohort (174 patients). The ACLF occurrence probability of these patients was statistically analyzed within 4 weeks. In the training cohort, multivariate logistic regression analysis was performed to determine the independent predictors of ACLF occurrence and to develop a new prediction model. The validation cohort was utilized to verify and evaluate the value of the new prediction model.

Within 4 weeks, 9.9% of the patients progressed to ACLF (12.0 ± 6.7 days). The new prediction model was characterized by $R = 3.090 + 0.035 \times$ Age (years) $- 0.050 \times$ PTA (%) $+ 0.005 \times$ TBIL (μmol/L) $+ 0.044 \times$ D/T (%) $- 0.072 \times$ Na (mmol/L) $+ 0.180 \times$ HBV DNA ($\log_{10}$IU/mL). The areas under the receiver operating characteristic curves of the training and validation cohorts in the new model were higher than those in the model for end-stage liver disease.

The new prediction model could be used by clinicians to recognize patients with AD of HBV-related CLD with high risks of progressing to ACLF.

Abbreviations: ACLF = acute-on-chronic liver failure, AD = acute deterioration, AFP = alpha fetoprotein, ALP = alkaline phosphatase, ALT = alanine aminotransferase, Ammo = ammonia, APASL = Asian Pacific Association for the Study of the Liver, APTT = activated partial thromboplastin time, AUC = area under the ROC curve, CHB = chronic hepatitis B, CHE = cholinesterase, CLD = chronic liver disease, CMA = Chinese Medical Association, Cre = cretinine, DBIL = direct bilirubin, DILI = drug-induced liver injury, D/T = direct bilirubin/total bilirubin, EASL-CLIF = European Association for the Study of the Liver-chronic liver failure, GGT = gamma-glutamyl transpeptidase, HBV = hepatitis B virus, HGB = hemoglobin, INR = international normalized ratio, LRA = logistic regression analysis, MELD = model for end-stage liver disease, Na = sodium, NACSELD = North American Consortium for the Study of End-stage Liver Diseases, NASH = nonalcoholic steatohepatitis, NPV = negative predictive value, PTA = prothrombin activity, PLT = platelets, PPV = positive predictive value, PT = prothrombin time, ROC = receiver operating characteristic, SAE = severe acute exacerbation, TBA = total bile acid, TBIL = total bilirubin, TC = total cholesterol, TG = triglyceride, ULN = upper limit of normal, WBC = white blood count, WGO = World Gastroenterology Organization.

Keywords: acute deterioration, acute-on-chronic liver failure, hepatitis B virus, prediction model

1. Introduction

Hepatitis B virus (HBV) infection is a global human health problem, and 350 million individuals are exposed to chronic HBV infection.[1] HBV can cause multiple diseases, such as chronic hepatitis, cirrhosis, hepatic carcinoma, and hepatic failure. In particular, acute-on-chronic liver failure (ACLF) is a unique type of severe disease. ACLF is defined in numerous research organizations, including the Asian Pacific Association for the Study of the Liver (APASL),[2] the European Association for the Study of the Liver–Chronic Liver Failure (EASL-CLIF),[3] the World Gastroenterology Organization (WGO),[4] the North American Consortium for the Study of End-Stage Liver Diseases (NACSELD),[5] and the Chinese Medical Association (CMA).[6] Although these definitions have some differences, in the simplest terms, ACLF is the abrupt hepatic decompensation in patients with chronic liver disease (CLD). According to diagnostic and treatment guidelines for liver failure proposed by the CMA in 2012, this disease is a serious acute liver function decompensation that occurs on the basis of HBV-related CLD, leading to bilirubin elevation and coagulation disorder (Total bilirubin [TBIL] ≥ 10 mg/dL (171 μmol/L) or a daily elevation ≥ 1 mg/dL

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(17.1 μmol/L), prothrombin activity (PTA) ≤ 40% (or international normalized ratio [INR] ≥ 1.50),[6] usually accompanied by infections, hepatic encephalopathy, hepatorenal syndrome, and upper gastrointestinal hemorrhage.[2,6,7] Characterized by rapid progression, difficult treatment, and high death rate, ACLF is the main cause of deaths in China due to liver diseases.[6] Liver transplantation can effectively treat late-stage ACLF,[8] but this strategy was limited to various problems, such as shortage of liver donors and high expenses of liver transplantation. If effective recognition and early warning are provided for patients with HBV-related CLD, which easily progresses to ACLF, individual and specific treatment can be administered before this condition occurs. The prognosis of patients with HBV-related ACLF should be improved and consequently contribute to the reasonable distribution of liver transplantation resources.

ACLF occurs on the basis of acute deterioration (AD) of preexisting CLD.[2,9] Definitions of severe acute exacerbation (SAE)–chronic hepatitis B (CHB), prophase liver failure, and AD of CLD have been proposed following the prewarning signs of HBV-related ACLF. SAE-CHB is defined as follows: intermittent elevation of aminotransferase activity to more than 10-fold of the upper limit of normal (ULN) value or more than twice the baseline value; and TBIL ≥ 3.0 mg/dL; PTA < 70%.[10] Prophase liver failure was described by diagnostic and treatment guidelines for liver failure proposed by the CMA in 2012 as follows: AD in CLD; extreme fatigue, anorexia, emesis, and abdominal distension; 51.3 μmol/L ≤ TBIL ≤ 171.1 μmol/L and daily elevation of TBIL ≥ 17.1 μmol/L; and bleeding tendency, 40% < PTA ≤ 50% or 1.5 < INR ≤ 1.6.[6] Zhang et al[11] observed that prophase liver failure shows the following characteristics: AD in CLD; extreme fatigue and evident symptoms in the digestive tract; rapid occurrence of jaundice, daily elevation of TBIL ≥ 34.2 μmol/L or TBIL ≥ 171.1 μmol/L; alanine aminotransferase (ALT) ≥ 10 ULN; and 40% < PTA < 60%.[11] Xia et al[12] characterized prophase liver failure as follows: AD in CLD; extreme fatigue accompanied by appetite loss, abdominal distension, nausea, and emesis; 85.5 μmol/L ≤ TBIL ≤ 171.1 μmol/L or daily elevation of TBIL ≥ 17.1 μmol/L; and 40% ≤ PTA ≤ 60%, or 1.28 ≤ INR ≤ 1.50. Another definition of prophase liver failure indicated that AD of CLD yields the following parameters: AD in CLD; serum TBIL ≥ 51 μmol/L; and 40% ≤ PTA ≤ 70%.[13]

The diagnostic criteria for prophase liver failure and AD-related CLD may have some problems. These criteria require different levels of TBIL and PTA possibly because patients with liver cirrhosis are not included in some research. Some studies fail to include patients with pure HBV-related CLD, and others use partially small sample sizes. Studies have yet to determine whether ALT should be included in the diagnostic criteria, which may be related to several influencing factors of ALT and its inference on the determination of disease severity. Some patients with high-HBV DNA load suffer from HBV reactivation, resulting in AD of HBV-related CLD and HBV-related ACLF, and patients with model for end-stage liver disease (MELD) > 30 scores are characterized by poor prognosis.[14] HBV DNA load is also an independent predictor of prognosis for patients with HBV-related ACLF.[15] Hence, the levels of HBV DNA load may be necessary to identify whether patients with AD of HBV-related CLD progress to ACLF.

AD possibly occurs in patients with HBV-related CLD, and some high-risk patients may suffer from ACLF. AD of HBV-related CLD is defined in our study as follows: having HBV-related CLD foundation for CHB and HBV-related cirrhosis; stable preexistent state but rapid AD manifestations, such as fatigue, anorexia, and jaundice, within 4 weeks; laboratory examination with bilirubin elevation and coagulation disorder; TBIL > 3 mg/dL (51.3 μmol/L) and PTA < 60%, and 40% < PTA < 60% when TBIL ≥ 10 mg/dL (171.1 μmol/L).

This retrospective study aimed to define the independent predictors of patients with AD of HBV-related CLD that progressed to ACLF within 4 weeks. A prediction model was also established to accurately evaluate possible progression to ACLF.

2. Methods

2.1. Patient enrollment and study design

Patients with AD of HBV-related CLD hospitalized in Beijing 302 Military Hospital of China from October 1, 2014 to October 31, 2016 were selected for retrospective analysis.

The grouping criteria were as follows: having HBV-related CLD foundation for CHB and HBV-related cirrhosis; preexistent state of illness is stable but with AD manifestations within 4 weeks; laboratory examination prompts bilirubin elevation and coagulation disorder; TBIL > 51.3 μmol/L and PTA < 60%, and 40% < PTA < 60% when TBIL ≥ 171.1 μmol/L; having complete medical history and length of stay ≥ 28 days; and drugs influencing serum sodium (Na), such as diuretics and tolvaptan, were not used 3 days before hospitalization.

The exclusion criteria were as follows: other concurrent virus infections, such as Hepatitis A virus, Hepatitis C virus, Hepatitis D virus, Hepatitis E virus, Human immunodeficiency Virus, Epstein-Barr virus, cytomegalovirus, and Parvovirus B19; concurrent hepatic lesions because of other factors, such as autoimmune liver disease, alcoholic hepatitis, drug-induced liver injury (DILI), and nonalcoholic steatohepatitis (NASH); concurrent diseases resulting in bilirubin elevation, such as hemolytic jaundice, nonhemolytic jaundice, and obstructive jaundice; metabolic liver diseases, including Wilson disease and hemochormatosis; malignant tumor; extrahepatic diseases seriously influencing life; usage of chemotherapeutics, immunosuppressors, and corticosteroids within 1 year; patients with length of stay < 3 days or with incomplete laboratory results.

A total of 885 patients satisfied the grouping criteria. Of these patients, 131 were excluded; 31 were detected with other virus infections; 28 were suffering from alcoholic hepatitis; 24 were found with DILI; 12 were manifesting NASH; 5 were exhibiting hemolytic jaundice, nonhemolytic jaundice, and obstructive jaundice; 2 were displaying Wilson disease; 13 were diagnosed with malignant tumors; 5 were suffering from serious extrahepatic diseases; 5 were applying chemotherapeutics, immunosuppressors, and corticosteroids within 1 year; 1 was pregnant; and 17 were described with incomplete medical histories. Finally, 754 patients were selected in this research. Of the selected patients, 580 were hospitalized from October 1, 2014 to March 31, 2016 and were classified into the training cohort, and a prediction model was established on the basis of these patients. Furthermore, 174 patients were hospitalized from April 1, 2016 to October 31, 2016, and they were classified into the validation cohort. The obtained prediction model was validated on the basis of these patients (Fig. 1).

2.2. Candidate predictor variables

We retrospectively collected data, which included gender, age, having liver cirrhosis foundation or not, probability and time of ACLF progression, and clinical and laboratory variables, such as ALT, aspartate amino transférase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), TBIL, direct bilirubin/TBIL (D/T), total bile acid (TBA), prothrombin time

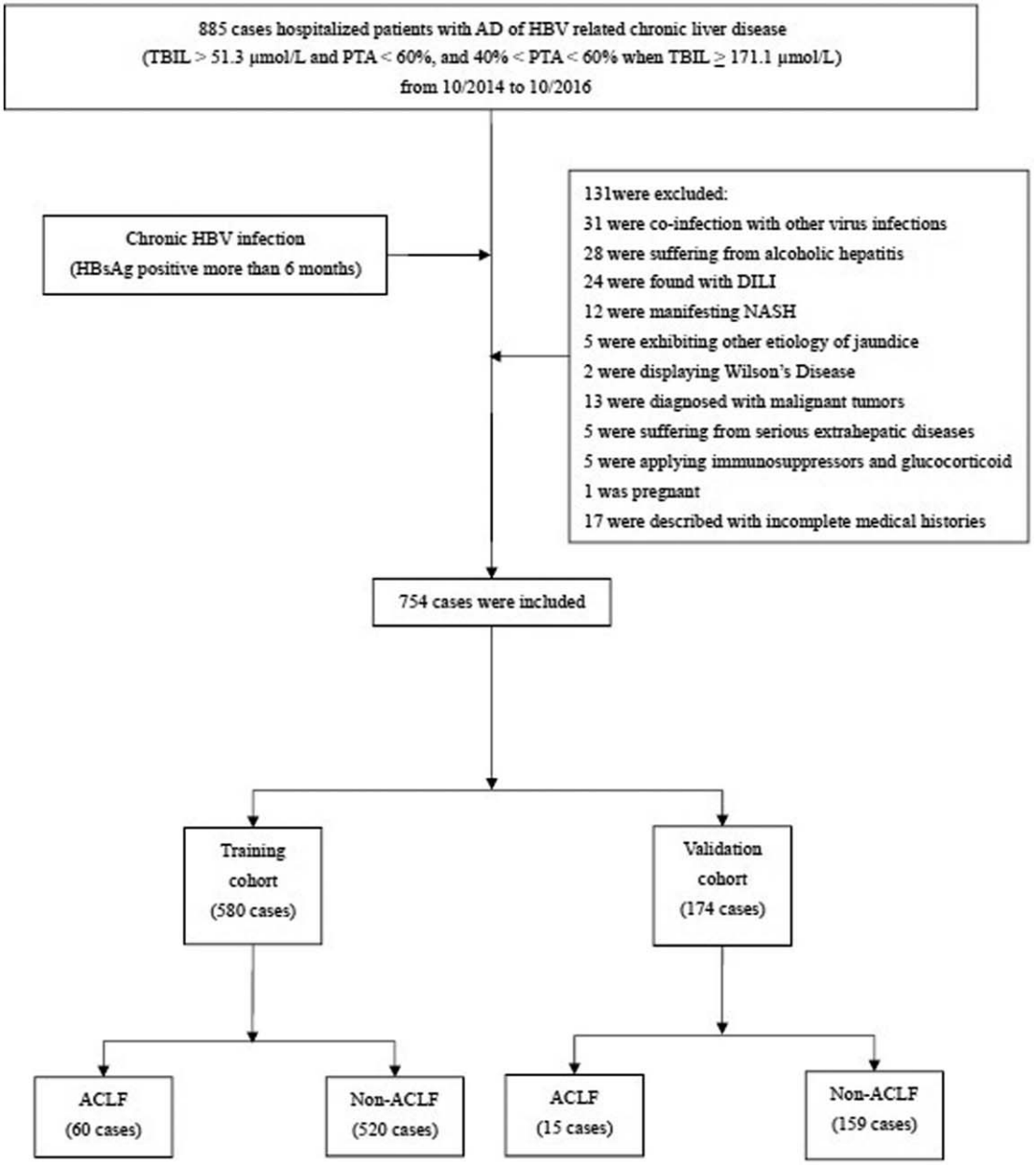

Figure 1. Outline of the screening and case selection protocol. ACLF = acute-on-chronic liver failure, AD = acute deterioration, DILI = drug-induced liver injury, HBV = hepatitis B virus, NASH = nonalcoholic steatohepatitis, PTA = prothrombin activity, TBIL = total bilirubin.

(PT), INR, PTA, activated partial thromboplastin time (APTT), total cholesterol (TC), triglyceride (TG), cholinesterase (CHE), créatinine (Cre), Na, ammonia (Ammo), alpha fetoprotein (AFP), HBV DNA ($\log_{10}$IU/mL), white blood count (WBC), hemoglobin (HGB), platelets (PLT), hepatitis B surface antigen, liver radiologic data, and endoscopy data.

2.3. Definitions

ACLF is defined by the CMA as a clinical syndrome of acute or subacute liver function decompensation based on CLD within a short term manifested as follows: extreme fatigue with evident symptoms in the digestive tract; rapid progression of jaundice, TBIL is greater than ULN value by 10 times or daily elevation ≥ 17.1 μmol/L; bleeding tendency, PTA ≤ 40% (or INR ≥ 1.5) (other causes are excluded); decompensated ascites; and with or without concurrent hepatic encephalopathy.[6]

Diagnosis criteria for cirrhosis are determined according to hepatic pathology, clinical symptoms and signs, laboratory indexes, liver radiologic data, and endoscopy data.

The severity of liver disease was assessed using the MELD score. The MELD score formula was $3.78 \times \ln[\text{TBil (mg/dL)}] + 11.2 \times \ln[\text{INR}] + 9.57 \times \ln[\text{Cr (mg/dL)}] + 6.43 \times$ (constant for liver disease etiology = 0 if cholestatic or alcoholic, otherwise = 1).[16]

2.4. Ethics statement

The protocol was conformed to the provisions of the Declaration of Helsinki (as revised in Seoul, Korea, October 2008) and was

approved by the Human Ethical Committee of Beijing 302 Military Hospital of China. Due to the retrospective nature of the study, written informed consent could not be obtained from all patients.

2.5. Statistical analysis

Categorical variables were expressed as number (%), and continuous variables were described as mean ± SD or median (interquartile range, Q1–Q3). Continuous variables were compared through Student *t* test. Mann–Whitney *U* test was used to compare the parameters under non-normal distribution. Categorical data were compared by the χ^2 test or Fisher exact test, if appropriate. For the training cohort, univariate logistic regression analysis (LRA) was first used to screen candidate factors. Candidate variables ($P < .05$) entered into a multivariate LRA following a forward stepwise approach. Based on the results from the multivariate LRA, a new model was developed. ROC curves were performed to compare the efficacy of MELD score and new prediction model through MedCalc 12.7.7 software. The areas under the ROC curves (AUCs) from the 2 models were compared by using DeLong method. All statistical analyses were implemented through SPSS 19.0 software (IBM, Armonk, NY). For all analyses, $P < .05$ was considered to be statistically significant.

3. Results

3.1. Patient characteristics of training and validation cohorts

Among the 754 grouped patients, 598 were males and 156 were females. Furthermore, the average age was 49.8 ± 11.3 years old. A total of 670 (88.9%) patients had pre-existing liver cirrhosis, and the baseline MELD score was 16.9. Within 4 weeks, 75 (9.9%) patients progressed to ACLF, and the time duration for ACLF progression was 12.0 ± 6.7 days. The training cohort had 580 patients, with 458 males and 122 females, and their average age was 50.1 ± 11.4 years old. Of these patients, 508 (87.6%) initially suffered from liver cirrhosis, with a baseline MELD score of 16.8. Within 4 weeks, 60 (10.3%) patients progressed to ACLF, and the duration for ACLF progression was 12.5 ± 6.6 days. The validation cohort consisted of 174 patients, with 140 males and 34 females, and their average age was 50.6 ± 10.8 years old. In this group, 162 (93.1%) patients were initially diagnosed with liver cirrhosis, and the baseline MELD score was 17.2. Within 4 weeks, 15 (8.6%) patients progressed to ACLF, and the time duration to progress to ACLF was 9.9 ± 6.9 days. The proportion of patients with liver cirrhosis and ALP was higher in the validation cohort than in the training cohort ($P < .05$). Moreover, ALT in the validation cohort was lower than that in the training cohort ($P < .05$), and no significant difference was found between the 2 cohorts in other factors ($P > .05$) (Table 1).

Table 1

Baseline characteristics of the total cohort, the training cohort, and the validation cohort.

Characteristics	Total cohort (n = 754)	Training cohort (n = 580)	Validation cohort (n = 174)	*t*	Z	χ^2	*P**
Male, n, %	598 (79.3)	458 (79.0)	140 (80.5)			0.182	.670
Age, y	49.8 ± 11.3	50.1 ± 11.4	50.6 ± 10.8	−0.541			.589
Cirrhosis, %	670 (88.9)	508 (87.6)	162 (93.1)			4.116	.042
ACLF, %	75 (9.9)	60 (10.3)	15 (8.6)			0.444	.505
Time for progressing to ACLF, d	12.0 ± 6.7	12.5 ± 6.6	9.9 ± 6.9	1.382			.171
ALT, IU/L	62.5 (32.0, 204.5)	65.0 (34.0, 224.8)	54.5 (25.0, 155.5)		−2.408		.016
AST, IU/L	98.5 (56.0, 224.0)	100.0 (57.0, 220.8)	92.0 (46.8, 235.3)		−1.437		.151
ALP, IU/L	151.0 (115.0, 198.0)	147.5 (114.0, 194.8)	163.5 (116.8, 211.2)		−2.242		.025
GGT, IU/L	61.0 (30.0, 117.0)	61.5 (32.0, 117.0)	57.5 (23.0, 115.8)		−1.719		.086
TBIL, μmol/L	102.7 (67.8, 167.7)	99.0 (66.2, 165.9)	109.5 (70.2, 193.2)		−1.396		.163
D/T, %	70.0 (56.0, 76.0)	70.0 (56.0, 76.0)	69.0 (55.0, 75.0)		−1.250		.211
TBA, umol/L	94.5 (43.8, 168.0)	99.0 (43.3, 165.8)	89.5 (44.5, 179.5)		−0.483		.629
PT, s	16.8 (15.6, 18.9)	16.8 (15.6, 19.1)	16.9 (15.7, 18.4)		−0.442		.658
INR	1.5 (1.4, 1.6)	1.5 (1.3, 1.6)	1.5 (1.4, 1.6)		−0.473		.636
PTA, %	47.0 ± 8.9	46.7 ± 9.1	47.7 ± 8.2	−1.272			.204
APTT, s	43.2 ± 10.4	43.2 ± 10.5	43.1 ± 10.0	0.106			.916
TC, mmol/L	2.3 ± 1.1	2.3 ± 1.1	2.3 ± 1.2	0.082			.935
TG, mmol/L	0.9 (0.6, 1.4)	0.9 (0.6, 1.4)	0.9 (0.6, 1.4)		−0.492		.623
CHE, IU/L	2436.9 ± 1252.7	2456.1 ± 1270.7	2372.8 ± 1192.2	0.769			.442
Cre, umol/L	78.0 (67.0, 92.0)	78.0 (67.0, 91.0)	77.5 (67.0, 94.0)		−0.006		.996
Na, mmol/L	135.8 ± 4.7	135.8 ± 4.8	135.8 ± 4.5	0.106			.916
Ammo, umol/L	51.2 (34.4, 71.3)	51.6 (34.8, 71.9)	49.3 (33.9, 67.0)		−1.135		.256
AFP, ug/mL	26.7 (5.2, 162.4)	31.7 (5.7, 177.8)	20.0 (3.8, 127.1)		−1.956		.050
HBV DNA, log10	3.4 ± 2.4	3.5 ± 2.4	3.2 ± 2.3	1.859			.063
WBC, $\times 10^9$/L	4.9 (3.3, 7.3)	5.0 (3.4, 7.3)	4.6 (3.0, 6.8)		−1.240		.215
HGB, g/L	117.1 ± 24.9	117.9 ± 24.6	114.5 ± 25.7	1.587			.113
PLT, 10^9/L	67.0 (44.0, 109.3)	67.5 (43.0, 111.0)	65.0 (45.0, 106.5)		−0.249		.803
MELD score	16.9 (13.8, 20.3)	16.8 (13.7, 20.2)	17.2 (13.9, 20.4)		−0.461		.645

Categorical variables expressed as number (%), non-normal continuous variables as median (Q1, Q3) and normal continuous variables as mean ± SD.

ACLF = acute-on-chronic liver failure, AFP = alpha fetal protein, ALP = alkaline phosphatase, ALT = alanine aminotransferase, Ammo = ammonia, APTT = activated partial thromboplastin time, AST = aspartate amino transferase, CHE = cholinesterase, Cre = cretinine, D/T = direct bilirubin/total bilirubin, GGT = gamma-glutamyl transpeptidase, HGB = hemoglobin, INR = international normalized ratio, MELD = Model for End-Stage Liver Disease, Na = sodium, PLT = platelets, PT = prothrombin time, PTA = prothrombin activity, TBA = total bile acid, TBIL = total bilirubin, TC = total cholesterol, TG = triglyceride, WBC = white blood count.

* *P* value of comparisons between the training cohort and the validation cohort patients.

Table 2

Baseline characteristics of ACLF group and non-ACLF group in the training cohort.

Characteristics	ACLF group (n = 60)	Non-ACLF group (n = 520)	*t*	Z	χ^2	*P**
Male, %	49 (81.7)	409 (78.7)			0.294	.588
Age, y	54.4 ± 11.0	49.6 ± 11.3	3.107			.002
Cirrhosis, %	56 (93.3)	452 (86.9)			2.033	.154
ALT, IU/L	94.0 (53.3, 220.8)	61.0 (33.0, 229.3)		−2.133		.033
AST, IU/L	170.0 (93.0, 333.0)	91.0 (56.0, 210.3)		−4.022		<.001
ALP, IU/L	185.0 (137.5, 232.5)	144.5 (112.0, 187.5)		−4.204		<.001
GGT, IU/L	94.0 (53.3, 145.0)	59.5 (30.0, 114.8)		−3.262		.001
TBIL, μmol/L	170.5 (110.3, 346.6)	88.5 (64.0, 153.1)		−6.220		<.001
D/T, %	75.0 (70.0, 79.0)	69.0 (55.0, 76.0)		−4.736		<.001
TBA, umol/L	114.0 (67.3, 162.0)	91.0 (40.0, 168.0)		−1.393		.164
PT, s	18.4 (16.7, 20.2)	16.7 (15.5, 19.0)		−3.879		<.001
INR	1.6 (1.5, 1.7)	1.4 (1.3, 1.6)		−3.740		<.001
PTA, %	43.8 ± 7.4	47.1 ± 9.2	2.640			.009
APTT, s	45.1 ± 11.9	43.0 ± 10.3	1.474			.141
TC, mmol/L	2.0 ± 1.1	2.4 ± 1.1	−2.507			.012
TG, mmol/L	1.2 (0.7, 1.6)	0.9 (0.6, 1.4)		−1.899		.058
CHE, IU/L	2396.1 ± 1288.1	2463.0 ± 1269.7	0.386			.699
Cre, umol/L	80.5 (71.0, 129.5)	78.0 (67.0, 90.0)		−2.036		.042
Na, mmol/L	133.2 ± 5.5	136.1 ± 4.6	−4.615			<.001
Ammo, umol/L	55.1 (42.5, 81.7)	51.1 (34.1, 71.5)		−2.150		.032
AFP, ug/ml	66.8 (10.7, 393.4)	26.3 (5.6, 164.0)		−2.485		.013
HBVDNA, $\log_{10}$	4.4 ± 2.6	3.4 ± 2.3	3.007			.003
WBC, $\times 10^9$/L	7.4 (4.2, 10.7)	4.8 (3.3, 7.1)		−4.263		<.001
HGB, g/L	118.3 ± 26.5	117.9 ± 24.4	0.122			.903
PLT, $\times 10^9$/L	77.0 (51.0, 109.3)	67.0 (43.0, 111.0)		−0.414		.679
MELD score	20.9 (17.0, 25.5)	16.5 (13.6, 19.5)		−5.909		<.001

Categorical variables expressed as number (%), non-normal continuous variables as median (Q1, Q3) and normal continuous variables as mean ± SD. Comparisons between ACLF group and Non-ACLF group in the training cohort patients were performed by Student *t* test, Mann–Whitney *U* test, or χ^2 test.

AFP = alpha fetal protein, AKI = acute kidney injury, ALP = alkaline phosphatase, ALT = alanine aminotransferase, Ammo = ammonia, APTT = activated partial thromboplastin time, AST = aspartate amino transferase, CHE = cholinesterase, Cre = cretinine, D/T = direct bilirubin/total bilirubin, GGT = gamma-glutamyl transpeptidase, HE = hepatic encephalopathy, HGB = hemoglobin, INR = international normalized ratio, MELD = model for end-stage liver disease, Na = sodium, PLT = platelets, PT = prothrombin time, PTA = prothrombin activity, TBA = total bile acid, TBIL = total bilirubin, TC = total cholesterol, TG = triglyceride, UGIB = upper gastrointestinal bleeding, WBC = white blood count.

* *P* value of comparisons between ACLF group and non-ACLF group in the training cohort patients.

3.2. Patient characteristics of ACLF group and Non-ACLF group in the training cohort

The baseline indexes, including the age, ALT, AST, ALP, GGT, TBIL, D/T, PT, INR, Cre, Ammo, AFP, HBV DNA ($\log_{10}$IU/mL), WBC, and MELD, of the ACLF group in the training cohort were significantly higher than those of the non-ACLF group ($P < .05$). However, the PTA, TC, and Na in the ACLF group were significantly lower than those in the non-ACLF group ($P < .05$) (Table 2).

3.3. Logistic regression analysis of the training cohort

Univariate LRA was conducted on the baseline indexes of the training cohort. Categorical variables were differentiated and assigned with values according to whether they were positive or negative, and continuous variables were assigned with values according to actual numerical values. Age, GGT, PTA, TBIL, TC, D/T, Cre, Na, WBC, and HBV DNA ($\log_{10}$IU/mL) were screened out as meaningful variables and entered for multivariate LRA ($P < .05$).

Multivariate LRA showed that age, PTA, TBIL, D/T, Na, and HBV DNA ($\log_{10}$IU/mL) were independent influencing factors of ACLF occurrence in patients with AD of HBV-related CLD ($P < .05$) (Table 3). On the basis of the multivariate LRA results, a prediction model of ACLF occurrence in patients with AD of HBV-related CLD was established as $R = 3.090 + 0.035 \times \text{age (years)} - 0.050 \times \text{PTA (\%)} + 0.005 \times \text{TBIL (μmol/L)} + 0.044 \times \text{D/T (\%)} - 0.072 \times \text{Na (mmol/L)} + 0.180 \times \text{HBV DNA } (\log_{10}\text{IU/mL})$. Equation values of all patients with AD of HBV-related CLD were obtained from the prediction model. The ROC curve method was used to evaluate the obtained prediction model, as shown in the figure. In this model, the AUC value was 0.820 (95% CI: 0.787–0.851), the cut-off value was −2.12, sensitivity was 79.8%, specificity was 71.7%, positive predictive value (PPV) was 28.9%, and negative predictive value (NPV) was 96.1%. In addition, DeLong test showed that the score of this model (AUCs = 0.820) was superior to MELD score (AUCs = 0.733) in predicting ACLF occurrence in patients ($Z = 3.133$, $P = .002$) (Fig. 2). A total of 149 patients (high score group) had model scores greater than −2.12 and ACLF occurrence rate of 28.9%, and 431 patients (low scores group) yielded model scores ≤ −2.12 and ACLF occurrence rate of 3.9%. These 2 groups of patients significantly differed ($\chi^2 = 74.105$, $P < .001$).

3.4. Verify the new model of the validation cohort

According to the prediction model, the equation values of all patients with AD of HBV-related CLD in the validation cohort were obtained, and the ROC curve method was used to evaluate the obtained prediction model. As shown in the figure, the AUC

Table 3

Multivariate logistic regression analysis of independent predictors associated with progression into ACLF in the training cohort.

Variables	b	SE	Wald χ^2	*P* value	Odds ratio	95% CI	
						Lower	Upper
Age	0.035	0.014	6.680	.010	1.036	1.009	1.064
GGT	0.001	0.001	0.554	.457	1.001	0.999	1.003
PTA	−0.050	0.017	9.026	.003	0.951	0.920	0.983
TBIL	0.005	0.001	15.460	.000	1.005	1.002	1.007
D/T	0.044	0.017	6.601	.010	1.045	1.010	1.080
TC	−0.011	0.150	0.006	.940	0.989	0.737	1.327
Cre	−0.001	0.002	0.366	.545	0.999	0.995	1.003
Na	−0.072	0.031	5.395	.020	0.930	0.875	0.989
HBV DNA (log10)	0.180	0.066	7.544	.006	1.198	1.053	1.362
WBC	0.058	0.033	3.155	.076	1.060	0.994	1.130
Constant	3.090	4.398	0.494	.482	21.982		

Cre = cretinine, D/T = direct bilirubin/total bilirubin, GGT = gamma-glutamyl transpeptidase, HBV = hepatitis B virus, Na = sodium, PTA = prothrombin activity, TBIL = total bilirubin, TC = total cholesterol, WBC = white blood count.

value was 0.852 (95% CI: 0.790–0.901). In the new model, with the cut-off value of −2.12, sensitivity was 73.3%, specificity was 79.2%, PPV was 25.0%, and NPV was 96.9%. In addition, DeLong test showed that the model's AUCs were superior to MELD score (AUCs = 0.767) in the ability of predicting ACLF occurrence in patients ($Z = 2.042$, $P = .041$) (Fig. 3). A total of 44 patients (high score group) showed model scores > -2.12 and ACLF occurrence rate of 25.0%, and 130 patients (low scores group) revealed model scores ≤ -2.12 and ACLF occurrence rate of 3.1%. These 2 groups of patients significantly differed ($\chi^2 = 20.057$, $P < .001$).

4. Discussion

The definitions of ACLF from EASL-CLIF[3] and NACSELD[5] were based on patients with decompensated liver cirrhosis; the definitions of ACLF from APASL[2] were based on patients with hepatitis and compensated liver cirrhosis; and the definitions of ACLF from WGO[4] and CMA[6] were based on patients with hepatitis, compensated liver cirrhosis, and decompensated liver cirrhosis. This research found that 88.9% and 93.3% of patients with AD of HBV-related CLD and with ACLF had pre-existing liver cirrhosis, respectively. In comparison with the relevant pre-existent studies on patients with SAE-CHB,[17,18] the proportion of patients with liver cirrhosis in this research was evidently high, similar to the result obtained by Zhang et al.[13] Thus, patients with HBV-related ACLF in China not only provided a CHB basis but also initially suffered from liver cirrhosis. Therefore, patients with liver cirrhosis should also be included in the concept of prophase HBV-related ACLF. Moreover, those definitions from west countries could be applied in Chinese patients with ACLF, which may help doctors to judge the progression and prognosis of patients with ACLF.

We found that the ACLF and non-ACLF groups considerably differed in the main baseline indexes, such as MELD score, ALT, AST, TBIL, D/T, Cre, HBV DNA ($\log_{10}$IU/ml), INR, PTA, and serum Na. Thus, patients with AD of HBV-related CLD with serious baseline state of illness and higher levels of HBV DNA would progress to ACLF more easily. Through multivariate LRA study, age, PTA, TBIL, D/T, Na, and HBV DNA ($\log_{10}$IU/ml) were found to be independent predictors of ACLF occurrence in patients with AD of HBV-related CLD.

TBIL and PTA were necessary conditions measuring the severity of ACLF. ACLF was divided into 3 clinical stages—early stage, intermediate stage, and late stage—by diagnostic and treatment guidelines for liver failure proposed by the CMA in accordance with TBIL and PTA levels.[6] Twelve-week mortalities of patients with ACLF in early stage, intermediate stage, and late stage were 33.9%, 49.5%, and 77.2%, respectively. Furthermore, 24-week mortalities were 37.1%, 53.8%, and 78.5%, respectively. Patients with ACLF in the different stages were significantly different in prognosis, as decided by TBIL and PTA levels.[12] Biggins et al[19] found that serum Na < 126 mmol/L is an independent predictor of mortality in patients with cirrhosis who were listed for liver transplantation. Hyponatremia is an independent predictive factor of survival in patients with ACLF in

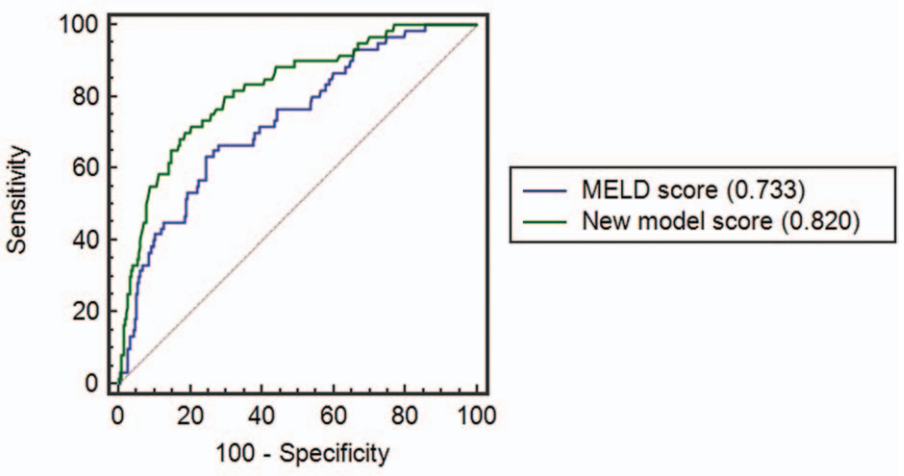

Figure 2. The ROC curve of the new model score and MELD score to predict AD of HBV related CLD patients to become ACLF in the training cohort. The new model (AUCs = 0.820) was superior to MELD score (AUCs = 0.733) in predicting ACLF occurrence from patients. ACLF = acute-on-chronic liver failure, AD = acute deterioration, AUCs = areas under the ROC curves, CLD = chronic liver disease, HBV = hepatitis B virus, MELD = model for end-stage liver disease, ROC = receiver operating characteristic.

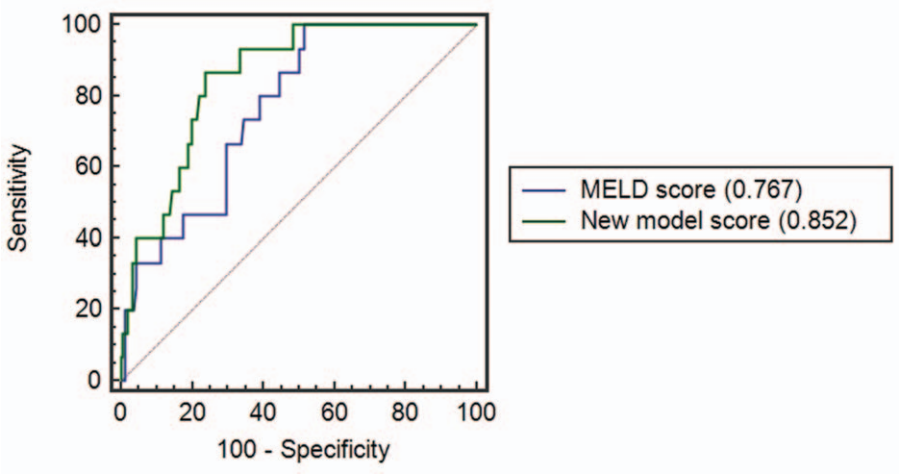

Figure 3. The ROC curve of the new model score and MELD score to predict AD of HBV related CLD patients to become ACLF in the validation cohort. The new model (AUCs = 0.852) was superior to MELD score (AUCs = 0.767) in predicting ACLF occurrence from patients. ACLF = acute-on-chronic liver failure, AD = acute deterioration, AUCs = areas under the ROC curves, CLD = chronic liver disease, HBV = hepatitis B virus, MELD = model for end-stage liver disease, ROC = receiver operating characteristic.

Europe; patients with hyponatremia and ACLF had a 3-month transplant-free survival of only 35.8% compared with 58.7% in those with ACLF without hyponatremia.[20] The influence of diuretics was excluded in our research, confirming that serum Na was one of the independent predictive factors of ACLF occurrence in patients with AD of HBV-related CLD. Some previous studies did not show a correlation between serum Na and patient prognosis in prophase liver failure. This result might be related to the small proportion of participants with liver cirrhosis and interference of diuretics on serum Na. HBV reactivation, HBV mutation, and withdrawal of nucleos (t)ide analogue therapy can lead to a high level of HBV DNA load. Mortality of liver failure based on HBV reactivation can reach 63% to 67%.[15,21] For patients with liver failure caused by HBV reactivation, nucleos (t)ide analogues therapy, including lamivudine,[22] entecavir,[23] and tenofovir,[15] could be used to improve the prognosis of patients. Therefore, for patients with AD of HBV-related CLD, if the level of HBV DNA load is high, appropriate antiviral therapy should be given or replaced as soon as possible, and supportive treatment should be given to prevent patients from progressing to ACLF. In addition, D/T is a new independent predictor in the prediction model and has not been concerned by previous literature. The increased level of D/T may be associated with decreased ability of liver to metabolize serum bilirubin. D/T should be given more attention in the treatment of AD of HBV-related CLD.

MELD, a classical model evaluating patients with end-stage liver disease waiting for liver transplantation, has been extensively applied to evaluate the prognosis of patients with HBV-related ACLF. However, those research results are inconsistent.[24–26] As a model of predicting ACLF occurrence from patients with AD of HBV-related CLD, MELD may have certain deficiencies. First, MELD only covers 3 indexes—TBIL, Cre, and INR—where INR is greatly influenced by experimental conditions that may affect MELD score.[27] Second, MELD does not include important indexes, such as age, serum Na, and HBV DNA, which may affect prediction accuracy. Verification through the training and validation cohorts revealed that the AUCs of the new model were greater than those of MELD. Furthermore, this new model is applicable to the prediction of ACLF occurrence in patients with AD of HBV-related CLD. The new model included 6 important variables, which can be easily obtained in practical work and are convenient for utilization by clinicians. According to the score of the new model, possible ACLF progression can be effectively anticipated, and more positive treatment can be offered to patients with high ACLF probability to reduce the chances of progression. Cut-off value at −2.12 of the new model was obtained through the training cohort. The patients who had higher than cut-off value in the training and validation cohorts had 28.9% and 25.0% chances to progress to ACLF, respectively. These patients belong to the category of prophase HBV-related liver failure. Pre-existent research showed that ALT and AST show not correlation with the severity or prognosis of HBV-related ACLF and prophase HBV-related liver failure.[28–30] In the present research, ALT and AST were also not independent influencing factors of ACLF occurrence in patients with AD of HBV-related CLD. ALT and AST rapidly and easily decreased, which was observed by clinicians because of the medical treatment given to patients and the bilirubin–enzyme separation phenomenon. Therefore, ALT and AST are inappropriate indexes in diagnosing AD of HBV-related CLD and prophase HBV-related liver failure.

This research is limited by the following factors. First, liver cirrhosis is diagnosed mainly by relying on clinical indexes and radiologic data, and few cases can be established with definite diagnoses through liver pathology and liver stiffness. As such, the early detection of liver cirrhosis is difficult and may influence the proportion of patients with liver cirrhosis. Second, some histories about HBV reactivation, HBV mutation, and withdrawal of nucleos (t)ide analogues therapy of patients were unclear. The role of HBV in the pathogenesis of AD of HBV-related CLD may be more apparent if the data are collected. Third, the complications of patients were unclear because they were not provided in the data. Likewise, the effects on the progression of AD of HBV-related CLD may be more apparent if the data are collected. Fourth, the patients in this research were admitted to the same hospital. If multicenter data are found, then the results may be more representative. Fifth, the new model was derived from a retrospective study. As such, the new model can be verified through future prospective studies.

In summary, the new model obtained in our research is characterized as follows: the new model is specialized for patients with AD of HBV-related CLD; all incorporated indexes are common and thus convenient for practical applications; the model can effectively identify patients with high risks of ACLF progression, allowing such patients to receive disease-specific treatment; the model provides favorable supplementation to diagnose and define patients with prophase HBV-related ACLF. This model is useful to evaluate the effects on monitoring and treating patients with AD of HBV-related CLD.

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Writing – original draft: Chen Li.
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