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Original Article

Novel Prognostic Models for Predicting the 180-day Outcome for Patients with Hepatitis-B Virus-related Acute-on-chronic Liver Failure

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Abstract

Background and Aims: It remains difficult to forecast the 180-day prognosis of patients with hepatitis B virus-acute-on-chronic liver failure (HBV-ACLF) using existing prognostic models. The present study aimed to derive novel-innovative models to enhance the predictive effectiveness of the 180-day mortality in HBV-ACLF. ***Methods:*** The present cohort study examined 171 HBV-ACLF patients (non-survivors, *n*=62; survivors, *n*=109). The 27 retrospectively collected parameters included the basic demographic characteristics, clinical comorbidities, and laboratory values. Backward stepwise logistic regression (LR) and the classification and regression tree (CART) analysis were used to derive two predictive models. Meanwhile, a nomogram was created based on the LR analysis. The accuracy of the LR and CART model was detected through the area under the receiver operating characteristic curve (AUROC), compared with model of end-stage liver disease (MELD) scores. ***Results:*** Among 171 HBV-ACLF patients, the mean age was 45.17 years-old, and 11.7% of the patients were female. The LR model was constructed with six independent factors, which included age, total bilirubin, prothrombin activity, lymphocytes, monocytes and hepatic encephalopathy. The following seven variables were the prognostic factors for HBV-ACLF in the CART model: age, total bilirubin, prothrombin time, lymphocytes, neutrophils, monocytes, and blood urea nitrogen. The AUROC for the CART model (0.878) was similar to that for the LR model (0.878, p=0.898), and this exceeded that for the MELD scores (0.728, p<0.0001). ***Conclusions:*** The LR and CART model are both superior to the MELD scores in predicting the 180-day mortality of patients with HBV-ACLF. Both the LR and CART model can be used as medical decision-making tools by clinicians.

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Introduction

Acute-on-chronic liver failure (ACLF) is a common type of clinical syndrome with rapid deterioration of liver function, organ failure(s) and high short-term mortality.[1] Hepatitis B virus (HBV) poses a serious threat to human health, due to its devastating effect on liver function.[2] In the Asia-Pacific region, HBV is the leading cause of chronic liver disease.[3]

At present, liver transplantation (LT) is still the most beneficial and feasible therapy for patients with ACLF.[4–5] However, 20–30% of patients remain at risk to be delisted from the transplant list, and wait-list mortality is high due to patients being too sick for LT and succumbing to the condition. Hence, it is a significant unmet need to accurately distinguish ACLF patients who are suitable for LT therapy, and seize the best chance for LT.[6] Therefore, an accurate prognostic scoring system is needed to guide and optimize the therapeutic strategy for patients with ACLF.[7] At present, the model of end-stage liver disease (MELD) score is the most commonly used tool for designating patients to the wait-list for LT.[8] However, among the candidates listed for LT, the MELD score may not capture the ACLF severity and adequately evaluate the outcome in the ACLF. Meanwhile, due to differences in patient background queues, the MELD score may not be reasonably applied for HBV-ACLF. Furthermore, although some prognostic scoring systems have been developed to predict the HBV-ACLF short-term (such as 30-day and 90-day) mortality, including the 30-day HBV-ACLFD model previously developed by the inves-

Keywords: Classification and regression tree; Acute-on-chronic hepatitis B liver failure; MELD scores; Logistic regression model.

Abbreviations: ACLF, acute-on-chronic liver failure; ALT, alanine transaminase; AST, aspartate transaminase; AUROC, area under the receiver operating characteristic curve; BUN, urea nitrogen; CART, classification and regression tree; CI, confidence interval; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HE, hepatic encephalopathy; HGB, hemoglobin; INR, international normalized ratio; L, lymphocyte; LT, liver transplantation; LR, logistic regression; M, monocyte; MELD, model for end-stage liver disease; N, neutrophil; OR, odds ratio; PLT, platelet; PTA, prothrombin activity; RBC, red blood cell; SD, standard deviation; TBIL, total bilirubin; WBC, white blood cell.

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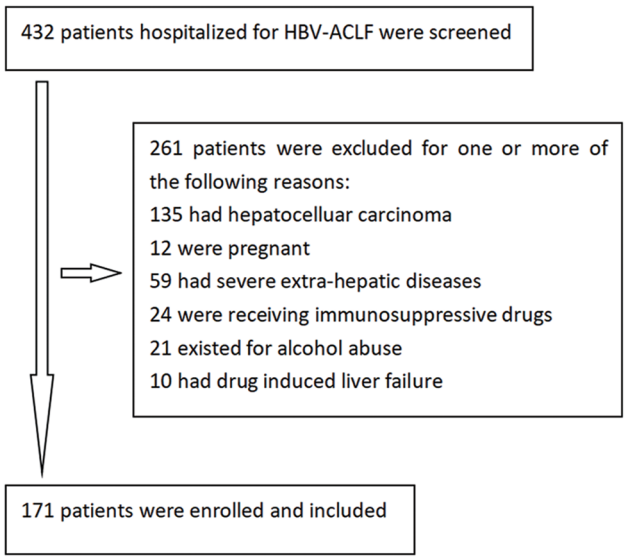

Fig. 1. Flow diagram of inclusion of study participants in the study.

tigators[9], the efficacy is still scanty to predict the mid-term (such as 180-day) mortality of patients with HBV-ACLF.

The present study aimed to derive novel predictive models to evaluate the 180-day mortality of patients with HBV-ACLF based on the backward stepwise logistic regression (LR) and classification and regression tree (CART) analysis, and to evaluate whether these new models are superior to the MELD scores, providing guidance for clinical treatment decision making.

Methods

Study design

A total of 445 patients, who were diagnosed with HBV-ACLF at Beijing You'an Hospital, Capital Medical University, from June 2014 and December 2018, were selected for the present study. Among these patients, merely 171 entered the final selection. The selection process for HBV-ACLF patients inclusion in the present study is presented in Figure 1.

The enrolment criteria for these patients corresponded to the Asian Pacific Association for ACLF.[10] The inclusion criteria were as follows: (a) patients who were at least 16 years-old; (b) patients who were HBV surface antigen (HBsAg)-positive for at least 6 months; (c) patients with a total bilirubin (TBIL) of >171 μmol/L and a sudden exacerbation of liver disease; (d) patients with an international normalized ratio (INR) of >1.5; (e) patients who had ascites within 4 weeks and/or had an onset of hepatic encephalopathy (HE). The exclusion criteria were as follows: (a) pregnant or lactating patients; (b) patients co-infected with human immunodeficiency virus; (c) patients with severe diseases, such as heart dysfunction, previous renal failure, cancer, etc.; (d) patients with infection upon admission to the hospital; (e) patients compounded by other causes of liver damage, such as hepatitis A, C, or E, autoimmune hepatitis, alcohol consumption, or hereditary liver diseases.

The study protocol was approved by the Ethics Committee on Clinical Trials of Beijing You'an Hospital, Capital Medical University. All methods and procedures related to the present study were morally accorded with the laws of the Declaration of Helsinki.

A total of 27 parameters were retrospectively collected as potential risk factors. The parameters included sex, age, serum creatinine level, blood urea nitrogen (BUN) level, aspartate transaminase (AST) level, aspartate alanine transaminase (ALT) level, albumin level, TBIL level [normal reference range: 5–21 μmol/L], serum sodium level, serum potassium level, ammonia level, prothrombin activity (PTA), INR, white blood cell (WBC), hemoglobin (HGB), red blood cell (RBC) count, platelet (PLT) count, lymphocytes (L), neutrophils (N), monocytes (M), time begin, HBV DNA, HBsAg, and complications such as hepatorenal syndrome, ascites, infection, pleural effusion, cirrhosis, and HE. The result (survival or death) for each subject with HBV-ACLF was recorded. The MELD equation was applied to calculate the score for severity as: $9.57 \times \ln(\text{creatinine, mg/dL}) + 3.78 \times \ln(\text{bilirubin, mg/dL}) + 11.20 \times \ln(\text{INR}) + 6.43$. The minimal values were forced to 1.0 for calculation purposes.[11]

LR analysis and nomogram generation

A multivariable LR analysis was performed for the prediction of HBV-ACLF. The candidate predictors were as follows: sex, age, creatinine, BUN, AST, ALT, albumin, TBIL, serum sodium level, serum potassium level, ammonia level, PTA, INR, WBC, RBC, HGB, PLT, L, N, M, time begin, HBV DNA, HBsAg, hepatorenal syndrome, ascites, infection, pleural effusion, cirrhosis, and HE.

In order to identify the significant predictors, 1,000 random samples were generated from the 171 patients through bootstrap resampling with replacement, and backward stepwise LR was conducted for each patient. Then, the predictors selected by the backward stepwise regression were included in the final model. Next, a 10-fold cross-validation was used to calculate the C-index and generate the calibrated statistics. Finally, the parameters for the final model were generated. Based on the results of the logistic regression, the 95% confidence interval (CI) and odds ratio (OR) were calculated. The performance of the model was assessed by sensitivity, and by evaluating the discriminative capacity via the area under the receiver operating characteristic curve (AUROC). A nomogram was created based on the LR analysis, and the nomogram was constructed using the rms package.

Analysis of the CART

A CART analysis was performed for the 171 patients, and it was verified whether this method could calculate more useful clinical results, when compared to the LR model. The candidate predictors were the same as those used in the LR model. The CART analysis divided the data (parent node) into two subsets (child nodes) through the function of the predictor variables. These two subsets were the new parent nodes, which were further split into two child nodes. This process was continued until all patients were classified. After finding the best split for each variable, the CART algorithm used the best overall split to divide the data, and assigned a prediction category for each subgroup. The CART recursively proceeded in this manner, until a predetermined stopping criterion was reached. The algorithm was allowed to go on indefinitely, enabling the model to identify the entirely or almost entirely homogeneous splits.

In the present study, the CART analysis was used to predict the 180-day mortality of patients with HBV-ACLF. The mortality rate, 95% CI and OR were determined. The 10-fold cross-validation was used to trim and optimize the tree, and minimize the relative misclassification. The C-index and the receiver operating characteristic curve were

Table 1. Baseline characteristics of the patients, stratified by mortality

Variable	Overall, *n*=171	Non-survivors, *n*=62	Survivors, *n*=109	*p*
Age in years	45.17 (12.49)	48.74 (12.54)	43.14 (12.05)	<0.0001
Men, *n*(%)	151(88.3)	51(82.3)	100(91.7)	0.064
Ascites, *n*(%)	103(60.2)	46(74.2)	57(52.3)	0.005
HE, *n*(%)	20(11.7)	13(20.9)	7(6.4)	0.004
Infection, *n*(%)	92(53.8)	38(61.3)	54(49.5)	0.138
K/Na, *n*(%)	17(9.9)	5(8.1)	12(11)	0.536
HBeAg, *n*(%)	91(53.2)	32(51.6)	59(54.1)	0.751
HRS, *n*(%)	5(2.9)	4(6.4)	1(0.9)	0.111
Pleural effusion, *n*(%)	7(4.1)	5(8.1)	2(1.8)	0.115
Cirrhosis, *n*(%)	137(80.1)	49(79)	88(80.7)	0.789
lgHBV DNA	4.76(1.93)	4.61(2.06)	4.84(1.87)	0.491
HBsAg	3,948.19 (5,194.35)	4,541.64 (7,356.64)	3,610.64 (3,403.74)	0.944
ALT	464.02 (577.17)	325.65 (305.42)	542.73 (674.12)	0.047
AST	377.83 (413.63)	342.99 (286.41)	397.66 (471.05)	0.393
TBIL	353.83 (138.49)	408.7 (146.06)	322.62 (124.20)	<0.0001
BUN	4.86 (2.49)	5.56 (2.78)	4.46 (2.22)	0.002
Cr	75.16 (36.97)	81.50 (42.99)	71.55 (32.72)	0.174
WBC	7.34 (3.52)	7.89 (4.28)	7.022 (2.99)	0.422
L	20.59 (8.58)	16.77 (6.74)	22.76 (8.78)	<0.0001
M	9.35 (3.78)	10.20 (4.38)	8.86 (3.32)	0.025
N	93.6 (65.55)	69.2 (18.06)	63.47 (7.38)	0.002
PTA	35.97 (9.3)	31.50 (8.58)	38.51 (9.62)	<0.0001
INR	2.11 (0.56)	2.36 (0.65)	1.97 (0.45)	<0.0001
RBC	3.88 (0.85)	3.82 (0.90)	3.91 (.82)	0.336
HGB	124.3 (21.0)	122.33 (21.95)	125.42 (20.46)	0.402
PLT	104.77 (51.73)	96.12 (52.58)	109.68 (50.83)	0.036
Time begin	22.72 (19.01)	23.44 (16.22)	22.31 (0.49)	0.081
ALB	31.06 (4.13)	30.85 (4.31)	31.18 (4.04)	0.615

ALB,albumin;ALT, alanine transaminase; AST, aspartate transaminase; BUN, urea nitrogen; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HE, hepatic encephalopathy; HGB, hemoglobin; HRS, hepatorenal syndrome;INR, international normalized ratio; L, lymphocyte; M, monocyte; N, neutrophil; PLT, platelet; PTA, prothrombin activity; RBC, red blood cell; TBIL, total bilirubin; WBC, white blood cell.

generated to evaluate the performance of the final decision tree.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD), and compared using the Mann-Whitney test, and unpaired or two-tailed *t*-test. Categorical variables were compared using the chi-square test. The predictive accuracy of the LR model was calculated with the concordance statistic, which ranged from 0.5 (no discrimination) to 1.0 (perfect discrimination). The calibration was assessed using the calibration plot, which was implied by a 45° diagonal line with the 1,000 bootstrap samples, in order to decrease the overfit bias.[12] The ROC curve analysis was performed using the MedCalc 17.0 software (Mariakerke, Belgium). The nomogram and CART analysis were performed using the R statistical software, version 4.0.2 (http://www.Rproject.org). The additional statistical analysis was analyzed using the SPSS 25 software (IBM Corp., Armonk, NY, USA). The reported statistical significance levels were all two-sided, and the statistical significance was set at 0.05.

Results

Baseline characteristics

A total of 171 patients who were diagnosed with HBV-ACLF were involved in the present study. The comparison of the clinical characteristics of HBV-ACLF patients stratified by mortality are presented in Table 1. There were no significant differences in sex distribution, potassium/sodium, cirrhosis, HBV DNA, and time begin between the non-survivor (death) group and survivor group ($p>0.05$). However, the differences in age, PTA, INR, TBIL and L were statistically

Table 2. Multivariable predictors of mortality of HBV-ACLF

Variable	β-coefficient	OR(95% CI)	*p*
HE	1.635	5.13 (1.282,20.512)	0.021
TBIL	0.006	1.006 (1.002,1.009)	0.001
PTA	−0.115	0.892 (0.845,0.941)	0.0001
L	−0.130	0.878 (0.825,0.935)	0.0001
M	0.215	1.240 (1.087,1.414)	0.001
Age	0.049	1.050 (1.014,1.087)	0.006

HE, hepatic encephalopathy; L, lymphocyte; M, monocyte; PTA, prothrombin activity; TBIL, total bilirubin.

significant between these two groups (p<0.0001).

LR analysis and nomogram

In order to deeply identify the independent predictors of mortality in the present study, multivariate backward stepwise LR analysis was performed. It was found that age, TBIL, PTA, L, M and HE were significantly associated with the 180-day mortality (Table 2). The C-index for the LR model with these predictors was 0.878. In the 1,000 bootstrap data, the calibration plot for the prediction indicated a good fit (Fig. 2), and the Brier score was 0.1898. Based on the results of the LR analysis, a nomogram was drawn to predict the patient's mortality rate (Fig. 3). A higher score calculated based on the sum of assigned points of each predictor in the nomogram corresponded to a higher probability of death.

CART analysis

In the CART model, TBIL was identified as the variable for the initial split, with an optimal value of 381.10 μmol/L, and L was selected as the variable for the second split, with a dis-

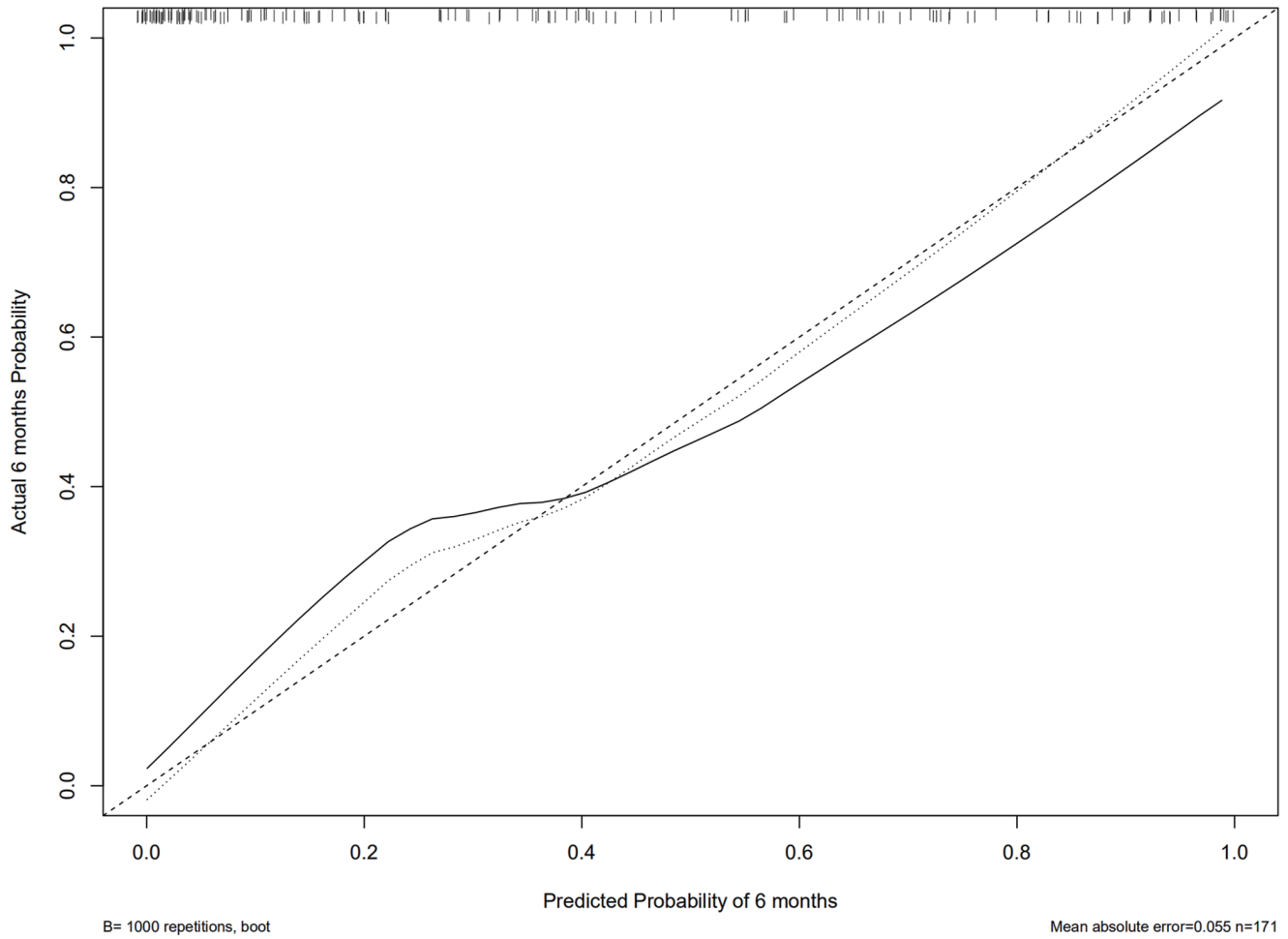

Fig. 2. Calibration plots for predicted using bootstraps.

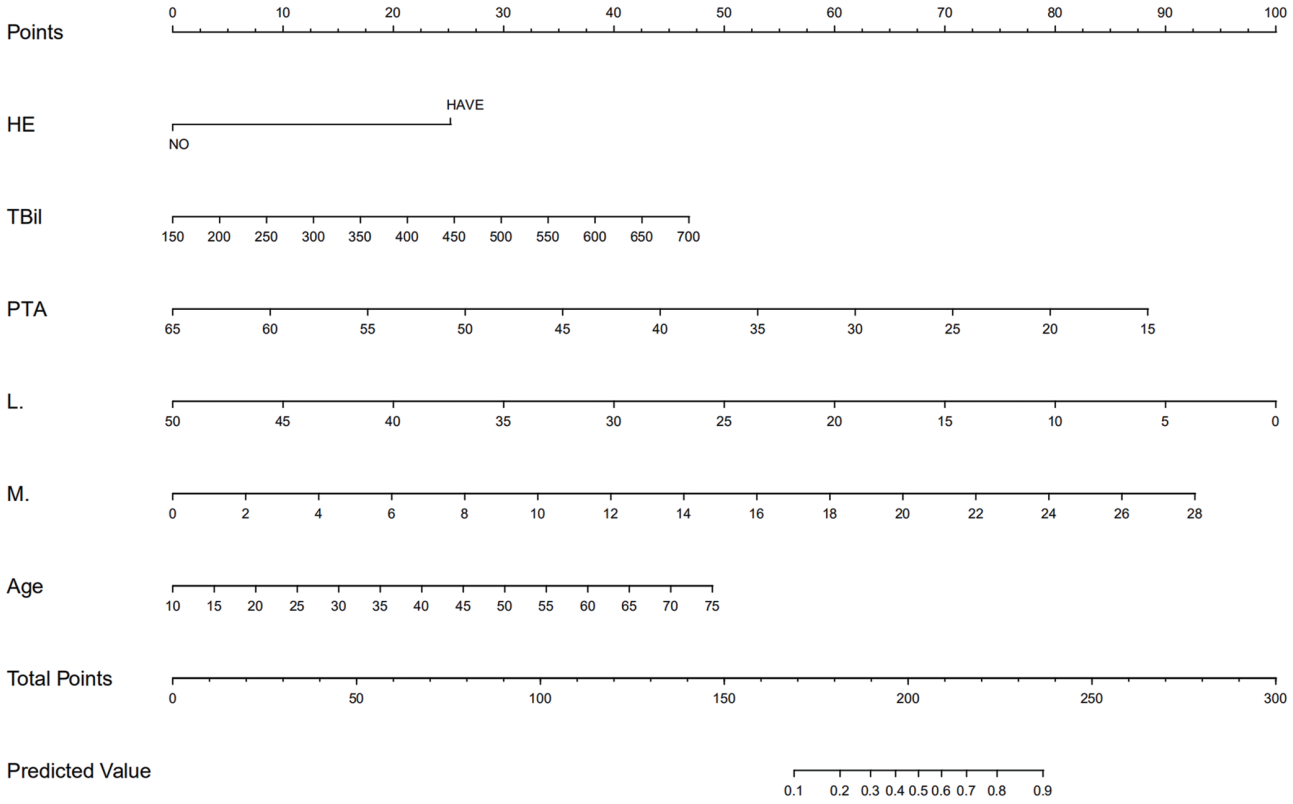

Fig. 3. The nomogram was developed by incorporating the following six parameters: age (years), total bilirubin (μmol/L), prothrombin activity, lymphocyte (%), monocyte (%), and HE. For example, a Hepatitis-B virus-related acute-on-chronic liver failure (HBV-ACLF) patient was 65 years-old, with total bilirubin (TBIL) of 400 μmol/L, L% of 40%, M% of 12%, prothrombin activity (PTA) of 35, and having hepatic encephalopathy (HE). The corresponding total points were: 40+20+20+40+55+25=200. The predicted value of death risk in the nomogram was about 50%.

crimination level of 13.78%. When L was >13.78%, the next best predictor for HBV-ACLF was PTA, with an optimal cut-off value of 33.2. For the node of patients who have a TBIL level of >381.1 μmol/L, an L of >13.78% and a PTA level higher than 33.2, M was selected as the additional significant variable, and this was dichotomized at a level of 10.96%.

Finally, a total of nine subgroups of patients were generated through the seven predictive variables chosen via the CART analysis: subgroup 1 (TBIL ≥381.10 μmol/L and L <13.78%), subgroup 2 (TBIL <381.10 μmol/L and BUN ≥7.915 mmol/L), subgroup 3 (TBIL <381.10 μmol/L, BUN <7.915 mmol/L, and age <56.00 years-old), subgroup 4 (TBIL ≥381.10 μmol/L, L ≥13.78%, PTA <33.20, and age <43.50 years-old), subgroup 5 (TBIL ≥381.10 μmol/L, L ≥13.78%, PTA <33.20, and age ≥ 43.50 years-old), subgroup 6 (TBIL ≥381.10 μmol/L, L ≥13.78%, PTA ≥33.20, and M ≥10.96%), subgroup 7 (TBIL ≥381.10 μmol/L, L ≥13.78%, PTA ≥33.20, and M <10.96%), subgroup 8 (TBIL <381.10 μmol/L, BUN <7.915 mmol/L, age ≥56.00 years-old, and N ≥65.10%), and subgroup 9 (TBIL <381.10 μmol/L, BUN <7.915 mmol/L, age ≥56.00 years-old, and N <65.1%) (Fig. 3). Each patient was sorted to subgroups based on flow chart of the derived CART. The mortality rates for each subgroup are presented in Figure 4. The C-index for the CART model with these predictors was 0.878.

Comparison among the LR, CART and MELD score

As shown in the Figure 5, the predictive power for the 180-day mortality for HBV-ACLF among the LR, CART and MELD score was determined. The CART analysis had an AUROC of 0.878 (95% CI: 0.810–0.923). The performance of the LR analysis was high, with an AUROC of 0.878 (95% CI: 0.820–0.923). However, there was no significant difference between the CART and LR model (p=0.9659). In Table 3, the MELD score had an AUROC of 0.728 (95% CI: 0.655–0.793), which was significantly lower than that for the LR and CART model (p<0.0001).

Discussion

HBV-ACLF is defined as a hazardous syndrome with multiorgan failure.[3–5] Worldwide, it has been demonstrated that LT brings survival profit for selected patients with ACLF. Due to the rapid progression and unpredictable results, accurate prognostic scoring systems are the precondition for optimizing the clinical therapeutic strategy for HBV-ACLF patients. Although the MELD score has been verified to promote the allocation of donor livers, this is still not an ideal indicator for HBV-ACLF patients.[13] Although several prognostic models have been developed to predict the HBV-ACLF short-term (such as 30-day and 90-day) mortality,[14–17] including the 30-day HBV-ACLFD model previously developed by the investigators,[9] there is still a lack of a prognostic model to predict the mid-term (such as 180-day) mortality of patients with HBV-ACLF. In the present study, the LR and CART models were developed to predict the 180-day mortality of patients with HBV-ACLF. Both the LR and CART models could be used as medical decision-managing tools by clinicians.

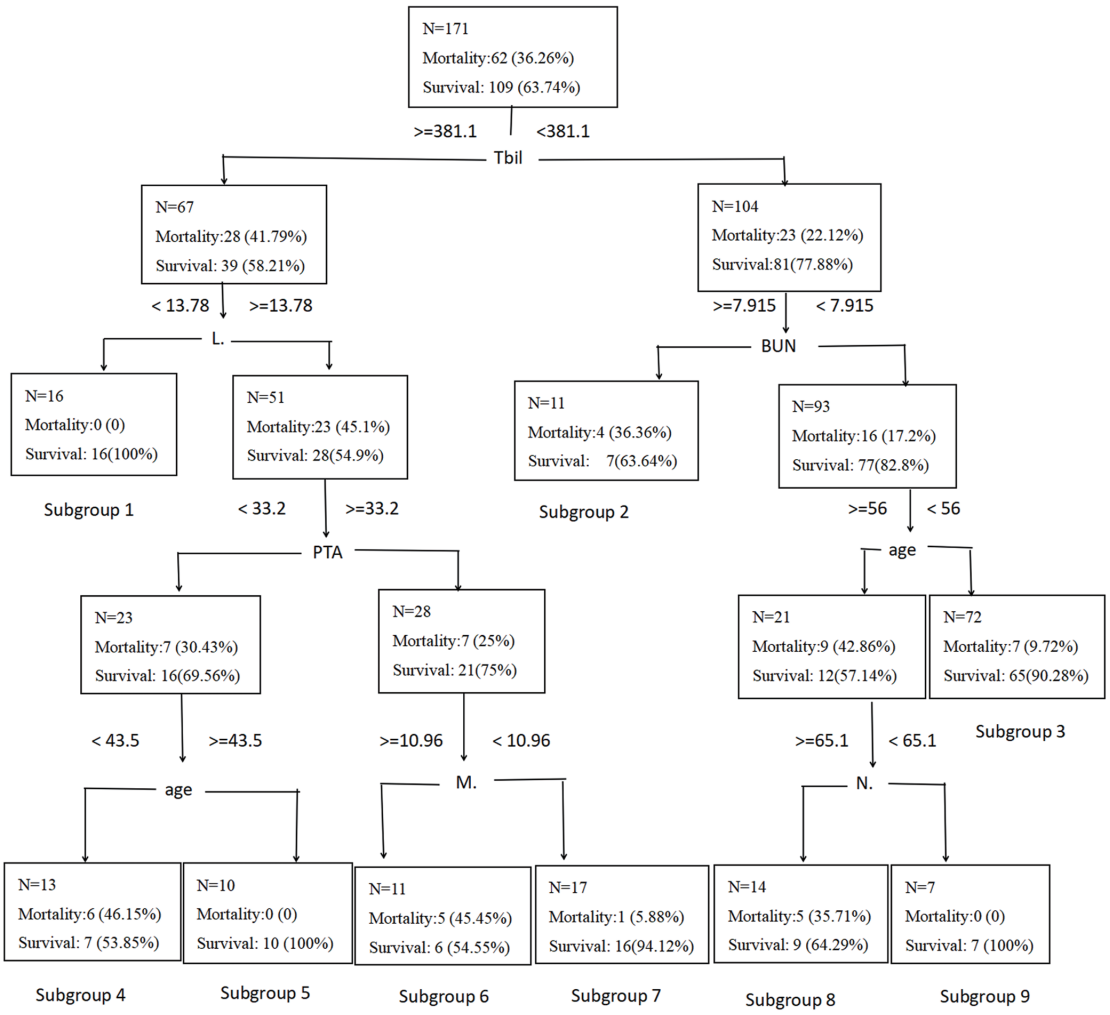

Fig. 4. Predictors from classification and regression tree (CART). Terminal subgroups of patients discriminated by the analysis were numbered from 1 to 9.

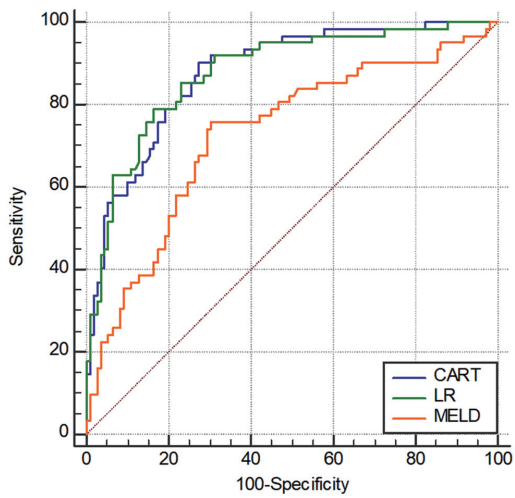

Fig. 5. ROC analysis of the predictive accuracy of the classification and regression tree (CART) model, logistic regression (LR) and model for end-stage liver disease (MELD) score to predict 180-day mortality of hepatitis-B virus-related acute-on-chronic liver failure (HBV-ACLF).

In the present study a new LR model was established, which included age, TBIL, L, M, HE and PTA as prognostic factors for the 180-day mortality. The AUROC for this prognostic model was significantly higher than that for the MELD score. Except for LR, a novel CART model was also developed to predict the 180-day outcome of HBV-ACLF patients. In the present study, the CART model included age, TBIL, PTA, L, M, N and BUN. These seven potential variables were the important predictors for the survival of HBV-ACLF patients. Both the LR and CART models appeared to perform better than the MELD score. Meanwhile, the investigators also made the LR models easier to use in clinic by drawing a nomogram.

Compared to traditional models, the CART model has many advantages. First, the CART can conduct highly biased clinical data, and reveal the complicated relationships among different variables. This generates a clearly visible decision tree that contains many binary splits, which are more accessible and convenient for clinical applications. Second, in the present study, the CART model had better predictive accuracy, when compared to the MELD score. At present, some organ function-based scoring systems, including the chronic liver failure-sequential organ failure assessment score, the CLIF Association ACLF score,[18] the chronic liver failure-sequential organ failure assessment score (, the Acute Physiology and Chronic Health Assessment II score,[19] and the sequential or-

Table 3. The predictive value of mortality of the CART score and other models

Models	AUROC	95% CI	*p*	Youden's index	Sensitivity, %	Specificity, %
CART	0.878	0.819–0.923	0.0001	0.6280	90.32	72.48
LR	0.878	0.820–0.923	0.0001	0.6255	85.48	77.06
MELD	0.728	0.655–0.793		0.4553	75.81	69.72

AUROC, area under the receiver operating characteristic curve; CART, classification and regression tree; CI, confidence interval; LR, logistic regression; MELD, model for end-stage liver disease.

gan failure assessment score, have also been used to make predictions for the mortality of ACLF. Compared to these scoring systems, the CART model is much easier to apply. Third, the CART model is more convenient for LT patients, in terms of estimating the risk stratification. Shi et al.[20] used a CART model to validate the 3-month mortality of patients with HBV-ACLF. This revealed the profit of the CART model to predict the HBV-ACLF risk stratification.

However, there were some limitations in the present study. The present study was a single-center retrospective study that mostly involved male patients. However, it was not easy to collect more data of the mid-term outcome of HBV-ACLF patients. Hence, further validation is needed through a larger study.

Conclusions

The LR and CART model was derived to predict the 180-day clinical outcomes in HBV-ACLF patients. These models can be helpful for doctors who need to make vital clinical decisions for patients with HBV-ACLF. However, larger multicenter studies and further evaluations are needed.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conception and design of the study (QM), collection of the data (JW, ZW), analysis of the data (RX, JY), and writing of the paper (RX, JY).

Data sharing statement

No additional data are available.

References

[1] Jia L, Xue R, Zhu Y, Zhao J, Li J, He WP, *et al*. The efficacy and safety of methylprednisolone in hepatitis B virus-related acute-on-chronic liver failure: a prospective multi-center clinical trial. BMC Med 2020;18(1):383. doi:10.1186/s12916-020-01814-4.
[2] Xue R, Zhu Y, Liu H, Meng Q. The clinical parameters for the diagnosis of hepatitis B virus related acute-on-chronic liver failure with sepsis. Sci Rep 2019;9(1):2558. doi:10.1038/s41598-019-38866-3.
[3] Hernaez R, Solà E, Moreau R, Ginès P. Acute-on-chronic liver failure: an update. Gut 2017;66(3):541–553. doi:10.1136/gutjnl-2016-312670.2.
[4] Tang LSY, Covert E, Wilson E, Kottilil S. Chronic hepatitis B infection: a review. JAMA 2018;319(17):1802–1813. doi:10.1001/jama.2018.3795.
[5] Xue R, Meng Q, Dong J, Li J, Yao Q, Zhu Y, *et al*. Clinical performance of stem cell therapy in patients with acute-on-chronic liver failure: a systematic review and meta-analysis. J Transl Med 2018;16(1):126. doi:10.1186/s12967-018-1464-0.
[6] Shalimar, Kumar D, Vadiraja PK, Nayak B, Thakur B, Das P, *et al*. Acute on chronic liver failure because of acute hepatic insults: etiologies, course, extrahepatic organ failure and predictors of mortality. J Gastroenterol Hepatol 2016;31(4):856–864. doi:10.1111/jgh.13213.
[7] Xue R, Meng Q, Li J, Wu J, Yao Q, Yu H, *et al*. The assessment of multipotent cell transplantation in acute-on-chronic liver failure: a systematic review and meta-analysis. Transl Res 2018;200:65–80. doi:10.1016/j.trsl.2018.05.006.
[8] Sundaram V, Jalan R, Wu T, Volk ML, Asrani SK, Klein AS, *et al*. Factors associated with survival of patients with severe acute-on-chronic liver failure before and after liver transplantation. Gastroenterology 2019;156(5):1381–1391.e3. doi:10.1053/j.gastro.2018.12.007.
[9] Xue R, Duan Z, Liu H, Chen L, Yu H, Ren M, *et al*. A novel dynamic model for predicting outcome in patients with hepatitis B virus related acute-on-chronic liver failure. Oncotarget 2017;8(65):108970–108980. doi:10.18632/oncotarget.22447.
[10] Sarin SK, Choudhury A, Sharma MK, Maiwall R, Al Mahtab M, Rahman S, *et al*. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL): an update. Hepatol Int 2019;13(6):826–828. doi:10.1007/s12072-019-09946-3.
[11] Schlegel A, Linecker M, Kron P, Györi G, De Oliveira ML, Müllhaupt B, *et al*. Risk assessment in high- and low-MELD liver transplantation. Am J Transplant 2017;17(4):1050–1063. doi:10.1111/ajt.14065.
[12] DuBrock HM, Goldberg DS, Sussman NL, Bartolome SD, Kadry Z, Salgia RJ, *et al*. Predictors of waitlist mortality in portopulmonary hypertension. Transplantation 2017;101(7):1609–1615. doi:10.1097/TP.0000000000001666.
[13] Gottlieb A, Kottmann M, Manka P, Bedreli S, Hadem J, Bechmann L, *et al*. How to define acute liver failure patients with pre-existing liver disease without signs of cirrhosis. Dig Dis 2019;37(2):147–154. doi:10.1159/000492869.
[14] Jilma-Stohlawetz P, Lysy K, Belik S, Jilma B, Quehenberger P. Interference in specialized coagulation assays affecting the protein C pathway: effects of marked haemolysis, hyperbilirubinaemia and lipaemia on chromogenic and clotting tests on two coagulation platforms. Int J Lab Hematol 2019;41(3):404–411. doi:10.1111/ijlh.13000.
[15] Shen Y, Wu SD, Wu L, Wang SQ, Chen Y, Liu LL, *et al*. The prognostic role of liver stiffness in patients with chronic liver disease: a systematic review and dose-response meta-analysis. Hepatol Int 2019;13(5):560–572. doi:10.1007/s12072-019-09952-5.
[16] Weiss N, Thabut D. Neurological complications occurring after liver transplantation: role of risk factors, hepatic encephalopathy, and acute (on chronic) brain injury. Liver Transpl 2019;25(3):469–487. doi:10.1002/lt.25420.
[17] Song DS, Kim TY, Kim DJ, Kim HY, Sinn DH, Yoon EL, *et al*. Validation of prognostic scores to predict short-term mortality in patients with acute-on-chronic liver failure. J Gastroenterol 2018;33(4):900–909. doi:10.1111/jgh.13991.
[18] Lee M, Lee JH, Oh S, Jang Y, Lee W, Lee HJ, *et al*. CLIF-SOFA scoring system accurately predicts short-term mortality in acutely decompensated patients with alcoholic cirrhosis: a retrospective analysis. Liver Int 2015;35(1):46–57. doi:10.1111/liv.12683.
[19] Christodoulou E, Ma J, Collins GS, Steyerberg EW, Verbakel JY, Van Calster B. A systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction models. J Clin Epidemiol 2019;110:12–22. doi:10.1016/j.jclinepi.2019.02.004.
[20] Shi KQ, Zhou YY, Yan HD, Li H, Wu FL, Xie YY, *et al*. Classification and regression tree analysis of acute-on-chronic hepatitis B liver failure: Seeing the forest for the trees. J Viral Hepat 2017;24(2):132–140. doi:10.1111/jvh.12617.