

# Establishment and Validation of ALPH-Q Score to Predict Mortality Risk in Patients With Acute-on-Chronic Hepatitis B Liver Failure

## A Prospective Cohort Study

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**Abstract:** Currently, there are no robust models for predicting the outcome of acute-on-chronic hepatitis B liver failure (ACHBLF). We aimed to establish and validate a new prognostic scoring system, named ALPH-Q, that integrates electrocardiography parameters that may be used to predict short-term mortality of patients with ACHBLF.

Two hundred fourteen patients were included in this study. The APLH-Q score was constructed by Cox proportional hazard regression analysis and was validated in an independent patient cohort. The area under the receiver-operating characteristic curve was used to compare the performance of different models, including APLH-Q, Child–Pugh score (CPS), model of end-stage liver disease (MELD), and a previously

reported logistic regression model (LRM).

The APLH-Q score was constructed with 5 independent risk factors, including age (HR = 1.034, 95% CI: 1.007–1.061), liver cirrhosis (HR = 2.753, 95% CI: 1.366–5.548), prothrombin time (HR = 1.031, 95% CI: 1.002–1.062), hepatic encephalopathy (HR = 2.703, 95% CI: 1.630–4.480), and QTc (HR = 1.008, 95% CI: 1.001–1.016). The performance of the ALPH-Q score was significantly better than that of MELD and CPS in both the training (0.896 vs 0.712, 0.896 vs 0.738, respectively, both  $P < 0.05$ ) and validation cohorts (0.837 vs 0.689, 0.837 vs 0.585, respectively, both  $P < 0.05$ ). Compared with LRM, APLH-Q also showed a better performance (0.896 vs 0.825, 0.837 vs 0.818, respectively).

We have developed a novel APLH-Q score with greater performance than CPS, MELD, and LRM for predicting short-term mortality of patients with ACHBLF.

(*Medicine* 94(2):e403)

Editor: Marek Sierżęga.

Received: September 24, 2014; revised: November 12, 2014; accepted: December 7, 2014.

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S-JW, H-DY, Z-XZ, Y-YX, W-JH, and Y-PC contributed to data collection. S-JW, F-LW, B-ZY, and W-JH contributed to data analysis. S-JW and H-DY drafted the manuscript. K-QS, M-HZ, F-LW, and Y-CF contributed to the study design. K-QS, W-JH, and M-HZ helped to draft the manuscript. Y-CF contributed to statistical analysis. Y-PC and M-HZ conceived the study. M-HZ was responsible for study supervision and obtaining funding.

This work was supported by grants from the Scientific Research Foundation of Wenzhou, Zhejiang Province, China (H20090014, Y20090269), Health Bureau of Zhejiang Province (2010KYB070), Research Foundation of Education Bureau of Zhejiang Province (Y201009942), Fresh Talent Program for Science and Technology, Department of Zhejiang Province (2013R413018, 2013R413035, and 2013R413015), Research Funds for Tian Qing Liver Diseases (TQGB20120057), and Project of New Century 551 Talent Nurturing in Wenzhou.

The authors have no conflicts of interest to disclose.

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ISSN: 0025-7974

DOI: 10.1097/MD.0000000000000403

**Abbreviations:** ACHBLF = acute-on-chronic hepatitis B liver failure, ACLF = acute-on-chronic liver failure, ALT = alanine aminotransferase, AST = aspartate aminotransferase, auROC = area under the receiver-operating characteristic curve, BMI = body mass index, CI = confidence interval, CPS Child–Pugh = score, DBP = diastolic blood pressure, ECG = electrocardiogram, HBeAg = hepatitis B e antigen, HBV = hepatitis B virus, HE = hepatic encephalopathy, HR = hazard ratio, HRS = hepatorenal syndrome, INR = international normalized ratio, LC = liver cirrhosis, LRM = logistic regression model, MELD = model of end-stage liver disease, PT = prothrombin time, PTA = prothrombin time activity, QTc = QT interval corrected for the heart rate,  $\gamma$ -GT =  $\gamma$ -glutamyl transferase, SBP = systolic blood pressure, SD = standard deviation, +PV = positive predictive value, –PV = negative predictive value, +LR = positive likelihood ratio, –LR = negative likelihood ratio.

## INTRODUCTION

In recent years, acute-on-chronic liver failure (ACLF) has been increasingly recognized as a specific clinical entity that occurs in patients with acute deterioration of diagnosed or undiagnosed chronic liver disease.<sup>1,2</sup> In China, due to the high prevalence of hepatitis B virus (HBV), acute-on-chronic hepatitis B liver failure (ACHBLF) accounts for the majority of ACLF.<sup>3</sup> ACHBLF has a rapidly progressive course and may lead to a high short-term mortality.<sup>4,5</sup> The most effective approved treatment for ACHBLF is liver transplantation.<sup>6,7</sup> However, due to the limited number of liver donors, an optimized prognostic scoring index is urgently needed to evaluate the patient's condition so that transplantation can be performed on patients with the greatest need.

Currently, several known models, such as the Child–Pugh score (CPS) and the model for end-stage liver disease (MELD), were used to assess the severity of liver disease. Unfortunately, they were mainly established on the basis of alcoholic-abuse population, rather than the viral-infected population and consequently have a poor predictive accuracy for ACHBLF patients,<sup>8,9</sup> which ranged from 0.601 to 0.760 for CPS and from 0.521 to 0.683 for MELD. To further increase the accuracy of prediction, we have established a logistic regression model (LRM), which was mainly based on available parameters, and it had shown better performance in predicting short-term mortality than existing scoring systems.<sup>10</sup> Recently, the robustness of the LRM model has been further validated elsewhere.<sup>8,11</sup>

As is well known, the liver and the heart are intimately related in both health and disease states. Patients with chronic heart failure may have liver damage; conversely, patients with end-stage liver disease may have heart failure or electrophysiological abnormalities, even in those who do not have a history of cardiac disease.<sup>12,13</sup> Recently, several electrophysiological abnormalities, such as chronotropic incompetence, electromechanical uncoupling, and electrocardiographic QT interval prolongation, have frequently been reported in the patients with liver disease, of which the QT prolongation interval is the most widely recognized.<sup>14</sup> The QT interval on the electrocardiogram is an indirect measure of the ventricular electrical depolarization and repolarization and should be corrected for the heart rate (named QTc).<sup>15</sup> Several studies had found that the presence of prolonged QTc might lead to a higher mortality in patients with liver diseases.<sup>6,16</sup> The QTc may be an additional prognostic means to identify patients with high-mortality risk.<sup>17</sup> Therefore, the establishment of an early accurate prediction of the prognosis combining with QTc in ACHBLF patients listed for liver transplantation is both necessary and feasible.

In this study, we integrated electrocardiography parameters including QTc with other clinical and biochemical variables to establish a new prognostic score, named APLH-Q score. We tested the accuracy of the APLH-Q score's prediction ability and compared it with existed scores in a prospective separated patient cohort.

## MATERIALS AND METHODS

### Study Protocol

We established and validated a clinical scoring system in two separate medical centers (training cohort: the First Affiliated Hospital of Wenzhou Medical University from March 2009 to December 2012; prospective validation cohort: Ningbo No. 2 Hospital from April 2012 to April 2013) with the same medical record systems.

The start date of the followup was the date of diagnosis of ACHBLF. All the patients were followed up for at least 3 months. An informed consent was obtained from each patient included in the study, and the research protocol of the study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University and the Ningbo No. 2 Hospital. The study was performed according to Standards for the Reporting of Diagnostic Accuracy Studies.<sup>18</sup>

### Patients Definition and Observation

ACLF was diagnosed according to the guidelines and recommendations of the Asian Pacific Association for the Study of the Liver in 2009.<sup>1</sup> In brief, ACLF is defined as acute hepatic insult manifesting as jaundice and coagulopathy, complicated

within 4 weeks by ascites or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease. ACHBLF is defined as ACLF caused solely by hepatitis B virus. Patients who meet the following criteria were excluded: infected and/or coinfecting with non-B hepatitis virus; alcohol abuse; autoimmune diseases; toxic or other causes that might lead to liver failure; past or current hepatocellular carcinoma; pregnancy; hematologic disorders; confirmed cardiovascular diseases and/or taking any agents contributing to a prolonged QTc interval, such as cordarone,  $\beta$ -blockers, quinolones; and liver transplantation, or serious diseases in other organ systems.

We took a detailed history of all the patients when they were in a hospital. Medical history was recorded upon admission. The basic characteristics of the patients were detected within the first 24 hours after the established diagnosis of ACHBLF. Physical examination, laboratory tests, and abdominal ultrasound scanning were performed. Meanwhile, a routine 12-lead electrocardiographic examination (ECG) made at a paper speed of 25 mm/s was performed for all the patients.

The care that was provided to the patients at both centers was the same and in accordance with the Asia-Pacific consensus recommendations.<sup>1</sup> This routinely included antiviral treatment, absolute bed rest, energy supplements and vitamins, intravenous drop infusion albumin maintenance water, electrolyte and acid–base equilibrium, and prevention and treatment complications, etc.

### Clinical Parameters

Clinical parameters included age, gender, body mass index, blood pressure, hepatic encephalopathy (HE), liver cirrhosis (LC), ascites, and hepatorenal syndrome (HRS). We reclassified the HE grade into 0: non-HE, 1: mild (grades 1–2), and 2: severe (grades 3–4) according to the West-Haven criteria.<sup>19</sup> LC was defined by the following combined parameters: a score greater than 2 according to the aspartate aminotransferase (AST) to platelet ratio using the formula:  $[\text{AST}/\text{upper limit of normal}]/\text{platelet count} (\times 10^9/\text{L}) \times 100^{20}$ , ultrasonographic evidence of a small-sized liver with and without splenomegaly/ascites, and an albumin level less than 35 g/L without other identifiable causes of hypoalbuminemia such as renal loss or gastrointestinal loss. HRS was defined as the low glomerular filtration rate, as indicated by serum creatinine of  $>1.5$  mg/dL or 24-hour creatinine clearance  $<40$  mL/min, without the presence of chronic kidney diseases.<sup>21</sup> The detection of ascites includes history, physical examination, abdominal ultrasound, and laboratory assessment of liver function, renal function, serum, and urine electrolytes. We reclassified ascites grade into 0: nonascites, 1: mild (grade 1), and 2: moderate to severe (grades 2–3).<sup>22</sup> Also, the diagnosis of bacterial or fungal infection was based on infection-positive cultures of blood, ascites, urine or sputum, and/or clinical findings suggestive of infections.

### Laboratory Parameters

Laboratory parameters included alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), albumin (ALB), platelet count, hemoglobin (Hb), serum creatinine (Cr), prothrombin time (PT), prothrombin time activity (PTA), international normalized ratio (INR), serum sodium, and potassium. HBV serologic markers were collected for each patient (Abbott, AXSYM). Serum HBV DNA was measured by quantitative PCR assay (Roche Amplicor, limit of detectability of 100 IU/mL) after admission. Hepatitis C virus

antibody and human immunodeficiency virus antibody were detected using ELISA (IEGAN, Freedom evolyzer/150). Anti-nuclear antibody (ANA) was evaluated using indirect immunofluorescence, and soluble liver antigen/liver pancreas antigen (SLA/LP), anti-liver/kidney microsomal antibody Type 1 (anti-LKM-1), and anti-liver cytosol antibody Type 1 (anti-LC-1) were evaluated using immunoblot analysis (Euroimmun, Lubeck, Germany).

**Electrocardiography Parameters**

All ECG data were reviewed visually, and any segments containing signal loss, noise, or extra-systole were discarded. The ECG parameters, including P-wave, PR interval, QRS interval, QT interval, and RR interval, were evaluated in Adobe Photoshop CS5 (Adobe Systems, San Jose, CA) with a scan version. Magnification of the ECG enabled a fine determination of the measurement points. The ECG traces were reviewed by two of the investigators (Zai-Xin Zheng and Ke-Qing Shi), who were blinded to the clinical parameters of the patients. The QT interval was also manually assessed and corrected according to the Bazett formula ( $QTc = QT \text{ interval} / RR \text{ interval}$ ).<sup>15</sup>  $QTc \geq 440$  milliseconds was classified as prolonged.

**Scoring Systems and Prognostic Models**

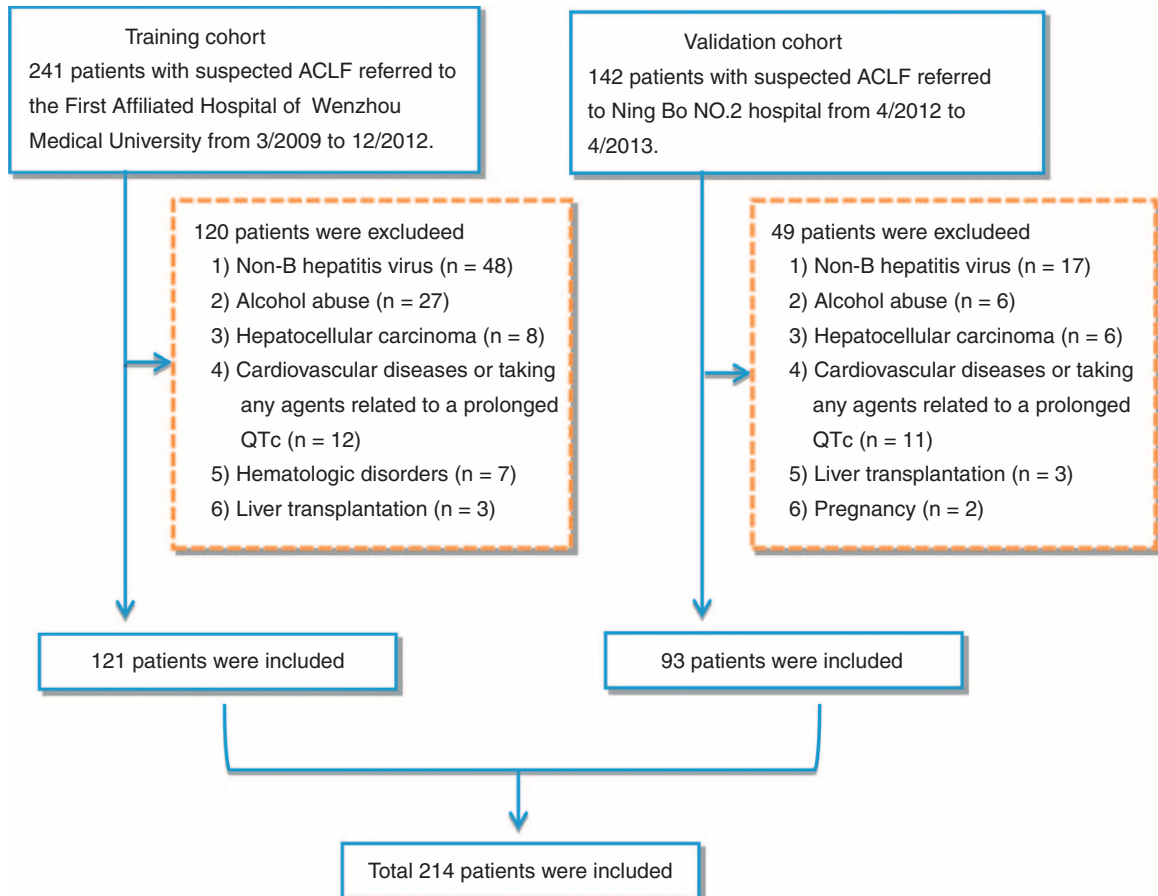
MELD scores were calculated according to the Malinchoc formula:  $R = 9.57 \times \ln(\text{creatinine [mg/dL]}) + 3.78 \times \ln(\text{bilirubin$

$[\text{mg/dL}]) + 11.2 \times \ln(\text{INR}) + 6.43 \times (\text{aetiology: } 0 \text{ if cholestatic or alcoholic, } 1 \text{ otherwise}).$ <sup>23</sup> CPS, which included HE, PT, ascites, total bilirubin, and serum albumin, was assessed according to the standard criteria.<sup>24</sup> In addition, an LRM constructed by our group was also calculated:  $P = -1.343 + 0.772 \times \text{HE} + 2.279 \times \text{HRS} + 0.85 \times \text{LC} + 1.026 \times \text{HBeAg} - 2.117 \times \text{PTA}/\text{age}.$ <sup>10</sup>

**Construction of the ALPH-Q Score**

For the training cohort, we performed univariate Cox proportional hazards regression analysis for determining the association of clinical and laboratory parameters with prognosis and survival time. Covariables with a *P* value of  $<0.01$  as per univariate regression analyses were included in a forward-conditional step-wise Cox proportional hazards regression to identify independent predictors for the prognosis of the patients with ACHBLF. For this analysis, the conditional probabilities for stepwise entry and removal of a factor were 0.05 and 0.10, respectively. The hazard or instantaneous risk of death  $h(t)$  at time  $t$  after randomization for a patient with variables  $x_1, \dots, x_n$  has the form  $h(t) = h_0(t) \exp(b_1x_1 + b_2x_2 + \dots + b_nx_n).$

A prognostic index ( $PI = b_1x_1 + b_2x_2 + \dots + b_nx_n$ ) can be calculated for each patient on the basis of the final model. Higher values for PI mean worse prognosis, and lower values mean better prognosis.<sup>25</sup> We then defined the PI as a new prognosis score, named ALPH-Q score, that was based on the final included five parameters (age, liver cirrhosis, PT, HE, and QTc).



**FIGURE 1.** A flow diagram of study participants.

To assess differences in prognosis efficiency between the ALPH-Q score and other models, area under the receiver-operating characteristic curve (auROC), which is a measure of discrimination, was calculated. The 3-month mortality was used to evaluate diagnostic performance of scoring systems for patients with ACHBLF in majority of studies<sup>26–28</sup>, in addition to this study. Furthermore, the standard index of validity, such as Youden index, sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value, was calculated according to the ROC results.

## Statistical Analysis

The Kolmogorov–Smirnov test was applied to determine whether sample data were likely to be derived from a normal distribution population. Continuous variables of normal and skewed distributions are expressed as mean  $\pm$  standard deviation (SD) and median (interquartile range), respectively. Categorical values were expressed by absolute and relative frequencies. Differences in variables were analyzed using Student *t* tests (for normally distributed data) or Wilcoxon signed rank test (for skewed distributed data). The chi-square test or the Fisher

**TABLE 1.** Characteristics of Patients With Acute-on-Chronic Hepatitis B Liver Failure, Stratified by Different Cohorts

Variable	Training Cohort (n = 121)	Validation Cohort (n = 93)	P Value
<b>Clinical parameters</b>			
Age, y	43.3 $\pm$ 12.0	47.8 $\pm$ 13.5	0.011
Male gender no. (%) <sup>*</sup>	96 (79.3%)	64 (68.8%)	0.079
Mortality no. (%)	51 (42.1%)	30 (32.3%)	0.139
BMI, kg/m <sup>2</sup>	22.8 $\pm$ 3.6	22.7 $\pm$ 3.7	0.941
SBP, mm Hg	121.6 $\pm$ 14.2	120.2 $\pm$ 15.2	0.480
DBP, mm Hg	74.4 $\pm$ 9.8	74.4 $\pm$ 10.5	0.974
HBeAg positivity no. (%) <sup>*</sup>	67 (55.4%)	44 (47.5%)	0.418
Hepatic encephalopathy no. (%) <sup>†</sup>	29 (24.0%)	16 (17.2%)	0.229
Liver cirrhosis no. (%) <sup>*</sup>	54 (44.6%)	45 (48.4%)	0.585
Infection no. (%) <sup>*</sup>	29 (24.0%)	49 (52.7%)	<0.001
Ascites no. (%) <sup>†</sup>	71 (58.7%)	52 (55.9%)	0.685
Hepatorenal syndrome no. (%) <sup>*</sup>	6 (5.0%)	3 (3.2%)	0.735
<b>Laboratory parameters</b>			
White blood cell (10 <sup>12</sup> /L)	6.0 (4.6, 8.0)	6.9 (5.4, 9.3)	0.002
Haemoglobin, g/L	132.8 $\pm$ 19.3	117.8 $\pm$ 21.9	<0.001
Platelet (10 <sup>9</sup> /L)	94.1 $\pm$ 43.0	106.9 $\pm$ 55.0	0.057
Serum sodium, mmol/L	137.1 $\pm$ 4.8	135.2 $\pm$ 5.6	0.010
Serum potassium, mmol/L	4.2 $\pm$ 0.84	4.0 $\pm$ 0.64	0.106
ALT, U/L	805 (247.5, 1228.5)	133 (73, 371.5)	<0.001
AST, U/L	503 (247.5, 894.5)	153 (117.3, 312.5)	<0.001
Albumin, g/L	32.4 $\pm$ 5.2	29.2 $\pm$ 5.9	<0.001
Alkaline phosphatase, U/L	169.7 $\pm$ 45.7	138.6 $\pm$ 60.2	<0.001
$\gamma$ -GT, U/L	106 (73.5, 165)	79.0 (47.5, 147.0)	0.007
Total bilirubin, $\mu$ mol/L	277 (201.5, 370.1)	288.0 (169.0, 368.0)	0.765
Total cholesterol, mmol/L	2.2 $\pm$ 0.89	2.3 $\pm$ 1.04	0.285
Creatinine, $\mu$ mol/L	67 (58, 79.8)	58 (49, 69)	<0.001
HBV DNA (log <sub>10</sub> IU/ml)	5.7 $\pm$ 1.7	5.5 $\pm$ 2.0	0.497
PT, s	27.4 $\pm$ 9.8	27.3 $\pm$ 7.7	0.913
PTA (%)	25.3 (19.4, 37.5)	31.9 (26, 41.2)	0.001
INR	2.28 (1.81, 2.99)	2.4 (2, 2.9)	0.642
<b>Electrocardiogram parameters</b>			
P-wave, ms	88.1 $\pm$ 11.6	90.8 $\pm$ 11.8	0.101
PR interval, ms	143.4 $\pm$ 20.0	144.6 $\pm$ 18.9	0.642
QRS interval, ms	85.9 $\pm$ 9.8	88.2 $\pm$ 11.3	0.115
QT interval, ms	380.1 $\pm$ 32.7	373.5 $\pm$ 42.3	0.202
QTc interval, ms	427.1 $\pm$ 35.5	435.6 $\pm$ 41.6	0.107
RR interval, ms	796.9 $\pm$ 163.5	748.6 $\pm$ 160.6	0.032
<b>Scoring systems</b>			
MELD score	27.6 $\pm$ 6.0	22.6 $\pm$ 7.5	<0.001
CTP score	11.2 $\pm$ 1.3	10.9 $\pm$ 1.6	0.044

$\gamma$ -GT =  $\gamma$ -glutamyl transferase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CTP = Child–Turcotte–Pugh, DBP = diastolic blood pressure, HBeAg = hepatitis B e antigen, INR = international normalized ratio, MELD = model for end-stage liver disease, PT = prothrombin time, PTA = prothrombin time activity, SBP = systolic blood pressure.

<sup>\*</sup> Dichotomous values.

<sup>†</sup> Categorical values.



exact test was used for categorical data, as appropriate. For all the analyses, a *P* value of <0.05 was considered statistically significant. A statistical analysis was performed using SPSS version 20.0 (SPSS, Chicago, IL) and MedCalc version 12.7 (MedCalc Software, Ostend, Belgium).

**RESULTS**

**Baseline Characteristics of the Study Sample**

Three hundred eighty three patients with suspected ACLF were enrolled in the study. After exclusion of those who did not

meet the inclusive criteria (Figure 1), 214 individuals (121 in the training cohort and 93 in the validation cohort) were finally included. As shown in Table 1, in the training cohort, the mean age was 43.3 ± 12.0 years, and the patients were predominantly men (79.3%), of which 42.1% patients (n = 51) died at the end of the followup. The most common complication of ACHBLF was ascites (71 patients, 58.7%). In the validation cohort, the mean age was 47.8 ± 13.5 years, and male was also predominant (68.8%), of which 32.3% patients (n = 30) died at the end of the followup. The training cohort had a higher mortality rate

**TABLE 2.** Characteristics of Patients With Acute-on-Chronic Hepatitis B Liver Failure, Stratified by Mortality

Variables	Training Cohort (n = 121)			Validation Cohort (n = 93)		
	Survival (n = 70)	Death (n = 51)	<i>P</i> Value	Survival (n = 63)	Death (n = 30)	<i>P</i> Value
Clinical parameters						
Age, y	38.7 ± 10.4	49.7 ± 11.2	<0.001	43.9 ± 12.2	56.0 ± 12.4	<0.001
Male gender no. (%) <sup>*</sup>	59 (84.3%)	37 (72.5%)	0.115	45 (71.4%)	19 (63.3%)	0.431
BMI, kg/m <sup>2</sup>	22.3 ± 3.6	23.5 ± 3.5	0.088	22.4 ± 3.6	23.4 ± 3.8	0.218
SBP, mm Hg	119.4 ± 13.1	124.6 ± 15.3	0.048	118.7 ± 13.3	123.3 ± 18.5	0.172
DBP, mm Hg)	74.1 ± 9.1	74.9 ± 10.7	0.054	74.1 ± 9.5	75.0 ± 12.5	0.741
HBeAg positive no. (%) <sup>*</sup>	40 (57.1%)	27 (52.9%)	0.646	25 (39.7%)	19 (63.3%)	0.033
HE no. (%) <sup>†</sup>	4 (5.7%)	25 (49.0%)	<0.001	4 (6.3%)	12 (40.0%)	<0.001
LC no. (%) <sup>*</sup>	17 (24.3%)	37 (72.5%)	<0.001	24 (38.1%)	21 (70.0%)	0.004
Infection no. (%) <sup>*</sup>	12 (17.1%)	17 (33.3%)	0.039	24 (38.1%)	25 (83.3%)	<0.001
Ascites no. (%) <sup>†</sup>	30 (42.9%)	41 (80.4%)	<0.001	33 (52.4%)	19 (63.3%)	0.320
HRS no. (%) <sup>*</sup>	3 (4.3%)	3 (5.9%)	0.696	1 (1.6%)	2 (6.7%)	0.242
Laboratory parameters						
White blood cell (10 <sup>12</sup> /L)	6.0 (4.6, 7.5)	6.0 (4.3, 7.5)	0.973	6.6 (5.1, 9.3)	8.0 (6.1, 9.3)	0.183
Haemoglobin, g/L	137.8 ± 17.3	125.8 ± 20.0	0.001	119.6 ± 22.3	114.0 ± 21.0	0.248
Platelet (10 <sup>9</sup> /L)	103.9 ± 46.1	80.6 ± 34.3	0.003	105.9 ± 50.6	109.0 ± 64.3	0.803
Serum sodium, mmol/L	138.1 ± 4.1	135.6 ± 5.3	0.005	136.0 ± 4.9	133.5 ± 6.5	0.042
Serum potassium, mmol/L	4.1 ± 0.85	4.3 ± 0.82	0.263	4.0 ± 0.68	3.9 ± 0.55	0.487
ALT, U/L	996.5 (356.3, 1319.7)	524 (157, 1122)	0.030	133 (74, 392)	140 (71, 369.3)	0.990
AST, U/L	611 (247.3, 974.8)	420 (245, 732)	0.231	137 (107, 238)	273.5 (129.5, 356)	0.030
Albumin, g/L	34.0 ± 5.2	30.3 ± 4.5	<0.001	28.9 ± 5.7	29.7 ± 6.0	0.558
Alkaline phosphatase, U/L	161.6 ± 40.7	181.1 ± 50.1	0.021	130.3 ± 52.1	155.8 ± 72.4	0.056
γ-GT, U/L	113 (77.8, 167)	91 (62, 152)	0.194	76 (47, 145)	83.5 (47.5, 150.3)	0.678
Total bilirubin, μmol/L	233.5 (190.0, 342.6)	343 (229, 464)	0.001	258 (140, 354)	313.5 (223.8, 464.7)	0.051
Total cholesterol, mmol/L	2.43 ± 0.86	1.85 ± 0.84	0.001	2.4 ± 0.95	2.2 ± 1.21	0.288
Creatinine, μmol/L	66 (57, 78)	69 (58, 87)	0.349	57 (48, 66)	66.5 (55.3, 79.8)	0.017
HBV DNA (log <sub>10</sub> IU/mL)	5.7 ± 1.7	5.8 ± 1.6	0.864	5.7 ± 1.59	5.1 ± 2.73	0.325
PT, s	24.9 ± 7.4	30.9 ± 11.7	0.002	26.5 ± 7.2	28.9 ± 8.3	0.147
PTA (%)	28.6 (21.1, 40.7)	23.1 (16.7, 28.6)	0.015	33.3 (24.6, 42.2)	28.7 (21.9, 41.1)	0.043
INR	2.2 (1.7, 2.8)	2.7 (2.2, 3.5)	0.001	2.3 (1.9, 2.8)	2.7 (2.0, 3.3)	0.108
Electrocardiogram parameters						
P wave, ms	87.6 ± 12.3	88.9 ± 10.6	0.553	89.4 ± 9.9	93.9 ± 14.9	0.151
PR interval, ms	141.5 ± 21.3	145.9 ± 18.1	0.239	143.1 ± 16.9	147.8 ± 22.8	0.276
QRS interval, ms	85.4 ± 10.1	86.5 ± 0.5	0.542	88.9 ± 10.6	86.7 ± 12.9	0.391
QT interval, ms	377.0 ± 30.7	384.3 ± 35.1	0.233	375.0 ± 39.5	370.3 ± 48.1	0.622
QTc interval, ms	418.3 ± 33.8	439.1 ± 34.5	0.024	429.2 ± 38.3	449.0 ± 44.7	<0.001
RR interval, ms	815.6 ± 167.3	771.2 ± 156.1	0.141	775.0 ± 149.5	693.0 ± 171.3	0.021
Scoring systems						
MELD score	25.7 ± 4.7	30.1 ± 6.7	<0.001	21.3 ± 6.0	25.4 ± 6.6	0.004
CPS	10.8 ± 1.18	12.0 ± 1.04	<0.001	10.8 ± 1.6	11.1 ± 1.5	0.298

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CPS = Child–Pugh score, DBP = diastolic blood pressure, HBeAg = hepatitis B e antigen, HE = hepatic encephalopathy, HRS = hepatorenal syndrome, INR = international normalized ratio, LC = liver liver cirrhosis, MELD = model for end-stage liver disease, PT = prothrombin time, PTA = prothrombin time activity, SBP = systolic blood pressure.

<sup>\*</sup> Dichotomous values.

<sup>†</sup> Categorical values.

than that in the validation cohort, but not statistically significant (42.1% vs 32.3%,  $P=0.139$ ).

Table 2 shows that patients who survived had a lower MELD score (25.7 vs 30.1,  $P<0.001$ ), CPS (10.8 vs 12.0,  $P<0.001$ ), systolic blood pressure (SBP, 119.4 mm Hg vs 124.6 mm Hg,  $P=0.048$ ), HE (5.7% vs 49.0%,  $P<0.001$ ), LC (24.3% vs 72.5%,  $P<0.001$ ), infection (17.1% vs 33.3%,  $P=0.039$ ), and ascites (42.9% vs 80.4%,  $P<0.001$ ) in the training cohort. The patients' conditions were confirmed in the validation cohort,

except for CPS (11.1 vs 10.8,  $P=0.298$ ), systolic blood pressure (123.3 mm Hg vs 118.7 mm Hg,  $P=0.172$ ), and ascites (63.3% vs 52.4%,  $P=0.320$ ). We had also found that the QT interval was not statistically different in the survival group and the death group of both cohorts (377.0 milliseconds vs 384.3 milliseconds,  $P=0.233$ ; 375.0 milliseconds vs 370.3 milliseconds,  $P=0.622$ ), but it had a longer QTc in the death group (418.3 milliseconds vs 439.1 milliseconds,  $P=0.024$ ; 429.2 milliseconds vs 449.0 milliseconds,  $P<0.001$ ).

**TABLE 3.** Univariate Analysis of the Associations Between Mortality and Clinical and Biochemical Characteristics in Patients With Acute-on-Chronic Hepatitis B Liver Failure in Training Cohort

Variables	B	HR	95% CI	P Value
<b>Clinical parameters</b>				
Age, y	0.058	1.060	1.036–1.085	<0.001
Gender*	0.447	1.563	0.845–2.892	0.155
BMI, kg/m <sup>2</sup>	0.070	1.072	0.993–1.158	0.075
SBP, mm Hg	0.025	1.025	1.004–1.047	0.020
DBP, mm Hg	0.012	1.012	0.983–1.042	0.427
HBeAg*	−0.092	0.912	0.526–1.581	0.743
HE <sup>†</sup>	1.196	3.308	2.182–5.014	<0.001
LC*	1.513	4.538	2.445–8.426	<0.001
Infection*	0.609	1.838	1.027–3.291	0.041
Ascites <sup>†</sup>	0.381	1.464	1.162–1.844	0.001
HRS*	0.310	1.363	0.425–4.378	0.603
<b>Laboratory parameters</b>				
White blood cell (10 <sup>12</sup> /L)	0.018	1.018	0.920–1.126	0.734
Haemoglobin, g/L	−0.018	0.983	0.971–0.995	0.005
Platelet (10 <sup>9</sup> /L)	−0.011	0.989	0.982–0.997	0.007
Serum sodium, mmol/L	−0.072	0.930	0.886–0.976	0.003
Serum potassium, mmol/L	0.153	1.165	0.856–1.586	0.331
ALT, U/L	0.000	1.000	0.999–1.000	0.199
AST, U/L	0.000	1.000	0.999–1.000	0.758
Albumin, g/L	0.922	−0.081	0.880–0.966	0.001
Alkaline phosphatase, U/L	0.007	1.007	1.002–1.013	0.013
γ-GT, U/L	−0.001	0.999	0.997–1.002	0.644
Total bilirubin, μmol/L	0.004	1.004	1.002–1.006	<0.001
Total cholesterol, mmol/L	−0.603	0.547	0.384–0.779	0.001
Creatinine, μmol/L	0.006	1.006	0.996–1.015	0.241
HBV DNA (log <sub>10</sub> IU/ml)	0.017	1.017	0.858–1.205	0.848
PT, s	0.050	1.051	1.027–1.076	<0.001
PTA (%)	−0.037	0.964	0.938–0.990	0.007
INR	0.465	1.593	1.270–1.998	<0.001
<b>Electrocardiogram</b>				
P-wave, ms	0.008	1.008	0.984–1.031	0.527
PR interval, ms	0.007	1.007	0.994–1.021	0.298
QRS interval, ms	0.007	1.007	0.979–1.036	0.629
QT interval, ms	0.004	1.004	0.996–1.012	0.358
QTc interval, ms	0.012	1.012	1.005–1.019	<0.001
RR interval, ms	−0.002	0.998	0.997–1.000	0.087
<b>Scoring systems</b>				
MELD score	0.095	1.099	1.054–1.146	<0.001
CPS	0.550	1.733	1.393–2.157	<0.001

γ-GT = γ-glutamyl transferase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CI = confidence interval, CPS = Child–Pugh score, DBP = diastolic blood pressure, HBeAg = hepatitis B e antigen, HE = hepatic encephalopathy, HR = hazard ratio, HRS = hepatorenal syndrome, INR = international normalized ratio, LC = liver cirrhosis, MELD = model for end-stage liver disease, PT = prothrombin time, PTA = prothrombin time activity, SBP = systolic blood pressure.

\* Dichotomous values.

† Categorical values. For gender, 0: woman, 1: man; for HBeAg, 0: negative, 1: positive; for LC, 0: non-LC, 1: LC; for infection, 0: non-infection, 1: infection; for ascites, 0: non-ascites, 1: mild (grade 1) and 2: moderate to severe (grades 2–3); for HE, 0: non-HE, 1: mild (grades 1–2) and 2: severe (grades 3–4).

**TABLE 4.** Multivariate Analysis of the Associations Between Mortality and Clinical and Biochemical Characteristics in Patients With Acute-on-Chronic Hepatitis B Liver Failure in Training Cohort

Variables	B	HR	95% CI	P Value
Age	0.033	1.034	1.007–1.061	0.012
LC*	1.013	2.753	1.366–5.548	0.005
PT	0.031	1.031	1.002–1.062	0.038
HE†	0.994	2.703	1.630–4.480	<0.001
QTc	0.008	1.008	1.001–1.016	0.036

CI = confidence interval, HE = hepatic encephalopathy, HR = hazard ratio, LC = liver cirrhosis, PT = prothrombin time.

\* Dichotomous values.

† Categorical values. For LC, 0: non-LC, 1: LC; for HE, 0: non-HE, 1: mild (grades 1–2), and 2: severe (grades 3–4).

**Construction of the ALPH-Q Score**

Table 3 shows that age, SBP, HE, LC, infection, ascites, Hb, platelet, serum sodium, ALB, alkaline phosphatase, TB, total cholesterol, PT, PTA, INR, QTc, MELD score, and CPS were significantly associated with mortality in the training cohort (all  $P < 0.05$ ).

The above variables were entered into the multivariate Cox proportional hazards regression analyses. As Table 4 has presented, age (HR = 1.034, 95% CI: 1.007–1.061,  $P = 0.012$ ), LC (HR = 2.753, 95% CI: 1.366–5.548,  $P = 0.005$ ), PT (HR = 1.031, 95% CI: 1.002–1.062,  $P = 0.038$ ), HE HR = 2.703, 95% CI: 1.630–4.480,  $P < 0.001$ ), and QTc (HR = 1.008, 95% CI: 1.001–1.016,  $P = 0.036$ ) were found to be the independent risk factors. As shown in Figure 2, patients with age  $\geq 45$  years or LC or HE or PT  $\geq 28$  seconds or QTc  $\geq 440$  milliseconds had a poorer overall survival compared with patients who did not have the characteristics mentioned above.

Finally, ALPH-Q score, a new prognostic score for ACHBLF patients, could be calculated by combining 5 independent risk factors with the regression coefficients. ALPH-Q score = 0.033 \* age + 1.013 \* LC + 0.031 \* PT + 0.994 \* HE + 0.008 \* QTc.

**Performance of ALPH-Q Score in the Training Cohort**

Figure 3A shows the ability of the ALPH-Q score to predict 3-months mortality risk in patients with ACHBLF. The performance of the new score was high, with an auROC of 0.896 (95% CI: 0.827–0.944). In the same dataset, LRM had an auROC of 0.825 (95% CI: 0.735–0.888), an MELD score of 0.712 (95% CI: 0.623–0.791), a CPS of 0.738 (95% CI: 0.650–0.814), significantly lower than that of the ALPH-Q score (all  $P < 0.001$ ). When using a best cut-off value of 6.778 for the ALPH-Q score, the sensitivity was 78.7%, the specificity was 85.1%, the positive likelihood ratio was 5.3, the negative likelihood ratio was 0.25, and the positive predictive and negative predictive values were 77.1 and 86.3, respectively (Table 5).

**Performance of ALPH-Q Score in the Prospective Validation Cohort**

As shown in Figure 3B, the auROC analysis was performed to test the robustness of the ALPH-Q score in the validation cohort. The auROC was 0.837 (95% CI:

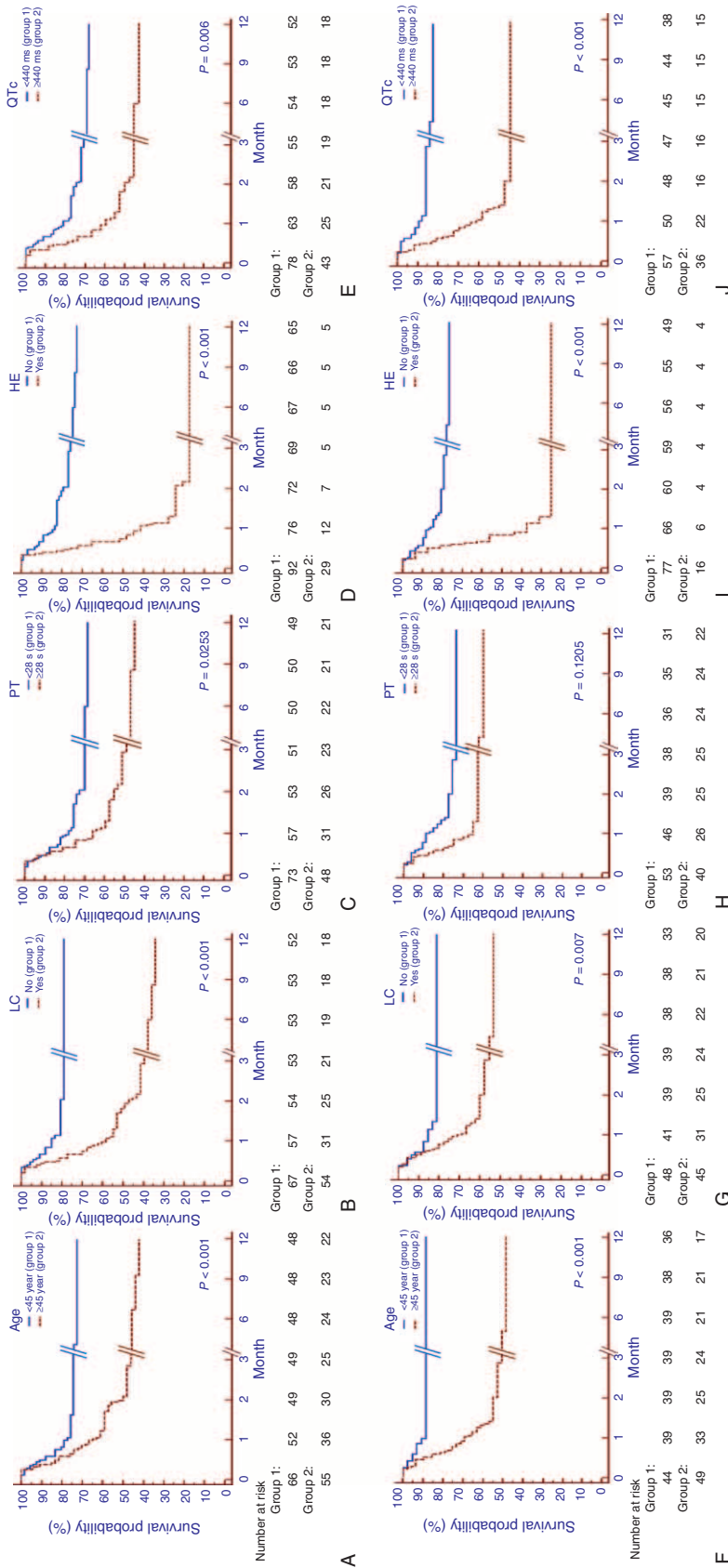
0.746–0.905), which was greater than 0.7 and suggested that the new model had its utility. The auROC of LRM, MELD, and CPS scoring systems was 0.818 (95% CI: 0.724–0.890), 0.689 (95% CI: 0.585–0.781), and 0.585 (95% CI: 0.478–0.686), respectively. The performance of the ALPH-Q score was significantly better than that of MELD and CPS ( $P = 0.033$ ,  $P < 0.001$ , respectively). No statistical difference was obtained between the ALPH-Q score and the LRM ( $P = 0.522$ ); however, the ALPH-Q score tended to be better than those of LRM (Table 5).

**DISCUSSION**

Recently, several models have been constructed for the selection of patients for liver transplantation, of which the CPS and MELD are the most widely known. However, all these models were established among European and American populations, and not using data from patients with ACLF. The etiology of ACLF differs by geographic location. The causes of ACLF among European and American patients are typically alcohol consumption, hepatitis C, and cholestasis, whereas, with high HBV prevalence, ACHBLF accounts for the majority of ACLF in China. Thus, a new logistic regression model (LRM), specific to ACHBLF, was established by our previous data and shown to have a better performance than CPS and MELD scores. However, the LRM merely considered liver-relative parameters. Furthermore, as a logistic analysis, the LRM may lose the information of the survival time inescapability and may have an effect on the predicting prognosis of ACHBLF.

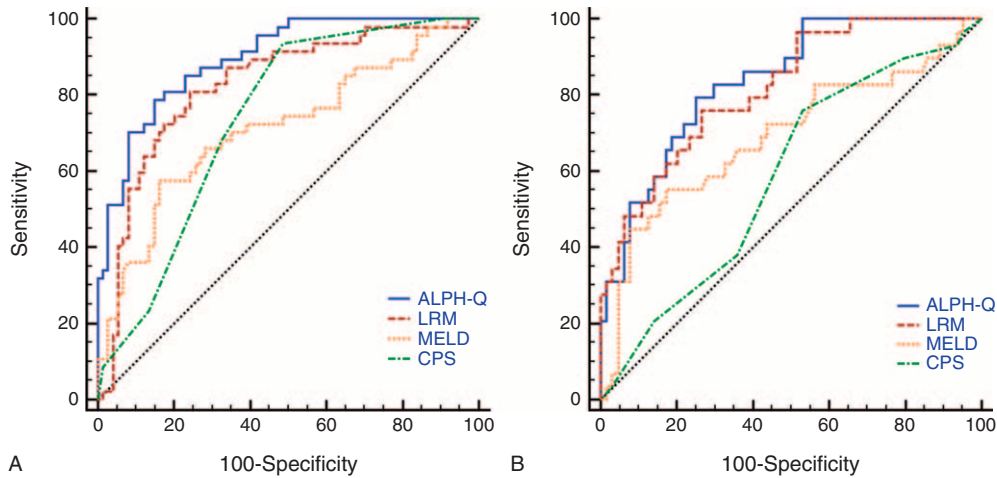
In this study, we established and validated an ALPH-Q score to predict the short-term prognosis of ACHBLF patients. To our knowledge, this is the first prognostic scoring system that has integrated a QTc parameter for the prediction of mortality in ACHBLF patients. On the basis of Cox proportional hazards regression analysis, the ALPH-Q score performed better than CPS, MELD, and LRM. In a prospective validation cohort, the improvement over CPS and MELD was 25.2% and 14.8%, respectively. No statistical difference was obtained between the ALPH-Q score and the LRM ( $P = 0.522$ ); however, the ALPH-Q score tended to be better than those of LRM.

Among the ALPH-Q scores, five independent factors were found to be associated with survival among patients with ACHBLF, namely, age, liver cirrhosis, prothrombin time, hepatic encephalopathy, and QTc. Age was associated with the risk of mortality, with older patients having worse survival rates. This result was similar in previous reports.<sup>9,10</sup> In this study, we found liver cirrhosis to be an independent risk factor. Cirrhosis represents the end stage of chronic liver disease, and although the definition of ACHBLF has no direct relation with liver cirrhosis, patients with underlying liver cirrhosis may have an increased morbidity, together with a poor life quality.<sup>29,30</sup> Our new score showed that PT is a useful risk factor. The extent of PT is based on the levels of blood coagulation factors that are synthesized in the liver, and a prolonged PT may reflect the decline in liver synthetic capacity.<sup>31</sup> Therefore, PT may become a common monitorable factor in patients with liver dysfunction. HE was a major clinical event in the natural history of cirrhosis that affects survival of patients. Some studies have indicated that HE correlates significantly with mortality in ACHBLF, particularly among patients with low MELD scores.<sup>9,10,32</sup> Thus, this clinical event should be considered. In our new prognostic score, HE played an important role and was the only subjective indicator.



**FIGURE 2.** Kaplan–Meier survival curve stratified for patients under different status of age, LC, PT, HE, and QTc. (A) In the training cohort, a shorter overall survival existed in patients with age  $\geq 45$  years or liver cirrhosis or hepatic encephalopathy or PT  $\geq 28$  seconds or QTc  $\geq 440$  milliseconds (all  $P < 0.05$ ). (B) In the validation cohort, the overall survival was the same as those in the training cohort, except that of those with PT  $< 28$  seconds and  $\geq 28$  seconds ( $P = 0.121$ ). HE = hepatic encephalopathy, LC = liver cirrhosis, PT = prothrombin time.





**FIGURE 3.** ROC analysis of the predictive accuracy of ALPH-Q score and other models to predict 3-mo mortality of acute-on-chronic hepatitis B liver failure in training cohort (A) and validation cohort (B).

The mutual interaction between the liver and the heart has been established for some time. A large number of studies have proved that the QTc may play an important role in the prognosis of patients with liver diseases and could be a useful indicator for patients who require liver transplantation.<sup>12,17,33</sup> On the basis of this study, we reconfirmed that QTc was a major predictive indicator on the prognosis of ACHBLF. Figure 3 shows that mortality among patients with prolongation of QTc interval was significantly higher than that of patients with normal QTc interval in the two cohorts (both  $P < 0.01$ ). Our analysis was in accordance with a previous study<sup>34</sup> that QTc prolongation in cirrhosis patient was correlated with the CPS.

Sudden deaths and ventricular arrhythmias had been reported to be related to the high-mortality risk with the prolongation of QTc;<sup>12,14</sup> however, the pathophysiology of QTc prolongation in ACHBLF remained unclear. Previous studies showed that the increased plasma norepinephrine concentration, an activator of the sympathetic nervous system (SNS), might play an important role in a prolong QTc.<sup>14,34,35</sup> However, other studies showed that there was no relation between QTc and SNS in these patients.<sup>36</sup> Portal hypertension and porto-systemic shunts had to be present to be responsible,<sup>37,38</sup> but this remains inconclusive.

There are, however, some limitations of this study. First, the ALPH-Q score was built on a single-center cohort and tested on another single-center cohort. It could be argued that data originating from other centers might lead to different conclusions. Thus, multicenter, prospective studies of larger populations with longer-term followup are needed. Furthermore, to exclude the effect of cardiovascular factors, patients with confirmed cardiovascular diseases or taking any agents affecting QTc interval before the establishment of ACHBLF were excluded, such as  $\beta$ -blockers, even if it is recommended in patients with portal hypertension associated with chronic liver diseases. A larger population and subgroup analysis for cardiovascular diseases should be needed in the further study. Finally, a dynamic analysis of ACHBLF in different stages is more important and meaningful than a single-point measurement.

In conclusion, we are the first to establish the new prognosis score that integrated QTc parameter, named the ALPH-Q score. The ALPH-Q score was superior to CPS, MELD, and LRM scoring systems in predicting short-term mortality risk in patients with ACHBLF and could be an ideal prognostic score to determine the order of these patients undergoing liver transplantation.

**TABLE 5.** Predictive Value of 3-Mo Mortality of the ALPH-Q Score and Other Models in the Training and Validation Cohorts

Models	auROC	95% CI	P Value	Youden Index	Cut-Off Point	Sensitivity (%)	Specificity (%)	+LR	-LR	+PV	-PV
Training cohort											
ALPH-Q	0.896	0.827–0.944		0.6386	6.778	78.7	85.1	5.30	0.25	77.1	86.3
LRM	0.825	0.745–0.888	<0.001	0.5653	0.1995	80.6	75.7	3.32	0.25	67.9	86.2
MELD	0.712	0.623–0.791	<0.001	0.4123	29.40	57.5	83.8	3.54	0.51	69.2	75.6
CPS	0.738	0.650–0.814	<0.001	0.4497	10.00	93.6	51.5	1.92	0.12	55.0	92.7
Validation cohort											
ALPH-Q	0.837	0.746–0.905		0.5431	6.900	79.3	75.0	3.17	0.28	59.0	88.9
LRM	0.818	0.724–0.890	0.522	0.4930	0.1685	75.9	73.4	2.86	0.33	56.4	87.0
MELD	0.689	0.585–0.781	0.033	0.3798	24.60	55.2	82.8	3.21	0.54	59.3	80.3
CPS	0.585	0.478–0.686	<0.001	0.2274	10.00	75.9	46.9	1.43	0.51	39.3	81.1

P value, compared with auROC of ALPH-Q. auROC = area under the receiver-operating characteristic curve, CI = confidence interval, +LR = positive likelihood ratio, -LR = negative likelihood ratio, +PV = positive predictive value, -PV = negative predictive value.

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