



Liver, Pancreas and Biliary Tract

## A new algorithm for predicting long-term survival in chronic hepatitis B patients with variceal bleeding after endoscopic therapy

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### ABSTRACT

**Background and aims:** A predictive algorithm for survival is urgently needed in clinical practice. This study aimed to establish an algorithm to predict long-term survival in chronic hepatitis B (CHB) patients with hepatic cirrhosis and variceal bleeding after endoscopic therapy.

**Methods:** This was a retrospective study in which 603 patients who followed-up for three years were randomly assigned into a training cohort and a validation cohort in a 2:1 ratio. A new score model was devised based on the result of Cox regression analysis in the training cohort, and was verified in the validation cohort.

**Results:** A prediction score model composed of age, neutrophil-lymphocyte ratio, gamma-glutamyl transpeptidase and MELD score was established. The score ranged from 0 to 11. Areas under the ROC curve of the score were 0.821 ( $p < 0.001$ , 95% CI: 0.769–0.873) and 0.827 ( $p < 0.001$ , 95% CI: 0.753–0.900) in the training cohort and validation cohort, respectively. Scores 0–4 and 5–11 identified patients as low-risk and high-risk categories, respectively. The cumulative 3-year survival rate was significantly higher in the low-risk group than in the high-risk group ( $p < 0.001$ ).

**Conclusion:** The new score model can be used to predict long-term survival in CHB patients with hepatic cirrhosis and variceal bleeding after endoscopic therapy.

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### 1. Introduction

China has one of the highest prevalences of chronic hepatitis B virus (HBV) infection worldwide, with nearly 40% of total chronic HBV infection cases, although vaccination strategies have progressively decreased the number of patients [1,2]. Consequently, nearly half a million people die from HBV-related cirrhosis and its complications each year, in which more than 20% of the deaths was related to gastroesophageal variceal (GOV) hemorrhage [3]. Portal hypertension, ultimately leading to GOV, is a natural outcome of cirrhosis. Clinically significant portal hypertension (CSPH) is defined as a threshold, which suggests that varices or its complications have developed [4,5]. Approximately 40% of cirrhotic patients with Child A and 85% with Child C were clinically diagnosed with GOV [6]. Although major progress has been made in pharmacologic and endoscopic therapies during the past decade, variceal bleed-

ing leads to high mortality in clinical practice. Approximately 60% of the patients developed re-bleeding after the first variceal hemorrhage [7], and 5–20% of the patients died within six weeks after variceal rupture [3,8,9].

In the last three decades, non-selective  $\beta$ -blockers and endotherapy have been widely used for prophylaxis in patients with variceal hemorrhage [10,11]. For patients with acute variceal bleeding, endoscopic sclerotherapy (EST) and endoscopic band ligation (EBL) were preferred [12]. Endoscopic variceal ligation (EVL) has a higher variceal recurrence rate since the deeper varices and perforating veins are difficult to completely ligate [13]. For patients with large varices, even combined treatment of EBL and EST led to up to 16.7% re-bleeding rate, especially in those who experienced post procedure pyrexia, and developed gastric antral vascular ectasia [14]. Since rupture bleeding can occur without any warnings or symptoms, and is a major cause of mortality in patients with varix [15], a warning marker or predictive algorithm for re-bleeding or long-term survival is urgently needed in clinical practice. In the present study, we retrospectively analyzed 828 HBV-related patients with variceal bleeding after endotherapy at our medical center during the past nine years, and developed a new algorithm to

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predict long-term survival based on 603 patients who followed-up for three years.

## 2. Patients and methodology

### 2.1. Patients

This was a retrospective cohort study, and the protocol was approved by the Ethics Committee of Beijing Ditan Hospital, Capital Medical University. Between September 2008 and December 2016, all chronic hepatitis B (CHB) patients with hepatic cirrhosis and variceal bleeding, who were treated by endoscopic therapy at the Beijing Ditan Hospital, Capital Medical University, China, were followed-up for the risk of death. The exclusion criteria were: (i) patients co-infected with hepatitis C virus, and other chronic liver diseases; (ii) patients with liver cancer, and other serious concurrent illness; (iii) patients with acute upper gastric mucosal lesions, and peptic ulcers. CHB infection was defined as HBsAg seropositive status at  $\geq 6$  months [16]. Liver cirrhosis was defined as an irregular and nodular liver imaged by ultrasonography, CT, or MRI, together with impaired liver synthetic functions. Other findings included small and shrunken liver, splenomegaly, and evidence of portosystemic collaterals [17].

### 2.2. Clinical data collection

Baseline data was defined as the data collected at the time of endotherapy for gastroesophageal varices. The data included the demographic data (age, gender) and laboratory indexes, such as white blood cell (WBC), neutrophil-lymphocyte ratio (NLR), platelet (PLT), hemoglobin (HGB), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), cholinesterase (CHE), total bilirubin (TBIL), albumin (ALB), creatinine (Cr), prothrombin time (PT), alpha fetoprotein (AFP), HBeAg and HBV-DNA. The portal vein diameter and spleen thickness, measured by trans-abdominal ultrasonography, were also noted. Child-Turcotte-Pugh score and MELD score were recorded.

### 2.3. Endotherapy and follow-up

All patients received their first endoscopy, and/or urgent endoscopic therapy within 12–24 h after admission at our medical center. Based on the drug therapy (Octreotide, Somatostatin, Terlipressin, and proton pump inhibitors), proper blood transfusion, and fluid therapy, all patients received endotherapy when their hemodynamic status was stable.

The endoscopic therapies were as follows: (i) for patients with esophageal variceal bleeding, endoscopic variceal ligation (EVL) was performed; (ii) for patients with gastric variceal hemorrhage, cyanoacrylate injection was used; (iii) for patients with GOV hemorrhage, the “sandwich therapy” (2 ml polidocanol+0.5 ml *n*-butyl-2 cyanoacrylate+2 ml polidocanol) was used (repeated injections, if necessary). Most patients with GOV1 and GOV2 varices received repeated endotherapy every 3–6 months of follow-up. For some patients with esophageal variceal bleeding, endoscopic injection sclerotherapy (EIS) was also performed. The appropriate therapy was chosen based on the clinical guidelines [18,19] and the specialists' preferences and experiences.

The follow-up ended on September 2017. The primary outcome was 3-year survival. The secondary outcome was 5-year survival. The median follow-up duration was 59 months. The longest follow-up duration was 111 months.

### 2.4. Antiviral therapy

Antiviral therapy is defined as the time before and/or after endoscopic treatment. Nearly 80% of the patients had received antiviral therapy after 2010 because it was recommended in the clinical guideline in China [20].

### 2.5. Statistical analysis

Statistical analysis was performed by SPSS version 19.0 (IBM Corp., Armonk, NY, United States) and GraphPad Prism version 7.0 (GraphPad Prism Software Inc., San Diego, CA, USA). Quantitative data with normal distribution were analyzed by Student's *t*-test, and expressed as mean  $\pm$  standard deviation. Data that did not accord with normal distribution were analyzed by Mann-Whitney *U* test, and expressed as median with interquartile range. Qualitative data were analyzed by chi-square test, and expressed as percentage.

Patients who followed-up for three years were randomly assigned into the training cohort and validation cohort in a 2:1 ratio. Univariate and multivariate Cox regression analyses were performed in the training cohort to determine the variables associated with 3-year survival. Risk of death was expressed as hazard ratio (HR) and 95% CI. The score model was established according to the Cox regression analysis result. The HRs were converted to integer risk scores and the final score was the sum of these values. It was then applied to the validation cohort. Accuracy of the new score model was estimated by areas under the receiver operating characteristics (AUROC) curve and its 95% CI. Sensitivity analysis was performed by analyzing all patients who followed-up for five years.

The score was categorized into low and high risk groups with a cutoff value (the highest sum of sensitivity and specificity). The Kaplan-Meier method was used to estimate the cumulative survival rate of different groups. The log-rank test was used to compare time-to-event curves between different groups. Two-sided *p*-values  $< 0.05$  were considered statistically significant.

## 3. Results

### 3.1. Patient characteristics

From September 2008 to December 2016, a total of 2886 patients underwent endoscopic therapy at the Beijing Ditan hospital. After excluding patients with peptic ulcer bleeding, laceration hemorrhage or Dieulafoy disease (221 patients), infected with HCV (244 patients), alcoholic liver disease (568 patients), autoimmune liver disease (54 patients), primary biliary cirrhosis (95 patients), and other non-HBV chronic liver diseases (241 patients); 1459 CHB patients remained. Of these, patients who failed to follow-up (272 patients) or had pre-existing hepatocellular carcinoma (359 patients) at baseline were excluded. The final analysis included 828 CHB patients with hepatic cirrhosis and variceal bleeding (Fig. 1).

The 1, 2, 3, 4 and 5-year cumulative survival rates were 91.6%, 87.2%, 80.9%, 74.3% and 67.1%, respectively. At a median follow-up of 59 months, 115 (19.1%) of 603 patients died in three years, of which three patients died of non-liver diseases and 112 patients died of liver diseases, including 32 patients who died of re-bleeding and 22 patients who died of HCC. A total of 143 (32.9%) patients died in five years, of which four patients died of non-liver diseases and 139 patients died of liver disease, including 36 patients who died of re-bleeding and 32 patients who died of HCC. Nine patients underwent a TIPS after bleeding.

The baseline characteristics of patients who followed-up for three years are shown in Table 1. Patients who died were older,

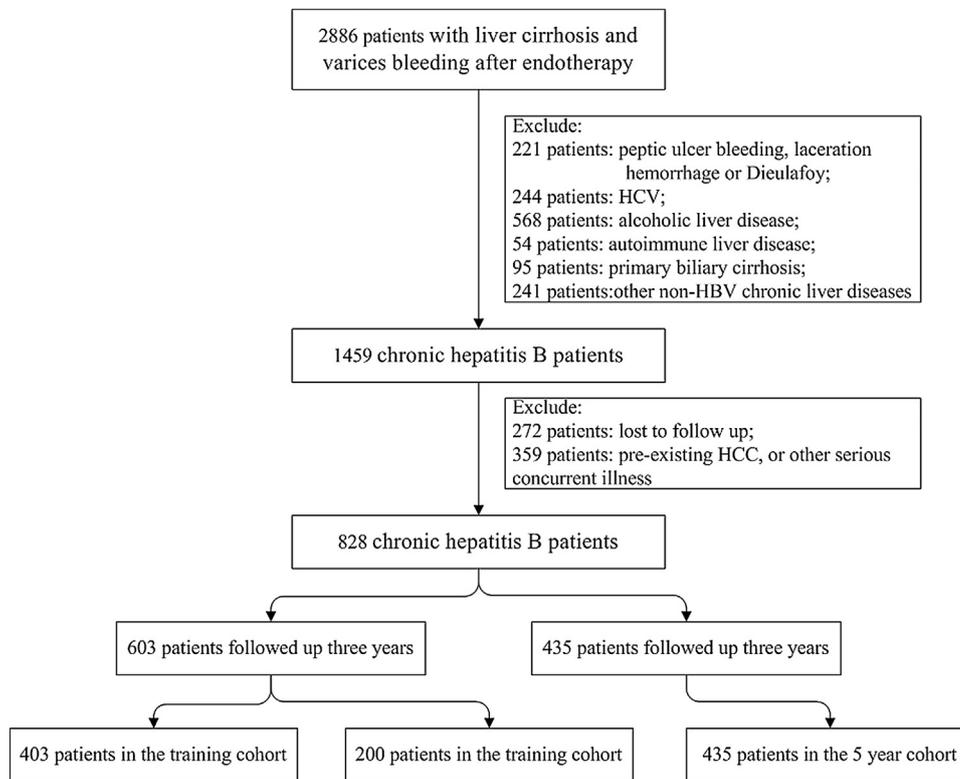


Fig. 1. Study design.

**Table 1**  
Characteristics of patients followed up 3 years.

Variable	Survival (n = 488)	Death (n = 115)	p
Age (year)	48.7 ± 10.3	53.9 ± 9.6	<0.001
Male sex	360 (73.8%)	82 (71.3%)	0.591
Ascites	338 (69.3%)	99 (86.1%)	<0.001
Hepatic encephalopathy	38 (7.8%)	22 (19.1%)	<0.001
portal vein thrombosis	27 (5.5%)	13 (11.3%)	0.025
Cyanoacrylate glue (ml)	1.0 (0.5–1.5)	1.0 (1.0–1.5)	0.027
Lauroacrylate glue (ml)	20.0 (10.0–40.0)	20.0 (10.0–40.0)	0.554
Antiviral therapy	392 (80.3%)	78 (67.8%)	0.004
WBC ( $\times 10^9/l$ )	3.6 (2.5–6.1)	4.0 (2.7–6.3)	0.277
NLR	3.0 (1.8–4.8)	4.8 (3.1–6.5)	<0.001
HGB (g/l)	95.1 ± 28.7	86.3 ± 27.0	0.003
PLT ( $\times 10^9/l$ )	62.0 (43.7–86.0)	56.4 (36.4–85.5)	0.118
ALT (U/l)	26.7 (19.1–40.3)	27.1 (18.8–48.0)	0.648
TBIL ( $\mu\text{mol/l}$ )	17.9 (13.3–27.8)	26.0 (17.1–45.7)	<0.001
ALB (g/l)	32.6 ± 6.2	30.0 ± 5.1	<0.001
GGT (U/l)	25.8 (15.6–35.8)	42.8 (21.7–64.4)	<0.001
CHE (U/l)	3340 (2460–4402)	2524 (1787–3379)	<0.001
Cr ( $\mu\text{mol/l}$ )	63.0 (53.4–72.4)	67.0 (54.4–87.4)	0.001
PT (s)	15.1 (14.0–16.4)	15.9 (14.4–18.4)	<0.001
AFP (ng/ml)	4.1 (2.2–7.9)	5.0 (2.5–13.6)	0.095
CTP class	142/248/98	12/56/47	<0.001
Meld score	6 (3–8)	9 (6–14)	<0.001

Data are presented as mean ± standard deviation, or number (percentage). EVL, endoscopic variceal ligation; WBC, white blood cell; NLR, neutrophil-lymphocyte ratio; HGB, hemoglobin; PLT, Platelet; ALT, alanine aminotransferase; TBIL, total bilirubin; ALB, albumin; GGT, gamma-glutamyl transpeptidase; CHE, cholinesterase; Cr, creatinine; PT, prothrombin time; AFP, alpha fetoprotein; CTP class, Child–Turcotte–Pugh class.

applied more cyanoacrylate glue, did not receive antiviral therapy, had higher NLR, lower HGB, higher TBIL, lower ALB, higher GGT, lower CHE, higher Cr, longer PT, higher MELD score and a large proportion of CTP class C. They also had higher proportion of ascites and hepatic encephalopathy (Table 1). Table S-1 lists the endoscopic therapies. There was no significant difference between the different therapies.

### 3.2. Factors associated with death risk

To establish a score model for predicting long-term prognosis in CHB patients with hepatic cirrhosis and variceal bleeding, 603 patients who followed-up for three years were randomly assigned into the training cohort and validation cohort in a 2:1 ratio. Factors associated with 3-year mortality were analyzed in the training cohort by univariate and multivariate Cox regression analyses.

In the training cohort, 79 (19.6%) of 403 patients died in three years. Table 2 shows the results of Cox regression analysis. By univariate analysis, age, antiviral therapy, HGB, NLR, ALT, GGT, TBIL, ALB, Cr, PT, HBV-DNA, AFP, MELD score and CTP score were found to be significant risk factors for the incidence of death in three years. By multivariate analysis, age, NLR, GGT and MELD score remained independent factors for the high risk of mortality (Table 3).

Further analysis was performed to identify the influence of each risk factor on the 3-year cumulative survival rate. The 3-year cumulative survival rate was 86.9% in the age ≤ 50 years group, while it was 73.0% in the age > 50 years group (Fig. 2A). It was significantly higher in the age ≤ 50 years group than that in the age > 50 years group. Similarly, the 3-year cumulative survival rate was 89.3% in the NLR ≤ 4.28 group, while it was 63.8% in the NLR > 4.28 group (Fig. 2B). The 3-year cumulative survival rate was 88.1% in the GGT ≤ 40.4  $\mu\text{l}$  group, while it was 59.6% in the GGT > 40.4  $\mu\text{l}$  group (Fig. 2C). The 3-year cumulative survival rate was 87.5% in MELD score ≤ 8 group, whereas it was 64.2% in MELD score > 8 group (Fig. 2D). It was significantly higher in the MELD score ≤ 8 group than in the MELD score > 8 group.

### 3.3. Prediction score model

A new score model was established based on the independent risk factors in the multivariate Cox regression analysis. It was devised on the basis of the HR value of each parameter (Table 4). The score ranged from 0 to 11. AUROC was 0.821 ( $p < 0.001$ , 95%

**Table 2**  
Factors associated with death risk in training cohort.

Variable	Univariate analysis HR (95%CI)	p	Multivariate analysis HR (95%CI)	p
Age (year)	1.038 (1.017–1.061)	0.001	1.048 (1.018–1.078)	0.001
Ligation	0.570 (0.308–1.054)	0.073		
Antiviral therapy	0.612 (0.377–0.995)	0.048		
WBC ( $\times 10^9/l$ )	1.026 (0.968–1.087)	0.387		
HGB (g/l)	0.992 (0.984–1.000)	0.044		
NLR	1.051 (1.022–1.081)	0.001	1.083 (1.019–1.152)	0.011
PLT ( $\times 10^9/l$ )	0.997 (0.993–1.002)	0.268		
ALT (U/l)	1.005 (1.003–1.007)	<0.001		
GGT (U/l)	1.009 (1.006–1.012)	<0.001	1.007 (1.003–1.011)	<0.001
TBIL ( $(\mu\text{mol/l})$ )	1.005 (1.003–1.007)	<0.001		
ALB (g/l)	0.937 (0.904–0.972)	0.001		
Cr ( $\mu\text{mol/l}$ )	1.007 (1.002–1.011)	0.003		
PT (s)	1.106 (1.033–1.183)	0.004		
HBeAg (positive)	1.358 (0.844–2.186)	0.208		
HBV-DNA (positive)	1.738 (1.002–3.015)	0.049		
AFP (ng/ml)	1.007 (1.004–1.009)	<0.001		
MELD score	1.119 (1.083–1.156)	<0.001	1.120 (1.075–1.168)	<0.001
Child–Pugh score	1.310 (1.189–1.444)	<0.001		

WBC, white blood cell; NLR, neutrophil–lymphocyte ratio; PLT, Platelet; ALT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; AFP, alpha fetoprotein.

**Table 3**  
Components of the score model.

Variable	HR (95%CI)	p	Risk score
Age > 50 (year)	1.799 (1.129–2.867)	0.013	2
NLR > 4.28	3.101 (1.932–4.977)	<0.001	3
GGT > 40.4 (U/l)	3.570 (2.274–5.603)	<0.001	4
MELD score > 8	2.376 (1.503–3.757)	<0.001	2

CI: 0.769–0.873) (Fig. 3D). We assigned the scores 0–4, 5–11 to the low-risk and high-risk categories according to the highest sensitivity and specificity of the score model. In the low-risk group, 237 (93.3%) patients survived for three years after endoscopic therapy. Correspondingly, the patients who survived in the high-risk group was 58.4%. The 3-year cumulative survival rate was significantly higher in the low-risk group than in the high-risk group ( $p < 0.001$ ) (Fig. 3A).

To verify its accuracy, the score model was then used in the validation cohort (200 patients). AUROC of the validation cohort was 0.827 ( $p < 0.001$ , 95% CI: 0.753–0.900) (Fig. 3E). In the validation cohort, the cumulative 3-year survival rate was 92.5% and 66.3% in the low-risk and high-risk groups, respectively (Fig. 3B). The cumulative survival rate was significantly higher in the low-risk group than in the high-risk group ( $p < 0.001$ ).

The prediction score model was further verified in a subgroup of patients (435 patients) who followed-up for five years. The 5-year survival rate of CHB patients with hepatic cirrhosis and variceal bleeding after endoscopic therapy was 67.1%. The AUROC of 5-year survival prognosis was 0.774 ( $p < 0.001$ , 95% CI: 0.727–0.822) (Fig. 3F). The cumulative 5-year survival rate was 82.3% and 43.5% in the low-risk and high-risk groups, respectively ( $p < 0.001$ ) (Fig. 3C).

The prognostic score was also compared with other currently used scores like MELD and Child–Pugh scores. The new score model (AUROC = 0.821, 95% CI: 0.769–0.873) was more accurate than the MELD score (AUROC = 0.705, 95% CI: 0.638–0.771) and the Child–Pugh score (AUROC = 0.687, 95% CI: 0.623–0.751) (Fig. S-1).

#### 4. Discussion

CHB infection, which frequently leads to liver cirrhosis, is a major public health problem worldwide [21,22], especially in China [23,24]. More than 70 million individuals are infected with HBV in

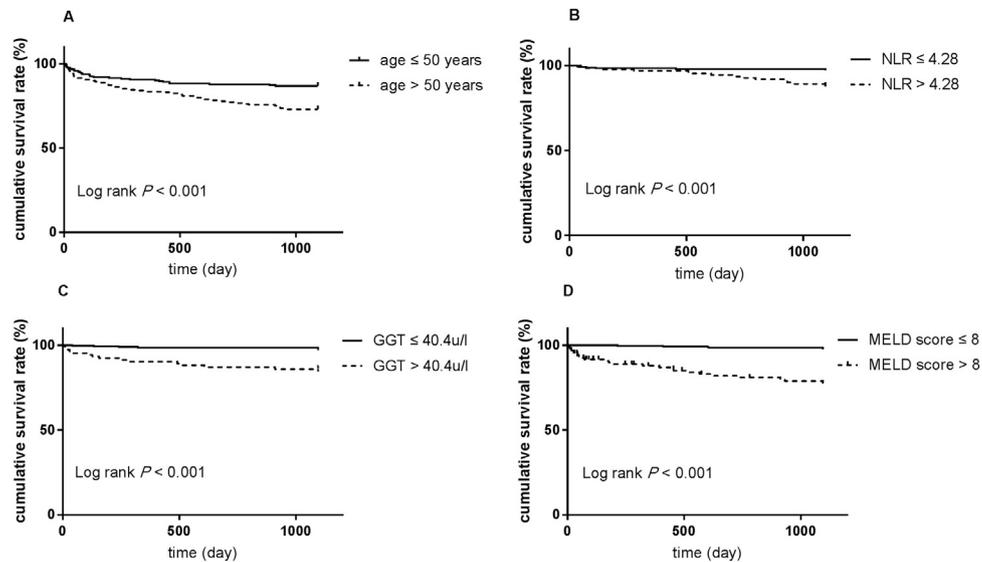
China [23]. Clinically, liver cirrhosis and gastroesophageal varices are end-stage diseases that invariably lead to death. Endoscopic therapy is the primary strategy for gastroesophageal varices. Therefore, a predictive algorithm for long-term survival of CHB patients with gastroesophageal varices after endoscopic therapy is urgently needed.

In this study, we established a predictive score model to predict 3-year survival in CHB patients with hepatic cirrhosis and variceal bleeding who were treated with endoscopic therapy. This model was easy to apply in clinical practice because it was composed of four routinely available clinical markers. It was not only accurate and sensitive for predicting 3-year survival but also applicable for predicting 5-year survival since it was validated in the patients who followed-up for five years.

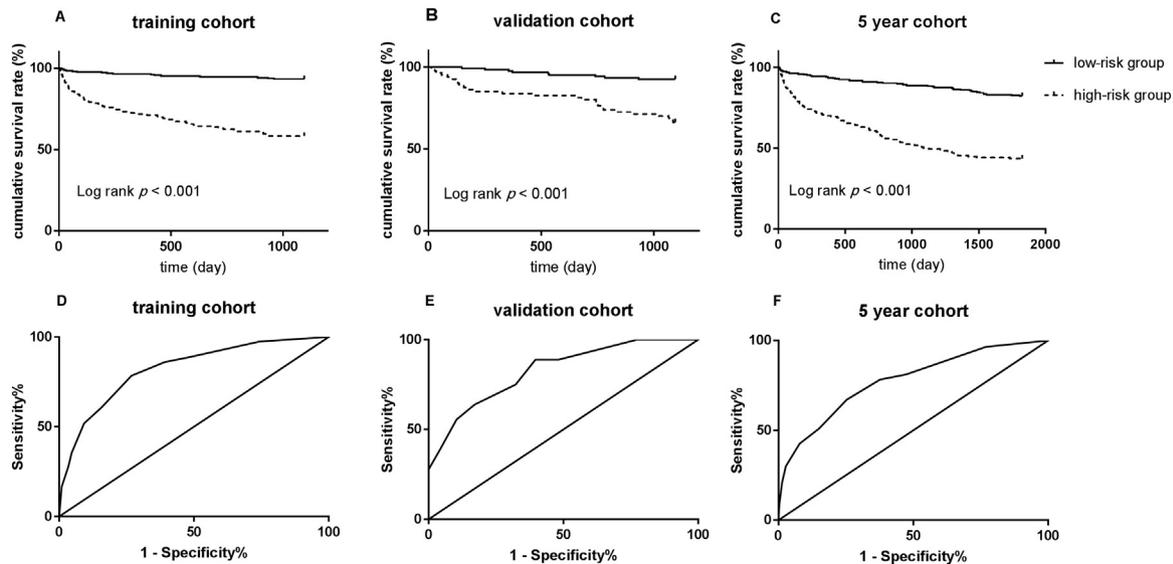
To the best of our knowledge, this is the first model and the largest cohort study to predict long-term survival of CHB patients after endoscopic therapy in the world. The risk score developed in this study can provide valuable insights to clinicians for long-term prediction after endoscopic therapy, and if necessary, to pay more attention to the high-risk individuals. Several management strategies may be considered, including more intensive follow-ups.

Various methods are used to predict gastroesophageal varices in chronic liver diseases [25–27]. However, there is no prediction model for long-term survival or re-bleeding after endoscopic therapy. Recent studies have shown that MELD score, Child–Pugh score, HVPG, units of packed red blood cells, administration of antibiotics, coexistence of HCC, and PPI administration are associated with re-bleeding as well as mortality in patients with gastroesophageal varices [28–31]. Previous studies mostly focused on risk factors that affect clinical outcomes. No study has combined non-invasive clinical parameters, used Cox regression analysis, and established a score model to predict death risk. Notably, our model is specifically applicable for patients with HBV, the main cause of chronic liver diseases in China.

The final clinical markers of this score model include age, NLR, GGT, and MELD score. Age was reported to be an independent factor associated with prognosis in several studies [32,33]. NLR is believed to be an important factor associated with prognosis. Higher NLR level is related to poor overall survival and disease-free survival [34,35]. Our study found that  $\text{NLR} > 4.28$  may be an indicator of poor overall survival in CHB patients with variceal bleeding after endoscopic therapy. Gamma-glutamyltransferase is involved



**Fig. 2.** The 3-year cumulative survival rate of patients in different groups. A, age  $\leq 50$  years group and age  $> 50$  years group ( $p < 0.001$ ). B,  $NLR \leq 4.28$  group and  $NLR > 4.28$  group ( $p < 0.001$ ). C,  $GGT \leq 40.4 \mu/l$  group and  $GGT > 40.4 \mu/l$  group ( $p < 0.001$ ). D, MELD score  $\leq 8$  group and MELD score  $> 8$  group ( $p < 0.001$ ).



**Fig. 3.** The 3-year cumulative survival rate of patients in the low-risk and high-risk groups. A, training cohort ( $p < 0.001$ ). B, validation cohort ( $p < 0.001$ ). C, 5-year cohort ( $p < 0.001$ ). The performance of the algorithm. D, training cohort. AUROC was 0.821 ( $p < 0.001$ , 95% CI: 0.769–0.873). E, validation cohort. AUROC was 0.827 ( $p < 0.001$ , 95% CI: 0.753–0.900). F, 5-year cohort. AUROC was 0.774 ( $p < 0.001$ , 95% CI: 0.727–0.822).

in biotransformation, nucleic acid metabolism, and tumorigenesis. Higher GGT indicates a poor survival [36]. Numerous studies have reported the validity of MELD score in predicting prognosis [37,38]. The present study confirmed MELD score as one of the independent risk factors in the multivariate analysis in CHB patients with variceal bleeding.

Antiviral therapy is a protective factor for long-term survival in CHB patients. Nevertheless, it is not in the final equation using multivariate Cox regression. Patients with HBV cirrhosis mostly received antiviral therapy after 2010 as it is recommended in the clinical guideline in China [20].

This study had several potential limitations. Firstly, it was a single center study, and multi-center studies are required for further verification. Secondly, retrospective cohort study has its inherent limitations as a clinical strategy for HBV infection or endoscopic treatment optimize over time. Importantly, some clinical complications of endotherapy, which influenced patients' outcome, such as portal vein thrombosis, spontaneous peritonitis, etc., were not

analyzed in this study. The model established in the present study is composed of routine serological indicators that are easy to acquire. Thirdly, liver stiffness measurement (LSM) plays an important role in the prognosis estimation in patients with liver cirrhosis. However, the LSM was started in November 2015 at our hospital. As this was a retrospective study and the patients were followed-up for at least three years, the LSM data of the patients was not available in the study.

## 5. Conclusion

The new algorithm, composed of age, NLR, GGT and MELD score, can predict long-term survival in CHB patients with variceal bleeding after endoscopic therapy. A prospective validation study is necessary in the future.

## Conflict of interest

None declared.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.dld.2019.01.004>.

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