Am J Transl Res 2023;15(5):3697-3704
www.ajtr.org /ISSN:1943-8141/AJTR0149139

Original Article

Construction of a risk prediction model for non-variceal upper gastrointestinal bleeding and rebleeding based on multi-dimensional indicators and its application research

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Received January 15, 2023; Accepted April 14, 2023; Epub May 15, 2023; Published May 30, 2023

Abstract: Objective: To construct a predictive model for the risk of rebleeding in non-variceal upper gastrointestinal bleeding (NVUGIB) based on multidimensional indicators to provide an assessment tool for early screening of rebleeding in NVUGIB. Methods: Retrospective analysis of the 3-month follow-up data of 85 patients with NVUGIB diagnosed at the Fifth Hospital of Wuhan from January 2019 to December 2021 who were discharged from the hospital after medical treatment. Patients were divided into a rebleeding group (n=45) and a non-rebleeding group (n=95) based on whether they rebleed during follow-up. The demographic characteristics, clinical characteristics and biochemical indicators of the two groups were compared. A multivariate logistic regression was used to analyze the influencing factors of NVUGIB rebleeding. A nomograph model was built using the screening results. The area under the working characteristic curve of the subject (AUC) was used to analyze the model differentiation, evaluate the model specificity and sensitivity, and verify the prediction performance of the model with the validation set. Results: There were significant differences in age, hematemesis, red blood cell count (RBC), platelet (PLT), albumin (Alb), prothrombin time (PT), TT, fibrinogen (Fib), plasma D-dimer (D-D), and blood lactate (LAC) levels between the two groups (all $P<0.05$). Logistic regression analysis shows that, age ≥75, hematemesis more than 5 times, PLT≤100*10^9/L, D-D>0.5 mg/L were associated with greater risk of rebleeding. The nomogram model was constructed based on the above four indicators. The AUC of the training set (n=98) for predicting the risk of NVUGIB rebleeding was 0.887 (95% CI: 0.812-0.962), the specificity was 0.882, and the sensitivity was 0.833. The AUC of the validation set (n=42) was 0.881 (95% CI: 0.777-0.986), the specificity was 0.815, and the sensitivity was 0.867. After 500 times of sampling by bootstrap method, the mean absolute error of the calibration curve of the validation set model was 0.031, indicating that the calibration curve and the ideal curve fit well, and the predicted value of the model was in good agreement with the actual value. Conclusion: Age ≥75, hematemesis >5 times, lower PLT, and higher D-D levels rise the risk of rebleeding in NVUGIB patients and have some reference value in clinical diagnosis and disease assessment.

Keywords: Non variceal upper gastrointestinal bleeding, rebleeding, prediction model

Introduction

Non-variceal upper gastrointestinal bleeding (NVUGIB) is bleeding from the gastrointestinal tract above the ligament of Trevor, with a mortality rate of 6% to 10%. The main clinical manifestations are melena, hematemesis, and dizziness. The clinical diagnosis of NVUGIB are often signs of peripheral circulatory failure such as decreased blood pressure, pale complexion, and rapid heart rate [1]. Patients were guided to do relevant examinations. Identifying the clinical symptoms and etiological composition of the disease is of great significance for timely diagnosis and disease assessment. There are clear descriptions of the diagnostic guidelines and clinical manifestations of NVUGIB in clinical practice. There is continuous international research reported changes in the clinical symptoms and etiological composition of the disease [2]. It is necessary to clarify the clinical features and epidemiology of the disease in depth and to strengthen the control measures. Internal medicine is the main treat-

ment for NVUGIB. The success rate of the treatment reaches 90%. Some patients are at risk of rebleeding after the treatment. Once rebleeding occurs, patients have a poor prognosis and a high-risk of death [3]. Identifying the risk factors of rebleeding immediately and providing effective targeted intervention are important means to decrease the risk of rebleeding and increase the prognosis. A logistic regression model is used to analyze the influencing factors of NVUGIB rebleeding in clinical practice. A logistic regression model has the characteristics of fast training speed and is easy to understand, but it cannot directly present the importance of each factor to the result variable. The nomogram model is a line segment graph with scale. This model is concise and self-evident, and has good guiding value in the field of disease prediction. We constructed a NVUGIB rebleeding risk prediction model based on multidimensional indicators to identify high-risk indicators and provide an assessment tool for early screening of NVUGIB rebleeding.

Objects and methods

Research objects

This study complies with the ethical guidelines of the Declaration of Helsinki. Retrospective analysis was conducted on medical record information of 85 NVUGIB patients diagnosed at the Fifth Hospital of Wuhan from January 2019 to December 2021. The included patients should meet the following criteria: (1) All patients met the diagnostic criteria in the 'Guidelines for the diagnosis and treatment of acute non-variceal upper gastrointestinal bleeding (2015)' [4]; (2) All patients had endoscopic indications and the bleeding was stopped by endoscopic diagnosis and treatment; (3) All patients age ≥18 years; (4) All patients had complete data. Exclusion criteria: (1) The patients with a history of surgery before bleeding; (2) The patients in pregnancy and lactation; (3) The patients with craniocerebral injury; (4) The patients complicated with malignant tumor of digestive system; (5) The patients with contraindications to endoscopic treatment; (6) The patients with blood system diseases.

Methods

Grouping method: Outcome measurement: whether the patient had rebleeding 7 days after treatment was used as an outcome indicator. After the endoscopic hemostasis treatment, patients were identified to have rebleeding if they had clinical symptoms such as melena and hematemesis during follow-up, combined with various vital signs and biochemical indicators.

Definition of rebleeding [5]: After drug therapy, endoscopic therapy, interventional embolization or surgery, one or more of the following conditions recur after upper gastrointestinal bleeding: (1) The frequency of melena and hematemesis increased, the stool was thin, accompanied by hyperactive bowel sounds; (2) The symptoms of peripheral circulatory failure were temporarily improved and worsened after active fluid rehydration and blood transfusion, or no improvement; (3) Blood urea nitrogen increased again with adequate rehydration and urine volume; (4) Reticulocyte count continued to rise, and red blood cell count, leukocyte volume and hemoglobin concentration decreased progressively.

Grouping: Patients with rebleeding within 7 days after treatment were included in the rebleeding group (n=45). Those with no bleeding within 7 days were included in the non-bleeding group (n=95).

Clinical data collection: (1) Demographic characteristics: gender, age, body mass index (BMI), hypertension, diabetes mellitus, coronary artery disease, and the use of bleeding-prone drugs (e.g.: antiplatelet drugs, nonsteroidal tired anti-inflammatory drugs, and glucocorticoids). (2) Clinical features: whether there was hematemesis, black stool, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), mean arterial pressure (MAP), and shock index at admission for the first bleeding. (3) Biochemical indicators: white blood cell count (WBC), red blood cell count (RBC), hemoglobin (HGB), platelet (PLT), albumin (Alb), blood urea nitrogen (BUN), prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (Fib), D-dimer (D-D), blood lactate (LAC); the above laboratory indicators were all completed before endoscopy, and all were the first laboratory results.

Establishment of nomogram model

Using the machine learning settings, all selected NVUGIB patients were divided into a training set (98 cases) and a validation set (42 cases) at

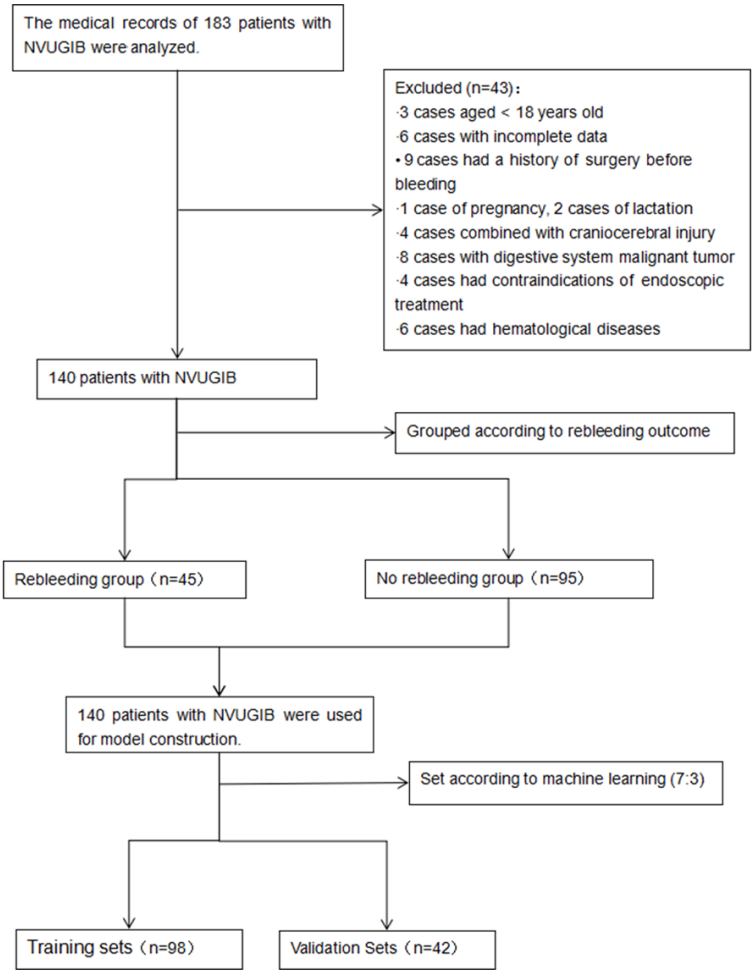

Figure 1. Research flow chart (PS: NVUGIB: non variceal upper gastrointestinal bleeding).

a ratio of 7:3. Based on the training set data, the logistic regression model was constructed using the lrm function in R Studio software. The validation set data was used for model validation. Variable input: Rebleeding were used as dependent variable of the regression model and the indicators related to rebleeding were used as independent variables. These variables were simultaneously entered into the regression model formula. The logistic regression equation is expressed as:

$$logit(P) = ln\frac{P}{1-P} = \beta_0 + \sum_{j=1}^{p}\beta_j x_j$$

β_0 is the intercept term or constant term of the equation, β_j is the partial regression coefficient of the equation, χ_j is the number of variables.

Statistical treatment

SPSS 24.0 statistical software was used for analysis of relevant data. Measured data were expressed as mean ± standard deviation ($\bar{x}\pm s$), and compared by t test; The counted data was expressed as frequency [n (%)] and compared by chi-square (χ^2) test. The nomogram model of NVUGIB rebleeding was constructed based on multivariate logistic regression analysis. The area under the curve (AUC) was used to analyze the model discrimination performance. The goodness of fit (Hosmer-Lemeshow) test was used to evaluate the model calibration; Use validation set data to verify the prediction efficiency of the model. Inspection standards: α=0.05.

Results

Analysis of the demographic characteristics of the two groups

The research and analysis process are shown in **Figure 1**. After follow-up, there were 45 case in the rebleeding group, accounting for 32.14%, and 95 case in the non-rebleeding group, accounting 67.86%. There was a significant difference in the age of the two groups of patients (P<0.05), but no significant differences in the sex, BMI, hypertension, diabetes, or coronary heart disease, taking hemorrhagic drugs compared (all P>0.05) (**Table 1**).

Analysis of clinical characteristics of the two groups

In clinical manifestations, there were 29 cases of hematemesis in the rebleeding group (64.44%), the proportion was significantly higher than that in the non-rebleeding group (29.47%) (P<0.05); Comparison of melena, sys-

Table 1. Demographic characteristics analysis [n (%), ($\bar{x}$±s)]

Features	Rebleeding group (n=45)	No rebleeding group (n=95)	χ^2/t	*P*
Gender (Male/Female)	25/20	62/33	1.223	0.269
Age (years)	75.04±5.62	71.02±5.63	3.956	<0.001
BMI (kg/m^2)	23.55±2.03	23.16±2.17	1.017	0.311
Hypertension (yes/no)	22/23	48/47	0.033	0.856
Diabetes (yes/no)	21/24	41/54	0.182	0.670
Coronary heart disease (yes/no)	23/22	46/49	0.152	0.696
Taking bleeding-prone drugs (yes/no)	25/20	39/56	2.588	0.108

PS: BMI: Body mass index.

Table 2. Analysis of clinical characteristics [n (%), ($\bar{x}$±s)]

Features	Rebleeding group (n=45)	No rebleeding group (n=95)	χ^2/t	*P*
Hematemesis >5 times (yes/no)	31/14	27/68	20.608	<0.001
Black stool >5 times (yes/no)	23/22	42/53	0.585	0.445
SBP (mmHg)	117.45±14.92	116.39±17.54	0.350	0.727
DBP (mmHg)	69.12±7.41	67.46±7.99	1.176	0.242
MAP (mmHg)	85.26±9.34	84.55±10.77	0.378	0.706
HR (b/min)	92.54±12.64	91.19±12.12	0.607	0.545
Shock index	0.85±0.33	0.79±0.24	1.154	0.251

PS: SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate.

tolic, diastolic blood pressure, mean arterial pressure, heart rate, and shock index of the two groups showed no significant differences (all *P*>0.05) (**Table 2**).

Comparison of biochemical indicators between the two groups

In laboratory examination, comparison of RBC, PLT, Alb, PT, TT, Fib, and D-D levels showed that there were significant differences between the two groups (all *P*<0.05). The two groups were compared in WBC, HGB, BUN, APTT, and LAC levels, and the differences were not significant (all *P*>0.05) (**Table 3**).

Multivariate logistic regression analysis of NVUGIB rebleeding

With rebleeding as the dependent variable, taking the indicators with significance in the analysis of patient demographics, clinical features, and biochemical indicators as independent variables. Logistic regression analysis shows that the age, hematemesis, PLT, and D-D were all risk factors. Age ≥75, hematemesis more than 5 times, PLT≤100×10^9/L and D-D>0.5 mg/L were associated with greater risk of rebleeding, see **Table 4**.

The nomogram model of NVUGIB rebleeding was constructed with the training set

Based on the training set data (n=98), a nomogram model of risk prediction was constructed using the four characteristic variables screened from multivariate logistic regression analysis. The corresponding scores related to each index were added to obtain a total points. It was converted into a predicted probability of NVUGIB rebleeding risk. See **Figure 2**.

Nomogram model results

The AUC of the nomogram model for predicting the risk of rebleeding in NVUGIB patients was 0.887 (95% CI: 0.812-0.962), the specificity was 0.882, and the sensitivity was 0.833. The results suggest that the nomogram model has good discrimination ability (**Figure 3A**). The calibration curve of the nomogram model was constructed by the original sampling of the Bootstrap method for 500 times, the mean absolute error was 0.044, and Hosmer-Lemeshow suggested no deviation between predicted and actual values (χ^2=4.483, *P*=0.811). It showed that the calibration curve fit well with the ideal curve, and the predicted

Table 3. Comparison of biochemical indicators ($\bar{x}\pm s$)

Index	Rebleeding group (n=45)	No rebleeding group (n=95)	χ^2/t	*P*
WBC (×10^9/L)	9.33±2.64	9.51±2.54	0.372	0.711
RBC (×10^12/L)	2.41±0.45	2.76±0.30	5.358	<0.001
HGB (g/L)	89.30±7.71	91.63±6.33	1.888	0.061
PLT≤100×10^9/L (yes/no)	34/11	32/63	21.484	<0.001
Alb (g/L)	29.33±4.41	32.71±3.89	4.603	<0.001
BUN (mmol/L)	9.29±2.52	9.50±2.54	0.462	0.645
PT (s)	13.91±1.98	13.06±1.95	2.385	0.018
APTT (s)	24.22±4.15	23.02±3.65	1.728	0.086
TT (s)	18.98±3.60	16.30±3.32	4.338	<0.001
Fib (g/L)	1.93±0.23	2.06±0.37	2.213	0.029
D-D>0.5 mg/L (yes/no)	32/13	27/68	22.823	<0.001
LAC (mmol/L)	1.67±0.40	1.48±0.34	2.888	0.005

PS: WBC: white blood cell count; RBC: red blood cell count; HGB: hemoglobin; Alb: albumin; PLT: platelet; BUN: blood urea nitrogen; PT: prothrombin time; APTT: activated partial thromboplastin time; TT: thrombin time; Fib: fibrinogen; D-D: D-dimer; LAC: lactic acid.

Table 4. Multivariate logistic regression analysis

Variable	*β*	*SE*	Wald χ^2	*P* value	*OR* (95% *CI*)
Age ≥75 years old	*0.196*	0.046	17.951	<0.001	1.217 (1.111-1.333)
Hematemesis >5 times	1.351	0.515	6.876	0.009	3.862 (1.407-10.605)
PLT≤100×10^9/L	1.838	0.541	11.558	0.001	6.283 (2.178-18.125)
D-D>0.5 mg/L	1.475	0.518	8.109	0.004	4.372 (1.584-12.067)
Constant	-17.808	3.613	24.296	<0.001	-

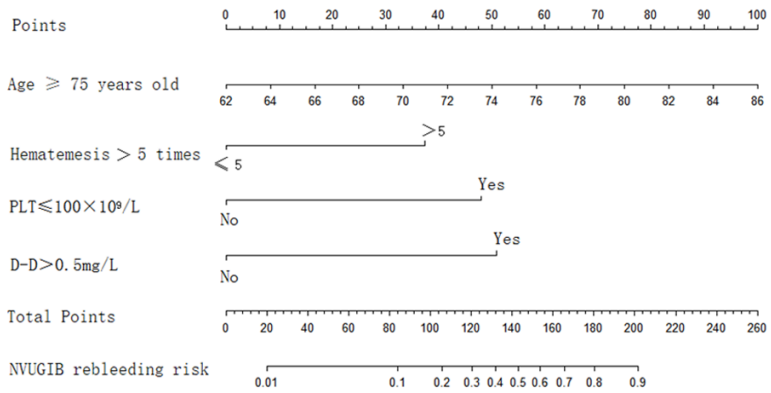

Figure 2. Nomogram prediction model of NVUGIB bleeding risk (PS: NVUGIB: non variceal upper gastrointestinal bleeding; PLT: platelet; D-D: D-dimer).

value of the model was in good agreement with the actual occurrence value (**Figure 3B**).

Nomogram model validation

The AUC of the nomogram for the validation set (n=42) was 0.881 (95% CI: 0.777-0.986), the specificity was 0.815, and the sensitivity was 0.867, suggesting a good discrimination of the nomogram model (**Figure 4A**). The average absolute error of the calibration curve of the validation set model was 0.031 (**Figure 4B**), indicating that the predicted value of the model is in good agreement with the corrected predicted value.

Discussion

NVUDIB is a common type of upper gastrointestinal bleeding. The clinical symptoms of the disease are hematemesis, melena, dizziness, fatigue, abdominal distension, and abdominal pain. Occasional symptoms included palpitations, sweating (referring to profuse sweating or cold sweat), syncope, and clammy limbs [6]. With the continuous improvement of medical standards, the treatment strategy, prevention plan, and management measures of NVUGIB have been improved.

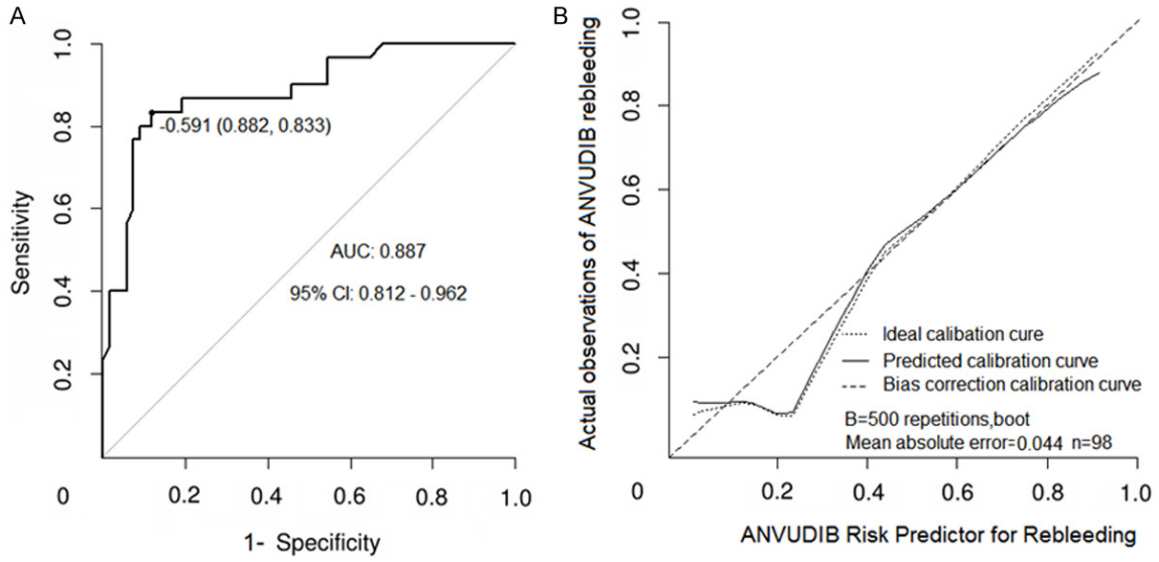

Figure 3. The predictive performance of the nomogram model on the training set. A: The receiver operating characteristic curve (ROC) of the training set; B: Calibration curve of the training set.

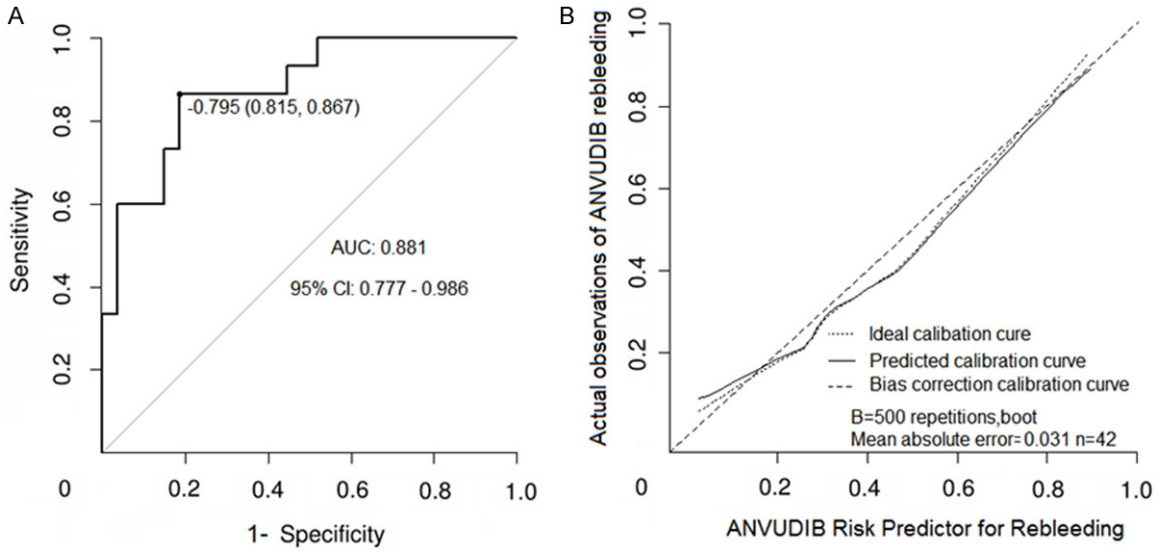

Figure 4. The predictive performance of the nomogram model on the validation set. A: The receiver operating characteristic curve (ROC) of the validation set; B: Calibration curve of the validation set.

Relevant domestic and foreign guidelines have summarized and updated acid suppression regimens. The rapid development and application of endoscopic therapy has significantly reduced the mortality rate and rebleeding rate of these patients [7]. As the accelerated aging of the population, the number of elderly patients with NVUGIB is increasing yearly, coupled with the fact that elderly patients usually have a combination of multiple underlying diseases, organ function decline often requires treatment with anticoagulants, antiplatelet drugs, and NSAIDs. Reducing the incidence of NVUGIB rebleeding has become a major clinical challenge. Rebleeding assessment is an important part of the prognosis of NVUGIB patients, and the occurrence of rebleeding can increase the risk of death by more than 10 folds [8]. This research, we searched for the influence factors of NVUGIB rebleeding from three dimensions, including demographic characteristics, clinical characteristics and biochemical indicators, and constructed a risk prediction model for NVUGIB rebleeding.

Previous studies have reported [9] that advanced age was associated with a higher risk of rebleeding and mortality in patients with NVUGIB. Patients ≥75 were more likely to have significant organ complications than those who were younger than 75 year old. These included diabetes and hypertension. These complications will reduce the ability of tissue repair, leading to non-healing or delayed healing after bleeding, and the risk of rebleeding after surgery is higher [10]. Clinicians and families should pay attention to the prevention of rebleeding in elderly patients to improve the prognosis. In a meta-analysis [11], active endoscopic bleeding, hemodynamic disturbance, ulcer, hemoglobin values, and the need for transfusion were considered to be the main predictors of rebleeding after treatment. If the patients are accompanied by unstable hemodynamics, or have the symptoms of massive hematemesis and melena, they are at high risk of rebleeding. It is necessary to seek medical attention immediately, take emergency endoscopic treatment, determine the bleeding site, and conduct hemostasis treatment in time [12]. In this study, the rebleeding group had more hematemesis than the non-rebleeding group, indicating that hematemesis more 5 times was a contributing factor to the patient's risk of rebleeding. No other studies have reported that hematemesis was an influence factor for rebleeding in patients with NVUGIB. This was presumed to be related to the small sample number of patients in this study. More verification is needed. The main function of PLT is coagulation and hemostasis. The plasma layer consisting of plasma proteins, coagulation factors, and fibrinolytic systems is the outer covering of PLT. It plays an important role in hemostasis after vascular injury [13]. Patients with low PLT can lead to prolonged bleeding time, severe damage to the body or rebleeding under stress [14]. The PLT levels were significantly lower in the rebleeding group in this study than the non-bleeding group. Univariate and multifactorial regression analyses showed that PLT was a protective factor against rebleeding in NVUGIB patients. The higher the PLT, the less likely it was that rebleeding would occur. In the study of Bonnet et al. [15], PLT aggregation dysfunction predicted bleeding risk in patients with decompensated cirrhosis. Plasma D-D is the main factor that reacts to fibrinolytic activity and blood formation and is considered a prognostic marker for gastrointestinal hemorrhage. D-D were higher in the rebleeding group than in the non-rebleeding group in this study, it was an influence factor for rebleeding after discharge from hemostatic treatment, and was positively associated with rebleeding; the higher the plasma D-D, the greater the risk of rebleeding in patients with NVUGIB [16]. A study [3] concluded that plasma D-D is a predictor of rebleeding in patients with NVUGIB. The presence of fibrinolysis and coagulation abnormalities in the body's vasculature caused an increase in D-D levels, showing the possibility of rebleeding in patients with NVUGIB. This proved a good predictive value.

There are many influencing factors for rebleeding in NVUGIB patients. It is very important to construct a risk prediction model with simple clinical application and strong self-evident. The nomogram model has been widely used in disease prediction and has a good prediction effect. There is a lack of exploration in the nomogram model of rebleeding risk in NVUGIB patients. In this study, four independent risk factors were screened based on three dimensions of demographic characteristics, clinical characteristics and biochemical indicators. A nomogram prediction model for rebleeding in NVUGIB patients was constructed using the training set. The AUC of the model to predict the risk of rebleeding in NVUGIB was above 0.8, suggesting that the model has strong predictive ability and high visualization, readability and accuracy. To verify the prediction performance of the model, an internal data (validation set) was used to authenticate the accuracy of the model. The AUC predicted by the validation set model was 0.881. This was equivalent to the prediction ability of the training set. The calibration curve of the validation set model was close to the ideal curve, suggesting that the nomogram model has good discrimination and small average absolute error, indicating that the model has a good consistency level. These results suggest that the nomogram has a certain predictive value for rebleeding in NVUGIB patients. Clinicians can use this nomogram model to scientifically and reasonably formulate preoperative decision-making and postoperative intervention programs to maximize the benefits of NVUGIB patients.

In summary, age ≥75, hematemesis >5 times, lower PLT, and higher D-D and LAC levels increase the risk of rebleeding in patients with NVUGIB, and it has certain reference value in clinical diagnosis and disease assessment. The nomogram model is simple, convenient,

easy to apply clinically, and easy to popularize in primary hospitals. Limitations of this study: this study was a single-center retrospective research. There may be selection bias and information bias. Prospective multi center research should be carried out in the future. Changes of age, hematemesis, PLT, and D-D should be dynamically observed to reduce the risk of rebleeding in patients with NVUGIB.

Disclosure of conflict of interest

None.

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