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Original Article

Retrospective analysis of risk factors for non-variceal upper gastrointestinal bleeding and construction of a nomogram prediction model

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Abstract: Aim: By analyzing the clinical data of patients with non-variceal upper gastrointestinal bleeding (NVUGIB), the independent risk factors for NVUGIB were found, and a risk prediction model was initially constructed. Methods: This retrospective analysis collected patients hospitalized in Laizhou City People's Hospital from January 2020 to January 2022. According to whether the patients had NVUGIB during hospitalization, they were divided into a bleeding group of 173 cases and a control group of 121 cases. We collected the medical records of the two groups, including general conditions, disease conditions, medication conditions, and laboratory test indicators. The independent risk factors of NVUGIB were screened by univariate and multivariate logistic regression analysis, and a prediction model was initially constructed. The nomogram was developed using R language. the establishment of a regression equation model was based on the above risk factors: *logit (P)* = -8.320 + 0.436 * history of peptic ulcer + Helicobacter pylori infection * 0.522 + use of anticoagulant and antiplatelet drugs * 0.881 + 0.583 * increased leukocyte count + prolonged international normalized ratio (INR) * 0.651 + hypoproteinemia * 0.535. By using receiver operating characteristic curves, area under curve and Hosmer-Lemeshow test, the discrimination and calibration of the model was evaluated, and a calibration curves were plotted. Results: Univariate and multivariate regression analysis identified that history of peptic ulcer, Helicobacter pylori infection, use of anticoagulant and antiplatelet drugs, increased leukocyte count, prolonged INR and hypoproteinemia were risk factors for NVUGIB. Those risk factors were used to construct a clinical predictive nomogram. The calibration curves for NVUGIB risk revealed excellent accuracy of the predictive nomogram model. The unadjusted C-index was 0.773 [95% CI, 0.515-0.894]. The area under the curve was 0.793982. Decision curve analysis showed that the predictive model could be applied clinically when the threshold probability was 20 to 60%. Conclusions: A history of peptic ulcer, Helicobacter pylori infection, use of anticoagulant and antiplatelet drugs, increased leukocyte count, prolonged INR, and hypoproteinemia may be independent risk factors for NVUGIB. Furthermore, this study initially established a risk prediction model for NVUGIB and developed a nomogram. It was verified that the model had good differentiation ability and consistency, andcould provide a practical reference for clinical work.

Keywords: Non-variceal upper gastrointestinal bleeding, risk factors, nomogram, retrospective analysis

Introduction

Upper gastrointestinal bleeding (UGIB) refers to the bleeding of the digestive tract that occurs above the flexor ligament, including the esophagus, stomach, duodenum, bile duct and pancreatic duct. UGIB is commonly divided into variceal upper gastrointestinal bleeding (VUGIB) and non-variceal upper gastrointestinal bleeding (NVUGIB) [1]. In many countries, the incidence of NVUGIB is five times greater than that of VUGIB. According to epidemiological studies, the annual incidence of NVUGIB is estimated to be 50 to 150 per 100,000 people and the mortality rate ranges from 2% to 14% [2-4]. In the UK, a survey showed that 14% of the patients with NVUGIB were hospitalized due to non-digestive diseases, while 25% of them were elderly people over 80 years old. The mortality rate of the NVUGIB patients in this survey was 33% [5]. Furthermore, recent studies have reported a positive correlation between NVUGIB morbidity and mortality with age [6].

Most studies on NVUGIB focus on the severity, prognosis, and rebleeding risk to patients, such

as using Rockall score to determine whether further endoscopic intervention is needed and Forrest score to assess the risk of rebleeding under endoscopy. Also, Glasgow Latchford score, Quick Sequential Organ Failure Assessment, AIMS65 score and Italian PNED score system are usually used to evaluate the severity and prognosis of the disease [7-9]. Unfortunately, there is currently no specific research or risk scoring system for NVUGIB in clinical practice. As such, this research intends to establish a prediction model for NVUGIB by analyzing the clinical medical records of patients.

Nomograms can effectively predict the occurrence of disease in individuals and have been utilized in various disciplines such as predicting the survival probability of cancer patients [10], the prognosis of liver failure [11] and the incidence of infectious diseases [12]. This study will utilize nomograms to quantify and display the independent risk factors of NVUGIB in patients. It is hoped that this would provide certain theoretical references for clinicians to carry out early assessment, screening, and prevention, which is an innovative approach. Ultimately, this study aims to explore the risk factors for NVUGIB in patients, and to develop a simple and intuitive nomogram model to predict its risk.

Materials and methods

Study design and ethics

This is a retrospective analysis, which collected patients hospitalized in Laizhou City People's Hospital from January 2020 to January 2022. This study was approved by the ethics committee of Laizhou City People's Hospital. This subjects were divided into a bleeding group (n=173) and a control group (n=121) according to whether NVUGIB occurred during hospitalization.

Inclusion criteria

(1) Patients who were 18 years or older; (2) Patients who were admitted within 48 hours after symptoms of UGIB; (3) Patients with NVUGIB confirmed by gastroscopy [13]: there was no varicose vein under endoscope, and the bleeding point was found; (4) Patients with severe bleeding requiring immediate endoscopic intervention or surgery; (5) Patients without severe peripheral circulatory failure, respiratory failure, gastrointestinal perforation or other contraindications to gastroscopy.

Exclusion criteria

Patients were excluded if they: (1) had undergone gastroscopy or refused gastroscopy for more than 48 hours; (2) had esophageal, gastric varices or other non-UGIB; (3) had lower gastrointestinal bleeding or bleeding in other parts of the body; (4) had multiple primary cancers; or (5) had incomplete clinical data.

Data collection and measurement

General information (age, sex, etc.), disease history (upper gastrointestinal ulcer, cardiovascular and cerebrovascular diseases, liver cirrhosis, hypertension and diabetes), recent drug use (non-steroidal anti-inflammatory drugs (NSAIDs) and hormone drugs) and general vital signs (blood pressure, heart rate, etc.) were collected at admission, while laboratory hematologic indicators (complete set of blood coagulation, blood routine and biochemistry) were examined.

Construction of the nomogram

Methods such as inputting and backward stepwise methods in univariate and multivariate logistic regressions and the step-by-step method in multiple linear regressions were used to select independent variables. Subsequently, a nomogram was constructed based on the independent determinants identified through multivariate Cox regression.

Validation of the nomogram

The performance of the nomogram was validated regarding discrimination capabilities, calibration, and clinical value. The discrimination capabilities were quantitatively assessed by the area under curve (AUC) of the receiver operating characteristic (ROC) curve (where 1 indicates perfect discrimination, and 0.5 indicates no discrimination). The calibration of the nomogram was investigated from the graphical representations of the consistency between the predicted probabilities and the observed outcomes based on 1,000 bootstrap resamples. Decision curve analysis was performed to validate the clinical value of the nomogram,

Table 1. Clinical characteristics of patients

	Bleeding group (n=173)	Control group (n=121)	t/χ^2	*P*
Age (years)	72.1±7.37	72.8±12.1	9.65	0.47
Sex			11.46	0.79
Male (n%)	97 (56.1%)	73 (60.3%)		
Female (n%)	76 (43.9%)	48 (39.7%)		
BMI (kg/m^2)	17.15±2.03	18.25±1.87	6.39	0.09
Smoke	45 (26.0%)	44 (36.4%)	7.547	0.006
Drink	37 (21.4%)	37 (30.6%)	7.063	0.008
Coronary heart disease	110 (63.4%)	16 (23.5%)	5.171	0.023
Helicobacter pylori infection	12 (6.9%)	3 (2.5%)	8.106	0.004
Heart failure	3 (1.7%)	2 (1.7%)	0.014	0.907
Diabetes	41 (23.7%)	33 (27.3%)	1.378	0.24
PUD	6 (3.5%)	9 (7.4%)	5.437	0.02
Hypertension	167 (96.5%)	118 (97.5%)	1.874	0.171
Cerebral apoplexy	155 (89.6%)	112 (92.6%)	6.664	0.01
Atrial fibrillation	17 (9.8%)	10 (8.3%)	5.301	0.021
Anticoagulant and antiplatelet drugs	51 (15.03%)	78 (64.5%)	76.791	<0.01
Nonorganic anti-inflammatory drugs	87 (50.3%)	72 (59.5%)	5.958	0.015
Glucocorticoid drugs	27 (15.6%)	48 (39.7%)	53.509	<0.01
White blood cell count ($\times 10^9/L$)	9.65±8.06	13.92±2.06	-13.3	<0.001
Hemoglobin (g/L)	124.79±22.1	104.41±22.7	-5.944	<0.001
Albumin (g/L)	43.57±11.9	33.56±10.8	-1.601	0.029
C-reactive protein (ng/L)	2.54±4.56	143.14±22.02	-7.235	<0.001
Procalcitonin (ng/mL)	0.23±0.09	1.63±1.32	-6.308	<0.001
INR	1.13±1.87	1.63±2.12	-8.225	<0.001
D dimer (μg/mL)	695.89±432.1	2840.59±874.2	-9.650	<0.001
Triglyceride (mmol/L)	1.18±1.44	2.42 (1.88, 3.68)	-3.327	0.001
LDL-C (mmol/L)	2.46±2.17	2.51±2.19	-0.079	0.973

Note: BMI: body mass indexes; PUD: Peptic Ulcer Disease; INR: international normalized ratio; LDL-C: Low density lipoprotein cholesterol. Significant difference as P<0.05.

assessing if the clinical utility of the nomogram increases the net benefits when realistic threshold probabilities are considered.

Statistical analysis

Data were analyzed with SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). Normality distribution was evaluated with the Kolmogorov-Smirnov test, and the results are expressed as mean - standard deviation, median (interquartile range), or percentage when appropriate. A two-tailed unpaired t test or Mann-Whitney U test was used for independent samples. Chi-square test was used to compare variables between patients without and with NVUGIB when appropriate. Univariate and multivariable logistic regression models were used to evaluate the presence of NVUGIB predictors. A two-sided *P* value <0.05 was considered significant.

Results

Basic clinicopathological characteristics

The comparison of the general clinical data of the two groups showed statistically significant differences in smoking and drinking history, peptic ulcer, coronary heart disease, atrial fibrillation, stroke, Helicobacter pylori infection, anticoagulant and antiplatelet drug use, nonsteroidal anti-inflammatory drug use, glucocorticoid drug use, white blood cell count, international normalized ratio (INR), D-dimer, hemoglobin count, albumin level, C-reactive protein, procalcitonin, and triglyceride level (P<0.05). See **Table 1**.

Table 2. Univariate logistic regression analyses

Factor	β	SE	P	OR	95% CI
Smoking history	0.578	0.375	0.007	1.613	1.144-2.273
Drinking history	0.579	0.284	0.009	1.615	1.127-2.315
Coronary heart disease	0.479	0.267	0.033	1.461	1.053-2.029
Helicobacter pylori infection	1.243	0.722	0.039	1.319	1.115-1.888
PUD	0.772	.0.539	0.033	2.164	1.115-4.202
Cerebral apoplexy	-0.261	0.736	0.389	0l63	0.22-1.803
Atrial fibrillation	-0.032	0.519	0.153	0.649	0.347-1.211
Anticoagulant and antiplatelet drugs	1.353	0.508	<0.01	4.279	3.041-6.023
Nonorganic anti-inflammatory drugs	1.369	0.18	<0.01	3.393	2.619-5.907
Glucocorticoid drugs	1.263	0.174	<0.01	3.528	2.487-5.034
Prolonged INR	4.531	1.034	<0.01	92.481	12.255-705.042
D dimer rise	1.473	0.176	<0.01	4.362	3.088-6.161
anemia	1.034	0.277	<0.01	2.811	1.802-4.386
Hypertriglyceridemia	0.425	0.198	0.031	2.53	1.038-2.254
Increased white blood cell count	3.843	0.507	<0.01	16.172	11.428-25.804
Hypoalbuminemia	2.087	0.37	<0.01	3.956	2.215-4.138
CRP rise	1.548	0.395	<0.01	2.255	2.901-6.239
PCT rise	1.573	0.514	<0.01	8.506	3.513-12.049

Note: PUD: Peptic Ulcer Disease; INR: international normalized ratio; CRP: C-reactive protein; PCT: Procalcitonin.

Table 3. Multifactor Logistic analysis

Factor	β	SE	X^2	P	OR	95% CI
History of peptic ulcer	2.568	0.383	16.743	<0.01	2.797	2.263-10.16
Helicobacter pylori infection	2.974	0.7	8.951	0.006	3.139	1.035-1.548
Anticoagulant and antiplatelet drugs	0.599	0.219	23.882	<0.01	2.715	1.769-4.167
Prolonged INR	4.059	1.131	8.313	<0.03	16.370	2.321-195.72
Increased white blood cell count	2.339	0.207	94.648	<0.01	16.370	6.521-16.491
Hypoalbuminemia	1.678	1.211	15.374	0.002	13.970	1.365-2.970

Note: INR: international normalized ratio.

Univariate logistic regression analyses

There were significant differences between the two groups in smoking and drinking history, peptic ulcer, coronary heart disease, Helicobacter pylori infection, anticoagulant and antiplatelet drug use, non-steroidal anti-inflammatory drug use, glucocorticoid drug use, increased leukocyte count, INR, D-dimer, anemia, hypoproteinemia, C-reactive protein, procalcitonin and hypertriglyceridemia (P<0.05). See **Table 2**.

Multivariate logistic regression analysis

Multivariate logistic regression analysis was carried out in factors showing significant differences by univariate analysis. It was found that history of peptic ulcer, Helicobacter pylori infection, use of anticoagulant and antiplatelet drugs, prolongation of INR, increase of white blood cell count and hypoproteinemia were independent risk factors for NVUGIB (**Table 3**).

Development of nomogram model

The prognostic predictors of NVUGIB were included in a prediction model established by R software (R 3.6.3). The prediction probability corresponding to the sum of the integral of each factor was the risk value of preterm birth (**Figure 1**). We established the regression equation model based on the above factors: *logit (P)* = -8.320 + 0.436 * history of peptic ulcer + Helicobacter pylori infection * 0.522 + use of anticoagulant and antiplatelet drugs *

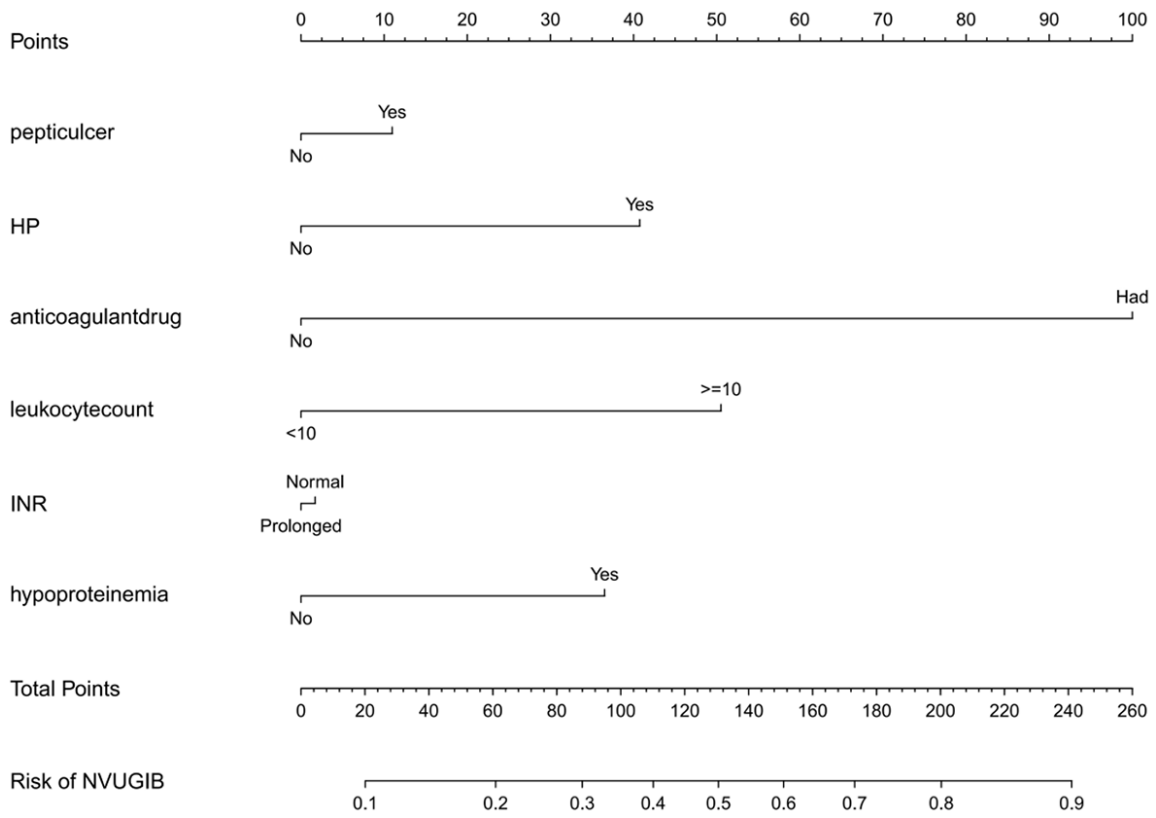

Figure 1. Nomogram for predicting the risk of non-variceal upper gastrointestinal bleeding (NVUGIB). HP: Helicobacter pylori infection; INR: international normalized ratio.

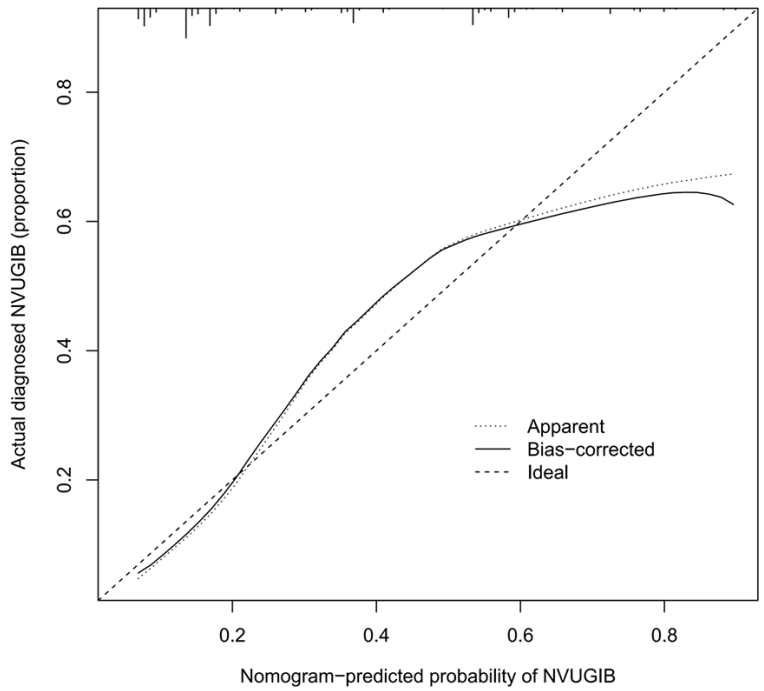

Figure 2. Calibration curves for predicting the risk of non-variceal upper gastrointestinal bleeding (NVUGIB).

0.881 + 0.583 * increased leukocyte count + prolonged INR * 0.651 + hypoproteinemia * 0.535.

Validation of nomogram model

The unadjusted concordance index (C-index) for the nomogram was 0.773 (95% confidence interval (CI), 0.515-0.894). The calibration plot of the nomogram is shown in **Figure 2**. The AUC for the nomogram was 0.793982 (**Figure 3**). This indicated that the nomogram model had a good discrimination and consistency in predicting NVUGIB.

The decision curve analysis

The decision curve analysis of the model is shown in the

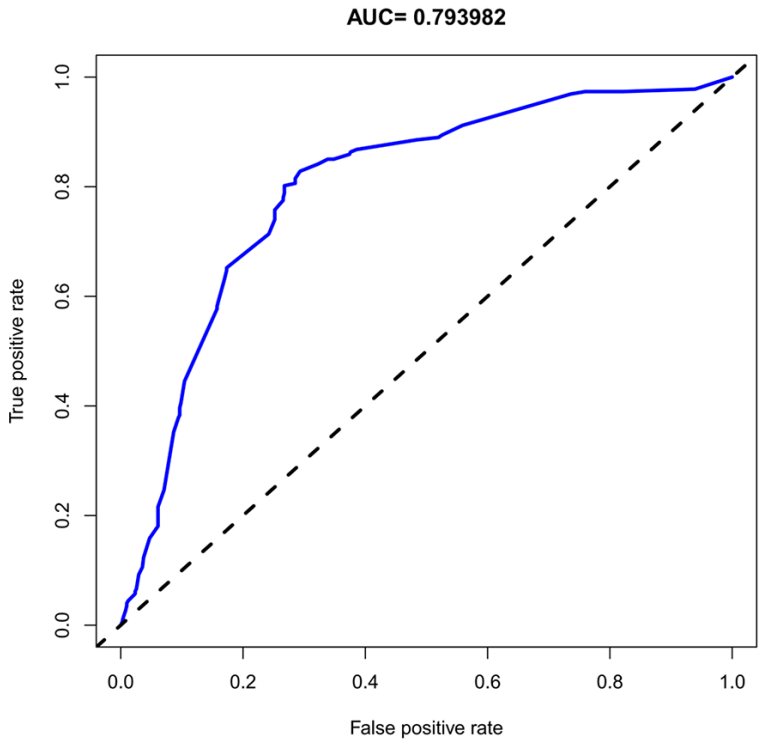

Figure 3. Receiver operating characteristic curve for predicting the risk of non-variceal upper gastrointestinal bleeding (NVUGIB). AUC: Area Under Curve.

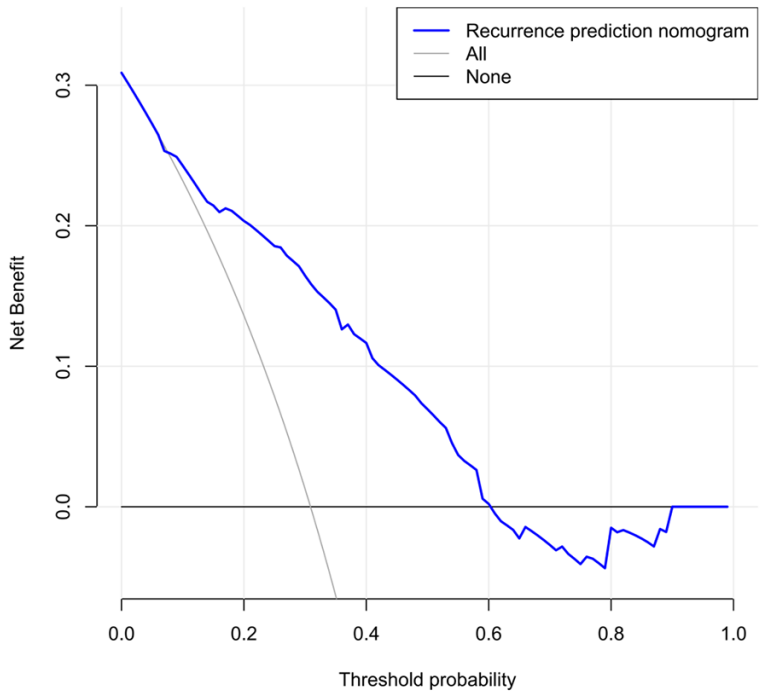

Figure 4. Decision curve analysis for the nomogram.

Figure 4. If the threshold probability of preterm birth of twin pregnancies was 20 to 60%, the validity of the model was increased. This indicates that this predictive model is suitable for clinical use.

Discussion

We collected clinical characteristics of the patients to generalize and screen risk factors for NVUGIB and constructed a predictive nomogram model to predict the risk of NVUGIB. A history of peptic ulcer, Helicobacter pylori infection, use of anticoagulant and antiplatelet drugs, prolongation of INR, increase of white blood cell count, and hypoproteinemia were identified as independent risk factors for NVUGIB. Our nomogram model was shown to good accuracy and clinical applicability, with a high C-index and AUC. The decision curve analysis demonstrated clinical usefulness of this nomogram for predicting NVUGIB. In addition, this model can enable early identification of high-risk population.

Peptic ulcer bleeding (PUB) is the main cause of NVUGIB, and new PUB cases account for 67% of all NVUGIB patients [14, 15]. A large number of studies have shown that Helicobacter pylori infection is the main cause of PUB, and the prevalence of Helicobacter pylori infection increases with age [16, 17]. The results of this study showed that the history of peptic ulcer (OR=4.797, 95% CI=2.263~10.165) and Helicobacter pylori infection (OR=1.139, 95% CI=1.035~1.548) were

risk factors for NVUGIB, which is consistent with the known research results. This may be related to the fact that patients with digestive tract ulcers often have no typical epigastric pain, vague symptoms, and cannot be diagnosed and treated early, leading to ulcer bleeding. Therefore, comprehensive diagnostic tools such as targeted questionnaires for the digestive tract, early detection, diagnosis and treatment of peptic ulcer, and eradication of Helicobacter pylori are important means to prevent patients from developing NVUGIB.

A large number of studies have found that the use of anticoagulants, antiplatelet drugs, and NSAIDs is a common cause of gastrointestinal mucosal damage and NVUGIB [18, 19]. Some studies have shown that NSAIDs can damage the gastric mucosa and cause NVUGIB by reducing prostaglandins in the gastric mucosa. A study showed that over 30% of the bleeding were related to the use of NSAIDs [20]. In this study, anticoagulant and antiplatelet drug use (OR=2.715, 95% CI=1.769~4.167) is an independent risk factor for NVUGIB. Therefore, for patients using anticoagulant and antiplatelet drugs a comprehensive geriatric assessment should be conducted in combination with the general situation, complications, and drug use of the patients to assess the multidimensional risk for gastrointestinal diseases.

INR is an index to evaluate blood coagulation function. The results of this study found that INR ≥1.21 (OR=21.314, 95% CI=2.321~195.727) was an independent risk factor for NVUGIB. At present, the research results on the relationship between INR and NVUGIB are not consistent [21]. Attar et al. [22] reported that when UGIB patients had an INR of ≤1.3, it was speculated that their bleeding type was more inclined to NVUGIB. The results of this study suggest that prolonged INR can be used to predict bleeding. This may be related to changes in hemodynamics, blood viscosity, and platelet function.

Leukocytes are an inflammatory marker. It is usually used to comprehensively reflect the degree of inflammation and immune status of the body. Research has shown that the increase of leukocyte count can indicate NVUGIB in UGIB patients [23]. It has also been pointed out that the increase of leukocyte count is related to the severity of NVUGIB and mortality of the patients, indicating that patients with severe bleeding need emergent endoscopic intervention [24].

Albumin has a variety of biological functions. At present, hypoproteinemia has been widely recognized and accepted as one of the risk factors for death in some diseases [25]. Mirsadraee et al. [26] found that serum albumin level <26 g/L at admission was an independent risk factor for NVGUIB. This study found that the level of albumin <35 g/L (OR=1.970, 95% CI=1.304~2.976) was an independent risk factor for NVUGIB. Previously, it was also found that in the intensive care unit, serum albumin level <30 g/L could be used to predict the probability of rebleeding in patients [27, 28]. Hypoalbuminemia is related to a variety of clinical conditions that make patients weak, such as malnutrition, diabetes, renal failure and chronic liver disease [29, 30] and one of the factors causing NVUGIB. A large number of prospective, multicenter studies are still needed in the future to further clarify the role and value of hypoproteinemia in predicting the morbidity and mortality of various diseases.

This study has some limitations. First, this is a retrospective study. Data sources are limited by the medical records, and some important medical record data of patients are not included, such as the control of concomitant diseases, the changes in laboratory test indicators, the types and dosage of drugs, the course of treatment, and the emotional and psychological state of patients at onset. Second, because the research population comes from a single hospital, there are certain limitations. Whether the prediction model can be applied to other populations is still uncertain. Therefore, a multicenter large sample study is needed for further verification.

To sum up, this study concluded six independent risk factors for NVUGIB: history of peptic ulcer, Helicobacter pylori infection, use of anticoagulant and antiplatelet drugs, increased leukocyte count, prolonged INR and hypoproteinemia. The preliminary establishment of risk prediction model and the development of nomogram are helpful for clinicians to make intuitive clinical evaluation and treatment decisions for elderly inpatients, and have certain values for preventing patients from developing NVUGIB.

Disclosure of conflict of interest

None.

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