Establishment and validation of a pathologic upgrade prediction nomogram model for gastric low-grade intraepithelial neoplasia patients after the eradication of Helicobacter pylori

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Research Article

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Abstract

Background: At present, there is no unified treatment for the evaluation and management of gastric low-grade intraepithelial neoplasia (LGIN) all over the world.

Methods: Patients who were Helicobacter pylori eradicated, with low-grade gastric intraepithelial neoplasia were gathered.Several demographic and clinicopathological characteristics were described and analyzed retrospectively by LASSO regression analysis and multivariable logistic regression. Then the predictive nomogram was established. C-index, the area under the receiver operating characteristic curve (AUC) , calibration plot and decision curve analysis (DCA) were used to evaluate the accuracy and reliability of the model.

Results: A total of 309 patients with LGIN were included, divided into training groups and validation groups randomly. LASSO regression analysis and multivariable logistic regression showed that six variables, gender, size, location, border line, number and erosion were independent risk factors for progression of gastric LGIN. The nomogram model displayed good discrimination with a C-index of 0.765 (95% confidence interval: 0.702–0.828). High C-index value of 0.768 could still be reached in the internal validation. The accuracy and reliability of the model was also verified by the AUC of 0.764 in the training group and 0.757 in the validation group. The calibration curve showed the model was in good agreement with the actual results as well. Decision curve analysis suggested that the predictive nomogram had clinical utility.

Conclusions: A predictive nomogram model was successfully established and proved to identify high-risk groups with possible pathologic upgrade in patients with gastric LGIN. It suggested that after identifying high-risk patients, strengthening follow-up or endoscopic treatment may benefit in improving the detection rate or reducing the incidence of gastric cancer, which providing a reliable basis for the treatment of LGIN.

Introduction

Gastric cancer is one of the common malignant tumors in the world. In 2020, there were 1.09 million new cases in the world, while the new cases and deaths of gastric cancer in China accounted for 44% and 49% of the world respectively [1]. Diagnosis early is very important in the prevention and treatment of gastric cancer. Correa cascade reaction is a widely accepted mode about the pathogenesis of gastric cancer [2]. It is considered that the carcinogenic effect of gastric cancer is the continuous progression from atrophic gastritis to intestinal metaplasia (IM), intraepithelial neoplasia (GIN) and finally to adenocarcinoma [3]. Low grade intraepithelial neoplasia (LGIN) is considered to be a precancerous lesion. According to the tumor classification of the World Health Organization in 2000, the recommended clinical treatment guidelines for gastric LGIN are as follows: (□) conservative treatment: drug treatment and follow-up; (□) endoscopic therapy: (a) lesion mucosal resection: endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD); (b) Lesion mucosal injury: the main methods include high-

frequency electrocoagulation, argon plasma coagulation, radiofrequency ablation, holmium laser treatment, microwave coagulation treatment, etc. According to the guidelines of the American Gastroenterology Association (AGA) [4] and the British Gastroenterology Association (BSG) [5], endoscopic resection is recommended regardless of the size of the adenoma and whether it is associated with dysplasia. The American Society of gastroenteroendoscopy (ASGE) guideline [4] recommends endoscopic resection for gastric LGIN lesions which can still be found after one year of follow-up. These clinical guidelines provide different treatment principles. At present, there is no unified solution for the evaluation and management of gastric LGIN all over the world. For patients with high-grade intraepithelial neoplasia (HGIN), endoscopic treatment is recommended in various clinical guidelines.

For drug treatment, follow-up or endoscopic treatment, clinicians mostly decide the diagnosis and treatment plan referring to their own clinical experience and the orders of patients. Although different clinical guidelines are inconsistent in the treatment of gastric LGIN, almost all guidelines recommend long-term follow-up. This suggestion increases the economic burden, psychological burden and potential medical risk of patients [6]. Current research shows that about 16.1–48.9% of biopsies diagnosed with gastric LGIN may have pathologic upgrade [7, 8]. Clinical strategies based only on follow-up or drug treatment may miss the great opportunity of optimal treatment, and there is also a risk about missed diagnosis or misdiagnosis. It suggests that early endoscopic intervention for patients with high-risk gastric LGIN can obtain great clinical and economic benefits [6, 9, 10]. Therefore, it is necessary to find a new method to predict and evaluate the possibility of gastric LGIN progression, which has great clinical value. The aim of this study is to develop an effective and simple predictive tool for evaluating the risk factors of gastric LGIN patients by endoscopic diagnosis, and then effectively predict the pathologic upgrade risk of patients with gastric LGIN. It could help to effectively identify high-risk groups who may develop into gastric cancer. So that incidence rate of gastric cancer can be reduced by intensive monitoring and active treatment, and avoid over examination and waste of medical resources, providing valuable guidance for clinical intervention of gastric LGIN patients.

Materials And Methods

Patients

The overall flow diagram is shown in the Fig. 1. The clinical data of 431 patients with gastric LGIN as the first diagnosed who underwent gastroscopy in the Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University from December 2015 to December 2020 were retrospectively analyzed. The inclusion criteria of this study were: (□) diagnosis as gastric LGIN at the first time; (□) reviewed gastroscopy at least one year later; (□) the result of examination about Helicobacter pylori(HP) by ^{13}C-Urea Breath Test (UBT) was positive, and reexamined it one month later after the completion of quadruple therapy to ensure eradication; (□) all patients did fine endoscopic examination: Mucosal lesions were observed and biopsied by two endoscopists with extensive experience using Narrow Band Imaging (NBI) and Magnifying Endoscopy (ME) under the painless endoscopy. At least one clear picture about the

biopsy site was left for the follow-up. The exclusion criteria are shown in Fig. 1. The study was approved by the Ethics Committee of the Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University.

Demographic and Clinicopathological Variables

All information was gathered from the medical record systems and telephone follow-up inquiries. Demographic data of patients were retrospectively collected and recorded, including age, gender, family history of gastric cancer and concomitant diseases. Endoscopic characteristics of lesions were recorded, including lesion diameter, lesion location, boundary, multiple, rough mucosa, mucosal swelling, morphological characteristics (heave, flat, depression), erosion ulcer, lesion color (redness, whiteness, yellowing). The patients who progressed to HGIN or cancer were divided into upgrade group and those without upgrade pathology were divided into stable group.

Statistical analysis

Random numbers were used to classify 70% (n=217) of all enrolled patients into the training group and 30% (n=92) into the validation group. The least absolute shrinkage and selection operator (LASSO) method was used to select the optimal predictive factors in risk factors from the patients with gastric LGIN. Multivariable logistic regression analysis was used to build a predicting model, incorporating the feature selected in the LASSO regression model. Based on the above factors, a nomogram model of pathologic upgrade prediction of gastric LGIN patients was constructed. Sociodemographic variables with the *P*-value of 0.1 were included in the model, whereas variables associated with clinical characteristics were all included. To quantify the discrimination performance of the nomogram, Harrell's C-index and the area under the receiver operating characteristic curve (AUC) was measured in both the training group and the validation group. In addition, calibration accuracy was evaluated by a calibration plot. And the clinical effectiveness was evaluated by a decision curve analysis (DCA).

Statistical analysis was performed using SPSS version 26.0 and the R software (Version 3.4.1; https://www.R-project.org).

Results

Baseline Patient Characteristics in Training Cohort

A total of 309 patients were in the study, with 217 patients in the training cohort and 92 in the validation cohort. In the training cohort, 115 patients maintained stable lesions on endoscopic biopsy during follow-up, while 102 patients progressed to HGIN or cancer. We statistically described several demographic and clinical characteristics of the two groups. The clinical data about the training cohort are shown in Table 1.

LASSO Regression Analysis and Multivariate Logistic Regression Analysis

The LASSO regression model was used to select the final 6 features with relatively high predictive outcome from the 11 features in the training set. It showed that gender, lesion size, location, border line, number and erosion were the more important predictors with non-zero coefficient, as shown in Figure 2. After multivariate logistic regression analysis, gender (male), lesion size(≥1cm), location (cardia or pylorus), border line (yes), number(single) and erosion(no) were identified as independent predictors of the occurrence of pathologic upgrade in patients with gastric LGIN (Table 2).

Development of a nomogram model of pathologic upgrade prediction

Based on the Lasso analysis, this study used six variables, gender, size, location, border line, number and erosion, to establish a nomogram model for predicting pathologic upgrade in gastric LGIN patients. As shown in Figure 3, each of these independent predictors was projected upward to the value of the “points” at the top level of the nomogram to obtain a score within the range of 0 to 100. Record the total score of these points, and then the corresponding probability of pathological progression was obtained through the total score line at the bottom of the nomogram. The higher the total score, the higher the risk of progression.

Meanwhile, the self-verification of the nomogram model was conducted. The C-index for the prediction nomogram was 0.765 (95% CI: 0.702–0.828) for the training cohort. Then we drew the ROC curve of predicted probability, and the AUC value for the prediction of pathologic upgrade risk was 0.764, suggesting that the nomogram prediction model has a great discrimination (Figure 4A). The calibration curve of the nomogram in gastric LGIN patients also demonstrated good agreement in this cohort (Figure 4B).

Validation of the Nomogram

In the validation cohort, there were 51 cases (55.4%) that progressed. C-index was 0.768(95% CI: 0.672–0.864), indicating that the prediction model has a good discriminability, The AUC value in the validation cohort was 0.757, although slightly smaller than that in the training cohort, which also indicated that the prediction model had good accuracy, as shown in Figure 5A. In addition, the Calibration curve showed that the nomogram prediction model had good consistency and fitting degree, as shown in Figure 5B.

Decision Curve Analysis of the Prediction Model

In addition, Decision Curve Analysis (DCA) calculates the net benefit to evaluate the clinical utility of the nomogram, which is presented in Figure 6. From the decision curves, it concluded that the nomogram could acquire great net benefits across a large range of high-risk thresholds (range 0.06 to 0.91).

Table 1. Different demographic and clinical characteristics between stable and upgrade groups.

Characteristics	n (%)		
	Stable group (n=115)	Upgrade group (n=102)	Total (n=217)
Age (years)			
< 60	49(42.6%)	45(44.1%)	94(43.3%)
≥ 60	66(57.4%)	57(55.9%)	123(56.7%)
Sex			
Female	46(40%)	30(29.4%)	76(35.0%)
Male	69(60%)	72(70.6%)	141(65.0%)
Size (cm)			
<1	103(89.6%)	71(69.6%)	174(80.2%)
⩾1	12(10.4%)	31(30.4%)	43(19.8%)
Location			
Antrum、Pylorus	80(69.6%)	58(56.9%)	138(63.6%)
Gastric body、Angle	33(28.7%)	39(38.2%)	72(33.2%)
Cardia、Fundus	2(1.7%)	5(4.9%)	7(3.2%)
Border			
None	42(36.5%)	12(11.8%)	54(24.9%)
Yes	73(63.5%)	90(88.2%)	163(75.1%)
Number			
Single	35(30.4%)	56(54.9%)	91(41.9%)
Multiple	80(69.6%)	46(45.1%)	126(58.1%)
Rough			
None	16(13.9%)	15(14.7%)	31(14.3%)
Yes	99(86.1%)	87(85.3%)	186(85.7%)
Swelling			
None	41(35.7%)	36(35.3%)	77(35.5%)
Yes	74(64.3%)	66(64.7%)	140(64.5%)
Shape			
Eminentia	84(73.0%)	67(65.7%)	151(69.6%)
Depression	11(9.6%)	26(25.5%)	37(17.1%)
Flat	20(17.4%)	9(8.8%)	29(13.4%)
Erosion			
None	58(50.4%)	74(72.5%)	132(60.8%)
Yes	57(49.6%)	28(27.5%)	85(39.2%)
Color			
White	37(32.2%)	29(28.4%)	66(30.4%)
Red、Yellow	78(67.8%)	73(71.6%)	151(69.6%)

Table 2. Multivariable logistic regression of predictors for pathologic upgrade in gastric LGIN patients

Characteristics	n (%)		
	Stable group (n=115)	Upgrade group (n=102)	Total (n=217)
Age (years)			
< 60	49(42.6%)	45(44.1%)	94(43.3%)
≥ 60	66(57.4%)	57(55.9%)	123(56.7%)
Sex			
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White	37(32.2%)	29(28.4%)	66(30.4%)
Red、Yellow	78(67.8%)	73(71.6%)	151(69.6%)

Note: β is the regression coefficient.

Abbreviations: CI, confidence interval.

Discussion

According to the degree of cell atypia and structural disorder, gin is divided into low-grade intraepithelial neoplasia (LGIN) and high-grade intraepithelial neoplasia (HGIN). LGIN includes mild dysplasia and moderate dysplasia, and HGIN includes severe dysplasia and carcinoma in situ. For patients with pathological diagnosis of gastric HGIN, endoscopic treatment is recommended by most guidelines, but there has been controversy about the treatment of gastric LGIN. Park etc. found that 26.9% (7 / 26) of

gastric LGIN progressed to HGIN or cancer during a median follow-up of 58 months [11]. After excluding misdiagnosis, Zou etc. found that 12.2% [12 / 98) of patients with gastric LGIN had pathological progression, with a median progression time of 39.5 months [9]. A recent study showed that about 23% gastric LGIN can progress to cancer, while the incidence of HGIN was higher (60% - 85%) [12]. These data suggested that the risk of gastric LGIN progression to malignancy could not be ignored. For patients with high-risk of pathologic upgrade, we have sufficient reason to recommend early endoscopic treatment, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Our nomogram model can effectively identify gastric LGIN patients with different risk levels for different degrees of clinical intervention, so as to achieve higher clinical benefits.

Six risk factors were identified and included in this study: patient gender, lesion size, location, border line, number and erosion. A national multicenter study [13, 14] showed that gender was an independent risk factor for high risk of gastric cancer, with OR 2.52 (1.92 to 3.30), $P < 0.001$, which was consistent with our results. However, our results show that there is no significant correlation between gastric LGIN progression and age, which is inconsistent with the study of CAI et al. [13], but consistent with previous studies [6, 15], which may be related to the age structure and population size. In this study, the lesion diameter was distinguished as ≥ 1cm and < 1cm, showed to be an independent risk factor for the risk of pathologic upgrade in patients with gastric LGIN. This is consistent with the guideline of endoscopic mucosal dissection [16] of the European Society of gastrointestinal endoscopy, which recommends endoscopic mucosal dissection for lesions > 1.5cm. The size of the lesion is considered to be a consistent feature of malignant tumor progression, but the threshold of risk classification may need to be confirmed by a larger sample size. What's more, in this study, the location of lesions in gastric fundus or cardia, boundary, single onset or no erosion can increase the risk of pathological progression of patients with gastric LGIN. Kang et al. retrospectively analyzed the data of 1006 cases of gastric LGIN resected by endoscopic submucosal dissection [17]. They believed that the lesion size ≥ 1 cm and various surface changes (erythema, nodule, depression and erosion) were significantly related to the diagnosis of gastric LGIN. Yuqian C et al. suggested that multiple location was also an independent risk factors for prolonged or advanced progression in patients with LGIN through univariate and multivariate analysis [6]. Our research also found lesion location might impact the pathologic progression, and we pointed out that the fundus/cardia lesions may be more likely to progressing into HIGH or cancer. Although there are few studies focusing on gastric LGIN at present, from the existing research results, we can find that the model constructed in this study has strong reliability for the risk prediction of pathological progression in patients with gastric LGIN.

However, referring to the published studies, it was considered that the erosion on the lesion surface was also a risk factor, which is different from the conclusion of this study. This may be related to the fact that the selected cases reported above were not strictly screened for cases with negative HP infection or turned negative after treatment. There is a great correlation between the surface erosive ulcer and HP infection as reported [18-22]. Therefore, it is still doubtful whether the erosive ulcer at the lesion site in the above report can be used as an independent risk factor without excluding HP factors. In this study, all patients selected were positive for HP after the first examine and underwent quadruple bactericidal

therapy. HP eradication was confirmed one month after completion of the treatment course. We controlled for variables of HP infection. And it could conclude that the lesion surface erosion and ulcer may be the protective factors for the pathological upgrading of gastric LGIN, although it still needs to be further confirmed by more studies in the future.

As a risk prediction nomogram, it shows good potential in clinical trial design and evaluation, and has been widely used in prognostic models. In this study, nomogram was used for the first time to construct the prediction model of whether gastric LGIN patients would have pathological progression. ROC curve analysis and calibration line were used to show the prediction accuracy of nomogram. Compared with the risk prediction model constructed by univariate and multivariate regression analysis [6], the use of LASSO regression and nomogram made the analysis more intuitive, and the specific risk score also makes the prediction more accurate.

During the follow-up of this study, it was found that some patients had pathological reversal. It was even reported that 49.4% of cases were reversed during an average follow-up of 15 months [24]. Some studies pointed out that this part of cases with pathologic upgrade may be due to the difference of gastroscopic biopsy materials or pathological misdiagnosis when gastric LGIN was first diagnosed [23,25]. In a study of 138 cases about gastric LGIN, the difference between preoperative endoscopic biopsy (PEB) and postoperative pathological examination (PPE) was analyzed. It was found that 47.8% of cases had pathological upgrading due to misdiagnosis [10]. However, at present, most patients are diagnosed as gastric LGIN through gastroscopic biopsy for the first time, which inevitably has the risk of missed diagnosis and misdiagnosis. Therefore, for different gastric LGIN patients, the prediction of their risk is particularly important, which can also reduce the clinical risk to a certain extent.

Our research also has some limitations. Firstly, this nomogram model is based on retrospective single center data set, which weakens the credibility of the risk prediction model and reduces its application scope. Secondly, this study only carries out self-verification and internal validation. External validation is also important to prove the accuracy of the model, and may lead to statistical analysis deviation after elimination. In order to establish a perfect prediction model, the risk prediction model of pathologic upgrade in patients with gastric LGIN still needs further multi center and large sample clinical research in order to provide more evidence.

Conclusions

In summary, this study developed a nomogram model of pathologic upgrade prediction in patients with gastric LGIN. This model can provide a valuable reference for clinical treatment decision-making in patients with gastric LGIN.

Declarations

Ethics approval and consent to participate

All experimental protocols were approved by the Ethics Committee of the Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University. Informed consent was obtained from all subjects. And all methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

All authors have read and approved the final version of the manuscript, and consented for publication.

Availability of data and materials

All data generated in this study are available from the corresponding author upon request.

Competing interests

The authors declare that there are no conflicts of interest.

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Authors' contributions

Yejiao Ruan and Xuanping Xia conceptualized and designed the study. Yejiao Ruan, Zhenzhai Cai and Xuanping Xia was responsible for conception, design, quality control of this study, reviewed, and edited the manuscript. Guangrong Lu performed data extraction, statistical analyses. Yejiao Ruan and Yuesheng Zhu were major contributors in writing the manuscript. Xianhui Ma, Yating Shen, Yuning Shi, Xuchao Zhang and Zheng Zhu participated in data extraction and statistical analyses. All authors have read and approved the final version of the manuscript.

Acknowledgments

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Figures

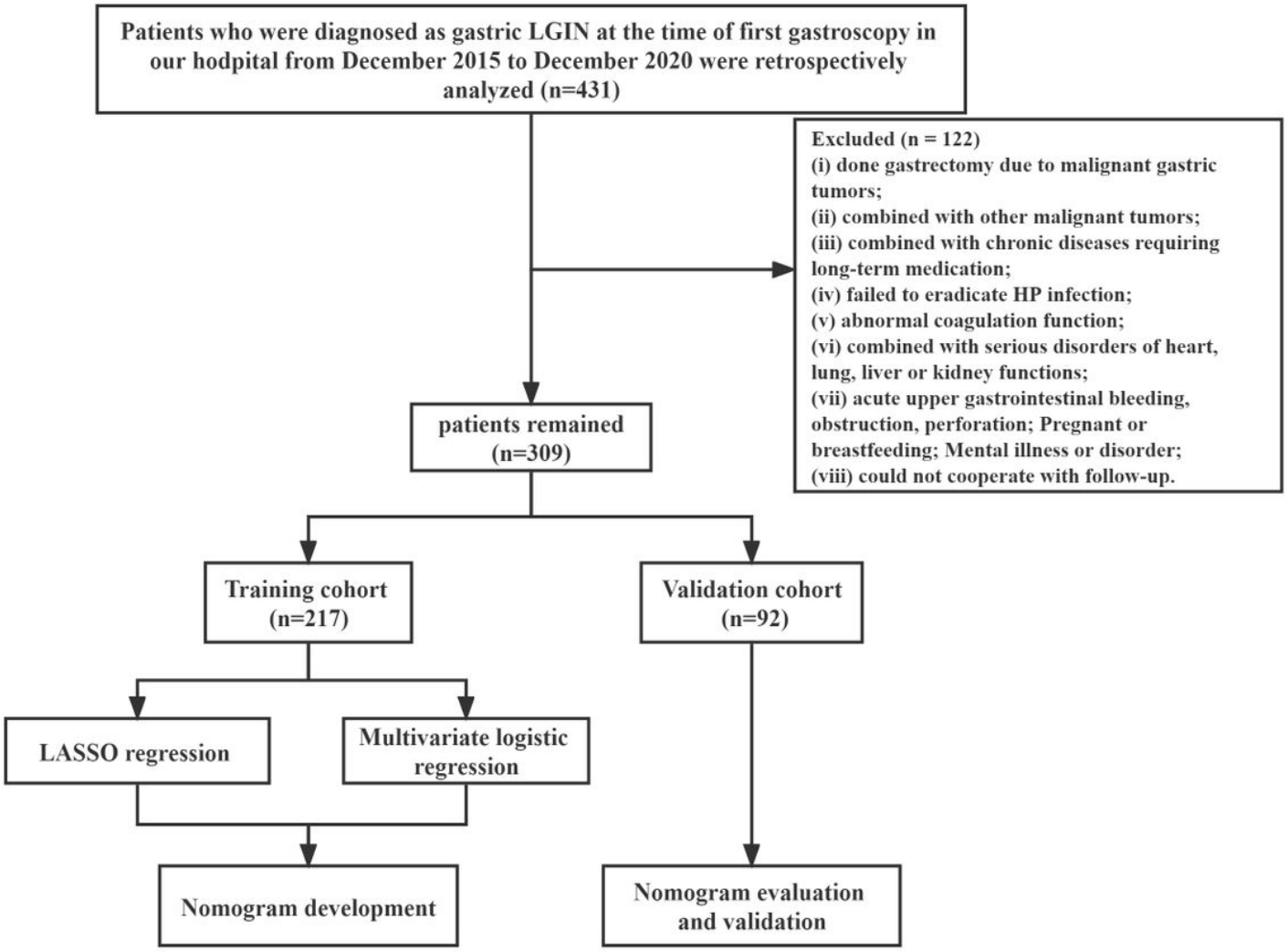

Figure 1

Study flow diagram.

Abbreviations: LGIN, low-grade intraepithelial neoplasia; LASSO, least absolute shrinkage and selection operator.

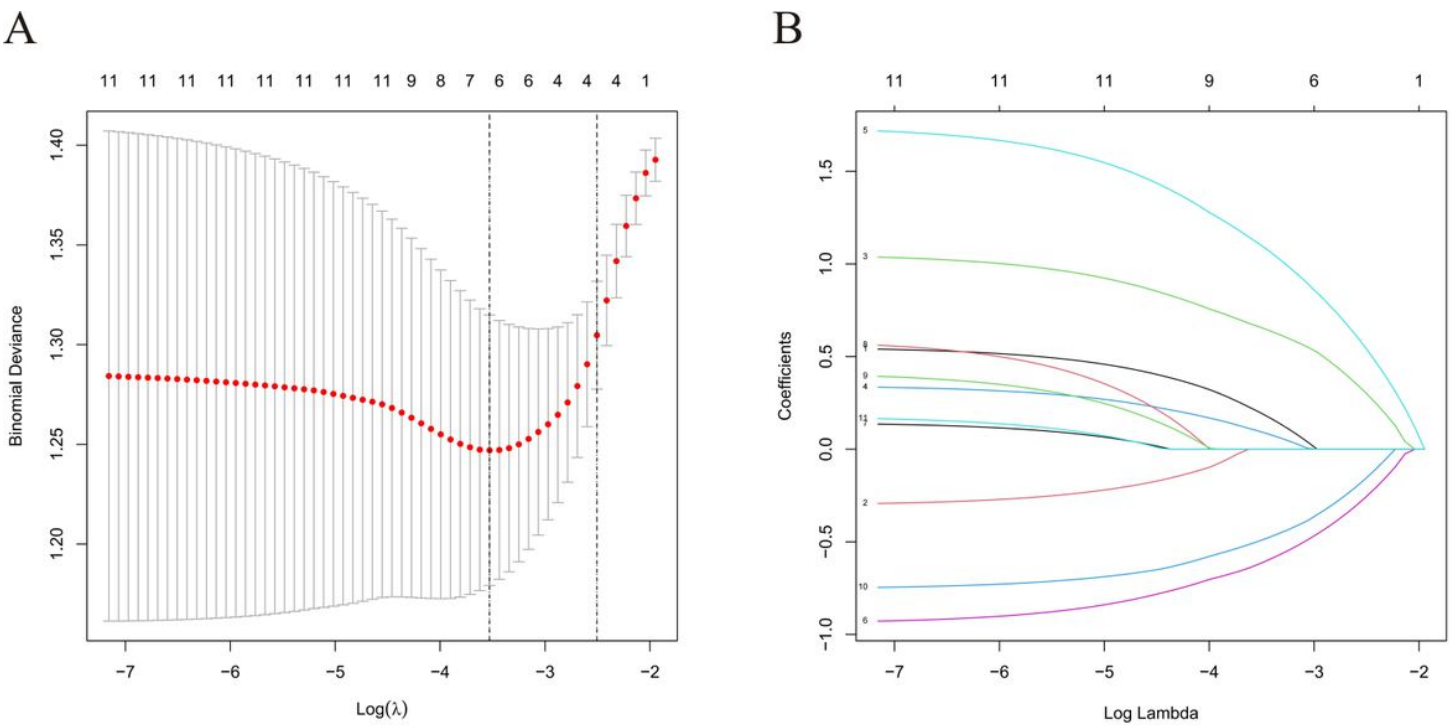

Figure 2

Demographic and clinical feature selection using the LASSO binary logistic regression model. **(A)** Optimal parameter (lambda) selection in the LASSO model used fivefold cross-validation via minimum criteria. The partial likelihood deviance (binomial deviance) curve was plotted versus log(lambda). Dotted vertical lines were drawn at the optimal values by using the minimum criteria and the 1 SE of the minimum criteria (the 1-SE criteria). **(B)** LASSO coefficient profiles of the 11 features. A coefficient profile plot was produced against the log(lambda) sequence. Abbreviations: LASSO, least absolute shrinkage and selection operator; SE, standard error.

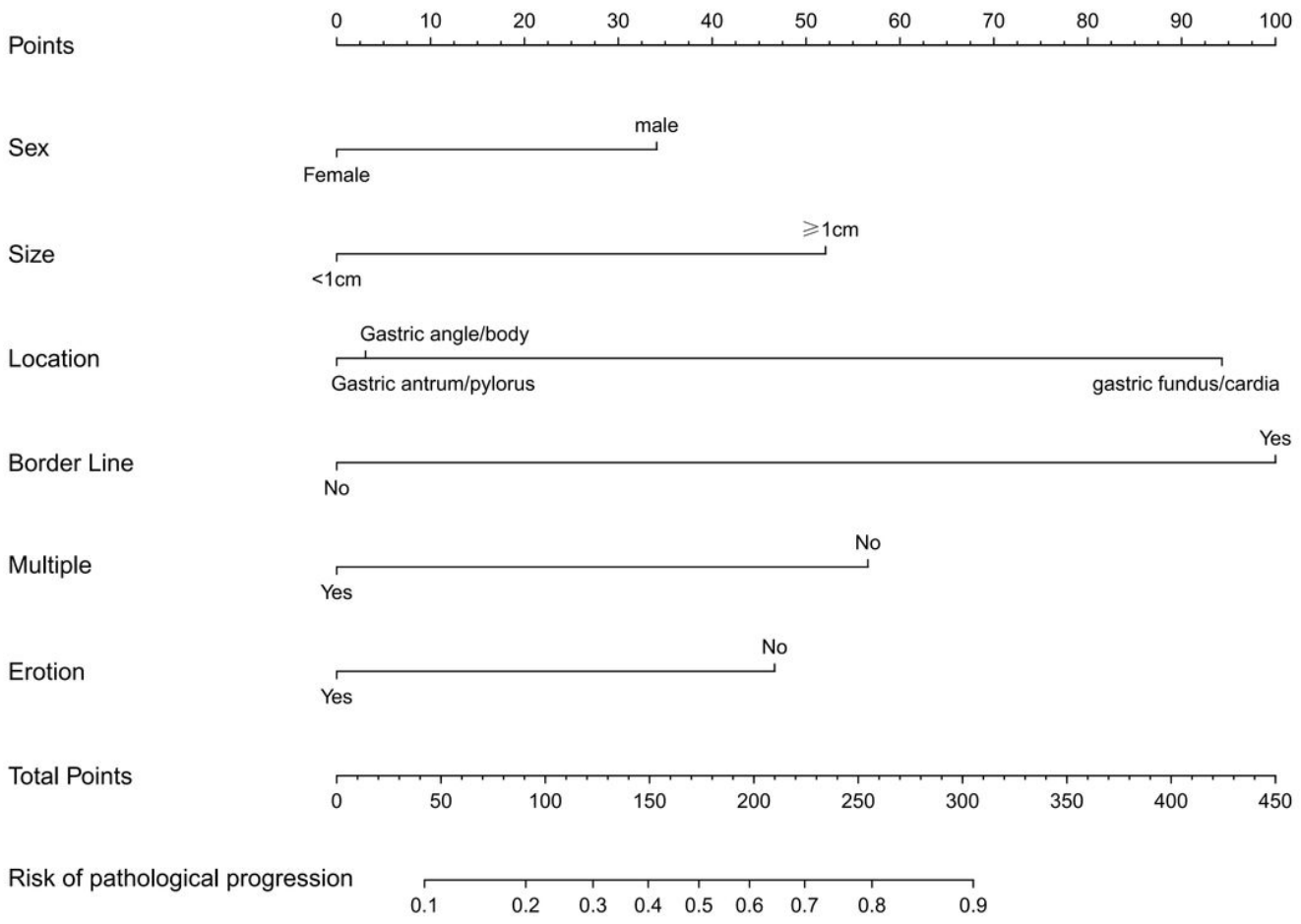

Figure 3

Developed gastric LGIN pathologic upgrade nomogram. An individual patient's value is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable value. The sum of these numbers is located on the Total Points axis, and a line is drawn downward to the Risk of pathological progression axis to determine the risk of pathologic upgrade in patients with gastric LGIN.

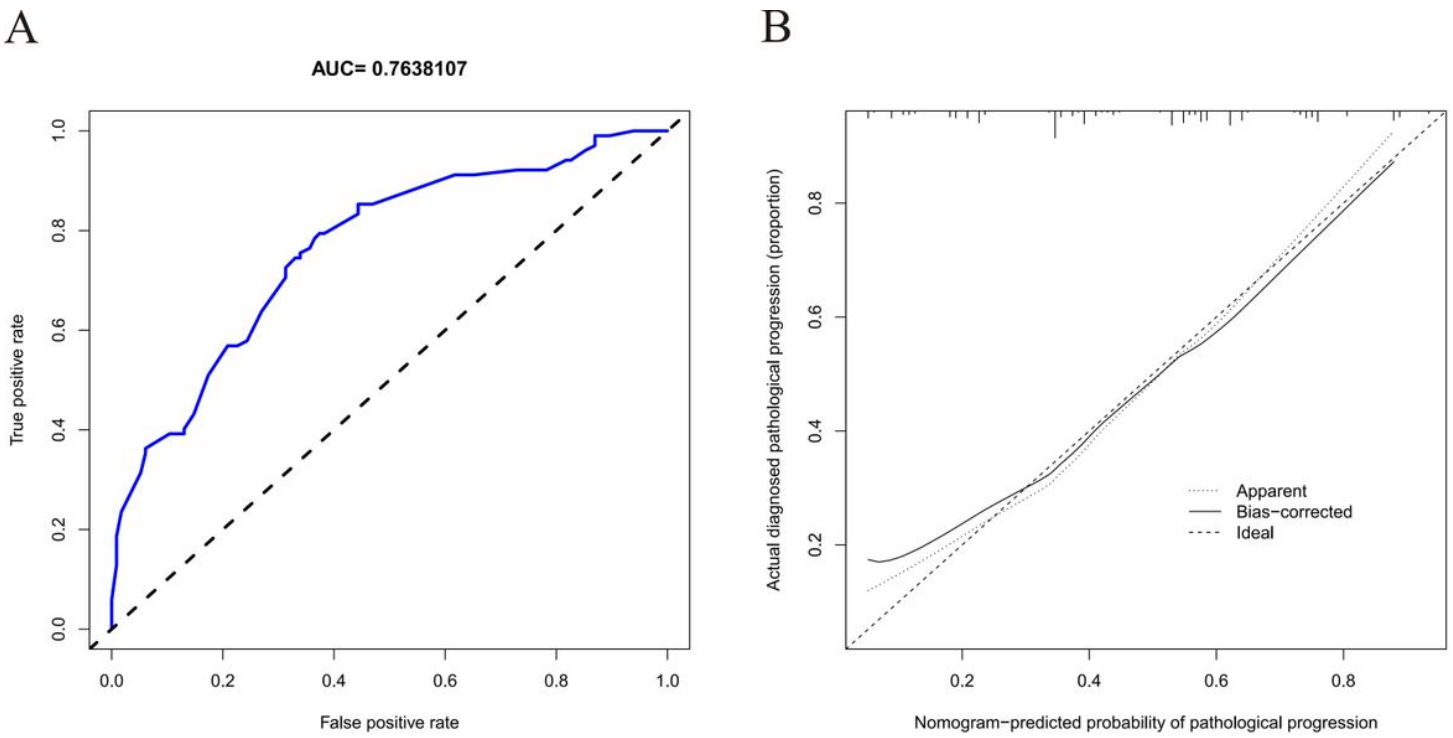

Figure 4

The evaluation of the performance of the nomogram predicting the risk of pathologic upgrade in patients with gastric LGIN in the training cohort. **(A)** ROC curve of the nomogram in the training cohort. The AUC was 0.763; **(B)** Calibration curve in the training cohort.

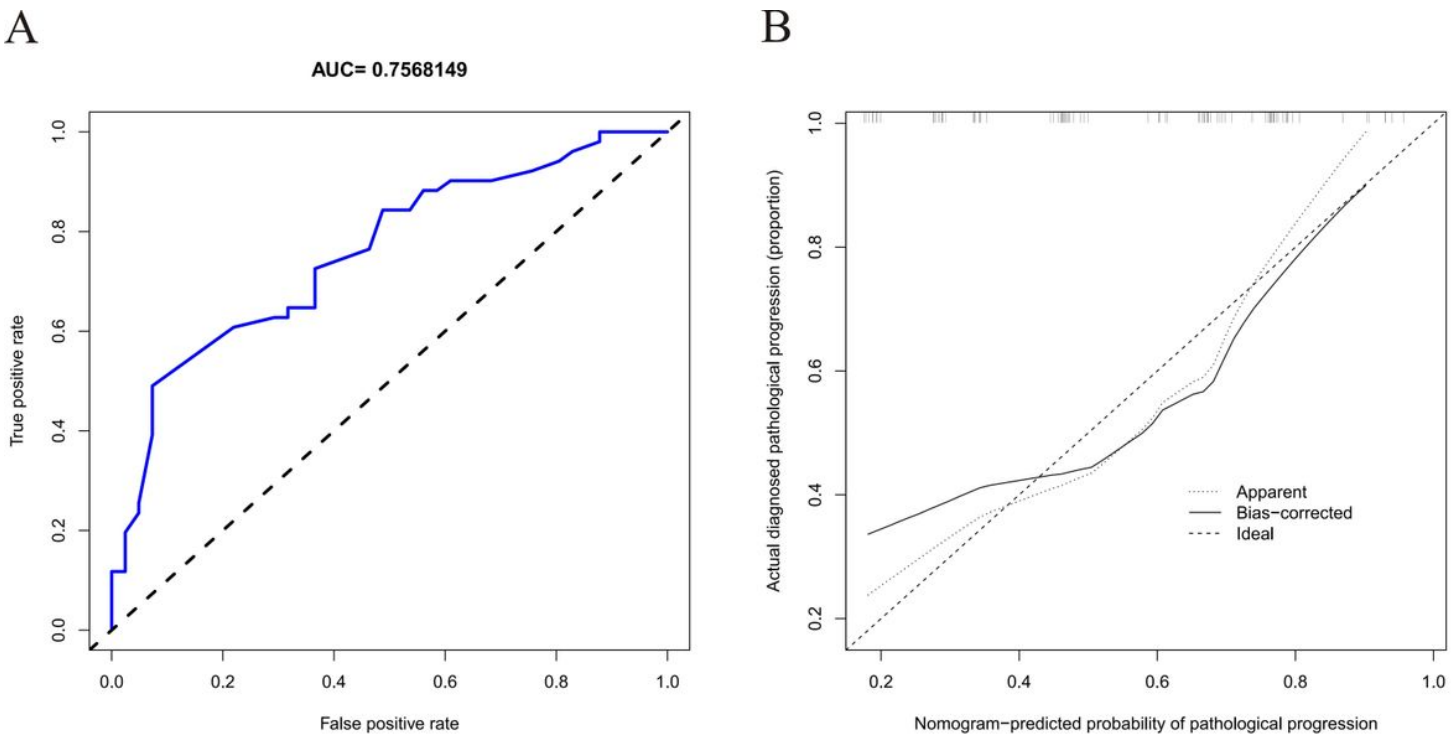

Figure 5

The evaluation of the performance of the nomogram predicting the risk of pathologic upgrade in patients with gastric LGIN in the validation cohort. **(A)** ROC curve of the nomogram in the validation cohort. The AUC was 0.757; **(B)** Calibration curve in the validation cohor

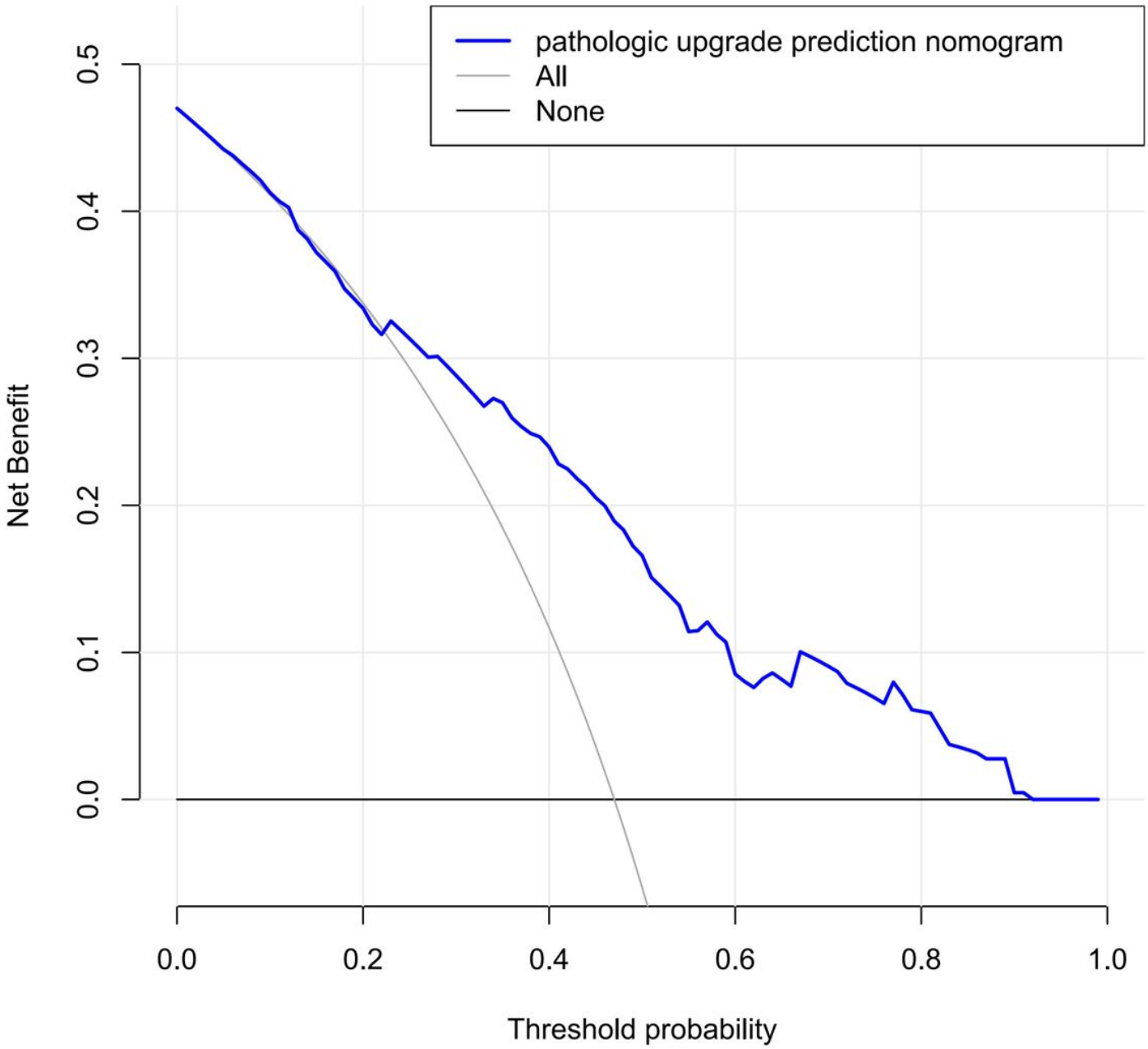

Figure 6

Decision curve analysis for the validation set. A horizontal line indicates that all samples are negative and not treated, with a net benefit of zero. An oblique line indicates that all samples are positive. The net

benefit has a negative slope.