Predictive Value of Nomogram Based on Kyoto Classification of Gastritis to Diagnosis of Gastric Cancer

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Abstract

Background and Aim. It is of importance to predict the risk of gastric cancer (GC) for endoscopists because early detection of GC determines the determines the selection of best treatment strategy and the prognosis of patients. The aim of the study was to evaluate the utility of a predictive nomogram based on Kyoto classification of gastritis for GC.

Methods. It was a retrospective study that included 2639 patients who received esophagogastroduodenoscopy and serum pepsinogen (PG) assay from January 2020 to November 2020 at the Endoscopy Center of the Department of Gastroenterology, Wenzhou Central Hospital. Routine biopsy was conducted to determine the benign and malignant lesions pathologically. All cases were randomly divided into the training set (70%) and the validation set (30%) by using bootstrap method. A nomogram was formulated according to multivariate analysis of training set. The predictive accuracy and discriminative ability of the nomogram were assessed by concordance index (C-index), area under the curve (AUC) of receiver operating characteristic curve (ROC) as well as calibration curve and were validated by validation set.

Results. Multivariate analysis indicated that age, sex, PG I/II ratio and Kyoto classification scores were independent predictive variables for GC. The C-index of the nomogram of the training set was 0.79 (95% CI: 0.74 to 0.84) and the AUC of ROC is 0.79. The calibration curve of the nomogram demonstrated an optimal agreement between predicted probability and observed probability of the risk of GC. In the validation set, the C-index was 0.86 (95% CI: 0.79 to 0.94) with a calibration curve of better concurrence.

Conclusion. The nomogram formulated was proven to be of high predictive value for GC.

Introduction

Despite the many advancements made in the past few decades, cancer still has a high prevalence worldwide and is one of the main causes of death in the population. Gastric cancer (GC) is the fourth most common malignant tumor and the second leading cause of cancer-related death in the world (1). GC has notable regional, ethnic and socioeconomic status differences in its distribution. The incidence rate of GC in men is 2 to 3 times that of women (2). East Asia, Eastern Europe and South America have the highest incidence of GC, while North America and Africa the lowest (1). GC is a multi-factor disease, with environmental and genetic factors work in its etiology. Some of these risk factors such as age, race, gender (3) and family history (4) are not changeable, while others such as Helicobacter pylori (HP) infection (5), tobacco smoking (6) and physical activity (7) are.

Due to the development of endoscopic technology, the gastric mucosa can now be observed in detail to indirectly infer the pathological diagnosis. Clinically, the risk of GC is usually assessed according to the state of chronic gastritis observed by endoscope. Numerous gastritis classifications have been proposed, among which Kyoto classification of gastritis is one of the most common classification systems. The Kyoto classification of gastritis, promoted at the 85th Congress of the Japan Gastroenterological

Endoscopy Society, is based on the past gastritis classifications and adopts more objective gastroscopy results. This classification considers HP infection, the site of gastritis and pathological histology, and evaluate the endoscopic findings and diagnosis. It consists of 19 endoscopic features, such as atrophy, intestinal metaplasia, enlarged fold, nodularity and diffuse redness, which are used in the prediction of the risk of gastric cancer. This classification gives us a unified way to describe gastritis of different individuals.

Previous studies have proven the value of Kyoto classification of gastritis in predicting gastric cancer, but they are all qualitative analysis. Nomogram is commonly used to predicting a certain clinical ending or the probability of a type of event. Based on multi-factor regression analysis, it is a statistical prognostic model that generates clinical event probability in graphical way using multiple clinical indicators or biological properties. It transforms the complex regression equation to simple and visualized graphics, making the result of the prediction model more readable and higher usage value. Thus, we retrospectively collected the cases of patients who were underwent esophagogastroduodenoscopy in our center, analyzed the clinical factor as well as the endoscopic features and established a nomogram based on Kyoto classification to predict the risk of gastric cancer.

Patients And Methods

Patients

Cases of esophagogastroduodenoscopy at Wenzhou Central Hospital, Zhejiang University (China) from January 2020 to November 2020 were retrospectively collected. The inclusion criteria were as follows: referral for esophagogastroduodenoscopy, patients aged ≥ 18 years, with serum pepsinogen (PG) assay and confirmed histopathological diagnosis through endoscopic approach or surgery. The exclusion criteria were the history of surgical gastrectomy of gastric neoplasm. Of 16412 esophagogastroduodenoscopy cases from January 2019 to November 2019 at the Endoscopy Center of the Department of Gastroenterology, 13777 cases were excluded due to the lack of solid histopathological diagnosis or serum PGs and 2639 cases were enrolled in our study. The study protocol was approved by our ethical review board of Wenzhou Central Hospital, number L2021-03-001x.

Methods

A retrospective study was designed to assess the utility of the novel nomogram, which is based on Kyoto classification of gastritis, serum PGs and other demographic factors, such as age and sex. Esophagogastroduodenoscopy (GIF-HQ290/GIF-290Z of Olympus Corporation, Tokyo, Japan) combined with routine biopsy of normal tissues or suspicious lesions and serum PG assay were carried out on every case enrolled. The histopathological diagnosis was made by two experienced pathologists. For the cases of discrepancy in diagnosis between the two pathologists, these were reviewed by a third one to make an arbitration for future analysis. The Malignant lesion was defined as gastric cancer, high grade

intraepithelial neoplasia (HGIN). Low grade intraepithelial neoplasia (LGIN) cases were reviewed by a senior endoscopist and pathologist to differentiate benign and malignant lesions.

The Kyoto classification of gastritis of gastric cancer risk consist of five endoscopic finds: atrophy, intestinal metaplasia, mucosal swelling, nodularity and diffuse redness. The score ranges from 0 to 8. Higher score indicates higher risk of current HP infection and gastric cancer. A Kyoto classification score of 0 means that there is no HP infection, ≥ 2 indicates current HP infection and ≥ 4 may indicates high risk of gastric cancer. (8) Every case of esophagogastroduodenoscopy was scored by two experienced endoscopists (Lin JJ and Zhou QJ) according to Kyoto classification of gastritis and disagreement was solved by a third endoscopist (Pan J) with over 20 years of experience in endoscopy.

Pepsinogen is the precursor of pepsin, which was a protease secreted by gastric chief cells. The level of serum PGs reflects the morphology and function of different parts of the gastric mucosa, which can be used to detect gastric cancer caused by atrophic gastric mucosa. Serum PG assay was conducted before esophagogastroduodenoscopy and was considered into our research.

Statistical analysis

R Software for Linux of version 4.1.0 was used throughout the statistical analysis. Categorical variables ware compared using the Chi-square test or Fisher's exact test. Continuous variables were compared using the t test. Univariate analysis was adopted to calculate the Odd Ratio (OR) of each factor and its p value. Factor with p value of < 0.05 was used for multivariate analysis. Finally, the cohort was randomly divided into training set (70%) and validation set (30%) by using bootstrap method of R package of caret (version 6.0–88). A nomogram was formulated based on the results of the multivariate analysis on training set using the R package of rms (version 6.2-0). The performance of the nomogram model was assessed by concordance index (C-index), area under the curve (AUC) of receiver operating characteristic curve (ROC) and calibration curve. The higher the C-index and AUC, the more accurate was the nomogram model. The closer the calibration curve of both training set and validation set to the diagonal, the more robust was the model prediction. P values of < 0.05 were considered statistically significant.

Results

Clinical Characteristics of All Patients

In training set, there were 1848 cases who received esophagogastroduodenoscopy and routine biopsy combined with serum pepsinogen assay. In the validation set, there were 791 patients enrolled. The baseline characteristics of all the patients of our study are listed in Table 1. The medium age of training set and validation set were both 56 years, ranging from 19 to 93 and 19 to 92 years, respectively. LGIN cases, which were reassessed by an experienced endoscopist and pathologist, and HGIN cases combined with gastric cancer cases were divided into the gastric cancer group (n = 2534 of all cases), whereas the rest cases of benign pathological results were considered as benign group (n = 102 of all cases).

Table 1
Baseline Characteristics of Patients

Baseline Characteristics	Training Set (n = 1848)		Validation Set (n = 791)	
	No. of Patients	Percent	No. of Patients	Percent
Age (years)				
< 50	454	24.6%	197	24.9%
50–70	1165	63.0%	499	63.1%
≥ 70	229	12.4%	95	12.0%
Sex				
Male	971	52.5%	396	50.1%
Female	877	47.5%	395	49.9%
PG I (μg/L)				
Medium	103.15		106.50	
Range	3.00–711.70		3.00–618.0	
PG II (μg/L)				
Medium	9.42		9.62	
Range	1.69–378.50		1.78–352.95	
PG I/II Ratio				
Medium	11.15		11.34	
Range	0.31–62.33		0.20–29.88	
HP Antibody				
Negative	665	36.0%	285	36.0%
Positive	1183	64.0%	506	64.0%
Atrophy				
None, C1	587	31.8%	245	31.0%
C2 and C3	1060	57.4%	461	58.3%
O1 – O3	201	10.9%	85	10.7%
Intestinal Metaplasia				
None	790	42.7%	333	42.1%
Antrum	827	44.5%	360	45.5%

Baseline Characteristics	Training Set (n = 1848)		Validation Set (n = 791)	
	No. of Patients	Percent	No. of Patients	Percent
Corpus and Antrum	231	12.5%	98	12.4%
Enlarged Fold				
Absence	1204	65.2%	498	63.0%
Presence	644	34.8%	293	37.0%
Nodularity				
Absence	1838	99.5%	786	99.4%
Presence	10	0.5%	5	0.6%
Diffuse Redness				
None	1026	55.5%	428	54.1%
Mild (with RAC)	709	38.4%	310	39.2%
Severe	113	6.1%	53	6.7%
Kyoto Classification Scores				
≤ 1	697	37.7%	301	38.1%
2–3	607	32.8%	252	31.9%
≥ 4	544	29.4%	238	30.1%
Pathology				
Benign	1771	95.8%	763	96.5%
LGIN* and HGIN	40	2.2%	13	1.6%
Gastric Cancer	37	2.0%	15	1.9%

Abbreviations: PG, pepsinogen; RAC, Regular arrangement of collecting venules; LGIN, low grade intraepithelial neoplasia; HGIN, high grade intraepithelial neoplasia.

*LGIN cases were reviewed by an experienced endoscopist and pathologist to determine whether they were malignant.

Independent Predictive Factors of Training Set

Univariate analysis of the training set was conducted and indicated that age, sex, PG I/II ratio, HP antibody, atrophy, intestinal metaplasia, enlarged fold, diffuse redness and Kyoto classification scores were probable predictive factors (Table 2). Multivariate analysis showed age, sex, PG I/II ratio and Kyoto classification scores were independent predictive factors for gastric cancer (Table 3).

Table 2
Univariate Analysis of the Training Set

Variable	OR	95% CI	P value
Age	1.06	1.04–1.09	< .001
Sex (female v male)	0.49	0.29–0.79	.004
PG I/II Ratio	0.88	0.83–0.93	< .001
HP Antibody	4.45	2.32–9.62	< .001
Atrophy			
None, C1			
C2 and C3	14.48	4.48–88.76	< .001
O1 – O3	41.55	12.22–259.82	< .001
Intestinal Metaplasia			
None			
Antrum	3.12	1.70–6.09	< .001
Corpus and Antrum	6.61	3.34–13.63	< .001
Enlarged Fold (Presence v Absence)	4.41	2.73–7.33	< .001
Diffuse Redness			
None			
Mild (with RAC)	2.62	1.59–4.44	< .001
Severe	4.50	2.07–9.25	< .001
Kyoto Classification Scores	1.67	1.46–1.93	< .001
Abbreviations: PG, pepsinogen; RAC, Regular arrangement of collecting venules.			

Table 3
Multivariate Analysis of the Training Set

Variable	OR	95% CI	P value
Age	1.05	1.03–1.07	< .001
Sex (female v male)	0.56	0.33–0.92	.025
PG I/II Ratio	0.92	0.86–0.97	.003
HP antibody	0.90	0.39–2.23	0.806
Kyoto Classification Scores	1.50	1.26–1.78	< .001
Abbreviations: PG, pepsinogen; RAC, Regular arrangement of collecting venules.			

Predictive Nomogram for the Risk of Gastric Cancer

The predictive nomogram consisting of the predictive variable proven in multivariate analysis was formulated and shown in Fig. 1. The C-index of the nomogram was 0.79 (95% CI: 0.74 to 0.84) and the AUC of ROC is 0.79 (Fig. 2). The calibration curve of the nomogram showed an excellent agreement between predicted probability and observed probability of the risk of gastric cancer (Fig. 3A).

Validation of the Nomogram

In the validation set, the C-index was 0.86 (95% CI: 0.79 to 0.94). The calibration curve was shown in Fig. 3B, which indicated an even better concurrence between predicted probability and observed probability.

Discussion

The occurrence and development of gastric cancer is a multi-step and gradual process. Reasonable screening and risk prediction of high-risk groups of gastric cancer, and dynamic follow-up have always been key steps in the process of early diagnosis and treatment of gastric cancer. Serum pepsinogen assay is one of the non-invasive tests. It was reported that the serum pepsinogen assay was better than the serum gastrin assay when measuring the gastric mucosal state because gastrin is mainly produced by the endocrine G cells of the gastric antrum (9, 10). Yoshida et al followed a cohort of 4655 healthy asymptomatic subjects for 16 years and came to the conclusion that the serum PG assay was useful for the screening of GC, especially for the intestinal-type GC (11). Yanaoka et al conducted a cohort study of 5209 middle-aged male subjects for 10 years and concluded that subjects with a low PG I/II ratio are at high risk of GC and a thorough endoscopy is required for them (12). Japanese scholar Miki first adopted the ABC method for clinical risk assessment of early gastric cancer. This method combines the detection of serum HP antibody and serum pepsinogen to determine the high-risk population that may develop into gastric cancer in the future (13). However, it was found that the method was mainly for tumors located at

gastric body and fundus during the application process, which made it easy to miss tumors of gastric antrum. Thus, in 2015, the new ABC method was first proposed at the International Symposium on Early Gastric Cancer Screening in China. The new ABC method replaces the serum HP antibody in the ABC method with serum G-17. Subsequent research results also showed that the new ABC method could improve the sensitivity and specificity of early gastric cancer screening in the Chinese population compared with the ABC method (14). But when it came to the best cut-off value, there were still differences in different regions. Cai Q et al (15) developed a novel risk prediction rule to further stratify risk for GC in the Chinese GC risk population. It quantified various risk factors such as age, gender, HP antibody and serum gastric secretion function for the first time. Based on the risk prediction rule, the strategy of precise endoscopic examination should be adopted for people at high risk of gastric cancer and appropriate follow-up strategy should be adopted for people at low risk, which improves screening efficiency and saves medical resources.

However, the esophagogastroduodenoscopy is an irreplaceable part for gastric status and risk prediction of gastric cancer. Endoscopic gastritis was proven by Schindler who used gastroscope to observe the gastric mucosa for the first time and proposed the existence of endoscopic gastritis in 1930s (16). In 1960s, Kimura Takemoto established the diagnostic criteria of atrophic gastritis and described the appearance of an atrophic transitional zone of gastritis, which was known as the endoscopic atrophic border for the first time (17). The Kimura-Takemoto classification was published in 1969 and is still an indispensable method for the diagnosis and classification of gastritis in Japan. In 1983, HP was found in the gastric mucosa of patients with gastritis by Warren and Marshall et al. (18), which completely changed the strategy of gastritis classification. Therefore, the Sydney System for the classification of gastritis was proposed (19, 20). It took consideration of the position of gastritis, histopathological results and endoscopic status. Later the Operative Link on Gastric Intestinal Metaplasia (OLGIM) classification was promoted to predict the risk of GC focusing on intestinal metaplasia (21). The Kyoto classification of gastritis, advocated at the 85th Congress of the Japan Gastroenterological Endoscopy Society, adopts more objective gastroscopy results, such as atrophy, intestinal metaplasia, enlarged fold, nodularity and diffuse redness (Fig. 4), to establish a global standard for gastritis classification. The efficacy of Kyoto classification of gastritis to GC risk prediction have been proven by Sugimoto, Shichijo, Sakitani and Fujimoto et al (22–25).

Although upper gastrointestinal endoscopy allows doctors to estimate the risk of gastric cancer based on the findings of the background gastric mucosa, the secretion capacity of gastric mucosa is also significant for the risk prediction. None of the researches mentioned above took demographic factor, serum pepsinogen and endoscopic features into consideration to build up a statistical model to visualize the prediction. Hence, this research was conducted. This study demonstrated that patients background data, such as age and sex, as well as PG I/II ratio and Kyoto classification scores are independently associated with GC risk. Nomograms have been adopted and proven to be useful in prediction (26). The monogram formulated based on these factors was excellent, with C-index of 0.79 and calibration curve of optimal agreement between predicted probability and observed probability. Old age and male sex are independent factor for GC, which is consistent with the previous study of Kaneko et al (27). The higher

the Kyoto classification scores were, the more risk were the subjects to GC with the OR of 1.48, which is concordant with the findings of Sugimoto et al (22). The significance of the study is that demographic factors, such as age and sex, and serological indicators of pepsinogen were considered and combined with Kyoto classification of gastritis to build up a novel nomogram model, which made the prediction more visible. Predicting the lesion type before pathological diagnosis of biopsy could determine the concentration of endoscopist and lead to a more careful and thorough endoscopy. As for each item of Kyoto classification of gastritis, atrophy, intestinal metaplasia, enlarged fold and diffuse redness were positive correlated with GC, but nodularity showed no association with GC. This result is also corresponding to the finding of Sugimoto and Toyoshima (22, 28).

However, there are still some limitations of this study. It was found that HP antibody had no meaning in predicting gastric cancer in our cohort. We assumed that it was because a large-scale population-based HP screening and eradication had been carried out in our region, which made HP antibody unable to reflect the status of HP infection. Furthermore, this study was a retrospective and single-center study. The validation set of the nomogram came from the part of the whole subjects which were divided randomly using bootstrap method. Thus, an external validation was required to further validate the nomogram. In addition, further investigations using prospective study designs are required to evaluate the accuracy and discriminative ability of the nomogram model.

Conclusion

In conclusion, age, sex, PG I/II ratio and Kyoto classification scores are independent factors for GC prediction. The nomogram proposed in this study was proven to be of high predictive value for GC. Further studies are needed to determine whether it can be applied to other situations.

Abbreviations

GC: gastric cancer PG: pepsinogen C-index: concordance index AUC: area under the curve ROC: receiver operating characteristic curve HP: Helicobacter pylori HGIN: high grade intraepithelial neoplasia LGIN: low grade intraepithelial neoplasia OR: odd ratio

Declarations

Ethics approval and consent of participate

This population-based study complies with ethical guidelines of the Declaration of Helsinki (1975) and was approved by the Ethics Committee of the ethical review board of Wenzhou Central Hospital(number L2021-03-001x). The data were anonymous, so the requirement for informed consent was waived(the application for non informed consent has been approved by the ethics committee).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of interests

There are no conflicts of interest between authors.

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Author Contributions

Lin JJ designed the study and collected data. Su H analyzed data and wrote the manuscripts. Zhou LY designed the study and revised the manuscripts. Zhou QJ and Guan YQ collected data. Pan J revised the manuscripts and approved the final article.

Lin JJ and Su H contributed to this article equally.

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Figures

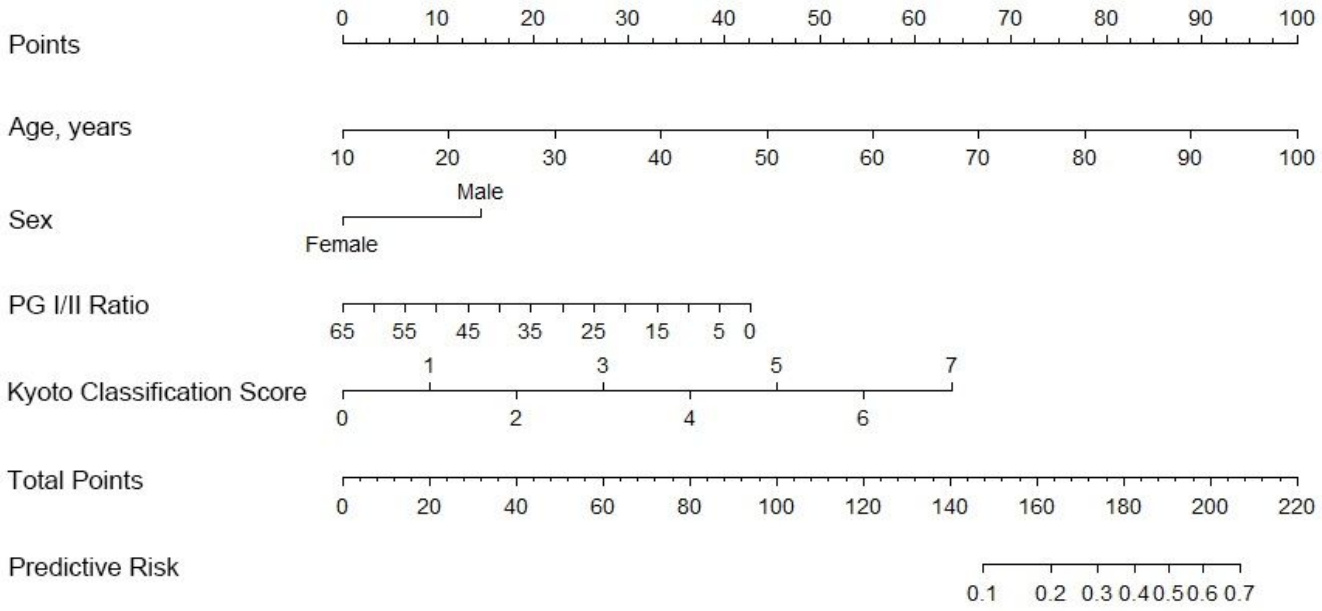

Figure 1

Gastric Cancer Risk Predictive Nomogram. Abbreviations: PG, pepsinogen.

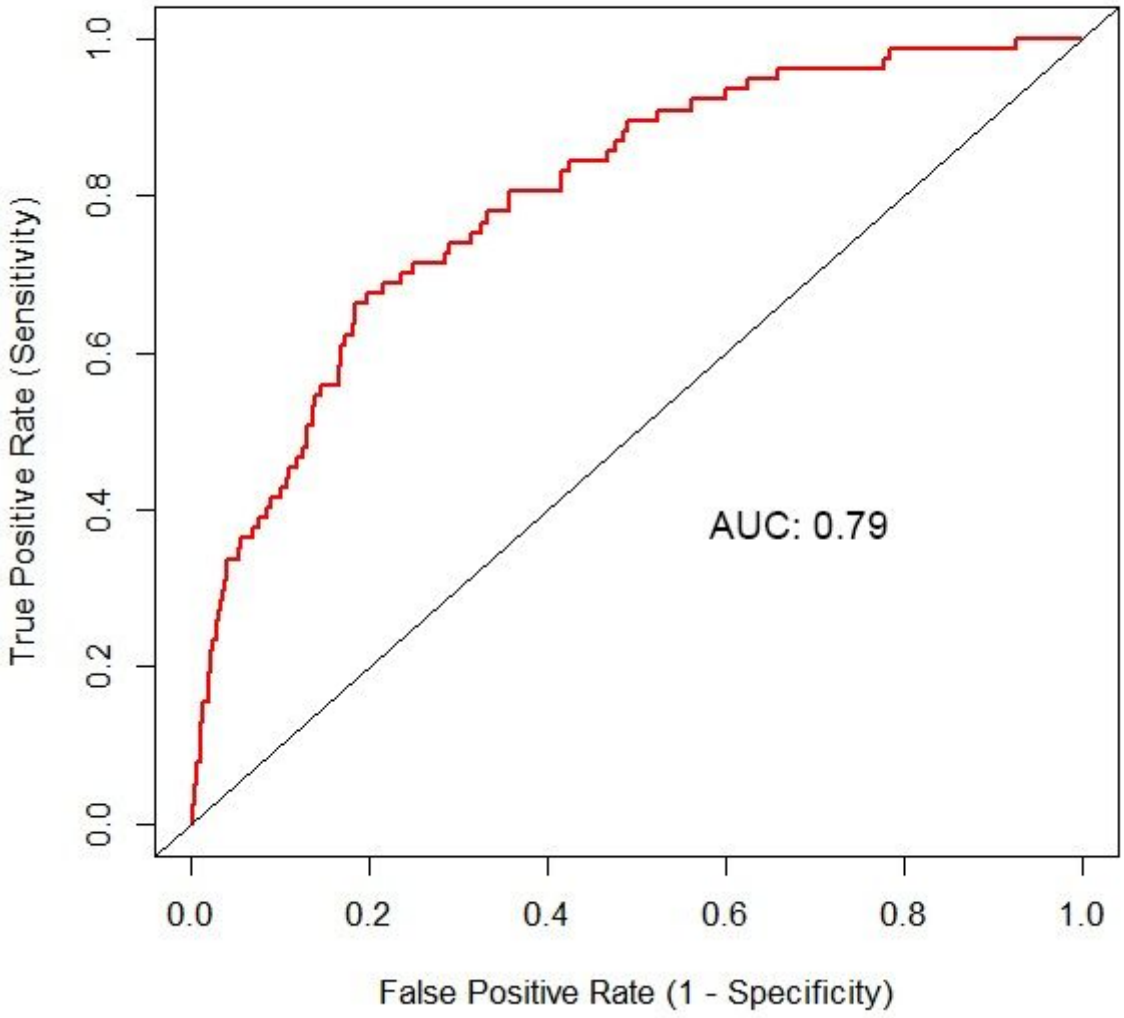

Figure 2

ROC of the Nomogram to Predict the Risk of Gastric Cancer

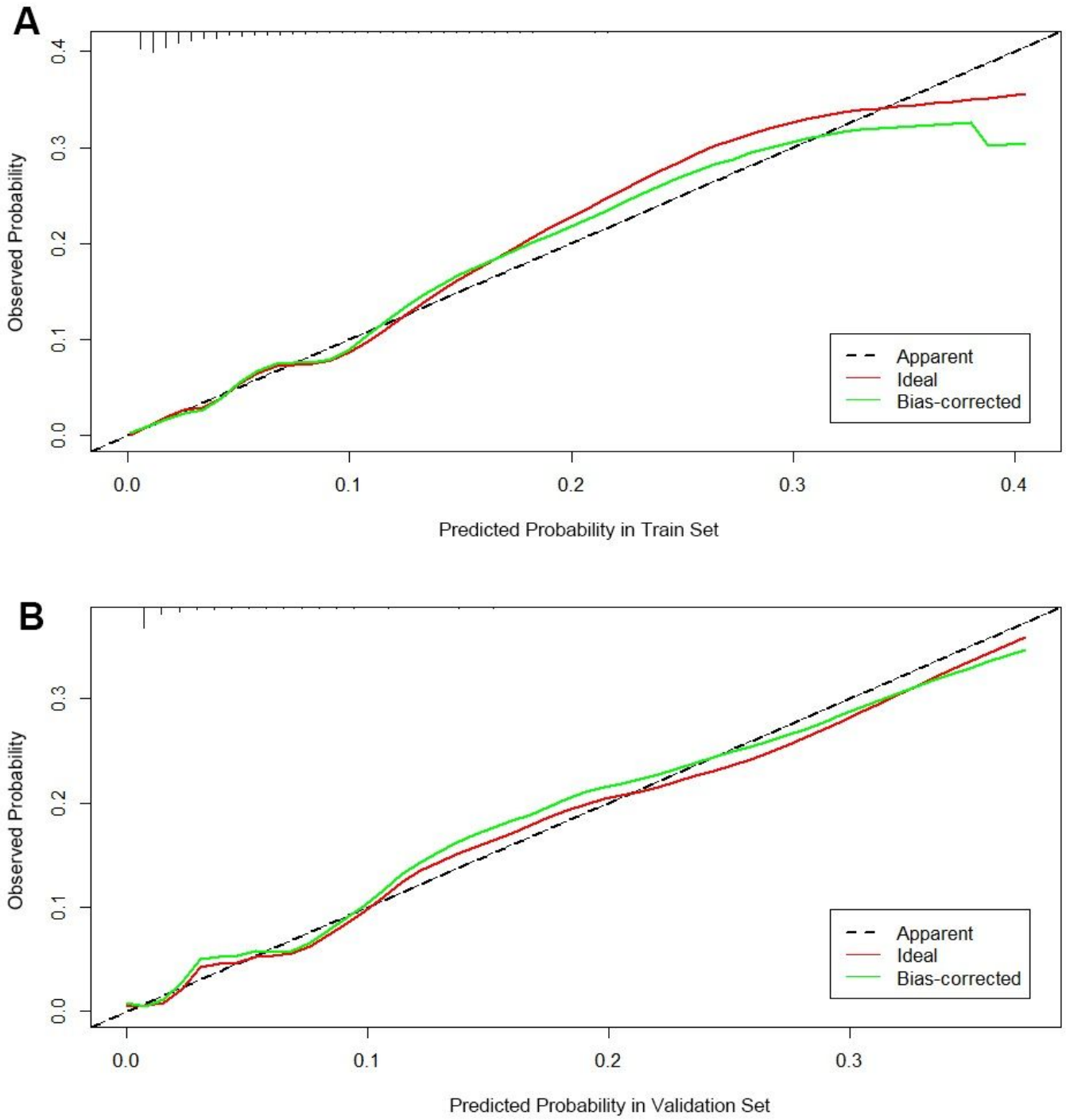

Figure 3

The Calibration Curve of the Nomogram to Gastric Cancer Risk Prediction

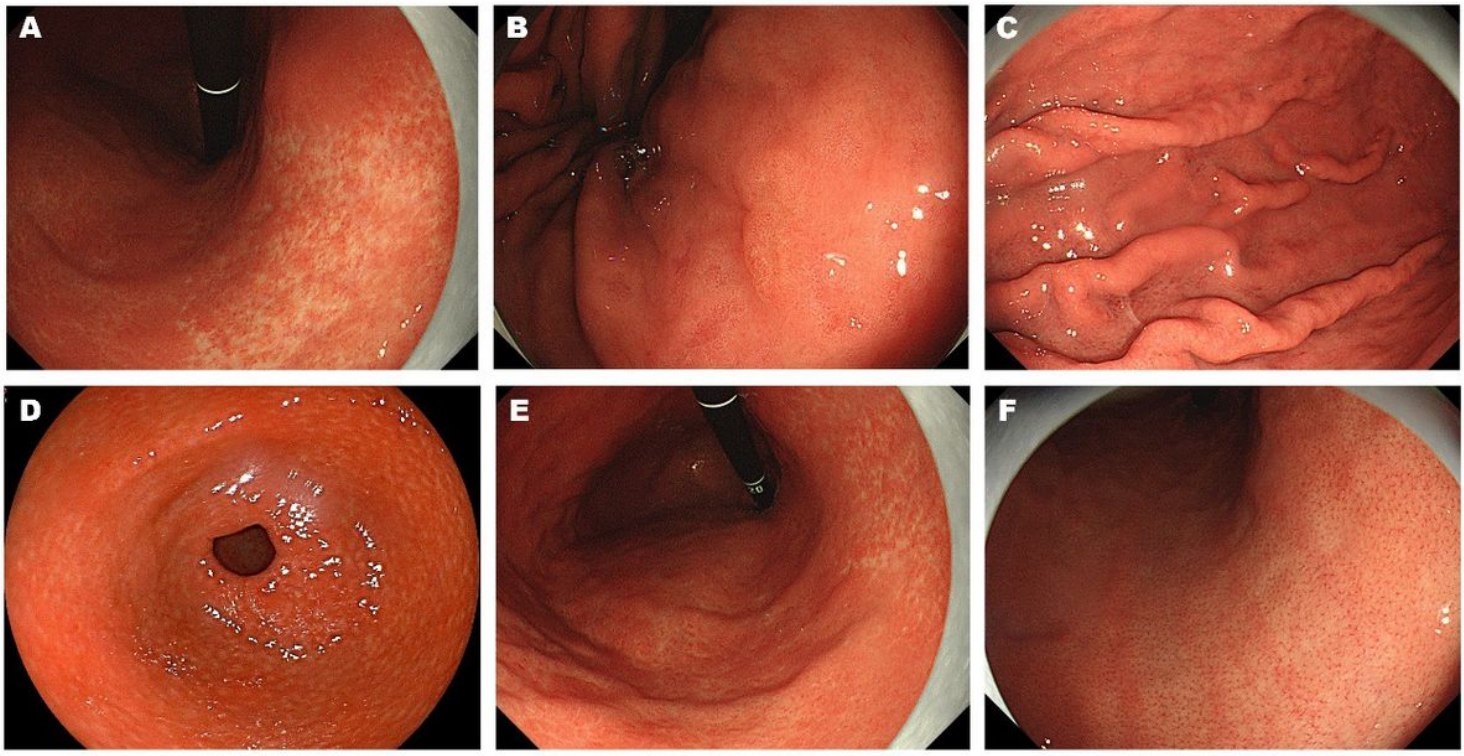

Figure 4

Endoscopic Features of Stomach Based on the Kyoto Classification of Gastritis. A: Atrophy; B: Intestinal Metaplasia; C: Enlarged Fold; D: Nodularity; E: Diffuse Redness; F: Regular Arrangement of Collecting Venules.