Predicting reflux symptom recurrence: The impact of gastroesophageal junction indicators and body mass index among outpatients

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Abstract. The present study aimed to evaluate the efficacy of the prediction model in predicting reflux symptom recurrence among outpatients with reflux esophagitis (RE). A total of 261 outpatients diagnosed with RE complicated by anatomical alterations at the gastroesophageal junction and reflux symptoms were included in the study. Through follow-up, patients were divided into a General group (149 cases) and a Recurrent group (112 cases). Receiver operating characteristic curves of the related factors and prediction model were analyzed to compare the efficacy of each element in predicting reflux recurrence. A prediction model was constructed for predicting reflux recurrence using the axial length of the hiatal hernia (HH), the diameter of the esophageal hiatus, Hill classification, and body mass index (BMI) as risk factors. The cutoff values of the aforementioned factors for predicting reflux recurrence were: an axial length of HH >2 cm, esophageal hiatus diameter ≥3 cm, Hill grade >III, and BMI >25.1 kg/m^2. The multivariate prediction model constructed using the aforementioned four indicators together with chronic atrophic gastritis and *Helicobacter pylori* infection had the area under the curve of 0.801 (95% confidence interval: 0.748-0.854), and the cutoff value of 46.8 had a sensitivity and specificity of 71.4% and 75.8%, respectively. The predictive model in the present study can be used for the primary assessment of reflux recurrence in patients with RE.

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Introduction

Reflux esophagitis (RE) is classified as an upper gastrointestinal disease that is characterized by symptoms of regurgitation, heartburn and esophageal mucosal injury. Most of these symptoms are caused by regurgitation of gastric or duodenal contents into the esophagus. RE is a type of gastroesophageal reflux disease (GERD) with high incidence and recurrence rates. The occurrence of RE is attributed to the interaction of multiple factors, including the impaired anti-reflux function of the gastroesophageal junction (GEJ), low motility state of the stomach and esophagus, and decreased clearing ability of the extra-esophageal organs to regurgitation. Among these factors, damage to the anatomical structure of the GEJ is the most critical causative factor for the occurrence of RE (1). Gastroscopy is the preferred examination in the diagnosis and treatment of GERD. Abnormalities of the GEJ, including the severity of the esophageal mucosa injury, axial length of the hiatal hernia (HH), degree of relaxation of the cardia, and morphological changes in the gastroesophageal flap valve (GEFV), can be observed directly through gastroscopy. Reflux symptoms can recur or persist in patients with GERD and an abnormal anatomical morphology of the GEJ (2,3). A previous review showed that 17 to 45% of 21,736 patients still experienced reflux symptoms after treatment with proton-pump inhibitors (PPIs) (4).

The GERD clinical guidelines of numerous countries point out that the objective of GERD treatment should primarily consider cost-effectiveness (5,6). The initial evaluation methods of GERD include a PPI test, questionnaire and gastroscopy evaluation. When further diagnosis and treatment are required, including clarifying the degree and nature of regurgitation, endoscopic treatment and preoperative evaluation, objective examinations including multichannel intraluminal impedance-pH testing (MII-pH), high-resolution esophageal manometry (HRM) are needed.

Numerous studies have analyzed the risk factors for RE. However, only a few studies have examined the predictive factors for reflux recurrence by observing the structural abnormalities of the GEJ during endoscopy. In the present

study, reflux recurrence and the efficacy of PPI treatment were evaluated through a Reflux Disease Questionnaire (RDQ) and collected data on gastroscopic findings and general information of patients with different degrees of reflux symptom recurrence. The prediction model and receiver operating characteristic (ROC) curves were constructed to evaluate the clinical predictive values of reflux recurrence.

Materials and methods

Patients. An analysis was performed on patients who were treated in four hospitals from September 2020 to December 2021 for RE with structural abnormalities of the GEJ and reflux symptoms including regurgitation, heartburn, noncardiogenic chest pain, and food reflux. The present study protocol was approved (approval no. T20211223001) by the Ethics Committee of Linfen People's Hospital affiliated to Shanxi Medical University (Taiyuan, China). Inclusion criteria: Patients who were diagnosed using painless gastroscopy and responded to a 6-week treatment of esomeprazole were included in the study. Exclusion criteria were as follows: i) Patients diagnosed with other digestive system diseases, including achalasia of the cardia, esophageal cardia laceration, nodular gastritis, bile reflux gastritis, peptic ulcer, Zollinger-Ellison syndrome, refractory RE, secondary RE, gastroesophageal varices, gastroesophageal carcinoma, upper gastrointestinal surgery history, and digestive tract malformation; ii) those with non-digestive system diseases, such as depression and other psychiatric illnesses, severe dysfunction of important organs; iii) those with other conditions that required drug intake that affect the gastrointestinal function during treatment, including non-steroidal anti-inflammatory drugs, hormonal drugs, calcium antagonists, and other drugs. Patients who did not receive the standard treatment or had incomplete case information were also excluded from the study. The screening process is illustrated in Fig. 1. Among all the patients (n=261) participating in this study, there were 158 men and 103 women, ranging in age from 21 to 83 years old.

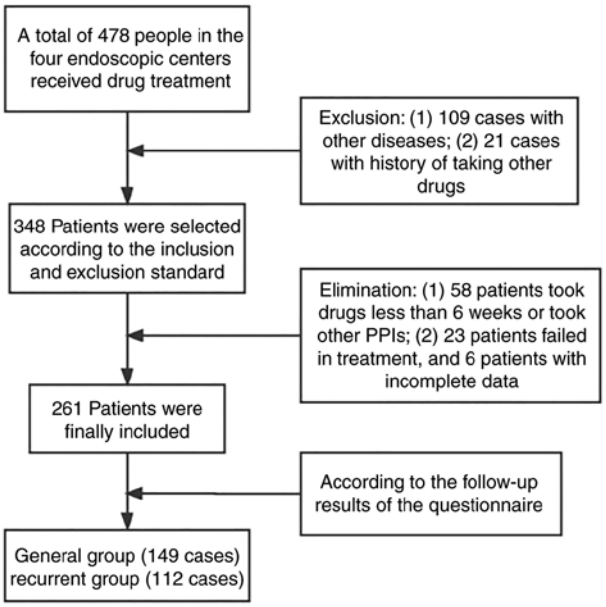

Figure 1. Case screening process.

Treatment and grouping criteria. The treatment administered was in accordance with the Chinese GERD guidelines (7). Esomeprazole (20 mg) was administered twice daily (i.e., 30 min before breakfast and before bedtime) for 6 weeks as the initial treatment, and the maintenance treatment was esomeprazole 20 mg administered once, if necessary. Patients were evaluated using the RDQ before the initial treatment and at the first and third months after the initial treatment to determine whether the initial treatment was effective or if the symptoms recurred (Table SI) (8). Effective treatment or no recurrence was defined as a decrease in RDQ score of ≥50% before the initial treatment; otherwise, the treatment was considered invalid or recurrent (9,10). Patients who responded to the initial treatment were screened and divided into general and recurrent groups according to the RDQ score and GERD guidelines. On the third month after the initial treatment, patients with severity and frequency scores of ≤2 points for any reflux symptoms were assigned to the general group while patients who met one of the following conditions were assigned to the recurrent group: i) the frequency score was >2 points regardless of the severity of reflux symptoms; ii) severity score was >2 points. The follow-up time for all patients is regular, so there is no difference in the follow-up time between the two groups of patients. During the follow-up, no patients in the General group needed maintenance treatment. By contrast, 67 patients in the recurrent group reported receiving maintenance therapy with Esomeprazole 20 mg once a day for 1 to 10 days after the initial treatment, while 19 patients remained on Esomeprazole.

Data collection. The general information of the patients, including sex, age, body mass index (BMI), *Helicobacter pylori* (*H. pylori*) infection, smoking and drinking history, was collected during the follow-up. Gastroscopic findings include RE grade, GEFV grade, axial length of HH, esophageal hiatus diameter, chronic superficial gastritis and chronic atrophic gastritis (CAG).

RE grade was assigned based on the Los Angeles classification (11), GEVF was evaluated using the Hill classification, CAG was graded based on the Kimura-Takemoto classification (12) and *H. pylori* infection was diagnosed by the urea breath test. The distance from the diaphragmatic hiatus to the incisors subtracted by the distance from the dentate line to the incisors was defined as the axial length of the HH (13,14). During gastroscopy, images were captured after observing the morphology of GEFV for at least 30 sec and the diameter of the esophageal hiatus was assessed on these images. Using the endoscope shaft (~1 cm) as the reference, the algebraic multiple relationship between the esophageal hiatus diameter and endoscope shaft was measured (15). The diameters of the esophageal hiatus of all patients were evaluated and recorded by the same researcher. Since the diameter of the esophageal hiatus cannot be measured directly, a scoring system was used to represent the range of esophageal hiatus diameters for statistical analysis. Based on the measurement results, 1 cm ≤ diameter <2 cm was defined as 1 point, 2 cm ≤ diameter <3 cm was defined as

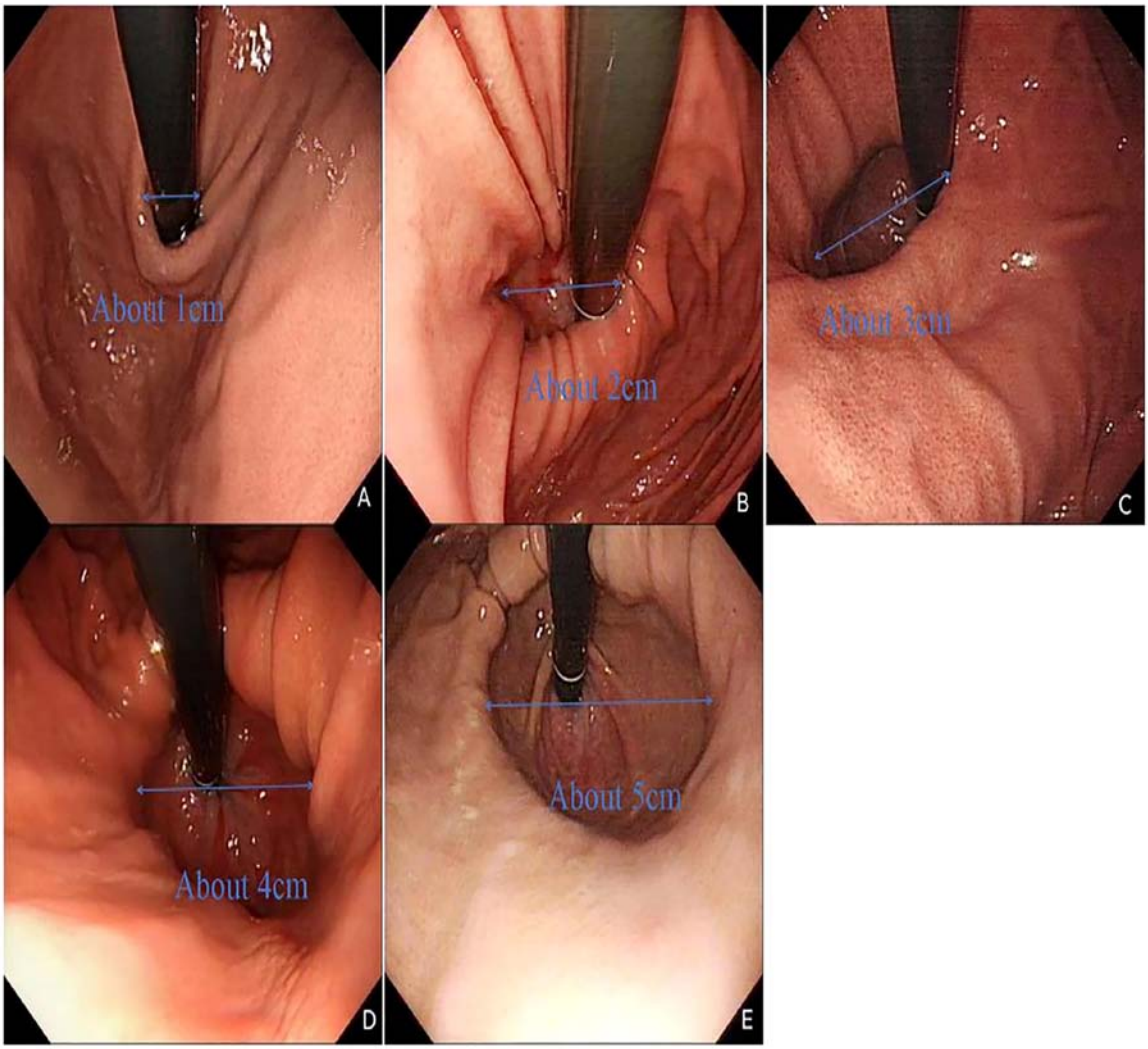

Figure 2. Endoscopic images of different degrees of esophageal hiatus diameter. (A) Normal cardia for 1 point. (B) The esophageal hiatus diameter is ~2 cm for 2 points. (C) ~3 cm for 3 points. (D) ~4 cm for 4 points. (E) ~5 cm for 5 points.

2 points, 3 cm ≤ diameter <4 cm was defined as 3 points, 4 cm ≤ diameter <5 cm was defined as 4 points and diameter ≥5 cm was defined as 5 points. The endoscopic images of each score are shown in Fig. 2. Two types of gastroscope (GIF-H290, Olympus Corporation; and EG760, FUJIFILM Wako Pure Chemical Corporation) were used in these assessments.

Statistical analysis. Data were analyzed using SPSS V25.0 (IBM Corp.). All the quantitative data were normally distributed. Quantitative data were expressed as the mean ± standard error and independent samples t-test was used for comparison. Qualitative data were expressed as rate (%) and chi-square test was used for comparison. Correlations between the continuous variables (i.e., axial length of the HH) and ordinal categorical variables (i.e., RE grade and recurrence) were analyzed using the Kendall correlation coefficients. The factors with P<0.2 in the univariate analysis were included in the logistic regression analysis. The ROC curves and nomogram were built using R version 4.2.2 (www.r-project.org). P<0.05 was considered to indicate a statistically significant difference.

Results

Sex, BMI, axial length of HH, esophageal hiatus diameter score, RE classification, Hill classification, smoking history, and drinking history between the two groups were significantly different. The results of univariate analysis are shown in Table I. Univariate analysis revealed that sex, smoking and alcohol consumption were closely associated with reflux symptom recurrence (P<0.001); however, these three factors were not independent risk factors for reflux recurrence after excluding the interaction among the factors through logistic regression analysis.

The factors with P<0.2 in the univariate analysis were included in the logistic regression analysis. Axial length of HH, esophageal hiatus diameter score, Hill classification, and BMI were independent risk factors for reflux recurrence. The results are shown in Table II. A total of 148 patients were classified as grade III, including 41 (27.7%) cases in the recurrent group and 107 (72.2%) cases in the general group; 113 patients were classified as grade IV, including 71 (62.8%) patients in the recurrent group and 42 (37.1%) cases in the general group. The average BMI of the general

Table I. The factors included in the present study and the results of univariate analysis.

Factors	General group (n=149)	Recurrent group (n=112)	t-value	P-value
Sex			11.41	0.001
Female (%)	72 (48.3%)	31 (27.7%)		
Male (%)	77 (51.7%)	81 (72.3%)		
Age (years)	55.2±12.2	56.7±10.3	-0.24	0.275
Body mass index (kg/m^2)	24.4±2.3	25.6±2.2	-3.83	<0.001
Reflux esophagitis				
Grade A (%)	78 (52.2%)	42 (37.5%)		
Grade B (%)	57 (38.3%)	45 (40.2%)		
Grade C (%)	12 (8.1%)	15 (13.4%)		
Grade D (%)	2 (1.3%)	10 (8.9%)		
Hill				
Grade III (%)	107 (71.8%)	41 (36.6%)	32.28	<0.001
Grade IV (%)	42 (28.1%)	71 (63.3%)		
The axial length of hiatal hernia (cm)	1.97±0.51	2.40±0.54	-6.09	<0.001
Esophageal hiatus diameter score	2.48±0.62	3.07±0.62	-6.74	<0.001
Superficial gastritis				
No	60 (40.2%)	50 (44.5%)	0.50	0.479
Yes	89 (59.7%)	62 (55.4%)		
Atrophic gastritis				
No (%)	89 (59.7%)	62 (55.4%)	5.06	0.080
C1/C2 (%)	50 (33.6%)	48 (42.9%)		
C3/O1 (%)	10 (6.7%)	2 (1.8%)		
Drinking				
No	122 (81.8%)	78 (69.6%)	5.35	0.021
Yes	27 (18.1%)	34 (30.4%)		
Smoking				
No				
Yes				
Helicobacter Pylori infection				
No	123 (82.6%)	99 (88.4%)	1.72	0.190
Yes	26 (17.4%)	13 (11.6%)		

and recurrent groups were 24.4±2.3 and 25.6±2.2 kg/m^2, respectively.

The axial length of the HH, esophageal hiatus diameter score, Hill classification, and BMI were used as test variables, and recurrence was used as a classification variable to construct the ROC curves (Fig. 3). In Table III, the AUC values of each factor are summarized. The cut-off value of the esophageal hiatus diameter score was >2 points, corresponding to the esophageal hiatus diameter of ≥3 cm. The differences in the AUC between the prediction model and each factor were statistically significant (P<0.000). The prediction model showed a higher accuracy in predicting reflux recurrence than each factor alone.

The nomogram was developed based on clinical experience and a literature review using the four independent risk factors, CAG and *H. pylori* infection (Fig. 4). The higher total point value for the six indicators, the greater the probability of reflux recurrence. In multivariate prediction model, the reflux recurrence score of 0.468 showed the most accurate prediction. The cut-off value of 46.8 revealed accuracy, sensitivity, specificity, positive predictive value and negative predictive value of 74.0, 71.4, 75.8, 69.0 and 77.9%, respectively (Table IV). The multivariate prediction model for reflux recurrence was established using the data from all patients and showed a ROC of 0.801 (95% confidence interval: 0.748-0.854) (Fig. 5). In addition, the AUC of the two prediction models was not significantly different (P=0.552). The calibration curve revealed favorable predictive accuracy between the predicted and actual reflux recurrence (mean absolute error=0.023) (Fig. 6).

Discussion

The occurrence of RE is attributed to the interaction of multiple factors. The abnormal anatomical morphology of the GEJ weakens the anti-reflux function and the low motility state decreases the clearance ability of the esophagus and prolongs acid exposure time, which not only aggravate

Table II. Results of Logistic regression analysis and risk factors for reflux symptoms recurrence.

Risk factors	β	SE	Wald	P-value	OR (95% confidence interval)
Sex (man)	0.548	0.354	2.394	0.122	1.730 (0.864~3.462)
Hill grade IV	0.875	0.366	5.722	0.017	2.399 (1.171~4.912)
Reflux esophagitis classification			3.716	0.294	
Grade B	-0.564	0.920	0.376	0.852	0.829 (0.114~6.014)
Grade C	-0.945	0.892	1.122	0.540	0.569 (0.094~3.451)
Grade D	-1.436	0.959	2.242	0.134	0.238 (0.036~1.559)
Chronic atrophic gastritis			0.356	0.837	
C1/C2	0.079	0.952	0.007	0.934	1.083 (0.168~6.991)
C3/O1	0.265	0.957	0.076	0.782	1.303 (0.200~8.504)
The axial length of hiatal hernia	0.970	0.347	7.810	0.005	2.638 (1.336~5.207)
Esophageal hiatus diameter score	0.984	0.293	11.264	0.001	3.676 (1.506~4.754)
Body mass index	0.160	0.069	5.402	0.020	1.173 (1.025~1.342)
Helicobacter Pylori infection (Yes)	-0.906	0.486	3.474	0.062	0.404 (0.156~1.048)
Drinking	0.409	0.443	0.852	0.356	1.505 (0.632~3.584)
Smoking	0.210	0.502	0.175	0.676	1.234 (0.461~3.300)

Table III. The prediction model for predicting reflux symptom recurrence.

Predictors	AUC	95% CI	Cut-off value	Sensitivity (%)	Specificity (%)	P-value
The axial length of HH (cm)	0.681	0.630~0.733	>2	39.29	88.59	P_1<0.000
Esophageal hiatus diameter score	0.719	0.665~0.773	>2	83.93	48.99	P_2<0.000
Hill classification	0.676	0.618~0.734	> grade III	63.39	71.81	P_3<0.000
BMI (kg/m^2)	0.639	0.571~0.706	>25.1	69.64	63.09	P_4<0.000
Prediction model	0.797	0.734~0.851	>0.539	65.18	81.88	

Prediction model developed by axial length of HH, esophageal hiatus diameter, Hill grade and BMI. P_1, P_2, P_3 and P_4 respectively reflect the statistical differences between the AUC of prediction model and the AUC of the axial length of HH, esophageal hiatus diameter score, Hill classification and BMI. HH, hiatal hernia; ROC, receiver operating characteristic curve; AUC, area under the curve; 95% CI, 95% confidence interval; BMI, body mass index.

regurgitation, but also affects the efficacy of PPI treatment (6). Reflux symptoms can recur or persist in patients with GERD and an abnormal anatomical morphology of the GEJ (2). In the present study, the anatomical morphology of the GEJ of patients with different severity of regurgitation was analyzed. Previous studies have indicated that factors, including HH and abnormal GEFV affect the efficacy of PPI treatment for GERD (16,17), but BMI does not (18). In the present study, it appeared that patients with axial length HH >2 cm, esophageal hiatus diameter ≥3 cm, Hill grade IV, and BMI >25.1 kg/m^2 at the same time are vulnerable to severe regurgitation and may require long-term maintenance treatment.

In the current study, the optimal cut-off value of BMI was >25.1 kg/m^2 and patients with recurrent regurgitation accounted for 58.2% (78/134). Pandolfino *et al* (19) analyzed the relationship between obesity and pressure of the EGJ; it was revealed that patients with BMI >25 kg/m^2 had significantly higher intragastric pressure than those with BMI <25 kg/m^2. This finding indicated that the gastroesophageal pressure in the GEJ increases with BMI, causing the anti-reflux function to become unstable. Furthermore, patients with a BMI >30 kg/m^2 were more likely to develop HH and GERD, further supporting the results of the present study.

The morphology of the gastric mucosal fold and its fit with the endoscopic shaft reflects the anti-reflux function of the GEJ. Hill *et al* classified GEFV into four grades based on the appearance of the GEJ; grades I and II were normal, while grades III and IV were abnormal (20). In a meta-analysis examining the predictive value of the Hill classification on GERD (21), 3,914 patients were included in seven studies, and the sensitivity and specificity of abnormal GEFV in the diagnosis of RE were 54.8 and 75.7%, respectively. The Hill classification provides diagnostic information on the morphology of the EGJ and quantifies the severity of GERD, which facilitates the selection of a therapeutic regimen and observation of prognosis.

The endoscopic evaluation of sliding HH includes the axial length of the HH and esophageal hiatus diameter; however, presently, there is no unified standard for its endoscopic diagnosis and classification (2,22). Schlottmann *et al* (23)

Table IV. The efficacy of the multivariate prediction model in predicting reflux recurrence.

Cutoff	Accuracy	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive by prediction model
63.8	0.709	0.482	0.879	0.750	0.693	72 (0.276)
56.1	0.743	0.616	0.839	0.742	0.744	93 (0.356)
46.8	0.740	0.714	0.758	0.690	0.779	116 (0.444)
39.1	0.732	0.759	0.711	0.664	0.797	128 (0.490)
26.9	0.648	0.839	0.503	0.560	0.807	168 (0.644)
26.4	0.655	0.857	0.503	0.565	0.824	170 (0.651)
15.1	0.579	0.964	0.289	0.505	0.915	214 (0.820)
12.0	0.548	0.973	0.228	0.487	0.919	224 (0.858)
10.3	0.540	0.991	0.201	0.483	0.968	230 (0.881)
7.2	0.494	0.991	0.121	0.459	0.947	242 (0.927)
6.3	0.475	0.991	0.087	0.449	0.929	247 (0.946)
4.2	0.464	1.000	0.060	0.444	1.000	252 (0.966)
2.4	0.448	1.000	0.034	0.438	1.000	256 (0.981)

Multivariate prediction model developed by axial length of HH, esophageal hiatus diameter, Hill grade, BMI, CAG, and *H. pylori* infection. HH, hiatal hernia; BMI, body mass index; CAG, chronic atrophic gastritis; *H. Pylori, Helicobacter pylori*.

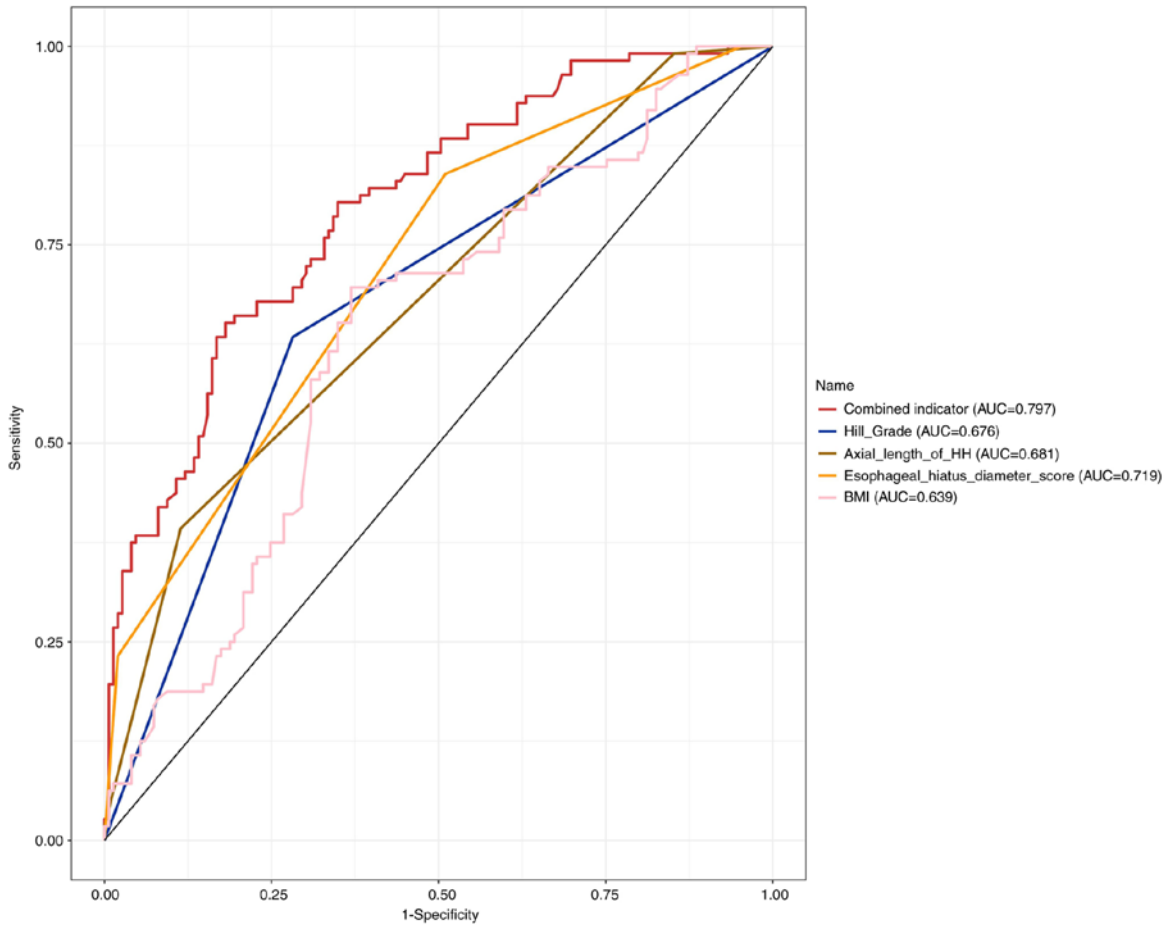

Figure 3. ROC curves of prediction model, the axial length of HH, esophageal hiatus diameter score, Hill classification and BMI. 1-specificy: false positive rate, which is equal to 1-specificity (%). HH, hiatal hernia; ROC, receiver operating characteristic curve; AUC, area under the curve.

measured the axial length of HH using barium radiography and divided the study population into three groups: HH <3, 3-5, and >5 cm. Regurgitation occurred more frequently and esophagitis and reflux symptoms were more severe in patients

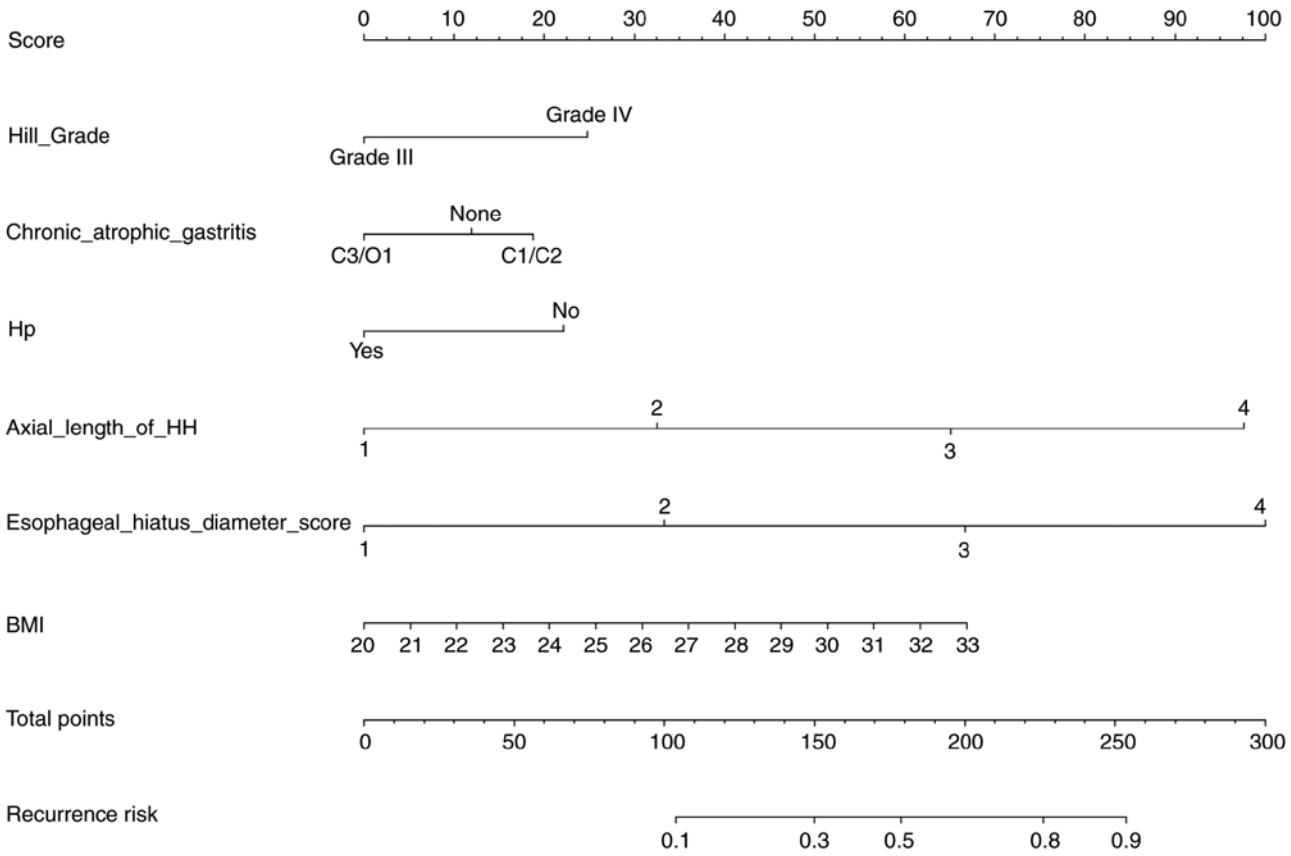

Figure 4. Nomogram for the multivariate prediction model of reflux recurrence.

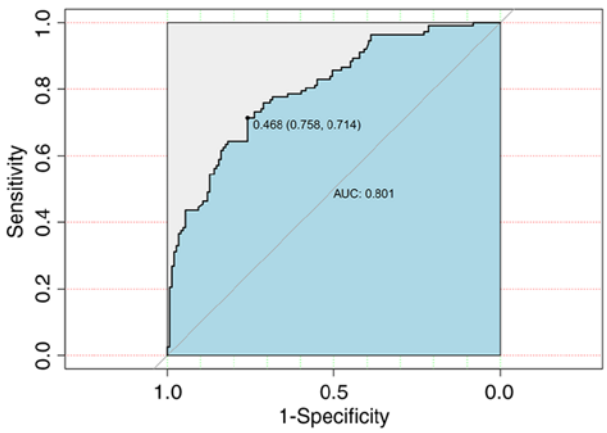

Figure 5. ROC curves of the multivariate prediction model of reflux recurrence. ROC, receiver operating characteristic curve; AUC, area under the curve.

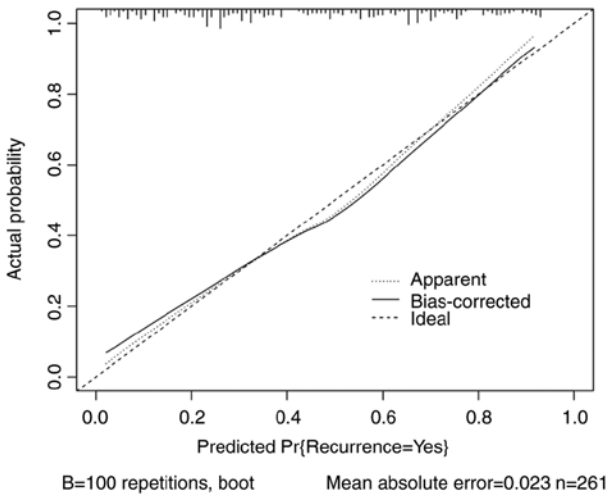

Figure 6. Calibration curve of the multivariate prediction model in predicting reflux recurrence.

with longer axial length of HH; in the current study, the average axial lengths of HH in the general and recurrent groups were 1.97±0.51 and 2.40±0.54 cm, respectively. Additionally, the Kendall tau-β correlation coefficients between the axial length of HH and RE classification and recurrence were 0.198 and 0.366, respectively (P<0.001), which were similar to the study conducted by Schlottmann *et al*.

A previous research showed that the average axial length of HH and Hill classification in patients with GERD were greater than those in non-GERD patients (1.9 and 2.7 cm vs. 1.6 and 2.2 cm). There was no statistical difference between the Hill classification and axial length of HH; however, in clinical practice, the Hill classification was more accurate in measurement than that of axial length of HH (24). In the present study, there was no statistical significance in the AUC between the Hill classification and axial length of HH (P=0.880), which indicates that the Hill classification was not superior to axial length of HH in predicting reflux symptom recurrence. The combination of the axial length of HH, esophageal hiatus diameter, Hill classification, and BMI showed a higher

accuracy in predicting reflux symptom recurrence than that of each individual factor (P<0.001).

The relationship between *H. pylori* infection and GERD has not yet been resolved (25). Gastric atrophy and hyposecretion of gastric acid often occur in patients with *H. pylori* infection. Therefore, it is mostly considered believe that *H. pylori* infection is negatively correlated with RE, which may protect vulnerable individuals from GERD (26). Similarly, the effect of CAG on gastric mucosa is analogous to that of *H. pylori* infection (27). To construct a reasonable and complete prediction model, combined with the authors' clinical experience and literature review, atrophic gastritis and *H. pylori* infection were included in the multivariate prediction model, even if they are not independent risk factors for reflux recurrence. Specifically, the results may be more definitive when the sample size increases. In a similar study, a prediction model with a sample size of 494 patients showed improved discriminative power (28).

Actually, MII-pH or HRM have not yet been popularized in all medical institutions of developing countries including China, but patients with GERD are very common (5,29). Without complicated symptoms, outpatients or physical examination patients with GERD alone, usually do not require to be subjected to other examinations than endoscopy from a cost-effective perspective. There were several limitations to the present study. Given the patients' condition in the present study, the data were measured using RDQ and gastroscopy without other objective examination, including MII-pH or HRM. The esophageal hiatus diameter was indirectly measured by directly comparing the esophageal hiatus diameter and endoscope shaft, scores were used to reflect the range of the esophageal hiatus diameter and perform statistical analysis. The sample size may not be sufficient due to the exclusion criteria and patient compliance. Certain patients discontinued their treatment voluntarily after a slight improvement in symptoms. Further study with a larger sample size and more objective examination is required to confirm the efficacy of the prediction model in the present study.

This prediction model is more suitable for primary clinical evaluation without imposing additional burdens on outpatients. Patients with an axial length of HH >2 cm, esophageal hiatus diameter ≥3 cm, Hill grade >III, and BMI >25.1 kg/m^2 are prone to have reflux recurrence or require PPI maintenance treatment. In clinical practice, patients who present with *H. pylori* infection and CAG are relatively less likely to develop reflux recurrence. However, this feature was not represented in the prediction model of the present study. Meanwhile, a reference was provided for diagnosing refractory RE and screening high-risk populations with poor drug efficacy or recurrent reflux.

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Availability of data and materials

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

Authors' contributions

XC, QW and JL conceived and designed the study. JL performed statistical analysis. QW and JL analyzed the data. QW, YS, JF, JR and ZW performed data collection. QW and JL confirm the authenticity of all the raw data. All authors contributed to the writing of the manuscript and reviewed, read and approved the final manuscript.

Ethics approval and consent to participate

The present study was conducted in accordance with the tenets of the Declaration of Helsinki. The present study protocol was approved (approval no. T20211223001) by the Ethics Committee of Linfen People's Hospital affiliated to Shanxi Medical University (Taiyuan, China). According to the Shanxi Medical University Ethics Committee, the study patients were notified of the study and permitted the opportunity to refuse participation in the study.

Patient consent for publication

With regard to the informed consent of participants, the Ethics Committee of Linfen People's Hospital affiliated to Shanxi Medical University made a decision based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects, which states that non-intervention studies are deemed exempt from patients' consent and, instead, researchers must notify the study subjects about the information regarding study contents on a home page, and guarantee an opportunity when the study subjects could refuse consent. All patients participating in the present study received written informed consent.

Competing interests

The authors declare that they have no competing interests.

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