



# Analysis of Risk Factors and Establishment of a Prediction Model for Endoscopic Primary Bile Reflux: A Single-Center Retrospective Study

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**Background:** Endoscopic primary bile reflux is one of the main diagnostic criteria for bile reflux gastritis (BRG). Presently, the risk factors and prediction models of endoscopic primary bile reflux (EPBR) in gastropathy patients who cannot or will not undergo endoscopy due to contraindications are not clear. Thus, this study aimed to evaluate the risk factors of EPBR and to establish and verify a prediction model.

**Methods:** A series of 844 patients (564 subjects with EPBR and 280 control subjects) were retrospectively selected for this study and divided into a training set ( $n = 591$ ) and a validation set ( $n = 253$ ) according to the usual ratio of 70:30% for the subsequent internal validation of the logistic regression model for EPBR. Fifteen parameters that might affect the occurrence of EPBR were collected. Subsequently, univariate and stepwise logistic regression analyses were introduced to reveal the risk factors and the multivariate prediction model. An R package was dedicated to the corresponding internal validation of the EPBR model.

**Results:** The univariate analysis showed that gender, age, smoking, *Helicobacter pylori* (*H. pylori*) infection status, metabolic syndrome (MS), non-steroidal anti-inflammatory drugs (NSAIDs) use history, and previous medical histories of chronic liver diseases, cholelithiasis, and erosive gastritis were statistically significant between the two groups ( $P < 0.05$ ). Multivariate regression described that being a male [OR (95% confidence interval (CI)) = 2.29 (1.50–3.50),  $P < 0.001$ ], age  $\geq 45$  years old [OR (95% CI) = 4.24 (2.59–6.96),  $P < 0.001$ ], *H. pylori* infection status [OR (95% CI) = 2.34 (1.37–4.01),  $P = 0.002$ ], MS [OR (95% CI) = 3.14 (1.77–5.54),  $P < 0.001$ ], NSAIDs use history [OR (95% CI) = 1.87 (1.03–3.40),  $P = 0.04$ ], cholelithiasis history [OR (95% CI) = 3.95 (2.18–7.18),  $P < 0.001$ ] and erosive gastritis history [OR (95% CI) = 6.77 (3.73–12.29),  $P < 0.001$ ] were the risk factors for the occurrence of EPBR. Based on the results of these risk factors, an EPBR prediction model with an adequate calibration and

excellent discrimination was established [area under the curve (AUC): 0.839, 95% CI = 0.806–0.872].

**Conclusions:** Being a male, age  $\geq 45$  years old, *H. pylori* infection, histories of MS, NSAIDs use, cholelithiasis, and erosive gastritis appear to be the risk factors for EPBR, and our favorable prediction model might be an option for the prediction of EPBR.

**Keywords:** primary bile reflux, endoscope, risk factors, prediction model, retrospective study

## INTRODUCTION

Bile reflux gastritis, also known as alkaline reflux gastritis (ARG), refers to the chronic inflammation, erosion, and even ulceration in the gastric mucosa caused by excessive duodenal fluid (including bile, pancreatic, and intestinal fluid) refluxing into the stomach (1). The action component of duodenal reflux fluid is bile acid, which has an accumulative damaging effect on the gastric mucosal barrier and can induce chronic inflammation, erosion, ulcers, gastroesophageal reflux, and even carcinogenesis (2–4). As a common digestive disease, bile reflux gastritis (BRG) accounts for about 22.6% of chronic gastritis (5). Bile reflux gastritis that originated in a non-operative stomach is referred to as primary bile reflux gastritis (PBRG), while BRG that occurred after gastric pylorus surgery is called secondary bile reflux gastritis (SBRG). Endoscopic primary bile reflux is part of the most important diagnostic criteria for PBRG (6, 7). Long-term endoscopic primary bile reflux (EPBR) may also lead to the hyperplasia of gastric epithelial pits and esophageal squamous epithelium, and may even be associated with intestinal metaplasia or cancer (8). However, to date, the etiologies and risk factors of EPBR are not well-understood, especially for gastropathy patients who cannot or will not undergo further endoscopy due to contraindications.

Past two conflicting studies have explored the influence of psychological factors and *H. pylori* infection on EPBR (4, 5). Another study revealed that EPBR might be involved with sex, age, and fasting time (9). These findings provided a preliminary basis for further research. Our study aimed to further elucidate more possible factors related to the occurrence of EPBR, and eventually, to design a prediction model that provides a valuable evaluation tool for patients with EPBR. The significance of this study is to offer clues for clinical empirical diagnosis and treatment.

## MATERIALS AND METHODS

### Study Design and Participants

A total of 1,029 patients admitted to the Tongji Hospital of Tongji University from January 2017 to December 2020 were assigned the analytical data, including 711 subjects with EPBR and 318 control subjects. The studies involving human participants were reviewed and approved by the Ethics Committee of Tongji Hospital, School of Medicine, Tongji University. The patients or participants involved in this study had provided their written informed consent. Three endoscopists performed gastroscopies, and all of them were skilled in endoscopic procedures and had

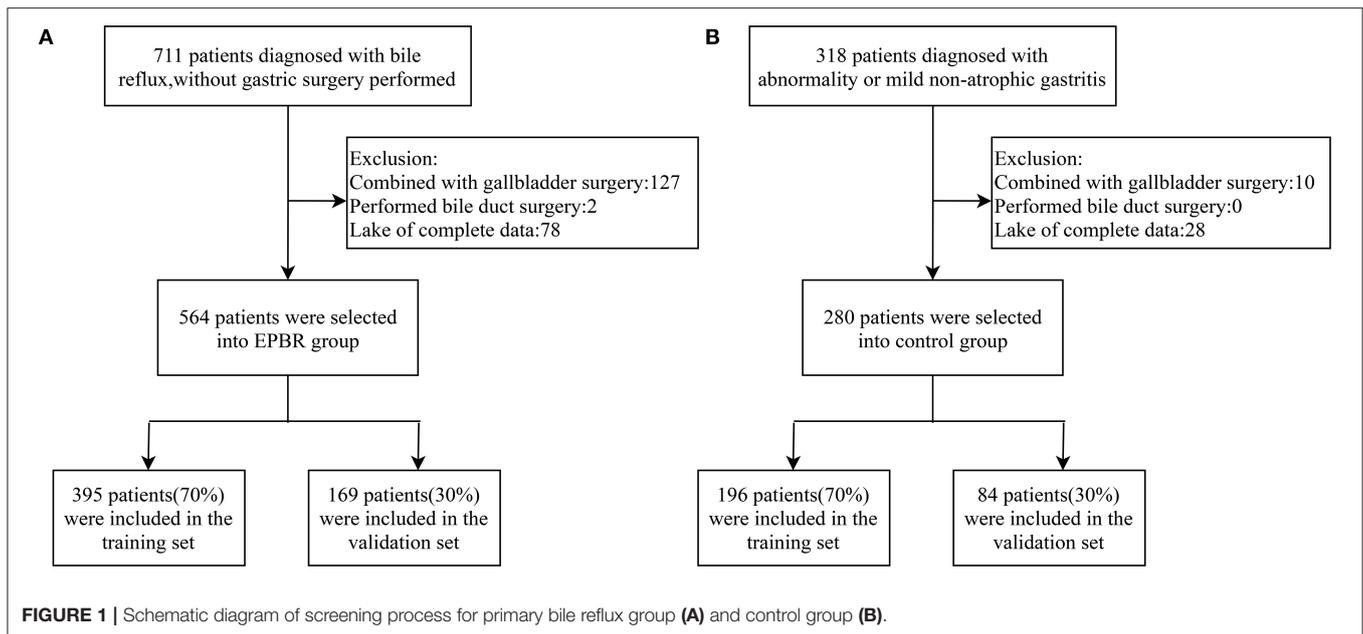
the same diagnostic criteria for EPBR. All the patients were excluded from gastric surgery and had not taken proton pump inhibitors (PPI) or ursodeoxycholic acid in 7–10 days prior to endoscopy. The same exclusion criteria in the two groups were applied to one of the following: patients with histories of gastrectomy, cholecystectomy, other biliary surgery (they are generally considered as predisposing factors for SBRG), and incomplete clinical medical data (Figures 1A,B). Consequently, a series of 844 patients with complete medical records were retrospectively divided into the EPBR group ( $n = 564$ ) and the control group ( $n = 280$ ) (Figures 1A,B). The control group means no abnormality or only mild non-atrophic gastritis under the gastroscope. For the subsequent internal validation of the logistic regression model for EPBR, the two groups were successively selected to build the training set and the validation set according to the usual ratio of 70%:30% (training set:  $n = 591$ , validation set:  $n = 253$ ) (Figures 1A,B).

The patients with EPBR were enrolled as endoscopically confirmed. The determination of excessive EPBR in the stomach under endoscopy was mainly based on the mucus lake bile staining when the endoscope is entered into the gastric cavity (10). According to the color of the mucus lake, the EPBR severity was classified into four levels: mucus lake is clear and transparent (Grade 0); mucus lake is clear and light yellow (Grade I); mucus lake is yellow and clear (Grade II); the mucous lake is pale yellow or dark green (Grade III) (6, 11). The EPBR of grade 0–I, also called physiological reflux, is unlikely to cause digestive symptoms and pathological gastric mucosal lesions. Instead, EPBR of grade II–III may induce upper gastrointestinal symptoms and pathological gastric mucosal lesions, which is considered as pathological reflux (12).

### Clinical Variables

In the present study, the succeeding 15 parameters that might influence the occurrence of EPBR were gathered after obtaining the informed consent of the patients. Fifteen parameters that might affect the occurrence of EPBR, namely, gender, age, body mass index (BMI), smoking, alcohol consumption, *Helicobacter pylori* (*H.pylori*) infection status, metabolic syndrome (MS), non-steroidal anti-inflammatory drugs (NSAIDs) use history, psychological factors, allergic constitution, gastrointestinal symptoms, and previous medical histories of chronic liver diseases, cholelithiasis, erosive gastritis, and pancreatic diseases were collected.

The medical history of psychotropic medication of the patient and the anxiety and depression scale was used as the criteria to assess whether the patient had mental health factors.



The diagnostic criteria for MS proposed by the International Diabetes Federation (IDF) in 2005 were adopted (13). The specific diagnostic definitions for MS were as follows: central obesity (waist circumference as the tangent point, male  $\geq 90$  cm, female  $\geq 80$  cm) and any two of the following four indicators: (1) raised triglycerides (TG)  $>1.7$  mmol/L, or specific treatment for this lipid abnormality; (2) reduced HDL-cholesterol (HDL-C):  $<1.03$  mmol/L in men and  $<1.29$  mmol/L in women, or being correspondingly treated; (3) raised blood pressure:  $\geq 130/85$  mmHg, or treatment of previously diagnosed hypertension; (4) raised fasting plasma glucose (FPG):  $\geq 5.6$  mmol/L or previously diagnosed type 2 diabetes. The gastrointestinal symptoms referred to abdominal pain, abdominal distension, heartburn, bitter taste, or vomiting bile before endoscopy, with at least one of which was regarded as having gastrointestinal symptoms. Moreover, the eligible contents of chronic liver diseases were viral hepatitis, fatty liver, cirrhosis, and liver malignancy. Cholelithiasis meant cholecystitis, gallstones, and malignant tumors of the biliary tract. The patients with pancreatic diseases included acute or chronic pancreatitis and pancreatic tumors. The selection principle of the 14 potential risk factors above for inducing or deteriorating EPBR mainly hinged on previous literature and our clinical practice experience (14–18).

## Statistical Analysis

The statistical analysis was conducted with SPSS version 20.0 (IBM Corp., Armonk, New York, United States) and R software (version 4.0.2; <http://www.Rproject.org>) using an alpha level of 0.05. The quantitative data with normal distribution were calculated for the mean with SDs, and the quantitative data with abnormal distribution were expressed as median with interquartile ranges, whereas the frequencies were determined by the categorical values. The Chi-square test or Fisher's exact probability method, the Student *t*-test, and Wilcoxon rank-sum

test was employed for the analysis of the categorical, continuous, and ordinal variables between the groups, respectively. The predictors of the variables were tested in univariate and multivariate logistic regression analyses for their association with EPBR. The discriminatory ability of the logistic regression model was quantified using the receiver operating characteristic (ROC) curve and the area under the curve (AUC). The calibration of the nomogram was performed by plotting the observed outcome probabilities. The Hosmer–Lemeshow (H–L) test was employed to evaluate how well the percentage of the observed probability matched the percentage of the predicted probability. A  $P < 0.05$  was considered statistically significant.

## RESULTS

### Description of the Subjects

According to the inclusion and exclusion criteria, 564 subjects in the reflux group and 280 subjects in the control group were screened, respectively (Figures 1A,B). The training set used for establishing the logistic regression model consisted of 395 subjects from the reflux group and 196 subjects from the control group. Meanwhile, 169 subjects from the reflux group and 84 subjects from the control group constituted the validation set and were assigned to the internal validation of the EPBR prediction model (Figures 1A,B). The equilibrium test showed that there was no system selection bias between the two data sets (Supplementary Table 1). Therefore, it is reasonable and feasible to establish a logistic regression model through the above data sets.

### Univariate Analysis

Our univariate analysis studies revealed that there were statistically significant differences in gender, age, smoking, *H. pylori* infection status, MS, histories of NSAIDs use, chronic

**TABLE 1** | Univariate analysis of the risk factors for bile reflux in the training set.

Factor	Total (n = 591)	Bile reflux		P-value
		No (n = 196)	Yes (n = 395)	
<b>Gender, n (%)</b>				<0.001
Female	296 (50.08)	127 (64.80)	169 (42.78)	
Male	295 (49.92)	69 (35.20)	226 (57.22)	
Age, Mean ± SD	50.18 ± 13.72	43.27 ± 13.60	53.62 ± 12.44	<0.001
<b>Age, n (%)</b>				<0.001
<45	194 (32.83)	110 (56.12)	84 (21.27)	
45–59	201 (34.01)	51 (26.02)	150 (37.97)	
≥60	196 (33.16)	35 (17.86)	161 (40.76)	
Height, M (Q <sub>1</sub> , Q <sub>3</sub> )	1.65 (1.60, 1.72)	1.66 (1.60, 1.73)	1.65 (1.60, 1.71)	0.367
Weight, Mean ± SD	64.23 ± 13.45	65.04 ± 15.85	63.82 ± 12.08	0.346
BMI, Mean ± SD	23.14 ± 3.87	23.28 ± 4.47	23.07 ± 3.54	0.579
<b>BMI, n (%)</b>				0.625
<18.5	59 (9.98)	20 (10.20)	39 (9.87)	
18.5–23.9	300 (50.76)	102 (52.04)	198 (50.13)	
≥24	232 (39.26)	74 (37.76)	158 (40.00)	
<b>NSAIDs use history, n (%)</b>				0.005
No	491 (83.08)	175 (89.29)	316 (80.00)	
Yes	100 (16.92)	21 (10.71)	79 (20.00)	
<b>Chronic liver diseases, n (%)</b>				0.002
No	521 (88.16)	184 (93.88)	337 (85.32)	
Yes	70 (11.84)	12 (6.12)	58 (14.68)	
<b>Cholelithiasis, n (%)</b>				<0.001
No	447 (75.63)	176 (89.80)	271 (68.61)	
Yes	144 (24.37)	20 (10.20)	124 (31.39)	
<b>H. pylori infection status, n (%)</b>				<0.001
No	446 (75.47)	166 (84.69)	280 (70.89)	
Yes	145 (24.53)	30 (15.31)	115 (29.11)	
<b>Psychological factors, n (%)</b>				0.101
No	408 (69.04)	144 (73.47)	264 (66.84)	
Yes	183 (30.96)	52 (26.53)	131 (33.16)	
<b>Allergic constitution, n (%)</b>				0.075
No	473 (80.03)	165 (84.18)	308 (77.97)	
Yes	118 (19.97)	31 (15.82)	87 (22.03)	
<b>Erosive gastritis, n (%)</b>				<0.001
No	421 (71.24)	178 (90.82)	243 (61.52)	
Yes	170 (28.76)	18 (9.18)	152 (38.48)	
<b>Smoking, n (%)</b>				0.011
No	478 (80.88)	170 (86.73)	308 (77.97)	
Yes	113 (19.12)	26 (13.27)	87 (22.03)	
<b>Alcohol consumption, n (%)</b>				0.259
No	531 (89.85)	180 (91.84)	351 (88.86)	
Yes	60 (10.15)	16 (8.16)	44 (11.14)	
<b>Metabolic syndrome, n (%)</b>				<0.001
No	460 (77.83)	171 (87.24)	289 (73.16)	
Yes	131 (22.17)	25 (12.76)	106 (26.84)	
<b>Pancreatic diseases, n (%)</b>				0.171
No	562 (95.09)	183 (93.37)	379 (95.95)	
Yes	29 (4.91)	13 (6.63)	16 (4.05)	
<b>Gastrointestinal symptoms, n (%)</b>				0.129
No	342 (57.87)	122 (62.24)	220 (55.70)	
Yes	249 (42.13)	74 (37.76)	175 (44.30)	

**TABLE 2** | Logistic multivariate analyses of risk factors for primary bile reflux in the training set.

Factor	β	S.E	Wald	P	OR	95% CI	
						Lower	Upper
Constant	-1.860	0.241	59.405	<0.001			
Gender (Male)	0.829	0.216	14.723	<0.001	2.291	1.500	3.500
<b>Age</b>							
<45					Ref.		
45–59	1.445	0.253	32.729	<0.001	4.243	2.586	6.961
≥60	1.937	0.275	49.477	<0.001	6.935	4.043	11.896
NSAIDs use history (Yes)	0.628	0.307	4.169	0.041	1.874	1.025	3.423
Cholelithiasis (Yes)	1.374	0.304	20.378	<0.001	3.952	2.176	7.176
H. pylori infection (Yes)	0.851	0.274	9.643	0.002	2.342	1.369	4.008
Erosive gastritis (Yes)	1.912	0.305	39.410	<0.001	6.766	3.725	12.290
Metabolic syndrome (Yes)	1.143	0.290	15.478	<0.001	3.135	1.774	5.539

liver diseases, cholelithiasis, and erosive gastritis between the two groups ( $P < 0.05$ ) (Table 1).

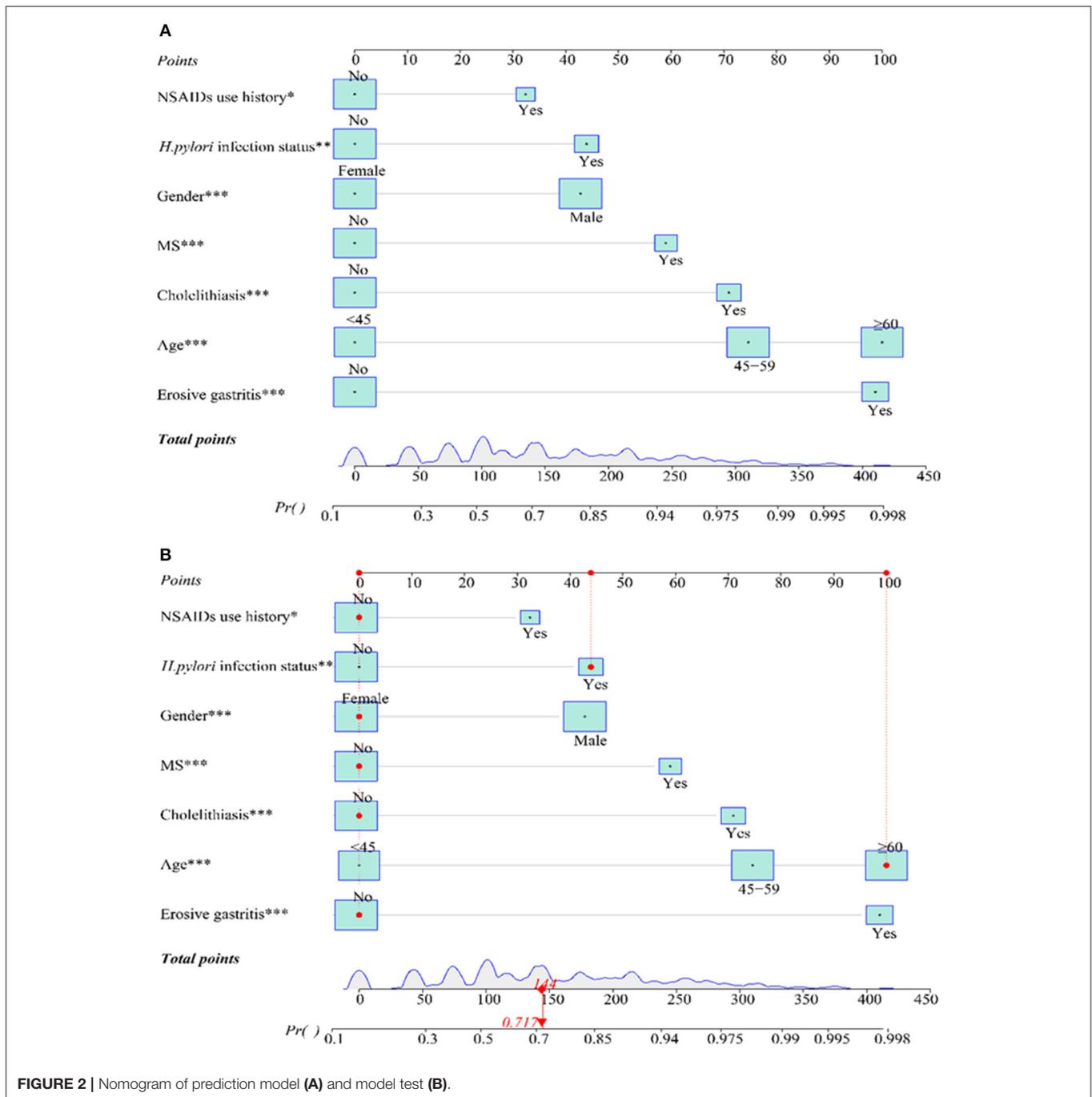
## Multivariate Analysis

Multivariate regression described that being male [OR (95% confidence interval (CI) = 2.29 (1.50–3.50),  $P < 0.001$ ], age  $\geq 45$  years old [OR (95% CI) = 4.24 (2.59–6.96),  $P < 0.001$ ], H. pylori infection status [OR (95%CI) = 2.34 (1.37–4.01),  $P = 0.002$ ], MS [OR (95% CI) = 3.14 (1.77–5.54),  $P < 0.001$ ], NSAIDs use history [OR (95% CI) = 1.87 (1.03–3.40),  $P = 0.04$ ], cholelithiasis history [OR (95% CI) = 3.95 (2.18–7.18),  $P < 0.001$ ], and erosive gastritis history [OR (95% CI) = 6.77 (3.73–12.29),  $P < 0.001$ ] were the risk factors for the occurrence of EPBR (Table 2).

## Establishment of the Prediction Model

Based on the results of the multivariate analysis, a formula for predicting the probability of EPBR was computed as follows:  $P = e^X / (1 + e^X)$ ,  $X = 0.829X_1 + 1.445 X_2$  or  $1.937X_2 + 0.628X_3 + 1.374X_4 + 0.851X_5 + 1.912X_6 + 1.143X_7 - 1.860$  (Table 2). The values of the various parameters in the formula were different:  $X_1 =$  gender (female = 0, male = 1);  $X_2 =$  age (<45 = 0, 45–59 = 1 for 1.445  $X_2$ ;  $\geq 60 = 1$  for 1.937  $X_2$ );  $X_3 =$  NSAIDs use history (no = 0, yes = 1);  $X_4 =$  cholelithiasis history (no = 0, yes = 1);  $X_5 =$  H. pylori infection status (no = 0, yes = 1);  $X_6 =$  erosive gastritis history (no = 0, yes = 1); and  $X_7 =$  MS history (no = 0, yes = 1). The cut-off value of the prediction model was 0.667.

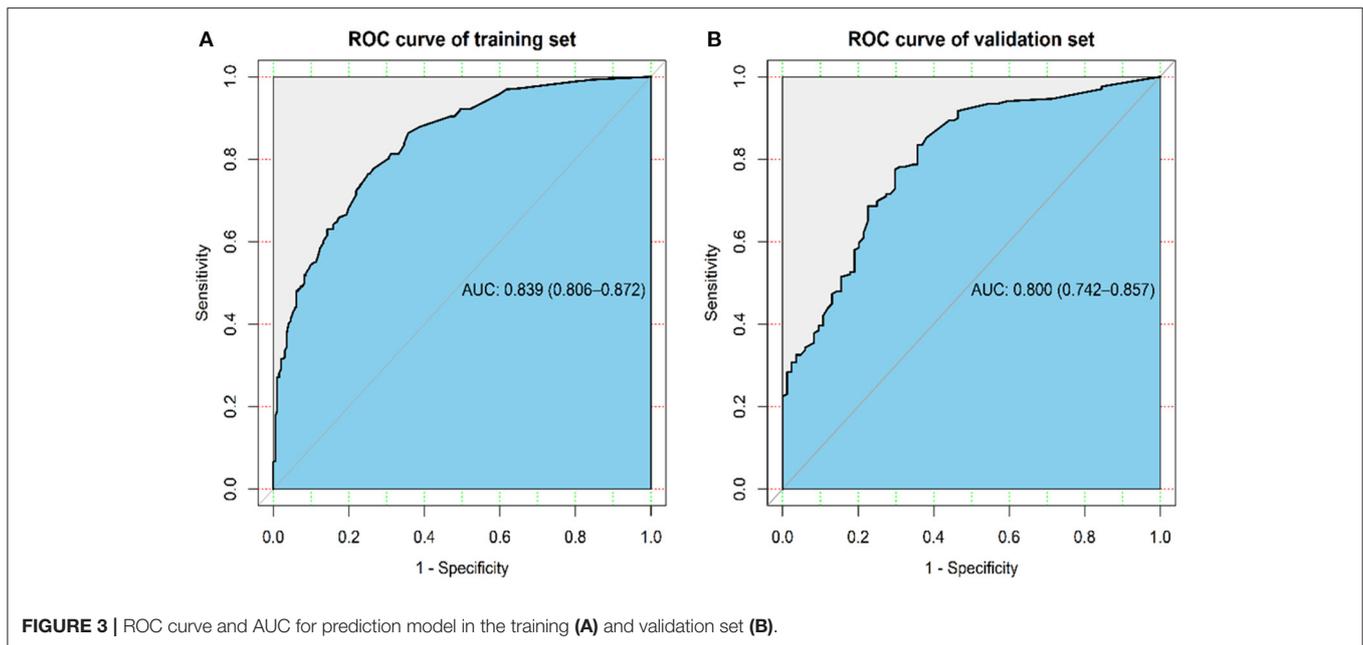
A nomogram that depicted the multivariate impact of each risk factor was further developed (Figure 2A). A further descriptive explanation and example of the logistic regression model was as follows: we randomly selected a patient from the data, who was with the clinical characteristics of female, age  $\geq 60$  years old, NSAIDs use history, no cholelithiasis history,



and *H. pylori* infection, no erosive gastritis, and MS history. Consequently, the logistic regression model score for this patient was 144 and the corresponding probability of EPBR occurrence was 0.717. Seeing that this score exceeded the cut-off value (0.667), this patient should be identified with a serious probability of EPBR. As expected, the de facto confirmed EPBR in this patient and provided a testament for the accuracy of the internal validation for the prediction model (Figure 2B).

## Prediction Model Evaluation and Internal Validation

The ROC analysis for the logistic regression model was computed to judge its clinical discrimination. As shown in Figure 3, the ROC analysis revealed that this model had an eminent discrimination ability due to the results of AUC 0.839 (95% CI, 0.806–0.872) in the training set (Figure 3A) and 0.800 (95% CI, 0.742–0.857) in the validation set (Figure 3B), respectively.



In addition to these evaluations, the H–L test was adopted for the calibration of the logistic regression model. The calibration plots for the probabilities of EPBR described that the logistic regression model was adequately calibrated, with no indication of systematic under- or overestimation of EPBR rate (Figures 4A,B). As a cut-off value is 0.667, the regression model features, such as the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), were 0.765 (95% CI = 0.723–0.806), 0.750 (95% CI = 0.689–0.811), 0.860 (95% CI = 0.824–0.897), and 0.612 (95% CI = 0.551–0.674) in the training set and 0.686 (95% CI = 0.616–0.756), 0.774 (95% CI = 0.684–0.863), 0.859 (95% CI = 0.801–0.918), and 0.551 (95% CI = 0.461–0.641) in validation set, respectively (Table 3).

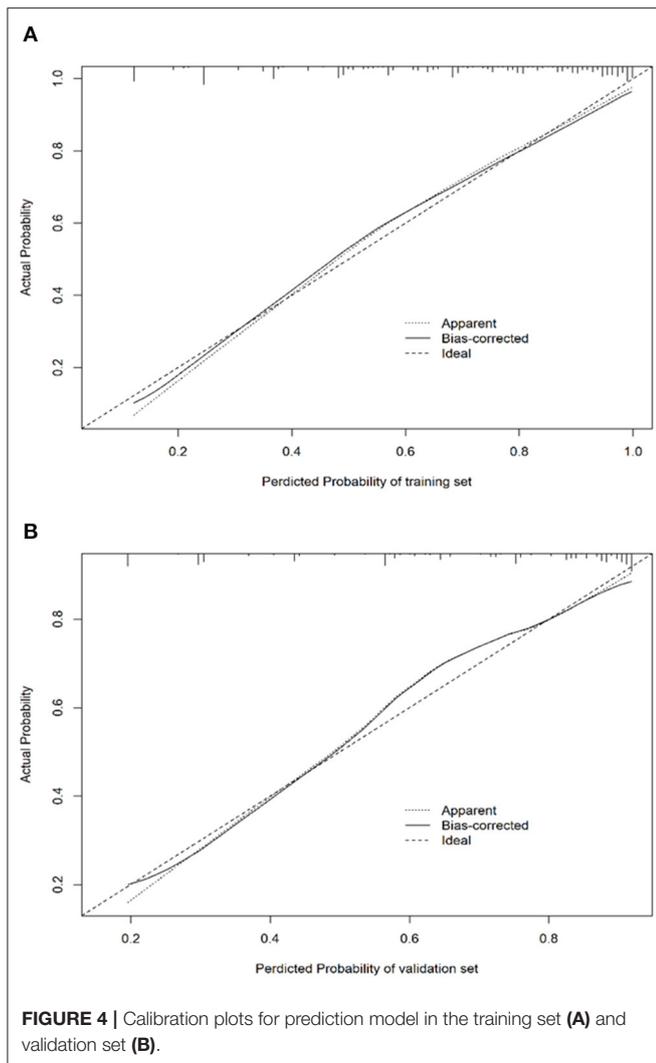
## DISCUSSION

In general, the coordinated movement of the stomach and duodenum rarely causes EPBR. However, when the duodenum becomes antiperistaltic and the pyloric closure is incomplete, in the meantime, bile will flow back into the stomach (19). Accompanied by delayed gastric emptying, bile acids continue to interact with the gastric mucosa and finally result in well-recognized damage (20). Any factor that causes gastrointestinal motility disorder and anatomical abnormality can cause pathologic duodenogastric reflux. Endoscopic primary bile reflux was classified as primary and secondary type (21), depending on whether the patient has a gastrectomy history. In addition to other endoscopic features such as the co-existence that changes mucosa: hyperemia, fragility, and erosions, EPBR is one of the mandatory diagnostic criteria for PBRG (6, 7). For patients who cannot or will not undergo endoscopy due to contraindications, the determination of EPBR is particularly critical for clinical empirical treatment. Furthermore, our clinical

experience is not identical to the predictors of EPBR reported in most historical studies. Therefore, the purpose of this study was to summarize the predictors and prediction models of EPBR in a real-world setting with a large sample size.

In this retrospective study, 15 clinical parameters that possessed a strong possibility of predicting EPBR were analyzed, and seven risk factors including being male, age  $\geq 45$  years old, *H. pylori* infection, previous medical histories of NSAIDs use, cholelithiasis, erosive gastritis, and MS were accessed for the first time. Furthermore, after validating the regression formula through the ROC and H-L test, the evidence from our retrospective study suggested that the prediction model for EPBR provides a favorable reference for clinical empirical treatment.

As a recognized etiologic agent, *H. pylori* colonizes the gastric mucosa and causes gastritis, peptic ulcers, and gastric cancer (21, 22). Even now, the relationship between EPBR and *H. pylori* infection remains controversial (23). Several studies attempted to address the association of EPBR and *H. pylori* infection with the occurrence and development of chronic gastritis and gastric cancer (9, 14, 24–26). One study implied that bile acid, which continued in gastric juice, had the extraordinary capabilities of promoting ulcer healing and inhibiting the growth of *H. pylori* (27). In contrast, substantial data believed EPBR to be consistently reduced after successful *H. pylori* eradication. The *H. pylori* infection status may affect EPBR by increasing gastrin secretion and altering the duodenal movement (28). This notion meant that the two had a synergistic effect in inducing chronic gastritis (5). A multi-center study of 2,283 subjects from 14 institutions in Japan found that a high concentration of EPBR increased the risk of intestinal metaplasia regardless of the *H. pylori* infection status (29). Partially contrary to the findings of previous literature reports, our results demonstrated that *H. pylori* infection and erosive gastritis history coexisted in our prediction model. It is well-known that the prolonged exposure



**FIGURE 4 |** Calibration plots for prediction model in the training set (A) and validation set (B).

**TABLE 3 |** Features of the prediction model in the training and validation set.

Index (95% CI)	Training set	Validation set
AUC	0.839 (0.806–0.872)	0.800 (0.742–0.857)
Sensitivity	0.765 (0.723–0.806)	0.686 (0.616–0.756)
Specificity	0.750 (0.689–0.811)	0.774 (0.684–0.863)
PPV	0.860 (0.824–0.897)	0.859 (0.801–0.918)

of gastric mucosa to bile acid and *H. pylori* infection may result in histopathological changes (30, 31). Our study proves to be a likely overlap between *H. pylori*-associated gastritis and BRG. Consequently, the sensitive identification and appropriate treatment of EPBR should be admitted while considering the presence of *H. pylori* infection.

Moreover, a history of NSAIDs use, besides *H. pylori* infection and EPBR, is likewise a common cause of chronic gastritis (32–34). Data from *in vivo* studies has shown that administration of NSAIDs decreased the prostaglandin concentration in the gastric

mucosa but did not increase the mucosal damage in *H. pylori*-induced gastritis, which is ascribed to the elevated expression of cyclooxygenase-2 (COX-2) induced by *H. pylori* (8). In our multivariate logistic regression model, *H. pylori* infection and the history of NSAIDs use were incorporated into the prediction model as risk factors. However, the relationships between *H. pylori* infection, NSAIDs use, and EPBR in gastric mucosal damage are intricate, which is yet to be clarified by more basic and clinical researches.

During the past few years, several studies have shown that EPBR is more frequent in elderly male patients, which may be associated with an increased rate of gastrectomy and operation of the biliary tract (35). However, a study reported no distinguishable differences in EPBR occurrence between the younger (median age 25 years) and older (median age 51 years) healthy volunteers (36). Another related study believed that the rate of EPBR in women and middle-aged patients was higher than in men and in young and elderly patients (9). Here we demonstrated that EPBR was more common in male patients aged 45 years or older. An appropriate interpretation of the above conclusions imputes to population characteristics or genetic background and synchronously implies that a multi-center prospective study with a larger sample size is needed.

It is currently generally accepted that bile reflux is frequently disclosed in patients with chronic calculous cholecystitis patients (67–80%) and cholecystectomy (89%) (11, 37). Previous studies have evaluated that the predisposition toward EPBR in patients with cholelithiasis can probably be associated with changes in the gut hormone induced by biliary tract disease (12, 38, 39). There was no clear evidence to suggest that EPBR is clinically related to MS patients in previous studies. Meanwhile, in our clinical practice, we realized that EPBR patients are often accompanied by MS. Our results go beyond the previous reports, showing that MS is also a risk factor for EPBR. Existing studies have emphasized that the occurrence of MS is always related to age and gender (40–43). These results underscored the idea that the prevalence of MS tended to be higher with age in women than in men, driven primarily by an increase in abdominal obesity and a decrease in the HDL-C levels (44). Although, whether MS interacts with age, gender, and other factors to play an essential role in EPBR remains undefined. At present, the prevalence of MS continues to rise globally (45), and the frequency of cardio-cerebrovascular events is concerned with MS. Here we demonstrated that EPBR requires more attention instead of just the frequency of cardio-cerebrovascular events associated with MS. In the future, it will be necessary to explore the relationship between MS and EPBR after excluding the other risk factors.

The limitations of the present studies naturally include only a single-center retrospective experience, and more clinical data from other medical institutions for external validation are urgently needed. Meanwhile, gastric cancer may be misdiagnosed as acid reflux, leading to certain false positives in our study, which needs to be paid attention to. Moreover, the diagnosis of EPBR is just configured based on endoscopy without 24 h gastric bilirubin monitoring, and its causal relationship, as well as underlying mechanisms, should be further confirmed through prospective and in-depth studies.

In conclusion, being male, age  $\geq 45$  years old, *H. pylori* infection, histories of MS, NSAIDs use, cholelithiasis, and erosive gastritis appear to be the risk factors for EPBR. Meanwhile, this favorable prediction model might be an option for the prediction of EPBR.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Tongji Hospital, School of Medicine, Tongji University. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

LC and GZ acquired and analyzed the data and participated in drafting the manuscript. LS, YD, FZ, and CY provided comprehensive case data and analyzed the data. FZ contributed to the concept and design of the work, reviewed, and revised the manuscript. All authors contributed to the article and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmed.2021.758771/full#supplementary-material>

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