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Original Article

Effects of proton pump inhibitors plus gastroprokinetic agents on laryngopharyngeal reflux disease and factors influencing prognosis

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Abstract: Objective: To assess the efficacy of proton pump inhibitors (PPIs) combined with gastroprokinetic agents for laryngopharyngeal reflux disease (LPRD) and to explore factors associated with prognosis. Methods: A retrospective analysis was performed in 120 patients with LPRD treated at our institution from January 2023 to December 2024. They were classified into a combination group (n=60, PPI plus gastroprokinetic agents) and a monotherapy group (n=60, PPI alone). The two groups were compared before and after treatment in terms of the Reflux Symptom Index (RSI) score, Reflux Finding Score (RFS), 24-hour pharyngeal pH monitoring indicators, treatment efficacy, and the incidence of adverse events. Univariate and multivariate logistic regression analyses were conducted to identify factors influencing prognosis. Results: After treatment, the combination group showed significantly lower RSI and RFS scores, lower Ryan score, number of reflux episodes, and percentage of reflux time than the monotherapy group (P<0.05). A significantly higher overall response rate was observed in the combination group than in the monotherapy group (91.67% vs. 73.33%, P<0.05). Disease duration ≥12 months, concomitant hiatal hernia, body mass index (BMI) ≥28 kg/m^2, and smoking history served as independent risk factors for LPRD prognosis (P<0.05). Combination therapy was a protective factor (P<0.05). Conclusions: PPIs combined with gastroprokinetic agents are more effective than PPIs alone for patients with LPRD. This combination therapy alleviates patients' symptoms and improves their signs. Disease duration, BMI, hiatal hernia, smoking history, and treatment regimen are important factors influencing prognosis. Comprehensive interventions may improve patient prognosis.

Keywords: Proton pump inhibitor, gastroprokinetic agent, laryngopharyngeal reflux disease, treatment efficacy, prognostic factor

Introduction

Laryngopharyngeal reflux disease (LPRD) is a condition characterized by the reflux of gastric contents beyond the upper esophageal sphincter into the larynx and pharynx, resulting in a variety of associated symptoms and signs. With changes in lifestyle and advances in diagnostic techniques, the detection rate of LPRD has been increasing in recent years [1, 2]. Patients with LPRD may present with hoarseness, chronic cough, and globus sensation, and may also develop laryngeal mucosa damage and vocal cord lesions, which can significantly impair their quality of life [3, 4]. Proton pump inhibitors (PPIs) are widely used as the primary treatment for LPRD. They inhibit gastric acid secretion and reduce injury of reflux to the pharyngeal mucosa [5]. However, monotherapy with PPIs is not always effective in the treatment of LPRD. Symptoms in some patients do not significantly improve. This may be because the pathogenesis of LPRD involves not only gastric acid damage but also factors such as impaired gastric motility and esophageal clearance [6, 7]. Gastroprokinetic agents such as mosapride may enhance gastrointestinal motility, facilitate gastric emptying, and increase

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lower esophageal sphincter (LES) tone [8]. In theory, this may help reduce reflux through multiple mechanisms.

Recently, increasing attention has been given to the combined use of PPIs and gastroprokinetic agents in patients with LPRD. However, the results remain inconsistent. Moreover, few studies have explored prognostic factors in LPRD. Therefore, we conducted a retrospective analysis to compare the efficacy of PPIs combined with gastroprokinetic agents versus PPIs alone in patients with LPRD. We also explored relevant factors influencing prognosis. The aim was to provide evidence to support rational use of medicine and individualized therapy.

Methodology

Study design

The retrospective controlled research protocol was permitted by the Ethics Committee of Hangzhou Fuyang Hospital of Traditional Chinese Medicine. The research was carried out in accordance with the Declaration of Helsinki. Based on the hospital's information system, patients with LPRD who were treated as inpatients or outpatients in the Otolaryngology Department of our institution from January 2023 to December 2024 were included.

Inclusion criteria: (1) Diagnosis of LPRD based on established criteria [9], with a Reflux Symptom Index (RSI) score >13 and/or a Reflux Finding Score (RFS) >7; (2) Age between 18 and 75 years; (3) Newly diagnosed LPRD or no prior standardized treatment; (4) Treatment duration ≥8 weeks, with complete follow-up data; (5) Good treatment adherence, with medications taken as prescribed.

Exclusion criteria: (1) Patients requiring surgical treatment for gastroesophageal reflux disease; (2) Patients with a history of gastrointestinal surgery; (3) Patients with malignant tumors; (4) Patients with severe cardiac, hepatic, or renal insufficiency; (5) Pregnant or lactating women; (6) Patients with known allergy to the study medications; (7) Patients with other conditions that may cause laryngopharyngeal symptoms, such as chronic sinusitis or acute exacerbation of allergic rhinitis; (8) Patients receiving concomitant medications that may affect gastric acid secretion or gastrointestinal motility.

One hundred and twenty patients were screened according to the aforementioned eligible criteria. Among them, 60 patients receiving PPI combined with gastroprokinetic agents were classified into the combination group, while 60 patients receiving PPI alone were classified into the monotherapy group.

Therapeutic methods

Both groups of patients received lifestyle guidance, including avoiding overeating, fasting for 3 hours before sleep, maintaining a bed head evaluation of 15-20 cm, smoking cessation, alcohol restriction, avoiding spicy and irritating foods, and weight reduction.

The combination group received omeprazole enteric-coated capsules (Life Technology (Zhongshan) Biological Pharmaceutical Co., Ltd.; specification: 20 mg/capsule; No. H20054926) twice daily, administered orally 30 minutes before breakfast and dinner, in combination with mosapride citrate dispersible tablets (Chengdu Kanghong Pharmaceutical Group Co., Ltd.; specification: 5 mg/tablet; No. H20031110) three times daily, administered orally before meals, for 8 weeks.

The monotherapy group received omeprazole enteric-coated capsules (Life Technology (Zhongshan) Biological Pharmaceutical Co., Ltd.; specification: 20 mg/capsule; No. H20054926), twice daily, administered orally 30 minutes before breakfast and dinner, for 8 weeks.

Outcome measures

Primary outcomes: (1) The RSI score [10]: The RSI scale, developed by Belafsky et al., was used to assess reflux-associated symptoms. It consists of nine items: hoarseness, throat clearing, sensations of a lump in the throat, difficulty swallowing, coughing after eating or lying down, breathing difficulties, troublesome cough, excessive throat mucus or postnasal drip, and heartburn, chest pain, or indigestion. Each item was scored on a scale of 0-5, with a total score of 0-45. Higher scores indicate more severe symptoms. (2) The RFS score [6]: Laryngoscopy was performed to assess eight items, including subglottic edema, ventricular obliteration, erythema/hyperemia, vocal fold edema, diffuse laryngeal edema, posterior commissure hypertrophy, granuloma, and thick

Table 1. Comparison of general data between the two groups (mean ± SD)/[n (%)]

General data	Combination group (n=60)	Monotherapy group (n=60)	t/χ^2	P
Mean age (years)	48.35±12.46	47.82±11.93	0.238	0.812
Sex (men/women)	26/34	28/32	0.134	0.714
Disease duration (months)	14.26±8.54	13.78±7.96	0.318	0.751
BMI (kg/m^2)	24.58±3.42	24.86±3.28	0.458	0.648
Smoking history	22 (36.67)	20 (33.33)	0.142	0.706
Alcohol consumption	18 (30.00)	16 (26.67)	0.160	0.689
Hypertension	15 (25.00)	17 (28.33)	0.165	0.685
Diabetes mellitus	12 (20.00)	10 (16.67)	0.218	0.640
Hiatal hernia	8 (13.33)	10 (16.67)	0.253	0.615

BMI: body mass index.

endolaryngeal mucus. The total score ranges from 0 to 26. Higher scores indicate more severe symptoms. (3) 24-hour pharyngeal pH monitoring: Ryan score [11] was assessed.

Secondary outcomes: (1) Baseline data of patients were collected, including age, sex, disease duration, body mass index (BMI), smoking and alcohol history, and comorbidities. (2) Clinical efficacy was assessed after 8 weeks of treatment. Treatment efficacy was classified as markedly effective (≥70% reduction in both RSI and RFS scores), effective (30%-69% reduction in both scores), or ineffective (<30% reduction in either RSI or RFS score). The overall response rate = (number of markedly effective cases + effective cases)/total number of cases × 100% [12]. (3) Adverse events during the treatment period were recorded, including diarrhea, abdominal pain, headache, rash, and nausea. (4) Prognosis assessment: Patients were followed up clinically for three months after treatment. A good prognosis was defined as an RSI score ≤13 and an RFS ≤7; otherwise, the prognosis was considered poor [13].

Statistical methods

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to assess whether continuous variables were normally distributed. Continuous data with normal distribution were shown as mean and standard deviation (SD). The independent samples t-test was used for comparisons between groups, and the paired t-test was applied for differences within the same group before and after treatment. Categorical variables were described by number of cases and percentages [n (%)]. The chi-square test or Fisher's exact test was used for comparisons between groups. Univariate analysis of factors associated with prognosis was performed using the independent-samples t-test or chi-square test, and multivariate analysis was conducted using binary logistic regression. Statistically significance was defined as $P<0.05$. Prior to multivariate regression analysis, the variance inflation factor (VIF) was used to diagnose collinearity of the included variables. The VIF of each variable was <5, indicating no serious collinearity and a stable model. In addition, based on the expected effect size (OR≈2.5), α=0.05 (two-sided), and statistical power of 80%, the estimated sample size required for each group was approximately 50 cases. In this study, 60 cases were included in each group, and the sample size met the statistical power requirements.

Results

Comparison of baseline data between groups

The two groups did not differ significantly in baseline data, including sex, age, disease duration, and BMI ($P>0.05$, **Table 1**).

Comparison of pre- and post-treatment RSI scores between groups

Pre-treatment scores for each item and the total RSI scores did not differ significantly between the two groups ($P>0.05$). After treatment, both groups exhibited significant reductions in scores for each item and the total RSI scores compared with baseline scores ($P<0.05$). The combination group exhibited significantly reduced post-treatment scores compared to the monotherapy group ($P<0.05$, **Figure 1**).

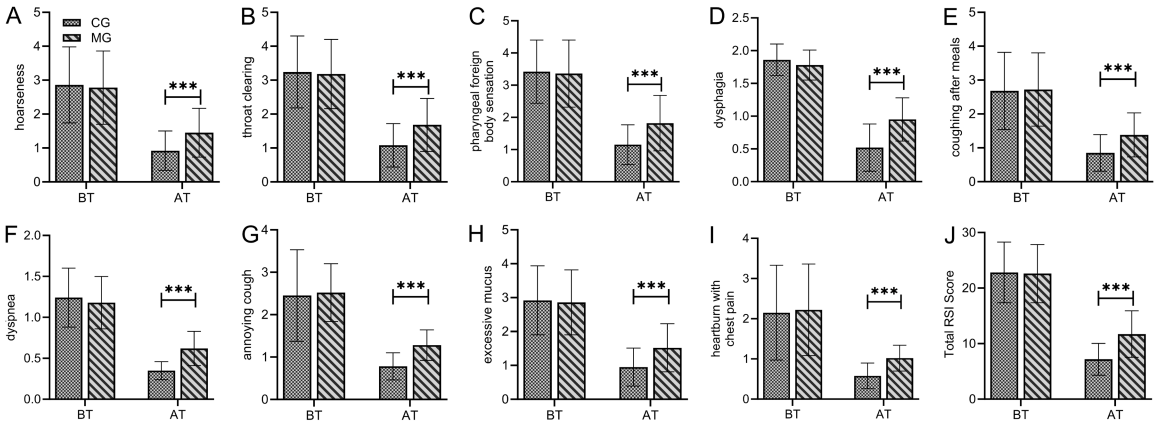

Figure 1. Comparison of RSI scores before and after treatment between the two groups. Before treatment, the two groups did not have significant differences in scores for each item and the total RSI scores (P>0.05). After treatment, the combination group exhibited markedly lower scores for hoarseness (A), throat clearing (B), sensations of a lump in the throat (C), difficulty swallowing (D), coughing following meals or when lying down (E), breathing difficulties (F), troublesome cough (G), excessive throat mucus or postnasal drip (H), heartburn, chest pain, or indigestion (I), and total RSI scores (J) in contrast to the monotherapy group (P<0.05). Note: RSI: Reflux Symptom Index; CG: combination group; MG: monotherapy group; BT: before treatment; AT: after treatment. ***P<0.001.

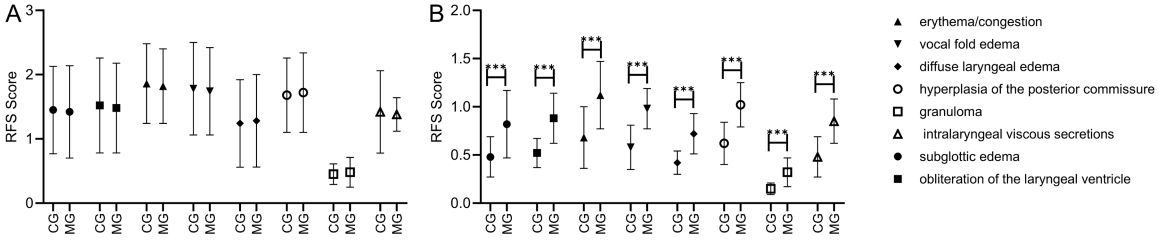

Figure 2. Comparison of RFS scores before and after treatment between the two groups. Before treatment, the two groups exhibited no significant differences in scores for each item and the total RFS scores (P>0.05) (A). The combination group demonstrated significantly lower scores for each item than the monotherapy group after treatment (P<0.05) (B). Note: RFS: Reflux Finding Score; CG: combination group; MG: monotherapy group; BT: before treatment; AT: after treatment. ***P<0.001.

Comparison of pre- and post-treatment RFS scores between groups

Pre-treatment scores for each item and the total RFS scores did not differ significantly between the two groups (P>0.05). After treatment, the two groups exhibited significant reductions in scores for each item and the total RFS scores compared with pre-treatment scores (P<0.05), and the combination group exhibited significantly lower scores than the monotherapy group (3.93±1.62 vs. 6.71±2.48, t=7.290) (P<0.001, **Figure 2**).

Comparison of pre- and post-treatment Ryan scores between groups

Before treatment, the groups did not exhibit significant differences in the Ryan scores (P>0.05). Twenty-four hours following treatment, the combination group exhibited significantly lower Ryan scores compared with the monotherapy group (P<0.05, **Figure 3**).

Comparison of clinical efficacy between groups

The combination group exhibited a significantly higher effective rate (56.67% vs. 35.00%) and overall response rate (91.67% vs. 73.33%) compared with the monotherapy group (P<0.05, **Figure 4**).

Comparison of the incidence of adverse events between groups

The combination group (16.67%) did not differ significantly compared with the monotherapy group (11.67%) in terms of the overall rate of adverse events (P>0.05, **Table 2**).

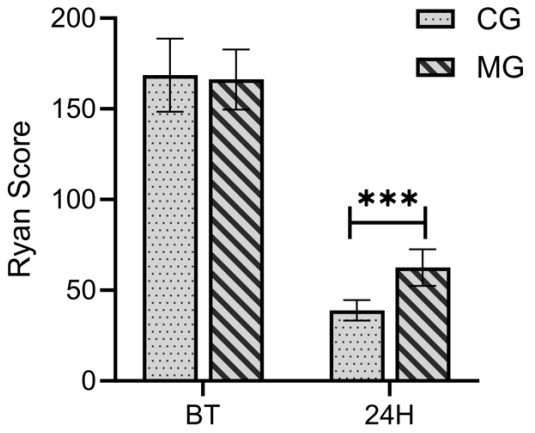

Figure 3. Comparison of pre- and post-treatment Ryan scores between the combination and monotherapy groups. The pre-treatment Ryan scores did not differ significantly between the two groups (P>0.05). Twenty-four hours following treatment, the combination group exhibited significantly lower Ryan score than the monotherapy group (P<0.05). Note: CG: combination group; MG: monotherapy group; BT: before treatment; 24H: 24 hours following treatment. ***P<0.001.

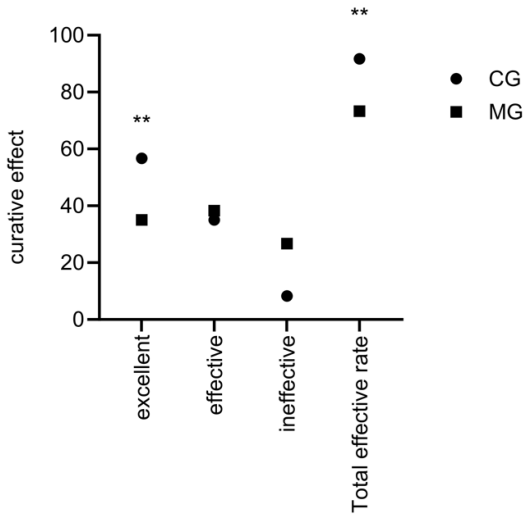

Figure 4. Comparison of clinical efficacy between the two groups. The markedly effective rate (56.67%) and overall response rate (91.67%) in the combination group were elevated compared with the monotherapy group (35.00% and 73.33%, respectively; P<0.05). Note: CG: combination group; MG: monotherapy group; BT: before treatment; 24H: 24 hours after treatment. **P<0.01.

Univariate analysis of prognostic factors for LPRD

At the 3-month follow-up, among the 120 patients, 78 (65.00%) had a favorable prognosis and 42 (35.00%) had a poor prognosis. Univariate analysis revealed that disease duration, BMI, smoking history, concomitant hiatal hernia, and treatment regimen were associated with the prognosis of LPRD (P<0.05, **Table 3**).

Multivariate logistic regression analysis of prognostic factors for LPRD

Prognosis was used as the dependent variable (favorable = 0, poor = 1). Variables that were significant in the univariate analysis were entered into the multivariate logistic regression model. The results showed that disease duration ≥12 months, concomitant hiatal hernia, BMI ≥28 kg/m^2, and smoking history were identified as independent risk factors for LPRD prognosis (P<0.05), whereas combination therapy was identified as a protective factor (P< 0.05, **Table 4**; **Figure 5**).

Discussion

The primary finding of this study was that, in patients with LPRD receiving standardized lifestyle interventions, the overall response rate to PPI combined with gastroprokinetic agents was higher than that compared to PPI alone. The primary outcomes, including RSI, RFS, and Ryan scores from 24-hour pharyngeal pH monitoring, showed greater improvement in the combination group. These findings are consistent with clinical experience suggesting that single-target treatments may be insufficient to fully manage reflux symptoms. This indicates that combing multiple treatment approaches may have important value in LPRD management.

LPRD is not only caused by excess gastric acid, but also by impaired gastric motility, slow esophageal clearance, and upper esophageal sphincter dysfunction [5, 14]. While PPI monotherapy can reduce laryngeal damage caused by acid reflux, it is less effective for non-acid reflux or reflux associated with impaired gastric motility. This shows its limitation when used alone. Mosapride is a selective 5-HT4 receptor agonist that enhances gastrointestinal motility by increasing acetylcholine release. It accelerates gastric emptying and increases LES tone. This can make up for small effect of PPIs on movement in the digestive system [15, 16]. PPIs and gastroprokinetic agents work together and help reduce reflux better.

Table 2. Comparison of the incidence of adverse events between the two groups [n (%)]

Adverse events	Combination group (n=60)	Monotherapy group (n=60)	χ^2	P
Diarrhea	3 (5.00)	2 (3.33)	0.209	0.648
Abdominal pain	2 (3.33)	1 (1.67)	0.342	0.559
Headache	2 (3.33)	2 (3.33)	0.000	1.000
Rash	1 (1.67)	1 (1.67)	0.000	1.000
Nausea	2 (3.33)	1 (1.67)	0.342	0.559
Overall incidence	10 (16.67)	7 (11.67)	0.593	0.441

The Ryan score is widely used to evaluate LPRD, as it integrates the frequency, duration, and intensity of reflux events [17, 18]. In our study, the combination group exhibited a significant reduction in the Ryan score after treatment, indicating a substantial decrease in reflux events. Previous studies have reported that gastroprokinetic agents can reduce the frequency and duration of reflux by accelerating gastric emptying and decreasing intragastric pressure [7, 19]. These findings are consistent with our results. Regarding safety, the two groups didn't show significant difference in the incidence of adverse events. Patients in both groups mostly had mild gastrointestinal symptoms. This indicates that the combination therapy has good tolerability [20]. Notably, mosapride may aggravate diarrhea and abdominal pain. Our study reported a low incidence of adverse events. This may be related to patient sample selection and interindividual variability in drug tolerance. Nevertheless, individual responses to mosapride should still be carefully monitored in clinical practice. For patients experiencing significant discomfort, the treatment regimen should be adjusted promptly.

Multivariate regression findings of our study demonstrated that disease duration ≥12 months was an independent risk factor for unfavorable prognosis. Patients with a longer disease course often experience repeated mucosal injury. Local fibrosis and proliferative alteration weaken mucosal repair capacity, and the response to pharmacotherapy is corresponding weakened [14]. Anatomically, hiatal hernia damages the antireflux barrier integrity. Even after standard treatment with medicine, reflux may still continue to occur because of a hernia sac [21]. BMI ≥28 kg/m^2 may increase intra-abdominal pressure and displace the diaphragm, thereby reducing LES pressure. Moreover, obesity is frequently associated with metabolic syndrome, which may further impair gastrointestinal motility [22]. Smoking may also hinder recovery from LPRD through multiple mechanisms, including reduced sphincter pressure, increased gastric acid secretion, delayed gastric emptying, and disruption of the mucosal barrier [23]. Combination therapy emerged as a protective factor in the model. Its therapeutic benefit may be attributed to its simultaneous effects on gastric acid suppression and gastrointestinal motility improvement. This helps promote mucosal healing and long-term symptom relief.

Based on the analysis of the above risk factors, for LPRD patients with disease duration ≥12 months, BMI ≥28 kg/m^2, hiatal hernia, or long-term smoking, it is recommended to provide more active lifestyle interventions in addition to standardized combination therapy, and to appropriately extend the course of treatment (which may be extended to 12-16 weeks as appropriate). Patients were followed up at 3-month intervals after treatment completion to dynamically assess RSI/RFS scores and pH monitoring indicators and to detect recurrence in a timely manner. In patients with concomitant hiatal hernia who respond poorly to pharmacotherapy, the feasibility of laparoscopic hiatal hernia repair should be evaluated in a timely manner. Smoking cessation interventions should be strengthened in smokers, and individualized weight reduction strategies should be developed in obese patients to reduce the risk of reflux and improve long-term outcomes.

Our study has several clinical implications. Patients with LPRD who present with risk factors such as prolonged disease duration, obesity, hiatal hernia, or smoking may require more intensive lifestyle modifications in addition to standard combination therapy. When necessary, the course of treatment should be extended, and the feasibility of surgery should be evaluated. This study also has some deficiencies. Since it was conducted retrospectively at a single center, the generalizability of its conclusions may be limited. The results from these

Table 3. Univariate analysis of prognostic factors for LPRD

Factors		Favorable prognosis (n=78)	Poor prognosis (n=42)	χ^2	P
Age	<50 years	42 (53.85)	20 (47.62)	0.420	0.517
	≥50 years	36 (46.15)	22 (52.38)		
Sex	Men	34 (43.59)	20 (47.62)	0.179	0.672
	Women	44 (56.41)	22 (52.38)		
Disease duration	<12 years	48 (61.54)	15 (35.71)	7.303	0.007
	≥12 months	30 (38.46)	27 (64.29)		
BMI	<28 kg/m^2	62 (79.49)	24 (57.14)	6.642	0.010
	≥28 kg/m^2	16 (20.51)	18 (42.86)		
Smoking history	No	56 (71.79)	22 (52.38)	4.495	0.034
	Yes	22 (28.21)	20 (47.62)		
Alcohol consumption	No	57 (73.08)	27 (64.29)	1.016	0.314
	Yes	21 (26.92)	15 (35.71)		
Hypertension	No	60 (76.92)	28 (66.67)	1.459	0.227
	Yes	18 (23.08)	14 (33.33)		
Diabetes mellitus	No	66 (84.62)	32 (76.19)	1.264	0.261
	Yes	12 (15.38)	10 (23.81)		
Hiatal hernia	No	72 (92.31)	30 (71.43)	8.889	0.003
	Yes	6 (7.69)	12 (28.57)		
Treatment regimen	Combination therapy	48 (61.54)	12 (28.57)	11.885	0.001
	Monotherapy	30 (38.46)	30 (71.43)		

LPRD: laryngopharyngeal reflux disease; BMI: body mass index.

Table 4. Analysis of multivariate logistic regression model for prognostic factors in LPRD

Factors	β	SE	Wald χ^2	P	OR	95% CI
Disease duration ≥12 months	1.124	0.428	6.892	0.009	3.08	1.33-7.12
BMI ≥28 kg/m^2	0.986	0.412	5.728	0.017	2.68	1.20-6.00
Smoking history	0.842	0.396	4.522	0.033	2.32	1.07-5.04
Concomitant hiatal hernia	1.386	0.485	8.168	0.004	4.00	1.55-10.34
Combination therapy (vs. monotherapy)	-1.245	0.418	8.872	0.003	0.29	0.13-0.65

LPRD: laryngopharyngeal reflux disease; BMI: body mass index; SE: standard error; OR: odds ratio; 95% CI: 95% confidence interval.

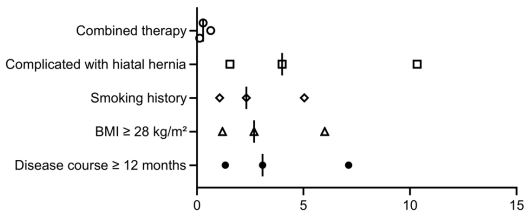

Figure 5. Multivariate analysis of prognostic factors in LPRD. Note: LPRD: laryngopharyngeal reflux disease; BMI: body mass index.

120 cases should be verified with larger-sample research. The follow-up lasted only three months and the long-term efficacy and recurrence rates are not clear. This study primarily relied on validated scales such as RSI and RFS for efficacy assessment. Although these scales are widely used in clinical practice, their subjective nature may introduce observer bias. Future research should combine objective instrument assessments with independent raters to further improve reliability. In addition, this study did not include patient-reported outcomes such as quality of life and swallowing function, nor did it systematically record follow-up dropouts or quantitative measures of patient adherence. These limitations should be taken into account when interpreting the findings. Finally, our research did not assess different dosages or treat-

ment regimens. In addition, it did not include assessments of quality of life or health economics. Further multicenter randomized controlled trials should focus on refining the parameters of combination therapy regimens and assessing their long-term benefits.

For patients with LPRD, the combined use of PPIs and gastroprokinetic agents is better than PPIs alone. The combination therapy alleviates patients' symptoms, improves signs, and reduces reflux indicators, exhibiting good safety. Disease duration ≥12 months, hiatal hernia, BMI ≥28 kg/m^2, and smoking history are independent factors for LPRD prognosis, while combination therapy is a protective factor. Combination therapy should be prioritized in the treatment of LPRD, in conjunction with lifestyle interventions. LPRD patients with risk factors should receive more comprehensive interventions to enhance clinical outcomes.

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Disclosure of conflict of interest

None.

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