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## Prospective Study

# Nissen fundoplication vs proton pump inhibitors for laryngopharyngeal reflux based on pH-monitoring and symptom-scale

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## Abstract

### AIM

To compare the outcomes between laparoscopic Nissen fundoplication (LNF) and proton pump inhibitors (PPIs) therapy in patients with laryngopharyngeal reflux (LPR) and type I hiatal hernia diagnosed by oropharyngeal pH-monitoring and symptom-scale assessment.

### METHODS

From February 2014 to January 2015, 70 patients who were diagnosed with LPR and type I hiatal hernia and referred for symptomatic assessment, oropharyngeal pH-monitoring, manometry, and gastrointestinal endoscopy were enrolled in this study. All of the patients met the inclusion criteria. All of the patients

underwent LNF or PPIs administration, and completed a 2-year follow-up. Patients' baseline characteristics and primary outcome measures, including comprehensive and single symptoms of LPR, PPIs independence, and satisfaction, and postoperative complications were assessed. The outcomes of LNF and PPIs therapy were analyzed and compared.

## RESULTS

There were 31 patients in the LNF group and 39 patients in the PPI group. Fifty-three patients (25 in the LNF group and 28 in the PPI group) completed reviews and follow-up. Oropharyngeal pH-monitoring parameters were all abnormal with high acid exposure, a large amount of reflux, and a high Ryan score, associated reflux symptom index (RSI) score. There was a significant improvement in the RSI and LPR symptom scores after the 2-year follow-up in both groups ( $P < 0.05$ ), as well as typical symptoms of gastroesophageal reflux disease. Improvement in the RSI ( $P < 0.005$ ) and symptom scores of cough ( $P = 0.032$ ), mucus ( $P = 0.011$ ), and throat clearing ( $P = 0.022$ ) was significantly superior in the LNF group to that in the PPI group. After LNF and PPIs therapy, 13 and 53 patients achieved independence from PPIs therapy (LNF: 44.0% vs PPI: 7.14%,  $P < 0.001$ ) during follow-up, respectively. Patients in the LNF group were more satisfied with their quality of life than those in the PPI group (LNF:  $62.49 \pm 28.68$  vs PPI:  $44.36 \pm 32.77$ ,  $P = 0.004$ ). Body mass index was significantly lower in the LNF group than in the PPI group (LNF:  $22.2 \pm 3.1$  kg/m<sup>2</sup> vs PPI:  $25.1 \pm 2.9$  kg/m<sup>2</sup>,  $P = 0.001$ ).

## CONCLUSION

Diagnosis of LPR should be assessed with oropharyngeal pH-monitoring, manometry, and the symptom-scale. LNF achieves better improvement than PPIs for LPR with type I hiatal hernia.

**Key words:** Laryngopharyngeal reflux; Hiatal hernia; Laparoscopic Nissen fundoplication; Proton pump inhibitor; pH-monitoring; Gastroesophageal reflux disease

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**Core tip:** Laryngopharyngeal reflux disease is often associated with hiatal hernia and gastroesophageal reflux disease. Although the role of oropharyngeal pH-monitoring in the diagnosis of laryngopharyngeal reflux is clear, little is known regarding the anti-acid and anti-reflux therapeutic outcome by pH-monitoring and symptom-scale diagnosis. Laparoscopic Nissen fundoplication and proton pump inhibitors (PPIs) are effective in patients with laryngopharyngeal reflux and type I hiatal hernia. Nissen fundoplication shows better symptom relief than PPIs administration, and it also controls body mass index of patients. Our findings shed new insight into diagnosis and management for patients with laryngopharyngeal reflux disease.

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## INTRODUCTION

Laryngopharyngeal reflux (LPR) is a common condition in patients with gastroesophageal reflux disease (GERD). The effect of GERD on the upper aero-digestive tract seriously affects the quality of life of patients, with symptoms such as hoarseness, rhinitis, pharyngalgia, foreign body sensation, throat clearing, chronic cough, and laryngospasm<sup>[1,2]</sup>. All of these clinical presentations of LPR are considered as extraesophageal symptoms for distinguishing typical symptoms of GERD, such as heartburn and regurgitation. The incidence rate of reflux-induced laryngitis ranges from 18%-80%<sup>[3,4]</sup>. The association between GERD and hiatal hernia has been well confirmed, including sliding hernia (type I), paraesophageal hernia (type II), and mixed hernia (types III and IV)<sup>[5]</sup>. Recently, evidence has suggested that hiatal hernia is one of the major risk factors for the occurrence of LPR in patients with GERD<sup>[4]</sup>. The management strategies for LPR, GERD, and type I hiatal hernia are similar, which involve controlling the occurrence of reflux and reducing reflux-induced symptoms. Common management methods include lifestyle modification, anti-acid therapy, and anti-reflux surgery. To the best of our knowledge, few studies have focused on the treatment outcome of patients with LPR and type I hiatal hernia, especially regarding comparison of anti-acid therapy and anti-reflux surgery with lifestyle modification.

Currently, diagnosis of LPR mainly includes empirical therapeutic trials of proton pump inhibitors (PPIs), the reflux symptom index (RSI) score, pH-monitoring and laryngoscopy<sup>[6]</sup>. Among these diagnostic methods, PPIs do not have objective evidence for diagnosis of LPR. Additionally, the placebo effect of anxiety in patients without LPR cannot be excluded. Laryngoscopic findings, such as erythema and edema, are also nonspecific signs of LPR<sup>[7]</sup>. The reflux finding score, a clinical severity rating scale based on laryngoscopic findings, has poor reliability in detecting LPR<sup>[8,9]</sup>. Monitoring of pH can directly detect increased esophageal or laryngopharyngeal acid exposure by a pH probe. Therefore, it is regarded as the best evidence for diagnosis of LPR<sup>[10]</sup>. Some studies have documented LPR using a new pH sensor<sup>[9,11]</sup> and others have investigated the pH threshold for identifying patients with an abnormal pharyngeal pH environment<sup>[12,13]</sup>. However, few studies have shown the therapeutic outcome in patients with LPR who were diagnosed by

oropharyngeal pH-monitoring. Moreover, abnormal laryngopharyngeal acid exposure can indicate the presence of pathological reflux, but it does not provide proof of causality for symptoms of LPR. Therefore, evidence of LPR should be combined with pH-monitoring and special symptom-scales, such as the RSI score<sup>[14]</sup> and single symptom score<sup>[15]</sup>.

Therefore, in this study, we investigated two different therapeutic strategies for LPR with hiatal hernia: anti-reflux surgery and anti-acid therapy both with lifestyle modifications. We assessed the postoperative 6-mo and 2-year outcomes based on diagnosis by oropharyngeal pH-monitoring and the symptom-scales. In particular, we analyzed the integrated results of pH-monitoring, manometry, and endoscopy, which may demonstrate the characteristics of patients with LPR and hiatal hernia.

## MATERIALS AND METHODS

### Patients

Medical records of 70 patients with LPR and type I hiatal hernia who manifested laryngopharyngeal symptoms, who underwent laparoscopic Nissen fundoplication (LNF), or were administered PPIs therapy alone between February 2014 and January 2015, were obtained. The following criteria were met before enrolment: Patients complaint with laryngopharyngeal symptoms (hoarseness, globus, throat clearing/pain, mucus, and chronic cough) were suspected by the otolaryngologist, the LPR symptom occurred at least once a week, and lasted at least 6 mo; RSI score  $\geq 13$ ; type I hiatal hernia (increase of the squamo-columnar junction by  $> 2$  cm, and without paraesophageal hernia); absence of significant esophagitis (Los Angeles grades A and B esophagitis); abnormal Ryan score during 24-h oropharyngeal pH-monitoring; and abnormal lower esophageal sphincter (LES) pressure as detected by esophageal manometry. Patients were symptomatically stable and generally medically fit for anti-acid or surgical anti-reflux treatments. Patients with broncho-pulmonary disease, central nervous system diseases, connective tissue diseases, previous pharyngolaryngeal, esophageal or gastric surgery, esophageal stricture, a shortened esophagus, impaired distal esophageal peristalsis, Barrett's esophagus, autoimmune diseases, collagen vascular disease, and/or coagulation disorders were excluded. This prospective, observational study was approved by the Institutional Review Board at the Second Artillery General Hospital of Chinese People's Liberation Army and Xuanwu Hospital. Informed consent was obtained from each participant according to the Helsinki Declaration.

### Oropharyngeal pH-monitoring

The diagnosis of LPR was confirmed using the 24-h oropharyngeal Restech pH recorder system (Respiratory Technology Corp., San Diego, CA,

United States) and LPR symptom-scale (outcome assessment). Patients were instructed to stop taking any anti-acid medications at least 1 wk before insertion of the probe. The pH probe was inserted through the patient's nose and advanced slowly to its destination in the back of the oropharynx just 5 mm below the tip of the uvula. Placement of the probe in the oropharynx was verified by observing the flashing light at the tip of the probe. Patients were asked to keep a diary indicating the time of meals and the time spent in the supine and upright positions. Meal periods were excluded in the final analyses. The data recorder was downloaded to a dedicated software program (DataView Lite V3; Respiratory Technology Corp.) and correlated with the patient's diary. Tracings were all manually evaluated by a single operator. Thresholds for the detection of acidic reflux were 5.5 for the upright position and 5.0 for the supine position. The percentage of time spent below these thresholds was then calculated. The Ryan score was also calculated using the same pH thresholds for the upright and supine positions. This score was obtained by combining the following three different parameters: (1) the number of reflux episodes; (2) the duration of the longest reflux episode; and (3) the percentage of time spent below the defined threshold. A score greater than 9.41 in the upright position and/or 6.81 in the supine position was regarded as LPR<sup>[12,16]</sup>.

### High-resolution manometry and gastrointestinal endoscopy

A solid-state manometric catheter assembly with 36 circumferential sensors spaced in 1-cm intervals was used (Sierra Scientific Instruments, Los Angeles, CA, United States). Before the recording, the transducers were calibrated, and a thermal compensation program was applied using external pressure. The catheter was passed *via* the nose and positioned to provide simultaneous recordings from the hypopharynx and the esophagus to the stomach. Ten 5-mL water swallows were provided to evaluate peristalsis. Upper esophageal sphincter (UES) and LES pressure, the size of hiatal hernia, and esophageal body contractions were recorded for data analysis. Moreover, hiatal hernia, reflux esophagitis, and esophageal metaplasia were determined by gastrointestinal (GI) endoscopy, which was independent of pH-monitoring and manometry. If esophagitis was present, it was graded according to the Los Angeles classification<sup>[17]</sup>.

### Treatment

Patients were allocated to the PPI or LNF group according to their own preference and physical conditions after the following instructions: PPIs medication focused on the anti-acid, which need life-long medication but could not cause other damage or complication on upper gastrointestinal, whereas, LNF was an invasive operation, aiming to make a one-way flap by fundus for anti-reflux, with more possibility of injury and



complications, but a lower recurrence rate. Of the 70 patients, 39 were treated with esomeprazole 40 mg every day for 61–96 d (mean, 78 d). LNF was carried out in the remaining 31 patients. Briefly, LNF was performed with five ports under general anesthesia. After dissecting the gastrohepatic ligament with a harmonic scalpel, a widow was created behind the lower esophagus. The diaphragmatic crura were then carefully dissected and the distal esophagus was mobilized at approximately 5 cm. In all cases, the gastric fundus was dissected by dividing short gastric vessels. The diaphragmatic crura were sewn behind the esophagus with 1–2 non-absorbable sutures. A posterior 360° with a 2-cm-long fundoplication was constructed with 2–3 interrupted non-absorbable stitches. After operation, omeprazole 40mg i.v. was administered once for gastric mucosal protection.

We also suggested that lifestyle modifications (head elevation during bedtime, no fatty foods and eating close to bedtime, eating more frequently with smaller meals, and reduction of cigarettes, alcohol, or caffeine) should be adopted for all of the patients. Body mass index [BMI, body weight (kg) divided by the square of standing height (m)] was calculated before treatment and after treatment at a 2-year follow-up.

### Assessment of outcome

Comprehensive symptom LPR was evaluated on the basis of symptom scoring using the RSI. The RSI accurately documents symptoms with LPR with a nine-item self-administered outcome instrument. An RSI score greater than 13 is considered to indicate LPR<sup>[18,19]</sup>. The single symptom score was used to measure the frequency and severity of each symptom, including heartburn, regurgitation, cough, globus, mucus, hoarseness, throat pain and clearing. Data on these outcome measures were collected through a standardized questionnaire as previously described<sup>[20,21]</sup>. More specifically, the total of the frequency score (5 points) and the severity score (5 points) for each of these measures was designed as the symptom score out of 10 points. The questionnaires were prepared in simplified Chinese and administered to the patients before and after treatment. Other outcome measures included PPI independence (PPIs was prescribed and administered continually over 3 d for recurrent GERD and LPR symptoms that were excluded from PPI independence in LNF or PPI group), satisfaction, and complications.

### Statistical analysis

Data are expressed as mean  $\pm$  SD or number (%) unless specified otherwise. For statistical analyses, normality was assessed by the Kolmogorov-Smirnov test. Data were analyzed by the independent-/paired-sample Student's *t* test (Table 1) or nonparametric tests (Tables 2–4, Figures 1 and 2) based on the normality of data distribution. Independent-sample *t*-test and Mann-Whitney *U* test were performed for

independent samples in LNF and PPI groups (Figures 1 and 2, Tables 2–4), whereas paired-sample *t* test and the Wilcoxon test for within-group paired samples (Table 4). The statistical analysis software, SPSS-17.0 (SPSS Inc., Chicago, IL, United States), was used. Statistical review of the study was performed by a professional statistician. Differences were considered significant when  $P < 0.05$ .

## RESULTS

### Baseline measurements

Consecutive patients who were diagnosed with LPR with type I hiatal hernia and met our inclusion criteria were enrolled between February 2014 and January 2015 in this study. Patients were divided into two groups based on the patients' choice to undergo an LNF surgery or PPIs administration. A total of 39 patients were included in the PPI group and 31 patients were included in the LNF group. A total of 61 patients were still in the study at the 6-mo follow-up, and 53 patients (25 patients in the LNF group and 28 patients in the PPI group) completed the 2-year follow-up (follow-up time ranged from 1.7 to 2.5 years; average of 2 years). The demographic data for each group are listed in Table 1. Baseline demographic data were similar between the LNF and PPI groups, including the mean age, sex distribution, and pre-treatment values for the RSI and BMI. And 66.7%–74.2% patients also suffered from typical GERD symptoms (regurgitation and/or heartburn) in the LNF and PPI groups. The number of presenting complaints and the RSI were not significantly different between the two groups, except for globus (LNF group: 27/31 vs PPI group: 20/39,  $P = 0.003$ ).

### Characteristics of diagnostic examinations

The results of diagnostic examinations are summarized in Table 2, including 24-h oropharyngeal pH-monitoring, high-resolution manometry, and GI endoscopy. Almost all of the patients demonstrated more reflux events and a longer duration of acid exposure in the upright position, with a much higher Ryan value than the standard upright-threshold (Ryan score = 9.41), regardless of the groups. The mean supine Ryan score still exceeded 6.81, which was the upper limit of the normal value. Although the presenting complaints varied, there was no significant difference in pH-monitoring between the two groups. For manometric investigation, 13 of 70 patients presented with ineffective or abnormal esophageal motility, with a significant difference between the two groups (LNF group: 3/31 vs PPI group: 10/39,  $P = 0.090$ ). LES pressure values ranged from 11.78 to 14.84 mmHg, which were lower than the normal value<sup>[22,23]</sup>. UES pressure was lower in the LNF group than in the PPI group ( $P = 0.045$ ). Hiatal hernia was assessed by high-resolution manometry and GI endoscopy. Manometry showed hiatal hernia in 57/70 patients (LNF

**Table 1** Baseline demographics, clinical characteristics and proportions for laparoscopic Nissen fundoplication and proton pump inhibitor groups

Characteristic/parameter	LNF	PPI	P value
No.	31	39	
Age (yr)	47.2 ± 10.7	51.3 ± 12.5	0.218
Sex			0.670
Male	14 (45.2)	19 (48.7)	
Female	17 (54.8)	20 (51.3)	
BMI (kg/m <sup>2</sup> )	23.9 ± 3.8	25.0 ± 3.1	0.285
RSI score	15.3 ± 3.5	14.2 ± 4.0	0.759
Presenting complaint			
Regurgitation <sup>1</sup>	21 (67.7)	26 (66.7)	0.926
Heartburn <sup>1</sup>	23 (74.2)	28 (71.8)	0.826
Cough	18 (58.1)	21 (53.8)	0.729
Mucus	14 (45.1)	12 (30.7)	0.222
Globus	27 (87.1)	20 (51.3)	0.003 <sup>2</sup>
Hoarseness	12 (38.7)	10 (25.6)	0.248
Throat pain	12 (38.7)	10 (25.6)	0.248
Throat clearing	10 (32.2)	9 (23.1)	0.398

<sup>1</sup>Represents gastroesophageal reflux disease typical symptoms; <sup>2</sup>Represent statistical significant *P* values (*P* < 0.05). Values are given as mean ± SD or *n* (%). LNF: Laparoscopic Nissen fundoplication; PPI: Proton pump inhibitor; BMI: Body mass index; RSI: Reflux symptom index.

group: 24/31, PPI group: 33/39). However, endoscopy showed endoscopic hiatal hernia in 46/70 patients (LNF group: 16/31, PPI group: 30/39). Additionally, 13 patients in the LNF group and 12 in the PPI group had esophagitis as shown by endoscopy (Table 2).

### Efficacy

When we completed the 2-year follow-up, all of the data were collected to assess the efficiency of controlling symptoms of LPR. To assess relief from symptoms, we evaluated each symptom *via* a questionnaire that was scaled by frequency and severity. There were no significant differences in the pre-treatment symptom scores between patients in the PPI and LNF groups. The LPR and GERD typical symptom scores for cough, mucus, globus, hoarseness, and throat pain and clearing improved in both groups at the 6-mo and 2-year follow-up. The overall mean value of the symptom score decreased from 7.71 to 1.12 after both treatments (Table 3). Evaluation at the 2-year follow-up showed significantly better improvement in cough, mucus, and throat clearing of the LNF group than in the PPI group (Figure 1), as well as typical symptoms of GERD, including regurgitation and heartburn (Figure 2). The symptom scores for globus, hoarseness and throat pain were not significantly different between the two groups. However, the post-treatment symptom score for globus was lower in the LNF group than in the PPI group (LNF group: 2.95 ± 2.75 vs PPI group: 5.43 ± 2.50, *P* = 0.013 at 6 mo and LNF group: 2.77 ± 2.87 vs PPI group: 5.28 ± 2.86, *P* = 0.017 at 2 years, Table 3). We also observed no improvement in the LPR and GERD symptom scores in a few patients in both groups. This finding indicated no effect of LNF or PPI in

**Table 2** Characteristics on the oropharyngeal pH-monitoring, manometry and endoscopy between laparoscopic Nissen fundoplication and proton pump inhibitor groups

Characteristic/examination parameter	LNF	PPI	P value
Oropharyngeal pH-monitoring			
Acid exposure (upright, %)	11.77 ± 18.95	8.49 ± 15.66	0.416
Acid exposure (supine, %)	4.25 ± 12.79	3.28 ± 7.92	0.182
Number of reflux events (upright)	53.84 ± 97.48	34.93 ± 65.35	0.195
Number of reflux events (supine)	7.44 ± 18.42	5.14 ± 9.22	0.232
Ryan score (upright)	335.13 ± 491.08	274.57 ± 459.10	0.617
Ryan score (supine)	8.98 ± 16.18	7.23 ± 7.81	0.217
High-resolution Manometry			
LES pressure (mmHg)	11.78 ± 8.07	14.84 ± 9.73	0.236
UES pressure (mmHg)	43.8 ± 28.33	67.08 ± 42.51	0.045 <sup>1</sup>
Dysperistalsis	3 (9.7)	10 (25.6)	0.090 <sup>1</sup>
Hiatal hernia	24 (77.4)	33 (84.6)	0.449
GI endoscopy			
Esophagitis (grade A)	10 (32.2)	10 (25.6)	0.549
Esophagitis (grade B)	3 (9.7)	2 (5.1)	0.470
Hiatal hernia	16 (51.6)	30 (76.9)	0.027 <sup>1</sup>

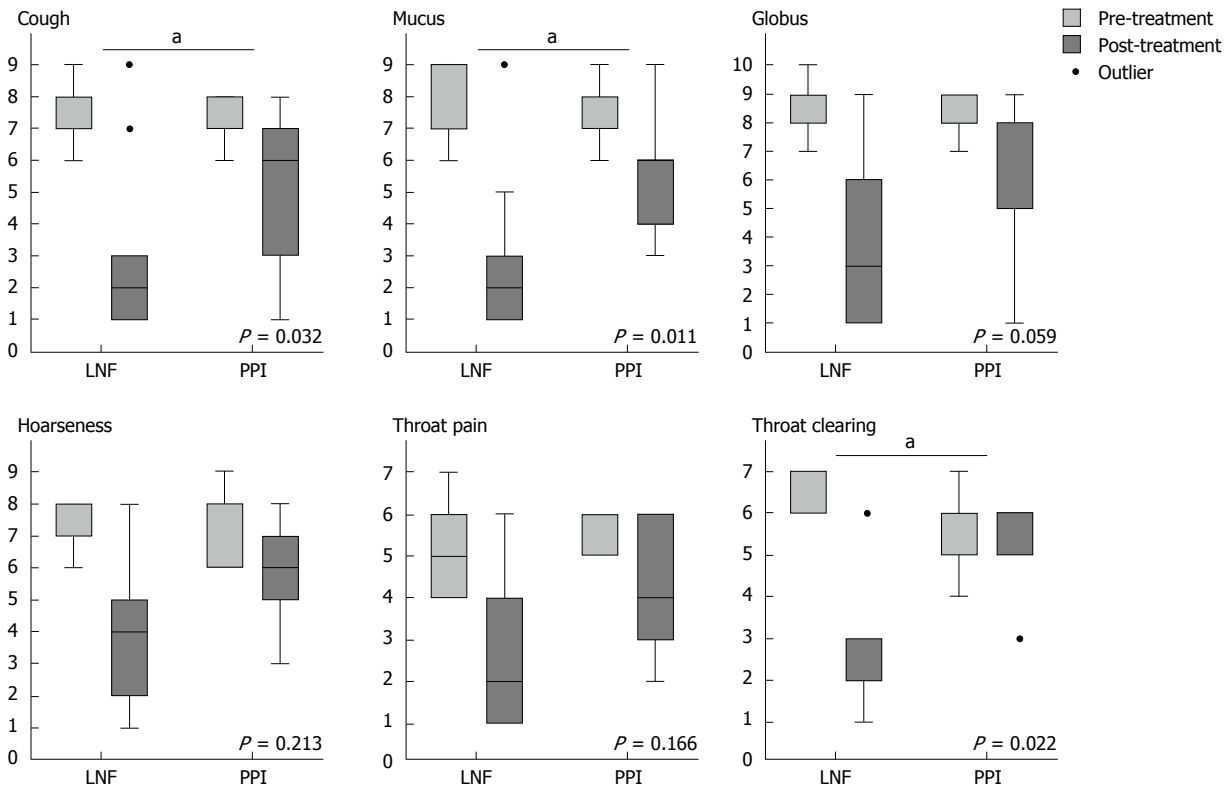
<sup>1</sup>Represent statistical significant *P* values (*P* < 0.05). Values are given as mean ± SD or *n* (%). LNF: Laparoscopic Nissen fundoplication; PPI: Proton pump inhibitor; LES: Lower esophageal sphincter; UES: Upper esophageal sphincter.

three patients (Figures 1 and 2).

### Comprehensive assessment and satisfaction

The comprehensive LPR diagnostic scale of the RSI score was assessed in this study. All 70 patients reported one or more symptoms that were included in the RSI scale. Forty-three (81.1%) patients had an RSI score ≥ 13 during the 2-year follow-up. The RSI score decreased after treatment in the LNF and PPI groups. Importantly, the mean RSI score in patients who had LNF surgery was significantly lower (9.7 ± 4.1) than that in patients who had PPIs administration (12.8 ± 3.1) at the 2-year follow-up (*P* = 0.004). Similar results were observed in the rate of a positive RSI score between the two groups (*P* = 0.003). Interestingly, 11 (44.0%) patients in the LNF group achieved independence of PPIs at the 2-year follow-up. However, only two (7.1%) patients were completely weaned off of PPIs in the PPI group (*P* < 0.001). Moreover, we found that the mean BMI was significantly decreased after LNF compared with before LNF (24.9 kg/m<sup>2</sup> vs 22.2 kg/m<sup>2</sup>, *P* < 0.001). However, the mean BMI of the PPI group did not significantly change before and after treatment (25.0-25.1 kg/m<sup>2</sup>, *P* = 0.991). There was a significant difference in BMI between the LNF and PPI groups at the 2-year follow-up (LNF group: 22.2 ± 3.1 vs PPI group: 25.1 ± 2.9, *P* = 0.001), but not at pre-treatment (Table 4).

From baseline to the 2-year follow-up, the mean satisfaction score of patients improved by 62.49 ± 28.68 in the LNF group and 44.36 ± 32.77 in the PPI group. Patients were more satisfied with their quality of life after undergoing LNF than with PPI therapy (*P* = 0.004, Table 4). However, three (12%) patients



**Figure 1** Comparison of the laryngopharyngeal reflux symptom score between the laparoscopic Nissen fundoplication and proton pump inhibitor groups before treatment and at the 2-year follow-up. Range, upper and lower quartiles, and median values are shown. Represents significant  $P$  values ( $^aP < 0.05$ ) for a difference in improvement of symptoms between the LNF and PPI groups.  $P$  values are also shown in the right lower corner of each box. LNF: Laparoscopic Nissen fundoplication; PPI: Proton pump inhibitor.

**Table 3** Comparison of the laryngopharyngeal and gastroesophageal reflux disease typical symptom score between laparoscopic Nissen fundoplication and proton pump inhibitor groups before treatment and at 6-mo and 2-year follow-up

Characteristic/symptom score (No. of LNF/PPI)	Baseline ( $n = 70$ )			6-mo follow-up ( $n = 61$ )			2-yr follow-up ( $n = 53$ )		
	LNF	PPI	$P$ value	LNF	PPI	$P$ value	LNF	PPI	$P$ value
Regurgitation <sup>2</sup> (17/20)	6.47 ± 0.62	6.24 ± 0.56	0.385	1.41 ± 1.69	2.53 ± 1.15	0.022 <sup>1</sup>	1.12 ± 1.47	2.53 ± 1.26	0.005 <sup>1</sup>
Heartburn <sup>2</sup> (19/20)	6.33 ± 0.68	6.30 ± 0.59	0.100	1.33 ± 1.06	2.60 ± 1.69	0.008 <sup>1</sup>	0.94 ± 1.10	3.05 ± 2.20	0.001 <sup>1</sup>
Cough (15/16)	7.71 ± 0.82	7.67 ± 0.46	0.804	2.34 ± 2.37	4.40 ± 2.10	0.022 <sup>1</sup>	2.28 ± 2.12	5.00 ± 2.28	0.012 <sup>1</sup>
Mucus (11/9)	7.09 ± 0.83	7.22 ± 0.44	0.824	2.82 ± 2.24	4.77 ± 1.85	0.055 <sup>1</sup>	3.27 ± 2.18	5.29 ± 1.78	0.020 <sup>1</sup>
Globus (23/14)	6.10 ± 0.66	7.01 ± 0.88	0.268	2.95 ± 2.75	5.43 ± 2.50	0.013 <sup>1</sup>	2.77 ± 2.87	5.28 ± 2.86	0.017 <sup>1</sup>
Hoarseness (10/7)	7.30 ± 2.78	7.33 ± 2.55	0.954	3.80 ± 2.69	5.00 ± 2.65	0.409	3.50 ± 2.76	4.33 ± 2.53	0.546
Throat pain (11/4)	7.20 ± 1.03	7.50 ± 0.58	0.552	3.70 ± 2.98	5.50 ± 2.65	0.100	3.20 ± 3.46	4.25 ± 2.06	0.166
Throat clearing (6/7)	7.67 ± 0.52	7.14 ± 0.52	0.063	3.33 ± 2.06	6.00 ± 1.53	0.034 <sup>1</sup>	2.83 ± 2.40	6.28 ± 1.51	0.020 <sup>1</sup>

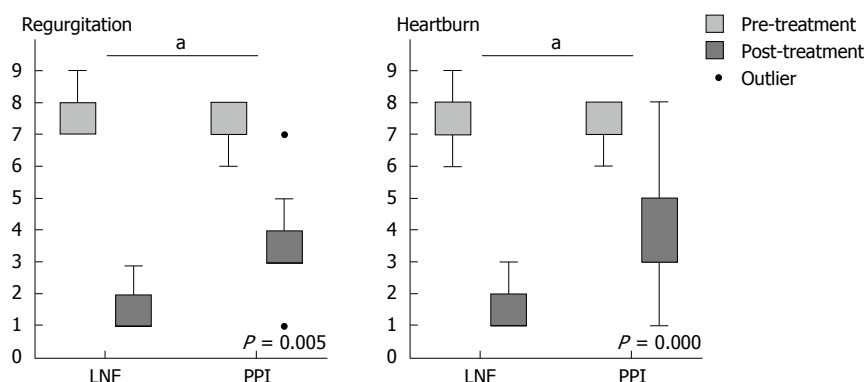
<sup>1</sup>Represent statistical significant  $P$  values ( $P < 0.05$ ); <sup>2</sup>Represents gastroesophageal reflux disease typical symptoms. Values are given as mean ± SD. LNF: Laparoscopic Nissen fundoplication; PPI: Proton pump inhibitor.

suffered from severe dysphagia after LNF surgery, and this was relieved after bougie dilation treatment. No patients experienced perforation, infection, or death.

## DISCUSSION

LPR remains a controversial issue with inconsistent data on epidemiology, etiology, diagnosis, and management, even though LPR and GERD are both caused by reflux of stomach contents. The association between GERD and hiatal hernia is well known; hiatal hernia is present in 83% of patients with GERD.

Additionally, the prevalence of GERD is 68% in patients with hiatal hernia<sup>[24,25]</sup>. Recent studies have shown that LPR is found in 70% of patients with GERD, 53% patients with GERD and LPR have hiatal hernia, and approximately 50% of patients with GERD and hernia have common symptoms of LPR<sup>[4,26]</sup>. In our study, we found that 67.7%-74.2% of patients with LPR and type I hiatal hernia had typical GERD symptoms, similar to a previous study<sup>[26]</sup>. We also found that esophagitis was present in 35.7% of patients with LPR. Indeed, hiatal hernia appears to be an important risk factor for occurrence of LPR as GERD. A method of treating



**Figure 2** Comparison of the typical gastroesophageal reflux disease symptom score between the laparoscopic Nissen fundoplication and proton pump inhibitor groups before treatment and at the 2-year follow-up. Range, upper and lower quartiles, and median values are shown. Represents significant  $P$  values ( $^2P < 0.05$ ) for a difference in improvement of symptoms between the LNF and PPI groups.  $P$  values are also shown in the right lower corner of each box. LNF: Laparoscopic Nissen fundoplication; PPI: Proton pump inhibitor.

**Table 4** Comparison of outcome between laparoscopic Nissen fundoplication and proton pump inhibitor administration by 2-year follow-up

Characteristic/parameter	LNF ( $n = 25$ )	PPI ( $n = 28$ )	$P$ value
BMI ( $\text{kg}/\text{m}^2$ )			
Pre-treatment	$24.9 \pm 3.8$	$25.0 \pm 3.1$	0.285
Post-treatment	$22.2 \pm 3.12$	$25.1 \pm 2.9$	0.001 <sup>1</sup>
RSI score (value)			
Pre-treatment	$15.3 \pm 3.5$	$14.2 \pm 4.0$	0.759
Post-treatment	$9.7 \pm 4.12$	$12.8 \pm 3.12$	0.004 <sup>1</sup>
RSI score ( $\geq 13$ ), $n$ (%)			
Pre-treatment	19 (76.0)	24 (85.7)	0.284
Post-treatment	7 (28.0) <sup>2</sup>	19 (67.9) <sup>2</sup>	0.003 <sup>1</sup>
PPI independence, $n$ (%)	11(44.0)	2 (7.14)	0.000 <sup>1</sup>
Satisfaction, $n$ (%)	$62.49 \pm 28.68$	$44.36 \pm 32.77$	0.004 <sup>1</sup>

<sup>1</sup>Represent statistical significant  $P$  values between LNF and PPI group;

<sup>2</sup>Represent statistical significant  $P$  values between pre-treatment and post-treatment for 2-year follow-up ( $P < 0.05$ ). Values are given as mean  $\pm$  SD or  $n$  (%). LNF: Laparoscopic Nissen fundoplication; PPI: Proton pump inhibitor.

hernia or GERD might also improve symptoms of LPR. Therefore, this study was designed to focus on the comparison of diagnosis and treatment for LPR with hiatal hernia.

Currently, diagnosis of LPR mainly includes empirical therapeutic trials of PPIs, the RSI scale, laryngoscopy, and pH-monitoring<sup>[6]</sup>. Among these diagnostic methods, PPI trials and the RSI scale are subjective methods, which cannot provide direct pathophysiological evidence of LPR. The reflux finding score, which is based on laryngoscopic findings, also has poor reliability in detecting LPR<sup>[8,9]</sup>. Recent evidence has suggested no relationship between clinical findings of LPR, laryngoscopy, and the reflux finding score<sup>[26]</sup>. Monitoring of pH can directly detect increased esophageal or laryngopharyngeal acid exposure by a pH probe, and is thus regarded as the best evidence for diagnosis of LPR. Advances in oropharyngeal pH-monitoring have been made, such as the oropharyngeal pH-monitoring system. This

system is a sensitive and minimally invasive device for determining acid reflux in oropharynx<sup>[10,13]</sup>. Our study was designed to diagnose LPR by combining a comprehensive RSI scale/single symptom score and pH-monitoring to assess the consistent reflux events and the occurrence of symptoms. Monitoring of pH showed that all patients had positive pH-monitoring (Ryan score) with an RSI score  $\geq 13$ . This finding suggested that oropharyngeal pH-monitoring and the RSI have the same diagnostic value for LPR. Moreover, oropharyngeal pH-monitoring showed more reflux events and a longer duration of acid exposure in the upright position than in the supine position. The potential reasons for these findings could be due to the following: (1) increased abdominal pressure induces high-level reflux and acid has direct laryngeal contact in the upright position; (2) feeding and acid secretion stimulate the vagal afferents to promote irregular contraction of the distal/proximal esophagus in the daytime; and (3) activity of the laryngopharynx in the daytime affects the nozzle structure<sup>[27]</sup>, as hypothesized by our group. A recent study proposed that, in the upright position, intragastric air rushes proximally with the assistance of increased intra-abdominal pressure, and the resultant gastric distension triggers relaxation of the intra-thoracic portion of the LES *via* stretch receptors in the stomach<sup>[28]</sup>. Our result of a higher Ryan score in the upright position than in the supine position is consistent with the LPR characteristics of aerosol of acidic contents.

The primary determinants of severity of GERD are a dysfunctional anti-reflux barrier and impaired esophageal clearance<sup>[29]</sup>. Disruption of the anti-reflux barrier can be related to a hypotensive LES ( $< 10$  mmHg), dysperistalsis, and hiatal hernia<sup>[29-31]</sup>. All of these factors may contribute to the occurrence of symptoms of LPR. Our study showed that LES pressure was reduced to approximately 10-15 mmHg. Additionally, a high incidence of dysperistalsis and hiatal hernia was shown by esophageal high-resolution manometry and GI endoscopy. High-resolution



manometry had a greater sensitivity than endoscopy for diagnosis of hiatal hernia in this study. Additionally, we analyzed the UES pressure of patients with LPR. Unfortunately, we obtained a different baseline of UES pressure before treatment, and no studies have focused on normal values of UES pressure or the relationship between UES pressure and LPR. However, our center has proposed a mechanism of LPR by using a special pharyngeal nozzle structure, and measured hypertensive UES pressure in a rat model<sup>[32,33]</sup>.

Hiatal hernia impairs LES function by reducing its length and pressure, and appears to be an important risk factor for the occurrence of LPR. LPR symptoms are likely to be cured by surgery for hernia repair and fundoplication. However, the guideline for management of GERD<sup>[34]</sup> suggests that the strength of evidence is insufficient, with no consistent benefit attributed to surgery for LPR. PPIs therapy is the first choice for LPR in patients who also have typical symptoms of GERD or objective evidence of GERD by endoscopy or reflux monitoring.

The efficacy of empirical PPIs therapy for suspected LPR has been previously investigated. PPIs therapy reduced the incidence rate of LPR symptoms by 50.3% in one study (range: 38%-90%)<sup>[35]</sup>. Another study specified that abnormal pH testing was an inclusion criterion, and the rate for responding to PPIs was 59.1%<sup>[36]</sup>. In our study, comprehensive symptoms (RSI scale) markedly improved in 10 patients, and the mean RSI score significantly decreased after PPIs treatment. However, the rate of independence from PPIs (2 patients, 7.14%) was low. Additionally, some symptoms were not significantly relieved in some patients in the PPI group, such as globus, hoarseness, and throat pain and clearing. Some studies have suggested that symptoms persisted or recurred in the long-term follow-up, even though some patients used a double dose of PPI twice daily<sup>[37,38]</sup>.

LNF has become the surgical gold standard for GERD treatment. LNF can repair diaphragmatic crura to correct the anatomical problem of hiatus, and establish a wrap to provide an anti-reflux barrier. Nevertheless, the guideline<sup>[34]</sup> suggests that controlling symptoms of LPR is not satisfied by Nissen fundoplication. In our study, we focused on patients with LPR with a clear diagnosis of hiatal hernia, and compared LNF with PPIs administration, which is the first recommended choice for LPR. We found that LNF was effective in reducing the RSI score, and the frequency and severity of LPR and typical GERD symptoms. Additionally, LNF was superior to empirical PPIs therapy in all aspects, especially in independence from PPIs, and patients' satisfaction with LNF tended to be better than that with PPIs therapy. These findings demonstrated that anti-reflux surgery could be as effective for LPR as for GERD. However, the accuracy of diagnosis of LPR could be a problem. With strict screening *via* multichannel intraluminal impedance-pH<sup>[39,40]</sup> or oropharyngeal pH-

monitoring, symptoms of LPR are likely to demonstrate improvement following anti-reflux surgery.

Another important factor related to the occurrence of GERD is BMI, which affects the efficacy of anti-reflux surgery for LPR<sup>[41]</sup>. In our study, BMI ranged from 21.1 to 28.1 kg/m<sup>2</sup>, with no difference between the LNF and PPI groups. However, all of the patients were instructed to adopt lifestyle modifications. BMI was remarkably decreased only in the LNF group during the 2-year follow-up. Some studies have suggested that obesity is associated with GERD<sup>[42]</sup> and an increased BMI is associated with increased esophageal acid exposure<sup>[43]</sup>. Therefore, LNF could play a role in maintaining or reducing BMI, which affects the progress of GERD, as well as symptoms of LPR. However, this effect of LNF still needs to be observed in a long-term investigation.

A limitation of this study is that it was an uncontrolled, nonrandomized study, which made it impossible to control for baseline demographics. Although all of the patients underwent either anti-reflux or anti-acid therapy, the methods of therapy were not randomly chosen. Oropharyngeal pH-monitoring is a costly and time-consuming technique, which is still not widely available for use in patients for follow-up. Only improvement of symptoms was used to evaluate the effect of treatment, such as the RSI and specific symptoms score. Another limitation of the study is its small sample size and the loss of follow-up. Only 75.7% of patients finally completed the 2-year follow-up. A multicenter, randomized, controlled trial with more samples is required to reach a conclusion regarding the superiority of anti-reflux surgery for controlling LPR.

In conclusion, current knowledge on diagnosis of LPR needs to be expanded with multiple diagnostic strategies, including oropharyngeal pH-monitoring and high-resolution manometry. These strategies should be combined with classical techniques, such as GI endoscopy and symptom-scale assessment. Anti-reflux surgery and anti-acid therapy are effective in patients with LPR and type I hiatal hernia. LNF shows better improvement than PPIs administration, and it also controls BMI of patients in short time. Our findings shed new insights into the diagnosis and management for patients with LPR.

## COMMENTS

### Background

Laryngopharyngeal reflux (LPR) is considered as extraesophageal symptoms for distinguishing typical symptoms of gastroesophageal reflux disease (GERD). Evidence has suggested hiatal hernia is a risk factor for the occurrence of LPR as well as GERD. Common diagnosis and management for LPR depend on empirical proton pump inhibitors (PPIs) therapy; however, it cannot solve the hiatal hernia. Few studies have focused on the outcome of LPR patients following anti-reflux surgery, like laparoscopic Nissen fundoplication. The current trial was designed to evaluate anti-acid and anti-reflux therapy for LPR with type I hiatal hernia.

### Research frontiers

LPR symptoms are much harder to be improved than GERD typical symptoms,



such as heartburn and regurgitation. GERD could be cured by anti-reflux surgery, thus increasing studies focused on the outcome of laparoscopic fundoplication to find the best therapeutic strategy for LPR. Meanwhile, oropharyngeal pH-monitoring is still in debate for diagnosing LPR, the integrated results of symptom-scale and oropharyngeal pH-monitoring could demonstrate the characteristics of LPR.

### Innovations and breakthroughs

The literature suggests that the LPR patient should be assessed with oropharyngeal pH-monitoring and symptom-scale, combination of manometry and endoscopy, which could avoid the misdiagnosis of hiatal hernia. LNF achieves better improvement than PPIs for LPR with type I hiatal hernia, and could play a role in controlling BMI in short-term.

### Applications

This study provides clinical evidence to support the effect of laparoscopic Nissen fundoplication on LPR patients diagnosed by oropharyngeal pH-monitoring and symptom-scale.

### Terminology

Oropharyngeal pH-monitoring: A pH probe is inserted in laryngopharyngeal to detect acid exposure for continual 24 h. The pH-monitoring system includes a pH sensor with a teardrop shape to avoid becoming covered with food or mucus, a recorder to store the message and a new parameter calculation system (Ryan score) with different pH thresholds for upright and supine positions. Reflux symptom index (RSI): the scale accurately documents laryngopharyngeal symptoms with 9 item self administered outcome instrument, ranges from 0 to 45 (worst possible score). RSI more than 13 is considered as LPR diagnosis.

### Peer-review

The authors have performed an interesting single-centre, comparative study. The outcomes of interest are well described and defined in the manuscript.

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