



# Laryngopharyngeal reflux in patients with reflux esophagitis

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## INTRODUCTION

Gastroesophageal reflux disease (GERD) has been known to be a common medical condition affecting approximately 35%-40% of the adult population in the Western world<sup>[1,2]</sup>. Forty-four of all Americans suffer from heartburn at least once per month, 20% at least once per week<sup>[3]</sup>. The role of GERD in causing extra-esophageal symptoms is also increasingly being recognized<sup>[4]</sup>. Chronic laryngeal signs and symptoms associated with GERD are often referred to as reflux laryngitis or laryngopharyngeal reflux (LPR)<sup>[5]</sup>. But, not all episodes of GERD are associated with LPR and not all patients with LPR have typical features of GERD<sup>[6]</sup>. Classic reflux symptoms (heartburn and regurgitation), which are referred to as "typical GERD," may be absent in more than half the patients presenting with extra-esophageal manifestations<sup>[7,8]</sup>. The "silent reflux" contributes to the difficulty in making a definite and correct diagnosis. The extra-esophageal manifestations of GERD provide the most challenging areas to perform good research<sup>[9]</sup>.

Furthermore, the prevalence of LPR in the patients with GERD has not been studied well in the past. The kind of patients with GERD who are more associated with LPR is still unknown. The cause-and-effect relationship between GERD and LPR remains elusive.

In patients with esophageal syndromes of GERD, reflux esophagitis (RE) is more easily diagnosed definitely by endoscopy than others. The objectives of our current study were to determine the prevalence of LPR in the patients with RE and to find out the factors that contribute to the development of LPR.

## Abstract

**AIM:** To assess the prevalence of laryngopharyngeal reflux (LPR) in patients with reflux esophagitis and disclose factors contributing to the development of LPR.

**METHODS:** A total of 167 patients who proved to have reflux esophagitis by endoscopy were enrolled. They received laryngoscopy to grade the reflux findings for the diagnosis of LPR. We used validated questionnaires to identify the presence of laryngopharyngeal symptoms, and stringent criteria of inclusion to increase the specificity of laryngoscopic findings. The data of patients were analyzed statistically to find out factors related to LPR.

**RESULTS:** The prevalence rate of LPR in studied subjects with reflux esophagitis was 23.9%. Age, hoarseness and hiatus hernia were factors significantly associated with LPR. In 23 patients with a hiatus hernia, the group with LPR was found to have a lower trend of esophagitis grading.

**CONCLUSION:** Laryngopharyngeal reflux is present in patients with reflux esophagitis, and three predicting factors were identified. However, the development of LPR might be different from that of reflux esophagitis. The importance of hiatus hernia deserves further study.

## MATERIALS AND METHODS

### Recruitment of patients

Consecutive patients who were diagnosed to have RE by gastroendoscopic examination due to various symptoms, such as epigastric pain, acid regurgitation, heartburn, nausea, abdominal fullness sensation, and so on, at the gastrointestinal clinic of Cathay General Hospital from September 2006 to October 2007 were enrolled. These qualified patients then were referred to the otorhinolaryngologic clinic for the further work-up of a laryngoscopic examination. Written, informed consent had to be provided by the participants before the endoscopic examination.

To improve the specificity of our study, the inclusion criteria of the patients were very strict. Patients were excluded from the study if they had a history of respiratory or gastrointestinal malignancy; radiation therapy to the head and neck, lung, or gastrointestinal tract; gastroesophageal surgery; use of H<sub>2</sub>-receptor antagonists or proton pump inhibitors in previous 1 mo; past or present smoker; excessive alcohol consumption; chronic cough attributable to known chronic pulmonary or tracheobronchial disease; professional voice users (e.g. singer, teacher); excessive voice use; exposure to occupational or environmental pollutants; history of seasonal allergic rhinitis; pharyngolaryngeal infection in the previous 3 mo; tracheal intubation in the previous 12 mo and use of inhaled corticosteroids<sup>[10,11]</sup>.

### Gastroendoscopic examination

All subjects received conventional endoscopic imaging, as well as imaging with the narrow-band imaging (NBI) system by using a video endoscope (GIF-H 260; Olympus Optical Co, Ltd, Tokyo, Japan). A group of experienced endoscopists performed the endoscopic examination. NBI is a novel, non-invasive optical technique that adjusts reflected light to enhance the contrast between the esophageal mucosa and the gastric mucosa<sup>[12]</sup>. The Los Angeles classification was used to grade esophagitis. A hiatus hernia was diagnosed if the hernia sac was more than 2 cm in length. We did not include patients suspected to have Barrett's esophagus due to diagnostic complexity.

### Questionnaire

The qualified participants needed to complete a questionnaire by answering "yes" or "no" with the aid of research nurses, right after the gastroendoscopic examination. It was used to identify the presence of any throat or reflux symptoms (cough, hoarseness, throat clearing, sore throat, thick drainage, globus sensation, bad taste in the mouth, swallowing problems, chest pain). Subjects were also asked to score the severity of each symptom based on a graded scale of 1 to 4 [1 = rare (once a month or less), 2 = occasional (2-3 times a month), 3 = frequent (several times a week); 4 = all the time (several times daily)]. The graded scales of more than 2 were considered significant, and the symptoms with such a scale could be included into the study<sup>[13]</sup>.

### Laryngoscopic examination

Each patient at the otorhinolaryngologic clinic underwent an endoscopic examination (Hopkins 70°C Telescope, Model 8706 CA, Karl Storz, Germany) of the larynx by two well-trained otolaryngologists, both with experience of over 10 years and good consensus, to grade the laryngoscopic findings. The otolaryngologists were not aware of the results of the questionnaire before the laryngoscopic examination. A reflux finding score (RFS) was obtained based on the laryngeal examination scoring system by Belafsky *et al*<sup>[14]</sup>. A RFS of > 7 was considered abnormal and to have LPR. Laryngeal signs suspected to be reflux-related were determined based on an agreement of the two experts.

### Statistical analysis

Statistical analyses were performed using the Stata 8.0 for Window (STATA Corp, College Station, TX). Patient characteristics were compared using the Student's *t* test and Pearson's  $\chi^2$  test for proportions. A logistic regression model was used to adjust for confounding covariates including age, sex, BMI, disease (presence or absence), a hiatus hernia (presence or absence), and the grading of LA classification (A, B, C) *etc*. A two-tailed *P* value of less than 0.05 was taken to indicate statistical significance.

## RESULTS

Two hundred twenty-two patients with endoscopically proven RE initially were included in the study. However, 13 patients did not visit otorhinolaryngeal clinic due to personal reasons and 42 patients were excluded because they did not meet the strict inclusion criteria. Therefore, a total of 167 patients (80 males and 87 females) were enrolled in this study. The demographic characteristics of the studied subjects are listed in Table 1. 96.4% of the patients belonged to the groups of esophagitis grade A and B; only 3.6% were of grade C. A hiatus hernia was found in 13.8% of the patients.

Table 2 shows comparisons of demographic characteristics of patients with and without LPR. Among the 167 patients, 23.9% (40 cases) were diagnosed to have LPR. The difference in age between the patients with and without LPR was significant (45.2 *vs* 49.9 years, *P* = 0.04). The patients with LPR were younger than the ones without LPR. The presence of hoarseness symptom was significantly higher in the group with LPR (55.0% *vs* 26.8%, *P* = 0.001). In addition, a hiatus hernia was found more frequently in the group with LPR (27.5% *vs* 9.5%, *P* = 0.004).

If we combined the symptom of hoarseness and presence of a hiatus hernia together, the prediction of LPR was much higher (odds ratio increased up to 12.3, Table 3).

We also made a detailed analysis in the patients with a hiatus hernia. The distribution of esophagitis grading between the groups with and without LPR were compared. Of interest, in 23 patients with a hiatus hernia, the group with LPR (11 patients) had a relatively lower trend of esophagitis grading (LA grade A/B/C:

Table 1 Demographic characteristics of 167 patients

Demographic characteristics	<i>n</i>
Gender (male/female)	80/87
Age (yr)	
mean $\pm$ SD	48.8 $\pm$ 12.8
Range	21-81
BMI (kg/m <sup>2</sup> )	
mean $\pm$ SD	23.4 $\pm$ 3.2
Range	16.1-36.3
LPR symptoms (%)	
Hoarseness	56 (33.5)
Globus	56 (33.5)
Cough	46 (27.5)
Throat clearing	59 (35.3)
LA grade (%)	
A	118 (70.7)
B	43 (25.7)
C	6 (3.6)
Hiatus hernia (%)	23 (13.8)

BMI: Body mass index; LPR: Laryngopharyngeal reflux; LA grade: The grade of Los Angeles classification of esophagitis.

Table 2 Comparisons of demographic characteristics of patients with and without LPR

	LPR ( <i>n</i> = 40)	Non-LPR ( <i>n</i> = 127)	<i>P</i>
Gender (%)			0.67
Male	18 (45.0)	62 (48.8)	
Female	22 (55.0)	65 (51.2)	
Age (yr)	45.2 $\pm$ 11.9	49.9 $\pm$ 12.9	0.04
BMI (kg/m <sup>2</sup> )	23.3 $\pm$ 3.2	23.4 $\pm$ 3.2	0.88
LPR symptoms (%)			
Hoarseness	22 (55.0)	34 (26.8)	0.001
Globus	14 (35.0)	42 (33.1)	0.82
Cough	12 (30.0)	34 (26.8)	0.69
Throat clearing	16 (40.0)	43 (33.9)	0.47
LA grade (%)			0.68
A	29 (72.5)	89 (70.1)	
B	9 (22.5)	34 (26.8)	
C	2 (5.0)	4 (3.1)	
Hiatus hernia ( <i>n</i> , %)	11 (27.5)	12 (9.5)	0.004

BMI: Body mass index; LPR: Laryngopharyngeal reflux; LA grade: The grade of Los Angeles classification of esophagitis.

9, 81.8%/2, 18.2%/0, 0%), whereas the group without LPR (12 patients) had a higher trend of grading (LA grade A/B/C: 4, 33.3%/6, 50.0%/2, 16.7%). The difference was statistically significant ( $P = 0.04$ ).

## DISCUSSION

The association between LPR and GERD has not been firmly established yet<sup>[6]</sup>. Not all patients with GERD will develop LPR. On the other hand, it is estimated that 50%-60% of chronic laryngitis and difficult-to-treat sore throat may be related to GERD<sup>[8]</sup>. The causal association between acid reflux and laryngitis is highly plausible considering the close anatomical relationship. The vagally mediated reflexes (bronchospasm, laryngospasm and cough) stimulated by esophageal acid is also implicated in the pathogenesis of GERD-related extra-esophageal disorder<sup>[11,15]</sup>.

Table 3 Logistic regression analyses on predictors of LPR

	Odds ratio	
	Model 1	Model 2
Gender		
Female	-	-
Male	0.72	0.82
Age	0.96 <sup>†</sup>	0.96 <sup>†</sup>
BMI	0.98	0.99
LPR symptoms		
Hoarseness	4.12 <sup>†</sup>	-
Globus	1.77	1.21
Cough	0.91	1.23
Throat clearing	0.82	1.24
LA grade		
A	-	-
B	0.81	0.76
C	2.35	2.21
Hiatus hernia	4.78 <sup>†</sup>	-
Hiatus hernia and Hoarseness	-	12.3 <sup>†</sup>

BMI: Body mass index; LPR: Laryngopharyngeal reflux; LA grade: The grade of Los Angeles classification of esophagitis. <sup>†</sup>*P* value is significant at the 0.05 level.

Currently, there is no “gold-standard” for the diagnosis of LPR. Ambulatory 24-h dual or triple probe pH-metry was once considered the best method for reflux testing<sup>[16]</sup> but the position of the probes makes the measurement not easy to interpret, and there is no consensus about the pathological reflux at the level of laryngopharynx<sup>[6]</sup>. Moreover, extra-esophageal reflux is also intermittent. A negative pH study does not rule out extra-esophageal reflux<sup>[17]</sup>. The empiric therapy with aggressive acid suppression, usually BID dosing of proton-pump inhibitors (PPIs), is currently recommended as the most practical and cost effective approach for the patients suspected with extra-esophageal presentations of GERD<sup>[16]</sup>. Nevertheless, this therapeutic trial for the diagnosis of LPR could not provide direct evidence of pathologic imaging changes of patients, about which most clinicians want to learn.

Laryngeal examination with special emphasis on the posterior location of tissue injury can be helpful for the diagnosis of LPR<sup>[18]</sup>. The severity of mucosal injury may be graded according to the RFS by Belafsky 2001<sup>[14]</sup>. The RFS is an 8-item clinical severity scale based on findings during fiberoptic laryngoscopy. However, this RFS system has been criticized to have high inter- or intra-observer variability and low specificity for reflux laryngitis<sup>[6,10,19]</sup>. Therefore, it is very important to exclude meticulously other potential etiologies that can lead to laryngeal irritation. In our study, we did a very stringent selection of the patients to avoid the secondary causes of chronic laryngitis, such as smoking, alcohol, excessive voice use, allergies, or asthma.

The NBI system we used on gastroendoscopic examinations could offer a better image of capillary patterns and, thus, enhance the contrast between the esophageal and gastric mucosa and facilitate the endoscopic evaluation of esophagitis<sup>[20,21]</sup>. The better depictions of small erosive foci improves the intra- and inter-observer reproducibility in the grading of esophagitis, especially

in the grading of class A or B esophagitis<sup>[12]</sup>, which was very helpful in our study.

In our study, LPR was present in 23.9% of the studied subjects with RE. In the past, Koufman described posterior laryngitis in 74% and laryngeal edema with erythema in 60% of all patients with GERD<sup>[16]</sup>. Tauber *et al* also reported 85% of GERD-positive patients had posterior laryngitis and 69% had laryngitis with an interarytenoid erythema and edema<sup>[22]</sup>. Our prevalence rate of LPR is much lower than theirs; the different sample size of patients and method of enrollment in our research must have influenced the results. Because we used very stringent criteria to enroll the patients, it was possible that we missed some cases and underestimated the prevalence rate of LPR. In fact, this kind of report is quite rare in the literature. Most papers dealt only with the prevalence rate of GERD (ranging 20%-50%) in patients with LPR<sup>[4,21,23,24]</sup>.

Our results indicated that age, hoarseness and a hiatus hernia could be the predicting factors of LPR in the patients with RE. However, gender, body mass index, and the severity of esophagitis were not associated. A large cohort study performed by Jaspersen *et al* reported female gender, higher age, severe esophagitis, longer duration of GERD and smoking were significantly related to the extra-esophageal disorder<sup>[25]</sup>. Their risk factors were not the same as ours, which might be caused by the recruitment method they used. Though the case number of their study was large, they did not exclude the patients strictly and included patients who smoked. The patients they studied did not receive a laryngoscopic examination, and solely relied on the "symptom questionnaire" for the diagnosis of extra-esophageal disorders, which could be another factor that would induce diverse outcomes.

Increased GERD severity due to degradation of the gastroesophageal junction and impaired esophageal clearance was found in the elderly<sup>[26]</sup>. Yet, age as a factor contributing to LPR seldom has been mentioned before. In the present study, the RE patients with LPR were of a younger age than the patients without LPR. This finding is contradictory to the result of Jaspersen's study, in which they noted higher age was a risk factor for the occurrence of extra-esophageal disorder<sup>[25]</sup>. The opposite results again might be attributed to the different recruitment and research methods. However, the drawback of our study was that we had fewer patients. According to our findings, higher age, which implies the probable longer duration of GERD, is not essential for the development of LPR. In addition, our study also indicated the severity of RE had nothing to do with the occurrence of LPR. Therefore, the existence of LPR seems to be not associated with the duration or severity of RE.

LPR may have several clinical symptoms. Among them, throat-clearing, persistent cough, globus and hoarseness are the most common complaints<sup>[24]</sup>. In our study, the prevalence of hoarseness in all the patients was 33.5%. When we made comparison between the patients with and without LPR, the rate of hoarseness became 55.0% *vs* 26.8%, which was statistically significant. Our result indicated that more than 50% of the RE

patients with LPR had the symptom of hoarseness. As for the other symptoms (globus, throat discomfort and persistent cough), we did not find significant differences between the two groups.

Hoarseness is a common complaint of the patients at the otorhinolaryngologic clinic. Underlying causes include malignancy, vocal cord palsy, polyps and nodules of the vocal cords, laryngitis and functional disorders. Acute laryngitis is usually infective, whereas chronic laryngitis may result from a spectrum of insults including cigarette smoking, dehydration, acid reflux and muscular imbalance<sup>[6]</sup>. Hoarseness is not specific for LPR. Therefore, we must exclude several other possible causes before we can make sure the laryngitis-related hoarseness is induced solely by acid reflux. In our patients with RE, an additional symptom of hoarseness might reflect that the acid reflux has gone beyond the upper esophageal sphincter and injured the vocal cord. Extra-esophageal manifestation of GERD, thus, might be incurred.

Hiatus hernias have a higher detection rate in Western populations, ranging between 14.5% and 22%<sup>[27]</sup>. In the Far East, the prevalence rate is much lower, 7% of 464 subjects in Taiwan<sup>[28]</sup>, 2.9% of 11943 subjects in Singapore<sup>[29]</sup>, and 17.5% of 6010 individuals in Japan were reported<sup>[30]</sup>. In a recent series in Taiwan, hiatus hernia was found in 18.8% of patients with erosive esophagitis<sup>[31]</sup>. In our research, it was 13.8% of the studied subjects, which was also higher than that of the normal population here.

A hiatus hernia can disrupt both the anatomy and physiology of the normal anti-reflux mechanism. It is associated with decreased esophageal peristalsis; it also increases the cross-sectional area of the esophago-gastric junction and acts as a reservoir allowing reflux from the hernia sac into the esophagus during swallowing. The presence of a hiatus hernia is associated with symptoms of gastroesophageal reflux, and increased prevalence and severity of RE<sup>[27]</sup>. Because the presence of a hiatus hernia would increase esophageal acid exposure, it is emerging as an important factor in the pathogenesis of GERD<sup>[27]</sup>.

In our study, a confirmed hiatus hernia was found to be a risk factor contributing to LPR in the patients with RE. Considering the possible mechanism of reflux-related extra-esophageal disorders, it will not be surprising to disclose the importance of a hiatus hernia in these patients. With the existence of a hiatus hernia, the acid reflux could be potentiated and would result in more mucosal injury up to larynx. Animal studies have shown that even minute amounts of gastric acid and pepsin on laryngeal mucosa can induce significant inflammation and edema<sup>[32,33]</sup>. Further work is still needed to understand how a hiatus hernia influences the progression of GERD and its complications. At present, a hiatus hernia is known to be a marker of severe GERD<sup>[27]</sup> and must have a contributing effect in the pathogenesis of LPR.

In our patients with a hiatus hernia, we also analyzed their grade of esophagitis. Between the groups with and without LPR, the result was quite interesting and surprising. In this category, the patients with LPR had



a milder form of esophagitis than the ones without LPR. This finding again supports the concept that the development of LPR is not related to the severity of RE. To the contrary, LPR can be seen more frequently in the patients with mild RE when a confirmed hiatus hernia is present. Of interest, Li *et al* just reported that a hiatus hernia was found to be associated with more severe esophagitis in patients with RE<sup>[34]</sup>. Therefore, the development of LPR must be different from that of simple RE without LPR. Moreover, our patients who coexisted with a hiatus hernia and hoarseness had a very high odds ratio for LPR. Combining these two factors clinically, we could predict the presence of LPR more accurately in the patients with RE.

Regretfully, we had only 6 patients (3.6%) with LA grade C esophagitis and no patient with grade D. Thus, in our research, several factors could not be viewed and studied with the entire esophagitis spectrum from grade A to D. Another drawback of our study is that we did not include patients suspected to have Barrett's esophagus or endoscopically suspected esophageal metaplasia, which could be another intriguing field to see the relationship between GERD and extra-esophageal syndromes.

In conclusion, our study revealed that age, hoarseness and a confirmed hiatus hernia were the factors related to LPR in the patients with RE. LPR could be associated with RE, but the definite cause-and-effect relationship is still unknown. Our research was only a hospital-based study; more case numbers and convincing data are necessary in the future. Based on the aforementioned findings, the development of LPR seems to be different from that of RE. The importance of a confirmed hiatus hernia in LPR deserves further study.

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## COMMENTS

### Background

The role of gastroesophageal reflux disease (GERD) in causing laryngopharyngeal reflux (LPR) is being increasingly recognized, but the cause-and-effect relationship between them remains elusive.

### Research frontiers

This research is to assess the prevalence of LPR in the patients with reflux esophagitis (RE), and also to identify the factors contributing to the development of LPR.

### Innovations and breakthroughs

The prevalence rate of LPR in our studied subjects with RE was 23.9%. Age, hoarseness, and hiatus hernia were the factors significantly associated with LPR. In addition, the patients who coexisted with a hiatus hernia and hoarseness had a very high odds ratio (12.3) for LPR. Another interesting finding was that in 23 patients with a hiatus hernia, the group with LPR was incidentally revealed to have lower trend of esophagitis grading.

### Applications

LPR is present in patients with RE and three predicting factors could be identified. Combining the two factors of hoarseness and hiatus hernia together, we could predict the presence of LPR more accurately in the patients with RE. However, the development of LPR seems to be different from that of RE, based

on the findings of this research. The importance of hiatus hernia in LPR deserves further study.

### Peer review

In this study, the authors ascertained the association of LPR with GERD and analyzed the factors related to the development of LPR. The results could be very important because the readers could learn the newest knowledge and understand the future perspectives in this field.

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