Preliminary study on symptoms and signs of patients with laryngopharyngeal reflux disease infected with *Helicobacter pylori*

HAIXIANG ZHANG[1,2*], HUANHUAN DANG[3,4*], XIN WANG[3], YUXIANG ZHAO[3] and JINPING WANG[3]

[1]Shaanxi Provincial Key Laboratory of Infection and Immune Diseases, Shaanxi Provincial People's Hospital, Xi'an, Shaanxi 710068, P.R. China; [2]Shaanxi Engineering Research Center of Cell Immunology, Shaanxi Provincial People's Hospital, Xi'an, Shaanxi 710068, P.R. China; [3]Department of Otolaryngology, Shaanxi Provincial People's Hospital, Xi'an, Shaanxi 710068, P.R. China; [4]Medical College of Yan'an University, Yan'an, Shaanxi 716000, P.R. China

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Abstract. The aim of the present study was to investigate the symptoms and signs of laryngopharyngeal reflux disease (LPRD) in patients infected with *Helicobacter pylori* (HP) and provide a clinical reference for the treatment of such patients. From January 2023 to October 2024, HP tests were performed on 97 outpatients who received a diagnosis of LPRD at the Department of Otolaryngology, Shaanxi Provincial People's Hospital, among whom 60 patients were HP-positive and 37 patients were HP-negative. The symptom and sign scores of the patients who were HP-positive and HP-negative were statistically compared. After treatment, the symptom scores of patients who were HP-positive (treated with anti-HP quadruple therapy) and patients who were HP-negative (treated with acid suppression therapy) were analysed. The results showed that significant differences in dysphagia symptoms (P=0.038) and vocal cord oedema signs (P=0.026) were observed between patients who were HP-positive and HP-negative. After treatment, the total Reflux Symptom Index (RSI) scores were significantly decreased in both groups (HP-positive group, Z=6.733, P<0.001; HP-negative group, Z=4.546, P<0.001). Moreover, the improvement in RSI scores was significantly greater in the HP-positive group compared with in the HP-negative group (Z=-4.12; P<0.001). In conclusion, after being infected with HP, the symptoms of dysphagia and the signs of vocal cord oedema in LPRD increase significantly; therefore, HP infection may exacerbate the severity of LPRD.

Correspondence to: Professor Jinping Wang, Department of Otolaryngology, Shaanxi Provincial People's Hospital, 256 Youyi West Road, Xi'an, Shaanxi 710068, P.R. China
E-mail: 306070789@qq.com

*Contributed equally

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Introduction

Laryngopharyngeal reflux disease (LPRD) is an inflammatory condition caused by the reflux of gastric and duodenal contents into the laryngopharyngeal region, leading to mucosal irritation and damage (1). The incidence of LPRD in Otorhinolaryngology-Head and Neck Surgery Outpatient Clinics in China is relatively high, reaching up to 10.15%, and the prognosis of this disease is not optimistic (2). Older age, history of smoking and drinking are risk factors for LPRD. It manifests as chronic throat clearing, globus pharyngeus, hoarseness, throat swelling discomfort and recurrent pain and can even cause laryngeal cancer (3), thereby markedly affecting quality of life of patients (4). Owing to the complexity of symptoms and signs, varied pathological mechanisms and differential responses to treatments, broader therapeutic approaches are needed to improve patient outcomes (5).

Helicobacter pylori (HP) is a common pathogen associated with gastrointestinal diseases and is considered to be the most important risk factor for gastric cancer (GC) (6). The International Agency for Research on Cancer reported that H. pylori eradication could reduce the risk of developing GC (7). Studies suggest that HP exacerbates or induces extragastrointestinal diseases (8), including by colonising the extragastric mucosa to contribute to LPR (9). The present study was performed to investigate whether HP is a pathogenic factor in LPRD, identify the characteristic symptoms and signs of HP infection in patients with LPRD and evaluate the efficacy of anti-HP therapy in alleviating symptoms, with the aim of providing new insights into the clinical management of LPRD (10).

Materials and methods

Patient selection. From January 2023 to October 2024, 97 patients who received a diagnosis of LPRD based on the Reflux Symptom Index (RSI) and Reflux Finding Score (RFS) (11,12) at the Department of Otolaryngology, Shaanxi Provincial People's Hospital (Xi'an, China) were enrolled. The inclusion criteria were as follows: i) A diagnosis of reflux laryngitis on the basis of the RSI and/or RFS; ii) a symptom duration >1 month; and iii) age ≥18 years. The exclusion criteria were as

follows: i) A history of laryngopharyngeal trauma or systemic diseases; ii) HP treatment within 3 months prior to LPRD diagnosis; iii) proton pump inhibitor (PPI) treatment within 1 month of enrolment; and iv) laryngopharyngeal tumours. All participants provided written informed consent and the study was approved by the Ethics Committee of Shaanxi Provincial People's Hospital (approval no. 2023K-S181); the study protocol adhered to The Declaration of Helsinki.

Clinical assessment. The RSI includes the following nine items: Hoarseness or voice problems; throat clearing; excessive mucus or postnasal drip; difficulty swallowing food, liquids or pills; coughing after eating or lying down; breathing difficulties or choking episodes; sensation of a foreign body in the throat; heartburn; and stomach ache. Each item was scored from 0 (no symptoms) to 5 (most severe symptoms), with a total RSI score of 45. The RFS evaluated pseudosulcus vocalis, ventricular obliteration, erythema/hyperaemia, vocal cord oedema, diffuse laryngeal oedema, posterior commissure hypertrophy, granuloma and thick mucus, and each item in the scale was scored from 0 (no abnormality) to 26 (most severe). An RSI >13 and/or an RFS >7 indicated LPRD.

HP detection. All enrolled patients underwent local sampling using pharyngeal swabs. A sterile swab was vigorously rubbed back and forth at least three times on the surface of each of the pharyngeal tonsils. After collection, the tail of the swab was removed along the crease, and the head of the swab was placed in a sterile centrifuge tube for further use. The collected pharyngeal swabs were processed within 4 h using a Hi-Swab DNA Kit (Tiangen Biotech Co., Ltd.) to extract total DNA according to the manufacturer's instructions. HP was detected using the *Helicobacter pylori* SYBR qPCR Kit (cat. no. JN4360A; Shanghai Jining Biotechnology Co., Ltd.) for fluorescence-based quantitative PCR (qPCR). The PCRs were performed using a real-time fluorescence qPCR analyser (FQD-96C; Hangzhou Bioer Co., Ltd.). The amplification protocol was as follows: An initial denaturation step at 95˚C for 5 min, an annealing step at 95˚C for 15 sec and an extension step at 60˚C for 1 min; this process was repeated for a total of 40 cycles. Samples with a cut-off of ≥40 were considered negative, whereas those with a cut-off of ≤35 were considered positive.

Medication based on grouping. Patients were divided into two groups based on the HP detection results. Patients who were HP-negative were treated with a PPI (esomeprazole sodium enteric-coated tablets, 20 mg twice daily) for 2 weeks, whereas patients who were HP-positive were treated with anti-HP quadruple therapy (consisting of esomeprazole sodium enteric-coated tablets, 20 mg twice daily; clarithromycin tablets, 500 mg twice daily; amoxicillin capsules, 1 g twice daily; and bismuth potassium citrate capsules, 220 mg twice daily) for 2 weeks. In addition, all patients were required to follow the recommended lifestyle and dietary habits for 2 weeks of medication, including limiting the time of the last meal and avoiding alcohol, coffee, tea and sweets, and were subsequently required to continue to follow the recommended lifestyle and dietary habits for 1-2 months depending on the relief of symptoms. After 2 weeks, a senior physician who was blinded to the treatment groups uniformly followed up all patients either by outpatient visits or telephone for posttreatment evaluation.

Statistical analysis. SPSS 25.0 software (IBM Corp.) was used for statistical analysis. The normally distributed data are expressed mean ± SD and an independent sample student's t test was used for comparisons between groups. The non-normally distributed data are expressed as medians and quartiles (P25, P75), and the Wilcoxon paired-rank sum test was used for comparisons between groups. The count data are expressed as absolute values and relative frequencies, and a χ^2 test or a Fisher's exact test was used for comparisons between groups. Univariate logistic regression was used to calculate probabilities [odds ratio (OR)] and 95% confidence intervals to analyse risk factors for the disease. $P<0.05$ was considered to indicate statistically significant difference.

Results

General characteristics. No significant differences in age, height, weight, BMI or sex were observed between patients who were HP-positive (n=60) or HP-negative (n=37) (all $P>0.05$; Table I).

RSI and RFS comparison. Compared with patients who were HP-negative, the patients with HP-positive infection exhibited significantly greater rates of dysphagia (46.7 vs. 27.0%; $P=0.038$) and vocal cord oedema (58.3 vs. 35.1%; $P=0.026$). Further univariate logistic regression analysis revealed that the regression coefficient (OR) of dysphagia symptoms was 2.526 and that of vocal cord oedema was 2.585. These findings indicate that the risk of HP infection in patients with dysphagia or vocal cord oedema was 1.526 and 1.437 times greater, respectively (Table II).

Comparison of the RSI before and after treatment. RSI scores significantly improved in both groups after treatment, with a greater improvement in the HP-positive group ($Z=1.807$; $P=0.071$) compared with the HP-negative group (Table III).

Compared with patients who were HP-negative, the patients with HP-positive infection demonstrated greater improvements in throat clearing ($P=0.001$), excessive mucus ($P=0.008$), troublesome cough ($P=0.005$) and globus sensation ($P<0.001$). Moreover, the total RSI score in the HP-positive group was significantly lower compared with that in the HP-negative group ($Z=-4.12$; $P<0.001$) (Table IV).

Discussion

LPRD is characterised primarily by the reflux of gastric contents into the laryngopharyngeal region, leading to symptoms such as cough, throat clearing, hoarseness and phlegm production. Numerous patients with LPRD experience notable impairments in emotional, physical and social aspects of their quality of life (13). Owing to the diverse clinical manifestations and pathophysiological mechanisms of LPRD, there is considerable variability in symptom presentation and treatment efficacy (12). HP, a common pathogenic bacterium residing in the gastric mucosa, is known to cause excessive

Table I. General characteristic of patients with laryngopharyngeal reflux disease.

Characteristic	HP-positive (n=60)	HP-negative (n=37)	t/χ^2	P-value
Age, years	46.77±13.82	45.24±13.93	0.526	0.600
Height, m	1.68±0.09	1.66±0.09	0.845	0.401
Weight, kg	67.44±12.45	65.74±12.49	0.644	0.521
BMI, kg/m^2	23.72±3.32	23.90±3.44	0.241	0.810
Sex			0.005	0.945
Male	28	17		
Female	32	20		

HP, *Helicobacter pylori*; BMI, body mass index.

Table II. Comparison of Reflux Symptom Index and Reflux Finding Score between HP positive and negative in patients with LPRD.

	HP test					
LPRD symptoms and signs	Positive (n=60), n (%)	Negative (n=37), n (%)	χ^2	P-value	OR	95% CI
Hoarseness or a problem with voice	30 (50.0)	20 (54.1)	0.151	0.698	0.850	0.374-1.932
Throat clearing[a]	59 (93.3)	34 (91.9)	-	0.317	5.206	0.521-52.038
Excess throat mucous or postnasal drip	49 (81.7)	28 (75.7)	0.502	0.479	1.432	0.529-3.876
Difficulty swallowing food, liquids or pills	28 (46.7)	10 (27.0)	4.322	0.038	2.526	1.043-6.119
Coughing after you ate or after lying down	22 (36.7)	10 (27.0)	0.962	0.327	1.563	0.638-3.828
Breathing difficulties or choking episodes	19 (31.7)	12 (32.4)	0.006	0.937	0.965	0.402-2.321
Troublesome or annoying cough	27 (45.0)	19 (51.4)	0.370	0.543	0.775	0.341-1.762
Foreign body sensation in the throat[a]	57 (95.0)	33 (89.2)	-	0.699	2.303	0.485-10.928
Heartburn, chest pain, stomach ache	46 (76.7)	25 (67.6)	0.966	0.326	1.577	0.634-3.926
Sulcus of the false vocal folds[a]	11 (18.3)	4 (10.8)	-	0.571	1.852	0.543-6.314
Laryngeal ventricle disappears	31 (51.7)	14 (37.8)	1.760	0.185	1.756	0.762-4.049
Erythema/congestion[a]	58 (96.7)	37 (100.0)	-	0.503	0.000	0.000-∞
Vocal cord oedema	21 (35.0)	21 (56.8)	4.413	0.036	2.437	0.177-0.950
Diffuse laryngeal oedema	42 (70.0)	30 (81.8)	1.469	0.226	0.544	0.202-1.466
Posterior coalition hyperplasia[a]	55 (91.7)	37 (100.0)	-	0.157	0.000	0.000-∞
Granuloma[a]	7 (11.7)	5 (13.5)	-	0.770	0.854	0.247-2.888
Adhesion of thick mucus in the larynx	47 (78.3)	27 (73.0)	0.364	0.547	1.339	0.518-3.464

[a]Fisher's exact test. HP, *Helicobacter pylori*; LPRD, laryngopharyngeal reflux disease; CI, confidence interval; OR, odds ratio.

gastric acid secretion, leading to chronic gastritis, gastric ulcers, nausea, bloating and even gastric cancer. Extensive research has established a strong association between HP infection and various gastrointestinal diseases (14,15). Some scholars suggest that HP infection may exacerbate LPRD signs and symptoms (16), with HP colonisation in the extragastric mucosa potentially contributing to LPR (9). Tezer *et al* (17) discovered an association between HP positivity and LPRD; in addition, Siupsinskiene *et al* (18) reported a notable relationship between HP positivity and LPR-related signs such as vocal cord oedema, diffuse laryngeal oedema and posterior commissure hypertrophy. Furthermore, a 2008 clinical study revealed that HP eradication therapy markedly alleviated some symptoms in patient with LPRD (19). Therefore, it is crucial to identify which symptoms and/or signs may indicate HP infection in patients with LPRD and whether anti-HP therapy can improve symptoms and/or signs in these patients.

In the present study, 97 patients with LPRD were enrolled, and no significant differences in age, height, weight, BMI or sex were observed between patients who were HP-positive and HP-negative. However, a comparative analysis of the RSI and RFS revealed significant differences between patients with LPRD who were HP-positive and HP-negative in terms of dysphagia symptoms and vocal cord oedema signs. These findings align with those of studies by Shen *et al* (16), Siupsinskiene *et al* (18) and Bulmer *et al* (20),

Table III. Comparison of RSI scores in the two groups of patients with LPRD before and after treatment.

	HP-positive (n=60)				HP-negative (n=37)			
LPRD symptoms	Before	After	Z	P-value	Before	After	Z	P-value
Hoarseness or a problem with voice	0.5	0.0	4.500	<0.001	1.0	0.0	3.133	0.002
Clearing throat	5.0	2.0	6.406	<0.001	5.0	3.0	4.181	<0.001
Excess throat mucous or postnasal drip	3.0	0.0	5.953	<0.001	2.0	2.0	3.695	<0.001
Difficulty swallowing food, liquids or pills	0.0	0.0	4.696	<0.001	0.0	0.0	1.807	0.071
Coughing after eating or after lying down	0.0	0.0	4.001	<0.001	0.0	0.0	2.565	0.010
Breathing difficulties or choking episodes	0.0	0.0	3.767	<0.001	0.0	0.0	2.701	0.007
Troublesome or annoying cough	0.0	0.0	4.122	<0.001	0.0	0.0	3.111	0.002
Foreign body sensation in the throat	5.0	1.0	6.284	<0.001	5.0	3.0	3.959	<0.001
Heartburn, chest pain, stomach ache	3.0	0.0	5.746	<0.001	0.0	0.0	4.065	<0.001
RSI total score	19.0	6.0	6.733	<0.001	17.0	11.0	4.546	<0.001

HP, *Helicobacter pylori*; LPRD, laryngopharyngeal reflux disease; RSI, Reflux Symptom Index.

Table IV. Comparison of RSI between the two groups of patients with LPRD after treatment.

	HP test			
LPRD symptoms	Positive (n=60), %	Negative (n=37), %	Z	P-value
Hoarseness or a problem with voice	47.47	51.49	-0.83	0.407
Throat clearing	41.86	60.58	-3.24	0.001
Excess throat mucous or postnasal drip	43.43	58.03	-2.65	0.008
Difficulty swallowing food, liquids or pills	48.50	49.81	-0.31	0.760
Coughing after eating or after lying down	48.08	50.49	-0.60	0.555
Breathing difficulties or choking episodes	47.96	50.69	-0.79	0.433
Troublesome or annoying cough	44.04	57.04	-2.80	0.005
Foreign body sensation in the throat	41.15	61.73	-3.56	<0.001
Heartburn, chest pain, stomach ache	45.60	54.51	-1.84	0.066
RSI total score	39.78	63.95	-4.12	<0.001

HP, *Helicobacter pylori*; LPRD, laryngopharyngeal reflux disease; RSI, Reflux Symptom Index.

indicating an association between HP infection and LPRD, with HP infection potentially exacerbating the severity and progression of LPRD (21,22). The pathogenicity of HP may be related to inflammatory cytokines or oxidative stress responses (8), promoting disease onset and progression (23). The mechanism may involve HP-induced dysfunction of the oesophageal sphincter, exacerbating sphincter damage and leading to oesophagitis and oesophageal contraction disorders (24). Gastric acid reflux can injure the laryngopharyngeal mucosa (25), and HP infection may promote pharyngolaryngeal aggregation of activated pepsin from pharyngeal pepsinogen II, exacerbating pharyngeal infection (26). Gastric acid and pepsin stimulate the downregulation of CAIII in the vocal cord mucosa (columnar epithelium), making the vocal cords more susceptible to damage from reflux, further contributing to vocal cord oedema. Therefore, in clinical practice, patients with LPRD who present with dysphagia or vocal cord oedema on laryngoscopy should be suspected of having concurrent HP infection, and HP testing should be considered to facilitate targeted diagnostic and therapeutic approaches.

In the present study, after 2 weeks of treatment, all symptoms were significantly alleviated in the patients with HP-positive LPRD, compared with pretreatment. Patients with HP-negative LPRD also showed alleviation of most symptoms, except for difficulty swallowing food, liquids or pills. Owing to the inability of numerous patients to return for follow-up laryngoscopy, the evaluation of signs such as vocal cord oedema was limited. After treatment, compared with the HP-negative group, the HP-positive group demonstrated significantly greater improvement in total RSI scores, as well as in throat clearing, excessive pharyngeal mucus or postnasal drip, troublesome cough and globus sensation. These results are consistent with those of Shen *et al* (16), suggesting that HP eradication therapy is more effective compared with PPI therapy alone in improving RSI scores in patients with LPRD. Currently, PPI therapy is the mainstay of LPRD

treatment; however, patients with non-acid or mixed reflux may not respond to PPIs (27). Moreover, long-term use of PPIs may lead to side effects such as increased risk of intestinal infections, atrophic gastritis and impaired nutrient absorption, affecting multiple organ systems. Some of these risks are irreversible, thus requiring caution (28). Additionally, there is no standardised diagnostic or therapeutic approach for LPRD (10,29); therefore, the present study explored the use of targeted anti-HP quadruple therapy (PPI + bismuth compound + two different types of antibiotics) in patients with HP-positive LPRD, which resulted in considerable symptom relief and improved treatment efficacy. This approach offers a new therapeutic strategy for otolaryngologists in LPRD management and warrants further research and clinical application.

However, anti-HP therapy faces several challenges, including low gastric pH, high bacterial load, impaired mucosal immunity, poor patient compliance due to complex treatment regimens and the increasing prevalence of antibiotic resistance (30). Furthermore, the use of antimicrobial agents poses considerable safety concerns in children, pregnant women and elderly individuals and should be avoided (31,32). Therefore, selecting appropriate treatment regimens is crucial. In the present study, anti-HP therapy was administered only to patients with HP-positive LPRD, avoiding unnecessary treatment and ensuring more precise therapeutic interventions.

Additionally, conventional HP detection methods such as the C^{13}/C^{14} urea breath test (16), which primarily target gastric HP, were not suitable for the present research focused on pharyngeal infection. The current study employed qPCR analysis of pharyngeal swab samples for HP detection, which provides higher sensitivity and specificity in identifying this pathogen in the laryngopharyngeal region (21).

The present study has several limitations. First, the use of subjective assessment tools such as the RSI and RFS may introduce bias; second, the lack of a placebo control group limits the strength of the findings; third, the relatively small sample size may have introduced bias; and finally, the inability to perform follow-up laryngoscopy in numerous patients limited the comprehensive evaluation of posttreatment signs.

In summary, the present study demonstrated that HP serves a role in the pathogenesis and progression of LPRD. Clinicians should consider that the probability of HP infection in patients with LPRD is relatively high presenting with dysphagia and vocal cord oedema and implement appropriate diagnostic and therapeutic measures to improve the diagnosis and treatment outcomes of LPRD.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HZ and JW were responsible for study conception and design. HZ, HD and JW wrote and edited the main manuscript. HZ, HD, XW, YZ and JW performed data analysis and prepared the tables. JW supervised the project, and reviewed and revised the manuscript. HD and JW confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethical approval and consent to participate

The present study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Shaanxi Provincial People's Hospital in China (approval no. 2023K-S181). Written informed consent to participate the study was obtained from each patient.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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