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Original article

Post treatment improvement of laryngopharyngeal reflux diagnosed using a novel algorithm: A cohort study

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Abstract. *Purpose:* To compare pre- and post-treatment measurements in patients diagnosed with laryngopharyngeal reflux (LPR), and to compare patients with gastroesophageal reflux disorder (GERD) who exhibit symptoms of laryngopharyngeal reflux to those who do not, using a combined algorithm. *Methods:* This prospective cohort study involved 384 patients and used the following algorithm: a Reflux Symptom Index (RSI) questionnaire score of >13, videolaryngostroboscopy with an assessment of the Reflux Finding Score (RFS) >7, pH strips of mucus from the laryngopharynx, and acoustic analysis of the voice in singers with voice disorders. Patients with LPR and GERD were treated with proton pump inhibitors at a dose of 20 mg twice a day and were given lifestyle and dietary changes recommendations for one month. The patients were monitored for six months. *Results:* After treatment, RSI and RFS results in patients with LPR and GERD significantly improved from 19.9±6.4 & 9.1±1.7 and 18.7±5.3 & 10.10±2.4 respectively ($p<0.001$). In patients without the symptoms of LPR, the laryngopharyngeal medium pH ranged from min 5.5 to max 7.5, and in cases of suspected LPR and GERD, it ranged from min 5 to max 8 and min and 4.5 to max 8.5 respectively. The acoustic voice analysis scores changed after therapy, p-value<0.05. *Conclusion:* The lack of a gold standard and the inaccessibility of diagnostic methods make LPR diagnosis a very complex task. However, using the proposed diagnostic algorithm, the post treatment scores were improved. More studies are needed to validate the algorithm for early diagnosis of LPR. (www.actabiomedica.it)

Key words: laryngopharyngeal reflux, reflux symptom index, reflux finding score, acoustic voice analysis, pH indicator

Introduction

The term laryngopharyngeal reflux (LPR) refers to an inflammatory state of the tissues of the upper respiratory tract that results in morphological changes and involves both direct and indirect effects of reflux of gastroduodenal contents (1). A distinction between LPR and gastroesophageal reflux disease (GERD) is that patients with GERD have pathology and dysfunction of the lower esophageal sphincter, whereas those with LPR have a dysfunction of the upper esophageal sphincter (2).

An analysis of the literature conducted by researchers in Europe, the United States of America (USA), and South Korea found that LPR symptoms affect 4-10% of outpatient otolaryngology and head and neck surgery patients (3), and up to 50% of laryngology patients (4). There is no data on the prevalence

of LFR in Kazakhstan, but the prevalence of GERD was found to be 40.5% in the city of Aktobe during the survey of 1140 adults who had heartburn as the main symptom (5). Aktobe residents also had a true prevalence of 17.6% for GERD (5). A further source claims that LFR affects 10% of patients undergoing treatment in otolaryngology, more than 50% of patients suffering from voice disorders in the USA and it is unknown how prevalent LFR disease is in Europe (6, 3). There is a high economic and social burden associated with LPR and its complications in the USA, where initial assessment and treatment cost an average of $5,438 for each patient. As a result of LPR in the USA, there are $50 billion in annual costs, five times the cost of GERD. There are several factors that contribute to the higher healthcare burden associated with LPR, including testing delays, ineffective treatments, and the widespread use of proton pump inhibitors (PPIs) (7). According to existing data, there are various consequences of LPR: scar of the vocal folds, Barrett's esophagitis that leads to long-term damage to the vocal cords (8) and contributes to the development of tumor-like laryngopharyngeal diseases (9), a subsequent formation of nodules, polyps, Reinke's edema (10), leukoplakia, and carcinoma of the vocal cords (11, 12). According to one study, gastric proton pump acid secretion, expressed in the laryngeal mucosa, may induce mitochondrial damage and gene expression changes associated with inflammation and cancer in the local cells (13).

Researchers identified different causes of reflux in the study: dysfunction of the stomach wall and protective structure, which leads to reflux of stomach contents; also, it was found that obstructive sleep apnea syndrome may be one of the causes of LPR (14). When the esophagus is overloaded with acid, high negative chest pressure can hinder the discharge of reflux and cause gastric reflux (8). Eating unhealthy foods, depression, stress (9), cigarette smoking and alcohol consumption, among other factors, can all contribute to reflux (6).

LPR symptoms can manifest in a wide range of ways in the head and neck region, such as voice changes, chronic cough, pharyngeal globus, hoarseness, and postnasal drip (6). An experiment found pepsin in the tear ducts when hypopharyngeal-nasal gas refluxed (15). There is a possibility of LPR in patients with demineralization and caries in the oral cavity (16). In one case series study, the authors report atypical manifestations of LPR in patients, such as recurrent aphthosis or burning in the mouth, recurrent belching and abdominal disorders, posterior nasal congestion, recurrent acute suppurative otitis media, severe vocal cord involvement, dysplasia, and recurrent acute nasopharyngitis, lacrimation, aspiration or tracheobronchitis (17).

As pointed out by the authors, excessive treatment and delayed diagnosis are the primary problems with LPR (18). In a survey involving 824 otolaryngologists from 65 countries, only 21.1% were aware that non-acidic LPR exists and 43.2% of them were satisfied with their knowledge of LPR. This study concluded that it would be beneficial to have international guidelines for defining, diagnosing, and treating LPR to improve knowledge and treatment throughout the world (19).

Early diagnosis of LPR can help to prevent or reduce the complications of LPR. Therefore, we attempted to develop a unified algorithm for diagnosis during outpatient appointments that includes: the reflux symptom index (RSI) questionnaire score of >13; videolaryngastroboscopy with the assessment of the reflux finding score (RFS)>7; pH-strips of mucus from the laryngopharynx; acoustic analysis of the voice of singers with voice disorders. This algorithm could be beneficial in settings with limited resources and low awareness (lack of daily pH-metry, impedancemetry, endoscopic laryngoscopy; lack of specialists; poor awareness of specialists about LPR).

The aim of this study was to assess pre- and post-treatment measurements in patients with LPR, who were diagnosed following our proposed algorithm, and GERD, and to compare the clinical RSI and RFS measurements in patients with LPR and GERD before treatment.

Methods

The study included 384 patients and was conducted between January 2021 and February 2022 in a specialized outpatient otorhinolaryngology medical

center of Almaty city. A Local Ethics Committee of the Asfendiyarov Kazakh National Medical University approved the study (Study ID: 1399). The study has been registered with the Clinical Trials Registry (Study ID: NCT04771221). All participants provided written informed consent for the study. The main group consisted of patients who complained of sore throat, cough, burning sensation, frequent sore throat, difficulty swallowing, lump in the throat, the sensation of a foreign body in the throat, voice change, heartburn, and belching but were not diagnosed with LPR and/or GERD before; the control group consisted of patients with early diagnosis of GERD; and the patients without the above complaints or prior diagnosis of LPR and/or GERD were included to the third group. The criteria for inclusion in the study were: filling in the informed consent of the patient, age from 18 to 74 years, without severe somatic diseases, and for the main group and patients with GERD complaints of sore throat, cough, burning sensation in the throat, cough, frequent pain in the throat, difficulty swallowing, lump in the throat, the sensation of a foreign body in the throat, voice change, heartburn, and belching. The following criteria for exclusion were used: absence of consent to participate in a scientific study, age under 18, severe somatic disorders, organic gastrointestinal and ENT lesions, pulmonary pathologies, allergic manifestations of respiratory diseases (seasonal hay fever, bronchial asthma, etc.), acute respiratory diseases and neurologic disorders in general. RSI questionnaires were completed by patients and doctors together. Belafsky and coauthors originally developed the RFS and RSI questionnaires (20, 21). The Kazakh version of the RSI was translated and validated by the authors (22). An item's RSI score can vary from 0 (no problems) to 5 (severe problems), with a maximum total score of 45. In patients with LPR and GERD, the condition of the larynx was assessed using rigid endoscopic laryngoscopy and video laryngstroboscopy with a diameter of 5.0 mm, a viewing angle of 90°, and a working length of 158 mm of the ENT combine (Heinemann, Xion, Germany). It was confirmed that there were no additional features of the larynx, such as nodules, polyp, and dysplasia, which could cause a change in the voice. There was a range of RFS scores from 0 (normal larynx) up to 26 (exceptional larynx). Patients without LPR symptoms were not evaluated using laryngoscopy due to their lack of complaints. In patients with an RSI score of > 13 and an RFS score of > 7, LPR was suspected.

Monitoring of daily pH was not carried out due to the lack of this equipment. Instead, all participants had their hypopharyngeal mucus pH measured using pH strips on an empty stomach or 2 hours after eating. LPR patients with voice professions and voice impairments were analyzed using the LingWAVES program for acoustic voice analysis. Acoustic analysis of the voice was based on the following indicators: optimal shimmer (amplitude variations during normal speaking conditions), quiet shimmer (amplitude variations during soft speaking conditions), loud shimmer (amplitude variations during loud speaking conditions), optimal jitter (frequency variations during normal speaking conditions), quiet jitter (frequency variations during soft speaking conditions), loud jitter (frequency variations during loud speaking conditions), Dysphonia Severity Index (DSI) (overall assessment of voice quality), and norm profile coverage (the extent to which the patient's voice parameters fall within the normal range for a healthy voice). Patients with voice professions who had symptoms of LPR and a diagnosed voice impairment accounted for 20 patients in the group.

Patients who had LPR or GERD were prescribed PPIs at a dose of 20 mg twice daily (omeprazole or pantoprazole). Alongside medication, patients received detailed lifestyle and dietary recommendations. Specifically, they were advised to follow a low-fat, low-quick-release sugar, high-protein, alkaline, and plant-based diet for 6 to 12 weeks (1). Recommendations also included avoiding late meals, reducing caffeine and alcohol intake, and elevating the head of the bed during sleep (3). Patients with voice impairments were additionally recommended voice therapy (18). A month later, the initial indicators were reassessed. If the following criteria were met—Reflux Symptom Index (RSI) score below 13, Reflux Finding Score (RFS) below 7, pH measures between 6.5-7.5, and improvements in acoustic voice analysis parameters—PPIs were discontinued. Patients were then advised to continue with dietary and lifestyle modifications. When the criteria were not fully met, the therapeutic regimen

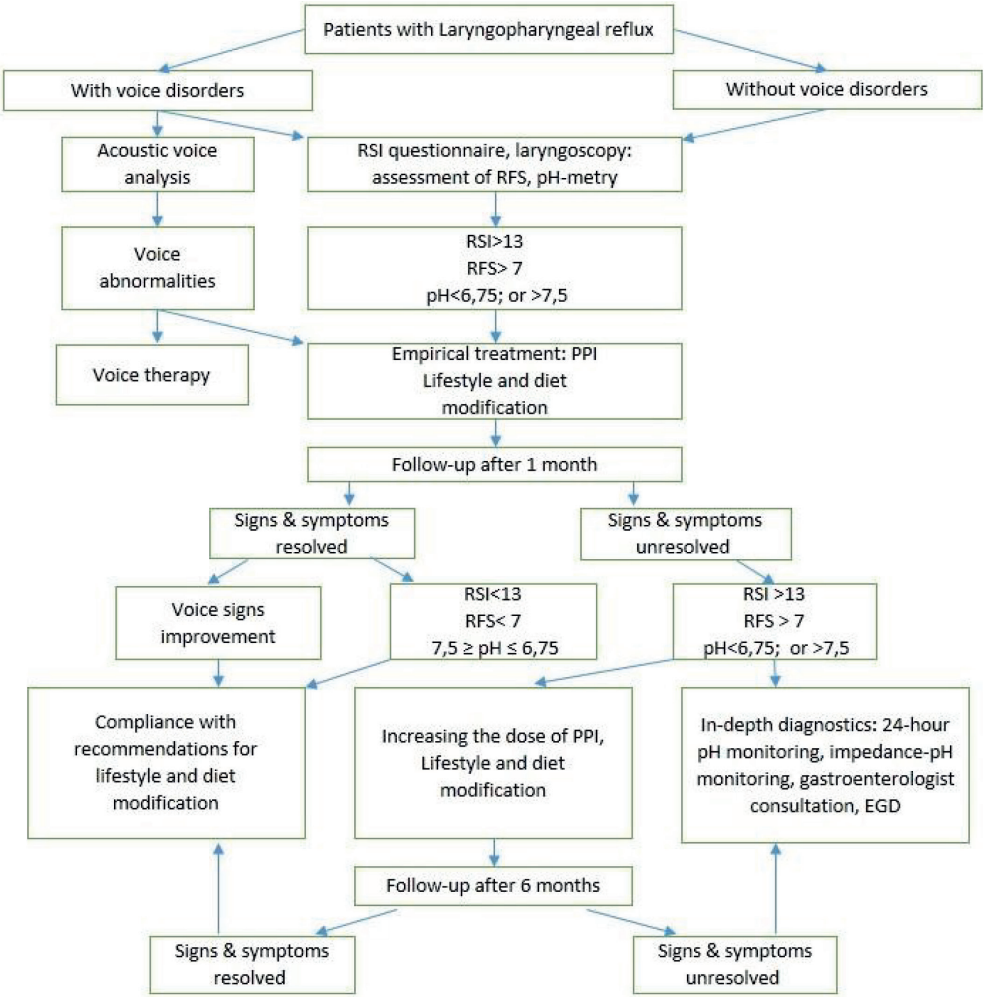

Figure 1. Proposed LPR diagnosis algorithm.

Abbreviations: RSI = reflux symptoms index; RFS = reflux finding score; PPI = proton pump inhibitor; EGD = esogastroduodenoscopy.

was extended up to 6 months. In cases where no improvement was observed, further research and specialist consultations were considered (Figure 1). In cases where no improvement was observed, further research and specialist consultations were considered.

Statistical methods

The statistical analysis was performed with SPSS software (version 25, Inc., Chicago, Illinois). To represent the clinical and epidemiological data of patients, mean and standard deviation for continuous data, and frequency with percentage for discrete data were calculated.

For testing the null hypothesis, we used the paired t-test to calculate the average of the differences between paired observations. First, we compared pre- and post-treatment results in each group to assess effectiveness of the treatment when LPR is diagnosed.

Secondly, we compared clinical measurements between LPR and GERD patients before the treatment to identify meaningful parameters in diagnostic methods that will help diagnose LPR in a timely manner. Statistical significance was determined at the p-value of <0.05.

Results

Study population/Demographics

The study included 3 groups of patients: patients with LPR (149 patients), patients with GERD (86 patients), and patients without symptoms of LPR (WSLPR) (149 patients). All clinical and epidemiological data are shown in Table 1.

The clinical measurements of three patient groups before and after treatment

There was a significant difference between pretreatment and post-treatment values for the RSI total score, RFS total score, and pH values in the LPR and GERD groups after implementation of the proposed diagnostic algorithm and treatment (Table 2). WSLPR group patients had a lower than 13 RSI. In patients with LPR and GERD before treatment, RSI was higher than 13 in all, RFS was higher than 7, pH index in the LFR group was 94%, GERD 96.5%, WSLPR 4% acidic, neutral in patients with LPR 2.7%, WSLPR 97.3% and in the GERD group was not observed, and an alkaline was detected in both LPR and GERD, between 3.3 and 3.5%, but no alkaline was detected in the WSLPR group.

There was no treatment for the WSLPR group.

There was a significant difference between pretreatment and post-treatment values for all RSI and RFS indicators in the LPR group, but not for the "Cough after eating or lying position" and "Dyspnea or breathing difficulties" RSI indicators and "Diffuse laryngeal edema", "Granulation", "Thick endolaryngeal mucus" RFS indicators in the GERD group (Table 3).

Pre- and post-treatment comparison of acoustic voice analysis data of LPR patients shows that almost all parameters except quiet jitter were statistically different after treatment (Table 4).

Between group comparison of the RSI and RFS parameters at the baseline

Almost all clinical parameters in the RSI questionnaire for the LPR and GERD groups did not have a statistically significant difference, except for the "Dyspnea or breathing difficulties" symptom. For the RFS score the following parameters had a statistically significant difference: "Ventricular obliteration", "Diffuse laryngeal edema", "Posterior commissure hypertrophy" and "Granulation" (Table 5).

Table 1. Epidemiological and Clinical Characteristics of Patients.

Characteristics	LPR	GERD	WSLPR
Mean age (SD)	41.9±14.4	41.5±15.7	35.9±11.2
Gender (N, %)			
Male	38 (25.5)	35 (40.7)	42 (28.2)
Female	111 (74.5)	51 (59.3)	107 (71.8)
Smoking (N, %)			
Yes	63 (42.3)	64 (74.4)	27 (18.2)
No	86 (57.7)	22 (25.6)	122 (81.9)
Alcohol (N, %)			
Yes	67 (45.0)	47 (54,7)	17(11,4)
No	82 (55.0)	39 (45,3)	132(88,6)
ENT disease (N, %)			
Yes	109 (73.2)	74 (86)	96(64.4)
No	40 (26.8)	12 (14)	53(35.6)
GIT disease (N, %)			
Yes	77 (51.7)	85 (99)	42 (28.2)
No	72 (48.3)	1 (1)	107 (71.8)

Abbreviations: ENT = ear, nose, and throat; GERD = gastroesophageal reflux disease; GIT = gastrointestinal tract; LPR = laryngopharyngeal reflux; RSI = reflux symptoms index, RFS = reflux finding score; SD = standard deviation; WSLPR = without symptoms of LPR.

Discussion

The main findings of our study are:

1. Algorithm Effectiveness: The combined use of the RSI questionnaire (score >13), videolaryngostroboscopy with RFS assessment (score >7), pH-strips of mucus from the laryngopharynx, and acoustic voice analysis can detect LPR early and prevent complications.
2. RSI Measures: Statistically significant differences ($p<0.05$) were found between the LPR and GERD groups for RSI measures.

Table 2. Comparison of pretreatment and post-treatment clinical indicators among different groups

	Pretreatment			Posttreatment		Diff	
	LPR mean±SD	**GERD mean±SD**	**WSLPR mean±SD**	**LPR mean±SD**	**GERD mean±SD**	**LPR mean±SD (95% CI)**	**GERD mean±SD (95% CI)**
RSI	19.88±6.42	18.72±5.35	4.38±3.29	5.99±3.66	6.40±2.74	-1.39±5.09 (-14.72;-13.07)**	-1.23±5.92 (-13.59;-11.06)*
RFS	9.06±1.72	9.93±2.36	-	3.25±1.42	3.59±1.38	-5.81±1.67 (-6.08;-5.54)**	-6.34±2.77 (-6.93;-5.74)**
pH 4.5-6.25 (%)	93.96%	96.51%	4.06%	0.67%	0	-	-
pH 6.5-7.5 (%)	2.68%	0	97.31%	99.33%	100%	-	-
pH 8.0-8.5 (%)	3.36%	3.49%	0	0	0	-	-
mean±SD	5.71±0.54	5.69±0.62	6.83±0.28	6.85±0.24	6.83±0.20	1.14±0.50 (1.06;1.22)**	1.13±0.63 (1.01;-1.27)**

Abbreviations: GERD = gastroesophageal reflux disease; LPR = laryngopharyngeal reflux; WSLPR = without symptoms of LPR. p<0.001**

3. RFS Measures: Statistically significant differences (p<0.05) were found between the LPR and GERD groups for RFS measures.
4. pH Values Comparison: Comparison of pH values before and after treatment in LPR and GERD groups, as well as a control group without LPR symptoms.
5. Acoustic Measurements: Analysis of pretreatment and posttreatment acoustic measurements in LPR patients with voice disorders.

There are several benefits to using the RSI questionnaire. In addition to being simple and affordable, the RSI questionnaire is an effective way to diagnose LPR at an early stage. General practitioners, along with otorhinolaryngologists, can use it to identify symptoms that patients do not immediately recall. Because RSI is assessed on a 5-point scale, some patients may underestimate or overestimate their symptoms. The best results are achieved when patients complete the questionnaire together with their otorhinolaryngologist. The RSI questionnaire has been translated, adapted, and validated in many languages to detect LPR symptoms and evaluate treatment effectiveness. The Kazakh version of RSI has shown high test-retest reliability and good clinical validity (22). In our study, both in the LPR group and in the GERD group, before treatment, the RSI was above 13 and RFS was above 7. Posttreatment, those indicators improved. Statistically significant mean differences (p<0.05) of the RSI measures between the LPR and GERD were cough after eating or lying position, dyspnea or breathing difficulties, cough, and heartburn/chest pain.

It has been suggested that RFS may not be specific and that laryngeal signs may not be used to detect reflux changes in many situations (e.g., in smokers, after upper respiratory tract infection, etc.) (23). Another study found that the presence of LPR was associated with smoking and other causes (20). In our study, 42.3% of LPR patients and 74.4% of GERD patients smoked. For those patients, cessation of smoking was recommended. Considering those patients with LPR and GERD had more health-risk behaviors than patients in the WSLPR group, it can be confirmed that smoking and alcohol, as found in other studies, were associated with LPR. The majority of LPR and GERD patients had chronic ENT diseases, as did the WSLPR patients. Half of the patients with LPR had GIT problems. Among GERD patients, only one patient denied the presence of chronic pathologies with the GIT, and among WSLPR patients, only 28.2% noted the presence of problems with the GIT. These

Table 3. Reflux Symptoms Index and Reflux Finding Score Changes (symptom scores are represented with mean ± standard deviation)

	Pre-treatment		Post-treatment		Diff	
	LPR mean±SD	**GERD mean±SD**	**LPR mean±SD**	**GERD mean±SD**	**LPR mean±SD (95% CI)**	**GERD mean±SD (95% CI)**
Reflux Symptoms Index						
1. Voice disorder	2.46±1.65	2.52±1.96	0.38±0.67	0.17±0.49	-2.09 ± 1.6 (-2.35; -1.82)**	-2.35 ± 1.99 (-2.78; -1.92)**
2. Throat clearing	3.34±1.32	3.58±1.60	1.08±1.03	1.01±1.06	-2.26±1.63 (-2.53; -2.00)**	-2.57±1.79 (-2.95; -2.18)**
3. Flowing mucus into throat	2.96±1.66	2.65±1.84	1.18±1.07	1.48±1.10	-1.78±1.87 (-2.08; -1.47)**	-1.17±2.02 (-1.61; -0.74)**
4. Difficulty swallowing	1.59±1.60	1.85±1.55	0.69±0.85	1.03±0.98	-0.90±1.54 (-1.15; -0.65)**	-0.81±1.91 (-1.22; -0.41)**
5. Cough after eating or lying position	1.66±1.50	1.13±1.23	0.60±0.80	0.86±0.94	-1.07± 1.55 (-1.32; -0.82)**	-0.27± 1.59 (-0.61; -0.07)
6. Dyspnea or breathing difficulties	1.62±1.54	0.57±1.00	0.39±0.66	0.43±0.69	-1.23±1.53 (-1.48; -0.98)**	-0.14±1.15 (-0.38; -0.11)
7. Cough	1.30±1.44	0.85±1.10	0.29±0.55	0.47±0.81	-1.01±1.40 (-1.24; -0.79)**	-0.38±1.41 (-0.69; -0.08)*
8. Globus sensation	2.63±1.73	2.26±1.77	0.87±1.04	0.63±0.12	-1.76±1.81 (-2.05; -1.47)**	-1.63±1.90 (-2.04; -1.22)**
9. Heartburn, chest pain	1.79±1.69	3.30±1.80	0.59±0.96	0.43±0.95	-1.20±1.90 (-1.50; -0.89)**	-2.87±1.81 (-3.26; -2.48)**
Reflux Finding Score						
Subglottic edema	0.78±0.97	0.86±0.10	0.00±0.00	0.00±0.00	-1.78±0.97 (-0.94; -0.62)**	-0.86±0.10 (-1.07; -0.65)**
Ventricular obliteration	0.68±0.95	1.70±0.78	0.36±0.77	0.41±0.82	-0.32±1.23 (0.52; -0.12)*	-1.28±1.30 (-1.56; -1.00)**
Diffuse hyperemia/erythema	2.40±0.10	2.32±0.74	0.48±0.83	0.31±0.72	-1.92 ± 1.21 (-2.11; -1.72)**	-2.01 ± 0.10 (-2.20; -1.82)**
Vocal fold edema	1.46±0.71	1.47±0.59	0.56±0.60	0.62±0.74	-0.90±0.07 (-1.04; -1.76)**	-0.85±0.93 (-1.05; -0.65)**
Diffuse laryngeal edema	1.43±0.58	1.16±0.78	0.66±0.53	1.09±0.76	-0.77±0.81 (-0.90; -0.64)**	-0.07±1.11 (-0.31; -0.17)
Posterior commissure hypertrophy	1.89±0.50	2.15±0.54	0.89±0.67	1.07±0.79	-0.99±0.72 (-1.11; -1.87)**	-1.08±1.04 (-1.30; -0.86)**
Granulation	0.28±0.70	0.09±0.42	0.0±0.00	0.05±0.30	-0.29±1.23 (-0.55; -0.13)*	-0.05±0.53 (-0.16; -0.07)
Thick endolaryngeal mucus	0.19±0.59	0.08±0.38	0.00±0.00	0.0±0.00	-0.19±0.05 (-0.28; 0.09)**	-0.08±0.38 (-0.16; 0.00)

*p<0.05; **p<0.005
Abbreviations: CI = confidence interval; Diff. = mean difference; GERD = gastroesophageal reflux disease; LPR = laryngopharyngeal reflux; SD = standard deviation.

Table 4. Pretreatment and Posttreatment Acoustic Measurements of LPR patients with voice disorders.

Parameters	Pretreatment			Posttreatment			Diff.±SD (95%CI)
	Mean±SD	Minimum - Maximum	Range	Mean±SD	Minimum - Maximum	Range	
Optimal shimmer	39.00±1.89	36.05-42.04	5.99	26.97±2.61	24.41-31.82	7.41	1.02±2.12 (11.04; 13.02)*
Quiet shimmer	18.92±3.05	11.68-25.13	13.45	5.51±1.71	3.75-9.81	6.06	1.34±3.31 (11.86; 14.95)*
Loud shimmer	59.68±7.03	31.17-65.24	34.07	72.74±10.30	57.17-96.2	39.03	-1.31±12.41 (-18.86; -7.25)*
Optimal jitter	4.10±0.56	2.79-4.78	1.99	5.41±0.55	4.8-6.8	2	-1.30±0.49 (-1.53;-1.08)*
Quiet jitter	0.71±2.06	0.15-9.41	9.26	0.16±0.25	0.04-1.14	1.1	0.55±2.04 (-0.4;1.50)
Loud jitter	17.08±1.57	10.7-18.12	7.42	21.44±1.90	19.01-24.85	5.84	-4.36±2.33 (-5.45;-3.26)*
DSI	3.44±0.59	2.1-4.1	2	5.04±0.46	4.4-5.7	1.3	-1.60±0.78 (-1.96;-1.23)*
Norm profile coverage	2.45±1.19	1-5	4	15.4±3.68	10-23	13	-1.30±3.20 (-14.45;-11.45)*

*$p<0.05$
Abbreviations: SD = standard deviation, DSI = dysphonia severity index. Diff = difference, CI = confidence interval.

findings suggest that GIT pathologies are not always the cause of LPR. Research has shown that RFS can discriminate individuals with pH-confirmed pharyngeal reflux with a sensitivity of 87.8% and a specificity of 37.5%, respectively (24). The prevalence of pseudosulcus, interarytenoid thickening, and Reinke's edema was higher in patients with LPR symptoms as opposed to those without (24). In other studies, arytenoid erythema and/or edema were used to indicate LPR in 72% of patients with physical findings, while mucosal hypertrophy of the posterior larynx was demonstrated in 64% of participants, which were typically relied upon for clinical diagnosis (25). Statistically significant mean differences ($p<0.05$) in our study between the LPR and GERD groups were for the following RFS measures: ventricular obliteration, diffuse laryngeal edema, posterior commissure hypertrophy, and granulation. Physicians should exercise caution in establishing a causal relationship between changes in the larynx and a patient's vocal complaints. By using multiple mucous membrane signs, reflux patients can be detected more accurately using laryngoscopy. LPR is more difficult to diagnose than typical GERD due to the absence of specific symptoms like heartburn and regurgitation, and the variety of clinical manifestations (9). There are various pH-metry assessment methods such as multichannel intraluminal impedance combined with pH-metry (MII-pH) or hypopharyngeal-esophageal intraluminal impedance pH (HEMI-pH) that are very sophisticated to perform during a routine visit to an otorhinolaryngologist (26, 27).

In our study, we determined the pH of the larynx using pH-sensitive litmus paper. Direct acid exposure to the laryngeal mucosa damages its epithelium, which usually occurs in the esophagus, but in the larynx, acid can only come from the esophagus. Epithelial cilia are difficult to move at pH 5.0, and they are absent at pH 2.0 (2). This is confirmed in our study by the fact that chronic ENT disease associated with chronic foci of infection is often found in patients with LPR (73.2%) and GERD (86%). Moreover, otorhinolaryngologists should consider the importance of suppressing acidity from the GIT in the treatment of chronic ENT diseases. The treatment of reflux should also aim

Table 5. Reflux Symptoms Index and Reflux Finding Score Changes. Symptom scores are represented with mean ± standard deviation

	LPR	GERD	Diff. (95 CI)
Reflux Symptoms Index			
1. Voice disorder	2.46±1.65	2.5±1.95	0.06 (-0.41; 0.53)
2. Throat clearing	3.34±1.32	3.58±1.60	0.24 (-0.14; 0.62)
3. Flowing mucus into throat	2.96±1.66	2.65±1.84	-0.31 (-0.77; 0.15)
4. Difficulty swallowing	1.59±1.60	1.85±1.55	0.26 (-0.16; 0.68)
5. Cough after eating or lying position	1.66±1.50	1.13±1.23	-0.53 (-0.90; -0.16)*
6. Dyspnea or breathing difficulties	1.61±1.54	0.57±1.00	-1.15 (-1.31; -1.08)**
7. Cough	1.30±1.44	0.85±1.10	-0.45 (-0.81; -0.10)*
8. Globus sensation	2.63±1.73	2.26±1.78	-0.38 (-0.84; 0.09)
9. Heartburn, chest pain	1.78±1.70	3.30±1.80	1.52 (1.06; 1.99)**
Reflux Finding Score			
Subglottic edema	0.78±0.97	0.86±0.10	0.08 (-0.18; 0.34)
Ventricular obliteration	0.68±0.95	1.70±0.78	1.10 (1.07; 1.25)**
Diffuse hyperemia/erythema	0.40±0.10	2.32±0.74	-0.07 (-0.31; 0.17)
Vocal fold edema	1.46±0.71	1.47±0.59	0.01 (-0.17; 0.19)
Diffuse laryngeal edema	1.43±0.58	1.16±0.78	-0.27 (-0.44; -0.09)**
Posterior commissure hypertrophy	1.89±0.50	2.15±0.54	0.27 (0.13; 0.40)**
Granulation	0.28±0.70	0.09±0.42	-0.19 (-0.35; -0.03)**
Thick endolaryngeal mucus	0.19±0.59	0.08±0.38	-0.11 (-0.25; 0.03)

*p<0.05; **p<0.005
Abbreviations: CI = confidence interval; Diff. = mean difference; GERD = gastroesophageal reflux disease; LPR = laryngopharyngeal reflux; NS = nonsignificant.

at preserving the buffering ability and pH of saliva by correcting changes in saliva to avoid the destruction of the oral mucosa and teeth (16). In a study comparing litmus paper and intragastric pH sensors, it was found that there was a good correlation between the two pH measurements (r2 = 0.93, p < 0.001) (28). Based on this, it can be concluded that the determination of intragastric pH using pH-sensitive litmus paper is both sensitive and specific when using a nasogastric pH probe as a reference (28). In patients with a high probability of stress gastric ulcers, this method (testing the pH of gastric juice using a pH indicator) is easy, cheap, and reliable (28). A separate study has found that saliva tests (saliva pH, pepsin content, bile acids) perform better than RSI questionnaires and RFS scales in diagnosing LPR in patients with recurrent respiratory papillomatosis (29). In a study examining salivary pepsin testing at optimal times, the results showed that testing at waking up, one to two hours after breakfast and lunch, and one hour after dinner can help identify LPR (13). As a result, in our study, we sampled mucus from participants on an empty stomach or one and two hours after eating. The physiological pH for the oral cavity and upper respiratory tract is 6.4-7.2 (30). In our study, in WSLPR patients, the pH of the pharyngeal mucus was in the range of 6.5-7.5. In patients with LPR and GERD, more acidic than alkaline pH was determined pretreatment, and posttreatment the pH changed closer to the physiological norm. For patients with voice professions and voice disorders, we conducted an acoustic analysis of the voice using the LingWAVES registration program, which is considered the gold standard in other studies (31). Acoustic voice analysis in patients with LPR revealed that objective LPR patients had significantly higher frequency perturbations than subjective patients with LPR and

those without LPR symptoms on all four frequency perturbation measures (local jitter, absolute jitter, jitter rap, and ppq jitter) (32). Another study concluded that patients with functional dysphonia could be identified through a two-parameter panel (jitter and shimmer) of acoustic analysis (33). The reflux symptom index was significantly correlated with jitter; jitter and shimmer improved during the first 2 months of treatment and continued to improve for 3–4 months after treatment. Acoustic parameters were found to be effective indicators of laryngopharyngeal reflux disease treatment (34). There is a consistent correlation between improvements in voice quality and the treatment of LPR patients. An objective and quantitative correlation of perceived vocal quality is established using the dysphonia severity index (DSI), where a DSI of -5 indicates strongly dysphonic voices, and +5 indicates perceptually normal voices (35). The worse the patient's voice data, the lower their index, making DSI beneficial for assessing therapeutic progress in dysphonia patients. Despite this, we recommend carefully comparing our results with those in the literature, as there are many different approaches to calculating acoustic parameters. Acoustic measurement results are affected by the software used, the algorithms employed, the type of vowel recorded, the duration of the analyzed segment, and the method used to select the interval (36). In our study, we assessed the improvement of the condition and the effect of treatment using indicators such as optimal shimmer, quiet shimmer, loud shimmer, optimal jitter, quiet jitter, loud jitter, DSI, and norm profile coverage, all of which showed improvement after therapy.

We recommended voice therapy to patients with LPR who had voice changes in addition to the main treatment, helping to restore reversible mucosal changes caused by acid reflux and shorten treatment time (37).

The data obtained indicates that the methods used to diagnose LPR vary greatly. LPR symptoms have low specificity, and many results go unnoticed; there is no gold standard for diagnosis according to a systematic review of 1,227 articles involving 4,735 patients with LPR and tools for assessing clinical manifestations (26). Due to inadequate early diagnosis and a lack of epidemiological studies in the general population, the actual incidence and prevalence of LPR remain unclear (38). Doctors need a thorough understanding of modern views on LPR, current patient care standards, and the need for more interdisciplinary research to prevent complications resulting from the high prevalence of LPR and its potentially serious consequences (including laryngeal cancer) (39).

Empirical treatment trials and objective reflux testing are the two main diagnostic approaches. A 2-month empirical testing regimen of proton pump inhibitors (PPIs) can be convenient but may lead to overtreatment and delayed diagnosis if the patient's symptoms are not related to LPR. In their conclusion, the authors emphasize that non-reflux etiologies must be assessed, including laryngoscopy or videostroboscopy. If an objective diagnosis is desired or the patient's symptoms do not respond to empirical treatment, pH-metry with or without impedance should be used (18). Clinics focus mainly on medical and surgical treatment, while simultaneously.

A PPI test detects acid-associated disorders by assessing the relief of symptoms after PPI administration, which can be used to differentiate acid-associated disorders from GERD, non-esophageal GERD, or functional dyspepsia (40). This test reduces gastric juice secretion, decreases pepsin activity, and blocks the inflammatory response, thereby minimizing direct damage to the throat by inhibiting H+-K+-ATPase on stomach wall cells (41). Despite the effectiveness of PPIs in treating LPR, as shown in numerous clinical studies, some adverse reactions necessitate a prolonged treatment cycle (42). To optimize patient management, medication should be administered at the lowest effective dose, and other medications should be adjusted to minimize adverse interactions (2). Studies indicate that LPR symptoms are more effectively treated with PPIs administered twice daily rather than once daily (26). However, the long-term use of PPIs has been associated with increased risks of gastrointestinal infections, pneumonia, Clostridium difficile colitis, osteoporosis, and bone fractures (43). Yet, no major observational studies confirm the risks associated with PPIs (1). A systematic review and meta-analysis of 1,140 publications showed moderate superiority of PPIs over placebo, highlighting the importance of considering diet as an adjunct treatment (44). In our

LPR diagnostic algorithm, we recommend taking PPIs (omeprazole or pantoprazole) at a dose of 20 mg twice daily for one month, followed by a six-month follow-up. Each patient requires an individualized approach, with treatment adjustments as needed to balance the benefits and risks of therapy and achieve the desired outcomes. LPR symptoms may gradually resolve, potentially eliminating the need for antireflux medications. Patients require ongoing support to modify their lifestyles, including weight loss, smaller meal sizes, and avoiding lying down for three hours post-meal (45). Other studies corroborate that medications and surgical interventions must be complemented by dietary modifications, such as reducing fat and acid intake, avoiding carbonated and caffeinated beverages, and minimizing alcohol and tobacco use (2). These dietary recommendations were integral to our study as well.

A significant limitation of our study was the lack of daily pH-metry or impedancemetry due to equipment unavailability. pH strips were used as a substitute, which may impact generalizability. Further research is needed to validate our algorithm and assess the clinical benefits and cost-effectiveness of different decision-making thresholds in clinical practice.

Significance for practice and future research.

Our decision support algorithm holds promise for enhancing the sorting of patients with suspected LFR in various medical specialties and transforming their treatment through more accurate diagnosis. While impedance meters are time-consuming and resource-intensive, our diagnostic algorithm could lead to significant cost savings and improved healthcare system efficiency. A prospective study is necessary to assess the clinical benefits and cost-effectiveness of different decision-making thresholds for the algorithm in clinical practice. Further studies are required to finalize conclusions that may influence changes in LPR diagnosis and treatment.

Conclusion

The absence of a gold standard and the inaccessibility of diagnostic methods complicate LPR diagnosis. However, the proposed diagnostic algorithm showed improved post-treatment scores. Further studies are needed to validate our algorithm for early LPR diagnosis, potentially aiding otorhinolaryngologists and patients in regions with limited specialist availability and equipment.

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