

Predictive Value of Digestive Enzymes in Patients With Reflux-Induced Chronic Cough

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Abstract

Objective. To investigate the presence and clinical value of salivary elastase, pepsin, trypsin, cholesterol, and bile salts in the development of laryngopharyngeal reflux disease-related chronic cough (LPRD-CC).

Study Design. Prospective controlled study.

Setting. University hospital study.

Methods. Patients with LPRD at the 24-hour hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring were recruited from two European hospitals. Symptoms and findings were evaluated with the reflux symptom score (RSS), quality-of-life RSS (QoL-RSS), and the reflux sign assessment (RSA) at baseline and following 3 months of treatment. Pepsin, trypsin, elastase, cholesterol, and bile acids were measured in the saliva of patients. Clinical presentation and enzyme patterns were compared between patients with LPRD-CC versus patients without chronic cough. Predictive values of digestive enzymes on clinical patterns were assessed.

Results. Of the 104 recruited patients, 54 had LPRD-CC and 50 did not. Patients with chronic cough demonstrated significantly lower pharyngeal upright reflux events but higher RSS compared to those without chronic cough. The CC group demonstrated significant reduction of RSS (164.4 ± 104.5 vs 105.1 ± 103.2) and RSA (27.7 ± 6.6 vs 21.6 ± 8.1) following treatment. RSS (78.4 ± 51.3 vs 50.2 ± 49.7) and RSA (24.8 ± 7.9 vs 21.5 ± 10.3) were similarly reduced in the non-CC group. The chronic cough group maintained significantly higher scores in otolaryngological RSS ($P = .033$), respiratory RSS ($P = .036$), overall RSS ($P = .035$), and RSS quality of life (RSS-QoL) ($P = .007$). Salivary elastase demonstrated moderate correlation with both chronic cough presence ($r_s = 0.325$) and RSS ($r_s = 0.353$), while salivary bile salts correlated strongly with RSS-QoL ($r_s = 0.564$). In patients with chronic cough, esophageal acid exposure time showed a significant negative correlation with salivary pH ($r_s = -0.443$).

Conclusion. LPRD patients with chronic cough demonstrated higher symptom severity than those without, with salivary elastase and bile salts as potential predictors of clinical findings.

Keywords

biomarkers, cough, diagnosis, digestive, enzymes, gastroesophageal, laryngopharyngeal, otolaryngology, otorhinolaryngology, reflux

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Laryngopharyngeal reflux disease (LPRD) is defined as a disease of the upper aerodigestive tract resulting from the direct and/or indirect effects of gastroduodenal content reflux, inducing morphological and/or neurological changes in the upper aerodigestive tract.¹ The most prevalent symptoms associated with LPRD include globus sensation, throat clearing, and chronic cough, the last occurring in approximately 60% of cases.^{2,3} LPRD-related chronic cough (LPRD-CC) significantly affects patients' quality of life (QoL), leading to substantial economic burdens on health care systems.^{4,5} The pathophysiology of LPRD-CC remains unclear. The current hypotheses include microaspiration, esophageal dysmotility, nonacid reflux, pepsin-induced upper aerodigestive tract mucosa injuries, and the reflex theory, which consists of stimulation of the

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subesophageal mucosal receptors by reflux contents and the related activation of the cough center through the esophagus, ultimately causing the bronchial cough reflex.⁶ To date, a paucity of research has investigated the role of digestive enzymes on the upper aerodigestive tract mucosa of patients with LPRD-CC.

This preliminary study investigated the presence and clinical value of salivary elastase, pepsin, trypsin, and bile salts in the development of LPRD-CC.

Methods

Patients with demonstrated LPRD at the 24-hour hypopharyngeal-esophageal multichannel intraluminal impedance-pH (HEMII-pH) were consecutively enrolled from January 2022 to May 2024 from the Otolaryngology–Head and Neck Surgery departments of two European hospitals: CHU Saint-Pierre (Brussels, Belgium) and the Elsan Polyclinique of Poitiers (Poitiers, France). According to the Dubai consensus,¹ the LPRD diagnosis was based on the identification of more than one pharyngeal reflux event at the 24-hour HEMII-pH monitoring. Gastrointestinal (GI) endoscopy was performed in patients aged 60 years or older, those presenting with gastroesophageal reflux disease (GERD) symptoms or findings, and individuals with a history of GERD-related complications.⁷ Patients were retrospectively stratified into two groups based on the presence of chronic cough (cough item of the reflux symptom score [RSS] ≥ 1), which was defined as a cough lasting over 8 weeks.⁸

Exclusion criteria for both groups included the following: excessive smoking, alcohol dependence, pregnancy, neurological or psychiatric illness, upper respiratory tract infections within the last month, current use of antireflux treatments (eg, proton pump inhibitors [PPIs], antihistamines, alginates, and magaldrates) or inhaled corticosteroids, previous neck surgery or trauma, vocal fold lesions (benign or malignant), history of ear, nose, and throat radiotherapy, active seasonal allergies, chronic pulmonary obstructive disease, asthma, and other non-LPRD etiology of chronic cough.

The study protocol was approved by the local ethics committee (CHU Saint-Pierre Committee, protocol no. BE076201837630). Patients were invited to participate, and informed consent was obtained.

HEMII-pH Monitoring

The Versaflex Z[®] catheter (Digitrapper pH-Z Testing System; Medtronic) was introduced transnasally in the morning before breakfast. The catheter is composed of eight impedance segments and two pH electrodes, tailored to the patient's esophageal length. Six impedance segments were positioned along the esophagus zones (Z1-Z6), positioned at 19, 17, 11, 9, 7, and 5 cm above the lower esophageal sphincter (LES). The remaining two sensors were positioned 1 and 2 cm above the cricopharyngeal

sphincter in the hypopharyngeal cavity. The two pH electrodes were placed 2 cm above the LES and 1 to 2 cm below the cricopharyngeal sphincter. After 24 hours, HEMII-pH tracings were downloaded (Digitrapper; Medtronic) and analyzed using a standardized method.^{1,7} A distal reflux event was defined when reflux reached the two impedance sensors closest to the LES. A pharyngeal reflux event occurred when reflux reached the two hypopharyngeal sensors. Consistent with the Dubai consensus,¹ LPRD was diagnosed as the occurrence of more than one hypopharyngeal reflux episode. Acidic pharyngeal reflux events consisted of events with a pH < 4.0 , whereas those with pH ≥ 4.0 were defined as nonacidic pharyngeal reflux events. The GERD diagnosis was established in accordance with the Lyon consensus criteria, in which patients reported either a Los Angeles grade C or D esophagitis, long-segment Barrett's esophagus, peptic esophageal strictures, or a distal acid pH (pH < 4.0) exposure time exceeding 6% of the 24-hour monitoring period.⁹

Saliva Enzyme Measurements

Saliva samples were collected using Salivette devices (Sarstedt) following the 24-hour HEMII-pH completion. Each participant provided two samples (up to 2 mL per sample) under standardized conditions: fasting state, immediately postawakening, and before dental hygiene procedures. Two Salivette devices were required per participant to ensure adequate volume for enzyme analyses. Saliva samples were frozen at -20°C during storage. Test DRI pH-Detect (Thermo Scientific), total bile acids Assay Kit (Diazyme Lab), and cholesterol (CHOL2) were analyzed on Cobas 8000, and trypsin (DuoSet Human Trypsin [pan], R&D Systems). Elastase (BS-86-01 SK15 from BioServ Diagnostics) and pepsin (BioMatik) were measured with enzyme-linked immunosorbent assay (ELISA). The Peptest device was not selected due to insufficient validation of its analytical performance. Note that the thresholds for distinguishing LPRD and asymptomatic individuals were reported in a recent study.¹⁰ The diagnosis of LPRD was suggested for salivary cholesterol levels < 2.1 mg/dL, elastase > 49 $\mu\text{g/mL}$, and salivary pH > 7.6 .

Clinical Evaluations

Patients prospectively completed the French versions of the RSS,¹¹ which is a 22-item patient-reported outcome questionnaire including the most prevalent otolaryngological (N = 9), digestive (N = 9), and respiratory (N = 4) symptoms. Each symptom was scored by multiplying its frequency (0-5) and severity (0-5) ratings, resulting in individual symptom scores ranging from 0 to 25. The sum of these symptom scores is calculated to obtain the RSS total score, ranging from 0 to 550. Of the respiratory items, troublesome cough was used to detect the occurrence of cough, and to rate its severity (1-25). The oral, laryngeal, and pharyngeal signs were evaluated by two blinded

board-certified otolaryngologists (J.R.L. and F.B., a retired laryngologist) with the reflux sign assessment (RSA).¹²

LPRD severity was determined with the IFOS classification, using the quality-of-life reflux symptom score (QoL-RSS).¹³ The severity stratification defined mild disease as QoL-RSS ranging from 6 to 25, moderate disease as QoL-RSS ranging from 26 to 38, and severe disease as QoL-RSS exceeding 38.¹³

Therapeutic Regimen

The treatment was based on the European guidelines for treating LPRD,⁷ considering an antireflux diet, lifestyle changes, and a 3-month standardized therapy combining PPI (pantoprazole 40 mg/day) with postmeal alginates (Gaviscon®, Reckitt Benckiser) or antacids (Riopan®, Takeda), both administered three times daily. The treatment strategy was based on the HEMII-pH features: GERD and acidic LPRD patients received PPI with alginate, whereas nonacidic LPRD patients were treated with alginate or magaldrate. A standardized antireflux dietary and lifestyle protocol was recommended for all patients.⁷

Statistical Analyses

Statistical analysis was conducted using the Statistical Package for the Social Sciences for Windows (SPSS version 29.0; IBM Corp.). Demographics, enzyme measures, and clinical findings were compared between LPRD-CC and LPRD without CC with the Mann-Whitney *U* test and chi-square depending on the data characteristics. The pretreatment to posttreatment changes in clinical scores were evaluated with the Wilcoxon rank test. A bivariate correlation was conducted between the salivary enzyme levels and the clinical findings through a Spearman analysis. Spearman correlation coefficients were considered as low ($k < 0.40$), moderate ($k = 0.40-0.60$), and strong ($k > 0.60$). A significance level of $P < .05$ was used.

Results

A total of 104 adult patients with positive HEMII-pH results completed the evaluations, including 54 patients with LPRD-CC and 50 controls. The LPRD-CC group included 36 females (66.7%) and had a mean age of 54.2 ± 15.0 years, whereas the control group included 24 females (48.0%) with a mean age of 49.0 ± 15.4 years. The body mass index, proportion of mild, moderate, and severe reflux diseases, GI endoscopy features, and proportion of GERD were similar in patients with LPRD-CC and controls (**Table 1**). Patients with LPRD-CC demonstrated significantly higher numbers of supine pharyngeal reflux events compared to patients without chronic cough.

Salivary Enzymes and Biomarkers

The salivary levels of digestive enzymes and biomarkers of patients with LPRD-CC and controls are reported in **Table 2**. Consistent with the analytical performance

study,¹⁰ the mean values of salivary pH and digestive enzymes of patients with LPRD-CC and without CC reached the thresholds for considering the LPRD diagnosis. The mean salivary cholesterol levels of patients and controls did not reach the cutoff established for determining healthy individuals (≥ 2.1 mg/dL) from LPRD patients (< 2.1 mg/dL). Patients with LPRD-CC had significantly higher salivary levels of pepsin and bile acids compared to those without chronic cough.

Clinical Presentations and Therapeutic Findings

Baseline symptoms, RSS, and RSA subscores and total scores of groups are described in **Table 3**. PPIs were prescribed in 10/54 (18.5%) patients with CC and 17/50 (34.0%) patients without CC, respectively. Most otolaryngological, digestive, and noncough respiratory symptoms demonstrated significantly higher scores in patients with LPRD-CC compared to others. There were no significant differences across groups for oral, laryngeal, and pharyngeal findings.

At 3-month posttreatment, the LPRD-CC group showed significant reductions in all subscores (otolaryngological, digestive, and respiratory) and total RSSs. The baseline cough item score of RSS (9.9 ± 10.1) significantly reduced following 3 months of treatment (3.3 ± 6.4 ; $P = .001$). LPRD-CC patients also demonstrated significant decreases in pharyngeal, laryngeal, and total RSA scores (**Table 4**). Patients without chronic cough showed significant reductions only in otolaryngological and digestive subscores and total RSSs, with improvements limited to laryngeal and total RSA scores (**Table 5**). Only the LPRD-CC group exhibited significant improvement in RSS-QoL scores from baseline to posttreatment. Although the reduction of symptom scores was significant in both groups, the comparison of the 3-month RSS subscores and total scores revealed that the CC group exhibited higher otolaryngological ($P = .033$), respiratory ($P = .036$), and total RSS ($P = .035$) compared to the non-CC group (**Tables 4 and 5**).

Clinical Findings and Enzyme Associations

The bivariate correlation analysis reported that salivary elastase level is significantly correlated with the cough severity ($r_s = 0.325$; $P = .031$) and the baseline RSS ($r_s = 0.353$; $P = .017$). A significant moderate association was found between the salivary bile salt measurements and the baseline RSS-QoL ($r_s = 0.564$; $P = .010$). The acid exposure time was moderately and negatively associated with the salivary pH ($r_s = -0.433$, $P = .030$). Finally, there was a moderate association between the number of nonacidic pharyngeal reflux events and the posttreatment respiratory RSSs ($r_s = 0.429$; $P = .046$).

Discussion

The pathophysiology of LPRD-CC remains incompletely understood.¹⁴⁻¹⁶ In this study, although patients with

Table 1. Demographics and Clinical Features of Patients

Characteristics	Chronic cough N = 54	No-chronic cough N = 50	P-value
Mean age (range, y)	54.2 ± 15.0	49.0 ± 15.4	NS
Body mass index (mean, SD)	25.0 ± 4.6	24.5 ± 5.0	NS
Gender (N, %)			
Female	36 (66.7)	24 (48.0)	NS
Male	18 (33.3)	26 (52.0)	
Severity of laryngopharyngeal reflux symptoms			
Mild reflux (<26)	23 (42.6)	23 (46.0)	NS
Moderate reflux (26–38)	12 (22.2)	7 (14.0)	NS
Severe reflux (>38)	19 (35.2)	20 (40.0)	NS
Gastrointestinal endoscopy findings	N = 26	N = 38	
Normal	7 (26.9)	8 (21.0)	NS
Esophagitis (LA)	8 (30.8)	16 (42.1)	NS
Hiatal hernia	10 (38.5)	11 (28.9)	NS
LES insufficiency	12 (46.2)	12 (31.6)	NS
Gastritis	2 (7.7)	17 (44.7)	.003
<i>Helicobacter pylori</i> infection	1 (3.8)	1 (2.6)	NS
HEMII-pH feature (mean, 95% CI)			
Pharyngeal events			
Pharyngeal acid reflux events	12.3 ± 18.5	9.1 ± 14.3	NS
Pharyngeal nonacid reflux events	14.8 ± 18.6	19.7 ± 25.4	NS
Total number of pharyngeal events	27.1 ± 24.3	29.8 ± 28.2	NS
Position events			
Pharyngeal event upright	23.8 ± 21.2	24.1 ± 19.7	NS
Pharyngeal event supine	6.1 ± 5.8	1.8 ± 2.1	.001
Number of patients with GERD (N, %)	13 (24.1)	13 (26.0)	NS
Acid exposure time, %	17.8 ± 25.4	15.3 ± 26.9	NS

Abbreviations: GERD, gastroesophageal reflux disease; HEMII-pH, hypopharyngeal-esophageal multichannel intraluminal impedance-pH testing; LA, Los Angeles; LES, lower esophageal sphincter; N, number; NS, nonsignificant; SD, standard deviation.

Table 2. Digestive Enzyme and Biomarker Measurements

Enzyme/biomarker measurements	Units	Thresholds	LPRD-CC	LPRD	P-value
Saliva pH	-	>5.93	7.16 ± 0.75	6.98 ± 0.65	NS
Cholesterol	mg/dL	<2.05	1.15 ± 0.50	1.20 ± 0.48	NS
Pepsin (ELISA)	ng/mL	>30.28	35.50 ± 32.77	86.00 ± 104.93	.001
Bile salts	μmol/L	>0.39	0.50 ± 0.47	1.56 ± 3.78	.025
Elastase	μg/mL	>49.2	70.74 ± 44.47	68.28 ± 43.19	NS
Trypsin	pg/mL	>250.03	689.70 ± 705.01	700.73 ± 666.39	NS

Abbreviations: ELISA, enzyme-linked immunosorbent assay; LPRD-CC, laryngopharyngeal reflux disease with chronic cough; NS, nonsignificant.

LPRD-CC exhibited similar profiles to non-CC patients for GI endoscopy findings, pharyngeal pH reflux events, and GERD features, they demonstrated significantly higher otolaryngological, digestive, and respiratory symptom scores. Our observations are consistent with the findings of a previous large-cohort study (326 LPRD-CC vs 197 non-CC patients), which demonstrated that CC was associated with greater severity of otolaryngological, digestive, and RSSs at baseline.³ In 2019, Yu et al compared symptom severity between LPRD-CC and atopic CC patients using the reflux symptom index (RSI).

Their study demonstrated more severe otolaryngological and digestive symptoms in LPRD-CC patients compared to those with atopic CC. Moreover, they observed a predominance of gaseous nonacidic proximal esophageal reflux events at the 24-hour MII-pH in LPRD-CC patients, which corroborates our findings.¹⁴ The minimal contribution of GERD and distal esophageal acid exposure to the development of CC was corroborated by Ang et al who studied 50 patients with suspected LPRD-related CC. Their investigation showed that acid exposure time was rarely elevated in these patients, while highlighting the

Table 3. Clinical Symptoms and Finding Presentations of Patient Groups

Reflux symptom score	Chronic cough	No-chronic cough	P-value
Ear, nose, and throat symptoms			
1. Voice disorder	7.3 ± 8.8	3.3 ± 5.6	.019
2. Throat pain	9.2 ± 8.6	4.5 ± 6.5	.001
3. Pain during swallowing time	5.6 ± 7.1	3.2 ± 5.8	.023
4. Dysphagia	5.4 ± 7.3	3.1 ± 6.2	.034
5. Throat clearing	11.7 ± 9.1	8.0 ± 9.0	.035
6. Globus sensation	10.8 ± 9.7	6.7 ± 8.3	.014
7. Excess throat mucus	12.7 ± 9.2	8.3 ± 9.3	.013
8. Ear pressure/pain	5.4 ± 6.8	3.3 ± 5.0	NS
9. Tongue burning	6.9 ± 9.6	1.2 ± 4.5	.001
Ear, nose, and throat total score	75.0 ± 54.2	41.6 ± 28.7	.001
Digestive symptoms			
1. Heartburn	10.3 ± 8.8	6.2 ± 8.4	.003
2. Regurgitations or burps	7.6 ± 8.4	3.7 ± 6.1	.004
3. Abdominal pain	6.8 ± 8.0	3.9 ± 7.3	.001
4. Diarrhea	3.0 ± 4.7	1.4 ± 3.0	.049
5. Constipation	3.8 ± 6.6	2.9 ± 5.8	NS
6. Indigestion	4.5 ± 6.2	2.1 ± 5.1	.002
7. Abdominal distension/flatus	9.9 ± 8.3	5.9 ± 8.0	.004
8. Halitosis	6.3 ± 7.8	3.5 ± 6.9	.009
9. Nausea	4.3 ± 5.8	1.8 ± 4.9	.001
Digestive total score	55.5 ± 41.0	31.4 ± 30.3	.002
Respiratory symptoms			
1. Cough after eating/lying down	9.6 ± 10.1	1.4 ± 3.5	.001
2. Cough	9.9 ± 7.9 ^a	0.0 ^a	.001
3. Breathing difficulties	6.5 ± 7.6	1.1 ± 2.9	.001
4. Chest pain	7.9 ± 8.8	3.0 ± 6.0	.001
Respiratory total score	33.9 ± 24.7	5.5 ± 8.6	.001
RSS: score total	164.4 ± 104.5	78.4 ± 51.3	.001
Quality of life score	44.5 ± 23.3	23.3 ± 13.7	.001
Reflux sign assessment			
Oral score	5.6 ± 1.7	5.2 ± 2.1	NS
Pharyngeal score	9.5 ± 4.4	7.9 ± 4.3	NS
Laryngeal score	12.9 ± 4.5	11.2 ± 5.7	NS
RSA total score	27.7 ± 6.6	24.8 ± 7.9	NS

Abbreviations: NS, nonsignificant; RSA, reflux sign assessment; RSS, reflux symptom score.

^aBecause this item was used for inclusion criteria, the nonchronic cough group score was 0.

superior diagnostic capability of MII-pH monitoring in detecting nonacidic reflux events.¹⁶ The results of these studies were inconsistent with the observations of Li et al who compared the clinical presentations of GERD patients

with and without CC. Despite different inclusion criteria than ours (GERD vs LPRD), Li et al revealed that GERD-CC patients exhibited higher RSS, prolonged acid exposure times, elevated DeMeester scores, and increased frequency of proximal acidic reflux events (detected by MII-pH) compared to GERD patients without chronic cough.¹⁵

The moderate impact of GERD and the apparent significance of nonacidic pharyngeal reflux events led us to measure the salivary pancreaticoduodenal enzymes with optimized activity under alkaline conditions. Although LPRD-CC patients exhibited lower salivary pepsin and bile salt concentrations, both groups showed elastase and bile salt levels exceeding established pathological thresholds, with LPRD-CC patients demonstrating significantly higher salivary pH values.¹⁰ Statistical analyses identified salivary elastase as a significant predictor of both cough severity and baseline RSSs, whereas bile salt concentrations demonstrated significant correlation with RSS-QoL. Although correlation does not imply causation, these findings may support the hypothesis that alkaline-activated digestive enzymes may contribute to upper aerodigestive tract mucosal inflammation in LPRD-CC. The potential role of elastase in the development of respiratory symptoms related to GERD was supported by Sacco et al, who detected elastase in bronchoalveolar fluid of children with GERD at the GI endoscopy.¹⁷ However, until now, no study had investigated its role in the development of LPRD irrespective of the presence of cough. Given that elastase demonstrates optimal activity within a pH range of 6.5 to 8.5, its presence in both salivary and respiratory specimens from LPRD patients suggests a potential pathophysiological role in mucosal damage and subsequent clinical symptoms.

From a therapeutic standpoint, the identification of key enzymes involved in the mucosal inflammation is important toward optimizing LPRD-CC treatment strategies. To date, PPIs have historically been considered the standard of care; their therapeutic efficacy in LPRD-CC management has not been conclusively demonstrated regarding meta-analysis.¹⁸ In this study, both LPRD-CC and non-LPRD-CC groups exhibited comparable significant reductions in symptom scores, notwithstanding the more severe clinical presentation of LPRD-CC patients.

The adequate posttreatment outcomes may be attributed to the use of alginates and antacids that act for reducing reflux events, chelating some digestive enzymes (pepsin, elastase, and bile acids), and providing mucosal protection against enzymatic activity, independent of pH-mediated enzyme activation.⁷ The potential benefit of alternative medications, either as monotherapy or in combination with PPIs for LPRD-CC treatment, was demonstrated by Yu et al, who reported enhanced efficacy when combining PPIs with prokinetics.¹⁴ In our study, PPIs were prescribed to 18.5% of patients with CC and 34.0% of those without CC. Future large-scale cohort

Table 4. Pretreatment to Posttreatment Changes in Stress, Symptoms, and Endoscopic Findings in Chronic Cough Patients

Clinical symptom/sign outcomes	Chronic cough patients (N = 54)		Z	P-value
	Pretreatment	3 mo posttreatment		
Perceived stress scale	27.4 ± 7.2	32.0 ± 10.7	−1.41	NS
Reflux symptom score				
Otolaryngological RSS	75.0 ± 54.2	50.1 ± 47.4	−2.71	.007
Digestive RSS	55.5 ± 41.0	34.5 ± 38.0	−2.98	.003
Respiratory RSS	33.9 ± 24.7	20.5 ± 25.6	−2.91	.004
RSS total score	164.4 ± 104.5	105.1 ± 103.2	−3.07	.002
RSS QoL total score	44.5 ± 23.3	33.2 ± 25.5	−4.27	.001
Reflux sign assessment				
Oral	5.6 ± 1.7	4.8 ± 1.7	−0.44	NS
Pharyngeal	9.5 ± 4.4	7.9 ± 4.3	−1.97	.049
Laryngeal	12.9 ± 4.5	8.6 ± 5.7	−3.22	.001
RSA total score	27.7 ± 6.6	21.6 ± 8.1	−3.23	.001

Abbreviations: mo, month; NS, nonsignificant; QoL, quality of life; RSA, reflux sign assessment; RSS, reflux symptom score; Z, group difference.

Table 5. Pretreatment to Posttreatment Changes in Stress, Symptoms, and Endoscopic Findings in Patients Without Chronic Cough

Clinical outcomes	No-chronic cough patients (N = 50)		Z	P-value
	Pretreatment	3 mo posttreatment		
Perceived stress scale	28.2 ± 8.0	26.00 ± 6.4	−1.49	NS
Reflux symptom score				
Otolaryngological RSS	41.6 ± 28.7	21.2 ± 15.2	−3.81	.001
Digestive RSS	31.4 ± 30.3	22.3 ± 31.3	−2.19	.028
Respiratory RSS	5.5 ± 8.6	6.7 ± 16.6	−0.70	NS*
RSS total score	78.4 ± 51.3	50.2 ± 49.7	−3.23	.001
RSS QoL total score	23.3 ± 13.7	16.5 ± 13.6	−1.54	NS
Reflux sign assessment				
Oral	5.2 ± 2.1	5.4 ± 2.2	−1.19	NS
Pharyngeal	7.9 ± 4.3	7.4 ± 5.1	−0.17	NS
Laryngeal	11.2 ± 5.7	9.6 ± 5.3	−2.09	.037
RSA total score	24.8 ± 7.9	21.5 ± 10.3	−2.06	.040

Abbreviations: mo, month; NS, nonsignificant; QoL, quality of life; RSA, reflux sign assessment; RSS, reflux symptom score; Z, group difference.

studies should examine how findings change from pretreatment to posttreatment, specifically comparing patients with acid versus nonacid pharyngeal reflux events, while also accounting for PPI prescription patterns.

The use of 24-hour HEMII-pH and the measurements of several gastroduodenal salivary enzymes are the primary strengths of this study. These approaches address a significant limitation in existing literature, where conventional MII-pH or single, dual- or triple-probe pH monitoring has been used for LPRD diagnosis without consideration of pharyngeal reflux events or nonacid refluxate components. The careful exclusion of confounding conditions associated with chronic cough, including asthma, chronic obstructive pulmonary disease, and allergy, is an additional strength.

The primary limitation of this study is the absence of a validated, cough-specific patient-reported outcome measure.

Additionally, several potentially confounding variables were not assessed, including dietary patterns, lifestyle factors, and autonomic nervous system dysfunction, all of them being influencing factors of pharyngeal reflux pathophysiology.¹⁹⁻²¹

The potential heterogeneous distribution of these variables across patient groups may have impacted our findings. In addition, CC might not be solely due to LPRD/GERD, as some alternative causes have not been excluded, including neurogenic cough and chronic aspiration. The chronic aspiration etiology makes particular sense regarding the LPR-related sensory mucosa impairments.^{22,23} The sensory mucosa variability across individuals and the sensory alterations in patients with CC²³ can support the lack of significant association between the severity of reflux, endoscopic findings of GERD and LPRD, and symptom burden. Moreover, in LPRD, a large number of studies investigating the relationship between symptom, sign, and

HMII-pH finding severities did not find significant associations,^{21,24,25} which is attributed to a substantial variability of mucosa sensitivity across individuals. Finally, results suggest that CC patients have increased supine pharyngeal reflux events, which represents an important observation for understanding the pathophysiology of LPRD/GERD-related CC. However, since nighttime/supine chronic cough occurrence was not investigated in detail, the interpretation of this finding remains limited.

Conclusion

LPRD patients with chronic cough demonstrated higher symptom severity than those without. Salivary elastase and bile salt levels emerged as significant predictors of clinical manifestations, with salivary elastase concentrations demonstrating a positive correlation with cough severity. Further basic science studies are needed to understand the role of elastase, bile salts, and other alkaline-activated enzymes in respiratory mucosal inflammation among patients with LPRD-associated chronic cough.

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Author Contributions

Jerome R. Lechien, data interpretation, revising the manuscript for important intellectual content; final approval of the version to be published, final approval, and accountability for the work; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. **Nathalie De Vos** and **Sven Saussez**, analysis data conduction, proofread of the last version of the paper.

Disclosures

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