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Distinct Clinical Physiologic Phenotypes of Patients with Laryngeal Symptoms Referred for Reflux Evaluation

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Abstract

BACKGROUND & AIMS: Heterogeneous presentations and disease mechanisms among patients with laryngeal symptoms account for misdiagnosis of laryngopharyngeal reflux (LPR), variations in testing and suboptimal outcomes. We aimed to derive phenotypes of patients with

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laryngeal symptoms based on clinical and physiologic data and to compare characteristics across phenotypes.

METHODS: 302 adult patients with chronic laryngeal symptoms were prospectively enrolled at three centers between 1/2018–10/2020 [age 57.2±15.2 years; 30% males; BMI 27.2±6.0 kg/m^2]. Discriminant analysis of principal components (DAPC) was applied to 12 clinical and 11 physiologic variables collected in stable condition to derive phenotypic groups.

RESULTS: DAPC identified five groups, with significant differences across symptoms, hiatal hernia size, and number of reflux events ($p<0.01$). Group A had the greatest hiatal hernia size (3.1cm±1.0;$p<0.001$) and reflux events (37.5±51;$p<0.001$), with frequent cough, laryngeal symptoms, heartburn and regurgitation. Group B had the highest body mass index (28.2kg/m^2±4.6;$p<0.001$) and salivary pepsin (150ng/ml±157;$p=0.03$), with frequent cough, laryngeal symptoms, globus, heartburn and regurgitation. Group C frequently reported laryngeal symptoms (93%;$p<0.001$), and had fewest esophageal symptoms (9.6%;$p<0.001$) and reflux events (10.7±11.0;$p<0.001$). Group D commonly reported cough (88%;$p<0.001$) and heartburn. Group E (18%) was oldest (62.9y±14.3;$p<0.001$) and distinguished by highest integrated relaxation pressure.

CONCLUSIONS: DAPC identified distinct clinico-physiologic phenotypes of patients with laryngeal symptoms referred for reflux evaluation: Group A, LPR and gastroesophageal reflux disease (GERD) with hiatal hernia; Group B, Mild LPR/GERD; Group C, No LPR/No GERD; Group D, Reflex cough; Group E, Mixed/Possible obstructive esophago-gastric junction. Phenotypic differences may inform targeted clinical trials design and improve outcomes.

Keywords

Gastro-esophageal reflux disease; Esophageal manometry; Proton pump inhibitor

INTRODUCTION

One-third of the adult population experiences laryngeal complaints such as throat clearing, dysphonia, or chronic cough. Laryngeal symptoms can arise from various etiologies including allergy, post-nasal drip, vocal cord dysfunction, visceral hypersensitivity, or laryngopharyngeal reflux (LPR). LPR is an extra-esophageal syndrome of gastroesophageal reflux disease (GERD) in which retrograde reflux of gastric contents leads to chronic laryngeal irritation.[1–3] While laryngeal symptoms are not synonymous with LPR, up to 80% of symptomatic individuals seeking consultation may receive a diagnosis of LPR with the vast majority treated with empiric proton pump inhibitor (PPI) therapy.[4–7] Furthermore, LPR is often diagnosed in the absence of typical esophageal symptoms of GERD.[1] These empirical one-size-fits-all approaches for heterogeneous non-specific laryngeal complaints drive variations observed in physiologic testing and suboptimal efficacy of conventional medical and surgical anti-reflux therapies.[3,8] Thus, methods to delineate mechanisms of symptomatology and clarify whether GERD is a culprit are critically needed.

Recent efforts to phenotype patients with reflux symptoms based on clinical characteristics and physiologic profiles have been described to allow distinct and personalized management in GERD.[9] Consequently, the paradigm is shifting away from the historic approach that

largely focused on empiric acid suppression, and moving towards a phenotype-driven, personalized approach to GERD. Similarly, unsupervised clustering for identification of patient subpopulations have been successfully applied to other disease states such as heart failure, cancer and diabetes.[10] These approaches are needed among patients with laryngeal symptoms to understand symptom pathogenesis, appropriately diagnose LPR, and formulate tailored, personalized management approaches. Therefore, we aimed to cluster patients with laryngeal symptoms referred for reflux evaluation based on a range of clinical and physiologic data using unsupervised phenotype modeling and compare characteristics across phenotypes.

METHODS

Study Design & Subjects

This multi-center study analyzed prospectively collected data between January 2018 to October 2020 from patients with laryngeal symptoms. The study was approved by the Institutional Review Board at participating sites and data share agreements were executed (University of California San Diego, La Jolla, CA; University of Colorado, Aurora, CO; Brigham and Women's Hospital, Boston, MA).

Adults presenting with at least 8 weeks of one or more extra-esophageal symptom (dysphonia, sore throat, throat clearing, cough, or globus), with or without concomitant esophageal symptoms, who underwent esophageal high-resolution impedance-manometry (HRIM) were enrolled. Patients with history of prior foregut or otolaryngolic surgery, foregut or otolaryngologic malignancy, chronic lung disease and eosinophilic esophagitis were excluded.

Data Collection & Management

The prospective dataset included 302 subjects with 12 clinical parameters (n=302), 4 HRIM metrics (n=302), 6 ambulatory reflux monitoring metrics (n=251), and 1 salivary biomarker value (n=77). Clinical parameters included demographics, presenting symptoms, use of PPI, and validated patient-reported symptom instruments.

HRIM was performed using a 36-channel solid-state catheter (Manoscan 360; Medtronic, Minneapolis, Minnesota; or Diversatek, Highlands Ranch, Colorado) and a standardized protocol of ten supine 5ml wet swallows. Metrics collected included upper esophageal sphincter (UES) resting pressure, median lower esophageal sphincter (LES) integrated relaxation pressure (IRP), manometric hiatal hernia size (separation between crural diaphragm and LES), % of ineffective swallows, and % of complete bolus clearance. Validated symptom instruments included GerdQ[11] and reflux symptom index (RSI)[12] scores.

Ambulatory reflux monitoring performed included MII-pH monitoring (Reflux 6.1; Medtronic, Minneapolis, Minnesota; or Diversatek, Highlands Ranch, Colorado) or wireless pH monitoring (Bravo; Medtronic, Minneapolis, Minnesota). MII-pH catheter configurations included single-pH electrode in the distal esophagus, or dual-pH electrodes in the distal esophagus and at the UES. Patients that underwent ambulatory reflux monitoring were instructed to follow their baseline regular diet during monitoring. Data collected from

ambulatory reflux monitoring included study type, on/off acid suppression, total acid exposure time (% time pH below 4.0), number of reflux events, number of full column reflux events, number of LPR events, and distal mean nocturnal baseline impedance (DMNBI). The pH-impedance studies were manually reviewed, with reflux events defined by at least 50% drop in impedance from baseline and propagating in retrograde fashion from the distal most electrode pairs. LPR reflux events were defined by an impedance reflux event reaching the most proximal electrode pairs. Unstimulated fasting salivary pepsin was collected, processed within seven days of collection, and quantified for salivary pepsin concentration using the Peptest lateral flow device (LFD) (RD Biomed Ltd) per previously published protocols.[13 14]

Phenotype-Based Clustering Using Discriminant Analysis of Principal Components

The primary outcome was phenotypic cluster grouping based on discriminant analysis of principal components (DAPC), an unsupervised multivariate method involving principal components analysis, K-means clustering and discriminant analysis to detect and visualize clusters of related individuals across a population structure.[15] The steps to conduct the DAPC analysis are outlined in a tutorial, which we followed and briefly outline here.[15] First, an *a priori* selection of variables to include in the model was identified, motivated by potential clinical utility and to minimize missingness in the available data while maximize sample size. The variables included in the primary model included age, body mass index (BMI), hiatal hernia size, normalized LES IRP, the percent of ineffective swallows (distal contractile integral < 450 mmHg-s-cm), and presence of symptoms related to cough, throat symptoms (a composite of voice hoarseness, sore throat, or throat clearing), globus, regurgitation, heartburn and chest pain. Second, k-means clustering was used to identify between 3 to 6 initial clusters, where this range was *a priori* selected to maintain a reasonable number of clusters to evaluate for potential clinical utility. Third, the k-means clusters were then used in the DAPC, where the optimal number of principal components was selected based on the a-score when peaked or a lower value when plateaued to avoid over-fitting the data, with the number of discriminant functions retained based on the change in eigenvalues for adding additional functions. Finally, this “optimal” DAPC model was used to assign group membership based on the individual probability to generate figures, summarize performance, and propose potential phenotypes. Evaluation of the DAPC analyses for the different group sizes was conducted to select the number or groups that balanced the overlap of group membership while providing clinically meaningful differences.

To evaluate if detailed ambulatory reflux monitoring can provide fine mapping of patients beyond the clinical and HRIM parameters, a subgroup analysis of subjects that had available ambulatory reflux monitoring data was conducted to evaluate potential group membership. To evaluate if clinical presentation alone could reliably identify phenotypes, a sensitivity analysis was conducted to evaluate potential group membership based on symptoms alone in the model. Cramér’s V was calculated to estimate the association between the primary grouping with the subgroup and sensitivity groups.

Comparison of variables across DAPC phenotypes used an overall F-test for an unadjusted linear regression model for continuous measures and a chi-squared test for categorical measures. All categorical measures were summarized as count (percent) and all continuous measures as mean (standard deviation). An adjusted median LES IRP was calculated by dividing the observed value with the established normative cutoff (15 mmHg for Medtronic and 20 mmHg for Diversatek) to normalize across the two systems. All analyses were conducted in R v3.6.3 (Vienna, Austria) and DAPC was implemented using the adegenet package[17] and Cramér's V was implemented using the DescTools package.[15]

RESULTS

In total, 302 subjects were enrolled [90 (30%) males, mean age of 57.2 years (SD 15.2), mean BMI of 27.2 kg/m2 (SD 6.0)]. The predominant extra-esophageal symptom reported was throat clearing (237, 78%), followed by dysphonia (172, 57%), globus (160, 53%), cough (159, 52%), and sore throat (45, 15%). Typical esophageal symptoms of GERD reported included 110 (36%) with heartburn, 93 (31%) with regurgitation, and 47 (16%) with non-cardiac chest pain.

Primary Outcome: Phenotypic Cluster Groups

DAPC analysis of the complete data set (n=302) identified five distinct groups: 26 (9%) group A, 72 (24%) group B, 94 (31%) group C, 57 (19%) group D, and 53 (17%) group E (Figure 1A). Probability of a subject being correctly assigned to each group were high for groups A, B, and E (95%, 81%, and 77%, respectively) and lower for groups C and D (68% and 55%, respectively) (Figures 1B & 1C). Of all included variables the loading variables significantly influencing cluster groups were hiatal hernia size, median IRP, and presenting symptoms (Figure 2).

Distribution of Variables Across Phenotypic Cluster Groups (Figure 3)— Notable differences among cluster groups are summarized below (p-values reflecting comparisons across all five groups) and displayed in Table 1.

Demographics: Group B was youngest (52.2 years (SD 13.3)) and group E was oldest (62.9 (14.3)) ($p<0.001$). Groups A and B had higher BMI (27.4 kg/m2 (SD 4.6) and 28.2 (6.1)) compared to Groups C, D, and E (26.8 (6.4), 26.8 (5.1), 26.4 (6.6)), respectively.

Presenting Symptoms: With regards to extra-esophageal symptoms, cough was reported by the majority in Groups A (85%), B (67%), and D (88%) ($p<0.001$). Laryngeal symptoms (dysphonia, throat clearing, and/or sore throat) were reported by the majority in Groups A (69%), B (99%), C (93%), and D (84%) ($p<0.001$). Globus was reported by the majority in Groups B (81%) and C (68%) ($p<0.001$). With regards to esophageal symptoms, regurgitation was reported by the majority in group A (58%) and B (82%) ($p<0.001$), and heartburn in group B (83%) ($p<0.001$).

High Resolution Manometry: Hiatal hernia size was greatest in Group A (3.1cm (SD 1.0) and smallest in Group C (0.0 (SD (0.0); $p<0.001$). Median IRP was greatest in Group E (normalized ratio 0.9 (0.6); $p<0.001$). Group A exhibited the greatest proportion of

ineffective swallows (46% (SD 32); p=0.03). For UES metrics, Group A exhibited the lowest UES basal (74.8 mmHg (38)) and residual (0.7 (7.5)) pressures.

Other Variables: Ambulatory reflux monitoring data were available for 252 (83%) patients. Group A exhibited the greatest number of total (37.6 (SD 51); p<0.001) and LPR (7.2 (17.4); p=0.13) reflux events. Mean DMNBI was lowest in Group A (1790 ohms (SD 1340; p=0.01). Acid exposure time on PPI was highest in Group A (3.8% (SD 6.2); p=0.09) and off PPI was highest in group E (4.2% (SD 8.0); p=0.05). Mean salivary pepsin concentrations were highest in Group B (150 ng/ml (SD 157)) and Group A (107 (SD 117); p=0.03).

Post-hoc Clinical Characterization of Phenotypic Cluster Groups—In order to provide clinical context, we labeled the five cluster groups based on the results of the DAPC of clinico-physiologic characteristics as follows: LPR/GERD with hiatal hernia (Group A), mild LPR/GERD (Group B), no LPR/GERD (Group C), reflex cough (Group D), and mixed with possible obstructive EGJ process (Group E). (Figure 4)

Comprehensive Sub-Group Model Inclusive of Symptom Presentation, High Resolution Manometry, & Ambulatory Reflux Monitoring Table 2

DAPC sub-group analysis limited to subjects who underwent ambulatory reflux monitoring (n=251) identified three cluster groups (Cramér's V of 0.21 (95% CI: 0.07 to 0.27) with the primary analysis, Supplemental Table). Sub-Group A (n=9) was reminiscent of an LPR/GERD with hiatal hernia phenotype characterized by greatest hiatal hernia, presentation with regurgitation, BMI, salivary pepsin concentration, acid exposure time, number of reflux events, and lowest DNMBI. 0% of sub-group A had membership in the original Group C (no LPR/no GERD). Sub-Group B (n=64) was reminiscent of mild GERD and commonly presented with cough, laryngeal symptoms and esophageal symptoms, and had a moderate salivary pepsin concentration. Patients in Sub-Group B most frequently had membership in the primary Groups B (mild LPR/GERD) (33%) and D (cough reflex) (25%). Sub-Group C (n=178) was characterized by frequent cough and laryngeal symptoms, smallest hiatal hernia size and the lowest salivary pepsin concentration. Sub-Group C (reminiscent of no LPR and no GERD) had rare membership in the primary Group A (LPR/GERD with hiatal hernia; 11/178, 6%).

Sensitivity Analysis: Symptoms Only Model

DAPC analysis including only symptoms (n=302) identified five cluster groups, with a Cramér's V of 0.51 (95% CI: 0.44, 0.56) with the primary analysis (Supplemental Table). Of note, of the 94 patients originally assigned to the primary Group C (no LPR/no GERD) phenotype clustering based on symptoms alone correctly assigned 75 (80%) into a cluster with rare esophageal symptoms.

DISCUSSION

Assessment of patients with laryngeal symptoms referred for reflux evaluation has remained challenging for clinicians and investigators. Patients may present with a variety of

throat symptoms that mimic other otorhinolaryngologic conditions, often without typical esophageal symptoms of GERD.[2] While empiric acid suppression therapy is often the first-line treatment, the response is variable[16] and prior studies on the efficacy for surgical intervention for suspected LPR have been inconclusive.[3] These variations illustrate the significant heterogeneity of patients with laryngeal symptoms suspected to have LPR. Effective management would, therefore, require careful selection of patients and therapies tailored to the underlying mechanisms. This first-of-its-kind study applied sophisticated phenotyping methods to explore potential clinical physiologic phenotypes of patients with laryngeal symptoms undergoing evaluation for reflux.

This study of 302 adults presenting with laryngeal symptoms who underwent HRIM at three centers identified five distinct clinico-physiologic phenotypes. Groups A and B likely represents a spectrum of GERD with esophago-pharyngeal reflux. Notably a small proportion (8.6%) had membership in Group A (*LPR/GERD with hiatal hernia*), a group characterized by disrupted anti-reflux barrier and higher reflux burden. Group B (*LPR/mild GERD*) shares characteristics with group A, though less often has a hiatal hernia and more often has positive symptom-reflux association, suggesting a milder spectrum of GERD with potential of reflux hypersensitivity overlap. On the other hand, Group C (*No LPR/No GERD*) likely represents a non-GERD pathology with isolated laryngeal symptom presentation and least suggestion of reflux physiology. Of note membership was most prevalent for Group C (30.9%). Groups D and E are less well characterized and in sensitivity analyses share overlap between phenotypes resembling GERD as well as those without GERD (Supplemental Table). Group D (*Reflex cough*) may be comprised of patients whose laryngeal symptoms (cough) were in part reflux-related, perhaps through the described vagally-mediated reflex mechanism leading to bronchoconstriction, rather than esophago-pharyngeal reflux.[17,18] Group E (*Mixed/possible obstructive EGJ*) may include patients with an obstructive physiology across the EGJ, which may lead to poor bolus clearance, chronic esophageal distention, and increased pressurization in the proximal esophagus. It is important to note that an elevated supine median IRP on manometry does not equate to LES dysfunction, and the elevated IRP may be related to catheter artifact or effect of hiatal hernia.

Our results of this proof-of-concept study illustrate the value of systematic assessment through clinico-physiologic phenotyping and personalized management, particularly prior to escalated anti-reflux therapy. We applied the results from this study to develop a post-hoc classification tree model in which 81% of patients were classified in the correct phenotype. Literature to-date has not identified any single diagnostic test as being adequately predictive for an accurate diagnosis of LPR and treatment outcome. Given the current lack of a “gold standard” diagnosis for LPR, tailored management based on clinical and physiologic phenotyping using a multitude of data may provide a cost-effective and efficient approach to these challenging patients with laryngeal symptoms.

Using results from our phenotyping, potential clinical algorithms may be formulated for a sensible tailored management approach. In a potential model generated from our current data (Figure 5), assessment for esophageal symptoms (heartburn or regurgitation), BMI, or presence of hiatal hernia may serve as the initial step to dichotomize patients into the

GERD groups A (LPR/GERD + Hiatal hernia) or B (LPR/mild GERD) versus groups C (No LPR/No GERD), D (Reflex Cough) or E (Mixed/Possible obstructive EGJ). Notably, our sensitivity model based solely on symptom presentation correctly assigned 80% of patients into the no LPR/noGERD phenotype (Group C), supporting a pre-test probability that patients presenting with laryngeal symptoms in the absence of typical esophageal symptoms likely do not have LPR. This potential diagnostic approach to laryngeal symptoms echoes concepts in the clinical model by Patel et al., which identified that the overall risk of pathologic reflux among patients with refractory esophageal or extraesophageal symptoms was independently associated with heartburn, elevated BMI, asthma and presence of hiatal hernia.[20]

After this initial step of dichotomization, evaluation strategies may then follow to allow efficient phenotyping and tailored therapy. Patients with LPR and pathologic GERD with hiatal hernia (group A) would be the optimal candidates for escalated anti-reflux therapy, including potential surgical intervention.[8] Patients with LPR and mild reflux or reflux hypersensitivity (group B) and those with reflux-induced reflex cough (group D) may benefit from “mild” anti-reflux management with acid suppression or alginates.[21] Invasive interventions such as anti-reflux surgery should generally be avoided due to unclear benefits in these groups. Neuromodulation or behavioral interventions may be particularly beneficial for patients in group B with reflux hypersensitivity.[22] Gabapentin, other neuromodulators, and voice therapy for cough suppression, desensitization, and avoidance strategies may be useful for group D patients with reflex cough.[23] Patients with no LPR/no GERD (group C) warrant assessment and management of other etiologies, such as laryngeal abnormalities, vocal cord dysfunction, allergies/post-nasal drip, oropharyngeal dysphagia, or airway hypersensitivity. Finally, a sub-group with confirmed obstructive physiology at the EGJ on supportive testing may benefit from LES directed therapy. Further research is needed to understand response to treatment and outcomes across distinct phenotypes.

Our exploratory study has several strengths, including the multi-center cohorts, prospective data collection, and relatively large sample size for a study of LPR patients. There are also limitations to our study. Treatment response was not assessed, as this proof-of-concept study was designed as the first-of-its-kind to identify distinct clinical and physiologic phenotypes. A next step will be to validate this analysis incorporating outcome data. Modality of ambulatory reflux monitoring was not standardized and for this reason, ambulatory reflux monitoring data were not included in the primary DAPC model, but rather in the sensitivity analysis. Nonetheless, given the lack of a “gold standard” test and clear consensus of the optimal ambulatory reflux monitoring for evaluating LPR, and the limited availability of some of these newer technologies, the inclusion of all available types of ambulatory reflux monitoring likely improved the generalizability of our results. This study included the well-established extra-esophageal symptoms such as dysphonia, sore throat, throat clearing, globus, cough, however symptoms that may potentially suggest LPR such as halitosis or odynophagia were not within inclusion criteria. Finally, the included patients came from three tertiary care institutions with subspecialists in LPR that were referred to HRM which may include more severe or refractory patients compared to the general population. However, these refractory patients also likely represent the diagnostically challenging

patients most frequently referred to gastroenterologist offices for evaluation, and would, therefore, most benefit from a tailored management approach.

In conclusion, distinct clinical physiologic phenotypes were identified in a multi-center prospective study utilizing DAPC among 302 patients with laryngeal symptoms referred for reflux evaluation. This exploratory study affirms and highlights that patients with suspected LPR are heterogeneous and a reflux physiology is not always present. Distinct clinical presentations and physiologic differences may explain variability in presentation, treatment response, and prognosis. Identifying phenotypic differences may improve outcomes and inform future targeted clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Rena Yadlapati: Institutional Consulting Agreement: Medtronic, Ironwood Pharmaceuticals, Diversatek; Consultant: Phathom Pharmaceuticals; Research support: Ironwood Pharmaceuticals; Advisory Board with Stock Options: RJS Mediagnostix

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Abbreviations:

LPR	laryngopharyngeal reflux
DAPC	discriminant analysis of principal components
BMI	body mass index
RSI	reflux symptom index
GERD	gastroesophageal reflux disease
PPIs	proton pump inhibitors
HRIM	high-resolution impedance-manometry
UES	upper esophageal sphincter
LES	lower esophageal sphincter
IRP	integrated relaxation pressure
DMNBI	distal mean nocturnal baseline impedance
LFD	lateral flow device

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WHAT YOU NEED TO KNOW

Background:

- Laryngopharyngeal reflux is commonly suspected with poorly delineated evaluation and management pathways
- Patients with laryngeal symptoms suspected to have LPR are heterogeneous with variation in mechanisms of symptoms, presence of gastro-esophageal reflux, and treatment outcome.

Findings:

- Discriminant analysis of principal components across 302 patients with chronic laryngeal symptoms referred for reflux evaluation identified five distinct phenotypic groups described as LPR and gastroesophageal reflux disease (GERD) with hiatal hernia (Group A); Mild LPR/GERD (Group B); No LPR/No GERD (Group C); Reflex cough (Group D); Mixed/Possible obstructive esophago-gastric junction (Group E).

Implications for patient care:

- Distinct groups of patients with laryngeal symptoms referred for reflux evaluation exist and can be identified through clinical physiologic phenotypes
- Phenotypic differences may inform targeted clinical trials design and improve outcomes

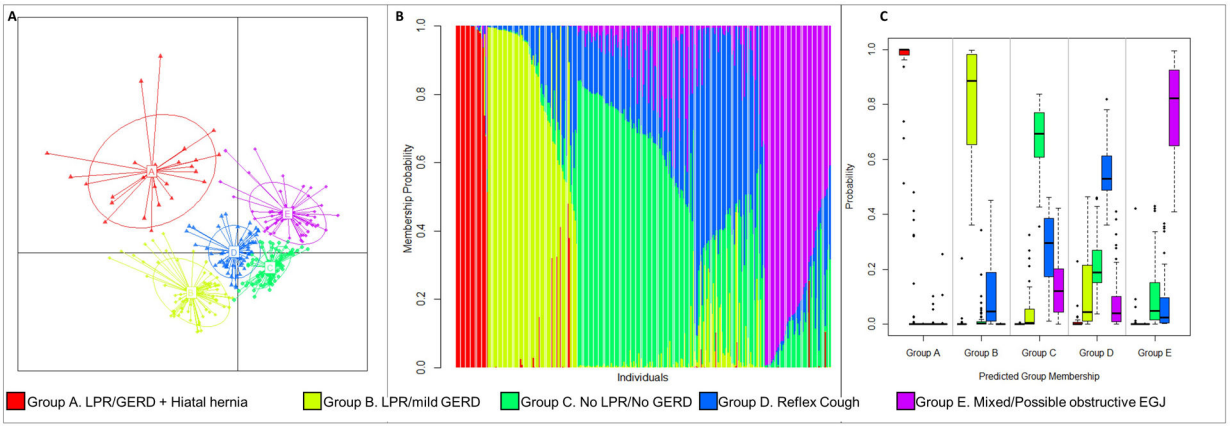

Figure 1. Five Phenotype Cluster Groups.

1A)Group A, B, E do not overlap with the other five groups; groups C and D have minimal overlap. 1B)Waterfall plot of individual probabilities for five groups. X-axis represents a patient; y-axis represents membership probability. 1C)Boxplot of posterior probability for each group based on group membership

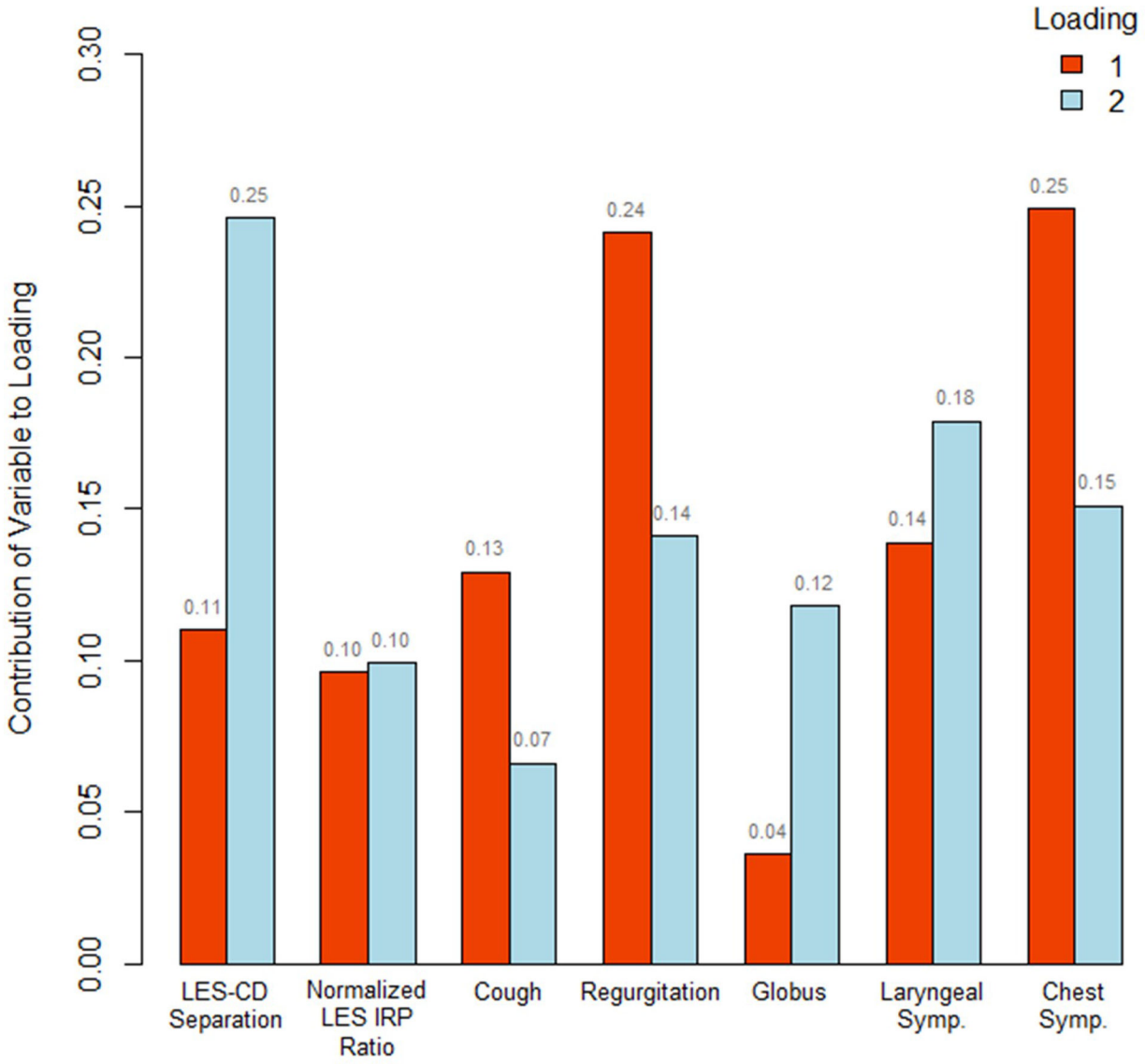

Figure 2. Loading Variables Driving Group Membership.

The total contribution of variable to loading sums to 1.0 within each loading (1 and 2). This barplot is a graphical representation of loading variables that had a measure >0.001, and reflect a relative measure of the contribution of each original variable to the discriminant functions of the DAPC.

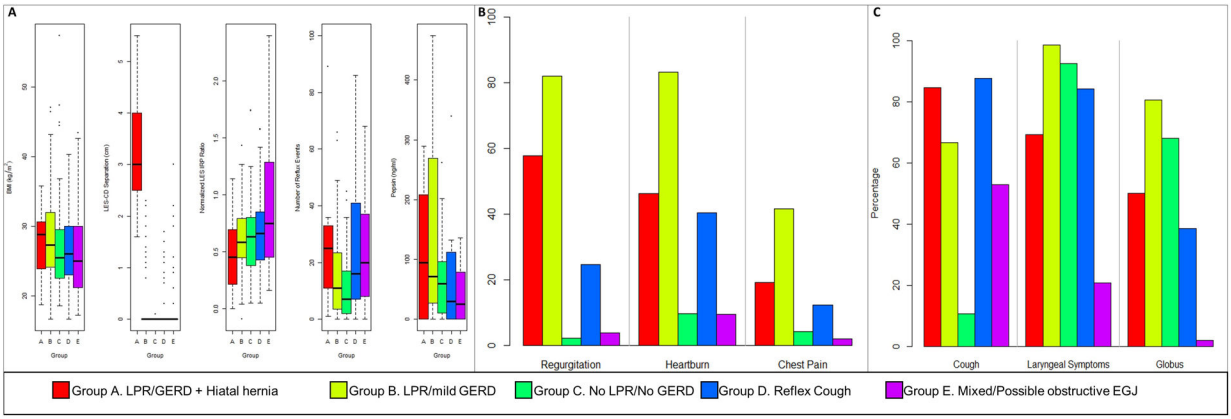

Figure 3.
Distribution of Variables Within Each Group.

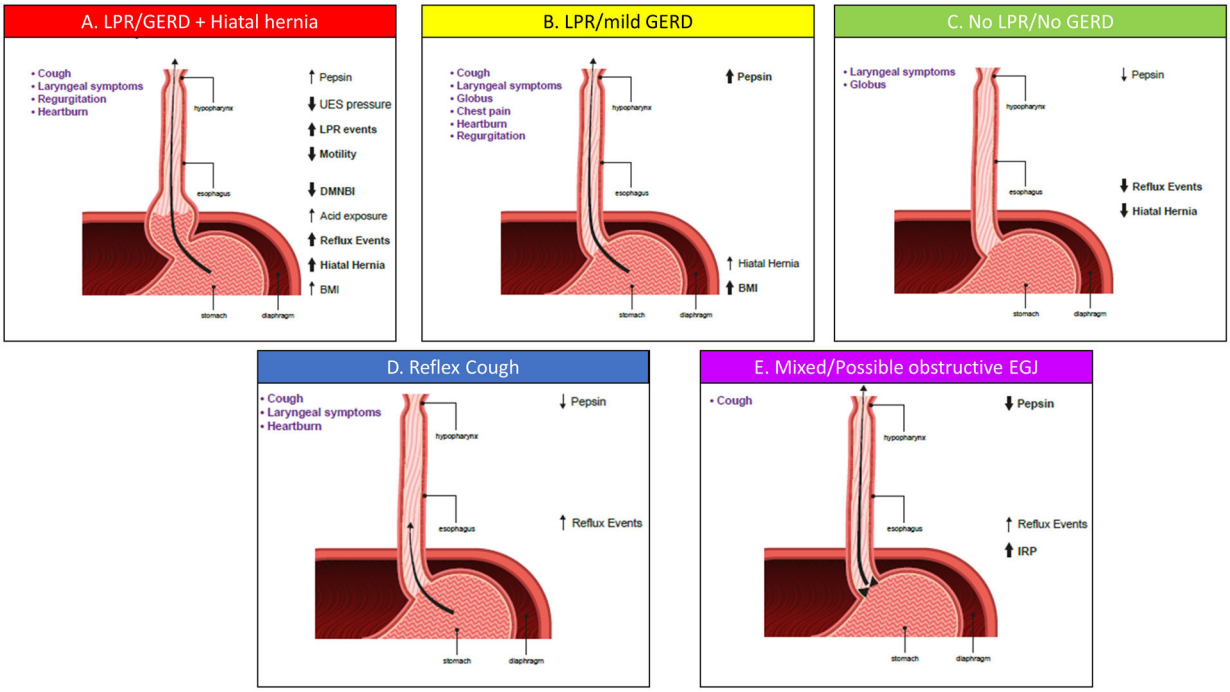

Figure 4. Representative Depiction of Phenotypic Cluster Groups.

Five distinct clusters depicted based on symptom presentation (left bullets) and clinical/physiologic profiles (right arrows) with arrow representing directionality and degree (bolding) of relationship. Group A: Commonly presented with hiatal hernia, ineffective esophageal peristalsis, cough, laryngeal symptoms, heartburn and regurgitation; higher BMI, AET on PPI, number of reflux and LPR events, salivary pepsin; lowest DMNBI. Group B: Presented with highest BMI and salivary pepsin concentration; commonly presented with cough, laryngeal symptoms, globus, heartburn and regurgitation. Group C: Lowest proportion with hiatal hernia and number of reflux events; commonly presented with laryngeal symptoms and globus, however rarely with esophageal symptoms. Group D: highest proportion of patients with cough and commonly presented with heartburn. Group E: presented with the highest mean LES IRP, and predominantly with symptoms of cough; lowest salivary pepsin concentration.

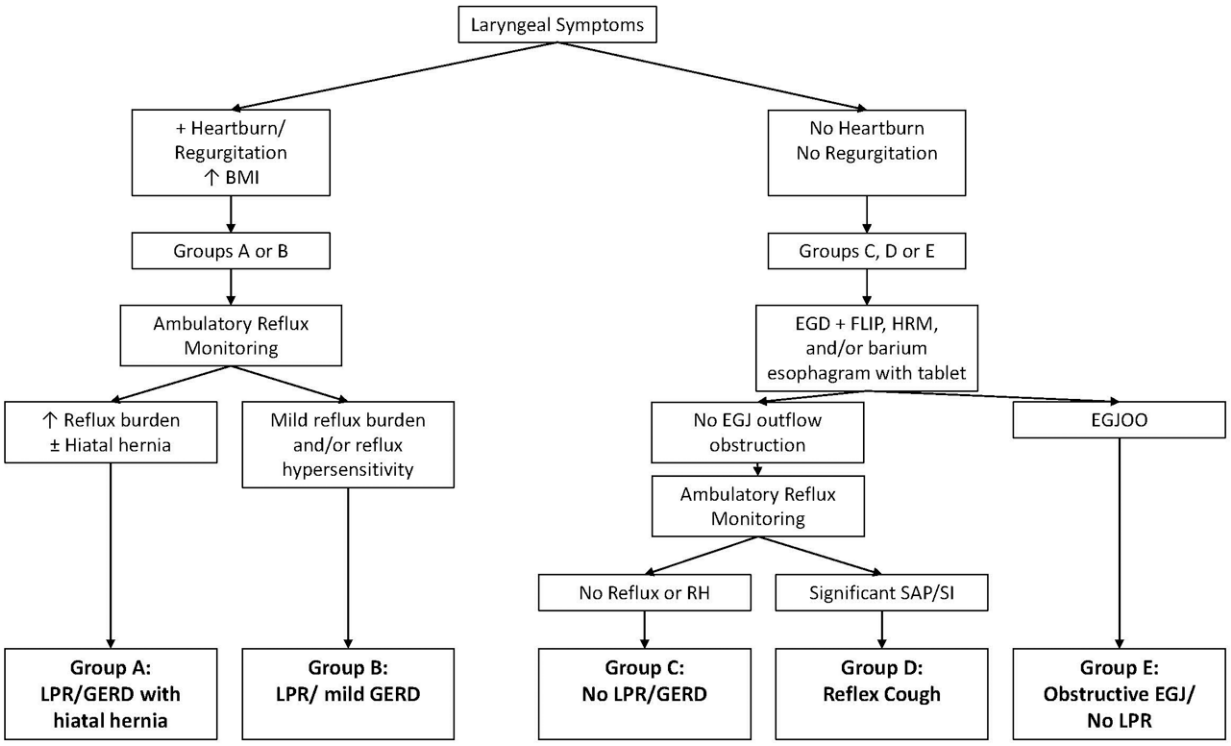

Figure 5. Conceptual Diagram of Clinical Approach to Identifying Phenotypes of Patients with Suspected LPR.

This diagram synthesizes results from this study and clinical experiences. The first step is assessment of symptoms, BMI, and presence of hiatal hernia. Patients with high BMI and concomitant heartburn/regurgitation likely fall into GERD groups A (*LPR/GERD with hiatal hernia*) or B (*LPR/mild GERD*), and testing including ambulatory reflux monitoring should be performed for further characterization. Those without heartburn/regurgitation likely belong to group C (*no LPR/no GERD*) or possibly group D (*reflex cough*) or E (*Mixed/Possible obstructive EGJ*). Evaluation can include upper gastrointestinal endoscopy with real-time functional luminal impedance-planimetry, esophageal HRM, and/or barium esophagram. In absence of obstructive physiology, ambulatory reflux monitoring should be performed to further stratify patients into groups with GERD (groups A, B, or potentially D) versus those without GERD (group C).

Table 1.

Distribution of Clinical and Physiologic Variables Across Phenotype Clusters

	Phenotype Clusters					
	LPR/GERD hiatal hernia	**Mild LPR/ GERD**	**No LPR/No GERD**	**Reflex Cough**	**Mixed/Possible Obstructive EGJ**	
	A (n=26)	**B (n=72)**	**C (n=94)**	**D (n=57)**	**E (n=53)**	**p-value**
Demographics						
Age (years)	53.6 (14.0)	52.2 (13.3)	58.8 (15.5)	56.5 (16.3)	62.8 (14.3)	<0.001
Male	8/26 (30.8%)	20/72 (27.8%)	29/94 (30.9%)	19/57 (33.3%)	13/53 (24.5%)	0.87
BMI (kg/m^2)	27.4 (4.6)	28.2 (6.1)	26.8 (6.4)	26.8 (5.1)	26.4 (6.6)	0.46
Symptom Presentation						
Cough	22/26 (84.6%)	48/72 (66.7%)	10/94 (10.6%)	50/57 (87.7%)	28/53 (52.8%)	<0.001
Laryngeal Symptoms	18/26 (69.2%)	71/72 (98.6%)	87/94 (92.6%)	48/57 (84.2%)	11/53 (20.8%)	<0.001
Voice Hoarseness	11/26 (42.3%)	54/72 (75.0%)	68/94 (72.3%)	32/57 (56.1%)	7/53 (13.2%)	<0.001
Sore Throat	4/26 (15.4%)	22/72 (30.6%)	4/94 (4.3%)	12/57 (21.1%)	3/53 (5.7%)	<0.001
Throat Clearing	16/26 (61.5%)	66/72 (91.7%)	82/94 (87.2%)	43/57 (75.4%)	7/53 (13.2%)	<0.001
Globus	13/26 (50.0%)	58/72 (80.6%)	64/94 (68.1%)	22/57 (38.6%)	1/53 (1.9%)	<0.001
Regurgitation	15/26 (57.7%)	59/72 (81.9%)	2/94 (2.1%)	14/57 (24.6%)	2/53 (3.8%)	<0.001
Heartburn	12/26 (46.2%)	60/72 (83.3%)	9/94 (9.6%)	23/57 (40.4%)	5/53 (9.4%)	<0.001
Chest Pain	5/26 (19.2%)	30/72 (41.7%)	4/94 (4.3%)	7/57 (12.3%)	1/53 (1.9%)	<0.001
High Resolution Manometry						
Hiatal Hernia Size (cm)	3.1 (1.0)	0.3 (0.6)	0.0 (0.0)	0.2 (0.5)	0.3 (0.7)	<0.001
Hernia Present	25 (96.2%)	17 (23.6%)	2 (2.1%)	12 (21.1%)	11 (20.8%)	<0.001
Normalized LES IRP Ratio	0.5 (0.3)	0.6 (0.3)	0.6 (0.3)	0.7 (0.3)	0.9 (0.6)	<0.001
Median LES IRP (Medtronic) (mmHg) [N=110]	6.8 (5.0)	10.7 (5.0)	12.6 (7.2)	13.3 (5.4)	20.0 (9.1)	<0.001
Median LES IRP (Diversatek) (mmHg) [N=192]	9.2 (6.4)	11.1 (4.7)	11.9 (5.5)	10.7 (4.8)	11.9 (5.5)	0.48
Percent ineffective swallows	45.7 (32.3)	22.9 (30.9)	28.2 (26.7)	28.6 (31.7)	32.3 (35.3)	0.03
Mean UES Basal Pressure (mmHg) [N=206]	74.8 (38.1)	89.4 (64.1)	99.3 (50.6)	91.0 (57.2)	105.0 (69.7)	0.42
Ambulatory Reflux Monitoring						
Number of Reflux Events [N=251]	37.6 (51.4)	19.2 (25.9)	10.7 (11.0)	26.2 (27.2)	23.4 (18.4)	<0.001
Number of LPR Events [N=187]	7.2 (17.4)	2.4 (3.6)	4.8 (7.4)	2.3 (4.1)	3.0 (5.8)	0.13
Overall acid exposure time (%) [N=258]	2.6 (4.1)	1.5 (4.1)	1.4 (2.4)	1.6 (2.6)	3.9 (6.9)	0.01
Acid exposure time off PPI (%) [N=204]	1.9 (1.9)	1.6 (4.4)	1.5 (2.6)	1.5 (2.5)	4.2 (8.0)	0.05
Acid exposure time on PPI (%) [N=54]	3.8 (6.2)	0.8 (2.2)	0.5 (1.1)	2.0 (3.1)	3.3 (2.7)	0.09

	Phenotype Clusters					
	LPR/GERD hiatal hernia	**Mild LPR/ GERD**	**No LPR/No GERD**	**Reflex Cough**	**Mixed/Possible Obstructive EGJ**	
	A (n=26)	**B (n=72)**	**C (n=94)**	**D (n=57)**	**E (n=53)**	**p-value**
DMNBI (Ohms) [N=226]	1.8 (1.3)	2.8 (1.3)	2.2 (1.2)	2.5 (1.2)	2.1 (1.0)	0.01
Symptom index	56.5 (33.5)	41.5 (39.2)	29.4 (36.3)	39.1 (29.0)	34.8 (19.7)	0.61
Positive SAP for extra-esophageal symptom (>95%)	3/7 (42.9%)	14/24 (58.3%)	3/6 (50.0%)	14/22 (63.6%)	5/11 (45.5%)	0.80
Other Variables						
Salivary pepsin concentration (ng/ml) [N=77]	107.2 (116.7)	150.5 (156.6)	77.7 (85.7)	68.2 (88.3)	40.1 (40.8)	0.03
GerdQ Score [N=213]	8.9 (3.2)	8.5 (2.7)	7.0 (2.6)	7.6 (2.9)	7.1 (3.0)	0.01
RSI Score [N=258]	24.8 (12.8)	22.7 (8.9)	17.8 (9.0)	20.5 (9.0)	16.8 (13.1)	<0.01

Body mass index (BMI); Lower esophageal sphincter (LES); Integrated relaxation pressure (IRP); Upper esophageal sphincter (UES); Laryngopharyngeal reflux (LPR); Proton pump inhibitor (PPI); Distal mean nocturnal baseline impedance (DMNBI); Symptom association probability (SAP); Reflux symptom index (RSI); Gastroesophageal reflux disease (GERD); Esophagogastric junction (EGJ).

Table 2.

Distribution of Clinical and Physiologic Variables Across Clusters in Sub-Group Analysis

	SubGroup Clusters		
	Sub Group A (n=9)	**Sub Group B (n=64)**	**Sub Group C (n=178)**
Demographics			
Age (years)	45.4 (7.39)	43.4 (13.8)	63.0 (12.3)
Male	3 (33.3%)	21 (32.8%)	53 (29.8%)
BMI (kg/m^2)	28.0 (3.98)	26.4 (6.42)	27.1 (5.92)
Symptom Presentation			
Cough	7 (77.8%)	39 (60.9%)	84 (47.2%)
Laryngeal Symptoms	7 (77.8%)	50 (78.1%)	149 (83.7%)
Voice Hoarseness	4 (44.4%)	34 (53.1%)	114 (64.0%)
Sore Throat	4 (44.4%)	17 (26.6%)	13 (7.3%)
Throat Clearing	6 (66.7%)	43 (67.2%)	143 (80.3%)
Globus	5 (55.6%)	30 (46.9%)	106 (59.6%)
Regurgitation	4 (44.4%)	26 (40.6%)	38 (21.3%)
Heartburn	3 (33.3%)	28 (43.8%)	57 (32.0%)
Chest Pain	2 (22.2%)	18 (28.1%)	22 (12.4%)
High Resolution Manometry			
LES-CD separation; Hiatal Hernia Size (cm)	1.4 (1.4)	0.4 (0.8)	0.3 (0.9)
Hernia Present	5 (55.6%)	11 (17.2%)	21 (11.8%)
Normalized LES IRP Ratio	0.6 (0.6)	0.7 (0.4)	0.6 (0.3)
Percent ineffective swallows	45.6 (40.6)	7.73 (11.5)	38.1 (31.3)
Mean UES Basal Pressure (mmHg)	58.2 (10.2)	84.9 (47.3)	102 (63.5)
Ambulatory Reflux Monitoring			
Number of Reflux Events	112 (47.3)	29.3 (20.4)	11.8 (11.5)
Overall acid exposure time (%)	3.97 (5.66)	1.89 (4.1)	1.94 (4.1)
Acid exposure time off PPI (%)	3.96 (4.29)	1.98 (4.66)	1.96 (4.29)
Acid exposure time on PPI (%)	3.99 (7.81)	1.64 (1.91)	1.85 (3.18)
DMNBI (Ohms)	2.02 (1.36)	2.7 (1.38)	2.26 (1.15)
Positive SAP for extra-esophageal symptom (>95%)	6 (66.7%)	31 (62.0%)	60 (51.3%)
Other Variables			
Salivary pepsin concentration (ng/ml)	106 (125.3)	77.3 (100.9)	43.5 (71.1)
GerdQ Score	9.4 (2.61)	7.75 (2.93)	7.59 (2.77)
RSI Score	25.5 (11.9)	19.3 (9.56)	19.9 (9.98)

Body mass index (BMI); Lower esophageal sphincter (LES); Integrated relaxation pressure (IRP); Upper esophageal sphincter (UES); Laryngopharyngeal reflux (LPR); Proton pump inhibitor (PPI); Distal mean nocturnal baseline impedance (DMNBI); Symptom association probability (SAP); Reflux symptom index (RSI); Gastroesophageal reflux disease (GERD); Esophagogastric junction (EGJ).