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Original Article

Distal Mean Nocturnal Baseline Impedance Predicts Pathological Reflux of Isolated Laryngopharyngeal Reflux Symptoms

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Background/Aims
Diagnosis of isolated laryngopharyngeal reflux symptoms (ILPRS), ie, without concomitant typical reflux symptoms (CTRS), remains difficult. Mean nocturnal baseline impedance (MNBI) reflects impaired mucosal integrity. We determined whether esophageal MNBI could predict pathological esophagopharyngeal reflux (pH+) in patients with ILPRS.

Methods
In this cross-sectional study conducted in Taiwan, non-erosive or low-grade esophagitis patients with predominant laryngopharyngeal reflux symptoms underwent combined hypopharyngeal multichannel intraluminal impedance-pH monitoring when off acid suppressants. Participants were divided into the ILPRS (n = 94) and CTRS (n = 63) groups. Asymptomatic subjects without esophagitis (n = 25) served as healthy controls. The MNBI values at 3 cm and 5 cm above the lower esophageal sphincter (LES) and the proximal esophagus were measured.

Results
Distal but not proximal esophageal median MNBI values were significantly lower in patients with pH+ than in those with pH– (ILPRS in pH+ vs pH–: 1607 Ω vs 2709 Ω and 1885 Ω vs 2563 Ω at 3 cm and 5 cm above LES, respectively; CTRS in pH+ vs pH–: 1476 vs 2307 Ω and 1500 vs 2301 Ω at 3 cm and 5 cm above LES, respectively, $P < 0.05$ for all). No significant differences of any MNBI exist between any pH– subgroups and healthy controls. The areas under the receiver operating characteristic curve in the ILPRS group were 0.75 and 0.80, compared to the pH– subgroup and healthy controls ($P < 0.001$ for both), respectively. Interobserver reproducibility was good (Spearman correlation 0.93, $P < 0.0001$).

Conclusion
Distal esophageal MNBI predicts pathological reflux in patients with ILPRS.
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Key Words
Diagnosis; Esophageal pH monitoring; Gastroesophageal reflux; Laryngopharyngeal reflux

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Introduction

Laryngopharynx reflux (LPR) is an extraesophageal manifestation of gastroesophageal reflux disease (GERD), involving excessive backflow of gastric content into the laryngopharynx.[1] Diagnosis of LPR is challenging, particularly for those with isolated LPR symptoms (ILRPS), ie, without concomitant typical reflux symptoms (CTRS), due to protean and non-specific laryngeal symptoms/signs[2] and normal esophageal mucosa in the majority of patients.[3]

Reflux theory (direct damage of laryngeal mucosal surface by refluxate exposure) and reflex theory (indirect vagal reflex arc between the esophagus and airway triggered by acid reflux) have been proposed as mechanisms of LPR symptom generation.[4] However, little is known about the mechanism of absent esophageal symptoms and physiological characteristics in patients with ILPRS. Recently, Lien et al[5] used 24-hour combined hypopharyngeal multichannel intraluminal impedance-pH (HMII-pH) to define pathological esophagopharyngeal reflux, ie, excessive acid exposure time in the distal esophagus, and/or pharyngeal acid reflux episodes ≥ 2/day. They found that both ILPRS and CTRS groups (63% and 57%) with pathological esophagopharyngeal reflux responded equally well to proton pump inhibitors (PPIs) therapy, compared to the non-refluxers (32%).[5] In addition, patients with ILPRS were less likely to respond to the esophageal acid perfusion test, and had fewer pharyngeal pathological reflux episodes compared to its counterpart. These findings imply that the generation of symptoms in patients with ILPRS may involve a vago-vagal-mediated "reflex" or central sensitization, rather than "reflux" mechanism.[6] In the recent America Collage of Gastroenterology guidelines for GERD, upfront reflux monitoring is recommended in patients with ILPRS before PPIs therapy.[7] Given the absence of concomitant esophageal symptoms, obtaining evidence of reflux in this challenging subset of patients is of paramount importance in the clinical setting.[1]

Mean nocturnal baseline impedance (MNBI) is an impedance-pH metric assessing impaired mucosal integrity of the esophagus owing to chronic reflux, and has been proposed to segregate GERD patients from healthy controls.[8] Low MNBI (< 2292 Ω) in the distal esophagus predicts the response to anti-reflux therapy and is also considered to be an adjunctive diagnosis of GERD according to the Lyon Consensus.[9] In contrast, data on MNBI in patients with LPR are limited. Kavitt et al[10] conducted a case-control study to measure mucosal impedance (MI) in patients with LPR symptoms during endoscopy. They found that patients with pathological reflux in the distal esophagus detected by wireless pH monitoring have a lower MI than those without.[10] However, data in patients with ILPRS remain unknown, and the diagnostic ability of MI, including sensitivity and specificity, was not evaluated in that study.

In this study, we hypothesized that distal esophageal MNBI values in non-erosive or low-grade esophagitis patients with ILPRS may predict pathological esophagopharyngeal reflux. Based on the 2 distinct phenotypes, ie, CTRS and ILPRS, we compared MNBI values in both distal and proximal esophagus between patients with and without pathological esophagopharyngeal reflux. We also evaluated the diagnostic ability of MNBI and determined the best cutoff values for separating patients with pathological reflux from those with physiological reflux and from healthy controls.

Materials and Methods

This was prospective multicenter cohort study evaluating referral patients with LPR symptoms. The Institutional Review Board of Taichung Veterans General Hospital approved the protocol (#CF16150B) in accordance with the Declaration of Helsinki and Good Clinical Practice. All participants signed an informed consent form prior to undergoing the investigations.

Patient Population

Patients with suspected LPR symptoms referred from otolaryngologic outpatient clinics in tertiary medical centers were prospectively enrolled during the period from June 2016 to June 2019.

Patients (aged > 20 years) with a chief complaint of chronic laryngitis symptoms for more than 3 months, such as hoarseness, cough, throat clearing, or globus (at least moderate severity) were evaluated for eligibility, which included comprehensive history taking, laryngoscopic signs based on the Reflux Finding Score,[11] and

an upper gastrointestinal endoscopy. Participants also filled out a LPR-specific questionnaire, the Chinese version Reflux Symptoms Index to evaluate the symptom severity.[12,13]

Participants were excluded if there was any evidence of the following conditions: severe esophagitis (Los Angeles classification Grade C or D), Barrett's esophagus, or any common non-reflux etiologies of chronic laryngitis, as stated previously.[5] Healthy subjects recruited from flyers served as controls. To obtain the norms of MNBI, patients were excluded from the study if they had airway or reflux symptoms, were taking acid suppressive therapy, had any grade esophagitis or endoscopic suspected esophageal metaplasia, or had evidence of pathological reflux on the HMII-pH test.

Study Design

Eligible participants underwent 24-hour combined hypopharyngeal multichannel intraluminal impedance-pH (HMII-pH) monitoring. The catheter was composed of 2 pH sensors (hypopharynx and distal esophagus) and 6 pairs of impedance electrodes (catheter models ZAI-BL-54, -55, and -56; Sandhill Scientific, Highlands Ranch, CO, USA). We selected catheters according to subjects' esophageal length. The proximal pH probe was positioned 1 cm above the proximal margin of the upper esophageal sphincter (UES) and the distal pH probe was placed at 5 cm (± 1 cm) above the proximal margin of the lower esophageal sphincter (LES), determined by high resolution manometry (SOLAR GI HRIM, MMS, Enschede, Netherlands). There were 6 impedance pairs, with 2 located at the hypopharynx, 2 at the proximal esophagus (2 ± 1 cm and 4 ± 1 cm below the UES), and 2 at the distal esophagus (3 ± 1 cm and 5 ± 1 cm above LES), respectively. Participants recorded their meals, supine or upright position, and symptom events throughout the period of data acquisition while off PPI for at least 7 days. After recording, the impedance pH data were uploaded and analyzed using Bioview Analysis software (Sandhill Scientific, Highlands Ranch, CO), which calculated acid exposure time (AET%) in the distal esophagus automatically.

Measurements and Data Analysis

Pathological esophagopharyngeal acidic reflux, or pH (+) was defined as: 1) ≥ 2 pharyngeal acid reflux episodes; and/or 2) excessive distal esophageal acid reflux, ie, the percent time with pH < 4 at 5 cm above the LES (total > 4.2%, or upright > 6.3%, or supine > 1.2%) during the 24-hour recording period.[5,14] Patients with suspected LPR were divided into 2 groups based on the presence or absence of concomitant typical reflux symptoms, ie, CTRS or ILPRS, respectively. CTRS was defined as the presence of heartburn or regurgitation at least twice per week with mild symptoms, or once per week with moderate to severe symptoms. Each group was further divided into pH (+) and pH (–) groups.

MNBI values were determined by averaging 3 nocturnal 10-minute periods (at 1:00 AM, 2:00 AM, and 3:00 AM) selected to avoid events such as reflux, swallows, and pH drops during the recumbent period, at 3 impedance electrodes (3 ± 1 cm and 5 ± 1 cm above LES and 4 ± 1 cm below the UES, or proximal esophagus).[15] Two independent observers read the tracings manually to assess interobserver agreement of MNBI values.

Statistical Methods

Demographic data, clinical presentations, and impedance-pH values were compared between the pH (+) and pH (–) groups in both CTRS and ILPRS patients. Categorical variables were compared using Pearson chi-square tests. Continuous variables were compared using Kruskal-Wallis tests. P-value < 0.05 was considered significant. We also conducted receiver operating characteristic (ROC) analysis and calculated the area under the curve (AUC) for pairwise comparisons and evaluation of the diagnostic performance of MNBI for the prediction of pH (+). The sensitivity and specificity were calculated with best cutoff points of the MNBI normal threshold based on the maximal Youden index. Interobserver agreement of the MNBI readings and correlation between MNBI and AET% were evaluated by Spearman rank correlation test.

To determine the appropriate sample size, we used a conservative estimate of standard deviation of 1513 Ω,[16] and assumed a difference of 1300 Ω and 1100 Ω in impedance values between pH (+) and pH (–) for the CTRS and ILPRS groups, respectively. Based on this model, 57 and 81 subjects with a pH (–) to pH (+) ratio of 2:1 in each corresponding groups may provide 80% power with a significant level of 0.025. (https://clincalc.com/Stats/SampleSize.aspx).

Results

Baseline Characteristics

A total of 157 subjects with suspected LPR completed impedance-pH tests, including 63 and 94 subjects in the CTRS and ILPRS group, respectively (Fig. 1). Among them, 23 (36%) and 31 (33%) subjects in the corresponding groups had pathologic reflux. Twenty-five healthy subjects were included in the control group.

The baseline characteristics are shown in Table 1. There was no significant differences in age, gender, or ENT first visit (consulting

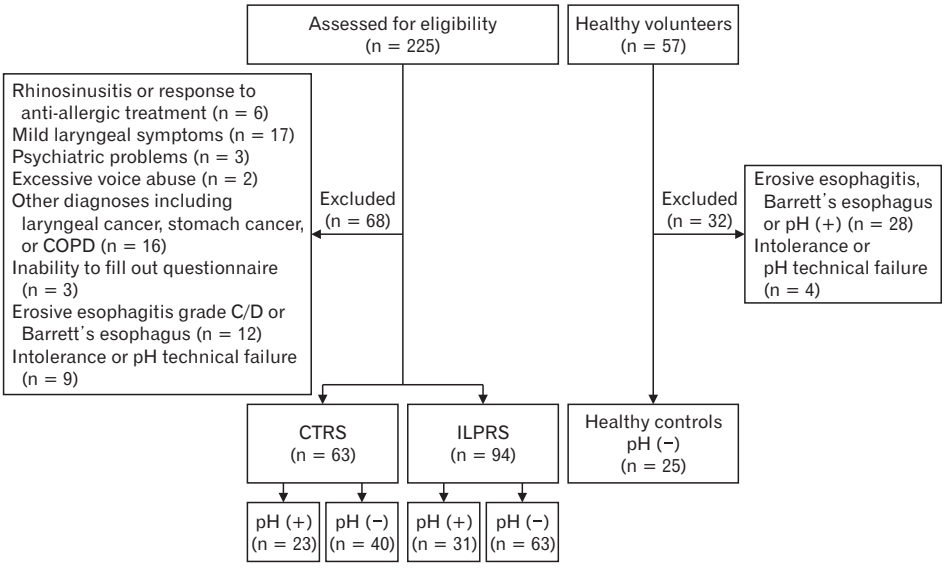

Figure 1. Flow chart of study population. CTRS, concomitant typical reflux syndrome; ILPRS, isolated laryngopharyngeal reflux symptoms; COPD, chronic obstructive pulmonary disease.

otolaryngologists first for their primary laryngeal symptoms) between the pH (+) and pH (–) groups in both CTRS and ILPRS groups. The healthy controls were slightly younger than those in the CTRS and ILPRS groups. In the CTRS group but not the ILPRS group, patients with pH (+) had higher body mass index than those with pH (–) ($P < 0.05$). Other clinical features including endoscopic findings, major laryngeal symptoms, symptom durations, comorbidities, and rates of previous use of suppressive agents were similar between the pH (+) and pH (–) groups in both CTRS and ILPRS patients.

Mean Nocturnal Baseline Impedance

In the CTRS group, median (interquartile range) MNBI values at 3 cm above LES were significantly lower in those with pH (+) (1476 Ω; 920-1848 Ω) than in those with pH (–) (2307 Ω; 1920-2894 Ω, $P < 0.001$) and healthy controls (2639 Ω; 2342-2846 Ω, $P < 0.0001$). A similar trend was found at 5 cm above LES (Fig. 2 and Table 2). In the ILPRS group, significant differences, though to a lesser extent, were also found at 3 cm and 5 cm above LES between pH (+) and pH (–). In contrast, there were no differences among groups at the proximal esophagus. There were also no differences in the MNBI values at 3 cm and 5 cm between healthy controls and participants with pH (–) in both CTRS and ILPRS groups. The MNBI values at 3 cm above LES negatively correlated with AET% ($r = -0.55$, $P < 0.0001$ and −0.41, $P < 0.0001$ in the CTRS and ILPRS groups, respectively). The Spearman rank correlation coefficient for interobserver agreement of MNBI values at 3 cm above LES was 0.93 ($P < 0.0001$).

Diagnostic Efficacy of Mean Nocturnal Baseline Impedance

For the ILRPS group, ROC analysis revealed AUC of 0.75 and 0.80 when compared to the pH (–) group and healthy controls, respectively, for the diagnosis of pH (+). The sensitivity and specificity were respectively 0.65 and 0.71 when compared with the pH (–) group, and 0.65 and 0.88 when compared to healthy controls (Fig. 3 and Table 3).

Discussion

In this study, we prospectively assessed the feasibility of MNBI in the prediction of pathologic reflux or pH (+) in patients with suspected ILPRS and mild esophagitis or normal esophageal mucosa. To this purpose, the relationship of MNBI values and pH (+) in patients with the presence of CTRS and in healthy controls was also evaluated. We found that distal MNBI values were significantly lower in patients with pH (+) than those in patients with pH (–), for both ILPRS and CTRS groups. In addition, distal MNBI may also predict pH (+) in both groups. In contrast, proximal MNBI values were comparable among groups. There were no differences of MNBI between patients with pH (–) and healthy controls for both ILPRS and CTRS groups, regardless of proximal or distal esophagus.

In line with the findings of Kavitt et al,[10] we found that distal MNBI differentiated patients with pH (+) from those with pH (–) or healthy controls.[10] Similarly, in a large-scale (n = 239) retrospec-

Table 1. Demographic Data and Clinical Features of the Study Population

Demographic and clinical features	CTRS[a]		ILPRS[b]		Healthy controls (n = 25)
	pH (+)[c] (n = 23)	pH (–) (n = 40)	pH (+)[c] (n = 31)	pH (–) (n = 63)	
Demography					
Age (yr)	57 (48, 63)	53 (47, 61)	56 (49, 62)	56 (48, 64)	40 (34, 56)[g,h,i]
Male gender	12/23 (52.1)	13/40 (32.5)	22/31 (70.9)	40/63 (63.4)	6/25 (24.0)[h,i]
BMI (kg/m^2)	25.9 (24.4, 27)[j]	22.6 (21.4, 24.6)	24 (20.5, 25.7)	23.1 (21.6, 24.8)	22.2 (20.8, 23.2)[g]
ENT first visit	17/23 (73.9)	28/40 (70.0)	28/31 (90.3)	57/63 (90.4)	-
Clinical presentations					
Major laryngeal symptom					
Globus sensation	5/23 (21.7)	11/40 (27.5)	6/31 (19.3)	15/63 (23.8)	-
Throat pain	8/23 (34.7)	11/40 (27.5)	7/31 (22.5)	13/63 (20.6)	-
Hoarseness	5/23 (21.7)	11/40 (27.5)	10/31 (32.2)	22/63 (34.9)	-
Cough	3/23 (13.0)	6/40 (15.0)	6/31 (19.3)	9/63 (14.2)	-
Throat clearing	2/23 (8.7)	1/40 (2.5)	2/31 (6.5)	4/63 (6.3)	-
Typical GERD symptoms	23/23 (100.0)	40/40 (100.0)	0/31 (0.0)	0/63 (0.0)	-
Symptom duration, month	24 (12, 54)	24 (12, 42)	18 (6, 36)	12 (6, 36)	-
Previous acid suppressive therapy use (%)	18/23 (78.2)	34/40 (85)	14/31 (45.1)	33/63 (52.3)	-
Anti-reflux medication response	4/18 (22.2)	12/33 (36.3)	6/14 (42.8)	10/31 (32.2)	-
Diabetes mellitus	1/23 (4.3)	1/40 (2.5)	1/31 (3.2)	3/63 (4.8)	0/25 (0.0)
Hypertension	5/18 (27.7)	7/40 (17.5)	5/31 (16.1)	13/63 (20.6)	1/25 (4.0)
Endoscopic findings					
Erosion esophagitis					
No esophagitis	3/23 (13.0)	10/40 (25.0)	4/31 (12.9)	10/63 (15.8)	25/25 (100.0)
Esophagitis grade A	18/23 (78.2)	25/40 (62.5)	23/31 (74.1)	49/63 (77.7)	0/25 (0.0)
Esophagitis grade B	2/23 (8.7)	5/40 (12.5)	4/31 (12.9)	4/63 (6.3)	0/25 (0.0)
Hiatus hernia	1/23 (4.3)	2/40 (5.0)	2/31 (6.5)	3/63 (4.8)	0/25 (0.0)
Peptic ulcer	2/23 (8.7)	4/40 (10.0)	3/31 (9.7)	9/63 (14.2)	3/25 (12.0)
Helicobacter pylori	6/19 (31.5)	7/36 (19.4)	7/28 (25.0)	12/56 (21.4)	7/24 (29.1)
Reflux Finding Score[d]	8 (5, 11)	6 (4, 9)	7 (3, 9)	7 (5, 10)	-
Patient report outcome					
Reflux Symptom Index total score[e]	19 (14, 23)	18 (11, 23)	13 (8, 18)	11 (6, 16)	0 (0, 2)
Heartburn, frequency[f]	3 (2, 5)	3 (1, 4)	0 (0, 2)	0 (0, 1)	-
Heartburn, severity[f]	3 (2, 3)	2 (0, 3)	0 (0, 2)	0 (0, 1)	-
Acid regurgitation, frequency[f]	3 (2, 4)	3 (3, 4)	1 (0, 3)[j]	0 (0, 1)	-
Acid regurgitation, severity[f]	3 (2, 3)	3 (2, 4)	1 (0, 2)[j]	0 (0, 1)	-

[a]Concomitant typical reflux syndrome (CTRS) is defined as regurgitation or heartburn at least twice a week with mild symptom, or once a week with moderate/severe symptom.
[b]Isolated laryngopharyngeal reflux symptoms (ILPRS) is defined as patients with laryngopharynx reflux (LPR) without CTRS.
[c]pH (+), pathological esophagopharyngeal reflux, is defined as the presence of (1) excessive pharyngeal acid reflux (PAR), ie, ≥ 2 episodes of PAR; and/or (2) excessive distal esophageal acid reflux, ie, ≥ 4.2% of 24-hr, or ≥ 6.3% of upright position, or ≥ 1.2% of supine position.
[d]Score range from 0 to 26, with higher scores suggesting more severe laryngitis.
[e]Score range from 0 to 45, with higher scores indicating more severe symptoms.
[f]Score range from 0 to 5 for symptom frequency or severity, with higher scores suggesting worse quality of life.
[g]$P < 0.05$ for CTRS pH (+) vs healthy controls.
[h]$P < 0.05$ for ILPRS pH (+) vs healthy controls.
[i]$P < 0.05$ for ILPRS pH (–) vs healthy controls.
[j]$P < 0.05$ for pH (+) vs pH (–).
BMI, body mass index; ENT, ear, nose, and throat.
Pearson χ^2 tests were used for dichotomous variables, whereas Mann–Whitney *U* tests were used for continuous variables.
Data are expressed as median (interquartile range) or n (%).

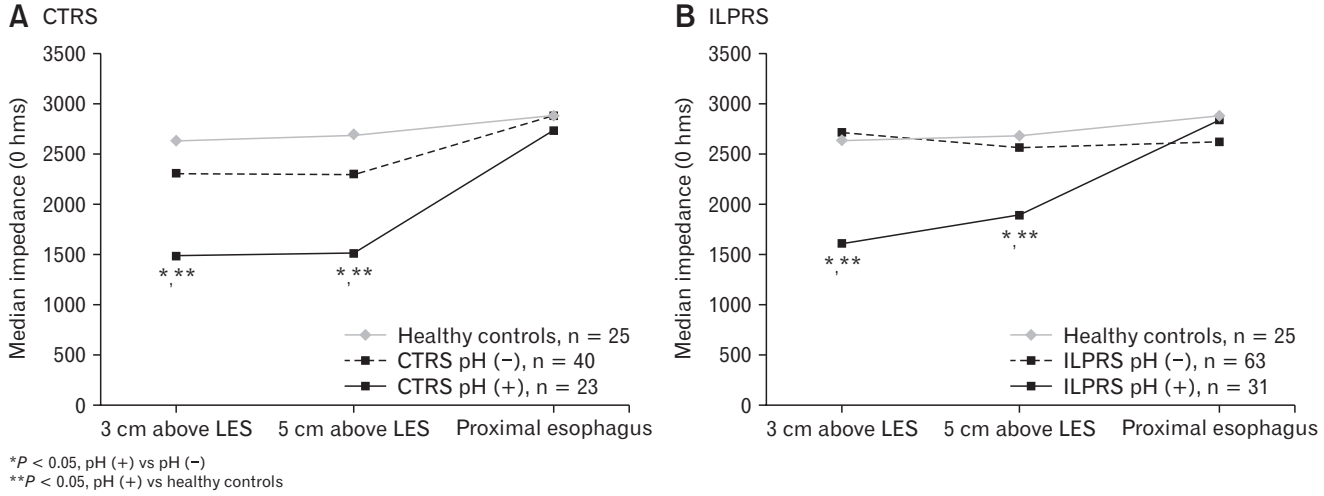

Figure 2. The median mean nocturnal baseline impedance (MNBI) measurements for the study groups at each of the measured sites (3 cm and 5 cm above the lower esophageal sphincter (LES) and proximal esophagus) in the concomitant typical reflux syndrome (CTRS) (Fig. 2A) and isolated laryngopharyngeal reflux symptoms (ILPRS) groups (Fig. 2B). MNBI values were lower in patients with pH (+) than those with pH (–) and healthy controls at 3 cm and 5 cm above LES in both the CTRS and ILPRS groups. However, MNBI values were similar over the proximal esophagus among all groups.

Table 2. Comparison of Acid Exposure Time, Acidic Reflux Episodes, and Mean Nocturnal Baseline Impedance Values of 24-Hour pH-impedance Between Patients With and Without Pathological Esophagopharyngeal Reflux in the Concomitant Typical Reflux Syndrome, Isolated Laryngopharyngeal Reflux Symptoms Groups, and Healthy Controls

Reflux parameters	CTRS[a]		ILPRS[b]		Healthy controls (n = 25)
	pH (+)[c] (n = 23)	pH (–) (n = 40)	pH (+)[c] (n = 31)	pH (–) (n = 63)	
24-hr pH test finding					
Distal esophageal acid exposure (%)	4.6 (2.3, 7.4)[d]	0.7 (0.1, 1.3)	4.6 (3.1, 9.2)[d]	0.2 (0.1, 1)	0.3 (0.1, 0.9)[e,f]
Excessive distal esophageal acid reflux	19/23 (82.6)[d]	0/40 (0)	27/31 (87.0)[d]	0/63 (0)	0/25 (0.0)[e,f]
Pharyngeal acid reflux events	1 (0, 6)[d]	0 (0, 0)	0 (0, 2)[d]	0 (0, 0)	0 (0, 0)[e,f]
Excessive pharyngeal acid reflux	11/23 (47.8)[d]	0/40 (0)	8/31 (25.8)[d]	0/63 (0)	0/25 (0.0)[e,f]
Number of reflux events					
Proximal esophagus					
Acid reflux events	14 (7, 24)[d]	4 (1, 7)	13 (6, 20)[d]	2 (1, 5)	7 (4, 10)[e,f,g]
Total events	25 (15, 32)[d]	10 (7, 18)	23 (12, 31)[d]	9 (5, 17)	30 (20, 45)[e,f]
Distal esophagus					
Acid reflux events	25 (17, 36)[d]	10 (4, 17)	26 (15, 34)[d]	8 (2, 16)	2 (0, 3)[e,f]
Total events	45 (31, 71)[d]	32 (23, 43)	50 (29, 54)[d]	30 (17, 43)	10 (7, 14)[e,f]
MNBI value					
Proximal esophagus	2730 (2205, 3213)	2873 (2144, 3391)	2835 (2113, 3565)	2616 (2173, 3168)	2885 (2481, 2972)
Distal esophagus					
5 cm	1500 (609, 2630)[d]	2301 (1664, 3002)	1885 (618, 2587)[d]	2563 (1818, 3405)	2690 (2183, 3032)[e,f]
3 cm	1476 (920, 1848)[d]	2307 (1920, 2894)	1607 (1049, 2441)[d]	2709 (1796, 3360)	2639 (2342, 2846)[e,f]

[a]Concomitant typical reflux syndrome (CTRS) is defined as regurgitation or heartburn at least twice a week with mild symptom, or once a week with moderate/severe symptom.
[b]Isolated laryngopharyngeal reflux symptoms (ILPRS) is defined as patients with laryngopharynx reflux (LPR) without CTRS.
[c]pH (+), pathological esophagopharyngeal reflux, is defined as the presence of (1) excessive pharyngeal acid reflux (PAR), ie, ≥ 2 episodes of PAR; and/or (2) excessive distal esophageal acid reflux, ie, ≥ 4.2% of 24-hr, or ≥ 6.3% of upright position, or ≥ 1.2% of supine position.
[d]$P < 0.05$ for pH (+) vs pH (–).
[e]$P < 0.05$ for CTRS pH (+) vs healthy controls.
[f]$P < 0.05$ for ILPRS pH (+) vs healthy controls.
[g]$P < 0.05$ for CTRS pH (–) vs healthy controls.
Data are expressed as median (interquartile range) or n (%).

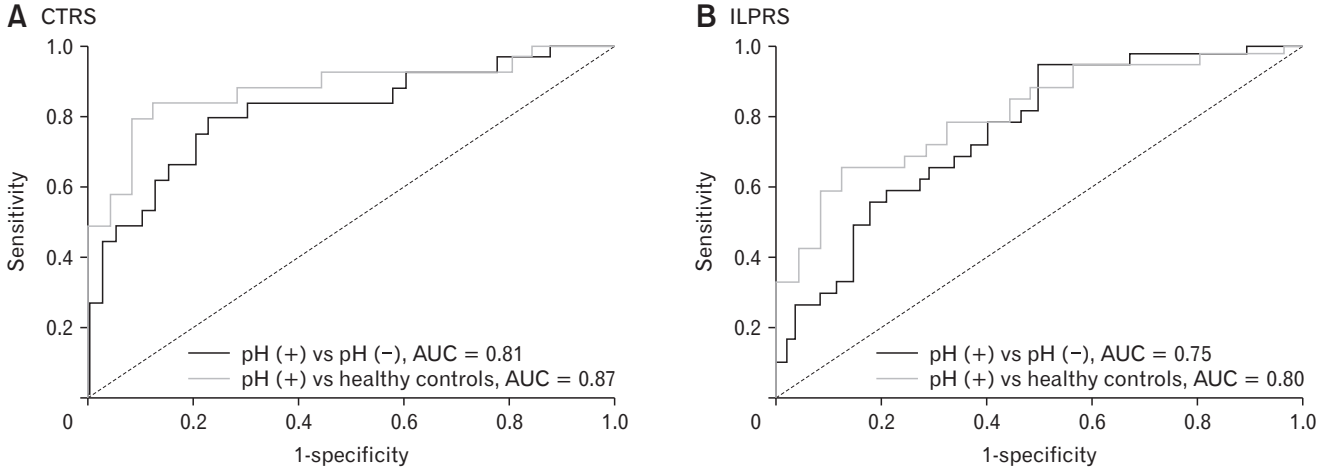

Figure 3. Receiver operating characteristic (ROC) curves in the concomitant typical reflux syndrome (CTRS) (A) and isolated laryngopharyngeal reflux symptoms (ILPRS) (B) groups. AUC, area under the curve.

Table 3. Diagnostic Accuracy of Mean Nocturnal Baseline Impedance in Laryngopharyngeal Reflux Phenotypes

Comparison of MNBI between pH (+) and control groups	AUC	Cut-point	Sensitivity	Specificity	Relative risk (95% CI)
Patients pH (+) vs pH (–)					
CTRS[a] + ILPRS[b]	0.77	2059	0.72	0.71	6.3 (3.0-13.1)
CTRS[a]	0.81	1864	0.78	0.78	12.4 (3.6-42.8)
ILPRS[b]	0.75	2059	0.65	0.71	15.0 (3.3-68.1)
Patients pH (+) vs healthy controls					
CTRS[a] + ILPRS[b]	0.83	2065	0.72	0.88	19.1 (5.0-73.2)
CTRS[a]	0.87	2038	0.83	0.88	34.8 (6.9-175.6)
ILPRS[b]	0.80	2065	0.65	0.88	13.3 (3.2-54.8)

[a]Concomitant typical reflux syndrome (CTRS) is defined as regurgitation or heartburn at least twice a week with mild symptom, or once a week with moderate/severe symptom.
[b]Isolated laryngopharyngeal reflux symptoms (ILPRS) is defined as patients with laryngopharynx reflux (LPR) without CTRS.
MNBI, Mean nocturnal baseline impedance; AUC, area under the ROC curve.
Best cutoff points for MNBI at 3 cm above the LES were based on maximal Youden index.

tive cohort study, Ribolsi et al[17] found that patients with suspected LPR and pathological MNBI (< 2292 Ω) in the distal esophagus may predict PPI-responsiveness with a sensitivity of 71% and a specificity of 57%.

When combined the CTRS and ILPRS groups, our study found a sensitivity of 72% in the prediction of pathological esophagopharyngeal reflux, and a specificity of 71% and 88% when comparing to patients with pH (–) and healthy controls, respectively (Table 3). When divided into the CTRS and ILPRS groups, substantial differences were observed in our study. In the CTRS group, there was an area under the ROC curve of 0.81-0.87 and a moderately negative correlation coefficient of −0.55 ($P < 0.0001$) with AET%, suggest a comparable diagnostic accuracy compared with patients with typical GERD in the literature.[15,18] However, a relatively lower area under the ROC curve of 0.75-0.80 and a lower correlation coefficient of −0.41 ($P < 0.0001$) with AET% found in the ILPRS group, seem to indicate a lower diagnostic accuracy of MNBI compared to its counterpart. In addition, the median distal MNBI value tends to be higher in the ILPRS group than that in the CTRS group (1607 vs 1476, Table 2), suggesting a possible link of mucosal integrity to the symptom perception in the distal esophagus despite similar AET% between them.[19] These results also support the recent findings that patients with ILPRS and pathological reflux are relatively insensitive to acid in the distal esophagus despite similar AET% and PPI-responsiveness to those with CTRS.[5]

One may postulate a lower MNBI value in the proximal esophagus in patients with LPR. In a large-scale retrospective observational study (n = 242), Chen et al[20] compared MNBI values among 4 groups defined by symptoms, ie, CTRS, ILPRS, GERD only, and healthy controls. They found decreased MNBI values in the proximal esophagus in patients with CTRS compared to the other 3 groups, suggesting a possible diagnostic role of proximal esophageal mucosal integrity. However, in their ILPRS group, both AET% and distal MNBI values were similar to those in the healthy controls. Although the reasons are unclear, defining patients with ILPRS by symptom alone may include patients without objective evidence of pathological reflux.

The merit of our studies is 2-fold. First, using the HMII-pH catheters to diagnose pathological esophagopharyngeal reflux in this study may be more reliable than using traditional dual pH-metry, because the configuration of HMII-pH incorporated 2 trans-upper esophageal sphincter impedance channels to trace the refluxate along the entire esophagus to the hypopharynx for the detection of pharyngeal acid reflux episodes.[21] Second, the criteria of pathological esophagopharyngeal reflux in this study comprised of acid (pH < 4) and part of weakly acid (pH between 4 and 5) reflux episodes and pathological AET% in the distal esophagus have been shown to predict PPI responsiveness in patients with ILPRS.[5] One of the potential contributions of our study is to support the future implications for the newly developed esophageal balloon-incorporated MI test performed via direct mucosal contact during endoscopy particularly in patients with suspected ILPRS.[22]

There were some limitations in this study. First, our patients were all ethnic Chinese and only recruited from tertiary centers. Some of them have been prescribed PPIs for variable durations despite suspending the medications for more than 1 week prior to the HMII-pH test. Thus, the sensitivity and specificity may not be applicable to other ethnicities, primary care settings, or PPI-naive patients. Second, PPI responsiveness was not evaluated in our study, as the primary interest in this study was the objective evidence of GERD test in patients with ILPRS.

In conclusion, distal esophageal MNBI measurement is valuable in the prediction of pathological esophagopharyngeal reflux in patients with suspected LPR, in both the CTRS and ILPRS groups. The diagnostic ability of distal MNBI in the CTRS group seems to be superior to that seen in the ILPRS group, although further studies assessing associations of treatment outcomes to MNBI values are warranted.

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