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Original Article

Baseline Impedance via Manometry Predicts Pathological Mean Nocturnal Baseline Impedance in Isolated Laryngopharyngeal Reflux Symptoms

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Background/Aims
Distal mean nocturnal baseline impedance (MNBI) measuring via pH-impedance may be valuable in diagnosing patients with suspected laryngopharyngeal reflux (LPR). However, its wide adoption is hindered by cost and invasiveness. This study investigates whether baseline impedance measured during high-resolution impedance manometry (HRIM-BI) can predict pathological MNBI.

Methods
A cross-sectional study in Taiwan included 74 subjects suspected of LPR, who underwent HRIM (MMS) and pH-impedance testing (Diversatek), after stopping proton pump inhibitors for more than 7 days. Subjects with grade C or D esophagitis or Barrett's esophagus were excluded. The cohort was divided into 2 groups: those with concomitant typical reflux symptoms (CTRS, n = 28) and those with isolated LPR symptoms (ILPRS, n = 46). HRIM-BI measurements focused on both distal and proximal esophagi. Pathological MNBI was identified as values below 2065 Ω, measured 3 cm above the lower esophageal sphincter.

Results
In all subjects, distal HRIM-BI values correlated weakly with distal MNBI(r = 0.34-0.39, $P < 0.005$). However, in patients with ILPRS, distal HRIM-BI corelated moderately with distal MNBI(r = 0.43-0.48, $P < 0.005$). The areas under the receiver operating characteristic curve was 0.78 ($P = 0.001$) with a sensitivity of 0.83 and a specificity of 0.68. No correlation exists between distal HRIM-BI and distal MNBI in patients with CTRS, and between proximal HRIM-BI and proximal MNBI in both groups.

Conclusions
Distal HRIM-BI from HRIM may potentially predict pathological MNBI in patients with ILPRS, but not in those with CTRS. Future outcome studies linked to the metric are warranted.
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Key Words
Diagnosis; Electric impedance; Esophageal pH monitoring; Laryngopharyngeal reflux; Manometry

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Introduction

Laryngopharyngeal reflux (LPR) is an extraesophageal manifestation of gastroesophageal reflux disease (GERD), characterized by laryngeal symptoms such as coughing, hoarseness, and throat clearing, along with signs like edema, erythema, and vocal cord granuloma.[1,2] Identifying isolated LPR symptoms (ILPRS), ie, those without concurrent typical reflux symptoms (CTRS), poses a considerable challenge due to the overlapping complexity with various non-reflux etiologies and the typically normal appearance of the esophageal mucosa in most patients.[3,4]

The American College of Gastroenterology recently recommended the use of pH-impedance monitoring for GERD diagnosis over empirical proton pump inhibitor (PPI) therapy in patients with suspected ILPRS.[5,6] This guidance is based on the observation that most patients with suspected ILPRS do not actually have reflux,[7,8] and prolonged PPI use can delay the identification of non-reflux conditions and increase healthcare costs.[9] Moreover, the Lyon Consensus highlighted that impedance metrics, such as the mean nocturnal baseline impedance (MNBI), obtained through ambulatory pH-impedance monitoring, may enhance diagnostic precision,[10] leading to an expected increase in the demand for these tests.

MNBI, calculated by averaging the baseline impedance during 3 nocturnal recording periods over the entire sleep period, serves as a marker of mucosal integrity.[11] It can reflect the severity of chronic reflux burden and often moderately correlates with acid exposure time. A reduced MNBI, particularly in the distal esophagus, may predict the effectiveness of anti-reflux interventions,[12] and is also recognized as an additional diagnostic criterion for GERD as outlined in the Lyon Consensus.[10] Moreover, the utility of MNBI extends to predicting response to anti-reflux therapy in individuals suspected of having LPR[13-15] and may even predict a decline in lung function in patients with idiopathic pulmonary fibrosis after a lung transplant.[16]

Despite the promising diagnostic potential of pH-impedance technology, its cost, availability, invasiveness, and the need for manometry for catheter placement could limit its widespread use.[17] As an alternative, high-resolution esophageal manometry with impedance (HRIM) has the theoretical capability to assess esophageal epithelial integrity. Studies have explored HRIM's effectiveness in measuring baseline impedance (HRIM-BI), with a key study by Ravi et al[18] showing that HRIM-BI can differentiate GERD patients based on their esophageal acid exposure. However, variations in HRIM-BI readings across different manufacturers and its moderate to weak correlation with MNBI in LPR patients suggest that these 2 methods may not be interchangeable.[19,20] Besides, the diagnostic accuracy of HRIM-BI, including its sensitivity and specificity in patients with suspected ILPRS, remains to be clarified.

In our study, we hypothesize that HRIM-BI could predict pathological MNBI in patients with non-erosive or low-grade esophagitis and ILPRS. Recognizing the distinct phenotypes of CTRS and ILPRS, we compared HRIM-BI values between patients with and without pathological MNBI in both the distal and proximal esophagi. We also assessed the diagnostic potential of HRIM-BI and established optimal cutoff values to differentiate patients with pathological MNBI from those with physiological MNBI and healthy controls.

Materials and Methods

This prospective, multicenter study evaluated individuals referred for symptoms suggestive of LPR. The research protocol (#CF16150B) received approval from the Institutional Review Board at Taichung Veterans General Hospital, in compliance with the ethical standards of the Declaration of Helsinki and Good Clinical Practice guidelines. Before any assessments were conducted, all participants provided their informed consent by signing a designated form.

Participant Population

From September 2016 to June 2019, we enrolled individuals experiencing symptoms associated with LPR. These participants were referred from otolaryngology outpatient clinics at tertiary medical centers, including Taichung Veterans General Hospital, China Medical University Hospital, and Chung Shan Medical University Hospital in Taiwan. To be eligible, participants had to be older than 20 years and report a chief complaint of persistent laryngitis symptoms lasting for at least 3 months. Such symptoms encompassed hoarseness, coughing, throat clearing, or a sensation of a lump in the throat (globus) of more than moderate severity. The eligibility evaluation included a detailed medical history review, examination for laryngoscopic signs using the Reflux Finding Score,[21] and an upper gastrointestinal endoscopy. Moreover, participants completed the Chinese version of the Reflux Symptoms Index questionnaire to assess the severity of their LPR-related symptoms.[22,23]

We excluded individuals showing signs of severe esophagitis (Los Angeles classification grade C or D), Barrett's esophagus,

or any common non-reflux related causes of chronic laryngitis, including but not limited to achalasia, allergy, and cancer. This also extended to those who were unable or unwilling to complete the study.[24] Healthy control subjects, identified through the distribution of flyers, were excluded if they reported airway or reflux symptoms, were undergoing acid suppressive therapy, showed any degree of esophagitis, or had suspected esophageal metaplasia identified during endoscopy. Additionally, subjects with a pathological MNBI defined as value below 2065 Ω at 3 cm above the upper margin of the lower esophageal sphincter (LES), as determined by ambulatory pH-impedance testing from a prior study,[25] were also excluded (Fig. 1).

Study Design

Participants who met the inclusion criteria underwent comprehensive diagnostic procedures, including HRIM (SOLAR GI HRIM; MMS, Enschede, Netherlands) and 24-hour ambulatory hypopharyngeal multichannel intraluminal impedance-pH (HMII-pH; Diversatek Healthcare, Highlands Ranch, CO, USA) monitoring. These were conducted after a minimum of 7 days without PPI and other acid suppressants use. HRIM was performed before HMII-pH monitoring. During the HMII-pH monitoring phase, participants were advised to maintain their usual activities and diet, with the exception of avoiding acidic beverages and refraining from anti-reflux medications. They also kept a detailed diary of their meal consumption, body position (whether supine or upright), and any symptoms they experienced.

High-resolution Impedance Manometry Measurements

For HRIM, we utilized a 4 mm solid-state catheter fitted with 32 pressure sensors (spaced 1 cm apart) and 16 adjacent impedance segments (each 2 cm apart) from SOLAR GI HRIM. The assessment, conducted by an experienced investigator, adhered to the Chicago classification version 3.0, starting with a minimum of a 1-minute adaptation period, a 30-second baseline measurement, and then ten 5 mL saline swallows in a supine position.[26] Participants were instructed not to swallow during the baseline measurement period.

Data from the HRIM-BI were uploaded and analyzed using the Medical Measurement Systems Analysis software (MMS). Baseline impedance was determined by selecting a 15-second interval during the baseline period of the HRIM procedure. This data was then transferred to a spreadsheet for manual calculation of the mean impedance at each sensor level.[18] Measurements of the proximal esophagus were taken at 2 ± 1 cm, 4 ± 1 cm, and 6 ± 1 cm below the upper esophageal sphincter (UES), and those of the distal esophagus were taken at 2 ± 1 cm, 4 ± 1 cm, 6 ± 1 cm, and 8 ± 1 cm above the LES.

Multichannel Impedance-pH Monitoring

The HMII-pH catheter comprised 2 pH sensors (located in the hypopharynx and distal esophagus) and 6 pairs of impedance electrodes (ZAI-BL-54, -55, and -56 catheter models). The selection of the catheter was based on each subject's esophageal length. We positioned the proximal pH probe 1 cm above the upper margin of the UES, and the distal probe was placed approximately 5 cm (with a possible variation of ± 1 cm) above the LES's upper margin. The 6 pairs of impedance electrodes were strategically arranged: 2 in the hypopharynx (1 at 1 cm above the UES and another across the UES), 2 in the proximal esophagus (at 2 ± 1 cm and 4 ± 1 cm below the UES), and 2 in the distal esophagus (at 3 ± 1 cm and 5 ± 1 cm above the LES).[27]

Analysis of impedance and pH data was performed using the Bioview Analysis software (Diversatek Healthcare), which automatically calculated the acid exposure time (AET) in the distal esophagus. To assess the MNBI levels, we focused on 3 impedance electrodes (3 ± 1 cm above LES, 5 ± 1 cm above LES, and 4 ± 1 cm below the UES or proximal esophagus) during nocturnal supine positioning. Specifically, three 10-minute intervals (around 1 AM, 2 AM, and 3 AM) were chosen manually, excluding instances of swallowing, reflux, and pH drops. The MNBI level was calculated by averaging the 3 measurements.[11] To reassure the reliability, we also used the simplified method for MNBI automated calculation by the software.[28] Furthermore, we examined the proximal-to-distal ratios of MNBI to mitigate individual variations.

Statistical Methods

The study divided participants into 2 groups: those with concurrent typical reflux symptoms (CTRS) and those with isolated LPR symptoms (ILPRS), determined by whether they experienced heartburn and/or regurgitation. CTRS was identified if participants reported heartburn or regurgitation at least twice weekly with mild symptoms or at least once weekly with moderate to severe symptoms. The participants were then further categorized based on the absence (MNBI[–]) or presence (MNBI[+]) of pathological mean nocturnal baseline impedance (< 2065 Ω at 3 cm above the LES), within both the CTRS and ILPRS groups. We analyzed demographic information, clinical manifestations, HRIM metrics

such as distal contractile integral, HRIM-BI, and contractile segment impedance, and HMII-pH measurements, including AET, number of reflux episodes, and MNBI values, across the MNBI-categorized groups. We employed Pearson chi-square tests for categorical data and Kruskal-Wallis tests for continuous variables. The Spearman rank correlation test was used to check the consistency of MNBI measurements between manual and software-based evaluations, and to investigate correlations among HRIM-BI and MNBI, MNBI and AET, and AET and HRIM-BI. Furthermore, receiver operating characteristic (ROC) analysis was conducted to assess the diagnostic performance of HRIM-BI in identifying pathological MNBI in participants with suspected LPR symptoms, using area under the curve (AUC) for pairwise comparisons. Sensitivity and specificity were calculated at the best cutoff points derived from the maximal Youden index for the normal HRIM-BI threshold. A *P*-value of less than 0.05 was considered statistically significant.

To calculate the appropriate sample size, we determined that a sample of 29 participants would be sufficient to identify a correlation coefficient of 0.5 within each group, with an alpha (α) level of 0.05 and a power of 80%.[29] For assessing diagnostic accuracy, we considered a standard deviation estimate of 200 Ω[19] and anticipated a difference of 250 Ω and 200 Ω in impedance measurements between pathological and normal MNBI values for the CTRS and ILPRS groups, respectively. Following this model, having 28 participants in the CTRS group and 47 participants in the ILPRS group, with a pathological to normal MNBI ratio of 1:1 for CTRS and 1:3 for ILPRS, respectively, is expected to provide an 80% power at a significance level of 0.025. Due to the preliminary nature and limited size of our study, we did not conduct analyses on potential confounders, effect modifiers, or perform sensitivity analyses.

Results

Baseline Characteristics

The baseline characteristics of study population including 23 healthy individuals are shown in Table 1. Participants suspected of having LPR were older and had more comorbidities specifically hypertension and post-nasal drip than the healthy controls. The ILPRS/MNBI(+) group had a higher percentage of males, while those in the CTRS/MNBI(+) group had a higher BMI when compared to the healthy control group. Moreover, individuals identified as CTRS/MNBI(+) and ILPRS/MNBI(+) exhibited increased Reflux Finding Scores relative to their counterparts.

Acid Exposure Time and Number of Reflux Episodes

Participants with pathological MNBI, ie, CTRS/MNBI(+) and ILPRS/MNBI(+), exhibited higher distal esophageal AET in the distal esophagus and higher number of acid reflux episodes in the proximal esophagus than their counterparts (Table 2). The number of acid reflux episodes in the hypopharynx was also higher in those with MNBI(+) than those with MNBI(−) in the CTRS group but was not different in the ILPRS group. Similarly, both CTRS/MNBI(+) and ILPRS/MNBI(+) exhibited a lower median MNBI value in the corresponding impedance channels of the proximal and distal esophagi, and a higher proximal/distal MNBI ratio, compared to their counterparts.

Baseline Impedance via Manometry

The HRIM-BI values in the distal esophagus (2 ± 1 cm, 4 ± 1 cm, 6 ± 1 cm, and 8 ± 1 cm above the LES) and contractile segment impedance at 3 cm and 5 cm were significantly lower and the proximal/distal HRIM-BI ratio was significantly higher in the ILPRS/MNBI(+) group compared to their counterparts (Table 2 and Supplementary Table). However, the HRIM-BI values were not different between the CTRS/MNBI(+) and CTRS/MNBI(−) groups at all impedance channels. The HRIM-BI values in the proximal esophagus were comparable across all MNBI-categorized groups (Table 2).

Correlation Coefficients and Diagnostic Efficacy of Baseline Impedance Measured During High-resolution Impedance Manometry

The Spearman rank correlation coefficients between manual and software methods for MNBI calculation ranged from 0.85 to 0.95 across all impedance channels. At 3 cm above LES, the MNBI values correlated moderately with AET, with a correlation coefficient of 0.74 for the CTRS group and 0.46 for the ILPRS group. In all subjects, the distal HRIM-BI correlated weakly (r = 0.34-0.39, $P < 0.005$) with distal MNBI and correlated poorly with AET. Notably, within the ILPRS group but not in the CTRS group, there was a moderate correlation between the distal HRIM-BI (2 ± 1 cm, 4 ± 1 cm, 6 ± 1 cm, and 8 ± 1 cm above LES) and distal MNBI (r = 0.43-0.48, $P < 0.005$) (Fig. 2 and Table 3). Besides, in the ILPRS group, ROC analysis of MNBI(+) revealed AUC of 0.78 and 0.76 when compared to MNBI(−) subjects and healthy controls, respectively. The sensitivity/specificity were 0.83/0.68 and 0.72/0.74 when compared to MNBI(−) subjects and healthy controls, respectively

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

Demographic and clinical features	CTRS[a]		ILPRS[b]		Healthy controls (n = 23)
	MNBI(+) (n = 14)	MNBI(–) (n = 14)	MNBI(+) (n = 18)	MNBI(–) (n = 28)	
Demography					
Age (yr)	58 (54, 63)[f]	53 (44, 60)[g]	57 (51, 60)[h]	55 (48, 63)[i]	43 (33, 53)
Male gender	7 (50.0)	4 (28.5)	13 (72.2)[h]	15 (53.5)	7 (30.4)
BMI (kg/m^2)	25.5 (23.1, 26.2)[f]	22.9 (21.0, 24.7)	23.9 (22.1, 24.8)	22.8 (20.9, 24.7)	22.2 (20.8, 23.5)
ENT first visit	11 (78.5)	11 (78.5)	17 (94.4)	27 (96.4)	-
Clinical presentations					
Major laryngeal symptom					
Globus sensation	4 (28.5)	3 (21.4)	5 (27.7)	4 (14.2)	-
Throat pain	3 (21.4)	5 (35.7)	5 (27.7)	5 (17.8)	-
Hoarseness	4 (28.5)	3 (21.4)	5 (27.7)	12 (42.8)	-
Cough	1 (7.1)	3 (21.4)	1 (5.6)	5 (17.8)	-
Throat clearing	2 (14.2)	0 (0.0)	2 (11.1)	2 (7.1)	-
Typical GERD symptoms	14 (100.0)	14 (100.0)	0 (0.0)	0 (0.0)	-
Symptom duration, month	36 (24, 57)	27 (12, 60)	19 (9, 45)	12 (6, 24)	-
Previous acid suppressive therapy use	11 (78.5)	12 (85.7)	11 (61.1)	13 (46.4)	-
Anti-reflux medication response	2 (18.1)	4 (33.3)	3 (27.2)	6 (46.1)	-
Diabetes mellitus	0 (0.0)	0 (0.0)	1 (5.6)	1 (3.6)	0 (0.0)
Hypertension	3 (21.4)[f]	1 (7.1)[g]	3 (16.6)[h]	4 (14.2)[i]	1 (4.3)
Post nasal drip	7 (50.0)[f]	6 (46.1)[g]	6 (33.3)[h]	14 (50)[i]	0 (0.0)
Endoscopic findings					
Erosion esophagitis					
No esophagitis	1 (7.1)[f]	3 (21.4)[g]	3 (16.6)[h]	3 (10.7)[i]	23 (100.0)
Esophagitis grade A	11 (78.5)	10 (71.4)	13 (72.2)	24 (85.7)	0 (0.0)
Esophagitis grade B	2 (14.2)	1 (7.1)	2 (11.1)	1 (3.6)	0 (0.0)
Esophagitis grade C	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hiatus hernia	1 (7.1)	1 (7.1)	1 (5.6)	1 (3.6)	0 (0.0)
Peptic ulcer	1 (7.1)	1 (7.1)	3 (16.6)	0 (0.0)	4 (17.3)
Helicobacter pylori	4 (33.3)	2 (14.2)	3 (18.7)	5 (21.7)[i]	8 (36.3)
Reflux Finding Score[c]	0 (0, 6)[j]	0 (0, 0)	3 (0, 7)[j]	0 (0, 0)	-
Patient report outcome					
Reflux Symptom Index total score[d]	19 (13, 22)[f]	19 (11, 24)[g]	12 (9, 18)[h]	12 (8, 17)[i]	0 (0, 3)
Heartburn, frequency[e]	2 (0, 3)	3 (1, 5)	0 (0, 2)	0 (0, 1)	-
Heartburn, severity[e]	2 (1, 2)	3 (2, 4)	0 (0, 2)	0 (0, 1)	-
Acid regurgitation, frequency[e]	3 (2, 4)	3 (3, 5)	1 (0, 2)	1 (0, 1)	-
Acid regurgitation, severity[e]	3 (2, 3)	3 (3, 4)	1 (0, 2)	1 (0, 2)	-

[a]Concomitant typical reflux syndrome (CTRS) is defined as regurgitation or heartburn at least twice a week with mild symptoms, or once a week with moderate/severe symptoms.

[b]Isolated laryngopharyngeal reflux symptoms (ILPRS) is defined as patients with laryngopharyngeal reflux without CTRS.

[c]Scores range from 0 to 26, with higher scores suggesting more severe laryngitis.

[d]Scores range from 0 to 45, with higher scores indicating more severe symptoms.

[e]Scores range from 0 to 5 for symptom frequency or severity, with higher scores suggesting worse quality of life.

[j]$P < 0.05$ for mean nocturnal baseline impedance (MNBI)(+) vs MNBI(–).

[f]$P < 0.05$ for CTRS MNBI(+) vs healthy controls.

[g]$P < 0.05$ for CTRS MNBI(–) vs healthy controls.

[h]$P < 0.05$ for ILPRS MNBI(+) vs healthy controls.

[i]$P < 0.05$ for ILPRS MNBI(–) vs healthy controls.

Pearson χ^2 tests were used for dichotomous variables, whereas Mann–Whitney *U* tests were used for continuous variables except that *t* tests were used when age and BMI were expressed as continuous variables (normal distribution).

BMI, body mass index; ENT, ear, nose, and throat; GERD, gastroesophageal reflux disease.

Data are presented as median (interquartile range) or n (%).

Table 2. Importance Clinical Metrics 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 = 23)
	MNBI(+) (n = 14)	MNBI(–) (n = 14)	MNBI(+) (n = 18)	MNBI(–) (n = 28)	
24-hr pH test finding					
AET	3.4 (2.1, 7.4)[e,f]	0.3 (0, 1.1)	3.7 (1.3, 6.2)[e,g]	0.6 (0.1, 1.3)	0.3 (0.2, 1.1)
Excessive distal esophageal acid reflux[c]	9 (64.2)[e,f]	1 (7.1)	10 (55.5)[e,g]	4 (14.2)	2 (8.7)
Pharyngeal acid reflux episodes	0 (0, 1)[e,f]	0 (0, 0)	0 (0, 0)[g]	0 (0, 0)[h]	0 (0, 0)
Excessive pharyngeal acid reflux[d]	3 (21.4)[f]	0 (0.0)	3 (16.6)	2 (7.1)	0 (0.0)
Number of reflux events					
Proximal esophagus					
Acid reflux episodes	8 (5, 15)[e,f]	3.5 (0, 6)	10 (5, 22)[e,g]	2 (1, 9)	3 (1, 3)
Total episodes	16 (8, 26)	9 (6, 18)	18 (11, 31)[g]	10 (6, 25)	10 (7, 14)
Distal esophagus					
Acid reflux episodes	20 (15, 30)[f]	14 (4, 28)	25 (11, 34)[g]	10 (3, 25)	7 (5, 10)
Total episodes	42 (25, 45)	33 (24, 44)	45 (28, 52)	33 (20, 50)	31 (22, 45)
Proximal to distal reflux episode ratio (proximal total events/distal total events)	0.4 (0.3, 0.6)	0.3 (0.2, 0.4)	0.4 (0.4, 0.6)[g]	0.4 (0.3, 0.5)	0.4 (0.3, 0.4)
MNBI value					
Proximal esophagus	2448 (2114, 2775)[e]	3215 (2611, 3432)	2108 (1879, 3042)[e,g]	2978 (2298, 3570)	2898 (2481, 3185)
Distal esophagus					
5 cm	926 (385, 1713)[e,f]	2955 (2335, 3198)	1441 (516, 1885)[e,g]	2824 (2540, 3892)	2690 (2183, 3049)
3 cm	1439 (855, 1619)[e,f]	2724 (2267, 3338)	1531 (1118, 1681)[e,g]	2839 (2500, 3586)	2636 (2433, 2969)
Proximal to distal MNBI ratio (Proximal/distal 3 cm)	2.0 (1.2, 3.2)[e,f]	1.0 (0.9, 1.4)	1.5 (1.3, 2.5)[e,g]	1.0 (0.7, 1.3)	1.0 (0.9, 1.1)
HRIM-BI value					
cm below the UES					
2 ± 1 cm	985 (768, 1284)	918 (812, 1142)	1087 (742, 1322)	1001 (849, 1410)	1006 (834, 1315)
4 ± 1 cm	753 (635, 1078)	740 (663, 951)	841 (659, 1047)	925 (702, 1179)	821 (672, 1091)
6 ± 1 cm	697 (576, 940)	663 (556, 765)	761 (558, 1197)	796 (624, 1133)	769 (600, 901)
Proximal average	802 (688, 1102)	778 (727, 966)	943 (661, 1159)	953 (695, 1220)	848 (732, 1033)
cm above the LES					
8 ± 1 cm	780 (609, 1230)	806 (667, 1043)	664 (613, 904)[e]	997 (760, 1232)	903 (599, 1271)
6 ± 1 cm	829 (745, 1376)	949 (725, 1190)	786 (631, 1150)[e]	1047 (885, 1315)	937 (675, 1313)
4 ± 1 cm	890 (727, 1352)	943 (788, 1128)	856 (637, 991)[e]	1231 (882, 1462)	1182 (744, 1428)
2 ± 1 cm	881 (673, 1140)	1008 (712, 1219)	716 (614, 991)[e,g]	1343 (863, 1501)	1221 (811, 1388)
Distal average	837 (692, 1316)	896(811, 1143)	798 (619, 932)[e]	1087 (914, 1387)	1112 (721, 1349)
Proximal to distal HRIM-BI ratio (Proximal average/distal average)	0.9 (0.8, 1.1)	0.9 (0.7, 1.3)	1.2 (0.8, 1.4)[e]	0.8 (0.7, 1.1)	1.0 (0.6, 1.3)

[a]Concomitant typical reflux syndrome (CTRS) is defined as regurgitation or heartburn at least twice a week with mild symptoms, or once a week with moderate/severe symptoms.
[b]Isolated laryngopharyngeal reflux symptoms (ILPRS) is defined as patients with laryngopharyngeal reflux without CTRS.
[c]Excessive distal esophageal acid reflux is defined as subjects with abnormal distal esophageal pH defined as percent time pH < 4 of ≥ 4.2% of 24-hr, or ≥ 6.3% of upright position, or ≥ 1.2% of supine position.
[d]Excessive pharyngeal acid reflux is defined as pharyngeal acid reflux ≥ 2 episodes.
[e]$P < 0.05$ for mean nocturnal baseline impedance (MNBI)(+) vs MNBI(–).
[f]$P < 0.05$ for CTRS MNBI(+) vs healthy controls.
$P < 0.05$ for CTRS MNBI(–) vs healthy controls.
[g]$P < 0.05$ for ILPRS MNBI(+) vs healthy controls.
[h]$P < 0.05$ for ILPRS MNBI(–) vs healthy controls.
Pearson χ^2 tests were used for dichotomous variables, whereas Mann–Whitney *U* tests were used for continuous variables.
AET, % of acid exposure time in the distal esophagus; HRIM-BI, baseline impedance measured during high-resolution impedance manometry; UES, upper esophageal sphincter; LES, lower esophageal sphincter.
MNBI(+) denotes MNBI < 2065.
Data are presented as median (interquartile range) or n (%).

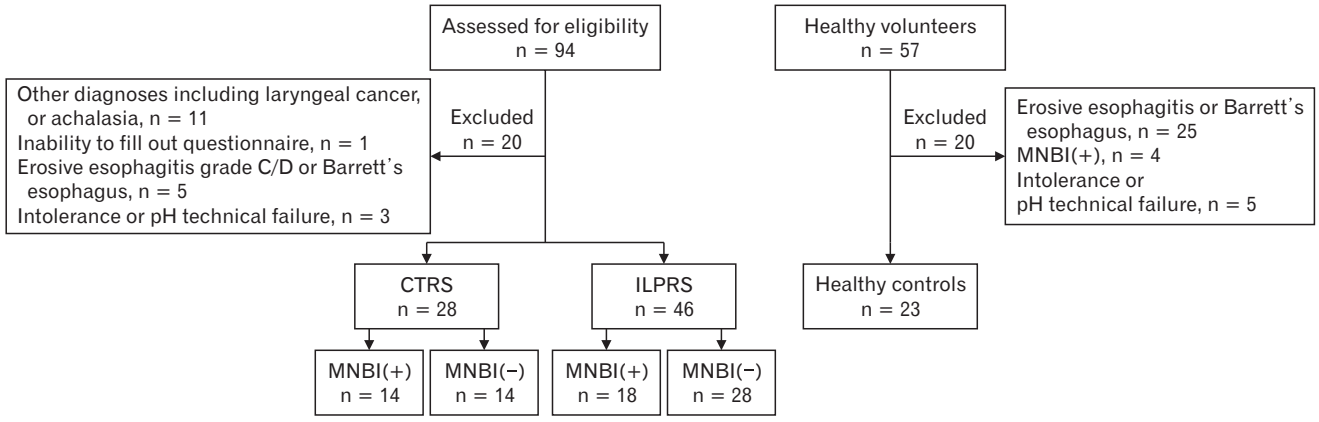

Figure 1. Flow chart of study population. MNBI, mean nocturnal baseline impedance; CTRS, concomitant typical reflux syndrome; ILPRS, isolated laryngopharyngeal reflux symptoms.

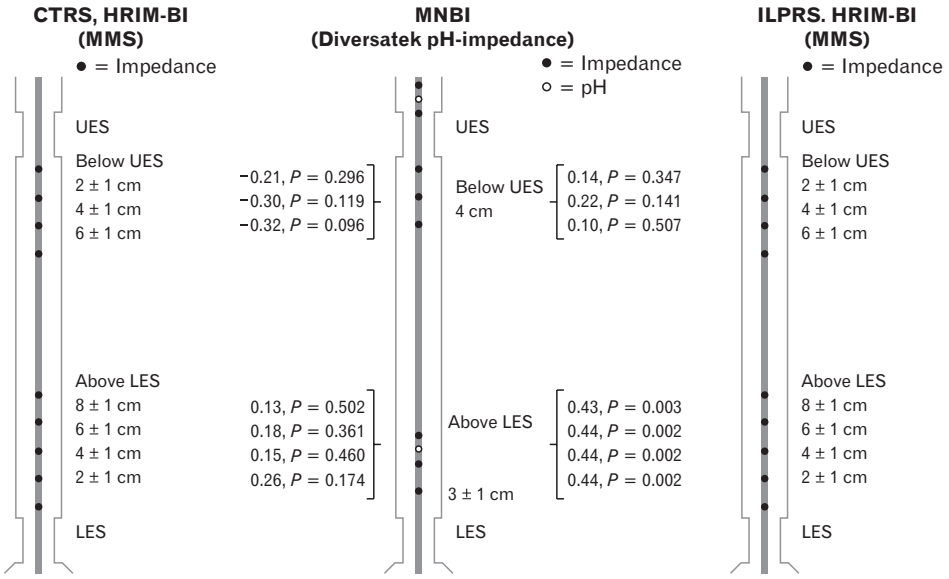

Figure 2. Spearman correlation coefficients between baseline impedance measured during high-resolution impedance manometry (HRIM-BI) and mean nocturnal baseline impedance (MNBI). CTRS, concomitant typical reflux syndrome; ILPRS, isolated laryngopharyngeal reflux symptoms; UES, upper esophageal sphincter; LES, lower esophageal sphincter.

(Fig. 3 and Table 4). Conversely, ROC analysis in the CTRS group showed poor diagnostic efficacy.

Discussion

This study investigated the utility of HRIM-BI measured during HRIM as a predictor of pathological MNBI in patients with ILPRS. Our findings reveal a moderate correlation between distal HRIM-BI and distal MNBI specifically in the ILPRS group. This suggests that HRIM-BI could potentially offer a simpler approach to diagnosing a condition that significantly impacts patients' quality of life.

Although AET is a highly reproducible measure for monitoring reflux to predict treatment outcome, it has diagnostic sensitivity limitations due to variations from day to day and its failure to identify proximal reflux.[30] The MNBI, as an emerging metric, correlates with symptom outcome when AET provides inconclusive results (between 4% and 6%)[31] or even normal AET[11] during reflux monitoring. From a mechanistic standpoint, a moderate inverse relationship between distal MNBI and AET in GERD ($r = -0.5$, $P < 0.001$)[32] and LPR patients ($r = -0.65$, $P < 0.001$),[20] including our research ($r = -0.56$, $P < 0.001$) may reflect mucosal integrity as a surrogate marker of the severity of chronic acid injury. However, the lower correlation coefficient for ILPRS (−0.46) compared to CTRS (−0.74) in this study, in line with Luo et al's findings,[25] suggests a link between baseline impedance and symptoms. This may

Table 3. Correlation Coefficients Between Baseline Impedance Measured During High-resolution Impedance Manometry, Mean Nocturnal Baseline Impedance, and Percent of Acid Exposure Time

HRIM-BI and AET	All patients (n = 74)				CTRS[a] (n = 28)				ILPRS[b] (n = 46)			
	MNBI			Distal esophageal acid exposure (%)	MNBI			Distal esophageal acid exposure (%)	MNBI			Distal esophageal acid exposure (%)
	Proximal esophagus	Distal esophagus (5 cm)	Distal esophagus (3 cm)		Proximal esophagus	Distal esophagus (5 cm)	Distal esophagus (3 cm)		Proximal esophagus	Distal esophagus (5 cm)	Distal esophagus (3 cm)	
HRIM-BI												
cm below the UES												
2 ± 1 cm	0.04	−0.08	0.02	0.01	−0.21	−0.04	−0.02	0.05	0.14	−0.09	0.03	−0.02
4 ± 1 cm	0.06	−0.06	0.07	0.02	−0.30	0.002	−0.01	0.20	0.22	−0.11	0.10	−0.07
6 ± 1 cm	−0.02	−0.03	0.08	0.06	−0.32	−0.04	−0.05	0.18	0.10	−0.06	0.10	0.02
Proximal average	0.05	−0.06	0.06	0.04	−0.29	−0.03	−0.04	0.13	0.18	−0.09	0.07	0.01
cm above the LES												
8 ± 1 cm	0.10	0.21	0.34[d]	−0.12	−0.04	0.03	0.13	−0.12	0.18	0.31[c]	0.43[d]	−0.13
6 ± 1 cm	0.16	0.27[c]	0.35[d]	−0.10	−0.03	0.09	0.18	−0.11	0.25	0.38[d]	0.44[d]	−0.12
4 ± 1 cm	0.11	0.23	0.34[d]	−0.07	−0.06	0.02	0.15	−0.05	0.23	0.35[c]	0.44[d]	−0.13
2 ± 1 cm	0.09	0.23	0.38[d]	−0.18	0.007	0.05	0.26	−0.18	0.15	0.31[c]	0.44[d]	−0.23
Distal average	0.13	0.26[c]	0.39[d]	−0.14	−0.04	0.05	0.18	−0.09	0.24	0.37[d]	0.48[d]	−0.18
24-hr pH test												
AET	−0.22	−0.49[e]	−0.56[e]	-	−0.29	−0.63[e]	−0.74[e]	-	−0.20	−0.39[d]	−0.46[d]	-

[a]Concomitant typical reflux syndrome (CTRS) is defined as regurgitation or heartburn at least twice a week with mild symptoms, or once a week with moderate/severe symptoms.
[b]Isolated laryngopharyngeal reflux symptoms (ILPRS) is defined as patients with laryngopharyngeal reflux without CTRS.
[c]$P < 0.05$, [d]$P < 0.01$, [e]$P < 0.001$ for Spearman correlations.
HRIM-BI, baseline impedance measured during high-resolution impedance manometry; AET, % of acid exposure time in the distal esophagus; MNBI, mean nocturnal baseline impedance; UES, upper esophageal sphincter; LES, lower esophageal sphincter.

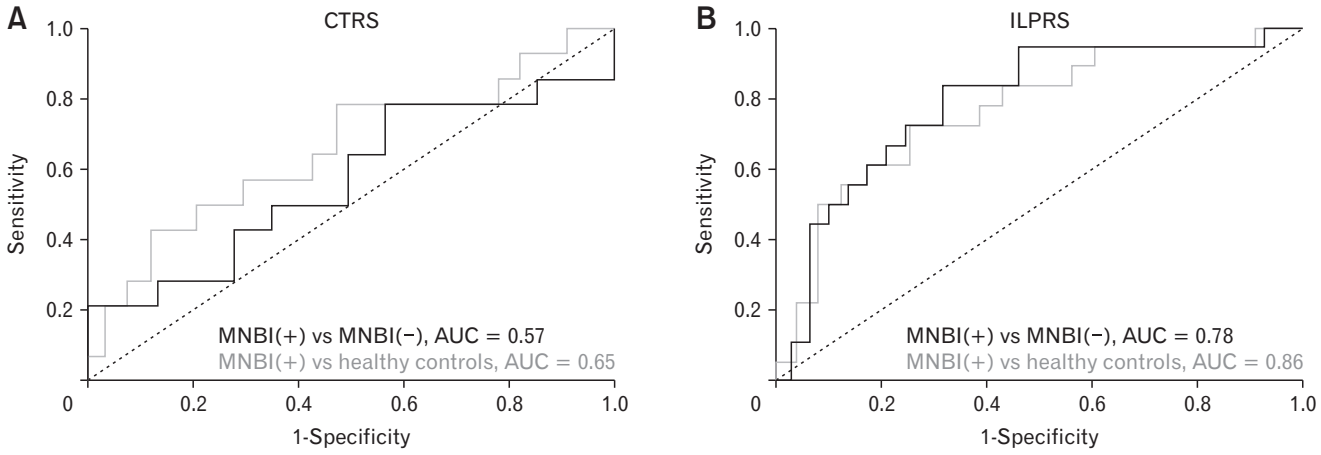

Figure 3. Receiver operating characteristic curves in concomitant typical reflux syndrome (CTRS) (A) isolated laryngopharyngeal reflux symptoms (ILPRS) (B) groups. MNBI, mean nocturnal baseline impedance; AUC, area under the curve.

Table 4. Diagnostic Accuracy of Baseline Impedance Measured During High-resolution Impedance Manometry for Pathological Mean Nocturnal Baseline Impedance

Comparison of HRIM-BI between MNBI (+) and control groups	AUC	Cut-point	Sensitivity	Specificity	Relative risk (95% CI)	*P*-value
Patients MNBI(+) vs MNBI(–)						
CTRS[a] + ILPRS[b]	0.70	1095	0.75	0.62	4.9 (1.8-13.4)	0.004
CTRS[a]	0.57	1143	0.79	0.43	2.8 (0.5-14.4)	0.400
ILPRS[b]	0.78	1066	0.83	0.68	10.6 (2.4-46.0)	< 0.001
Patients MNBI(+) vs healthy controls						
CTRS[a] + ILPRS[b]	0.71	886	0.63	0.74	4.7 (1.5-15.3)	0.020
CTRS[a]	0.65	1180	0.79	0.52	4.0 (0.9-18.2)	0.090
ILPRS[b]	0.76	886	0.72	0.74	7.4 (1.8-30.0)	0.009

[a]Concomitant typical reflux syndrome (CTRS) is defined as regurgitation or heartburn at least twice a week with mild symptoms, or once a week with moderate/severe symptoms.
[b]Isolated laryngopharyngeal reflux symptoms (ILPRS) is defined as patients with laryngopharyngeal reflux without CTRS.
HRIM-BI, baseline impedance measured during high-resolution impedance manometry; MNBI, mean nocturnal baseline impedance; AUC, area under the receiver operating characteristic curve.
Best cutoff points for MNBI at 3 cm above the SCJ were based on maximal Youden index.

underscore the interplay between chronic reflux burden, sensation,[33] and mucosal integrity, and highlights ILPRS as a distinct phenotype within LPR.[24]

While both MNBI and HRIM-BI measure baseline impedance, their correlation varies across different studies. Ravi et al[18] found a moderate correlation in GERD patients ($r = 0.59$, $P < 0.0001$), similar to Horton et al's findings in symptomatic patients with normal AET ($r = 0.58$, $P = 0.005$).[19] However, Zikos et al[20] observed a weak to moderate correlation ($r = 0.34$-0.50, $P = 0.05$) in patients suspected of having LPR, indicating that these 2 metrics might not be directly comparable. In our research, we consistently identified a moderate correlation ($r = 0.43$-0.48, $P < 0.001$) between distal HRIM-BI and distal MNBI in patients suspected of having ILPRS, but not in those with CTRS. Additionally, the diagnostic efficacy showed AUC values of 0.78 and 0.76 when compared to MNBI-negative patients and healthy controls, respectively. The findings were further supported by lower values of another novel impedance metric, contractile segment impedance, observed in the distal esophagus of individuals suspected to have ILPRS and pathological MNBI (Supplementary Table). Overall, our findings indicate that HRIM-BI could be a promising diagnostic tool in the future.

This study found no correlation between MNBI and HRIM-BI in patients with CTRS, potentially due to 2 patient-related fac-

tors. Firstly, the optimal duration of PPI discontinuation for esophageal mucosa impedance to return to baseline is unclear. Kessing et al. showed significantly lower median distal baseline impedance after a 7-day PPI cessation,[34] but it is uncertain if this period is sufficient for those with heightened acid sensitivity, which is associated with slow recovery after acid challenge.[33] This study noted higher positive acid perfusion tests and greater previous PPI use in CTRS patients (Supplementary Table and Table 1). Secondly, esophageal dysmotility, linked to mucosal injury or baseline impedance,[35] is more common in CTRS patients.[24] This can complicate interpreting impedance in patients with low distal baseline impedance,[36] as indicated by a trend of lower median distal contractile integral in CTRS patients compared to their counterparts (961 vs 1149 mmHg·s·cm, Supplementary Table). Additionally, distal contractile segment impedance, a metric highly correlated with HRIM-BI,[37] was associated with pathological MNBI in ILPRS patients but not in the CTRS group (Supplementary Table). Limitations in the HRIM-BI measurement technique, such as short capture periods,[18] poor correlation with AET,[20] and manufacturer differences,[19] may introduce further bias. These factors necessitate further investigation before HRIM-BI can be reliably used clinically.

The value of our study is 2-fold. First, it focuses on ILPRS, a subgroup for which the ACG guidelines suggest initial reflux testing via pH-impedance,[6] despite these patients often showing a low occurrence of positive AET.[7,8] HRIM emerges as an appealing option for healthcare providers. This method provides a faster and more cost-efficient diagnostic pathway, reduces the discomfort associated with impedance-pH metric evaluations, and may decrease the dependency on extended empirical PPI therapy, thereby lowering healthcare expenses. Our research underscores this approach for individuals suspected of having ILPRS and/or in cases where pH-impedance monitoring is unavailable.[38] Secondly, HRIM enables the concurrent evaluation of potential motility disorders that could be causing the symptoms, and integrates HRIM-BI as an adjunctive measure to predict pathologic reflux within a single procedure.

We recognize limitations of our study, including its cross-sectional design, and the modest sample size drawn exclusively from tertiary centers, composed entirely of ethnic Chinese participants. This composition may limit the generalizability of our findings. Moreover, we did not assess treatment outcomes. Future studies should aim to replicate these findings in larger, more diverse populations and explore the longitudinal relationship between HRIM-BI measurements and treatment outcomes. Research should also focus on differentiating between different phenotypes of GERD and LPR based on HRIM-BI to refine the diagnostic criteria and treatment strategies.

In conclusion, our study highlights the potential of HRIM-BI as a valuable diagnostic tool in predicting pathological MNBI within the ILPRS group, offering a more accessible alternative to pH-impedance monitoring. However, its effectiveness is constrained when applied to the CTRS group. The distinctive mucosal impedance profile observed may suggest varied underlying pathophysiological mechanisms in these 2 distinct phenotypes. While our findings are promising, they also underscore the necessity for ongoing research to validate the clinical utility and to integrate it effectively into the diagnostic pathway for LPR.

Supplementary Material

Note: To access the supplementary table mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm24051.

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