J Neurogastroenterol Motil, Vol. 28 No. 1 January, 2022
pISSN: 2093-0879 eISSN: 2093-0887
https://doi.org/10.5056/jnm20277
Journal of Neurogastroenterology and Motility

Original Article

Role of the Mean Nocturnal Baseline Impedance in Identifying Evidence Against Pathologic Reflux in Patients With Refractory Gastroesophageal Reflux Disease Symptoms as Classified by the Lyon Consensus

Yanhong Wu, Zihao Guo, Chuan Zhang,* and Yutao Zhan*

Department of Gastroenterology, Beijing Tong Ren Hospital, Capital Medical University, Beijing, China

Background/Aims
Mean nocturnal baseline impedance (MNBI) is a new reflux metric for mucosal integrity. It remains unclear whether MNBI can help identify evidence against pathological reflux by the Lyon Consensus in patients with refractory gastroesophageal reflux disease (GERD) symptoms.

Methods
Three hundred and forty-nine patients with refractory GERD symptoms enrolled in this study were subjected to high-resolution manometry, 24-hour multichannel intraluminal impedance-pH (MII-pH) monitoring, and endoscopy. Conventional indexes (ie, reflux events and acid exposure time) and the novel index (MNBI) of MII-pH monitoring were extracted and analyzed. The value of MNBI in diagnosing patients with evidence against pathologic reflux was evaluated by receiver-operating-characteristic analysis.

Results
There were 102 (29.2%) patients with evidence against pathologic reflux, 149 (42.7%) with inconclusive or borderline evidence and 98 (28.1%) with conclusive evidence for pathologic reflux. The MNBI was significantly higher while the proportion of pathological MNBI was significantly lower in subjects with evidence against pathologic reflux than in patients with inconclusive or borderline evidence and in patients with conclusive evidence for pathologic reflux (2444.3 [1977.9-2997.4] vs 1992.8 [1615.5-2253.6] and vs 1772.3 [758.6-2161.3], both $P < 0.001$; 42.2% vs 79.7% and vs 80.0%, both $P < 0.05$). When identifying evidence against pathologic reflux in patients with refractory GERD symptoms, the MNBI yielded an area under the curve of 0.749 ($P < 0.001$) at a cut-off value of 1941.8 Ω.

Conclusions
The MNBI has a good diagnostic value for evidence against pathological reflux in patients with refractory GERD symptoms. For its simplicity and reproducibility, we believe that MNBI should be referred to in reports of impedance-pH tracings by physicians.
(J Neurogastroenterol Motil 2022;28:121-130)

Key Words
Electric impedance; Esophageal pH monitoring; Gastroesophageal reflux

Received: December 14, 2020 Revised: March 24, 2021 Accepted: April 15, 2021

*Correspondence: Chuan Zhang and Yutao Zhan are equally responsible for this study.
Chuan Zhang, MD
Department of Gastroenterology, Beijing Tong Ren Hospital, Capital Medical University, No.1, Dongjiaominxiang, Dongcheng District, Beijing 100730, PR China
Tel: +86-010-58268473, Fax: +86-010-58268473, E-mail: 15801227696@139.com
Yutao Zhan, MD
Department of Gastroenterology, Beijing Tong Ren Hospital, Capital Medical University, No.1, Dongjiaominxiang, Dongcheng District, Beijing 100730, PR China
Tel: +86-010-58268474, Fax: +86-010-58268474, E-mail: yutaozhan@263.net
Yanhong Wu and Zihao Guo contributed equally to this study.

Introduction

Gastroesophageal reflux disease (GERD) is becoming increasingly prevalent worldwide. Refractory GERD, which is considered to be the persistence of typical reflux symptoms that are unresponsive to proton pump inhibitor (PPI) treatment, is challenging in clinical practice.[1] However, not all patients with refractory reflux symptoms are GERD patients.[2] Given current concerns about the safety[3] and financial burden[4] of PPI treatment, it is becoming increasingly important to identify these non-GERD patients to avoid unnecessary PPI therapy and determine proper subsequent treatments.

The reflux evidence for refractory GERD symptoms is classified as evidence against pathological reflux, inconclusive or borderline evidence for pathological reflux, or conclusive evidence for pathological reflux as per the Lyon Consensus.[5] The evidence against pathological reflux is drawn from normal endoscopic manifestations as well as the percentage of acid exposure time (AET) < 4% and reflux episodes < 40 in multichannel intraluminal impedance and pH (MII-pH) monitoring off PPIs. However, normal endoscopic manifestations exist widely in patients with heartburn,[6,7] and traditional reflux parameters of MII-pH monitoring also have many shortcomings. For example, although AET could reflect the cross-sectional acid burden, it is subject to day-to-day variation.[8] In addition, identification of reflux events has to be confirmed manually, and sometimes there are discrepancies on what constitutes a reflux event even among experts.[9-11]

Mean nocturnal baseline impedance (MNBI) based on MII-pH monitoring is a novel metric that can be obtained manually in a few minutes using a simple formula and has a very high inter-observer reproducibility rate.[6,12] It is considered to be a potential objective reflux metric and a marker that reflects longitudinal reflux burden, mucosal integrity,[13] and the severity of esophageal mucosal damage, which has proved to be useful in both separating reflux-unrelated (functional heartburn [FH]) patients from reflux-related (GERD[14-17] and reflux hypersensitivity [RH][18,19]) patients and as an independent potential predictor of symptoms responding to anti-reflux therapy.[20-23] Low MNBI is adjunctive evidence for inconclusive or borderline evidence for pathologic reflux (AET 4-6%, reflux episodes 40-80, or Los Angeles [LA] A or B), and can increase the impression of conclusive evidence for pathologic reflux.[5] However, to the best of our knowledge, the contribution of MNBI towards evidence against pathological reflux for patients with refractory GERD symptoms as classified by the Lyon Consensus has not been explored. In this study, we aim to evaluate the role of MNBI in identifying evidence against pathological reflux in patients with refractory GERD symptoms.

Materials and Methods

Subjects

Adult patients (age > 18 years) who underwent endoscopy, high-resolution manometry (HRM), and MII-pH monitoring over a 4-year period (between October 2015 and January 2020) were enrolled consecutively in this retrospective study. The inclusion criteria consisted of patients with reflux symptoms (regurgitation and heartburn) refractory to PPIs. Patients with reflux symptoms improvement < 50% in the context of the use of a standard dose of PPI treatment for at least 8 weeks were referred to have refractory GERD symptoms.[1] The exclusion criteria were inadequate or incomplete studies and studies on patients who were pregnant or had poor treatment adherence, tumors, presence of eosinophilic or infectious esophagitis, prior thoracic, esophageal, gastric or foregut surgery, or major motor disorders (jackhammer esophagus, absent contractility, distal esophageal spasm, esophagogastric junction outflow obstruction, and achalasia), as determined by HRM based on

the Chicago classification version 3.0 criteria.[24]

The Beijing Tong Ren Hospital Medical Ethics Committee approved the study (trxhzcfa01). All patients had signed informed consent (trxhzczp01).

Endoscopic Examination

Upper gastrointestinal (GI) endoscopic examination was performed for all patients using a GIF-260 upper GI endoscope (Olympus, Hamburg, Germany). Esophagitis was graded from LA A to LA D.[7]

Esophageal High-resolution Manometry

HRM was performed after an overnight fast using a 22-channel transnasal multi-lumen polyvinyl catheter (diameter, 3.6 mm; Medical Measurement Systems Inc [MMS], Williston, VT, USA), which was perfused continuously with distilled water at a rate of 0.15 mL/min by a low-compliance pneumohydraulic capillary infusion system (Solar GI; MMS). Esophageal motility was assessed by using 5 mL of ambient temperature water at 30-second intervals for at least 10 water swallows as previously described.[25]

Multichannel Intraluminal Impedance and pH Monitoring

Immediately after HRM, the pH-impedance catheter (8 impedance rings and 1 pH ring, Ref. No 261A; Given Imaging, Los Angeles, CA, USA) was placed in the nose such that the distal esophageal pH sensor was 5 cm proximal to the lower esophageal sphincter (LES) as located by HRM, and 6 impedance sensors were positioned 3, 5, 7, 9, 15, and 17 cm above the LES. MII-pH was monitored after PPI withdrawal for at least 2 weeks and recorded continuously for at least 23 hours. The number of reflux events, the AET, the symptom index (SI)/symptom association probability (SAP), and the MNBI were recorded.

Physiological reflux episodes and physiological AET were defined as < 40 and $< 4\%$, respectively. Pathological reflux events and pathological AET were defined as > 80 and $> 6\%$, respectively. When reflux episodes were between 40 and 80, or the AET was at 4-6%, they were considered to be inconclusive or borderline evidence.[5] The SAP and SI were defined as positive when $\geq 95\%$ and $\geq 50\%$ respectively and positive reflux-symptom association was defined as the SI $\geq 50\%$ and/or SAP $\geq 95\%$.[26-28]

The MNBI was evaluated when the patient was in a supine position at night. The 3 stable 10-minute time periods (around 1 AM, 2 AM, and 3 AM) avoiding reflux episodes, swallows, artifacts, or pH-drops were manually selected by 2 observers (Y.W. and Z.G.) in a blinded fashion as previously described.[6,12] If disagreement occurred, a senior expert (C.Z.) would participate in making the final decision. The baseline impedance of each impedance channel was the mean baseline impedance of the 3 stable 10-minute periods.[6,12] The MNBI values were considered to be the average baseline impedance of 3, 5, 7, and 9 cm above the LES.[22] MNBI less than 2292 Ω was defined as abnormal.[6] Data from pH-impedance monitoring were extracted from a special digital datalogger-MMS (Ohmega, Medical Measurement Systems, Enschede, the Netherlands).

Group Definition

Patients were classified into 3 groups as per the Lyon Consensus.[5] Group 1 or the evidence against pathological reflux (evidence against GERD) group included patients with normal endoscopic findings as well as AET $< 4\%$ and reflux episodes < 40 on pH-impedance monitoring off PPIs. Of these, patients with normal endoscopic findings, normal AET, negative reflux-symptom association in the setting of esophageal symptoms were considered as FH, and patients with normal endoscopic findings, normal AET, but positive reflux-symptom association were classified as RH by the Rome IV.[29] Group 2 or the inconclusive or borderline evidence for pathologic reflux (inconclusive or borderline evidence of GERD) group included patients with LA grades A or B esophagitis, AET 4-6%, or reflux episodes 40-80. In addition, adjunctive evidence (ie, reflux-symptom association, reflux episodes > 80, and low MNBI) could add confidence for a GERD diagnosis. Group 3 or the conclusive evidence for pathologic reflux (conclusive evidence of GERD) group included patients with LA grades C or D, long-segment Barrett's mucosa, or peptic strictures based on endoscopy or AET $> 6\%$ on ambulatory pH or pH impedance monitoring, any one of which was adequate for diagnosing GERD.

Statistical Methods

Continuous data were expressed as mean ± standard deviation and compared using the one-way ANOVA among 3 groups if the data followed a normal distribution. If the value of P was less than 0.05, post hoc comparisons were made using the Bonferroni correction. Otherwise, they were reported as median (interquartile range) and compared using the Kruskal-Wallis H test among the 3 groups. The pairwise comparison was performed if $P < 0.05$. Qualitative data were reported as numbers (percentages), and categorical data were compared by the chi-squared test using the Bonferroni correction. The applicability of MNBI in diagnosing evidence against GERD in patients with refractory GERD symptoms was evaluated

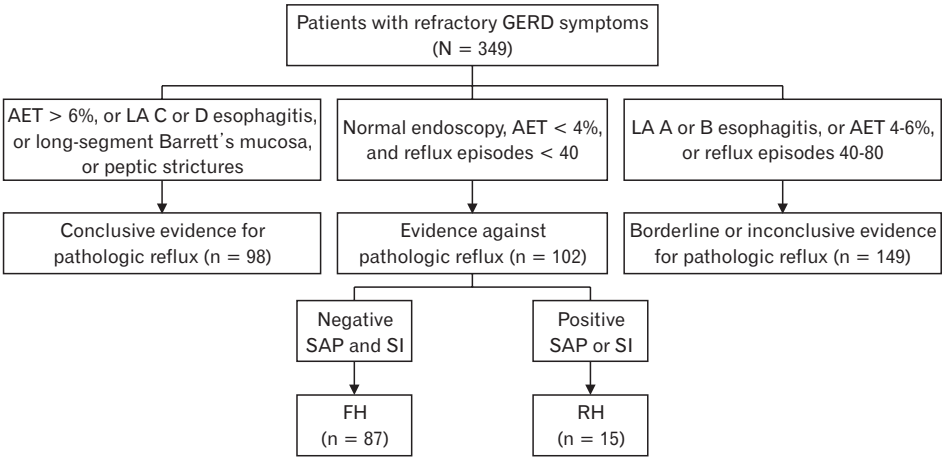

Figure 1. Flow chart of 349 patients with refractory gastroesophageal reflux disease (GERD) symptoms as classified by the Lyon Consensus and Rome IV. AET, acid exposure time; LA, Los Angeles; SAP, symptom association probability; SI, symptom index; FH, functional heartburn; RH, reflux hypersensitivity.

Table 1. Baseline Characteristics, Reflux Parameters of Multichannel Intraluminal Impedance and pH Monitoring and Endoscopy Results for Evidence Against Gastroesophageal Reflux Disease, Inconclusive or Borderline Evidence of Gastroesophageal Reflux Disease, and Conclusive Evidence of Gastroesophageal Reflux Disease in 349 Patients With Refractory Gastroesophageal Reflux Disease Symptoms

Items	Evidence against GERD (Group 1, n = 102)	Inconclusive evidence of GERD (Group 2, n = 149)	Conclusive evidence of GERD (Group 3, n = 98)	*P*-value
Age (yr)	55.9 ± 13.0	58.7 ± 12.9	60.4 ± 11.4	0.036
$P = 0.034$ for Group 1 vs Group 3; $P = 0.237$ for Group 1 vs Group 2; $P = 0.910$ for Group 3 vs Group 2				
Male gender	27 (26.5%)	58 (38.9%)	45 (45.9%)	0.015
$P < 0.05$ for Group 1 vs Group 3; $P > 0.05$ for Group 1 vs Group 2, Group 3 vs Group 2				
BMI (kg/m^2)	23.5 ± 3.7	23.8 ± 3.7	24.4 ± 3.2	0.159
$P = 0.193$ for Group 1 vs Group 3; $P > 0.999$ for Group 1 vs Group 2; $P = 0.447$ for Group 3 vs Group 2				
AET (%)	0.6 (0.1-1.3)	2.5 (0.9-4.3)	8.6 (6.4-15.8)	< 0.001
$P < 0.001$ for all pairwise comparisons				
Reflux events (n)	24.5 (17.0-36.0)	42.0 (24.0-73.0)	37.5 (19.0-70.5)	< 0.001
$P = 0.001$ for Group 1 vs Group 3; $P < 0.001$ for Group 1 vs Group 2; $P > 0.999$ for Group 3 vs Group 2				
Acidic refluxes (n)	1.0 (0.0-3.0)	5.0 (1.0-8.8)	19.0 (7.0-33.3)	< 0.001
$P < 0.001$ for all pairwise comparisons				
Weakly acidic refluxes (n)	15.0 (9.0-23.3)	22.5 (12.0-41.8)	12.0 (5.0-24.0)	0.001
$P = 0.987$ for Group 1 vs Group 3; $P = 0.002$ for Group 1 vs Group 2; $P = 0.065$ for Group 3 vs Group 2				
Weakly alkaline refluxes (n)	4.0 (1.0-11.3)	8.0 (3.0-17.0)	2.0 (0.0-9.0)	< 0.001
$P = 0.142$ for Group 1 vs Group 3; $P = 0.015$ for Group 1 vs Group 2; $P < 0.001$ for Group 3 vs Group 2				
MNBI (Ω)	2444.3 (1977.9-2997.4)	1992.8 (1615.5-2253.6)	1772.3 (758.6-2161.3)	< 0.001
$P < 0.001$ for Group 1 vs Group 3, Group 1 vs Group 2; $P = 0.025$ for Group 3 vs Group 2				
Pathological MNBI	43 (42.2%)	118 (79.7%)	78 (80.0%)	< 0.001
$P < 0.05$ for Group 1 vs Group 3, Group 1 vs Group 2; $P > 0.05$ for Group 3 vs Group 2				
Endoscopy results				< 0.001
Normal	102 (100.0%)	40 (26.8%)	20 (20.4%)	
LA-A or B	0	109 (73.2%)	45 (45.9%)	
LA-C or D or BE	0	0	33 (33.7%)	

GERD, gastroesophageal reflux disease; BMI, body mass index; AET, acid exposure time; MNBI, mean nocturnal baseline impedance; LA, Los Angeles; BE, Barrett's esophagus.
Values are presented as mean± SD, median (interquartile range), or n (%).
Differences were significant when $P < 0.05$.

by receiver operating characteristic analysis with calculation of the area under the curve (AUC) and the cutoff value. The diagnostic agreement was evaluated by using the interclass correlation coefficient. $P < 0.05$ was required for statistical significance. SPSS 22.0 software (IBM, Armonk, NY, USA) was used to perform statistical analysis.

Results

Demographic, Clinical Characteristics and Distribution of Evidence Against Gastroesophageal Reflux Disease, Inconclusive or Borderline Evidence of Gastroesophageal Reflux Disease, and Conclusive Evidence of Gastroesophageal Reflux Disease in Patients With Refractory Gastroesophageal Reflux Disease Symptoms

A total of 376 patients with refractory GERD symptoms were screened. Twenty-seven patients affected by reflux episodes, swallowing, or artifact were excluded from the study. Finally, a total of 349 patients with refractory GERD symptoms were enrolled in the study. Their mean age was 58.3 ± 12.6 years and their mean body mass index was 23.9 ± 3.6 kg/m^2. Among them, 219 (62.8%) were females.

There were 102 (29.2%) patients with evidence against GERD, 149 (42.7%) with inconclusive or borderline evidence of GERD, and 98 (28.1%) with conclusive evidence of GERD. Among those with evidence against GERD, 87 (85.3%) patients were FH, and 15 (14.7%) patients were RH (Fig. 1). In addition, as shown in Table 1, the mean age and the proportion of male patients were significantly lower in patients with evidence against GERD than in patients with conclusive evidence of GERD (55.9 ± 13.0 vs 60.4 ± 11.4, $P = 0.034$; 26.5% vs 45.9%, $P < 0.05$; respectively). There were no significant differences in body mass index among these 3 groups.

Comparison of Acid Exposure Time, Reflux Events by Multichannel Intraluminal Impedance and pH Monitoring and Endoscopic Findings Among These 3 Groups

As shown in Table 1, patients with evidence against GERD showed significantly lower AET than patients with inconclusive or borderline evidence of GERD and patients with conclusive evidence of GERD (0.6 [0.1-1.3] vs 2.5 [0.9-4.3] and vs 8.6 [6.4-15.8], respectively, both $P < 0.001$).

Patients with evidence against GERD had significantly lower total number of reflux events than patients with inconclusive or borderline evidence and patients with conclusive evidence of GERD (24.5 [17.0-36.0] vs 42.0 [24.0-73.0] and vs 37.5 [19.0-70.5]; $P < 0.001$ and $P = 0.001$, respectively). Although the total number of reflux events was also lower in patients with conclusive evidence of GERD than in patients with inconclusive or borderline evidence of GERD, the difference was not statistically significant ($P > 0.999$). When further classifying refluxes into acidic refluxes, weakly acidic refluxes, and weakly alkaline refluxes, the number of acidic reflux events was significantly higher in patients with conclusive evidence of GERD than in patients with inconclusive or borderline evidence of GERD and in patients with evidence against GERD (19.0 [7.0-33.3] vs 5.0 [1.0-8.8] and 1.0 [0.0-3.0], respectively; both $P < 0.001$). It was also significantly higher in

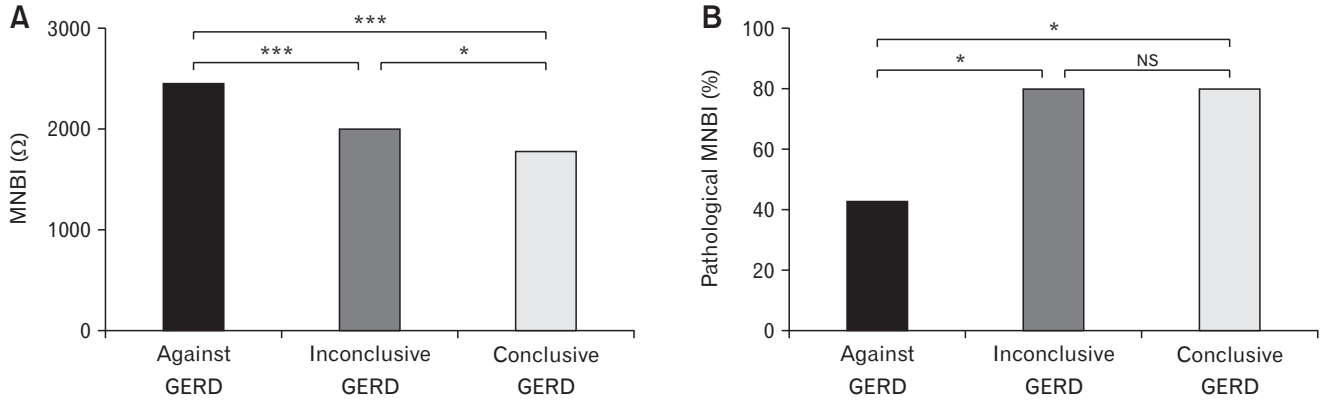

Figure 2. The values of mean nocturnal baseline impedance (MNBI) (A) and the proportion of pathological MNBI (B) in patients with evidence against gastroesophageal reflux disease (GERD), in patients with inconclusive or borderline evidence of GERD, and in patients with conclusive evidence of GERD. NS, not significant. *$P < 0.05$, ***$P < 0.001$.

patients with inconclusive or borderline evidence of GERD than in patients with evidence against GERD (5.0 [1.0-8.8] vs 1.0 [0.0-3.0]; $P < 0.001$). The weakly acidic reflux events were predominant in patients with evidence against GERD and in patients with inconclusive or borderline evidence of GERD.

The endoscopic findings were normal in all patients with evidence against GERD. Among patients with inconclusive or borderline evidence of GERD, 109 LA grades A or B and 40 normal endoscopic findings were found, accounting for 73.2% and 26.8%, respectively. By contrast, among patients with conclusive evidence of GERD, 33 LA grades C, D or BE, 45 LA grades A or B, and 20 normal endoscopic findings were found, accounting for 33.7%, 45.9%, and 20.4%, respectively (Table 1).

Comparison of the Mean Nocturnal Baseline Impedance Among These 3 Groups and the Role of the Mean Nocturnal Baseline Impedance in Identifying Patients With Evidence Against Gastroesophageal Reflux Disease

We obtained interclass correlation coefficient (interclass correlation coefficient = 0.982) of MNBI values between the 2 observers (Supplementary Figure). Patients with evidence against GERD had significantly higher MNBI than patients with conclusive evidence of GERD and patients with inconclusive or borderline evidence of GERD (2444.3 [1977.9-2997.4] vs 1772.3 [758.6-2161.3] and vs 1992.8 [1615.5-2253.6], respectively; both $P < 0.001$) (Table 1 and Fig. 2A). Patients with evidence against GERD displayed a significantly lower proportion of pathological MNBI than patients with conclusive evidence of GERD and patients with inconclusive or borderline evidence of GERD (43 [42.2%] vs 78 [80.0%] and vs 118 [79.7%], respectively; both $P < 0.05$) (Table 1 and Fig. 2B).

In patients with evidence against GERD, RH showed significantly lower MNBI compared with FH (2231.4 [1899.1-2453.2] vs 2510.1 [1998.8-3087.9]; $P = 0.042$) (Fig. 3A). In patients with borderline or inconclusive evidence of GERD, 50 (33.6%) patients had a positive reflux-symptom association and 99 (66.4%) patients had a negative reflux-symptom association. The MNBI was lower in patients with a positive reflux-symptom association than in patients with a negative reflux-symptom association, but there was no statistical difference (1912.0 [1347.5-2259.8] vs 2048.5 [1710.9-2254.6], $P = 0.172$) (Fig. 3B).

When using MNBI to identify patients with evidence against GERD, it yielded an AUC of 0.749 (95% CI, 0.690-0.807; $P < 0.001$) at a cutoff value of 1941.8 Ω, with a sensitivity of 0.814 and specificity of 0.534 (Fig. 4).

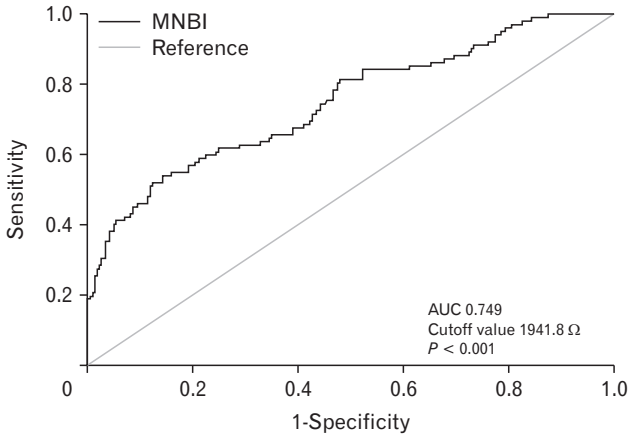

Figure 4. Receiver operating characteristic (ROC) curves of using mean nocturnal baseline impedance (MNBI) to identify evidence against gastroesophageal reflux disease (GERD) in patients with refractory GERD symptoms. In ROC analysis, MNBI yielded an area under the curve (AUC) of 0.749 (95% CI, 0.690-0.807; $P < 0.001$) with a cutoff value of 1941.8 Ω.

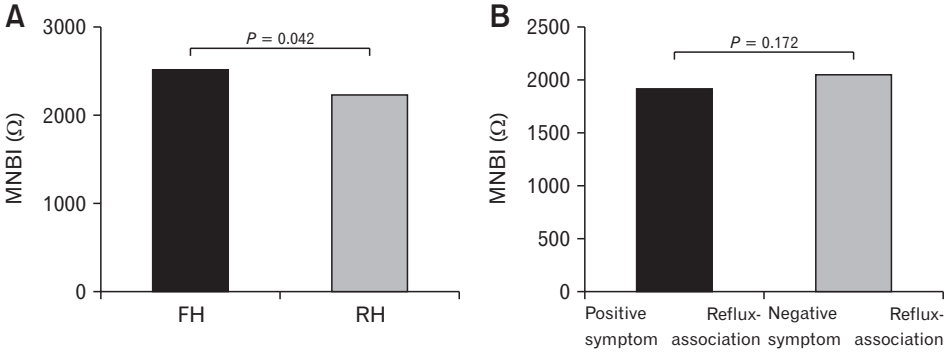

Figure 3. The values of mean nocturnal baseline impedance (MNBI) in functional heartburn (FH) and reflux hypersensitivity (RH) of evidence against gastroesophageal reflux disease (GERD) group (A) and the values of MNBI in patients with a positive reflux-symptom association and in patients with a negative reflux-symptom association of borderline or inconclusive evidence of GERD group (B).

Table 2. The Value of the Mean Nocturnal Baseline Impedance in Separating Functional Heartburn From Gastroesophageal Reflux Disease or Reflux Hypersensitivity of Previous Studies

Author (year)	Off or On PPI MII-pH	Subject groups	Group classification criteria	Assessment of the MNBI	MNBI (Ω)	Role of MNBI
Frazzoni et al[14] (2017)	On PPI therapy	RRE (n = 39)	Persistence of mucosal breaks	3 cm above the LES	1145 (662-1879)	Distinguishing PPI-refractory NERD from FH (with an AUC 0.677 [0.605-0.748])
		HRE (n = 41)	Regressions of mucosal breaks		1741 (1273-2951)	
		NERD (n = 68)	Negative endoscopy findings, but AET > 3.2%, and/or number of reflux events < 48, and/or positive SAP/SI[a]		2374 (1755-2835)	
		FH (n = 41)	Negative endoscopy findings, AET < 3.2%, number of reflux events < 48, and negative SAP/SI[b]		3488 (2965-4069)	
Tenca et al[15] (2017)	Off PPI at least 10-14 days	NERD (n = 25)	Normal endoscopy findings and AET > 4.2%	5 cm above the LES	971 ± 180	Distinguishing GERD from FH (with an AUC 0.960 and a cutoff value of 2934 Ω)
		FH (n = 25)	AET < 4.2%, normal total number of reflux events, and negative SAP/SI[b]		3889 ± 728	
Yoshimine et al[16] (2019)	Not mentioned	ENRD (n = 59)	AET > 4.2% or positive SI/SAP[a]	5 cm above the LES	2229.9 ± 1042.9	Distinguishing FH from PPI-refractory NERD (with an AUC 0.73 [0.63-0.84] and a cutoff value of 2874.1 Ω)
		FH (n = 32)	AET < 4.2% and negative SI/SAP[b]		3061.2 ± 762.1	
Sun et al[17] (2019)	Off PPI for a week	EE (n = 24)	With mucosal breaks at endoscopy	The average of distal 4 channels	1243.4 (908.5-1686.6)	Distinguishing FH from EE, NERD, and RH (with an AUC 0.721 and a cutoff value of 1890.6 Ω)
		NERD (n = 46)	Normal endoscopy, AET > 6% and/or reflux episodes > 80		1506.5 (1104.4-2085.6)	
		RH (n = 52)	Normal endoscopy and AET, but positive SAP/SI[a]		2451.2 (1911.6-2764.5)	
		FH (n = 78)	Without objective evidence of reflux, negative SAP/SI[b]		2477.3 (2010.6-2986.2)	
Frazzoni et al[18] (2016)	Off PPI for 2 weeks	NERD (n = 125)	PPI-responsive heartburn, endoscopy-negative, and abnormal AET	3 cm above the LES	1378 ± 699	Distinguishing RH from FH (with an AUC 0.864 [0.809-0.919])
		RH (n = 108)	Negative upper endoscopy, normal AET, and positive SAP/SI[a]		2274 ± 774	
		FH (n = 70)	Endoscopy-negative hearburn unaffected by PPI therapy, normal AET, and negative SAP/SI[b]		3443 ± 873	
Gao et al[19] (2017)	Off PPI for a week	FH (n = 147)	Normal endoscopy, normal AET, negative SAP/SI[b]	3 cm above the LES	2972.0 ± 775.6	Distinguishing FH from RH (with an AUC 0.643 [95% CI, 0.570-0.716])
		RH (n = 91)	Normal endoscopy and AET, but positive SAP/SI[a]		2485.3 ± 939.2	
		HC (n = 36)			3290.1 ± 613.5	

[a]SAP ≥ 95% and/or SI ≥ 50%.
[b]SAP < 95% and SI < 50%.
PPI, proton pump inhibitor; MII-pH, multichannel intraluminal impedance and pH; MNBI, mean nocturnal baseline impedance; RRE, refractory reflux esophagitis; HRE, healed reflux esophagitis; NERD, non-erosive reflux disease; FH, functional heartburn; AET, acid exposure time; SAP, symptom association probability; SI, symptom index; LES, lower esophageal sphincter; GERD, gastroesophageal reflux disease; AUC, area under the curve; ENRD, Endoscopic-negative reflux disease; EE, erosive esophagitis; RH, reflux hypersensitivity; HC, healthy controls.

Discussion

In this retrospective study, we evaluated the value of the MNBI in differentiating evidence against pathological reflux from inconclusive or borderline evidence of GERD and conclusive evidence of GERD in patients with refractory GERD symptoms. The present study showed that up to 29.2% of patients with refractory GERD symptoms showed evidence against GERD. The MNBI value was significantly higher while the proportion of pathological MNBI was significantly lower in patients with evidence against GERD than in patients with inconclusive or borderline evidence of GERD and in patients with conclusive evidence of GERD. When using MNBI to identify patients with evidence against GERD, it yielded an AUC of 0.749 ($P < 0.001$) at a cutoff value of 1941.8 Ω with a sensitivity of 0.814 and specificity of 0.534. Accordingly, we concluded that MNBI may help identify evidence against GERD in patients with refractory GERD symptoms. In addition to conventional reflux parameters, MNBI should be also reported by physicians in MII-pH monitoring.

In the present study, females accounted for the majority of the large cohort, consistent with a previous study showing that being female was a predictive factor of PPI-refractory GERD symptoms.[30] In addition, patients with conclusive evidence of GERD were significantly older than patients with evidence against GERD, which may attribute to the mechanical impairment of the esophagogastric junction of elder patients, resulting in pathological reflux and its accompanying syndromes.[31] Also, patients with conclusive evidence of GERD had a significantly higher proportion of males than patients with evidence against GERD, which was in line with a previous study showing that the proportion of males was higher in patients with GERD than in patients with FH.[14] Evidence against pathological reflux was found in 29.2% of the total enrolled patients in this study. Among these patients, FH (85.3%) was more predominant than RH (14.7%). Therefore, not all patients with refractory GERD symptoms were true GERD patients, which could be the reason that many patients failed to respond to PPI treatments.[2]

Endoscopy and conventional impedance-pH monitoring are imperfect in identifying patients with evidence against pathologic reflux. Up to 70% of patients with heartburn showed negative findings in upper endoscopic examinations in clinics.[6,7] Accordingly, the proportion of patients with evidence against GERD may be overestimated. Therefore, impedance-pH monitoring is often performed and traditional reflux parameters (ie, AET and reflux events) and SAP are routinely evaluated. AET, which can be reliably extracted from automatic analysis, is the most reproducible among all traditional reflux parameters,[32,33] but it is subjected to day-to-day variation.[8] Moreover, previous studies have shown that automatic software analysis of reflux episodes could lead to false positive reflux episodes and overestimation of reflux episodes, which may influence the results of the symptom association analysis.[34,35] Therefore, a time-consuming manual review of the tracing is needed although there may be inter-observer and intra-observer variability on what constitutes a reflux event.[9-11]

Low esophageal baseline impedance reflects the severity of acid reflux and epithelial structural abnormalities of the esophageal mucosa.[36] Subsequently, the standardized measurement of baseline impedance, namely MNBI, was proposed.[6,12] As a novel metric, MNBI is based on MII-pH monitoring. Thus, it requires no additional testing. In addition, it can be obtained manually in a few minutes and has a very high inter-observer repeatability rate[6] and resistance to circadian variations.[37]

It is crucial to differentiate non-GERD (ie, FH) patients from GERD (ie, erosive esophagitis and non-erosive reflux disease) patients for prescribing different treatments. The MNBI has proven to be useful in distinguishing FH from GERD[14-17] and FH from RH,[18,19] with a high diagnostic accuracy off- as well as on-PPI therapy (Table 2), and in predicting symptomatic responses to antireflux therapy.[20-23] However, no study has explored its role in identifying evidence against GERD in patients with refractory GERD symptoms as classified by the Lyon Consensus, which includes evidence against GERD group, conclusive evidence of GERD group, and inconclusive or borderline evidence of GERD group.[5]

Given that, we evaluated the value of MNBI used for differentiating evidence against GERD from inconclusive or borderline evidence of GERD and conclusive evidence of GERD in patients with refractory GERD symptoms. We found that MNBI was significantly higher while the proportion of pathological MNBI was significantly lower in patients with evidence against GERD than in other patients. Because patients with evidence against GERD often have a physiological reflux burden, the degree of their mucosal integrity damage is lighter than that of other patients, thus leading to a higher MNBI.

Unexpectedly, the proportion of patients with pathological MNBI (42.2%) was very high in patients with evidence against GERD. According to the Lyon Consensus, pathological MNBI was defined as less than 2292 Ω.[5] Frazzoni et al[6] performed a prospective study with 289 GERD patients and 50 healthy controls in Italy, which showed that 2292 Ω may be used as the cutoff impedance values to distinguish GERD patients from healthy controls.

However, normative MNBI cutoff values may vary between regions and ethnicities. A single-center study from China showed that 1764 Ω could be used as the cutoff impedance values to discriminate patients from healthy controls, which included 92 patients with typical reflux symptoms and 10 healthy controls.[38] Given this, we speculate that abnormal MNBI cutoff values may be lower than 2292 Ω in Asian populations, which may explain the high proportion of pathological MNBI (< 2292 Ω) in patients with evidence against GERD in our study. Studies involving a larger sample size of healthy controls will be needed in Asia.

In line with previous studies,[18,19] our study also showed the MNBI was significantly lower in RH than in FH, which may be associated with impairment of mucosal integrity resulting from dilated intercellular spaces in RH.[18] Patients with positive reflux-symptom association had similar MNBI to those with negative reflux-symptom association in borderline or inconclusive evidence of GERD group. That may be because the group of borderline or inconclusive evidence of GERD is very heterogeneous,[5] so there may be no direct relationship between the reflux-symptom association and MNBI in borderline or inconclusive evidence of GERD group.

In addition, we found that MNBI showed a good diagnostic value to differentiate patients with evidence against GERD from other patients, with an AUC of 0.749 ($P < 0.001$) at a cutoff value of 1941.8 Ω. The value of MNBI in identifying evidence against pathological reflux in patients with refractory GERD symptoms as classified by the Lyon Consensus was first found in our study, which was crucial for prescribing different treatments.

Our study has certain strengths. Firstly, it includes a large cohort of patients with refractory GERD symptoms. Secondly, it is the first study to evaluate the value of MNBI in differentiating evidence against GERD from conclusive evidence of GERD and inconclusive or borderline evidence of GERD in patients with refractory GERD symptoms as classified by the Lyon Consensus.

However, some limitations are associated with this study. Primarily, it was a retrospective analysis of a single-center institution. Given this, there may be potential selection bias although patients were enrolled consecutively between 2015 and 2020. Secondarily, the study did not include healthy volunteers. The study aimed to investigate the role of MNBI in identifying evidence against pathological reflux in patients with refractory GERD symptoms, which was crucial for prescribing different treatments. Consequently, patients with refractory GERD symptoms were enrolled in the study without including healthy controls. Healthy controls may be good subjects if the study aimed to evaluate the role of MNBI in differentiating GERD patients from healthy controls.

Overall, we found that MNBI has a good diagnostic value for evidence against pathological reflux in patients with refractory GERD symptoms. For its simplicity and reproducibility, we believe that MNBI should be referred to in reports of MII-pH tracings by physicians.

Supplementary Material

Note: To access the supplementary figure 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/jnm20277.

Financial support: This study was supported by the Digestive Medical Coordinated Development Center of Beijing Hospitals Authority (Grant No. XXT09).

Conflicts of interest: None.

Author contributions: Yanhong Wu and Zihao Guo performed the data collection, analyzed and interpreted the data, and drafted the manuscript, and both are to be considered as first authors; and Chuan Zhang and Yutao Zhan were responsible for designing, editing, and revising the draft.

References

1. Fock KM, Talley N, Goh KL, et al. Asia-Pacific consensus on the management of gastro-oesophageal reflux disease: an update focusing on refractory reflux disease and Barrett's oesophagus. Gut 2016;65:1402-1415.
2. Herregods TV, Troelstra M, Weijenborg PW, Bredenoord AJ, Smout AJ. Patients with refractory reflux symptoms often do not have GERD. Neurogastroenterol Motil 2015;27:1267-1273.
3. Savarino V, Dulbecco P, Savarino E. Are proton pump inhibitors really so dangerous? Dig Liver Dis 2016;48:851-859.
4. Shaheen NJ, Hansen RA, Morgan DR, et al. The burden of gastrointestinal and liver diseases, 2006. Am J Gastroenterol 2006;101:2128-2138.
5. Gyawali CP, Kahrilas PJ, Savarino E, et al. Modern diagnosis of GERD: the Lyon Consensus. Gut 2018;67:1351-1362.
6. Frazzoni M, Savarino E, de Bortoli N, et al. Analyses of the post-reflux swallow-induced peristaltic wave index and nocturnal baseline impedance parameters increase the diagnostic yield of impedance-pH monitoring of patients with reflux disease. Clin Gastroenterol Hepatol 2016;14:40-46.
7. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999;45:172-180.
8. Penagini R, Sweis R, Mauro A, Domingues G, Vales A, Sifrim D.

Inconsistency in the diagnosis of functional heartburn: usefulness of prolonged wireless pH monitoring in patients with proton pump inhibitor refractory gastroesophageal reflux disease. J Neurogastroenterol Motil 2015; 21:265-272.
9. Ciecierega T, Gordon BL, Aronova A, Crawford CV, Zarnegar R. More art than science: impedance analysis prone to interpretation error. J Gastrointest Surg 2015;19:987-992.
10. Loots CM, van Wijk MP, Blondeau K, et al. Interobserver and intraobserver variability in pH-impedance analysis between 10 experts and automated analysis. J Pediatr 2012;160:441-446, e441.
11. Ravi K, DeVault KR, Murray JA, Bouras EP, Francis DL. Inter-observer agreement for multichannel intraluminal impedance-pH testing. Dis Esophagus 2010;23:540-544.
12. Martinucci I, de Bortoli N, Savarino E, et al. Esophageal baseline impedance levels in patients with pathophysiological characteristics of functional heartburn. Neurogastroenterol Motil 2014;26:546-555.
13. Ribolsi M, Gyawali CP, Savarino E, et al. Correlation between reflux burden, peristaltic function, and mucosal integrity in GERD patients. Neurogastroenterol Motil 2020;32:e13752.
14. Frazzoni M, de Bortoli N, Frazzoni L, et al. The added diagnostic value of postreflux swallow-induced peristaltic wave index and nocturnal baseline impedance in refractory reflux disease studied with on-therapy impedance-pH monitoring. Neurogastroenterol Motil 2017;29:e12947.
15. Tenca A, de Bortoli N, Mauro A, et al. Esophageal chemical clearance and baseline impedance values in patients with chronic autoimmune atrophic gastritis and gastro-esophageal reflux disease. Dig Liver Dis 2017;49:978-983.
16. Yoshimine T, Funaki Y, Kawamura Y, et al. Convenient method of measuring baseline impedance for distinguishing patients with functional heartburn from those with proton pump inhibitor-resistant endoscopic negative reflux disease. Digestion 2019;99:157-165.
17. Sun YM, Gao Y, Gao F. Role of esophageal mean nocturnal baseline impedance and post-reflux swallow-induced peristaltic wave index in discriminating Chinese patients with heartburn. J Neurogastroenterol Motil 2019;25:515-520.
18. Frazzoni M, de Bortoli N, Frazzoni L, et al. Impairment of chemical clearance and mucosal integrity distinguishes hypersensitive esophagus from functional heartburn. J Gastroenterol 2016;52:444-451.
19. Gao F, Gao Y, Chen X, Qian J, Zhang J. Comparison of esophageal function tests in Chinese patients with functional heartburn and reflux hypersensitivity. Gastroenterol Res Pract 2017;2017:3596148.
20. Frazzoni L, Frazzoni M, de Bortoli N, et al. Postreflux swallow-induced peristaltic wave index and nocturnal baseline impedance can link PPI-responsive heartburn to reflux better than acid exposure time. Neurogastroenterol Motil 2017;29:e13116.
21. Ribolsi M, Guarino MPL, Tullio A, Cicala M. Post-reflux swallow-induced peristaltic wave index and mean nocturnal baseline impedance predict PPI response in GERD patients with extra esophageal symptoms. Dig Liver Dis 2020;52:173-177.
22. Patel A, Wang D, Sainani N, Sayuk GS, Gyawali CP. Distal mean nocturnal baseline impedance on pH-impedance monitoring predicts reflux burden and symptomatic outcome in gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2016;44:890-898.
23. Rengarajan A, Savarino E, Della Coletta M, Ghisa M, Patel A, Gyawali CP. Mean nocturnal baseline impedance correlates with symptom outcome when acid exposure time is inconclusive on esophageal reflux monitoring. Clin Gastroenterol Hepatol 2020;18:589-595.
24. Kahrilas PJ, Bredenoord AJ, Fox M, et al. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil 2015;27:160-174.
25. Savarino E, de Bortoli N, Bellini M, et al. Practice guidelines on the use of esophageal manometry-A GISMAD-SIGE-AIGO medical position statement. Dig Liver Dis 2016;48:1124-1135.
26. Bredenoord AJ, Weustern BL, Sout AJ. Symptom association analysis in ambulatory gastro-oesophageal reflux monitoring. Gut 2005;54:1810-1817.
27. Kushnir VM, Sathyamurthy A, Drapekin J, Gaddam S, Sayuk GS, Gyawali CP. Assessment of concordance of symptom reflux association tests in ambulatory pH monitoring. Aliment Pharmacol Ther 2012;35:1080-1087.
28. Patel A, Sayuk GS, Gyawali CP. Parameters on esophageal pH-impedance monitoring that predict outcomes of patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol 2015;13:884-891.
29. Aziz Q, Fass R, Gyawali CP, Miwa H, Pandolfino JE, Zerbib F. Functional esophageal disorers. Gastroenterology 2016;150:1368-1379.
30. Delshad SD, Almario CV, Chey WD, Spiegel BMR. Prevalence of gastroesophageal reflux disease and proton pump inhibitor-refractory symptoms. Gastroenterology 2020;158:1250-1261, e2.
31. Boeckxstaens G, El-Serag HB, Smout AJ, Kahrilas PJ. Symptomatic reflux disease: the present, the past and the future. Gut 2014;63:1185-1193.
32. Wiener GJ, Morgan TM, Copper JB, et al. Ambulatory 24-hour esophageal pH monitoring. Reproducibility and variability of pH parameters. Dig Dis Sci 1988;33:1127-1133.
33. Horton AJ, Clayton SB. Optimization of impedance-measured reflux events in GORD utilizing acid exposure time. BMC Gastroenterol 2020;20:179.
34. Roman S, Bruley des Varannes S, Pouderoux P, et al. Ambulatory 24-h oesophageal impedance-pH recordings: reliability of automatic analysis for gastro-oesophageal reflux assessment. Neurogastroenterol Motil 2006;18:978-986.
35. Hemmink GJ, Bredenoord AJ, Aanen MC, Weusten BL, Timmer R, Smout AJ. Computer analysis of 24-h esophageal impedance signals. Scand J Gastroenterol 2011;46:271-276.
36. Zhong C, Duan L, Wang K, et al. Esophageal intraluminal baseline impedance is associated with severity of acid reflux and epithelial structural abnormalities in patients with gastroesophageal reflux disease. J Gastroenterol 2013;48:601-610.
37. Kessing BF, Bredenoord AJ, Weijenborg PW, Hemmink GJ, Loots CM, Smout AJ. Esophageal acid exposure decreases intraluminal baseline impedance levels. Am J Gastroenterol 2011;106:2093-2097.
38. Xie C, Sifrim D, Li Y, Chen M, Xiao Y. Esophageal baseline impedance reflects mucosal integrity and predicts symptomatic outcome with proton pump inhibitor treatment. J Neurogastroenterol Motil 2018;24:43-50.