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Value of adjunctive evidence from MII-pH monitoring and high-resolution manometry in inconclusive GERD patients with AET 4–6%

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Abstract

Objectives: Gastro-esophageal reflux disease (GERD) is a common disease in gastroenterology outpatients. However, some patients with typical reflux symptoms does not satisfy diagnostic criteria. This study was to explore the value of adjunctive evidence from multichannel intraluminal impedance-pH (MII-pH) monitoring and esophageal high-resolution manometry (HRM) in inconclusive GERD patients with acid exposure time (AET) 4–6%.

Methods: Endoscopy, MII-pH monitoring and esophageal HRM were retrospectively analyzed from consecutive patients with typical reflux symptoms in a tertiary hospital from 2013 to 2019. Patients were categorized as conclusive or inconclusive GERD according to AET. Adjunctive evidence for GERD diagnosis from Lyon Consensus were collected and analyzed.

Results: Among 147 patients with typical reflux symptoms, conclusive GERD was found in only 31.97% of patients ($N = 47$). The remaining 100 patients (68.03%) were inconclusive GERD, of whom 28% ($N = 28$) had AET 4–6%. These patients suffered similar reflux burden and impaired esophageal movement. Inconclusive GERD patients with AET 4–6% had lots of positive adjunctive evidence from HRM and MII-pH monitoring. In receiver operating characteristic analysis, mean nocturnal baseline impedance (MNBI) and post-reflux swallow-induced peristaltic wave index (PSPWI) had an area under the curve (AUC) of 0.839 (CI: 0.765–0.913, $p < 0.001$) and 0.897 (CI: 0.841–0.953, $p < 0.001$), respectively, better than total reflux episode (AUC of 0.55, $p = 0.33$). When MNBI was combined with PSPWI, the AUC was elevated to 0.910 (CI: 0.857–0.963, $p < 0.001$).

Conclusions: Inconclusive GERD patients with AET 4–6% have similar acid burden and esophagus motility dysfunction to GERD patients. MNBI and PSPWI are pivotal adjunctive evidence for diagnosing GERD when AET is borderline.

Keywords: acid exposure time, gastro-esophageal reflux disease, Lyon Consensus, ROC AUC

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Introduction

Gastro-esophageal reflux disease (GERD) refers to various symptoms and/or complications caused by gastric contents refluxing into the esophagus, mouth, or lungs,[1–3] with a worldwide prevalence of 33%,[3] resulting in poor quality of life, impaired social activity, and heavy economic burden.[4]

GERD is often empirically diagnosed by typical symptoms (heartburn and regurgitation),[5] and then tested for a response to proton pump inhibitors (PPI) therapy. When PPI test is negative or when alarm symptoms raise suspicion for complications or other diseases, diagnostic tests such as upper endoscopy, esophageal pH/pH-impedance monitoring, and esophageal manometry are warranted. However, there is not a single "gold standard" to diagnose patients with GERD because of the different diagnostic tests with sometimes inconclusive results,[4] causing big dilemmas in clinical practice.[6]

Compared with patients in Western countries, Chinese have lower reflux burden.[7] According to the Lyon Consensus, few patients with GERD typical symptoms can be diagnosed as GERD. Some patients with acid exposure time (AET) 4–6% who have heartburn and/or regurgitation respond to PPI well or actually suffer esophageal mucosa impairment but do not satisfy Lyon criteria. The Lyon Consensus recommends total reflux episodes, symptom index (SI) / symptom-association probability (SAP), mean nocturnal baseline impedance (MNBI) and post-reflux swallow-induced peristaltic wave index (PSPWI) from multichannel intraluminal impedance-pH (MII-pH) monitoring and esophago-gastric junction contractile integral (EGJ-CI), ineffective esophageal motility (IEM) and hiatus hernia from high-resolution manometry (HRM) as adjunctive evidence to help diagnose suspicious patients with confidence.[8] However, no unified thresholds for them have been built until now. Our study aimed (1) to investigate the difference and similarities of reflux monitoring, endoscopic findings, and esophageal motility among patients with AET > 6%, AET 4–6% and AET < 4%; (2) to explore the value of adjunctive evidence from MII-monitoring and HRM in diagnosing inconclusive GERD patients with AET 4–6%.

Methods

Patients

Consecutive adult patients (⩾18 years old) who had typical GERD symptoms (heartburn or regurgitation lasting for at least 3 months with negative PPI test) in the Gastrointestinal Motility Center at the First Affiliated Hospital of Nanjing Medical University from 2013 to 2019 were enrolled in our retrospective study. They all underwent evaluation of upper endoscopy, MII-pH monitoring and esophageal HRM off anti-reflux therapy (at least 1 week). Exclusion criteria were as follows: previous foregut surgery; organic lesions on upper endoscopy (including eosinophilic esophagitis); major esophageal motor disorders on HRM with outflow obstruction (achalasia, distal esophageal spasm, Jackhammer esophagus, etc); on antacids, prokinetics, or PPIs 7 days before or during the esophageal function testing. This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (NO.2020-SR-307). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Upper endoscopy

The patients had upper endoscopy examination before esophageal HRM and 24-hour MII-pH monitoring. Upper endoscopy was performed according to international guidelines. The severity of reflux esophagitis (RE) was graded according to the Los Angeles classification. Patients were then classified as (1) endoscopy negative or (2) RE (LA Grade A–D). All subjects underwent endoscopy (off PPI > 1 week) at least 1 month before esophageal function testing.

HRM

Patients were assigned to undergo esophageal HRM (Given Imaging) to locate the lower esophageal sphincter (LES) and exclude major motility disorders before 24-hour MII-pH monitoring. Transducers were calibrated at 0 and 300 mmHg using externally applied pressure before testing. A 4.2 mm outer diameter 36-channel solid-state catheter with pressure sensors located at 1-cm intervals was inserted by a trained nurse, in a semi-recumbent position after overnight fast, through an anesthetized nostril. At least three distal pressure sensors were placed in the stomach. Then a HRM catheter was taped to the patient's nose. The manometric protocol included a 30-s baseline recording and 10 5 mL swallows of ambient temperature water at 30-s intervals. The studies were analyzed manually by two independent experienced physicians through using the Manoview software (Given Imaging).

The collected parameters included: (a) esophagogastric junction (EGJ) parameters: LES length, LES resting pressure, integrated relaxation pressure (IRP), hiatus hernia and EGJ-CI; EGJ-CI was considered as abnormally low when the value was below 39.3 mm Hg/cm,[9] (b) peristalsis parameters: distal contractile integral (DCI), ineffective swallows. According to the Chicago

Classification Criteria version 3.0,[10] IEM was defined by 50% or more ineffective swallows (DCI < 450 mmHg·s·cm).

24 h MII-pH monitoring

Patients underwent 24-hour MII-pH monitoring using an ambulatory monitoring system (Given Imaging), which has a portable data logger with impedance-pH amplifiers and a catheter containing one pH channel and six impedance channels. Before recording, patients were asked to fast overnight. The pH electrodes were calibrated using pH 4.0 and pH 7.0 buffer solutions before monitoring. LES was located by esophageal manometry. The catheter was placed through the nostril to distal esophagus with pH electrode 5 cm above the LES. Six impedance electrodes were positioned at 3, 5, 7, 9, 15, and 17 cm proximal to the LES. After placement of the catheter, patients were instructed to return to daily diet and activities, keeping a diary to record the onset of all GERD-related symptoms, meal times, and changes in posture.

AET was defined as pathological if the time pH <4 exceeded 6% of the total recording time after excluding meal times. The collected parameters included: AET%, DeMeester Score, long reflux episode, acid episode, weakly acid reflux episode, non-acid episode, total reflux episode, SI, SAP, MNBI, and PSPWI.

The MNBI was calculated using the method described by Martinucci *et al.*[11] which involves extracting and averaging baseline impedance values at three stable nocturnal 10-min periods at 1:00 AM, 2:00 AM, and 3:00 AM. Previous reports have shown that distal MNBI (at the 3-cm and 5-cm markers) but not proximal MNBI correlates with AET. For the purpose of this study, baseline impedance was calculated and averaged at the 5-cm channel to correspond to total distal AET, and was considered abnormal if less than 2292 ohms.[11,12] PSPW was defined as an antegrade 50% drop in impedance occurring within 30 s after a reflux event, originating in the proximal impedance channels, reaching the most distal impedance channel, and followed by at least 50% return to the baseline. PSPWI was obtained when dividing the number of PSPWs by the number of reflux events. PSPWI was regarded as abnormal when <61%.[13] MNBI and PSPWI in this study were calculated manually by two experienced physicians, respectively.

In our study, patients with conclusive GERD were diagnosed according to the Lyon Consensus.

Statistics

Data were presented as either the mean (SD) or the median (25th, 75th) according to whether it was normally distributed. Categorical data were compared using the X2-squared test. Comparisons among groups were performed using one-way ANOVA or non-parametric test according to different data. For multiple comparisons, Bonferroni's correction was applied. Receiver operating characteristic curve (ROC) was used to evaluate diagnostic value of different parameter. Differences were considered significant when $p < 0.05$. Data analysis was performed using a standard software package (SPSS 20.0; IBM, Armonk, NY, USA).

Results

Groups

A total of 147 patients (70 males, mean age 51.88 ± 12.70) with typical GERD symptoms were finally included. They were divided into three groups based on their AET. Among them, 47 (31.97%) patients were found with AET > 6%, 28 patients (19.05%) were with AET 4–6% and the remaining 72 patients (48.98%) were presented with normal AET (AET < 4%) (Figure 1(1)).

Endoscopy outcomes

As shown in Figure 1(2), among patients with AET >6%, 34 (72.34%) of them had RE while seven (14.89%) patients presented LA grade C&D RE. Some 14 (50%) and 18 (25%) patients were found with LA grade A&B RE in patients with AET 4–6% and AET < 4%. Therefore, 47 patients (31.97%) were diagnosed with conclusive GERD according to the Lyon Consensus. Patients with AET >6% and AET 4–6% suffered more RE than patients with AET <4% ($p < 0.001$ and $p = 0.03$). However, no significant difference was observed between patients with AET >6% and AET 4–6% ($p = 0.081$).

MII-pH monitoring outcomes

As shown in Table 1, patients with AET > 6% had higher AET and DeMeester score, more acid and long reflux episodes than patients with AET 4–6% and AET < 4% (all ps < 0.05). Among

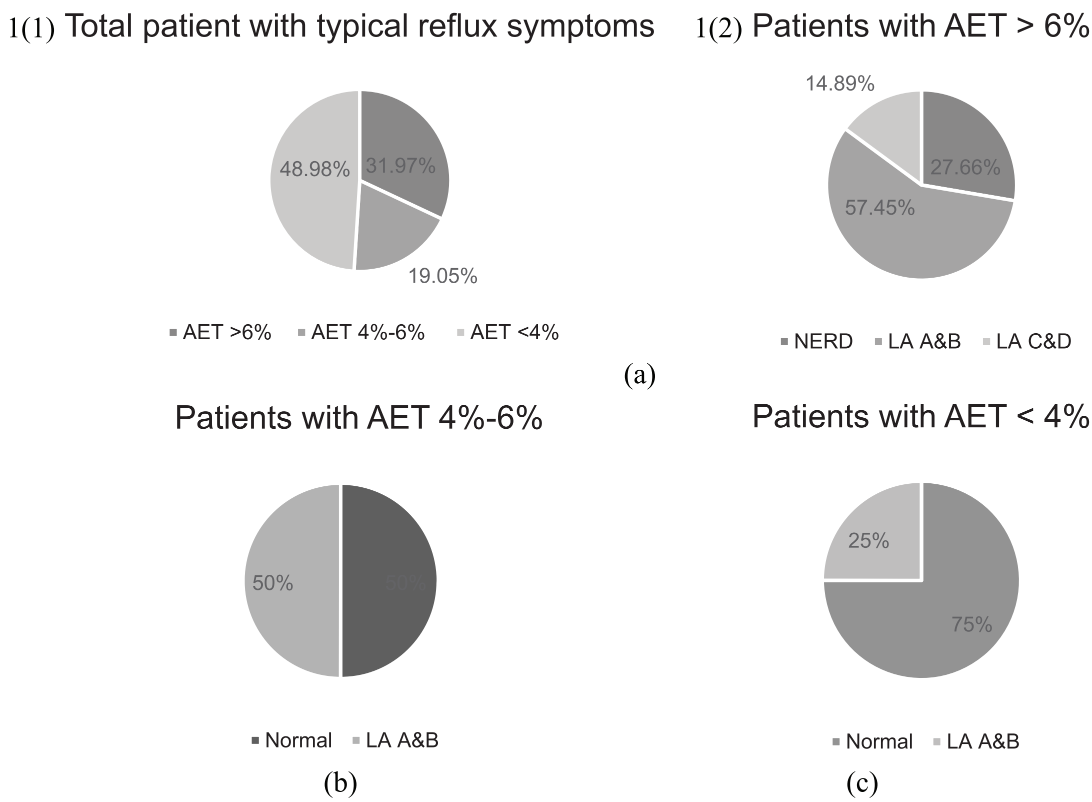

Figure 1. Distribution of patients with typical reflux symptoms based on AET (1(1)) and endoscopy findings (1(2)).
AET, acid exposure time; NERD, non-erosive reflux disease; LA, Los Angeles classification.

Table 1. Characteristics of MII-pH monitoring in patients with typical reflux symptoms.

	AET <4% (*n* = 72)	AET 4–6% (*n* = 28)	AET >6% (*n* = 47)	*p* value
AET%	0.9 ± 1.63	4.9 ± 1.1[a,b]	11.3 ± 12.8	<0.001
DeMeester score	4.5 (6)	18.9 (5.27)[a,b]	41.2 (59.3)	<0.001
Long reflux episode	0 (1)	1 (3)[a,b]	7 (10)	<0.001
Acid episode	9 (15.5)	26 (25.75)[a,b]	19 (29)	<0.001
Weakly acid episode	19 (20.5)	22 (25)[a]	22 (34)	0.676
Non-acid episode	0 (1)	0 (3.75)	0 (1)	0.634
Total reflux episode	35.5 (35.5)	56.5 (43)[a]	49 (63)	0.002
SI >50%	12.5%	39.29%[a]	51.06%	<0.001
SAP >95%	20.83%	50%[a]	46.81%	0.002
MNBI	3388.5(1639.5)	1911(1464)[a]	1131(1168)	<0.001
PSPWI (%)	84.08 ± 9.26	78.57 ± 10.47[a,b]	59.83 ± 16.38	<0.001

[a]$p < 0.05$, compared between patients with AET <4% and patients with 4% ⩽ AET ⩽ 6%.
[b]$p < 0.05$, compared between patients with AET >6% and patients with 4% ⩽ AET ⩽ 6%.
AET, acid exposure time; SI, symptom index; SAP, symptom-association probability; MNBI, mean nocturnal baseline impedance; PSPWI, post-reflux swallow-induced peristaltic wave index.

patients with AET < 6%, patients with AET 4–6% had significantly higher AET and DeMeester score, more acid, weakly acid, long and total reflux episodes than those of patients with AET < 4% (all *p*s < 0.05). When compared with patients with AET > 6%, patients with AET 4–6% had similar weakly acid and total reflux episode (all *p*s > 0.05).

We found that patients with AET 4–6% had more total reflux episodes, higher ratio of SI > 50%/ SAP > 95% and lower MNBI than patients with AET < 4%, but similar to patients with AET > 6%. PSPWI in patients with AET 4–6% was lower than that in patients with AET < 4% (p = 0.044) but higher than AET > 6% (p < 0.001). Some 25% inconclusive GERD with AET 4–6% had reflux episode > 80, 39.29% had SI > 50%, 50% had SAP > 95% and 60.71% had low MNBI (< 2292 ohms), which was similar to patients with AET > 6% and higher than patients with AET < 4% (Figure 2). However, the ratio of PSPWI < 61% in patients with AET 4–6% was similar to that in patients with AET < 4% but lower than that in patients with AET > 6%.

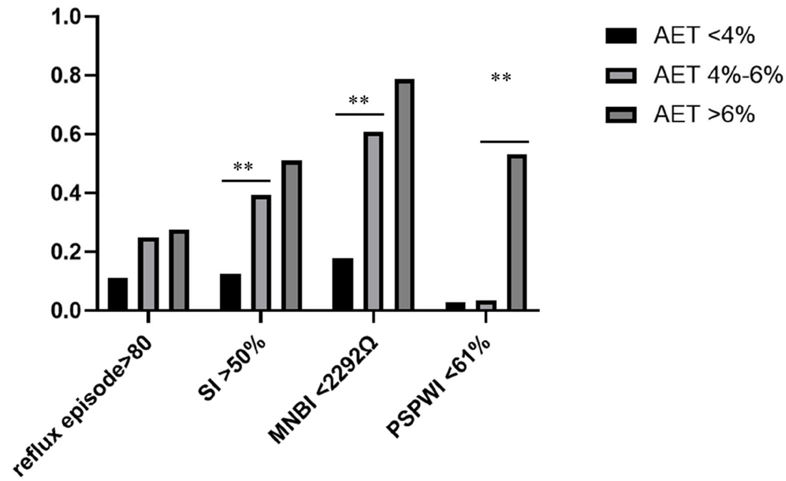

Figure 2. Adjunctive evidence from MII-pH monitoring for GERD diagnosis in three groups.
AET, acid exposure time; SI, symptom index; MNBI, mean nocturnal baseline impedance; PSPWI, post-reflux swallow-induced peristaltic wave index; GERD, gastro-esophageal reflux disease.

Diagnostic value of adjunctive evidence in MII-pH monitoring

ROC analysis of adjunctive MII-pH evidence for GERD was further conducted. As shown in Figure 3, MNBI had an area under the curve (AUC) of 0.839 (CI: 0.765–0.913, p < 0.001) and the cut-off value was 1838 ohms with sensitivity 76.6% and specificity 81.0%, better than total reflux episode (AUC of 0.55, p = 0.33). The positive predictive value (PPV) for MNBI < 1838 ohms was 65.45% and negative predictive value (NPV) was 88.04%. PSPWI also showed good diagnostic value with AUC 0.897 (CI: 0.841–0.953, p < 0.001) and the cut-off value was 72.5% (sensitivity 85.1%, specificity 85.0%). The PPV for PSPWI < 72.5% was 62.50% and NPV was 92.39%. When MNBI was combined with PSPWI, AUC was elevated to 0.910 (CI: 0.857–0.963, p < 0.001).

Based on our findings, the diagnostic sensitivity of SI > 50% in GERD patients was 51.06% while specificity was 80.0%, with a PPV of 54.55% and NPV of 77.67%. And the diagnostic sensitivity of SAP > 95% was 46.81% while specificity was 71.0%, with a PPV 43.14% and NPV 73.96%. When SI > 50% was combined with SAP > 95%, the specificity rose to 85% while sensitivity declined to 36.17%.

Esophageal HRM outcomes

Patients with AET > 6% showed lower LES resting pressure (LESP), IRP, and average DCI than patients with AET 4–6% and AET < 4% (all p < 0.05), indicating weaker anti-reflux barrier. Among patients with AET < 6%, patients with AET 4–6% also showed weaker anti-reflux barrier function than patients with AET < 4%, especially in EGJ-CI (p = 0.029). However, there was no difference in EGJ-CI between patients with AET 4–6% and AET > 6% (p = 0.614). The ineffective swallows of patients with AET 4-6% was similar to that of patients with AET > 6%, which was more than that of patients with AET < 4% (p = 0.012) (Table 2).

Also, the adjunctive HRM evidence was evaluated. We found that 42.86% inconclusive GERD with AET 4–6% had hypotensive EGJ-CI, 10.71% had hiatus hernia, and 50.0% had IEM, which was similar to patients with AET > 6% and higher than patients with AET < 4%, especially in hypotensive EGJ-CI (p = 0.01) (Figure 4).

Diagnostic value of adjunctive evidence in HRM

As shown in Figure 5, EGJ-CI had AUC of 0.576 with no significant difference (p = 0.139). According to our results, IEM had a diagnostic sensitivity of 63.83% and specificity of 65.0% in GERD patients, with a PPV 46.15% and NPV 79.27%, while hiatus hernia had a diagnostic sensitivity of 19.15% and

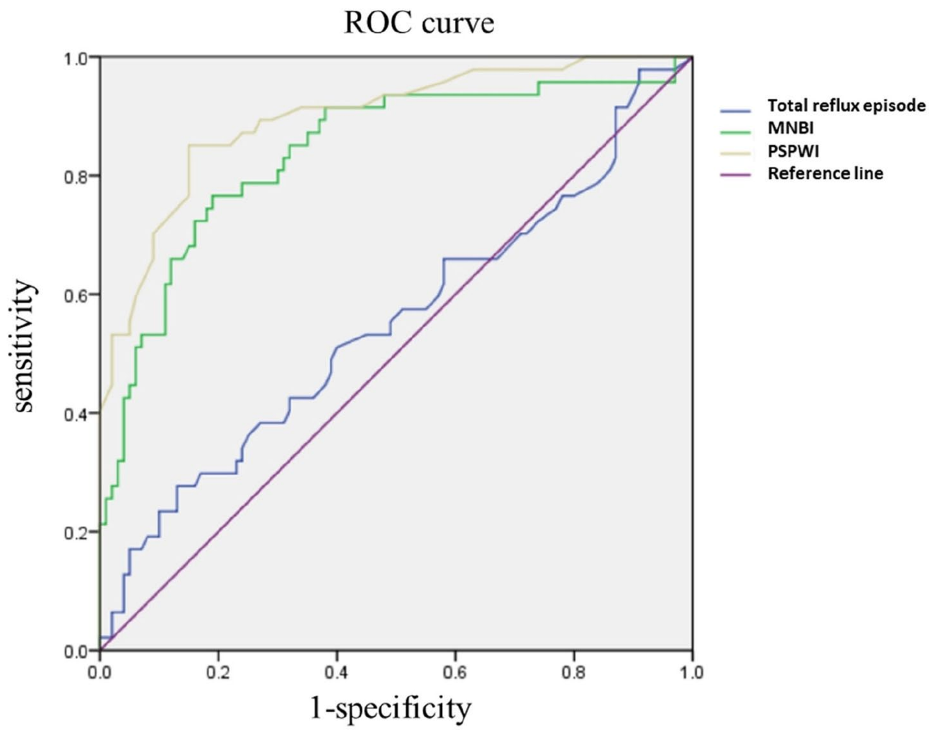

Figure 3. ROC analysis of adjunctive evidence from MII-pH monitoring for GERD diagnosis.
MNBI, mean nocturnal baseline impedance; PSPWI: post-reflux swallow-induced peristaltic wave index; MII-pH, multichannel intraluminal impedance-pH; GERD, gastro-esophageal reflux disease.

Table 2. Characteristics of esophageal HRM in patients with typical reflux symptoms.

	AET <4% (*n* = 72)	AET 4–6% (*n* = 28)	AET >6% (*n* = 47)	*p* value
LESP (mmHg)	21.86 ± 7.85	19.14 ± 6.53[b]	14.77 ± 6.62	<0.001
IRP (mmHg)	12.29 ± 5.45	10.68 ± 3.81[b]	7.61 ± 4.25	<0.001
LESL (cm)	3.67 ± 0.62	3.39 ± 0.86	3.10 ± 0.87	<0.001
LESL in abdomen (cm)	2.88 ± 0.76	2.35 ± 1.02[a,b]	1.73 ± 1.35	<0.001
EGJ-CI	68.77 ± 28.61	46.91 ± 27.93[a]	48.27 ± 22.89	0.013
Average DCI	899.13 ± 76.07	924.35 ± 819.88[b]	590.21 ± 599.46	0.03
Ineffective swallows	1.31 ± 2.74	3.0 ± 3.50[a]	3.28 ± 3.08	0.013
IEM (%)	29.17%(21/72)	50%(14/28)	63.83%(30/47)	0.001
Hiatus hernia	0	10.71%(3/28)	19.14%(9/47)	0.105

[a]$p < 0.05$, compared between patients with AET < 4% and patients with 4% ⩽ AET ⩽ 6%.
[b]$p < 0.05$, compared between patients with AET > 6% and patients with 4% ⩽ AET ⩽ 6%.
HRM, high-resolution manometry; AET, acid exposure time; LESP, lower esophageal sphincter resting pressure; IRP, integrated relaxation pressure; LESL, lower esophageal sphincter length; EGJ-CI, esophago-gastric junction contractile integral; DCI, distal contractile integral; IEM, ineffective esophageal motility.

specificity of 97.0%, with a PPV 75.0% and NPV 71.85%.

Discussion

GERD impairs patients' physical and mental health, quality of life, and social activity. How to identify GERD more sensitively and specifically is the main problem troubling clinicians. Upper endoscopy and MII-pH monitoring can detect the presence of reflux and mucosal impairment.[14] According to the Lyon Consensus, LA-C/D is diagnosed as GERD. However, endoscopy can hardly measure reflux details or discern symptoms related to reflux. A study showed the detection rate of RE was only 4.30%[15] in Chinese patients, which was much lower than that of 11.8%–15.5% in Western countries,[16,17] so GERD patients with mild or no mucosal impairment might be omitted. In our study, there is no difference between patients with AET > 6% and AET 4–6% regarding RE incidence, indicating patients with AET 4–6% suffered mild but somewhat similar esophagitis as GERD patients.

MII-pH monitoring is pivotal to confirm the diagnosis in patients with LA-A/B and non-erosive reflux disease (NERD). Based on the Lyon Consensus, AET > 6% can confirm GERD and predict PPI response. However, a study[7] on Chinese patients suggests more than 60% with EE are diagnosed with inconclusive GERD (AET < 6%) and 56.25% of them have positive response to PPI treatment. Among them, approximately 14% patients have borderline AET 4–6% and they have similar demographic characteristics and motor pattern compared with patients with AET > 6%. The study also reveals that patients with AET 4–6% have similar reflux pattern (weakly acid and total reflux episode, SI, MNBI, and PSPW index) as patients with AET > 6%. In our study, patients with AET 4–6% had similar weakly acid and total reflux episode as patients with AET > 6%. According to the above findings, it is doubted that whether the Lyon criteria are too strict to diagnose GERD in Chinese population. So how to handle the inconclusive diagnosis of GERD is still a challenge.

Reflux burden appears to be worse in poor anti-reflux barrier such as lower LESP and EGJ-CI, hiatus hernia, and IEM patients.[18] HRM shows great advantage of presenting esophageal body contraction and assessing EGJ function. Our

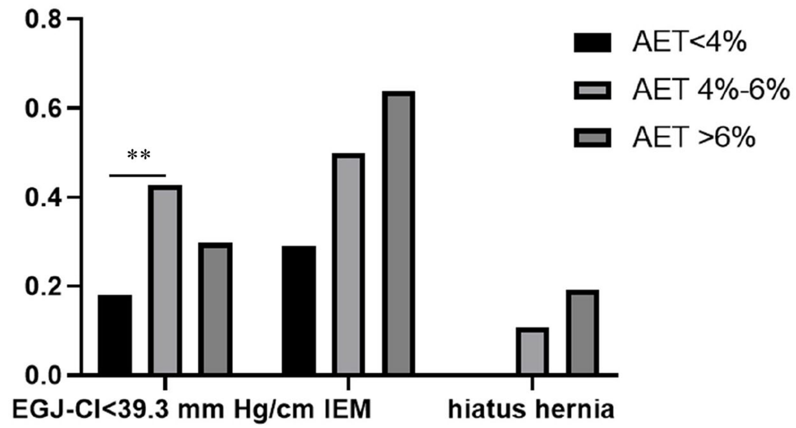

Figure 4. Adjunctive evidence from esophageal HRM for GERD diagnosis in three groups.
AET, acid exposure time; EGJ-CI, esophago-gastric junction contractile integral; IEM, ineffective esophageal motility.

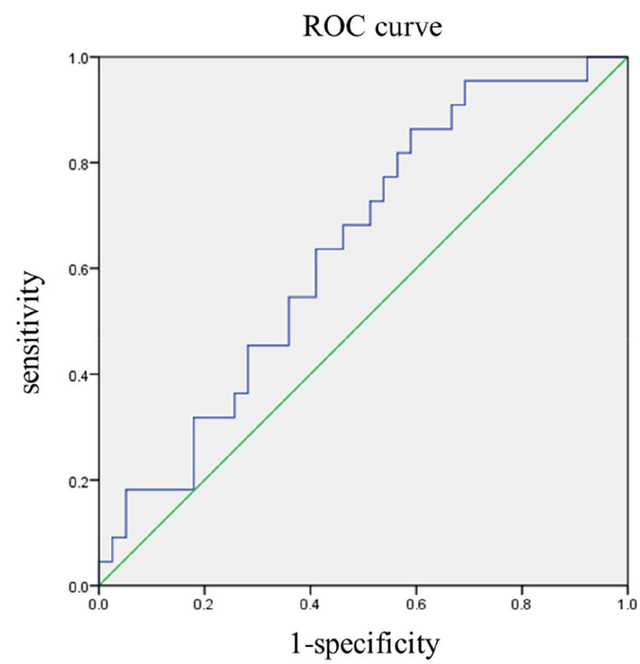

Figure 5. ROC analysis of IEM from esophageal HRM for GERD diagnosis.
IEM, ineffective esophageal motility; HRM, high-resolution manometry; GERD, gastro-esophageal reflux disease.

study revealed impaired anti-reflux barrier and esophagus body motion were similar between patients with AET 4–6% and AET > 6%, which may partly explain the reflux pattern in these patients.

Despite the limitations of currently available esophageal tests and the lack of normative values for novel metrics, the Lyon Consensus recommends several adjunctive evidences to enhance clinicians' confidence for a conclusive diagnosis. According to our results, patients with AET 4–6% had similar ratios of adjunctive evidences (most of both MII-pH monitoring and HRM) as patients with AET > 6%, more than patients with AET < 4%, indicating AET 4–6% could predict more abnormality of esophagus function. Whether AET 4–6% combined with adjunctive evidence from the Lyon Consensus could help diagnose GERD needs to be further explored.

This study suggested that patients with AET 4–6% and AET > 6% suffered similar total reflux episodes, which was more than patients with AET < 4% did. However, ROC curve did not show total reflux episodes alone had diagnostic value for GERD. Previous studies reported that number of reflux episodes alone is not predictive of treatment outcome,[19–21] which is in agreement with our finding. Therefore, additional clinical findings should be considered together with reflux events when diagnosing GERD.[22]

AET has false negative results in about 30% of patients with RE.[23,24] With the emergence of MII-pH monitoring, SAP and SI have been applied to document a direct link between reflux episodes and symptoms, increasing the ability to diagnose GERD, especially in endoscopy-negative, pH-negative patients.[5] Our study found the sensitivity value of SI > 50% was 51.06% and specificity value was 80%, both higher than SAP > 95%, indicating SI can be used as a complementary tool with good specificity in GERD diagnosis.

SI and SAP have a predictive value for the effect of anti-reflux treatment, which is independent of AET[21,25,26] and has a high degree of reproducibility.[27] The SI and SAP are complementary. Our results also showed SI > 50% combined with SAP > 95% had high diagnostic specificity for GERD. If one test is positive and the other is negative, this represents a gray area and further interpretation with other parameters (AET, total reflux episodes, MNBI, etc. . .) is needed.[14]

Baseline impedance reflects the integrity of the esophageal mucosa[28] and is a hallmark of pathological reflux.[29,30] Lower MNBI values could be generated from the presence of reflux as well as poorly cleared food or saliva. Patients with EE, NERD, and inconclusive GERD with typical symptoms all have lower MNBI values than healthy subjects.[31] MNBI correlates with symptom response to anti-reflux therapy in the NERD population with persistent symptoms refractory to PPI therapy, especially when AET is borderline.[32] A previous study showed that the vast majority of patients with AET 4–6% had low MNBI and likely had pathologic GERD. Among them, nearly three-quarters with low MNBI improved with anti-reflux therapy.[32] Besides, it showed that MNBI was negatively correlated to acid-related parameters, such as episodes of acid reflux, DeMeester score, and AET.[33]

Based on our results, patients with AET 4–6% and AET > 6% both had lower MNBI than patients with AET < 4%. ROC curve analysis revealed MNBI had an advantage in diagnosing GERD with high sensitivity and specificity, so MNBI is crucial for GERD diagnosis in suspected patients with AET 4–6%. However, normative values for MNBI have not been unified to date. The cut-off value for MNBI (1838 ohms) in this study was lower than that of patients in Western countries (2292 ohms), and it might be related to our small sample size or the difference (e.g. genetic mechanisms, exposure to different meals and refluxate, etc) between patients from different regions. Therefore, more studies involving larger sample size and more medical centers are needed to explore the threshold in Chinese patients.

In our study, PSPWI of patients with AET 4–6% was significantly lower than that in patients with AET < 4%. ROC curve analysis suggested that PSPWI was an excellent adjunctive evidence for GERD. PSPWI was developed to evaluate chemical clearance and it is significantly lower in patients with RE and NERD.[13,34] A previous study reported that in 103 pH-negative NERD cases (normal AET) the diagnostic accuracy of PSPW index was 86% in the 65 SAP/SI-positive cases and 82% in the 38 SAP/SI-negative cases.[13] However, we did not find similarities in PSPWI of patients with AET 4–6% and AET > 6%. While PSPWI may have complementary value for suspected GERD,[35] there is not enough evidence for its clinical use. Similar to MNBI, the threshold for PSPWI has not been confirmed around the world so further studies are still warranted.

Previous studies indicated that PSPWI and MNBI were abnormal in the vast majority of definitely

PPI-responsive heartburn cases with normal AET and negative SAP/SI[13,36] and predicted PPI responsiveness better than AET.[37] We also found the diagnostic value for GERD was obviously elevated when PSPWI was combined with MNBI.

The new metric EGJ-CI is a comprehensive reflection of the barrier function. EGJ-CI negatively correlates with acid exposure in the supine position and the total reflux episode.[38] The present study showed EGJ-CI values of patients with AET 4–6% were obviously lower than that of patients with AET $<$4% and were similar to that of patients with AET $>$6%. However, ROC curve did not find its significant diagnostic value. The use of EGJ-CI has been enhanced by evidence of elevated reflux burden when EGJ-CI is low,[9,39,40] whereas whether EGJ-CI can help diagnose GERD in suspected patients still needs to be investigated.

It was found that hiatus hernias showed high specificity in GERD diagnosis. Previous studies indicate HRM has higher specificity in the detection of hiatus hernia than endoscopy[41] and a hiatus hernia is predictive of abnormal acid burden,[42,43] contributing to lower MNBI.[44] According to our results, inconclusive GERD with hiatus hernia can be considered as GERD with high probability.

Absent or failed esophageal peristalsis predicts higher esophageal reflux burden, lower MNBI, and more reflux symptoms.[42,45,46] Diener *et al.*[47] reported that GERD patients with IEM were linked to longer acid exposure, more frequent and longer reflux episodes, and slower esophageal acid clearance. However, we found that IEM did not have high sensitivity or specificity in identifying GERD. According to previous findings, abnormal acid burden associates best with “severe” IEM where $>$70% sequences are ineffective,[42] which could partly explain our results (we defined IEM as $>$50% ineffective swallows).

Our enrollment was symptom-based and emulated a real-world setting of suspected GERD patients regardless of whether they were RE or not. We confirm that the Chinese population has a low reflux burden and suspected GERD patients may be omitted just based on Lyon criteria. Our study revealed patients with AET 4–6% have acid burden and esophagus motility dysfunction similar to GERD patients. MNBI and PSPWI are promising MII-pH metrics to help diagnose GERD with confidence when AET is borderline. However, total reflux episode, SI/SAP, EGJ-CI, hiatus hernia, and IEM were not reliable predictors for GERD according to our findings. Based on our findings and previous studies, whether the AET threshold should be adjusted to 4% instead of 6% in Chinese patients still needs further evaluation.

There are also some limitations in this study. First, we performed this research through a retrospective analysis in a single tertiary care center where patients had severe symptoms, which might lead to data scarcity and lack of universality. Second, the suspected GERD patients were enrolled only based on typical symptoms instead of standardized GERD Questionnaire. Furthermore, data of response to PPI management were not collected and analyzed, which might not differentiate patients with reflux hypersensitivity or functional heart burn.

In conclusion, the majority of Chinese patients with typical reflux symptoms suffer low reflux burden and are diagnosed as inconclusive GERD based on the Lyon Consensus. Patients with AET 4–6% shared similar reflux and esophagus motility characteristics with GERD patients. MNBI and PSPWI could enhance clinicians’ confidence to diagnose inconclusive GERD especially when these two metrics are combined. However, their clinical utility and unified thresholds need further investigation.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Ethical Approval

This study was approved by the Ethical Committee of the First Affiliated Hospital of Nanjing Medical University (No. 2020-SR-307) and it agrees with the 1975 Helsinki declaration.

Informed Consent

All patients involved have signed the informed consent.

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