


Diagnostic accuracy of multichannel intraluminal impedance-pH monitoring for gastroesophageal reflux-induced chronic cough

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Abstract

Objectives: To elucidate the accuracy and advantages of Multichannel intraluminal impedance-pH monitoring (MII-pH) in diagnosing gastroesophageal reflux-induced chronic cough (GERC). **Methods:** The patients with suspected GERC were recruited and underwent MII-pH, GERC was confirmed by subsequent anti-reflux treatment despite the findings of MII-pH. Its diagnostic accuracy in identifying GERC were evaluated by receiver operating characteristic (ROC) analysis and compared with that of 24-h esophageal pH monitoring. **Results:** Among 158 patients completing both MII-pH and anti-reflux therapy, GERC was diagnosed in 136 patients, including acid GERC in 96 patients (70.6%), non-acid GERC in 30 patients (22.0%), neither one of both GERC in 10 patients (7.4%). For the identification of GERC, MII-pH presented with the sensitivity of 92.6%, specificity of 63.6%, positive predictive value of 94.0%, negative predictive value of 58.3% and area under ROC curve of 0.863, which was totally superior to 24-h esophageal pH monitoring. As the essential criteria of MII-pH, esophageal acid exposure time and symptom associated probability had a limited diagnostic value when used alone, but improved greatly the diagnostic yield when used in combination, even with a suboptimal efficacy. **Conclusion:** MII-pH is a more sensitive test for identifying GERC, but with a suboptimal diagnostic efficacy.

Keywords

Esophageal acid exposure time, cough, esophageal pH monitoring, gastroesophageal reflux, symptom associated probability

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Introduction

Gastroesophageal reflux-induced chronic cough (GERC) is a special gastroesophageal reflux disease (GERD) with the predominant cough and a common cause of chronic cough.^{1–3} Presently, ambulatory 24-h esophageal pH monitoring is a main laboratory tool employed for the diagnosis of GERC.⁴ However, it can only detect acid reflux but not non-acid reflux, and may easily under-diagnose GERC caused by non-acid reflux. Thus, the unmet clinical need appeals

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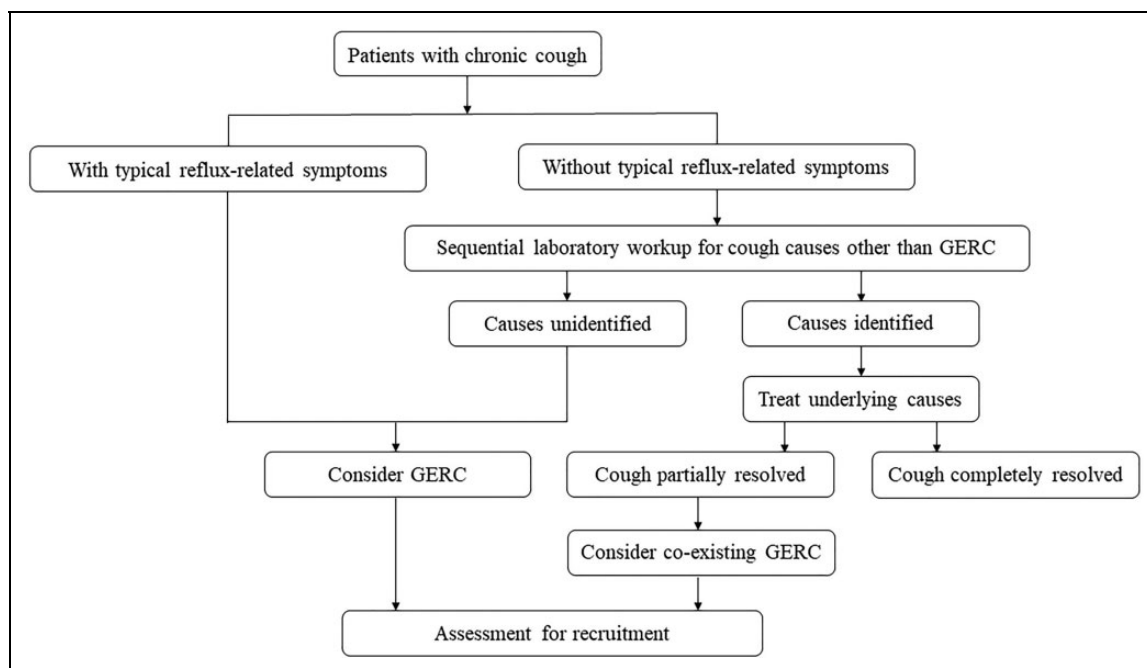


Figure 1. Patients' flow diagram for the recruitment. GERC: gastroesophageal reflux-induced chronic cough.

a diagnostic method for GERC with a higher sensitivity and specificity.

Multichannel intraluminal esophageal impedance-pH monitoring (MII-pH) has been recommended as an important means for detecting gastroesophageal reflux since it can effectively analyze the characters and components of refluxates including the identification of liquid and gas reflux as well as the differentiation of acid and non-acid reflux.⁵ However, there were only a few studies on the evaluation of MII-pH in GERC.⁶ In a preliminary study, we have noticed the usefulness of MII-pH in diagnosing GERC.⁷ Thus, we performed a prospective investigation to evaluate the efficacy of MII-pH in identifying GERC in a larger number of patients with suspected GERC.

Materials and methods

Patients

Consecutive patients with cough lasting for ≥ 8 weeks referred for possible GERC to our respiratory clinic were recruited into this study from July 2016 to July 2019. Inclusion criteria were anyone of followings: (1) chronic cough with co-existing typical reflux-related symptoms such as regurgitation and heartburn; (2) potential GERC was considered when the other common causes of chronic cough including cough variant asthma, upper airway cough syndrome, eosinophilic bronchitis were excluded after a sequential

laboratory workup according to an established algorithm³; (3) concomitant GERC was suspected when the therapy pointed to the current cause of chronic cough could not resolve cough completely.⁸ Patients' flow was shown in Figure 1 where patients would enter assessment for the study at the top of Figure 2. Exclusion criteria included: (1) refusal or intolerance to MII-pH; (2) women in pregnancy or lactation.

It is a single-center observational study. The protocol was approved by the Ethics Committee of Tongji Hospital (No. K-1017-019). Written informed consent was obtained from each participant before enrollment.

MII-pH

MII-pH was conducted off acid suppression for at least one week as described previously.⁹ On the testing day, the patients appeared to the esophageal laboratory in our hospital after an overnight fasting and were asked to keep in a sitting or supine position. After the location of lower esophageal sphincter by previous esophageal manometry (Solar GI, Medical Measurement System B.V., Netherlands), a 2.1-mm diameter combined MII-pH catheter consisting of six impedance channel amplifiers (K6011-E10632, Unisensor, Switzerland) and an antimony pH probe (819100, Medical Measurement System B.V., Netherlands) was transnasally inserted into the

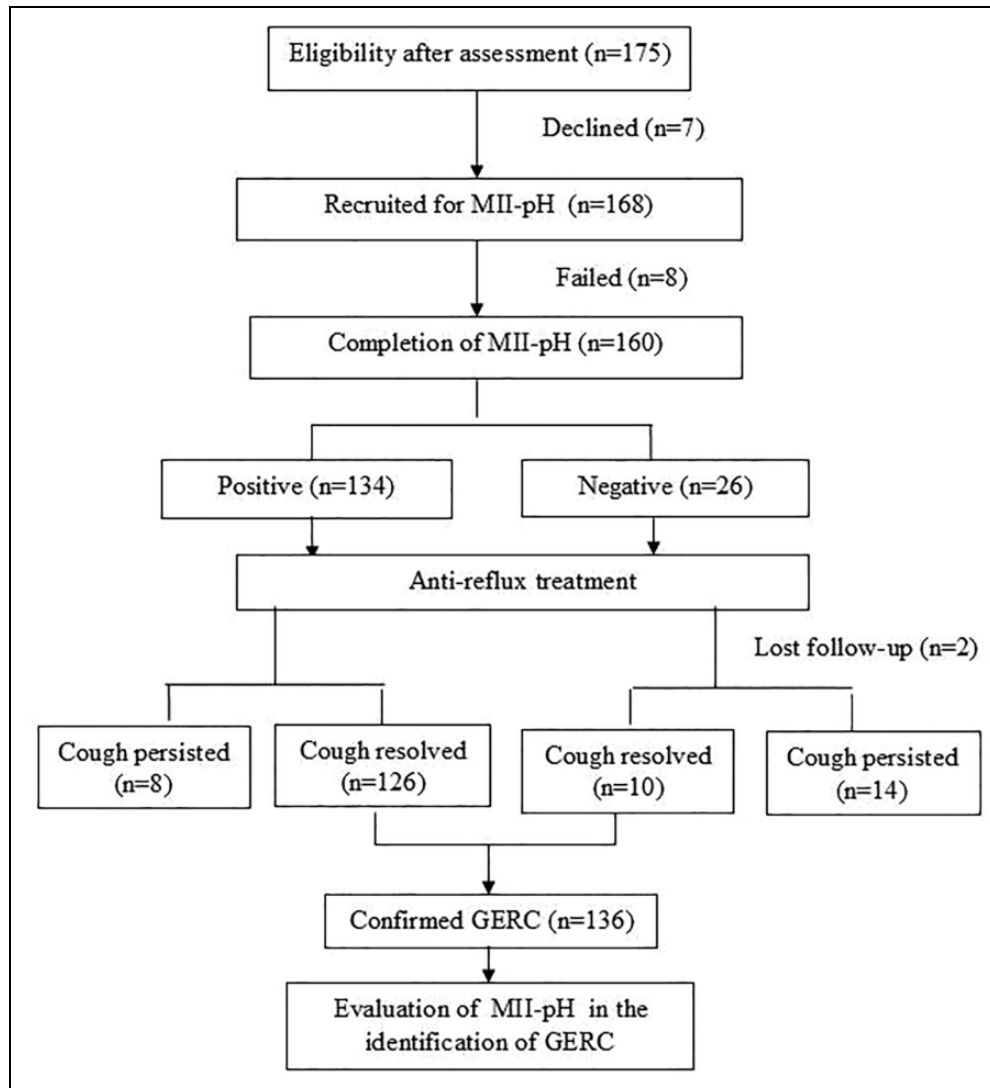


Figure 2. Consort flow diagram of the study. GERC: gastroesophageal reflux-induced chronic cough; MII-pH: multi-channel intraluminal impedance-pH monitoring.

esophagus, with impedance channel amplifiers located at 3, 5, 7, 9, 15 and 17 cm above the manometrically determined lower esophageal sphincter, and pH probe positioned 5 cm above the proximal border of lower esophageal sphincter. Prior to the procedure, the pH probe was calibrated at pH 4.0 and 7.0 according to the manufacturer's instructions. The catheter was connected to a portable data logger (Omega, Medical Measurement System B.V. Netherlands) that collects the data from all seven channels with 50 Hz frequency over 24 h. The patients were instructed to maintain their usual life style, and keep a diary to record the timing of the start and end of meals, changes in position and symptoms.

Using specific software (Database soft, 8.7 version, Medical Measurement System B.V., Netherlands), the

data were automatically analyzed but manually reviewed for reflux episodes, which are classified as liquid, gas and mixed reflux on the basis of impedance values, and categorized into acidic (pH < 4.0) and non-acidic consisting of weakly acidic (pH 4.0–7.0) and weakly alkaline reflux (pH > 7.0).¹⁰ Symptom association probability (SAP) for acid and non-acid reflux was calculated to establish the temporal association between cough and MII-detected liquid-containing reflux.^{6,11} Briefly, the entire recording was divided into consecutive 2-min time windows and evaluated for the presence of reflux. Combined with cough time and number recorded on diary cards, each time window of the recording was classified into reflux alone, reflux followed by cough, only cough but no reflux and neither reflux nor cough. When a cough

occurred in the 2-min time window after the start of a reflux event, it was considered “associated to reflux.” The probability (P-value) that the observed association between reflux (acid or nonacid) and cough occurred by chance, was calculated from the contingency table containing the number of the above different types of 2-min windows with Fisher’s exact test. The SAP was expressed as $(1.0-P) \times 100\%$. Esophageal acid exposure time (AET) was expressed as total time percentage of esophageal pH < 4 over the whole monitoring time and used as a global measure of esophageal acid exposure. Abnormal reflux was defined as AET > 6% and/or SAP for acid and nonacid reflux $\geq 95\%$ ⁵ and used for the diagnostic criteria of GERC.

For the comparison with pure 24-h esophageal pH monitoring, the data of MII-pH in the same patients were re-analyzed by ignoring the tracings of impedance channel sensors and only reviewing the recordings of pH to simulate and collect the data of 24-h esophageal pH monitoring, with AET >6% and/or SAP for acid reflux $\geq 95\%$ as the positive criteria of abnormal acid reflux.

Diagnostic criteria of GERC

The diagnosis of GERC were confirmed when the patients met all the following criteria: (1) the presence of chronic cough, with or without typical reflux symptoms; (2) MII-pH revealed abnormal acid (for acid GERC) or nonacid reflux (for nonacid GERC), defined by a positive AET and/or SAP for acid or nonacid reflux as described above; (3) cough disappeared or substantially improve with medical anti-reflux therapy.^{5,9}

Studying procedures

Initial assessment of patients included the collection of general information, the recording of cough severity and performance of MII-pH. Cough severity was evaluated by the validated Chinese version¹² of cough symptom score described by Hsu et al.¹³ Despite the findings of MII-pH, all the patients received an 8 weeks of standard anti-reflux therapy comprising omeprazole, 20 mg twice daily 30 min before meals, and domperidone, 10 mg three times daily. When the initial treatment failed and MII-pH revealed the abnormal reflux, the patients were given an augmented anti-reflux trial, either by doubling the dose of omeprazole to 80 mg daily or replacing domperidone with baclofen 20 mg three times daily¹⁴ or gabapentin 300 mg three times daily.¹⁵ The patients received

follow-ups every 2 weeks, and their response to therapy and cough symptom score were recorded at each time. GERC was definitely confirmed when cough was completely resolved or significantly improved (cough symptom score decreased by >50%) in response to the anti-reflux treatment.¹⁵ Patients with abnormal acid reflux were diagnosed as acid GERC while these with abnormal non-acid reflux were defined as non-acid GERC.¹⁶

Statistical analysis

Data with normal distribution were expressed as mean \pm SD, whereas those with skewed distribution were expressed as medians (25%, 75% interquartile). Receiver operating characteristic (ROC) analysis was employed to evaluate the efficacy of AET and SAP in identifying GERC. The diagnostic efficacy of MII-pH and 24-h esophageal pH monitoring was compared by chi square test. The consistence of diagnosis was evaluated with Kappa test. SPSS 14.0 software (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. A P-value <0.05 was accepted as statistically significant.

Results

General information

A total of 175 patients with suspected GERC met the inclusion criteria, accounting for 29.8% of 587 patients with chronic cough referred during the study period. Except for seven patients who declined and eight patients who failed to undergo MII-pH because of intolerance to intubation, 160 patients received MII-pH examination. Two patients lost to follow-up after the initiation of anti-reflux treatment. Finally, 158 patients completed both MII-pH and anti-reflux therapy (Table 1, Figure 2).

Etiological diagnosis

One hundred thirty-six patients (86.1%) favorably responded to anti-reflux therapy and were conclusively diagnosed as having GERC, including acid GERC in 96 patients (70.6%), non-acid GERC in 30 patients (22.0%), and mixed acid with non-acid GERC in 10 patients (7.4%). Their cough was relieved in response to the therapy containing omeprazole in 101 patients (74%), baclofen in 26 patients (19%) and gabapentin in 9 patients (7%), respectively. Among 22 patients failing to anti-reflux treatment and recruited by inclusion criteria one, their cough was

finally explained by cough variant asthma in six, eosinophilic bronchitis in four, atopic cough in three and psychogenic cough in two. In the remaining seven patients, no etiology could be identified.

MII-pH in identifying GERC

One hundred thirty-four (84.8%) patients had a positive finding of MII-pH, including the purely increased AET in 69 (51.5%) patients, only positive SAP for acid reflux in 10 (7.5%) patients, only positive SAP for non-acid reflux in 30 (22.4%) patients and both positive AET and SAP in 25 (18.6%) patients. Finally, GERC were confirmed in 126 (94.0%) patients. Among the remaining 24 patients with normal MII-pH, cough was favorably responsive to empirical anti-reflux treatment in 10 (41.7%) patients (Figure 2).

Table 1. General information of the patients.

Items	Value
Case number (male/female)	158 (70/88)
Age (years, $x \pm s$)	44.3 \pm 14.6
Cough duration (months)	12 (6, 48)
Cough symptom score	
Daytime	3 (3, 4)
Nighttime	1 (1, 2)
FEV ₁ (% predictive value)	100.0 \pm 13.6
FVC (% predictive value)	100.9 \pm 14.1
FEV ₁ /FVC	86.5 \pm 10.4

FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity. Cough duration and cough symptom score were expressed as medium (interquartile).

Totally, 18.4% GERC (25 cases) was overlapped identified by both AET and SAP, 44.9% GERC (61 cases) exclusively identified by AET, and 29.4% GERC (40 cases) exclusively identified by SAP. 7.3% GERC (10 cases) failed to be identified by either AET or SAP (Figure 3).

By using AET or SAP as a diagnostic criteria, the efficacy of MII-pH in identifying GERC was shown in Table 2. AET presented with a moderate sensitivity, specificity and area under curve, a high positive predictive value and a low negative predictive value and Kappa value. In contrast, all of total SAP, SAP for acid reflux or non-acid reflux had a low sensitivity, negative predictive value and Kappa value, a high specificity and positive predictive value, and a moderate area under curve. However, the combination of AET with SAP (either one was positive) obviously improved the diagnostic accuracy of MII-pH in identifying GERC.

Comparison of MII-pH with 24-h esophageal pH monitoring in identifying GERC

MII-pH had a higher sensitivity, positive predictive value, Kappa value and area under than those of pure 24-h esophageal pH monitoring, with a similar specificity and negative predictive value (Table 3, Figure 4).

Discussion

Laboratory tests available for GERC include barium esophagography, esophagoscopy and 24-h esophageal pH monitoring.¹⁷ Since barium esophagography and

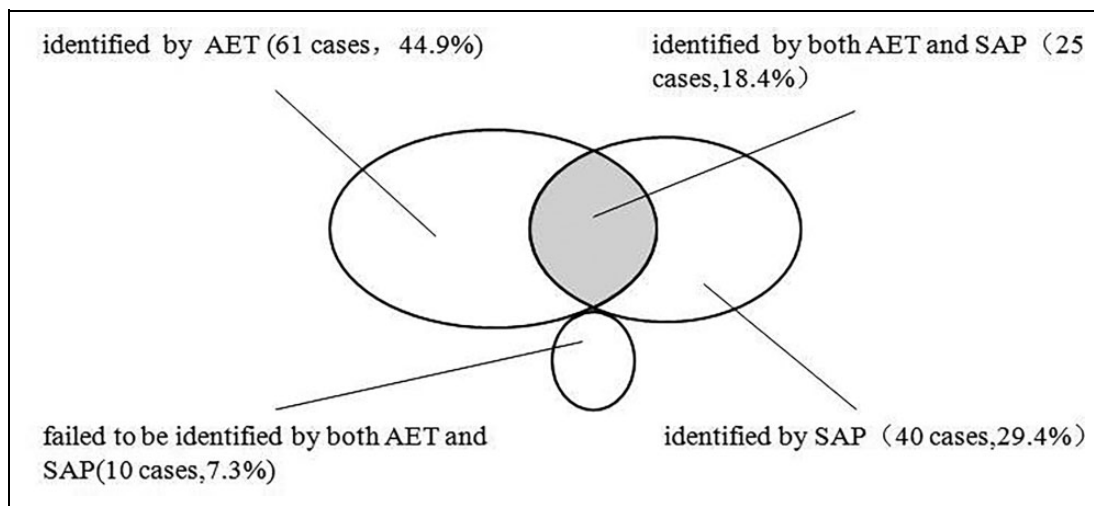


Figure 3. Identifying proportion of GERC by AET and SAP. AET: esophageal acid exposure time; GERC: gastroesophageal reflux-induced chronic cough; SAP: symptom association probability.

Table 2. Diagnostic efficacy of MII-pH in diagnosing GERC.

Parameters	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Kappa	Area under ROC curve
AET and SAP	92.6	63.6	94.0	58.3	0.512	0.863
AET	63.2	63.6	91.5	21.9	0.149	0.657
SAP for acidic reflux	25.7	100	100	17.9	0.088	0.721
SAP for non-acidic reflux	22.1	100	100	17.2	0.073	0.714

AET: esophageal acid exposure time; GERC: gastroesophageal reflux-induced chronic cough; MII-pH: multichannel intraluminal esophageal impedance-pH monitoring; ROC: receiver operating curve; SAP: symptom association probability.

Table 3. Comparison on the efficacy between MII-pH and 24-h esophageal pH monitoring in identifying GERC.

Method	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Kappa
MII-pH	92.6	63.6	94.0	58.3	0.542
24-h esophageal pH monitoring	70.6	63.6	92.3	25.9	0.213
χ^2 value	25.9	...	0.277	7.583	—
P-value	0.000	...	0.599	0.006	All <0.01

GERC: gastroesophageal reflux-induced chronic cough; MII-pH: multichannel intraluminal esophageal impedance-pH monitoring.

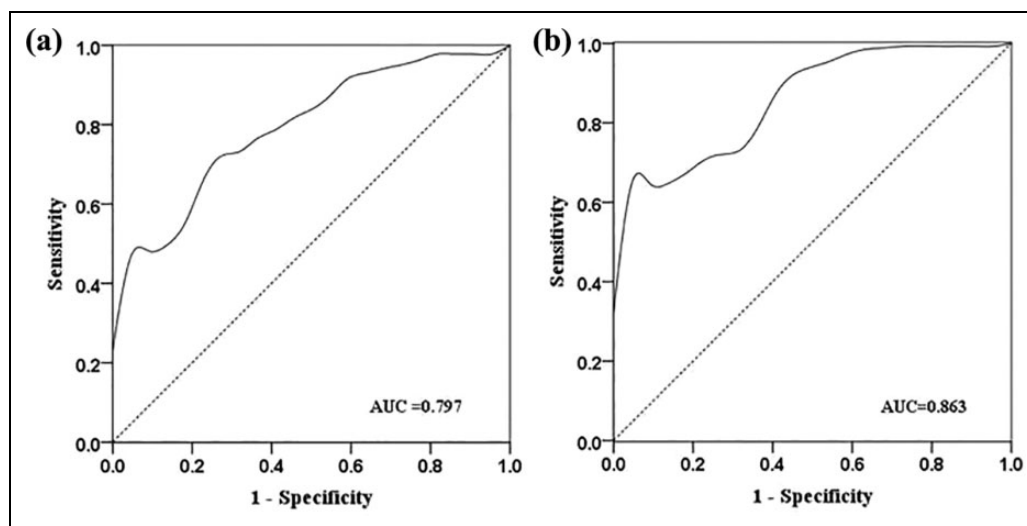


Figure 4. Receiver operating curve (ROC) of multichannel intraluminal impedance-pH monitoring (MII-pH) and 24-h esophageal pH monitoring in identifying gastroesophageal reflux-induced chronic cough (GERC). AUC: area under the curve, sensitivity and 1-specificity by positive esophageal acid exposure time and symptom association probability (SAP) (A: MII-pH; B: 24-h esophageal pH monitoring).

esophagoscopy only reveal the positive findings in only 35–50% patients with GERC,^{18,19} they are not recommended as the first-line choice in identifying GERC. 24-h esophageal pH monitoring, a preferred test for diagnosing GERC, has a higher sensitivity and specificity than barium esophagography and esophagoscopy.¹⁷ Nevertheless, it cannot identify non-acid and gas reflux as well as the moving direction of

intraesophageal liquids and alimentary bolus, and thus have no ability to recognize the cough due to non-acid reflux.¹⁰

The study has demonstrated that MII-pH is superior to 24-h esophageal pH monitoring in identifying GERC. Nevertheless, its specificity and negative predictive value was the same as those of 24-h esophageal pH monitoring. These findings are consistent

with the previous observations of our preliminary report with a small sample size that MII-pH additionally identifies non-acid GERC when keeping the same ability to measure acid reflux as 24-h esophageal pH monitoring,⁷ regardless of a slightly higher sensitivity but lower specificity in the present study. Therefore, MII-pH may make up the defects of 24-h esophageal pH monitoring in lacking the ability to detect non-acid reflux, and present with a better diagnostic accuracy for GERC in clinical practices.

The diagnosis of GERC depends essentially on AET and SAP according to the current guideline for the management of chronic cough.^{4,5} This study has demonstrated that both AET and SAP have their own merits in predicting GERC, with a moderate sensitivity and specificity in AET and a low sensitivity but high specificity in SAP. Therefore, these parameters present with a limited efficacy alone and are unable to meet the needs for the diagnosis of GERC. However, when either positive AET or SAP is used in combination as the objective criteria of GERC, the diagnostic yield has been greatly improved and the shortcomings of single indicator have been maximally compensated.

Despite its advantages over 24-h esophageal pH monitoring, MII-pH has its inherent limitations, with a suboptimal sensitivity and specificity in identifying GERC. Currently, there is no general consensus on how to best interpret the results of MII-pH. AET has nothing to do with the non-acid reflux. SAP only reflects the cough within two-minute time window after the occurrence of reflux episodes, which only accounts for 56–81% of the total count of cough.²⁰ During MII-pH, the patients often forget to record the cough events or mislabel the cough time, leading to the inaccuracy in the calculation of SAP.²¹ The positive rate of SAP was only 35% in the patients with suspected GERC,²² could be only increased to 48–71% even MII-pH was combined with synchronous esophageal manometry or cough frequency recording.²³ In the situation that GERC is highly probable by clinical manifestation but with a negative MII-pH, the empirical anti-reflux therapy is still necessary to be instituted to minimize the misdiagnosis and under-diagnosis.²⁴ In the study, 10 patients with the negative findings of MII-pH were finally confirmed to suffer from GERC with subsequent empirical anti-reflux treatment.

In the present study, the favorable response to anti-reflux therapy was set as the gold standard for definite GERC. Despite its advantage on verifying the cause-effect relation between reflux and cough, the

failure to anti-reflux therapy cannot exclude the possibility that the patients with positive findings of MII-pH still had GERC since some patients with abnormal reflux (especially with non-acid reflux) were resistant to antireflux medicinal treatment but might have responded to anti-reflux surgery.²⁵ Therefore, it is predictable that the diagnostic efficacy and accuracy of MII-pH for potential GERC might be underestimated by the means of outcome assessment used in the study.

One may criticize the therapeutic gain of anti-reflux therapy was mainly due to placebo effect since it is an uncontrolled treatment with omeprazole and domperidone. It is true that the placebo effect cannot be excluded, which might contribute up to 50% of the therapeutic efficacy in the study²⁶ and limit the strength of conclusions. However, the purpose of the study is to demonstrate the diagnostic accuracy and yield of MII-pH by observing the antireflux response in the patients with potential GERC and not to verify the efficacy of anti-reflux medicinal therapy. Moreover, anti-reflux medicinal therapy employed in the study are logically expected to be effective for GERC when considering their benefits in the treatment of gastroesophageal reflux disease.^{4,5} We do not believe placebo effects of omeprazole and domperidone can completely explain the high therapeutic success rate (81.6%) in the cohort of the patients with chronic cough.

In conclusion, MII-pH is a more reliable and sensitive test currently available for identification of GERC, and can recognize non-acid GERC failing to be detected by 24-h esophageal pH monitoring. It improves the diagnostic yield of GERC and is gradually replacing 24-h esophageal pH monitoring for the identification of GERC in clinical practice. However, MII-pH has its inherent limitations similar to 24-h esophageal pH monitoring with suboptimal diagnostic efficacy. For the suspected GERC patients with a negative MII-pH, the implementation of empirical anti-reflux is a remedy to avoid the misdiagnosis and under-diagnosis of GERC.

Authors' note

Na Li and Qiang Chen contributed equally as co-first authors.

Author contributions

Na Li had full access to the data in the study and was responsible for data integrity and the accuracy of the data analysis. Na Li and Qiang Chen were in charge of case

collection, processing and statistical analysis of data, interpretation of the results and writing the manuscript. Qiang Chen also participated the critical review of the manuscript. Siwan Wen, Mengru Zhang, Ran Dong, Xianghuai Xu and Li Yu participated in case collection and critical review of the manuscript. Zhongmin Qiu was in charge of study design, program coordination, and review and correction of the manuscript.


Declaration of conflicting interests

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