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Diagnostic value of reflux episodes in gastroesophageal reflux-induced chronic cough: a novel predictive indicator

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Abstract

Background: Multichannel intraluminal impedance and pH-monitoring (MII-pH) is an essential testing modality for gastroesophageal reflux-induced chronic cough (GERC), while the existing diagnostic criteria still have some inherent defects. This study aimed to explore the diagnostic value of a direct and objective index, reflux episodes, and related parameters in MII-pH in different types of GERC.

Methods: Patients with chronic cough suspected of gastroesophageal reflux disease who successfully received MII-pH were enrolled. The differences in MII-pH parameters were analyzed among patients with different etiologies and the predictive diagnostic value of reflux episodes and related parameters were analyzed in patients with GERC, acid GERC, and non-acid GERC, and compared with existing diagnostic criteria.

Results: A total of 190 patients with suspected GERC who underwent MII-pH were enrolled; 131 of these patients were finally diagnosed with GERC. When the reflux episodes were used to diagnose GERC, the area under the curve (AUC) was 0.684; when the acid reflux episodes and the ratio of acid reflux episodes were used to diagnose acid GERC, the AUCs were 0.769 and 0.854; when the non-acid reflux episodes and the ratio of non-acid reflux episodes were used to diagnose non-acid GERC, the AUCs were 0.735 and 0.705, respectively. When the non-acid reflux episodes >58 and the proportion of non-acid reflux episodes $>68.18\%$ were used alone or in combination to diagnose non-acid GERC, their diagnostic value was significantly better than SAP or SI (all $ps<0.05$).

Conclusion: The number of reflux episodes has a good diagnostic value for GERC, especially in the diagnosis of non-acid GERC.

Keywords: cough, diagnosis, gastroesophageal reflux, multichannel intraluminal impedance-pH monitoring

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Introduction

Gastroesophageal reflux-induced chronic cough (GERC) is a common extraesophageal manifestation of gastroesophageal reflux disease (GERD) as well as one of the most important causes of chronic cough.[1–3] Patients with GERC tend to have a long disease course and low quality of life.[4,5] Multichannel intraluminal impedance-pH monitoring (MII-pH) is an essential test for gastroesophageal reflux, which allows the detection of times, pH, and the gas and liquid phases of reflux episodes.[2,6] According to the pH value of the reflux episodes, GERC can be divided into acid GERC and non-acid GERC. MII-pH is the only way to detect non-acid GERC. At present, various guidelines have proposed that acid exposure time (AET), DeMeester score, symptom-associated probability (SAP), and symptom index (SI) can be used to diagnose GERC.[7–9] AET and DeMeester score only represent the severity of

acid reflux; thus, SAP and SI are still the only means of diagnosing non-acid GERC. However, the algorithm defects and patients' poor compliance have restricted the application of SAP and SI. Therefore, there are still some defects in the existing diagnostic criteria, and objective indicators are needed to predict GERC.[10,11] As the most objective indicator in MII-pH, the diagnostic value of reflux episodes per 24 h in GERC has not yet been evaluated. The Lyon Consensus proposed that >80 reflux episodes per 24 h indicated GERD.[1] Therefore, we speculated that the number of reflux episodes and its related indicators might be better predictors of GERC, and a prospective study was carried out to explore the value of reflux episodes with different pH values in diagnosing different types of GERC. We present this protocol in accordance with the STAndards for Reporting of Diagnostic (STARD) accuracy studies reporting checklist.

Methods

Patients

Consecutive patients with suspected GERC and referred to our hospital for MII-pH were enrolled from October 2017 to February 2021. The inclusion criteria were as follows: (1) Patients with a cough lasting >8 weeks but with normal chest radiography or computed tomography (CT) images and with accompanying typical reflux-related symptoms, such as acid regurgitation and heartburn; (2) other common causes of chronic cough, including cough-variant asthma, upper respiratory tract cough syndrome, eosinophilic bronchitis, or atopic cough were excluded. The flow chart of patients' enrollment is shown in Figure 1. The exclusion criteria were as follows: (1) refusal or intolerance of MII-pH, (2) patients who took acid suppressants 1 week prior to MII-pH, (3) women with pregnancy or during breast feeding, and (4) patients lost to follow-up.

Laboratory investigations

MII-pH. MII-pH was performed as previously described[12,13] after the patients had stopped taking acid suppressants for at least 1 week. Briefly, a combined MII-pH catheter was transnasally inserted into the patient's esophagus, with six impedance channel sensors (K6011-E10632, Unisensor, Switzerland) located 3, 5, 7, 9, 15, and 17 cm above the lower esophageal sphincter, which was determined by esophageal manometry. An antimony pH electrode (819100, Medical Measurement System B.V., Netherlands) was positioned 5 cm above the proximal border of the lower esophageal sphincter. A connected portable data logger (Ohmega; Medical Measurement System B.V., Netherlands) stored data from all seven channels over 24 h. Reflux episodes recorded on the tracings of MII-pH were manually characterized by their impedance value as liquid, gas, or mixed liquid–gas reflux or characterized by pHmetry as acid ($pH < 4.0$), weakly acidic ($4.0 < pH < 7.0$), or weakly alkaline ($pH > 7.0$) reflux,[14] with the latter two collectively referred to as non-acid reflux. SAP was used to indicate the correlation between the cough recorded by the patient on the diary card and the reflux episodes that occurred in the previous 2 min. SI referred to the percentage of reflux-related coughs out of the total number of coughs.[8,15]

The reflux episode was defined as the sum of liquid reflux, gas reflux, and mixed reflux that occurred during MII-pH.[1] The acid reflux episode was the number of reflux episodes with $pH < 4.0$ that occurred within 24 h during MII-pH; the ratio of acid reflux was the ratio of the number of acid reflux episodes to the total number of reflux episodes. The non-acid reflux episode was the number of refluxes with $pH \geq 4.0$ that occurred within 24 h during MII-pH, indicating the sum of weekly acid and weekly alkaline reflux episodes. The ratio of non-acid reflux was calculated as the ratio of the number of non-acid reflux episodes to the total number of reflux episodes. The counts of reflux episodes were manually corrected per the Wingate consensus.[16]

Other laboratory tests. Patients underwent lung function and histamine bronchial provocation tests in accordance with the standard operating procedure proposed by the Respiratory Branch of the Chinese Medical Association.[17] Induced sputum cell analysis and MII-pH were performed according to the method previously reported.[18] Cough sensitivity was measured by the modified capsaicin challenge test reported by Fujimura *et al.*[19] The minimum capsaicin concentration that induced ≥2 or ≥5 coughs by inhalation of the capsaicin solution was the cough threshold C2 and C5, respectively, and was used as an index of cough sensitivity.

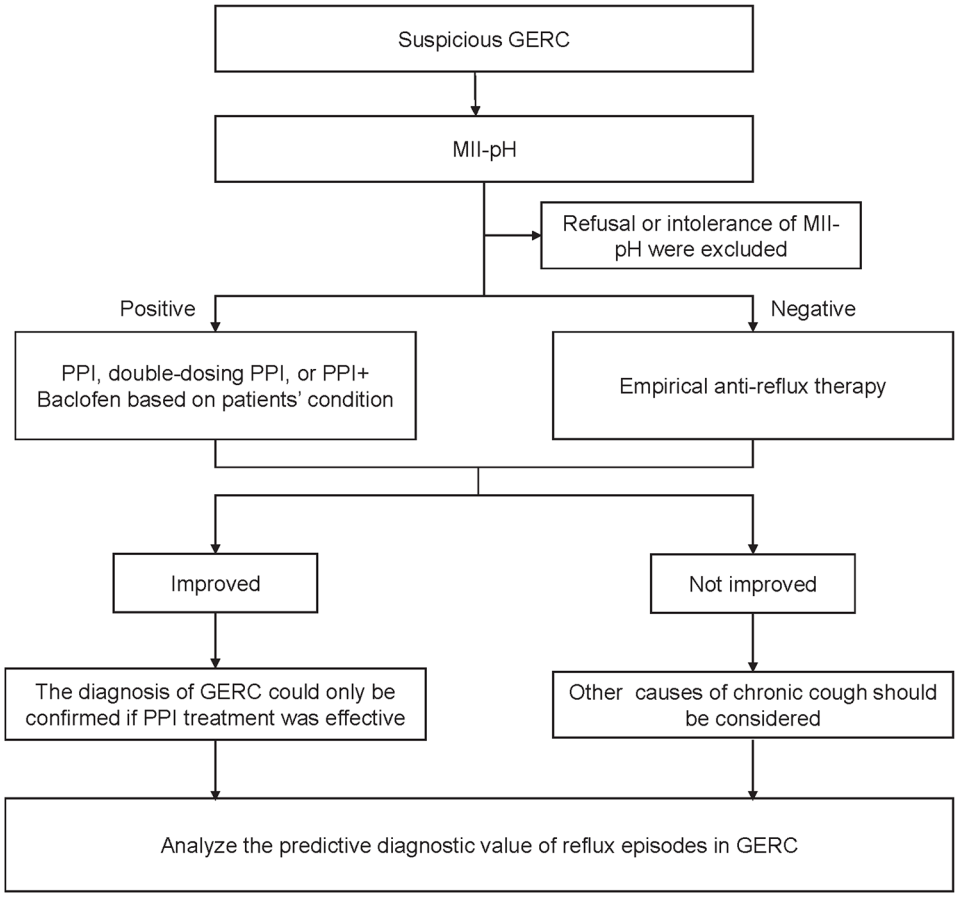

Figure 1. The flow of patients through the study. Positive: Positive results according to the diagnostic criteria of GERD proposed by American College of Chest Physicians. Negative: Negative results according to the diagnostic criteria of GERD proposed by American College of Chest Physicians.
GERC, gastroesophageal reflux-induced chronic cough; MII-pH, multichannel intraluminal esophageal impedance and pH monitoring; PPI, proton pump inhibitor.

Diagnosis of GERC

The diagnosis of GERC was in accordance with the 'Guidelines for the Diagnosis and Treatment of Cough (2015 Edition)' and the diagnostic criteria of GERD proposed by the American College of Chest Physicians.[2,8] Briefly, the diagnostic criteria included mainly daytime cough; an MII-pH indicated DeMeester score of >14.72, SI $\geqslant 50\%$, and/or SAP $\geqslant 95\%$; and cough responsive to a stepwise anti-reflux therapy (cough symptom score decreased by $>50\%$).[8] If the DeMeester score >14.72, acid SI $\geqslant 50\%$, and/or acid SAP $\geqslant 95\%$, the patient was diagnosed with acid GERC. If acid reflux is negative, patients with DeMeester score $\leqslant 14.72$, non-acid SI $\geqslant 50\%$, and/or non-acid SAP $\geqslant 95\%$ were diagnosed with non-acid GERC.[12] Diagnosis of GERC was also confirmed if MII-pH was negative and the cough was still responsive to a stepwise anti-reflux therapy.[20]

Study design

This is a prospective study. According to the above-mentioned diagnostic criteria, patients with suspected GERD were enrolled to undergo MII-pH to clarify the etiology. A standard anti-reflux therapy [omeprazole 20 mg (b.i.d.) plus mosapride 10 mg (t.i.d.)] was first introduced in patients with suspected GERC. If cough remission was not achieved, the dose of proton pump inhibitor was doubled [omeprazole 40 mg (b.i.d.)] and continued for 8 weeks. Patients who responded to the double-dosing were maintained on this treatment until their cough resolved. If the cough did not resolve, baclofen was introduced

[omeprazole 20 mg (b.i.d.), baclofen 10–20 mg (t.i.d.)] for 4 weeks[21] and mosapride was discontinued. If a favorable response was achieved, the treatment was maintained until cough resolution. Patients with negative MII-pH results were treated with empirical anti-reflux therapy. If the cough symptoms improved, GERC was diagnosed. Otherwise, GERC was excluded.

Sample size

The sensitivity and the specificity of reflux episodes in diagnosing GERC are 0.5 and 0.8, respectively, according to our preliminary experimental results. After other laboratory tests, the probability of being diagnosed with GERC by MII-pH is 0.6. According to the formula $Z^2_{1-\alpha/2} * S_N * (1-S_N) / L^2 *$ Pervalence, $Z^2_{1-\alpha/2} * S_P * (1-S_P) / L^2 * (1-$ Pervalence), and a calculated 15% loss to follow-up rate, 189 patients with suspected GERC needed to be included. Our final analysis was conducted on 190 included patients.[22,23]

Statistical analysis

Normally distributed data were expressed as mean ± SD, while those with skewed distribution were expressed as medians (25%–75% interquartile range). One-way analysis of variance (ANOVA) or non-parametric test (Kruskal–Wallis H test). Correlation analyses were performed using Spearman's rank correlation coefficient. Area under the curve (AUC), sensitivity, specificity, positive predictive value, negative predictive value, Youden's index of reflux episodes, episodes of acid and non-acid reflux, and their ratios to reflux episodes in diagnosing GERC, acid GERC, and non-acid GERC were analyzed to establish the best cut-off value for the diagnosis of GERC, acid GERC, and non-acid GERC. Different AUCs were compared using the DeLong test. Statistical analysis was performed with SPSS version 21.0 (a relatively newer version). $p < 0.05$ was considered statistically significant.

Results

Basic information

A total of 542 patients with chronic cough attended the Department of Respiratory and Critical Care Medicine of our hospital between October 2017 and February 2021. Among them, 217 (40.04%) patients with chronic cough underwent MII-pH testing. After excluding 27 patients who were lost to follow-up or had incomplete data, 190 patients were eventually included in the study. Of these, 43 underwent gastroduodenoscopy and 11 had erosive esophagitis, but none of them had Barrett's esophagus. The distribution of etiologies is shown in Table 1. One hundred thirty-one patients were finally diagnosed with GERC, accounting for 24.17% of all chronic cough patients. One hundred twenty-five of these patients (125/131, 95.42%) with positive MII-pH results responded to anti-reflux therapy, and six (6/131, 4.58%) patients with negative MII-pH results were diagnosed with GERC after responding to anti-reflux therapy. There were 113 GERC patients with single etiology and 18 with multiple etiologies. Among all GERC patients, 87 (45.79%) were diagnosed with acid GERC; 44 (23.16%) were diagnosed with non-acid GERC; and the remaining 59 (31.05%) were excluded from GERC after further examination or empirical treatment (Table 1). The basic information of the three groups is shown in Table 2.

Comparison of MII-pH parameters among acid GERC, non-acid GERC, and non GERC patients

The results of MII-pH parameters and reflux ratio of the three groups are shown in Table 3. Significant differences in AET were observed among them ($H = 132.877$, $p < 0.001$). The AET of acid GERC patients was significantly higher than that of non-acid GERC patients and non-GERC patients. There were significant differences in the DeMeester scores among the three groups ($H = 135.316$, $p < 0.001$). The DeMeester score of acid GERC patients was significantly higher than those of the other two groups. There were significant differences in SAP and SI among the three groups ($H = 9.126$, $p = 0.010$; $H = 12.696$, $p = 0.002$). The SAP and SI of acid GERC and non-acid GERC patients were significantly higher than those of non-GERC patients.

As for the reflux episodes, there was a significant difference in the reflux episodes among the three groups ($H = 20.916$, $p < 0.001$). The number of reflux episodes in non-acid GERC patients was significantly higher than those of the other two groups. The reflux episodes of acid GERC patients were significantly higher than those of non-GERC patients. There was a significant difference in the acid reflux episodes among the three groups

Table 1. The etiology distribution of 190 chronic cough patients.

Cause of cough	*n*	%
Single etiology GERC	113	59.47
Dual etiologies GERC	18	9.47
GERC + CVA	5	2.63
GERC + AC	6	3.16
GERC + EB	4	2.11
GERC + UACS	3	1.58
Non-GERC	59	31.05
UACS	11	5.79
AC	6	3.16
CVA	5	2.63
EB	9	4.74
Psychogenic cough	3	1.58
OSAHS-related cough	2	1.05
ACEI	2	1.05
CVA + UACS	5	2.63
EB + UACS	4	2.11
AC + UACS	3	1.58
Unexplained cough	9	4.74

AC, atopic cough; ACEI, angiotensin-converting enzyme inhibitor; CVA, cough-variant asthma; EB, eosinophilic bronchitis; GERC, gastroesophageal reflux-induced chronic cough; OSAHS, obstructive sleep apnea–hypopnea syndrome; UACS, upper airway cough syndrome.

($H = 43.802$, $p < 0.001$), and the acid reflux episodes of acid GERC patients were significantly higher than those of the other two groups. There was a significant difference in the non-acid reflux episodes among the three groups ($H = 17.507$, $p < 0.001$). The non-acid reflux episodes in patients with non-acid GERC were significantly higher than those of the other two groups, and the non-acid reflux episodes in acid GERC patients were significantly higher than those of non-GERC patients.

In the comparison of reflux ratio, there was a significant difference of the acid reflux ratio among the three groups ($H = 47.456$, $p < 0.001$). The acid reflux ratio of patients with acid GERC was significantly higher than that of the other two groups. Among the three groups, there was a significant difference in the ratio of non-acid reflux ($H = 49.298$, $p < 0.001$). The ratio of non-acid reflux in patients with acid GERC was significantly lower than that of the other two groups.

Diagnostic value of reflux episodes, SAP, SI, DeMeester score, and AET in GERC

The diagnostic values of reflux episodes, SAP, SI, DeMeester score, and AET for GERC are shown in Figure 2. When reflux episodes were greater than 97, the Youden index reached a maximum value of 0.296, and the sensitivity and the specificity were 46.56% and 83.05%, respectively. The diagnostic values of AET and DeMeester score were better than those of reflux episodes, SAP, and SI (DeLong's test, $p < 0.05$). There was no significant difference among reflux episodes, SAP, and SI (DeLong's test, all ps > 0.05).

Diagnostic value of acid reflux episodes, acid reflux ratio, acid SAP, acid SI, DeMeester score, and AET in acid GERC

The diagnostic value of acid reflux episodes, acid reflux ratio, acid SAP, acid SI, DeMeester score, and AET for acid GERC is shown in Figure 3. The acid reflux episodes showed good value in diagnosing acid GERC. When the cut-off value of acid reflux episodes was 12.5, the sensitivity and the specificity were 89.53% and 52.88%, respectively. The acid reflux ratio indicated a higher diagnostic value in diagnosing acid GERC. When the cut-off value of acid reflux ratio was 31.08%, the sensitivity and the specificity were 82.56% and 76.92%, respectively. When DeMeester score and AET were used to diagnose acid GERC, the diagnostic value was better than others (DeLong's test, all ps < 0.001), while there was no significant difference between DeMeester score and AET. The diagnostic values of acid reflux episodes and acid reflux ratio were better than those of acid SAP and acid SI (DeLong's test, all ps < 0.001). There was no difference between acid reflux episodes and acid reflux ratio, as well as between acid SAP and acid SI (DeLong's test, all ps > 0.05).

Table 2. General clinical characteristics of patients.

Variables	Acid GERC ($n=87$)	Non-acid GERC ($n=44$)	Non-GERC ($n=59$)
Age(years)	50.94 ± 15.72	46.44 ± 15.46	47.07 ± 12.64
Gender (F/M)	45/42	23/21	32/27
Course of cough (m)	9.00 (32.00)	11.50 (32.00)	24.00(36.00)
Cough symptom score			
Daytime	3.00 (1.00)	3.00 (1.25)	3.00(1.00)
Nighttime	2.00 (1.00)	1.00 (1.25)	1.00(2.00)
Cough sensitivity			
C2 (μmol/L)	0.49 (1.95)	0.49 (1.46)	0.49(0.49)
C5 (μmol/L)	1.95 (7.31)	0.74 (4.39)	0.49(0.97)
Lung function (%, $\bar{x} \pm s$)			
FEV1 predicted (%)	95.17 ± 14.85	97.45 ± 10.96	98.10 ± 18.08
FVC predicted (%)	99.79 ± 15.53	99.12 ± 15.78	102.45 ± 14.94
FEV1/FVC%	82.87 ± 9.86	84.52 ± 11.63	80.66 ± 7.54

C2, capsaicin solution concentration with ≥2 coughs; C5, capsaicin solution concentration for ≥5 coughs; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GERC, gastroesophageal reflux–induced chronic cough.
The data of age and lung function were expressed as mean ± SD. Except for age and lung function, data were expressed as medians (interquartile).

Diagnostic value of non-acid refluxs episodes, non-acid reflux ratio, non-acid SAP, and non-acid SI in non-acid GERC

The diagnostic values of non-acid reflux episodes, non-acid reflux ratio, non-acid SAP, and non-acid SI for non-acid GERC are shown in Figure 4. The non-acid reflux episodes had good diagnostic value in diagnosing non-acid GERC. When the cut-off value of non-acid reflux episodes was 58, the sensitivity and the specificity were 68.89% and 71.72%, respectively. The non-acid reflux ratio also had a good value in diagnosing non-acid GERC. When the cut-off value of the non-acid reflux ratio was 68.18%, the sensitivity and the specificity were 86.67% and 61.38%, respectively. When non-acid SAP and non-acid SI were used to diagnose non-acid GERC, the diagnostic value was moderate. There was no significant difference among these receiver-operating characteristic (ROC) curves (DeLong's test, $p > 0.05$).

Comparison of the diagnostic values of different criteria in non-acid GERC

According to the above results, we, respectively, used the following six diagnostic criteria to predict non-acid GERC: (i) non-acid reflux episodes >58; (ii) non-acid reflux ratio $>68.18\%$; (iii) non-acid SAP $\geqslant 95\%$; (iv) non-acid SI $\geqslant 50\%$; (i) and (ii); and (i) or (ii). The predictive diagnostic value was further compared among these criteria (Table 4, Figure 5).

Among the six diagnostic criteria, there were significant differences in sensitivity, specificity, negative predictive value, and positive predictive value (all $ps < 0.001$). In terms of predicted diagnostic value, criteria (iii) and (iv) were less valuable in diagnosing non-acid GERC. According to the DeLong test, there was no significant difference among criteria (i), (ii), [(i) and (ii)], as well as [(i) or (ii)], which all had a higher diagnostic value for non-acid GERC than criterion (iii) and

Table 3. Comparison of different variables of MII-pH among three groups.

Variables	Acid GERC ($n=87$)	Non-acid GERC ($n=44$)	Non-GERC ($n=59$)	p value
AET (%)	7.50 (8.28)[a, b]	1.40 (1.60)	0.90(1.80)	<0.001
DeMeester score	26.18 (26.48)[a, b]	5.68 (5.77)	3.23(6.13)	<0.001
SAP (%)	73.50 (94.23)[b]	81.30 (91.60)[b]	0.00(72.60)	0.010
Acid SAP (%)	0.00 (78.77)[b]	0.00 (65.28)	0.00(0.00)	0.026
Non-acid SAP (%)	0.00 (0.00)[a]	70.10 (91.23)[b]	0.00(65.38)	0.002
SI (%)	22.50 (40.00)[b]	16.70 (45.50)[b]	0.00(14.30)	0.002
Acid SI (%)	0.00 (10.30)	0.00 (7.10)	0.00(0.00)	0.139
Non-acid SI (%)	0.00 (0.00)[a]	14.30 (34.70)[b]	0.00(5.83)	< 0.001
Reflux episodes(n)	95.00 (88.75)[a, b]	109.00 (85.00)[b]	54.00(45.00)	0.001
Acidic reflux (n)	37.00 (43.25)[a, b]	19.00 (21.00)	7.00(21.00)	< 0.001
Percentage of acidic reflux (%)	48.84 (27.95)[a, b]	22.68 (18.89)	16.67(29.07)	< 0.001
Non-acidic reflux (n)	55.00 (41.25)[a]	84.00 (90.00)	43.00(33.00)	< 0.001
Weakly acidic reflux (n)	36.50 (44.75)[a]	57.00 (53.50)[b]	24.00(25.00)	< 0.001
Weakly alkaline reflux (n)	6.50 (17.25)[a, b]	18.00 (42.00)	12.00(22.00)	< 0.001
Percentage of non-acidic reflux (%)	51.16 (27.95)[a, b]	77.32 (18.89)[b]	83.33(29.07)	< 0.001
Percentage of weakly acidic reflux (%)	39.87 (24.76)[a]	56.32 (31.16)	48.00(28.63)	0.001
Percentage of weakly alkaline reflux (%)	4.00 (18.19)[a, b]	17.28 (25.41)	25.37(36.89)	< 0.001
Gas reflux (n)	25.00 (42.50)[a]	36.00 (38.50)	15.00(18.00)	0.027
Liquid reflux (n)	15.50 (20.00)	20.00 (28.50)	13.00(15.00)	0.064
Mixed reflux (n)	39.00 (33.25)[b]	50.00 (48.50)[b]	19.00(31.00)	< 0.001
Acid clearance (s)	13.00 (3.13)[a, b]	12.00 (4.75)	11.00(5.50)	0.001
Proximal extent (n)	0.00 (5.60)[b]	0.00 (1.00)	0.00(0.00)	< 0.001
Percentage of proximal extent (%)	3.21 (13.88)[b]	0.00 (15.58)[b]	0.00(0.00)	< 0.001

AET, acid exposure time; GERC, gastroesophageal reflux-induced chronic cough; MII-pH, multichannel intraluminal esophageal impedance and pH monitoring; SAP, symptom-associated probability; SI, symptom index.
Data were presented as median (25%–75% interquartile range)
[a]$p<0.05$ compared with non-acid GERC group.
[b]$p<0.05$ compared with non-GERC group.

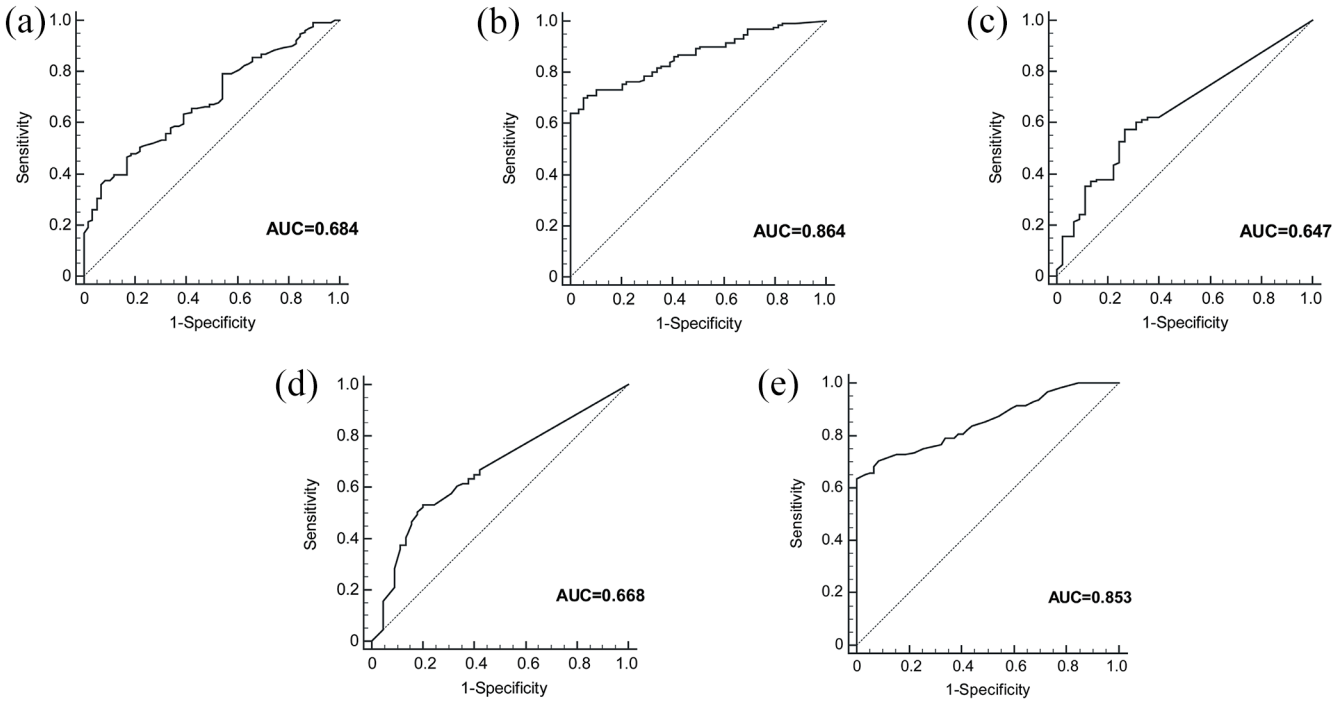

Figure 2. The diagnostic value of reflux episodes, SAP, SI, and DeMeester score for GERC. (a) Receiver-operating characteristic (ROC) curve of reflux episodes in predicting GERC; (b) ROC curve of DeMeester in predicting GERC; (c) ROC curve of SAP in predicting GERC; (d) ROC curve of SI in predicting GERC; and (e) ROC curve of AET in predicting GERC.

criterion (iv) (all $ps < 0.05$). Among them, criteria [(i) and (ii)] had the highest specificity, reaching 83.45%, while criteria [(i) or (ii)] had the highest sensitivity of 93.33%.

Discussion

This study found that AET and DeMeester score were better than reflux episodes, SAP, and SI in diagnosing GERC. Compared with non-GERC patients, the reflux episodes in patients with GERC were significantly higher. Among them, the reflux episodes in patients with non-acid GERC were more than those of acid GERC, while the acid reflux ratio in patients with acid GERC was significantly higher. The non-acid reflux episodes were more in non-acid GERC patients than those of the other two groups. Reflux episodes >97 was of medium diagnostic value in patients with suspected GERC. For the diagnosis of acid GERC, the diagnostic value of DeMeester score was higher than that of acid reflux episodes, acid SAP, and acid SI. When non-acid reflux >58 and non-acid reflux ratio >68.18% were used alone or in combination for diagnosing non-acid GERC, the diagnostic value was significantly better than non-acid SAP and non-acid SI.

GERC is an important extraesophageal manifestation of GERD, which is also one of the common causes of chronic cough.[24,25] In recent years, with changes in people's lifestyles, improvement of the awareness of GERC, and the development of corresponding diagnostic methods, the proportion of GERC in the causes of chronic cough has increased year by year.[26–29] In this study, patients with suspected GERC were examined and treated with common remedies before enrollment, so GERC accounted for the majority of patients' enrollment in the study. Similar to our previous studies, cough symptom and cough sensitivity in acid GERC patients did not significantly differ from non-acid GERC patients; therefore, it was difficult to distinguish acid GERC from non-acid GERC based on cough symptoms and cough sensitivity alone.[6] Although MII-pH is an important tool for diagnosing GERC, the diagnostic criterion is not uniform, and experts have an inconsistent understanding of it.[11,25] As the most

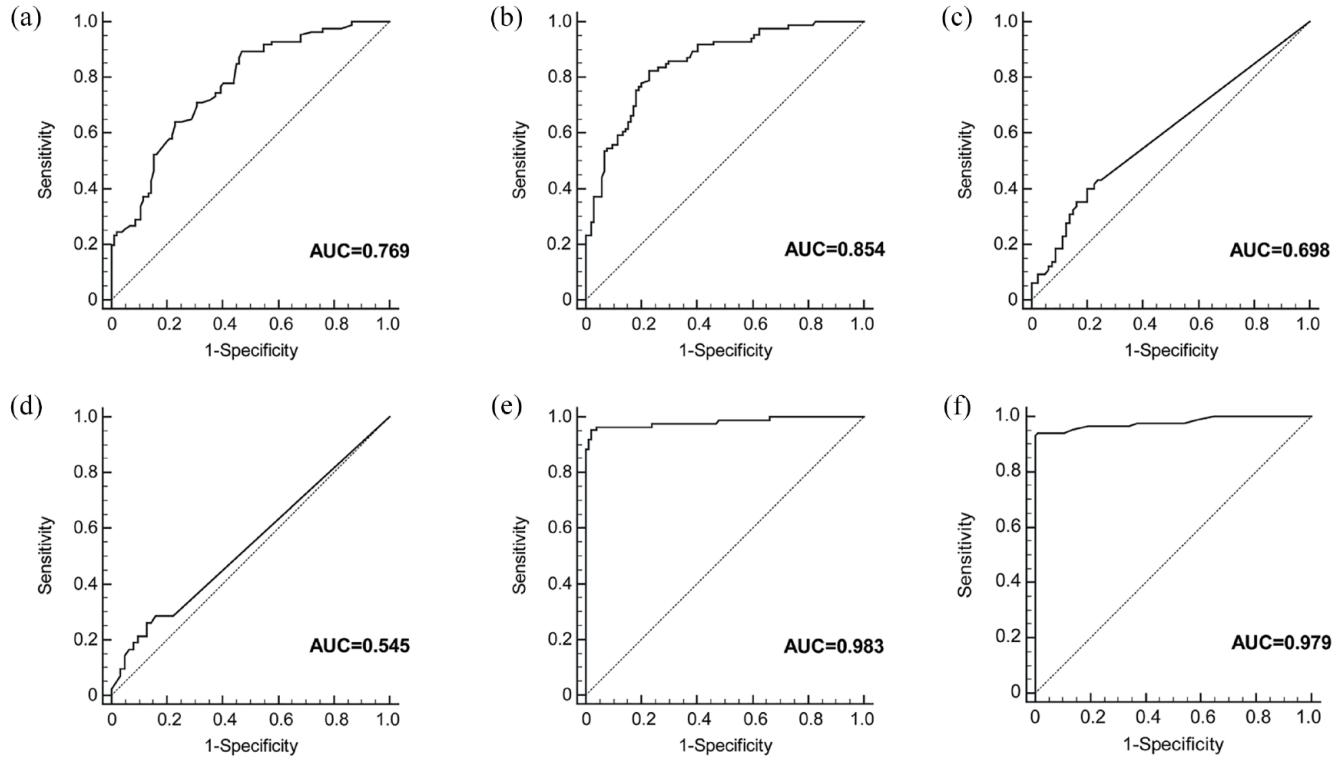

Figure 3. The diagnostic value of acid reflux episodes, acid reflux ratio, acid SAP, acid SI, and DeMeester score for acid GERC. (a) Receiver-operating characteristic (ROC) curve of acid reflux episodes in predicting acid GERC; (b) ROC curve of acid reflux ratio in predicting acid GERC; (c) ROC curve of acid SAP in predicting acid GERC; (d) ROC curve of acid SI in predicting acid GERC; (e) ROC curve of DeMeester score in predicting acid GERC; and (f) ROC curve of AET in predicting acid GERC.

objective indicator of MII-pH, the reflux episodes per 24 h are often overlooked. At present, the diagnostic criteria for the reflux episodes are non-uniform, both at national and international levels. For the first time in the Lyon Consensus, it was proposed that patients can be diagnosed with GERD if reflux episodes per 24 h were >80,[1] while in the Chinese population, patients can be diagnosed when it is only >73 episodes/24 h.[30] However, its diagnostic value in GERC is not clear. This study is the first to explore the diagnostic value of reflux episodes in predicting GERC, acid GERC, and non-acid GERC. In this study, it was found that >97 reflux episodes had a good diagnostic value for GERC, which also reflected the increased number of reflux episodes in GERC patients.

GERC can be divided into acid GERC and non-acid GERC according to the pH value of reflux contents. This study found that the diagnostic value of the acid reflux episodes was not better than that of the DeMeester score and AET. DeMeester score and AET suggest the severity of acid reflux. AET is reactive to acid reflux. DeMeester score is an indicator of the overall acid exposure of the esophagus, including total reflux episodes, the percentage of time when pH < 4 in the standing position, the percentage of time when pH < 4 in the lying position, the percentage of total time when pH < 4 (AET), the number of reflux attacks ⩾5 min, and the longest reflux attack time. The DeMeester score is the sum of the six parameters calculated according to the formula: (actual detection value − average)/standard deviation + 1. Therefore, it is theoretically better to indicate acid reflux than the reflux episodes. In this study, acid reflux showed excellent diagnostic value for acid GERC, similar to a previous study.[31] Even if the number of reflux episodes is not high in such patients, the DeMeester score will also increase owing to other indicators, such as the increased time of pH < 4 in the standing and lying positions. Therefore, the number of reflux episodes in acid GERC is not as valuable as non-acid GERC.

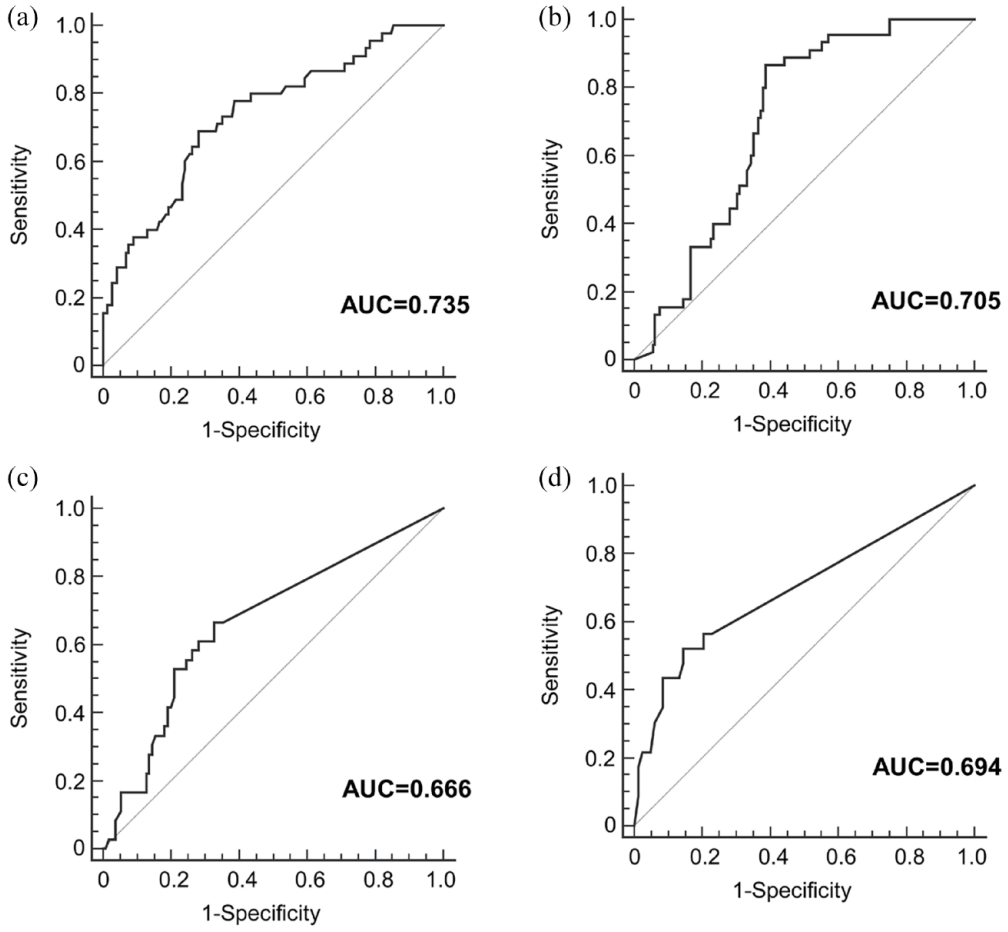

Figure 4. The diagnostic value of non-acid reflux episodes, non-acid reflux ratio, non-acid SAP, and non-acid SI for non-acid GERC. (a) Receiver-operating characteristic (ROC) curve of non-acid reflux episodes in predicting non-acid GERC; (b) ROC curve of non-acid reflux ratio in predicting non-acid GERC; (c) ROC curve of non-acid SAP in predicting non-acid GERC; and (d) ROC curve of non-acid SI in predicting non-acid GERC.

In the previous diagnostic criteria, SAP and SI were important indicators, especially for the diagnosis of non-acid GERC. They, respectively, represent the percentage of reflux-related coughs in the total cough and the percentage of cough-related refluxes in the total refluxes. Among them, SAP is the most commonly used, and its diagnostic value is better than the SI and symptom sensitivity index. According to the pH value of the reflux material, SAP is divided into acid SAP and non-acid SAP, which respectively represent the possibility of acid reflux and non-acid reflux as the cause of cough. Studies have shown that the two have high sensitivity but low specificity. A previous study in China has confirmed that SAP $>$ 80% and SI $>$ 45% can increase the specificity, which can reduce the missed diagnosis rate.[32] In clinical practices, poor patient compliance, low education level, too many symptoms, or failure to record symptoms at work or at night and other circumstances often lead to incomplete records and false negatives. If reflux episodes occur frequently, the association with reflux episodes will become inaccurate, and the SI and SAP may be relatively high. The increase in sample size and the use of SAP have some limitations in the real world.[10,33,34] Therefore, it is urgent to find a more objective indicator to confirm the existence of reflux. However, this study found that for suspected GERC, the reflux episodes have a certain diagnostic value, especially for non-acid GERC, wherein the number and ratio of non-acid reflux alone or in combination is better than previous SAP and SI, and has better clinical significance.

Table 4. Comparison of diagnostic value of different criteria in non-acid GERC.

	AUC	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio	Kappa
(1) Non-acid reflux episodes > 58	0.703	68.89	71.72	0.417	0.881	2.370	0.447	0.322
(2) Non-acid reflux ratio > 68.18%	0.737	86.67	60.69	0.396	0.936	2.174	0.226	0.330
(3) Non-acid SAP ⩾ 95%	0.531	16.67	90.09	0.353	0.769	1.682	0.925	0.082
(4) Non-acid SI ⩾ 50%	0.581	18.18	98.82	0.800	0.824	15.455	0.828	0.238
(1) and (2)	0.728	62.22	83.45	0.538	0.877	3.759	0.453	0.433
(1) or (2)	0.715	93.33	49.66	0.365	0.960	1.854	0.134	0.280
X^2		224.614	92.262	58.093	23.36			
p value		< 0.001	< 0.001	0.001	< 0.001			

AUC, area under the curve; GERC, gastroesophageal reflux-induced chronic cough; SAP, symptom-associated probability; SI, symptom index.

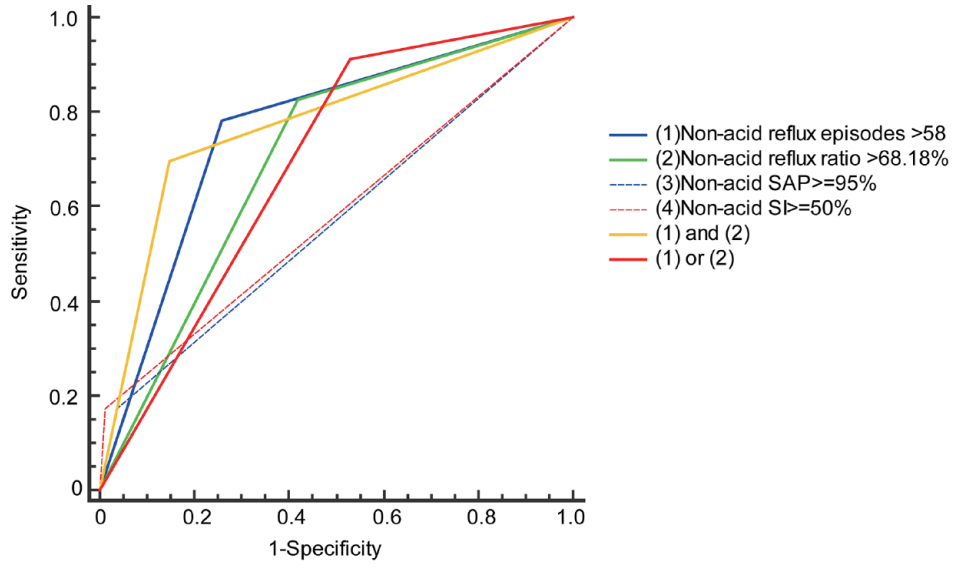

Figure 5. The diagnostic value of (1) non-acid reflux episodes > 58; (2) non-acid reflux ratio > 68.18%; (3) non-acid SAP ⩾ 95%; and (4) non-acid SI ⩾ 50%.

At present, there are two theories explaining the mechanisms of GERC. One is that neurogenic inflammation of the airway is caused by the distal esophagus-bronchial reflex. The other theory believes that proximal reflux directly stimulates the throat, causing chronic inflammation that causes an irritable state of the larynx, which in turn leads to the formation of cough hypersensitivity syndrome.[35–37] A study found that GERD patients with respiratory symptoms had more total reflux episodes and proximal reflux episodes than patients with GERD without respiratory symptoms.[38] Our previous study also found that GERC patients with pharyngeal symptoms had

more proximal and non-acid reflux episodes.[39] Researchers further investigated the correlation between reflux and cough symptoms, and showed that proximal reflux plays an important role in the development of cough and that the onset of cough is likely related to the increased number of reflux episodes and the non-acid component of them.[25] In this study, we found that proximal reflux episodes in acid GERC and non-acid GERC were more than non-GERC patients which indicated the importance of proximal reflux in the pathogenesis of GERC. This implies that proximal reflux is an important determinant of GERC and further confirms the importance of the reflux theory in the pathogenesis of GERC.

Except for different clinical characteristics, there are certain differences between the treatment of acid GERC patients and non-acid GERC patients.[40] Studies have shown that GERD and GERC patients whose standard anti-reflux therapy is ineffective are mainly caused by non-acid refluxes,[34,41–43] and these patients should also be given gastrointestinal motility drugs and baclofen as soon as possible to relieve symptoms early, reduce the course of therapy,[21,44] and reduce the overall burden for patients. Therefore, early identification of this type of reflux is of great significance in GERD-related diseases.

Our study has some limitations. Compared with the other two groups, there were more patients in the acid GERC group. There may be a selection bias, which needs to be confirmed by further expansion of the sample size. Future studies can establish the diagnosis of non-acid GERC based on the cut-off value established in this study, conduct treatment, and further validate the results of the study.

Conclusion

To our knowledge, this is the first study to discuss the diagnostic value of the 24-h reflux episodes in MII-pH for the diagnosis of various types of GERC and its diagnostic threshold. We found that the reflux episodes have a certain diagnostic value for GERC, and a higher diagnostic value for the diagnosis of non-acid GERC. Non-acid reflux episodes >58 and non-acid reflux ratio $>68.18\%$ are better than SAP and SI when used to diagnose non-acid GERC, which can assist clinicians in the early diagnosis of GERC, especially the early detection of non-acid GERC.

Declarations

Ethics approval and consent to participate

Our study was registered in the Chinese Clinical Trials Register (www.chictr.org.cn/) (ChiCTR-DDD-17012587). The study protocol was approved (No. LL(H)-2016-396) by the Ethics Committee of Tongji Hospital. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) as well as the Helsinki Declaration of 1975, as revised in 2000. Written informed consent was obtained from all individuals before study enrollment.

Consent for publication

All the authors approved the final version of the manuscript.

Author contributions

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Competing interests
The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

Availability of data and materials
The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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