Can acid exposure time replace the DeMeester score in the diagnosis of gastroesophageal reflux-induced cough?

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Abstract

Background: The objective of this study was to compare the predictive accuracy of the acid exposure time (AET) with the DeMeester score (DMS) for gastroesophageal reflux–induced cough (GERC).

Methods: A total of 277 patients who underwent multichannel intraluminal impedance pH monitoring (MII-pH) were enrolled, and their clinical information and laboratory results were retrospectively analyzed. The diagnostic value of AET for GERC was compared with that of the DMS, symptom association probability (SAP), and symptom index (SI).

Results: A total of 236 patients met the inclusion criteria, 150 patients (63.65%) were definitely diagnosed with GERC, including 111(74%) acid GERC and 39 (26%) nonacid GERC. The optimal cutoff value of AET for diagnosing GERC was AET > 4.8%, and its diagnostic value was equal to that of DMS > 14.7 (AUC = 0.827 *versus* 0.818, $p = 0.519$) and was superior to that of SAP (AUC = 0.827 *versus* 0.689, $p = 0.000$) and SI (AUC = 0.827 *versus* 0.688, $p = 0.000$). When using both DMS > 14.7 and AET > 4.8% or either of the two for the diagnosis of GERC, the diagnosis rate was not improved over using DMS > 14.7 alone. The diagnostic value of AET and DMS for acid GERC were both high and equivalent (AUC = 0.925 *versus* 0.922, $p = 0.95$). The optimal cutoff value of AET for diagnosing acid GERC was AET > 6.2%.

Conclusion: AET and DMS are both equal in discriminating GERC. A GERC diagnosis should be considered when AET > 4.8%, whereas an acid GERC diagnosis should be considered when AET > 6.2%.

Keywords: acid exposure time, chronic cough, DeMeester score, gastroesophageal reflux, multichannel intraluminal impedance pH monitoring

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Introduction

Gastroesophageal reflux-induced cough (GERC) is a special type of gastroesophageal reflux disease (GERD) and is one of the common causes of chronic cough.[1,2] The main test for diagnosing GERC is 24-hour esophageal pH monitoring or combined multichannel intraluminal impedance pH monitoring (MII-pH).[2] The acid exposure time (AET) refers to the time that esophageal pH is < 4 out of the whole monitoring time, and the pH is often monitored at the distal esophagus [5 cm above the lower esophageal sphincter (LES)].[3] The DeMeester score (DMS)

is a composite score of six parameters that measures acid exposure during prolonged ambulatory pH monitoring, including AET, and has been used to diagnose GERD since the 1970s.[3,4] In addition, the DMS is an important indicator for GERC diagnosis[5–7] and is included in the guidelines for the diagnosis and treatment of cough.[8]

Based on its pH value, GERC can be divided into two major subtypes, designated as acid (pH ⩽ 4) and nonacid GERC, including weakly acid (4.1 < pH < 7) and weakly alkaline (pH ⩾ 7). Both DMS and AET are reliable parameters for

the identification of abnormal acid reflux.[9,10] As an important indicator to evaluate abnormal reflux, DMS has been widely used to diagnose GERD.[4,11] However, the DMS was not adopted by the more recent GERD consensus—the Lyon Consensus. Instead, AET > 6% is considered the most reliable parameter to define GERD.[12] There are little data that show that DMS is superior—or inferior—to AET in the diagnosis of GERD, including GERC. This study retrospectively analyzed the clinical information and laboratory results of patients treated for chronic cough who underwent MII-pH monitoring in our department within the past 4 years, to identify the diagnostic value of AET for GERC.

Methods

Patients
A total of 277 patients with chronic cough from our respiratory clinic between May 2016 and May 2020 and who underwent MII-pH were included in this study. Complete medical history, physical examination, and capsaicin cough sensitivity test, chest x-ray, lung function test, histamine bronchial provocation test, induced sputum cytological examination, and MII-pH of those patients were analyzed to identify the causes of chronic cough according to the established step-by-step algorithm.[1] According to the guideline,[8] MII-pH monitoring was not performed in all the patients. Patients who underwent MII-pH monitoring were those who had typical symptoms (such as typical upper gastrointestinal symptoms) after a detailed inquiry and the empirical evaluation of the physician, as well as patients with chronic cough excluding other causes. The preliminary diagnosis of other patients [ie, cough-variant asthma (CVA), upper airway cough syndrome (UACS), atopic cough (AC), and eosinophilic bronchitis (EB)] who have not received MII-pH monitoring is based on detailed medical history and examination, and the definitive diagnosis was established after effective treatment for preliminary diagnosis. GERC was considered when the patient met all of the following criteria:[1,8,11,13] (1) cough lasting for no less than 2 months, with or without typical upper gastrointestinal symptoms such as regurgitation, heartburn, or chest pain; (2) one or more of the following items of MII-pH: (a) abnormal acid reflux: DMS > 14.7 and/or an acid reflux symptom association probability (SAP) > 95% and/or an acid reflux symptom index (SI) > 50%; (b) abnormal nonacid reflux: nonacid (weakly acidic or weakly alkaline) reflux SAP > 95% and/or nonacid SI > 50%; (3) effective antireflux therapy (8-week course of omeprazole 20 mg twice daily plus mosapride 5 mg thrice daily), or doubling the dose of omeprazole (40 mg twice daily) or neuromodulators use (baclofen 10–20 mg thrice daily) as add-on therapy if antireflux therapy failed.[5,6] Patients with abnormal acid reflux were diagnosed with acid GERC, and patients without abnormal acid reflux were diagnosed with nonacid GERC. Several patients were ultimately diagnosed with GERC combined with other etiologies because their cough partially improved after targeted treatment for non-GERC diagnosis (such as AC, EB, UACS, etc.), and the cough disappears completely after a combination of antireflux therapy. The reflux-related symptom score was assessed using the gastroesophageal reflux diagnostic questionnaire (GerdQ).[14] The cough symptom score described by Hsu et al.[15] was used to assess cough severity.

The exclusion criteria were as follows: (1) No SAP or SI because cough symptoms were not recorded on a diary card as required during MII-PH monitoring; and (2) incomplete medical records. The study was approved by the Ethics Committee of Tongji Hospital (K-2020-025).

Laboratory examination
Lung function test and the histamine bronchial provocation test were performed according to the guidelines established by the Respiratory Society of the Chinese Medical Association.[16] Induced sputum cytological examination was performed as described previously.[17] The capsaicin cough sensitivity test was evaluated according to the European Respiratory Society (ERS) guidelines[18] and using the modified method initially described by Fujimura et al.,[19] with the lowest capsaicin inhalation concentration required to induce ≥ 2 (C2) or ≥ 5 (C5) coughs as the subject's cough threshold.

Esophageal manometry and motility measurements, and pH monitoring were performed according to guidelines.[5,20] The subjects discontinued all proton pump inhibitors (PPIs) and/or histamine H2 receptor antagonists for at least 7 days and had fasted for more than 10 hours before examination. A four-channel manometric

catheter (7521PV, MMS, Netherlands) was inserted into the stomach directly below the LES at a depth of approximately 65 cm. During perfusion pressure measurement, the patient was in the supine position, and the baroreceptor was placed at the patient's midaxillary level. After recording the pressure, the manometric catheter was withdrawn 1.0 cm every 15 seconds. After each pull, the sequence was recorded on the computer, and the distance and position of the manometric catheter from the nasal cavity were determined. During this process, the software recorded any changes in pressure information to determine the positions of the LES and upper esophageal sphincter. On this basis, impedance-pH monitoring (Ohmega, MMS) was performed, with 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 esophagus after esophageal manometry, with the pH electrode 5 cm above the LES and six impedance channel sensors at 3, 5, 7, 9, 15, and 17 cm above the LES. A portable data logger (Ohmega; Medical Measurement System BV) stored data with 50 Hz frequency from all seven channels over 24 hours. Each subject was asked to document reflux symptoms and eating and sleeping times on an issued diary card. Automatic analysis which performed by Commercial software (MMS database, v8.7) combined with manual analysis to detect the total number of reflux episodes (>80 reflux episodes per 24 hours are definitively abnormal), the number of proximal reflux episodes (15 cm above the LES), the number of distal reflux episodes (15 cm below LES), the esophageal acid clearance time (the time required for pH to recover to $\geqslant 4.0$ after acid reflux), and other monitoring indicators. Other important indicators were as follows:

AET: AET was defined as the total time (%) with pH below 4, divided by the total time of monitoring. But there is no uniform standard for the normal value of AET; AET has been defined as pathological if the time at pH < 4 exceeded 4.2%[10,21] or 5%[22] of the total recording time. The Lyon Consensus proposes that AET < 4% be considered definitively normal (physiological) and > 6% be considered definitively abnormal with intermediate values between these limits being inconclusive.[12]

DMS: This composite score measures the overall esophageal acid exposure level and includes six parameters:[23] (1) total number of reflux episodes, (2) % total time esophageal pH < 4 (AET), (3) % upright time esophageal pH < 4, (4) supine time esophageal pH < 4, (5) number of reflux episodes $\geqslant 5$ minutes, and (6) longest reflux episode (minutes). The DMS is the sum of the 6 parameter scores, and the simplified formula for scoring each component is as follows: component score = (Pt value − mean + 1) / standard deviation (SD). In this study, the DMS was automatically calculated by software, and reflux exceeding the threshold value (14.7) 9 was considered abnormal reflux.

SAP and SI: SAP/SI is for cough specifically. SAP was used to represent the temporal association between cough recorded by patients on diary cards and reflux that had occurred during the preceding 2-minute period, SI is defined as the number of reflux-related symptom episodes (cough)/ total number of symptom episodes × 100%.

Review of clinical information
Based on the general information of the included patients, MII-pH monitoring parameters, pulmonary function, capsaicin cough sensitivity, cough symptom score, and GerdQ score, the diagnostic value of AET, DMS, SAP, and SI for GERC was analyzed. The various MII-pH monitoring parameters were compared between GERC patients and non-GERC patients, and AET and DMS were compared between acid GERC and nonacid GERC patients.

Statistical analysis
Normally distributed data are expressed as $\chi^2 \pm$ SD, nonnormally distributed data are expressed as the median (interquartile range), and after logarithmic transformation, the C2 and C5 data are expressed as the geometric mean ± SD. Sex and coughing properties were compared between groups by the χ^2 test. Analysis of variance was used to compare the data of the acid GERC group, nonacid GERC group, and non-GERC group when the variance was homogeneous. A nonparametric test for several independent samples (Kruskal–Wallis rank sum test) was used to compare the data of the three groups when the variance was not homogeneous. The area under the receiver operating characteristic (ROC) curve

(AUC) (AUCROC), sensitivity, specificity, positive predictive value, negative predictive value, and Youden index of the AET, DMS, SAP, and SI for diagnosing GERC and acid GERC were calculated to determine the optimal AET cutoff values to diagnose GERC and acid GERC. DeLong test was used to compare AUCROC values. SPSS 24.0 statistical software package (IBM, USA) was used for statistical analysis. A $p < 0.05$ was statistically significant.

Results

General information

A total of 277 patients with chronic cough who underwent MII-pH monitoring during the study period were initially included in this study. Of the 277 patients, heartburn accounted for 20.2% ($n = 56$), regurgitation 37.2% ($n = 103$), belching 17% ($n = 47$), cough with eating (during or soon after meals) 13% ($n = 36$). None of the patients had previous fundoplication or foregut surgery, 56 were examined with gastroduodenoscopy, and 12 patients had erosive esophagitis. According to the Chicago Classification of esophageal motility v3.0:[24] patients with major disorders of peristalsis accounted for 9.4% ($n = 26$), those with minor disorders of peristalsis accounted for 45.1% ($n = 125$), and those with normal esophageal motility accounted for 45.5% ($n = 126$).

Eighteen patients who did not complete the diary card as required and 23 patients with incomplete follow-up data were excluded. Of the final 236 patients, 150 (63.6%) had GERC, accounting for 22.6% of all 664 patients with chronic cough in the same period. Among the 150 GERC patients, 127 had only 1 etiology, and 20 had dual etiologies; GERC plus CVA was diagnosed in 5 patients, GERC plus AC was diagnosed in 6 patients, GERC plus EB was diagnosed in 5 patients, and GERC plus UACS was diagnosed in 4 patients. Three patients had 3 etiologies, including 2 patients with GERC plus UACS and CVA, and 1 patient with GERC plus UACS and obstructive sleep apnea syndrome. Among the 150 GERC patients, there were 111 patients with acid GERC and 39 patients with nonacid GERC.

After empiric treatment, the diagnose of 86 non-GERC patients (36.4%) were determined. General information of all 236 patients with chronic cough is shown in Table 1.

**Table 1.** General information of 236 patients with chronic cough.

Variable	Value
Sex (male/female)	105/131
Age (years)	48.92 ± 16.20
Cough duration (months)	10.00 (26.50)
Cough symptom score	
Daytime score	3.00 (1.00)
Night score	2.00 (2.00)
Lung function tests	
Forced expiratory volume in 1 s (FEV_1) (% of predicted)	97.66 ± 15.44
FVC (% of predicted)	97.60 ± 9.29
FEV1/FVC%	80.48 ± 10.75
Capsaicin cough threshold	
C2	0.81 ± 0.31
C5	1.20 ± 0.38

Data are presented as mean ± SD, median (interquartile range), or No. (%) unless otherwise indicated.
C2, capsaicin solution concentration required for ⩾2 coughs; C5, capsaicin solution concentration for ⩾5 coughs; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; SD, standard deviation.

Comparison of MII-pH variables between acid GERC, nonacid GERC, and non-GERC

Both AET [7.10 (11.55) *versus* 0.90 (1.70), Z = 8.721, $p = 0.000$] and DMS [22.97 (38.19) *versus* 3.28 (5.55), Z = 8.542, $p = 0.000$] were higher in GERC patients than non-GERC patients (Figure 1).

All the important indicators of MII-pH monitoring was present in Table 2. Comparison between the acid GERC, nonacid GERC, and non-GERC groups showed that except for the proximal extent variable, all the MII-pH parameters differed between the groups. The AET, DMS, GerdQ, and number of acid reflux episodes in acid GERC patients were significantly higher than those in nonacid GERC and non-GERC patients. The number of weakly alkaline reflux and the number of gas reflux in acid GERC patients were significantly lower than those in nonacid GERC and
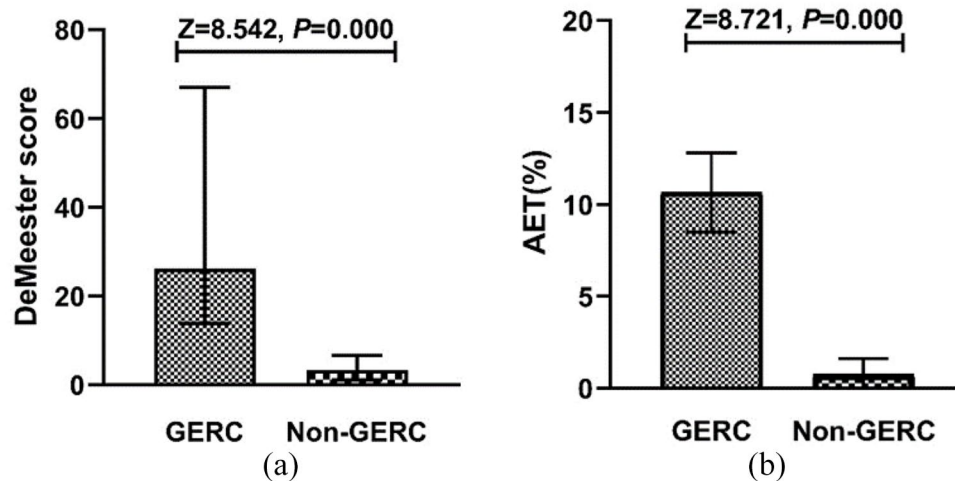
Figure 1. Comparison of AET and DMS between the GERC and non-GERC groups. (a) Comparision of DMS between the GERC and non-GERC groups.(b)Comparision of AET between the GERC and non-GERC groups. AET, acid exposure time; DMS, DeMeester score; GERC, gastroesophageal reflux–induced cough.

Table 2. Comparison of GerdQ score and variables of MII-pH between acid GERC, nonacid GERC, and non-GERC patients.

Items	Acid GERC (n = 111)	Nonacid GERC (n = 39)	Non-GERC (n = 86)	p value
GerdQ	8.56 ± 2.33*#	7.88 ± 2.24	6.65 ± 1.46	0.004
AET (%)	10.90 (20.50)*#	1.40 (3.20)	0.90 (1.70)	0.000
DMS	36.89 (81.27)*#	5.42 (10.74)	3.28 (5.55)	0.000
SAP (%)	74.20 (92.30)#	86.00 (96.40)#	0.00 (84.95)	0.005
SI (%)	5.40 (33.30)*#	20.00 (31.60)#	0.00 (15.40)	0.015
Total number of reflux episodes (n)	64.00 (80.00)*#	90.00 (74.00)#	52.00 (53.50)	0.001
Acidic reflux (n)	29.00 (38.33)*#	19.00 (18.50)#	8.50 (20.50)	0.000
Weakly acidic reflux (n)	24.00 (33.78)*	45.00 (45.80)#	23.00 (37.00)	0.002
Weakly alkaline reflux (n)	3.25 (11.00)*#	10.00 (22.10)	12.50 (27.25)	0.000
Gas reflux (n)	11.80 (19.25)*#	22.30 (31.63)	25.00 (31.00)	0.001
Liquid reflux (n)	12.50 (19.93)*	20.50 (24.08)#	10.85 (17.25)	0.008
Mixed reflux (n)	35.50 (52.00)*#	46.00 (47.85)#	25.00 (37.00)	0.041
Proximal extent (n)	8.50 (15.40)	3.15 (9.05)	19.20 (68.80)	0.132
Acid clearance(s)	12.50 (3.75)#	11.00 (7.25)#	10.00 (5.50)	0.021

AET, acid exposure time; DMS, DeMeester score; GerdQ score, gastroesophageal reflux diagnostic questionnaire score; GERC, gastroesophageal reflux–induced cough; SAP, symptom association probability; SI, symptom index.
*Compared with the nonacid GERC group, $p < 0.05$; #compared with the non-GERC group, $p < 0.05$.

non-GERC patients. The SAP, SI, total number of reflux episodes, numbers of acid reflux and mixed reflux episodes, and acid clearance time in GERC (both acid GERC and nonacid GERC) patients were higher than those in non-GERC patients.
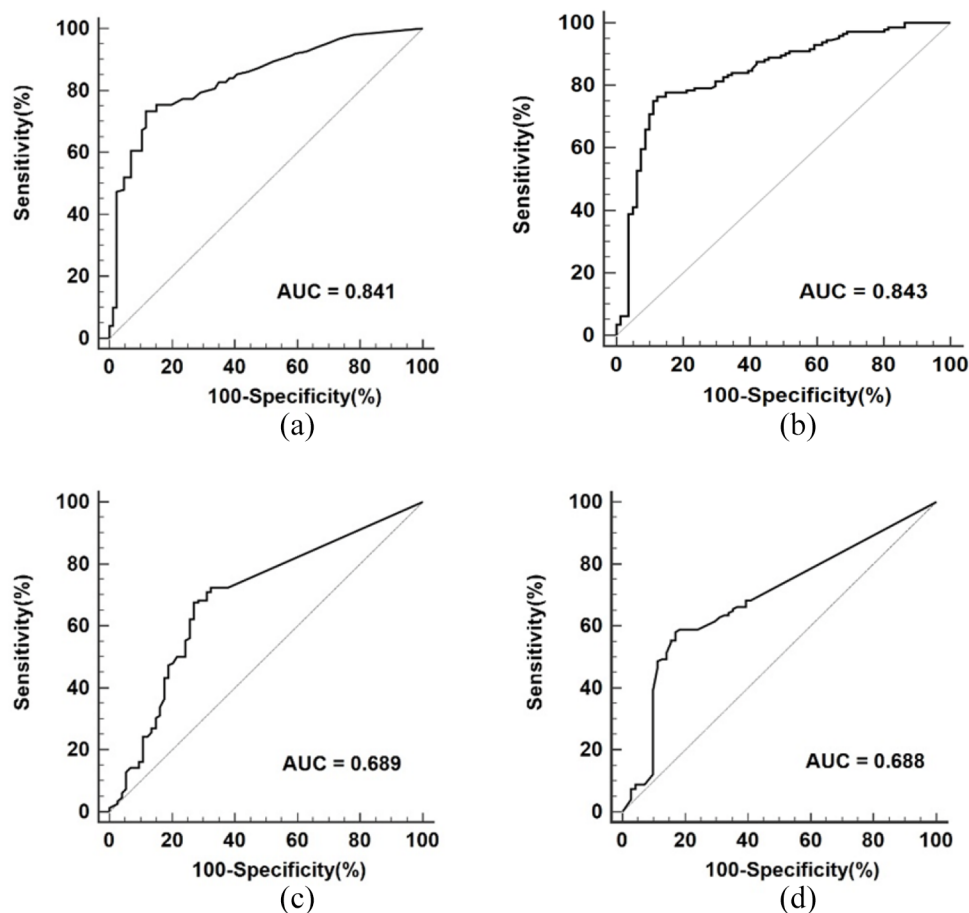
Figure 2. ROC curves of MII-pH parameters for the diagnosis of GERC. (a) The AUC_{ROC} for AET in the diagnosis of GERC. The optimal AET cutoff for diagnosing GERC was AET > 4.8%. (b) The AUC_{ROC} for DMS in the diagnosis of GERC. (c) The AUC_{ROC} for SAP in the diagnosis of GERC. (d) The AUC_{ROC} for SI in the diagnosis of GERC.
AET, acid exposure time; AUC, area under the curve; DMS, DeMeester score; GERC, gastroesophageal reflux–induced cough; ROC, receiver operating characteristic; SAP, symptom association probability; SI, symptom index.

AET and DMS were not significantly different between nonacid GERC patients and non-GERC patients (Table 2).

Predictive value of the AET, DMS, SAP, and SI for GERC

ROC curves of the AET, DMS, SAP, and SI in predicting GERC are shown in Figure 2. When predicting GERC, the AUC_{ROC} of AET was 0.841 ($p = 0.000$), and the AUC_{ROC} of the DMS was 0.843 ($p = 0.000$). The DeLong test showed that both indicators had relatively high predictive value for GERC ($Z = 0.795$, $p = 0.427$) and were comparable. When using the SAP to predict GERC, the AUC_{ROC} was 0.689 ($p = 0.000$), and

the predictive value ranked second to that of AET ($Z = 3.511$, $p = 0.000$). When using the SI, the AUC_{ROC} was 0.688 ($p = 0.000$), and the predictive value was inferior to that of AET ($Z = 3.612$, $p = 0.000$).

As shown in the Table 3, the sensitivity ($\chi^2 = 111.281$, $= 0.000$), positive predictive $= 0.000$), positive predictive value ($\chi^2 = 4.576$, $= 0.032$), negative predictive $= 0.032$), negative predictive value ($\chi^2 = 28.312$, $p = 0.000$), Youden index, Kappa value, AUC_{ROC} of SAP > 95% and SI > 50% were significantly lower than AET > 4.8% and DMS > 14.7. There was no significant difference in Specificity ($\chi^2 = 0.288$, $p = 0.426$) between these four indicators. Therefore, the ability of

Table 3. Comparison of AET > 4.8%, DMS > 14.7, SAP > 95%, and SI > 50% in predicting GERC.

Standard	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	AUC$_{ROC}$	Youden index	Kappa value
AET > 4.8%	73.33	88.37	91.67	65.52	0.827	0.617	0.574
DMS > 14.7	70.00	89.63	92.11	63.11	0.818	0.607	0.547
SAP > 95%	24.32	87.83	80.00	36.72	0.561*#	0.122	0.090
SI > 50%	12.17	90.14	72.00	32.99	0.515*#	0.023	0.016
χ^2	111.281	0.288	4.576	28.312			
p	0.000	0.426	0.032	0.000			

AET, acid exposure time; AUC, area under the curve; DMS, DeMeester score; GERC, gastroesophageal reflux–induced cough; ROC, receiver operating characteristic; SAP, symptom association probability; SI, symptom index.
*DeLong test showed that compared with the AUC$_{ROC}$ of DMS > 14.7 in diagnosis GERC, $p < 0.05$.
#DeLong test showed that compared with the AUC$_{ROC}$ of AET > 4.8% in diagnosis GERC, $p < 0.05$.

Table 4. Comparison of AET > 4.8% and AET > 6% in predicting GERC.

Standard	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	AUC$_{ROC}$	Youden index	Kappa value
AET > 4.8%	73.33	88.37	91.67	65.52	0.809	0.617	0.574
AET > 6%	60.67	93.02	93.81	57.55	0.768	0.537	0.475
χ^2	4.884	0.620	0.116	1.369	2.250		
p	0.018	0.292	0.541	0.190	0.024		

AUC, area under the curve; AET, acid exposure time; GERC, gastroesophageal reflux–induced cough; ROC, receiver operating characteristic.

SAP and SI in discriminating GERC *versus* non-GERC was inferior to that of AET and DMS.

Optimal AET cutoff value for predicting GERC
ROC curve analysis showed that the optimal AET cutoff value for predicting GERC based on the Youden index was 4.8%. When using AET > 4.8%, the sensitivity was 73.33%, the specificity was 88.37%, the positive predictive value was 91.67%, and the negative predictive value was 65.52%. The comparison of AET > 4.8% with AET > 6% (mentioned in the Lyon Consensus) in predicting GERC showed that the AUC$_{ROC}$ of the former was higher (0.809 *versus* 0.768, Z = 2.254, $p = 0.024$), and the sensitivity was also higher (73.33% *versus*

60.67%, $\chi^2 = 4.884$, $p = 0.018$); thus, the predictive value was superior (Table 4).

The predictive diagnostic value of AET > 4.8%, DMS > 14.7 alone, and their combination for GERC
When using any combination of DMS > 14.7 and AET > 4.8% in predicting GERC, the sensitivity, specificity, positive predictive value, negative predictive value, Youden index, and kappa value were not significantly different from those when using AET > 4.8% alone or DMS > 14.7 alone (Table 5). Pearson correlation analysis showed that there was a remarkable correlation between DMS > 14.7 and AET > 4.8% ($r = 0.892$, $p = 0.000$).

Table 5. The predictive diagnostic value of AET > 4.8%, DMS > 14.7 alone, and their combination for GERC.

Standard	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	AUC$_{ROC}$	Youden index	Kappa value
AET > 4.8%	73.33	88.37	91.67	65.52	0.827	0.617	0.574
DMS > 14.7	70.00	89.63	92.11	63.11	0.818	0.607	0.547
AET > 4.8% and DMS > 14.7	72.67	75.33	91.60	64.96	0.809	0.610	0.567
AET > 4.8% or DMS > 14.7	75.33	88.37	91.67	65.52	0.804	0.607	0.578
χ^2	0.156	0.052	0.011	0.018			
p	0.692	0.819	0.918	0.895			

AET, acid exposure time; AUC, area under the curve; DMS, DeMeester score; GERC, gastroesophageal reflux–induced cough; ROC, receiver operating characteristic.
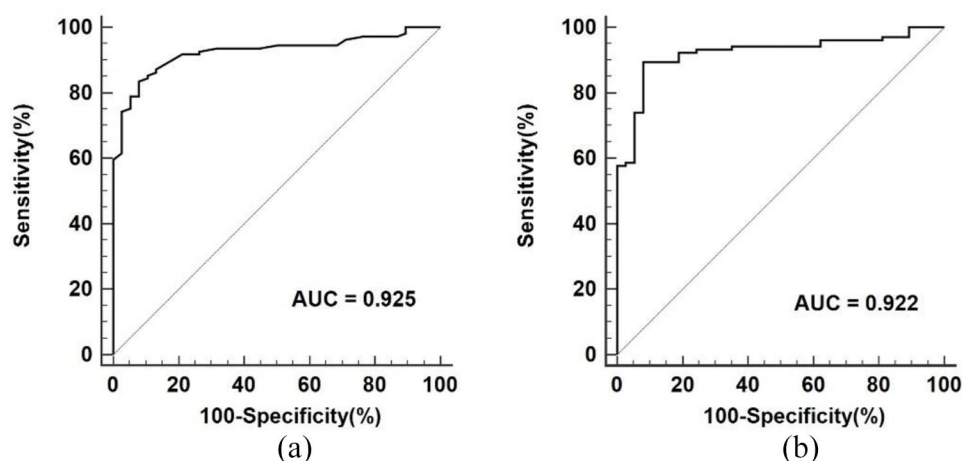
Figure 3. Comparison of the diagnostic value of AET and DMS for acid GERC. (a) The AUC$_{ROC}$ for AET in the diagnosis of acid GERC. The optimal AET cutoff for diagnosing acid GERC was AET > 6.2%. (b) The AUC$_{ROC}$ for DMS in the diagnosis of acid GERC.
AET, acid exposure time; AUC, area under the curve; DMS, DeMeester score; GERC, gastroesophageal reflux–induced cough; ROC, receiver operating characteristic.

Comparison of the predictive value of AET and the DMS between acid GERC and nonacid GERC

The predictive value of AET and the DMS for diagnosing acid GERC was relatively high. When using AET, the AUC$_{ROC}$ was 0.925, and when using the DMS, the AUC$_{ROC}$ was 0.922. The diagnostic value of those two indicators was equal (Z = 0.09, p = 0.928) (Figure 3). When using AET to predict nonacid GERC, the AUC$_{ROC}$ was 0.323, and when using the DMS, the AUC$_{ROC}$ was 0.320. Both indicators had no diagnostic value.

Discussion

GERC includes acid and nonacid (weakly acidic or weakly alkaline) GERC, and acid GERC is more common. MII-pH monitoring is the gold standard test for GERC. The DMS and AET are critical indicators of the test's results for defining acid exposure. The DMS is a weighted score consisting of 6 parameters, i.e. the total number of reflux episodes, AET in the upright position, AET in the supine position, total AET, the number of reflux episodes ≥ 5 min, and duration of the longest reflux.[4,25]

DMS was initially reported by DeMeester *et al.* based on the 24-hour pH monitoring results of 15 volunteers without typical gastroesophageal reflux symptoms.[23] In a subsequent study by DeMeester *et al.* with an asymptomatic control group and patients with typical gastroesophageal reflux symptoms, 84% of patients with gastroesophageal reflux symptoms had abnormal DMS, which further confirmed the diagnostic value of DMS for GERD.[4] The authors confirm the validity of the score and the threshold value of 14.7 in a later study.[9] Since the 1970s, DMS has been widely used to diagnose GERD.[4,9,11,26] An abnormal DMS is more frequent in patients with endoscopic esophagitis.[26] DMS correlates with the severity of mucosal injury,[26] hiatal hernia size,[27] and esophageal dysfunction[28] and the presence of Barrett's esophagus.[29] In recent years, although different technologies for pH monitoring have been developed, such as wireless capsules and various types of catheters for esophageal pH monitoring, the DMS remains a valuable indicator for identifying pathologic *versus* physiologic reflux[29] and is also a positive indicator for GERC diagnosis.[5–8,14]

Early studies confirmed that among the 12 pH monitoring metrics, including the six DMS parameters, AET is the most reproducible in normal volunteers and GERD patients (93%), and the repeatability in suspected GERD patients is also relatively high (up to 84%).[30] For diagnosing GERD, AET has higher specificity and sensitivity than other MII-pH parameters.[31] AET is reliably extracted from automated analysis and is predictive of response from medical and surgical reflux therapy in GERD patients.[32–34] Patel *et al.*[33] conducted a 5-year follow-up study on symptom improvement in GERD patients after antireflux therapy and found that AET > 4.0% could significantly predict the global symptom severity improvement. In addition, Ribolsi *et al.*[35] performed MII-pH examinations on 156 suspected GERC patients, and patients with a pathological AET showed a twofold greater probability of a PPI response than patients with a normal AET, suggesting that the AET also plays a predictive role in the treatment of reflux-induced cough symptoms.

The more recent Lyon consensus[12] was based on the Porto Consensus[36], which was the worldwide leading consensus on gastroesophageal reflux. The Lyon Consensus proposes that AET <4% be considered definitively normal (physiological) and >6% be considered definitively abnormal with intermediate values between these limits being inconclusive; thus, further analyses of the AET should be combined with other indicators, such as the SAP, SI, and number of reflux episodes.

Although there were no worldwide unified diagnostic criteria for GERC, the diagnostic criteria in our study are based on Chinese guidelines[8,11] as well as our previous studies.[1,5,6,14] But there is no doubt that both DMS and AET are effective indicators for the diagnosis of GERD; DMS was not adopted by the Lyon Consensus, but there were little data that show that the DMS is superior—or inferior—to AET in diagnosing GERC. This study confirmed that AET and DMS had comparable diagnostic value, both significantly higher than that of SAP or SI. The results of this study also showed that when AET was used to diagnose GERC, the optimal cutoff value was AET > 4.8%, which is lower than the AET > 6% in the Lyon Consensus. In fact, when using AET > 4.8%, the sensitivity and AUC_{ROC} were significantly higher than when using AET > 6%, indicating that the diagnostic value of AET > 4.8% was higher than that of AET > 6% for GERC. The subjects of this study were GERD patients with cough as the main manifestation and were slightly different from the subjects in the Lyon Consensus, so we believe that diagnosis for GERC by AET > 4.8% could avoid omission diagnosis and improve diagnostic efficiency in GERC, to better satisfy the clinical requirements of clinicians and patients. Our results is consistent with the findings of Patel *et al.* and Ribolsi *et al.*, who found that PPI responders did have significantly higher AET (>4%).[33,35]

In this study, both AET > 4.8% and DMS > 14.7 had similarly high diagnostic value for GERC. However, when either or both of them were satisfied, the diagnosis rate of GERC was not improved compared with using one indicator alone. In addition, we found the correlation between these two indicators is very remarkable. Therefore, we believe that either can be used to diagnose GERC.

This study also confirmed that both AET and DMS had a relatively high diagnostic value for acid GERC and a relatively low diagnostic value for nonacid GERC, and the optimal cutoff value for AET in the diagnosis of acid GERC was 6.2%. The proportion of nonacid reflux among

gastroesophageal reflux could be as high as 40%.[37] It is difficult to avoid the missed diagnosis of non-acid GERC when using either DMS or AET, and neither of them could be used to establish the causal relationship between reflux and cough. Therefore, it is necessary to add other indicators, such as the number of episodes of reflux, SAP, and SI, to improve the diagnostic rate of GERC. In the study, there were also differences in some other indicators which represent the pH and properties of the reflux episode (ie, gas, liquid, or mixed; acidic, weakly acidic, or weakly alkaline) between acid GERC, nonacid GERC, and non-GERC. The results have been presented in detail (Table 2) and were almost consistent with our previous studies.[38,39]

This study has some limitations. This was a retrospective study. MII-pH has not been highly accepted by patients because of its invasiveness, and guidelines of different countries have not recommended that MII-pH should be performed in all patients with chronic cough.[2,8,13,18] Among the patients with chronic cough treated in our department, only the suspected GERC patients who underwent MII-pH monitoring were recruited in this study which strictly follows the Chinese guidelines,[8] so there was a certain bias in the inclusion criteria. More patients with chronic cough who voluntarily accept MII-pH monitoring will be enrolled in our prospective study to verify the conclusions of this study. Ideally, the patients' response to treatment should be assessed by the objective measurement of cough frequency with a cough monitor. Since we can't access the cough monitor at present. The therapeutic outcome evaluated by cough symptom score is inevitably affected by the subjectivity of the questionnaire, which is inferior to cough frequency monitoring for the reliability of the results.

Conclusion
AET has high diagnostic value for GERC, especially acid GERC. AET and DMS are both equal in discriminating GERC. It should be pointed out here that our study somewhat contradicts the proposals of the Lyon Consensus. A GERC diagnosis should be considered when AET > 4.8%, whereas an acid GERC diagnosis should be considered when AET > 6.2%. Combining AET with DMS cannot improve the GERC diagnostic rate.

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References
1. Ding H, Xu X, Wen S, *et al.* Changing etiological frequency of chronic cough in a tertiary hospital in Shanghai, China. *J Thorac Dis* 2019; 11: 3482–3489.

2. Kahrilas PJ, Altman KW, Chang AB, *et al.* Chronic cough due to gastroesophageal reflux in adults: CHEST guideline and expert panel report. *Chest* 2016; 150: 1341–1360.

3. Neto R, Herbella F, Schlottmann F, *et al.* Does DeMeester score still define GERD? *Dis Esophagus* 2019; 32: doy118.

4. Johnson LF and DeMeester TR. Development of the 24-hour intraesophageal pH monitoring composite scoring system. *J Clin Gastroenterol* 1986; 8 (Suppl. 1): 52–58.

5. Dong R, Xu X, Yu L, *et al.* Randomized clinical trial: gabapentin vs baclofen in the treatment of suspected refractory gastro-esophageal reflux-induced chronic cough. *Aliment Pharmacol Ther* 2019; 49: 714–722.

6. Xu X, Lv H, Yu L, *et al.* A stepwise protocol for the treatment of refractory gastroesophageal reflux-induced chronic cough. *J Thorac Dis* 2016; 8: 178–185.

7. Shaheen NJ, Crockett SD, Bright SD, *et al.* Randomised clinical trial: high—dose acid suppression for chronic cough—a double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2011; 33: 225–234.

8. Asthma Workgroup, Society of Respiratory Diseases, Chinese Medical Association. Guidelines for the diagnosis and treatment of cough (2015). *Chin J Tuberc Respir Dis* 2016; 39: 323–354.

9. Jamieson JR, Stein HJ, DeMeester TR, *et al.* Ambulatory 24-h esophageal pH monitoring: normal values, optimal thresholds, specificity, sensitivity, and reproducibility. *Am J Gastroenterol* 1992; 87: 1102–1111.

10. Chen J, Guo B, Guo Z, *et al.* Association of serum gastric inhibitory polypeptide and pancreatic polypeptide levels with prolonged esophageal acid exposure time in refractory gastroesophageal reflux disease. *Medicine* 2019; 98: e15965.

11. Wu J, Wang Z, Hu Z, *et al.* Multidisciplinary consensus on the diagnosis and treatment of gastroesophageal reflux disease in China. *Chin J Front Med Sci* 2020; 7: 1–28.

12. Gyawali CP, Kahrilas PJ, Savarino E, *et al.* Modern diagnosis of GERD: the Lyon Consensus. *Gut* 2018; 67: 1351–1362.

13. Irwin RS. Chronic cough due to gastroesophageal reflux disease ACCP evidence-based clinical practice guidelines. *Chest* 2006; 129 (Suppl. 1): 80S–94S.

14. Xu X, Chen Q, Liang S, *et al.* Comparison of Gastroesophageal Reflux Disease Questionnaire and multichannel intraluminal impedance pH monitoring in identifying patients with chronic cough responsive to antireflux therapy. *Chest* 2014; 145: 1264–1270.

15. Hsu JY, Stone RA, Logan-Sinclair RB, *et al.* Coughing frequency in patients with persistent cough: assessment using a 24 hour ambulatory recorder. *Eur Respir J* 1994; 7: 1246–1253.

16. Pulmonary function Workgroup, Society of Respiratory Diseases, Chinese Medical Association. Guidelines for pulmonary function tests (part 2)—pneumometer examination. *Chin J Tuberc Respir Dis* 2014; 37: 481–486.

17. Yu L, Wei W, Wang L, *et al.* Upper-airway cough syndrome with latent eosinophilic bronchitis. *Lung* 2010; 188: 71–76.

18. Morice AH, Millqvist E, Bieksiene K, *et al.* ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *Eur Respir J* 2020; 55: 1901136.

19. Fujimura M, Sakamoto S, Kamio Y, *et al.* Effects of methacholine induced bronchoconstriction and procaterol induced bronchodilation on cough receptor sensitivity to inhaled capsaicin and tartaric acid. *Thorax* 1992; 47: 441–445.

20. Ribolsi M, Balestrieri P, Holloway RH, *et al.* Intrabolus pressure and esophagogastric gradient, assessed with high-resolution manometry, are associated with acid exposure and proximal migration of refluxate. *Dis Esophagus* 2016; 29: 1020–1026.

21. Savarino E, Zentilin P, Tutuian R, *et al.* The role of nonacid reflux in NERD: lessons learned from impedance-pH monitoring in 150 patients off therapy. *Am J Gastroenterol* 2008; 103: 2685–2693.

22. Streets CG and DeMeester TR. Ambulatory 24-hour esophageal pH monitoring: why, when, and what to do. *J Clin Gastroenterol* 2003; 37: 14–22.

23. Johnson LF and Demeester TR. Twenty-four-hour pH monitoring of the distal esophagus. A quantitative measure of gastroesophageal reflux. *Am J Gastroenterol* 1974; 62: 325–332.

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. DeMeester T, Wang C, Wernly J, *et al.* Technique, indications, and clinical use of

24 hour esophageal pH monitoring. *J Thorac Cardiovasc Surg* 1980; 79: 656–670.

26. Schlottmann F, Andolfi C, Herbella FA, *et al.* GERD: presence and size of hiatal hernia influence clinical presentation, esophageal function, reflux profile, and degree of mucosal injury. *Am Surg* 2018; 84: 978–982.

27. Xenos E. The role of esophageal motility and hiatal hernia in esophageal exposure to acid. *Surg Endosc* 2002; 16: 914–920.

28. Gerson L, Boparai V, Ullah N, *et al.* Esophageal and gastric pH profiles in patients with gastro-esophageal reflux disease and Barrett's esophagus treated with proton pump inhibitors. *Aliment Pharmacol Ther* 2004; 20: 637–643.

29. Ayazi S, Lipham J, Portale G, *et al.* Bravo catheter-free pH monitoring: normal values, concordance, optimal diagnostic thresholds, and accuracy. *Clin Gastroenterol Hepatol* 2009; 7: 60–67.

30. 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.

31. Schindlbeck NE, Heinrich C, König A, *et al.* Optimal thresholds, sensitivity, and specificity of long-term pH-metry for the detection of gastroesophageal reflux disease. *Gastroenterology* 1987; 93: 85–90.

32. Patel A, Sayuk GS and Gyawali CP. Parameters on esophageal pH-impedance monitoring that predict outcomes of patients with gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2015; 13: 884–891.

33. Patel A, Sayuk GS and Gyawali CP. Acid-based parameters on pH-impedance testing predict symptom improvement with medical management better than impedance parameters. *Am J Gastroenterol* 2014; 109: 836–844.

34. Wang AJ, Wang H, Xu L, *et al.* Predictors of clinical response of acid suppression in Chinese patients with gastroesophageal reflux disease. *Dig Liver Dis* 2013; 45: 296–300.

35. Ribolsi M, Savarino E, De Bortoli N, *et al.* Reflux pattern and role of impedance-pH variables in predicting PPI response in patients with suspected GERD-related chronic cough. *Aliment Pharmacol Ther* 2014; 40: 966–973.

36. Roman S, Gyawali CP, Savarino E, *et al.* Ambulatory reflux monitoring for diagnosis of gastro-esophageal reflux disease: update of the Porto consensus and recommendations from an international consensus group. *Neurogastroenterol Motil* 2017; 29: 1–15.

37. Sifrim D, Mittal R, Fass R, *et al.* Review article: acidity and volume of the refluxate in the genesis of gastro-esophageal reflux disease symptoms. *Aliment Pharmacol Ther* 2007; 25: 1003–1017.

38. Xu X, Yang Z, Chen Q, *et al.* Comparison of clinical characteristics of chronic cough due to non-acid and acid gastroesophageal reflux. *Clin Respir J* 2015; 9: 196–202.

39. Yu Y, Wen S, Wang S, *et al.* Reflux characteristics in patients with gastroesophageal reflux-related chronic cough complicated by laryngopharyngeal reflux. *Ann Transl Med* 2019; 7: 529.

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