Original Article on Novel Insights into Chronic Cough

Predictive value of clinical features for anti-reflux therapy response in suspected gastroesophageal reflux-induced chronic cough

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Background: Not all gastroesophageal reflux-induced cough (GERC) patients respond to anti-reflux treatment. It is not certain whether reflux-related symptoms or other clinical characteristics could indicate a successful response to anti-reflux treatment. In this study, we aimed to investigate the relationship between clinical features and anti-reflux response.

Methods: We retrospectively analyzed the clinical characteristics of suspected GERC who had reflux-related symptoms or reflux evidence based on abnormal 24-hour esophageal pH value monitoring, or who had no evidence of other common causes of chronic cough in our chronic cough database with a standard case report form. All patients experienced anti-reflux treatment with proton pump inhibitors (PPIs) plus prokinetic agents for at least 2 weeks and were divided into responders and non-responders based on the treatment response.

Results: Among 241 patients with suspected GERC, 146 (60.6%) showed a successful response. There was no significant difference in regard to the proportion of reflux-related symptoms, and results of 24-hour esophageal pH value monitoring between responders and non-responders. Compared with non-responders, responders had higher proportions of nasal itching (21.2% *vs.* 8.4%; P=0.014), tickle in the throat (51.4% *vs.* 35.8%; P=0.025) and lower proportion of pharyngeal foreign body sensation (32.9% *vs.* 54.7%; P=0.001). Multivariate analysis showed that nasal itching [hazard ratio (HR): 1.593, 95% confidence interval (CI): 1.025–2.476, P=0.039], tickle in the throat (HR: 1.605, 95% CI: 1.152–2.238, P=0.005), pharyngeal foreign body sensation (HR: 0.499, 95% CI: 0.346–0.720, P<0.001) and sensitivity to at least one cough trigger (HR: 0.480, 95% CI: 0.237–0.973, P=0.042) were associated with the therapeutic response.

Conclusions: Over half of suspected GERC patients benefited from anti-reflux therapy. A few clinical features rather than reflux-related symptoms might indicate a response to anti-reflux treatment. Further study is needed for the predictive value.

Keywords: Gastroesophageal reflux-induced chronic cough; reflux-associated symptoms; extraesophageal symptoms; anti-reflux therapy

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Introduction

The common causes of chronic cough include cough variant asthma (CVA), eosinophilic bronchitis (EB), upper airway cough syndrome (UACS), and gastroesophageal reflux-induced cough (GERC). GERC accounts for 4.6–41% of chronic cough (1-3) and impaired significantly the quality of life (4,5). Etiological diagnosis of chronic cough is a key step to a favorable treatment response. It requires multiple investigations, such as spirometry, bronchial challenge, induced sputum test for differential cells, and 24-hour esophageal pH value monitoring. These investigations, especially 24-hour esophageal pH value monitoring are time-consuming, expensive, and unavailable in the primary care setting. Our previous study found that a few clinical features could indicate a single common cause of chronic cough, such as nocturnal cough for CVA, postnasal dripping and history of sinusitis for UACS, heartburn, belching, acid regurgitation and cough after meals for GERC (6). Empiric therapy based on clinical characteristics is recommended in primary care (7).

According to the American College of Chest Physicians (ACCP) Clinical Practice Guideline for cough due to gastroesophageal reflux disease (GERD), GERC should be considered if chronic cough patients present with typical reflux-related symptoms, or had no evidence of other common causes of chronic cough (2,8). For these patients with suspected GERC, anti-reflux treatment is recommended (2,8). However, this recommendation was based on observational studies with a small sample and a low level of evidence (9,10). A previous study found that only 35% of patients with chronic cough responded favorably to proton pump inhibitor (PPI) treatment after excluding asthma (11).

For patients with chronic cough, reflux-related symptoms may indicate a diagnosis of GERC to some extent, in comparison with other common causes of chronic cough (6). However, it remains unknown whether reflux-related symptoms and other clinical features could predict the response to anti-reflux therapy in suspected GERC patients. It would be meaningful to identify a few clinical features for predicting anti-reflux therapy response. Therefore, we conducted this retrospective study to investigate the relationship between the clinical features and the response to anti-reflux therapy in suspected GERC patients from a chronic cough database with standard case report form. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1046/rc).

Highlight box

Key findings

- Over half of the suspected gastroesophageal reflux-induced cough patients benefited from anti-reflux therapy. A few clinical features rather than reflux-related symptoms might indicate a response to anti-reflux treatment.

What is known and what is new?

- Among patients with chronic cough, anti-reflux treatment is recommended in patients with typical reflux-related symptoms or in who had no evidence of other common causes of chronic cough. It remains unknown whether reflux-related symptoms and other clinical features could predict the response to anti-reflux therapy in suspected GERC patients.
- A few clinical features rather than reflux-related symptoms might indicate a response to anti-reflux treatment.

What is the implication, and what should change now?

- Nasal itching, tickle in the throat, pharyngeal foreign body sensation and sensitivity to at least one cough trigger could be used as a screening tool to guide the anti-reflux therapy.

Methods

This was a retrospective observational study. Data were collected from a chronic cough database in the First Affiliated Hospital of Guangzhou Medical University from 2006 to 2021. We enrolled the chronic cough patients who presented cough as the sole or predominant symptom lasting at least 8 weeks with normal chest X-ray. A subset of patients come from our previous prospective studies (12,13). The standard case report form was used to record demographics, clinical features, laboratory results, primary diagnosis, response to therapy, and final diagnosis as described previously. Spirometry, bronchial challenge, and induced sputum test for differential cells were performed in all patients, and 24-hour esophageal pH value monitoring was performed in a subset of patients (2,14). DeMeester score and symptom association probability (SAP) were recorded in the chronic cough database. Pathological reflux was defined as a distal DeMeester score ≥12.7 or distal SAP ≥95% (15).

The inclusion criteria for patients with suspected GERC were as follows: (I) presence of typical reflux-related symptoms, including acid regurgitation, belching, heartburn, or abnormal 24-hour esophageal pH value monitoring results; or (II) no evidence of CVA, EB, UACS, atopic cough, and other potential causes, and no response to treatment directed to these potential

causes of chronic cough; (III) anti-reflux therapy for at least 2 weeks, PPIs (omeprazole or esomeprazole, 20 mg, bid) plus prokinetic agents (domperidone, 10 mg, tid or mosapride, 5 mg, tid) were administered in all suspected GERC patients. We excluded the patients who underwent anti-reflux therapy combined with other therapy and patients with multi causes of chronic cough in this study.

The patients with suspected GERC were divided into responders and non-responders according to the response to anti-reflux treatment. Responders were defined as patients who had a self-reported resolution of cough after anti-reflux treatment. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (No. 2020150). All patients gave informed consent for their data to be analyzed.

Statistical analyses

Data were expressed as frequency (percentage), mean ± SD, or median (interquartile range). Statistical comparisons between groups were performed with unpaired Student's *t*-test for normally distributed data, Mann-Whitney U tests for skewed data, and χ^2 tests or Fisher exact tests for categorical variables. A Cox regression test was used to identify the variables that were independent predictors of the response to anti-reflux treatment. Variables whose P value <0.1 in univariable models was put into the multivariable model. Multiple Cox regression analysis was conducted with the method of forward stepwise (likelihood ratio). For those clinical features that indicated response to anti-reflux therapy (P<0.05), sensitivities, specificities, and area under curve (AUC) were calculated. For patients who did not complete 24-hour esophageal pH value monitoring, we handled missing data as missing without data imputation. Rstudio (Version 1.4.1717.0; Free Software Foundation, Inc., Boston, MA, USA) was used for statistical analyses.

Results

The relationship between clinical features and response to anti-reflux therapy

A total of 241 patients with suspected GERC were enrolled. Among this group of eligible patients, 111 (46.1%) patients were female and the median age was 37.0 [interquartile range (IQR), 30.0–49.0] years. The median course of the disease was 30.0 (IQR, 12.0–72.0) months.

Among 241 patients evaluated in this study, cough resolved in 146 (60.6%) patients. The demographic characteristics of responders and non-responders are shown in *Table 1*. Responders showed a significantly higher proportion of nasal itching (21.2% *vs.* 8.4%; P=0.014) and tickle in the throat (51.4% *vs.* 35.8%; P=0.025) than non-responders whereas the proportion of pharyngeal foreign body sensation (32.9% *vs.* 54.7%; P=0.001) was significantly lower in responders. One hundred and four (71.2%) responders presented at least one of the reflux-associated symptoms (acid regurgitation, nausea, belching, heartburn, and chest tightness) while 56 (58.9%) non-responders showed at least one of them (P>0.05). The frequency of trigger-eating (32.2% *vs.* 34.7%), acid regurgitation (36.3% *vs.* 36.8%), nausea (28.8% *vs.* 20.0%), belching (39.7% *vs.* 27.4%), heartburn (19.2% *vs.* 14.7%), chest tightness (31.5% *vs.* 31.6%), the presence of acid regurgitation or heartburn (42.5% *vs.* 41.1%), and the number of reflux-related symptoms did not differ between responders and non-responders (P>0.05) (*Table 1*, *Figure 1*).

For all patients recruited in this study, the univariate Cox regression analysis indicated that potential factors associated with the response to anti-reflux therapy were reflux-associated symptoms, sensitive to at least one cough trigger, tickle in the throat, pharyngeal foreign body sensation, nasal itching and rhinitis (P<0.1). Multivariate analysis showed that nasal itching [hazard ratio (HR): 1.593, 95% confidence interval (CI): 1.025–2.476, P=0.039] and tickle in the throat (HR: 1.605, 95% CI: 1.152–2.238, P=0.005) were predictive factors for a response to therapy while pharyngeal foreign body sensation (HR: 0.499, 95% CI: 0.346–0.720, P<0.001) and sensitive to at least one cough trigger (including dust, cooking fume, cold air, supine position, cigarette smoke, exercise, talking, alcohol, eating or others) (HR: 0.480, 95% CI: 0.237–0.973, P=0.042) were associated with no response to anti-reflux therapy (*Table 2*).

The combination of nasal itching, tickle in the throat, pharyngeal foreign body sensation, and sensitive to at least one cough trigger had low sensitivity of 0.497 and specificity of 0.805 to predict the successful response to anti-reflux treatment, with an AUC of 0.713.

The relationship between clinical features and response to anti-reflux therapy in GERC patients with abnormal results of 24-hour pH esophageal monitoring

In 89 patients with abnormal pH value monitoring results,

Table 1 Demographic characteristics of respondents and non-respondents in all patients

Variables	Total (n=241)	Responder (n=146)	Non-responder (n=95)	P value
Female, n (%)	111 (46.1)	67 (45.9)	44 (46.3)	1.000
Age (years), median (Q1, Q3)	37.0 (30.0, 49.0)	38.0 (30.0, 50.0)	36.0 (29.5, 47.0)	0.740
Course of disease (months), median (Q1, Q3)	30.0 (12.0, 72.0)	24.0 (12.0, 84.0)	36.0 (12.0, 72.0)	0.771
VAS at admission, median (Q1, Q3)	60.0 (50.0, 80.0)	60.0 (50.0, 80.0)	60.0 (50.0, 75.0)	0.631
Cough phase, n (%)				
Cough in daytime	225 (93.4)	135 (92.5)	90 (94.7)	0.669
Cough after sleep	67 (27.8)	43 (29.5)	24 (25.3)	0.574
Cough after waking up	95 (39.4)	55 (37.7)	40 (42.1)	0.580
Nonproductive cough, n (%)	177 (73.4)	111 (76.0)	66 (69.5)	0.329
Sensitive to at least one cough trigger, n (%)	228 (95.8)	135 (93.8)	93 (98.9)	0.094
Trigger-eating, n (%)	80 (33.2)	47 (32.2)	33 (34.7)	0.787
After meal	55 (22.8)	32 (21.9)	23 (24.2)	0.797
During meal	31 (12.9)	21 (14.4)	10 (10.5)	0.498
Reflux-related symptoms, n (%)	160 (66.4)	104 (71.2)	56 (58.9)	0.067
Acid regurgitation	88 (36.5)	53 (36.3)	35 (36.8)	1.000
Nausea	61 (25.3)	42 (28.8)	19 (20.0)	0.168
Belching	84 (34.9)	58 (39.7)	26 (27.4)	0.067
Heartburn	42 (17.4)	28 (19.2)	14 (14.7)	0.475
Chest tightness	76 (31.5)	46 (31.5)	30 (31.6)	1.000
Acid regurgitation or Heartburn	101 (41.9)	62 (42.5)	39 (41.1)	0.933
Acid regurgitation or Belching or Heartburn	129 (53.5)	83 (56.8)	46 (48.4)	0.250
Number of reflux-related symptoms, n (%)				0.493
0–2	186 (77.2)	110 (75.3)	76 (80.0)	
3–5	55 (22.8)	36 (24.7)	19 (20.0)	
Nasal symptoms, n (%)	121 (50.2)	70 (47.9)	51 (53.7)	0.460
Sneezing	53 (22.0)	33 (22.6)	20 (21.1)	0.901
Nasal itching	39 (16.2)	31 (21.2)	8 (8.4)	0.014
Runny nose	50 (20.7)	30 (20.5)	20 (21.1)	1.000
Postnasal dripping	44 (18.3)	28 (19.2)	16 (16.8)	0.773
Nasal congestion	65 (27.0)	38 (26.0)	27 (28.4)	0.794
Shortness of breath, n (%)	51 (21.2)	30 (20.5)	21 (22.1)	0.898
Pharyngeal symptoms, n (%)	211 (87.6)	129 (88.4)	82 (86.3)	0.788
Tickle in the throat	109 (45.2)	75 (51.4)	34 (35.8)	0.025
Tickle below the throat	49 (20.3)	31 (21.2)	18 (18.9)	0.789
Pharyngeal foreign body sensation	100 (41.5)	48 (32.9)	52 (54.7)	0.001

Table 1 *(continued)*

Table 1 *(continued)*

Variables	Total (n=241)	Responder (n=146)	Non-responder (n=95)	P value
Frequent throat clearing	109 (45.2)	66 (45.2)	43 (45.3)	1.000
Mucus adhesion to the throat	87 (36.1)	52 (35.6)	35 (36.8)	0.955
Medical history, n (%)				
Rhinitis	41 (17.0)	31 (21.2)	10 (10.5)	0.047
Sinusitis	33 (13.7)	21 (14.4)	12 (12.6)	0.845
Gastrointestinal disorders	61 (25.4)	40 (27.6)	21 (22.1)	0.422
Hypertension	11 (6.5)	10 (8.8)	1 (1.8)	0.105
24-hour pH-metry	n=137	n=94	n=43	
Distal DeMeester score, median (Q1, Q3)	12.5 (4.7, 23.0)	14.6 (5.2, 24.8)	10.4 (2.9, 17.9)	0.058
Distal DeMeester score ≥12.7, n (%)	67 (48.9)	51 (54.3)	16 (37.2)	0.095
Distal SAP, median (Q1, Q3)	88.8 (31.0, 99.0)	87.8 (38.8, 99.0)	92.0 (0.0, 99.0)	0.890
Distal SAP ≥0.95, n (%)	52 (38.0)	36 (38.3)	16 (37.2)	1.000
Abnormal pH results, n (%)	89 (65.0)	64 (68.1)	25 (58.1)	0.348

Trigger-eating, cough occurs after meal or during meal. Q1, the first quartile; Q3, the third quartile; VAS, a 10 cm scale to evaluate severity of cough, with higher score meaning more severe cough; SAP, symptom association probability; VAS, visual analogue scale. Abnormal pH results, distal DeMeester score ≥12.7 or distal SAP ≥95%.

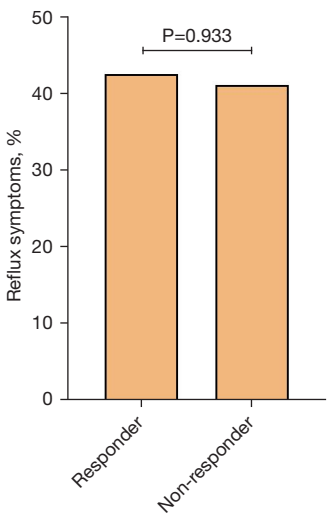

Figure 1 The proportion of patients with reflux symptoms in 241 patients who experienced anti-reflux treatment for longer than 2 weeks. Reflux symptoms: acid regurgitation or heartburn.

60 (67.4%) showed a good response to anti-reflux therapy, whereas the remaining 29 (32.6%) reported an unfavorable response. Compared with non-responders, the responders presented a similar frequency of cough trigger and reflux-related symptoms, but a higher proportion of nasal itching (26.7% *vs.* 3.4%; P=0.020) and tickle in the throat (65.0% *vs.* 31.0%; P=0.005) (*Table 3*).

Comparison of 24-hour esophageal pH-value monitor results between responders and non-responders

Among 137 patients who completed 24-hour ambulatory esophageal pH-monitor, 94 (68.6%) showed successful responses to anti-reflux treatment. Distal DeMeester score, [14.6 (5.2, 24.8) *vs.* 10.4 (2.9, 17.9)], the proportion of patients with distal DeMeester score ≥12.7 (54.3% *vs.* 37.2%), distal SAP [87.8 (38.8, 99.0) *vs.* 92.0 (0.0, 99.0)], the proportion of patients with distal SAP ≥0.95 (38.3% *vs.* 37.2%), and the proportion of pathological reflux results (68.1% *vs.* 58.1%) did not differ between responders and non-responders (P>0.05) (*Table 1*, *Figure 2*).

Discussion

This study investigated the relationship between clinical features and response to anti-reflux therapy in a group of suspected GERC patients. In this study, we found that more than half of patients benefited from anti-reflux therapy

Table 2 Univariate and multivariable Cox regression analysis of predictors of the onset of response to anti-reflux therapy in all patients

Characteristics	Univariable analysis			Multivariable analysis		
	HR	95% CI	P	HR	95% CI	P
Gender	1.080	0.779–1.495	0.645	1.317	0.910–1.907	0.144
Age	1.005	0.992–1.018	0.465	1.001	0.987–1.015	0.908
Cough triggers*	0.555	0.282–1.090	0.087	0.480	0.237–0.973	0.042
Reflux-related symptoms	1.398	0.977–2.001	0.067	1.391	0.962–2.011	0.079
Tickle in the throat	1.646	1.189–2.281	0.003	1.605	1.152–2.238	0.005
Pharyngeal foreign body sensation	0.538	0.381–0.761	<0.001	0.499	0.346–0.720	<0.001
Nasal itching	1.673	1.125–2.488	0.011	1.593	1.025–2.476	0.039
Rhinitis	1.788	1.201–2.660	0.004	1.457	0.933–2.276	0.098

*, cough triggers: cough induced by dust, cooking fume, cold air, supine position, cigarette smoke, exercise, talking, alcohol, eating or others. HR, hazard ratio; CI, confidence interval.

Table 3 Demographic characteristics of respondents and non-respondents in patients with abnormal 24-hour esophageal pH value monitoring results

Variables	Total (n=89)	Responder (n=60)	Non-responder (n=29)	P value
Female, n (%)	33 (37.1)	20 (33.3)	13 (44.8)	0.413
Age (years), median (Q1, Q3)	37.0 (30.0, 50.0)	36.0 (30.0, 51.5)	38.0 (33.0, 44.0)	0.990
Course of disease (months), median (Q1, Q3)	36.0 (24.0, 96.0)	36.0 (16.5, 96.0)	39.0 (24.0, 96.0)	0.349
VAS at admission, median (Q1, Q3)	60.0 (50.0, 80.0)	60.0 (50.0, 80.0)	60.0 (50.0, 80.0)	0.833
Cough phase, n (%)				
Cough in daytime	81 (91.0)	56 (93.3)	25 (86.2)	0.430
Cough after sleep	23 (25.8)	20 (33.3)	3 (10.3)	0.039
Cough after waking up	34 (38.2)	21 (35.0)	13 (44.8)	0.508
Nonproductive cough, n (%)	66 (74.2)	46 (76.7)	20 (69.0)	0.603
Sensitive to at least one cough trigger, n (%)	85 (96.6)	56 (94.9)	29 (100.0)	0.548
Trigger-eating, n (%)	34 (38.2)	25 (41.7)	9 (31.0)	0.462
After meal	23 (25.8)	16 (26.7)	7 (24.1)	1.000
During meal	14 (15.7)	12 (20.0)	2 (6.9)	0.133
Reflux-related symptoms, n (%)	62 (69.7)	44 (73.3)	18 (62.1)	0.402
Acid regurgitation	42 (47.2)	30 (50.0)	12 (41.4)	0.591
Nausea	30 (33.7)	19 (31.7)	11 (37.9)	0.729
Belching	34 (38.2)	24 (40.0)	10 (34.5)	0.788
Heartburn	21 (23.6)	15 (25.0)	6 (20.7)	0.855
Chest tightness	27 (30.3)	20 (33.3)	7 (24.1)	0.523
Acid regurgitation or Heartburn	48 (53.9)	34 (56.7)	14 (48.3)	0.605
Acid regurgitation or Belching or Heartburn	55 (61.8)	39 (65.0)	16 (55.2)	0.508

Table 3 *(continued)*

Table 3 *(continued)*

Variables	Total (n=89)	Responder (n=60)	Non-responder (n=29)	P value
Number of reflux-related symptoms, n (%)				1.000
0–2	64 (71.9)	43 (71.7)	21 (72.4)	
3–5	25 (28.1)	17 (28.3)	8 (27.6)	
Nasal symptoms, n (%)	52 (58.4)	38 (63.3)	14 (48.3)	0.262
Sneezing	27 (30.3)	21 (35.0)	6 (20.7)	0.258
Nasal itching	17 (19.1)	16 (26.7)	1 (3.4)	0.020
Runny nose	20 (22.5)	16 (26.7)	4 (13.8)	0.274
Postnasal dripping	18 (20.2)	13 (21.7)	5 (17.2)	0.837
Nasal congestion	29 (32.6)	20 (33.3)	9 (31.0)	1.000
Shortness of breath, n (%)	11 (12.4)	7 (11.7)	4 (13.8)	0.744
Pharyngeal symptoms, n (%)	78 (87.6)	52 (86.7)	26 (89.7)	1.000
Tickle in the throat	48 (53.9)	39 (65.0)	9 (31.0)	0.005
Tickle below the throat	23 (25.8)	15 (25.0)	8 (27.6)	0.998
Pharyngeal foreign body sensation	24 (27.0)	12 (20.0)	12 (41.4)	0.061
Frequent throat clearing	40 (44.9)	24 (40.0)	16 (55.2)	0.262
Mucus adhesion to the throat	26 (29.2)	15 (25.0)	11 (37.9)	0.313
Medical history, n (%)				
Rhinitis	15 (16.9)	15 (25.0)	0 (0.0)	0.002
Sinusitis	9 (10.1)	7 (11.7)	2 (6.9)	0.712
Gastrointestinal disorders	29 (33.0)	19 (32.2)	10 (34.5)	1.000
Hypertension	5 (6.5)	5 (9.3)	0 (0.0)	0.314

Trigger-eating, cough occurs after meal or during meal. Q1, the first quartile; Q3, the third quartile; VAS, a 10 cm scale to evaluate severity of cough, with higher score meaning more severe cough; VAS, visual analogue scale.

in patients who had evidence of reflux (reflux-related symptoms or abnormal results of 24-hour pH esophageal monitoring) or who had no evidences of other common causes of chronic cough (12,15,16). Nasal itching, tickle in the throat, pharyngeal foreign body sensation, and sensitive to cough triggers were associated with anti-reflux therapy response in suspected GERC patients.

In ACCP guidelines on GERC, anti-reflux treatment was recommended to chronic cough patients after other common causes of chronic cough were excluded, even though patients did not have concomitant reflux-related symptoms (2,8). In this study, around one-third of patients did not benefit from anti-reflux therapy. These patients might have reflux symptoms or evidence of reflux, but the reflux might not be the cause of the cough (4). In addition, this ineffectiveness might be attributed to refractory reflux-related cough (6). The proportion of patients with common causes decreased and the proportion of patients with unexplained cough or refractory chronic cough increased in our center in recent years (6) because more chronic cough patients with common causes could be diagnosed and treated in primary care clinics or secondary health care after the promotion of Chinese guidelines on cough. These patients with refractory reflux-related cough might need intensive anti-reflux treatment, such as doubling the dose of PPIs, neuromodulators, or even surgery. In addition, although most patients with suspected GERC would respond to anti-reflux therapy within 2 weeks (17,18), the cough might improve after longer treatment occasionally. We could not rule out that a few patients might need

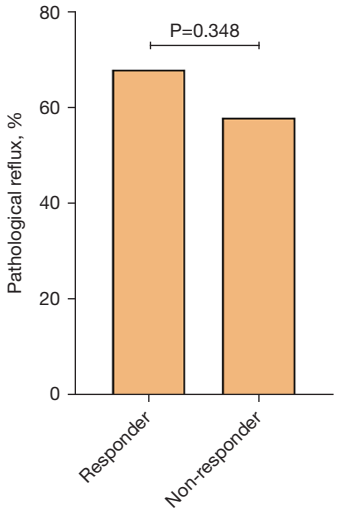

Figure 2 The proportion of patients with abnormal pH results in 137 patients who underwent 24-hour ambulatory esophageal pH-monitor. Pathological reflux: distal DeMeester score ≥12.7 or distal SAP ≥0.95; SAP, symptom association probability.

longer-duration treatment to improve their cough.

The relationship between reflux-related symptoms and the anti-reflux therapy efficacy in suspected GERC is still controversial. Previous data found that symptom scores of reflux-associated symptoms were not associated with definite, sustained improvement in cough for >3 months, although the symptom score in this article was not clearly defined (19). In our study, reflux-related symptoms were also not associated with anti-reflux therapy efficacy. However, Xu *et al.* (20) reported that a comprehensive questionnaire could identify responsiveness to anti-reflux therapy in suspected GERC. This comprehensive questionnaire comprised the severity of reflux-related symptoms, quality of sleep related to symptoms, and additional medication targeting heartburn and/or regurgitation in the preceding week, with a scale ranging from 0 to 3 for each item. An overall score ≥8 indicated a response to anti-reflux treatment for 8 weeks. These results suggested that higher reflux-related symptom scores might indicate a better response to anti-reflux therapy for GERC.

It is surprising that higher proportions of nasal itching and tickle in the throat were found in responders to anti-reflux treatment. It is well known that a variety of extraesophageal symptoms could be caused by direct stimulation of the pharynx, larynx, or airway or indirect stimulation of neurogenic inflammation. Laryngopharyngeal reflux may induce chronic laryngitis or laryngopharyngitis (21), which often presents with throat clearing, pharyngeal foreign body sensation, cough, throat pain, vocal changes, and/or hoarseness (22). To our best knowledge, the relationship between nasal itching and reflux has never been reported. However, it has been reported that reflux was related to rhinitis or sinusitis (4,23). We postulate that the higher proportion of nasal itching in responders might be due to rhinitis triggered by reflux. Similarly, the tickle in the throat may be a special presentation of acid reflux or laryngopharyngeal reflux. In addition to the reflux mechanism, a vagally mediated reflex process in distal esophageal reflux could also cause extraesophageal symptoms (24). The reflex mechanism could explain why most reflux events occurred in the distal esophagus in patients with chronic cough (80%) (25-27). Acidification of the distal esophagus could stimulate acid-sensitive receptors that may interact with pulmonary bronchi and other upper airway structures via a vagally mediated arc (28). This sensory neuronal dysfunction might lead to hypersensitive somatic sensation in the upper airway and present as a constant itch in the throat and nose, causing a neuronal sensitization process (29) and indicating a good response to acid inhibitors. However, the mechanism of neuronal sensitization linking distal reflux and cough remains unclear. Further study needs to figure out the relationship between reflux, nasal itching, and tickle in the throat. In contrast to nasal itching and tickle in the throat, we found that a higher proportion of pharyngeal foreign body sensation existed in non-responders. Pharyngeal foreign body sensation might reflect chronic cough hypersensitivity or refractory chronic cough, indicating poor response to PPI and prokinetics (30,31).

We only compared the DeMeester score and SAP between responders and non-responders. No significant difference was found. According to the 2018 Lyon Consensus, new parameters, AET, and total reflux episodes also come up with definite acid reflux. We did not analyze the two variables in the current study. We began to establish our chronic cough database after 2000, DeMeester score and SAP were recorded in our chronic cough database and were recommended as primary diagnostic variables at that time according to the National Guidelines on the Diagnosis and Management of Cough in China (15). There are several limitations in this study. First, in our clinic, if cough did not improve after four weeks of anti-reflux therapy, anti-reflux empirical treatment would end usually, those patients

were defined as non-responders. Not all non-responders were real non-responders since cough might improve after longer treatment occasionally. However, we found that most patients with GERC showed a positive response to anti-reflux treatment within 2 weeks (18). Second, multichannel intraluminal impedance-pH monitoring (MII-pH) was not in use in the early stage of this study. Weakly acidic or weakly alkaline reflux episodes might be missed (32). Third, oesophageal manometry was not used to evaluate impaired oesophageal and gastric motility in this study. It might be valuable to screen out the population that would respond to anti-reflux therapy. In this study, we tried to find clinical features to predict the response of anti-reflux treatment and a lot of variables were compared in the current study. We could not rule out completely the possibility of false positives. Nonetheless, these results could provide a reference for subsequent studies. More prospective studies are needed to further investigate the relationship between these clinical features and the efficacy of anti-reflux therapy for suspected GERC.

Conclusions

Our study showed that over half of suspected GERC patients benefited from anti-reflux therapy. Reflux-related symptoms could not predict the anti-reflux response. Higher proportions of nasal itching, tickle in the throat and a lower proportion of pharyngeal foreign body sensation were found in responders, which might indicate a positive response to anti-reflux treatment in patients with suspected GERC. Further study is needed to identify the predictive value of these clinical features.

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Footnote

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