Original Article on Cough Section

Improved diagnostic yield of symptom association probability involving only cough for gastroesophageal reflux-induced chronic cough

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Background: Use of symptom association probability (SAP) is recommended for identifying gastroesophageal reflux-induced chronic cough (GERC). This study aimed to compare the diagnostic yield of SAPs involving only cough (C-SAP) or total symptoms (T-SAP) for GERC identification.

Methods: Patients with both chronic cough and other reflux-related symptoms underwent multichannel intraluminal impedance-pH monitoring (MII-pH) between January 2017 and May 2021. C-SAP and T-SAP were calculated based on the patient-reported symptoms. GERC was definitively diagnosed by the favorable response to anti-reflux therapy. The diagnostic yield of C-SAP in identifying GERC was evaluated by receiver operating characteristic curve analysis and compared with that of T-SAP.

Results: MII-pH was performed in 105 patients with chronic cough, and GERC was confirmed in 65 (61.9%), including 27 (41.5%) cases of acid GERC and 38 (58.5%) cases of non-acid GERC. The positive rates of C-SAP and T-SAP were comparable (34.3% *vs.* 23.8%, P>0.05), but C-SAP exhibited a higher sensitivity (53.85% *vs.* 33.85%, χ^2=8.117, P=0.004) and similar high specificities (97.5% *vs.* 92.5%, P>0.05) compared with T-SAP for GERC identification. C-SAP was also more sensitive for recognition of acid GERC (51.85% *vs.* 33.33%, χ^2=7.386, P=0.007) and non-acid GERC (65.79% *vs.* 39.47%, χ^2=14.617, P<0.001). More GERC patients with positive C-SAP needed intensified anti-reflux therapy for cough resolution when compared with those with negative C-SAP (82.9% *vs.* 46.7%, χ^2=9.449, P=0.002).

Conclusions: C-SAP was superior to T-SAP for the identification of GERC and may improve the diagnostic yield of GERC.

Keywords: Cough; diagnostic accuracy; diagnostic yield; gastroesophageal reflux; symptom association probability (SAP)

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Introduction

Gastroesophageal reflux-induced chronic cough (GERC) is a specific type of gastroesophageal reflux disease (GERD) characterized by a predominant cough and is a common cause of chronic cough (1-4). When diagnosing GERC, it is important to obtain objective evidence of abnormal reflux and establish the assumed cause-effect relationship of the reflux-cough sequence. Multichannel intraluminal impedance and pH monitoring (MII-pH) is used to assess acid and non-acid reflux episodes, as well as their temporal association with cough (5). Thus, MII-pH is recommended as the most useful laboratory investigation for GERC diagnosis (6,7).

According to the Lyon Consensus, esophageal acid exposure time (AET), symptom association probability (SAP), and the number of reflux episodes are the main MII-pH metrics used for identifying GERC (5). The SAP is a measure that uses statistical calculations to express the probability that a truly significant symptom-reflux relationship does not exist by chance, and it is considered positive at ≥95% (8,9). The current Chinese guideline for cough management recommends a positive SAP as one of the diagnostic criteria for GERC (10). However, the calculation process of SAP has not been standardized yet.

There are two approaches for SAP calculation: taking all the recorded reflux-related symptoms including cough into account or considering only cough as a relevant component (11-14). While the former is widely employed for the diagnosis of GERD (5), the latter has only been used for determining the relationship between reflux and chronic cough in several studies and has not been applied for GERC identification in clinical practice (11,14). Which SAP is superior and more suitable for GERC diagnosis remains to be elucidated.

Therefore, we conducted a prospective clinical investigation to compare the efficacies of SAPs calculated by the above two methods in identifying GERC and tried to improve the diagnostic yield of GERC. We present the following article in accordance with the STARD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1016/rc).

Highlight box

Key findings

- Symptom association probability involving only cough (C-SAP) was superior to that involving total symptoms (T-SAP) for the diagnosis of gastroesophageal reflux-induced chronic cough (GERC), and its use might improve diagnostic efficacy.

What is known and what is new?

- A positive SAP was recommended for identifying GERC but with a low sensitivity. The calculation of SAP includes both C-SAP and T-SAP in clinical practice.
- Which SAP is superior and more suitable for the diagnosis of GERC and prediction of therapeutic efficacy needs the assessment.

What is the implication, and what should change now?

- C-SAP might be a more precise criterion for GERC diagnosis and could be used to replace T-SAP, even though its efficacy was still suboptimal.

Methods

Patients

Consecutive patients referred to our respiratory clinic for evaluation of potential GERC were enrolled between January 2017 and May 2021. Eligible inclusion criteria for participation were as follows: (I) aged between 18 and 70 years old; (II) cough lasting for >8 weeks, with concomitant other reflux-related symptoms such as regurgitation and heartburn; (III) other possible causes of chronic cough including cough variant asthma, upper airway cough syndrome, and eosinophilic bronchitis were excluded after a sequential laboratory work-up; and (IV) successful MII-pH. The exclusion criteria were as follows: (I) other co-existing causes of chronic cough; (II) neither cough events nor other reflux-related symptoms were reported, or fewer than four cough events were recorded during MII-pH; or (III) patients had incomplete clinical information or were lost to follow-up.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Committee of Tongji Hospital (No. LL(H)-2016-396) and registered as ChiCTR-DDD-17012587 in the Chinese Clinical Trials Registry (http://www.chictr.org/). Written informed consent was obtained from all participants before enrollment.

MII-pH

MII-pH was performed when subjects had been off acid suppression treatment for at least 1 week as described previously (15). Briefly, a MII-pH catheter containing an antimony pH probe (819100, Medical Measurement System B.V., Enschede, Netherlands) and six impedance channel amplifiers (K6011-E10632, Unisensor, Seraing,

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Belgium) was transnasally inserted into the esophagus. The pH electrode was positioned 5 cm and impedance channel amplifiers were located at 3, 5, 7, 9, 15, and 17 cm above the proximal border of lower esophageal sphincter as determined by high-resolution manometry just prior to MII-pH. The signals were collected from all seven channels with 50 Hz frequency over 24 h using a portable digital data logger (Ohmega, Medical Measurement System B.V.) connected to the MII-pH catheter. The patients were instructed to maintain their normal daily life and push an event marker on the digital data logger whenever cough or other reflux-related symptoms occurred. They were also asked to keep a journal to record the timing of meals, recumbent position, and symptom episodes in detail. These data were used to check the appropriate use of the event button and distinguish the type of symptoms. No significant adverse events occurred during the above tests.

The downloaded data were automatically analyzed and manually reviewed using specific software (Database soft, 8.7 version, Medical Measurement System B.V.). The reflux episodes were classified as liquid, gas, or mixed reflux based on the impedance values, and categorized into acidic (pH <4.0), weakly acidic (pH 4.0–7.0) and weakly alkaline reflux (pH >7.0), with the latter two defined as non-acidic reflux (16). AET and the number of reflux episodes were also analyzed.

The SAP was calculated to determine the temporal association between symptoms recorded in the journal and MII-detected reflux (including acidic and non-acidic reflux) according to the protocol described previously (12,17). The entire recording of MII-pH was divided into consecutive 2-min time windows and assessed for the presence of reflux in each time window. In combination with symptom time and the number of all the symptoms recorded in the journals, each 2-min period of the recording was classified into reflux alone (R+S–), reflux followed by symptom (R+S+), only symptom but no reflux (R–S+), and neither reflux nor symptom (R–S–). When a symptom occurred in the 2-min span after a reflux event, it was considered as "associated to reflux". A contingency table was constructed for each patient containing the numbers of the different types of 2-min windows using Fisher's exact test, appropriately adjusted where low numbers occurred in one of the four fields. The probability (P value) was then calculated to determine if the observed association between reflux and symptom occurred by chance, and the SAP was expressed as (1.0–P)×100%. An SAP value ≥95% was considered positive.

For comparison between the two calculation methods, SAPs in each patient were independently re-analyzed by only reviewing the recordings of cough episodes (not the other reflux-related symptoms such as regurgitation and heartburn) marked in the journal during MII-pH, and these were labeled as C-SAP. The SAP involving the total symptoms (cough and all the other reflux-related symptoms) was termed T-SAP. The SAPs for acidic and non-acidic reflux events were also calculated for individual patients based on the pH of the refluxates, reflecting the likelihood of acidic and non-acidic reflux as the cough cause, respectively.

Study procedures

This was a single-center observational study. Initial patient assessment included the collection of general information, cough severity recording, and MII-pH testing. Cough severity was scored using the validated Chinese version (18) of the cough symptom score developed by Hsu *et al.* (19), which rates daytime and nighttime cough from 0 (no coughing) to 5 (most intense coughing). Regardless of the MII-pH results, all patients with potential GERC received an 8-week of standard anti-reflux therapy comprising omeprazole (20 mg twice daily 30 min before meals) and domperidone (10 mg three times daily), followed by an intensified anti-reflux trial that included an increase in the omeprazole dose to 80 mg daily or add-on therapy with baclofen or gabapentin when the initial treatment failed and refractory GERC was suspected (20). The patients were followed up every 2 weeks, and their responses to therapy and cough symptom score were rated each time. GERC was definitively confirmed when cough was completely resolved or significantly improved (cough symptom score decreased by >50%) in response to the anti-reflux therapy, in addition to objective evidence of abnormal gastroesophageal reflux defined as any AET >6%, SAP ≥95%, or >80 reflux episodes/24 h. Patients with abnormal acidic and non-acidic reflux were diagnosed with acid GERC and non-acid GERC, respectively (16). When cough failed to improve after all the anti-reflux trials, empirical therapy targeting the other causes such as cough variant asthma, upper airway cough syndrome, eosinophilic bronchitis and atopic cough was performed even though the initial negative relevant laboratory findings. The diagnosis was considered as probable if a favorable response to the therapy specific to the etiology was observed (21).

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Statistical analysis

According to our published observations (6,22) and the literature data (11,13,14), prospective statistical power calculation indicated that the minimum of 103 patients would be required to provide 80% power to detect a 25% difference in sensitivity between C-SAP and T-SAP using a 5% two-sided test. In addition to the predicted 6% dropout or lost follow-up, the final recruited numbers were 110 patients.

Data with normal distributions are expressed as mean ± SD, whereas those with skewed distribution are expressed as medians (25%, 75% interquartile range). Receiver operating characteristic (ROC) curve analysis was performed to determine the efficacies of SAPs in diagnosing GERC. Student's *t*-tests, Mann-Whitney tests, χ^2 tests, DeLong's tests, and Kappa tests were used for the comparisons between groups where applicable. SPSS 23.0 software (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. Differences were considered significant at $P<0.05$.

Results

General information

A total of 213 patients with suspected GERC who underwent MII-pH met the recruitment criteria during the research period. Ninety-eight subjects were excluded because of cough reported alone (n=69), fewer than four cough episodes (n=12), no symptom recording (n=10), and only other reflux-related symptoms without cough bursts (n=7) during MII-pH. Ten other patients were excluded due to incomplete MII-pH recordings (n=5), failure to completion of anti-reflux therapy course (n=3), and loss to the follow-up (n=2). Finally, 105 patients were included in the analysis. The study flow diagram and general patient characteristics are shown in *Figure 1* and *Table 1*.

Sixty-five (61.9%) patients favorably responded to anti-reflux treatment and were definitively diagnosed with GERC, including 27 (41.5%) cases of acid GERC and 38 (58.5%) cases of non-acid GERC. For therapeutic response of GERC, standard anti-reflux treatment was effective in 22 (33.8%) patients while subsequent intensified anti-reflux therapy benefited the other 43 (66.2%) patients, including omeprazole dose increased to 80 mg daily in 11, add-on therapy with baclofen in 7 and with gabapentin in 25. Intensified anti-reflux treatment was more frequently needed in non-acid GERC (30/38) than in acid GERC (13/27) for cough resolution (78.9% *vs.* 48.1%, χ^2=6.687, P=0.01). Among 40 non-responders, their cough could be explained by cough variant asthma (n=12), upper-airway cough syndrome (n=8), eosinophilic bronchitis (n=7), atopic cough (n=5), and unknown causes (n=8) based on the therapeutic response to subsequent empirical treatment.

Symptoms and SAP distributions

The distribution of symptoms recorded by patients during MII-pH is shown in *Figure 2A*. All participants reported cough as their predominant symptom. Regurgitation was present in 69 of 105 (65.7%) patients, while heartburn was reported in 47 (44.8%) patients. There was a wide distribution of SAPs that ranged from 0% to 100%, but most concentrated on the 0 or between 50–100% for both C-SAP and T-SAP (*Figure 2B*).

Comparison of C-SAP with T-SAP in identifying GERC

In 105 patients, the positive C-SAP and T-SAP rates were 34.3% (36 cases) and 23.8% (25 patients), respectively (*Figure 1*). No statistically significant difference was found between them (P>0.05). GERC was confirmed in 35 of 36 (97.2%) patients with a positive C-SAP and 22 of 25 (88.0%) patients with a positive T-SAP. C-SAP had a higher sensitivity, positive predictive value, accuracy, Youden index, and area under the curve (AUC) than T-SAP for the identification of GERC (*Table 2*). Both had high and comparable specificities (97.5% *vs.* 92.5%, χ^2=5.556, P=0.121). Their negative predictive values were low and similar (*Table 2*).

For the identification of GERC, there was a 27.7% (18 cases) overlap between SAPs. Additionally, C-SAP and T-SAP exclusively predicted 26.2% (17 cases) and 6.2% (4 cases) of GERC, respectively. Approximately 40.0% (26 cases) of GERC cases were not predicted by either SAP (*Figure 3*).

C-SAP and T-SAP for acid and non-acid GERC

A sub-analysis showed that C-SAP had a distinctly higher sensitivity than T-SAP in identifying both acid and non-acid GERC. Furthermore, the AUC was significantly larger for C-SAP than T-SAP for the diagnosis of non-acid GERC. However, the other ROC analysis metrics were similar between C-SAP and T-SAP (*Table 3*).

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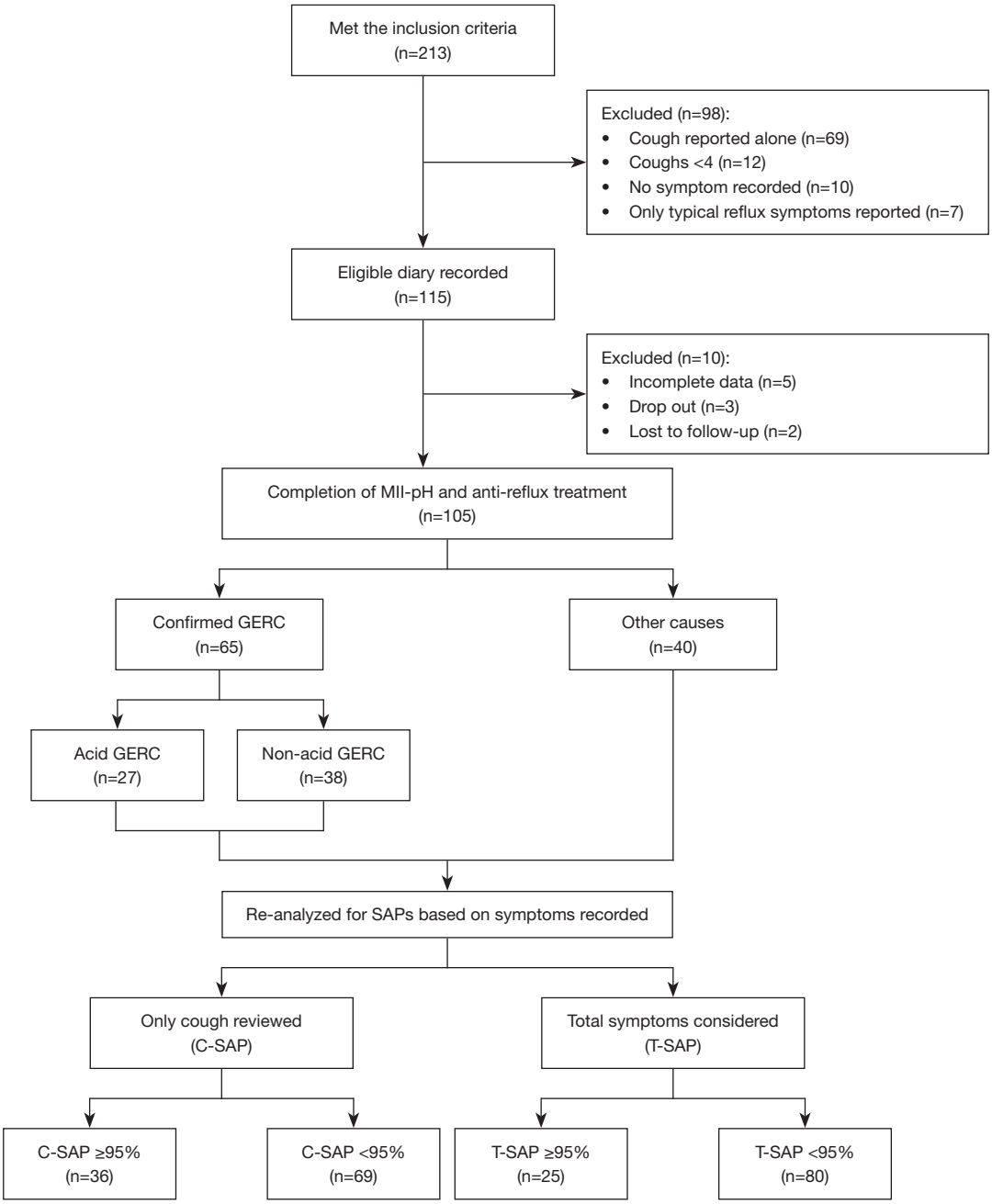

Figure 1 Flow diagram of the study. GERC, gastroesophageal reflux-induced chronic cough; SAP, symptom association probability; C-SAP, SAP calculated with only cough; T-SAP, SAP calculated with total symptoms.

Comparison between GERC patients with positive and negative C-SAPs

In 65 GERC patients, the positive C-SAP group accounted for 53.8% (35 cases) while the negative C-SAP group accounted for 46.2% (30 cases). More GERC patients (29/35) with positive C-SAP were resistant to standard anti-reflux treatment and needed the intensified anti-reflux therapy to resolve their cough when compared with those (14/30) with negative C-SAP (82.9% *vs.* 46.7%, χ^2=9.449, P=0.002). However, there was no significant difference in the other clinical characteristics such as age and gender

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Table 1 Subjects' demographic characteristics

Characteristic	Value
Male/female (n)	45/60
Age (year), mean ± SD	46.0±14.9
Cough duration (month), median [IQR]	12 [6–36]
Cough symptom score, median [IQR]	
Daytime	3 [3–4]
Nighttime	1 [1–2]
Number of coughs, median [IQR]	9 [6–18]
Number of reflux episodes, median [IQR]	83 [50–113]
Esophageal acid exposure time, mean ± SD	4.73±12.29
Pulmonary function test, mean ± SD	
FEV1 (% predictive value)	97.16±14.54
FVC (% predicted)	122.69±149.81
FEV1/FVC (%)	82.00±9.50

SD, standard deviation; IQR, interquartile range; FEV1, forced expiratory volume in one second; FVC, forced vital capacity.

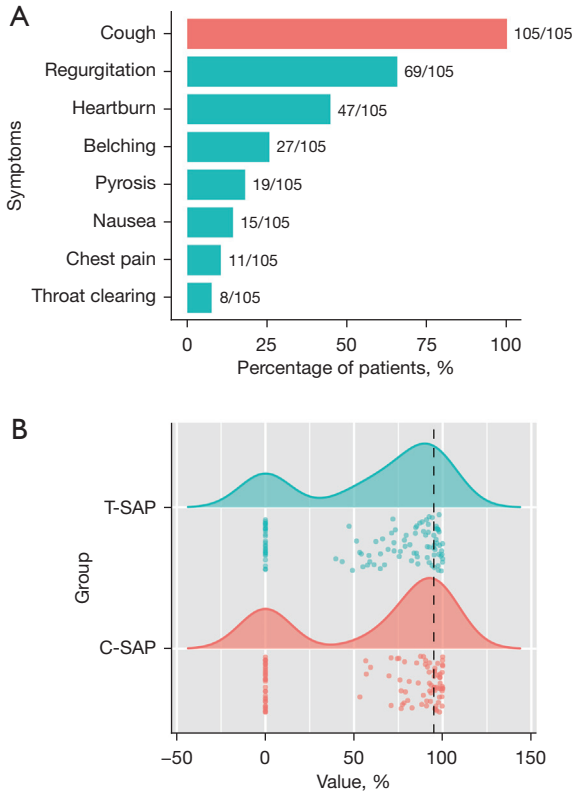

Figure 2 Symptoms and SAP distribution. (A) Percentages of patients with various symptoms; (B) distributions of C-SAP and T-SAP. The black dotted line represents a 95% threshold. SAP, symptom association probability; C-SAP, SAP calculated with only cough; T-SAP, SAP calculated with total symptoms.

distribution, cough duration or score and MII-pH variables between GERC patients with positive and negative C-SAPs (data are not shown).

Discussion

The SAP analysis seems to be an appropriate method to precisely document the temporal association between reflux events and symptom episodes during MII-pH (5). It can be calculated by selecting either cough alone or all the reflux-related symptoms (12). Nevertheless, few international cough guidelines have attempted to develop a uniform standard calculation method of SAP for GERC (8,11-13,17,23). Significant concerns were raised about the validity of clinical decision-making based on a positive SAP. In the present study, we assessed the diagnostic accuracy of C-SAP (cough only) and T-SAP (total symptoms involved) in a cohort of suspected GERC patients with both cough and other reflux-related symptoms. GERC was definitively confirmed by a favorable response to a standard or intensified medical anti-reflux therapy. Our results demonstrate that both C-SAP and T-SAP had moderate abilities to identify GERC with high and comparable specificities. C-SAP was superior to T-SAP since it achieved a higher diagnostic yield for GERC, as evidenced by a distinctly higher sensitivity, positive predictive value, accuracy, Youden index, and larger AUC. C-SAP was also more sensitive than T-SAP in predicting both acid and non-acid GERC. These findings indicate that C-SAP may be a more precise criterion for GERC diagnosis, and its use could improve diagnostic efficacy.

The reliability of SAP is critically dependent on the reliable execution of the reflux monitoring procedure and accurate analysis protocols, including careful selection of symptoms of interest (5). A previous study showed that 43.2% of patients with a positive SAP were observed for reflux-related cough, while SAP for other reflux-related symptoms were positive in 44.0% of patients, and only 10.8% of patients had a positive SAP for both other reflux-related symptoms and cough (13). This suggests that other reflux-related symptoms such as regurgitation and heartburn are not necessarily valuable when attempting

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Table 2 Diagnostic efficacy of SAPs to identify GERC based on a 95% threshold

Items	C-SAP	T-SAP	χ^2 value	P value
AUC	0.757	0.632	–	<0.001
Youden index	0.513	0.263	–	–
Sensitivity, %	53.85	33.85	8.117	0.004
Specificity, %	97.50	92.50	5.556	0.121
PPV, %	97.22	88.00	5.838	0.016
NPV, %	56.52	46.25	2.422	0.120
Accuracy, %	70.48	56.19	4.204	0.040
κ value	0.451	0.221	–	–
χ^2 value	28.975	9.475	–	–
P value	<0.001	0.002	–	–

SAP, symptom association probability; GERC, gastroesophageal reflux-induced chronic cough; C-SAP, SAP calculated with only cough; T-SAP, SAP calculated with total symptoms; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value.

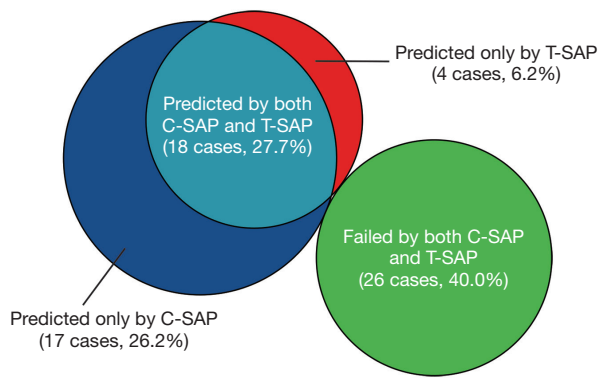

Figure 3 Predicted proportion of GERC by C-SAP and T-SAP. GERC, gastroesophageal reflux-induced chronic cough; SAP, symptom association probability; C-SAP, SAP calculated with only cough; T-SAP, SAP calculated with total symptoms.

to determine the temporal association between reflux and cough. In keeping with this observation, we found a higher sensitivity for GERC identification with C-SAP compared to T-SAP. A likely explanation for this is that cough, as an extra-esophageal symptom of GERD, may be induced either by reflux or by non-reflux causes. In the patients with GERC diagnosed by a positive T-SAP, it is possible that regurgitation and heartburn resolved, whereas cough failed to improve after the initiation of consequent anti-reflux therapy (24). It was originally believed that cough was less responsive to anti-reflux treatment than other reflux-related symptoms (25), which can be defined as refractory GERC (26). Actually, unlike regurgitation and heartburn, cough itself was probably irrelevant to reflux episodes, and C-SAP may more robustly establish reflux-cough causality.

Accumulating evidence suggests that a positive SAP is an independent predictor for a favorable response to anti-reflux treatment in patients with chronic cough (5,27,28). Theoretically, C-SAP should be expected to have a lower sensitivity and higher specificity for GERC identification when the other reflux-related symptoms were removed from the calculation because there would be an obvious decrease in the number of total marked symptoms. It is therefore surprising that the sensitivity of C-SAP was higher than that of T-SAP without affecting specificity. Actually, C-SAP showed slightly higher specificity for GERC diagnosis than T-SAP, but the difference did not reach statistical significance. Since the rate of positive SAPs mostly depends on the symptoms that occur within the 2-min time windows of MII-pH records containing a reflux event, the percentage of reflux-related symptoms rather than the absolute number of all symptoms matters for SAP calculations (11). In the context of GERC, cough is induced by reflux and is more prone to fall within the 2-min time window, thus leading to a higher sensitivity of C-SAP. Our results provide additional evidence that SAP is an effective indicator for GERC prediction and support replacing T-SAP with C-SAP in the identification of GERC.

Both non-acid and acidic reflux events were associated with cough (5,12,15). Like acidic reflux in acid GERC, non-acidic reflux was mainly responsible for non-acid GERC (15).

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Table 3 Diagnostic efficacies of SAPs for acid and non-acid GERC

Items	SAPs for acid GERC				SAPs for non-acid GERC			
	C-SAP	T-SAP	χ^2 value	P value	C-SAP	T-SAP	χ^2 value	P value
AUC	0.746	0.660	–	0.072	0.792	0.653	–	0.013
Youden index	0.493	0.284	–	–	0.583	0.294	–	–
Sensitivity, %	51.85	33.33	7.386	0.007	65.79	39.47	14.617	<0.001
Specificity, %	97.44	98.72	1.020	0.312	92.54	91.04	0.272	0.602
PPV, %	87.50	90.00	0.409	0.523	83.33	71.43	4.065	0.044
NPV, %	85.39	81.05	0.567	0.451	82.67	72.62	2.914	0.088
Accuracy, %	85.71	81.90	0.595	0.440	82.86	72.38	3.470	0.063
χ^2 value	37.724	23.912	–	–	40.420	14.115	–	–
κ value	0.569	0.404	–	–	0.611	0.338	–	–
P value	<0.001	<0.001	–	–	<0.001	<0.001	–	–

SAP, symptom association probability; GERC, gastroesophageal reflux-induced chronic cough; C-SAP, SAP calculated with only cough; T-SAP, SAP calculated with total symptoms; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value.

When acid and non-acid reflux events were considered separately, more acid and non-acid GERC (especially a higher percentage of non-acid GERC) were identified by C-SAP than by T-SAP, suggesting that concomitant other reflux-related symptoms were not good predictors for acid or non-acid GERC. The reason why non-acid GERC was more likely to be diagnosed by C-SAP than T-SAP may be explained by the recruited patients; we selected a larger number of patients with non-acid GERC who might record fewer other reflux-related symptoms but more cough events than those with acid GERC. We previously demonstrated that non-acid GERC had less frequent regurgitation and heartburn than acid GERC (22), and weakly acidic reflux was mainly related to cough hypersensitivity in non-acid GERC (15). When T-SAP alone was used to diagnose GERC, it had a roughly equal ability to identify both acid and non-acid GERC, which was consistent with our previous study (6). These findings revealed that refluxate acidity was not the only factor involved in the reflux-induced cough, and C-SAP might be more useful for identifying both acid and non-acid GERC.

Besides its more efficient identification for potential GERC, a positive C-SAP may predict the necessity and success of intensified anti-reflux trial, as indicated by the data regarding C-SAP in the study. It is clinically significant and important. In real-world practice, chronic cough with concomitant other reflux-related symptoms in patients leads generally to an empirical trial of proton pump inhibitors (4). If it fails or the reflux-related symptoms other than cough are absent, MII-pH is often ordered to examine the etiology underlying chronic cough, especially when patients are referred to cough specialists since easy to treat causes have usually been eliminated (6). With a positive C-SAP alone or in combination with pathological AET by MII-pH, one can be sure of GERC diagnosis and initiate the medical anti-reflux therapy immediately or become confident to implement the intensified anti-reflux treatment when the previous trial with proton pump inhibitors fails and refractory GERC is considered (20).

Despite its advantage of higher sensitivity compared to T-SAP, C-SAP was only positive in less than half of patients with suspected GERC. Therefore, both C-SAP and T-SAP have limited diagnostic efficiencies and are unable to meet the needs for GERC identification. However, the diagnostic yield can be greatly improved when C-SAP is used in combination with AET or the number of reflux episodes over 24 h, as shown in our previous study (6).

There were several limitations of this study. First, SAP calculation depends on the symptoms reported by the patients. During MII-pH, the patients often forget to record the symptom events including cough and fail to label the symptom on time (29). One criticism is that SAPs may be inaccurate if the symptom reports are unreliable. MII-pH combined with synchronous cough frequency recording could greatly improve C-SAP accuracy (11). However, cough frequency recording is only used for study purpose

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at present and has not been employed in clinical practice. Second, it is not possible to record the other reflux-related symptoms. The SAP calculation used in the study is still recommended in the Lyon Consensus (5). Third, the placebo effect of anti-reflux therapies cannot be excluded since the study was uncontrolled. However, the therapies are logically expected to be effective for GERC based on their benefits in the treatment of GERD (5) and previous observations (4,20). Furthermore, it may be suggested only the patients without pathological reflux should be recruited to evaluate the efficacy of C-SAP in the study as the patients with pathological reflux would undergo anti-reflux treatment anyway. However, the pathological reflux does not always guarantee the therapeutic success of anti-reflux treatment in patients with suspected GERC (30) and cannot replace SAP in the diagnosis of GERC (6). Thus, we included the patients with pathological reflux since the study purpose was to compare the diagnostic yield of C-SAP and T-SAP for GERC and the resolution of cough but not the other reflux-related symptoms was designed as the primary outcome in response to anti-reflux therapy. Finally, cough resolution in response to anti-reflux therapy was set as the gold standard and may underdiagnose definitive GERC since some patients may not respond to treatment but still have GERC. It is therefore possible that C-SAP may be more valuable for GERC diagnosis than demonstrated when considering the outcome assessment used in the study.

Conclusions

C-SAP was superior to T-SAP for the identification of GERC, especially non-acid GERC in that it had higher sensitivity and a similar high specificity. C-SAP may therefore improve the diagnostic yield of GERC, even though its efficacy was suboptimal.

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Footnote

Provenance and Peer Review: This article was a standard submission to the series "Cough Section" published in *Journal of Thoracic Disease*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1016/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1016/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Tongji Hospital (No. LL(H)-2016-396). Informed consent was taken from all the patients.

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