

Peer Review File

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Reviewer A

This is an interesting report that assessed the diagnostic yield of symptom association probability of cough (C-SAP) by gastroesophageal reflux.

Major comments:

Comment 1: The finding is very reasonable. However, I think clinicians can suspect of GERD as a cause of chronic cough if patients had cough in combination with reflux-related symptoms such as heart burn and regurgitation. In real-world practice, a three-month trial of medical anti-reflux therapy is recommended to diagnose GERD. Therefore, it is unclear whether detection of C-SAP is clinically helpful to diagnose GERD in the real-world practice. In this article, it is not assessed whether C-SAP is superior to anti-reflux therapy trial when diagnosing GERD. Do the authors think is C-SAP superior to a three-month treatment trial for GERD? Can the authors recommend to perform MII-pH before PPI trial? Should we consider to perform MII-pH more when patients with chronic cough are referred to cough specialists? If so, what situation performing MII-pH is considered? Please discuss the above concerns clearly if C-SAP is clinically useful for diagnosis of GERD.

Reply 1: Thank Reviewer 1 for his/her professional comment. It is true GERD will be suspected when patients with chronic cough present with concomitant other reflux-related symptoms such as regurgitation and heartburn and a three-month of medical anti-reflux trial will be recommended to the patients with suspected GERD in real-world practice. However, only 25-60% patients with GERD have the other reflux-

related symptoms (Chest. 1993;104(5):1511-7; 2006; 129:80S-94S.). Moreover, the co-existing regurgitation and heartburn do not guarantee the success of anti-reflux trial in the patients with chronic cough because chronic cough may not be associated with reflux (Chron Respir Dis. 2021; 18: 14799731211006682.). Therefore, the other reflux-related symptoms are helpful but not indispensable for diagnosis of GERC. In fact, the objective evidence of abnormal reflux (>6% AET) and positive reflux-cough association (SAP) provided by MII-pH are very useful criteria to establish the diagnosis of GERC as recommended by Lyon consensus and Chinese guideline for management of chronic cough (Gut. 2018;67(7):1351-62; J Thorac Dis. 2018;10(11):6314-6351.). Generally, MII-pH can be performed in the following situations: 1) the other common causes of chronic cough such as cough variant asthma, upper airway cough syndrome and eosinophilic bronchitis are excluded and the potential GERC is considered; 2) patients with suspected GERC but without other reflux-related symptoms such as regurgitation and heartburn; 3) empirical PPI anti-reflux trial fails in the patients with suspected GERC only based on other concomitant reflux-related symptoms (Gut. 2018;67(7):1351-62; J Thorac Dis. 2018;10(11):6314-6351.). Therefore, MII-pH is more often ordered in the patients with chronic cough referred to cough specialist since 75% patients with GERC may have cough as their sole symptom (Chest. 1993;104(5):1511-7.), and it can be performed before PPI trial if other reflux-related symptoms are absent (Gut. 2018;67(7):1351-62.). The patients in our cohort kept in line with above conditions as described in inclusion criteria of the manuscript. Nevertheless, we selected the suspected GERC patients with chronic cough as well as the other reflux-related symptoms for MII-pH in order to compare the efficacy of C-SAP and T-SAP.

However, in what situation MII-pH should be performed is not an issue

investigated in the study and therefore we did not discuss the problems in the manuscript. Our purpose is to improve the diagnostic yield and accuracy of MII-pH in the patients with potential GERC when MII-pH has to be undergone. It is impossible that C-SAP is superior to anti-reflux trial when diagnosing GERC since the favorable response to anti-reflux therapy is a prerequisite and gold standard for the GERC diagnosis according to the guidelines for cough management (J Thorac Dis. 2018;10(11):6314-6351.). In our study, an interesting finding is that a positive C-SAP improved the diagnostic gain of MII-pH when compared with T-SAP, as verified by medical anti-reflux therapy. It is clinically relevant and significant since a positive C-SAP during MII-pH means a higher probability of GERC and a higher success rate in response to consequent medical anti-reflux therapy.

Changes in the text: According to the opinion of Reviewer 1, we have added the description regarding in what situations MII-pH should be performed in the Discussion section (see Page 16, line 318-Page 17, line 324), and discuss the concern in the Discussion section (see Page 16, line 316-Page 17, line 328).

Comment 2: Please state that how many patients who are refractory to PPI but respond to additional therapies against GERC. I think diagnostic accuracy of C-SAP by MII-pH in such population is important. If a certain number of patients with GERC diagnosed by the presence of C-SAP is refractory to PPI trial for cough, the authors can emphasize the importance of the detection of C-SAP by MII-pH.

Reply 2: We appreciate the reviewer 1 for this excellent comment. Among 65 patients with GERC, 43 (66.2%) were resistant to standard anti-reflux treatment but responded to intensified anti-reflux therapy including baclofen and gabapentin. Moreover, there were 29 (29/35, 82.9%) GERC patients with positive C-SAP failed to standard anti-

reflux therapy but responded to intensified anti-reflux therapy including add-on therapies with baclofen and gabapentin, which was more frequent when compared with those with negative C-SAP (82.9% vs. 46.7%, $\chi^2=9.449$, $p=0.002$). With a positive C-SAP by MII-pH, we can be sure of GERC diagnosis and initiate the medical anti-reflux therapy immediately. Even though PPI trial fails, the intensified anti-reflux treatment can be implemented. Without a positive C-SAP, one cannot be so confident for treating refractory GERC after PPI trial fails.

Changes in the text: We have added these data in the revised Results section (see Page 11, line 201-207; Page 13, line 239-242) and discuss the C-SAP importance in Discussion section (see Page 17, line 324-328.).

Comment 3: Please state that the characteristic of patients with GERC whose C-SAP is positive by comparing to those without C-SAP (i.e. prevalence of symptoms of GERD, cough duration, and subjective cough frequency).

Reply 3: We compared the characteristics between GERC patients with positive and negative C-SAPs as Reviewer 1 suggested, and found more GERC patients (29/35) with positive C-SAP 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%, $\chi^2=9.449$, $p=0.002$). However, we did not find any other significant difference between the two groups.

Changes in the text: We have added the statement in the Results section (see Page 13, line 237-245), and discussed the findings in the Discussion section (see Page 16, line 316-318).

Comment 4: Did non-acidic reflex evoke cough more frequently than acidic reflex?

Reply 4: Currently, there is no clear evidence to support non-acidic reflux evokes cough more frequently than acidic reflux does. Actually, acid reflux impairs esophageal mucosa severer when compared with non-acidic reflux. In the case of non-acidic reflux, esophageal and cough hypersensitivity as well as airway inflammation may explain the mechanism underlying cough (World J Methodol. 2015;5(3):149-56. Respirology. 2011;16(4):645-52.). Our previous study showed that non-acid GERC accounts for 43.7% of all GERC (Clin Respir J, 2015; 9(2):196-202.). With the wide use of MII-pH, non-acid reflux has been increasingly detected in GERC patients and thus received more attention in recent years, as supported by the fact non-acid GERC accounts for 58.5% in the present study.

Minor comments:

Comment 1: Please remove Figure 4 because it is overlapping Tables 2 and 3.

Reply 1: We have removed the Figure 4 as required.

Comment 2: It might not be easy to understand Figure 3 for readers. Venn's diagram might be better to explain figure legends.

Reply 2: We have transformed the Figure 3 into Venn's diagram as required.

Changes in the text: We have modified the figure legend as advised (see Page 24, line 490-493).

Reviewer B

This study compares the diagnostic value of SAPs involving only cough (C-SAP) or total symptoms (T-SAP) for gastroesophageal reflux-induced cough (GERC). The

results showed that the positive rates of C-SAP and T-SAP were comparable, but C-SAP exhibited a higher sensitivity and similar high specificities, indicating C-SAP is superior to T-SAP for the identification of GERC. I have a few concerns:

Comment 1: According to the definition of authors, the total symptoms included cough and typical reflux-related symptoms. However, the reflux-related symptoms included regurgitation, heart burn, belching, nausea, chest pain, throat clearing, throat pain. These symptoms (nausea, chest pain, throat clearing, throat pain) are not really typical reflux symptoms. If only the typical symptoms were enrolled for analysis, the results may be different. Can the authors provide the results?

Reply 1: Thank Reviewer 2 for his/her excellent comment. Actually, we enroll all the reflux-related symptoms into the calculation of SAP as Reviewer 2 points out. Despite some symptoms such as nausea, chest pain, throat clearing and throat pain may not be really typical reflux symptoms, we usually look them as a typical reflux symptom during SAP calculation in daily clinical practice, as indicated in Figure 2A in the manuscript. Thus, we never calculate the SAP only involving regurgitation and heartburn, which is not consistent with routine work in gastroesophageal motility laboratory, and nor with our research purpose in the study.

Changes in the text: To avoid misunderstanding, we have replaced the typical reflux symptoms with other reflux-related symptoms. The revision can be seen by red mark in the revised manuscript.

Comment 2: In the screening, other possible causes of chronic cough had been ruled out, including cough variant asthma, upper airway cough syndrome, and eosinophilic bronchitis after a sequential laboratory work-up (methods), however, among 40 non-

responders, there were cough variant asthma (n=12), upper-airway cough syndrome (n=8), eosinophilic bronchitis in (n=7), atopic cough (n=5), it seems difficult to understand, and how those patients could be diagnosed based on the therapeutic response to subsequent empirical treatment?

Reply 2: We apologize for any confusion due to the unclear description in the exclusion and diagnosis of other cough causes. In the screening stage, the other common causes of chronic cough were excluded based on the negative laboratory findings such as bronchial challenge, induced sputum cytology and sinus CT scan. However, laboratory investigations have their inherent limitation of false positive and negative findings (Chin Med J (Engl). 2011;124(24):4138-43.). Among 40 non-responders to intensified anti-reflux therapy, we sequentially gave the empirical therapy targeting the other common causes of chronic cough even though the initial negative laboratory findings. When patients' cough responded to inhaled salbutamol plus oral theophylline, cough variant asthma was considered since cough responsive to bronchodilators was an essential feature of cough variant asthma (Respir Investig. 2021;59(3):270-90.); when responded to first generation of antihistamines/decongestants, upper airway cough syndrome was considered because silent upper airway cough syndrome may not present with the other symptoms and medical history related to rhinitis or nasal disorder (Chest. 2006;129(1 Suppl):63S-71S.); when responded to inhaled or systematic corticosteroids but resistant to bronchodilators and with a mild increase of eosinophils in induced sputum (more than 1% but less than 2.5%), atypical eosinophilic bronchitis was considered (Chest. 2010;138(6):1418-25.); and when responded to second generation of antihistamines, atopic cough was considered (Respir Investig. 2021; 59(3):270-90. J Thorac Dis. 2018;10(11):6314-6351.). The empirical therapy specific to the cause of chronic

cough is useful for management of chronic cough, especially for common causes of chronic cough including GERD established by PPI trials (Allergy Asthma Proc. 2011; 32(3):193-197.). Since the cause of chronic cough responsive to specific empirical treatment is suggestive but not definite, we described the patients' cough could be explained by causes such as cough variant asthma, did not mean the causes were definitely established. Since this issue was not a purpose of study, we did not discuss it in the manuscript.

Changes in the text: We have modified our text as advised (see Page10, line 168-173).