

Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-22-1046>

First-Round Peer Review

Reviewer A

Comment 1: In the abstract, the conclusion reads confusingly (“Despite a higher proportion of...with suspected GERC), which looks like none of these uneven variables have predicative value.

Reply 1: Thanks for your comments. We found the proportion of a few variables was higher in suspected GERC patients who responded to anti-reflux treatment, the proportion was not very high, and it is not certain whether these variables, especially nasal itching, were related to reflux. We think the predictive value of these variables for anti-reflux efficacy needs to study further in the future. In order to reduce the confusion for readers, we have modified the conclusion mildly as follows: *“A few clinical features rather than reflux-related symptoms might indicate response to anti-reflux treatment in patients with suspected gastroesophageal reflux, further study is needed for the predictive value.”*

Changes in the text: Line 41-Line 43

Comment 2: Instead of the capital P value, please use “p”.

Reply 2: Thank you for pointing out the mistakes. We have changed the capital P to the lowercase ‘p’.

Changes in the text: Line 38 - Line 40, Line 450, Line 483, Line 486, Line 489- Line 494

Comment 3: Line 57. “Overt anormal”? Just use “abnormal” instead.

Reply 3: Thanks for your suggestion. The “overt” has been deleted.

Changes in the text: Line 334

Comment 4: Line 64. Which kind of PPI? Did all the patients have a uniform prescription of PPI? Also, Dominic Sykes and Alyn Morice recently reported that two-thirds of patients with refractory respiratory symptoms had oesophageal dysmotility (Sykes DL, Crooks MG, Hart SP, Jackson W, Gallagher J, Morice AH. Investigating

the diagnostic utility of high-resolution oesophageal manometry in patients with refractory respiratory symptoms. *Respir Med* 2022; 202: 106985). That the drug actually worked was PPI or prokinetic agents is a question worthy of further thought.

Reply 4: The PPIs that were used in this study were omeprazole in most patients and esomeprazole in a few patients. The drug name, dosage, and times were added in the Method section. We agreed that many patients with reflux might have oesophageal dysmotility, which was also reported in other studies. Therefore, we continue to use the combination treatment of PPI plus prokinetic agents in patients with GERC in our clinical practice based on the National Guidelines for Diagnosis and Management of Cough in China. As you pointed out, we could not determine whether the efficacy of anti-reflux was due to PPI or prokinetic agents. PPI, in the current study, we think that the two drugs worked together in most patients. Further study is needed.

Changes in the text: Line 346- Line 347

Comment 5: According to the 2018 Lyon Consensus, new parameter “AET” and “total reflux episodes” were also come up to definite acid reflux. I’m wondering why the authors did not mention them.

Reply 5: We begin to establish our chronic cough database after 2000, DeMeester score and Symptom Association Probability (SAP) are recommended as primary diagnostic variables at that time according to the National Guidelines on the Diagnosis and Management of Cough in China (1). AET and the number of reflux episodes were not recorded in our early database, and it is too difficult to find these data from early hard disks because of the upgrading of computers.

Changes in the text: None

Comment 6: Line 81. Please use “ $p < 0.05$ ”.

Reply 6: We have corrected it.

Changes in the text: Line 450

Comment 7: Line 84. “were” should be “was”.

Reply 7: We have corrected it.

Changes in the text: Line 453

Comment 8: Patients with laryngeal symptoms in this study (approx. 40%-50%) seem

fewer than other studies (> 90%).

Reply 8: In our study, we found that the prevalence of a single pharyngeal symptom was 40-50% whereas the prevalence of total pharyngeal symptom, i.e., report of at least one pharyngeal symptom (including tickle below the throat, tickle below the throat, pharyngeal foreign body sensation, frequent throat clearing, mucus adhesion to the throat), was nearly 90%. These results were in line with previous research (2,3).

Changes in the text: Line 493-Line 494

Comment 9: Maybe worthy to compare HRM results, if possible.

Reply 9: Thanks for your suggestion. HRM might unravel the association between impaired motility and treatment response, we are regretful that HRM is not available in our hospital. The discussion for oesophageal manometry was added in the Discussion section.

Changes in the text: Line 1099 - Line 1103

Reviewer B

Comment 1: Defining outcomes – e.g how are outcomes such as 'favourable response' defined?

Reply 1: Thanks for your suggestion. We defined the response based on the reported outcome after 2 weeks of anti-reflux treatment in the current study. The definition of response has been modified in the Methods section.

Changes in the text: Line 440

Comment 2: There is a lack of validated questionnaires (e.g VAS or LCQ) or objective tests (e.g objective cough monitoring or tussive challenge) to define if patients have responded or not. This significantly reduces the validity and impact of the results.

Reply 2: Thanks a lot for your comment. This was a retrospective observational study. We feel regretful that VAS and LCQ were not fully recorded for all patients in our database. Thus, a self-reported resolve of cough was used as an outcome instead. Subsequent patients that would be recruited in our database will be evaluated by validated questionnaires and objective tests.

Changes in the text: None

Comment 3: The large number of variables compared means that false positives should be expected with a significance cut-off of $p < 0.05$. This should be discussed.

Reply 3: Thanks for your suggestion. We try to find a few useful clinical features to predicate the response of anti-reflux treatment, a lot of variables are compared in the current study. Indeed, we could not rule out completely the possibility of false positives. We added discussion according to your suggestion.

Changes in the text: Line 1101 - Line 1103

Comment 4: From where does the decision to use PPI and prokinetics come from? Is this evidence / guideline based? Which PPI or prokinetic was used?

Reply 4: PPIs plus prokinetics had been recommended as first-line treatment in national guidelines on diagnosis and management of cough in China and the American College of Chest Physicians (ACCP) Clinical Practice Guideline (4-9). The PPIs used in this study were omeprazole or esomeprazole. The prokinetics we used were domperidone in most patients or mosapride in a small number of patients. The drug name, dosage, and frequency were added in the Method section.

Changes in the text: Line 346-Line 347

Comment 5: Punctuation and grammar need considerable review.

Reply 5: Thanks a lot for your careful review. Punctuation and grammar have been checked and corrected.

Changes in the text: Line 35, Line 159, Line 348, Line 453, Line 458, Line 517-Line 519, Line 526, Line 528

Comment 6: Punctuation around references needs to be consistent.

Reply 6: Punctuation around references has been checked and corrected.

Changes in the text: Line 154, Line 161, Line 162, Line 165- Line 168, Line 170, Line 335, Line 339, Line 340, Line 527, Line 682, Line 684-Line 686, Line 696, Line 697, Line 883, Line 884, Line 886, Line 891, Line 893, Line 894, Line 899, Line 1093, Line 1097

Comment 7: Grammar around plurals needs review, as there are frequent errors.

Reply 7: I am sorry for our carelessness. Thank you. The grammar around plurals has been checked and corrected.

Changes in the text: Line 35, Line 159, Line 338, Line 518, Line 519, Line 528

Comment 8: Multiple sentences are too long and difficult for readers to comprehend. Consider shortening.

Reply 8: Thanks for your suggestion. Several long sentences have been shortened.

Changes in the text: Line 153-Line 154, Line 165, Line 1090, Line 1098- Line 1099

Comment 9: Consider subheadings within Results to break it up.

Reply 9: Thanks a lot for your suggestion. Subheadings were added to break up results.

Changes in the text: Line 456, Line 509-Line 510, Line 516

Comment 10: Line 31; Unclear if GERD or chronic cough impair quality of life.

Reply 10: Thanks for pointing out the mistakes. GERD is one of the common causes of chronic cough. Previous studies showed that chronic cough could impair quality of life, so could GERD (10,11). In this study, “GERD could impair the quality of life” was reserved. Statements and references have been corrected.

Changes in the text: Line 154

Comment 11: Line 33; Induced sputum is not routinely recommended in guidance, nor is it widely available clinically.

Reply 11: Indeed, induced sputum test is not routinely recommended in ACCP and ERS guidelines or widely available clinically. However, it is recommended as the first-line investigation in Chinese guidelines on cough, considering airway eosinophilia-related conditions are very common in chronic cough patients, and induced sputum test is conducted as routine tests, approximately 7000-8000 induced sputum tests are finished annually in our center. If a properly induced sputum test could not be conducted, empiric treatment of corticosteroids should be the next step (5).

Changes in the text: None

Comment 12: Line 36; Expand on "few clinical features could indicate single common causes of chronic cough".

Reply 12: Thanks for your advice. We found that a few clinical features could indicate single common causes of chronic cough, such as nocturnal cough for cough variant asthma, postnasal dripping and history of sinusitis for upper airway cough syndrome, heartburn, belching, acid regurgitation and cough after meals for GERD. These sentences have been added to the Introduction section.

Changes in the text: Line 159- Line 161

Comment 13: Line 38-41; Long sentence, consider revision. Does guidance suggest offering empiric treatment of PPI to those in who other conditions have been excluded?

Reply 13: Thanks for your comment. This long sentence has been shortened and revised. According to the American College of Chest Physicians (ACCP) Clinical Practice Guideline for cough due to GERD (4,12) and National Guidelines of Diagnosis and Management of Cough in China (1), cough due to GERD should be considered if chronic cough patients present with typical reflux-related symptoms, or had no evidence of other common causes of chronic cough. For these patients, anti-reflux treatment was recommended. These contents are presented in Recommendations No.3 in ACCP cough guideline 2006 (12) and in Table 1 in ACCP cough guideline 2016 (4).

Changes in the text: Line 165

Comment 14: Line 43; How do you define favourable response?

Reply 14: As we mentioned in Reply 1, the response was defined as self-reported resolution of cough after 2 weeks of anti-reflux treatment. The definition of response has been elaborated and modified in the Methods section.

Changes in the text: Line 440

Comment 15: Line 68; How do you define if cough has resolved? Patient or clinician reported? PRO? Objective cough counts?

Reply 15: As we mentioned in Reply 1, the resolution of cough was defined based on the patient-reported outcome of cough after 2 weeks of anti-reflux treatment.

Changes in the text: Line 440

Comment 16: Line 87; Interesting that patients are younger and majority male, in comparison to usual chronic cough cohort (older, majority female). This needs comment in the discussion. Do patients with suspected GERD have a different demographic?

Reply 16: The demographic characteristics of the chronic cough population in China are different from those of the western chronic cough population. In China, we found that patients with chronic cough had a roughly equal sex distribution and a middle-aged predominance, which was contrary to an older female predominance in chronic cough patients in Western countries (13,14). The demographic characteristics that patients with suspected GERD were predominantly younger and majority male in our study was roughly in line with the previous study (15). Since the demographic characteristics of chronic cough patients in China have been reported in another paper, we did not discuss

this question in this study.

Changes in the text: None

Comment 17: Line 90; How is 'cough resolved' defined.

Reply 17: As we mentioned in Reply 1, the response was defined as patient-reported resolution of cough after 2 weeks of anti-reflux treatment. The definition of response has been elaborated in the Methods section.

Changes in the text: Line 440

Comment 18: Line 113; Mix of figures and words for numbers, try to be consistent. Do figures relate to responders?

Reply 18: Thanks for your comment. The sentence has been revised into “Among 94 responders, 37 (39.4%) patients had both typical reflux-related symptoms and abnormal pH value monitoring results, 13 (13.8%) and 27 (28.7%) patients had typical reflux-related symptoms or abnormal pH monitor results alone, respectively, and 17 (18.1%) had neither of them.”

Changes in the text: Line 518- Line 520

Comment 19: Line 114; Revise grammar / punctuation (e.g 'and' after full stop).

Reply 19: Thanks for pointing out the errors. This sentence has been revised.

Changes in the text: Line 520

Comment 20: Line 122; Repetition of information from before. Not clear what is being compared (a higher proportion of ... compared to ...).

Reply 20: The repetition is used for subgroup analysis. We compared the clinical features between responders and non-responders who were diagnosed as GERC through 24-hour pH value monitor. According to ACCP clinical practice guidelines for GERC, for patients who failed to improve with an intensive anti-reflux diet, lifestyle modification, maximum acid suppression, and prokinetic therapy, anti-reflux surgery could be considered. This comparison in patients with the confirmed diagnosis was to discriminate specific groups who would respond to anti-reflux therapy or probably respond to anti-reflux surgery. However, we did not identify any useful clinical features.

Changes in the text: None

Comment 21: Line 123; 'Nearly significant' is not an appropriate term. Pharyngeal foreign body did not reach significance ($p>0.05$).

Reply 21: Thanks for pointing out the mistakes. The sentence “*and a nearly significant lower proportion of pharyngeal foreign body sensation (20.0% vs. 41.4%; $p = 0.061$)*” has been deleted.

Changes in the text: Line 522

Comment 22: Line 137; Unless previous studies cited were in your centre, it is unclear why temporal change in the underlying diagnosis in your centre should affect response to anti-reflux therapy.

Reply 22: Thanks for pointing out this. The previous study we cited was conducted in our center. Due to the promotion of Chinese guidelines on cough, more patients with common causes of chronic cough might be diagnosed and treated successfully in primary or secondary health care, which might result in an increasing number of patients with unexplained chronic cough or refractory chronic cough patients in our clinic. To make readers understand easily, “other center” has been changed to “primary care or secondary health care”.

Changes in the text: Line 687, Line 688

Comment 23: Line 142; How is 'partial response' to therapy defined?

Reply 23: If patients were relieved from cough to some extent but without complete resolution after 4 weeks of anti-reflux, partial response was defined.

Changes in the text: None

Comment 24: Line 148; Which symptoms scores? For GERC?

Reply 24: The symptom scores evaluated the severity of reflux-associated symptoms. This study found that symptom scores were not associated with definite, sustained improvement in cough for >3 months. In this retrospective study, symptom scores were not clarified. To make it easier for readers to comprehend, the symptom scores were further elaborated on in the Discussion section.

Changes in the text: Line 694, Line 695

Comment 25: Line 150; This sentence does not make sense, needs review of structure and grammar.

Reply 25: Thanks for your suggestion. The sentence has been revised.

Changes in the text: Line 696

Comment 26: Line 186; Concomitant oesophageal manometry would also be useful, should be commented on.

Reply 26: Thanks for your comments. The discussion on oesophageal manometry was added.

Changes in the text: Line 1091, Line 1092

Comment 27: Line 193; It is not correct that 'there are no useful clinical features', more that 'this study did not identify any useful clinical features'

Reply 27: Thanks for pointing out the mistakes. The conclusion has been revised.

Changes in the text: Line 1099-Line 1102

Comment 28: Study has potentially useful conclusions, however revisions are required.

Reply 28: Thanks for your suggestion. We have revised the conclusion to “*A few clinical features rather than reflux-related symptoms might indicate response to anti-reflux treatment in patients with suspected gastroesophageal reflux, further study is needed for the predictive value*”.

Changes in the text: Line 1099-Line 1102

Comment 29: Please review specific comments as above. The writing style, grammar and punctuation need considerable review. How you defined outcomes such as responders/non-responders require explanation. Is there scope to include validated questionnaires/outcomes e.g VAS, LCQ, cough monitoring? Possible false positive biases should be discussed.

Reply 29: Thanks a lot for your comments and suggestions. We have reviewed the comments thoroughly. The writing style, grammar, and punctuation have been revised. Please see our reply about the definition of outcomes above (Reply 14 and 15). Possible false positives bias has been discussed in the Discussion section.

Changes in the text: Line 440, Line 1101-Line 1105

Reference:

1. Asthma Workgroup of Chinese Society of Respiratory Diseases (CSRD) CMA. [Guidelines for diagnosis and management of cough (2015)]. Zhonghua Jie He He Hu Xi Za Zhi 2016;39(05):323-354.
2. Yang C, Feng Z, Chen Z, et al. The risk factors for urinary incontinence in female adults with chronic cough. BMC Pulm Med 2022;22(1):276.
3. Song W-J, Kim J-Y, Jo E-J, et al. Capsaicin cough sensitivity is related to the older female predominant feature in chronic cough patients. Allergy, asthma & immunology research

- 2014;6(5):401-408.
4. 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(6):1341-1360.
 5. Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129(1 Suppl).
 6. Asthma Group of Chinese Thoracic S. [Chinese national guideline on diagnosis and management of cough(2021)]. *Zhonghua Jie He He Hu Xi Za Zhi* 2022;45(1):13-46.
 7. Asthma Workgroup of Chinese Society of Respiratory Diseases (CSRDCMA). [Guidelines for diagnosis and management of cough (draft)]. *Zhonghua Jie He He Hu Xi Za Zhi* 2005;28:738-744.
 8. Asthma Workgroup of Chinese Society of Respiratory Diseases (CSRDCMA). [Guidelines for diagnosis and management of cough (2009)]. *Zhonghua Jie He He Hu Xi Za Zhi* 2009;06:407-413.
 9. Asthma Workgroup CSRDCMA. The Chinese national guidelines on diagnosis and management of cough (December 2010). *Chin Med J (Engl)* 2011;124(20):3207-3219.
 10. French CL, Irwin RS, Curley FJ, Krikorian CJ. Impact of chronic cough on quality of life. *Arch Intern Med* 1998;158(15):1657-1661.
 11. Kanemitsu Y, Kurokawa R, Takeda N, et al. Clinical impact of gastroesophageal reflux disease in patients with subacute/chronic cough. *Allergol Int* 2019;68(4):478-485.
 12. Irwin RS. Chronic cough due to gastroesophageal reflux disease: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129(1 Suppl):80S-94S.
 13. Morice AH, Jakes AD, Faruqi S, et al. A worldwide survey of chronic cough: a manifestation of enhanced somatosensory response. *Eur Respir J* 2014;44(5):1149-1155.
 14. Lai K, Long L, Yi F, et al. Age and Sex Distribution of Chinese Chronic Cough Patients and Their Relationship With Capsaicin Cough Sensitivity. *Allergy Asthma Immunol Res* 2019;11(6):871-884.
 15. Xu X, Chen Q, Liang S, Lv H, Qiu Z. 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(6):1264-1270.

Second-Round Peer Review

Reviewer A

Comment 1: Use of past tense not correct - implies that things have changed now, use present tense as below:

Line 21 "...patients respond to anti-reflux treatment."

Line 48 "GERC accounts for"

Line 60 "is recommended"

Reply 1: Thanks for pointing out the mistakes. The manuscript has been corrected according to your suggestion.

Changes in the text: Line 22. Line 55. Line 70.

Comment 2: Line 66 "predict" (not predicate).

Reply 2: Thanks for your suggestion. We have changed “predicate” to “predict”.

Changes in the text: Line 77. Line 286. Line 292.

Comment 3: Line 68 Full stop missed.

Reply 3: Full stop have been added.

Changes in the text: Line 78.

Comment 4: Line 80 "in a subset of patients" (instead of in a part).

Reply 4: We have corrected it.

Changes in the text: Line 88.

Comment 5: Line 156 Is it correct that "more than half of patients benefited from anti-reflux therapy after patients who had evidence of reflux were ruled out"? So >50% of those without reflux benefited from Tx? Is this from -ve 24hr testing? Or a typo ie is it meant to be "no evidence of reflux"?

Reply 5: Thanks a lot for your comment. It is a typo. We have revised the sentence to “In this study, we found that more than half of patients benefited from anti-reflux therapy 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”.

Changes in the text: Line 181-184.

Comment 6: Line 198 Punctuation "reflux, nasal itching, and tickle in the throat"

Reply 6: We have corrected the punctuation.

Changes in the text: Line 261

Comment 7: Line 208 You say "As mentioned above.." but I can not find any mention of stopping treatment after "4 weeks" even though you mention how in primary care treatment may be stopped too early.

Reply 7: Thanks for pointing out the mistakes. We have revised the sentence to “In our clinic, if cough did not improve after four weeks of anti-reflux empirical therapy, anti-

reflux treatment would end usually.

Changes in the text: Line 280-281.