Peer Review File

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First Round Peer Review

Reviewer A

Major comments

Comment 1:

The performance ability (sensitivity etc.) of CXR has been reported. My understanding of the study design is that the studied population is a selected cohort who underwent both CXR and CT based on the criteria described on pg 3 lines 67-69. The performance ability of CXR reported therefore does not apply to the entire unselected chronic cough cohort. The pre-test probability was not that of an unselected chronic cough cohort. This should be discussed more clearly in the discussion and the conclusion of the abstract.

Reply 1:

Thank you for this prompt remark. Indeed, the study included only adults with CC, who were referred to cough clinic and we did not include patients with CC, who were successfully treated by GPs. Following your comment, we added this information in the title, abstract (page 2, line 35 and 50), methods (page 4 line 111), discussion (page 9/10, line 265-271) and conclusions (page 12, 365,368) . It has also been mentioned in the limitations of the study in the original version of the manuscript.

Changes in the text:

We modified the title (page 1, line 1), abstract (page 2, line 35 and 50), methods (page 4 line 111), discussion (page 9/10, line 265-271) and conclusions (page 12, 365 and 368).

Comment 2:

Following on from the previous comment, it may be an overstatement to define the

outcomes of the studies as diagnostic accuracy of CXR in management of CC as only a selected cohort was assessed. The impact of CXR in the management of patient who did not require a CT was not assessed in this manuscript.

Reply 2:

Thank you for your apt comment. I understand it refers to two aspects: 1. The study included patients referred to cough clinic and 2. not all patients in the study had chest CT performed. As per point 1: the reason for referring patients to a cough clinic is an unsatisfactory response to antitussive treatment in GP practice. Thus our patients are these with difficult-to-treat cough. Initially, we do not treat all of them as refractory CC, as many of them did not have all diagnostic tests or trials of therapy before referral. As per point 2: indeed, not all patients had thoracic CT performed, but the criteria to refrain from chest CT were very sparse (page 5, line 123-135). The most important criterion to abandon CT was disappearance or reduction of cough as a result of causal treatment. If such a situation had occurred, the indication for chest CT became unjustified. To sum up both points, we emphasized the limitations by specifying our cohort in the title (page 1, line 1), abstract (page 2, line 35 and 50) and main text (page 4 line 101, page 4 line 111, page 9/10 line 262-271, page 12 line 365 and 368).

Changes in text:

We add information in the title (page 1, line 1), abstract (page 2, line 35 and 50) and main text (page 4 line 101, page 4 line 111, page 9/10 line 262-271, page 12 line 365 and 368).

Comment 3:

Were the respiratory specialist, who assessed the CXR and CT, also involved in the clinical management of the patients? If so, was there any blinding when the CXR and CT were reviewed please?

Reply 3:

Thank you for this important question. As this study was a retrospective analysis of our real life practice, the radiologist was blinded to patients' diagnosis related to CC and respiratory specialists were involved in management of patients. In response to your question, we added information in page 5 line 124-125.

Change in the text:
We added information on page 5, line 124-125.

Comment 4
The criteria used to proceed to CT in this study seem understandably very similar to the ERS cough guidelines: abnormal CXR/physical examination and refractory to treatment. I note the authors also included risk of lung malignancy as a criterion which would seem logical to all respiratory physicians. Would the authors therefore feel that their current study in essence support the ERS cough guidelines recommendations please? If so, it may be worth discussing further in the discussion as the ERS guidelines do clearly state that the recommendation is only conditional. The study is potentially providing further support for the ERS guidelines recommendation.

Reply 4:
Thank you for this comment. We think that CT should be recommended not only if CXR or physical examinations reveal any abnormalities (what stands in ERS guidelines), but also in all patients with refractory, idiopathic CC or patients with risk for lung cancer. Such broader approach seems more consistent with ACCP recommendations (2006, 2018). Following your question, we added comment in discussion (page 9, line 240-242)
Change in text:
We added a comment in the discussion (page 9, line 240-242)

Comment 5:
Pg 9 paragraph 4 ("We believe the high...") discussed how CT may accelerate the diagnostic process and help to avoid patient anxiety from a CXR report. I do not understand how this could be avoided without widespread implementation of CT chest. Meanwhile, the findings of the study are in a selected cohort of patients. How do the authors propose CT chest use can be implemented to avoid anxiety from a CXR report?

Reply 5:
Thank you for raising this point. We just wanted to emphasize the high percentage of false positive CXR among our patients with CC. It justifies performing CT, as results

of thoracic CT may change further diagnostic steps. In response to your doubts we deleted questionable sentence in this paragraph.
Change in text: We deleted one sentence in page 10, last paragraph (line 296-318).

Minor comment

1. I am not entirely sure if there is a typographical error on pg 8 line 216-217.

Reply 1: thank you very much for you remark. We tried to identify the potential typing error, and we could only come up with 2.3 fold (i.e. 2.3 times higher), so we changed it to 2.3-fold. We hope that this is what the Reviewer was referring to.
Change in the text: we corrected page 9, line 237

2. In Figures 3 and 4, it would be useful not to use the abbreviations NS, ES and S. It would help any readers who simply want to quickly review the figures.

Reply 2:
Thank you for this remark. We have changed it according to your suggestions.
Change in text: Full expressions instead of abbreviations were added in Figure 3 and 4

Reviewer B

In this manuscript, authors discussed the impact of chest CT scans on management of patients with chronic cough. This manuscript is of great importance and instructive for usefulness of chest CT scans in management of chronic cough. I have a few comments.
Comment 1:
It is not easy to determine what is being “significant changes” in CXR. Does “significant change” and “normal” mean the same finding in this study? It should be useful if you add the details in your definition of “significant changes”.

Reply 1
Thank you for this important remark. We used “significant change in CXR” in the context of abnormalities potentially related to CC. Following your question, we changed significant change for significant abnormalities (page 5, line 122)

Change in the text: We changed text (page 5, line 122)

Comment 2

It is important to clarify what was definition for abnormalities in chest CT scans. It is not clear in some cases. For example, does bronchiectasis all related to chronic cough? (Some patients with bronchiectasis did not complain chronic cough.) The authors need to confirm whether abnormal findings of chest CT scans are critical lesions related to cough.

Reply 2:

Thank you for this important comment. We share your doubt. As cough may be a symptom of many pulmonary and extra pulmonary diseases, we assume that any lung, mediastinal, heart or esophagus (organs innervated by vagus nerve) abnormalities found in either CXR or chest CT may be related to CC. The decrease of cough due to treatment related to pathologies found in chest imaging was treated as final confirmation of causal relationships (information in Table 2) However, not in all patients treatment was possible or effective (e.g. patients with breast cancer metastases to the lungs, patient with sarcoidosis or few patients with hiatal hernia) but it does not mean that there was no relationship between abnormalities in thoracic CT and cough. As we supposed that in some cases treatment might not be possible or effective, we defined significant abnormalities as ones influencing on identifying causal diagnosis or modification of further CC diagnostics or management. Following your remark, we changed the explanation of significant abnormalities in the text (page 5 line 122-123).

Change in the text: We modified the text on page 5, line 122-123

Comment 3

Pre-test clinical suspicion based on patient's medical history (for example, cancer, immunocompromised, and autoimmune etc.) is likely to affect the outcome or probability of abnormal chest CT. There are baseline factors such as underlying illnesses that may potentially influence the decision and outcome. Was there an evaluation of the patient's past chest CT scans?

Reply 3

Thank you for raising this valuable point. Following your question, we added information about history of malignancy, autoimmune diseases in the text (page 7, line 187-188). We also added information about evaluation of past chest CT scanning, if available (page 6, line 150-151) .

Change in the text: We added information on page 7, line 187-188 and page 6, line 150-151

Comment 4

Please add references in Table 1 if you any references.

Reply 4

Thank you for this important comment. We added references both in the text and Table 1 (Collins J, Stern EJ. Chest Radiology, the Essentials. II ed.,Lippincott Williams & Wilkins, Philadeplhia 2008; Expert Panel on Thoracic Imaging, Kuzniewski CT, Kizhner O, Donnelly EF, et al. ACR Appropriateness Criteria® Chronic Cough. J Am Coll Radiol. 2021;18(11S): S305-S319.)

Change in the text: We added references in the text (page 6, line 153) and Table 1 (page 20, line 527)

Comment 5

Table 2: The authors need to check some cases in Table 2. For example, in GERD cases, clinician can consider GERD medications without chest CT scan if there is no improvement of chronic cough despite three months chronic cough treatment. Will Chest CT scan clearly help these patients for changing their management?

Reply 5

Thank you for your remark. The patients with suspicion of GER were treated with diet and PPI, but if hiatal hernia was found in CT, treatment of GER was intensified. In 3/8 patients in whom features of hiatal hernia were found in CT, intensification of anti-reflux therapy led to decrease of cough. The other 5 patients were referred to consider surgical treatment.

Change in the text: none

Comment 6:
Page 5 line 110-111. Please clarify this sentence.

Reply 6:
We assume that the Reviewer refers to the sentence about the interval between CXT and CT.
The median time-interval between performing CXR and CT was 11 weeks as we managed patients according to our step-wise protocol shown in e-Figure 1. CXR was performed in the initial step, while CT used to be perform later (step 3).
Should this modification not be in line with the expectations of the Reviewer, we are ready to modify the text according to the Reviewer's suggestions.
Change in the text: we added reference to e-Figure 1 page 5, line 120

Second Round Peer Review

Comment 1
This is a retrospective study, but it appears that CT scans were performed strictly following the predetermined criteria (line 92-97 and 123-129). It is difficult to believe that the rules were strictly followed in usual clinical practice, just as they can be done in a prospective study.

Reply 1:
Thank you for very apt remark. In fact, this study was performed in our cough center as a part of larger project on different aspects of chronic cough (CC) diagnosis and therapy. As the diagnostic work-up of patients with CC can be quite complex, we developed and implemented a four-steps diagnostic algorithm (e-figure 1) based on previous recommendations on CC management (ACCP 2006, 2018). Thoracic CT in patients with CC and relevant smoking history or other risk factors for lung cancer has been included in the algorithm. This at least in part resulted from a necessity of particular vigilance due to high incidence of lung cancer in Central East Europe.

Specific indications for thorax CT are presented in the manuscript. Besides, this study had been planned as a continuation of our previous study on the role of imaging in CC diagnosing (Truba et al., Adv Resp Med 2018). Therefore, we made every effort to strictly follow the inclusion criteria. As detailed study protocol has neither been developed before the study onset nor register in clinical trial registry, we felt we should not label our study as prospective.

Change in text: none

Comment 2

A main concern in determining the positivity (line 99) is that the diagnosis does not always indicate the cause of chronic cough. Without such consideration, this is too simplistic to calculate the diagnostic utility. There were 8 cases with hiatal hernia, but in many cases, it is not related to chronic cough. Also, line 272-273 is not supported by firm evidence.

Reply 2

Thank you for this comment. We fully agree with your opinion. The major problem in interpretation of the results of diagnostic tests in patients with CC is whether there is a causal relationship between abnormal finding and CC or there is a simple coincidence with no causal relations. This refers not only to radiological findings but also to other tests, e.g. pH- or impedance monitoring, videolarynogoscopy, allergy tests. Bearing in mind the above uncertainty of the true significance of the diagnostic test results we assumed that the cure or improvement in the level of CC after specific therapy is a necessary prerequisite to consider the abnormality as the cause of CC (information in Table 2). Unfortunately, the specific therapies could not be applied to all patients, including those with pulmonary metastases of breast carcinoma, patient with sarcoidosis not requiring systemic corticoids or a few patients with hiatal hernia. This, however, does not prove that there was no relationship between CT abnormalities and CC. Moreover, as we supposed that in some cases treatment might not be possible or its effect might be limited, we extended our definition of potential causal relationship to those situations when CT findings changed further diagnostic approach or management. In this context, we would like to stress that in all patients with CC and

hiatal hernia, treatment of GER was modified (intensified). In 3/8 patients intensification of anti-reflux therapy led to cough reduction (Table 2) while the remaining 5 patient were referred to consider surgical treatment. To underline the difficult issue of the causal relationship between CT findings and CC, a sentence pointing this problem was added to the study limitations. We sincerely hope, the Reviewer will be satisfied with this amendment.

Change in text: We added a sentence in limitations of the study, page 11, line 307-310 in version with track changes.

Thank you for pointing out our inaccuracy in line 272-273. We confirm that the statement represented our opinion and was not supported by the study results (*Indeed, in our daily practice, we observe that a significant proportion of patients with CC are referred to thoracic CT scanning during the early steps of the diagnostic work-up undertaken by respiratory physicians, usually before they are referred to our cough center).* In response to your doubts we decided to delete the questionable sentence.

Change in text: We deleted one sentence in page 10, last paragraph (line 276).