Peer Review File

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Review Comments

Thank you for the opportunity to review this paper. The authors construct a diagnostic model to identify those with pre-COPD, small airway disease (SAD), and COPD – all among patients with chronic cough. This is a very interesting topic and identifying patients at-risk for COPD that already have symptoms is highly important for improve follow-up and intervention.

With that being said, there are significant flaws in how the authors address their findings.
First, the method use has no connection to "screening" but rather to "case finding"! The authors include only patients with symptoms from a very limited population of 200+ subjects – obviously not screening of a large population.
Second, doing a CT scan to detect pre-COPD or COPD is really not feasible as a case finding method. Spirometry, the diagnostic method for COPD or pre-COPD, is a very easy to perform toll and more accessible than CT, without radiation of course… Therefore, the authors should contextualize their study as a way to identify COPD or pre-COPD among patients that already have CT – for example those undergoing screening chest CT, which are widely done nowadays.
Having said the above, the methods are robust and of high quality given the prospective design and in-depth CT analysis. The results are also strong and indicate on a promising tool that should be validated in the future.

Reply: We appreciate the reviewer's insightful distinction between screening and case-finding. We agree that our cohort (symptomatic patients referred for CT) aligns with case-finding rather than population screening. As suggested, we have modified the expression of "screening" to clarify the study's focus on case-finding in symptomatic patients and reframed the study's purpose to emphasize utility in patients already scheduled for CT. We also clarified that spirometry remains the gold standard for pre-COPD/COPD diagnosis, and our model serves as a complementary tool for CT-screened subpopulations.
Changes in the text: We have emphasized that the study was based on the existing CT scans in the Abstract section (see Page 2, line 31-35) and the Methods section (see Page 6, line 130-131). We redefined the study value in the Abstract section (see Page 3, line 48-49), the Introduction section (see Page 6, line 117-125) and the Conclusion section (see Page 17, line 371-374). We have modified the expression of "screening" to "idenfying pre-COPD in symptomatic patients" throughout the text.

More minor issues:

1. Table 2 is too long and should include the main relevant variables with additional supplemental table for the rest. This is also true for Table 3.

Reply 1: We have divided Table 2 into into a main table focusing on whole-lung, left lung, and right lung CT parameters, while moving the results for each lung lobes to a supplemental table (Addition table 1). We have applied the same methodology to Table 3.
Changes in the text: We have streamlined Table 2 and Table 3, and the rest parameters are presented in Additional Table 1 and Additional Table 2.

2. In the multivariate analysis, did collinearity tested? especially Between the CT variables.

Reply 2: Thank you for raising this critical point. We employed the Variance Inflation Factor (VIF) for detection. A VIF value was calculated for each variable included in the multivariate model. A common threshold of VIF < 10 was used to indicate that multicollinearity was not at a level that would unduly influence the stability and interpretability of the model coefficients. All retained variables had VIF values below this threshold. Based on this analysis, we confirmed that no significant multicollinearity existed between the CT variables retained in the final model. This ensures that the independent contribution of each variable to the outcome can be reliably interpreted.
Changes in the text: We have updated the Methods section (see Page 11, line 225-226) to include Variance Inflation Factor (VIF) testing to assess multicollinearity among the predictor variables, and adjusted the final model in the Results section (see Page 12-13, line 253-266), Tables (Table 4, Table 5, Additional table 3 and Additional table 4) and Figures (Figure 1, Figure 2 and Addiitional figure 3).

3. When you note about sensitivity and specificity, this should be for a specific cutoff, which is not provided.

Reply 3: The measures of sensitivity and specificity are intrinsically linked to a specific classification cutoff point on the prediction scale, and we apologize for this omission in the previous text. We have now included this crucial detail in the revised manuscript to ensure the results are unambiguous and reproducible.
Changes in the text: We have added the cutoff point in Table 5 and Additional Table 6.

4. I think additional novel biomarkers that might be incorporated to identify patients with pre-COPD or COPD should be included in the discussion. A prospective study evaluated the nanoparticles in smokers' sputum and showed correlations with their concentrations and CAT score and pulmonary functions, making it a potential tool (DOI: 10.2217/nnm-2022-0269). This example and other should be included.
Reply 4: Thank you for your valuable suggestion. Novel biomarkers also offer promising avenues for early COPD detection. We have integrated the example of

sputum nanoparticles, along with other emerging biomarker candidates, into the Discussion section as requested.

Changes in the text: We have added the research advancements of novel biomarkers in the Discussion (see Page 15-16, line 319-331)