Peer Review File

Reviewer Comments

The article highlights the promise of radiomics in the diagnosis of pulmonary IFI as well as the potential to improve diagnostic accuracy by marrying this method with clinical variables. One methodological concern I have is the large number of patients excluded on the basis of missing data given the overall small size of the cohort.

Comment 1: On page 3, line 5, the authors should replace the phrase "immunocompromised patients" with language to specify this study is limited to patients with hematologic malignancy

Reply 1: We have modified our text as advised (see Page 3, line 5-6).

Changes in the text: "This retrospective study involved 235 patients with hematologic malignancy…"

Comment 2: On page 3, lines 21-22 it may be helpful to eliminate the phrase "overall superior" since the combined model's performance was the same as that of a senior radiologist in diagnosing IFI. The combined model outperformed a junior radiologist in discriminating IFI and bacterial pneumonia, and outperformed a senior radiologist in diagnosing bacterial pneumonia, but not IFI.

Reply 2: We have eliminated the phrase "overall superior" as advised (see Page 3, line 21-22).

Changes in the text: We deleted the sentence "The diagnostic performance of the combined nomogram was overall superior to that of the practicing radiologists."

Comment 3: On page 4, line 2, again would suggest authors replace the phrase "severely immunocompromised" with language to specify patients with hematologic malignancy.

Reply 3: We have modified our text as advised (see Page 4, line 2).

Changes in the text: "The clinical-radiomics nomogram can serve as a promising predictive tool for IFI in patients with hematologic malignancy…"

Comment 4: On page 4, lines 2-3, would avoid speculating about effects of findings on clinical outcomes as implementation of the nomogram and its effects are outside the scope of this study.

Reply 4: We have eliminated the speculation as advised (see Page 4, line 2-3).

Changes in the text: We deleted the sentence "and thus may assist clinicians in individualized treatment to improve clinical outcomes".

Comment 5: On page 7, line 9, would advise that the authors also reference the 2020 revision and update of the EORTC/MSGERC definitions: DOI: 10.1093/cid/ciz1008.

Reply 5: We have replaced the reference as advised (see Page 23, line 9-16, reference 6).

Changes in the text: Donnelly JP, Chen SC, Kauffman CA, et al. Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis 2020;71:1367-76.

Comment 6: On page 7, line 16, would advise the authors to provide further clarification of the term "incomplete clinic-etiology data." The large number of patients excluded on the basis of missing data may bias the study results. Would recommend further clarification on which data were missing, pattern of missingness, and any sensitivity analyses that may have been performed.

Reply 6: Thank you for your kind advice. In this study, we collected clinic-etiology data including basic information, comorbidities, symptoms and laboratory findings, to demonstrate the potential additional value of clinic-etiology data to improve the predictive performance. Due to the intrinsic nature of this retrospective study, many patients were excluded on the basis of missing data (such as routine blood test or C-reaction protein mg/dL) in the medical record. The detailed information on clinic-etiology data is provide in the Supplementary Table 1. We have clarified this point per your advice (see Page 7, line 17-18).

Changes in the text: "patients had incomplete clinic-etiology data (basic information, comorbidities, symptoms and laboratory findings, Supplementary Table 1) available for re-evaluation".

Comment 7: On page 7, lines 6-18, would advise the authors to clearly state how bacterial pneumonia and pulmonary IFI are being defined for this study. Based on inclusion criteria it seems bacterial pneumonia is being defined as pulmonary consolidation >5mm in diameter on CT in the presence of suspected pulmonary infection and an upper or lower respiratory culture positive for a bacterial organism,

and that pulmonary IFI is being defined as "probable" IFI according to EORTC/MSGERC criteria.

Reply 7: We added the definition of bacterial pneumonia and pulmonary IFI in the text (see Page 7-8).

Changes in the text: "All patients with proven or probable pulmonary IFI were diagnosed according to the consensus EORTC/MSG criteria. Proven IFI was defined by histopathologic evidence following percutaneous needle aspiration biopsy. Probable IFI was defined by the presence of host factors, an area of consolidation on CT, and mycological evidence of fungal infection from culture analysis of bronchoalveolar lavage fluid or serum, or microbiologic evidence of galactomannan positivity (8). Diagnosis of bacterial pneumonia was based on a positive culture of respiratory tract specimen for a bacterial organism, such as sputum or bronchoalveolar lavage fluid and pulmonary consolidation > 5 mm in diameter on CT"

Comment 8: On page 11, line 15, would advise that the authors confirm the same definitions for bacterial pneumonia and pulmonary IFI are being used in the pilot study cohort.

Reply 8: We have modified our text as advised (see Page 12, line 10-11).

Changes in the text: "The inclusion, exclusion criteria and the definitions for bacterial pneumonia and pulmonary IFI mentioned above were used in the pilot study cohort."

Comment 9: On page 16, lines 13 – 15, would clarify how the cited study defined pulmonary IFI and bacterial pneumonia and whether this may be contributing to the observed frequency of radiological findings in patients with one disease entity vs the other.

Reply 9: The definitions for bacterial pneumonia and pulmonary IFI used in our study are similar to those in the cited study. We have clarified this point per your advice (see Page 17, line 14-16).

Changes in the text: "although we used similar definitions for bacterial pneumonia and pulmonary IFI. This can be attributed to the distribution bias from different patient population."

Comment 10: On page 17, line 5, would recommend modifying the phrase "favorable classification" since this implies comparison, yet there is no gold standard test with which to compare the radiomics model's performance.

Reply 10: We have modified our text as advised (see Page 18, line 4-519).

Changes in the text: "In this study, we found that the radiomics features of pulmonary

lesions could be used to facilitate IFI diagnosis".

Comment 11: On page 18, lines 16-20, would advise the authors to either revise these statements or eliminated them altogether. The recommendation of clinical intervention is not justified by the findings of this study as prescription of antifungal therapy based on the nomogram is beyond the scope of this study. Further the authors state that early initiation of antifungal therapy on this basis will improve clinical outcomes. This statement is not justified by the evidence presented. Finally, I would advise the authors to avoid commenting on implementation of their tool since this is also beyond the scope of this study.

Reply 11: We have eliminated the description as advised (see Page 19-20).

Changes in the text: We deleted "For those with a higher risk of IFI after calculating the total points, we suggest early initiation of antifungal treatment to improve clinical outcome. Our developed combined nomogram based on easily available CT images and clinical laboratory data was applicable to implement in routine clinical practice." in the revised manuscript.

Comment 12: In the discussion section, the authors do not comment on the findings of their prospective pilot work. I would advise them to include discussion of these results.

Reply 12: We have modified our text as advised (see Page 19, line 15-18).

Changes in the text: "On the basis of our results in the prospective pilot study, the combined model performed equally well (12/15, 80.0%) in the diagnosis of pulmonary IFI as compared to a senior radiologist, and outperformed a junior radiologist in discriminating IFI and bacterial pneumonia."

Comment 13: In Table 1, a superscript "a" appears beside one of the reported p-values, yet no corresponding explanation is included in the caption

Reply 13: We have corrected the mistake in the revised Table 1. The superscript should be "*".

Comment 14: In Table 2, a superscript "a" appears beside several of the P-values, but no corresponding explanation is included in the caption.

Reply 14: We have corrected the mistake in the revised Table 2. The superscript should be "*".

Comment 15: In Table 3, please provide an explanation of the outcome used in this

regression analysis (ie pulmonary IFI) to orient the reader in their interpretation of the reported beta-coefficients.

Reply 15: To construct prediction models, the variables were enrolled into linear regression models (e.g. multivariate logistic regression). For example, a radiomics score (Radscore) was calculated for each patient through a linear combination of selected features weighted by their respective coefficients. In this study, the Radscore was calculated using the following formula:

Radscore = 4.327×original_shape_Sphericity+2.942×original_glcm_Imc1-1.747×original_glcm_Imc2+4.45×wavelet-LLH_firstorder_Kurtosis+2.004×wavelet-LLL_firstorder_RobustMeanAbsoluteDeviation+3.919×wavelet-LLL_glcm_Correlation+0.501×wavelet-LLL_glcm_JointEnergy-0.978×wavelet-LLL_glcm_Imc1+3.403×wavelet-LLL_glcm_Imc2+1.908×wavelet-LLL_glcm_MaximumProbability-2.48×wavelet-LLL_glszm_LargeAreaHighGrayLevelEmphasis+0.109×wavelet-LLL_gldm_LargeDependenceHighGrayLevelEmphasis-0.021.

These regression analysis with the reported beta-coefficients have been widely used in radiomics and AI related research.

Comment 16: In Table 3, would advise the authors to report results as odds ratios rather than coefficient values and to provide 95% confidence intervals and p-values.

Reply 16: Thank you for your advice. Odds ratios are really important variables for logistic regression models to calculate the relative risk. However, because the variables in the models were selected by the machine learning algorithm, the corresponding values (odds ratios, 95% confidence intervals and p-values) can not be provided by the R software (scikit learn package). Classically, the selected features weighted by their respective coefficients are reported in radiomics and AI related research.

Comment 17: In Table 3, to the extent possible, would replace the variable names in the Radiomics Model with ones that are easier to read. These variable names are not intuitive and can be disorienting to the reader.

Reply 17: Thank you for your advice. The variable names in the radiomics model are standard radiomics features in related research fields, to facilitate other readers to repeat the relevant experiment and generalize the reported results. Thus, the variable names are not recommended to be replaced.

Comment 18: In Table 4, would again orient the reader with respect to the outcome (pulmonary IFI). Would include positive and negative predictive values as well.

Reply 18: We have added positive and negative predictive values in the revised Figure