Peer Review File

Article information: https://dx.doi.org/10.21037/tlcr-23-171

Reviewer A

This is a very well written paper, with interesting perspectives. Actually, I think it will lead the way for new works.

Reply: Dear Reviewer, I would like to take this opportunity to express my sincere gratitude for your time and efforts in reviewing my article. Your positive feedback and encouragement have been instrumental in enhancing the quality of the final manuscript and I am truly honored to have had the benefit of your insights and encouragement.

Reviewer B

Reply：Dear Reviewer, I cannot thank you enough for your invaluable contribution to this paper.

Your thoughtful comments and suggestions have helped me to refine my ideas and articulate my arguments more clearly and convincingly. appreciate the time and energy you have invested in reading and critiquing my work, and I am impressed by your level of professionalism.

Comment 1: First, the title needs to indicate the development and validation of a diagnostic model for TMB status based on CT radiomics and clinical factors.

Reply 1: we are grateful to the reviewer by this good suggestion.

Changes in the text: we have modified our text as advised (see Page 1, line3-4): Establishing a predictive model for TMB status based on CT radiomics and clinical features of non-small cell lung cancer patients.

Comment 2: Second, the abstract needs further revisions. The background did not explain why CT radiomics can accurately predict the TMB status and what the knowledge gap is on the radiomics-based diagnostic model.

Reply 2: we are grateful to the reviewer by this good suggestion

Changes in the text: we have modified our text as advised (see Page 2, line43-46): Due to the the potential of radiomic signatures to identify microscopic genetic and molecular differences, thus radiomics is considered a suitable tool for judging the TMB status probably.

Comment 3: The methods need to describe the inclusion of subjects, assessment of clinical factors and CT radiomics, and the calculation of accuracy parameters of the diagnostic model.

Reply 3: we are grateful to the reviewer by this good suggestion

Changes in the text: we have modified our text as advised (see Page 3, line52-56): 14 Clinical features (sex, age, smoking history, allergy history,history of surgical anesthesia, family lung cancer/malignant tumor history, lymphatic metastasis, pathological type/stage/differentiation degree, multiple primary lung cancer, lesion location, multifocal lesion) related to TMB status were screened out.

Comment 4: The results need to first summarize the clinical characteristics of the study sample and the proportions of high and low TMB status.

Reply 4: we are grateful to the reviewer by this good suggestion

Changes in the text: we have modified our text as advised (see Page 3, line63-66):Compared with the TMB-L group(143 patients), the average age in the TMB-H group(46 patients), was older, the proportion of males, heavy smokers, adenocarcinoma, advanced stage, lymph node metastasis was higher, and the tumors with advanced stage accounted for a higher proportion.

Comment 5: The authors need to consider to tone down the current conclusion since it remains unclear whether the model has satisfactory sensitivity and specificity.

Reply 5: we are grateful to the reviewer by this great suggestion

Changes in the text: we have modified our text as advised (see Page 3, line66-71):10 radiomics features that were significantly correlated with the TMB status. The prediction efficiency of the intra-tumoral model was better than that of the peritumoral model (AUC: 0.819 vs. 0.726; Accuracy: 0.773 vs. 0.632, specificity: 0.767 vs 0.558). The efficacy of the prediction model based on radiomic features was significantly better than that of the clinical model (AUC: 0.822 vs. 0.683; specificity: 0.786 vs 0.643).

Comment 6: Third, in the introduction of the main text, the authors need to review available alternative methods for predicting or diagnosing the TMB status and have comments on their limitations.

Reply 6: we are grateful to the reviewer by this great suggestion

Changes in the text: There is some discussion in the article (see Page 14, line415-430):

Comment 7: Because the current study focused on the model combined clinical factors and CT radiomics, in this part the authors need to explain the accuracy of radiomics alone and why it is necessary to combine clinical factors and CT radiomics to improve the diagnostic accuracy.

Reply 7: we are grateful to the reviewer by this great suggestion

Changes in the text: There is some discussion in the article (see Page 16, line503-506):

Changes in the text: we have modified our text as advised (see Page 16, line506-508): The prediction efficiency of the clinical model was better than that of the radiomics model (Accuracy: 0.825 vs. 0.754, specificity: 0.884 vs 0.744).

Comment 8: The methodology of the main text needs to accurately describe the clinical research design, sample size estimation, and randomization method of the generation of training and validation samples.

Reply 8: we are grateful to the reviewer by this good suggestion.

Radiomics is a big data approach with a larger sample size and the higher model fit. This study is an exploratory study of TMB status by radiomics model, with strict inclusion and exclusion criteria, so the final sample size is relatively small. Meanwhile, based on the small proportion of patients with high TMB expression in clinical practice, we controlled the proportion of patients in the two groups at about 3:1. Finally, it is found that the omics model has certain predictive value of TMB state, and can be further optimized in studies with larger sample size in the future. In addition, some people believe that the sample size estimation of the literature omics model generally does not use the sample size estimation method of traditional statistical methods.

Changes in the text: None.

Comment 9: The sample size seems to be small, in particular that of the validation sample, which does not allow the stable estimation of accuracy parameters. In statistics, the authors need to report the threshold values of AUC for a good diagnostic test, as well as those of

sensitivity and specificity. Please also describe their threshold values for a good diagnostic test. Please ensure P<0.05 is two-sided.

Reply 9: we are grateful to the reviewer by this great suggestion.

Changes in the text: we have modified our text as advised (see Page 10-11, line310-313):
Using the best threshold points（0.338）, in the training set,the calculated accuracy of the model was 0.788, sensitivity is 0.469, specificity is 0.89; in the validation set,the accuracy is 0.852, sensitivity is 0.643, specificity is 0.884.

Changes in the text: we have modified our text as advised (see Page 10, line278):
P<0.05 is two-sided.

Changes in the text: we have modified our text as advised (see Page 12, line346-349):
In the validation set, the AUC of the intra-tumoral model and the peritumoral model was 0.816 and 0.728, the accuracy was 0.773 and 0.632, sensitivity is 0.786 and 0.857, specificity is 0.767 and 0.558,respectively, and the AUC of the combined radiomics model was 0.819, the accuracy was 0.754, sensitivity is 0.786 , specificity is 0.744 .

Changes in the text: we have modified our text as advised (see Page 12, line361-364):
Using the best threshold points（0.243）, in the training set,the calculated accuracy of the model was 0.754, sensitivity is 0.643, specificity is 0.791; in the validation set,the accuracy is 0.811, sensitivity is 0.812, specificity is 0.82.

Reviewer C

1. Ethics:

Please provide the ID/number of ethical approval.

Reply: revised.

2. The citation of references in your text is not in order. Please check the citation of references 53-56; they appear behind in references 57-58, which is not allowed.

Reply: revised.

3. Table 1:

1) Please indicate the meaning of “Differentiated degree*” in Table 1 footnote.

Differentiated degree*		
Low	33 (23.1)	20 (43.5)
Medium	59 (41.3)	14 (30.4)
High	51 (35.6)	12 (26.1)

2) Please indicate how the data are presented in Age. mean ± SD?

Age (years)	54.8±10.5	60.9±9.7	**0.001**

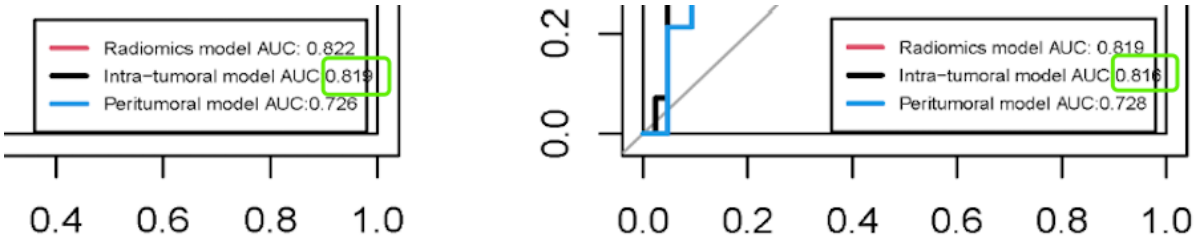
Reply: revised.

4. Figure 3:

1) The data in the abstract below is inconsistent with Figure 3B.

were significantly correlated with the TMB status. The prediction efficiency of the intra-tumoral model was better than that of the peritumoral model (AUC: 0.819 vs. 0.726; Accuracy: 0.773 vs. 0.632, specificity: 0.767 vs 0.558). The efficacy of the

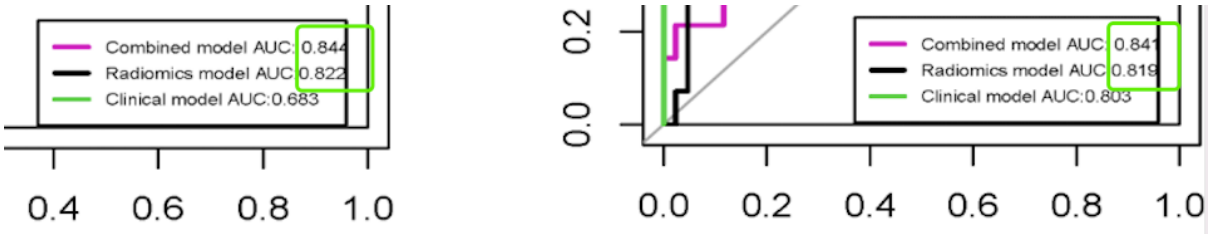
2) The numbers are covered and not clear. Please modify.



Reply: revised.

5. Figure 4:

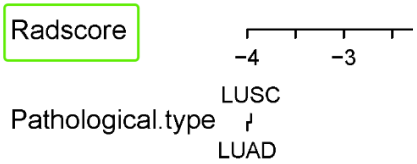
The numbers are covered and not clear. Please modify.



Reply: revised.

6. Figure 5:

Please revise “Radscore” to “Rad-score”.



Reply: revised.