Peer Review File

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Reviewer A

Comment 1： Please have the manuscript edited by English-speaking professionals.

Reply 1: We had premium editing for the manuscript by managing editor Dr. James Allen of Oxford Science Editing Ltd (https://www.oxfordscience.org), and we added the acknowledgement for his editing work in the "Acknowledgement" section.

Changes in the text: Changes were mainly in the "Acknowledgement" section (page 20, line 429-431).

Comment 2： Abstract. In the background part, please clearly indicate the objective of this study. In the part of methods, please describe the variables of clinical characteristics and assessment of survival outcomes. Experimental methods for detecting mutation, TMB and immune cells should also be briefly described. Please also provide the main statistical method. In the part of method, please provide detailed figures and P values to support these findings. In the conclusion part, the authors should be cautious to use "a precise predictor of prognosis in LUAD" because the above findings only support the association between prognosis and TMB and immune infiltrates without detailed data on the predictive effect of TMB and immune infiltrates.

Reply 2: We have revised the background part in "Abstract" section to indicate the

objective of this study more clearly, and we also modified the experimental methods more specific with detailed P values and indicators. We replaced the “precise predictor of prognosis in LUAD” with “better predictor of prognosis in LUAD” to make more rigorous description in the article.

Changes in the text: Changes were mainly in the “Abstract” section (page 2, line 38-42; page 2-3, line 43-54; page 4, line 70-71).

3. **Comment 3:** In this part, the authors may consider to have a brief review on known prognostic biomarkers of LUAD and TP53mut LUAD and comment on their limitations to indicate the need for a novel biomarker. The current review on TP53mu is inadequate, for example, please provide detailed data on how many patients with TP53mut are not beneficial from immunotherapy.

Reply 3: We have revised the “Introduction” section according to the comments of reviewers. Firstly, we have detailed the current review on responses of *TP53*^{mut} patients to immunotherapy on page 5, line 91-95, and we have added a brief review on known immune prognostic signatures for the prediction of overall survival and therapeutic responses in lung cancer in paragraph 2 of the “Introduction” section, and the comments on their limitations to indicate the need for a novel biomarker in paragraph 3 of the “Introduction” section.

Changes in the text: Changes were mainly in the “Introduction” section (page 5, line 91-95; page 5, line 98-102; page 6, line 115-131).

Comment 4: Methodology. In the part of data source, please describe the clinical variables and prognosis outcomes in the dataset in detail, because the authors used them. It would be helpful to describe how the patients were followed, because this is a clinical research. I also suggest the authors to move all statistical analytic approaches such as survival analysis, K-M analysis, and Wilcoxon rank-sum test to the part of statistics.

Reply 4: We have revised the "Methods" section according to the comments of reviewers. Firstly, we grouped the samples based on their *TP53* gene with and without mutation, and had a supplementary description in the "Methods" section. Then we detailed the clinical variables and prognosis outcomes as age (years), sex (female and male), T (tumor size), N (metastatic lymph node), M (distant metastasis), American Joint Committee on Cancer tumor-node-metastasis (AJCC TNM) stage (I~IV stage), and survival outcome mainly including overall survival time (OS) in the "Methods" section. Furthermore, as the reviewer suggestion we moved all statistical analytic approaches to the part of statistics.

Changes in the text: Changes were mainly in the "Methods" section (page 7, line 145-150; page 7-8, line 158; page 9, line 192-198; page 10, line 200-205).

Comment 5: Statistics. These descriptions on statistical methods are repeating the above analyses, so I suggest the authors to re-organize the part of methodology. Please indicate $P<0.05$ is two-sided. Because in the results part, the authors mentioned ROC method and AUC, the authors should describe how the ROC analysis was conducted

here. Please also describe the generation of training and validation sample. Based on the results, AUC value is poor, so the authors need to consider whether they would keep this analysis. If not, please consider the sentences in the last paragraph of introduction part, I think there is no need to mention the construction of “precise prognostic model for immunotherapy”.

Reply 5: We have revised the “Methods” section according to the comments of reviewers, and provided a supplemental description of ROC analysis in the part of TMBPI construction. However, we finally decided to keep this part analysis though its AUC value is poor, and we have removed all the descriptions of “precise prognostic model for immunotherapy” in the manuscript.

Changes in the text: Changes were mainly in the “Methods” section (page 9, line 192-198).

Comment 6: In the discussion part, please have some detailed comments on the implications of findings and have some suggestions on future research directions on unaddressed issues of the current study.

Reply 6: We have revised the “Discussion” section according to the comments of reviewers, and provided some new insights for better understanding of poor prognosis of tumor patients and some suggestions for future research.

Changes in the text: Changes were mainly in the “Discussion” section (page 19, line 403-417).

Reviewer B

Comment 1: The author reported "tumor mutation burden combined with immune infiltrates in lung adenocarcinoma with TP53 mutation as a special prognostic indicator". This manuscript is well-written and the contents is very interesting. Please mention your thought how to improve the prognosis about TP53mut patients with low-TMB or high TMBPI in Discussion.

Reply 1: We have revised the "Discussion" section according to the comments of reviewers, and mentioned "activation of immunity to increase the infiltration of effector B cells in TIME" was a possible way for improving the prognosis of *TP53*^{mut} patients with low-TMB or high TMBPI in the "Discussion" section.

Changes in the text: Changes were mainly in the "Discussion" section (page 19, line 415-417).

Reviewer C

The authors did an interesting job. Using TCGA database, they explored the utility of a novel composite biomarker, TMB with immune cell infiltrate, in TP53-mutated LUAD. They found that higher TMB levels with effector B cell and dendritic cell infiltrates were associated with favorable prognosis in those population. This study is well-designed, well-organized, and provides a novel prognostic model for immunotherapy setting.