Peer Review File

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Reviewer A

This manuscript explored the differentially expressed DDR genes, and then built a DDR-related prognostic model. Specifically, a total of 514 patients with LUAD from TCGA database were divided into distinct subtypes to characterize the diversity within the DDR pathway. DDR-activated and DDR-suppressed subgroups showed distinct clinical characteristics, molecular characteristics, and immune profiles. Nine genes were identified as hub DDR-related genes, including CASP14, DKK1, ECT2, FLNC, HMMR, IGFBP1, KRT6A, TYMS, and FCER2. By using the expression levels of these selected genes, the corresponding risk scores for each sample was predicted. The distinct characteristics of DDR subtypes may offer valuable insights into the clinical management and decision-making in LUAD.

1) The overall writing has some formatting issues, like wording, spacing, and some redundancy. I suggest the authors check the grammar and avoid any typos. More importantly, the writing needs improvement for readers to understand more easily.
Reply 1：We have improved the writing as advised.

2) The method part is lack of details. More detailed descriptions are needed to explain the method.
Reply 2：We have added details in the method part as advised(see Paragraph Methods).

3) I strongly recommend the authors to make figures with high resolution, as well as consistent font styles with the manuscript.
Reply 3：We have changed the figures with higher resolution as advised.

4) I would recommend the authors to include some discussions on related studies using different omics data (PMID: 33461059; PMID: 35284940), which helps expand the scope of the study.
Reply 4：We have included some discussions on related studies using different omics data (PMID: 33461059; PMID: 35284940,see reference).

Reviewer B

The paper titled “Predictive value of a DNA damage repair-related gene-based prediction model for the prognosis of lung adenocarcinoma” is interesting. The distinct characteristics of DDR subtypes offer valuable insights into the clinical management and decision-making in LUAD. We successfully developed a 9-gene risk signature associated with DDR in LUAD, which demonstrated its potential as an effective and stable classification tool for clinical practice. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) What are the differences in clinical features, molecular features, immune cell components, gene mutations, DDR pathway activation status and clinical outcomes among patients with different subtypes? It is suggested to add relevant contents.

Reply1 : DDR gene-based subtypes exhibited distinct clinical characteristics, molecular characteristics and different immune profiles(see RESULT Paragraph 2-4)

2) All figures are not clear enough. It is recommended to provide clearer figures again.

Reply2：We have changed the figures with higher resolution as advised.

3) What is the greatest advantage of the prediction model in this study? What is the biggest problem we are facing? It is suggested to add relevant content to the discussion.

Reply3:Our study contributes to the understanding of DDR heterogeneity and the identification of DDR subtypes in patients with LUAD. The distinct characteristics of DDR subtypes offer valuable insights into the clinical management and decision-making of LUAD. We have successfully developed a 9-gene risk signature associated with DDR in LUAD, which demonstrated its potential as an effective and stable classification tool for clinical practice. Moreover, our DDR subtype signature holds promise as a biomarker for guiding immunotherapy in patients with LUAD. However, further research and validation are required to fully elucidate the clinical implications and utility of the risk score in guiding treatment decisions for patients with LUAD. Relevant content has been added to the discussion.

4) What is the relationship between DNA damage repair gene mutations and increased neoantigen load and activated T cell infiltration in lung adenocarcinoma? It is recommended to add relevant contents.

Reply4: We will further investigate the relationship between DNA damage repair gene mutations and increased neoantigen load and activated T cell infiltration in lung adenocarcinoma. Thanks for the reminder.

5) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Molecular subtyping and IMScore based on immune-related pathways, oncogenic pathways, and DNA damage repair pathways for guiding immunotherapy in hepatocellular carcinoma patients, PMID: 36636061”,“The DNA damage repair-related gene

PKMYT1 is a potential biomarker in various malignancies, PMID: 35070764". It is recommended to quote the articles.
Reply5:We have quoted the advised articles in the introduction part.

6) This study is based on bioinformatics analysis. It is recommended to increase in vivo and in vitro experimental studies, which may be more meaningful.
Reply6: We will increase in vivo and in vitro experimental studies in further research. Thanks for the reminder.

Reviewer C

1) First of all, my major concern for this study is that most of the AUC values are lower than 0.75 even 0.70, so the predictive accuracy of the predictive model is limited.

Reply1:We tried to validate the accuracy of our model in other external data. In the GSE13213 dataset (containing 117 lung adenocarcinoma samples), we found that the AUC value of the 1-year OS survival prediction of this model was 0.87, and the AUC value of the one-year OS survival prediction of this model in the TCGA data was around 0.75, so our model may have high accuracy in the prediction of 1-year OS survival in lung adenocarcinoma. In view of the fact that many lung cancer patients are already in the middle and advanced stages at the time of presentation, the one-year OS survival prediction is still of great significance in lung adenocarcinoma. Our model can accurately predict the one-year OS survival of lung adenocarcinoma patients.
In addition, we also found significant differences in OS survival and DFS survival between samples in the high and low risk groups based on our model in multiple data cohorts, which means that the model can well distinguish the prognosis of lung adenocarcinoma.

2) Second, the title needs to indicate the development and validation of the prediction model.

Reply2: We have changed the title as advised.

3) Third, the abstract is not adequate. The background did not explain why DDR genes could accurately predict the prognosis. The methods did not describe the clinical sample used, the generation of training and validation samples, prognosis outcomes, and statistical methods for assessing the predictive accuracy. The results need to present the findings on the prediction accuracy parameters in both the training and validation samples. The correlation coefficients and accurate P values should be presented. The conclusion needs comments for the clinical implications of the findings.

Reply3: We have revised the abstract part as advised.

4) Fourth, the introduction needs to have an extensive review on what has been known on the prognostic biomarkers and prognosis prediction models in LUAD, analyze the limitations and knowledge gaps of prior studies, and explain why DDR genes can accurately predict the prognosis.

Reply4: We have revised the introduction part as advised.

5) Fifth, in the methodology of the main text, the authors need to describe the sample used in detail, including clinical factors, follow up procedures, and prognosis outcomes. In statistics, please provide the threshold AUC values for a good prediction model.

Reply5: We have revised the method part as advised.

6) Finally, please consider to cite several related papers: 1. Liu T, Hu A, Chen H, Li Y, Wang Y, Guo Y, Liu T, Zhou J, Li D, Chen Q. Comprehensive analysis identifies DNA damage repair-related gene HCLS1 associated with good prognosis in lung adenocarcinoma. Transl Cancer Res 2023;12(10):2613-2628. doi: 10.21037/tcr-23-921. 2.Shao C, Wang Y, Pan M, Guo K, Molnar TF, Kocher F, Seeber A, Barr MP, Navarro A, Han J, Ma Z, Yan X. The DNA damage repair-related gene PKMYT1 is a potential biomarker in various malignancies. Transl Lung Cancer Res 2021;10(12):4600-4616. doi: 10.21037/tlcr-21-973. 3. Li H, Sha X, Wang W, Huang Z, Zhang P, Liu L, Wang S, Zhou Y, He S, Shi J. Identification of lysosomal genes associated with prognosis in lung adenocarcinoma. Transl Lung Cancer Res 2023;12(7):1477-1495. doi: 10.21037/tlcr-23-14.

Reply 6: We have quoted the advised articles in the manuscript.

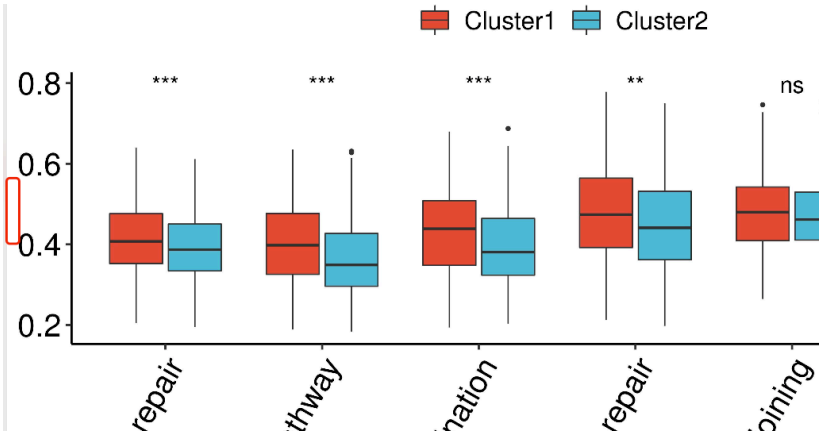
Reviewer D

1. Please check if there's a reference missing in this sentence since you've mentioned Wu et al.'s study.

171 outcomes for patients with LUAD(15). Wu *et al*. also investigated the survival benefits
172 associated with high tumor mutational burden (TMB) or DDR gene mutations in
173 patients with LUAD with high stromal or immune scores. These findings underscore

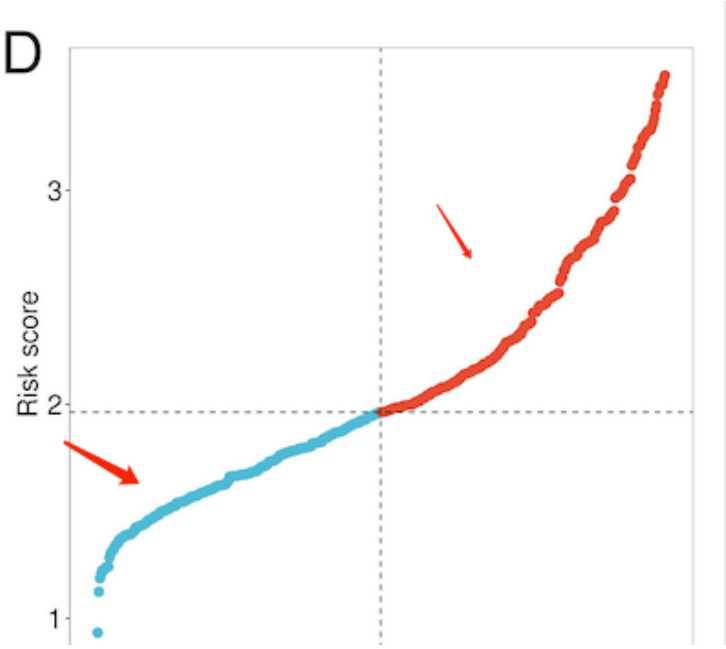
Reply: The missing reference has been added.

2. Figure 3: Please supplement the description of Y-axis.



Reply: Figure 3 has been revised as advised.

3. Figure 7D: Please also define the red and blue dots in the figure and resend us updated Figure 7.



Reply: Figure7 has been revised as advised.

4. Figure 9F is not included in your submitted figure 9, please check its citation in text.

378 significant correlations between the risk score and gender, T stage age and pathologic
379 stage (*Figure 9C-9F*).

Reply: We have revised “Figure 9F” to “Figure 9E” in the manuscript.