Peer Review File

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Review comment-Reviewer A

The authors enrolled about 500 LUADs from the TCGA database, and constructed a TNF family-related lncRNA signature to predict patient survival as well as response to immunotherapy. The manuscript is generally well written, with little to no grammatical or statistical errors. However, there are few issues that need to be clarified or revised.

1. In the "Methods - Data collection" section, the authors mentioned collecting data of 539 LUAD patients from the TCGA database. However, the authors subsequently mentioned that only 493 patients were randomly assigned to training and testing datasets, which means that 46 patients were excluded from the initial 539 patients. What were the reasons for excluding these cases? The authors should explain their exclusion criteria if these cases were indeed excluded.
Answer: Thank you for your value suggestion. Patients who had incomplete clinical data and OS < 30 days were excluded. Thus, 493 LUAD patients were eventually included in the study. We added exclusion criteria (see Page 4, line 127-128).

2. In the Results section, the authors stated that high expression of HLA-DQB1-AS1 had longer survival than those with low expression. However, in the 2nd paragraph of Discussion, the authors also stated that HLA-DQB1-AS1 interacts with ZRANB2 protein to promote proliferation and inhibit apoptosis in hepatocellular carcinoma, which would suggest that higher expression of HLA-DQB1-AS1 should have a negative impact on survival. The authors should discussion this conflicting data between their findings and the previous literature.
Answer: Thank you for your value suggestion. We have added the relevant discussion (see Page 10, line 311-316).

3. In the third paragraph of Discussion, the authors stated that TIDE is a better predictor for anti-PD1 and anti-CTLA4 therapies compared to PD-L1 and tumor mutation load. However, tumor mutation "burden" is more commonly used to describe the number of mutations per megabase.
Answer: Thank you for your value suggestion. Jiang *et al* developed TIDE and demonstrated that compared to widely used ICB response biomarkers, tumor mutation load, *PD-L1* level and interferon gamma response, the TIDE signature achieved consistently better performance for both anti-PD1 and anti-CTLA4 therapies using both RNA-Seq and NanoString data (see reference 45).

Review comment-Reviewer B

The utilization of the LASSO-Cox regression model by the authors to forecast the prognosis and immunotherapy response in lung adenocarcinoma patients by analyzing the expression of Tumor necrosis factor-related lncRNAs is a significant and valuable contribution towards the management of lung adenocarcinoma. I have the following concerns:

1. There are so many regression models, why did the authors choose Lasso-cox regression? Why did the authors do 10-fold cross validation? What is the theoretical foundation for making this decision?

Answer: Thank you for your value suggestions. Because we had a large number of predictor variables, so we tried to use Lasso-cox regression to select only the most important ones for predicting the target variable. Moreover, we tried several k value, k=10 provided us the best balance between bias and variance.

2. In the method, it says "The enrolled 493 LUAD patients were randomly
125 assigned into a training dataset and a testing dataset in a 1:1 ratio.", why chose 493 patients? Do the 493 patients belong to the 539 LUAD patients?

Answer: Thank you for your value suggestion. Patients who had incomplete clinical data and OS < 30 days were excluded. Thus, 493 LUAD patients were eventually included in the study. (see Page 4, line 127-128).

3. What's the statistic method used for p value calculation? The authors only mentioned 2-sided test. Please provide the name of the method in the paper.

Answer: Thank you for your value suggestion. Student's t-test was used to analyze significance among variables (see Page 6, line 174-175).

4. What does p value mean in KEGG analysis?

Answer: Thank you for your value suggestion. The smaller the p value, the more significant the enrichment in KEGG analysis.

5. Generally, this is an interesting study. However, to improve the general quality of your study, you can look at some similiar studies for your future project, such as PMID: 34363761, PMID: 34913723, PMID: 34807232.

Answer: Thank you for recommending these articles. They are very interesting study and would provide us with new research ideas.

Review comment-Reviewer C

The paper titled (Tumor necrosis factor-related lncRNAs predict prognosis and immunotherapy response for patients with lung adenocarcinoma) constructed and validated a prognostic predictive signature of LUAD patients based on TNF-related lncRNAs, and the signature showed good performance to predict immunotherapy response. It may provide new strategies for individualized treatment of LUAD patients. However, there are still some concerns need to be solved.

1. Most importantly, it is more meaningful to validate the predictive signature by in vivo/in vitro experiments.

Answer: Thank you for your value suggestion. Some in vitro and in vivo experiments had studied the prognostic value of these lncRNAs. For example, Yao et al found that LINC01137 was overexpressed in the NSCLC tumor tissues compared with healthy tissues, and patients with low expression of LINC01137 were likely to exhibit better outcomes. HLA-DQB1-AS1 was demonstrated to promote cell proliferation and inhibit apoptosis in hepatocellular carcinoma.

2. The words in some figures are too small to read. The figures in this manuscript could be further optimized and improved.

Answer: Thank you for your value suggestion. We have provided the high-resolution version of all pictures separately.

3. Please check and revise y axis in figure 6C.

Answer: Thank you for your value suggestion. We have revised y axis in figure 6C. Please see figure 6C.

4. Please revise “pvalue” to “P value” and “Hazard ratio” to “Hazard ratio (95% CI)” in figure 7A.

Answer: Thank you for your value suggestion. We have revised them. Please see figure 7A.

5. Please revise some grammatical errors. For example, “signature has can efficiently predict” should be revised to “signature can efficiently predict” in Line 87.

Answer: Thank you for your value suggestion. We have revised this grammatical error (see Page 3, line 89).

Review comment-Reviewer D

The paper titled “Tumor necrosis factor-related lncRNAs predict prognosis and immunotherapy response for patients with lung adenocarcinoma” is interesting. The results constructed and

validated a prognostic predictive signature of LUAD patients based on TNF-related lncRNAs, and the signature showed good performance to predict immunotherapy response. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) What are the patterns and prognostic roles of TMB and immune infiltration in LUAD? It is recommended to add relevant content.

   Reply: Thank you for your value suggestion. We will explore the patterns and prognostic roles of TMB and immune infiltration in LUAD in future research.

2) What are the relationships between the signature and immune landscape, genomic integrity, clinical characteristics, drug sensitivity, and immunotherapy efficacy? It is suggested to add relevant contents.

   Reply: Thank you for your value suggestion. We had added the relevant contents in the discussion. (see Page 9, line 285-289)

3) This study is based on bioinformatics analysis. It is suggested to increase in vivo and in vitro experimental verification, which may be more meaningful.

   Reply: Thank you for your value suggestion. Some *in vitro* and *in vivo* experiments had studied the prognostic value of these lncRNAs. For example, Yao *et al* found that LINC01137 was overexpressed in the NSCLC tumor tissues compared with healthy tissues, and patients with low expression of LINC01137 were likely to exhibit better outcomes. HLA-DQB1-AS1 was demonstrated to promote cell proliferation and inhibit apoptosis in hepatocellular carcinoma.

4) It may be more meaningful to suggest to increase the functional research of related key lncRNAs.

   Reply: Thank you for your value suggestion. Several studies have reported function of related key lncRNAs. For example, LINC01137 functions as an oncogenic lncRNA in OSCC and NSCLC, and miR-22-3p can directly target LINC01137 and negatively regulate its expression and function. HLA-DQB1-AS1 interacted with zinc finger RANBP2-type containing 2 (ZRANB2) protein to promote proliferation and inhibit apoptosis in hepatocellular carcinoma.

5) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Expression of interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α) in non-small cell lung cancer and its relationship with the occurrence and prognosis of cancer pain, PMID: 35016421 ”,“Comprehensive analysis of necroptosis-related long noncoding RNA to predict prognosis, immune status, and immunotherapeutic response in clear cell renal cell carcinoma, PMID: 36644185”. It is recommended to quote this article.

Reply: Thank you for your value suggestion. We had cited these articles in this paper. (see Page 3, line 91 and Page 4, line 103)

6) The biological characteristics of TNF-related lncRNA and its research progress in tumors should be added to the discussion.

Reply: Thank you for your value suggestion. We had added the relevant contents in the discussion. (see Page 9, line 275-278)

7) How does lncRNA interact with other signal networks in the progression of LUAD? What dual role does it play in increasing/inhibiting tumor progression? It is recommended to add relevant contents.

Reply: Thank you for your value suggestion. We had added the relevant contents in this paper. (see Page 3, line 96-102)

Review comment-Reviewer E

1. Figure 2:

a. Please add the header for the first column.

b. Please revise "Hazard ratio" to "Hazard ratio (95% CI)".

Answer: Thank you for your value suggestions. We have added the header for the first column and revised "Hazard ratio" to "Hazard ratio (95% CI)". Pleased see Figure 2-revised.

2. Figure 5:

a. Please check and revise this typo in the figure.

b. Please revise it to "1 year".

Answer: Thank you for your value suggestions. We have revised these typos in Figure 5. Pleased see Figure 5-revised.

3. Figure 6:

a. Please check and revise this typo in the figure.

b. Please revise it to "1 year".

Answer: Thank you for your value suggestions. We have revised these typos in Figure 6. Pleased see Figure 6-revised.

4. Figure 7

a. Please define "*, ***" in figure legends.

Answer: Thank you for your value suggestions. We have defined "*, ***" in figure legends. Pleased see the legends of Figure 7.

b. Please remove "(%)" from here.

Answer: Thank you for your value suggestion. We have removed "(%)" from Figure 7D. Pleased see Figure 7-revised.

5. Figure 10: Please define "**, ***" in figure legends.

Answer: Thank you for your value suggestion. We have defined "**, ***" in figure legends. Pleased see the legends of Figure 10.

6. Figure 6

Please delete them.

Answer: We have deleted them. Pleased see Figure 6-revised.

7. Figure 7

Please revise "pvalue" to "p value";

Please revise "Hazard ratio" to "Hazard ratio (95% CI)".

Answer: Thank you for your value suggestions. We have revised them. Pleased see Figure 7-revised.