

Peer Review File

Article information: <https://dx.doi.org/10.21037/tcr-23-199>

Reviewer A

Major Comment 1: The authors claimed that cancer-associated fibroblast gene expression pattern is a prognostic factor. Simultaneously, the authors asserted that high immunoscore and immune cell infiltration are prognostic factors in lung adenocarcinoma. The authors should prove that cancer-associated fibroblast gene expression pattern is an independent prognostic factor unrelated to high immunoscore and immune cell infiltration.

Reply 1: The risk scores of this model, immune score and immune cell infiltration degree were analyzed by multivariate regression. The results showed that the risk score of this model was an independent risk factor for prognosis. At the same time, it may be because all four genes in this research model are related to fibroblasts, so the expression of fibroblasts is also closely related to the prognosis of this model.

Changes in the text:

We added a description of Multivariate regression analysis of the risk scores of the model with the immune score and the degree of immune cell infiltration (see Page 9, line 282-285, Page 25, line 649, Figure 7F).

The modified parts are marked in red.

Major Comment 2: The authors identified 4 genes as representative cancer-associated fibroblast-related genes. Are these genes expressed in cancer-associated fibroblasts?

Reply 2: These four genes are all expressed in Cancer-associated fibroblasts, and the Cancer-associated fibroblast related genes (CAFRGs) were screened in GeneCards database (<https://www.genecards.org/>, The Human Gene Database, where we can get almost all the information of known human genes.) .

Changes in the text: We added a description of GeneCards (see Page 4, line 119-120)

The modified parts are marked in red.

Minor comment 1: Line 119. The authors should describe how CAFRGs were selected.

Moreover, what is GENECARD?

Reply 1: GeneCards (The Human Gene Database, <https://www.genecards.org/>) is a comprehensive database of searchable genes, where we can get almost all the information of known human genes. We screened CAFRGs from GeneCards.

Changes in the text:

We added a description of GeneCards (see Page 4, line 119-120)

The modified parts are marked in red.

Minor comment 2: Line 210. What does “immunoassays” mean? Moreover, there is no description on immunoassay procedures in Methods. The authors should describe the procedures in detail.

Reply 2: “immunoassays” means “immune infiltration analysis”. We have added a description of immune infiltration analysis, and elaborated the details in the method.

Changes in the text:

We have modified our text as advised (see Page 7, line 209-210)

We added a description of immune infiltration analysis, and elaborated the details in the method (see Page 5, line 140-148)

The modified parts are marked in red.

Reviewer B

1. Please structure your Abstract as: **Background**, Methods, Results, and Conclusions.

Reply and Change 1: The manuscript has been revised (see Page 1, line 11).

2. Please define below abbreviations in Abstract, you should ensure all abbreviated terms are defined the first time they appear in the Abstract.

of **CAFRGs** in the occurrence, diagnosis and development of lung adenocarcinoma.

Methods: RNA data and corresponding clinical information of lung adenocarcinoma patients were acquired from TCGA (**The Cancer Genome Atlas**) database.

Consensus clustering was performed to identify different molecular subgroups.

The tumor immune states of different subgroups were determined

by ESTIMATE, MCP and **ssGSEA** analyses. In order to elucidate the potential

mechanism of **CAFRGs**, functional enrichment analysis including **GO**, **KEGG** and

Reply and Change 2: The manuscript has been revised. (see Page 1, line 10-30).

3. For clarification, Original Article must include "**Statistical Analysis**" in “Methods” section in the main text (i.e., "Statistical Analysis" should be ranked as a subtitle independently under "Methods" section, and you should expand this part for your manuscript). If there's none, please give your reason.

Reply and Change 3: The manuscript has been revised. (see Page 6, line 164-174).

4. You should use the last name of the first author, please check the main text.

321 **Ahmed** et al. (23) found in a mouse lung adenocarcinoma model experiment that

322 CAFs overexpress FGF9 (fibroblast factor 9), FGF2 (fibroblast factor 2), etc., to

552 23. Hegab AE, Ozaki M, Kameyama N, et al. Effect of FGF/FGFR pathway blocking on lung

553 adenocarcinoma and its cancer-associated fibroblasts [J]. J Pathol, 2019, 249(2):193-205.

Reply and Change 4: The manuscript has been revised.

5. Please check if any references are missing in below sentences since you've mentioned “Studies”.

Studies have pointed out that tumor progression is closely related to the dynamic changes of TIME(Tumor Immune MicroEnvironment). The abnormal activity of

Reply and Change 5: The manuscript has been revised.(see Page 3,line 66-67).

6. Table 1: Please check if the table header should be completed.

4 **Table1 Characteristics of patients in the training and validation cohort.**

	Training cohort (n = 499)	Validation cohort (n = 82)	P-value

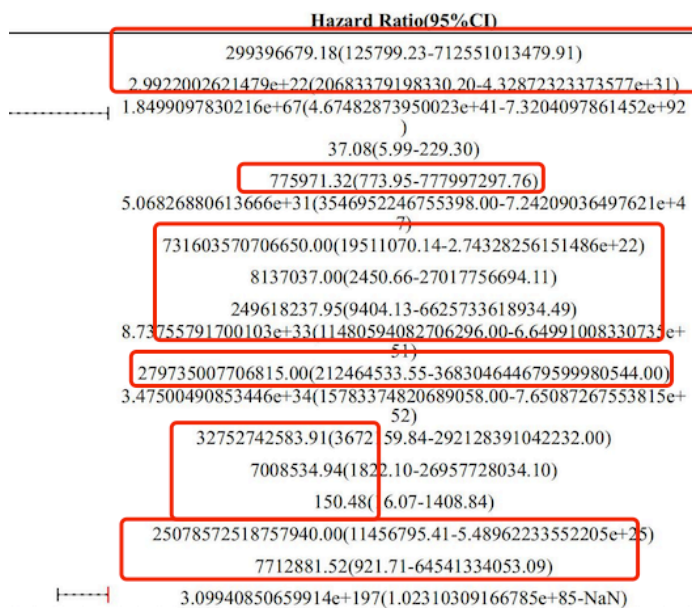
Reply and Change 6: The table has been modified.(see Page 20,line 575-588, table 1-revised).

7. Please provide **editable** version of Figure 1 in Word/PPT format since it's a flow diagram.

Reply and Change 7: See Figure 1-revised in a separate attachment.

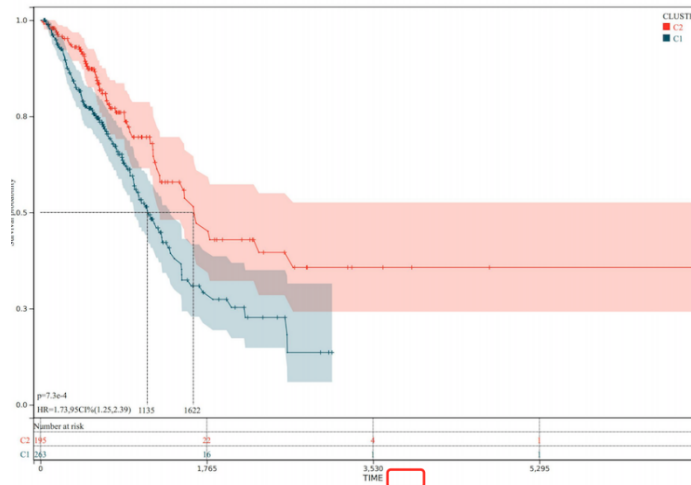
8. Figure 8: Please check if those numbers are correct and no need to modify. Please double check.

Reply and Change 8:The picture has been modified.(see Page 22,line 619, Figure 2-revised).



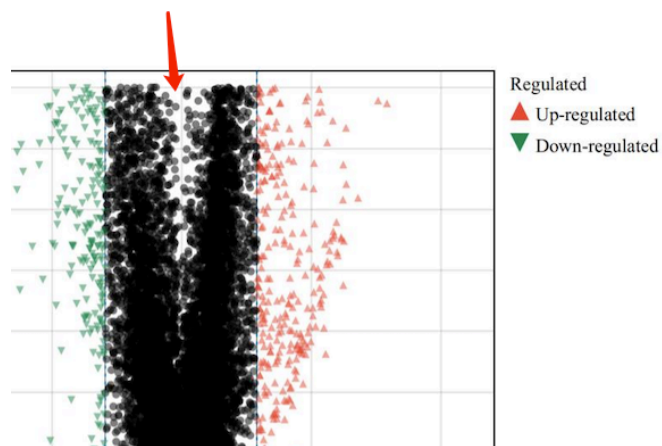
9. Figure 3: Please provide the unit for the figure.

Reply and Change 9:The picture has been modified.(see Page 23,line 630, Figure 3-revised).

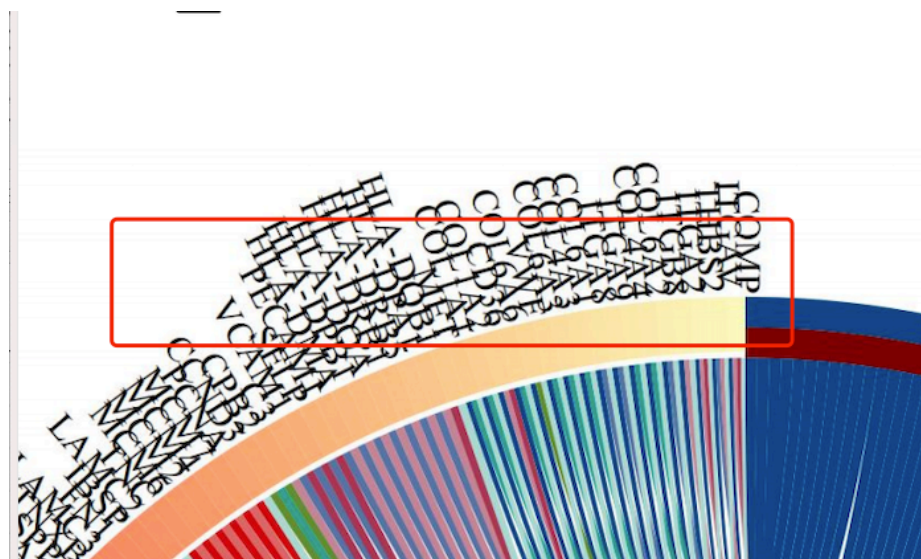


10. Figure 5

a. Please also define those black dots in Figure 5A.

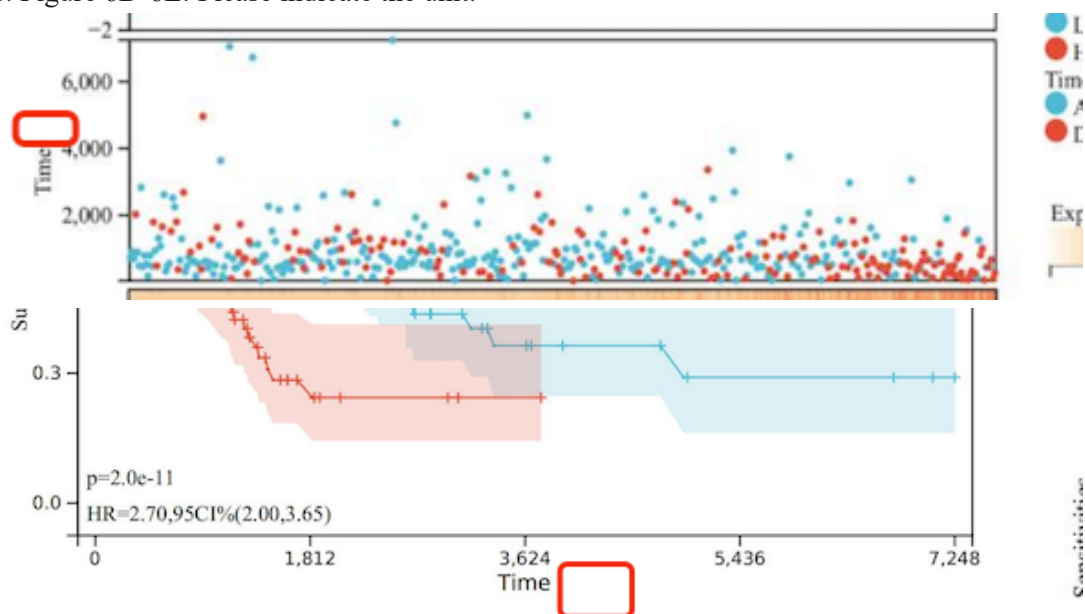


b. Figure 5E: The words are overlapped and cannot be identified, please check and revise.



Reply and Change 10: The picture has been modified.(see Page 25,line 647-649, Figure 5-revised).

11. Figure 6D-6E: Please indicate the unit.

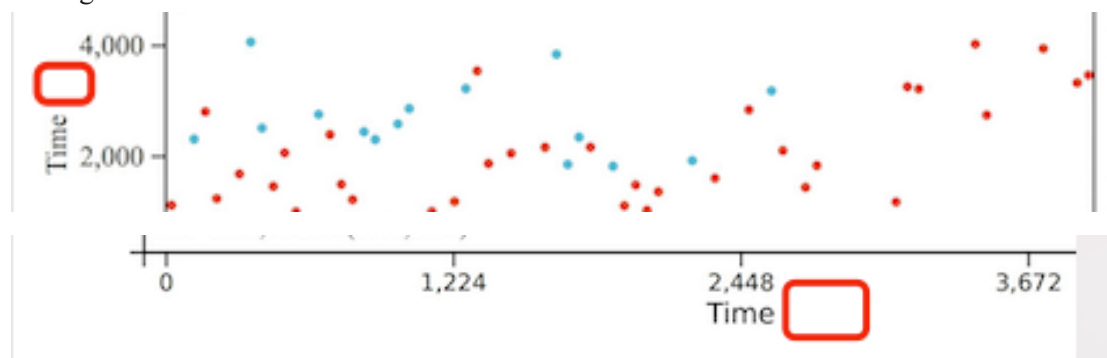


Reply and Change 11:The picture has been modified.(see Page 26,line 652-654, Figure 6-revised).

12. Figure 7 is not clear enough to be published, please revise and resend us a higher resolution version in JPG/TIFF format as separate file.

Reply and Change 12:The picture has been modified.(see Page 27,line 658-660, Figure 7-revised).

13. Figure 8: Please indicate the unit.

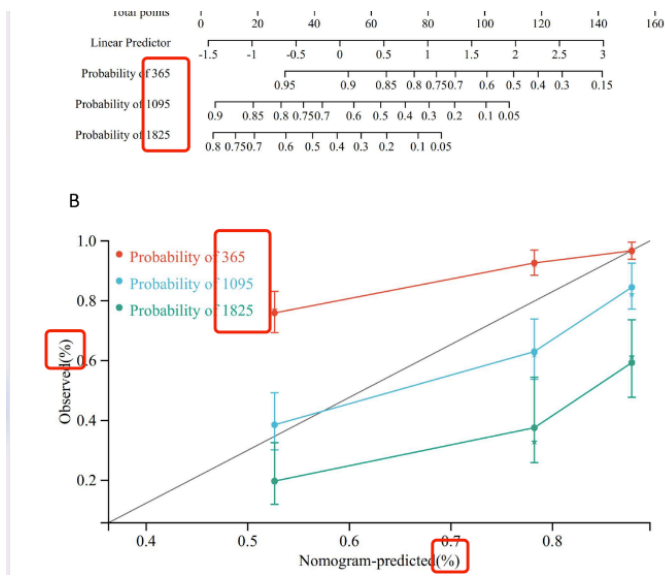


Reply and Change 13:The picture has been modified.(see Page 28,line 661, Figure 8-revised).

14. Figure 9:

a. Please revise 365/1095/1825 to 1-year/3 years/5 years respectively.

b. Please remove “(%)” from X- and Y-axis in Figure 9B since the numbers on the axis are 0-1.0.



Reply and Change 14:The picture has been modified.(see Page 29,line 665, Figure 9-revised).

15. Figure 1 was not cited in your paper, please cite it consecutively in text.

Reply and Change 15:(see Page 6,line 163,).