Peer Review File

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Reviewer A

Comment 1: In the highlight box you left "Report here about what this manuscript adds"

Reply 1: We apologize for the mistake that a statement in template was left in highlight box. We removed it.

Changes in the text: The sentence was removed in highlight box. (page3, line62)

Comment 2: lines 107 - how did you determine that there were insufficient samples?

Reply 2: In this study, insufficient sample size was defined as no more than 20 samples recorded in TCGA database. To date, all 33 types of primary tumors were sufficient for analysis, but the sample sizes of all recurrent tumor types were less than 20. SKCM has a sample size over 300 in metastatic type. However, there is lack of metastatic sample collection in other tumors.

Changes in the text: Methods was updated to describe the request about sample size clearly and without ambiguity. (page5, line116) Total sample size was also updated to fit the Table.1. (page5, line113)

Comment 3: As a part of Figure 4D, consider adding a T-Test between the two datasets to add statistical significance to the graph.

Reply 3: We added the T-test to Figure 4D using R package ggpubr.

Changes in the text: Figure 4D was replaced to add lines and significant symbols in each facets.

Comment 4: As part of your literature search in other work in identifying biomarkers, there are papers using neural networks to identify TCGA biomarkers you may want to add.

Reply 4: Neural network is a prevalent and robust algorithm in feature selection, especially in identifying biomarkers. Implement of neural networks may improve classification performance in this study. So we worked on establishing the pipeline of neural network, but realized that all results, tables and figures will be changed after this improvement. Unfortunately, the heavy workload make it difficult for us to submit the revision of manuscript before deadline. Therefore, We plan to apply this algorithm in future researches and keep current algorithm in this study.

Changes in the text: A statement of future work prospects using neural network

algorithm was added in Discussion section. (page12, line395)

Reviewer B

Comment 1: The abstract is not sufficient and needs further modification. The research background did not indicate the clinical needs of the research focus.

Reply 1: We rewrite some sentences in abstract to emphasize the clinical needs of the research focus, and condensed expression in the methods part. Results with direct clinical significance such as radiation therapy response was also added.
In addition, we defined 'tumor embryo distance' as TTSG index and make it consistent in the entire manuscript and in figure legends.

Changes in the text: Multiple modifications was made in abstract. (page2, line23)

Comment 2: Can the new tumor expression features constructed in this study effectively predict the response of cancer patients to immunotherapy and chemotherapy? It is recommended to add relevant contents.

Reply 2: We tested the performance of predicting the response of cancer patients to immunotherapy and chemotherapy using the expression features. Random forest algorithm and SVM algorithm were tried as predictive algorithm. However, the AUC of ROC was ranged from 0.66 to 0.71 and no more than 0.75, indicating the predictive performance was limited. So we decided not to add these results into content.

Changes in the text: No changes were made in text.

Comment 3: What is the biggest limitation of the method of this research? How to overcome? It is recommended to add relevant content to the discussion.

Reply 3: We revised the study and summarized two limitations as follow: Firstly, this study is a reanalysis of TCGA data only *in silico*, without validation and implement using histologic or clinic experiments. Secondly, advanced feature selection algorithms, such as neural network algorithms, were not used in selection of TTSG.

Changes in the text: limitations and prospects in further studies were added into discussion. (page12, line395)

Comment 4: All figures are not clear enough. It is recommended to provide clearer figures again.

Reply 4: Figures were not clear in the review version (in PDF format) of the manuscript probably due to high compress level in Word software and in this review platform. We resubmitted separate files for each figure, and checked all figures and ensured them with a sufficient resolution.

Changes in the text: No change was needed in the text.

Comment 5: This study is based on bioinformatics analysis. It is recommended to increase in vivo and in vitro experimental studies, which may be more meaningful.

Reply 5: Experiments in vivo and in vitro are meaningful validation and further explore for this bioinformatics study. However, it was difficult to add wet experiments results into this study within 3 weeks which is the deadline of revision. We consider that lack of experiment validation as a limitation for this study and should be focused on in future.

Changes in the text: A limitation was added in discussion. (page12, line395)

Comment 6: The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as "Estimating the prognosis of esophageal squamous cell carcinoma based on The Cancer Genome Atlas (TCGA) of m6A methylation-associated genes, J Gastrointest Oncol, PMID: 35284129". It is recommended to quote the article.

Reply 6: We take this advice and add the paper mentioned above into citation. Introduction was modified and some unnecessary content was removed.

Changes in the text: The introduction part was modified and the citation was added (page4, line75). Several citations were also replaced to make reference updated. (page13, line423)

Comment 7: What are the characteristics of tumor infiltrating immune cells? What is the therapeutic significance? It is recommended to add relevant contents.

Reply 7: We divided all samples into high group and low group based on the value of embryo tumor distance. The total immune cell fraction was significantly higher in the Low group in all tumor types, except UCEC and LUAD. The increase in the total immune cell fraction mainly consisted of macrophage M2 cells. The embryo tumor distance had a lower correlation with CD4 memory T cell activation and a higher correlation with dendritic cell activation. Tissues with higher embryo tumor distances were enriched in dendritic cell activation.
Patients with higher embryo distances had longer overall survival time compared to patients with lower distances. The radiation therapy effect of CESC and LGG was reduced in low group.

Changes in the text: Section 3.6 was modified to clarify the contents above. (page10, line312)