Peer Review File

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Reviewer A

Comment 1: -Renal cell carcinoma (RCC) is essentially a metabolic disease characterized by a reprogramming of energetic metabolism (PMID: 36960789; PMID: 30983433, PMID: 36430837,PMID: 36310399). In particular the metabolic flux through glycolysis is partitioned (PMID: 29371925, PMID: 28933387, PMID: 25945836), and mitochondrial bioenergetics and OxPhox are impaired, as well as lipid metabolism (PMID: 30538212; PMID: 32861643, PMID: 29371925, PMID: 36430448). In this scenario it has been shown that ERS-related activation of unfolded protein response (UPR) has a role in regulating cell metabolism and in particular lipid metabolism. These findings should be referenced and discussed.

Reply 1: We have modified our text as advised. (See Page 20, line 506-511)

Comment 2: -In addition, renal cell carcinoma is one of the most immune-infiltrated tumors (PMID: 31527133, PMID: 30738745). Emerging evidence suggests that the activation of specific metabolic pathway have a role in regulating angiogenesis and inflammatory signatures (PMID: 32345771, PMID: 28359744). Features of the tumor microenvironment heavily affect disease biology and may affect responses to systemic therapy (PMID: 37189689; PMID: 33265926; PMID: 36902242; PMID: 37373581). ERS can modulate immune cell infiltration and regulate immunoflogosis. These processes should be explored and discussed.

Reply 1: We have modified our text as advised. (See Page 20, line 511-513 and Page 21, line 553-555)

Reviewer B

Line 70 spelling error
Line 71 conceptual error: consider immunotherapy
Line 74 please cite Fotia et al PMID 37000341

Reply: We have modified our text as reviewer's comment. (See Page 5, line 90-91 and line 94-95)

Reviewer C

1. Reporting Checklist

a) Please fille these items. If it is not applicable, please fill N/A.

	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	PAGE 9-10, LINE	materials and methods,
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	PAGE 9-10, LINE	materials and methods,
Risk groups	11	D;V	Provide details on how risk groups were created, if done.		
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.		
Results					
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	N/A. The data was from the public datasets.	N/A. The data was from the public datasets.
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.		
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).		
Model development	14a	D	Specify the number of participants and outcome events in each analysis.		
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.		
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).		
	15b	D	Explain how to the use the prediction model.		
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.		
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).		
Discussion					
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).		
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.		
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, and results from simila studies, and other relevant evidence.		
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.		
Other information					
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.		
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.		

Reply: We have fulfilled the *TRIPOD reporting checklist* and attached to email.

2. Ethical Statement

Authors should also state that the study conformed to the provisions of the Declaration of Helsinki (as revised in 2013), available at: https://www.wma.net/wp- content/uploads/2016/11/DoH-Oct2013-JAMA.pdf

Describe this information in both the "Method" section of Main Text and the "Ethical Statement" section of Footnote.

- *Suggested wording: "The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional/regional/national ethics/committee/ethics board of ******* (No. the registration number of ethics board) and informed consent was taken from all the patients."*

Reply: We have modified our text as advised (see Page 10, line 248-252 and Page 23, line 610-614).

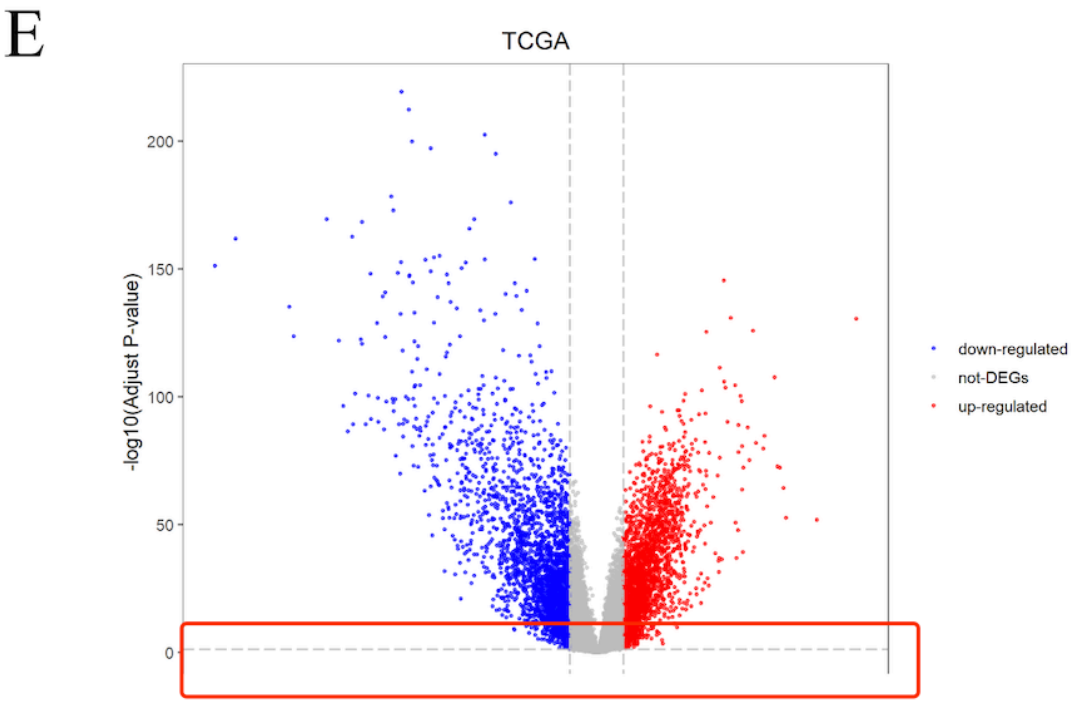
3. Figures and table

ALL abbreviations used in each table/figure or table/figure description should be defined in a footnote below the corresponding table/figure.

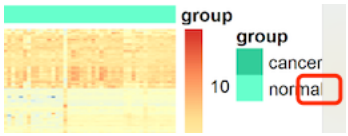
Reply: We have modified our figure legends as advised.

4. Figure 1

a) Please provide the description of the x-axis in 1E.

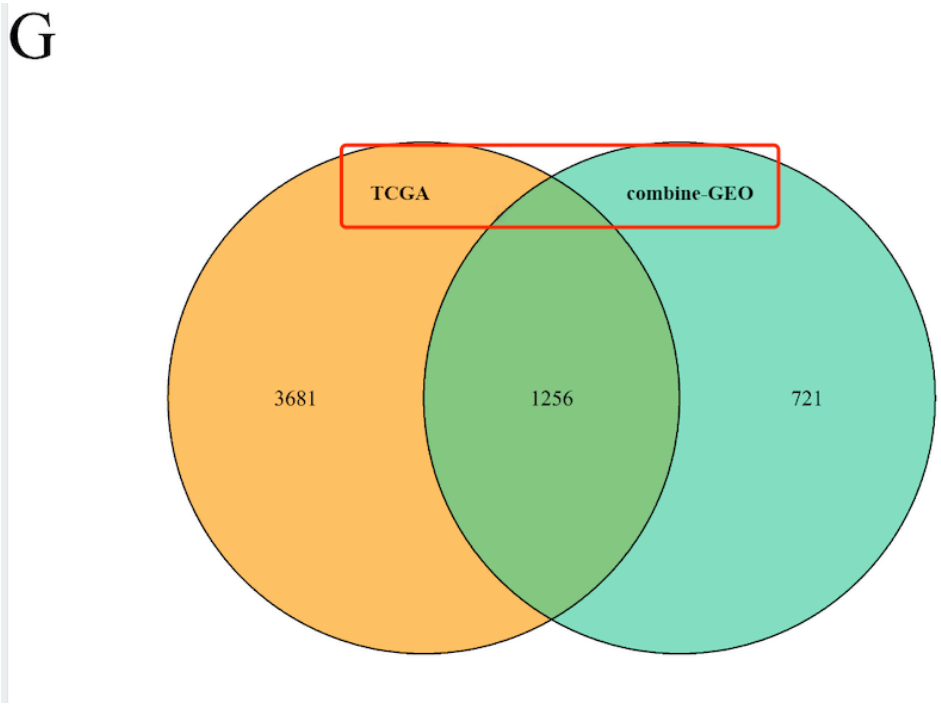


b) The word “normal” is not complete in 1D-E, please revise.



c) Please check if the figure matches the legend.

699 tissue. G: Venn diagram of differentially expressed genes. The green circle represents
700 the differentially expressed genes of the TCGA data set, and the yellow circle represents
701 the differentially expressed genes of the integrated GEO data set. Take the intersection

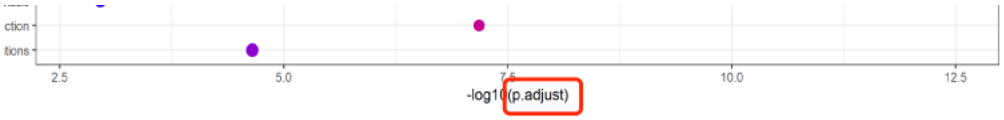


Reply: We have revised the figure 1 and figure legend as advise (see Page 24, line 633-634).

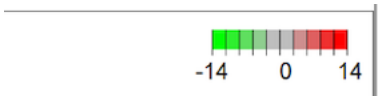
5. Figure 2

a) Please check if the figure matches the legend.

717 the color indicates different GO Term. E: KEGG pathway enrichment analysis, the
718 abscissa is -log10 (pvalue), the ordinate is the pathway name, the node size indicates
719 the number of genes enriched in the pathway, and the node color indicates -log10
720 (pvalue). F: Significantly enriched KEGG pathway, hsa04145: Phagosome. G:



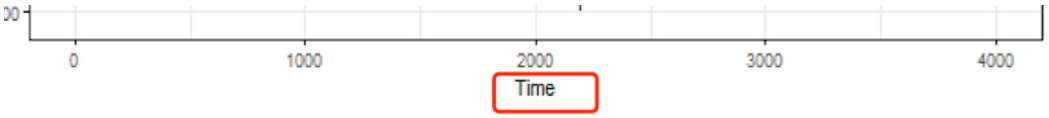
b) Please provide the meaning of this color bar.



Reply: We have revised the figure legend of figure 2 (see Page 25, line 652, 654 and 656-657).

6. Figure 10

Please provide the unit for the x-axis of 10A-D.

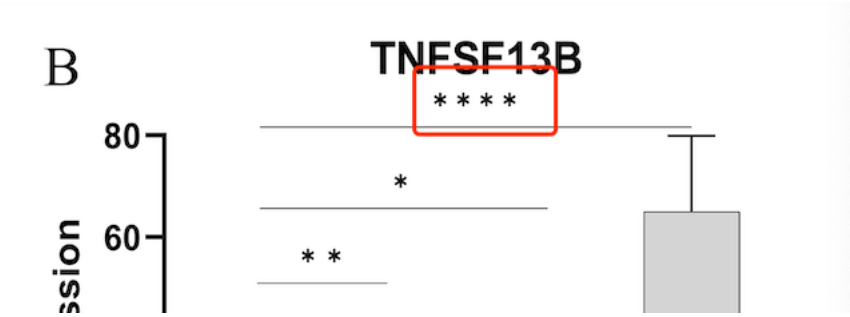


Reply: We have corrected the x-axis of figure 10A-D.

7. Figure 12

a) Please check if the figure matches the legend.

lines and renal tubular epithelial cell line. B: *, ** and *** represent the significant



Reply: We have revised the figure legend of figure 12 (see Page 29, line 771-773).

8. References/Citations

a) Please double-check if more studies should be cited as you mentioned “studies”. OR use “study” rather than “studies”.

102 studies have shown that ERS plays an important role in the occurrence and development
103 of tumors and protects tumor cells from drug-induced stress and radiation damage.(12)

b) Please double-check if citations should be added as you mentioned “studies”.

*Please note that the references should be cited in order of their appearance in the text. If the studies are not included in the reference list, please also update the current version.

104 Studies have shown that ERS can maintain the survival of renal cancer cells and can be
105 used as a new anticancer mechanism for the treatment of renal cancer. At present, there