

## Peer Review File

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### Reviewer A

1. In the introduction section, it is necessary to clarify what problems are still unclear, which leads to the purpose of this study.

Reply: Thanks for your comments. In the revised manuscript, we have further clarified the clinical problems and the purpose of this study.

Changes in the text:

“However, whether *MPP7* functions in the pathogenesis and progression of ccRCC with the possible mechanisms are still not clear. Previous studies indicate that several biomarkers correlate with the clinical prognoses of ccRCC patients. For instance, PTP4A3, GPX1, TAZ were all reported with the clinical prognosis of renal cancer and function via different signaling pathways (14-16). However, the association between MPPs and ccRCC has not been reported before. Therefore, we intended to investigate the potential role of *MPP7* in ccRCC by conducting bioinformatics-based analyses using a variety of databases and tools.” (Page 4, Paragraph 1)

“In this multi-dimensional bioinformatics-based study, we tried to analyze the associations between *MPP7* and the clinical prognosis, while investigating the corresponding relations by data analyses.” (Page 4, Para 2)

2. In the discussion part, the author repeated the results again, which is unnecessary, the authors should analyze the clinical practical value and significance of these results.

Reply: In the revised manuscript, we have further added the clinical practical value and the significance of the results.

Changes in the text:

“Therefore, *MPP7* could become a potential biomarker for prognostic prediction, combined with other key factors, while could function in the pathogenesis and progression of ccRCC in relation to mitochondrial or immune functions regulation.” (Page 11, Para 2)

“Therefore, *MPP7* could be a useful biomarker and a potential therapeutic target for ccRCC patients. However, the effects of *MPP7* on tumor proliferation, invasion and metastasis should be validated using both cellular and animal experiments with strict controls.” (Page 12, Para 1)

“Therefore, we can speculate that *MPP7* functions in TME by affecting the immune status of TME.” (Page 13, Para 1)

“However, the relationship between *MPP7* and mitochondrial functions is still not clear and further studies are needed to explore the role of *MPP7* on redox status, energy metabolism, mitochondrial dynamics and cell death.” (Page 13, Para 2)

3. What are the limitations of this study?

Reply: In the discussion part, we have provided with the limitation of this study in the last paragraph.

4. The manuscript should be reviewed by an English language text Editor, as there is a number of grammar, syntax, and lexicon errors.

Reply: The whole text has been edited by a native English speaker and we have further checked for a second time.

6. The quality of the figures should be improved.

Reply: We have provided with Figures of high-resolution at initial submission, while the quality of the figures may be impaired during peer-reviewing process.

## Reviewer B

First, the title needs to indicate that this is a bioinformatics analysis. The title is also not accurate since the study revealed that only the combination of MPP7 and clinical factors can accurately predict the prognosis.

Reply: Thanks for your comments. In the revised manuscript, we have further changed the title by adding “a bioinformatics analysis based on TCGA database”. As to the second recommendation, we have shown that the combination of MPP7 with other clinical factors could accurately predict the prognosis, while we also showed that the expression levels of MPP7 correlated with survival status and clinical prognosis in both Figure 3A-3C and Table 2. Moreover, we have changed the word “potent” to “potential” to make the title more accurate. Changes in the text: Please refer to the manuscript file.

Second, the abstract needs some revisions. The background did not indicate the potential clinical significance of this research focus and the objective of this study. The methods need to describe the clinical factors and prognosis outcomes in the datasets used. The results need to quantify the findings by providing statistics such as expression levels, HR values, and P values. Please also report the AUC values of the prognosis prediction model based on MPP7 and other clinical factors. The conclusion needs comments for the clinical implications of the findings, not to repeat the main findings again.

Reply: We have revised the abstract according to your suggestions. We have added the clinical significance and the objective of this study. Meanwhile, the clinical factors and prognosis outcomes were added. In the results section, some of the detailed statistics were added, however, some statistics were not added due to limit of word count. The conclusion was also revised to address the clinical implications of the findings. Changes in the text: Please refer to the manuscript file.

Third, the introduction of the main text needs to review what has been known on the of prior studies to indicate the clinical needs for identifying new prognostic biomarkers and their associated mechanisms. The authors need to explain the potential clinical significance of the research focus on MPP7.

Reply: In the revised manuscript, we have added the contents about the current knowledge about the prognostic biomarkers in ccRCC with the limitations and knowledge gaps. Changes in the text: Please refer to the changes in the Introduction section.

Fourth, in the methodology of the main text, please describe the research design and clinical factors and prognosis outcomes in the datasets. The authors need to describe the statistical analysis for the prognosis prediction accuracy of MPP7 and other clinical factors, including how the nomogram model was developed and validated, as well as the calculation of AUC, sensitivity and specificity for assessing the predictive accuracy. It is also necessary to report the threshold values of these parameters for a good prediction model. It seemed that there is no validation sample, which is necessary. According to the results of multiple Cox regression analysis, MPP7 is only one of the prognostic predictors, so the authors should consider to revise the text of the introduction to emphasize the combination of MPP7 and other factors, because the prognostic role of MPP7 is weak. There is no need to report the diagnostic AUC value of MPP7 for distinguishing tumors from normal tissues because this is not the focus of this study.

Reply: Thanks for your detailed comments and suggestions. As to the research design, the clinical factors and prognosis outcomes were all described in the first and third paragraph of the Method section. Moreover, the detailed statistical information has also been provided in different sections of the Methods section. The threshold value was already provided in the results section, while the validation sample of the prediction model was not provided since that we did not have enough data of ccRCC cohort to build the validation model. As to the description of the Cox regression, we have revised the text in the manuscript to emphasize the

combination of MPP7 and other factors as the prognostic predictor. We have deleted the contents of diagnostic AUC value of MPP7 for distinguishing tumors from normal tissues. Changes in the text: Please refer to the changes in the manuscript.

### Reviewer C

1. Please check if any more references need to be added in the below sentences since you mentioned “reports”, but only one reference was cited.

Previous reports have shown that changes in polarity-associated proteins affect epithelial polarity, thereby regulating cell proliferation, migration, and tumorigenesis

(6). MPPs are a class of cell polarity-related proteins comprising a total of seven

Reply: We have revised accordingly.

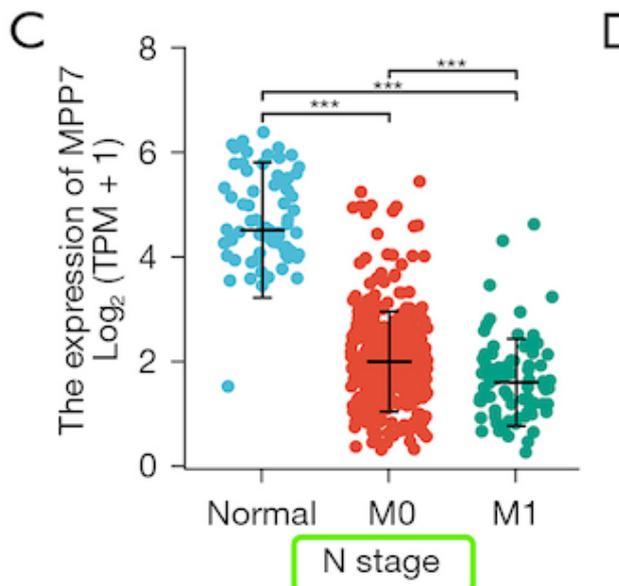
2. Figure 1E:

As cell images are all from HPA database, it’s needed to indicate the URL for each cell image in Figure 1E legend. Please provide.

Reply: We have provided with the URL for each image in Figure 1E in the legends.

3. Figure 2C:

The below N stage should be “M stage”.

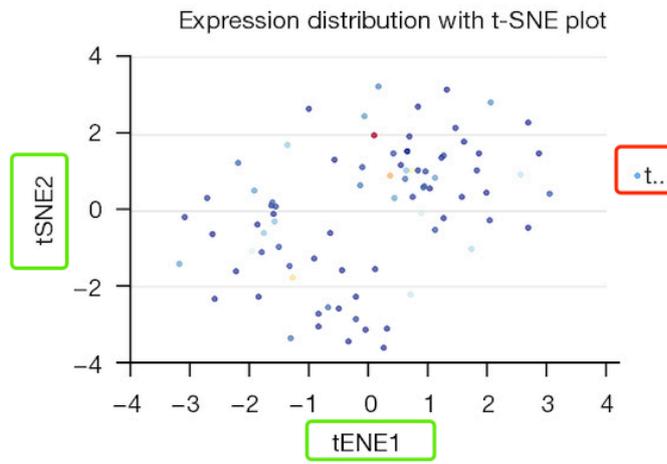


Reply: We have corrected it in the revised Figure 2.

4. Figure 5C:

The x/y-axis of Figure 5C should be “t-SNE 1” and “t-SNE 2”. Please revise. And please check the below red box. Is the word “t...” is correct and complete?

C



Reply: We have corrected it in the revised Figure 5.

5. Figure 7:

Figure 7C is not clear enough. Please resubmit Figure 7 in higher resolution.

Reply: Since that Figure 7C is generated through the TIMER website, therefore, the resolution can not be increased further.