

Peer Review File

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Reviewer A

Comment 1: I suggest the authors to indicate the development of the prognosis prediction model and the prognosis outcome, OS, in the title.

Reply 1: Thank you very much for your advice! Explicitly mentioning "Development of prognostic prediction models" and "prognostic outcomes" in the title may be more appealing to the target audience and more accurately reflect the core content and contributions of our research. Such a title not only highlights the focus of the research, but also allows potential readers to quickly understand the main idea of the paper. So, we took your advice!

Changes in the text: we have modified our text as advised (see Page 1, line 1-4).

Comment 2: Please revise the abstract to make it more accurate. The background needs to specify the clinical needs for this research focus and what the current knowledge gap is. The methods need to specify the clinical variables and prognosis outcomes in the datasets, the training and validation samples, and the instrumental variables used for the mendelian randomization analysis. The results need to report the accuracy of the prognosis prediction model, quantify the findings from MR analysis, and the findings from the transcriptomics analysis. Comments for the clinical implications of the findings are needed in the conclusion sentence.

Reply 2: Thanks again for your advice! Our previous abstracts were indeed too simplistic and did not accurately describe our research. So, we have revised our abstract.

Changes in the text: we have modified our text as advised (see Page 1, line 6-21).

Comment 3: In the introduction, a brief review on what has been known on the prognostic biomarkers, prognosis prediction models, in GC and analyses on the limitations of prior studies are needed. The authors need to clarify the controversy to be addressed by using MR analysis and explain the differences between prognosis significance analysis of BMG and the MR analysis, for example, the different research questions.

Reply 3: Thanks for your suggestions! We reviewed the current understanding of prognostic biomarkers and prognosis prediction models in gastric cancer and analyzed the limitations of previous studies. In addition, we explain the controversies that MR Analysis seeks to resolve, and explain the differences between analyses of the prognostic significance of BMG and MR Analyses.

Changes in the text: we have modified our text as advised (see Page 2, line 49-78).

Comment 4: In the methodology of the main text, please describe the clinical samples, clinical variables, and prognosis outcomes in the datasets used. The authors need to report the generation of training and validation samples, and the threshold AUC values

for a good prognosis prediction model. More details of the MR analysis is needed such as the selection of instrumental variables and sensitivity analysis. Please ensure $P < 0.05$ is two-sided.

Reply 4: Your suggestions are very helpful to us! We have again increased our materials and methods content as requested. In order to be able to introduce our research in more detail.

Changes in the text: we have modified our text as advised (see Page 3, line 108-111; Page 4, line 142-143; Page 4-5, line 184-214).

Comment 5: Please consider to review and cite several potentially related papers:

1. Cui MY, Yi X, Zhu DX, Wu J. Aberrant lipid metabolism reprogramming and immune microenvironment for gastric cancer: a literature review. *Transl Cancer Res* 2021;10(8):3829-384
2. doi: 10.21037/tcr-21-655. 2. Xu W, Ding H, Zhang M, Liu L, Yin M, Weng Z, Xu C. The prognostic role of fatty acid metabolism-related genes in patients with gastric cancer. *Transl Cancer Res* 2022;11(10):3593-3609. doi: 10.21037/tcr-22-761.
3. Zhu H, Luo M, Wang P, Peng H, Cheng Z, Li H. Comprehensive bioinformatics analysis for MEF2 family genes in gastric cancer. *Transl Cancer Res* 2022;11(11):4057-4069. doi: 10.21037/tcr-22-373.
4. Feng X, Zhao T, Liu X, Liu Y, Gao Y. Serum iron status and the risk of lung cancer: a two-sample Mendelian-randomization study. *J Thorac Dis* 2023;15(11):6291-6300. doi: 10.21037/jtd-23-1645.

Reply 5: Thanks for your suggestions! We have added these references to increase the persuasiveness of our article, thanks again for your suggestions!

Changes in the text: we have modified our text as advised (see Page 1, line 32; Page 2, line 48 and 68).

Reviewer B

1. Abstract

- 1) It is needed to describe the aim/objective of this study in the Background.
- 2) Please provide the full name of LASSO and ROC in the Abstract.

Reply : Thanks for your reminding, we have added this part of information.

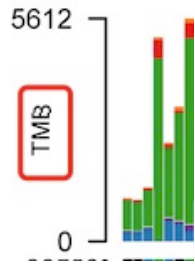
2. Main text

- 1) Please check all abbreviations in the main text, such as AJCC, TNM, DAPI, etc. All abbreviated terms should be full when they first appear.
- 2) Please provide website link/URL for Molecular Signature Database and The Cancer Genome Atlas (TCGA) database.

Reply : Thanks for your reminding, we have added this part of information.

3. Figures

- 1) Figure 2: Please define TCGA.
- 2) Figure 3: the word is not clear. Please define "TMB".



3) Figure 3: please add an abbreviation for The Cancer Genome Atlas Program.

606 Figure 3 BMG mutation map of TCGA [data sets](#)

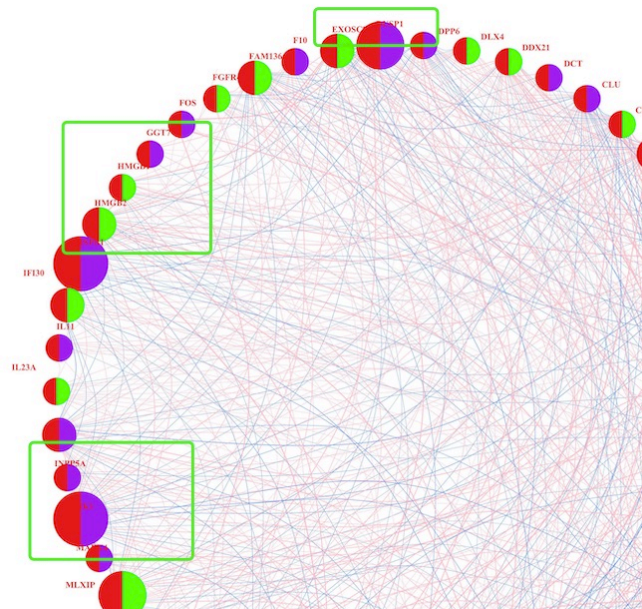
607 BMG, butyrate metabolism [The Cancer Genome Atlas Program](#)

4) Figure 3, 4, 5, 7, 8: please check the full name of BMG. Where is “G”?

606 Figure 3 BMG mutation map of TCGA [data sets](#)

607 BMG [butyrate metabolism](#) [The Cancer Genome Atlas Program](#)

5) Figure 4: the word is not clear. Please check through and revise.

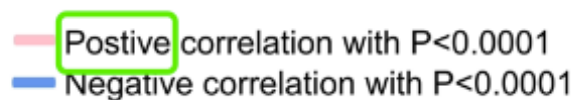


6) Figure 4: please unify the highlighted information.

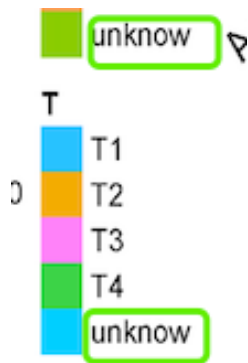
610 Figure 4 [BMS](#) prognostic correlation network

611 [BMG](#), butyrate metabolism

7) Figure 4: There is a typo.



8) Figure 5D, 7D: There is a typo.

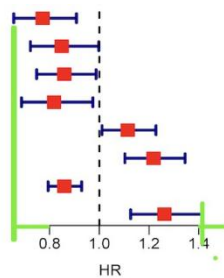


9) Figure 6: Please define TCGA.

10) Figure 7: please define HR, CDF, TCGA.

11) Figure 7A: Please revise “pvalue” to “P value” and “HR” to “HR (95% CI)”.

12) Figure 7A: please extend the x-axis.



13) Figure 8: the citation of Figure 8D and E is missing in the text. Please check and revise.

14) Figure 8E: Please provide description for Figure 8E.

15) Figure 8C-E: There is a typo.

Patients (increasing risk score)

16) Figure 9: the citation of Figure 9 is missing in the text. Please check and revise.

17) Figure 9: please indicate the meaning of **, ***.

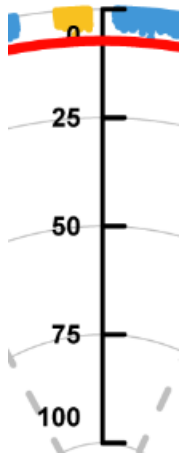
18) Figure 9: please define OS, AUC.

19) Figure 9B: Please remove (%) from the x/y-axis.

20) Figure 10: please define MSI, MSS.

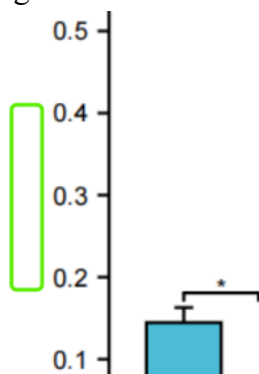
21) Figure 11: please indicate the meaning of different colors.

22) Figure 11: What the bar stands for?



23) Figure 12: please define SNP.

24) Figure 13A: Please add the description of Y-axis.



25) Figure 13B: Please provide the scale bar or magnification.

26) Figure 13: please define PCR, GC, NC.

Reply : Thanks for your reminding, we have corrected the error in the above picture.

4. Tables

1) Table 1 and S2: please revise “pval” to “P value”.

2) Please unify the description of Table S1.

453 Supplementary **Table 1**. Prognostic model↵

Table 1 Model construction coefficient↵

3) Table S2: please define SNP in the table footnote.

4) Table S3: please define PCR in the table footnote.

5) Table S3: please provide table head for each column.

6) Please check the citation of Table S2 and S3. “Model” is related to Table S3, not S2. “14 SNPs” is related to Table S2, not S3.

344 BMGs (Figure 8B and C). Supplementary **Table 2** describes the **model** formulation. We divided the

373 test. **Fourteen SNPs** were selected for further analysis (Supplementary Table 3). Our results provided

374 no evidence for an association between BMG and GC (Table 1) (Figure 12).↵

7) The citation of Table S4 is missing in the text. Please check and revise.

Reply : Thanks for your reminding, we have corrected the errors in the above form and

checked the position of the table.