

Reviewer A

The manuscript investigates the role of MMP11 as a prognostic biomarker in pancreatic adenocarcinoma (PAAD) and its association with immune infiltrates. The authors utilized various databases like TCGA, GEPIA, TIMER, and TISIDB to perform a comprehensive bioinformatics analysis, aiming to elucidate the clinical significance and expression level of MMP11 in PAAD. Exploring the relationship between MMP11 expression and immune cell infiltration provides valuable insights into potential therapeutic strategies. The manuscript presents significant findings and is well-structured but requires revisions to improve clarity and add experimental validation to support the bioinformatics data.

1- Provides a solid background in Introduction on PAAD and MMP11 but could be more concise.

Reply1: Thank you for your feedback.

Changes in the text: we have modified our text as advised (see Page 3, line 4 and page 3, line 11)

2- The manuscript lacks detailed information on the clinical characteristics of the patient samples used, including their source, inclusion, and exclusion criteria. Please provide if available.

Reply2: All mRNA information and clinical data of patients were obtained from The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) databases.

Changes in the text: we have modified our text as advised (see Page 3, line 31-33)

3- Methods used for determining cut-off points for MMP11 expression levels (high vs low) in the statistical analyses are not described.

Reply3: Added statistical analysis.

Changes in the text: we have modified our text as advised (see Page 5, line 22-27).

4- Although the manuscript mentions evolving biomarkers of resistance, a deeper discussion on the role of biomarkers in personalizing PDAC treatment would be valuable (10.1016/j.pan.2024.01.009). This could include current challenges in biomarker identification, validation, and how they might be used to guide therapy selection and predict treatment response or resistance.

Reply4: Thank you for your feedback.

Changes in the text: we have modified our text as advised (see Page 12, line 11-15).

5- While the conclusions summarize the findings well, the manuscript could better discuss the implications for future research and potential clinical applications of targeting MMP11 in PAAD.

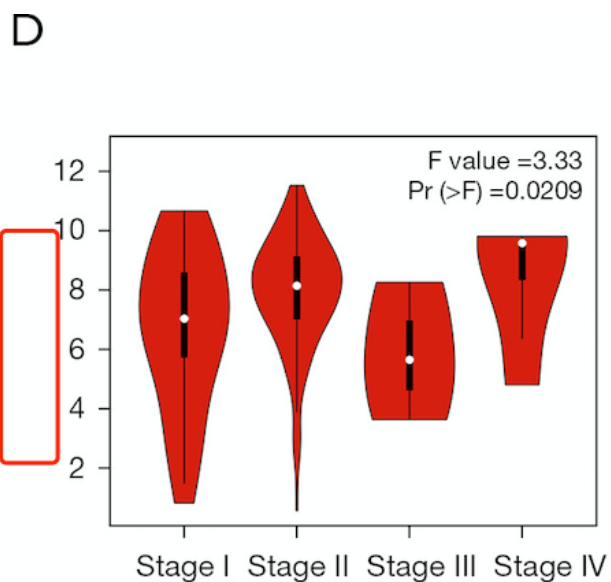
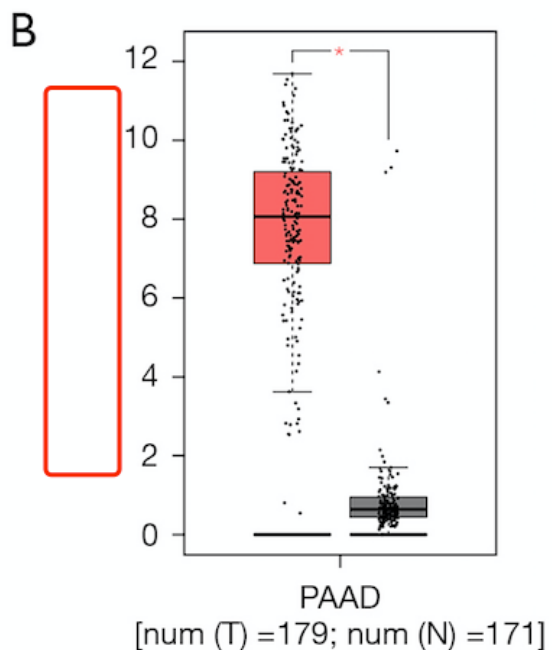
Reply5: Thank you for your feedback.

Changes in the text: we have modified our text as advised (see Page 14, line 18-22).

Reviewer B

1. Figure 1

Figure 1B, D: Please provide a caption for the Y-axis.



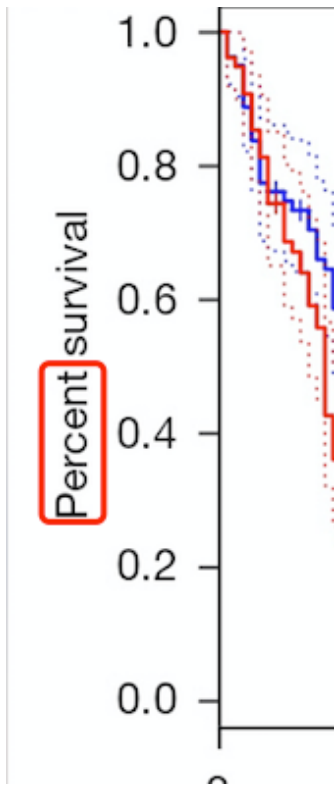
Reply: It has been modified.

2. Figure 3

a. The correct format for the y-axis should be one of the following, please revise.

a) If the description is “Percent survival”, the numbers should be 0-100.

b) If the description is “Survival”, the numbers should be 0-1.0.



b. Figure 3G-L: It is “RFS” in figure legend, but it is “DFS” in figure. Please unify.

8 LGG, MESO, PAAD, and UVM). (G-L) RFS curves for six cancers (i.e., KICH, LGG,
 9 PRAD, UVM, HNSC, and UCEC). *MMP11*, matrix metalloproteinase 11; TPM,



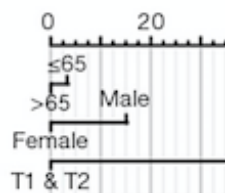
Reply: It has been modified.

3. Figure 4

Please indicate the unit of age.

H

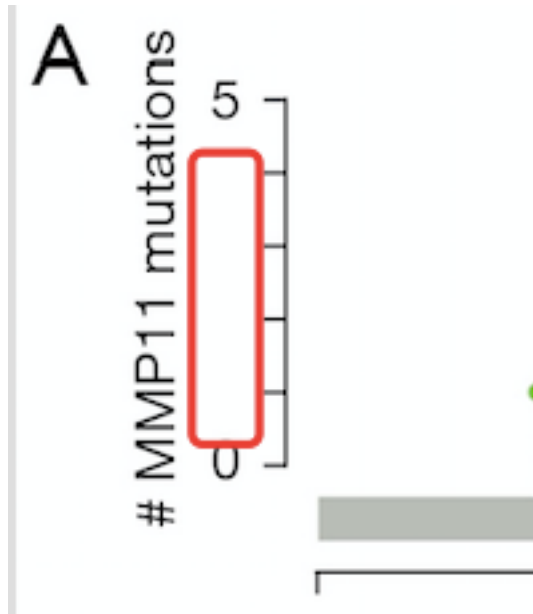
- Points
- Age
- Gender
- T stage
- Metastasis



Reply: It has been modified.

4. **Figure 5**

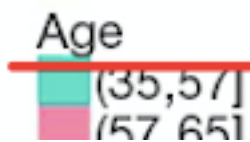
Please supplement the numbers.



Reply: It has been modified.

5. **Figure 6**

a. Please indicate the unit of age.



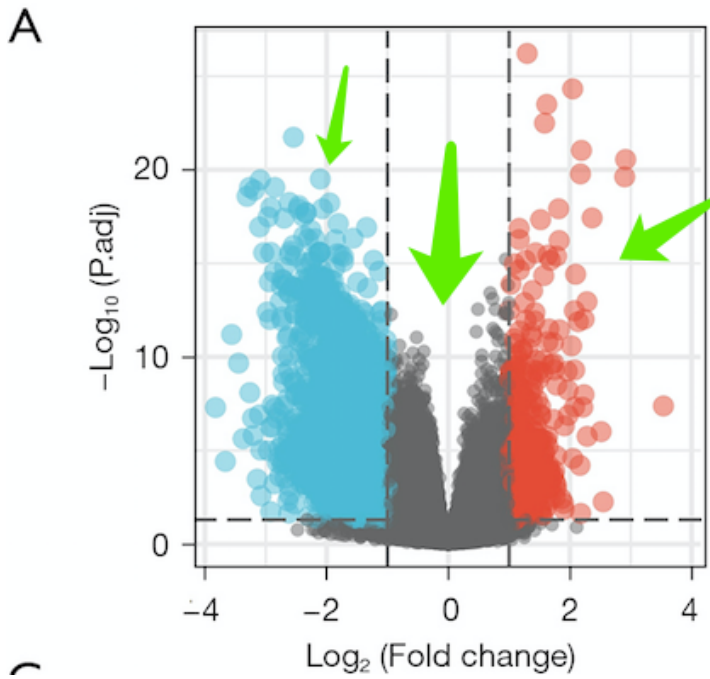
b. It seems that there are words in the bottom, but it is very vague. Please check.



Reply: a. It has been modified. b. The text at the bottom can be ignored, and online databases cannot provide clearer images.

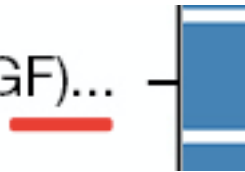
6. **Figure 7**

a. Figure 7A: Please explain the meaning of these different color dots in figure or figure legend.



b. Figure 7E: this term is incomplete. Please revise.

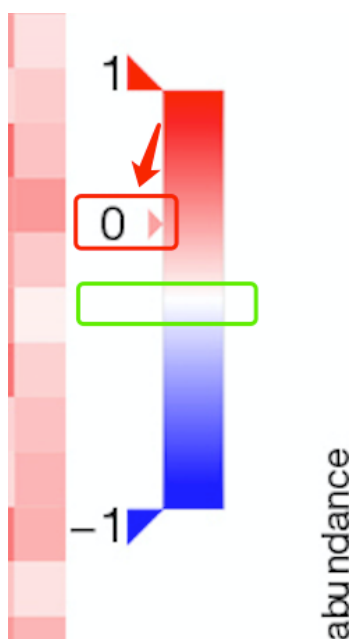
insulin-like growth factor (IGF)...



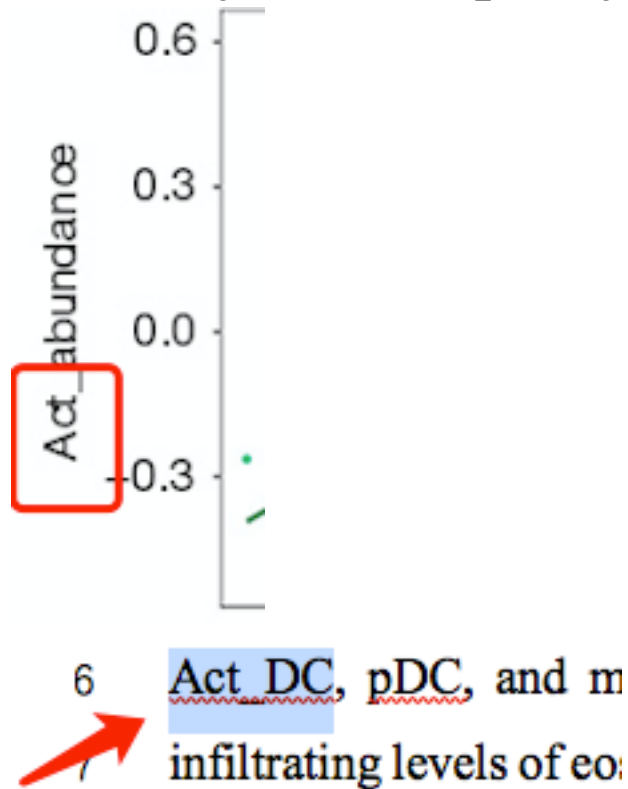
Reply: a. It has been Modified. (page30/line3-6); b. It has been modified.

7. Figure 9

a. The number 0 is in wrong place. Please revise.

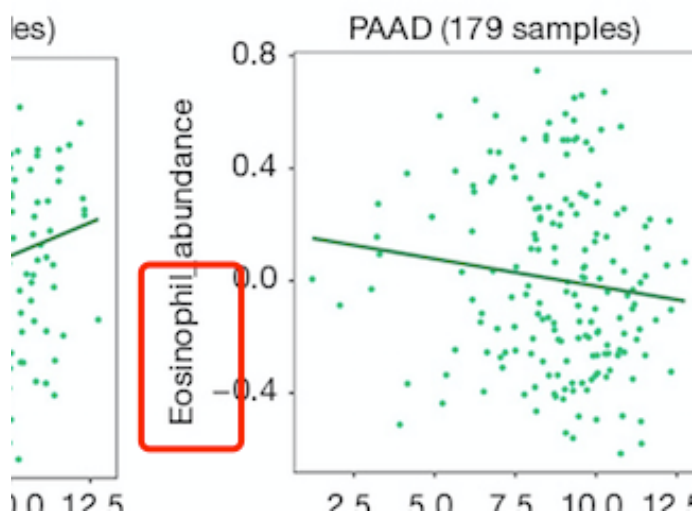


b. It is “Act” in figure 9B, but it is “Act_DC” in figure legend.



c. Please confirm whether “Eosinophil” should also be mentioned in the figure legend (B).

- 4 significantly positively associated with the infiltrating levels of Tcm_CD8, Tem_CD8,
- 5 Tcm_CD4, Tfh, Tgd, Th1, Th2, Treg, NK, CD56bright, CD56dim, MDSC, NKT,
- 6 Act_DC, pDC, and macrophages in PAAD, and was negatively correlated with the
- 7 infiltrating levels of eosinophils in PAAD. PAAD pancreatic adenocarcinoma: *MMP11*

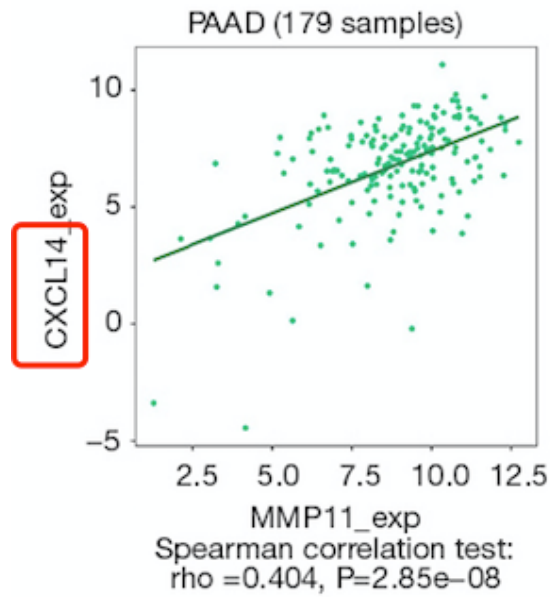


Reply: It has been modified.

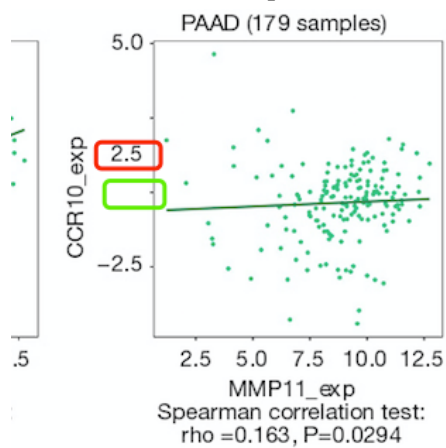
8. Figure 10

a. Please confirm whether “CXCL14” should also be mentioned in the figure legend (B).

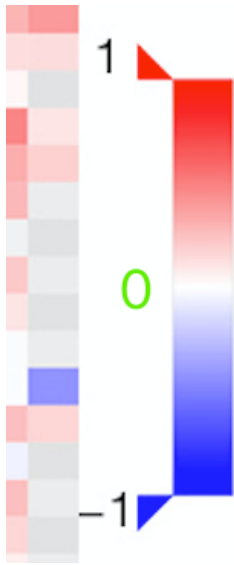
14 tumors. (B) *MMP11* expression in PAAD was correlated with chemokines, including
15 CCL3, CCL7, CCL13, CCL14, CCL17, CCL18, CCL22, CX3CL1, CXCL5, CXCL8,
16 and CXCL10. (C) Heatmap analysis of the correlation between *MMP11* and chemokine



b. This number is not parallel with the bar.

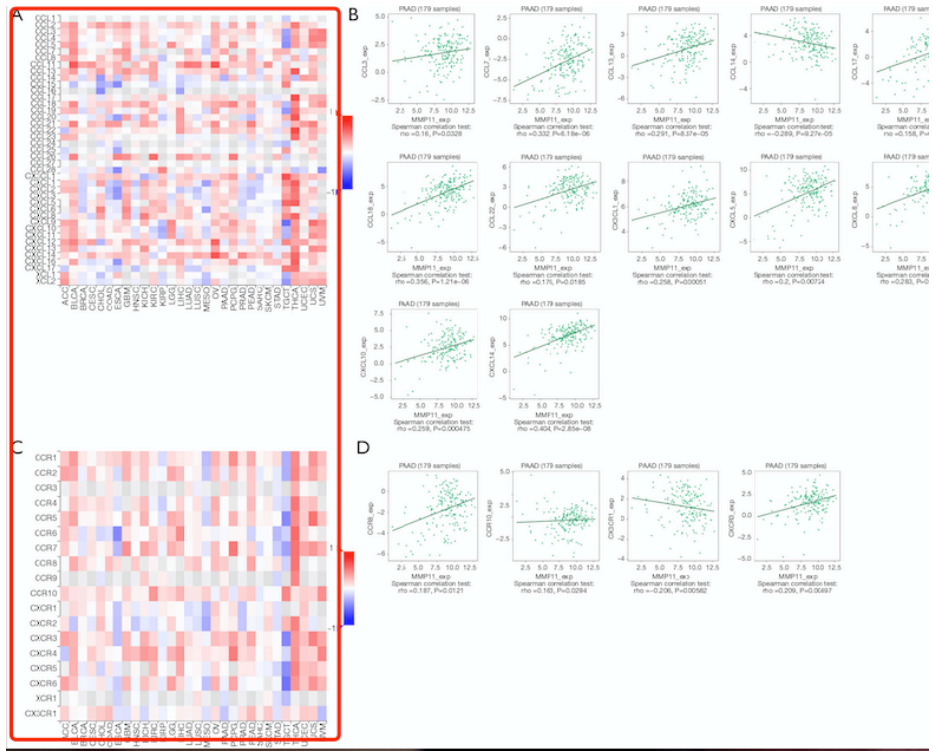


c. Figure 10A, C: Number 0 is missing. Please add.



d. Figure 10A, C is a heatmap. Please revise.

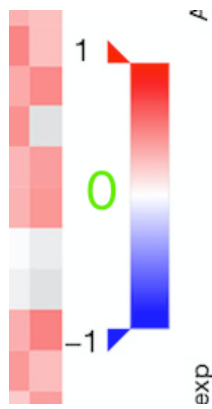
10 cell infiltration into tumors. The heatmap results showed that some chemokines and
 11 chemokine receptors were closely associated with the expression of *MMP11* in human
 12 tumors (Figure 10A, 10B). An association was also found between *MMP11* expression
 13 and chemokines in PAAD. Notably, *MMP11* expression was significantly associated
 14 with *CCL3*, *CCL7*, *CCL13*, *CCL14*, *CCL17*, *CCL18*, *CCL22*, *CX3CL1*, *CXCL5*,
 15 *CXCL8*, *CXCL10*, and *CXCL14* (Figure 10C). Additionally, we showed that *MMP11*
 16 expression was also significantly associated with chemokine receptors, including *CCR2*



Reply: It has been modified.

9. Figure 11A and figure 12

Number 0 is missing. Please add.



Reply: It has been modified.