

Peer Review File

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Reviewer A

Firstly, I would like to congratulate the authors on this original article. RNA analysis in patients with gastric cancer is a current topic.

I would appreciate the authors' insights on whether it would be more valuable to evaluate lymph node metastasis/tumor deposits instead of liver metastasis. From a clinical perspective, patients with liver metastasis do not have a proposed curative treatment, whereas patients with lymph node metastasis benefit from surgical or chemo treatments. What are your thoughts regarding a prognostic tool that can assess the RNA of primary and nodal tumors to predict the development of systemic metastatic disease?

Once you've conducted this analysis, what would be the direct clinical applications?

Reply: Firstly, I would like to express our gratitude for your effort in reviewing our manuscript. Regarding the predictive tool evaluating the RNA of primary tumors and lymph node tumors to forecast the development of systemic metastatic diseases, we are indeed interested in this area. Our team believes that such a predictive tool holds value in assessing patients' surgical and treatment options. Furthermore, our analysis has identified potential targets, including APOD, JUN, CXCL5, TNFAIP3, IL7R, and CD94. Among these genes, APOD, JUN, and CXCL5 are likely significant factors in the occurrence of liver metastasis in gastric cancer. We have also unveiled distinctions in the tumor microenvironment between gastric cancer and liver metastasis. Clinically, targeting these genes or their products might offer avenues to inhibit metastasis.

Minor corrections in the text:

(line)

20: Gastric cancer liver metastasis is a malignant metastatic disease.
Redundant phrase. Please rewrite or remove.

Reply: we have modified our text as advised. (see Page1 line 20)

Changes in the text: Liver metastasis is one of the most common distant metastatic sites for gastric cancer.

329: Tumor progression by the metastasis of gastric cancer to other organs may be different due to the interaction between cancer cells and tumor resident immune cells.
Please rewrite for better understanding.

Reply: we have modified our text as advised. (see Page 8 line 329)

Changes in the text: The progression of gastric cancer as it spreads to other organs might vary due to interactions between cancer cells and immune cells residing in the tumor.

335: The phenotypes of different immune cells between them in PT compared to Li were mostly associated with malignancies.
Didn't get the idea. Please explain.

Reply: we have modified our text as advised. (see Page8 line 335). Here, we want to emphasize that the states of certain immune cells in the tumor microenvironment of the primary site of gastric cancer may be suppressed or, alternatively, they promote the malignant progression of the tumor. Due to inaccuracies in the previous language description, misunderstandings arose, which we have now corrected.

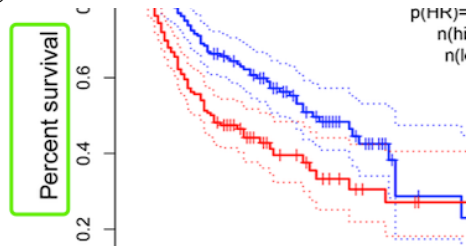
Changes in the text: The PT and Li sites harbor distinct immune cell populations, comprising Exhausted-T cells and TNFAIP3 high NK cells within the PT microenvironment. Functionally, these cells exhibit immunosuppressive traits or are associated with tumor progression.

Reviewer B

- Figure 2F: the word is not completed. Please check.



- Figure 2H-K: Please revise "Percent survival" to "Survival", since the rate is 0-1.



- Figure 4F-G: Please revise "Percent survival" to "Survival".
- Figure 4F: Please unify the p value.

253 survival of patients with LIHC ($P = 0.01$, $HR < 1$), while the high expression of TNFAIP3 was a poor
254 prognostic factor ($P = 0.39$, $HR > 1$) (Figure 4F-G). The survival analysis of patients with STAD also

Logrank $p=0.017$
 $HR(\text{high})=0.65$

- Figure 5F: Please indicate the meaning of the red, grey and blue bots.
- Please indicate the magnification for cell maps in Figure 8 legend.

Reply: We fixed bugs in figures, supplementary figures, as well as in the texts. Figure-revised files were resubmitted as attachment "Figure-revised.zip"

- Your Supplementary Figures are missing to submit. Please resubmit.

Reply: We resubmitted supplementary figures and legends as attachment “Supplementary Figures and Legends.zip”.