

Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: In this manuscript, the authors present a prognostic risk model for liver cancer patients, incorporating five genes from the ubiquitin proteasome system. While the topic is of significant relevance and the study yields interesting findings, this is not the inaugural research to offer a prognostic signature rooted in the ubiquitin proteasome system for predicting the patient outcomes in liver cancer. Moreover, there are several critical points that need to be addressed. Major issue: -The Figure 3 (Correlation analysis of expression levels and risk score with clinical parameters) is missing. Instead, the image of Figure 2 is repeated. Minor -In the Background section, the authors should refrain from elaborating on well-established foundational knowledge concerning ubiquitin. Instead, a comprehensive elucidation of liver cancer diagnostics would be highly beneficial. -The authors should ensure to properly reference and discuss the following studies that bear direct relevance to the current work: -Zhang J, Liu L, Wang Z, Hou M, Dong Z, Yu J, Sun R and Cui G. Ubiquitin-proteasome system-based signature to predict the prognosis and drug sensitivity of hepatocellular carcinoma. *Front. Pharmacol.* (2023) 14:1172908. doi: 10.3389/fphar.2023.1172908 -Liu, Zy., Li, Yh., Zhang, Qk. et al. Development and validation of a ubiquitin-proteasome system gene signature for prognostic prediction and immune microenvironment evaluation in hepatocellular carcinoma. *J Cancer Res Clin Oncol* (2023) 149, 13363–13382. <https://doi.org/10.1007/s00432-023-05189-w> -The authors should consider showing a volcano plot of DEGs between liver cancer and normal samples in the enrichment analysis. -In the Discussion section, the sentence “However, there is no report on the effect of PSMA8 expression level on the development of tumors.” should be reconsidered, since there are two studies that relate the expression of PSMA8 and the development of tumors: Wang Z, Huang C, Wu J, Zhang H, Shao Y and Fu Z. Analysis of the Prognostic Significance and Immune Infiltration of the Amino Acid Metabolism-Related Genes in Colon Adenocarcinoma. *Front. Genet.* (2022) 13:951461. doi: 10.3389/fgene.2022.951461; and Chiao C-C, Liu Y-H, Phan NN, An Ton NT, HDK, Anuraga G, Minh Xuan DT, Fitriani F, Putri Hermanto EM, Athoillah et al. Prognostic and Genomic Analysis of Proteasome 20S Subunit Alpha (PSMA) Family Members in Breast Cancer. *Diagnostics.* (2021) 11(12):2220. <https://doi.org/10.3390/diagnostics11122220>, where high PSMA8 expression levels were associated with good prognoses.

1. The Figure 3 (Correlation analysis of expression levels and risk score with clinical parameters) is missing.

Answer: Thank you for your reminder! The figure 3 have been added into the

Figure 3

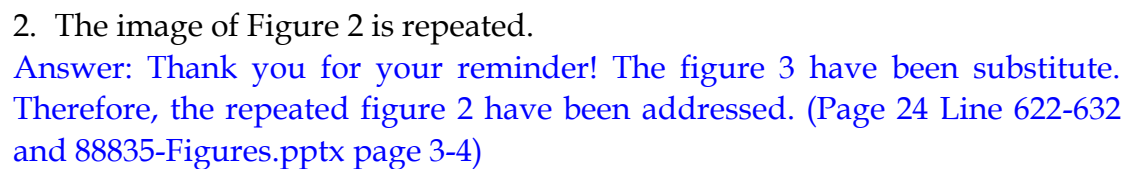


Figure 2

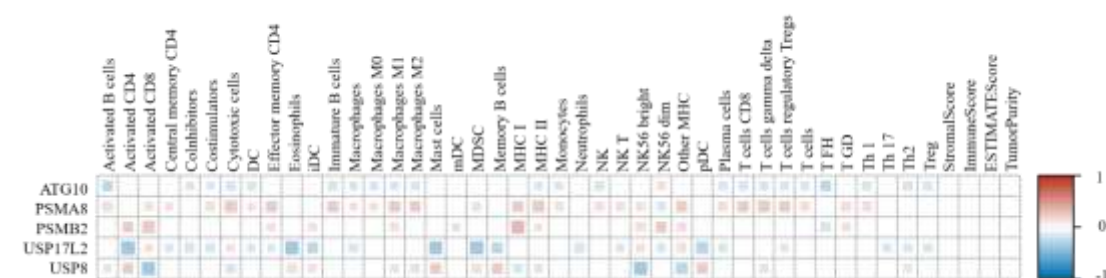
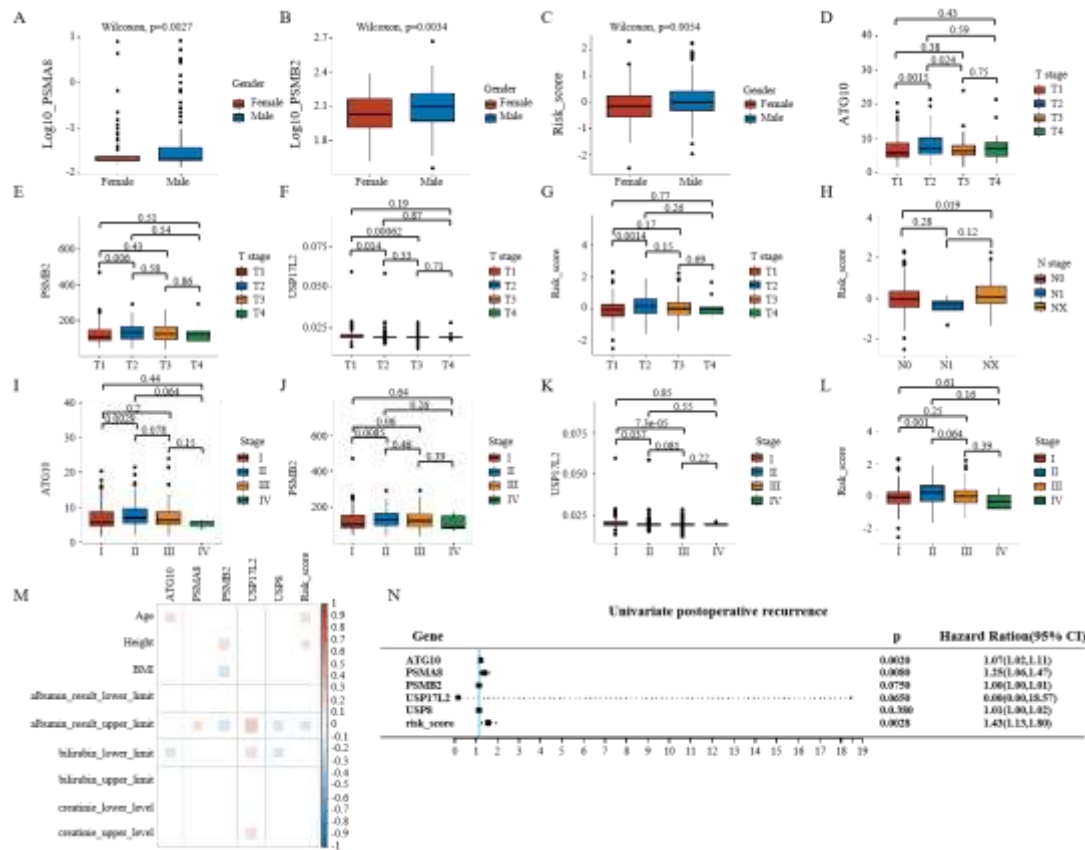


Figure 3



3. In the Background section, the authors should refrain from elaborating on well-established foundational knowledge concerning ubiquitin. Instead, a comprehensive elucidation of liver cancer diagnostics would be highly beneficial.

Answer: Thank you for your insight and meaningful suggestions! The basic knowledge about ubiquitin have been partially substituted by supplementing the epidemiological investigation and diagnostic methods of liver cancer. (Page 4 Line 106-Page 5 Line 122 and Page 5 Line 129-136)

4. The authors should ensure to properly reference and discuss the following studies that bear direct relevance to the current work: “Ubiquitin-proteasome system-based signature to predict the prognosis and drug sensitivity of hepatocellular carcinoma” and “Development and validation of a ubiquitin-proteasome system gene signature for prognostic prediction and immune microenvironment evaluation in hepatocellular carcinoma”.

Answer: Thank you for your constructive and insight guidance! I have added the two papers into the introduction of my manuscript. Based on TCGA datasets and 961 UPSGs (ubiquitin proteasome-system genes), Liu et al. found DCAF13, CDC20, and PSMB5 has excellent performance to predict the survival of liver cancer patients. Zhang et al. identified seven UPS-based prognostic signatures, while ATG10 was correlation with liver cancer development and prognosis through autophagy, immune response and tumor

metastasis. Therefore, proteasome inhibitors, as a potential and effective anti-tumor drug, have attracted a growing body of attention and research. (Page 5 Line 129-136)

5. The authors should consider showing a volcano plot of DEGs between liver cancer and normal samples in the enrichment analysis.

Answer: Thanks! The volcano plot about the DEGs between liver cancer and normal samples have been added into the Figure 4. (Page 9 Line 253-254 and 88835-Figures.pptx Page 5)

6. In the Discussion section, the sentence “However, there is no report on the effect of PSMA8 expression level on the development of tumors.” should be reconsidered, since there are two studies that relate the expression of PSMA8 and the development of tumors: “Analysis of the Prognostic Significance and Immune Infiltration of the Amino Acid Metabolism-Related Genes in Colon Adenocarcinoma” and “Prognostic and Genomic Analysis of Proteasome 20S Subunit Alpha (PSMA) Family Members in Breast Cancer”.

Answer: I am sincere gratitude for your meticulous review and valuable insights on my manuscript. Your attention to detail and sense of responsibility have greatly benefited me, contribution to the refinement and accuracy of my research work. The sentence (“However, there is no report on the effect of PSMA8 expression level on the development of tumors.”) has been removed. Following your suggestion, I have incorporated the content regarding the PSMA8 reports into the discussion section of my manuscript. These two studies have significantly enhanced my understanding of the research topic, adding substantial value to the quality and depth of the article. PSMA8 could affect the progression and prognosis of colorectal cancer due to the strong association with PSMB2. And, the higher PSMA8 expression levels were correlation with good prognoses for breast cancer through epigenetic regulation. In our study, it was found that it is positively correlated with the prognosis of patients with liver cancer. (Page 11 Line 288-293)

Once again, thank you for your patient guidance and invaluable suggestions. Your expert insights have provided crucial support to my research endeavors. I look forward to the opportunity to share my future research outcomes with you and benefit from your guidance.