Peer Review File

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Reviewer A

The study provides a thorough exploration of apoptosis, autophagy, and necroptosis pathways, integrating these into prognostic models for HCC. This novel approach is a key strength as it addresses the importance of multiple cell death pathways in cancer progression.
1. The manuscript presents an extensive analysis of the cell death pathways and their predictive models. However, certain sections, such as the Kaplan-Meier curves in Figures 2-4, could benefit from the addition of exact p-values for the survival differences between high- and low-risk groups. This would make the statistical significance of the results more transparent to the reader.
2. While overall survival (OS) has been analyzed, the addition of relapse-free survival (RFS) and Distant Metastasis-Free Survival(DMFS) would provide a more comprehensive understanding of the impact of these predictive models, especially in the context of HCC, which has a high recurrence rate. RFS is a critical factor in evaluating long-term patient outcomes, and including this data would enhance the clinical relevance of the models.

Reply:
1. We sincerely thank the reviewer for their valuable feedback. Regarding the suggestion to include exact p-values in the Kaplan-Meier curves, we agree that this would enhance transparency. However, for some comparisons, the p-values are extremely small ($p < 0.0001$), making it impractical to present more precise values. In these cases, we have reported the p-values as $p < 0.0001$ in accordance with standard reporting practices. We hope this addresses the concern, and we will clarify this in the revised manuscript.
2. Thank you for your valuable feedback and suggestions regarding the inclusion of relapse-free survival (RFS) and distant metastasis-free survival (DMFS) data. We agree that these metrics are crucial for a comprehensive understanding of the predictive models, especially in the context of hepatocellular carcinoma (HCC).
Unfortunately, we are currently unable to obtain RFS and DMFS data due to limitations in the available datasets we utilized for our analysis. The databases we accessed primarily focused on overall survival (OS) metrics, and comprehensive data on recurrence and metastasis rates were not included.
While we recognize that this limitation may affect the depth of our analysis, we believe that our current findings still provide meaningful insights into the prognostic capabilities of the models presented. We hope to explore the inclusion of these important survival metrics in future research as more comprehensive datasets become available.
We appreciate your understanding and will ensure to discuss this limitation in the revised manuscript.
Thank you once again for your insightful comments.

Reviewer B

Pros:
Rich Data Use: The study uses large, diverse databases, improving the study's robustness.
Validated Models: The findings are confirmed using independent data, enhancing their reliability.
Insightful: Offers new insights into how genes influence liver cancer and patient survival.

Cons:
Complex Methods: The statistical methods are complex, which might be hard for non-experts to understand.
Based on Past Data: It relies on retrospective data, which can introduce biases.
Lacks Direct Tests: There's no experimental testing of the genes, which is necessary to understand their roles fully.

Reply:
Thank you very much for your thoughtful and constructive review of our manuscript. We genuinely appreciate the time and effort you invested in evaluating our work.
Pros:
We are delighted to hear that you found our use of large, diverse databases to be a strength of the study. We aimed to enhance the robustness of our findings through comprehensive data analysis, and it's gratifying to know that you recognize this effort. Additionally, we are pleased that the validation of our models through independent data sources resonated with you, as we believe this adds significant reliability to our conclusions. Your acknowledgment of the new insights into how genes influence liver cancer and patient survival motivates us to continue our research in this important area.
Cons:

1. **Complex Methods:** We fully understand your concern regarding the complexity of the statistical methods used in our study. We strive to make our research accessible to a wider audience, and in our revised manuscript, we will work to provide clearer explanations and more context around these methods. We will include simplified descriptions and, if possible, visual aids to help non-experts better grasp our approach.
2. **Based on Past Data:** While we recognize that our reliance on retrospective data can introduce biases, we believe that the scale and diversity of the datasets we utilized provide a robust foundation for our findings. In our revision, we will discuss the potential limitations of retrospective studies more explicitly, along with their implications for our results. We appreciate your insight on this matter, and we will be sure to address it comprehensively.
3. **Lacks Direct Tests:** We acknowledge the importance of experimental validation in understanding the roles of specific genes. Our study primarily aims to provide a bioinformatics perspective, which we hope will inspire further experimental research. We will emphasize this point in our revision and suggest that future studies could

build on our findings to conduct the necessary experimental tests.

Once again, we sincerely thank you for your valuable comments and suggestions. Your feedback is instrumental in improving our manuscript, and we are committed to addressing your concerns thoroughly in our revision.