**Peer Review File**

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**Reviewer A:**

Comment 1: In this study, the authors characterized exosome-related genes in HCC livers obtained from the database such as the exoRbase and the International Cancer Genome Consortium database. Overall, this study has been well conducted but all of the data were obtained from the database. It is better to perform the clinical verification of selected genes (XPO1, IFI30, FBXO16, CALM1, MORC3) in HCC. The authors also need to consider some in vitro assays to explore the functional roles of selected genes (XPO1, IFI30, FBXO16, CALM1, MORC3) in HCC. The correlation of selected genes (XPO1, IFI30, FBXO16, CALM1, MORC3) and immune checkpoint genes (PD-L1, PD-L2, TIGHT and IDO1) should be discussed.

**Reply 1: Thank you very much for your kindly comments on our manuscript. There is no doubt that these comments are valuable and very helpful for revising and improving our manuscript. In what follows, we would like to answer the questions you mentioned and give detailed account of the changes made to the original manuscript. We analyzed the survival of five genes in the model respectively, which were statistically significant. (Figure S1). Figure S2 Then we identified the 10 genes most related to these five genes in the model and made enrichment analysis, which may explain the function of these genes on HCC to a certain extent (GO.xlsx). From which we may conclude, these genes are mainly involved in the pathway of immune cell regulation, p53 and cell cycle. These genes may exert their functions through these pathways in tumors. Next, we discussed the correlation between the selected genes and immune checkpoint genes. (Figure S3). Figure S3**

Comment 2: To use an abbreviation, write the full name in the first appearance.

**Reply 2: We have made corresponding changes in the text and written the full name in the first appearance of abbreviations.**

**Reviewer B:**

Comment 1: In figure 1, they identified 19 DEincRNAs, 45 DEmiRNAs, 47 DEmRNAs and 2 DEcircRNAs to construct their network. However, their results did not find the significant change between HCC and normal group. All heat-maps first show results similar to HCC and normal.

**Reply 1: Thank you for your letter and comments concerning our manuscript. These comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made corrections which we hope meet with approval. The previous heat map was indeed misleading, perhaps due to improper threshold adjustment. In order to avoid misleading readers, we deleted heat maps.**

Comment 2: In figure 2, they have a strong bias in grouping clinical patients into high-risk groups and low-risk groups. And they did not explain why they only selected 5 genes for further analysis. In addition, the demographics of these patients are unclear.

**Reply 2: To clarify the bias between the two groups, we did chi square analysis on the demographic data of the two groups. And five genes were selected by LASSO regression (appearing over 500 times out of a total of 1000-fold cross-validation repetition), and the detailed process is shown in the appendix. (boot_result-1000.xlsx) In order to express our research process more clearly, we added a flow chart (Figure 1).**

Comment 3: Although the authors tried to link these five genes with HCC. However, the data they performed is ambiguous. They should explain why the list of five genes can be annotated in the cell cycle, glycolysis, peroxisome, PPAR pathway, purine and pyrimidine biosynthesis. And they are located on different chromosomes and have no significant correlation in HCC.

**Reply 3: Then we identified the 10 genes most related to these five genes in the model and made enrichment analysis, which may explain the function of these genes on HCC to a certain extent (GO.xlsx). From which we may conclude, these genes are mainly involved in the pathway of immune cell regulation, p53 and cell cycle. These genes may exert their functions through these pathways in tumors.**

Comment 4: Clinicopathological factors that can be used for HCC include serum index (AFP, ALT, AST…), hepatitis status and various parameters. They should expand their table and recalculate these events.

**Reply 4: Thank you for your valuable comments. We have added other index to minimize bias, and re-do the univariate Cox regression, multivariate Cox regression and nomogram. (Figure 4) It is regrettable that due to the defect of public databases, some index such as ALT/AST cannot be found.**

Comment 5: In this study, they did not describe the correlation or results between immune response and HCC. They must declare the potential regulatory mechanisms between the 5-genes signature and the immune system.

**Reply 5: We did a GSEA score to find the most relevant pathways, which may play a role between immune response and HCC. (gsva_output.xlsx) And the receptor interacting protein kinase 1 (RIPK1) may represent an essential signaling node in cell death and inflammation.1**

Comment 6: They mentioned that the signature is related to the M2 macrophage response in HCC. However, in their results, no M1/M2 shift or inverse correlation was observed. Most importantly, the immune response should be examined by specific surface markers rather than RNA level.

**Reply 6: Thank you for your inspiring comment. We originally wanted to express the strength of the interaction between cells, but now it was a bit misleading. We have deleted Figure 5C. The main specific surface markers of M2 macrophage are CD， and we made a graph to show the relationship.(Figure S4)**

Comment 7: Recently, the survival period of HCC patients has been prolonged and improved. In their figure 2, it also shows that the average survival rate is more than 5 years. Therefore, they need to readjust their arguments and discussions.

**Reply 7: Thanks to advances in treatment, the survival time of HCC patients is indeed longer than that in the past. In our training model and validation model, we divided patients into high and low risk group, 36/307 of training and 23/209 of validation and this ratio is similar. We made changes in the corresponding discussion section.**

Comment 8: They should explain several correlations of immune events (Fig. 5C) and why they are concerned about these immune checkpoint molecules in figure 6. Unless there is information about whether the patient has received immunotherapy, it cannot be verified and determined.

**Reply 8: The high-risk group has higher Treg, so we wanted to see if the reason for the poor prognosis was related to the immune microenvironment. Our patients**

**had never used immunotherapy, and the language in corresponding Results part was somewhat misleading. We have deleted these contents.**

Comment 9: The pixels in Figure 1 and 5 are poor.

**Reply 9: We have modified the image with poor pixels.**

Comment 10: The detailed case number of each analysis should be listed.

**Reply 10: We have listed the detailed case number of each analysis. Line 80, 82. And in order to express our research process more clearly, we added a flow chart (Figure 1). Reference: 1.Schneider AT, Gautheron J, Luedde T, et al. RIPK1 Suppresses a TRAF2-Dependent Pathway to Liver Cancer. Cancer Cell. 2017 Jan 9;31(1):94-109. doi: 10.1016/j.ccell.2016.11.009. Epub 2016 Dec 22. PMID: 28017612.**