We gratefully appreciate the reviewer's constructive suggestions and questions. Our responses to the questions are shown below.

Reviewer: 1

Number ID:03882844

1.Comments: I congratulate author for advancing the field of liver cancer

1.Answer: Thank you for your suggestion and we appreciate your approval of our research.

Reviewer: 2

Number ID:02954382

Comments: 1. Title. Does the title reflect the main subject/hypothesis of the manuscript? Yes, the title of the manuscript is concise, informative and reflect the main subject of the manuscript 2 Abstract. Does the abstract summarize and reflect the work described in the manuscript? Yes, and that was done concisely, and very clearly 3. Key words. Do the key words reflect the focus of the manuscript? Yes 4. Introduction. Does the manuscript adequately describe the background, present status and significance of the study? Yes. This manuscript shortly, and clearly describe the background, present status, and what authors aimed by this study 5. Methods: This section is clearly written by authors, and is OK, including all subsections 6. Results This section is concisely written by authors, including all subsections 7. Discussion Is OK 8. References. Does the manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections? Does the author self-cite, omit, incorrectly cite and/or over-cite references? In this manuscript are cited important and authoritative references 9. Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate? Yes, the manuscript is clearly, concisely, and coherently presented. Language and grammar are appropriate 10. Illustrations and tables. Are the figures, diagrams and tables sufficient, good quality and appropriately illustrative of the paper contents? Do figures require labeling with arrows, asterisks etc., better legends? Tables and Diagrams are of good quality, illustrative, and reflect the paper contents.

Answer: Thank you for your careful review, and we sincerely appreciate your suggestions.

Reviewer: 3

Number ID:02451447

Comments: 1. Among them, the Glycolytis group has significantly more immune cell infiltration: NK cells, CD4 T cells, Treg cells, mast cells, etc. But glycolysis was seen to have the shortest median survival time of tumours. The authors discussed the possibilities of Treg and ROS in this glycolytic group HCCs. Studies have shown higher intratumoral inflammatory infiltrate is associated with better prognosis and response to ICB (PMID: 28624577 and PMID: 29603348). The authors may need to analyze more details of infiltrating immune cell types such as CD4 and CD8, since these are closely related to ICB treatment response and survival.

1.Answer: By using the “Cibersort” method, we obtained significantly higher infiltration of NK cells, CD8 T cells, and M1M2 cells in the FAO group than in the Glycolytis group. This may be consistent with the results that FAO group has a better prognosis and better response to ICB. However, the immune cell infiltration phenotype could not predict response to ICB alone. The effect of ICB therapy depends on the intricate and dynamic interactions between tumor cells, immune cells, and

other cells. In microenvironment, the complex interactions between tumor cells, immune cells and other immune modulators may inhibit or enhance the immune response. Some of our methods get the opposite results to what was expected, which may require further studies of the relationships in more depth in conjunction with the underlying experiments. It must be acknowledged that this may be related to the different etiology of HCC that you mentioned later. Thank you for your valuable suggestion. We will further analyze the disease and explore the reasons for them in a follow-up study.

2. The current does not consider etiologies of HCC. Are there any difference in the metabolic pathways between viral hepatitis and non-alcoholic liver disease associated HCCs? Recent study has shown HCC arising from non-alcoholic liver disease does not benefit from the ICB treatment. Patients with NASH-driven HCC who received ICB treatment showed reduced overall survival compared to patients with other etiologies (PMID: 33762733). If the authors can further analyze the proposed 4 groups in viral or non-viral (NASH) will be very helpful. The etiologies of the HCCs can also be found from the database the authors used for this study.
2.Answer: Dear reviewer, your proposal is very novel and topical. Unfortunately, we were not able to find required clinical data in the TCGA and ICGC databases. We have tried to conduct the study in the GEO database but could not get the desired results due to the lack of data. We also hope to find ways to include this variable for analysis in subsequent studies. Thank you very much for your suggestions, which have broadened our horizon greatly.

3. Page 7: "In terms of SNP, the most frequent mutation gene of the Glycolysis group is TP5": The TP5 should be TP53, right?
3.Answer: Sorry for the omission of characters in our writing. Thank you very much for your careful review, and again, thank you from the bottom of my heart.

4. Page 8: "The low-risk group and FAO group were more sensitive to ICB treatment". It is unclear what is the low-risk group?
5. Page 8: "We used this method to compare the high- and low-risk groups of the prediction model and found that the low-risk group could benefit, regardless of ICB treatment or common chemotherapy drugs". Same question as above, how the low and high-risk groups were defined? Please describe it clearly in the methods section.
4.5. Answer: After establishing the prognostic model, we obtained a risk score according to the gene expression of different samples. Samples higher than the median value of the modeling group were divided into high-risk group, and those with lower were divided into low-risk group. We have added this grouping description to the methods section and thank you for your valuable suggestions and careful review.

Answering reviewers for second round review

Dear Editor, Thank you very much for giving us another chance to improve the manuscript. Our responses to the questions are shown below.

Comments: The authors have made significant improvement in this revised version. I only have a minor suggestion for the authors which was my second comment in last version. Although the authors did not find anything in the so far available database, please briefly discuss that these genes discussed in this paper might be etiologically different, based on the reference I gave last time (Here I am copying my original comment and the author's reply for your reference). Otherwise, I have no more comments. 2. The current does not consider etiologies of HCC. Are there any difference in the metabolic pathways between viral hepatitis and non-alcoholic liver disease associated HCCs? Recent study has shown HCC arising from non-alcoholic liver disease does not benefit from the ICB treatment. Patients with NASH-driven HCC who received ICB treatment showed reduced overall survival compared to patients with other etiologies (PMID: 33762733). If the authors can further analyze the proposed 4 groups in viral or non-viral (NASH) will be very helpful. The etiologies of the HCCs can also be found from the database the authors used for this study.

Answer: Dear reviewer, your proposal is very novel and topical. Unfortunately, we were not able to find required clinical data in the TCGA and ICGC databases. We have tried to conduct the study in the GEO database but could not get the desired results due to the lack of data. We also hope to find ways to include this variable for analysis in subsequent studies. Thank you very much for your suggestions, which have broadened our horizon greatly. Answer: Thank you for your suggestion. After reviewing the relevant literature we found that cirrhosis induced by different etiologies can make a difference in the response of HCC patients to ICB. In contrast, the metabolic

profile of patients with NAFLD is characterized by hyper-glycolysis. Our study concluded that samples in the metabolic subgroup with active glycolytic gene expression had lower benefit from ICB. Although we were not able to identify in the data whether patients had cirrhosis of different etiological origin. However, from the metabolic perspective, it is still supported that ICB therapy is superior in the subgroup with active fatty acid oxidation genes than in the subgroup with active glycolytic gene expression. We have discussed it accordingly in the revised manuscript. Thank you very much for your valuable suggestions. Yours sincerely, Lei Qin