

Dear Editor:

Thank you very much for your decision letter and advice on our manuscript (Manuscript NO.: 65808) entitled “PPP2R3A gene might be a predictor of poor prognosis for hepatocellular carcinoma patients after liver transplantation”. We also thank the reviewers for the constructive comments and suggestions. We have revised the manuscript accordingly, and all amendments are indicated by red font in the revised manuscript. Since the automatically generated manuscript has no color, in order to make you better see the changes, we upload the revised manuscript to the supplementary materials. In addition, our point-by-point responses to the comments are listed below this letter.

We hope that our revised manuscript is now acceptable for publication in your journal and look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Jia-jia He, author,

Qing Zhang, Correspondence Author.

First of all, we would like to express our sincere gratitude to the reviewers for their constructive and positive comments.

Replies to Reviewer 1

1. The study designs and methods are appropriate, and the interpretations of the results are reasonable. Authors should also mention criteria other than Hangzhou criteria for AFP used for post-transplant survival and prognosis.

Response: Thank you for your insightful suggestion. Other criteria involving AFP have been mentioned in the Introduction section (page 4, lines 24-28).

2. Authors should explain why they use a semi-quantitative method for PPP2R3A expression. Could a quantitative method be better for measuring PPP2R3A expression?

Response: Semi-quantitative scoring standards are more commonly used in immunohistochemistry. I have explained the reason for choosing semi-quantitative scoring in this study in the Experimental methods section (page 8 lines 8-11).

3. The limitations of the study should be stated in the discussion section.

Response: Thanks for your thoughtful suggestion. Accordingly, the limitations of the study have been added in the Discussion of the revised manuscript (page 23 lines 15-21).

Replies to Reviewer 2

1. The title of the manuscript does not reflect precisely the main message of the study and presents it as if with some uncertainty.

Response: Thanks for raising this critical issue. The general title has been replaced.

2. More to that the conclusion in the Abstract and the conclusion section in the body

text do not exactly match each other.

Response: Thanks for your thoughtful suggestion. The conclusions in the abstract and the conclusions in the main text have been revised (page 3 lines 8-9).

3. The authors have stated that “Only the Hangzhou standard includes the molecular marker alpha-fetoprotein (AFP)...”. Metro Ticket Project should also be mentioned as it similarly suggests evaluating “Post-transplant survival according to HCC pre-transplant staging and AFP”.

Response: This part of the content has been added to the revised manuscript (page 4, lines 24-28).

4. General characterization of the study population is fine in terms of the used patient selection standard. However, the Milan criteria for liver transplantation in HCC are still assumed as an index selection system in various practice guidelines. It would be very important to know the results of OS and RFS in case the patients were classified according to Milan system. This data would be beneficial for a larger international acceptance allowing for direct comparison of presented data. Recalculating and presenting additional version of your data based on Milan in- and out- criteria would be of importance fostering a discussion whether the Milan criteria are too stringent and have to be universally updated. Reliable data is needed to show the validity or weakness of this classical selection system.

Response: Thanks for your thoughtful suggestion. Several contents have been added in the Results of in the revised manuscript (page 13, lines 10-13; page 15, lines 9-22; page 16, lines 1-2; Table 5 and Figure 6) to address this issue. In addition, we reorganized the data and found that the number of patients meeting the Milan criteria was small (25), so only the 1- and 3-year survival rate and the recurrence-free survival rate were analyzed.

5. There is too much emphasis (excessive information) on the role of PPP2R3A in other tumors (citations 26 to 30).

Response: Examples in the revised manuscript have been appropriately simplified.

6. Language Misprints, word omissions, capital letters.

Response: Correction has been made in the revised manuscript.

Replies to editor

1. Self-cited references.

Response: Citations 25 to 26 is self-cited references, 5 new references have been added: 12, 13, 38, 43, 44.

2. The title is too long, and it should be no more than 18 words.

Response: Title has been streamlined.

3. The “Author Contributions” section is missing.

Response: The “Author Contributions” section has been added.

4. The authors did not provide the approved grant application form(s).

Response: The approved grant application form(s) has been sorted out.

5. The authors did not provide original pictures.

Response: The original pictures have been sorted out.

6. The “Article Highlights” section is missing.

Response: The “Article Highlights” section has been added.

Other

1. The “Relationship between PPP2R3A and the clinicopathological features of tumors” in the Results section missed an indicator, which has now been added (page 11, lines 1). Corresponding discussions were also made in the Discussion (page 21,

lines 20-23).

2. In the Results section (Prognostic significance of PPP2R3A combined with AFP), the 1, 3, and 5 years survival rates and recurrence-free survival rates of each group have been added in order to better observe and compare the differences between the groups (page 14, lines 2-7; page 14, lines 13-18).

3. Because the school requires that the unit of the tutor must be added to the school, the corresponding author of the manuscript has two units. All other authors were in the knowledge, no conflicts of interest.