

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Prognostic factors influencing the short-term and long-term survival of hepatocellular carcinoma patients with portal vein tumor thrombosis treated with chemoembolization" (tracking number 62325). Those 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 read the comments carefully and have made correction which we hope meet with approval. Revised portions are marked in red with track changes. The main corrections in the paper and the responds to the reviewers' comments are as following:

Reviewer 1 (Number ID: 05408183)

1. First, why have no independent predictors for long-term survival been evaluated?

Response: Thanks for the reviewer's comment! We have added an assessment of independent factors affecting long-term prognosis. We used ROC curves to evaluate the predictability of the number of tumors and pathology for long-term survival. Number of tumors (AUC:0.665, 95%CI: 0.568-0.763, P=0.004) had the best predictive ability, followed by gross pathology (AUC: 0.620, 95% CI: 0.510-0.730, P=0.035).

These two indicators have good predictive power for long-term prognosis. The details can be found in *Figure3* and *Line 216-219, Page 10*.

2. Second, why is there no univariate analysis of survivors versus non-survivors at 12 months after TACE?

Response: Thanks for the reviewer's comment! I am very sorry, we did not put the univariate analysis of survivors versus non-survivors at 12months in a prominent position. In the text, TABLE 4 showed the results of univariate analysis, and we also mentioned the results of univariate analysis in *Line 206-209, Page 9-10*.

3. Third, the number of cases is OK, why is there no validation cohort to verify?

Response: Thanks for the reviewer's comment! This is a very good suggestion. The reason why we did not validate cohort that our study is a single-center study. And because of the restriction of inclusion and exclusion criteria, although we collected data from January 2015 to July 2019, there were only 181 cases, so we did not set up a verification group. But, in the discussion section, we have proposed that We need multicenter and larger sample research to further verify in the future. The details can be found in *Line 274-276, Page13*.

4. Finally, the author may be able to establish a nomogram to predict the postoperative survival of HCC patients with PVTT.

Response: Thanks for the reviewer's comment! This is a very good suggestion. There are two reasons why we did not add nomogram: First, this study was a single-center and retrospective study, and it was difficult to avoid selective bias. Second, the independent prognostic factors influencing the short-term and long-term survival of hepatocellular carcinoma patients with portal vein tumor thrombosis treated with chemoembolization are fewer in the study. If it could be based on the results of multicenter, large sample size and prospective studies to plot nomogram, it may have more clinical significance.

Reviewer 2(Number ID: 01560036)

Interesting paper within the scope of the Journal. Some practical advises according to your findings will be useful for readers.

Response: Thanks for the reviewer's comment!

Reviewer 3(Number ID: 05038583)

1. Specific comments as expected from China based study, majority of patients had hepatitis B. In our experiences, there HCC behavior is slightly different from other causes. Generalizability of this study to the

North America may be limited. I do not believe author can modify this point.

Response: Thanks for your comment. We must admit that viral hepatitis is the main cause of liver cancer in china, which is different from North America and may limit the application of our research results in North America. Therefore, researches in other countries or regions may be needed to make up for the shortcoming of our study. The details can be found in *Line 263-267, Page 12*.

2. Due to the sample size, AUC is not high. However, this study may aim for future study with larger population size.

Response: Thanks for your comment. we have collected HCC patients with portal vein tumor thrombosis who underwent TACE from January 2015 to July 2019, but may be limited by the inclusion criteria, only 181 patients were included in our study. Perhaps because of the small sample size, AUC value is not high, but the AUC value is still statistically significant. The larger and multicenter studies are needed to further validate the results in the future. The details can be found in *Line 273-276, Page13*.

3. Pre-albumin is not a routine test that our liver transplant center order for HCC unless sarcopenia or malnutrition is suspected. This makes it a little harder to apply in the North American settings.

Response: Thanks for your comment. Prealbumin is a commonly indicator for evaluating liver function in china. Compared with albumin, prealbumin has a shorter half-life and can sensitively reflect liver synthesis function. Some HCC patients with PVTT may have normal albumin, but prealbumin has decreased. If we only refer to the albumin level, we may not be able to accurately determine the liver function status, so prealbumin is included in our study.

4. For Table 2 and 4, it would be better to say survivor rather than Live and non-survivor than died.

Response: Thanks for the reviewer's kind suggestions. We have modified the Live and Died in Table 2 and Table 4 to survivor and non-survivor. The details can be found in *Table 2 and 4, Page 21 and 24*.

5. ChE for serum cholinesterase on abstract which was not used in the main text. It is better to be consistent.

Response: Thanks for the reviewer's kind suggestions. We have uniformly used ChE instead of serum cholinesterase in the article.

6. I have not seen serum cholinesterase was ordered on any patient on our transplant center. I am not sure the cost related to the testing in the North America. This may be a limiting factor to apply these finding to our clinical settings.

Response: Thanks for the reviewer's kind suggestions. Serum cholinesterase is a routine indicator for evaluating liver function in china. In the short-term survival group, serum cholinesterase in survivor group was lower than those in the non-survivor group, and univariate analysis showed that serum cholinesterase was a statistically significant indicator for short-term prognosis. The result suggested that serum cholinesterase may be a meaningful indicator to assess whether patients are suitable for TACE.

7. MELD scores for this sample population appears lower than our center for HCC. This is likely related to underlying HBV as a cause of HCC.

Response: Thanks for the reviewer's kind suggestions. The median MELD score of our overall population is 7.67(range:6.08-9.54). Because most of patients with viral hepatitis, our MELD score may be higher than that of patients whose cause of liver cancer was alcoholic or cholestatic. We have added relevant content to the discussion section. The details can be found in *Line 267-270, Page 12*.

8. In the methods section, it would be helpful to discuss what factors were selected in multivariate analysis.

Response: Thanks for the reviewer's kind suggestions. This is a very good opinion. The statistically significant indicators in the univariate analysis($P<0.05$) were selected in multivariate analysis in the study. We have added this part to the method section. The details can be found in *Line 159-161, Page 7*.

Your help and assistance is highly appreciated and I am looking forward to hearing from you.

Best regards

Yours sincerely,

Jian Gao