ANSWERING REVIEWERS

August 25, 2012

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 12849-review.doc).

Title: Significance of platelet count and platelet-based models for hepatocellular carcinoma recurrence

Author: Qing Pang, Jing-Yao Zhang, Xin-Sen Xu, Si-Dong Song, Kai Qu, Wei Chen, Yan-Yan Zhou, Run-Chen Miao, Su-Shun Liu, Ya-Feng Dong, Chang Liu

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 12849

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers

Reviewer (1): 2534208 (no comment)

Answer: We carefully perform a linguistic revision, again and again. Then we sent our manuscript to Ameditor, one of the polishing companies your journal specified, to improve our language. We have provided the "language certificate" according to the demand of the journal.

Reviewer (2): 2540301

(1) The authors conclude that both plt counts > 145, and high platelet based indices both adversely affect HCC recurrence. However, the indices that the authors have shown to adversely predict HCC recurrence all have an inverse relationship of platelets to risk of recurrence as against a direct relation of plt > 145 to HCC recurrence. The authors have not explained this dichotomy but it could result from using to study too many variables in a smaller sample size (30 variables/172 patients).

Answer: Thanks for the constructed suggestion. To explain the dichotomy, we increased the analyses of the potential reasons why both PLT and the indices (an inverse relationship with PLT) adversely predict HCC recurrence, in the second paragraph from bottom in the discussion, that is, “First and most important, although there was an adverse relationship between PLT and platelet-based indices, high levels of all predicted a high HCC recurrence. This dichotomy may due to the fact that although thrombocytopenia/low

PLT has been identified as a crucial risk factor for HCC formation and prognosis, it was identified as a favorable factor for HCC prognosis in our study and several others. In addition, our limited study population included numerous variables which may have contributed to the discrepancy. ”

(2) Looking at Table 2, I congratulate the authors that most of their patients did not have cirrhosis and were candidates for resection but as they have illustrated that patients with larger tumors had more recurrences- another corollary to this is that- pts’ without cirrhosis often have larger tumor sizes which may be associated with higher platelets and consequently higher risk of recurrence. The authors have also alluded to this when they found that in cirrhotics the platelet count was not a significant factor in predicting recurrence.

Answer: Thanks very much for this discover and rational explanation for our results. To explain this, we estimated the association between cirrhosis and tumor size in our population (*Supplementary Table 2*). We found that tumor size was not found to be significantly associated with to cirrhosis status. However, non-cirrhotic patients had a higher rate of elevated PLT levels in comparison with cirrhotic patients (39.8% vs. 27.1%). In addition, in our manuscript, we increased the analysis of the potential cause why PLT may predict recurrence especially in non-cirrhotic patients in our cohort. We thought that the limited number of individuals within each subgroup may also explain this result, and thus further study is need for verification.

(3) Again in table 2, the survival for the whole population is 52 months, while that for the recurrence group is 23 months and that for the no recurrence group is 39 months- this suggests that there may be some outliers and the authors may be better served looking at IQR for survival. Finally in Table 2, the mortality in the no recurrence group is 81% compared to 10% in the recurrence group- does it mean that people without recurrence were dying earlier due to their primary tumor and therefore could not be followed long enough?

Answer: Please forgive us for our incautions. We have corrected these number errors in Table 2. The numbers of death and living patients were incautiously reversed previously, and now have been corrected. The median survival time in non-recurrent patients was 87 months, and we miscalculated previously.

(4) A scatter plot comparing platelet values to survival would be helpful. On similar lines, the Kaplan Meir curves should come with the patients at different time intervals to see a large # of people had dropped off after the first year.

Answer: We drew scatter plots comparing platelet values to survival and recurrence (*Supplementary Figure 1A-1C*), and increased the different time intervals in the Kaplan Meir curves to see a large # of people had

dropped off after the first year. In addition, we increased boxplots which may intuitively reflect the relations between platelets and postoperative recurrence as well as survival.

(5) I do not agree with the conclusion "regular tesing PLT level and maintaining it at a normal range, is supposed to be pivotal to get a favorable outcome"- I did not see any evidence to that regard being presented.

Answer： We, the authors, discussed this issue, and agreed with the reviewer's view. So we omitted the sentence "regular tesing PLT level and maintaining it at a normal range, is supposed to be pivotal to get a favorable outcome", which had weak evidence to support the view.

(6) I feel that there may be a signal that high platelet levels may predict recurrence especially in non cirrhotics however to prove that the authors may need to divide the groups based on tumor size and cirrhosis and compare them across a fewer variables.

Answer: Thanks for this crucial suggestion. To further prove our findings, we analyzed the data again, and estimated whether PLT and its based models could be affected by tumor size, which was a major confounder in our study. For this, we increased Figure 8, and demonstrated that PLT, PAGA, and PAPAS were all useful indictors no matter tumors were bigger than 5cm or not. In addition, we estimated the association of cirrhosis and tumor size with several variables (we increased *Supplementary Table 2*).

Reviewer (3/4): 2936408

(1) In table 2, the authors mentioned that the survival for the whole population is 52 months, while that for the recurrence group is 23 months and that for the no recurrence group is 39 months. Is there a mistake? It should be explained.

Answer: Please forgive us for our incaution. The median survival time in non-recurrent patients was 87 months, and we miscalculated previously.

(2) In discussion part, the researchers conclude that both platelet counts > 145, and high platelet based indices both adversely affect HCC recurrence.However, the plt based indices which adversely predict HCC recurrence have an inverse relationship of platelets to risk of recurrence as against a direct relation of plt > 145 to HCC recurrence. The authors should explained this dichotomy in a detailed manner.

Answer: Thanks for the constructed suggestion. To explain the dichotomy, we increased the analyses of the potential reasons why both PLT and the indices (an inverse relationship with PLT) adversely predict HCC recurrence, in the second paragraph from bottom in the discussion, that is, "First and most important, although there was an adverse relationship between PLT and platelet-based indices, high levels of all

predicted a high HCC recurrence. This dichotomy may due to the fact that although thrombocytopenia/low PLT has been identified as a crucial risk factor for HCC formation and prognosis, it was identified as a favorable factor for HCC prognosis in our study and several others. In addition, our limited study population included numerous variables which may have contributed to the discrepancy. “

(3) English grammary mistakes should be corrected.

Answer: We carefully perform a linguistic revision, again and again. Then we sent our manuscript to Ameditor, one of the polishing companies your journal specified, to improve our language. We have provided the "language certificate" according to the demand of the journal.

Reviewer (5): 2936403

(1) If taking cirrhosis and tumor size into consideration, do the results still support the conclusion provided by the authors?

Answer: Thanks very much for this constructive suggestion. To prove our findings, we further analyzed the data again, and estimated whether PLT and its based models could be affected by tumor size, which was a major confounder in our study. For this, we increased Figure 8, and demonstrated that PLT, PAGA, and PAPAS were all useful indictors no matter tumors were bigger than 5cm or not.

(2) The authors addressed that the survival for the whole population is 52 months, whereas that for the recurrence-group is 23 months and that for the no recurrence-group is 39 months, which seems unreasonable. Please explain it.

Answer: Please forgive us for our incaution. The median survival time in non-recurrent patients was 87 months, and we miscalculated previously.

(3) The authors conclude that platelet>145 and high platelet-based indices inversely correlated the HCC recurrence. However, the indices proposed have inverse relationship to that of platelet to recurrence, which seems conflicting. Please explain it.

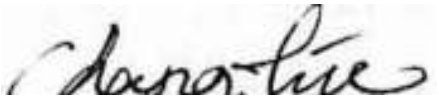
Answer: Thanks for the constructed suggestion. To explain the dichotomy, we added the analyses of the potential reasons why both PLT and the indices (an inverse relationship with PLT) adversely predict HCC recurrence, in the second paragraph from bottom in the discussion, that is, “First and most important, although there was an adverse relationship between PLT and platelet-based indices, high levels of all predicted a high HCC recurrence. This dichotomy may due to the fact that although thrombocytopenia/low PLT has been identified as a crucial risk factor for HCC formation and prognosis, it was identified as a favorable factor for HCC prognosis in our study and several others. In addition, our limited study population included numerous variables which may have contributed to the discrepancy. “

In conclusion, we adopted all the suggestions by the reviewers, and did our best to answer all the questions. We improved some imperfections in our manuscript according to the comments and concerns by the reviewers, especially the errors in Table 2, the potential confounder of tumor size and the incomplete discussion. Hope these will make it more acceptable for publication.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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