17 September, 2017

Dear Professor Damian Garcia-Olmo,

**Title: Prediction of hepatocellular carcinoma development by APRI in primary biliary cholangitis**

Thank you for your letter concerning the revision of our manuscript. The manuscript has been revised according to the reviewers' comments. The changes have been highlighted in the manuscript for your reference. The followings are the point-by-point responses to the reviewers' comments.

We hope that the reviewers and editors will find this revised version acceptable for publication in the World Journal of Gastroenterology.

Yours sincerely,

Man-Fung Yuen

**Language**

*Concerning the language of the manuscript, we have asked for advice from our colleague who is a native English speaker.*

**Reviewers' Comments to Author**

## Reviewer 00724450

Dear Editor, Cheung et al. presented a study and they found that APRI score can be a good predictive marker for HCC development in PBC patients. I read the paper and I believe this can be a new finding and add some contributions to the literature even HCC patients were small number. I believe we need many more predictive markers for HCC risks patients and APRI score may be a good follow up marker for PBC patients. Manuscript was well written, method and results were good designed and discussion section was satisfactory. Thanks to authors fort his paper…

*Our response:*
*We thank you for your comments.*

## Reviewer 00013213

Your retrospective study investigated the ability of APRI AND APRI-R1 tests in the prediction of HCC in PBC patients. Although your study included a relatively small sample size, yet your data indicated an AUROC of 0.77 for APRI-r1 in the predictive ability which is acceptable but not a robust one. Minor comments need your revision:

1-Page 13, lines 9-11: It is not appropriate to mention results of other studies compared to yours in results but better to be referred to in discussion.

*Our response:*
*We thank you for your comments. The sentence "*A study with the same cohort of patients assessed by different prognostic models for prediction of long-term transplant-free survival was recently published" *describes that the current study was based on the same cohort of patients was now included in the Discussion Part instead on page 17 lines 3-5.*

2-Your data indicated that cirrhosis had high significant predictive ability for HCC with HR more than that of APRI-r1. Based on your data, why have not you tried to obtain a model using discriminative functional analysis and consuming both cirrhosis and APRI-r1. This may yield a more robust predictive index for HCC in PBC.

*Our response:*

*We thank you for your comments. We have calculated the AUROC of cirrhosis also (0.71, 95% C 0.56 – 0.86) and included this result on page 15 line 21 and in Table 5. However, after we group cirrhosis & APRI-r1 > 0.54 into one single risk factor, the AUROC was only 0.62 (95% CI 0.48 – 0.77). In view of the AUROC crossing 0.50, we decided not to include this result.*

3-One of limitations of your study is the lack of validation cohort.

*Our response:*
*We thank you for your comments. We acknowledge this limitation, and stated that further studies to validate our findings are required (page 19 lines 15-17).*

## Reviewer 02567669

This paper deals with APRI-r1 as a novel prognostic marker for the development of HCC in patients with PBC. The cohort of 144 patients is of intermediate size. Using a lot of statistical calculations (partly difficult to understand for a gastroenterologist not completely familiar with these methods) the authors clearly show that this parameter, in particular in combination with treatment response to UDCA is a good prognostic parameter for the development of HCC. The paper may be published as it is.

*Our response:*
*We thank you for your comments.*

## Reviewer 01551089

1. It is noted that your manuscript needs careful editing by someone expertised in English paying attention to grammer, spelling, and sentnese structuer so that the introduction and results of the research are more clear.

2. Furthermore, there is a lack of explanation of statistical methods used in Signature Sequence Analysis(Line 171).

3. It is not clear why RNA structures obtained for sequences derived from T samples were not different from the corresponding NT samples in patients 2, 3 and 4(Line 264).

*Our response:*
*We find that the reviewer's comments were not for our manuscript.*

## Reviewer 00068723

The authors investigate the usefulness of APRI-rl for the prediction of HCC in PBC. They concluded that APRI-rl was a candidate for the prediction. Table 1a showed no correlation between the occurrence of HCC in PBC and AST, while lower platelet was correlated with HCC. The results were rationale because low platelet count was associated with liver cirrhosis. Apparently, the authors' conclusion was the same meaning as HCC occurred in advanced liver cirrhosis.

The authors should clearly state the superiority of APRI-rl over platelet.

*Our response:*
*We thank you for your comments. Thrombocytopenia also had satisfactory performance (AUROC 0.71, 95% CI 0.56 - 0.86), although slightly worse than that of APRI-r1 (AUROC 0.77, 95% CI 0.64 – 0.88). The AUROC of thrombocytopenia in predicting HCC was now included on page 15 lines 22 and Table 5.*

Also serum bilirubin was strongly associated with HCC in PBC. This was rationale because higher serum bilirubin was also associated with advanced liver cirrhosis. The authors should discuss the reason why they chose APR-rl related with platelet, not serum bilirubin.

*Our response:*
*We thank you for your comments. Bilirubin was not found to be a significant independent risk factor for HCC development as shown in Table 2. We have calculated the AUROC of hyperbilirubinemia in predicting HCC (AUROC 0.64, 95% CI 0.49 – 0.77) with the result included in Table 5.*

Maybe liver fibrosis was one of the discussion points.

*Our response:*
*We thank you for your comments. Hyperbilirubinemia is a known risk factor for liver transplantation and death in PBC patients in previous studies, but not found to be a significant independent risk factor for HCC development in the current study. This is likely because APRI is more specifically related to fibrosis/cirrhosis, while hyperbilirubinemia can be due to cholestasis from PBC per se or advanced liver disease (page 18 lines 10-14).*

It would be helpful if comparison of occurrence of HCC in PBC, autoimmune hepatitis (AIH), and viral hepatitis. The information would make clear the significance of not only the occurrence of HCC in PBC, but also this manuscript.

*Our response:*
*We thank you for your comments. Previous studies have already shown that APRI predicts HCC in patients with viral hepatitis (both HBV and HCV), while studies on autoimmune hepatitis are lacking.*

*However, we acknowledge that further studies to investigate the usefulness of APRI in predicting HCC in other chronic liver diseases are warranted (e.g. autoimmune hepatitis, non-alcoholic fatty liver diseases). As APRI reflects fibrosis/cirrhosis status, it is expected to have more or less consistent predictive performance in various liver diseases. We have included this into the Discussion section on page 19 lines 17-21.*