ANSWERING REVIEWERS

December 30, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6109-Edited_JL_clean.docx).

Title: Risk Calculators for Hepatocellular Carcinoma in Patients Affected with Chronic Hepatitis B in Asia

Author: Hwai-I Yang, Mei-Hsuan Lee, Jessica Liu, Chien-Jen Chen

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6109

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

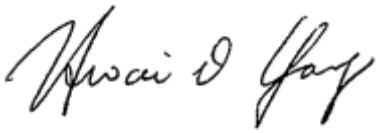
2 Revisions have been made according to the suggestions of the reviewers, and have been highlighted in the revised manuscript. We also generated a point-by-point Responses to Reviewers' Comments as the attachment.

3 References and typesetting were corrected.

4 The manuscript has been edited by one of our coauthors, Dr. Jessica Liu, who is a native speaker of English.

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

Sincerely yours,



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Responses to Reviewers' Comments

Comments from Reviewer 1

This is a updated and well written review on HCC risk calculators in untreated and NUC treated patients with CHB. The authors are encouraged to divide the review in two parts, untreated and treated patients.

Authors' response: We thank for the Reviewer's suggestion. Accordingly, we have changed two of our section titles into "Risk calculators for hepatocellular carcinoma in CHB patients without antiviral treatment" and "Extending the use of HCC risk scores in treatment research ".

Authors should also try to be more critical on the different issues raised by the application of HCC risk scores, rather than just summarizing the available data.

Authors' response: We thank for the Reviewer's suggestion and incorporated all issues raised by the Reviewer into the updated manuscript.

Title, add "in Asia"

Authors' response: We revised the title per the Review's suggestion.

Table 2: the Reach-B score has not been included

Authors' response: As we have indicated in the section "Risk calculators for hepatocellular carcinoma in CHB patients without antiviral treatment", only those HCC risk prediction models that have been developed by 2011 were summarized in Table 2. We also described in the same section that the REACH-B is actually a collaboration between those groups who published data in Table 2.

Table 3, title: what does "the most updated HCC risk score for …" mean ? Is this a new risk calculator ? is the Reach B risk score ? What the difference compared to those in table 2 ? is an evolution of reach B ?

Authors' response: Yes this is a new risk calculator which has been published in Hepatology this year. This is an evolution of the REVEAL nomogram rather than that of the REACH-B because it did not involve the external validation. In the second paragraph of the "Risk calculators for hepatocellular carcinoma in CHB patients without antiviral treatment " section, we also mentioned that this risk calculator was upgraded from the original REVEAL nomograms. To further clarify, we revised the table title to "the most updated hepatocellular carcinoma risk score for CHB patients upgraded from the REVEAL nomogram".

Also figure 2 refers to "the most updated HCC risk score", please explain Figure 2: the vertical axis is difficult to read, could you transform into HCC/year rates which is the standard HCC risk assessment ?

Authors' response: We revised the title of Figure 2 into "the updated REVEAL nomogram for the prediction of HCC risk" accordingly. It is difficult to transform the vertical axis into HCC/year because the nomogram was designed to estimate HCC risk within specific time frames. To overcome the readability of vertical axis, we put minor gridlines on the nomogram.

Page 4: an AUROC of 0.81 or 0.77 is not considered acceptable for many diagnostic or prognostic tests. How these numbers translate into individual predictions ? what is the 95% CI intervals for these AUROC?

Authors' response: We would like to emphasize that the AUROCs was generated by applying the REACH-B risk score to the validation cohort, which was quite different from the derivation cohort in many aspects. The AUROC may interpret as the discriminatory capability in predicting individual risk. An AUROC of 0.81 or 0.77 could be considered as fairly good. In order to respond to these concerns, we revised the section as "Although the derivation and validation cohorts were quite different in their

distributions of sex, age, HBeAg serostatus, ALT concentration, HBV DNA level, and cirrhosis, the risk score developed from the derivation cohort accurately and reliably estimated the HCC risk at 3, 5, and 10 years of follow-up in the validation cohort. The area under the receiver operating characteristic curve (AUROC) and the corresponding 95% confidence intervals (CI) were 0.811 (0.790-0.831), 0.796 (0.775-0.816), and 0.769 (0.747-0.790), respectively, in predicting 3-, 5-, and 10-year HCC risk, which indicate a fair discriminatory capability."

Page 4, last part: "the performance of the risk score improved when cirrhotic were excluded". The understanding from the paper is that the new score was developed for patients without cirrhosis.
Authors' response: Yes the REACH-B score was developed in non-cirrhotic patients. For clarification, we revised this sentence as "The performance of the risk score was improved when cirrhotic patients were excluded from the validation cohort.".

Please reconcile The overall paper is referring to a sort of "original" Reach-B score and a new one, incorporating HBsAg levels. Authors should try to make this difference more clear and illustrate both scores in table 3.
Authors' response: The new risk calculator published in Hepatology which incorporated HBsAg level as a predictor was sort of similar to the REVEAL nomogram rather than the "original" REACH-B score. The predictors of HCC in the new calculator included sex, age, ALT level, family history of HCC, HBeAg, HBV DNA, HBV genotype, and HBsAg level, which have been included in the REVEAL nomogram except for the last parameter. These two calculators both involved only internal validation. However, the REACH-B score did not include family history of HCC, HBV genotype, and HBsAg level, and one of the main theme of that paper was the external validation. For clarification, we revised the following sentences:
"The risk prediction model for HCC included age, sex, family history of HCC, and a combined variable encompassing HBeAg serostatus, serum HBV DNA and ALT levels, quantitative serum HBsAg level, and HBV genotype as the predicting parameters (Table 3; all parameters were included in the REVEAL nomogram except for quantitative serum HBsAg level)"; and "Taking the REACH-B score as a precedent, this upgraded version may hopefully be validated externally using clinical CHB patients to prove its accuracy, reliability, and added predictive capability over the original version in the near future."

Moreover, the authors refer to a "simplified model". Not clear which model is this.
Authors' response: We deleted "simplified" per the Reviewer's comment.

Page 5: the authors suggest possible uses of these risk calculators, however it is not clear how patients with a predicted risk of 3%/year could be managed differently compared to those for example with a 6% per year. What would be more important would be to identify a group of patients with a 5 year zero risk for HCC.
Authors' response: We thank for the Reviewer's constructive questions. As Figure 2 shows, the HCC risk that can be predicted by the risk score is a risk continuum. The risk is never zero, even in patients with the lowest scores. As the reviewer pointed out, the potential cut-off risk and corresponding management strategies is an important issue. However, the risk calculator only deals with risk estimation of HCC. The management of CHB patients should take other information into consideration such as benefits, adverse effects, as well as the cost-effectiveness of management strategies. International guideline development committees may integrate all of these factors when setting up threshold scores for beginning various clinical interventions. We inserted the above opinions in a paragraph in the main text.

Page 9. The Reach-B score was used in the tenofovir study, which however includes also cirrhotic patients. The authors should make a comment on this issue.

Authors' response: We thank for the Reviewer's insightful comment. We added the following sentences accordingly: "Of note, among patients with cirrhosis (25% of study patients), the observed numbers of HCC were closer to the curve of expected cases predicted by REACH-B. This result, however, does not necessarily rule out the long-term benefits of tenefovir, because the REACH-B score was generated from non-cirrhotic patients, which may have underestimated actual HCC risk in cirrhotic patients without treatment."

Comments from Reviewer 2

This model is very important for CHB patients and clinical practic. But, can we use it to predict the outcomes of patients who ongoing antiviral therapy?

Authors' response: We appreciate the Reviewer's comments. According to the results shown by Wong GL et al. (*Gastroenterology* 2013; 144(5): 933-944; reference 19), risk scores can be used to predict subsequent HCC development in patients treated with entecavir. However, because all of these scores were derived from and validated in treatment-free cohorts, and many potential predictors related to therapy and responses during and after treatment could not be collected, they may not be the optimal prediction tools for CHB patients under antiviral treatment. A risk calculator derived from treated patients, which includes pre-treatment, on-treatment, and post-treatment parameters, might best fit this purpose. We have incorporated this response to the manuscript accordingly.