Department of Medicine and Therapeutics
9/F Prince of Wales Hospital
30-32 Ngan Shing Street,
Shatin, Hong Kong.
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Lian-Sheng Ma
President and Editor-in-Chief
World Journal of Gastroenterology

Dear Prof Ma,

RE: Submission of Revised Version of Manuscript (ESPS Manuscript NO: 4588)

I would like to thank all the reviewers for their pivotal comments on our manuscript (**ESPS Manuscript NO: 4588**, entitled **"Risk prediction of hepatitis B virus-related hepatocellular carcinoma in the era of antiviral therapy"**). In response to your comments and suggestions, we have revised our manuscript accordingly. Please find enclosed the copy of our revised manuscript (with changes highlighted in red color) and point-by-point responses to your comments.

We hope my work can contribute to the high quality publications of the *Journal*. Thank you very much for your kind attention.

Yours sincerely,
Grace Lai-Hung Wong, MD

Responses to Editor's and Reviewers' Comments (ESPS Manuscript NO: 4588)

We would like to thank the Reviewers again for their important comments. Our responses to the comments are as follows:

Reviewer 1:

This review faces a crucial clinical point as the need of a proper tool to categorize the risk of HCC in HBV carriers. Many issues emerge in the contest of the applicability of HCC prediction scores (as dynamic changes in the risk scores during treatment) but the key message is the need of a different monitoring approach according with different HCC's risk profiles. This is crucial to select patients to antiviral treatment not only in order to control viral activity and disease progression but also to lessen (not to prevent) the risk of HCC occurrence. One concern, however, is the applicability of these scores in western patients. This review is complete and well structured. I have only a couple of hints: -Some phrases need an English language revision. -Few references for a review.

Response: We acknowledge the Reviewer's concern that the applicability of these scores in western patients remains uncertain as all of the scores were derived and validated in Asian patients. This is now addressed in the "CLINICAL APPLICATION OF RISK SCORES" section (page 14, paragraph 1). The English language is further polished by a native English-speaking editor. Some relevant references are now added. The number of reference is relatively small as this is a review of a very specialized area.

Reviewer 2:

Your manuscript reviewed validated scores for prediction of HCC in chronic HBV infection and you have illustrated very useful risk scores with high sensitivity and spicificity in prediction of HCC in those patients with hepatitis B infection with or without cihrosis. -However there are some remarks that warrant your response:

1-The term:Virologic Remission has been used in the manuscript in different paragraphs with different meanings; this needs more clarification.

Response: Virologic remission refers to undetectable on-treatment serum HBV DNA level. This is now clarified at its first appearance at page 7, paragraph 2.

2- Minor language corrections are required in in your manuscript.

Response: The English language is further polished by a native English-speaking editor.

Reviewer 3:

1. The authors have described the use of 3 prediction scores for the development of hepatocellular carcinoma in patients with chronic HBV hepatitis. They correctly note that blanket treatment and surveillance of all HBV patients would be a severe economic burden on any health system and thus it is necessary to identify high risk patients. The authors state that in the Reach-B study the patients did not have cirrhosis but do not detail how the cirrhosis was diagnosed. There are of course different methods of making the diagnosis of cirrhosis.

Response: Ultrasonography was used to define cirrhosis in the development cohort of the REACH-B score, which consisted of patients from the population-based prospective REVEAL-HBV database. This is now clarified in page 11, paragraph 1. We have discussed the issue of making the diagnosis of cirrhosis in the section of "FUTURE DIRECTION". There have been evolving data concerning the role of non-invasive tools to detect early cirrhosis, e.g. transient elastography, in the risk prediction of HCC.

2. I suggest the authors describe in more detail the "leave-one-out cross validation".
Response: The leave-one-out cross-validation involves using a single observation from the original sample as the validation data, and the remaining observations as the training data. This is repeated such that each observation in the sample is used once as the validation data. This is now added to page 8, paragraph 2.

3. One of the conclusions of the authors is that the results of the scores could be used to guide anti-viral therapy. This is too strong a conclusion- there are many other reasons for anti-viral therapy including preventing the development of cirrhosis and improving the quality of the patient's life which are not reflected in these scoring systems.
Response: The conclusion is now rephrased and tuned down to "Patients at high-risk category should be one of the indications of antiviral therapy" (page 16, paragraph 2).

4. In Table 1 , when mentioning risk factors for HBV -related HCC no mention is made of HIV.
Response: HIV is now added to Table 1, and also described in the text (page 6, paragraph 1).

5. The manuscript needs to be reviewed by a native English speaker.
Response: The English language is further polished by a native English-speaking editor.