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Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 26390
Title: Prediction and prophylaxis of hepatocellular carcinoma occurrence and postoperative recurrence in chronic hepatitis B virus-infected subjects
Reviewer's code: 02439754

Answer: We thank this reviewer for his/her comments. We revised our manuscript according to WJG's Guidelines and Requirements for Editorial, and reduced the volume of the text (word count for the main text is now 2419 with 49 references). We also revised the FUTURE CHALLENGE section to make the logic flow more smoothly, emphasing important characteristics of a prediction model derived from academic studies to be applied in clinical settings (The last paragraph of the FUTURE CHALLENGE section: Page 31, Line 20-22 & Page 32, Line 1-15).

Overall, a comprehensive review on the prediction models for prediction of HCC in HBV-infected patients in Asia, HCC staging for outcomes, and prediction models for HCC recurrence has been done in this manuscript. The main concern is that all are descriptive without any schemes, catoons, or tables for a concise summary or illustrations, which makes this manuscript is long and difficult to read out.

Answer: We thank the reviewer for the comments. We condensed the description of different HCC predicition models in the main text (Page 13, Line 9-22 & Page 14, Line 1-2 & Page 20, Line 6-21) and made a table (Table 1) to summarize and compare different models.

Specific comments:
1. Abstract and Introduction: Regarding epidemiology data about HCC incidence, predictive rates of HCC development and recurrence, 5-year survival and so on, only the data based on Chinese population or Mainland China were used. I suggest adding at least a global database for comparison and provide a global vision for the significance of the subject. I believe the readers of this journal are more interested to know the global data than just restricted in China.

Answer: We thank the reviewers for the comments. We fully appreciated the reviewer's point of view, and added epidemiology data (references 1-4) of HCC from a global perspective and revised the ABSTRACT and INTRODUCTION (now section HEPATITIS B VIRUS RELATED HEPATOCELLULAR CARCINOMA IS AN IMPORTANT PUBLIC HEALTH PROBLEM, Page 6, Line 3-18) accordingly. However, most of the HCC burden is in developing countries, and >80% HCC cases occur in Eastern Asia and sub-Saharan

Africa. Epidemiology data have shown that chronic HBV infection is the predominant risk factor of HCC in Asia and Africa; whereas HCV infection is a more prevalent cause of HCC in western countries as well as in Japan (reference 2: **El-Serag HB**. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology*. 2012;**142**:1264-1273.e1. [PMID: 22537432 DOI: 10.1053/j.gastro.2011.12.061]). Since this editorial is focusing on HBV-related HCC, so almost all of the studies are coundcuted in Asian regions such as mainland China, Hong Kong, Taiwan, and South Korea. It is undeniable that investigators from Asia do play a leading role in the field of HBV/HCC research, and most of the important literatures are published by Asian groups.

2. I strongly suggest having a table comparing different HCC prediction scores or algorithms published from different countries and research groups in the world.

Answer: We took the reviewer's suggestion and composed a table (Table 1) to summarize and compare different HCC predicition models from published literatures.

3. In terms of HCC staging for outcome prediction, there have been many reviews published. I will suggest just give a summary or comments on how to choose and use them for clinical practice.

Answer: We took the reviewer's suggestion and revised the manuscript accordingly. We summarized different HCC staging systems and briefly commented on how to choose and use them for clinical practice (Page 21, Line 12-21 & Page 22, Line 1-8).

4. A table for the reported HBV mutations with their frequency, associated treatments, and clinical implications and significance will be helpful for the readers.

Answer: We appreciated the reviewer's suggestion. However, since we revised our manuscript according to WJG's Guidelines and Requirements for **Editorial**, it seems too long to add an individual section for HBV mutations. It is an important component for the HBV-HCC predicition model. However, it is difficult to summarize the data in a table. To the best of our knowledge, only one published study carried out by our own group included the HBV mutation data in the HCC prediction system (reference 45: **Yin J**, Wang J, Pu R, Xin H, Li Z, Han X, Ding Y, Du Y, Liu W, Deng Y, Ji X, Wu M, Yu M, Zhang H, Wang H, Thompson TC, Ni W, Cao G. Hepatitis B Virus Combo Mutations Improve the Prediction and Active Prophylaxis of Hepatocellular Carcinoma: A Clinic-Based Cohort Study. *Cancer Prev Res (Phila)* 2015; **8**: 978-988 [PMID: 26290395 DOI: 10.1158/1940-6207.CAPR-15-0160]), although a lot of groups as well as our own have published articles demonstrating that some HBV mutations are significantly associated with HCC risk in HBV-infected subjects. The prophylactic effect of antiviral treatment on

HCC occurrence in HBV-infected subjects with the HBV mutations was only elucidated by our group (reference 45), although some groups in Taiwan, Hong Kong, Japan, France, Italy, and USA demonstrated the prophylactic effect of antiviral treatment on HCC occurrence in the HBV-infected subjects.

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Reviewer's code: 01221188

Answer: We thank the reviewer for spending time reviewing our manuscript and the kind remarks. In order to make this article more illustrateive and readable, we added a Table (Table 1) summarizing different HCC prediction models derived from HBV infected cohorts according to your suggestion.