November 3, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5577-review.doc).

Title: Significance of viral status on occurrence of hepatitis B-related hepatocellular carcinoma

Author: Li-Shuai Qu, Guo-Xiong Zhou

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 5577

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 reviewer

(1) Reviewer 1.

WJG-5577 Significance of viral status on occurrence of HBV-related HCC The paper addresses an interesting and important issue for which many novel findings have been reported in the recent years. A review appears thus valuable, is however also challenging. The following comments to the present draft should be taken into consideration:

1. The paper is basically well written, has however still some flaws in the English wording and should thus be revised by a native English speaking colleague / person. For example, on page 4, subtitle 'HBeAg and HCC', 4th and 5th line, the sentence "Before the introduction of DNA-testing, HBeAg has an immunomodulatory role ..." does not make sense.

Reply: Thank you very much for your attention. As suggested by the reviewer, we have revised the relevant passage in the manuscript. We do hope it will be relatively easy to understand now.

2. Some passages have apparently been transcribed from the reviewed article without understanding of the meaning leading to a senseless wording. For example, on page 5, last two lines, "4.5 log copies/mL" and "6.5 logs" is a wrong transcription from the original and completely incomprehensible for

the reader.

Reply: Thank you very much for your attention. We have carefully read and edited the entire manuscript. We hope this could significantly improved the language issues raised by the reviewers.

3. Citations appear inappropriately assigned. For examples, on page 7, 18th line, reference 36 should refer to associations on the human population level, describes however findings from animal experiments.

Reply: Thank you very much for careful reading of our manuscript and important proposal. We would like to thank the reviewer because he correctly pointed out that the reference 36 was inappropriately cited. According to the suggestion of the reviewer, we have carefully re-edit the reference. The article (El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012;142:1264-1273e1) was cited in the revised manuscript.

4. Summary and perspective: what are "serial" experiments? Generally, the conclusions appear somewhat unrelated to the preceding text. For example, why must examinations of patients with chronic HBV-infections be "frequent"? The subsequent sentence suggests the development of high throughput methods; are these the key messages of a review on HBV status and associated HCC?

Reply: Thank you very much for your kind reminds. As we all known, during past decades, various viral risk factors have been identified, such as seropositivity of HBeAg, high viral load, genotype, and specific viral sequence mutations. Most above important results were derived from several population-based, long-term prospective studies, such as REVEAL-HBV study in Taiwan. Serial important researches of the REVEAL-HBV Study Group (published in N Engl J Med, JAMA, and JNCI et al) revealed that viral risk factors was associated with the risk of HCC. In previous studies, most analysis of viral risk factors was based on a single blood sample obtained at recruitment, we could not assess the risk of changes in viral status on the development of HCC. Meanwhile, HBV DNA levels and viral mutations are

dynamic parameters in patients with chronic hepatitis B. The measurement of viral status from only one point in time may not give the complete picture of the relationship with severity of liver disease. In view of this, we think that measurement of viral load and mutations at multiple time points may offer the opportunity to helping those who are at high-risk of HCC to benefit from early diagnoses and interventions. According to the suggestion of the reviewer, we have carefully revised the "Summary and perspective" in the manuscript.

5. A recent review on HBV and HCC in Nature Reviews Cancer 13(2), p 123 ff, should be taken into consideration.

Reply: Thank you very much for your important proposal. We have carefully read the this important review. We have cited this latest article in the revised manuscript.

(2) Reviewer 2.

To whom it may concern, In the manuscript "Significance of viral status on occurrence of hepatitis B-related hepatocellular carcinoma" by Li-Shuai Qu et al, the authors summarized the viral factors involved in carcinogenesis of HBV-related HCC. It is comprehensive and well organized. Some minor concerns are listed below.

1. In the abstract, the authors mentioned that "…, we thus review the epidemiology of HBV-related HCC and viral factors…". However, the epidemiology apparently is not the topic of this review and should be removed.

Reply: Thank you very much for careful reading and kind reminds. We have revised the relevant passage in the abstract.

2. In introduction, authors stated that "… 350 million people with chronic HBV infection have a 15% to 25% risk of dying from HBV-related liver disease, including end-stage cirrhosis and HCC". This is a review focused on the correlation of viral status and HCC, the risk of dying from HCC should be separately listed other than combined with other end-stage liver diseases.

Reply: Thank you very much for your attention. We have revised the relevant passage in the introduction.

3. In the main text, section of "Serum HBV DNA levels and HCC" should be moved to the first section because it may be the most important viral factor which correlated with HCC. Also HBV DNA level was mentioned in the first two section "HBsAg levels and HCC" and "HBeAg and HCC".

Reply: Thank you very much for your important proposal. We have re-edit the manuscript according to the suggestions of the reviewer. We do hope it will be relatively easy to understand now.

4. The section of "Specific mutations and HCC" is too long. It would be better to trim it down because many discussions in this part are irrelevant with HCC.

Reply: Thank you very much for your suggestion. We have abbreviated the relevant passage in the section of "Specific mutations and HCC".

5. The authors made a comprehensive review on the viral factors and HCC. In the summary, they should not only state "several viral factors are critically involved in the development of HCC". It would be better for them to made a comparison among these factors in predicting or involvement in HCC.

Reply: Thank you very much for careful reading of our manuscript and important proposal. According to the suggestion of the reviewer, we have carefully revised the "Summary and perspective" in the manuscript. We do hope it will be relatively easy to understand now.

(3) Reviewer 3.

The authors comprehensively reviewed the recent progress in relation between HBV infection and risk of hepatocellular carcinoma. Almost all important literatures in this area have been included and commented. the writing style is good. minor concern: according to the summary by the authors, can we say HBV-DNA is the best test to evaluate the risk of HCC?

Reply: Thank you very much for your careful reading of our manuscript. According to the results from previous studies, a significant association

between elevated serum HBV DNA levels and increased risk of HCC was observed in all important studies despite differences in study design (cross-sectional versus longitudinal and community/hospital-based), health status of controls, method and detection limit for the determination of HBV DNA levels, HBV DNA levels selected as the referent group, and variables chosen for adjustment in the analyses. Meanwhile, the role of HBeAg, genotypes, and specific sequence mutations on development of HCC remain controversy. It was well established that serum level of HBV DNA could be used as a major independent risk predictor for HCC. However, serum level of HBV DNA is a dynamic parameter in patients with chronic hepatitis B. HBV DNA levels always fluctuate over time in most chronic hepatitis B patient. The measurement of viral load from only one point in time may not give the complete picture of the relationship with severity of liver disease. In view of this, we think that measurement of viral load at multiple time points may offer the opportunity to distinguish immunetolerant individuals with quiescent disease from those with more active immune response and consequent liver damage.

3 References and typesetting were corrected.

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

Sincerely yours, Dr. Guo-Xiong Zhou,

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