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March 3, 2023

Lian-Sheng Ma
Editorial Office Director, Company Editor-in-Chief, Editorial Office Science Editor
Baishideng Publishing Group

Dear Dr. Lian-Sheng Ma,

Please find enclosed the edited manuscript in Word format (file name: 83594-manuscript (revision).doc).

Title: Liver histopathological lesions is severe in patients with normal alanine transaminase and low to moderate HBV DNA replication

Author: Su-Wen Jiang, Xiang Lian, Ai-Rong Hu, Jia-Lin Lu, Zhe-Yun He, Xiao-Jun Shi, De-Dong Zhu, Zong-Yi Wang, Guan-Cheng Huang

Name of Journal: *World Journal of Gastroenterology*

Manuscript NO: 83594

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 reviewers

Reviewer 1:

(1) Response to comment: In the "Aim" of the abstract. I encourage the authors to use a different term than "put forward a suggestion on the scale". Rather the authors might use the term "impact" or "significance".

Response: Thanks for the reviewer's comments. We have made the correction which is marked in red in the "Aim" of the abstract: "To analyze the correlation of HBV DNA level and liver histopathological severity, and to explore the significance of HBV DNA for chronic hepatitis B with normal alanine transaminase (ALT)."

(2) Response to comment: In the "Methods" of the abstract. Please define both EASL and CMA.

Response: We have made the corrections which are marked in red in the "Methods" of the abstract: "HBV DNA ≤10^7 IU/mL (7.00 log IU/mL, the European Association for the Study of the Liver (EASL) guidelines) or ≤2×10^7 IU/mL (7.30 log IU/mL, the Chinese Medical Association (CMA) guidelines)".

(3) Response to comment: Please generally list the important factors for determining who should receive treatment for chronic hepatitis B instead of using "etc.".

Response: We have made the corrections which are marked in red in the "BACKGROUND": "Chronic hepatitis B (CHB) patients can be divided into treatment indication and non-treatment indication individuals according to ALT, HBV DNA, serum HBeAg status, disease status (liver cirrhosis, hepatocellular carcinoma (HCC), or liver failure), liver necroinflammation or fibrosis, patients' age, and family history of HCC or cirrhosis." Thanks for the reviewer's comments.

(4) Response to comment: The authors use both "2 x 10 ^3" and "2000" when describing HBV DNA levels. Please be consistent per the journal requirements.

Response: We have made the correction which is marked in red in paragraph 3 of the "Introduction" (Replace 2000 with 2×10^3.

(5) Response to comment: In the discussion, please provide some reasoning for why the authors think lower HBV DNA levels are associated with higher inflammation and fibrosis. Is there a pathological/biochemical explanation for these findings?

Response: We have added a brief discussion (explanation) which is marked in red in paragraph 5 of the "**Discussion**": "The high level of HBV DNA replication causes the deficiency and dysfunction of the HBsAg specific cytotoxic T lymphocytes, leading to the consequent immune tolerance. However, during the prolonged reproduction, HBV interacts with the host immune system, which can induce a cumulative immune damage. The hepatocytes suffer occult and persistent pathological apoptosis, with HBV DNA decreases accordingly, while the liver damage continues [40] ."

(6) Response to comment: Please provide an estimate of the number of the prevalence of patients in the 'gray zone'. This will add to the importance of your article.

Response: We have added a brief discussion which is marked in red in paragraph 1 of the "**Discussion**": "One retrospective cohort study [20] involved 3366 CHB patients came from 5 clinical centers of America and 7 towns of Taiwan, China which were followed up for at least 1 year and the mean time was 12.5 years. Staging of the disease was determined according to the American Association for the Study of Liver Diseases (AASLD) 2018 hepatitis B guidance [21]. The result showed that patients in the indeterminate phase count for 50.9% in American cohort and 31.8% in Taiwan, China with an average of 38.7%. Yao et al. [22] also adopted the same guidelines (ALT <ULN, male for 35 U/L and female for 25 U/L), and 4759 CHB patients in Nanjing, China were included among which 27.8% were in the indeterminate phase. " Thanks for the reviewer's comments.

(7) Response to comment: Unless this was determined, please list a limitation of the study was that HBV genotype was not determined.

Response: We have added a limitation of the study which is marked in red in paragraph 7 of the "**Discussion**": "The last, this study didn't determine the HBV genotypes. The dominant genotypes in China are genotype B and C with higher incidence of mother to child transmission, and genotype C infections are more prone to progress to HCC earlier [2,40]."

Reviewer 2:

Response to comment: The research topic is very interesting and challenging. I find it interesting that the authors comment a little on whether the HBV genotype profile may have some influence on the findings found.

Response: Thanks for the reviewer's comments. We have added a limitation of the study which is marked in red in paragraph 7 of the "**Discussion**": "The last, this study didn't determine the HBV genotypes. The dominant genotypes in China are genotype B and C with higher incidence of mother to child transmission, and genotype C infections are more prone to progress to HCC earlier [2,40]."

3 References and typesetting were corrected.

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

Sincerely yours,

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