

Re: *World Journal of Gastroenterology* Manuscript NO: 86691, Observational Study

Dear editor,

Thank you very much for your constructive comments regarding our manuscript entitled "Lowering the Threshold of Alanine Aminotransferase for Enhanced Identification of Significant Hepatic Injury in Chronic Hepatitis B Patients" (Manuscript No: 86691) for your journal. We have carefully considered each suggested revision and comment brought forward by the reviewers. Below, we have responded to the comments of the reviewers point by point, and the revisions have been indicated. The manuscript has also been polished by American Journal Expert. We hope that we have adequately addressed the queries raised by you and the reviewers.

We are looking forward to hearing from you and thank you very much for your help.

Sincerely,

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Responses to comments of Reviewer #1

The authors investigated the histological severity of liver disease in patients fitting the criteria of “grey zone” (GZ) among cases with HB infection (either chronic hepatitis B or simple infection). The definition of grey zone is based on ALT and HBV DNA levels, that are used to define the need for antiviral treatment. Based on a very large setting of cases (n = 1617) and 802 subjects fitting the criteria of GZ, they tested the histological severity in this last cohort, as well as the changes in treatment criteria according to reduction of cut-off ALT levels. Data confirm the need to rely on much lower ALT levels to effectively treat subjects at risk of disease progression (as also defined by surrogate biomarkers of progressive liver disease).

I have only minor comments.

1. The study is rather difficult to read, considering the multiple comparisons. As also commented by authors, the classification of GZ is not static, and may be assessed at any new contact. I invite the authors to comment on the classical finding that AST and particularly platelets are probably better estimates to define the severity of liver disease, compared with ALT.

Response: Thank you for the excellent and constructive suggestions. We acknowledge that the readability of this article has been compromised due to the comparative analysis of ALT thresholds advocated by various guidelines. We sincerely apologize for any errors present in this manuscript and any inconvenience they may have caused during your perusal. Consequently, the manuscript has undergone meticulous revision and editing, with the assistance of American Journal Expert.

The majority of current studies and guidelines have primarily focused on ALT treatment thresholds, such as those recommended by EASL 2017 (40 U/L), AASLD 2018 (35 U/L for men and 25 U/L for women), KASL 2022 (34 U/L for men and 30 U/L for women), JSH 2019 (30 U/L), and AASLD 2016 and GESA 2022 (30 U/L for men and 19 U/L for women). However, there is limited research on AST treatment thresholds. As mentioned earlier, AST and platelet levels may provide more accurate assessments of liver disease severity compared to ALT. We believe that further investigation in this area is necessary and will ultimately inform the future management of patients with liver disease.

In this study, we investigated the diagnostic performance of APRI, FIB-4 (utilizing ALT, AST, PLT), and GPR in identifying significant hepatic injury among patients within the grey zone. FIB-4 exhibited an AUROC of 0.713 and 0.645 in the HBeAg-positive and HBeAg-negative grey zones, respectively.

2. The suggestion that lowering the ALT threshold to 30/19 U/L improves the definition of cases progressing to advanced disease is in keeping with data dating back to 2002, when Prati et al (see *Ann Intern Med* 2002;137:1-9) updated the definition of normal ALT values in CHC. I do believe that it's time to accept these very low levels as "normal limits" in all cases.

Response: We sincerely appreciate the excellent suggestion. It is important to note that the current criteria for determining "normal" ALT levels were established based on populations that included individuals with subclinical liver disease (Prati et al. *Ann Intern Med* 2002;137:1-9). Previous studies have demonstrated that even when ALT levels fall within the normal range, they are still associated with the extent of liver inflammation and fibrosis. In our discussion, we thoroughly explore the necessity and advantages of lowering the treatment ALT threshold. By doing so, we believe that early initiation of

antiviral therapy in CHB patients can be facilitated, subsequently reducing the incidence of cirrhosis and HCC, especially during the GZ phases. We have incorporated this section into the text and included the above literature citations to provide evidence for our argument (Lines 25-28, page 13 in the revised manuscript).

3. The same is probably true for the effect of age, where the limit of 30 years appears totally insufficient to define cases at risk of future HCC. The more intense and earlier treatment, the best to reduce the risk.

Response: Thank you for your kind suggestion. We fully agree with your perspective that age should not be a barrier to commencing antiviral therapy in individuals diagnosed with chronic hepatitis B and exhibiting normal alanine aminotransferase levels. Instead, a more individualized approach should be taken, focusing on the patient's liver inflammation and fibrosis, to reduce the risk of misdiagnosis and underdiagnosis. This will enable timely initiation of antiviral therapy for patients with hepatitis B who require treatment and are at risk of disease progression. In our discussion, we have thoroughly examined the necessity and advantages of prioritizing antiviral treatment for patients under the age of 30 who are affected by hepatitis B.

Responses to comments of Reviewer #2

I was asked to review the paper entitled "Lowering the Treatment Threshold of Alanine Aminotransferase for Enhanced Identification of Evidenced Hepatic Injury in the Grey Zone" It is a very interesting paper, with clinical impact and possible clinical applications. It is a well-designed study, a strong point being that all the patients included have been evaluated by liver biopsy.

I have some suggestions that, in my opinion, would improve the manuscript:

Title

1. I think that the title should include "in chronic hepatitis B patients"

Response: Thank you for your kind suggestion. Your input aligns more closely with the research topic of this study. The title should not exceed 18 words. We have incorporated "in chronic hepatitis B patients" into the title, resulting in "Lowering the Treatment Threshold of Alanine Aminotransferase for Enhanced Identification of Significant Hepatic Injury in Chronic Hepatitis B Patients" (Lines 5-6, page 1 in the revised manuscript).

Abstract

2. You should mention how is the "grey zone (GZ)" defined.

Response: We appreciate the excellent suggestion. We have now included this part in the abstract. GZ CHB patients were classified into four groups: GZ-A (HBeAg positive, normal ALT levels, and HBV DNA $\leq 10^7$ IU/ml), GZ-B (HBeAg positive, elevated ALT levels, and HBV DNA $<10^4$ or $>10^7$ IU/ml), GZ-C (HBeAg negative, normal ALT levels, and HBV DNA ≥ 2000 IU/ml), and GZ-D (HBeAg negative, elevated ALT levels, and HBV DNA ≤ 2000 IU/ml) (Lines 12-15, page 3 in the revised manuscript).

3. "Evidenced hepatic injury" - I do not think that this is the most appropriate term - maybe "significant hepatic injury". I think it should be replaced throughout the manuscript.

Response: We apologize for the impropriety. As you suggested, "significant hepatic injury" may more precisely describe the inflammatory and fibrotic state of the liver, instead of "Evidenced hepatic injury". Previous studies have similarly defined $\geq G2$ and $\geq S2$ as significant liver inflammation and significant fibrosis, respectively. Due to the numerous alterations, we have

refrained from enumerating all of them, opting instead to indicate them in red within the revised document.

Results

4. I think that you should underline in the results and also in discussion the number of patients who would benefit for treatment if the proposed ALT limits would be used.

Response: Thanks for your valuable suggestions. As explained in the results section, A total of 794 patients with normal ALT levels ($ULN \leq 40$ U/L) were selected for further investigation; of these patients, 53.90% (428/794) necessitated antiviral therapy. The proportion of patients with $ALT \leq 40$ U/L who required antiviral therapy was 64.86% [(221+294)/794] according to the AASLD 2018 Clinical Practice Guidelines. Furthermore, the proportion of patients with $ALT \leq 40$ U/L who required antiviral therapy was 75.44% [(401+198)/794] according to the “expert opinion on expanding anti-HBV treatment for chronic hepatitis B” in China. We have included the above information in the results to demonstrate the benefit of lowering ALT treatment thresholds. (Lines 20-26, page 3, and line 1, page 4 in the revised manuscript).

Discussions

5. First paragraph - You say: “The study showed that 50.22% of the CHB patients fell into the GZ category” I think that you should say: “The study showed that 50.22% of the patients with HBV infection fell into the GZ category”.

Response: We are grateful for your careful review. In that sentence, “The study showed that 50.22% of the CHB patients fell into the GZ category” has been revised to “The study showed that 50.22% of the patients with HBV

infection fell into the GZ category". (Lines 11-12, page 12 in the revised manuscript).

6. See number 4

Response: Thanks for your kind suggestion. As explained in the discussion section, a total of 794 patients with normal ALT levels ($ULN \leq 40$ U/L) were selected for further investigation; of these patients, 53.90% (428/794) necessitated antiviral therapy. The proportion of patients with ALT ≤ 40 U/L who required antiviral therapy was 64.86% [(221+294)/794] according to the AASLD 2018 Clinical Practice Guidelines. Furthermore, the proportion of patients with ALT ≤ 40 U/L who required antiviral therapy was 75.44% [(401+198)/794] according to the "expert opinion on expanding anti-HBV treatment for chronic hepatitis B" in China. To demonstrate the benefit of lowering ALT treatment thresholds, we have included the above information in the discussion. (lines 18-24, page 13 in the revised manuscript).

7. Minor English polish is needed.

Response: We sincerely apologize for the mistakes in this manuscript and any inconvenience they may have caused during your reading. The manuscript has undergone thorough revision and editing with the assistance of American Journal Expert. These changes will not affect the content and structure of the paper. We appreciate your diligent review and sincerely hope that the corrections will meet with your approval.