PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 86691

Title: Lowering the Threshold of Alanine Aminotransferase for Enhanced Identification of Significant Hepatic Injury in Chronic Hepatitis B Patients.

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00159278

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Professor

Reviewer's Country/Territory: Romania

Author's Country/Territory: China

Manuscript submission date: 2023-07-02

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-07-03 06:28

Reviewer performed review: 2023-07-03 10:11

Review time: 3 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

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" Abstract 2. You should mention how is the "grey zone (GZ)" defined 3. "Evidenced hepatic injury" – I do not think that this is the most appropriate term – maybe "significant hepatic injury". I think it should be replace throughout the manuscript 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 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" . 6. See number 4   7. Minor English polishind is needed

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
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SPECIFIC COMMENTS TO AUTHORS

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 t 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. 2.

The suggesting that lowering the ALT threshold to 30/19 UI/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. 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.