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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 89634

Title: Cumulative effects of excess high-normal alanine aminotransferase levels in relation to new-onset metabolic dysfunction-associated fatty liver disease in China

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03912378
Position: Peer Reviewer
Academic degree: BSc, PhD
Professional title: Professor
Reviewer's Country/Territory: Australia
Author's Country/Territory: China

Manuscript submission date: 2023-11-07

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2023-12-12 05:27

Reviewer performed review: 2023-12-20 10:19

Review time: 8 Days and 4 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Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish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	[Y] Grade A: Excellent [ ] 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

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Scientific significance of the conclusion in this manuscript	[Y] Grade A: Excellent [ ] 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: [ ] Anonymous [Y] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This study addresses an important question: Within the range of ALT scores currently considered normal, 0-40 U/mL, does an ALT score of 21-40, with rising ALT score over a 3-year period indicate an increased risk of MAFLD? The study is well designed. The manuscript needs increased clarity, especially in abstract and introduction, addition of the ROC used to determine the cutoff of 18.5, and correction of errors. Also, why was there not a revisitation of the data using a 20 U/mL level as a criteria for entry to the study, and reanalyse the data using the 18.5 U/mL cutoff that was later derived.? The major limitation of the study lacking biopsy is noted in Discussion. Now that biopsy is far less frequent , which is appropriate, it is important that studies now turn to derive diagnostics that are not pinned to biopsy. Biopsy should be minimal in hepatology. ALT is higher in male than female and the follow-up cohort had 49% male: It would be interesting to know whether the analyses can be applied separately to males and females: Is 18.5 U/mL appropriate for both male and female if male and female were separated into two cohorts? Does the eALT work apply more strongly to males vs females? Details:

1. page 8: section 3.1: Error: 83.13% is % with MAFLD who had eALT, 21-40. It is not %

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who had normal ALT. This error is repeated in 1st para Discussion, page 10. 2. page 8: section 3.1: Error: the ALT levels are written in reverse order of the correct order [correct it to: "with median (IQR) ALT levels 24 (18–35) U/L and 17 (13–23) U/L, respectively (Fig. 2B)". 3. Page 8, section 3.2: Show the ROC and derivation of hALT as >18.5 U/mL. 4. There are several terms unique to this ms: aALT, hALT, ehALT, eALT etc; definitions of all in one place would help with clarity; in a table or fig. 5. Abstract needs a rewrite. I have some suggested edits at the end of this comments. List 6. Page 5: regarding ref 10: how about change to : Liver damage can occur in the presence of normal ALT levels [10] 7. Page 5: again, as in a number of places, there are statement that normal ALT is associated with MAFLD. This is not correct. Mafld can occur in the presence of normal ALT, but it is not an association with normal ALT. 8. Top of page 11: "this": what is this? Unclear. Re-write of abstract and Key points: Background: Within the normal range, elevated alanine aminotransferase (ALT) level is associated with an increased risk of metabolic-associated fatty liver disease (MAFLD). Aim: An association between repeated ALT levels that are high-normal and the risk of new-onset MAFLD was investigated prospectively. Methods: A cohort of 3553 participants followed for four consecutive health examinations during 4 years was selected. The incidence rate, cumulative times, equal and non-equal weight cumulative effect of excess high-normal ALT level (ehALT) were measured. Cox proportional hazards regression was used to analyze the association between the cumulative effect of ehALT and the risk of new-onset MAFLD. Results: 83.13% of participants with MAFLD had normal ALT levels. The incidence rate of MAFLD showed a linear increasing trend for the cumulative ehALT group. Compared with the low-normal ALT group, multivariate adjusted hazard ratios (HRs) in the third and fourth quartiles of the equal and non-equal weight cumulative effect of ehALT were 1.651 (95% CI 1.199–2.273) and 1.535 (95% CI 1.119–2.106), 1.616 (95% CI 1.162–2.246) and 1.580 (95% CI 1.155-2.162), respectively. Conclusion: Most participants

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with MAFLD had normal ALT levels. Long-term high-normal ALT levels showed a cumulative increased risk of new-onset MAFLD. Key points: Alanine transaminase (ALT) levels within the normal range may not require any intervention measures. However, if the liver function test ALT level is high-normal for several years, it is necessary to be alert whether metabolic-associated fatty liver disease has occurred and or prevention should be initiated.