

Dear Dr. Yuan Qi,

We thank you for your encouragement and advice. We would like to resubmit the manuscript entitled “Determination of upper cut-offs of serum ALT and AST in Chinese” (Manuscript #12546) for your further consideration as an original research article for publication in *World Journal of Gastroenterology*.

We appreciate the reviewers for their constructive comments and we have modified the manuscript, according to their advice in the revision. We believe that we have addressed all of the concerns raised by the reviewers. The major changes in the revision have been marked in red and please see our point by point responses below. We have carefully checked every sentence in the revision to eliminate/reduce any syntax error and to improve its readability. In addition, this manuscript has been proofread by two native English biologists from Medjaden, a professional publication service company. We think that this manuscript is easily understood in terms of a scientific story its language writing.

If I can be of any assistance regarding the process of this manuscript please feel free to contact me. I look forward to hearing from you soon.

Sincerely,

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First of all, we would like to express our sincere gratitude to the reviewers for their constructive and positive comments.

Replies to the Reviewer 1

Suggest that the table 1 is divided for a better understanding of the results.

Response: We appreciate his/her advice. We have re-formatted the Table 1. We believe that the current Table 1 is easy for readers to understand the results.

Suggest that the bibliographic references are updated, there is no 201 onwards.

Response: We appreciate his/her advice. We have updated the references, including two relevant references in the revision.

Suggest conclusions and job prospects are agregen.

Response: We have revised the conclusion and stated the job prospects as required in the revision as “In our future study, we will enlarge the sample size and include cohorts from different geographical areas, so that our results would be more reliable and would provide important evidence for the prevention and management of liver disorders”.

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Replies to the Reviewer 2

1. In Introduction: The author stated “This study questionnaire was approved by the Ethics Committee of China .”, yet I cannot find such an institution. Please provide the correct name of this institution and the

registration number of this study. Also in Introduction, it was stated “During the past few decades, population health and social economic conditions have seen notable changes in China.” This sentence should be revised.

Response: We are sorry for the confusion. “This study questionnaire was approved by the Ethics Committee of the First Hospital of Jilin University”, but not the Ethics Committee of China. We have corrected it in the revision. In addition, we have the sentence to “During the past few decades, social economic and people’s health conditions in China have notably changed” in the revision.

2. Please provide the exclusion criteria for the enrollment of this study.

Response: The exclusion criteria have been added in the section of Materials and Methods of the revision as “Exclusion criteria included: subjects with hepatic steatosis; liver cirrhosis; liver enlargement; a history of HBV or HCV infection; current administration of medicine and a history of ALT and/or AST > 60 U/L; triglyceride (TG) \geq 1.7 mmol/L; cholesterol \geq 6.0; low density lipoprotein (LDL) \geq 4.3 mmol/L; high density lipoprotein (HDL) < 1.04 mmol/L in men or <1.3 mmol/L in women; BMI \geq 23; alcohol consumption > 40 g/month; daily cigarette consumption > 30”.

3. What’s the definition of “drinker”? People with how much alcohol consumption can be classified as drinker? Also please define what HBV positive is.

Response: “drinker” was defined as one person with alcohol consumption > 40 g/month. HBV positive was defined as HBsAg positive. We have clarified the definition in the revision.

4. Table 1 cannot be displayed correctly. I cannot see the whole table.

Response: We are sorry for the confusion. Now, we have reformatted the Table to ensure its presentation clearly understandable.

5. In Results, the author stated “Furthermore, the lower levels of HDL were associated with the higher levels of serum AST ,” What’s the meaning by this statement? Does the author mean that HDL was negatively correlated with AST? Also in this section, the author wrote “Linear regression analysis revealed that a higher level of serum cholesterol was the strongest metabolic factor correlated with the abnormal levels of serum ALT, followed by higher levels of LDL and triglyceride. ” What did the author mean by using “higher levels”? Such a statement is confusing. Usually linear regression could suggest positive or negative correlation between factors no matter its lower or higher levels.

Response: Thanks for these helpful comments. We revised these statements as suggested.

We have changed the sentence to “HDL level was positively correlated with the serum AST levels, and serum cholesterol, LDL and triglyceride levels were positively correlated with serum ALT levels in this population” in the revision.

6. The author used “associated with” many times in the MS. What did the author mean by using “associated with”? Did it mean a correlation?

Response: In clinical epidemiology, while you stratify the data and calculate the difference in the rate between the stratifiers you only can claim the association, but not correlation. The correlation can only be used when you perform regression correlation analyses. Therefore, we used association to distinguish from correlation in the revision. Now, we have carefully checked these terms, based on the analytic methods.

7. In Discussion: The author stated “The concentrations of serum ALT and AST are the most commonly used serological markers”. “concentration of serum ALT” was also be used in other sentences in the MS. However, the serum levels of AST and ALT are usually indicated by activities rather than concentration. Also in Discussion, The author stated “In a retrospective study of 192 chronic hepatitis B patients, researchers showed that 59 patients (37%) with significant hepatic fibrosis and inflammation had persistently normal levels of ALT levels and that patients with high normal levels of serum ALT (> 25U/L) should be recommended for a liver biopsy [13][13].” I cannot understand this statement.

Response: We are sorry for our carelessness. Now, we have changed the concentrations to levels in the revision. In addition, we have changed the sentence to “In a retrospective study of 192 CHB patients, they found that 37% patients with significant hepatic fibrosis and inflammation had persistently normal levels of ALT and these patients with higher than normal levels of serum ALT (> 25U/L) had been recommended for a liver biopsy”.

8. The sentence “many “healthy” member individuals in the initial ALT studies might like to have some degrees of abnormalities in the liver function,” should be changed to “many “healthy” individuals in the initial ALT studies might have abnormalities in the liver function,”

Response: We have changed it, accordingly.

9. The author wrote “However, we found that the levels of serum triglycerides were correlated with the levels of serum ALT and AST.” But I cannot see any inconsistency before and after this sentence. I would suggest deleting “however”.

Response: We have changed it, accordingly.

10. Also in Discussion, it was stated “Most importantly, the new cut-off values of the levels of serum ALT and AST are valuable for the evaluation of liver function and diseases in adults in Northeast China.” Yet, the author did not evaluate his suggested upper normal limit of AST and ALT in patients with liver diseases in this manuscript. I wonder how the author had such a conclusion.

Response: We have deleted this inappropriate statement.

11. In Table 1: What is ex-drinker? Please define.

Response: We revised Table 1 and used “Drinking history” instead.

Replies to the Reviewer 3

The importance of the research and the significance of the research finding does not correspond to the journal’s aims and. Related work has been previously published and only a few new points have been added.

Response: We understood his/her comments. In this study, we for the firstly time conducted a large epidemiological study in Northern Chinese population. We determined the upper cut-off values of serum ALT and AST, and further stratification determined the potential risk factors associated with abnormal ALT and AST levels. Our study provides valuable insights into the evaluation of new cut-off values of the levels of serum ALT and AST. Establishment of new criteria for determination of the upper normal limits for serum ALT and AST may increase the sensitivity to evaluate chronic liver inflammation, and would also reduce the needs for unnecessary liver biopsy. Our findings would provide important

evidence for the prevention and management of liver disorders.