December 6, 2020
Dr. Lian-Sheng Ma.
Company Editor-in-Chief
World Journal of Gastroenterology

Dear Dr. Lian-Sheng Ma,

We are very grateful for the reviews provided by the editor and each of the external reviewers of this manuscript titled "**Prevalence of Advanced Liver Fibrosis and Steatosis in Type-2 Diabetics with Normal Transaminases: A Prospective Cohort Study**". The comments are encouraging, and the reviewers appear to share our judgement that this study and its results are clinically important. Please see below, in blue, our detailed response to comments.

Reviewer 1: Comments to the Author

1.1 - The authors report a study of the prevalence of advanced fibrosis in patients with type 2 diabetes mellitus. There were 59 patients who were compared to 26 in the control group. I think it is unfortunate that the control group is so small and it is not really explained where these patients were picked from.

Authors' Response: We thank the reviewer for this comment. Control group patients were recruited from gastroenterology clinic at our hospital. This has been added to the manuscript as well.

1.2 The ALT upper limit of normal of 40 is anachronistic- the current recommendations are for lower limits for men and women (Pacifico et al C; in Chim Acta 2013;422:29-39).

Authors' Response: We thank the reviewer for this comment. Inclusion criteria in our study were normal ALT defined by our lab as less than 40 U/L which is higher than the current accepted standard. Nevertheless, mean ALT level in the control and study group was 17 and 17.8 U/L. This has been also added as one of the limitations.

1.3 The authors do not clearly state when the M or XL probes were used for the ~Fibroscan determination, although tis is likely to be based on the patients BMI.

Authors' Response: We thank the reviewer for this comment. The probe selection was based on automatic recommendation as per the software which selects the probe based on thoracic perimeter measurement and skin capsule distance measurement. This comment has been added in the methods section under the subheading "Assessment of hepatic steatosis and fibrosis using transient elastography".

1.4 The definition of the metabolic syndrome employed may not have been accurate for people of Asian ethnicity- I am unsure as to how many of the patients this would be relevant for.

Authors' Response: We thank the reviewer for this comment. In our study, majority of the patients (>90%) were from Hispanic or African American race. Hence, metabolic syndrome definition as per the National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III) criteria was utilized.

1.5 I note that the patients in the control group were significantly older than the study group- this is another confounding factor. Despite these issues, the study is comprehensive, the data is discussed very well and the conclusions are valid. The authors conclusion that many patients with near normal ALT may have significant fibrosis may be valid- but it would be better if the control group was larger and had a lower normal level of normal for ALT.

Authors' Response: We thank the reviewer for this comment. Multiple studies have addressed age as a variable of influencing liver stiffness in normal subjects, and the results have been inconsistent, reporting no difference across age groups [PMID: 23116805, PMID: 30216377], higher LSM in older [PMID: 21068129] or younger [PMID: 20817625] age. Due to these inconsistent results in literature, we did not mention age as one of the confounding factor. However, now we have included this argument in the limitation section.

Reviewer 2: Comments to the Author

The present study mainly talk about the prevalence of advanced liver fibrosis and steatosis in patients with T2DM and normal transaminases. My comments are as follows: Seems that the has already been the leading cause of liver transplantation in some developed contries.
2.1 The name of NAFLD is including NASH, so it is immproper to say "Individuals with T2DM who develop NAFLD also carry a higher risk of progression to NASH"

Authors' Response: We thank the reviewer for this comment. We agree with reviewer's comment and her and accordingly we have changed the statement to the following - "individuals with T2DM who developed nonalcoholic steatosis also carry a higher risk of progression to NASH"

2.2. What about the criteria for control group, only no T2DM? Do they all had NAFLD or not?

Authors' Response: We thank the reviewer for this comment. These patients had no known history of fatty liver disease. We have clarified this in the methods section.

2.3. Liver biopsy is recommended for Metabolic Syndrome patients with NAFLD, so what's the meaning to compare MS in the diabetic and control group?

Authors' Response: We thank the reviewer for this comment. Our study results are consistent with the guidelines that presence of metabolic syndrome in patients with NAFLD predicts the presence of steatohepatitis and hence should alert the physicians to target these patients for a liver biopsy.

2.4. Age is also correlated to NAFLD, and the age in the study group is higher than that in control study, did the author consider this when they draw the conclusion?

Authors' Response: We thank the reviewer for this comment. Multiple studies have addressed age as a variable of influencing liver stiffness in normal subjects, and the results have been inconsistent, reporting no difference across age groups [PMID: 23116805, PMID: 30216377], higher LSM in older [PMID: 21068129] or younger [PMID: 20817625] age. Due to these inconsistent results in literature, we did not mention age as one of the confounding factor. However, now we have included this argument in the limitation section.

2.5. How the author explain that there was no differeneces between liver stiffness using elastography (kPa)?

Authors' Response: We thank the reviewer for this comment. Liver stiffness in the study group was higher as compared to control group but not statistically significant, and this is most likely due to small sample size.

2.6. The sample is too small for a study without biopsy.

Authors' Response: We thank the reviewer for this comment. We agree with the reviewer about small sample size of the study and accordingly have already mentioned that as one of the major limitations of the study. Our study is a prospective trial which has its own hurdles in recruiting patients. Nevertheless, we believe our prospective study results will further encourage other researchers to validate our findings in a larger sample size studies.

Science Editor: Comments to the Author

3.1 Scientific quality: The manuscript describes a prospective Study of the prevalence of advanced liver fibrosis and steatosis in T2DM and normal transaminases. The topic is within the scope of the WJG. (1) Classification: Grade C and Grade C; (2) Summary of the Peer-Review Report: This study mainly talks about the prevalence of advanced liver fibrosis and steatosis in patients with T2DM and normal transaminases. It is not proper to say "Individuals with T2DM who develop NAFLD also carry a higher risk of progression to NASH".

Authors' Response: We agree with reviewer's comment and accordingly we have changed the statement to the following - "individuals with T2DM who developed nonalcoholic steatosis also carry a higher risk of progression to NASH"

The control group is so small and it is not really explained where these patients were picked from.

Authors' Response: We thank the reviewer for this comment. Control group patients were recruited from gastroenterology clinic at our hospital. This has been added to the manuscript as well.

The questions raised by the reviewers should be answered; and

Authors' Response: Reviewers questions have been answered as detailed above.

(3) Format: There is 1 table and 4 figures. A total of 27 references are cited, including 8 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade B and Grade A. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the Signed Informed Consent, and the Institutional Review Board Approval Form. The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an unsolicited manuscript. The topic has not previously been published in the WJG. The corresponding author has not published articles in the BPG. 5 Issues raised:
(1) I found the title was more than 18 words. The title should be no more than 18 words;

Authors' Response: Title word limit has been adjusted to 18 words.

(2) I found no “Author contribution” section. Please provide the author contributions;

Authors' Response: Now included in the manuscript.

(3) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; and

Authors' Response: Please see attached files.

(4) I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text. 6 Re-Review: Required. 7 Recommendation: Conditionally accepted.

Authors' Response: Now included in the manuscript.

Once again, we thank reviewers’ helpful comments and hope that the revised version of the manuscript is suitable to World Journal of Gastroenterology, and look forward to its publication.

Sincerely,

The Authors