

Dr. Ke-Qin Hu MD

Dr. Koo Jeong Kang MD, PhD

Dr. Nikolaos Pirsopoulos MD, PhD

Editors-in-Chief

World Journal of Hepatology

June ***, 2021

Dear Drs. Hu, Kang, and Pirsopoulos,

We thank you and the reviewers for your helpful comments regarding our manuscript “Prevalence and risk factors of steatosis and advanced fibrosis using transient elastography in the United States’ adolescent population” (NO: 67866).

We are pleased to submit a revised version for your consideration as an original article in *World Journal of Hepatology*. We are grateful for the insightful and comprehensive reviewers’ comments and have taken into account the points made to incorporate the changes into our revised manuscript.

In the revised manuscript, we discussed the key factors that make our manuscript unique. We also added a couple limitations mentioned by the reviewers to ensure completeness of the manuscript.

We hope the revised manuscript is now suitable for publication in *World Journal of Hepatology*. Thank you again for your interest in our study’s findings.

Sincerely,

Yousef Elfanagely, MD

Resident Physician, Internal Medicine

Response to Reviewers

Reviewer #1:

1. It has been previously report
 - a. **Comment:** We acknowledge that a similar paper was published. We have included key differences that make our manuscript unique. As stated in the discussions portion of the paper: “This study reports the prevalence of steatosis and fibrosis in U.S. adolescents who participated in NHANES 2017-2018 as diagnosed by TE and CAP. We also identified predictors of steatosis grade and fibrosis stage in this study population. Although there was a recent study on a similar topic that utilized the same database from Ciardullo et al, 28 the study designs were distinct as follows: (1) the maximum age in this study is 17 since the age 18 and above was used as a cut-off for many adult questionnaires in NHANES (e.g., alcohol use, physical activity, and smoking); (2) we discretized the steatosis grades and fibrosis levels into 4 levels each; (3) Advanced fibrosis was defined as $\geq F3$ (≥ 8.6 kPa) rather than $\geq F2$ (≥ 7.4 kPa); (4) we included more risk factors that were widely known to be associated with NAFLD (e.g., smoking, physical activity, diet, and insulin resistance); (5) linear regression was used instead of logistic regression. For this reason, our results on prevalence and significant predictors are different from the previous study even though we used the same database.”
2. This important aspect has not been emphasized demonstrated that hypogonadism and low testosterone level is associated to an increased risk for NAFLD and NASH. Following this line, the authors should recognized that a limitation is the lack of an analysis of the association of NAFLD with the Tanner stages.
 - a. **Comment:** Thank you for this insightful point. We have included this as a limitation for the study in the discussions section of the manuscript. It reads: “Some variables not available in the NHANES include hormonal levels and Tanner stages of the participants. Hypogonadism and low testosterone level are associated with an increased risk for NAFLD and NASH(44). Low sex hormone binding globulin (SHBG) is a marker for NAFLD in women with oligomenorrhea and/or hirsutism(45). Since these variables were not included in the NHANES database, they were not accounted for.”
3. The authors should present data according to gender
 - a. **Comment:** We did not present the data according to gender because this is not the primary scope of the manuscript. Our paper was meant to study the prevalence and risk factors of steatosis and advanced fibrosis using transient elastography in the U.S. adolescent population.
4. The authors reported that several cardio-metabolic risk factors were predictors of fibrosis stage. A multi-regression analysis should be performed to assess the most relevant one during adolescence
 - a. **Comment:** A multi-regression analysis was performed. Statistically significant predictors of steatosis and fibrosis stage were summarized on Table 3 and 5.
5. It has been recently recognized that low SHBG level could predict to presence of NAFLD (Front Endocrinol (Lausanne)). In particular a SHBG level below 33-4 nM is considered to predict the presence of NAFLD. This biochemical marker of NAFLD should be commented and briefly discussed. Are there any hormonal data to evaluate the relationship between hepatic alterations and hormonal level?
 - a. **Comment:** Thank you for this insightful point. We have included this as a limitation for the study in the discussions section of the manuscript. It reads: “Some variables not available in the NHANES include hormonal levels and Tanner stages of the participants. Hypogonadism and low testosterone level are associated with an increased risk for NAFLD and NASH(44). Low sex hormone binding globulin (SHBG) is a marker for NAFLD in women with oligomenorrhea and/or hirsutism(45). Since these variables were not included in the NHANES database, they were not accounted for.”

Language Quality:

- Please resolve all languages issues in the manuscript
 - **Comment:** The manuscript was reviewed. All language issues were resolved.

Abbreviations:

- In general, do not use non-standard abbreviations, unless they appear at last two times in the text preceding the first usage/definition.
 - **Comment:**

Title:

- Please spell out any abbreviation in the title
 - **Comment:** The title no longer contains an abbreviation.

Running title:

- Please shorten the running title to no more than 6 words. Abbreviations are permitted.
 - **Comment:** The running title was reduced to 6 words (“Steatosis and fibrosis in the adolescent population”).

Abstracts:

- Abbreviations must be defined upon first appearance in the Abstract. Examples: Example 1: Hepatocellular carcinoma (HCC). Example 2: Helicobacter pylori (H. pylori).
 - **Comment:** Abbreviations were also included in the abstract.

Key words:

- Abbreviations must be defined upon first appearance in the Key words.
 - **Comments:** Abbreviations were defined upon first appearance in the Key words.