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July 28, 2019

Dr. Li-Jun Cui
Science editor

World Journal of Hepatology

Re: Manuscript NO 48729 "Characterization of Patients with Both Alcoholic and Nonalcoholic Fatty Liver Disease in a Large United States Cohort"

Dear Dr. Li-Jun Cui,

We are grateful to the editors and reviewers for their constructive comments and quick response. We have now addressed the questions and made point-by-point revisions. Attached please find copy of the latest manuscript version with changes highlighted in YELLOW. Thank you for your consideration.

Yours Respectfully,

George Khoudari, MD; Amandeep Singh, MD; Mazen Noureddin, MD; Danielle Fritze, MD; Rocio Lopez, MS, Imad Asaad, MD; Eric Lawitz E, MD; Fred Poordad, MD; Kris V Kowdley, MD; Naim Alkhouri, MD

PEER-REVIEW REPORT and Response

Name of journal: World Journal of Hepatology

Manuscript NO: 48729

Title: Characterization of Patients with Both Alcoholic and Nonalcoholic Fatty Liver Disease (BAFLD) in a Large United States Cohort

Reviewer's code: 02926997

Reviewer's country: Iran

Science editor: Li-Jun Cui

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Reviewer accepted review: 2019-05-26 23:33

Reviewer performed review: 2019-05-26 23:54

Review time: 1 Hour

SPECIFIC COMMENTS TO AUTHORS

Dear Associate Editor, Thank you for sending me the article entitled "Characterization of Patients with Both Alcoholic and Nonalcoholic Fatty Liver Disease (BAFLD) in a Large United States Cohort" for review. This cross sectional study evaluated the prevalence of NAFLD, ALD, and BAFLD in a cohort of American population. It also compared the degree of liver fibrosis based on a non-invasive model between NAFLD and BAFLD. The study concluded that a significant percentage of the American general population is afflicted by BAFLD and these patients tend to have more advanced liver fibrosis. There are some comments as the followings:

1- To clarify the possibility of selection bias, Please explain the National Health and Nutrition Examination Survey (NHANES) program (or at list reference to define the method of patient selection criteria).

The NHANES is a survey program conducted by the National Center for Health Statistics (NCHS), which is part of the Centers for Disease Control and Prevention (CDC). The program is designed to assess the health and nutritional status of adults and children in the US. It began in the early 1960s and became a continuous program in 1999. It examines a sample of 5,000 persons a year from different counties across the United States representing the US population of all ages. The survey includes interview questionnaires, standardized physical examination, and laboratory tests from blood samples collected at examination centers and analyzed at a central laboratory. The survey was approved by the Institutional Review Board at the Center for Disease Control and Prevention, and informed consent was obtained from all participants.

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This definition was added to the manuscript on page 10, line 157-166.

2- 2- Please refer to the Ethical considerations of the study.

NHANES was approved by the Institutional Review Board at the Center for Disease Control and Prevention, and informed consent was obtained from all participants.

3- 3- Please do not duplicate the data of tables in the text in result section.

We have now deleted the duplicated data from the text according to the reviewer's suggestions.

4- 4- Please delete the table 3 and just define data in the text.

We have now deleted table 3 and defined the data in the text, page 13, line 239-241 according to reviewer's suggestions.

PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 48729

Title: Characterization of Patients with Both Alcoholic and Nonalcoholic Fatty Liver Disease (BAFLD) in a Large United States Cohort

Reviewer's code: 02460576

Reviewer's country: China

Science editor: Li-Jun Cui

Reviewer accepted review: 2019-05-25 12:00

Reviewer performed review: 2019-05-29 08:53

Review time: 3 Days and 20 Hours

SPECIFIC COMMENTS TO AUTHORS

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This study assessed the clinical characteristics of patients with both alcoholic and nonalcoholic fatty liver disease in a large cohort, and the results showed that the prevalence of BAFLD is relative higher in America and patients with BAFLD have more advanced liver fibrosis than NAFLD patients. This study was interesting and the subjects were large. However, some defects could not be ignored. 1. How do the authors to distinguish the NAFLD and BAFLD? In my opinion, fatty liver disease may be caused by nonalcoholic factors or alcohol, but how to define the fatty liver disease was caused by both nonalcoholic factors and alcohol? Please explain it detailed.

We agree fatty liver disease can be caused by both alcohol and non-alcoholic factors, and this is exactly what our study entails and find individuals, which share modifiable alcoholic and non-alcoholic risk factors for fatty liver.

We first divided subjects into ALD and NAFLD groups based on criteria's used in previously published studies and then from these groups diagnosed BAFLD if they had NAFLD with either diabetes or metabolic syndrome and alcoholic liver disease.

This helped us identify patients from both ALD and NAFLD who had modifiable metabolic components (DM, Mets, obesity etc.)

2. If all the BAFLD patients were had either MetS or type 2 diabetes or part of them had the MetS or type 2 diabetes?

Not all of BAFLD had diabetes or Mets, it was either one or both of them along with h/o NAFLD and excess alcohol

3. In this study, NAFLD was diagnosed based on elevated alanine aminotransferase and overweight or obese, so the accuracy of NAFLD diagnosis may be suspectable.

We agree that using current criteria diagnosis of NAFLD is not accurate, but for such large population-based study, accurate measurement of NAFLD with US or biopsy is not feasible.

We added this to the limitation section in our manuscript page 17, line 376-378.

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4. If the age, sex of subjects in NAFLD group or BAFLD group were comparable? The authors should show them in table or described them in the results section.

These characteristics are listed in table 2. Please see table 2, page 27.

5. In the table 1, the prevalence of ALD is 0.40, the prevalence of BFLD is 0.84, whether it meaning that single alcohol-leaded fatty liver disease is less than the fatty liver disease which caused by nonalcoholic factor and alcohol?

It simply means alcoholic fatty liver is is less prevalent than NAFLD and BAFLD. As BAFLD included patients from both NAFLD and ALD, it leads to the larger number for BAFLD than ALD.

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PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 48729

Title: Characterization of Patients with Both Alcoholic and Nonalcoholic Fatty Liver Disease (BAFLD) in a Large United States Cohort

Reviewer's code: 03262644

Reviewer's country: Bosnia and Herzegovina

Science editor: Li-Jun Cui

Reviewer accepted review: 2019-05-24 04:00

Reviewer performed review: 2019-06-12 15:51

Review time: 19 Days and 11 Hours

SPECIFIC COMMENTS TO AUTHORS

This is interesting study conducted over the significant number of subjects addressing an important question of the prevalence and clinical featured of NAFLD in general population. In addition the authors have tried to address the issue of overlapping of NAFLD with excessive alcohol consumption which is frequently seen in NAFLD patients. The results are interesting, but to accept them as relevant and reliable several methodological issues should be clarified by the authors. Subjects, page 7: Definitions of NAFLD and BAFLD are not entirely clear to me. NaFLD has been defined as presence of BMI>25+ elevated ALT (>30 in M; >19 in F), which is acceptable in my opinion. With this definition significant number of patients with NAFLD and non-elevated ALT was missed and therefore this definition has its limitations. Which is more confusing to me is the definition of BAFLD. To be consistent I would have expected to define BAFLD as NAFLD+ heavy alcohol intake. However, in this study the diagnosis of BAFLD was

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narrowed by adding the presence of MetS or T2DM. I would expect that by narrowing BAFLD to only those patients with MetS or T2DM a certain number of patients would be missed as well. Also, the presumed severity of BAFLD should by definition be expectedly higher. This might have led to potentially underestimated prevalence of BAFLD. Authors should explain why did they decide to use such a definition of BAFLD.

We included diabetes and metabolic syndrome to define BAFLD as significant number of NAFLD and ALD patients could be lean or end-stage liver disease leading to underestimation of metabolic components. By adding diabetes and MetS we tried to capture patients with early stages where interventions can be applied.

Subjects, page 8: Which definition of MetS was used for this study?

MetS was defined as central Obesity plus at least 2 of the following: Diabetes, Hypertension, Hypertriglyceridemia or Low HDL

This was added to the methods in page 11, line 186 as per reviewer's suggestions.

Results, page 9 and Table 2: In line with the previous comment, it is confusing to me to compare NAFLD to BAFLD patients when all BAFLD patients by definition had presence of MetS or T2DM. Therefore, one should expect higher prevalence of the components of MetS and for T2DM in BAFLD group and for this reason I believe it is wrong to compare the presence of these components between 2 groups.

Patients with BAFLD met the criteria for NAFLD but also had either MetS or type 2 diabetes and consumed excessive amounts of alcohol defined as ≥ 3 drinks/day for men and ≥ 2 drinks/day for women. Not all NAFLD patients consumed alcohol leading to lesser number in BAFLD.

Prevalence of Advanced Fibrosis (AF) in Patients with NAFLD and BAFLD, page 10: Why did the authors use 2.67 cut-off as the threshold for advanced fibrosis? Why not 3.25?

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Even with this higher cut-off value PPV is weak of only around 50%..this should be also highlighted as limitation. Otherwise, FIB-4 is best used to rule-out advanced fibrosis (at cut-off value of 1.3).

Authors are kindly asked to compare their results on the estimates prevalence of advanced fibrosis in NAFL population to the existing data from other studies. The figures reported here seem to be too low.

2.67 had been previously used in various studies to define AF

The Utility of Noninvasive Scores in Assessing the Prevalence of Nonalcoholic Fatty Liver Disease and Advanced Fibrosis in Type 2 Diabetic Patients.

Singh A, Le P, Peerzada MM, Lopez R, Alkhouri N.

J Clin Gastroenterol. 2018 Mar;52(3):268-272. doi: 10.1097/MCG.0000000000000905.

In the study limitation section, page 17, line 376-378 we mentioned the following "we used non-invasive fibrosis scores to predict advance fibrosis which is not the gold standard method" according to the reviewer's suggestions

The manuscript reviewers' comments:

-The yellow highlighted sentences are rephrased as suggested by your comments.

-The authors' departments were added as suggested, line 9.

-ORCID numbers were added as suggested, page 2, line 40.

-Authors' contributions were added as suggested, page 3, line 52.

-Institutional review board statement was added as suggested, page 3, line 58

-Informed consent statement was added as suggested, page 3, line 61

-Core tip was added as suggested, page 8, line 101.

-All crosschecked phrases were rephrased as suggested by the reviewers and are highlighted in yellow in the manuscript file.

-All references were reformatted according to your suggestions.

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-Article highlights were added according to your suggestions, page 18, line 397.

-All abbreviations were added below tables and figures as per your suggestions.

-The decomposable table of figures was added according to your suggestions.