

PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 54031

Title: Non-alcoholic steatohepatitis and the risk of myocardial infarction: A population-based national study

Reviewer's code: 03262371

Position: Editorial Board

Academic degree: MD

Professional title: Academic Research, Doctor, Research Associate

Reviewer's Country/Territory: Iran

Author's Country/Territory: United States

Manuscript submission date: 2020-01-11

Reviewer chosen by: Ying Dou

Reviewer accepted review: 2020-02-18 18:04

Reviewer performed review: 2020-02-22 07:17

Review time: 3 Days and 13 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

Dear editor Thanks for the invitation. My only question is regarding the case selection. Why did author only select patients with MI in 2018-2019, but NAFLD cases form 1999 to 2019? I think it can make an important bias.

PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 54031

Title: Non-alcoholic steatohepatitis and the risk of myocardial infarction: A population-based national study

Reviewer's code: 02445091

Position: Editorial Board

Academic degree: PhD

Professional title: Professor

Reviewer's Country/Territory: India

Author's Country/Territory: United States

Manuscript submission date: 2020-01-11

Reviewer chosen by: Ying Dou

Reviewer accepted review: 2020-02-25 15:21

Reviewer performed review: 2020-02-26 15:52

Review time: 1 Day

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input type="checkbox"/> No
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SPECIFIC COMMENTS TO AUTHORS

In this retrospective study among 43,170 NASH patients in US using a large national database, the authors concluded that (1) NASH conferred a higher risk of MI compared to patients without NASH; (2) NASH had a comparable association with MI as advanced age, male gender and diabetes mellitus; (3) in an overall unadjusted model, the prevalence of MI was significantly high in patients with NASH. The following are the points raised by this reviewer. Major comments: Table 3 describes the absolute risk and relative risk of MI in patients with NASH compared to non-NASH. Did a gender base relative risk calculation possible among each age group? Minor comments: Many typographical errors found in the text that need to be corrected: 1. Core tip:.....severity might we? be able to... 2. Page 5: 'four fold increase in in? cardiovascular events

PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 54031

Title: Non-alcoholic steatohepatitis and the risk of myocardial infarction: A population-based national study

Reviewer's code: 04025443

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Doctor, Senior Researcher

Reviewer's Country/Territory: Russia

Author's Country/Territory: United States

Manuscript submission date: 2020-01-11

Reviewer chosen by: Jin-Zhou Tang (Quit in 2020)

Reviewer accepted review: 2020-03-25 03:13

Reviewer performed review: 2020-03-31 09:52

Review time: 6 Days and 6 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

This is an interesting and a large-scale study of the myocardial infarction (MI) incidence and conditions that coincide these event. The manuscript is well-written, provides new scientific data on the factors associated with MI within a year (2018-2019) on a country-based level. The methods used by the authors are absolutely relevant to this certain aim, but seems to be not fully appropriate for the study purpose. This makes the scientific value of the study questionable. Below are the concerns about the study. First - what was studied and in which groups? The aim of the study stated in the abstract and in the body of the manuscript differs. There is a discrepancy between time frame for identification of NAFLD/NASH patients and those with MI. Only cases of MI occurred within 1 year (2018-2019) were taken into the account while 20 years frame was taken for NAFLD. This does not allow to analyse neither risks nor incidence of MI in those with NAFLD and may be associated with an error related to random events. This approach can reveal the prevalence of NAFLD among the conditions found in patients with MI (if the study is focused on this condition) during a year (with a limitation of the coding, which, as it mentioned by the authors, could be not always correct). There is another limitation which was not mentioned by the authors. NAFLD is a chronic condition and currently we don't have effective and specific treatment for it. However, some of the non-specific (and not highly specific) measures may be taken and are advised by EASL and AASLD. The authors searched for NAFLD codes in the database for the period of 20 years. But what was going on with the patient after diagnosis had been established? It seems hardly possible that a patient with the diagnosis of NAFLD confirmed, for example, in 1999 have been doing nothing for twenty years. At least part of the patients should have been made one or several attempts to lose weight, become more physically active. Some of them might have been taken measures to lower serum

lipid concentrations, or affect insulin resistance, etc. The mentioned measures could make the risks of cardiovascular events lower. On the Fig. 1, and in table 3 the “risks” of MI in NASH patients are shown. According to the Methods section, these “risks” correspond to 1 year only which should be discussed appropriately (and which is not really correct). The relative risk of IM in patients with NASH in the age group 40-44 y.o. is more than twice higher compared to those of 60-64 y.o. On the one hand it may reflect the need for prophylaxis of CVD, but on the other hand (considering time trend and the disease progression) may require double check for an unintentional mistake. Thus, in case of the importance of NASH in the structure of cardiovascular disease, and probable increase of its influence along the condition presence, it should have made the chances of MI in NASH patients higher in the older group. May I suggest to analyse association between MI and the duration of time after diagnosis of NAFLD/NASH was established? Please explain a note of “Informed consent was obtained from all participants” in Ethical Statements (page 17). If so, whether the ICF form was approved by an IRB/LEC? Please consider revision of the figure and tables titles. (For example Fig. 1 – Risks of MI in different age groups and according to the presence of NASH. Tab 1 – “demonstrates” is not appropriate. Table 2 – there is no “prevalence”, but association of MI with certain conditions, Table 3 – please, explain the model “of what” is shown there. I cannot agree with the conclusion that NASH increases the risk of MI in the American population. This statement requires temporal association which was not studied. According to the data described, in those with MI, NASH is a prevalent condition. Sentences 2 and 3 in the Core tip are not relevant to the study.

PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 54031

Title: Non-alcoholic steatohepatitis and the risk of myocardial infarction: A population-based national study

Reviewer's code: 03317140

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: South Korea

Author's Country/Territory: United States

Manuscript submission date: 2020-01-11

Reviewer chosen by: Jin-Zhou Tang (Quit in 2020)

Reviewer accepted review: 2020-03-29 21:34

Reviewer performed review: 2020-04-02 04:14

Review time: 3 Days and 6 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The manuscript (54031) entitled " Non-alcoholic steatohepatitis and the risk of myocardial infarction: A population-based national study" provided new information using the Explorys database, the author performed a national-based population study to investigate the association between NASH, a more severe subtype of NAFLD, and myocardial infarction in the United States. Unfortunately, this paper provided weak evidence to reveal a new finding from their database. Therefore, I think this paper needs a major revision to publish in the World Journal of Hepatology.

1. Baseline characteristics : First of all, Table 1 should show a difference between total cohort and NASH cohort. I could not make sure that the author excluded fatty liver disease, alcoholic hepatitis, and alcoholic fatty liver disease from total cohort. If they included in total cohort, it gave us analysis errors.
2. NAFLD cohort : In principle, it is recommended to analyze the risks by NASH and NAFLD groups, because the effect of inflammation can be seen more clearly.
3. Classification of age : The number of patients by age is not clearly described, and this also describes baseline characteristics in other table or table 1, and subgroup analysis is needed to determine which factors closely affect MI development in each group. If the analysis by age group is not easy, it is necessary to see that the risk factors can be different for each age group by analyzing the data by cutting into 10-year-old units rather than analyzing them in 5-year-old units.
4. Definition of MI The distinction of MI is also ambiguous whether it is acute MI or old MI. Whether DM, HTN, and dyslipidemia are all well controlled by drugs or not is an important part of MI development. The author should describe about that.
5. Minor : Study design line 4, "from 1999 until 1999" is right?

PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

Manuscript NO: 54031

Title: Non-alcoholic steatohepatitis and the risk of myocardial infarction: A population-based national study

Reviewer's code: 02861252

Position: Editorial Board

Academic degree: MD

Professional title: Assistant Professor

Reviewer's Country/Territory: Turkey

Author's Country/Territory: United States

Manuscript submission date: 2020-01-11

Reviewer chosen by: Ying Dou

Reviewer accepted review: 2020-03-25 13:09

Reviewer performed review: 2020-04-08 12:00

Review time: 13 Days and 22 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

Very nice work The date should be corrected in the study design section only...

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Hepatology

Manuscript NO: 54031

Title: Non-alcoholic steatohepatitis and the risk of myocardial infarction: A population-based national study

Reviewer's code: 04025443

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Doctor, Senior Researcher

Reviewer's Country/Territory: Russia

Author's Country/Territory: United States

Manuscript submission date: 2020-01-11

Reviewer chosen by: Ying Dou

Reviewer accepted review: 2020-05-20 06:24

Reviewer performed review: 2020-05-22 05:56

Review time: 1 Day and 23 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Dear Editors! Thank you for the opportunity to re-review the manuscript. Unfortunately, I see no substantial changes in the manuscript. The authors provided their answer, however they insist on the correctness of methods used in the study. I tried to make the error much visible by providing the diagram of what has happened in the file attached. According to the methods and the response to reviewers, the authors tried to evaluate the events of acute myocardial infarctions (MI) happened along the period of 2018-2019 years with special emphasis on the patients with the diagnosis of non-alcoholic steatohepatitis (NASH) established in 1999-2019. This approach makes possible to obtain the information about the prevalence of NASH among the patients with MI in 2018-2019, but NOT the chances of MI in NASH patients. The authors are not fully correct about the exposure and the event, as this statement imply a causal relationship. However, the odds ratio does not, it is a measure of association between two (probably independent or associated with the other factors) events, especially in a retrospective studies. Narrowing the period for MI, and not taking into the account the possible events of MI happened on previous time interval we may underestimate the prevalence of MI in those with NASH and put ourselves under the risk of bias associated with the random events. According to the description of the odds ratio, this is the ratio of the odds of an event occurring in one group to the odds of it occurring in another group. Namely, all cases of MI should be calculated in patients with NASH for the same period. According to the manuscript, this is not odds of MI in NASH (page 7, Results), but odds of NASH in MI. Methods are described in somewhat weird way. For example, key point of statistical analysis comes as follows: "The prevalence of MI in each risk groups was calculated by dividing the number of patients with NASH in each risk group." (page 6, Statistical analysis). Again, it seems that it was not possible to obtain correct data, as there is an uncertainty on the presence of NASH in 2019, in case the diagnosis has been established in 1999.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Hepatology

Manuscript NO: 54031

Title: Non-alcoholic steatohepatitis and the risk of myocardial infarction: A population-based national study

Reviewer's code: 03317140

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Associate Professor

Reviewer's Country/Territory: South Korea

Author's Country/Territory: United States

Manuscript submission date: 2020-01-11

Reviewer chosen by: Ying Dou

Reviewer accepted review: 2020-05-22 07:32

Reviewer performed review: 2020-05-22 07:51

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS



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The manuscript (54031) was sufficiently revised according to the comments. However, please change the format of Tables 1 and 2 as shown in Table 3. Finally, I would like to suggest publishing this paper in the World Journal of Hepatology.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Hepatology

Manuscript NO: 54031

Title: Non-alcoholic steatohepatitis and the risk of myocardial infarction: A population-based national study

Reviewer's code: 02861252

Position: Editorial Board

Academic degree: MD

Professional title: Assistant Professor

Reviewer's Country/Territory: Turkey

Author's Country/Territory: United States

Manuscript submission date: 2020-01-11

Reviewer chosen by: Ying Dou

Reviewer accepted review: 2020-05-24 15:41

Reviewer performed review: 2020-05-24 15:49

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
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Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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Good work...