OPEN PEER REVIEW

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Hepatitis Monthly
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Peer Review Report for "Serum Mac-2 Binding Protein Glycosylation Isomer (M2BPGi) Can Predict Mild or Significant Liver Fibrosis in Non-Alcoholic Fatty Liver Disease"

Author(s): Yu-Ming Cheng, Chia-Chi Wang

Review Timeline:

Submit Date:	24 Apr 2021
Revised Date:	14 Jul 2021
Accepted Date:	21 Jul 2021

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | Revision (0)

8 May 2021

Dear AE,

In this manuscript, the authors evaluated the utility of M2BPGi for prediction of mild or significant liver fibrosis in patients with NAFLD. This report is of interest; however, there are several problems in this manuscript, and a major revision is needed before ready for publication.

Major points:
1) The authors used ARFI as standard reference of liver fibrosis stage. Please add a description of the advantages and disadvantages of ARFI as an index for assessing liver fibrosis, citing the literature.

2) In their Background, the authors state that ARFI is more accurate in diagnosing fibrosis, but at a higher cost. How high is the cost of ARFI compared to M2BPGi? If ARFI is clearly more accurate in diagnosing fibrosis than M2BPGi, then it would be appropriate to give priority to ARFI.

3) Conversely, FIB-4 index and APRI have the advantage of low cost.
Please also create ROC curves for FIB-4 index and APRI and compare them with M2BPGi to clearly show that M2BPGi is superior to FIB-4 index and APRI.

4) Was the M2BPGi useful in differentiating the F0 and F1 groups from the F2 and higher groups?

5) Results should be listed in separate paragraphs, with a title for each result.

Minor points:
1) In Page 5, line 2, NAFL should be changed to “NAFLD”.
2) In Page 5. Line 14, 30g/day should be changed to “30 g /day”.

REFEREE: Associate Editor | **Revision** (0) 27 Jun 2021

Dear Editor in Chief

Thanks for assigning me as associate editor to handle the manuscript NO.115400 entitled "Serum M2BPGi can Predict Mild or Significant Liver Fibrosis in Non-Alcoholic Fatty Liver Disease".
I appreciate the authors' work to do this study and write its manuscript. The subject is novel enough and the study methodology is correct. The manuscript needs revision. There are some concerns regarding the manuscript which should be addressed by the authors in this revision. See the peer-review comments attached. Also, the following issues should be addressed by the authors:

Title:
- Please use the "Mac-2 binding protein glycosylation isomer (M2BPGi)" instead of M2BPGi alone.
Abstract:
- Please select 3-5 proper keywords from PubMed MeSH-terms.
- The authors need to use the expanded version of abbreviations for the first time (e.g. AST and ALT in the abstract, HBV and HCV in the methods, IQR in the results).
- The authors should use the suitable references style according the journal's instruction.

Methods:
- The sampling frame is not clear. When? Where?
- The sampling technique is also unclear. What was the sampling technique? Were the patients randomly selected?
- The two above issues should be considered for the heathy controls. How did you selected the healthy controls? Where? When? By which sampling method?
- "42 participants were excluded due to V IQR/medium >15% in the data of ARFI." Please explain further about the reason for this exclusion in the methods section.

Results:

- This section needs more numerical results in its text (e.g. p-values). For example, "In this study population, the NAFLD patients were younger (P=XXX) and higher percentage of male gender (P=XXX) than healthy controls."
- Please specify the unit for M2BPGi level (e.g. COI), and use it after all M2BPGi levels in the results.

Seyed Moayed Alavian: EIC | **Revision** (0) 27 Jun 2021

Dear Authors,

Please follow the peer-review comments and submit a revision.

Regards,
EIC

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Response to reviewers' comments

Cheng et al.

Thanks for your invaluable comments and suggestions.

Reviewer #1: In this manuscript, the authors evaluated the utility of M2BPGi for prediction of mild or significant liver fibrosis in patients with NAFLD. This report is of interest; however, there are several problems in this manuscript, and a major revision is needed before ready for publication.

Major points:

1. The authors used ARFI as standard reference of liver fibrosis stage. Please add a description of the advantages and disadvantages of ARFI as an index for assessing liver fibrosis, citing the literature.
   Answer: Thanks for your comments. Since ARFI is incorporated in conventional ultrasonography, the complications of chronic liver disease, such as ascites or hepatocellular carcinoma could be assessed at the same time. However, the machine of ARFI is expensive and not available at local medical department. Although transient elastography can assess the severity of liver fibrosis, it displays reduced applicability in obese and NAFLD patients. The magnetic resonance elastography is expensive and remains understudied in NAFLD patients. The description and reference were added as your suggestion. (Page 10, paragraph 1)

2. In their Background, the authors state that ARFI is more accurate in diagnosing fibrosis, but at a higher cost. How high is the cost of ARFI compared to M2BPGi? If ARFI is clearly more accurate in diagnosing fibrosis than M2BPGi, then it would be appropriate to give priority to ARFI.
   Answer: Thanks for your comments. The cost of ARFI is about 50 US$ and M2BPGi costs about 17 US$ in our country. To the best of our knowledge, there was no report to compare the efficacy of diagnosing liver fibrosis between ARFI and M2BPGi. The description was added as your suggestion. (Page 10, paragraph 1)

3. Conversely, FIB-4 index and APRI have the advantage of low cost. Please also create ROC curves for FIB-4 index and APRI and compare them with M2BPGi to clearly show that M2BPGi is superior to FIB-4 index and APRI.
   Answer: Thanks for your comments. The accuracy of M2BPGi, APRI, and

FIB-4 in the diagnosis of liver fibrosis was calculated using receiver operating characteristics (ROC) analysis. Comparing F0 with ≥ F1, the AUC of M2BPGi, APRI and FIB-4 were 0.580, 0.562 and 0.547, respectively. Comparing F0-1 with F ≥ 2, the AUC of M2BPGi, APRI and FIB-4 were 0.680, 0.666 and 0.620, respectively. Therefore, M2BPGi had better diagnostic value for accessing liver fibrosis than APRI and FIB-4 index. The description and figures were added as your suggestion. (Page 8, paragraph 3 and figure 3a, 3b)

4. Was the M2BPGi useful in differentiating the F0 and F1 groups from the F2 and higher groups?
   Answer: Thanks for your comments. Comparing F0-1 with F ≥ 2, the AUC of M2BPGi was 0.680 (P = 0.024; Table 3), suggesting a surrogate marker to differentiate between normal-to-mild and significant fibrosis of NAFLD patients.

5. Results should be listed in separate paragraphs, with a title for each result.
   Answer: Thanks for your comments. The results were listed in separate paragraphs with a title as your suggestion.

Minor points:

1. In Page 5, line 2, NAFL should be changed to “NAFLD”.
   Answer: Thanks for your comments. The term was corrected as your suggestion.

2. In Page 5. Line 14, 30g/day should be changed to “30 g /day”.
   Answer: Thanks for your comments. The typo was corrected as your suggestion.

Associate Editor #1:

Dear Editor in Chief

Thanks for assigning me as associate editor to handle the manuscript NO.115400 entitled "Serum M2BPGi can Predict Mild or Significant Liver Fibrosis in Non-Alcoholic Fatty Liver Disease".

I appreciate the authors' work to do this study and write its manuscript. The subject is novel enough and the study methodology is correct. The manuscript needs revision. There are some concerns regarding the manuscript, which should be addressed by the authors in this revision. See the peer-review comments attached. Also, the following

issues should be addressed by the authors:

Title:

1. Please use the "Mac-2 binding protein glycosylation isomer (M2BPGi)" instead of M2BPGi alone.
   Answer: Thanks for your comments. The term was corrected as your suggestion.

Abstract:

1. Please select 3-5 proper keywords from PubMed MeSH-terms.
   Answer: Thanks for your comments. The PubMed MeSH term was added as your suggestion.

2. The authors need to use the expanded version of abbreviations for the first time (e.g. AST and ALT in the abstract, HBV and HCV in the methods, IQR in the results).
   Answer: Thanks for your comments. All the abbreviations for the first time were expanded as your suggestion.

3. The authors should use the suitable references style according the journal's instruction.
   Answer: Thanks for your comments. The references style was corrected according the journal's instruction.

Methods:

1. The sampling frame is not clear. When? Where?
   Answer: Thanks for your comments. This is a cross-sectional study using the baseline data from the participants of Tzu Chi NAFLD cohort (TCNC) in Taipei Tzu-Chi Hospital between May 2018 and December 2019. It was added as your suggestion (Page 4; paragraph 3).

2. The sampling technique is also unclear. What was the sampling technique? Were the patients randomly selected?
   Answer: Thanks for your comments. The subjects from health examination center were consecutively invited to join the study. NAFLD patients and healthy controls were enrolled after obtaining informed consent. The NAFLD patients were also randomly enrolled from outpatient department. It was added as you indicated (Page 4; paragraph 3).

3. The two above issues should be considered for the heathy controls. How did you select the healthy controls? Where? When? By which sampling method?

   Answer: Thanks for your comments. The subjects from health examination center of Taipei Tzu-Chi Hospital between March 2018 and December 2019 were consecutively invited to join the study. The participants including NAFLD patients and healthy controls were enrolled. It was added as your suggestion (Page 4; paragraph 3).

4. "42 participants were excluded due to V IQR/medium >15% in the data of ARFI." Please explain further about the reason for this exclusion in the methods section. **Answer: Thanks for your comments. The result of ARFI was expressed as median (M) in meters/second (m/s). Since the ratio of interquartile range to median (IQR/M) reflects the variability, the higher value means a poor quality and reduced accuracy of ARFI. Therefore, if IQR/M is >15%, the results were defined as unreliable and excluded in our study. The description was added as your suggestion. (Page 5, paragraph 2)**

Results:

1. This section needs more numerical results in its text (e.g. p-values). For example, "In this study population, the NAFLD patients were younger (P=XXX) and higher percentage of male gender (P=XXX) than healthy controls."

   Answer: Thanks for your comments. The numerical results were added as your suggestion.

2. Please specify the unit for M2BPGi level (e.g. COI), and use it after all M2BPGi levels in the results.

   Answer: Thanks for your comments. The unit of M2BPGi was specified (Page 6, paragraph 2) and added after all M2BPGi in the results as your suggestion.

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Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (1) 21 Jul 2021

Dear Editor in Chief

Thanks for assigning me as associate editor to handle the revised version of manuscript NO.115400 entitled "Serum Mac-2 binding protein glycosylation isomer (M2BPGi) can Predict Mild or Significant Liver Fibrosis in Non-Alcoholic Fatty Liver Disease".

I want to thanks to the author for revising their work. The authors correctly addressed all of the peer-review comments in this revision. This version of manuscript could be accepted for being published in Hepatitis Monthly.

Regards
Associate Editor

Seyed Moayed Alavian: EIC | **Revision** (1) 21 Jul 2021

Dear Authors,

I am delighted to inform that your manuscript is accepted for publication in Hepatitis Monthly journal.

Regards,
EIC