OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:
https://sites.kowsarpub.com/kowsar/knowledgebase/category/tree.html#opr.html

Hepatitis Monthly
Article DOI: 10.5812/hepatmon.102039
Published in: Hepatitis Monthly: 21(2); e102039

Peer Review Report for " Combined Serum Golgi Membrane Glycoprotein 73 Improves the Accuracy of Transient Elastography for Significant Fibrosis Detection in Patients with Chronic HBV Infections "

Author(s): Qiaoxia Zhou, Libo Yan, Lingyao Du, Xiaoqiong Tang, Hong Tang

Review Timeline:

Submit Date:	23 Feb 2020
Revised Date:	13 Feb 2021
Accepted Date:	13 Feb 2021

Revision (0)

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

Heidar Sharafi: Reviewer | **Revision** (0)

11 Oct 2020

Dear AE,

I reviewed the manuscript entitled "Combined serum Golgi membrane glycoprotein 73 improves accuracy of transient elastography for significant fibrosis detection in patients with chronic HBV infections". The authors assessed the performance of LSM, APRI, FIB-4 and GP73 for diagnosis of significant fibrosis. The results are interesting and can be published after considering the following comments:

Major Comment

It is very important to clarify the time frames of liver biopsy, LSM, lab tests (APRI, FIB-4 and GP73) and HBV management. Authors stated that the liver histology was assessed before initiation of HBV management however, it is not clear if it is true for LSM and lab tests. More, it should be clarify what was the time difference between biopsy, LSM and lab test. It is expected not to be far (>3 months) from each other otherwise the comparisons make no sense.

Minor Comments

1. The English expression and syntax should be carefully edited. Such as "stud", "chronical", "weather" and more.

2. How the cut-off value was selected? using Youden's index?

3. How the formula for the combined LSM and GP73 index was developed?

4. How the P value for comparison of GP73+LSM and LSM was calculated?

5. The results regarding the longitudinal study of indexes should be moved to results. How many patients were treated, followed and included in the latter analysis?

6. Use the equivalent USD instead of RMB.

7. These two sentences has to be rewritten to clarify their meaning:

"The sensitivity and specificity to regard GP73 as a biomarker of liver fibrosis also need to be detected. Besides, the limited number of HCC patients and healthy volunteers also restricted the current cohort study. "

8. In Table 2, for Se, Sp, PPV, NPV, LR+ and LR-, the 95%CI of each should be included as well.

Regards

Seyed Moayed Alavian: Associate Editor | **Revision** (0) 31 Oct 2020

Dear EIC,

The manuscript was reviewed by an expert and needs a revision.

Regards

Seyed Moayed Alavian: EIC | **Revision** (0) 31 Oct 2020

Dear Authors,

Thank you for your submission. Please 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.

Dear editor and reviewers,

Thanks for your email dated 30th Oct. 2020. We appreciate your constructive comments. We have corrected and modified the manuscript accordingly and the amendments are marked in red font in the revised manuscript. We also responded point by point to the suggestions raised by reviewer as listed below. We hope that the revised manuscript is acceptable for publication.

Replies to reviewer:

Major Comment

It is very important to clarify the time frames of liver biopsy, LSM, lab tests (APRI, FIB-4 and GP73) and HBV management. Authors stated that the liver histology was assessed before initiation of HBV management however, it is not clear if it is true for LSM and lab tests. More, it should be clarify what was the time difference between biopsy, LSM and lab test. It is expected not to be far (>3 months) from each other otherwise the comparisons make no sense.

Response：Thank you for your suggestions. The liver biopsy and LSM were carried out in 1 month before enrolled in this study and blood samples were collected in 15 days after registration for lab tests. All the examinations were carried out before HBV management. This information has been added to the Methods part in the manuscript and marked in red font (Page 4-5, line 106-108).

Minor Comments

1. The English expression and syntax should be carefully edited. Such as "stud", "chronical", "weather" and more.

Response: Thank you for your suggestion. The manuscript has been intensely edited for spelling mistakes and grammar errors. Modification was marked in red font.

2. How the cut-off value was selected? using Youden's index?

Response: Thank you for your question. The cut-off value was selected according to Youden's index, as mentioned in the manuscript line 137-138, page 6, "an optimal cut-off value was assessed to maximize the sum of sensitivity and specificity". The expression has been revised to "an optimal cut-off value was assessed according to the maximized Youden's index", which was marked in red font in the manuscript (Page 6, line 137-138).

3. How the formula for the combined LSM and GP73 index was developed?

Response: Thank you for your question. Logistic regression analysis was used to determine whether the variables related to fibrosis were independent risk factors. The variables with $P<0.05$ in univariate logistic regression analysis were introduced into multivariate logistic regression analysis, and were then selected using backward selection method. In the development of risk prediction models for significant fibrosis, the regression coefficients of the predictors were converted to integer risk scores by rounding the quotient from dividing the regression coefficients, and the final score was the sum of these two values.

4. How the P value for comparison of GP73+LSM and LSM was calculated?

Response: Thank you for your question. MedCalc statistical software was used to perform the DeLong test for diagnostic performance evaluation and the calculation of the areas under the receiver operating characteristic (ROC) curves, including the P value for comparison of GP73+LSM and LSM.

5. The results regarding the longitudinal study of indexes should be moved to results. How many patients were treated,

followed and included in the latter analysis?

Response: Thank you for your advice. Eighteen CHB patients undergoing a 4-years NA treatment were included. FibroScan was performed at the entry and the 4th year. Among the 18 patients receiving NA treatment, 2 patients received a single oral daily dose of 600 mg telbivudine (LDT), and the other 16 patients received 10 mg adefovir dipivoxil (ADV) in addition to daily LDT. The inclusion and exclusion criteria were the same as before (Page 4, line 92-96). Details of the results regarding the longitudinal study on the indicators have been added to results part in the manuscript. (Page 7, line 177-188).

6. Use the equivalent USD instead of RMB.

Response: Thank you for your suggestion. The RMB has been replaced with USD accordingly in this manuscript and marked in red font (Page 8, line 218).

7. These two sentences has to be rewritten to clarify their meaning:

"The sensitivity and specificity to regard GP73 as a biomarker of liver fibrosis also need to be detected. Besides, the limited number of HCC patients and healthy volunteers also restricted the current cohort study. "

Response: Thank you for your question. The two sentences have been replaced with the following expressions: “The sensitivity and specificity to regard GP73 as a biomarker of liver fibrosis caused by other etiologies still need to be detected. Besides, because of the relatively small number of HCC patients and healthy volunteers in this study, the predictive value of GP73 for HCC occurrence in CHB patients was limited.” (Page 9, line 227-230)

8. In Table 2, for Se, Sp, PPV, NPV, LR+ and LR-, the 95%CI of each should be included as well.

Response: Thank you for your question. The 95%CI of each index has been added to Table 2 (Page 13, line 317). The newly added data was marked in red font.

OPEN PEER REVIEW

Revision (1)

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

Heidar Sharafi: Reviewer | **Revision** (1) 18 Jan 2021

Dear AE,

I reviewed the revised manuscript. Authors addressed most of the comments correctly. I have few minor comments before acceptance for publication:

1. Authors should define what are the numbers in parenthesis in subheadings 4.1 and 4.4. IQR? or min and max?

2. Abbreviations in Table 2 should be defined in full term in the table caption. such as Se, Sp and others

3. In Figures 2 and 4, it should be defined what the bars and lines are representing.

Regards

Seyed Moayed Alavian: Associate Editor | **Revision** (1) 27 Jan 2021

Dear EIC,

The reviewer asked for more corrections.

Regards,

Seyed Moayed Alavian: EIC | **Revision** (1) 27 Jan 2021

Dear Authors,

Manuscript needs few minor amendments.

Regards,
EIC

OPEN PEER REVIEW

Revision (2)

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.

Dear editor and reviewers,

Thanks for your email dated 27th Jan. 2021. We appreciate your constructive comments. We have corrected and modified the manuscript accordingly and the amendments are marked in red font in the revised manuscript. We also responded point by point to the suggestions raised by reviewer as listed below. We hope that the revised manuscript is acceptable for publication.

Replies to reviewer:

1. Authors should define what are the numbers in parenthesis in subheadings 4.1 and 4.4. IQR? or min and max?

Response: Thank you for your comments. Numbers in parenthesis have been presented with the expression “range from”, represent the min and max numbers among the populations.

Before: The median LSM was 5.20 kpa (2.70-17.50 kpa) for no significant fibrosis, 10.15 kpa (3.80-43.00 kpa) for significant fibrosis (Figure 2A). In CHB patients, the median GP73 level was 64.05 (24.41-144.39) for those with no significant fibrosis (F0-F1), and 91.30 (31.81-200.05) ng/ml for those with significant fibrosis (F ≥2) (*P* <0.001) (Figure 2D).

……

At baseline, the median LSM value was 8.85 (4.9-22.0) kPa. After 4 years of NA treatment, the median LSM value was 4.7 (2.8-6.9) kPa. LSM of CHB patients significantly improved after 4 years of NA treatment (P<0.001). At baseline and 4 years after NA treatment, the median GP73 values were 80.91 (36.58-171.85) ng/mL and 55.11 (29.56-88.95) ng/mL, respectively (P=0.004). Similarly, the predictive model based on serum GP73 level and LSM were 0.47 (0.19-0.99), 0.16 (0.08-0.29) at baseline and year 4, respectively (P<0.001).

After: The median LSM was 5.20 kpa (range from 2.70 to 17.50 kpa) for no significant fibrosis, 10.15 kpa (range from 3.80 to 43.00 kpa) for significant fibrosis

(Figure 2A). In CHB patients, the median GP73 level was 64.05 (range from 24.41 to 144.39) for those with no significant fibrosis (F0-F1), and 91.30 (range from 31.81 to 200.05) ng/ml for those with significant fibrosis (F ≥2) (*P* <0.001) (Figure 2D).

……

At baseline, the median LSM value was 8.85 (range from 4.9 to 22.0) kPa. After 4 years of NA treatment, the median LSM value was 4.7 (range from 2.8 to 6.9) kPa. LSM of CHB patients significantly improved after 4 years of NA treatment (*P*<0.001). At baseline and 4 years after NA treatment, the median GP73 values were 80.91 (range from 36.58 to 171.85) ng/mL and 55.11 (range from 29.56 to 88.95) ng/mL, respectively (*P*=0.004). Similarly, the predictive model based on serum GP73 level and LSM were 0.47 (range from 0.19 to 0.99), 0.16 (range from 0.08 to 0.29) at baseline and year 4, respectively (*P*<0.001).

Page 6, line 149-154; Page 7, line 180-187.

2. Abbreviations in Table 2 should be defined in full term in the table caption. such as Se, Sp and others

Response: Thank you for your comments. Full terms of the abbreviations in Table 2 have been added to the table caption including Se, Sp, PPV, NPV, +LR, and -LR.

Before: LSM, liver stiffness measurement; GP73, Golgi membrane glycoprotein 73; FIB-4, fibrosis index based on the 4 factor; APRI, aspartate transaminase (AST)-to-platelet ratio index; AUC, area under the curve.

After: LSM, liver stiffness measurement; GP73, Golgi membrane glycoprotein 73; FIB-4, fibrosis index based on the 4 factor; APRI, aspartate transaminase (AST)-to-platelet ratio index; AUC, area under the curve; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio.

Page 13, line 314, Table 2.

3. In Figures 2 and 4, it should be defined what the bars and lines

are representing.

Response: Thank you for your comments. Detailed explanations for the lines and bars presented in Figure 2 and Figure 4 have been added to the figure legends.

Before:

Figure 2. Scatterplots of the data obtained with LSM, APRI, FIB-4, GP73 and LSM-GP73 against the fibrosis score. The LSM, APRI, FIB-4, GP73 and LSM-GP73 were higher in CHB patients with significant fibrosis ($P < 0.001$).

……

Figure 4. Longitudinal LSM values, GP73 and LSM-GP73 4 years after the start of nucleoside analog treatment.

After:

Figure 2. Scatterplots of the data obtained with LSM, APRI, FIB-4, GP73 and LSM-GP73 against the fibrosis score. The LSM, APRI, FIB-4, GP73 and LSM-GP73 were higher in CHB patients with significant fibrosis ($P < 0.001$). Lines in scatterplots represent the median values of each parameters with 95% confidence interval (95%CI) bars.

……

Figure 4. Longitudinal LSM values, GP73 and LSM-GP73 4 years after the start of nucleoside analog treatment. Each line connecting two plots represents an individual case before and after the nucleoside analog treatment. Floating bars represent the max and min values with the median lines.

Page 11, line 299-309.

We look forward to hearing from you regarding our submission. We would be glad to respond to any further questions and comments that you may have.

Yours sincerely,

OPEN PEER REVIEW

Revision (2)

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

Seyed Moayed Alavian: EIC | **Revision** (2) 13 Feb 2021

Dear Authors,

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

Regards,
EIC