Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

Answering reviewers

Critique Responses Summary

We would like to clarify that this submission is a series of two papers, that should be published simultaneously if accepted. We are not interested in publishing only one part of this series or publishing them in two separate journal issues. Please, let us know if this is not already the plan.

SPECIFIC COMMENTS TO AUTHORS: This study is very attractive with a large number of cases and bile acid index has high AUC values, which could be a diagnostic biomarker for liver diseases. (major)
Response: Thank you.

・Limitation is not mentioned. For example, severity is assessed by MELD score and whether it is compensated or decompensated, but stage is not assessed due to the lack of histological evaluation of the liver. I think there are some limitations that should be mentioned.
Response: We agree that the limitations of our study, even though already mentioned, were not emphasized. This study has the following limitations: (i) Severity of the liver diseases were assessed using MELD score, compensation status, and a panel of liver enzymes. However, liver histological evaluation was not included because it is not a routine practice to perform liver histology on all patients, but rather for specific patients as required by the hepatologists. (ii) We have enough subjects in this study to perform solid statistics, but smaller number of subjects in many individual disease subgroups. Also, distribution of subjects between disease groups was unbalanced.

We have now clarified this issue in the manuscript, which is highlighted in red. On page 22, line 17.

・There seems to be a lack of discussion of each disease in the analysis. For example, is there any discussion of the significance of secondary bile acidity in PBC due to bile stasis?
Response: We agree with the reviewer that the not all the individual disease subtypes were not discussed for the following reasons (i) we only discussed the ones with statistically significant results such as cirrhosis and hepatitis C, (ii) See comment 2 above, we clarified that a limitation of our study is having a relatively small number of subjects with uneven distribution in many individual disease subgroups

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

We have now clarified this issue in the manuscript, which is highlighted in red. On page 22, lines 6 and 17.

・How do you plan to use the bile acid index in human clinical practice? We would be grateful if you could describe your future prospects.

Response: In the 1st paper of this series, we demonstrated the statistical differences in bile acid indexes and their utility as biomarkers to differentiate between controls vs. cholestatic liver disease patients as well as among patients with various levels of disease severity.

In the 2nd paper, we have utilized BA indexes to build a survival model called "The Bile Acid Score (BAS)", which we showed was able to predict the prognosis into adverse events including death and liver transplant in liver patients.

We have now clarified this issue in the manuscript, which is highlighted in red. On page 23, line 21.

・I would be grateful if you could tell me why you included normal liver function in the inclusion. (Minor)

Response: Normal liver enzyme tests and history were inclusion criteria for the 103 healthy controls and not for the liver patients.

We have now clarified this issue in the manuscript, which is highlighted in red. On page 8, line 8.

・On Page 13, line 19, "non-12α-OH BA were 8.5-fold higher in patients" is noted. Is this a mistake for "8.15"?

Response: Yes, this was a mistake and now is corrected (8.15 or 8.2).

We have now clarified this issue in the manuscript, which is highlighted in red. On page 14, line 15.

・On page 14, line 11, "while there was no difference in the % amidation and % G-amidation between medium and low- MELD patients"is noted. However, in table 5, the % amidation appears to be significantly different. Is this correct?

Response: Correct, the % amidation was significantly different, but the magnitude of change was only 0.09 -fold higher, i.e., 9% increase in patients vs. controls.

We have now clarified this issue in the manuscript, which is highlighted in red. On page 15, line 3.

Baishideng Publishing Group

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

5 Issues raised:

(1) The "Author Contributions" section is missing. Please provide the author contributions;

Response: We have now added a section with author contributions, which is highlighted in red. On page 2, line 5.

(2) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

Response: We have now provided it.

(3) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

Response: We have now provided it.

(4) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout; and

Response: We have now added PMID and DOI numbers to the reference list. On page 27.

(5) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text.

Response: We have now added a section with article highlights, which is highlighted in red. On page 24 and 25, line 1.