Dear Editor,

Thank you for carefully reviewing our manuscript previously titled "**Serum metabolic profiling of targeted bile acids reveals potential novel biomarkers for primary biliary cholangitis and autoimmune hepatitis**" for possible publication in the World Journal of Gastroenterology. We are grateful to you and your reviewers for their constructive critique. We have revised the manuscript, highlighting our revisions in red. and have attached point-by-point responses detailing how we have revised the manuscript in response to the reviewers' comments below.

Thank you for your consideration and further review of our manuscript. Please do not hesitate to contact us with any further questions or recommendations.

Yours Sincerely,

Junqi Niu

Reviewer Comments:

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The aim is stated clear. The authors stated clearly what study found and how they did it. The title is informative and relevant. The references are relevant and recent. The cited sources are referenced correctly. Appropriate and key studies are included. The introduction reveals what is already known about this topic.

The research question is clearly outlined. The research question also justified given what is already known about the topic. The process of selection of the subjects was clear. The variables are well defined and measured appropriately. The study methods are valid and reliable. There are enough details provided in order to replicate the study. The data is presented in an appropriate way. The text in the results add to the data and it is not repetitive.

Statistically significant results are clear. It is clear which results are with practical meaning. Results are discussed from different angles and placed into context without being overinterpreted. The conclusions answer the aim of the study. The conclusions are supported by references and own results. The limitations of the study are not fatal, but they are opportunities to inform future research.

Specific comments on weaknesses of the article and what could be improved: Major points - none Minor points 1. Could you please discuss the clinical implications of the results 2. What would be your recommendations based on the obtained results?

Response:

- According to your advice,I add these sentences which were signed red marks.

- In autoimmune liver diseases, the dysfunction of bile acid metabolism occurs after liver injury, which may be related to bile stasis after liver injury, especially in primary biliary cholangitis, which is more drastic, and is related to the pathogenesis of PBC. After bile duct obstruction and sclerosis, bile acids cannot be transported and metabolized normally. Patients may present with jaundice and itchy skin.

  Bile acids can be used as a factor to judge the severity of the disease and as a basis for the diagnosis of the disease. It is necessary to further expand the sample size for research.

Reviewer #2:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision

Specific Comments to Authors: The manuscript presents interesting results. The methods used are novel and well selected. There is a need to correct punctuation and mistakes in the abstract and elsewhere in the manuscript text and tables, though, the main imperfection of this manuscript is results presentation. In present form the manuscript is difficult to read.

The result presentation should be changed to more understandable and reliable way. Here are some suggestions for improving this.

1. According to the manuscript title, a difference in blood BAs concentration between PBC and AIH was object of interest in this research. Moreover, only disparity in BAs composition was confirmed as putative noninvasive marker for PBC and AIH differentiation. Therefore, I would suggest to present only comprehensive results from BAs analysis and exclude other metabolites detected.

Non-bile acid content has been removed from the abstract. “The levels of 17 of the 26 potential biomarkers were elevated in the serum samples of PBC patients, while the levels of 9 of these 26 potential biomarkers were reduced in the serum samples of

PBC patients compared with HCs. The levels of 17 of the 25 potential biomarkers increased in the serum samples of AIH patients, while the levels of 8 of these 25 potential biomarkers decreased in the serum samples of AIH patients compared with HCs" .have been deleted.

Although other metabolites cannot be used to distinguish PBC from AIH, Although other metabolites cannot be used to distinguish PBC from AIH, we believe that the changes of these metabolites in the disease group are also of clinical significance.Also they are part of the results of our research work.

2. In the Table 1 TBA amount should be indicated for the Control.

Unfortunately, the healthy controls were not tested for TBA.This was a flaw in the design of the experiment.

3. Please, provide a raw amount of tested BAs in the serum of PBC, AIH and Controls, since lg10 was used in the further analyses.

It is listed as supplementary Table 1 at the end of this article.

4. If possible, an additional analysis of BAs changes in blood of PBC and AIH patients depending on disease duration would also be interesting.

This is also what we are interested in, and in the following study, we will also design this kind of experimental content. To observe the changes of BAs in the blood of patients with PBC and AIH over time, and to observe the relationship between the changes of disease and the changes of BA.

5. The diseases mentioned in this sentence are not autoimmune: "Clinical manifestations of AIH may have similarities to other autoimmune liver diseases, such as drug-induced hepatitis, alcoholic liver disease, inherited metabolic disorders, and hepatitis C virus infection" Please, specify.

Change to "Clinical manifestations of AIH may have similarities to other autoimmune liver diseases, such as drug-induced hepatitis, alcoholic liver disease, inherited metabolic disorders, and hepatitis C virus infection,such as regardless of the cause of liver disease, patients may present with fatigue, abdominal distention, skin and sclera yellow staining,laborotory test show liver dysfunction"

6. Clarify the information: "The Child-Pugh class A was found in 26 PBC cases, Child-Pugh class B in 19 PBC cases, and Child-Pugh class C in 9 PBC cases. The Child-Pugh class A was identified in 17 cases, followed by Child-Pugh class B in 9 cases."

Change to “There were 26 cases of Child-Pugh class A, 19 cases of Child-Pugh class B, and 9 cases of Child-Pugh class C in PBC patients. There were 17 Child-Pugh grade A and 9 Child-Pugh grade B patients with AIH”.

7. This is not informative: “The levels of 17 of the 26 potential biomarkers were elevated in the serum samples of PBC patients, while the levels of 9 of these 26 potential biomarkers were reduced in the serum samples of PBC patients compared with HCs. The levels of 17 of the 25 potential biomarkers increased in the serum samples of AIH patients, while the levels of 8 of these 25 potential biomarkers decreased in the serum samples of AIH patients compared with HCs.”

Results have been deleted in abstract.

8. This sentence needs to be reconstructed: “It may be due to the high similarity between PBC and AIH, both diseases are autoimmune liver diseases.” The only common feature of PBC and AIH is the autoimmune origin, bet the pathological mechanisms differ significantly. In PBC the liver injury starts from the autoimmune attack of the bile canalicular cell membranes, while in AIH – from autoimmune attack of hepatocytes.

Change to “uggesting that the changes of terminal metabolites in serum samples of patients with PBC and AIH were no special differences”.

Finally, since the additional blood samples were taking from patients for this research purposes, the Institutional Board approval is not sufficient. Authors should submit an approval from regional Bioethics Committee.

Unfortunately, we are unable to provide approval from the Regional Bioethics Committee currently. When we conducted this experiment,there was no Regional Bioethics Committee in our region.We can only provide approval from our hospital.