

Dear editor,

Thank you very much for your time and efforts. We have carefully revised the manuscript in accordance with the reviewers' comments point by point.

1. *It is not very clear in the introduction section the link between microbial changes and a possible benefit in the clinical practice, justifying the aim of the study.*

Response: Thank you for your suggestion. At present, current therapeutic options for ICP are very limited and novel approaches are desperately needed. This research intended to show a mechanism of ICP that is associated with the microbiota via changes in serum metabolites and to open the way to new strategies for treatment in ICP. In other areas, there are precedents for treating diseases with Fecal microbiota transplantation (FMT). In the field of the gut microbiota, we will also find the novel therapeutic strategies in ICP.

2. *Line 109: please amend several eminent studies linking intestinal inflammation and microbial shift: DOI:10.3748/wjg.v26.i22.3098, <https://doi.org/10.1038/s41598-019-49893-5>, <https://doi.org/10.1186/s12876-019-0930-3>, doi.org/10.1111/jgh.15183.*

Response: Thank you very much for your helpful advice, these literatures provide strong support for the significance of our research. They have been cited in “introduction” section of this study, which greatly improved our manuscript. The corresponding changes have been highlighted in the revised version.

3. *The link between metabolome and microbiota evaluation is not strict since metabolomics is influenced also by diet and several other factors. Do the author investigate these factors? Moreover, these limitations should be cited.*

Response: Thanks for this kind advise. Many factors influence serum metabolomics and gut microbiota, including diet, environment, stress, age, and other factors. In the current study, the age range of subjects, dietary differences,

and small sample size all limit the strength of conclusions about changes in serum metabolomics and gut microbiota. However, the results of this study should be considered hypothesis generating and should be confirmed in future studies with larger sample size.

4. *In the discussion section the authors should discuss what are the intervention that is possible to use in the clinical practice and which design should have further studies to confirm their results.*

Response: At present, there is no specific drug for the treatment of ICP in clinical practice, and the common treatment options include Yashifu, Smecta treatment and their combination intervention. Our group will study gut microbiota and metabolome changes before and after drug treatment to provide a new regimen for ICP treatment. In the future we will also conduct intervention studies using probiotics, probiotics and synbiotics to promote the establishment of beneficial microbiota and investigate whether it can have a positive impact on the health of ICP patients.

5. *The authors should better amend in the limitation section the use of a not wide-comprehensive methods for gut microbiota assessment*

Response: A limitation of this study is the small sample size, which causes the analysis of the differences in the gut microbiota to lack statistical significance. Our future studies will collect more samples to examine the changes in the gut microbiota of ICP patients. In addition, based on the analysis of 16S rRNA sequences, the reduction in microbial diversity simply indicates an imbalanced gut ecosystem, but does not provide us with more detailed information regarding the species and functions of certain microorganisms. Therefore, large-scale metagenomics and functional studies are needed to investigate the role of gut microbes in the molecular pathogenesis of ICP.

We hope that the manuscript has been revised in a manner that will make it

suitable for publication.

Thank you!

Yours sincerely,

Qiaoling Du, on behalf of all co-authors