

Editorial office, Scientific Editor, Dr. Yuan Qi
Baishideng Publishing Group Inc
8226 Regency Drive, Pleasanton
CA 94588, USA

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Dear Dr. Qi,

We were very pleased to read that our manuscript NO. 32918 can be reconsidered for publication in WJG. We enclose the revised version where the comments provided by both reviewers were carefully taken into account. Our point-by-point answers addressing individual comments are enclosed. We hope that our revised manuscript is now suitable for publishing in your journal.

Yours sincerely

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Answers to the reviewers:

Reviewer 1:

Comments to Authors

Interesting and complex article, a very good work and a beautiful writing. Congratulations! I found a little problem with one of the references (24) that has some typing error.

Response: We would like to thank the reviewer for appreciating our manuscript. The typing errors related to reference 24 were corrected.

Reviewer 2:

Comments to the Author

Bajer et al. present a cohort study examining microbial patterns in three cohorts: PSC with IBD, PSC without IBD, and Healthy Controls. The authors present a medium-sized cohort and attempt to focus on PSC as it compares to UC. But the study, both in terminology and methodology, becomes scattered, including PSC-IBD and AIH. The authors should streamline the study to keep terminology and their comparison groups consistent, and really focus the introduction on highlighting the aspects that make their study novel. At this time, I cannot recommend publication, and offer the following suggestions:

Major Points:

Table 1 – The authors nicely demonstrate IBD extent, activity, and recent medications. However, more information should be provided to show disease severity of the PSC – i.e. alk phos, direct bili, ALT, history of ERCP, etc.

Response: In order to demonstrate the PSC severity, we added a panel of liver enzymes and total bilirubin (while direct bilirubin was not routinely assessed in the subjects) into Table 1 as measured at the time of the sample collection. However, we were not able to collect reliable data on the history of ERCP for all patients, therefore, we did not include this information in table to avoid bias.

Figure 2 should include PSC and PSC-IBD juxtaposed, or at the very least, describe the results of this comparison in the text if this analysis did not reveal significant changes.

Response: The information on the lack of significant differences between PSC and PSC-IBD was added to the text, as requested by the reviewer.

The last paragraph of the Result section discusses Actinomycetales and its correlation with albumin. The associated Figure 4A depicts 8 data points or patients with PSC-AIH. However, from Table 1, it appears that those 8 patients represent both those with PSC-IBD and those with PSC and no IBD. It is not clear if the PSC column in Figure 4A represents PSC-IBD + PSC patients or if it is only PSC-IBD. These methods require clarification in the text or figure legend, and ensure they are consistent between PSC and the overlap columns. As the original figure stands, the authors may consider removing this figure and paragraph in the manuscript as the data seems to be weak and did not reach significance when adjusting for

specific diseases. Inclusion of the small number of patients with AIH did not seem to add to the value of the manuscript, and the authors may consider excluding this small group of 8 patients.

Response: As suggested by the reviewer, we excluded the text regarding PSC/AIH subgroup from the core tip, abstract and the discussion as these data are too weak to be stressed out. Furthermore, we deleted the respective Figure (4A). We kept short mention on the subject in the “Results” section, clearly stating that the results concern all patients with PSC (with or without IBD).

One strength of this study that the authors point out is that 100% of their PSC patients received UDCA as opposed to the other similar Sabino et al. study. It would be interesting to take this cohort and compare their microbiome profiles against the duration of UDCA treatment to answer the question the authors posed in the Discussion, i.e. does long term UDCA use lead to changes in microbiota (not just whether UDCA is or is not used).

Response: This is a very valid point and such comparison would without any doubt bring additional value to the manuscript. However, virtually all PSC subjects were recruited from the database of our chronic patients who had been treated with UDCA in the long-term manner. Moreover, as recently demonstrated by Tang et al. (doi: 10.1136/gutjnl-2016-313332), UDCA may change the microbiota composition within just few months and such changes may presumably be relatively stable thereafter. Furthermore, retrospective assessment of treatment length would be unreliable and may cause substantial bias.

In the “core tip” section, the authors state that these disease-specific microbial features may lead to establishing suitable biomarkers. It would be very interesting, perhaps for future studies, to see if they could create a panel of microbes that they found significantly changed among the different cohorts and see if this panel could predict the disease presentations.

Response: We would like to thank the reviewer for this excellent point. Indeed, the disease course prediction is an ultimate goal of this project, and we consider these data as a good starting point for this type of studies.

Minor Points:

Figure 2: Figure legend incorrectly references 2A and 2B (they are listed in reverse order as shown in the figure).

Response: The figure legend was corrected accordingly.

The discussion on Blautia that begins with “Torres et al. used biopsies...” should be shortened as it discusses largely insignificant findings. Similarly, since none of the PSC patients in this study were on biologics, the commentary on biologics and microbiota in the discussion could be removed as well.

Response: Both mentioned paragraphs in the “Discussion” section were substantially shortened.

There are multiple grammatical errors throughout the paper.

Response: We revised the manuscript once more for grammatical errors. We corrected several errors and typos throughout the text (e.g. adding space between two separate words, adjusting verb form, etc.).

Furthermore:

- the word "prospective" was deleted from the sentence "This single centre..." in the "Introduction" section
- the text of the Core-tip was slightly modified as we had to delete the passage regarding PSC/AIH
- the word "clinic" was changed to word "department" in the sentence "PSC, PSC-IBD, and UC patients for this single center..." in the "Patients and Methods" section
- a sentence regarding PCR protocol was added to "Patients and Methods" section