Editorial office, Scientific Editor, Xue-Jiao Wang, MSc
Beijing Baishideng BioMed Scientific Co., Limited
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China

Prague, October 20, 2018

Dear Ms. Wang,

We were very pleased to read that our manuscript NO. 41811 can be reconsidered for publication in WJG. We enclose the revised version where the comments provided by all three reviewers were carefully taken into an 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,

Lukas Bajer, MD

Department of Gastroenterology and Hepatology
Institute for Clinical and Experimental Medicine
Videnska 1958/9
140 21 Prague
Czech Republic
Telephone: +420-2-61362266
Fax: +420-2-61362615

Answers to the reviewers:

Reviewer 1:

Comments to Authors
In this retrospective study, the Authors aimed to assess the risk of recurrence of PSC after liver transplantation. This informative study showed that De novo colitis and acute cellular rejection are clinical conditions significantly predisposed towards recurrence of PSC after liver transplantation. However I have some comments. Material and methods should be shortened and changed to formal shape. In this section, numerated information should be omitted. Subtitles should be written as the same form in the abstract and main text (Methods vs Patients and methods). Beginning of the results should be clear and focused on the main patient's data. The present study was well discussed. After arrangement according to comments, this paper is acceptable for publication.

Response: We would like to thank the reviewer for valuable comments and for acknowledging our Discussion. As suggested by the reviewer, we have:

- shortened the ´Methods´ section
- omitted the numerated information
- synchronized the subtitles in abstract and main text
- adjusted the beginning of ´Results´ section by excluding redundant information and introducing the section right away with the text regarding key patients´ characteristics

Reviewer 2:

Comments to Authors
Although retrospective and analyzing the well known remanence of inflammatory bowel disease and primary sclerosing cholangitis after liver transplantation, the paper does a very nice analysis of the transplanted patients in a 21 year period with this problem. The paper deserves publication, because although not a review, the reader can also obtain a well-developed discussion that gives a global idea of the problem. Perhaps it will be of value to include a couple of paragraphs that give an update of new alternative treatment for both problems after liver transplantation.

Response: We would like to express our sincere gratitude to the reviewer for appreciating our manuscript. Treatment options for clinical conditions mentioned in the manuscript is without a doubt an interesting topic to elaborate on. However, the topic has been described in detail in dedicated review articles cited in the references and therefore we believe that it would be redundant to include this wide topic in our paper which is focused on original data presentation and is not aiming to review all aspects of current knowledge in its full extent.

Reviewer 3:

Comments to the Author

Bajer et al. present a single center, retrospective study examining the risk factors for recurrent PSC (rPSC) following liver transplantation (LT) for primary PSC. This study finds two risk factors – the presence of de novo colitis and history of ACR to be positively associated with rPSC. This study addresses an important area to better understand recurrent PSC after LT. The study's strengths include clear presentation of inclusion and exclusion criteria, and a thorough work up of each patient both pre- and post-LT. However, the following concerns dampen my enthusiasm for publication at this time:

Major Points:

It is unclear why the authors choose to only show univariate analysis of the risk factors in Table 2. It appears the study also conducted multivariate analyses, and this data (especially that of the overlap AIH/PSC subgroup analysis) should be shown in greater detail in the manuscript to better evaluate the study and risk factors.

Response: The results of performed multivariate analysis can be found in dedicated subsection of ´Results´ in the main text. We fully agree with the reviewer that the multivariate analysis on the subgroup with AIH/PSC overlap would certainly yield very interesting results. However, as ***all patients*** with AIH/PSC had rPSC, this factor cannot be included in multivariate analysis by definition (0 value in non-rPSC group). For certain other factors, such analysis would not be powerful enough as the study clearly acknowledges its limits in sample size.

More rationale needs to be provided for studying HLA typing, specifically what is the clinical impact that their findings may have.

Response: Certain HLA haplotypes were significantly associated with rPSC in previous studies (e.g. Alexander et al. *Liver Transpl* 2008; 14(2): 245-251) as mentioned in the ´Introduction´. As HLA-typing data were available (or, where possible, were obtained post hoc) in majority of our patients, our goal was clearly to determine the association with rPSC.

Albeit small numbers, the study had 8 of 15 patients (53%) with rPSC who needed re-transplant. It would be helpful to provide more description of these patients and their clinical characteristics.

Response: Based on the comment, we added a sentence describing the indications for other re-transplants.

There also seems to be some discrepancy as the last sentence in "Survival outcome" states a total of seven patients experienced re-transplant. Please clarify.

Response: This is not a discrepancy as one value concerns Total population and the other describes a Study cohort.

Regarding cases of rPSC – were there biochemical changes, i.e. increased alk phos or liver enzymes? Inclusion criteria include regular blood testing, so presumably this data is available.

Response: According to this comment, we added a brief mention specifying ´those with clinical suspicion´ as those with ´e.g. liver enzymes elevation´. However, we did not extend this further in the text as in our opinion, ALP levels do not have relevant information value in the context of the study.

The medical regimen for IBD treatment post-LT should be better described.

Response: The paragraph regarding post-LT treatment for IBD has been added to the ´Results´ section based on this comment.

In addition, it would be useful to know how the cases of de novo IBD presented – were they picked up on routine colonoscopy, or were they symptomatic and prompted colonoscopy, or changes in ESR and anemia? Is there any data on the natural history of the cases of de novo IBD or even the activity index at diagnosis?

Response: This is a very valid question. However, we are not able to provide entirely relevant answer on the matter due to retrospective nature of the data. Therefore, we did not include this in our results.

Can the authors speculate in the Discussion as to how we can either intervene or diagnose these cases earlier in the course?

Response: Based on this very relevant comment, we added a paragraph addressing this issue in the ´Discussion´.

Table 3 – what were the statistical methods used?

Response: Please, refer to ´Statistical analysis´ subsection: ´ Discrete variables were compared using Fisher's exact test (two-tailed) and expressed as number (*n*) and percentage (%)´.

Minor Points:
The patient population was examined from 1994-2015. Prior to 2004, Cyclosporine was the primary immunosuppressant. CSA can be used as treatment for IBD. An interesting analysis would be to examine for any difference between the rates of de novo IBD and rPSC between the two time periods.

Response: We fully agree with the reviewer that this would be very interesting comparison to focus on. Nevertheless, dividing the rPSC group (n = 11) would produce a sample size too small to bring any relevant results.

Page 10 - In total, 29 patients (61.7%) were diagnosed with IBD prior to OLT. They all had quiescent pancolitis (Mayo 0–1) with long-term aminosalicylate and ursodeoxycholic acid (8–

20 mg/kg/day) treatment. Does this mean the Ursodiol was used as IBD treatment? Or was it for the PSC? Please clarify.

Response: Based on this comment, we specified in the text that UDCA was ´used as potential chemopreventive agent against colorectal neoplasia´.

Furthermore, we have made following adjustments according to comments provided by Science Editor:

- Full approved grant applications have been uploaded as single pdf. file
- Audio core tip has been uploaded in mp3. format
- All blanks between text and [reference numbers] have been erased
- Article Highlights have been added to the manuscript body

All other required documents were already provided during original submission.

Moreover, we have amended following points according to provided Guidelines for Manuscript revision:

- We changed ´p – value´ to ´P – value´ throughout the Manuscript
- Numbers of rPSC cases have been added to ´Results´ section of the Abstract to better demonstrate how P value was obtained