

2016.04.26

Dear Editorial Board and reviewers:

Thank you for your consideration our article entitled “Comprehensive Risk Assessment for Early Neurologic Complications After Liver Transplantation, ESPS No. 25477” for publication in *World Journal of Gastroenterology*. We appreciate the comments we received and are resubmitting this manuscript for your consideration. We detail how we have addressed the reviewer’s comments in red below. Please find the “25477-Revised manuscript” document to follow these adjustments.

The first reviewer’s comments (code 00504828) and our revisions are as follows:

1. *Table 3 - what would be a potential factor(s) linking NC and significantly higher risk of alcoholic liver diseases? It looks to me that this is particularly something important to investigate. Although such investigation will be beyond the aim and scope of this study, it would be great if the authors can lightly develop a few sentence of discussion. If any previous published studies suggested such a link, I would definitely cite such papers to discuss.*

We would like to thank reviewer #1 for all the kind comments on our study. Alcoholic liver disease is always a consideration when referring to neurologic complication (NC) following liver transplantation because alcoholism patients have prevalent cognitive impairment (50-70%) and potential thiamine deficiency before transplantation. However, studies analyzing risk factors of NC after liver transplantation brought controversial results. The origins of NC in alcoholic liver disease are usually a combination of preoperative cognitive dysfunction, nutrient deficiency and hepatic encephalopathy, and it is difficult to differentiate these factors from a retrospective study. In this study, we attempted to review risk factors as comprehensive as possible, and tried to minimize confounding effects by using flexible statistical tools. Although alcoholic liver disease was more prevalent in the NC group, it failed to predict NC after adjustment by generalized additive model and multiple logistic regression. We still need controlled study with conscientious patient selection as well as complete neurologic examination before and after transplantation to answer the question. We have revised the fourth paragraph of discussion and had more discussion about the relationship between alcoholic liver disease and NC. We hope that it would help to clarify the problem gap for future work.

2. *Page 5, lines 15~16 “In the last decade, the risk factors...most of which were retrospective.” Appropriate literatures should be cited.*

We have added representative citations here.

3. *Very minor formatting issue. I guess that Page 6, "patients and methods" should begin from a new page (page break). Please check the instruction of the journal.*

We have made the change in format.

The second reviewer's comments (code 00504647) and our revisions are as follows:

*One weakness of this study, which obviously can not be corrected, is that diagnoses of neurological complications were not done by independent observer (preferably neurologist).*

We would like to thank reviewer #2 for all the supportive comments on our study. We acknowledge this limitation as the study is a retrospective review of regular clinical practice. Observer bias effects is possible in the non-randomized study design. As case-control studies often provide hints for further investigation, we aimed to consider all possible factors from liver recipient, donor, and surgeon. The eleven predictors for NC following liver transplantation that we identified have extended the concepts from prior case-control studies, which reminds clinician to watch for risk factors from donor and surgeon's experience.

Thank you very much for your time and consideration. If you have any questions about the manuscript or changes that we have made, please do not hesitate to contact us.

Sincerely,

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