

## The detailed point-by-point response

**Dear editors and reviewers,**

Thank you for sending us the comments of the editors and reviewers. We have read the comments very carefully and revised our manuscript point by point according to the comments raised by the editors and reviewers. The following was the reply to the editors and reviewers.

Reply to the editors and reviewers.

**Q1: Reviewer #1:**

**Specific Comments to Authors:** The research team conducted a report of three cases of tacrolimus-related HSOS after liver transplantation. I find the topic of this manuscript original and little investigated by the scientific literature up to now.

**A1:** Thank you for your interesting in our manuscript. In the present study, we reported three cases of tacrolimus-related HSOS after liver transplantation in our center. Our study and other studies confirmed that discontinuation of tacrolimus was the only effective treatment for HSOS following liver transplantation. We believe our case reports could reinforce the understanding of the development and progression of HSOS, a rare but severe complication after liver transplantation. The format of the manuscript was revised according to the requirements of the journal. We have revised our manuscript carefully and corrected all the English language expression errors. We used the underline to indicate where each of the revisions was located in the revised manuscript.

**Q2: Reviewer #2:**

**Specific Comments to Authors:** Excellent case series of a rare and interesting condition. I would only suggest an english review since I found some errors throughout the manuscript.

**A2:** Thank you for your interesting in our manuscript. In this study, we reported three cases of tacrolimus-related HSOS, a rare but severe complication after liver transplantation. The format of the manuscript was revised according to the requirements of the journal. Firstly, we have read the comments very carefully and revised our manuscript point-by-point according to the comments raised by the reviewer. We have checked it again and again and found some English language expression errors. We corrected all the errors and used underline to indicate where each of the revisions was located in the revised manuscript. Secondly, we send our revised manuscript to a professional English language editing company, American Journal Experts, for further language polishing. At last, we checked it again and again to ensure that all grammatical, syntactical, formatting and other related errors have been resolved. We hope that our revised manuscript could meet the publication requirement.

**Q3: Reviewer #3:**

**Specific Comments to Authors:** The article is within the scope of the journal, and the topic described is interesting. It is well written and easy to read. However, to be accepted, it must be improved in some aspects: a) The article must be structured. For example: introduction, state of the art, case description, discussion, and conclusions and future work. b) It is important to contextualize the proposed cases and compare them with other similar studies. c) It would be necessary to add a state of the art to find out what other studies have been carried out similar to the one proposed. d) A discussion section must be included where the results obtained are critically explained, compared with other studies and the limitations and advances of the study carried out are shown.

**A3:** Thank you for your interesting in our manuscript. In this study, we reported three cases of tacrolimus-related HSOS after liver transplantation. a) We restructured the manuscript. The format of the manuscript was revised according to the requirements of the journal. The state of art and conclusions were added in the revised manuscript. The future work was added and underlined in the discussion

section. b) We have reviewed the literatures on HSOS after liver transplantation, and the recent progresses in the early diagnosis and treatment of HSOS after liver transplantation were presented in Table 2 on Page 19-21 of the text. We have compared the etiology, symptoms, diagnosis methods and treatments of HSOS after liver transplantation. We found that tacrolimus and acute rejection were two main predisposing factors to induce HSOS after liver transplantation. The clinical manifestations, radiological, pathological features of tacrolimus-related HSOS were similar in these studies. Several recent studies showed that tacrolimus was the most possible predisposing factor inducing HSOS and withdrawal of the drug may be the only effective treatment. However, the detailed treatments were a little different in these studies. In some studies, the immunosuppressant therapy was switched from tacrolimus to cyclosporine A with mycophenolate mofetil continued. In other studies, tacrolimus was converted to sirolimus. In our study, tacrolimus was replaced by sirolimus, and mycophenolate mofetil was continued. Both of these two treatments relieved the clinical symptoms of HSOS. The results suggested that tacrolimus could be converted to either cyclosporine A or sirolimus. c) We added a state of the art on page 4 of the revised manuscript. In this section, the similarities of other studies and ours were compared and presented. We found that tacrolimus was the most possible predisposing factor to induce HSOS after liver transplantation, clinical manifestations of tacrolimus-related HSOS were similar and discontinuation tacrolimus may be the only effective treatment. d) In the discussion section, we explained the results objectively and critically. Since this study was a single center retrospective case report and the sample size was small. The evidences may be not convincing. In the future, multicenter large sample retrospective case-control studies and randomized controlled studies are needed to verify these results. Besides, we compared the results with other studies by reviewing the literatures of HSOS after liver transplantations. The similarities and differences of these studies were presented in Table 2 on Page 19-21 of the text. The recent progresses in the diagnosis and treatment of HSOS were also discussed. The advances of the study were also discussed in this section. All the three patients were timely diagnosed of HSOS based

on clinical symptoms, radiological and histological examinations. Besides, we found that enlarged liver with patchy enhancement on portal venous phase CT was the most important radiologic feature of HSOS, which was of great value in the diagnosis of HSOS. In addition, the results of our study and other studies indicated that discontinuation tacrolimus was the only effective treatment. Tacrolimus could be converted to either cyclosporine A or sirolimus. Both of these two methods were effective in the treatment of HSOS after liver transplantation. There were also some limitations in our study. Firstly, it was a single center retrospective case report and the sample size was small, so the evidences may be not convincing. In the future, well designed multicenter large sample retrospective case-control studies and randomized controlled studies are needed to verify these results. Besides, although we and other researchers speculated that tacrolimus may be the most possible predisposing factor to induce HSOS after liver transplantation, the mechanism of tacrolimus-related HSOS remains unclear. Further basic studies are needed to clarify the underlying mechanism.

**Q4:** Science editor:

The manuscript has been peer-reviewed, and it's ready for the first decision.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good)

**A4:** We have read the comments very carefully and revised our manuscript point-by-point according to the comments raised by the science editor. We have checked it again and again and found some English language expression errors. We corrected all the errors and used underline to indicate where each of the revisions was located in the revised manuscript. Secondly, we send our revised manuscript to a professional English language editing company, American Journal Experts, for further language polishing. At last, we checked it again and again to ensure that all grammatical, syntactical, formatting and other related errors have been resolved. We hope that our revised manuscript could meet the publication requirement.

**Q5: Company editor-in-chief:**

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please upload the approved grant application form(s) or funding agency copy of any approval document(s). Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the RCA. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the

author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>.

**A5:** We have read the comments very carefully and revised our manuscript point-by-point according to the comments raised by the Company editor-in-chief. The original figure documents were prepared and provided in a single PowerPoint file. We submitted them as "79834-Figures.pptx" on the system. The figures were uploaded to the file destination of "Image File". The standard three-line tables were provided. We submitted them as "79834-Tables.docx" on the system. The tables were uploaded to the file destination of "Table File". According to the suggestion of the Company editor-in-chief, we applied the tool RCA to review the latest highlight articles. After the literature reviewing, we supplemented the highlights of the latest cutting-edge research results in Table 2 on Page 19-21 of the text. The latest research results could reinforce the understanding of the development and progression of HSOS, a rare but severe complication after liver transplantation. We hope that our revised manuscript could meet the publication requirements.

If you have any question, please feel free to contact me. We will reply as soon as possible.

**Best wishes,**

**Lei-Da Zhang**