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Dear Prof. Ze-Mao Gong

Please find our revised manuscripts (**26479-Revised manuscript.docx**) enclosed that we wish to re-submit to World Journal of Gastroenterology. The newly described and added sentences in the revised manuscript are **colored as purple** for your convenience.

The information of the prevously submitted manuscript is
ESPS Manuscript NO: 26479
Title: Risk Factor of Ischemic-type Biliary Lesion after ABO-Incompatible Living Donor Liver Transplantation using B-cell Depletion Protocol.

Authors: Jun Bae Bang, Bong-Wan Kim, Young Bae Kim, Hee-Jung Wang, Hyun Yeong Lee, Joohyun Sim, Taegyu Kim, Kyeong Lok Lee, Xu-Guang Hu, Wei Mao

We acknowledge the comments made by the reviewers and have made a number of changes accordingly. We did our best to revise the manuscript according to your comments and questions. A list of these changes is included. I also enclose **a copy of point-by-point response to the referee comments** for your convenience.

All authors have contributed to the manuscript and approved the final version. This manuscript has not been submitted or accepted for publication elsewhere.

Sincerely,

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Editorial comment

Thank you for your comments. According to editorial comments about manuscript format, we revised the manuscript to satisfy the format of the World Journal of Gastroenterology.

1. We reduced the title length no more than 12 words.

2. Abstract was corrected to have no less 80 words of METHODS, and no less 120 words of RESULTS.

3. We fixed all format in the manuscript according to your comments.

4. We attach the all 13 documents for retrospective cohort study of the World Journal of Gastroenterology.

5. We did our best to answer from reviewers **as below**.

Thank you very much.

Bong-Wan Kim, MD, PhD,

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Reviewer 1

Reviewer's code: 00053888

COMMENTS TO AUTHORS

The authors have presented an interesting study of 27 patients who have undergone ABO incompatible liver transplantation. They present their own immunological protocol and the outcome of the 27 patients concentrating particularly on the incidence of ischaemic biliary injury. These data are very interesting and demonstrate that with careful attention to detail it is possible to achieve a satisfactory outcome in this group of patients.

COMMENTS	CHANGE MADE
There are a small number of grammatical errors in the manuscript that will no doubt be dealt with at a future editorial stage. One such example is 'further researches'.	Thank you for your comment. We corrected the English grammar by native speakers.
The discussion is too long and this could be partly addressed by moving the rationale for splenectomy in these patients to the introduction rather than having this in the discussion section. Otherwise this is a good manuscript & is worthy of publication.	Thank you. We agree with your comment. The DISCUSSION was shortened by deleting some additional explanations. The first sentence of the DISCUSSION was removed. The last 2 sentences of the 1st paragraph of the DISCUSSION were removed. In 2nd paragraph of the DISCUSSION, four reasons of splenectomy in our protocol were shortened to 3 reasons. In the 3rd paragraph in DISCUSSION was shortened by deleting general description of clinical symptoms and outcomes of ITBL (3rd sentence). In the 6th paragraph of the DISCUSSION, description of the role of NK cell in ADCC was shortened by deleting a general description of NK cell activity (5th sentence). Thank you again.

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Reviewer 2

Reviewer's code: 00054001

COMMENTS TO AUTHORS

The authors described occurrence and risk factor of ischemic-type biliary lesion (ITBL) after ABO incompatible adult living donor liver transplantation (ABO-I-ALDLT) with analyzing their institutions experiences. It seems very interesting attempt. However, In my own experiences with more than 100 cases of ABO-I-ALDLT, ITBL discussed in this manuscript has not been seen at all after the induction of B-cell depletion protocol using almost same as used in this manuscript. Therefore, I could not realize the significance of this condition. In order to specify the significance of this condition, the following issues must be discussed. 1. Long-term outcomes of total cases of ALDLT and comparison of those between ABO-identical/compatible and ABO-incompatible cases in the authors' institution must be given. Furthermore, causes of graft loss of each failed case were extensively discussed. 2. In the Section of Introduction, the authors addressed the AMR as the main cause of graft loss after ABO-I-ALDLT referring very old article concerning ABO-incompatible LT. The article used for the reference was very important but no longer suitable for addressing current problems regarding ABO-I-ALT. Moreover, the authors addressed ITBL as a consequence of AMR. The logical basis of this should be given. 3. I have an impression that currently reported ITBL cases were seen in institutions that do not use hepatic arterial infusion (HAI) or portal infusion (PI) therapy although difference between case with and without HAI was not significant in this manuscript. In our institution, HAI or PI has been used and no cases of ITBL were seen. Use of HAI or PI should be specifically discussed in Discussion section.

COMMENTS	CHANGE MADE
1. Long-term outcomes of total cases of ALDLT and comparison of those between ABO-identical/compatible and ABO-incompatible cases in the authors' institution must be given. Furthermore, causes of graft loss of each failed case were extensively discussed.	Thank you for your comment. We analyzed the reasons of graft losses, and added the overall survival rates of all ALDLT according to your comment. We also compared the survival rates between ABO-I ALDLT and ABO-identical/compatible ALDLT, and described in the "***clinical outcomes of recipients***" in the RESULT. Also we added the overall survival curve in "Figure 3".
In the Section of Introduction, the authors addressed the AMR as the main cause of graft loss after ABO-I-ALDLT referring very old article concerning ABO-incompatible LT. The article used for the reference was very important but no longer suitable for addressing current problems regarding ABO-I-ALT. Moreover, the authors addressed ITBL as a consequence of AMR. The logical basis of this should be given.	Thank you for your comment. We added a recent report from Japanese nationwide data analysis of ABO-I liver transplantation as a reference which showed the AMR was the main cause of patient's death after ABO-I LDLT. (Egawa H, et al., M. Present status of ABO-incompatible living donor liver transplantation in Japan. *Hepatology* 2008; **47**(1): 143-152) In the INTRODUCTION, we described the pathophysiology of the ITBL after ABO-I ALDLT would be from microcirculatory disturbance in the graft, which results from a graft endothelial inflammatory process triggered by

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	graft's endothelial reaction to the recipient's isoagglutinin. And in the DISCUSSION, we also described the pathophysiology of ITBL after ABO-I ALDLT in the 3rd paragraph.(It has been understood that the mechanism of ITBL development was thrombotic obstruction of the hepatic arteriole by accumulation of isoagglutinin-complement complex on the endothelial cells of ABO-I liver graft.)
I have an impression that currently reported ITBL cases were seen in institutions that do not use hepatic arterial infusion (HAI) or portal infusion (PI) therapy although difference between case with and without HAI was not significant in this manuscript. In our institution, HAI or PI has been used and no cases of ITBL were seen. Use of HAI or PI should be specifically discussed in Discussion section.	Thank you for your comment. First of all, we congratulate you on your excellent outcomes of ABO-I LDLT. We could understand your opinion but, our experience is unfortunately different from yours. There has been controversy in the use of local infusion therapy for ABO-I LDLT, especially after use of IVIG for a preventive measure of AMR. According to several previous studies, this might have to be investigated further to evaluate its feasibility. We specially discussed the use of local infusion therapy and added a new paragraph (3rd paragraph) in the DISCUSSION for local infusion therapy. Thank you again.

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Reviewer 3

Reviewer's code: 02729658

COMMENTS TO AUTHORS

1. Authors have to discuss how to treat NK cell problems. 2. Other possible factors except NK cells need more detail discussion. 3. Discussion needs to be shortened.

COMMENTS	CHANGE MADE
Authors have to discuss how to treat NK cell problems.	Thank you for your comment. We newly added an anti-NK cell research for prevention of the AMR in the experimental transplantation in the 8th paragraph of the DISCUSSION.
Other possible factors except NK cells need more detail discussion.	Thank you for your comment. Use of local infusion therapy could be a preventive strategy for development of ITBL after ABO-I ALDLT, although there was no concrete evidence in this study. We discussed the issue at the 3rd paragraph in the DISCUSSION.
Discussion needs to be shortened	Thank you. We agree with your comment. The DISCUSSION was shortened by deleting some additional explanations. The first sentence of the DISCUSSION was removed. The last 2 sentences of the 1st paragraph of the DISCUSSION were removed. In 2nd paragraph of the DISCUSSION, four reasons of splenectomy in our protocol was shortened to 3 reasons. The 4th paragraph in DISCUSSION was shortened by deleting general description of clinical symptoms and outcomes of ITBL (3rd sentence). In the 7th paragraph of the DISCUSSION, description of the role of NK cell in ADCC was shortened by deleting a general description of NK cell activity (5th sentence). Thank you again.