Format for ANSWERING REVIEWERS

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: H Tanaka WJH-revised).

Title: Reuse of liver grafts following the brain death of the initial recipient

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The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) The first comment from the reviewer # 02860775

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1. The donor or the initial recipient, who has the right to use the liver grafts? 2. Some liver disease may cause brain edema, whether this case has been taken consideration? 3. In the graph, the liver disease and cause of death of some donors is N/A, the youngest one is 4, so why do they want to be a donor? Whether because of the N/A has some influence on the conclusion?

Our reply to this comment:

Thank you for your comment about our paper.

Regarding the comment 1, in our case the reuse was carefully discussed in our transplant team and we decided to perform it. Then the informed consent was obtained from the family of the initial recipient first, and then obtained from the second recipient himself and his family. The review of the literatures revealed that not all the decision process for the reuse were clearly described, but we believe the situations were the same as ours.

Regarding the comment 2, as you pointed out, if the original disease of a liver recipient is an acute liver failure, the recipient may develop brain edema even after liver transplantation, and has the possibility to be brain dead. This situation has happened in six cases in our literature review.

Regarding the comment 3, we think that the reviewer pointed out that the data in 8 reuse transplants in the reference number 8 were missing. We believe the authors in the paper tried to collect the data from UNOS, but they could not. The missing data are off course interesting, but we do not think that would influence our conclusion.

The initial recipient in the reference number 14 was 4 years old, and actually the original donor was 8 years old. The authors in the paper described only, 'After informed conscent, ...', when they performed the reuse. So we do not know what decision process was undertaken at the time of the reuse from the pediatric recipient. We believe that in general, all the organ sharing organizations and transplant programs have strict guideline for donation from

children.

(2)The second comment from the reviewer # 02549484

In this manuscript, TANAKA et al. investigate whether the re-use liver retransplantation can be considered a reasonable clinical opportunity in marginal cases. Starting from a case report, the authors undertake a systematic survey of the literature. Although experience is still limited, the authors conclude that in this setting, outcomes of liver transplantation (patient/graft survival) are similar to those reported with conventional donors. The authors face with a still unsolved, very interesting transplant issue, which is of potential great impact due to the shortness of donors, but that so far, it has been reported in literature only sporadically. Although the manuscript is basically well written, a number of specific, major concerns are worth being addressed: 4. It is unclear to the reviewer how search of literature has been performed; in particular, the key words and the criteria of paper selection need to be clearly stated in the method section. 5. A critical point is the marginal recipient that theoretically may take advantage of reuse of liver grafts. This is an important issue, which is mostly missing in the Table provided by the authors. A careful discussion on the potential indications by reviewing data from literature whenever available is strongly claimed. 6. In case description, authors state: "Even though his HCC appeared to be stable … long-term survival without liver replacement was considered unlikely. The opportunity was discussed with the patient and his family …". This is a fundamental aspect with tremendous ethical implications. Unfortunately, no approval by the local Ethical Committee is mentioned by the authors in their case description. Furthermore, given its relevance this issue should be also properly outlined and commented in the discussion.

Our reply to this comment:

Thank you for your comments about our paper.

Regarding the comment 4, we added underlined descriptions as below in the Method section.

Regarding the comment 5, it is true that marginal recipients may take advantage of reuse of liver grafts, but ideally marginal recipients should take liver grafts with good quality from non-marginal donors to obtain good outcome. The situations that they should encounter and we actually encountered in the setting of reuse liver transplantation are as follows: when the potential donor of the liver for reuse is notified to their organ sharing organization, most of the transplant team would decline the offer, because the graft is considered to be quite marginal. But if a marginal recipient's access to the conventional list is limited as we stated in the Discussion, especially when the general condition is deteriorating or the extent of the tumor is almost beyond the inclusion criteria for liver transplantation. We are sorry to say that we could only retrieve the indication of the second recipients and outline them in the Table, but could not rate them precisely as marginal or non-marginal. We added the comments below with red line to clarify the difficult situation in the Discussion.

There has been no established guideline so far for the recipients' indication of reuse liver transplantation. A marginal recipient whose general condition is deteriorating or whose stage of malignancy is almost beyond the criteria for liver transplant and whose suitable donor is not available may take advantage of the reuse liver transplant.

Regarding the comment 6, approval of local Ethical committee was not described in any of the literature including our case. We believe that evaluation of brain death of the first recipient (reuse donor) had been precisely undertaken and informed consents were obtained from those families for possible donation in all the reported cases. If there is any ethical problem in the case of reuse liver transplants, that would be the same as liver transplants from marginal donors such as old donors, donors with fatty liver, or other conditions such that delayed graft function or poor outcome might be anticipated after the transplant compared to the transplants from

non-marginal donors.
The comments below with under line were added in the Discussion

Nowadays transplant programs are increasingly accepting marginal donors such as old donors, donors with fatty liver, or other conditions such that delayed graft function or poor outcome might be anticipated after the transplant compared to the transplants from non-marginal donors. The local Ethical committee should be ideally called before accepting the reuse liver, and this paper will help the committee understand the feasibility of the rare form of transplants.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Hepatology*

Sincerely yours,

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