

To the Editor-in-chief and the Science Editor of the *World Journal of Transplantation*,

Re: Submitted manuscript entitled “**Impact of machine perfusion of the liver on post-transplant biliary complications: a systematic review**”. [Manuscript NO: 41208]

We would like to thank the editor and reviewers for the helpful comments on our submitted manuscript. In accordance with them we have revised the manuscript, and are providing a point-by-point response to the comments below. All the changes in the original manuscript are highlighted in the revised version submitted. We hope the manuscript now meets the standard expected of the *World Journal of Transplantation*.

Sincerely,

Yuri Boteon (on behalf of all co-authors)

In response to Science Editor

We thank the editor for the comments. In accordance, we have provided a running title, an authors' contribution paragraph and a postcode for the authors' affiliations. The conflict of interest statement was moved to the title page as requested. All related documents as audio core tip, biostatistics review certificate, conflict of interest disclosure form, copyright license agreement, decomposable figures and PRISMA 2009 checklist were uploaded.

In addition, an article highlights section was written as requested. PubMed reference numbers and DOI were added to the reference list, as it was the names of all authors of the manuscripts.

In response to reviewer 02397506

We greatly appreciate your comments about the manuscript. As well recognised by the reviewer, the limited number of randomized controlled trials is a major limitation for the interpretation of the data available up to now on this subject. In accordance, we acknowledged this as a limitation of this review into the manuscript.

In response to reviewer 03291363

We thank the reviewer for the thoughtful analysis of the work. Please find a point-by-point response to the comments.

“2.The magnitude of this problem needs more explanation...”

We agree that clarification of the importance of the problem to the readers is fundamental to justify the work. In accordance, in the introduction, a detailed description of the problematic associated with post-transplant biliary complications is presented. Moreover, we have not only described the

incidence of those complications, but also its pathogenesis, diagnosis, consequences to patients and the options of treatment available.

“3.Nasralla et al which did not show any difference between normothermic machine perfusion and cold storage... Yet this hard conclusion is not mentioned in the conclusions”

The reviewer has made a valid point regarding the results reported by Nasralla *et al.* Indeed, there was no significant difference in bile duct complications between the intervention group that had NMP and the control group that had conventional static cold storage. This finding is reported in the first paragraph of the results (subsection “Normothermic machine perfusion and post-transplant biliary complications”). All figures are presented for an unbiased interpretation of the readers. Some details deserve attention, such as, just one patient in each group developed ITBL; and, for DCD livers the NAS rate varies between groups despite the difference not reaching statistical significance.

Apart from described in the results session, in the discussion (4th paragraph), we have acknowledged that, currently, the evidence of benefits of normothermic machine perfusion towards biliary complications is limited. Additionally, we have hypothesised the potential mechanistic reasons for this based on the existing literature. In the conclusion, we carefully report that, based on the studies available up to now, oxygenated hypothermic machine perfusion and normothermic regional perfusion exhibit better postoperative biliary outcomes in comparison with normothermic machine perfusion and non-oxygenated machine perfusion.

To sum up, the hard conclusion pointed out was discussed in diverse parts of the manuscript, as its consequences were.

“4.The other studies are small...” “5.There are multiple variable in the studies”

We agree with the reviewer that variability between studies characteristics, and the fact that most of the data originate from small pilot studies, are major limitations when interpreting the data presented. In accordance, in the 6th paragraph of the discussion, we have listed those and other points that need to be taken into consideration when assessing the studies available up to date.

“the selection for each modality is unclear... 7.There should be a study design to solve this problem not just “by randomised control trials”. What is the variable to be tested in the RCT; why select this type of machine perfusion; what is the comparator; how many centres; what are the numbers required”

We highly appreciated the reviewer’s comments regarding the limitations of the machine perfusion studies up to now. However, we would like to remind that the present manuscript is a systematic review. As a consequence, we reviewed the existing literature in a systematic way and then presented the results to the readers. All the findings were openly discussed in face of the limitations. Problems with the studies were acknowledged so readers can also interpret our results. Nevertheless, the concept and design of an ideal machine perfusion study is clearly out of the scope

of this manuscript. Therefore, despite interesting, the questions proposed by the reviewer are not appropriate to be answered by this study.

“8. Table 1 should have the study designed included”

We completely agree with the reviewer that reporting the studies design is important. In accordance we have included this information in table 2. This is because table 1 is already too busy, and identification of the trial is similarly presented in table 2.

“9. Overall I recommend a more critical examination of the validity of the studies”

We thank the reviewer for the recommendation. However we have critically assessed the manuscripts and presented openly to readers its limitations. All characteristics of the groups investigated and techniques of MP employed were described. A careful discussion of the findings was performed, taking into consideration its limitations, and there was no over-interpretation of the data at any point.

In response to reviewer 02726701

We are really thankful for your comments. Please find below a point-by-point response to them.

“My suggestion is to end each subsection (of the results) with a brief conclusion about the results description”

Thanks for the suggestion. This study was conceptualised as a systematic review. Therefore, into the results section the findings originated from the studies are only presented without an initial interpretation from the authors. This strategy allows an unbiased analysis of the data by the readers. A discussion section finally summarises the data and discuss the results.

Regarding, the hypothermic machine perfusion subsection specifically mentioned. Different protocols are presented in each paragraph, therefore, the results varies slightly between them as well. The advantages are more evident in the studies reported on the second and third paragraphs. Nevertheless, all the paragraphs describe benefits of this technique in different extent. A dedicated discussion section summarise the benefits showed by the individual studies presented in all the three paragraphs. To conclude, there is not inconsistent results of this technique. Therefore, we would prefer to maintain the current structured formatting of the manuscript.

“I did not find in the main text where it is mentioned Figure 1”

We thank the reviewer for the observation. Inadvertently the reference to figure 1 in the manuscript was in the wrong position. We apologise for the mistake and amended the manuscript accordingly.

“Table 1 requires some edition to fit properly all its content.”

Thanks for the observation. This is a consequence of the orientation of the page. This issue can be better handled by the publisher during the final formatting of the manuscript.

“Table 2 is confusing. It is mentioned just once in the HMP subsection, but it contained a lot of additional information”

We greatly appreciated the reviewer’s comment. In accordance with the comment we have explained further the content of table 2 into the manuscript.

In response to reviewer 00503243

We appreciated the complimentary comments from the reviewer. Thanks for spending your valuable spare time reviewing the manuscript.