

July 5, 2017

Dear editors of *World Journal of Gastroenterology*,

Thank you for considering our previous manuscript entitled **"Outcomes after Liver Transplantation in accordance with ABO Compatibility: A Systematic Review and Meta-Analysis (Manuscript NO. 34817)"** We are so happy to hear the news that the paper is available for publication with a pending satisfactory revision. We accepted all suggestions elaborated by four reviewers and tried to answer all questions to the best of our abilities. In our annotated version, we revised our previous manuscript by using Track Change function with marginal notes indicating changes (*e.g.*, Reviewer 00000000_Q1). Our specific responses to indications and suggestions are as follows:

Reviewer 02454185

COMMENTS TO AUTHORS

This is an interesting and controversial topic. I have several comments on this to improve it.

1. In the abstract, the authors need to explicitly state the type of study to be included in the systematic review.

Thank you for your thoughtful comment. As your recommendation, we have described the type of study included in this study in the abstract (page 3, line 11).

2. "Furthermore, ABO-I LT was associated with more incidences of antibody-mediated rejection, chronic rejection, cytomegalovirus infection, overall biliary complication"---quantitative data should be reported for these secondary outcomes.

As your recommendation, we have added quantitative data to abstracts (page 3, line 16 - 20).

3. "Graft survival in ABO-I LT could be enhanced in pediatric patients and those using rituximab."---this sentence is not supported in the data presented in the abstract , because they appear to be comparable.

We modified the sentence in the abstract to your recommendation. (page 3, line 27 - 28). The similar sentence has also been modified in core tip. (page 5, line 6- 7)

4. Detailed searching strategy should be presented in the supplemental file for each database.

We have attached supplementary file named "34817-Supplementary-Material-revision.docx" as your suggestion.

5. "The included studies were articles that compared ABO-I LT and ABO-C LT with a minimum of one outcome of interest." it is important to specify the type of studies to be included (RCT vs. observational; prospective vs. retrospective)

As you know, this meta-analysis was based on non-randomized controlled trials because it is practically impossible to randomly allocate patients into either ABO-C LT or ABO-I LT due to ethical issues. To date, RCT on this topic has never been reported. As your recommendation, we have described the type of study included in this study in the result section. (page 10, line 15)

6. For observational studies, the major drawback is the confounding. Do you use adjusted effect size for combination or use unadjusted one?

In our meta-analysis, there were no RCTs, and four cases/propensity score matched studies were included. Further, some of the rest of the articles included in this meta-analysis did not provide an adjusted OR (ABO-C vs. ABO-I) for the outcomes we are interested in. Thus, we contacted the corresponding or 1st author via e-mail with adjusted OR value or raw data, but there was no answer.

There is no documented consensus about or how to synthesize adjusted and unadjusted findings in a research synthesis. However, we had to choose between two options.

#1. To include only studies with adjusted finding

#2. To include both adjusted and unadjusted results while ignoring potential heterogeneity due to adjustment.

As you know, the concept of meta-analysis was devised to produce pooled results by merging RCTs without confounders. However, our research topic has an ethical issue that makes RCT impossible and has not been reported to date.

For the meta-analysis of the observational study, each of the methods # 1 and # 2 presented above have pros and cons. Although selecting studies (# 1) minimizes heterogeneity, it also reduces the number of studies available for synthesis. In many areas of inquiry, this would result in too few findings to synthesize. In this way, the selected studies may be non-representative and biased, and may lead to vastly different

conclusions^[1].

Another option is # 2. We refer to similar papers with this design^[2-5]. The problem with this method is that the unadjusted confounder causes heterogeneity in the pooled result. However, our results were no significant heterogeneities in most comparisons, such as graft survival, patient survival, and ABO-I-related complications. In addition, we attempted sensitivity tests and subgroup analyzes to minimize potential heterogeneities. Please consider these points.

7. Since most of included studies are small in sample size, it is necessary to discuss the “small study effect”, and perform sensitivity analysis restricting to large studies. Cite a useful reference (Crit Care. 2013 Jan 9;17(1):R2. doi: 10.1186/cc11919.) for this discussion and exploration.

It is a good point. As you know, in this meta-analysis, a potential publication bias was detected in the 1-yr patient survival. We confirmed this with funnel plot asymmetry and Egger's regression test. After adjustment for funnel plot asymmetry using the trim-and-fill method (Fig. 6B), ABO-I LT showed a significantly poorer 1-yr patient survival than ABO-C LT. We described in the discussion section that the main source of this publication bias could be the "small study effect", and we quoted the recommended article (page 18, line 12 – 15). In addition, the sensitivity test and subgroup analyses to complement the heterogeneities of the studies included in this meta-analysis are performed in the result section (page 12, line 24 – page 14, line 18) and Table 3.

Reviewer 00058381

COMMENTS TO AUTHORS

Major Comment:

1. Discussion: The details of the results (like CIs, etc.) already given in the “Results” section should not be repeated in the “Discussion” section. In this way, the readability of the discussion could be improved.

As you pointed out, we reduced the number of repetitive result presentations in the discussion section and made overall revisions.

Minor Comments:

1. Abstract: Abbreviated terms should be written out when first used.

The following points have been revised: ABO-Incompatible (ABO-I) (page 3, line 3),

liver transplantation (LT) (page 3, line 4), ABO-Compatible (ABO-C) (page 3, line 4), odds ratio [OR] (page 3, line 14), and confidence interval [CI] (page 3, line 14).

2. Supplementary Fig. 2: According to the figure legend, “patient survival” should be shown here. However, the last part of this figure is titled “5-yr graft survival”.

Thank you very much for your thoughtful comments. We corrected our mistake.

Reviewer 01559615

COMMENTS TO AUTHORS

This manuscript includes a systematic review and meta-analysis of outcomes after liver transplantation in accordance with ABO compatibility. Authors performed a well-designed meta-analysis. The flow diagram is adequate. Statistical approach is adequate for answering the questions regarding the study topic. Description of the results is well prepared.

1. However, findings are repeatedly presented in discussion part. Discussion should be shortened and, re-written. The plan of discussion should be designed regarding to order of presented results. Authors should be discussed the results, point by point, not to re-present.

As you pointed out, we have reduced the number of repetitive result presentations and described discussion sections according to the order of presented results (survival -> complications -> sensitivity and subgroup analyses [pediatric, rituximab, urgent indication, LDLT vs. DDLT] -> publication bias -> limitations -> conclusions).

Reviewer 00054465

COMMENTS TO AUTHORS

A well carried out meta-analysis.

We would like to express our deep appreciation for your positive evaluation of our article.

Thank you again for reconsidering our manuscript. We did our best to revise our previous manuscript. We hope the revised version would meet with deputy editor's and four reviewers' approval and be finally accepted.

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