

São Paulo, 19<sup>th</sup> January 2021

**ROUND 1**

To:

Professor Subatra Ghosh

WJG Editor-in-Chief

Dear Professor Ghosh,

Thank you very much for the important comments about our manuscript. We do believe that after reviewing this article according to the suggestions of the reviewers, a great improvement in the quality of the article was achieved. A careful revision was performed. The answers to the comments are described in detail below and the specific revision is **highlighted** in the reviewed manuscript.

Sincerely

Karina Gordon

**Corresponding author**

Karina Gordon, MD, PhD

Division of Anesthesiology Hospital das Clinicas of University of Sao Paulo School of Medicine

Av. Dr. Eneas de Carvalho Aguiar, 155 8th Floor

Zip code 01246-903 Sao Paulo, SP, Brazil

Phone/Fax: +55 11 2661-5367 E-mail: gordonkarina00@gmail.com

## Science Editor comments

1 Scientific quality: The manuscript describes a retrospective cohort study of the perioperative blood transfusion decreases long-term survival in pediatric living donor liver transplantation. The topic is within the scope of the WJG. (1) Classification: Grade B, Grade B and Grade C; (2) Summary of the Peer-Review Report: The manuscript reported a well-written manuscript with important findings. However, the discussion should be replenished. The questions raised by the reviewers should be answered; and (3) Format: There are 7 tables and 3 figures. A total of 53 references are cited, including 1 reference published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade B, Grade A and Grade B. A language editing certificate issued by American Manuscript Editors was provided. 3 Academic norms and rules: The authors provided the Institutional Review Board Approval Form. The authors need to provide the Biostatistics Review Certificate, the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement, and STROBE Statement with page number. No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an unsolicited manuscript. The topic has not previously been published in the WJG. 5 Issues raised: (1) The "Author Contributions" section is missing. Please provide the author contributions; (2) The authors did not provide original pictures. 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; and (3) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text. 6 Re-Review: Required. 7 Recommendation: Conditional acceptance.

1- However, the discussion should be replenished. The questions raised by the reviewers should be answered.

Response: The discussion was replenished as required, highlighted on pages 23, 24, 26 and 27. We respond to questions from all reviewers individually, point to point and accept all suggestions for improving this article, as described below.

2- The authors need to provide the Biostatistics Review Certificate

Response: The Biostatistics Review Certificate was annexed as required.

3- The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement

Response: The Conflict-of-Interest Disclosure Form and Copyright License was annexed as required

4-The authors need to provide STROBE Statement with page number.

Response: The STROBE Statement was annexed as required

5- The “Author Contributions” section is missing. Please provide the author contributions.

Response: Author contributions are highlighted on the Title page 2 and they were upload in the step 1 of review submission, as required.

6- The authors did not provide original pictures. 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.

Response: The original pictures were uploaded on the file named “61592-Figures.ppt”, as required.

Response: The original figures were annexed as required

7- The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text.

Response: The Article Highlights were annexed as required at the end of the main text (pages 28 and 29), as required.

### **Reviewer #1**

Karina Gordon, et al. have described the high volume perioperative transfusion is associated with early and late postoperative complications and mortality in small patients undergoing PLDLT, and confirmed the cutoff volume (RBC>27.5 mL/kg) was an independent risk factor for mortality, patient and graft survival. Given the lack of related research in young children, the topic is of certain potential interest.

#### Comments to the Author

1- I suggested the authors: The last paragraph in the Discussion seems to be superficial, I would like to see authors' commentary as experts, like how to treat weak children who need to high volume transfusion, to improve their prognosis.

Response: We thank you for your suggestion that enriched the end the of manuscript. We inserted expert comments highlighted on pages 26 and 27.

### **Reviewer #2**

#### Comments to the Author

1- In the first sentence of the Materials and Method section, I think “recipients” would be more appropriate than “receptors”.

Response: We thank you for your suggestions to improve this manuscript. The term “receptors” was replaced by “recipients” as suggested (page 4),

#### Comments to the Author

2. It was stated in the methods section that three patients who underwent retransplantation were excluded from the study. The reason for excluding these patients from the study is unclear. Shouldn't we consider retransplantation of these patients as a major complication according to your classification?

Response: Thank you for your observation. We considered retransplantation as a major complication. However, we excluded 3 cases of retransplantation, who had the first transplant performed in other centers. To clarify this information, we modified the flowchart in figure 1, renaming this cases as “patients referred after the first transplant”.

#### Comments to the Author

3. I think that in the first sentence of the third paragraph of the introduction section, “includes” is more appropriate instead of “covers”.

Response: The term was replaced as suggested (page 9).

#### Comments to the Author

4. In the "Late postoperative complications" section and in table 6; The "biliary fistula", "biliary stenosis", "hepatic artery thrombosis (HAT)", "portal vein thrombosis (PVT)", and "retransplantation" is classified as "graft related complication ". However, this

complications are not only related to graft. The biliary stenosis may be due systemic response to healing. Also late arterial thrombosis is mostly due to endothelial damage caused by immunologic mechanisms after transplantation. Therefore I think this classification is not appropriate. In addition, these complications may be encountered in the early postoperative period. Were not there any type of this complications (especially; "hepatic artery thrombosis", "portal vein thrombosis" and "biliary fistula") in early postoperative period in the study group.

Response: We agreed that biliary fistula", "biliary stenosis", "hepatic artery thrombosis (HAT)", "portal vein thrombosis (PVT)", and "retransplantation" are not only related to graft. Thereby, we replaced the expression "graft-related complications" for "LT specific complications" in the sections of Methods (page 12), Results (page 15 and 16) and Discussion (page 23), as well as in Table 4 and in the new Table 6.

We agreed with the reviewer comments, and we divided LT specific complications in early and late, as well the mortality rate, and they were displayed properly on Table 6, and excluded mortality rate of table 4. Results and Discussion were modified accordingly on pages 15 and 23-24, respectively.

## ROUND 2

Editor comments Still the discussion part in need for better in-depth engagement into the topic. References needs more updating.

**Response:** Additional comments were added to the discussion part, highlighted on pages 14, 15, 18, 19, 20 and 21. Moreover, references were updated and are numbered below, highlighted on manuscript pages 24-28: 02 Lu Q, Zhang J, Gao WM, Lv Y, Zhang XF, Liu XM. Intraoperative Blood Transfusion and Postoperative Morbidity Following Liver Resection. Medical science monitor : international medical journal of experimental and clinical research 2018; 24: 8469-8480 [PMID: 30470732 PMCID: PMC6270889 DOI: 10.12659/MSM.910978] 14 Nacoti M, Cazzaniga S, Colombo G, Corbella D, Fazzi F, Fochi O,

Gattoni C, Zambelli M, Colledan M, Bonanomi E. Postoperative complications in cirrhotic pediatric deceased donor liver transplantation: Focus on transfusion therapy. *Pediatr Transplant* 2017; 21(8) [PMID: 28681471 DOI: 10.1111/petr.13020] 21 Squires RH, Ng V, Romero R, Ekong U, Hardikar W, Emre S, Mazariegos GV. Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *Hepatology* 2014; 60(1): 362-398 [PMID: 24782219 DOI: 10.1002/hep.27191] 34 Cuenca AG, Kim HB, Vakili K. Pediatric liver transplantation. *Semin Pediatr Surg* 2017; 26(4): 217-223 [PMID: 28964477 DOI: 10.1053/j.sempedsurg.2017.07.014] 46 Chen XB, Xu MQ. Primary graft dysfunction after liver transplantation. *Hepatobiliary Pancreat Dis Int* 2014; 13(2): 125-137 [PMID: 24686540 DOI: 10.1016/s1499-3872(14)60023-0] 51 Kohli R, Cortes M, Heaton ND, Dhawan A. Liver transplantation in children: state of the art and future perspectives. *Arch Dis Child* 2018; 103(2): 192-198 [PMID: 28918383 DOI: 10.1136/archdischild-2015-310023] 52 Rawal N, Yazigi N. Pediatric Liver Transplantation. *Pediatr Clin North Am* 2017; 64(3): 677-684 [PMID: 28502445 DOI: 10.1016/j.pcl.2017.02.003] 53 Dreyzin A, Lunz J, Venkat V, Martin L, Bond GJ, Soltys KA, Sindhi R, Mazariegos GV. Long-term outcomes and predictors in pediatric liver retransplantation. *Pediatr Transplant* 2015; 19(8): 866-874 [PMID: 26362966 DOI: 10.1111/petr.12588] 60 Raffini L, Witmer C. Pediatric transplantation: managing bleeding. *J Thromb Haemost* 2015; 13 Suppl 1: S362-369 [PMID: 26149048 DOI: 10.1111/jth.12913] 61 Dukleska K, Vinocur CD, Brenn BR, Lim DJ, Keith SW, Dirnberger DR, Berman L. Preoperative Blood Transfusions and Morbidity in Neonates Undergoing Surgery. *Pediatrics* 2020; 146(5) [PMID: 33087550 DOI: 10.1542/peds.2019-3718] 62 Abuzeid AM, O'Keeffe T. Review of massive transfusion protocols in the injured, bleeding patient. *Curr Opin Crit Care* 2019; 25(6): 661-667 [PMID: 31574016 DOI: 10.1097/MCC.0000000000000668]