

Dear Editors and Reviewers,

We thank you very much for your evaluation of our manuscript “**Effect of cardiac output - guided hemodynamic management on acute lung injury in pediatric living donor liver transplantation: a randomized clinical trial**”. We really appreciate all your comments and suggestions! Please find our point-by-point responses in below and revisions/corrections which were highlighted in the re-submitted files. We believe that the manuscript was substantially improved.

Thank you for your time.

Sincerely,

**Xiaojing Dou, Qingping Wang, Weihua Liu, Yiqi Weng, Ying Sun, Wenli Yu**

**Reviewer #1 & #2:**

**Specific Comments to Authors:** This is a randomized controlled study to examined the effect of cardiac output based perioperative care on the incidence of acute lung injury.

We are grateful for the Reviewer’s encouraging comments and we hope that we have adequately addressed the problems raised.

**I have some comment.**

**1. Please put a line number for reviewer’s convenience.**

Thank you for the suggestion, and the line number was added accordingly.

**2. (P1, L16) Please explain the reason the authors focused the effect on postoperative lung not kidney injury.**

The justification that the focus on the effect on postoperative lung not kidney injury was in Line 99-110:”The incidence of acute lung injury (ALI) post-

liver transplantation (LT) has been reported to vary between 34.2% and 77.8% [4, 5]. ALI may lead to acute respiratory distress syndrome (ARDS), which is associated with adverse postoperative outcomes, such as prolonged hospital stay, high morbidity, and mortality [6]. ARDS is often caused by hemodynamic instability during surgery, which results in liver hypoperfusion and ischemia-reperfusion injury, exaggerating the inflammatory process [7]. Additionally, hemodynamic instability accompanied by the excess administration of fluids and blood products leads to fluid imbalance during LT. Clinical studies have demonstrated that intraoperative fluid overload is the primary risk factor for postoperative pulmonary complications (PPCs) [8]. Effective fluid management strategies can reduce the PPCs [9].”

3. (P1, L6 from the bottom) VIS needs an explanation.

The definition of VIS was added in Line 69.

4. (P1, L4 from the bottom) IL, TNF, cTnI, NT and BNP need an explanation.

The explanation of IL, TNF, cTnI, NT and BNP were added in P1, Line 71-72.

5. (P2, L4) acute kidney injury (ALI) is right?

We sorry for the mistake and it was now corrected in Line 82.

6. (P4, L16) What is FiO<sub>2</sub>?

FiO<sub>2</sub> is fraction of inspired oxygen and the explanation was added in Line 154.

7. (P4, L18) What is PETCO<sub>2</sub>?

PETCO<sub>2</sub> is Postapneic End-Tidal Carbon Dioxide Pressure and the explanation was added in Line 156-157.

8. (P4, L9 from the bottom, as PRAM/Mostcare) Does it mean that CI and SVI can be monitored by PRAM/Mostcare using the data from central venous catheter and a-line in the radial artery? Is the Swan-Ganz not needed? The detail of the mechanism is needed.

1. Yes, CI and SVI can be monitored by PRAM/Mostcare only by connecting a-line in the radial artery. Mostcare (Vytech Health, Padova, Italy) is a

hemodynamic monitoring device applying PRAM technology. It has advantages over other devices in the aspect of being minimally invasive (only the arterial line needs to be connected), not requiring direct or indirect calibration, and being suitable for pediatric patients weighing <20kg.

2. In our study, we used PRAM/Mostcare to monitor CO and other Hemodynamic parameters instead of Swan-Ganz catheters.

When monitor CO continuously in pediatric patients, Swan-Ganz catheters is extremely difficult and limited, probably due to their anatomical characteristics, biomaterial technology and surgical conditions. The target participants of our study were pediatric patients weighing under 20kg. It was very difficult to apply Swan-Ganz catheters continuously on CO monitoring in pediatric patients with liver transplantation.

In our center, CO was measured using the PRAM/MostCare device (Vytech Health, Padova, Italy) in pediatric liver transplantation since 2015. Studies results have already confirmed the feasibility and accuracy of PRAM/MostCare among pediatric liver transplantation recipients.

3. The details of PRAM/Mostcare mechanism

Pressure recording analytical method (PRAM) is a novel, arterial pulse contour-based method for measuring cardiac output (CO). PRAM is an invasive, continuous (beat-to-beat) method based on the theory of perturbations. PRAM measures CO by analyzing the morphology of both the pulsatile and continuous components of the arterial pressure waveform[1]. Another important characteristic of PRAM is that it uses a 1000-Hz sampling frequency, compared with the 100-Hz frequency typically used in other pulse contour analysis technologies[2]. Previous studies have found good correlation and agreement between PRAM and other methods for measuring cardiac output in animal models and adults[2]. And some studies have confirmed the effectiveness and accuracy of this technique in pediatric patients[3].

The PRAM monitor was connected to the arterial line and automatically

measures diastolic pressure in the waveform, and a vertical green line on the screen indicates the exact point of the waveform identified as the diastolic notch. This was classified as visible when the acting clinician was able to identify a true notch in the waveform, and not just a change in the slope where the device identified the diastolic pressure. The data recorded by the PRAM monitor included cardiac index (CI), stroke volume index (SVI), systemic vascular resistance index (SCRI), dP/dt, pressure pulse variation (PPV), and stroke volume variation (SVV).

9. (P5, L11 from the bottom) What is MAP?

MAP is mean arterial blood pressure and the Line 172.

10. (P5, L4 from the bottom) The definition of ALI should be described.

The definition of ALI was described in Line 49-50.

11. (P7, L3 from the bottom) Are there some data of ALI incidence after “human” liver transplantation (not rat)? I feel the incidences in the present study (45% in the control and 28 in the CO-G group) are high.

Thank you for your questions. Few studies reported the incidence of ALI among pediatric liver transplant recipients. Among the adult liver transplant recipients, there was a large variation in the reported ALI incidences, ranging from 34.2% and 77.8%. The references were in Line 432-436.

12. (P8, L4 from the bottom, P9, L17, P9 L7 from the bottom) Put a line between the subsections of Discussion section.

Thank you for your suggestions. The line between the subsections of Discussion section was added.

13. (P9, L7 from the bottom) The number of the subject was set by calculating  $\alpha < 0.05$  and beta power. Please explain the authors think the sample size in the present study is still small.

Thank you for pointing out the mistake and the correction was in Line 405-406.

14. (P9, L4 from the bottom) Put a line between the Discussion and Conclusion sections.

The line between the Discussion and Conclusion sections was added.

15. Figure legends are necessary which I can not find.

Figure legends were added in Line 585-587.

**(1) Science editor:**

1 Conflict of interest statement: Academic Editor has no conflict of interest. 2 Manuscript's theme: The topic is within the scope of the journal. 3 Academic misconduct: No academic misconduct was found. 4 Scientific quality: The authors submitted a manuscript. Effect of cardiac output - guided hemodynamic management on acute lung injury in pediatric living donor liver transplantation: a randomized clinical trial. The manuscript is overall qualified. (1) Advantages and disadvantages: The reviewers have given over all positive review and minor revisions suggested by both the reviewers. Core tip section is missing. Over all manuscript is well written. Few clarifications are required as reviewers suggested (I think reviewer report of both the reviewers is same, please check) (2) Main manuscript content: The authors state the purpose of the study clearly, the study design is appropriate and feasible, and the statistical methods used are correct. However, there are several flaws in methodology (3) Table(s) and figure(s): Tables are clear and legibly presented and figures are also okay (4) References: A total of 31 references are cited, including 9 references are latest and within 5 years. There are no self-cited references of the authors. The reviewer didn't request the authors to cite improper references published by him/herself. 5 Language evaluations: The English-language grammatical presentation needs to be improved little and minor language polishing required. 6 Medical ethics: All necessary ethics documents provided. Ethics statements clearly mentioned within manuscript 7 Specific comments:

The manuscript can be accepted after minor revision

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good)

We are grateful for the Science editor's encouraging comments. The language has been polished with certified institute and the certification was provided.

*(2) Company editor-in-chief:*

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Surgery, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. **Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.**

We are grateful for the company editor-in-chief's encouraging comments. The ppt file with decomposable Figures was provided.

Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

**Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.**

We are sure that the figures were original.

