Peer Review File
Article Information: https://dx.doi.org/10.21037/jtd-23-1510

Reviewer A

Comment 1: Would not include p-values in table 1 as this is generally not recommended and is a measure of inferential purpose.
Reply 1: Thank you for your kind suggestion. We have removed the p-values from Table 1.
Changes in the text: We have modified our Table1 as advised.

Comment 2: Would the authors further expand on the uniqueness of their findings as CPB, AKI, and myoglobin have been previously linked. Are we simply repeating a study in a different disease state or is there something specific about PEA that may explain the results?
Reply 2: Thank you for your kind comment. We believe it is valuable to investigate the correlation between postoperative myoglobin elevation and AKI in surgeries that require CPB, DHCA and long surgical durations. Similarly, PEA surgery belongs to this category of surgeries, so we conducted relevant research. Based on the comments from the other two reviewers, we have removed 15 PAS cases from the data (because CTEPH and PAS are totally different disease and prognosis) and collected additional clinical data from 9 CTEPH patients between April and September 2023. Further analysis of these 134 data revealed that Ln(POD0-sMb) still remains an independent risk factor for postoperative AKI, whether it is any-AKI or severe-AKI (Table 3). Unfortunately, CPB time is no longer an independent risk factor. The inconsistent result may be due to bias of the PAS data. In order to explore the risk factors associated with elevated serum myoglobin levels after PEA surgery, we included all variables mentioned in this article with a P-value of < 0.05 in univariate analysis into a multivariable linear regression analysis. Ultimately, we found that CAD, preoperative eGFR, preoperative mPAP, and CPB time had a significant influence on the Ln(POD0-sMb) level ($F = 11.459$, $P < 0.001$, adjusted $R2 = 0.239$) (Table 5). In conclusion, in PEA surgery, CPB time may influence the occurrence of AKI by affecting the elevation of postoperative myoglobin levels. Additionally, the influence of preoperative mPAP on postoperative serum myoglobin levels is unique to PEA surgery and does not exist in other cardiac surgeries ($\beta = 0.175$, $P = 0.032$; Table 5). In other cardiac surgeries[1], preoperative myoglobin levels are associated with higher postoperative myoglobin levels. However, this phenomenon does not occur in PEA surgery. Therefore, myoglobin exhibits its uniqueness in the occurrence of AKI following PEA surgery, rather than being a mere replication of different disease states.
Changes in the text: We have modified our Table1, Table 2, Table 3 and added Table 5. Relevant revised text see Page 10, line 184-192; Page 11, line 205-211; Page 12, line 232-241; Page 12-13, line 242-250.

Reviewer B

Comment 1: Authors explored the clinical impact of serum myoglobin level on postoperative AKI after PEA. However, they included patients both with chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary artery sarcoma (PAS). Certainly, PEA is a one optional

treatment for PAS; however, CTEPH and PAS are fundamentally different pathologies with different severities and prognoses. I think it is wrong to evaluate those two together. Authors have to focus on only the patients with CTEPH treated by PEA and re-evaluate the association of serum myoglobin with postoperative AKI after PEA.

Reply 1: Thank you for your insightful suggestion. We have removed 15 PAS cases from the data and collected additional clinical data from 9 patients between April and September 2023. We have merged the remaining 125 cases with these new cases, resulting in a total of 134 cases for further analysis.

Changes in the text: We have modified our Table1. Relevant revised text see Page 4, line 67-70.

Comment 2: Why did authors exclude the patients died within 7 days after surgery. They described that the secondary outcomes in this study included 30 days operative mortality. These patients should not be excluded when considering the development of postoperative AKI. （）

Reply 2: Thank you for your suggestion. According to the definition of AKI by KDIGO[2, 3], stage 1 is defined as an increase of ≥ 0.3 mg/dl (26.5 μmol/L) within 48 hours after surgery or an increase of 1.5 to 1.9-fold over baseline within 7 days. The classification of AKI stages requires observing the changes in sCr over a continuous period of 7 days. Patients who died within 7 days were excluded from the analysis due to incomplete sCr records, making it impossible to accurately assess their AKI status.

Comment 3: The preoperative baseline creatinine (pre-sCr) was defined as the mean outpatient concentration measured 7-365 days before hospitalization. This range of adoption periods seems too long. Shouldn't it be at least a month?

Reply 3: Thank you for your comment. Relevant literature indicates that the mean outpatient serum creatinine measured within a year of hospitalization most closely approximates nephrologist-adjudicated serum creatinine values[4]. Considering the longer time span of one year, as per your suggestion, we define pre-sCr as the mean outpatient serum creatinine within one month, and retrieve clinical data again to categorize AKI levels accordingly.

Changes in the text: We have modified our text as advised (see Page 5, line 91-92).

Comment 4: Authors described that pre-sMb was similar among patients with non-AKI, AKI, and severe AKI after PEA. I recommend that sMb should be included in Table 1.

Reply 4: Thank you for your kind reminder. We have added the pre-sMb and POD(0-7)-sMb data into the table1.

Changes in the text: We have modified our Table 1.

Comment 5: In the multivariate analysis, D-dimer at baseline is an independent predictor of postoperative AKI after PEA (OR 2.390, p value 0.044). It has been that D-dimer at the time of diagnosis are independent and significant predictors of outcome in CTEPH. Authors should discuss the significance and reason of D-dimer in postoperative AKI after PEA.

Reply 5: Thank you for your kind reminder. After removing the PAS data for further analysis, we found that D-dimer is no longer an independent risk factor for AKI or severe AKI. Interestingly, we discovered that apart from Ln(POD0-sMb), albumin is also an independent

risk factor for severe AKI, and the relevant reasons have been explained in the discussion.
Changes in the text: We have modified our text as advised (see Page 13, line 259-277).

Reviewer C

Comment 1: Patients who developed severe AKI had high rates of mortality and ECMO. I suppose that these patients could not have had satisfactory pulmonary hemodynamic results, thus they had high rates of mortality and ECMO. I wonder whether residual PH was associated with AKI.
Reply 1: Thank you for your constructive advice. We defined the mPAP ≥ 25mmg and PCWP ≤ 15mmHg measured by RHC 24 hours post-PEA as residual pulmonary hypertension (RPH). We collected and analyzed relevant clinical data, found no statistically significant association between RPH and AKI, whether it was AKI (P = 0.220) or severe AKI (P = 0.259) (Table S5, Table S6).
Changes in the text: We have modified our Table 1.

Comment 2: In addition, those patients had significant longer duration of ACC and CPB despite similar DHCA time to other groups. In case of postoperative ECMO, CPB time might be long, but I did not understand why they had such long duration of ACC.
Reply 2: Thank you for your friendly inquiry. First, based on our center's experience, we always stop pulmonary artery drainage after completing the pulmonary artery sutures to ensure there is no significant bleeding at the pulmonary artery incision and then finally opening the ascending aorta. If any bleeding is observed, timely intervention is performed. The timing of this step may vary from person to person. Secondly, based on the comments from the other two reviewers, we have removed 15 PAS cases from the data and collected additional clinical data from 9 CTEPH patients between April and September 2023. Further analysis of these 134 data showed that although there are still significant differences in CPB time and ACC time between the two comparions made, but there are no longer independent risk factors for post-PEA. We consider that the bias may be due to the PAS data, as CTEPH and PAS are fundamentally different pathologies with different severities and prognoses.

Comment 3: I wonder whether the authors investigated association of Jamieson or UCSD classification and the development of AKI. Generally speaking, Jamison type III disease is technically demanding, and requires longer DHCA and ACC time.
Reply 3: Thank you for your insightful comment. We collected clinical data on the UCSD classification and conducted an analysis, finding no statistically significant association between it and AKI, whether it was AKI (P = 0.531 for type I (reference); P = 0.284 for type II; P = 0.576 for type III) or severe AKI (P = 0.467 for type I (reference); P = 0.334 for type II; P = 0.575 for type III) (Table S5, Table S6).
Changes in the text: We have modified our Table 1.

Comment 4: It would be better to show postoperative mPAP and PVR.
Reply 4: Thank you for your kind suggestion. We have added the clinical data of mPAP and PVR measured by RHC 24 hours post-PEA.

Changes in the text: We have modified our Table 1. We have modified our text as advised (see Page 8, line 154-156).

Comment 5: I suppose that 3-hour ACC seemed to be long given that DHCA was 1 hour. In my experience, aortic clamp was applied after removal of central clot and the establishment of the dissection plane in the main rt. PA, and released during closure of lt. PA incision. I wonder whether the authors developed the dissection plane after aortic clamp.

Reply 5: Thank you for the friendly conversation. You have perceptively discovered that we developed the dissection plane after aortic clamp. The surgical procedures at our center are conducted according to the UCSD protocol[5], but we also have our own experiences. Firstly, we often expose the right pulmonary artery after aortic clamp because the space is limited before blocking the ascending aorta, making it inconvenient for dissection. Additionally, the right side tends to have more severe thrombosis, so we prioritize operating on the right side. Secondly, based on our experience, during the cooling process, the blood volume in the extracorporeal circulation reservoir tends to decrease. It requires intermittent supplementation of albumin and crystalloid fluids. If combined with cardiac arrest solution, it may further dilute the blood, making it unable to reach the desired hematocrit level at the time of circulatory arrest. Therefore, we often block the ascending aorta when the core temperature reaches 22-24°C and ventricular fibrillation occurs. Then, with the ascending aorta devoid of blood during cardiac arrest, we expose the right pulmonary artery and establish a dissection plane, removing some thrombi. At this moment, the core temperature has essentially dropped to 20°C, allowing for circulatory arrest. Thirdly, we have a practice of completely closing the incisions of the left and right pulmonary arteries before opening the ascending aorta. We even stop pulmonary artery drainage after completing the pulmonary artery sutures to ensure that there is no significant oozing or bleeding from the pulmonary artery incisions. This is because it can be challenging to expose the incisions of both pulmonary arteries, especially the left pulmonary artery, after the heart resumes beating. Bleeding or oozing from the pulmonary artery incisions can sometimes be catastrophic.

Comment 6: Regarding Table 1, I suppose preoperative data and surgical outcomes should be described separately. CPB, DHCA, ACC time should be described in minutes.

Reply 6: Thank you for your kind reminder. We have separated the description of preoperative data and surgical outcomes, and we have described CPB, DHCA, and ACC times in minutes.
Changes in the text: We have modified our Table 1.

Reviewer D

Comment 1: Please exclude the patients with sarcoma. CTEPH and pulmonary sarcoma are totally different disease and prognosis.

Reply 1: Thank you for your insightful comment. We have removed 15 PAS cases from the data and collected additional clinical data from 9 CTEPH patients between April and September 2023. We have merged the remaining 125 cases with these new cases, resulting in a total of 134 cases for further analysis.

Changes in the text: We have modified our Table1. Relevant revised text see Page 4, line 67-

70.

Comment 2: Please describe the patients with preoperative chronic kidney disease (eGFR<60) not eGFR<90 in Table 1. CKD could influence om post-operative AKI.
Reply 2: Thank you for your kind suggestion. We searched for eGFR data based on your recommendation and found that none of the patients had an eGFR lower than 60 ml/min/1.73m^2.
Changes in the text: Relevant revised text see Page 9, line 167-168.

Comment 3: How did you measure mean pulmonary arterial pressure? In the same content, mean PAP measured by RHC had significant differences whereas there were no significant differences in mean PA measured by ECG.
Reply 3: Thank you for your thoughtful comment. We apologize for the confusion caused by our oversight. We used RHC to measure mean pulmonary artery pressure. In Table 1, the term "ECG" was actually meant to be "TTE" (transthoracic echocardiography), and "mPA" referred to the diameter of the main pulmonary artery. The relevant statements have been corrected and clarified in Table 1 with appropriate footnotes.
Changes in the text: We have modified our Table1 and its footnotes.

Comment 4: What is the risk factor for high serum myoglobin level after PEA? Are there any differences between other cardiac surgeries?
Reply 4: Thank you for your insightful comment. It is indeed worthwhile to explore the risk factors associated with elevated serum myoglobin levels after PEA surgery. We included all variables mentioned in this article with a P-value of < 0.05 in univariate analysis into a multivariable linear regression analysis. Ultimately, we found that CAD, preoperative eGFR, preoperative mPAP, and CPB time had a significant influence on the Ln(POD0-sMb) level ($F = 11.459$, $P < 0.001$, adjusted $R2 = 0.239$) (Table 5). The influence of preoperative mPAP on postoperative serum myoglobin levels is unique to PEA surgery and does not exist in other cardiac surgeries ($\beta = 0.175$, $P = 0.032$). In other cardiac surgeries[1], preoperative myoglobin levels are associated with higher postoperative myoglobin levels. However, this phenomenon does not occur in PEA surgery. The factors we included can only explain a small portion of the increase of postoperative myoglobin levels after PEA surgery (adjusted $R2 = 0.239$). In the future, we will actively explore additional factors that may influence it.
Changes in the text: We added Table 5 and described the results on Page 11, line 205-211.

Comment 5: Please add the SGLT2 inhibitor, MRA, and ARNI not only ACEI/ARB and Diuretics as nephrotoxic agent uses.
Reply 5: Thank you for your kind and constructive suggestions. We have re-retrieved the clinical data and found that no patient took SGLT2 inhibitors or ARNI medications. The data for MRA medications has been added to Table 1. Unfortunately, the use of MRA medications did not show any statistically significant association with the occurrence of AKI ($P = 0.177$ for AKI and $P = 0.528$ for severe AKI) (Table S5, Table S6).
Changes in the text: We have modified our Table1.

Comment 6: In clinical situation, what are the benefits to focus on serum myoglobin level not

CPB time? Is serum myoglobin level just a surrogate marker of CPB time?

Reply 6: Thank you for your kind advice. Based on your suggestion, we have removed 15 PAS cases from the data and collected additional clinical data from 9 CTEPH patients between April and September 2023. Further analysis of these 134 data revealed that Ln(POD0-sMb) still remains an independent risk factor for postoperative AKI, whether it is any-AKI or severe-AKI. Unfortunately, CPB time is no longer an independent risk factor. According to our multiple linear regression analysis, there are many factors contributing to the elevation of postoperative myoglobin levels. Combined with other three variables, CPB time can only explain approximately 23.8% variation of postoperative sMb. This suggests that postoperative serum myoglobin levels are not a surrogate for CPB time and have a unique and broader significance than CPB. Monitoring postoperative myoglobin levels is beneficial for accurately assessing the occurrence of AKI.

Changes in the text: We added Table 5 and described the results on Page 11, line 205-211.

1. Chen S, Zhang C, Zhong Y, Tang B, Xie Q, Guo R, Qiao Z, Li C, Ge Y, Zhu J: Association between preoperative serum myoglobin and acute kidney injury after Stanford Type A aortic dissection surgery. Clin Chim Acta 2023, 541:117232.
2. Birnie K, Verheyden V, Pagano D, Bhabra M, Tilling K, Sterne JA, Murphy GJ: Predictive models for kidney disease: improving global outcomes (KDIGO) defined acute kidney injury in UK cardiac surgery. Crit Care 2014, 18(6):606.
3. Stevens PE, Levin A: Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 2013, 158(11):825-830.
4. Siew ED, Ikizler TA, Matheny ME, Shi Y, Schildcrout JS, Danciu I, Dwyer JP, Srichai M, Hung AM, Smith JP et al: Estimating baseline kidney function in hospitalized patients with impaired kidney function. Clin J Am Soc Nephrol 2012, 7(5):712-719.
5. Madani MM: Surgical Treatment of Chronic Thromboembolic Pulmonary Hypertension: Pulmonary Thromboendarterectomy. Methodist Debakey Cardiovasc J 2016, 12(4):213-218.