Peer Review File

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Comment 1: Please highlight your ATAAD outcomes (30 days mortality, 1 year mortality, STS composite outcomes, bleeding, reoperations, products, DHCA, adjuncts used, temperature, inotropes used etc. as an opening. This to be followed by AKI results.

Reply 1: Respected reviewer, first of all, thank you very much for taking the time to review this manuscript and for providing us with so many valuable comments. From your comments, we learned about your rigorous spirit of scientific research. Following your comments, we meticulously revised the manuscript and explained each point. There may be some problems we don't fully explain or offer satisfactory explanations based on your comments. In order to improve our research, we would sincerely appreciate your understanding and further comments.

Changes in the text: We added the ATAAD outcomes in Abstract, Results.

Comment 2: Comment on your volume of activity to highlight that you are a referral tertiary centre.

Reply 2: We added the comment on our centre.

Changes in the text: We added these in **Methods, Study design**.

Comment 3: Where is our current data? Your data are biased for selective population cohort. Update your data-analysis to match current time.

Reply 3: Dear Professor, we agree that the addition of current data may perform better in terms of bias reduction. In fact, we mainly focus on the risk factors and in-hospital outcomes of postoperative severe acute kidney injury in the present study. The data were collected during 6 consecutive years and the sample size was sufficiently large. Therefore, it may not be optimal but should be sufficient to draw a conclusion that postoperative severe acute kidney injury needs more emphasis. In addition, we do not yet have access to the current data because our data are collected every 5 years. The decision was based on consideration of practical issues, including ethical approval and data safety. The next five-year data are going to be analyzed in the near future.

Comment 4: Was your population a mix of familial and non-familial cohorts? Is this inclusive of Marfan and other connective tissue disorder?

Reply 4: Dear Professor, our study population is non-familial cohort. Our center relies on referrals as a possible underlying cause. This study population includes Marfan (Table 1), but not other connective tissue diseases by rarity and difficulties in diagnosis.

Comment 5: Were the population characteristic first comer?

Reply 5: Dear Professor, the patients who were diagnosed with isolated aortic hematoma, isolated thoracic aortic aneurysm, and isolated aortic ulcer underwent aortic CTA before the surgery. To better show the study design, we add the flow diagram.

Changes in the text: We added it in Figure 1.

Comment 6: Please add a table to illustrate “In patients with suspected aortic disease, computed tomography scans of the aorta and coronary artery were performed.”

Reply 6: Dear Professor, we added a flow diagram (Figure 1).

Comment 7: Conjecture bias. Your population cohort are all comers Type A aortic dissection, right?

Reply 7: Dear Professor, thank you very much for your nice reminder. We have corrected the wording accordingly and this sentence has now been amended to be more exact.

Changes in the text: We corrected it in **Methods, Study design.**

Comment 8: It’s imperative that you highlight evolution of your practice and why you have evolved your surgical technique to such. This will ameliorate collision bias between exposure and outcome.

Reply 8: Dear Professor, according to your suggestion, we add the evolution of our surgical technique and the main cause for this technology gaining popularity in China.

Changes in the text: We add these in **Methods, Surgical Technique**, paragraph 1.

Comment 9: Evidence based temperature selection should be portrayed not surgeon's preference. Rephrase

Reply 9: Dear Professor, it is amended to ‘Based on the patient’s condition’.

Changes in the text: We correct it in **Methods, Surgical Technique**, paragraph 2.

Comment 10: Page 6, line 138“... graft implantation.” Which graft? Denote commercial use.

Reply 10: Dear Professor, we added the commercial use. Tetrafurcate graft (Vascutek Terumo, Tokyo, Japan); FET (MicroPort Medical Co, Ltd., Shanghai, China)

Changes in the text: We add it in **Methods, Surgical Technique**, paragraph 2.

Comment 11: It's imperative that you consider propensity score modelling given the number of your population cohort being studied and also a derivative of risk odds ratio.

Reply 11: Dear Professor, thank you for giving us this valuable comment. According to your suggestion, we performed the propensity score matching (PSM). Matching was done on 6 variables, including female gender, BMI, diabetes, marfan syndrome, hypertension, and current smoker. The results remain similar between groups before and after PSM. The results are presented in table A and B.

In fact, we have questions about PSM in our study. We think PSM does not seem to be suitable for our study, so table A and B will not be presented in the manuscript. PSM is mainly used to study the effect of grouping variables on outcome variables after excluding the effect of confounding factors (matching variables). Our study is mainly to find out the risk factors from all the variables. The difficulty is that we cannot tell the difference between the confounding factors and risk factors. It has been challenging to find the right matching variables. Different matching variables will present different results after PSM. We sincerely hope to get your understanding and are pleased to have discussion with you.

Table A Baseline characteristics before and after PSM

	Before PSM			After PSM		
Variables	Non-Severe AKI (n=590)	Severe AKI (n=80)	P-value	Non-Severe AKI (n=80)	Severe AKI (n=80)	P-value
Demographics						
Age (years)*	46.5±10.0	49.4±11.1	0.019*	46.26±8.5	49.4±11.1	0.048*
Female gender	121 (20.5)	23 (28.7)	0.092	23 (28.7)	23 (28.7)	1.000
BMI (kg/m²)	26.4±4.3	26.9±4.5	0.338	26.8±3.5	26.9±4.5	0.835
Medical history						
Marfan	55 (9.3)	5 (6.3)	0.367	4（5）	5 (6.3)	0.732
syndrome						
Hypertension	495 (83.9)	66 (82.5)	0.750	68 (85.0)	66 (82.5)	0.668

Diabetes	18 (3.1)	2 (2.5)	0.786	2 (2.5)	2 (2.5)	1.000
Prior cardiovascular surgery	22 (3.7)	2 (2.5)	0.579	1 (1.3)	2 (2.5)	0.560
Prior CAD	1 (0.2)	1 (1.3)	0.096	0 (0.0)	1 (1.3)	0.316
Family history of dissections or aneurysms	9 (1.5)	1 (1.3)	0.849	1 (1.3)	1 (1.3)	1.000
Current smoker	274 (46.4)	30 (37.5)	0.132	29（36.3）	30 (37.5)	0.870
ATAAD presentation						
Chest pain	494 (83.7)	68 (85.0)	0.772	68 (85.0)	68 (85.0)	1.000
Back pain	261 (44.2)	40 (50.0)	0.331	39（48.8）	40 (50.0)	0.874
Abdominal pain	106 (18.0)	13 (16.3)	0.706	15（18.8）	13 (16.3)	0.677
Head or neck pain	13 (2.2)	3 (3.8)	0.395	4（5.0）	3 (3.8)	0.699
Preoperative malperfusion of organ						
Brain ischemia	55 (9.3)	12 (15.0)	0.112	6（7.5）	12 (15.0)	0.133
Myocardial ischemia	2 (0.3)	1 (1.3)	0.252	0（0.0）	1 (1.3)	0.316
Cardiac failure	14 (2.4)	1 (1.3)	0.524	2 (2.5)	1 (1.3)	0.560
Hypotension or shock	9 (1.5)	4 (5.0)	0.034	0（0.0）	4 (5.0)	0.043

Lower limb	41 (6.9)	20 (25.0)	<0.001*	7 (8.8)	20 (25.0)	0.006*
symptoms*						
Echocardiography						
DAA (mm)	45.0±7.5	45.5±7.1	0.583	44.2±7.3	45.5±7.1	0.266
LVEDD (mm)	51.5±6.2	50.2±6.7	0.086	51.5±6.0	50.2±6.7	0.198
LVEF (%)	60.2±4.4	59.9±5.5	0.613	60.5±3.5	60.0±5.5	0.419
Involvement of vessel branches						
Coronary artery*	106 (18.0)	34 (42.5)	<0.001*	17（21.3）	34 (42.5)	0.004*
Innominate	331 (56.1)	56 (70.0)	0.018*	51（63.7）	56 (70.0)	0.401
artery*						
Left common	285 (48.3)	47 (58.8)	0.080	45（56.3）	47 (58.8)	0.749
carotid artery						
Left subclavian	254 (43.1)	45 (56.3)	0.026*	35（43.8）	45 (56.3)	0.114
artery*						
Celiac trunk	249 (42.2)	34 (42.5)	0.960	34 (42.5)	34 (42.5)	1.000
Superior	151 (25.6)	24 (30.0)	0.400	21（26.3）	24 (30.0)	0.598
mesenteric artery						
Right renal	169 (28.6)	22 (27.5)	0.832	21（26.3）	22 (27.5)	0.858
artery						
Left renal artery*	254 (43.1)	48 (60.0)	0.004*	32（40.0）	48 (60.0)	0.011*
Laboratory results						
White blood cell	12.5±5.0	13.6±4.8	0.052	12.2±3.6	13.6±4.8	0.034

count ($\times 10^9$)						
Platelets ($\times 10^9$)*	182.5±62.3	165.6±55.8	0.021*	188.2±52.2	165.6±55.8	0.009*
SCr (μmol/L)*	96.9±45.3	125.1±51.4	<0.001*	89.8±28.3	125.1±51.4	<0.001*
Combined surgery						
Bentall or David procedure	149 (25.3)	24 (30.0)	0.363	18（22.5）	24 (30.0)	0.281
CABG*	64 (10.8)	24 (30.0)	<0.001*	6（7.5）	24 (30.0)	<0.001*
Duration of procedure (min)						
CPB time*	175.8±46.2	219.9±80.6	<0.001*	170.0±48.1	219.9±80.6	<0.001*
Cross-clamp time*	104.0±30.8	122.3±50.2	<0.001*	102.6±36.3	122.3±50.2	0.005*
HCA time*	17.6±6.8	20.3±7.7	0.001*	17.5±6.3	20.3±7.7	0.013*

Data are presented as the mean ± SD or n (%). *, Non-Severe AKI vs Severe AKI, P<0.05. BMI, body mass index; CAD, coronary artery disease; AKI, acute kidney injury; PSM = propensity score matching; ATAAD, acute type A aortic dissection; DAA, diameter of ascending aorta; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; SCr, serum creatinine; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; HCA, hypothermic circulatory arrest; SD, standard deviation.

Table B Univariate and multivariate analysis of risk factors for severe AKI (After PSM)

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Demographics				
Age (years) *	1.033 (1.000-1.066)	0.050*	1.054 (1.010-1.100)	0.016*
Female gender	1.000 (0.504-1.983)	1.000		
BMI (kg/m²)	1.008 (0.933-1.090)	0.834		
Medical history				
Marfan syndrome	1.267 (0.327-4.900)	0.732		
Hypertension	0.832 (0.358-1.931)	0.668		
Diabetes	1.000 (0.137-7.279)	1.000		
Prior cardiovascular surgery	2.026 (0.180-22.797)	0.568		
Prior CAD	-	1.000		
Family history of dissections or aneurysms	1.000 (0.061-16.270)	1.000		
Current smoker	1.055 (0.555-2.006)	0.870		
ATAAD presentation				
Chest pain	1.000 (0.420-2.382)	1.000		
Back pain	1.051 (0.566-1.954)	0.874		
Abdominal pain	0.841 (0.371-1.904)	0.678		

Head or neck pain	0.740 (0.160-3.419)	0.700		
Preoperative malperfusion of organ				
Brain ischemia	2.176 (0.774-6.120)	0.140		
Myocardial ischemia	-	1.000		
Cardiac failure	0.494 (0.044-5.556)	0.568		
Hypotension or shock	-	0.999		
Lower limb symptoms*	3.476 (1.377-8.775)	<0.008*	3.793 (1.185-12.139)	0.025*
Echocardiography				
DAA (mm)	1.0226 (0.981-1.072)	0.268		
LVEDD (mm)	0.968 (0.9221-1.017)	0.198		
Ejection fraction (%)	0.972 (0.908-1.041)	0.418		
Involvement of vessel branches				
Coronary artery*	2.739 (1.367-5.490)	<0.005*		
Innominate artery	1.327 (0.685-2.569)	0.402		
Left common carotid artery	1.108 (0.592-2.074)	0.749		
left subclavian artery	1.653 (0.885-3.087)	0.115		
Celiac trunk	1.000 (0.534-1.872)	1.000		
Superior mesenteric artery	1.204（0.604-2.402）	0.598		
Right renal artery	1.066（0.530-2.144）	0.858		
Left renal artery	2.250（1.195-4.236）	0.012*		

Laboratory results				
White blood cell count ($\times 10^9$) *	1.085 (1.005-1.171)	0.036*		
Platelets ($\times 10^9$) *	0.992 (0.986-0.998)	0.011*		
SCr (μmol/L) *	1.024 (1.014-1.035)	<0.001*	1.030 (1.017-1.043)	<0.001*
Combined surgery				
Bentall or David procedure	1.476 (0.726-3.002)	0.282		
CABG*	5.286 (2.025-13.799)	0.001*		
Duration of procedure (min)				
CPB time*	1.015 (1.008-1.022)	<0.001*	1.017 (1.009-1.025)	<0.001*
Cross-clamp time*	1.011 (1.003-1.020)	0.008*		
HCA time*	1.059 (1.011-1.109)	0.015*		

Data are presented as the mean ± SD or n (%). OR, odds ratio; CI, confidence interval; BMI, body mass index; CAD, coronary artery disease; AKI, acute kidney injury; ATAAD, acute type A aortic dissection; DAA, diameter of ascending aorta; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; SCr, serum creatinine; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; HCA, hypothermic circulatory arrest; SD, standard deviation.

Comment 12: Page 8, line 171, you are instigating the number of malperfusion, right? If so, you need to highlight this and run a separate analysis on this cohort.

Reply 12: Dear Professor, we add the result of preoperative malperfusion of organ in our table. We didn't instigate the malperfusion. From our results, it may be one of the causes for severe AKI.

Changes in the text: We added it in table 1 and 3.

Comment 13: Page 8, line 171, what is this statement? What do you mean by branch vessel involvement?

Reply 13: Dear Professor, it means branch vessel involved by aortic dissection. We introduced this description in the **Methods, Data definition**.

Changes in the text: we modified this in **Methods, Data definition**.

Comment 14: Page 8, line 172, is it a routine that coronary angiography performed in all patient or were those part of CTA? Please highlight as you mislead reader on this provocative statement. It would be best if you highlight your protocol of investigation in population characteristic section.

Reply 14: Dear Professor, thank you so much for catching these glaring and confusing errors. In fact, all the patients underwent preoperative coronary CTA or coronary angiography.

Changes in the text: we corrected it in **Methods, Study design**.

Comment 15: Page 8, line 182-184, why have you lumped those together? Please stratify as this is essential to differentiate between groups.

Reply 15: Dear Professor, we have removed the result of cross-clamp time and HCA time that do not seem to be relevant to the purpose of our study.

Comment 16: Page 8, line 184-185, why? Bias of performer? This very important and risk rejecting your article if not adjusted for.

Reply 16: Dear Professor, thank you for pointing out this problem. It is not bias of performer. We rewrote the results.

Changes in the text: we rewrote it in Results, Univariate analysis.

Comment 17: Page 8, line 184-189, rephrase, re-analysis and split groups. There will be statistical inference or inflation of results per se.

Reply 17: Dear Professor, we rewrite it and try our best to fulfill all the required changes. All the modifications according to your suggestions are marked in red in the revised manuscript.

Changes in the text: We rewrote it in **Results**.

Comment 18: Page 8, line 190-191, I'd like to know the comparative data analysis with/without AKI. It's important to portray this as this will show your risk stratification shrewdness!

Reply 18: Dear Professor, we added the comparative data analysis on in-hospital outcomes.

Changes in the text: We added it in **Results, In-hospital outcomes**.

Comment 19: It's important to highlight your long-term results and survival probability through KM curves stratified between groups.

Reply 19: Dear Professor, we agree that long-term outcome is clinically important, so is in-hospital outcome, especially after aortic surgery. There are also a lot of studies focusing on in-hospital outcomes(1-3). Severe AKI has a strong association with RRT and in-hospital adverse outcomes. Both in-hospital outcomes and long-term results deserve research. Our study focuses on in-hospital outcome this time. Long term results will be the subject of future work.

References:

1. Abebe A, Kumela K, Belay M, et al. Mortality and predictors of acute kidney injury in adults: a hospital-based prospective observational study. Sci Rep 2021;11:15672.
2. Arora T, Martin M, Grimshaw A, et al. Prediction of outcomes after acute kidney injury in hospitalised patients: protocol for a systematic review. BMJ Open 2020;10:e042035.
3. Benedetto U, Dimagli A, Kaura A, et al. Determinants of outcomes following surgery for type A acute aortic dissection: the UK National Adult Cardiac Surgical Audit. Eur Heart J 2021;43:44-52.

Comment 20: Page 9, line 200, where is your univariate analysis? Odds ratio? Propensity modelling and given your cohort number is impressive given its up to date, I would suggest a metaregression analysis as well. Sell it all on none.

Reply 20: Dear Professor, we added the univariate and multivariable analyses in table 3. According to your suggestion, we perform the propensity score matching (PSM). Matching was done on 6 variables, including female gender, BMI, diabetes, marfan syndrome, hypertension, and current smoker. The results remain similar between groups before and after PSM. The results are presented in table A and B.

Comment 21: Page 9, line 208, put your result of univariate analysis first, then flow to multivariate ones.

Reply 21: Dear Professor, we added the univariate and multivariable analyses in table 3.

Comment 22: Page 9, line 214, why did you perform ROC curve assay? Justify this scientifically.

Reply 22: Dear Professor, we delete it because ROC curve assay may be not helpful for presenting results.

Comment 23: Page 9, line 198-217, rephrase your Result section. This is your selling point.

Reply 23: Dear Professor, thank you again for your valuable comments and suggestions. We have tried our best to rephrase the result section and fulfill all the required changes. All the modifications according to your suggestions have been marked in red in the revised manuscript.

Comment 24: Page 10, line 229, weak statement. Nobody is interested in short-term outcomes.

Reply 24: Dear Professor, we agree that long-term result is clinically important, so is in-hospital outcome, especially after aortic surgery. There are also a lot of studies focusing on in-hospital outcomes. Severe AKI has a strong association with RRT and in-hospital adverse outcomes. Both in-hospital outcomes and long-term results deserve research. Our study focuses on in-hospital outcomes this time. Long term results will be the subject of future work.

Comment 25: Page 11, line 244-248, draw a comparison with other reported series to bring strength to your point.

Reply 25: Dear Professor, we added the comparison of our results with other reports.

Changes in the text: We added it in **Discussion**, paragraph 2.

Comment 26: Malperfusion needs to be highlighted in your result and as such can be included in your discussion. Your paragraph is bias of reporting. Please adjust.

Reply 26: Dear Professor, thank you for pointing out this problem. We added the result of preoperative malperfusion of organ in our results and tables.

Changes in the text: We add it in Results, Univariate analysis, table 1 and 3.

Comment 27: Rephrase the Discussion section once you depicted your re-analysis.

Reply 27: Dear Professor, we have tried our best to rephrase the Discussion section and fulfill all the required changes.

Changes in the text: We corrected it in Discussion, paragraph 1 and 2.

Comment 28: Page 14, line 297-298, what do you mean here?

Reply 28: Dear Professor, we delete it because it isn't suitable. We rewrite the limitations.

Changes in the text: We rewrite it in Limitations.

Comment 29: Page 14, line 299, "....mid-to-long-term results were not analyzed." Why?

Reply 29: Dear Professor, we deleted it and rewrote the limitations.

Changes in the text: We rewrote it in **Limitations**.

Comment 30: Page 14, line 299-300, "This factor may introduce variation between the results of different studies." Conjecture statement and not to be included in your limitations.

Reply 30: Dear Professor, we deleted it and **rewrite** the limitations.

Changes in the text: We **rewrite** it in **Limitations**.

Comment 31: Page 14, line 306-311, rephrase the Conclusion section accordingly.

Reply 31: Dear Professor, we tried our best to improve the manuscript and made major revisions in the manuscript. Finally, we came to the similar conclusions.

Comment 32: Please restructure your references accordingly.

Reply 32: Dear Professor, we have added some required references and also restructure your references accordingly where needed.

Comment 33: Table 1, where are your ROC curves?

Reply 33: Dear Professor, we deleted it this time because ROC curve assay might be not helpful for presenting results.

Commented 34: Table 1, comparative data reporting is preferred.

Reply 34: Dear Professor, we added it the table 1 and 3.

Comment 35: What is the total number of ATAAD operated during that period?

Reply 35: Respected reviewer, first of all, thank you very much for taking the time to review this manuscript and for providing us with so many valuable comments. From your comments, we learned about your rigorous spirit of scientific research. Following your comments, we meticulously revised the manuscript and explained each point. There may be some problems we don't fully explain or offer satisfactory explanations based on your comments. In order to improve our research, we would sincerely appreciate your understanding and further comments.
Dear Professor, 828 patients underwent aortic surgery for ATAAD. We have added the flow diagram of the study in Figure 1.

Comment 36: What is the % of patients who underwent TAR+FET?

Reply 36: Dear Professor, 81.3% (673/828) patients underwent TAR+FET. We have added the flow diagram of the study in Figure 1.

Comment 37: In the procedure the authors mention, "... replaced with a tetrafurcate graft, followed by a special stented graft implantation." Does this mean that the authors reconstruct the arch and then deploy the stent graft retrogradely?

Reply 37: Dear Professor, the stent-graft can be deployed by retrograde approach (femoral artery) in hybrid total arch repair. However, we excluded the patients who received hybrid total arch repair in this study. The stented graft was implanted anterogradely into the distal aorta after the anterior wall of the aortic arch was incised. After that, the stented graft was anastomosed to a tetrafurcate graft in an end-to-end fashion by continuous stitches.

Comment 38: What is the FET hybrid prosthesis used in these 670 patients?

Reply 38: Dear Professor, we have added the commercial use. Tetrafurcate graft (Vascutek Terumo, Tokyo, Japan); FET (MicroPort Medical Co, Ltd., Shanghai, China)

Changes in the text: We add it in Methods, Surgical Technique, paragraph 2.

Comment 39: The figures are not visible in the manuscript

Reply 39: Dear Professor, we deleted it this time because ROC curve assay may be not helpful for presenting results.

Comment 40: The authors mention that the cross-clamp time in non-severe AKI is 104.0±30.8 min, with a maximum of 134 minutes. This included Bentall's/David's procedure with TAR+FET. Right?

Reply 40: Dear Professor, yes, it includes Bentall's/David's procedure with TAR+FET.

Comment 41: Can you differentiate table 3 and table 4. Both almost appears with a few more variable in table 4. But the values in both are different.

Reply 41: Dear Professor, preoperative variables were included in table 3, pre- and intraoperative variables were included in table 4. The values in both were different because different variables were included in the twice logistic regression analysises. We delete the preoperative risk factors analysis (table 3) and revised table 4 to make it clearer.

Comment 42: What is the effect of cardioplegia on renal failure?

Reply 42: Dear Professor, the effects of cardioplegic solutions on acute kidney injury have rarely been studied, although acute kidney injury is a common complication following CPB. Cardioplegia applied to arrest the heart during CPB could exert effects on kidney, as large volumes of the cardioplegic solution enter the systemic circulation. The electrolyte compositions of cardioplegia are different from that of blood, and these solutions could affect end-organs such as the kidney. The intracellular accumulation of calcium has been associated with cellular injury. In addition, acute kidney injury includes tubular cell injury, which is characterized by apical membrane blebbing and cell swelling. The trend for the preservation of proximal tubular structure may be caused by the supplementation of the amino acids alanine, l-arginine and glycine to cardioplegia(4).

References:

4. Feirer N, Dieterlen MT, Klaeske K, et al. Impact of Custodiol-N cardioplegia on acute kidney injury after cardiopulmonary bypass. Clin Exp Pharmacol Physiol 2020;47:640-9.

Comment 43: It is surprising to see that the preoperative involvement of the renal artery (right or left) was not a significant factor both in univariate and multivariate analysis. Can the authors explain this?

Reply 43: Dear Professor, involvement of the left renal artery was a significant factor in univariate analysis, but multivariate analysis showed no statistical significance. We think that involvement of renal artery may not imply hypoperfusion on kidney. Different types and degrees of artery involvement might result in diverse effects on renal blood flow and renal function. In addition, early Intervention might improve the renal outcomes, such as adequate volume loading and emergency surgery.