

Peer Review File

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Reviewer A

Comment 1. There is a significant selection bias in the analysis. The patients in LVH group had lower median BMI, hemoglobin and more frequent renal dysfunction. Moreover, patients with LVH were more likely to experience cardiac tamponade and decreased left ventricular ejection function. These factors may worsen the clinical results in patients with LVH. The baseline variables should be adjusted using some techniques such as propensity score or weighting.

Reply 1: Thanks for the valuable advice. To reduce the potential confounding, propensity score matching in a 1:2 ratio was applied based on logistic regression. Clinical features and in-hospital outcomes after matching were summarized in Table 6, and we performed univariable logistic regression analyses for cases after matching (table 7). Covariates included in matching were as follows: cardiac tamponade, hyperlipidemia, Penn classification, emergency surgery and renal dysfunction. Changes in the text: table 6, table 7, page 11 L221-page 12 L 239.

Comment 2. “43.6% of patients with LVH underwent surgical repair within the first 24 hours of admission, while 37.7% of patients without LVH underwent emergent surgery.” Is this truly possible in the setting of acute type A aortic dissection?

Reply 2: Thank you for your comments. Despite the extremely high mortality of untreated ATAAD, surgical repair brings a substantial economic burden to patients as well, especially for patients with poor financial situations. Although immediate surgery was strongly suggested for every ATAAD patients, patients would receive aggressive medical therapy in the intensive care unit before obtaining consent for a procedure. In addition, about two thirds (128/193) patients were transported from other hospitals. In fact, most ATAAD patients in this series receive surgical repair within 3 days of admission, with only 9% (18/193) patients receiving surgery within 3-7 days of admission. Changes in the text: none.

Comment 3. Diagnosing hypertension is unacceptable. Authors listed that there was no statistical difference in the proportion of patients with hypertension. However, how diastolic BP can be higher in the LVH group?

Reply 3: Thanks for the reminder. Diagnosis of hypertension was added in the revised version (page 6 L 96-100). Despite the different diastolic BP in the LVH group, ATAAD patients might have taken antihypertensive agents before admission, especially for patients transported from other hospitals. Therefore, BP levels on admission deliver limited information about BP control status due to the possible antihypertensive agents using before admission might cover up some important information.

Changes in the text: page 6 L 96-100.

Comment 4. Categorization depending on the left ventricular remodeling is not right because left ventricular remodeling is an outcome. In addition, what is the core message through this supplementary categorization? It is hardly understandable.

Reply 4: We are sorry for causing your confusion. The original intention for the introduction of LVR was to compare in-hospital outcomes among different stages of left ventricular damage mediated by hypertension, as LVR was utilized for an early diagnosis of LVH. However, LVMI seemed to be better in reflecting the heart changes as a continuous variable. Therefore, we delete the LVR group analysis. Models based on LVMI were presented in Figure 1 B and Figure 2 B, and we believed that LVMI performed better than LVR in predicting postoperative outcomes.

Changes in the text: Figure 1, Figure 2, Supplementary Table 2, Supplementary Table 4, page 12 L 241- page 13 L262.

Comment 5. Table 4. Early clinical outcomes normally compared with logistic regression. Categorical comparison for clinical outcomes using fisher's exact test does not offer any additional information.

Reply 5: thanks for the reminder. clinical outcomes data in table 4 has been moved into table 3 in the revised version, and logistic regression results after matching were present in table 7. We believed the revised table 7 summarized the regression results of LVH and LVMI for postoperative outcomes.

Changes in the text: table 7, page 12 L 231-239.

Comment 6. The authors should check and provide collinearity. In addition, too many variables were included multivariable analysis.

Reply 6: we apologize for the mistake. Collinearity analyses for multivariable models were provided in Supplementary Table 3 and Supplementary Table 5 with tolerance and variance inflation factor for each variable included in the model. We also changed table 5, now only indicators with $p < 0.05$ were included in the multivariable analysis.

Changes in the text: Supplementary Table 3, Supplementary Table 5, table 5.

Comment 7. No information on the nomogram constructions. Please describe this in the method. What is difference of model 2 compared with model 1? This also should be included in the method.

Reply 7: we apologize for the mistake. Variables selection for model development was described in page 7 L 132-135, and interpretation of the nomogram model was added in page 12 L 245- page 13 L 248. The original model 1 and model 2 were introduced to compare in-hospital outcomes among different stages of left ventricular damage, which has been replaced with continuous variable LVMI. Therefore, we deleted model 1 and model 2. Model LVH and model LVMI were showed in revised figure 1 and figure 2.

Changes in the text: page 7 L 132-135, page 12 L 244- page 13 L 248, Figure 1, Figure 2.

Comment 8. "Ischemia (Penn Classification Ac, or Ab&c) and increased CPB duration made the greatest contribution to CMO in tAaAD patients after surgery in both model 1 and model 2. LVH/LVR, hyperlipidemia, and emergency surgery made a similar contribution to postoperative CMO.?" There is no explanation on how the authors interpret the nomograms. Please provide in the method and results.

Reply 8: thanks for the reminder. the interpretation of the nomogram model was added in page 12 L 245- page 13 L 248. As visualized regression results, each variable was assigned an exact point as indicated at the top of the point scale. The total point represents the probability of postoperative. Changes in the text: page 12 L 244- page 13 L 248, figure 1, figure 2.

Reviewer B

Comment 1. The key question to ask is if this is a risk factor that is modifiable and if there is anything different that can be done. LVH occurs commonly secondary to hypertension which is a common risk factor for ATAAD so it is to be expected that a high prevalence in ATAAD patients (nearly 30% in this series). It would be worth noting if the authors did anything differently during the conduct of the operation in the setting of LVH. For example, cannulation strategy, different cooling temperature, different myocardial protection strategies. Because if there is nothing different than can/should be done knowing that LVH is present, then this finding is of less significance.

Reply 1: Thanks for your valuable comment. Due to the single-center retrospectively designed nature of this study, limited variables were comparable. In table 3 we compared different cannulation strategies between two groups, including the femoral artery, axillary artery and femoral artery & axillary artery. However, moderate hypothermic circulatory arrest and antegrade Custodial-HTK solution were applied for surgical repair in our center, therefore current data was not enough to compare the protective effect of different surgical techniques for LVH patients, a prospective study might provide valid evidence for cooling temperature and myocardial protection strategies choosing for LVH ATAAD patients.

Changes in the text: table3, page 7, L 115-117.

Comment 2. It is interesting that the multivariable analysis characterized hyperlipidemia (OR 3.2) and LVH (OR2.7) both of which are unmodifiable as a similar risk factor to emergency surgery (OR 3.0) which would be expected to be higher.

Reply 2: Thanks for your comment. Hyperlipidemia is a common risk factor for cardiovascular diseases, including CHD and aortic disease. Previously study demonstrated an increased risk for in-hospital adverse cardiac events in hyperlipidemic patients after cardiac surgery, including cardiac

death, perioperative myocardial infarction and ventricular tachyarrhythmias (10.1016/j.jtcvs.2007.07.029; 10.1016/j.jjcc.2016.12.001). Lipid-lowering agents were proved to be effective in reducing mortality for patients undergoing cardiac surgery (10.1016/j.jtcvs.2010.08.002), however, high fat diet also prevented post-CPB AKI in swine (10.1186/cc13092). Hyperlipidemia might indicate other associated metabolic disorders, including obesity or insulin resistance. Thus, complex interactions exist between hyperlipidemia and cardiac surgery.

Despite that operation was suggested for ATAAD patients presenting within 48h of onset, emergency surgery was defined as surgical repair performed within first 24h of admission in this serie, because exact onset-surgery hours of some patients transported from other hospitals were unavailable. For patients attended to our hospital first, 86% (56/65) ATAAD patients received surgery within 48h of admission and 51% (33/65) ATAAD patients received surgery within 24h of admission. Therefore, the risk of emergency surgery might be underestimated in this series. Nevertheless, emergency surgery was still a strong predictor of poor outcomes, as showed in figure 1 and Supplementary Table 2.

Changes in the text: figure 1 and Supplementary Table 2.

Comment 3. Minor: would change the abbreviation of acute type A aortic dissection (ATAAD) which is more commonly accepted in the literature than (tAaAD).

Reply 3: Thank you for the reminder. The text has been modified as advised. We apologize for our mistake.

Changes in the text: abstract, introduction, methods, results and discussion.

Comment 4. Lines 60-62. I believe that the authors mean Bentall “procedure” and Wheat “procedure” and the term “etc.” should be replaced with something else more formal.

Reply 4: Thank you for the reminder. The text has been modified as advised.

Changes in the text: page 4 L64-65.

Comment 5. How much do the authors believe that the LVH is a surrogate of hypertension and more LVH is associated with more renal or neurologic disease or vulnerability to morbidities in those organ systems which explains the worse outcomes?

Reply 5: Thanks for your valuable comments. We performed univariable logistic regression analyses after adjusting based on propensity score matching in table 7, to estimate the potential association between LVH/LVMI and main postoperative events. After matching, LVH was a risk factor for CMO (OR: 2.769, 95% CI: 1.207-6.354, p=0.016). Increased LVMI was associated with several postoperative events, including CMO, CRRT, cardiac events, tracheotomy and atrial fibrillation. These results indicated that LVH might induce worse outcomes via potential renal and heart damage.

Changes in the text: table 7, page 12 L 231-239.

Comment 6. LVH was measured as LVMI as >115 for men and >95 for women. This makes LVH a binary- yes or no- phenomenon. Instead, it would be worth knowing if increasing severity was associated with worse outcomes. It would be worthwhile to run LVH as a continuous variable to see if more LVH was associated with worse outcomes.

Reply 6: Thank you for your valuable and constructive advice. We performed logistic regression analysis and developed nomograms based on LVMI as a continuous, which provide an estimate for patients with different LVMI. Models based on LVMI were presented in Figure 1 B and Figure 2 B, as increased LVMI, which indicated a severe LVH, was associated with a higher risk of poor outcome. Details of nomogram models were summarized in Supplementary Table 2 and Supplementary Table 2. Changes in the text: Figure 1, Figure 2, Supplementary Table 2, Supplementary Table 4, page 12 L 243- page 13 L262.

Comment 7. It's not clear to me what the distinction is with LVH vs. LV remodeling that the authors wish to differentiate. How is LVH different than LVR?

Reply 7: We are sorry for causing your confusion. The original intention for the introduction of LVR was to compare in-hospital outcomes among different stages of left ventricular damage mediated by hypertension, as LVR was utilized for an early diagnosis of LVH. However, LVMI seemed to be better in reflecting the heart changes as a continuous variable. Therefore, we delete the LVR group analysis. Models based on LVMI were presented in Figure 1 B and Figure 2 B, and we believed that LVMI performed better than LVR in predicting postoperative outcomes. Changes in the text: Figure 1, Figure 2, Supplementary Table 2, Supplementary Table 4, page 12 L 243- page 13 L 262.

Comment 8. It is notable in Table 3 that 60% of patients had surgery for ATAAD more than 24 hrs later. This seems to be a higher proportion than normal. Can the authors explain the delay?

Reply 8: Thank you for your comments. Despite the extremely high mortality of untreated ATAAD, surgical repair brings a substantial economic burden to patients as well, especially for patients with poor financial situations. Although immediate surgery was strongly suggested for ATAAD patients, patients would receive aggressive medical therapy in intensive care unit before obtaining consent for a procedure. In addition, about two thirds (128/193) patients were transported from other hospitals. In fact, most ATAAD patients in this series receive surgical repair within 3 days of admission, with only 9% (18/193) patients receiving surgery within 3-7 days of admission.

Changes in the text: none.

Comment 9. Do the authors have data on aortic size at presentation? Is there anything to support earlier

elective aortic surgery for patients with more significant degrees of LVH?

Reply 9: We did provide maximum ascending aortic diameters in table 3 (41.9 ± 7.6 mm for LVH vs. 40.9 ± 8.0 mm for nVLH, $p=0.448$). There seems no significant difference in ascending aortic diameters between two groups. However, additional information of aortic geometry was not compared in this study. As previously reported by Alberto Milan (10.1097/HJH.0000000000001844), LVH was associated with ascending aorta dilatation. Nevertheless, there is no direct evidence supporting earlier elective aortic surgery for LVH patients as far as we know.

Changes in the text: none.