Author’s response to reviews

Title: Preoperative uric acid predicts in-hospital death in patients with acute type A aortic dissection

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Author’s response to reviews:

Dear editors:

We would like to thank the editor for giving us a chance to revise the manuscript, and also thank the reviewers for giving us constructive suggestions which would help us in depth to improve the quality of the paper. Here we submit a new version of our manuscript with the title “Preoperative uric acid predicts in-hospital death in patients with acute type A aortic dissection”, which has been modified according to the reviewers’ suggestions. Efforts were also made to correct the mistakes and improve the English of the manuscript. We marked all the changes in red in the revised manuscript, and we also responded point by point to reviewer comments as listed below.

The following is a point-to-point response to the reviewer comments.
Reviewer 1:

- After analysis all data, you regard serum UA was an independent predictor for type a aortic dissection. The serum UA and Creatinine /BUN / were associated with kidney function, the survival group and no-group were different in several factor include UA /Creatine /BUN/D-dimer/Fibrinogen/plaelet and so on. the procedure and clamp time is different between two group. so i just regard no UA is predictor factor. the kidney function or the patient with low perfusion syndrome was the independent predictor, so what do you opinion?

- Answer: Thanks for the suggestion. We added preoperative eGFR<60ml/min/1.73 m2 and other variables reflecting organ ischemia (brain ischemia, coronary artery involvement and lower limb ischemia) to our model in the revised manuscript. After multivariate logistic regression analysis, serum UA was still a risk factor independent of preoperative kidney function and low perfusion syndrome.

- Changes: New variables reflecting organ ischemia were added to the regression model in the revised manuscript.

Reviewer 2:

- 1) Even if there is some association the question is why to analyze such an association if there are some meta-analyses available and provide the evidence on the UA and cardiovascular mortality. 2) What should we do with these results? How should we improve our clinical practice based on these results? When it comes to the aortic dissection, there are few known strong predictors of mortality. The question is how these results would add on the top of what we already know and how should we improve our practice having these results on mind?

- Answer: Thanks for the suggestion. Aortic dissection surgery is different from other regular cardiovascular surgery since it requires deep hypothermic circulatory arrest. Although there are evidences suggested that UA is a predictor of mortality for coronary artery bypass grafting and cardiac valve surgery, the relationship between UA and mortality after aortic dissection surgery, especially in those patients underwent deep hypothermic circulatory arrest, is still needed to be explored. The results of our present study could help to build a risk score system for aortic dissection surgery, and further indicates that targeting oxidative stress and inhibiting xanthine oxidoreductase might be a potential way to reduce the operation mortality.
- Power analysis should be done and sample size should be calculated so to give us an answer whether our database has enough patients to address our research question? This study has a particular focus on the subgroup of patients that underwent "total arch replacement". Therefore, we need to know if the study is adequately powered for analyses authors performed.

- Answer: Thanks for the suggestion. We performed power analysis using PASS 15 software for our data. In the overall patient population (n=186), group sample sizes of 40 and 146 achieve 92.899% power to reject the null hypothesis of equal means with a significance level (alpha) of 0.050 using a two-sided two-sample unequal-variance t-test. In the subgroup of “total arch replacement” (n=106), group sample sizes of 30 and 76 achieve 98.530% power to reject the null hypothesis of equal means with a significance level (alpha) of 0.050 using a two-sided two-sample unequal-variance t-test. The power analysis suggested that for the overall population and the subgroup of “total arch replacement”, our sample size was adequate.

- Changes: The results of power analysis were added to the “Result-subgroup analysis” section.

- How would authors explain that UA was associated with higher mortality in arch surgery, but that was not the case for ascending aorta? Again, the power analysis may actually give the answer.

- Answer: Thanks for the suggestion. In the subgroup of “ascending aorta/hemiarch replacement” (n=80), Group sample sizes of 10 and 70 achieve 7.504% power to reject the null hypothesis of equal means with a significance level (alpha) of 0.050 using a two-sided two-sample unequal-variance t-test. The power analysis suggested that the sample size of this subgroup did not provide the adequate power to support the negative conclusion.

- Changes: The results of power analysis were added to the “Result-subgroup analysis” section. A paragraph discussing the limitation of the present study was added to the discussion section.

- Discussion is well researched, however, serious methodological drawbacks are not addressed.

- Answer: Thanks for the suggestion. A paragraph discussing the limitation of the present study was added to the discussion section.
Reviewer 3:

- I would like to see the patients' preoperative diagnoses discriminated. This may help to understand mortality and other data found in the article. I would like the author to discuss further the other factors that were determinants of mortality. I'm wondering if would be possible to create a risk Bentall Score?

  - Answer: Thanks for the suggestion. We added other variables including chronic kidney disease, prior aortic stent implant, prior cardiac surgery, number of entry tears, organ ischemia (brain, coronary artery involvement, lower limb, eGFR<60ml/min/1.73 m2) in the revised manuscript.

  - Changes: New variables were analyzed in the revised manuscript.

Reviewer 4:

- Many risk factors were missing in the regression model. Since the outcome was in-hospital mortality, several important variables, such as coronary artery involvement (preop MI/ST-T elevation), malperfusion (AKI, intestinal ischemia..), CKD, transfusion, Marfan or other connective tissue diseases, prior cardiovascular surgery, number of entry tears, emergent vs urgent procedure, surgeons' experience, should be included in the analysis. Lacking these factors may very likely bias the results.

  - Answer: Thanks for the suggestion. We added variables including chronic kidney disease, prior aortic stent implant, prior cardiac surgery, number of entry tears, organ ischemia (brain, coronary artery involvement, lower limb, eGFR<60ml/min/1.73 m2) in the revised manuscript. The variable “onset to operation time” could partially represent urgency of the operation.

  - Changes: New variables were added to the regression model in the revised manuscript.

- Total arch, hemiarch replacement, and Bentall should be treated as a single categorical variable, since they were mutually exclusive.

  - Answer: Thanks for the suggestion. We bring in a categorical variable “extent of aortic replacement” (total arch replacement was defined as “1”, hemiarch replacement was defined as “2”, ascending aortic replacement was defined as “3”) in the revised manuscript. Bentall is a procedure for aortic root, which could be applied either in total arch replacement or ascending aortic/hemiarch replacement, thus was still treated as an independent variable.

  - Changes: A categorical variable “extent of aortic replacement” was introduced in the revised manuscript.
Using forward selection method to determine the variables included in the multivariate analysis is not ideal. Confounders and other factors related to in-hospital mortality should be included (i.e., based on science approach).

Answer: Thanks for the suggestion. The limitation of the present study is small sample size, while there are massive variables that might related to the operation mortality. In such situation, stepwise conditional regression is more suitable to create a predictive model.