Author’s response to reviews

Title: Metabolic Syndrome Increases Operative Mortality In Patients With Impaired Left Ventricular Systolic Function Who Undergo Coronary Artery Bypass Grafting: A Retrospective Observational Study

Authors:
Shuangkun Chen (757450275@qq.com)
Jiahui Li (lijiahui@tom.com)
Qianzhen Li (doctorlqz@163.com)
Zhiquang Qiu (qzlflm@126.com)
Xijie Wu (wuxijie@tom.com)
liangwan chen (chenshuangkun@tom.com)

Version: 1 Date: 28 Nov 2018

Author’s response to reviews:

Dear Editors and Reviewers:

Thank you for the opportunity to resubmit our revised manuscript. We thank you and the reviewers for your constructive suggestions and comments. Our point-by-point answers to the reviewers’ comments are below, with amendments highlighted in yellow.

We hope that the revised manuscript is now acceptable for publication. We look forward to hearing from you.

The main corrections in the paper and the responds to the reviewer’s comments are as flowing:

Reviewer 1#

General comments:
Q: An English proof-reading would be useful.
A: As the Reviewer's good instruction, we have tried our best to revise the English of the whole MS carefully. We hope that the language is now acceptable for the next review process. Special thanks to you for your good comments.
Q: I found it questionable that Urgent/emergency operation and Heart failure which were the factors with the highest association with post-operative mortality on univariate analysis (and the most clinically relevant) to become non-significantly associated with it in multivariate analysis. I recommend the analysis to be run through again to make sure of the results, and to use patients with NYHA class III/IV in these analyses instead of Heart failure.
A: Thank you for your advice. After running through the analysis again, we have arrived at the same conclusion: both urgent/emergency operation and patients with NYHA class III/IV did not increase mortality after CABG.

Q: There were more urgent/emergency operation in MetS group (although not statistically significant because of the low numbers), higher intubation time, more frequent use of IABP, and more frequent NYHA III/IV. All these factors pointed at that MetS group contains less hemodynamically stable patients which could have affect the prognosis rather that MetS itself.
A: Special thanks to you for your good comments. As the article notes (line 51-53 and line 172-178), MetS and its components acted as a combined risk factor for operative mortality, may lead to greater infarct size, resulting in LV dysfunction. Poor prognosis might be triggered by the unfavorable effects of MetS on left ventricular (LV) function. Therefore, MetS group contains less hemodynamically stable patients is explainable.

Specific comments:

Methods:
Q: Line 62: When was the echo done preoperatively because there is a difference if the echo is within 2-4 weeks or one year ago?
A: Echocardiographic results were obtained within 2 weeks prior to surgery in all patients. We have described this in the new manuscript.

Q: How many patients were excluded because of lacking LVEF measurements, and what is the distribution of MetS in this population?
A: We are sorry for the confusion. No patients were excluded because of lacking LVEF measurements.

Q: In statistical analysis section, you should specify which measure of relative risk you are using, in your case you are using logistic regression test which yield Odds ratio as a measure of the relative risk, this should also be clear in Tables 4 and 5, to write Odds ratio instead of relative risk.
A: We thank the reviewer for these good suggestions. We have modified the descriptions as to measure of relative risk we are using in the revised manuscript.

Results:
Q: In table 1 there was a significant difference in the no. of patients with Heart failure NYHA III/IV, this was not commented on in the results. This factor is very important for the outcomes.
A: Sorry for the error. As your mentioned, there was a significant difference in the no. of patients with Heart failure NYHA III/IV. We have described this in the new manuscript.

Q: In non-diabetic patients, when comparing the 2 groups, did you insure that the MetS patients do not have DM as part of their MetS criteria, it is not clear form the results?
A: Patients were considered to have MetS when 3 or more of the following 5 criteria: 1) obesity, defined as a body mass index (BMI) >25 kg/m2 based on the established Chinese criteria for obesity;
2) fasting glycemia ≥6.1 mmol/l or treatment with oral hypoglycemics or insulin; 3) triglycerides ≥1.69 mmol/l; 4) high-density lipoprotein (HDL) cholesterol <1.04 mmol/l in men and <1.29 mmol/l in women; and 5) blood pressure >130/85 mmHg or treatment with antihypertensive medication. In our study, about 49.4% MetS patients do not have DM as part of their MetS criteria (Table 1). We have described this in the new manuscript.

Q: The paragraph from line 136 "Mets was associated …" to the end of the results is very confusing with unnecessary repletion of comparison with the same group of patients (with no MetS and no DM). I would suggest it to be written more clearly and more simple, for example: in patients without DM, MetS was associated with higher risk of mortality whether DM was part of MetS or not (put numbers), while in diabetes patients MetS was not associated with higher risk (put numbers)
A: Thank you for your advice. The relevant descriptions has made an amendment in the new manuscript.

Discussion:
Q: Line 147-148, you should add references for the studies which studied the prevalence of MetS in CABG patients.
A: We have added references for the studies which studied the prevalence of MetS in CABG patients.

Q: Lines 174-175 "Our findings suggested that metabolic abnormalities associated with MetS might be key factors in CAD progression". There is nothing in your results which can support this claim.
A: We agree the reviewer's good advice. Although past clinical studies have demonstrated that metabolic abnormalities associated with MetS might be key factors in CAD progression, but the claim are simply unsubstantiated in the manuscript. We have removed this claim.

Q: Line 188, you need a reference to say that patients with MetS are not being treated appropriately.
A: Thank you for your advice. We have added a reference to demonstrate that patients with MetS are not being treated appropriately.

Q: Throughout the discussion, the authors concentrating about the primary prevention/treatment of MetS which is out of the scope of this study. To improve that, the focus should be on the patients with MetS who are referred to CABG.
A: It is really true as the Reviewer suggested that the discussion section should be focus on the patients with MetS who are referred to CABG. Thus, we have made corrections according to the Reviewer’s instructions. We have deleted the sentences which out of the scope of this study “For instance, CAD events in patients with MetS may be preventable and modifiable through optimal control of lipids, blood pressure, blood glucose and body weight. Considering that multiple pathogenic factors are involved in the effects of MetS on operative mortality, multifactorial intervention in MetS is required for the secondary prevention of CAD”, and added more relevant descriptions “For instance, multifactorial intervention in patients with MetS who are referred to CABG is required for improving poor prognosis, including optimal control of lipids, blood pressure, blood glucose and body weight”.

Q: In line 141 it is written that cardiac cause of death was 40%, while in the discussion line 179 it is written that most of deaths were of cardiac cause. What was the definition of cardiac death, and how it was confirmed?
A: We are very sorry for our negligence of describing what was the definition of cardiac death. Cardiac death is when the heart has been damaged so much that it is unable to supply enough blood to the organs of the body, and leading to death finally. Cardiac death may be secondary to multiple causes, which include ventricular fibrillation, myocardial infarction, low cardiac output syndrome and so on.
The most common cause of death was cardiac in 40% of the cases (6 deaths in all 15, 2 patients died from ventricular fibrillation, 4 patients died from low cardiac output syndrome). All these concentrations have been added in the revised manuscript (Table 6).

Q: From line 186 to 188 not relevant talking about preventive measure for MetS in CAD patients.
A: It is really true as the reviewer suggested that the relevant descriptions should not be included in the discussion. Therefore, the relevant descriptions has made an amendment in the new manuscript.

Table 1:
Q: Can you please explain how is that all of the study patients have LVEF<50% and 34.7% of them with NYHA class III/IV yet only 8.9% had heart failure?
A: “heart failure” refer to less heamodynamically stable (NYHA class IV) in the manuscript. As the Reviewer’s good advice, we have used “patients with NYHA class III/IV” in univariate and multivariable analyses instead of “Heart failure”.

Table 3:
Q: In the table title it is written ”in-hospital outcomes” but in the table is written 30-days mortality, were all patients admitted for 30 days?
A: We are very appreciated for the Reviewer good comments and corrections made for our manuscript. Indeed, not all patients admitted for 30 days. Thus, we have made corrections according to the Reviewer’s good instructions. We have modified “30-days mortality” to “in-hospital mortality ” in the new manuscript.

Table 4:
Q: Does the heart failure used in this table refer to that patients who were known with heart failure before the CABG or refer to those with NYHA III/IV which are mentioned in table 1. I think it is more relevant to use those with NYHA III/IV, also in multivariate analysis.
A: Heart failure used in the table refer to that patients who were known with NYHA class IV before the CABG. As the Reviewer's good advice, we have used “patients with NYHA class III/IV” in univariate and multivariable analyses instead of “Heart failure”, and we reached similar conclusions: patients with NYHA class III/IV was not associated with higher risk operative mortality.

Q: It is very hard to believe that DM is not associated with increased risk of mortality while hyperglycemia without DM is associated with increased risk.
A: We are very pleasure to answer the question. We have checked the data carefully, but the results that “DM is not associated with increased risk of mortality while hyperglycemia without DM is associated with increased risk” was indeed applicable through univariate analysis. This result may be due to the lack of awareness of diabetes in some patients and the acute stress reaction of myocardial infarction.

Table 5:
Q: In the method section it is written that factors with p <0.05 on univariate analysis were chosen to enter the multivariate analysis. In univariate analysis: HDL-cholesterol and fasting glycemia had a P<0.05, and it is not clear if they were used in the multivariate analysis. If they were used, this could lead to overfitting the model because they are components of MetS.
A: According to the Reviewer's good instruction, we have used HDL-cholesterol and fasting glycemia in the multivariate analysis. However, we get the same conclusion: MetS was strongly associated with an increased incidence of in-hospital mortality, but both HDL-cholesterol and fasting glycemia did not increase mortality. In order to avoid overfitting the model, HDL-cholesterol and fasting glycemia were not used in the multivariate analysis.
Conclusion:
Q: Line 208 I suggest to change "individuals" to "patients" and omit "frequently"
A: we have revised this sentence in the revised manuscript according to the Reviewer's advice.

Q: Line 210 I suggest to omit "have" so the sentence become "did not increase"
A: we have made corrections according to the Reviewer’s good instructions.

Q: Lines 212-214 from "Multifactorial" to "pharmacological intervention" are out of the scope of this study, therefore should not be included in the conclusion.
A: It is really true as the reviewer suggested that the relevant descriptions should not be included in the conclusion. we have deleted the irrelevant contents in the new manuscript.

Reviewer 2#
Q: In the Discussion section, the statement 'CAD events' is incorrect. Instead, it is more accurate if 'cardiovascular events'.
A: We have deleted the statement “CAD events”, and using "cardiovascular events" to express more accurate meaning.

Q: It appears to be that 4 and 21 references are written the same. It needs to be corrected.
A: Sorry for the error. We have made corrections according to the Reviewer’s instruction.