Author’s response to reviews

Title: Hospital mortality in acute coronary syndrome: adjustment of GRACE score by D-dimer enables a more accurate prediction in a prospective cohort study

Authors:

Tongtong Yu (workhard31@vip.163.com)
Yundi Jiao (jiaoyundi1987@163.com)
Jia Song (836214497@qq.com)
Dongxu He (1570057021@qq.com)
Jiake Wu (wujiake1107@163.com)
Zhijun Sun (sunzj@sj-hospital.org)
Zhaoqing Sun (sunzhaoqing@vip.163.com)

Version: 1 Date: 15 Aug 2019

Author’s response to reviews:

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled "Hospital mortality in acute coronary syndrome: adjustment of GRACE score by D-dimer enables a more accurate prediction in a prospective cohort study" (BCAR-D-19-00134). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. All changes in the text are marked in YELLOW HIGHLIGHT. The main corrections in the paper and the responds to the reviewer’s comments are as flowing:

Responds to the reviewer’s comments:

1. Response to comment (Technical Comments): (In the revision, please address the following:

1. Title page: Provide email of all authors (aus)
2. Authors Contributions: Use name initials for all aus
3. Funding: Role of funder
4. Transfer embedded figure legends after the reference
5. Acknowledgements: Missing
6. Rename Introduction to Background)

Response: Thank you for your comment. We have addressed the all things.

2. Response to comment (Reviewer 1): (1. The grammar of the manuscript will need major revision.)

Response: Thank you for your comment. We have invited an English native speaker to make a thorough revision of the written English throughout the manuscript.

3. Response to comment (Reviewer 1): (2. The exclusion of patients who received prior heparin before d-dimer suggest potential selection bias with exclusion of higher-risk patients.)

Response: Thank you for your comment. Indeed, some high-risk patients were excluded because of the use of unfractionated heparin or low molecular weight heparin, especially which were recommended for most high-risk patients at the early stage. We total agree with the potential selection bias. However, the use of heparin must be considered when studying D-dimer. We tried our best to reduce the bias, for example: we just excluded the patients whose samples collected within 5 hours after use of unfractionated heparin or 12 hours after use of low molecular weight heparin. Moreover, we have stated it in the “Limitations” section to improve the paper.

4. Response to comment (Reviewer 1): (3. Would be interesting to know the spread of d-dimer values, and also the range of d-dimer values for the three groups of patients (low, intermediate, high d-dimers). It would have been clinically more useful to have a cut-off value of d-dimer to identify the patients at the highest risk of in-hospital mortality. Also, I do not believe that classification of patients into three tertiles of d-dimers would be clinically relevant. It would have been more interesting to have a cut-off value of d-dimer which predicts the most in-hospital mortality.)

Response: Thank you for your comment. We think this comment is a great of value for our study. Also, this study has these things. The all individuals were divided into three groups according to the tertile of D-dimer level on admission (Low D-dimer group: ≤88 ng/mL [n=1975]; Intermediate D-dimer group: 89-179 ng/mL [n=1974]; High D-dimer group: >179 ng/mL [n=1974]), which was stated in the “Method” part. The cut-off values for D-dimer was 212 ng/mL with a sensitivity of 0.698 and a specificity of 0.724, which was stated in the “Results” part.

5. Response to comment (Reviewer 1): (4. The relationship of d-dimer with in-hospital mortality is also not well shown, linear, exponential, u-cu...Can the authors elaborate more on this.)

Response: Thank you for your comment. The univariate Logistic regression analysis showed that D-dimer was significantly predictive of in-hospital mortality (OR: 1.069, 95% CI: 1.046 – 1.093, p < 0.001, for per 100 ng/mL increase) (Table 2). After adjusting for covariates, D-dimer was still associated with in-hospital mortality. The result showed an increased in-hospital mortality risk of 6.0% for per 100 ng/mL increase in D-dimer concentration (OR: 1.060, 95% CI: 1.026 - 1.094, p < 0.001) (Table 2). Thank you again!
6. Response to comment (Reviewer 1): (5. Statistical expertise highly recommended for closer look of the comparison of the roc curves of the grace and grace+d-dimer. On the figure 2, the 2 curves look super-imposed, so I am not convinced that there are true differences between the 2 curves.)

Response: Thank you for your comment. We think this comment is a great of value for our study. The closer look of the comparison of the roc curves of the grace and grace+d-dimer came from the ‘p’ values. p=0.023 for C-statistic; p=0.032 for IDI; p=0.035 for NRI. They were all larger than 0.01. They were not very significant, but still significant (they were all smaller than 0.05). Thank you again!

7. Response to comment (Reviewer 1): (6. Why inclusion of only patients with PCI and not all patients with ACS?)

Response: Thank you for pointing this out. It has been confirmed that PCI can improve the prognosis of ACS patients. The number of ACS patients receiving PCI is increasing in China. ACS patients receiving PCI are already a big subgroup in ACS patients. So, we think assessing the relationship between D-dimer and in-hospital mortality in patients with ACS undergoing PCI is useful for the clinical practise.

8. Response to comment (Reviewer 2): (7- When testing the association between D-dimer and mortality, I suggest a parsimony model including predictors associated with a p-value < 0.1 as reported in table 1 to improve precision and avoid over-fitting.)

Response: Thank you for pointing this out. Table 1 just showed the difference among three groups. Appendix S1 showed the effects of the variables on in-hospital mortality in Univariate Analysis. We added three variables (History of Hypertension, Dyslipidemia and Platelet count) to the multivariable Logistic regression analysis. So, all variables with p<0.1 on univariate analysis in Appendix S1 were entered the multivariate analysis to improve precision and avoid over-fitting. Thank you again!

9. Response to comment (Reviewer 2): (8- Heparin treatment can lower D-dimer levels, this variable (patients with LMWH or heparin vs those without) should be included in the model.)

Response: Thank you for your comment. We did not include the variable (patients with LMWH or heparin vs those without), because all included patients received PCI, and heparin were used in them in our center. If the patients suffered from the end-stage liver or renal failure, known autoimmune diseases or steroid therapy, known malignancy, recent ischemic or hemorrhagic disease, and can not receive heparin, they were excluded in this study. So, the cases included in the study all received LMWH or heparin. At last, we excluded the patients whose samples collected within 5 hours after use of unfractionated heparin or 12 hours after use of low molecular weight heparin to reduce the effect of heparin on the DD. Thank you again!

10. Response to comment (Reviewer 2): (9- What are the "normal" value of D-dimer according to the local lab? I would suggest to test the association of D-dimer ≥ the upper limit of normal value and mortality, and, if statistically significant, derive a novel score by adding some points to the GRACE score for patients with D-dimer ≥ the upper limit of normal value.)
Response: Thank you for your comment. The "normal" value of D-dimer in our lab is less than 252 ng/mL. We also think your idea is great. However, this “normal” value bases on the “normal” people, who are different from the ACS patients included in our study. D-dimer is a marker of coagulation state and thrombosis.[1] Elevated levels of D-dimer are found in conditions associated with thrombosis. [1] ACS was complicated with thrombosis.

Reference:


11. Response to comment (Reviewer 2): (10- Linguistic revision from a native English-speaking medical translator should been done.)

Response: Thank you for your comment. We have invited an English native speaker to make a thorough revision of the written English throughout the manuscript.

12. Response to comment (Reviewer 2): (11- In the discussion section, too many data are reported: par 2 at page 11 seem a par of the results section.)

Response: Thank you for your comment. We have rewritten them.

13. Response to comment (Reviewer 2): (12- The authors should discuss the clinical implication of their finding. Do they suggest to use a new score for mortality risk estimation?)

Response: Thank you for your comment. Basing on our finding, it may be worth to monitor D-dimer in patients with ACS, which may help us identify the ACS patients at high risk. Also, in the future, the adequately powered randomized studies, targeting on attenuation of high D-dimer in ACS patients, should be performed to make sure whether decreasing high D-dimer in ACS patients can improve their prognosis or not. We have discussed them in the discussion section. A new score model including D-dimer is suggested by us. However, it may be inappropriate to get a new score model including D-dimer from this study, since this study comes from a single center and the number of the samples is not large enough. In the future, a multi-center global study should be conducted to get it, just like The Global Registry of Acute Coronary Events (GRACE) score.

14. Response to comment (Reviewer 2): (13- Only two study limitations are reported, whereas there are several limitations: single centre, heparin use, quite all the patients included in the study seem to have D-dimer below the normal value.)

Response: Thank you for your comment. According to your suggestion, we have specified them in the limitation section.

We tried our best to improve the manuscript and made changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in revised paper. We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval. Once again, thank you very much for your comments and suggestions.
Yours
Sincerely
Zhaoqing Sun