Author’s response to reviews

Title: N-terminal pro-brain natriuretic peptide levels had an independent and added ability in the evaluation of all-cause mortality in older Chinese patients with atrial fibrillation

Authors:

Shihui Fu (xiaoxiao0915@126.com)
Jie Jiao (249953590@qq.com)
Yi Guo (guoyi612@126.com)
Bing Zhu (sci6688@126.com)
Leiming Luo (lleim@sina.com)

Version: 1 Date: 08 Nov 2018

Author’s response to reviews:

BMC Geriatrics
November 1, 2018
Response letter

Dear editors:

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript. We appreciate the editors and reviewers very much for their positive and constructive comments and suggestions on our manuscript entitled "N-terminal pro-brain natriuretic peptide levels had an independent and added ability in the evaluation of all-cause mortality in older Chinese patients with atrial fibrillation".

Those comments and suggestions are all valuable and very helpful for us to revise and improve our paper, as well as very important to direct our researches. We have studied those comments carefully and tried our best to revise the paper. Attached please find the revised version, which we would like to submit for your kind consideration.
Responds to the editors and reviewers’ comments:

Editors:

1. In addition to the referee comments, please address the following editorial points: Please copy edit your manuscript throughout. See below for more information.

Thank you very much for your valuable suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. Under your guidance, we made the corresponding modification all through our manuscript.

2. Please provide a complete abstract, with details of your methods.

Thank you very much for your useful suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. Under your guidance, we made the corresponding modification our manuscript. Cox regression analysis was applied to determine the variables independently associated with all-cause mortality.

3. Please provide a code for ethical approval if possible.

Thank you very much for your kind suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. Under your guidance, we made the corresponding modification in the methods of our manuscript. The study was approved by Ethics Committee of Chinese People's Liberation Army General Hospital, China (Number: 038).

Reviewer 1

1. OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)? Yes - there is a clear objective. DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective? Yes - the approach is appropriate. EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results? Yes - experiments and analyses were performed appropriately. INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated? No - there are minor issues. OVERALL MANUSCRIPT POTENTIAL - Could an appropriately REVISED version of this work represent a technically sound contribution? Probably - with minor
revisions. PEER REVIEWER COMMENTS: GENERAL COMMENTS: In this study, the authors describe use of plasma level of N-terminal pro-brain natriuretic peptide (NT-proBNP) measurement in Chinese patients with atrial fibrillation as a predictor of patient prognosis. Cox regression analyses were used to measure the association between NT-proBNP levels and mortality. Similar analyses were used to assess two other measures called CHADS2 and CHA2DS2VASc scores. Combined measures of NT-proBNP with each of these scores as well as a model incorporating several measures, including age, hemoglobin, fasting blood glucose, glomerular filtration rate and NT-proBNP were also used to measure association with mortality. Of all methods, the model described in this study provided the highest c-statistic, suggesting that the model is the best predictor of patient mortality. This study provides important direction toward better predicting patient outcome based on various measures and is overall well-done. My primary concerns with the current manuscript are related to the amount of information provided, as detailed below. REQUESTED REVISIONS: What are CHADS2 and CHA2DS2VASc scores? Please define CHADS2 and CHA2DS2VASc scores or briefly indicate the factors included in these scores within the background sections. This information is needed for the reader to appreciate how these scores differ from NT-proBNP values are scores including these values.

Thank you very much for your valuable suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. Under your guidance, we make the corresponding modification in our manuscript. CHADS2 score includes age, congestive heart failure, hypertension, diabetes mellitus, and prior stroke or transient ischemic attack (TIA). CHA2DS2VASc score includes age, female gender, congestive heart failure, hypertension, vascular diseases, diabetes mellitus, and prior stroke or TIA.

2. Please describe what the ARISTOTLE and RE-LY trials are in the Background section when mentioning these trials.

Thank you very much for your kind suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. Under your guidance, we make the corresponding modification in our manuscript. NT-proBNP levels have been found to be associated with heart failure mortality in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, which consists of 18201 patients with AF treated with apixaban or warfarin. Meanwhile, NT-proBNP levels have demonstrated to be a significant predictor of all-cause mortality in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, which consists of 18113 patients with AF treated with dabigatran or warfarin.
3. In the background section, upon introduction of NT-proBNP, the authors should clarify that the level of NT-proBNP is the aspect of NT-proBNP that is correlated with patient prognosis, as opposed to other aspects of NT-proBNP, such as composition or localization, for example.

Thank you very much for your kind suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. Under your guidance, we added the levels all through our manuscript.

4. What are the "traditional scores" in prognostic evaluation of patients with these cardiovascular diseases that the authors refer to on line 23 of page 4? I assume the authors are referring to CHADS2 and CHA2DS2VASc, but it is not clear.

Thank you very much for your valuable suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. Traditional scores are not referring to CHADS2 and CHA2DS2VASc. Different cardiovascular diseases, such as coronary artery disease and heart failure, had different scores to make prognostic evaluation. NT-proBNP levels can also be applied to improve the roles of these scores in prognostic evaluation of patients with these cardiovascular diseases. Under your guidance, we make the corresponding modification all through our manuscript. N-terminal pro-brain natriuretic peptide (NT-proBNP) is a stable 76-amino acid N-terminal segment of pro-brain natriuretic peptide (pro-BNP), and significantly related to the prognosis in patients with different cardiovascular diseases, including coronary artery disease and heart failure. NT-proBNP levels can also be applied to improve the roles of traditional scores, such as Seattle Heart Failure Score (SHFS), in prognostic evaluation of patients with these cardiovascular diseases.

5. On Line 59 of page 8, the authors refer to the "multinormality assumption" Do you mean multivariate normality assumption?

Thank you very much for your kind suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. Under your guidance, we replaced multinormality assumption with multivariate normality assumption in our manuscript.

6. The details of the model based on NT-proBNP need to be provided. The authors state which factors are incorporated, but what else is involved in this model. What is the formula used to incorporate each of the factors? This information is needed if their model is to be used in further studies or in the clinic.
Thank you very much for your useful suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. What you side is quite right and valuable to clinical doctors. Under your guidance, we made the corresponding modification in our manuscript. The current analysis applied Cox regression analysis to select the variables independently associated with mortality to form a model based on NT-proBNP. As shown in Table 2, hazard ratios of different variables were obtained in the current analysis. They can be applied to develop a formula with these variables to make a prognostic evaluation. However, due to a lack of validation from large-scale studies, it may not be possible to determine this formula at present. In the future study, we will make a validation through large-scale study and report this formula when it has been confirm to be valid.

7. Minor points: Please define all abbreviations on first use. Abbreviations are also missing from the abbreviations section on page 11.

Thank you very much for your valuable suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. Under your guidance, we added the corresponding content in our manuscript.

8. The legend for Figure 1 should indicate that the graph includes c-statistics based on other methods, including the model generated in this study. Only three of the six methods shown in the graph are listed in the figure title.

Thank you very much for your kind suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. Under your guidance, we made the corresponding modification in our manuscript. Legend: Figure 1. Comparison of c-statistics between N-terminal pro-brain natriuretic peptide levels, CHADS2, CHA2DS2VASc scores, and model based on N-terminal pro-brain natriuretic peptide levels.

9. The manuscript should be edited for grammar.

We are very sorry for our unclear description. Thank you for your valuable suggestions very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. Under your guidance, we sought the help of an American expert to edit our manuscript. Certificate was provided by this expert and attached in our submission.
1. This study investigated whether N-terminal pro-brain natriuretic peptide (NT-proBNP) significantly improved mortality prediction in older Chinese patients with AF when added to CHADS2 and CHADS-VASc scores. The paper improved a bit after the correction made by the authors. However, I still think the paper needs improvements before it could be published. In your answer to my first question it is still not clear to me why the CHADS2 and CHA2DS2VASc scores need to be improved.

Thank you very much for your valuable suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. Under your guidance, we make the corresponding modification in our manuscript. Atrial fibrillation (AF) is the most common arrhythmia and has an increased prevalence in older patients, leading to poor prognosis for these patients. There is a need for a biomarker or a model of prognostic evaluation in older patients with AF, especially in China. CHADS2 and CHA2DS2VASc scores have been applied to evaluate their prognosis. But as the commonly applied scores to evaluate thrombotic risk, they are in need of improvement to achieve prognostic evaluation. N-terminal pro-brain natriuretic peptide (NT-proBNP) significantly related to poor prognosis in patients with different cardiovascular diseases, including coronary artery disease and heart failure. Moreover, NT-proBNP levels can also be applied to improve the roles of traditional scores, such as Seattle Heart Failure Score (SHFS), in prognostic evaluation of patients with these cardiovascular diseases. NT-proBNP levels have been found to be associated with heart failure mortality in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. Meanwhile, NT-proBNP levels have demonstrated to be a significant predictor of all-cause mortality in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. An addition of NT-proBNP levels to CHADS2 and CHA2DS2VASc scores or a model based on NT-proBNP levels may provide better methods to predict prognosis in patients with AF.

2. In your answer to my question 4, you stated that you added this information in the manuscript. However, I did not find a change in your text in that sense. Did I miss something?

Thank you very much for your useful suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. Under your guidance, we made the corresponding modification in our manuscript. Blood pressures were measured on two consecutive mornings, in the first afternoon and on two consecutive nights.
3. Answer to question 5: I understand correctly that CHF is 'congestive heart failure', not 'chronic heart failure'? Because in your definition you speak of long-term symptoms and signs? So people with acute heart failure were excluded? In the table you still used EF<40%.

Thank you very much for your useful suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. What you said is quite right. Patients with acute heart failure were excluded from the current analysis. There were patients with congestive heart failure with both congestive heart failure and EF<40%. There were patients with congestive heart failure but not with EF<40% (ejection fraction preserved heart failure). There were patients with EF<40% but not with congestive symptoms and signs (not acute heart failure).

4. I'm afraid your answer to question 6 is very blurry to me. As I stated above the rationale of your study is still not clear to me. Why all-cause mortality? Why the CHADS2 and CHA2DS2VASc scores need to be improved? And here you state they do not need improvement for stroke prediction, but they do for mortality prediction?

Thank you very much for your valuable suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. What you said is quite right. They do not need an improvement for stroke prediction, but they do for mortality prediction. Under your guidance, we made the corresponding modification in our manuscript. As the commonly applied scores to evaluate thrombotic risk including stroke, they are in need of improvement to achieve prognostic evaluation.

5. You report that most the patients died of multiple organ failure. When one out of four patients died of multiple organ failure during follow-up it seems we are dealing with a severely ill population? When performing risk prediction we want to identify a risk population that might benefit from an intervention that lowers the risk. What kind of interventions could help to prevent multiple organ failure? That CHADS2 and CHA2DS2VASc scores give the risk to develop a stroke in people with AF, and to prevent AF we can give anticoagulants. But I do not immediately see how you can translate this to death due to multiple organ failure?

Thank you very much for your kind suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. The current analysis included older patients with a median age of 85 years. There was a high prevalence of multiple organ failure in these patients. Under your guidance, we made the corresponding modification in our manuscript. Comprehensive management of high quality is very important to these patients. Shiwen Wang academician firstly defined multiple organ failure of elderly, and improved their
prognosis through comprehensive management. Model based on NT-proBNP levels could help clinical doctors to identify patients with high risk and poor prognosis, and provide comprehensive management of high quality for them to achieve prognostic improvement.

6. I disagree that you cannot calculate NRI and IDI at this time.

Thank you very much for your useful suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. We have sought the help of statistical experts to calculate NRI and IDI, but they said that the type of variables was not appropriate for NRI and IDI commonly applied for categorical variables. It is still unable to construct points-scoring systems based on an addition of NT-proBNP to CHADS2 and CHA2DS2VASc scores. Thus, it is impossible to observe the reclassification of patients by an addition of NT-proBNP to CHADS2 and CHA2DS2VASc scores, and apply NRI and IDI in the current analysis. The current analysis should be further validated in large-scale studies and different older populations, especially through the methods of net reclassification improvement and integrated discrimination improvement. Under your guidance, we add the corresponding content in our manuscript.

7. I understand this correctly that 100% of your study population received anticoagulation? This sentence is unclear to me. What kind of anticoagulation? Warfarin? DOAC?

Thank you very much for your valuable suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. Under your guidance, we make the modification in our manuscript. All patients received anticoagulation, such as warfarin or antiplatelet drugs. No DOAC has been applied in the current analysis.

8. The implication for practice is still unclear for me.

Thank you very much for your kind suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. Under your guidance, we make the corresponding modification in our manuscript. There has been no widely-accepted model based on a biomarker reflecting cardiac and renal dysfunction in older patients with AF, and there is a need to build a model based on NT-proBNP levels. The current analysis not only provided the evidence of an independent and added ability of NT-proBNP levels in the evaluation of all-cause mortality, but also constructed a model based on NT-proBNP levels to evaluate all-cause mortality in Chinese older patients with AF. Model based on NT-proBNP levels could help clinical doctors to identify patients with high risk and poor prognosis, and
provide comprehensive management of high quality for them to achieve prognostic improvement.

9. What is ‘nearly no’ study? Is there a study or not?

Thank you very much for your useful suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. Under your guidance, we make the modification in our manuscript. To our knowledge, no study has assessed whether NT-proBNP levels improve prognostic evaluation of CHADS2 and CHA2DS2VASc scores, especially in older Chinese patients.

10. I would not mention results in the methods section.

Thank you very much for your valuable suggestion. We are very sorry for our unclear description. What you said is very valuable and helpful for us to improve our paper. Under your guidance, we put them back to results in our manuscript.

11. I would mention the coefficient of variation in the methods section.

Thank you very much for your kind suggestion. We are very sorry for our linguistic problems. What you said is very valuable and helpful for us to improve our paper. Under your guidance, we added the corresponding content in our manuscript.

12. You stated language editing was done, but I do not notice any changes in this perspective?

We are very sorry for our unclear description. Thank you for your valuable suggestions very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. Under your guidance, we sought the help of an American expert to edit our manuscript, and all changes were marked in red in our manuscript. Certificate was provided by this expert and attached in our submission.
We have to apologize for giving you so many troubles because of confusing statements and other problems. We deeply appreciate your consideration and suggestions of our manuscript and look forward to receiving your comments. Your comments and suggestions give us not only the great help in revising the article, but also the significant revelation in our scientific research. Your kind guidance is our good luck. We wonder if the modification could meet your requirements. If you have any queries, please don’t hesitate to contact us.

Thank you and best regards.