Author’s response to reviews

Title: Predictive abilities of cardiovascular biomarkers to rapid decline of renal function in Chinese community-dwelling population: a 5-year prospective analysis

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Author’s response to reviews:

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Response letter

Dear Editors and Reviewers:

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 "Predictive abilities of cardiovascular biomarkers to rapid decline of renal function in Chinese community-dwelling population: a 5-year prospective analysis".

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 study the editors and reviewer's comments carefully and try 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:

Reviewer 1

1. This prospective multicentre analysis, performed in 1680 Chinese study participants which were recruited during a medical check-up program in several health service centers around Beijing, Shihui Fu et al. found a quite high overall median rate of renal function decline (1.46 mL/min/1.73m²/year) in 948 participants which had a follow up of 5 years. The authors found that mostly elderly, female patients and hypertensives experienced a rapid decline of renal function compared with others. In the multivariate analysis homocysteine and NT-proBNP were the only biochemical variables which were able to predict the primary outcome. Of interest arterial stiffness and compliance had no independent predictive power. This is an overall interesting prospective study but suffers from some major methodological flaws. Representative epidemiological studies are based on randomised sampling methods but there is no information provided concerning the selection procedures/selection methods of the study participants.

We are very sorry for the unclear description. Thank you for your valuable suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. This prospective and large medical check-up program was performed in 1680 participants at the health service centers in Beijing. A stratified cluster sampling design was applied in this survey. In the first stage of sampling, three districts (Fengtai, Shijingshan and Daxing) were selected from 18 districts in Beijing. In the second stage of sampling, four communities were selected from these districts. In the third stage of sampling, community-dwelling residents (Han Chinese and older than 18 years) were selected from these communities in the current analysis. There were 181 participants lost, and 1499 participants followed up for 5 years. Exclusion criteria were GFR below 60ml/min/1.73m² (12 participants), missing values for variables (487 participants) and death (52 participants). The final study population was comprised of 948 participants. Under your guidance, we make the corresponding modification in the manuscript.

2. Also although the number of participants lost to follow up was only 181 during follow up, almost 1/3 of the initial participants were excluded from the final analysis due to missing values of several variables rendering the overall study association and conclusions heavily biased and even not applicable. This is a major methodological flaw. Furthermore, no information about the missing participants are provided.

We are very sorry for the problem. Thank you for your kind suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. Although there
were only 181 participants lost during the follow-up of 5 years, 487 participants (30%) were excluded due to missing values for variables, and it was difficult to determine their all variable information. Under your guidance, we make the corresponding modification in the manuscript, and add a limitation paragraph in the manuscript. The current analysis had some limitations. There were 487 participants (30%) excluded due to missing values for variables, and it was difficult to determine their all variable information. However, there were only 181 participants lost during the follow-up of 5 years.

3. A quite remarkable finding is the overall median rate of renal function decline which is 1.46 mL/min/1.73m2/year and seems to be quite high, comparable to diabetic patients with CKD. Do the authors have an explanation for this finding?

We are very sorry for our less clear description. Thank you for your useful suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. Median baseline GFR level was 87.79 (79.27-96.89) mL/min/1.73m2, and median follow-up GFR level was 80.10 (72.02-87.89) mL/min/1.73m2 (p < 0.001 for change). Median rate of renal function decline was 1.46 (0.42-2.91) mL/min/1.73m2/year. As epidemiological results from Chinese community-dwelling population, it is different from data of European and American people. Prevention and therapy of renal function decline in European and American people obviously superior to that in Chinese community-dwelling population, and there was much room for improvement in China. Especially in Chinese community-dwelling population without GFR below 60 ml/min/1.73m2, less attention has been paid to renal function decline, not to say its prevention and therapy. Thank you very much again.

4. Several clinical and biochemical biomarker such as hs-cTnT, cfPWV, cAIx had no statistically impact on the GFR decline but other such as homocysteine and NT-proBNP levels had. What is the relevance of these findings? How can we lower the homocysteine and natriuretic peptide levels in patients at risk for declining GFR?

We are very sorry for the unclear description. Thank you for your valuable suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. The findings of this prospective analysis had public health relevance. Rapid decline of renal function has a growing prevalence in China. Given that there are limited interventions available, public health initiatives are needed for slowing the rapid decline of renal function. This prospective analysis confirmed that elevated homocysteine and NT-proBNP levels contributed to rapid
decline of renal function. Homocysteine might play an etiologic role in renal function decline through injuring the renal blood vessels. As a pro-oxidant, homocysteine could diminish the nitric oxide-mediated vasodilation, promote the thrombosis and impede the fibrinolysis. Elevated homocysteine levels could be a target of future intervention studies to slow the rapid decline of renal function, and folic acid might be a choice in clinical therapy of renal injury. Endogenous NT-proBNP at physiological levels affects the glomerular filtration and renal function. Glomerular hyperfiltration induces the glomerular hypertension and stretches the mesangial cells. Stretched cells secrete the cytokines that stimulate the production of extracellular matrix proteins, accumulation of which promotes the progression of renal injury. Moreover, natriuretic peptide receptor antagonist or angiotensin receptor blockade and neutral endopeptidase inhibition (ARNI, LCZ696) might be useful to prevent the renal injury [23,24]. Therefore, effective monitoring of NT-proBNP levels could play a significant role in slowing the rapid decline of renal function. Future studies are required to determine whether therapies changing the homocysteine and natriuretic peptide levels ultimately affect slowing the rapid decline of renal function. Effects of folic acid, natriuretic peptide receptor antagonist, angiotensin receptor blockade and neutral endopeptidase inhibition (LCZ696) and other medications associated with homocysteine and NT-proBNP levels on renal function are necessary to be paid special attention in pharmaceutical research and clinical practice. Under your guidance, we make the corresponding modification in the manuscript.

5. Originality: As the authors already stated in their work several cardiovascular biomarkers such as homocysteine, N-terminal pro B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) are already been explored in the setting of CKD and known to be elevated and associated with rapid kidney.

Thank you for your valuable comments very much. Your valuable comments are very valuable and helpful for us to improve our paper. As the established cardiovascular biomarkers, homocysteine, N-terminal pro B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) are considered to be elevated in patients with rapid decline of renal function, especially those with ESRD. Previous studies have observed the relationships between cardiovascular biomarkers and renal function decline in patients with glomerular filtration rate (GFR) below 60 ml/min/1.73m2, and yielded the controversial results. However, predictive abilities of cardiovascular biomarkers to renal function decline are more significant in community-dwelling population without GFR below 60 ml/min/1.73m2, and it is essential to analyze this problem in this population. Moreover, these cardiovascular biomarkers might play an etiologic role in renal function decline, and analyzing their relationships could promote the development of preventive strategies to slow the rapid decline of renal function. Predictive abilities can not be fully evaluated by cross-sectional and short-term studies, and long-term
prospective study is an optimal choice to explore the predictive abilities of cardiovascular biomarkers to renal function decline. Moreover, this problem differs between racial groups, and few studies about this problem have been performed in Chinese community-dwelling population. Therefore, aim of this prospective analysis was to evaluate the predictive abilities of cardiovascular biomarkers to renal function decline during the follow-up of 5 years in Chinese community-dwelling population without GFR below 60 ml/min/1.73m2. Thank you very much again.

6.* Scientific reliability/Research Question/Overall design of study /* Participants studied/ * Methods: This main aim of this study is clearly defined in the context of the provided data but the overall design of this study is rather vague since some important information are not adequate presented or missing. Although it is essential to perform long-term prospective study in order to explore and validate the predictive abilities of cardiovascular biomarkers concerning adverse outcomes a sound methodology and completeness of the study variables are equal important.

We are very sorry for the problem. Thank you for your kind suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. We study the editors and reviewer's comments carefully, and then try our best to revise our manuscript and make it more sound and completed. Thank you very much again.

7.Importance of work to other relevant readers: This work provides further insights and information for GFR function decline in a Chinese study population.

Thank you for your valuable comments very much. Your valuable comments are very valuable and helpful for us to improve our paper. Thank you very much again.

8.Ethics: approval was granted and all patients gave their consent for the use of clinical data.

We are very sorry for the unclear description. Thank you for your kind suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. The study protocol was approved by Ethics Committee of Chinese People’s Liberation Army General Hospital, China. Each participant provided written informed consent to be included in the study. Under your guidance, we make the corresponding modification in the manuscript.
9. References: The papers cited are relevant and updated. No glaring omissions of related literature were noted.

Thank you for your valuable comments very much. Your valuable comments are very valuable and helpful for us to improve our paper.

10. Specific comments: This manuscript need extensive language editing. The abstract has to been rewritten since the methodology section does not include crucial information on study design. The results section suffers from the same shortcomings. In the discussion section the reference to the work of other authors has be to adapted.

We are very sorry for the shortage of language. Thank you for your valuable suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. Under your guidance, we seek the help of an American expert to make the appropriate modification in the manuscript.

Reviewer 2:

1. The authors should explain why they used eGFR calculated based on MDRD formula instead of CKD-EPI.

We are very sorry for our less clear description. Thank you for your valuable suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. MDRD equation is more commonly used in clinical practice and epidemiological investigation compared with CKD-EPI equation. Moreover, MDRD formula but not CKD-EPI equation has Chinese modified version (CMDRD). CMDRD equation is more suitable for Chinese community-dwelling population and has superior accuracy than CKD-EPI equation. Under your guidance, we make the corresponding modification in the manuscript, and add a limitation paragraph in the manuscript. The current analysis had some limitations. MDRD equation rather than Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to evaluate renal function in the current analysis. However, MDRD equation is more commonly used in clinical practice and epidemiological investigation compared with CKD-EPI equation. Moreover, MDRD equation but not CKD-EPI equation has Chinese modified version (CMDRD). CMDRD equation is more suitable for Chinese community-dwelling population and has superior accuracy than CKD-EPI equation.
The authors should describe the length of duration of follow up in cases as they enrolled cases during 2007-2009.

We are very sorry for our less clear description. Thank you for your kind suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. Participants were enrolled from May 2007 to July 2009. The follow-up visit was performed from February 2013 to September 2013. Median length of duration of follow-up in cases was 5 years. Under your guidance, we make the corresponding modification in the manuscript.

Editors:

1. If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English. If you would like professional help in revising this manuscript, you can use any reputable English language editing service.

We are very sorry for the shortage of language. Thank you for your valuable suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. Under your guidance, we seek the help of an American expert to make the appropriate modification in the manuscript.

2. Please read the following information and revise your manuscript as necessary. If your manuscript does not adhere to our editorial requirements, this may cause a delay while this is addressed. Failure to adhere to our policies may result in rejection of your manuscript. In accordance with BioMed Central editorial policies and formatting guidelines, all manuscript submissions to BMC Nephrology must contain a Declarations section which includes the mandatory sub-sections listed below.

We are very sorry for the unclear description. Thank you for your kind suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. Under your guidance, we make the corresponding modification in the manuscript.

We have to apologize for giving you so many troubles because of language shortage 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.