Author's response to reviews

Title: Is abdominal aortic calcification superior over other vascular calcification in predicting mortality in hemodialysis patients? A retrospective observational study

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Author's response to reviews: see over
Dear editor,

Thank you very much for your letter on our manuscript entitled “The role of abdominal aortic calcification in predicting mortality in hemodialysis patients: a retrospective observational study”. We appreciate greatly the valuable comments and suggestions by you and the reviewers. We have now revised the manuscript according to the comments and suggestions raised by the referees. In the following, we respond to the comments point by point. All the changes are highlighted in red.

1. About copyediting - We have revised the style of written English by a professional native English speaker. The changes are highlighted in red.

2. We have included a Title Page with the title of the article, which has been changed in red color. And we think the title now provides a more accurate, clearer and more concise description of the reported work. The full names, institutional addresses, and e-mail address of all of the authors, and the corresponding author has also been included in Title Page.
Response to Referee 1 (Professor Teresa Adrago)

We thank the Professor Teresa Adrago for the nice comments. In the following, we addressed the issues raised by you. The changes were highlighted in red font.

Minor essential revisions:
1. Cardiovascular mortality was defined as death due to myocardial infarction, heart failure, sudden cardiac death, or stroke. See changes in Outcomes (page 4, line 16-17). Sudden death was also included, and the main cause of the sudden death for HD patients is cardiovascular events, we calculated sudden death as sudden cardiac death because it is impossible to exclude sudden death caused by other reasons including autonomic imbalance, uremia or inflammation.

2. We did not use the method mentioned by professor Lena Kauppila or KDIGO guideline. Because neither of the methods was included in a scoring system with pelvis, hands and abdominal radiographs at the same time. We don’t have adequate evidence to prove whether each 1 score for abdominal VC is the same as each 1 score for pelvis VC or for hands VC. We adopted this scoring system from Wang Mi (Wang MI, Wang Mei, Gan Liangying, et al. Relationship between plasma fetuin-A and vascular calcification in hemodialysis patients. Chinese Journal of Blood Purification, 2007; 6(5):263-266), which was adopted from Professor Teresa Adrago’s previous report with small modifications. We made the scoring system simple and focus on the relationship between presence or absence of a certain vascular calcification and patient outcome.

Discretionary revision:
1. Thanks for your kindly suggestion, we agreed with you and have changed the sentence. See Conclusions (page 11, line 11-13, highlighted in red).
Response to Referee 2 (Professor Dena Rifkin)

Thanks for your helpful comments!

1. With the relative small population and relative small events, especially cardiovascular mortality, a multicenter, prospective, large population, and well follow up study is expected to further confirm our conclusions, and we will keep going on this subject.

2. We have changed the figures; see Results (page 6, line 8, highlighted in red) and figures (Fig. 4 and Fig. 5).
Response to referee 3 (Professor Bojan Knap),

Thanks for your suggestions for our manuscript. It is very helpful for our research.

1. First, we agree with you that the title we have written provide too little information. After discussion in detail, we have changed the title to ‘Is abdominal aortic calcification superior over other vascular calcification in predicting mortality in hemodialysis patients? A retrospective observational study’.

2. The reviewer suggested more explanation about therapy of dialysis patients, especially therapy of secondary hyperparathyroidism, hypertension. We agree. And we have added description in Methods (page2, line 14-24, highlighted in red).

3. The reviewer suggested explanation cause of renal failure, because it’s important for VC in dialysis pts. We agree. Cause of renal failure is important for patient outcome. But in our population, primary glomerulonephropathy (62.2%) was the main cause, and we cannot find out the real cause in the patients who were diagnosed ESRD and diabetes and/or hypertension at the same time, because many people in China don’t take regular health examinations unless they don’t feel well. Many patients have already been in ESRD at their first time to see a doctor. But we still adjusted some important comorbidities such as diabetes, cardiovascular diseases for patient outcome analysis.

4. We did not present information about diet of pts with end-stage renal disease and also about phosphate binders, about their compliance with this medicine, which could be a problem. We agree with you that information is important, especially about the treatment. But this is a retrospective study, although we treated our patients according to the guidelines of K/DOQI, but the compliance of the patient is still difficult to evaluate. We have added descriptions in Methods (page2, line 15-18, highlighted in red) and also some explanations in Discussions section (page10, line 22-24, highlighted in red).

5. We agree with you we did not present information about vitamin D3 therapy and D vitamin analogues (calcitriol, paracalcitol and its doses), VC is thought to be associated with vitamin D; and vitamin D status may directly influence patient outcome, or indirectly influence patient outcome by affecting VC. Although we treated our patients according to the guidelines of K/DOQI, and we also analyzed the medicine information at the baseline, but no difference was found between patients died or survived, and the dosage varied according to the variation of iPTH, serum calcium, and serum phosphorus level, it is unlikely to present a comparably accurate dosage for data analysis. We have added descriptions in Methods section (page2, line 19-21, highlighted in red).

6. In discussion pathophysiologic background of VC and it’s correlation with therapy of patients, mood of life and their daily exercise habit is missing. We agree with you that mood of life and exercise is important. It was reported to affect blood pressure control, artery stiffness, endothelial dysfunction, etc. But lifestyle modification was reported to have no impact on change of coronary
artery calcium (Lehmann N, Paul A, Moebus S, Budde T, Dobos GJ, Michalsen A. Effects of lifestyle modification on coronary artery calcium progression and prognostic factors in coronary patients--3-year results of the randomized SAFE-LIFE trial Atherosclerosis. 2011, 219(2):630-6). Research also reported that exercise training reduced PWV but not OPG, suggesting that while an intervention of this nature improves vascular tone, it does not exert significant effects on serum biomarker related to calcification (Davenport C, Kenny H, Ashley DT, O'Sullivan EP, Smith D, O'Gorman DJ. The effect of exercise on osteoprotegerin and TNF-related apoptosis-inducing ligand in obese patients. Eur J Clin Invest. 2012, 42(11):1173-9). In Chinese population, smoking was reported to increase the risk of aortic arc calcification, while smoking cessation decreased the risk only in male light ex-smokers (Jiang CQ, Lao XQ, Yin P, Thomas GN, Zhang WS, Liu B, Adab P, Lam TH, Cheng KK. Smoking, smoking cessation and aortic arch calcification in older Chinese: the Guangzhou Biobank Cohort Study. Atherosclerosis. 2009 Feb; 202(2):529-34). But in our study population, all the ex-smokers (just a few in the study population) reported to discontinue smoking long before initiation of hemodialysis. Due to the inadequate evidence to support relationship between some lifestyle modifications or exercise and vascular calcification, and the limited baseline information in our study population, we did not discuss lifestyle and exercise in detail.

7. We agree that it would be necessary to know more about anamnesis and clinical data about heart disease, (echocardiography), peripheral artery disease, etc. to find the cause of death. It is important to know about the anamnesis of heart diseases; we agree and have presented the definitions of cardiovascular death in the Outcome (page 4, line 16-17, highlighted in red). But the sample is relatively small to study the relationship between different type of cardiovascular death and VC.

8. We agree that results section should include more clinical data, which are in connection with VC. It is a good idea to show more clinical data in connection with VC. But we could not include all, even some very important data with this retrospective study, because something like 25-hydroxyvitamin D was not measured at the baseline. But we still presented most of the relevant data including serum calcium, phosphorus, PTH, ALP, age, dialysis vintage, diabetes, hypertension, albumin (an indicator of nutrition), etc. We presented baseline data including factors associated with VC and factors reported to be associated with patient outcome.

9. We completely agree with you and thank you for your suggestion for future prospective observations in this group of patients with more clinical and medicine data, it’s a very good idea and we will keep going on not only in this group of patients but also in a larger, multicenter, better designed study.