Author’s response to reviews

Title: Impact of diabetes on sarcopenia and mortality in patients undergoing hemodialysis

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Author’s response to reviews:

Dear Dr. Hayley Henderson,

Thank you very much for reviewing our manuscript. We appreciate many valuable comments from four reviewers. We are resubmitting our manuscript to ‘BMC Nephrology’ after carefully considering the suggestions made by them. We have sincerely tried responding to each reviewer. We hope that the manuscript is now suitable for publication.
Reviewer #1:
Thank you very much for your valuable, precise comments.

Introduction
Line 79 - and importantly physical function. Sarcopenia is defined as loss of muscle mass and strength or function, and severe sarcopenia loss of mass, strength and function. This should be made clear.
: Thank you very much for your critical suggestion. We have added ‘physical function’ (Page 5, Line 79).

Line 80 - it would be helpful to state what the Asian criteria are in full as you are going to use these later in the study. You refer to this criteria several times and they must be stated in full either here or the methods for clarity.
: According to the reviewer’s suggestion, we have described the AWGS criteria in detail in ‘Methods’ (Page 9, Line 144-152).

Line 91-92 - you have already said sarcopenia is loss of muscle mass and strength, you do not need to repeat this - delete.
: We deleted this part (Page 6, Line 94-95).

Line 92 - we don't know what the Asian criteria are - see comment above - you need to include them in the introduction or methods.
: As described above, we added several sentences to describe the AWGS criteria in ‘Methods’ (Page 9, Line 144-152).

Line 95 - this paragraph - you don't really explain why you are focusing on HD patients. You say it is necessary to find out accurate figures for sarcopenia but you don't indicate why specifically HD.
Thank you very much for your important comments. We emphasized the reason why we focused on the HD patients.

Methods

Line 113 - retrospective ethics approval is not usual, nor only verbal consent. I think this requires explaining. In addition, the opt-out process requires explaining as this also is unusual.

This is not a prospective cohort study designed for research of sarcopenia. Although we had properly evaluated muscle mass by DXA and muscle strength by hand dynamometer, we didn’t originally intend to plan this study. Because this cohort was old, quite a lot of patients already died. We didn’t get written informed consent specific for this study. Therefore, we adopted the opt-out consent method.

Line 120 - how was handgrip strength tested. This is crucial since the hand used, the position and the process can all influence the result.

We added a few sentences to explain how to measure HS in more detail.

Line 127 - how was dry weight determined?

Basically, attending doctors determined dry weight in each patient, considering physical symptoms such as edema, blood pressure etc., the value of human atrial natriuretic peptide (hANP) more recently, and cardiothoracic ratio evaluated by chest X-Ray in Japan.

Line 131-132 - from where are these cut-offs derived. Please include the original reference.

As mentioned above, we adopted the cutoff values recommended by AWGS criteria (Ref. [2])

Results

Table 1 - numbers should be reported as % as well as actual numbers for gender.

We added ‘%’ (Page 23, Table 1).
Line 157-158 - of course HS and SMI are lower in the sarcopenic group because these are the diagnostic criteria you have used to define sarcopenia. It seems unnecessary to state this as though it was a finding.

: We deleted HS and SMI (Page 11, Line 181).

Discussion

Line 180 - it is over stating the results to say this cohort represents all Japanese patients undergoing HD. This study shows a 40% in this study cohort only. You have made no attempt to demonstrate that this cohort is in any way representative of all HD patients and it is a relatively small cohort. Please change this line.

: We agree with the reviewer. We don’t mean that our results could reflect in all Japanese patients undergoing HD. We revised a few sentences to avoid misunderstanding (Page 13, Line 220-224).

Line 184 - I am sure this cannot be the only study to show DM is an independent predictor of mortality. Please can you back up this state with comparisons of other work and/or say that these findings concur with others.

: Thank you very much for your comment. As the reviewer pointed out, DM is indeed one of well-known predictors of mortality in various populations. To our knowledge, there is no report that showed the independent impact of DM on mortality focusing on sarcopenia in patients undergoing HD. For example, it has been reported that DM was not associataed with sarcopenia in dialysis patients [OR 1.05, (95%CI: 0.51-2.19), p = 0.89] (Ref. [5]). In this study, the impact of DM on mortality was not examined. In contrast, DM was an independent risk factor for sarcopmenia [OR 7.64, (95%CI: 1.70-34.3), p = 0.008] (Ref. [7]). However, this study included only 131 patients on HD (10 patients with DM). Thus, it was not impossible to investigate the effect of DM on mortality.

Line 195 - can you say more than 'considerable variations' - please give some specific figures.

: We have revised a few sentences with specific figures (Page 14, Line 236-241).

Line 238 - The conclusion could be modified slightly to say ….The present study determined that the prevalence of sarcopenia among - this cohort of - patients undergoing HD was 40%.
According to the reviewer’s suggestion, we revised the sentence in ‘conclusions’ (Page 17, Line 295-296).

Reviewer #2:

…..This paper only showed that DM was associated with sarcopenia and mortality in HD patients and sarcopenia was not a predictive factor for mortality because DM had a stronger impact on mortality than sarcopenia…..Thus, this paper did support the significance of DM as a predictor for mortality in HD patients as previously shown, but did not support the significance of sarcopenia.

: Thank you very much for your critical and valuable comments. We completely agree with the reviewer. The reviewer #4 also gave us similar comments. We performed subgroup analyses according to age. As a result, sarcopenia had a significant impact on mortality only in elderly group (Age ≥ 60). We added these results and made major revisions (Page 12-13, Line 206-217) (Page 16, Line 274-280) (Supplementary Fig.1 and Supplementary Tables).

1. The prevalence of DM seemed to be low, about 30% (101/308) in this clinic, so the patients with DM seemed to be older and had higher frequency of sarcopenia. The reviewer really would like to know the characteristic of participants when dividing by with or without DM.

: Thank you very much for your request. We attached the table (Supplementary materials for reviewer #2 and #4). As the reviewer expected, patients with DM were significantly older than those without DM. However, we think that the difference was not too big. In addition, we performed additional analyses with or without DM (Supplementary materials for reviewer #2 and #4).

2. The ADL at baseline in the participants might be very important. Do all of the participants ambulate independently?

: As the reviewer pointed out, we didn’t write it clearly. We added one sentence about exclusion criteria (Page 7, Line 120). All participants could ambulate without assistance.
3. Did the authors measure some other markers related to low grade inflammation, oxidative stress, or advanced glycation end products (AGEs) accumulation, not CRP?

: Thank you very much for your important question. We realize what the reviewer means very well. Unfortunately, we didn’t measure those factors. Because the reviewer’s comments are critical, we described these points as one of limitations (Page 17, Line 287-289).

Reviewer #3:

…..However, there are several faults and limitations in the present study.

: Thank you very much for your critical and valuable comments. We try responding to the reviewer as follows.

Background

1. The prevalence of sarcopenia may be different by age. The authors should describe the mean age of Ref No. 5, 6, and 7.

: Thank you very much for your fine suggestion. We added information about age in each report [5][6][7]. We also added one sentence to emphasize the impact of aging on the prevalence of sarcopenia as well as the different criteria (Page 5-6, Line 87-92). As we respond to the reviewers #2 and #4, we realize the importance of aging with regard to sarcopenia-related mortality in this study.

2. The prevalence of sarcopenia was significantly higher in patients with diabetes than healthy subjects [10]. Is there any report in patients with chronic kidney disease and end-stage kidney disease?

: Thank you very much for your important question. We expect that sarcopenia may be highly prevalent in patients with CKD or ESKD. However, there is no report that directly compared the prevalence of sarcopenia between healthy subjects and patients with CKD or ESKD (HD) using AWGS criteria, so far. Very recently, it has been reported that the prevalence of sarcopenia in Chinese elderly (community-dwelling population) was 34.3% using AWGS criteria (mean age: 81.6 ± 3.3) (J Am Med Dir Assoc 2018;19:690-695). At least, unified criteria are required. In addition, adjustment of age may be necessary for direct comparison, as the reviewer pointed out. Just for information, recent Korean study showed that the prevalence of sarcopenia increased, as
the stage of CKD increased in men but not women, although AWGS criteria was not adopted (Moon et al., PLoS One 2015;10:e0130740). Since this discussion may confuse the reader, we would like to avoid it in our manuscript.

Methods

1. Exclusion criteria: The patients who had previous history of amputation should be excluded.

: According to reviewer’s suggestion, we added one sentence. Actually, we didn’t include patients with previous history of amputation (Page 7, Line 120). All participants could ambulate.

2. Diagnosis of sarcopenia: When did you measure the handgrip strength and skeletal mass index?

: DXA for SMI was performed 21–24 h after completing the dialysis session (Page 8, Line 137-139). HS was measured just before or after HD session. Unfortunately, we didn’t measure SMI and HS at the same time.

3 It means that the present study investigated the patients who were treated with hemodialysis in 1996-2000?

4. The duration of the present study should be described, i.e., "Observational period of this study was from January 1997 to December 2005".

: Thank you very much for your suggestion. We had started the observation in January 1997. As the reviewer mentioned, observational period of this study was from January 1997 to December 2005. We added this sentence (Page 9-10, Line 159-160).

5. Kt/V, nPCR, and history of cardiovascular disease should be included as independent variables in Cox regression multivariable analysis.

: Thank you very much for your critical suggestion. We included Kt/V and nPCR as independent variables in multivariate Cox proportional hazard analyses (Page 23, Table 1, Page 25, Table 3) (Supplementary Table 1, Supplementary Table 3). Unfortunately, we didn’t check the history of cardiovascular diseases.
Results

1. Important information are lacking in the present study. In common, diet intake, normalized protein catabolic rate, dialysis efficiency, phosphate, and history of cardiovascular disease may contribute to the prevalence of sarcopenia.

The authors should describe nPCR, serum UN, nPCR, Kt/V, cardiovascular comorbidity rate, and dialysate concentrations of calcium and glucose.

: We completely agree with the reviewer. As the reviewer pointed out, all factors may contribute to the prevalence of sarcopenia. However, we don’t have complete data. Wherever possible, we added the data (Page 23, Table 1). In addition, we acknowledged the lack of data as one of major limitations in this study (Page 17, Line 289-292). If that helps, dialysate concentrations of calcium and glucose were 3 mEq/L and 100 mg/dL, respectively.

2. Results section and Fig 1: the number of the patients should be described. 77 patients were transferred to other hospitals. This number is very high. Why did many patients move from your hospital?

: According to reviewer’s suggestion, we revised Fig.1. With regard to the move of patients, one of the reasons might be originated from the location of our hospital. Around our hospital, there are so many dialysis facilities including specialty clinic. In addition, we have the related-satellite clinics, too. For a reason of their convenience, some of them transferred to neighboring clinics.

3. Table 3: The authors described "Independent association between diabetes and all-cause mortality. This title should be revised.

: We agree with the reviewer. The title was inappropriate. We revised the title (Page 25, Table 3).

4. The causes of death should be given a detailed description.

: Thank you very much for your suggestion. We added the causes of death in detail (Page 11-12, Line 193-197).
5. I would like to know the information about the distribution of age in the sarcopenia group.

- We attached the figure which shows the distribution of age in the sarcopenia group (Supplementary materials for reviewer #3).

Reviewer #4:

Major comment

……. The author should add detailed explanation regarding non-association between sarcopenia and mortality in HD patients and revise conclusion section considering negative results. In addition, reviewer recommends subgroup analyses according to age group or the presence of DM, these analyses may explain negative results.

- Thank you very much for your critical and thoughtful comments. The reviewer #2 pointed out the similar issue. According to reviewer’s suggestion, we performed additional analyses according to age. Very interestingly, in elderly group (Age ≥ 60), sarcopenia was a significant predictor of mortality. We appreciate your fine suggestion. Because these findings are extremely important, we made major revision (Page 12-13, Line 206-217) (Page 16, Line 274-280) (Supplementary Fig.1 and Supplementary Tables). On the other hand, subgroup analyses with or without DM didn’t seem to provide a helpful and new information. For your reference, we added the results (Supplementary materials for reviewer #2 and #4)

Minor comment

Page 7, line 118: the arteriovenous fistula may be exchanged to "arteriovenous fistula or graft".

- Thank you very much for your suggestion. We have corrected It (Page 8, Line 128).

Page 7, line 120: Which machine for hand grip strength was used (for example, Takei or Sportstek)? Two references (ref 12 and 13) also did not explain the machine for hand grip strength. As far as I know, Takei is most popular machine for hand-grip strength in Japan.

- Thank you very much for your kind comments. We added the information of hand dynamometer (Page 8, Line 131).
Page 8, line 141: The author should add statistical software and version such as SPSS ver 23, SAS ver 20…

: According to reviewer’s suggestion, we added the information of statistical software (Page 10, Line 171-172).

Page 9, line 152: Can the author add the data regarding dialysis adequacy or dialysis modality (HD or HDF)? These variables would be associated with prevalence or incidence of sarcopenia.

: Thank you very much for your critical comments. We recognize that these factors might contribute to the prevalence of sarcopenia as well as mortality. Unfortunately, we didn’t have complete data. As the reviewer #3 recommended, we added the Kt/V for statistical analyses (Page 23, Table 1, Page 25, Table 3) (Supplementary Table 1, Supplementary Table 3). This factor seemed not to affect the prevalence of sarcopenia and mortality. With regard to dialysis modality, we think that several patients might undergo hemodiafiltration (HDF). We cannot confirm the accurate number. Anyway, we believe that the difference by small number of HDF patients didn’t have any impact on the results.

Page 10, line 168: Can the author add the data regarding cause of death (cardiovascular disease, infection, malignancy..)? These data may be helpful to understand the clinical impact of sarcopenia in HD patients.

: We added the detailed information about the causes of death (Page 11-12, Line 193-197).