Author’s response to reviews

Title: Associations between the measures of physical function, risk of falls and the quality of life in haemodialysis patients: a cross-sectional study.

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Associations between the measures of physical function, risk of falls and the quality of life in haemodialysis patients: a cross-sectional study

Dear Editor,

Thank you for the opportunity to improve our work and to give us the chance to resubmit the manuscript to BMC Nephrology. We are grateful for the editorial and reviewers’ comments and thank them for their appreciation.

The formulated comments are well taken; below you will find point-by-point responses to the comments and questions raised in the decision letter. Stated citations (page; line) refer to the revised version of the manuscript with track changes.

Yours sincerely,
Patrick Calders

1. EDITORIAL COMMENTS

- Your manuscript "Associations between the measures of physical function, risk of falls and the quality
We would like to thank you for the opportunity to improve our work and to give us the chance to resubmit the manuscript to BMC Nephrology. We are grateful for the editorial and reviewer comments and thank them for their appreciation.

REPORTING COMMENTS

1. 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. Please refer to the journal's Submission Guidelines web page for information regarding the criteria for each sub-section (https://bmcnephrol.biomedcentral.com/). Where a mandatory Declarations section is not relevant to your study design or article type, please write "Not applicable" in these sections.

   Answer: Adaptations have been conducted to the revised manuscript according to the BioMed Central editorial policies and formatting guidelines regarding the Declarations section.

   The following adaptations were conducted in the revised version of the manuscript:
   Declarations, pages 15, lines 336-337: “Consent for publication: Not applicable”
   Declarations, page 15, lines 344-345: “Competing interests: The authors declare that they have no competing interests.”

2. For the 'Availability of data and materials' section, please provide information about where the data supporting your findings can be found. We encourage authors to deposit their datasets in publicly available repositories (where available and appropriate), or to be presented within the manuscript and/or additional supporting files. Please note that identifying/confidential patient data should not be shared. Authors who do not wish to share their data must confirm this under this sub-heading and also provide their reasons. For further guidance on how to format this section, please refer to BioMed Central's editorial policies page. Further information about our editorial policies can be found at the following links:
   - Ethical approval and consent: http://www.biomedcentral.com/about/editorialpolicies#Ethics
   - Availability of data and materials section: http://www.biomedcentral.com/submissions/editorial-policies#availability+of+data+and+materials

   Answer: The authors agree with the editor that publishing datasets improves the transparency of articles, including this manuscript. Nevertheless, this database is only a small part of a whole and the main database is still being used by various PhD-applicants. As we cannot guarantee that the database is completely free of identifying data, publishing it would be not compliant with the General Data Protection Regulation (GDPR). However, if readers request the dataset with a reasonable argumentation, the authors of course are willing to provide the dataset to them in an anonymised way.

   The following sentence was adapted in Declarations of the manuscript:
   Declarations, page 15, lines 339-342: “Availability of data and materials: As the full dataset is still being used for other analyses, it has not been anonymized yet. The datasets (without any identifying information) used and/or analysed during the current study are available from the corresponding author on reasonable request”
2. RESPONSE TO REVIEWERS

REVIEWER #1

This is a very well designed and written analysis. I only have a few minor comments:
Answer: We thank the reviewer for his/her constructive criticism and interest in our work, and we have used his/her comments to improve the manuscript.

1. There are too many tables in the manuscript and some of them are difficult to read/can be presented in a more concise fashion
Answer: We thank the reviewer for this remark to improve the transparency of our manuscript. By channelling the data and information of this study, readers will be able to screen and find data more effectively. Consequently, irrelevant information was removed from three tables in the revised version of the manuscript, as the reviewer suggested. Nevertheless, we opted to maintain the number of tables as we are of the opinion that four is a rather normal number of tables for a paper. Also, we believe that supplementary data should be as comprehensive as possible and, therefore, no reductions were performed in the number of additional files as well. We hope the reviewer can identify him/herself with this reply.

Table 4 of the original version of the manuscript was made more clear by presenting only significant results. Evidently, the deleted data was cited in Results of the revised version of the manuscript. The following sentence was added to Results of the revised version of the manuscript with track changes:
Results, page 9, lines 220-222: “Additionally, a negligible relation was found between quadriceps strength and subjective fatigue. No measures of physical performance were associated with anxiety and sleep disturbance (Table 4).”

Data in Table S2 (see additional file 2) was reduced to one statistical model (i.e. including measures of muscle strength and 6MWT) for each measure of the risk of falls, instead of two statistical models (measures of muscle strength with and without the 6MWT respectively). Whereas the removed data of Table S2 was indeed irrelevant, no reference was added to Results of the revised version of the manuscript.

Table S4 in additional file 3 was presented as a landscaped design instead of a portrait design. Accordingly, in contrast to the original version of the manuscript, the rows and columns of Table S4 take an appropriate form that displays the data in a more transparent fashion. Additionally, p-values were removed and information regarding the statistical differences can be found in the tables’ legend.

2. It's unclear to me what "consecutive prevalent" means
Answer: The ‘consecutive prevalent’ was used to describe the permanent need for maintenance haemodialysis. We adapted the manuscript by changing ‘consecutive prevalent’ into ‘maintenance haemodialysis’.

The manuscript was adapted as follows:
Abstract, page 2, lines 33-34: “This cross-sectional multicentre study included patients on maintenance haemodialysis.”
Materials and methods, page 4, lines 86-88: “Patients on maintenance HD, who were included in a larger study (registration number on clinicaltrial.gov: NCT03910426, in two main dialysis centres were screened for eligibility between December 2016 and March 2018.”

Discussion, page 14, lines 309-310: “A strength of this research was that we included HD patients willing to participate, without exclusion of the weakest, and this from multiple dialysis units.”

3. I am also concerned about the small N and generalizability of this study
Answer: We understand the concerns of the reviewer. Green et al. have stated that the number of subjects per variable (SPV) is preferable 20, and that the minimum required SPV should be five (Samuel B. Green (1991) How Many Subjects Does It Take To Do A Regression Analysis, Multivariate Behavioral Research, 26:3, 499-510, DOI: 10.1207/s15327906mbr2603_7). This rule of thumb has been widely accepted and is the most stringent recommendation to ensure accurate prediction in subsequent subjects, albeit other authors suggest SPV’s of 15-20 and 10 for linear regression models (F.E. Harrel, Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis, ISBN: 3319194259). Interestingly, a recent study by Austin and Steyerberg found that a linear regression model requires only 2 SPV for adequate estimation of regression coefficients (R2), standard errors, and confidence intervals. Nevertheless, we don’t think that an SPV of 2 is appropriate in this study. The present study examined 6 different variables over 113 subjects, which results in an SPV of 19. Whereas our SPV is just below the most ideal ratio, we can accommodate with the reviewers remark by addressing this issue in the limitations of the revised version of the manuscript.

The following information was added to Discussion in the revised version of the manuscript:
Discussion, page 13, lines 304-308: “Second, the sample size of this study is small and does not exceed the rule of thumb of 20 subjects per variable, which is recommended by Green et al. However, the general linear model presented in this study has a subjects per variable-ratio of 19 and, thus, adequate estimations of regression coefficients, standard errors and confidence intervals can be performed.[51]”

The following citation was added to support the information mentioned above:

Assuming the sample size in this study is appropriate for the analyses performed, we believe that this cohort is representative for the population on haemodialysis in a North-European country. Furthermore, patients were recruited on an easy accessible basis in two main dialysis centres. These centres included five different low-care dialysis units and two different high-care dialysis units. Moreover, the heterogeneity between patients on haemodialysis is well established in the literature and is also presented in our cohort by the following minima and maxima: (1) age between 22-91 year old, (2) BMI between 14.7-42.3 kg/m2, (3) dialysis vintage between 0-191 months. Hence, we argue that our cohort is representative for a cohort on haemodialysis. Nevertheless, we do agree with the reviewer that, due to the heterogeneity in our cohort, our results are not applicable for all patients on haemodialysis.

The following information was added to the manuscript to stress the representativeness of our cohort:
Materials and Methods, page 4, lines 86-90: “Patients on maintenance HD, who were included in a larger study (registration number on clinicaltrial.gov: NCT03910426, in two main dialysis centres were screened for eligibility between December 2016 and March 2018. These dialysis centres included five...”
different dialysis units (two high-care and five low-care dialysis units) distributed throughout five different public hospitals.”

Overall, a very useful addition to the literature on this topic.
Answer: Thank you for the well-taken review.

REVIEWER #2

This is well-written paper which seeks to examine the association between the objective and subjective measures of physical function, the risk of falls and subcategories of HRQoL in prevalent HD patients.
Answer: We thank the reviewer for his/her well-taken observations and appreciate the suggestion to further highlight the methodology of this study.

1. Page 3, line 60, the authors refer to a 4.4 times higher risk of hip fractures without specifying the reference group or comparator.
Answer: We agree with the reviewer that the reference group should be added.

The following sentence was adapted in the manuscript:
Introduction, page 3, lines 58-61: “Next to decreased muscle strength, uremic polyneuropathy, autonomic dysfunction, hypotensive episodes, and polypharmacy contribute to an increased risk of falls as well, resulting in a 4.4 times higher risk for hip fractures in HD patients compared to age-matched healthy control subjects.[6, 7]”

2. Page 3, line 75, suggest 'insight into' not 'insight in'.
Answer: We thank the reviewer for this correct request.

As the reviewer suggested, we adapted the following sentence in the introduction:
Introduction, pages 3-4, lines 75-77: “Again, better insight into the association between subjective fatigue and objective physical function is important, as it can steer interventional strategies.”

3. Suggest for the authors to state the hypothesis of this study.
Answer: We thank the reviewer for broaching the absence of this information. The hypothesis of a study is indeed an important aspect of the statistical analysis and was therefore added to the introduction. Our primary assumption was that both psychosocial and physical domains of health-related quality of life are decreased and related to objective physical impairments.

The following sentence was added to the introduction of the revised version of the manuscript:
Introduction, page 4, lines 78-79: “We hypothesised that both psychosocial and physical domains of HRQoL are associated with objective measures of physical function in patients on HD.”

4. There is need for a brief description of the dialysis centres. Were they hospital-based, private or public etc.
Answer: Thank you for this very constructive remark. Patients were recruited in two main dialysis centres. These centres included five different low-care dialysis units and two different high-care
dialysis units. All these units are public services, as all dialysis units in Belgium

Based on the reviewer’s suggestion, the following information was added to the manuscript:
Materials and Methods, page 4, lines 86-90: “Patients on maintenance HD, who were included in a larger study (registration number on clinicaltrial.gov: NCT03910426, in two main dialysis centres were screened for eligibility between December 2016 and March 2018. These dialysis centres included five different dialysis units (two high-care and five low-care dialysis units) distributed throughout five different public hospitals.”

5. Inclusion criteria is not well-specified.
Answer: This study was part of a larger study that examined various clinical determinants of quality of life and mortality in patients with end-stage kidney disease (Registration number on clinicaltrial.gov: NCT03910426). Whereas the assessment of physical performance was added to the protocol by amendment after the initiation of the original study, only 122 out of 216 originally-included patients could be addressed. All patients with ESKD were eligible in the original study (original exclusion criteria; active inflammation, malignancy and cognitive disorders). Based on the reviewer’s suggestion, we have added the relevant information to Materials and Methods.

The following information was added to the revised version of the manuscript:
Materials and Methods, page 4, lines 86-93: “Patients on maintenance HD, who were included in a larger study (registration number on clinicaltrial.gov: NCT03910426, in two main dialysis centres were screened for eligibility between December 2016 and March 2018. These dialysis centres included five different dialysis units (two high-care and five low-care dialysis units) distributed throughout five different public hospitals. Exclusion criteria were the following: age < 18 years, pregnancy, active inflammation, malignancy, cognitive disorders, inadequate motor and verbal responses to verbal commands and questions, and recent (< 6 months) surgical musculoskeletal interventions.”

6. Please provide information of sample size calculation.
Answer: We thank the reviewer for this pertinent remark. No sample size calculation was performed in this cross-sectional study. Nevertheless, Green et al. have stated that the number of subjects per variable (SPV) is preferable 20, and that the minimum required SPV should be five in order to have a robust general linear model (Samuel B. Green (1991) How Many Subjects Does It Take To Do A Regression Analysis, Multivariate Behavioral Research, 26:3, 499-510, DOI: 10.1207/s15327906mbr2603_7). This rule of thumb has been widely accepted, it is the most stringent recommendation to ensure accurate prediction in subsequent subjects, albeit other authors suggest SPV’s of 15-20 and 10 for linear regression models (F.E. Harrel, Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis, ISBN: 3319194259). Interestingly, a recent study by Austin and Steyerberg found that linear regression models require only 2 SPV for adequate estimation of regression coefficients (R2), standard errors, and confidence intervals. Nevertheless, we don’t think that an SPV of 2 is appropriate in studies including a heterogeneous population, such as in this study. The present study examined 6 different variables over 113 subjects, which results in an SPV of 19. Whereas our SPV is just below the most ideal ratio, we can accommodate with the reviewers remark by addressing this issue in the limitations of the revised version of the manuscript.

The following information was added to Discussion in the revised version of the manuscript:
Discussion, page 13, lines 304-308: “Second, the sample size of this study is small and does not exceed
the rule of thumb of 20 subjects per variable, which is recommended by Green et al. However, the general linear model presented in this study has a subjects per variable-ratio of 19 and, thus, adequate estimations of regression coefficients, standard errors and confidence intervals can be performed.[51]"

The following citation was added to support the information mentioned above:

If the reviewer would like more information on the generalizability of this study, we refer the reviewer to the third question of reviewer #1.

7. How was missing data handled? Was there any pattern in the missing data?
Answer: It is indeed important to stress the point of missing data, as raised by the reviewer. Patients with missing data on a primary outcome were excluded and mainly the unavailability of data on quality of life questionnaires resulted in exclusion (N=9). A language barrier and the accompanied incomplete assessment of questionnaires accounted for six out of nine exclusions. Additionally, two subjects were excluded as they reported outliers on at least one measure of physical function. In this case, outliers were defined as unrealistic values (e.g. 6MWT +900 meters for a 84 year old man) and, thus, are not based on standard deviation. One other patient indicated wanting to stop the testing for personal matters and, subsequently, the test protocol was ceased. Evidently, this patient was excluded as well.
For the record, the main characteristics of the nine excluded patients are reported in a table below. Interestingly, although the language barrier and not a physical barrier was the main reason for missing data, patients scored apparently lower on the 6MWT compared to the cohort included in the study. Whereas the other physical examinations showed similar results compared to the included cohort, we may conclude that there are no major differences between our subjects with and without missing data. Furthermore, we believe that this information does not influence the reliability of our results or imply a selection bias. Nevertheless, we want to accommodate with the reviewers’ suggestion by addressing this issue in Results of the revised version of the manuscript.

The following information was added to Results of the manuscript:
Results, page 8, lines 185-188: “Nine patients with missing data were excluded, giving a response rate of 93%, albeit six patients for missing data on QoL questionnaires and three patients on measures of physical function. There were no major differences between the excluded and included subjects.”

<table>
<thead>
<tr>
<th>Descriptive Statistics</th>
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<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
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<td>Body Mass Index (kg/m2)</td>
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<td>29,2</td>
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<td>Months on dialysis (months)</td>
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<td>174</td>
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<tr>
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<td>2</td>
<td>12</td>
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<td>Sit to Stand</td>
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<td>10</td>
<td>50</td>
<td>28,86</td>
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<td>(sec)</td>
<td>Handgripforce (kg)</td>
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<td>11</td>
<td>42</td>
<td>25,57</td>
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<tr>
<td>-------</td>
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<tr>
<td></td>
<td>Quadriceps Force (N)</td>
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<td>6MWT (m)</td>
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<td>48</td>
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<tr>
<td>6MWT (%)</td>
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<td>9,02</td>
<td>55,20</td>
<td>29,8968</td>
<td>19,03300</td>
</tr>
</tbody>
</table>

8. The authors, under strengths of the study, make reference to 'multiple' dialysis centres. Were they not 2?
Answer: Thank you for this remark. We admit that the information in the original version of the manuscript was ambiguous. Patients were recruited in two main dialysis centres. These centres included five different low-care dialysis units and two different high-care dialysis units. All units were hospital-based.

Based on the reviewer’s suggestion, the following information was added to the manuscript:
Materials and Methods, page 4, lines 86-90: “Patients on maintenance HD, who were included in a larger study (registration number on clinicaltrial.gov: NCT03910426, in two main dialysis centres were screened for eligibility between December 2016 and March 2018. These dialysis centres included five different public dialysis units (two high-care and five low-care dialysis units) distributed throughout five different public hospitals.”

9. How many participants were approached? Were there any differences between those who were approached and those who participated in the study?
Answer: This study was part of a larger study that examined various clinical determinants of quality of life and mortality in patients with end-stage kidney disease (Registration number on clinicaltrial.gov: NCT03910426). Whereas the assessment of physical performance was added to the protocol by amendment after the initiation of the original study, only 122 out of 216 originally-included patients could be addressed. All patients with ESKD were eligible in the original study (original exclusion criteria; active inflammation, malignancy and cognitive disorders). Yet, as reported above, one patient ceased the physical examinations. Accordingly, one patients out of the 122-approached patients did not participate in the study. Regarding the differences between those who were approached and those who participated in the study, we refer the reviewer to the answer of question 7.

Finally, we would like to thank the reviewer to review our manuscript and its methodology with attention to detail.