Author’s response to reviews

Title: Assessing Protein Energy Wasting in a Malaysian Haemodialysis Population Using Self-Reported Appetite Rating: A Cross-Sectional Study

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Author’s response to reviews: see over
Dr Liffert Vogt  
Associate Editor  
BMC Neprology

Dear Dr. Vogt,

Re: Submission of Revised Manuscript MS ID: 5211732951582230

On behalf of the authors, I wish to thank the Editor and Reviewers for their useful comments and suggestions to improve the manuscript. We have undertaken the revision taking into account all the points raised. We are now resubmitting the above manuscript with title amended to “Assessing Protein Energy Wasting in a Malaysian Haemodialysis Population Using Self-Reported Appetite Rating: A Cross-Sectional Study”.

We have attached herewith a separate document with detailed point-by-point responses to comments highlighted by the Editor and Reviewers. Changes to the manuscript were made and submitted as a revised manuscript. We are very much looking forward to a favorable reply. Please do not hesitate to contact us if further revisions or clarifications are needed.

Yours sincerely,

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# RESPONSE TO REVIEWERS

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<th>No.</th>
<th>Reviewer comment</th>
<th>Author Response</th>
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<td><strong>Editor’s Comments</strong></td>
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<tr>
<td><strong>General comments</strong></td>
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<tr>
<td>1.</td>
<td>The latter conclusion is at least surprising when looking at Figure 2 and reading the text at the top of page 14. There, a graded increase in the proportion of patients with PEW with decreasing appetite can be seen. An explanation of the authors’ conclusion is clearly needed.</td>
<td>Based on Pearson $\chi^2$ analysis, the number of patients identified with protein energy wasting (PEW) is significantly different across the appetite rating scales ($p=0.005$). However, the minimum expected count was less than 5 where the number of PEW patients in the ‘very good’ and ‘poor’ appetite categories was very small. Hence, the 4-scaled appetite ratings were dichotomized to ‘normal’ and ‘diminished’ categories. After doing this, the association between PEW and dichotomized appetite category became non-significant (adjusted odds ratio: 1.71; 95% CI: 0.94-3.10].</td>
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<td>2.</td>
<td>Copy editing</td>
<td>The manuscript has been proof read by an English native speaker.</td>
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<td><strong>Reviewer #1 Comments</strong></td>
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<td>3.</td>
<td>The authors concluded that there is no significant relationship between appetite category and PEW. However, when I see Figure 2 and read the text at the top of page 14 there is a graded increase in the proportion of patients with PEW with decreasing appetite. The p-value is not provided in the text or in the legend of Figure 2 (or I have missed it). Please provide the p-value (and the test used to assess the p-value). Even of this is not significant, this might be because there are too few patients in the ‘poor’</td>
<td>Based on Pearson $\chi^2$ analysis, the number of patients identified with protein energy wasting (PEW) is significantly different across the appetite rating scales ($p=0.005$). However, the minimum expected count was less than 5 where the number of PEW patients in the ‘very good’ and ‘poor’ appetite categories was very small. Hence, the 4-scaled appetite ratings were dichotomized to ‘normal’ and ‘diminished’ categories. After doing this, the association between PEW and dichotomized appetite category became non-significant (adjusted odds ratio: 1.71; 95% CI: 0.94-3.10].</td>
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and in the ‘very good’ appetite category. So, I would be cautious with the conclusion that there is no relation between appetite and PEW, especially since appetite was strongly associated with various nutritional parameters.

4. Patient inclusion:
In the methods section, it is stated ‘terminally ill patients were excluded’. But what about patients with intercurrent illness (e.g. pneumonia, diverticulitis or central venous access related bacteremia) just before or during the study? Were these patients excluded? Was hospitalization an exclusion criterion?

There were 6 patients with poor appetite. I would suggest to give more information on these patients.

[i] The aspect of hospitalization during the data collection period is unlikely as the data collection was only conducted during a single interview within a week of patients’ consent immediately upon recruitment.

We have amended the patient selection statement to:

[ii] Added to methodology section
Patients with cognitive impairment or terminal illnesses such as HIV/AIDS or malignancy were excluded during the recruitment period. Additional exclusion criteria included patients with repeated history of hospitalization or inter-current illnesses in the six months prior to recruitment.

[iii] Added to result section in Line 335-338:
Of the six patients who were rated as having poor appetite, five were diagnosed with PEW. The BMI for these five patients ranged between 19-22 kg/m², serum albumin ranged between 30-46 g/dL and hsCRP ranged between 4.80-194.13 mg/L. In this group of six, one incidence of mortality was attributed to cardiac arrest six months post-data collection.

5. Page 11: How was lean tissue mass and fat mass measured/calculated?

View Line 199, Page 9

We have amended to provide a clearer description:

Body composition and hydration status were assessed using a portable whole-body bio-impedance spectroscopy device (Body Composition Monitor, Fresenius Medical Care, Bad Homburg, Germany). The use of this tool in assessing the hydration status in Malaysian HD population has been reported elsewhere [17]. Body composition
measurements were carried out before the dialysis session, with the patient resting in the supine position for approximately 15 minutes prior to the measurement. The electrodes were placed on the wrist of the non-fistula arm and on the ipsilateral ankle and subsequently connected to the device [18]. The hydration status, lean tissue mass (LTM) and fat mass (FM) generated by the instrument were based on a physiologic tissue model as described by Chamney et al. [19].

6. Page 15, Line 350-351:
It is stated that hsCRP is not correlated with appetite scores. In contrast, at line 357 it is stated ‘….patients reporting lower appetite scores had significantly increased hsCRP’. Please change one or two statements.

We have taken note of these comments and the following revisions were made to improve clarity:

[i] The statement in line 316-317 ‘For inflammatory status, patients reporting poor appetite had significantly greater hsCRP compared to the other 3 groups’ clearly states that hsCRP was significantly different across appetite ratings. Although we included hsCRP as a proposed biomarker for potential PEW diagnostic criteria, the adjusted odds ratio between diminished appetite and hsCRP was not significant.

[ii] We have included the following amendments for better clarity:

In line 365-366:
Other potential markers of PEW such as hand grip strength, triglyceride, total lymphocyte count and hsCRP did not correlate with the dichotomized appetite category.

In line 371-374:
When our patients were assessed using the 4-scaled appetite ratings, only those with the poorer appetite ratings had significantly higher hsCRP and lower dry weight, BMI, MAC, MAMC, MAMA, LTM, serum urea and creatinine, dietary energy and protein intakes as well as SF-36 total scores.

7. The English can be improved. The manuscript has been proof read by an English native speaker.
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<th>8.</th>
<th>What is meant with ‘Probing’, e.g. in the title if the manuscript, I would suggest changing the manuscript title.</th>
<th>Thank you for this comment. The manuscript title has been changed to: Assessing Protein Energy Wasting in a Malaysian Haemodialysis Population Using Self-Reported Appetite Rating: A Cross-Sectional Study</th>
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| 9. | My main concern reflects the interpretation of the data. The authors mention repeatedly that appetite does not reflect or correlate with PEW criteria. However, the prevalence of PEW is greatly different among the appetite rating categories (very good:17.6%, poor: 83.3%). Also, a strong relation between appetite and other nutritional markers was observed. From these data, it could be well argued that appetite is quite well related to different parameters of malnutrition. Could the authors please explain their argumentation in more detail? | Based on Pearson $\chi^2$ analysis, the number of patients identified with protein energy wasting (PEW) was significantly different across the appetite rating scales ($p=0.005$). However, the minimum expected count was less than 5 where the number of PEW patients in the ‘very good’ and “poor” appetite categories was very small. Hence, the 4 scale appetite ratings were dichotomized to ‘normal’ and ‘diminished’ categories. After doing this, the association between PEW and dichotomized appetite category became non-significant (adjusted odds ratio: 1.71; 95%CI: 0.94-3.10].

[ii] We agree that 4-scaled appetite ratings correlates with nutritional markers and this is consistent with reported literature. This is reflected in our statement in line 427. However, we could not find an association when testing the question whether appetite assessment correlated with the ISRNM PEW criteria.

We have revised Line 445-457 to reflect the above view with an explanation.

Amendment: In line with literature, we found that appetite assessment correlated well with markers of nutritional status but did not correlate with PEW. Although appetite assessment has been proposed as a potential diagnostic tool for PEW by the ISRNM [7], on the contrary we noted that the percentage of HD patients diagnosed with PEW in both diminished and normal appetite categories was similar. The ability to feel hunger may be masked by the anorexia-cachexia manifestation in PEW, leading these patients to misreport their appetite [5]. However, this simple appetite question still provides insights into poor oral intake in HD patients, serving as an early warning of
impending malnutrition and can therefore be easily applied by nurses where dieticians’ services are limited. Findings of our study observed that other potential diagnostic markers of PEW may lend greater evidence to linking appetite to PEW. Thus, there is a need to redefine the criteria for PEW to maximize the clinical utility of using appetite assessment in detecting PEW. Further research to elucidate PEW diagnostic criteria related to appetite assessment is warranted.

| 10. | The aim of the study needs some clarification. What is the hypothesis? | We have included this in Line 140-141: We hypothesize that self-reported appetite if correlated to markers of nutritional status, will also correlate with PEW diagnosis in the Malaysian HD population. |
| 11. | Cut-off levels for lean tissue mass: Why as a LTM below 29.6 kg chosen as cut-off, instead of the sex and age specific cut-off limits proposed by the manufacturer of the BCM? | The reasons for choosing these cut-offs are: [i] The BCM manufacturer has not provided dialysis population-specific cut-off limits for lean tissue mass (LTM) and fat mass (FM). The reference range was derived from measurements of 1000 healthy subjects aged between 18 and 75 years (http://www.bcm-fresenius.com/23.htm), which we deemed was not appropriate as studies have shown LTM and FM profiles to be significantly different between HD and healthy populations (Jha et al. 2006; van Biesen et al. 2013). [ii] Although LTM has been proposed as diagnostic criteria by ISRN (Fouque et al. 2008), no cut-off limit has been published. [iii] We had adopted a median cut-off limit for LTM specific to the Malaysian HD population in this study. [iv] We have adjusted both LTM and FTM for confounding variables (age, gender, ethnicity, income level, co-morbidities and dialysis vintage) for the logistic regression analyses. Jha V, Jairam A, Sharma MC, Sakhuja V, Piccoli A, Parthasarathy S. Body composition analysis with bioelectric impedance in adult Indians with ESRD: Comparison with healthy population. Kidney Int 2006, 69: 1649-1653. |

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<td>Thank you for this comment. We have taken note of this comment. Referencing has been revised.</td>
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<td><strong>13.</strong></td>
<td>The wording sometimes suggests a prospective study (e.g. abstract LTM “declined”, “appetite worsened”, whereas the study is cross sectional.</td>
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<td>Thank you for this comment. We take note of this comment and we have made corrections in the manuscript.</td>
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<td><strong>14.</strong></td>
<td>Figure 3 and 4: please specify what the vertical line represent</td>
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<td>We have included a footnote explanation for <strong>Figures 3a and 3b</strong>:</td>
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<td>A vertical line represents odds ratio of 1. A value of 1 indicates no association between diminished appetite and PEW. In the figure, the 95% interval is also presented. If the value of 1 falls within the interval, there is no significant association between diminished appetite and PEW. (Akobeng 2005).</td>
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