Author’s response to reviews

Title: OBSERVATIONAL STUDY OF PATIENTS IN SPAIN WITH AMYOTROPIC LATERAL SCLEROSIS: CORRELATIONS BETWEEN CLINICAL STATUS, QUALITY OF LIFE, AND DIGNITY

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Author’s response to reviews:

Dear Sirs,

In reference to the manuscript PCAR-D-17-00093 entitled “OBSERVATIONAL STUDY OF PATIENTS WITH AMYOTROPIC LATERAL SCLEROSIS IN SPAIN: CORRELATIONS BETWEEN CLINICAL STATUS, QUALITY OF LIFE AND DIGNITY” that is being considered for publication in BMC Palliative Care.

Please, find enclosed the detailed response to the editor and reviewer point raised, describing exactly what amendments has been made to the manuscript text and where these can be viewed. All the references have been checked in order to be validated.

The present work has not been published and is not being considered for publication elsewhere.

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
No conflict of interest has been declared by the authors

The study has been conducted in full accordance with the World Medical Association Declaration of Helsinki (2008)

Please find enclosed the answers to the Associate Editor and reviewer point by point

Dear Associate Editor:

1. To check your English use, including spellings such as rage instead of range, missing full stops and brackets. Check also they you have first spelt out first in full all abbreviations.

The grammar English of the manuscript and the use of abbreviations have been checked

2. Add to the abstract the statistical data to support the results on the QOL and DOL scales.

The statistical data have been added (Page 4 L16)

3. To state in the methods what are the research questions?

The research questions have been added in Methods section (Page 9 L8)

4. The methods ARE not clear on the design of this study. You refer to it as a trial, but it would be more fitting to call it a comparative study as it is not testing a form of intervention. Is study one better described as a cross-sectional observational study and part two a prospective observational study, perhaps this would make it clearer for the reader.

The changes in order to clarify the design of the study have been added in the Methods section (Page 10 L16)

5. Can you detail more on the participants as in whether they are from local town in Spain or drawn from a wider geographical area.

The information about the origin of the patients of the ALS Unit of our centre have been added in the Introduction section. (Page 7 L14)

6. In statistical analysis section in methods, please add in sentence ‘statistical’ before significant.

The information has been added (Page 10 L17)
7. Also in the methods section, can you provide for the international reader what is the El Escorial criteria for ALS?

The information to clarify the ALS criteria has been added in the Introduction section of the manuscript (Page 7 L7)

8. Like Reviewer 2 I would like more details on the selection of the health controls and whether your relatives could be viewed as biased in anyway. Please add this as a potential limitation in your discussion section. Also, are not relatives and family the same thing?

The information about the healthy control cohort has been added in the discussion section. The possible bias and limitation has been explained (page 15 L8)

9. The last sentence in the background should be pitched more neutral, rather than trying to demonstrate something (which could be interpreted as biased) it would be better to say you are exploring the potential value of quality of life and dignity on clinical status.

The sentence has been changed (P9 L11)

10. You do not provide details on patient response rate in the result section, so there is no indication of how representative your findings are of the population of interest. Please revise.

All the patients responded all the questionnaires. This data has been added to the manuscript (P11 L7 and P12 L3)

11. In results section, you need to make clear for all outcomes (clinical status, QOL and DOL) what the score direction of improvement is. As they are presented now it not clear if the results are showing better or worse status.

We have clarified the direction of improvement/worsening of all the outcomes (Page 12 L15)

12. Discussion section is not written in conventional style can you revise so the section 'speaks to' the following headings:

   What did the study set out to do

   What were your main findings

   Limitations and strengths of the study

   How it compares to other studies
Clinical and research implications of the findings.

Check tables and figures headings

The discussion section has been revised and corrected

13. Abbreviations section needs to say what the abbreviations stand for too!

The explanation of the meaning of all the abbreviations has been added (Page 16 L21)

14. As noted by Reviewer 2 the tables and figures are not presented according to journal style. Please consider whether the individual details as given in table 1 and 2 add anything to the paper, I would recommend that these could be grouped such as by clinical onset and gender, then provide an average and range of each item listed. The number of the tables and figures differ between the actual tables/figures and the text, please correct.

Following your advice, it was considered that tables did not take much more than explained in the text therefore, the tables have been deleted, all information that was not yet in the manuscript has been added in the results section

Dear Professor Chang:

1. The controls in this study were selected from the authors' families and relatives. Please explain why? Would these controls have potential biases?

We have been added the explanation of why this control cohort have been chosen and its potential limitation of the study in the discussion section (Page 15 L8)

2. In the results section in abstract and main document, the authors described that "Statistically significant differences were found in the QoL and DoL scales between ALS patients and healthy controls. (p=0.000)." This sentence needs to be revised as "Significantly statistical differences were found in the QoL and DoL scales between ALS patients and healthy controls (both p < 0.001)."

The changes have been done in the manuscript in the abstract and results section (Page 4 L15 and Page 11 L22 respectively)

3. Due to the small sample size, the authors should describe the statistical power of each insignificant finding. If a statistical power is low, the authors should not conclude that there are no significantly statistical differences. In this situation, I recommended the authors to list the statistical powers for each insignificant result or to include more subjects for analysis.
The reviewer is absolutely right. The power of the study is too low to conclude that there are no significant differences. The authors have changed the sense of the conclusion. “ALS is a neurodegenerative disease that clearly affects QoL and dignity. In this pilot study, we identified significant deteriorations in clinical status, functionality, and QoL, but not in DoL, as the disease progressed. It is likely that this preservation of dignity is multifactorial in nature, being closely related to the use of therapies derived from a multidisciplinary approach to the disease. We believe that DoL, not merely QoL, could be an important target in the management of ALS.” (Page 15 L19)

This limitation of the study and the possibility of develop in the future a new study with a higher number of patients have been added in the discussion section (Page 15 L3)

4. The presentation of Table 1 and Table 2 are not according to the journal style. Please revise these two tables.

Following the editor advice, it was considered that tables did not take much more than explained in the text therefore, the tables have been deleted, all information that was not yet in the manuscript has been added in the results section

Carlos Casasnovas