

Peer Review File

Article information: <https://dx.doi.org/10.21037/apm-23-386>

Reviewer A

Comment 1: Please define the terms of BiPAP & PEG in abstract and manuscript

Reply 1: Thank you. The definitions have been added to the abstract (Page 3, line 63-64) and to the manuscript (Introduction, page 5 line 108-109)

删除了: Replay

Comment 2 : Your current study title might contradict the results of the study, so I suggest rename the title: A prospective study for using cognitive decline as a predictor for survival and use of feeding/respiratory support for patients with motor neurone disease in Norway.

Reply 2: Thank you. The title has been changed according to your suggestion (Page 1, line 1-2). Consequently, the running title has been changed as well (Page 2, line 29)

删除了: Replay

Comment 3: Line 113, what is ECAS-N

Reply 3: Thank you. The explanation has been added to the Introduction (Page 6, line 102-103)

删除了: Replay

Comment 4 What is the rationale behind of not offering the PEG/BiPAP?

Reply 4: Thank you. We have added the explanation to the Introduction (Page 5, line 109)

删除了: Replay

Comment 5 What are the implications of your study? The small sample size contributes to the type II error for concluding the negative relationship of cognitive decline and use of support. I suggest not to put much emphasis on the relationship between them

Reply 5. Thank you. We have added explanation of the rationale for offering support by the BiPAP or by the PEG to the Introduction (line 92-96). We agree that the small sample size prevents statistical analysis. Therefore we also evaluated the results visually.

删除了: Replay

We agree that we cannot not put main emphasis on the relationship between the use of support and cognitive decline. However, we did not know that before the start of this study.

Reviewer B

Comment 1 The main limitation of the study is the sample size (n=31), which makes any speculation impossible. I suggest to the authors to broaden the sample to include other centres, as all data is easily obtainable.

Reply 1: Thank you. We agree with your comment. This study is terminated now. We added the statement about the multicenter studies to the Discussion (line 270)

删除了: Replay

Comment 2. In addition, other suggestions are related to neuropsychiatric battery. I suggest to extend the neuropsychological battery, the subdivide the patients according to Strongs classification

Reply 2. Thank you. We agree that extended battery might provide additional information about the cognitive status. Many different neuropsychological batteries have been used in the studies. Our study was designed with ECAS-test because the patients with ALS/MND are physically fragile. It is important to provide concise and informative test. The use of ECAS was based on our previous study which concluded that ECAS is informative and applicable among the other clinical tests in the consultations.

删除了: Replay

Reviewer C

Comment 1 Abstract- please specify which kind of management.

Reply 1. Thank you. We added word «medical management» (Page 3, line 53)

删除了: Replay

Comment 2. Unfluence, like reduce the length of the disease trajectory, complicate the course. There are studies indicating that cognitive decline impact negatively on the length of the illness trajectory.

Reply 2. Thank you, we have extended Background in the Abstract accordingly:

删除了: Replay

Cognitive decline may impact the length of illness trajectory. (Page, line 56-57)

Comment 3. What about invasive ventilator

Reply 3. Thank you. We have changed the text in Abstract. We included use of invasive respirator in the study, but none of the participants used that (Page 3, line 67 and page 4, line 70)

删除了: Replay

Comment 4. Key findings. I would soften this (implication) a bit and discuss this in the discussion

Reply 4. Thank you. We have changed the implication to: *The aids should be installed based on clinical evaluation, individual cognitive status may give additional information (Page 4, line 94-95)*

删除了: Replay

Comment 5. Introduction. ALS/MND-specific cognitive changes typically alter language, executive- and social functions and therefore may influence both use and implementing of advanced aids Suggested add: such as PEG (percutaneous endoscopic gastrostomy) and BiPAP (bilevel positive airway pressure device) (2).

Reply 5: Added to the sentence (Page 5, line 108-109)

删除了: Replay

Comment 6: Material and Methods. Participants. We wrote: We excluded ALS/MND patients who had great difficulties in writing or reading, as well as those with comorbidities in which cognitive function was impaired before the ALS diagnosis. Comment : due to the physical functioning, dyslexia , even cognitive dysfunction

Reply 6. Thank you. We agree that ALS, dyslexia and cognitive dysfunction may be the conditions which make writing and reading difficult. However, there are many other reasons for this dysfunction. Therefore, we did not change the text.

删除了: Replay

Comment 7. Material and methods .. assessed using Kaplan-Meier-plots (7) as well as other graphical methods. Like?

Reply 7. The statement changed to: visual evaluation of individual cases (line 167)

删除了: Replay

Comment 8. What about the patients with cognitive decline and their potential lack of disease recognition and their potential inability to fully grasp the implications of

providing consent? How did you ensure that this subgroup understood the information provided, their rights and their consent enrolled. Were all 31 participants able to give written consent.

Reply 8. Thank you. According to the legislation in Norway, all persons with problems to take care their interests will be given the legal guardian .None of the participants had an appointed guardian and all of them signed by themselves. All ECAS tests were performed after the written consent, as also approved by Ethical Committee. In addition, the study were always presented orally and discussed with the participant as well. All participants gave written consent. We did not change the manuscript.

删除了: Replay

Comment 9 What it means,? A bit fluffy.

Reply 9. Thank you. The sentence in question has been changed to: For BiPAP we observed patients living *several months* after early implementation of BiPAP but also some patients dying soon after receiving BiPAP (diamonds close to the diagonal)(Page 9,line 213)

删除了: Replay

Comment 10 Perhaps add other references supoting your findings

Reply 10 Thank you. We added the reference: The cognitive decline related to ALS will give estimate of prognosis. (Page 10, line 224)

删除了: Replay

Comment 10.I don't see the link between shorter survival- appropriate management abd Q&L Please unfold and perhaps link to other studies

Reply 10. Thank you. We have added reference to this sentence(17) (page 10, line 226)

删除了: Replay

Comment 11 : As a supportive intervention

Reply 11: Sentence changed to:Therefore the nutritional status will be important in ALS/MND care and PEG should be considered timely as a supportive intervention(Page 10, line 230)

删除了: Replay

Comment 12. In terms of BMI, physical functioning do you mean by deterioration?

Reply 12. Thank you. The sentence changed to: Our study demonstrates that installation procedure of feeding tube does not deteriorate *the physical condition* of individuals with ALS/MND.(Page, line 232)

删除了: Replay

Comment 13: what about clinical guidelines?

Reply: Thank you. There are no clinical guidelines regarding BiPAP/PEG installation

删除了: Replay

in ALS/MND in Norway

Comment 14. Can you tell from your functional rating if these patients had a slower ALS progression or from ECAS score, if they were cognitively intact

Reply 14. Thank you. The persons with ALS and cognitive decline had shorter survival. The additional analysis of survival and life prolonging aids in the subgroup with cognitive decline with BiPAP/PEG is not possible to do because few observations in this group.

删除了: Replay

Comment 15. Is this different or common practice around the world (to offer life prolonging aids for the ALS patients with cognitive decline)?

Reply 15. Thank you. It is unknown how the patients with ALS and cognitive decline will be managed. This issue has not been on focus before.

删除了: Replay

Comment 16. Perhaps draw parallel to what other studies have found on negative consequences in relation to these aids and cognitive deficits, e.g. difficulties in medical/intervention compliance or caregiver burden

Reply 16. Thank you. Unfortunately, there are not any other studies, which have investigated the relation between decisionmaking, cognitive decline in ALS and implementation of life-prolonging aids

删除了: Replay

Comment 17. And may this be due lack of collaboration between different departments and ALS team? Or why is that?

Reply 17. Thank you. In our ALS clinic, the specialist of respiratory diseases has been included to the ALS team in many years. One can speculate that the importance of cognitive decline in ALS as well as lack of studies showing benefit or lack of it for this subgroup (ALS with cognitive decline) has not been done before. Therefore the installation of aids was done according to the individual clinical evaluation.

删除了: Replay

Comment 18-19: And what have other studies found on this matter? Please elaborate- I don't understand the statement based on your study e.g. quality of life and disease phases

Reply 18-19. We have erased from the manuscript statement about the quality of life

删除了: Replay

Comment 20. And what would this information potentially mean for your study findings- what influence may this have had on your findings or not

Reply 20. Thank you. The information about no use or different use of PEG and BiPAP could influence the results of study

删除了: Replay

Comment 21. It could be interesting to know the reason behind his decision eg perhaps cognitive impaired or just not wanting to prolong life, afraid procedure etc

Reply 21. Thank you. Unfortunately the reason for denying has not been mentioned in the available documents

删除了: Replay

Comment 22. Measured on which instrument, Kings, ALS-FRS-R? If I understood it right, the implementation of PEG and/or BiPAP did not necessarily reduce the length of the disease course right? So why should this group not be offered the same events as those estimated to have longer course if you anticipate that this may positively impact on their quality of life?

Reply. Thank you. We agree. The reason of this study is that the impact of cognitive decline on installation of life prolonging aids have not been studied before. Therefore, there is no previous knowledge about this issue.

删除了: Replay

Comment 23-24: Consistency... Like a RCT or what would you suggest?

Reply 23-24. Thank you. The last sentences has been changed to: The study had a limited number of participants, therefore the *statistical* analysis of all details such as *optimal time to install life prolonging aids* were not possible. Future studies with multicenter design will answer for this question (Page 12, line 270).

删除了: Replay

Comment 25: Conclusion

Reply: Thank you. We have added conclusion to the end of text: The study demonstrated shorter survival for the patients with ALS/MND with cognitive decline compared to the patients without cognitive decline. The practice and implementation of both BiPAP and PEG did not differ among the ALS/MND patients with and without cognitive decline in Norway.

删除了: Replay

We thank for all grammatical comments. The text has been changed according to these comments.

Reviewer D

Comment 1. Introduction. Even though there are not many studies about cognitive changes, I saddest to present some findings from the literature in order to better contextualize the present study.

Reply 1: Thank you. We added the suggested 2 references (page 1,- line 280-284; ref 2,3)

删除了: Replay

Comment 2. Materials and methods. It is not specified that the two groups were divided according to the cut –off point of the ECAS-N total score. Related to this previous question, did all patients who belonged to the normal cognition group scored above the cut –off value off all ECAS-N subdomains?

Reply2. Thank you. We added the sentence about the groups to the text (Page 7, line 159- 160). Four participants had normal ECAS in total score, but scored lower than cut-off in the subscore,The sentence added to the Results(Page 9, line 196-7)

删除了: Replay

Comment 3. Material and methods. Besides this, do you intend to add any neuropsychological tests apart from the ECAS to determine the cognitive impairment of the patients in a more specific way?

Reply 3. Thank you. We used only ECAS test in this study.

删除了: Replay

Comment 4. Even though the ECAS behavioural scale score has not been considered, has it been somehow recorded whether patients presented apathy or other affective disorders?

Reply 4. Thank you. The patients were followed by the ALS team. Any other disease or condition had been recorded in the patient journal .However, the apathy or other affective disorders were not mentioned in the records.

删除了: Replay

Comment 5. Although it is understandable that the size of the sample hinders detailed analysis, with regard to analyzing the differences between groups, have t-tests or Mann-Whitney U tests been calculated?

Reply 5. Thank you. We did mentioned statistical analyses to confirm significance.

删除了: Replay

Comment 6. Are there previous studies associating cognitive impairment in decision-making for establishing PEG or BiPAP? If yes, I suggest indicating it in this section (lines 232-235).

Reply 6. Thank you. Unfortunately, there are not previous studies associating cognitive impairment in decision-making for establishing PEG or BiPAP. This was one reason of this study.

删除了: Replay

Comment 7. Have other variables such as date of diagnosis and symptom onset been recorded? Together with the baseline ALSFRSR value, they may have an effect on prognosis and may be relevant in this study. These variables should be included and/or discussed.

Reply 7. Thank you. We agree that some symptoms indicating ALS may be present before the diagnosis has been made. However the symptoms without any medical evaluations will be a source for potential bias. All participants were included during 4 months after the ALS diagnosis. We added the sentence to the results (Results,page 9 line 196-7)

删除了: Replay