Original Article | Palliative Medicine and Palliative Care for Other Serious or Advanced Diseases

A prospective study for using cognitive decline as a predictor for survival and use of feeding/respiratory support for patients with motor neuron disease in Norway

Tina Taule[1,2]^, Ole-Bjørn Tysnes[3]^, Jörg Aßmus[4]^, Tiina Rekand[3,4,5]^

[1]Department of Occupational Therapy, Orthopedic Clinic, Haukeland University Hospital, Bergen, Norway; [2]Faculty of Health and Social Sciences, Western Norway University of Applied Sciences, Bergen, Norway; [3]Department of Neurology, Neurologic Clinic, Haukeland University Hospital, Bergen, Norway; [4]Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway; [5]Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Contributions: (I) Conception and design: T Taule, OB Tysnes, T Rekand; (II) Administrative support: OB Tysnes, J Aßmus, T Rekand; (III) Provision of study materials or patients: T Taule, OB Tysnes, T Rekand; (IV) Collection and assembly data: T Taule, OB Tysnes, T Rekand; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Tiina Rekand, PhD. Department of Neurology, Neurologic Clinic, Haukeland University Hospital, Jonas Liesvei 65, N-5021 Bergen, Norway; Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway; Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. Email: tiina.rekand@helse-bergen.no.

Background: There is a need for knowledge regarding the medical management of motor neuron disease/amyotrophic lateral sclerosis (MND/ALS) with and without cognitive decline. It has scarcely been studied whether cognitive decline will influence the course of disease or interfere with the use of life-prolonging aids for respiration and nutrition. Cognitive decline may impact the length of illness.

Methods: Patients were prospectively recruited from an ALS outpatient clinic at Haukeland University Hospital. Participants underwent the standardized cognitive test Edinburgh Cognitive and Behavioral ALS Screen Norwegian version (ECAS-N), clinical examination, and were functionally assessed by the ALS Functioning Rating Scale-revised version (ALS-FRS-R). The time and indication for installation of a feeding tube [percutaneous endoscopic gastrostomy (PEG)] and/or respiratory aid [bilevel positive airway pressure device (BiPAP)] or invasive respirator were retrieved from the medical records. Kaplan-Meier tests were used to study the risk of death and the probability for implementing PEG and/or BiPAP in relation to time from diagnosis. The individual assessment was used for analyzing the establishment of aids in relation to point of death.

Results: A total of 40 patients were evaluated for the study, 31 of whom were finally included. None of the included patients did not use an invasive respirator. The patients were divided into two subgroups (normal cognition or cognitive decline, cut-off 92 points) according to their performance in the ECAS-N. The course of the disease, shown as a risk of death, was higher among the ALS/MND patients with cognitive decline compared to those with cognitive intact function throughout the study period. The cognitive status did not influence the fitting of aids. Use of aids did not influence the survival in subgroups significantly.

Conclusions: The study demonstrated shorter survival for the patients with ALS/MND with cognitive decline compared to those 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.

Keywords: Survival; amyotrophic lateral sclerosis (ALS); motor neuron disease (MND); cognition; aids

Submitted Apr 21, 2023. Accepted for publication Nov 01, 2023. Published online Jan 24, 2024.
doi: 10.21037/apm-23-386
View this article at: https://dx.doi.org/10.21037/apm-23-386

^ ORCID: Tina Taule, 0000-0002-0143-5650; Ole-Bjørn Tysnes, 0000-0002-7668-3157; Jörg Aßmus, 0000-0002-1688-8556; Tiina Rekand, 0000-0002-2506-9503.

Introduction

Amyotrophic lateral sclerosis (ALS) or motor neuron disease (MND) is primarily characterized by decreased motor function, but it may also include cognitive decline (1). The need for cognitive testing after diagnosis of ALS/MND has been generally accepted. However, cognitive changes as a predictor for management and prognosis have not been studied thoroughly (2,3).

ALS/MND-specific cognitive changes typically alter language and executive and social functions and therefore may influence both use and implementation of advanced aids such as percutaneous endoscopic gastrostomy (PEG) and bilevel positive airway pressure device (BiPAP) (4).

In general, there is a need for knowledge about clinical predictive factors for course of ALS/MND and about the management of complications (5). It is also unknown whether all patients with ALS/MND will benefit equally from the supportive measures such as feeding tube (PEG) and non-invasive respiratory assistance (BiPAP) or respirator. Use of those life-prolonging aids will alleviate respiratory and nutritional problems and even temporarily improve the functional status. However, the use of such aids is technically complicated and they require proper administration every day. Therefore, their adoption might be onerous for people with cognitive decline and improvement of their health will be uncertain.

The aim of this study was to evaluate cognition as a possible factor that alters the course of ALS. The study also evaluates whether the feeding tube and respiratory support will be implemented according to clinical need or the decision will be influenced by cognitive condition.

Before the start of the study, four hypotheses were formulated:

(I) Patients with low baseline scores on the Edinburgh Cognitive and Behavioral ALS Screen Norwegian version (ECAS-N) will not be offered advanced life-prolonging treatment in the form of feeding tube (PEG) or implementation of respiratory aids (BiPAP mask) or respirator.

(II) Patients with cognitive decline at baseline will have different point of time to establish feeding tube (PEG) in relation to clinical need.

(III) Patients with cognitive impairment related to ALS at baseline will have different timing for implementation of respiratory aids (BiPAP mask or respirator).

(IV) Consequently, ALS patients' cognitive status may predict the length of disease.

We present this article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-23-386/rc).

Highlight box

Key findings

- The study confirms shorter survival for the patients with amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND) with cognitive decline compared to those without cognitive decline.

What is known and what is new?

- Installation of feeding tube [percutaneous endoscopic gastrostomy (PEG)] and/or non-invasive respiratory mask [bilevel positive airway pressure device (BiPAP)] is not dependent on cognitive status in Norway.
- Installation of PEG and/or BiPAP do not influence the length of survival.

What is the implication, and what should change now?

- The aids should be installed based on clinical evaluation; individual cognitive status may give additional information.
- Shorter survival in patients with ALS/MND and cognitive decline predicts shorter timeline for installation of life-prolonging aids.

Methods

Study design

The study was performed prospectively as a cohort study.

Protocol and registration

The study was registered at ClinicalTrials.gov (registration number NCT03578796; available at https://clinicaltrials.gov/ct2/show/NCT03578796). The protocol has been published (6).

Participants

The patients were recruited from the ALS/MND outpatient clinic at Haukeland University Hospital within 4 months after being diagnosed with ALS/MND (6). Between 30 April 2017 and 1 May 2021, the study participants were included in conjunction with their first visit to the hospital.

To ensure equal results of tests among participants, only persons who were native Norwegian speakers were included. 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. These exclusions were necessary to avoid

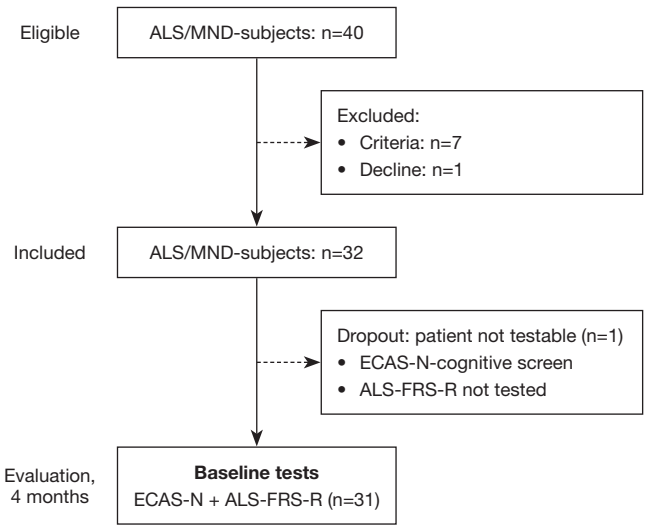

Figure 1 Flow diagram for inclusion to the study. ALS/MND, amyotrophic lateral sclerosis/motor neuron disease; ALS-FRS-R, ALS-Functional Rating Scale-Revised; ECAS-N, Edinburgh Cognitive and Behavioral ALS Screen-Norwegian version.

confusion about results derived from the cognitive tests.

Data collection

Participants underwent the standardized cognitive test ECAS-N after attending for the first time (6). The ECAS is a brief, well-established screening test for detecting cognitive and behavioral changes in patients with ALS. It has been designed for mapping of ALS-specific cognitive challenges (4) and has previously been thoroughly evaluated (6,7). The cut-off value for ECAS-N total score (≤92 points) indicated cognitive impairment. The clinical decision of implementation of aids were made by specialists who were unaware of the results of ECAS-N. The two groups were divided according to the cut-off point of the ECAS-N total score. Physical and medical information were assessed using the ALS Functioning Rating Scale-Revised (8).

The use of aids, point of time for installation, and evaluations were derived from the patient records.

Sample size

Annually from 2012 to 2017, 12 to 15 patients were diagnosed with ALS at our clinic. Based on this census (unpublished data), a total of 50 to 60 patients were expected to be included in the current study over a 4-year period.

Statistical analysis

Data were analyzed using SPSS version 26.0 (9); R 4.2.1 (10); and MATLAB version 9.0 (11). Due to minimal variation in the data, the ECAS-N psychosis score and behavioral screening were not included in the analysis.

The patients were divided in two subgroups according to their performance in ECAS-N (ALS with normal cognition and ALS with cognitive decline).

Descriptive statistics were used to characterize the sample at baseline. The time to death as well as the time to implementation of feeding or respiratory aids for patients with or without cognitive decline were assessed using Kaplan-Meier plots (12) as well as visual evaluation of individual cases. Due to the low number of events, we abstained from testing for differences.

Ethical considerations

The Regional Ethical Research Committee of the Western Norwegian Health Authority approved this study (reference number 2016/2187/REK west). The study was undertaken with the understanding and written informed consent of each participant. The study conformed with the World Medical Association Declaration of Helsinki (as revised in 2013) (13).

Results

A total of 40 patients were evaluated for the study, 31 of whom were eligible and could be included. The inclusion process is shown in *Figure 1*. All participants were included to the study latest 4 months after their ALS/MND diagnosis.

The baseline characteristics of the participants are displayed in *Table 1*. We did not find any significant differences between the patients with or without cognitive decline. Notably, none of the patients younger than 60 years showed cognitive decline. Some four participants had normal ECAS in the total score, but scored lower than normal cut-off in the subscore.

Figure 2 shows the time-dependent risks for death (*Figure 2A*), for installation of PEG (*Figure 2B*) and BiPAP (*Figure 2C*) for patients with and without cognitive decline, as well as the median time to event. According to the confidence bands, there were no significant differences between the curves for any of the outcomes. Although not significant

Table 1 The clinical characteristics of participants

Variables	Cognitive decline	
	Yes (ECAS-N ≤92) (n=11)	No (ECAS-N >92) (n=20)
Sex, female, n [%]	4 [36]	7 [35]
Age, >60 years, n [%]	11 [100]	14 [70]
ECAS-N baseline†	90 [73–92]	109 [94–123]
ALS with bulbar onset, n [%]	1 [9]	3 [15]
ALS-FRS-R†	37 [23–45]	40 [26–45]

†, median [minimum–maximum], *t*-test. ALS-FRS-R, Amyotrophic Lateral Sclerosis-Functioning Rating Scale-Revised; ECAS-N, Edinburgh Cognitive and Behavioural ALS Screen-Norwegian version; ALS, amyotrophic lateral sclerosis.

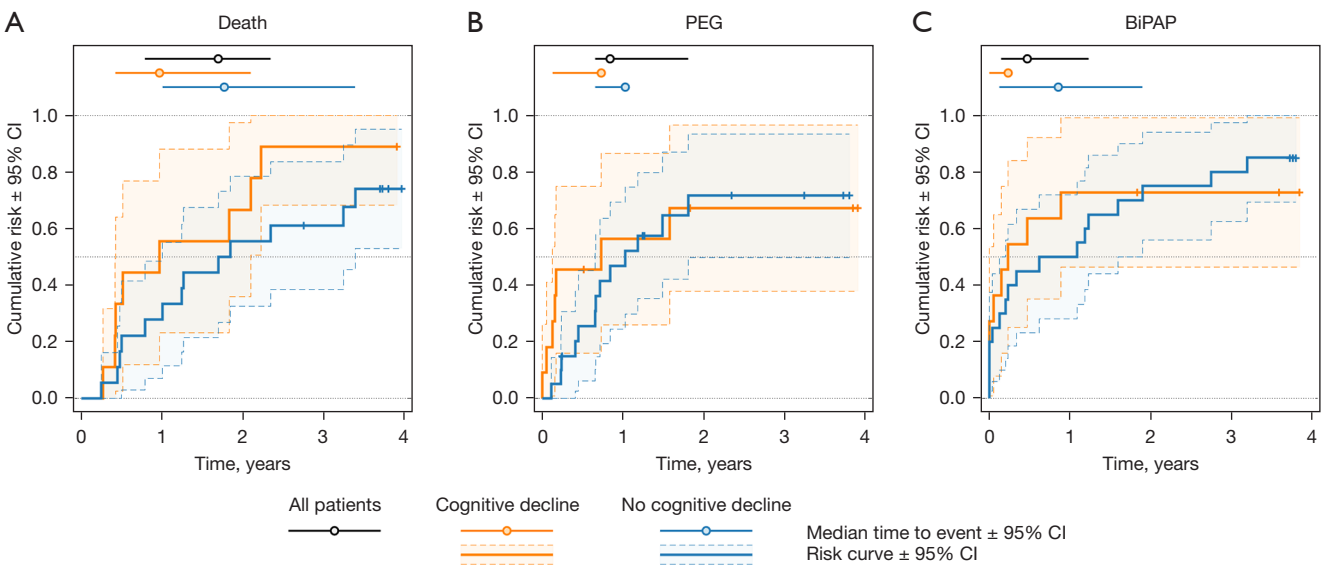

Figure 2 Cumulative risk for death (A), installation of feeding tube (PEG) (B) or non-invasive respiratory aid (BiPAP) (C). CI, confidence interval; PEG, percutaneous endoscopic gastrostomy; BiPAP, bilevel positive airway pressure device.

[overlap of confidence intervals (CIs) with the median values], we observed that all three events appeared earlier in median for the patients with cognitive decline, namely, death after 0.97 (0.42–2.0) years whereas 1.8 (1.0–3.3) years without cognitive decline. For some of the measures, there were too few events after median time to compute the upper limit of the CI.

There were ten patients who were deceased or were alive without the PEG and four patients without BiPAP in this study.

Figure 3 shows for each patient the time to death or last observation versus the time to PEG (*Figure 3A*)/BiPAP (*Figure 3B*), respectively.

For PEG, we observed a number of patients dying without PEG (left pointing triangles on diagonal) whereas others lived quite long with early PEG (diamonds in the lower part of the figure). We did not observe patients dying soon after receiving PEG (no diamonds close to the diagonal). 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). We did not observe a different pattern of the disease for patients with or without cognitive decline, neither for PEG nor for BiPAP.

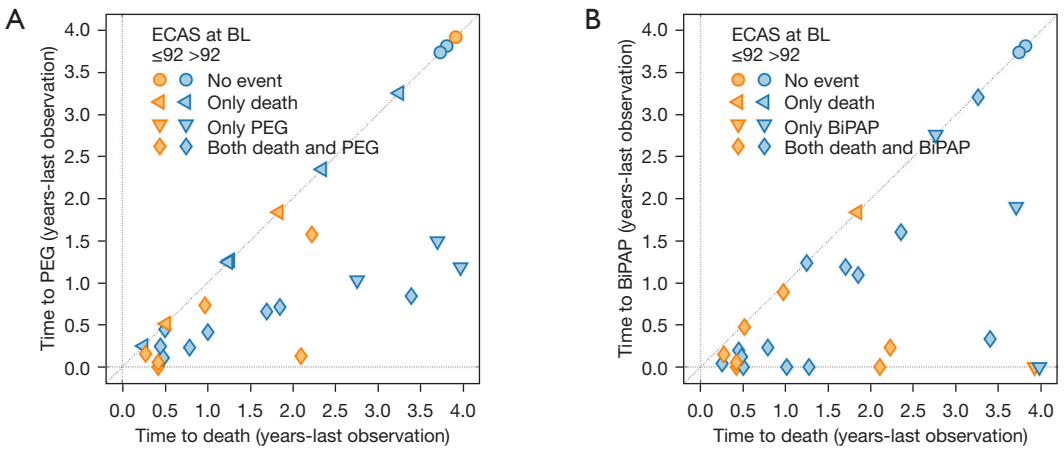

Figure 3 Observation of individual cases. ECAS, Edinburgh Cognitive and Behavioral ALS Screen; BL, baseline; PEG, percutaneous endoscopic gastrostomy; BiPAP, bilevel positive airway pressure device; ALS, amyotrophic lateral sclerosis.

All patients were included with complete data.

Discussion

This study shows that cognitive decline after the onset of ALS will predict shorter course of ALS. The finding confirms our hypothesis and supports the previously shown connection between the cognitive changes and shortened survival in ALS/MND (14-19). Our study indicates that cognitive decline should be mapped after ALS/MND diagnosis and should be measured by a clinically applicable tool such as the ECAS. The cognitive decline related to ALS will give an indication of prognosis (14-19). The prediction of shortened survival will help the patients as well as caregivers and specialists to implement appropriate management to achieve best possible quality of life for all patients with ALS/MND (9).

There are no randomized studies that have investigated the effect of feeding tube in ALS (17-19). Previous studies as well as a meta-analysis have demonstrated however that body mass index will influence survival (10,11,20). Therefore, the nutritional status will be important in ALS/MND care and PEG should be promptly considered as a supportive intervention. Our study demonstrates that the installation procedure of feeding tube does not deteriorate the physical condition of individuals with ALS/MND.

The implementation of non-invasive respiratory aids has been studied before and is a usual approach in the course of ALS/MND (11). In our study, the respiratory evaluations were performed regularly every 3 months and a BiPAP mask was offered according to the clinical evaluation. The installation itself as well as time of installation of BiPAP did not significantly change the course of ALS/MND. It should be noted that some patients continued to live for a long period with respiratory support.

According to clinical understanding, unnecessary changes in nutritional state and respiration will weaken the patient. In Norway, the feeding tube will usually be implemented before the installation of BiPAP, except if the patient has respiratory problems as the first and leading symptoms. Our study demonstrated that the cognitive status did not influence decisions to establish PEG or BiPAP. We did not notice any negative consequences by offering these aids to all eligible patients.

Our results show that the aids were implemented in the same point of time and with the same frequency regardless of normal or declined cognition; this finding contradicts our hypotheses. However, the dependency of survival on cognitive status could therefore have been analyzed without any additional adjustments. The analysis of single cases showed that installation of aids and point of time for death were not related to each other.

Respirator with tracheostomy as an invasive aid was not installed for any of the study participants. Therefore, the analysis only included patients who used non-invasive respiratory support, BiPAP mask, and the results cannot be generalized for all respiratory aids. The decision to install a BiPAP mask was made based on clinical evaluation of respiratory function and did not differ between the patients with and without cognitive decline.

Despite that the decisions for installation of PEG or BiPAP did not differ in both subgroups, the course of ALS

remained different: the patients with cognitive decline had a shorter course of disease. Based on evaluation of single cases, the aids did not change the course in both subgroups. This leads to the assumption that the aids have similar life-prolonging characteristics independent of a patient's cognitive status. In our study, we did not analyze how the prescribed use of PEG and BiPAP were executed at home. Meanwhile, the assistance from local home nurses is not limited in Norway and changes in prescribed use were not reported. Therefore, we believe that use of the aids was generally as prescribed. In addition, the patients were regularly followed up at the outpatient clinic by the specialists, and any aberration should have been discovered. In this study, one patient did not want to establish a feeding tube despite clinical indication and his wishes were respected.

This study did not answer whether patients with predicted short survival will benefit from the aids. Our study did not reveal any additional problems related to the PEG and BiPAP. 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 are required to answer this question.

Conclusions

The study demonstrated shorter survival for the patients with ALS/MND with cognitive decline compared to those 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.

Acknowledgments

Funding: This work was supported by the Western Norwegian Regional Health Authority (No. 912158, 2017 to T.T.).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-23-386/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-23-386/dss

Peer Review File: Available at https://apm.amegroups.com/article/view/10.21037/apm-23-386/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-23-386/coif). T.T. reports funding from the Western Norwegian Regional Health Authority under Grant number 912158, 2017. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study conformed with the World Medical Association Declaration of Helsinki (as revised in 2013). The Regional Ethical Research Committee of the Western Norwegian Health Authority approved this study (reference number 2016/2187/REK west). The study was undertaken with the understanding and written informed consent of each participant.

References

1. Beeldman E, Raaphorst J, Klein Twennaar M, et al. The cognitive profile of ALS: a systematic review and meta-analysis update. J Neurol Neurosurg Psychiatry 2016;87:611-9.
2. Elamin M, Phukan J, Bede P, et al. Executive dysfunction is a negative prognostic indicator in patients with ALS without dementia. Neurology 2011;76:1263-9.
3. Westeneng HJ, Debray TPA, Visser AE, et al. Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model. Lancet Neurol 2018;17:423-33.
4. Strong MJ, Abrahams S, Goldstein LH, et al. Amyotrophic lateral sclerosis - frontotemporal spectrum disorder (ALS-

FTSD): Revised diagnostic criteria. Amyotroph Lateral Scler Frontotemporal Degener 2017;18:153-74.
5. Creemers H, Grupstra H, Nollet F, et al. Prognostic factors for the course of functional status of patients with ALS: a systematic review. J Neurol 2015;262:1407-23.
6. Taule T, Spilde Morland A, Arnevik Renså M, et al. Edinburgh Cognitive and Behavioral Amyotrophic Lateral Sclerosis Screen (ECAS) in Norway: Protocol for validation and a prospective cohort study. Contemp Clin Trials Commun 2019;14:100347.
7. Taule T, Morland AS, Aßmus J, et al. Translation, cultural adaptation, and validation of a screening test for cognitive and behavioural changes in amyotrophic lateral sclerosis. Disabil Rehabil 2022;44:7069-77.
8. Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci 1999;169:13-21.
9. Ng L, Khan F, Young CA, et al. Symptomatic treatments for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev 2017;1:CD011776.
10. Dardiotis E, Siokas V, Sokratous M, et al. Body mass index and survival from amyotrophic lateral sclerosis: A meta-analysis. Neurol Clin Pract 2018;8:437-44.
11. Dorst J, Ludolph AC, Huebers A. Disease-modifying and symptomatic treatment of amyotrophic lateral sclerosis. Ther Adv Neurol Disord 2017;11:1756285617734734.
12. Collett D. Chapter 2: Some non-parametric procedures. In: Modelling Survival Data in Medical Research (Chapman & Hall/CRC Texts in Statistical Science). 3rd ed. Philadelphia, PA: Chapman & Hall/CRC; 2014.
13. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191-4.
14. Xu Z, Alruwaili ARS, Henderson RD, et al. Screening for cognitive and behavioural impairment in amyotrophic lateral sclerosis: Frequency of abnormality and effect on survival. J Neurol Sci 2017;376:16-23.
15. Ye S, Jin P, Chen L, et al. Prognosis of amyotrophic lateral sclerosis with cognitive and behavioural changes based on a sixty-month longitudinal follow-up. PLoS One 2021;16:e0253279.
16. Agosta F, Spinelli EG, Riva N, et al. Survival prediction models in motor neuron disease. Eur J Neurol 2019;26:1143-52.
17. Nguyen C, Caga J, Mahoney CJ, et al. Behavioural changes predict poorer survival in amyotrophic lateral sclerosis. Brain Cogn 2021;150:105710.
18. Cheng HWB, Chan KY, Chung YKJ, et al. Supportive & palliative interventions in motor neurone disease: what we know from current literature? Ann Palliat Med 2018;7:320-31.
19. Hardiman O. Management of respiratory symptoms in ALS. J Neurol 2011;258:359-65.
20. Braun MM, Osecheck M, Joyce NC. Nutrition assessment and management in amyotrophic lateral sclerosis. Phys Med Rehabil Clin N Am 2012;23:751-71.

Cite this article as: Taule T, Tysnes OB, Aßmus J, Rekand T. A prospective study for using cognitive decline as a predictor for survival and use of feeding/respiratory support for patients with motor neuron disease in Norway. Ann Palliat Med 2024;13(1):86-92. doi: 10.21037/apm-23-386