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Clinical Short Communication

Disease progression impacts health-related quality of life in amyotrophic lateral sclerosis

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ABSTRACT

Objectives: To determine the impact of disease progression on health-related quality of life in amyotrophic lateral sclerosis (ALS).
Methods: A total of 161 patients with ALS were enrolled. Assessments included the revised ALS Functional Rating Scale and the ALS Assessment Questionnaire (ALSAQ-40). Data analysis comprised linear regression and multivariate analyses.
Results: ALSFRS-R score ($\beta = 0.75$, $p < 0.001$), depression ($\beta = 0.08$, $p < 0.001$), pain ($\beta = 0.07$, $p < 0.001$), hopelessness ($\beta = 0.07$, $p = 0.001$), and progression rate ($\beta = 0.02$, $p = 0.02$) explained 76% of the ALSAQ-40 summary index variance. Progression rate alone explained 7% of the ALSAQ-40 summary index variance. The subdomains of emotional well-being, followed by ADL, and finally communication and eating were most strongly influenced by progression rate.
Conclusion: Our study demonstrates the importance of physical health for emotional well-being. In particular, slower disease progression is associated with higher levels of emotional well-being in ALS.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a multi-systemic neurodegenerative disorder that is characterized by motor neuron degeneration and several non-motor symptoms [1,2]. No cure currently exists and treatment mainly aims to improve or sustain quality of life (QoL) and health-related QoL. Various factors influence QoL and health-related QoL in ALS. Importantly, depression and hopelessness are associated with poor QoL in ALS [3–6]. Anxiety adversely affects QoL and is more prevalent in ALS patients relative to the general population [7]. In addition to psychological components, physical dysfunction (e.g dysphagia and pain) is also associated with worsening of QoL [8,9]. However, the impact of disease progression on health-related QoL in ALS remains to be fully elucidated. This issue is of special importance, because the deterioration of physical ability in ALS is highly variable [10]. Here, we hypothesized that health-related QoL differs between patients who experience a rapid decline in physical function (i.e. over a few months) and those with a more protracted disease trajectory.

2. Methods

2.1. Subject recruitment and assessments

In total, 200 patients were consecutively recruited from the outpatient clinic of the Department of Neurology, Jena University Hospital between May 2013 and December 2017. Data from 161 patients were subsequently used for analyses owing to incomplete questionnaire responses. Clinical and epidemiological characteristics did not differ between patients with full and incomplete data. Written informed consent was obtained from all participants and the study was approved by the local Ethics committee (#3633-11/12). Inclusion criteria were: diagnosis of definite, probable, laboratory-supported probable, or possible ALS (as determined by the revised El-Escorial criteria) [11]. Exclusion criteria were: delirium, acute infection, inability to understand and fulfill questionnaires, presence of tracheostomy.

The revised ALS Functional Rating Scale (ALSFRS-R) was used to quantify physical impairment [12]. Health-related QoL was measured

Abbreviations: ADL, Activities of Daily Living; ALS, Amyotrophic Lateral Sclerosis; ALSAQ-40, Amyotrophic Lateral Sclerosis Assessment Questionnaire; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale Revised; ECAS, Edinburgh Cognitive and Behavioral Amyotrophic Lateral Sclerosis Screen; QoL, Quality of Life; SI, Summary Index

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using the German ALS Assessment Questionnaire (ALSAQ-40) [13]. The ALSAQ-40 assesses five domains: physical mobility (10 items), activities of daily living/independence (10 items), eating and drinking (3 items), communication (7 items) and emotional well-being (10 items). Patient responses are marked on a Likert-type scale. Answers from each of the five scales are then transformed onto a scale of 0–100 (where 0 = maximum health, 100 = poorest health). Questions refer to the patient's condition during the past 2 weeks. The internal consistency, reliability, construct validity, and psychometric robustness of the ALSAQ-40 have been previously confirmed by several independent studies, indicating that it provides a meaningful and acceptable instrument for assessing HRQoL in ALS [13–15] that is also sensitive to changes over time [16,17].

In addition, the presence and pervasiveness of depressive symptoms (ALSAQ-40 item 38), hopelessness (ALSAQ-40 item 34), dysphagia (ALSFRS-R item 3), and pain (ALSAQ-40 item 7) were determined. Disease progression rate was calculated as [48 - current ALSFRS-R score]/disease duration in months (Kimura et al. 2006). Cognition was assessed with the Edinburgh Cognitive and Behavioral ALS Screen (ECAS) [18,19]. The ECAS is a multi-domain neuropsychological screening tool that assesses executive function, social cognition, verbal fluency and language (ALS-specific), as well as memory and visuospatial abilities (both not specific to ALS).

2.2. Statistics

The SPSS software package (version 25.0; IBM Corporation, USA) was used for all statistical analyses. Prior to statistical analysis, data were checked for outliers. Normality was assessed using the Shapiro-Wilk's Test. Clinical parameters between patients in different King's stages were compared using either the Chi-square test or an Anova with post-hoc Bonferroni-correction, depending on normality distribution. Correlations between the ALSAQ-40 and clinical variables were assessed using the Pearson's and Spearman's tests for normally and non-normally distributed data, respectively. Multiple linear regression with step-wise forward selection was used to evaluate the relationship between the ALSAQ-40 summary index (SI) (dependent variable) and clinical variables. Variables known to be relevant for health-related QoL (depression, hopelessness, pain, dysphagia, ALSFRS-R), the calculated disease progression rate and the presence of dementia (according to the total ECAS score) were included as independent variables. Auto-correlation was excluded by the Durbin-Watson statistic. The Bayesian Information Criterion was used to select the “best” subset of predictor variables to compare the fit of the models. Finally, a multivariate regression model with the ALSAQ-40 sub-domains as dependent variables and progression rate as the independent variable was performed. Statistical significance was set at $p < 0.05$.

2.3. Data availability

Anonymized data from this study will be shared with qualified investigators on reasonable request.

3. Results

All clinical data are detailed in Table 1. The majority of patients were in Kings Stages 2 and 3. Patients in different King's stages did not significantly differ in terms of age, sex, ALS sub-type and ECAS total score. As expected, patients in later King's stages (4 and 5) had significantly lower ALSFRS-R scores and higher ALSAQ-40 SI ($p < 0.05$). The worst health-related QoL was observed in the ALSAQ-40 sub-domains of ADL, communication, and mobility.

Depressive symptoms were frequently reported by patients, with 19.8%, 26.5%, 16%, and 5.6% complaining of having depressive thoughts occasionally, sometimes, often and always, respectively. The pervasiveness and frequency of depressive symptoms correlated with both the progression rate and the ALSAQ-40 SI (Fig. 1A, B). The total ALSFRS-R score and progression rate significantly correlated with the ALSAQ-40 SI (Fig. 1C, D).

Table 1
Patient demographics and clinical parameters (n = 161).

Age [mean, SD, years]	61.8	11.5
Disease duration [mean, SD, months]	23	20
Female [n, %]	66	41
Limb onset [n, %]	104	64.6
Bulbar onset [n, %]	57	35.4
Disease progression rate [mean, SD]	0.9	1.0
Disease severity		
• ALSFRS-R total (item 1–12, max 48) [mean, SD]	34.8	8.6
• ALSFRS-R bulbar (item 1–3, max 12) [mean, SD]	8.6	3.4
• ALSFRS-R cervical (item 4–6, max 12) [mean, SD]	6.8	3.7
• ALSFRS-R lumbar (item 7–9, max 12) [mean, SD]	6.5	3.7
• ALSFRS-R respiratory (item 10–12, max 12) [mean, SD]	9.8	2.5
Kings stage 1 [n, %]	26	16.1
Kings stage 2 [n, %]	38	23.6
Kings stage 3 [n, %]	56	34.8
Kings stage 4 [n, %]	33	20.5
Kings stage 5 [n, %]	8	5.0
ECAS total score [mean, SD]	95	19
Health-related quality of life		
• ALSAQ-40 Summary index [mean, SD]	39.0	19.0
• ALSAQ-40 Mobility [mean, SD]	40.3	30.1
• ALSAQ-40 Activity of daily living [mean, SD]	44.0	31.6
• ALSAQ-40 Eating [mean, SD]	24.4	29.6
• ALSAQ-40 Communication [mean, SD]	43.2	36.2
• ALSAQ-40 Emotional well-being [mean, SD]	34.6	23.1

Revised ALS Functional Rating Scale (ALSFRS-R), ALS Assessment Questionnaire (ALSAQ-40), Edinburgh Cognitive and Behavioral ALS Screen (ECAS), Progression rate = (48 – current ALSFRS-R)/Disease duration in months, standard deviation (SD).

In the final model, the total ALSFRS-R score ($\beta = 0.75$, $p < 0.001$), depression ($\beta = 0.08$, $p < 0.001$), pain ($\beta = 0.07$, $p < 0.001$), hopelessness ($\beta = 0.07$, $p = 0.001$), and progression rate ($\beta = 0.02$, $p = 0.02$) explained 76% of the ALSAQ-40 SI variance ($F(10,149) = 51.8$, $p < 0.001$, adjusted $R^2 = 0.76$). Dysphagia and the presence of dementia were not significant predictors. Progression rate alone explained 7% of the ALSAQ-40 SI variance ($F(1,159) = 14.0$, $p < 0.001$, adjusted $R^2 = 0.07$).

In the multivariate regression analysis, the subdomains of emotional well-being, followed by ADL, and finally communication and eating were most strongly influenced by PR (Fig. 1E).

4. Discussion

The present study confirms that physical function and psychological factors are important predictors of health-related QoL in ALS [5,6,20–25]. Here, physical ability and depression had the strongest influence on health-related QoL. The influence of the ALSFRS-R score on health-related QoL is unsurprising, as the ALSAQ-40 is predominantly weighted towards physical function. While substantial evidence for depression being a core predictor of health-related QoL in ALS already exists, the present study has revealed that the progression rate is also a relevant and independent predictor of health-related QoL in ALS.

There is also evidence from other chronic disorders that psychological well-being is related to slower disease progression [26]. In particular, the importance of physical health for emotional well-being has been reported [27]. Accordingly, the emotional well-being subdomain was most strongly influenced by disease progression in our analysis. Interestingly, a meta-analysis showed that physically diseased patients with higher levels of emotional well-being have better recovery and survival rates than patients with low levels of emotional well-being stress [28].

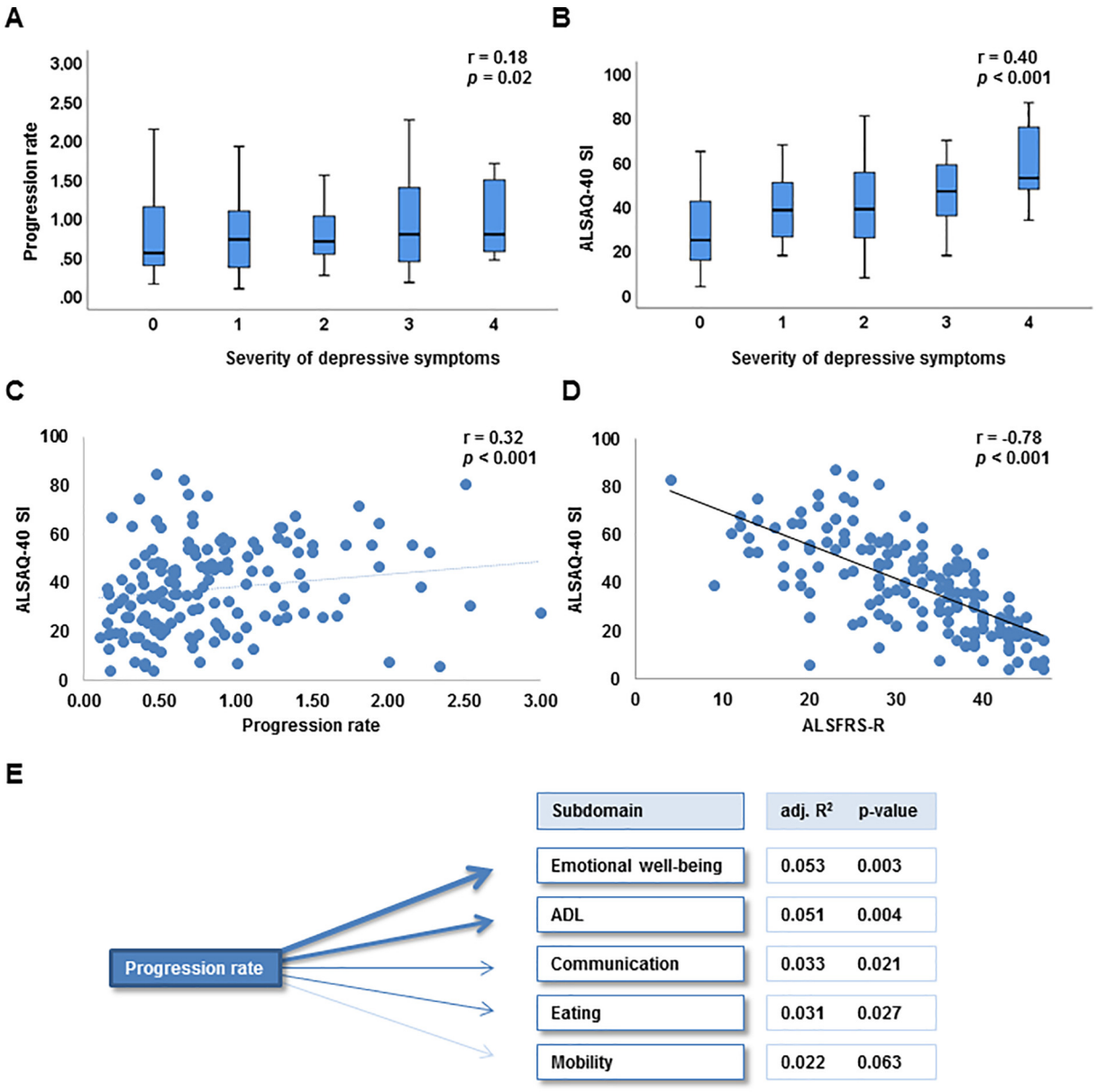

Fig. 1. Relationship between health-related quality of life and clinical factors in ALS.
Depressive symptoms (never (0), occasionally (1), sometimes (2) often (3) and always (4)) correlated with A) progression rate and B) ALS Assessment Questionnaire 40 summary index (ALSAQ-40 SI). The ALSAQ-40 summary index (SI) is plotted against C) disease progression rate and D) the revised ALS Functional Rating Scale (ALSFRS-R) score. E) Multivariate analysis shows that progression rate exerts the strongest influence on emotional well-being, followed by activities of daily living (ADL), communication and eating.

The present study is not without limitations. Its cross-sectional design constrains any analysis of the causative links between progression and health-related QoL. Further, while the progression rate as calculated here is commonly used in ALS research, longitudinal indices would be more reflective of overall disease progression.

The present study was also not designed to assess the impact of cognitive deficits on health-related QoL. Varying degrees of cognitive and behavioral disturbances are commonly reported in ALS [29,30]. A previous study with 86 ALS patients reported that severe cognitive deficits (as assessed by the ALS Cognitive-Behavioral Screen) were not associated with a decline in general QoL [31]. Conversely, another study with 31 ALS patients reported that their QoL scores (Schedule for Evaluation of Individual Quality of Life-Direct Weighting) correlated negatively with the presence of self-rated everyday cognitive difficulties [24]. However, this association may have been influenced by the subjectivity inherent in self-reporting. It is also worth acknowledging that behavioral data was not included for patients as the objective of the study wasn't focused on this and there are significant logistical constraints with obtaining this data; however, behavioral changes may also impact the QoL of patients and their caregivers. Lastly, while we have included the presence of dementia as a cofactor, the complex interplay between cognitive deficits, QoL and caregiver burden needs further analysis.

5. Conclusion

The present study demonstrated that higher levels of emotional well-being correlate with slower disease progression in ALS. However we acknowledge that the cross-sectional design of the study may limit the generalization of these results. Future studies should therefore evaluate the longitudinal interplay among disease progression, emotional well-being and survival in ALS.

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Declaration of interest statement

The authors have no conflicts of interest to declare.

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