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ORIGINAL ARTICLE

The Dynamics of Quality of Life in ALS Patients and Caregivers

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Abstract
Background Quality of life (QOL) in people with amyotrophic lateral sclerosis (ALS) and their caregivers may depend on disease progression, premorbid characteristics (e.g., personality or demographics), or idiosyncratic effects (e.g., life events unrelated to the disease). Furthermore, effects may differ for patients and caregivers; physical decline may impact the caregiver more than the patient.
Purpose The present study examined QOL in ALS patients and their caregivers over the course of the illness.
Methods Longitudinal data from ALS patients (N=55) and caregivers (N=53) yielded estimates of the sources of and changes over time in total QOL as well as individual domains (psychological existential, physical, and social) as measured by the McGill Quality of Life Questionnaire.
Results For both patients and caregivers, about half of QOL variance emerged from stable individual differences. Passage of time did not affect QOL in patients, but total QOL and particularly QOL related to physical symptoms declined over time in caregivers. Gender was mostly unrelated to QOL in patients and caregivers, but younger caregivers had lower QOL across a number of domains.
Conclusions Low QOL among ALS patients is likely due to pre-existing individual differences, whereas both individual differences such as demographics (e.g., age) and disease progression are likely to affect QOL among caregivers.

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Keywords ALS · Quality of life · Well-being · Disease progression

Abbreviations

ALS	Amyotrophic lateral sclerosis
QOL	Quality of life
SIS	Single item score
ICC	Intraclass correlation
MLM	Multilevel modeling
MI	Multiple imputation
ALS-FRS	Amyotrophic lateral sclerosis functional rating scale
MAR	Missing at random

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive and invariably fatal neurodegenerative disease with few options for treatment and no cure. Most people with ALS die within 5 years of the onset of symptoms after experiencing progressive paralysis. Because life-extending treatments are limited to one drug that extends life by only a few months, quality of life (QOL) is an important theoretical and clinical issue for people with ALS. Furthermore, caregiving is a significant role in ALS, with most people with ALS cared for at home, many of them until their death [1]. The burden of caring for a person with ALS who may need assistance with almost every activity of daily living means that QOL is an important issue for ALS caregivers as well.

People with ALS may derive a sense of well-being or subjective QOL from several different sources. One reasonable hypothesis is that QOL decreases over time as

physical functioning declines. However, recent studies suggest that QOL is not likely determined by disease progression or loss of physical function [2]. For example, despite compromised physical function, the majority of people with ALS rated their QOL as 8 or better on a scale of 1 to 10 [3, 4]. Several studies have found that even when people with ALS are supported by mechanical ventilation, they are generally satisfied with their quality of life, are not depressed, and have a positive worldview (e.g., [5, 6]).

The effect of disease progression on QOL, however, differs for caregivers. One report found that caregivers of people with ALS spend an average of 11 h a day in caregiving, even when they are receiving assistance from hospice or other professional services, and 50% of these caregivers reported feeling physically and psychologically unwell [1, 7]. Caregivers do appear to be adversely affected by disease progression (e.g., [3, 4, 8–10]). Clinical impairment directly affects caregiver burden [11, 12]. Studies of spousal caregivers' QOL found that as their spouses' health declined over time, caregivers' scores on measures of physical and mental health also declined, while their spouses' QOL remained stable [1, 13, 14]. A recent review of 32 studies of the impact of ALS on caregivers found that nearly 50% of European ALS caregivers score below the population norms on measures of physical health [15].

Beyond disease progression, another source of QOL for both people with ALS and their caregivers is premorbid personal characteristics such as personality, social relationships, and demographic characteristics. The characteristics and degree of psychological health that were part of a person's personality and life circumstances before a diagnosis with ALS are likely to carry over into his or her life after diagnosis and likewise for caregivers [16]. For example, reports indicate that individual differences in optimism, flexibility, humor, and spirituality are important in predicting QOL for people with ALS, and these are likely to carry over from the premorbid period [17–20]. Likewise, social relationships established before onset of the disease may provide a resource that enhances QOL. Psychological well-being and QOL are strongly influenced by the social support provided to people with ALS [8, 21]. Demographic factors such as age and gender may also be important. In one study, younger people with ALS tend to report higher QOL than older people [17].

The same variation in individual characteristics may be important for caregiver QOL. For example, among dementia caregivers, although there is some increase in psychological distress with disease progression, there is also substantial evidence for stability in caregiver well-being over time and across transitions such as transfer to a nursing home [22, 23]. Individual differences in personality characteristics such as neuroticism and optimism as well as social support account for part of this stability [24, 25]. One study of ALS caregivers found that social support at initiation of the study was the best predictor of change in psychological distress over time [10].

Finally, ALS does not preclude other life events that may affect QOL for patients and caregivers. ALS does not preclude the ordinary and even extraordinary joys and sorrows of life, such as births and deaths. These individual changes that are unrelated to the disease and to premorbid characteristics would be expected nonetheless to affect QOL.

The Present Study

The present study examined the sources of QOL in people with ALS and their caregivers. To do so, we utilized self-reported QOL assessments from a longitudinal study that allowed us to model changes in QOL over the course of time after ALS diagnosis. Previous studies have either been cross-sectional [8] or used analysis strategies that did not allow for differences between people in how much time had already passed since substantive milestones such as diagnosis [3, 4]. Using multilevel modeling, we report on QOL changes across the scope of the disease rather than the scope of the study. We measured QOL using the McGill Quality of Life (MQOL) Questionnaire, which assesses multiple domains of well-being independently (e.g., physical, psychological), including positive contributions to QOL and a person's meaning in life and personal growth (i.e., existential well-being), which potentially increases in seriously ill patients [26]. Although definitions and measures of QOL are numerous, according to the World Health Organization, QOL is a general and subjective term referring to “the physical, mental, and social well-being” of individuals, “and not merely the absence of disease or infirmary”[27]. Many QOL measures target particular or unspecified components of QOL, lack conceptual clarity, and are problem-focused (i.e., fail to assess positive contributions to QOL) [28–30]. However, the measure employed in the present study is widely accepted because it was developed to measure health-related QOL, including positive contributions to well-being, in terminally ill patients.

In addition, we estimated both between-person variance (i.e., differences between people in QOL) and within-person variance (i.e., differences within people in QOL). More between-person variance would imply differences that persist through the course of the disease and are likely to be attributable to premorbid characteristics. Conversely, more within-person variance would imply that QOL is mainly due to changing circumstances, including systematic changes over time such as those that might occur with disease progression as well as idiosyncratic changes that might occur due to other influences and events. These

variance estimates provide guidance as to where future investigations should look for influences on QOL in ALS patients and caregivers. For example, a preponderance of within-person variance would suggest that scientists should not pursue between-person factors such as personality to explain QOL; likewise, a preponderance of between-person variance would suggest that scientists should not pursue within-person factors such as disease progression.

In line with previous research, we hypothesized that QOL would be more stable over time for people with ALS than for their caregivers and that the latter would experience a decline in QOL with disease progression that would not be true for the former. Further, we expected that there would be significant individual differences in QOL for both people with ALS and their caregivers, such that differences in QOL between subjects would be evident early in the disease course and persist over time. Finally, we hypothesized an increase over time specifically in the existential domain for people with ALS and their caregivers. Research on post-traumatic growth and goal shifts in people with chronic disease and their caregivers suggests growth in existential and spiritual domains [31], and experimental evidence indicates that this growth is likely a function of long-term confrontations with mortality [32].

Methods

Participants

Fifty-five clinic patients with ALS (64% male and 36% female) and 53 of their spouses or caregivers (33% male and 67% female) participated in the study. Patients ranged from 27 to 81 years old (M=58.4, SD=11.5), while their caregivers ranged in age from 30 to 77 years (M=56.02, SD=12.25). Ninety-eight percent of patients and 96% of caregivers were Caucasian and 2% and 4%, respectively, were Hispanic. Of the patients, 93% were married, 2% were divorced, 2% were separated, and 4% were widowed. Patients' education ranged from 3 to 19 years (M=12.57, SD=2.69), and caregivers' education ranged from 2 to 18 years (M=12.51, SD=2.31). Annual household income range for patients prior to their diagnosis ranged from $5,001–10,000 to 75,001 or more (median range=$40,001–45,000). Upon beginning the study, time since ALS diagnosis ranged from 0 (i.e., 1 day) to 8.56 years, with a median of 0.40 years (M=0.98 years, SD=1.68 years).

Procedure

Participants were recruited for the study though ALS clinics at the Universities of Kentucky and New Mexico. Patients were eligible for participation if they met the El Escorial Criteria, which require the presence of lower (LMN) or upper motor neuron (UMN) degeneration or the progressive spread of symptoms or signs within a region or to other regions and the absence of evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration and/or observed clinical and electrophysiological signs [33].

Every 6 months up to 5 years, patients and their caregivers were separately mailed survey packets and envelopes in which to return completed questionnaires. If patients were unable to complete the questionnaires due to physical limitations, they were instructed to ask another individual (not their caregiver) to assist them. Participants were provided a stamped return envelope in which to return their completed questionnaires. Patients and caregivers completed between one and 11 assessments. Over the duration of the study, patients completed an average of 3.02 assessments (SD=2.26), and caregivers completed an average of 3.23 assessments (SD=2.25). The median number of completed assessments for both patients and caregivers was 2. Although an attempt was made to assess participants every 6 months, the time between consecutive assessments ranged from 67 to 566 days, likely for reasons related to disease progression (e.g., increased caregiving demands, decreased mobility and functional status, availability of assistance to complete questionnaires) and other factors (e.g., continued work responsibilities). In all, there were 166 completed patient assessments and 168 completed caregiver assessments (see Table 1). It should be noted that attrition was not related to any baseline demographic (age, gender, race, education), psychological (depression, hopelessness, QOL), or functional (ALS-FRS) characteristics.

Table 1 Data contributions by patients and caregivers

No. of waves	Person		Total
	Patient	Caregiver	
1	20	11	31
2	8	16	24
3	8	6	14
4	8	9	17
5	2	1	3
6	3	3	6
7	5	3	8
8	0	2	2
11	1	1	2
Total	55	52	107

Measures

McGill Quality of Life Questionnaire

This is a 16-item self-report scale measuring subjective well-being in terminally ill populations [30]. The scale is comprised of five subscales relating to physical symptoms, physical well-being, psychological well-being, existential well-being, and social support. In addition, the total score averages well-being across all domains (α=0.80), and the single item score is derived from a single item and reflects participants' overall quality of life. Items are measured on a Likert-scale ranging from 0 to 10, with lower scores indicating poor quality of life and higher scores indicating good quality of life.

ALS Functional Rating Scale

This is a ten-item self-report scale used to assess activities of daily living for people with ALS (e.g., speech, handwriting, dressing/hygiene, walking; [34]). The scale consists of four scales relating to coordinated upper limb motions, bulbar function, breathing, and gross, less finely controlled activities. The total score averages item responses (α=0.90). Item test–retest reliability has been demonstrated (≥0.88). Participants rate the difficulty of specific tasks. Lower scores on a 1 to 4 scale indicate more functional difficulty. Caregivers did not complete this measure.

Data Analysis

This study employed a variable occasion design [35], in which the number of assessments and the interval between those assessments both varied. Such designs are effectively analyzed using multilevel modeling (MLM; [36]). Unlike conventional repeated-measures models that require each person to have complete data for all possible waves and that each wave be of equal interval, MLM extracts as much information as possible from the available data without any loss of data. Even individuals with only one data point can be used in estimation, although individuals with more data points will typically have a larger influence on the estimates.

MLMs also array the estimates along a substantively meaningful range of time points. In this case, we set the intercept of the model at date of diagnosis, although we also explored alternative centering strategies. Longitudinal studies to date that align individual estimates by study start and end date ignore the possibility that intercepts and nonlinear slopes may differ relative to important disease milestones such as diagnosis.

The MLM in the current study provides three important pieces of information about QOL. First, similar to regression, the model provides the intercept (predicted QOL at diagnosis) and slope (predicted, systematic change in QOL over time). Second, variance estimates provide information about variability within and between individuals. Finally, the model provides information about variability in the intercept and slope parameters, that is, whether there are individual differences in initial QOL and in the effects of time, age, and gender on QOL.

The MLM analysis proceeded as follows. An initial model with no predictors estimated the amount of variance in QOL that was attributable to variance within people vs. between people. These estimates were used to calculate the intraclass correlation (ICC). A higher ICC indicates that between-subjects variance dominates over within-subjects variance. A second model estimated the effect of time on QOL. Level 1 (within-person) variance for person i at time j was modeled as follows:

$$\mathrm{QOL}_{ij} = \beta_{0j} + \beta_{1j}(\mathrm{time}) + R_{ij}(\mathrm{error\ term})$$

The level 1 models were integrated into level 2 (between-person) models; where there was a statistically significant random intercept or slope, error terms (U_j) reflect that variability. However, there were no models including random-slope effects that converged on a valid solution or that resulted in a significant change in the −2 log likelihood fit statistic. Therefore, the level 2 models were as follows:

$$\beta_{0j} = \gamma_{00} + U_j$$

$$\beta_{1j} = \gamma_{10}$$

For models that included age and sex, they were included as predictors of random intercept variance. Therefore, these level 2 models were as follows:

$$\beta_{0j} = \gamma_{00} + \gamma_{01}(\mathrm{age}) + \gamma_{02}(\mathrm{sex}) + U_j$$

$$\beta_{1j} = \gamma_{10}$$

Furthermore, our approach also allowed us to estimate nonlinear effects of time on QOL related to disease course, for example, if QOL diminished quickly shortly after diagnosis and stabilized thereafter. These models included a quadratic time variable in the level 1 model. As in the linear models, time was always included as a fixed rather than random variable in these analyses as random-slope models did not converge on valid solutions.

The time variable was centered around time since diagnosis, which is likely a pivotal event pertaining to QOL, and was thus considered appropriate to model the effects of time [37, 38]. Therefore, intercepts reflected the model's estimate of QOL at time of diagnosis rather than study entry. We also tested two alternative centering strategies in which time was centered around symptom onset and death. There were some missing data for these centering variables. Twenty-five percent of patients were missing diagnosis date and date of onset, and 38% of

patients were missing date of death. Most patients (N=40) had two of the three dates available, and the majority of participants had data for our main centering strategy, date of diagnosis. However, these data are believed to be missing at random, which is a typical and relatively safe assumption [39], and thus accommodated by our analyses. Furthermore, the centering variable, time since diagnosis, establishes only where the intercept will fall. The intervals between questionnaire dates were not imputed, and therefore, linear slopes were minimally affected by imputation of the centering variables.

Missing data were imputed from the available data (the other two dates as well as dates of entry and dropout from the study) using Multiple Random Imputation [40] in SAS. In the first step, carried out by PROC MI using MCMC due to the non-monotone missing data pattern, multiple possible values (i.e., five sets) of the missing dates are generated. Within this step, we restricted the range of imputed values so that date of diagnosis would not precede date of onset or proceed date of death. Next, we analyzed each of five imputed data sets using PROC MIXED, which generated multilevel models for each set of data. Last, we combine the results from these five analyses using PROC MIANALYZE, which provides estimates of the parameters, standard errors, and between and within imputation variability [41]. The stability of the solution with different centering values (and therefore different patterns of imputation) further supports the reliability of this approach. Furthermore, participants whose date of diagnosis was imputed did not differ from those participants with a diagnosis date with regard to age, gender, race, education, QOL, depression status, or functional status.

Each MQOL subscale was modeled separately for patients and caregivers. The models were tested using SAS PROC MIXED with maximum likelihood estimation [42]. γ weights are reported with their standard error and 95% confidence intervals. γ is analogous to the unstandardized beta weight and reflects predicted change in QOL with passage of each month of time. The range of standard effect sizes η, calculated from the F statistics of the five imputations, is also reported. η can be interpreted on the same scale as r: 0.10 effects are considered small, 0.30 medium, and 0.50 large [43]. The figure is based on model estimates through the range of existing data, which was available from 0.03 months after diagnosis (i.e., 1 day) to 80 months after diagnosis. We trimmed the model estimates at 80 months, even though ten data points beyond 80 months were available, in order to restrict the model conservatively to a time frame that would be expectable for a reasonable number of ALS patients. A recent examination of the natural history of ALS indicated that approximately 20% of patients were living 7–10 years after symptom onset [44].

Results

Patients' QOL

Sources of Variance

Table 2 summarizes the sources of variance in patients' QOL. ICCs suggested that about half of the total variance in QOL was due to stable differences between patients and half was due to instability within patients. That is, there was evidence that some patients had higher QOL than others, but also that patients' QOL fluctuated over time. In general, psychological aspects of QOL (psychological, existential, and social) tended to be more stable than physical aspects and therefore most likely to be characterized by individual differences at the time of diagnosis. Therefore, the models suggested that patients started out with significant differences in their QOL, particularly psychosocial aspects of QOL.

Effects of Time

Patient fluctuations in QOL were not systematically related to time since diagnosis on any dimension of QOL, as

Table 2 Sources of variability in patients' and caregivers' QOL

	Patients		Caregivers	
	ICC	Intercept variance (SE)	ICC	Intercept variance (SE)
QOL subscale				
Total	0.56	1.20 (0.31)**	0.66	1.96 (0.50)**
Single item	0.18	1.61 (1.02)	0.34	2.83 (1.07)**
Physical	0.44	3.17 (0.94)**	0.40	3.32 (1.18)**
Physical symptoms	0.36	3.46 (1.18)**	0.22	2.34 (1.09)*
Psychological	0.55	2.71 (0.73)**	0.51	2.61 (0.73)**
Existential	0.64	1.77 (0.64)**	0.77	3.22 (0.74)**
Social support	0.66	1.74 (.43)**	0.60	3.56 (0.99)**
ALS-FRS	0.51	57.59 (16.75)**	–	–

The ICC reflects the proportion of variance that is due to differences between individuals; the remaining proportion is variance due to differences within individuals. The median ICC value and its corresponding intercept are reported. The range in ICCs did not exceed 0.06. These are therefore highly stable estimates

*p<0.05, significant individual differences; **p<0.01, significant individual differences

Table 3 MLM of QOL domains and functional rating for patients and caregivers

Scale/domain	Patients		Caregivers	
	Gamma (95% CI)	Intercept (95% CI)	Gamma (95% CI)	Intercept (95% CI)
MQOL scale				
Total score	0.04 (−0.11–0.19)	6.64 (6.22–7.06)	−0.25* (−0.43 to −0.07)	7.16 (6.62–7.69)
Single item scale	−0.25 (−0.66–0.16)	6.62 (5.77–7.46)	−0.17 (−0.50–0.15)	6.45 (5.61–7.30)
Social support	0.05 (−0.11–0.21)	8.26 (7.79–8.73)	−0.09 (−0.34–0.16)	8.01 (7.27–8.76)
Psychological well-being	0.08 (−0.14–0.31)	6.56 (5.92–7.20)	−0.08 (−0.33–0.17)	6.43 (5.74–7.12)
Existential well-being	0.05 (−0.09–0.20)	7.62 (7.14–8.09)	−0.07 (−0.24–0.10)	7.83 (7.21–8.32)
Physical well-being	0.04 (−0.23–0.32)	6.20 (5.45–6.96)	−0.27 (−0.57–0.04)	6.89 (6.04–7.74)
Physical symptoms	−0.10 (−0.42–0.23)	4.64 (3.79–5.50)	−0.52* (−0.87 to −0.17)	6.49 (5.59–7.40)
ALS Functional Rating Scale				
Total score	−2.44 (−3.91 to −0.97)	33.51 (30.37–36.66)*	–	–

*$p<0.01$

reflected by the γ weights given in Table 3: total score (γ=0.04, SE=0.07, CI=−0.11 to 0.19, ns), the single item (γ=−0.25, SE=0.19, CI=−0.66 to 0.16, ns), physical well-being (γ=0.04, SE=0.14, CI=−0.23 to 0.32, ns), physical symptoms (γ=−0.10, SE=0.16, CI=−0.42 to 0.23, ns), psychological well-being (γ=0.08, SE=0.11, CI=−0.15 to 0.31, ns), existential well-being (γ=0.05, SE=0.07, CI=−0.09 to 0.20, ns), or social support (γ=0.05, SE=0.08, CI=−0.11 to 0.21, ns). This finding occurred in the context of significant changes in physical functioning: Time since diagnosis predicted decreases in patients' functional rating (γ=−2.44, SE=0.68, CI=−3.90 to −0.97, ns, $p<0.01$, η=0.39–0.47).

Nonlinear effects of time were also tested; however, none of these terms was statistically significant. The largest effect was for the single item scale (γ=0.08, SE=0.05, CI=−0.02 to 0.19, η=0.11–0.19), where patients' single item score tended to decrease initially, but then returned to and exceeded baseline levels.

Caregivers

Sources of Variance

Table 2 summarizes the sources of variance in caregivers' QOL. As was true for patients, about half of the total variance in QOL was due to stable differences between caregivers and half was due to instability within caregivers. Therefore, there was evidence that some caregivers had higher QOL than others, but also that their QOL fluctuated over time. As was true for patients, psychological aspects of QOL (psychological, existential, and social) tended to be more stable than physical aspects and most highly characterized by differences between people. Therefore, the models for caregivers closely resembled those for patients and suggested that caregivers started out with significant differences in their QOL, particularly psychosocial aspects of QOL.

Effects of Time

Unlike patients, variability in QOL for caregivers was systematically related to time since diagnosis, with QOL decreasing over time on the dimensions of total QOL and physical symptoms as reflected by the γ weights given in Table 3 (total, γ=−0.25, SE=0.09, CI=−0.43 to −0.07, $p<0.01$, η=0.41–0.49; symptoms, (γ=−0.52, SE=0.17, CI=−0.87 to −0.17, $p<0.01$, η=0.27–0.36). Other subscales showed some decrease in QOL over time, but these were not significant differences: the single item (γ=−0.17, SE=0.16, CI=−0.50 to 0.15, ns), physical well-being (γ=−0.27, SE=0.15, CI=−0.57 to 0.04, ns), psychological well-being (γ=−0.08, SE=0.12, CI=−0.33 to 0.17, ns), existential well-being (γ=−0.07, SE=0.09, CI=−0.24 to 0.10, ns), and social support (γ=−0.09, SE=0.12, CI=−0.34 to 0.16, ns).

Nonlinear effects of time were also tested; however, none of these terms was statistically significant. The largest effect was for existential well-being (γ=0.04, SE=0.03, CI=−0.02 to 0.10 η=0.09–0.24), where existential well-being initially tended to decrease but returned to and exceeded baseline levels.

Alternative Centering Strategies

We explored whether these results differed when the intercept was set to onset of disease or to death. There were very few differences as a function of different approaches to centering the time variable. There were no differences when time was centered around disease onset. When time was centered around date of patient death, there were significant

changes in patients' single item QOL rating (γ=0.61, SE=0.29, CI=0.02 to 1.20, p<0.05, η=0.17–0.29) and caregivers' physical well-being (γ=0.51, SE=0.25, CI=0.00 to 1.00, p<0.05, η=0.13–0.23). However, when time was centered around patients' death, caregivers' physical symptoms ratings were not significant.

Effects of Age and Gender

For both patients and caregivers, older age was associated with increased social support ratings (patients, γ=0.04,SE=0.02, CI=0.01 to 0.08, p<0.05, η=0.28–0.31); caregivers, γ=0.09,SE=0.02, CI=0.01 to 0.08, p<0.05, η=0.28–0.31). Caregivers' older age was also associated with higher well-being in all domains: total QOL (γ=0.05 (CI=0.03–0.07), F(1,68)=11.25, p<0.01, η=0.38), existential well-being (γ=0.05 (CI=0.03–0.07), F(1,70)=13.32, p<0.01, η=0.40), physical well-being (γ=0.08 (CI=0.04–0.12), F(1,71)= 10.23, p<0.01, η=0.35), psychological well-being (γ=0.05 (CI=0.09–0.01), F(1,70)=5.60, p<0.05, η=0.27), and the single item score (γ=0.06 (CI=0.02–0.10), F(1,71)=5.89, p<0.05, η=0.28). There was a significant effect of gender on psychological well-being in patients (γ=−1.04 (CI=−1.33 to −0.75), F(1, 61)=3.99, p<0.05, η=0.06), such that males reported higher QOL.

Discussion

In the present study, ALS patients maintained high QOL in every domain despite simultaneous decreases in functional status. The relatively high and stable level of QOL in ALS patients despite the physical progression of the disease is consistent with previous research [45]. People with ALS, when asked about the determinants of their own QOL, refer to the importance of "psychological and existential issues, social support, and spirituality" rather than physical function ([46], p. 1939). Consistent with this response, the current study found that individual differences and idiosyncratic events were each responsible for 50% of the variance in ALS patients' QOL. It is possible then that characteristics such as personality, social relationships, and spirituality could be more important for QOL in ALS than the progression of the disease per se and should be explored in future research.

In contrast, caregivers reported significant decreases in QOL, particularly regarding physical symptoms, suggesting that ALS caregiving could result in decreased quality of life over time. Previous investigations suggest that caregivers' levels of depression and anxiety are closely related to the degree of the patient's incapacitation [47–50]. Similar "costs of caring" have also been examined in those who provide treatment for individuals experiencing a traumatic event, such as therapists and doctors. This "compassion fatigue" is said to describe the secondary stress resulting from witnessing a traumatizing event of a significant other and may be similar to ALS caregivers' experiences [51]. It is likely that over time, caregivers in the present study were required to perform a greater number of physical tasks, such as transferring the patient from his or her bed to the wheelchair to the car and back, retrieving items that the patient needed or could no longer access from remote areas of the house, or transporting augmentative communication devices, all of which took a toll on their energy and led them to report decreased QOL related to their total and especially physical health.

However, caregivers' QOL, like patients', also had a preponderance of influence from stable individual differences, and the fact that the passage of time accounted for only part of the within-person changes in QOL suggests that caregivers, like patients, are significantly affected by idiosyncratic influences that fluctuate over time, such as life events. ALS caregivers appear to be more impacted by disease progression than, for example, dementia caregivers [22, 23] but their QOL is also, like dementia caregivers, significantly affected by their personal characteristics [10].

One such personal characteristic is age. There has been little examination of developmental effects in ALS caregivers, and the finding that younger age is associated with worse QOL differs somewhat from findings in dementia caregiving, in which older age associates with worse outcomes (e.g., [52]). However, the age range in dementia caregiving studies tends to be restricted to older adults. The present study included a wide range of ages, including adults in early middle age. Such caregivers may find the process of coping with their spouse's illness to violate normal life course expectations and therefore suffer a greater loss of QOL. Older caregivers may also have more peers with experientially similar experiences of spousal caregiving, which has a positive effect on social support and psychological well-being [53], corresponding to our findings of increased social support and well-being across all domains in older ALS caregivers.

Notably, patients' and caregivers' existential well-being—their sense of having a meaningful existence—was maintained over the course of the study. There was a nonlinear tendency for caregivers to report decreased existential well-being immediately following diagnosis, but it eventually returned to and exceeded initial. The simultaneous decline in Total QOL and trend towards an increase in Existential QOL is consistent with evidence that ALS caregiver burden is positively correlated with finding positive meaning [1]. However, high ICCs for existential well-being of both patients and caregivers suggests that although there is some fluctuation over time, much of the variance in this domain is due to stable individual differences at baseline. This highlights a need for future longitudinal studies of existential

well-being and its growth or maintenance over the course of chronic diseases such as ALS.

Several limitations to this study bear discussion. First, because none of the patients in this study were receiving mechanical ventilation, these results do not inform QOL in this population of people with ALS and their caregivers; for example, up to 70% of caregivers for those on mechanical ventilation report health problems and expressed that their levels of QOL decreased dramatically with the introduction of the patient's ventilator [54]. Second, the patients' physical symptom scores from the McGill QOL scale are difficult to interpret because patients may have recorded different symptoms at each assessment point. Therefore, a lack of significant decrease in physical symptoms QOL in the patients may reflect moving targets rather than lack of decline in physical capacities, which is perhaps better reflected in the ALS Functional Rating Scale (ALS-FRS). Finally, our sample of patients may have represented a restricted range because they were receiving multidisciplinary care, which has been shown to have a positive impact on QOL. For example, multidisciplinary care compared to general care for ALS has been linked to better mental QOL and prolonged survival (e.g., an increment of 7.5 to 10 months), and some authors suggest that comprehensive medical care is a critical component in preserving patients' QOL throughout the disease course [16, 55–57].

It should be recognized that as the study progressed, fewer patients and spouses remained in the study. This is not surprising in a naturalistic, longitudinal study of patients and caregivers coping with a terminal and demanding illness that makes it unlikely that 5 years of continuous and available data could be obtained, not least because many patients die within that time frame. However, the strength of our data analysis (MLM) is that complete data across the span of the study are not necessary to fit a model, and MLM is even considered ideal for longitudinal quality-of-life studies in which number of data points and intervals between data points both vary [58, 59]. Additionally, for missing centering variables that were imputed (e.g., time since diagnosis), we used an acceptable multiple random imputation method [39, 60].

QOL is a "critically important endpoint in ALS", considering the fact that no current options exist for cure ([45], p. 233), and many feel it should be a major focus of clinical care and interventions (e.g., [8, 11, 16]). Furthermore, evidence suggests that higher QOL may result in longer survival with ALS [61, 62]. Our results suggest that when people with ALS report low QOL, it is reasonable to assume that this was probably true at diagnosis or the result of idiosyncratic factors, as disease progression does not seem to markedly influence their well-being. In contrast, caregivers reporting low QOL may have either had low QOL at the time of diagnosis, experienced idiosyncratic events, or experienced a decrease in QOL with extended caregiving. These declines in QOL are significant because they may reflect or portend adverse effects on caregivers' mental and physical health. The influence that caregivers have on experience of the disease suggests that the potential for both patient and caregiver QOL when coping with this terminal disease may be maximized by clinicians' careful attention. Further, those whose QOL is lowest at early stages in the disease will be in most need of this attention throughout the disease course.

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