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Patient-Reported Problematic Symptoms in an ALS Treatment Trial

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Abstract

Objectives—This study was undertaken to determine which symptoms are perceived to be most problematic for patients with ALS and how their severity changes over time.

Methods—A retrospective study was performed of data from a randomized, double-blind, placebo-controlled trial of ceftriaxone in ALS. Participants completed the ALS Specific Quality of Life Instrument (ALSSQOL) at baseline and at intervals up to 96 weeks. Ten ALSSQOL items ask participants to rate how problematic symptoms are (the subjective feeling of burden of these symptoms), ranging from 0 (no problem) to 10 (tremendous problem). Six are non-bulbar (pain, fatigue, breathing, strength and ability to move, sleep, and bowel and bladder) and four are bulbar (eating, speaking, excessive saliva, and mucus).

Results—There were 82 subjects (56% men, mean age 53 ± 10.3 years) with ALSSQOL data for weeks 0 and 96. All 10 symptoms became more problematic over time. For non-bulbar symptoms, strength/ability to move and fatigue were the most problematic. Speaking was the most problematic bulbar symptom.

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Disclosures of Interest

Dr. Simmons has received reimbursement from Neuralstem, Inc., for serving on a Data Safety Monitoring Board for an ALS therapeutic trial. Other authors have no conflicts of interest to disclose.

Conclusions—Although all the symptoms in the ALSSQOL were acknowledged as problematic, some had greater impact than others. All became more problematic over time. This should help prioritize research into symptom management, and assist individual clinicians in their approach to patient care.

Keywords

amyotrophic lateral sclerosis; quality of life; fatigue; strength; speech

Introduction

The management of patients with amyotrophic lateral sclerosis (ALS) is aimed at providing optimal supportive care(1), most often in a multidisciplinary setting based on guidelines such as those of the American Academy of Neurology and the EFNS Task Force (2–5). This form of care has been shown to prolong lifespan and to positively impact quality of life (QOL) in patients with ALS in most(6–10), but not all (11,12), comparative studies of multidisciplinary care versus other forms of care. A key part of the supportive care is the management of a wide variety of symptoms. An attempt to identify a core group of symptoms that are of importance to this patient group was undertaken during the development of the ALS Specific Quality of Life Instrument (ALSSQOL), which includes 6 non-bulbar and 4 bulbar symptoms relevant to ALS (13). The perception by patients of the magnitude of the problem posed by each of these 10 items has not been assessed. Knowledge of the relative importance of these items should permit researchers to better prioritize the development of interventions for symptom management. An understanding of the changes in these problems over time should aid clinicians as they address symptom management and attempt to optimize QOL in individual patients. The objectives of this study were to determine which symptoms are perceived to be the most problematic for patients with ALS and how the severity of those problems changes over time.

Subjects and Methods

This was a retrospective study using a limited data set from a multi-center, three-stage randomized, double-blind, placebo-controlled study on ceftriaxone in ALS, conducted between Sept 4, 2006, and July 30, 2012 (ClinicalTrials.gov NCT00349622) (14), a study that did not show efficacy. The main inclusion and exclusion criteria were an El Escorial diagnosis(15) of possible ALS or higher, vital capacity of more than 60% of predicted, and symptom duration of less than 3 years. Participants completed the ALS Specific Quality of Life Instrument(13) and the ALS Functional Rating Scale-Revised(16), and performed spirometry at baseline, 4 weeks, 16 weeks, and every 16 weeks thereafter throughout the trial, for a total of 8 assessments. For inclusion in the data set, participants must have completed a minimum of 96 weeks in the trial. The study was approved by our Institutional Review Board.

Instruments

The ALS Specific Quality of Life Instrument: The ALSSQOL (13) is an ALS-specific measure of overall QOL, assessing health-related and non-health-related factors. It assesses

overall QOL via six specific domains, and has been validated on a national US sample of adult men and women who were receiving care for their disease in ALS multidisciplinary clinics. In addition to its suitability for use in a multidisciplinary ALS clinic, the instrument has been used to assess patients not receiving multidisciplinary care(12). Each of its 59 items uses a 0–10 point Likert scale, with 0 being the least desirable situation, and 10 the most desirable. The instrument contains 6 domains of QOL: Negative Emotion, Interaction with People and the Environment, Intimacy, Religiosity, Physical Symptoms, and Bulbar Function. An Average Total Score is obtained by adding the individual item scores and dividing by the total number of items, resulting in a score that varies from 0 (worst QOL) to 10 (best QOL). The first 10 items of the ALSSQOL ask participants to rate how problematic a variety of symptoms have been in the last 7 days, ranging from 0 (no problem) to 10 (tremendous problem). Six of the items are non-bulbar symptoms (pain, fatigue, breathing, strength and ability to move, sleep, and bowel and bladder) and the other four are bulbar (eating, speaking, excessive saliva, and mucus).

The ALS Functional Rating Scale-Revised: The ALSFRS-R(16) is a widely-used, 12-item, ALS-specific questionnaire assessing physical function in the bulbar, upper limb, lower limb, and respiratory domains. Each item is scored from 0 (poorest function) to 4 (normal function), and the scores are added to produce a total score from 0 (worst) to 48 (normal).

Statistical Methods

Only subjects with non-missing data at weeks 0 and 96 for ALSSQOL average were included in the analyses. The 10 individual symptoms of interest from the ALSSQOL (ranging from 0–10) were also categorized in terms of severity (0=None, 1–3=Mild, 4–6=Moderate, and 7–10=severe). All variables were summarized with means and standard deviations for continuous variables and frequencies and percentages for categorical variables. The means for ALSFRSR total score, average % predicted FVC, ALSSQOL, and the 10 individual symptoms of interest were plotted over time. The distribution of the continuous outcome variables was evaluated prior to analysis using histograms and box plots. A normal distribution was found. Comparisons were made between week 0 and week 96 for ALSFRSR total score, average % predicted FVC, and ALSSQOL using a paired t-test, for the individual symptoms in their original format (0–10) using a Wilcoxon signed rank test, and for the individual symptoms categorized as severity using Bowker's test of symmetry. Statistical significance was taken as $p < 0.05$. Additionally, we analyzed the differences from week 0 to the other seven time points leading up to week 96 by using either a linear mixed effects model for repeated measures applied to all time points at once or by using individual Wilcoxon signed rank tests at each time point. The choice of the applied method depended on the distribution of the outcome variable, but for both methods we adjusted the p-values for the seven comparisons made for each outcome variable using the Bonferroni correction for multiple comparisons. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

There were 82 subjects for whom there was complete ALSSQOL data for week 0 and week 96. Fifty-four (56%) of the subjects were men. The mean age was 53 ± 10.3 years. Physical function (ALSFRSR), respiratory function (FVC) and QOL decreased over the course of the trial (See Table 1).

The average item scores of the 6 non-bulbar symptoms and 4 bulbar symptoms over the course of the 96 weeks of the trial are plotted in Figures 1 and 2 respectively. All 10 of the symptoms demonstrated an increase over time in patients' perception of the degree to which they were problems (Tables 2 and 3). Some symptoms were rated as considerably more problematic, on average, than others. Moreover, the distribution of the severity ratings for all of the symptoms shifted towards being more severe over time (Tables 2 and 3). For non-bulbar symptoms, strength and ability to move followed by fatigue were the most problematic symptoms. Others were less problematic and were clustered together. For the bulbar symptoms, the most problematic was speaking, with others clustered lower.

When comparing the severity ratings for each of the 10 symptoms at each time point (4, 16, 32, 48, 64, 80, and 96 weeks) to baseline, the time at which the difference from baseline first became statistically significant varied between symptoms, occurring as early as 4 weeks for eating, but as late as 96 weeks for bowel and bladder. For pain and for fatigue, differences from baseline were statistically significant at some data collection points but not others (at weeks 16, 32, 64, and 96, but not 48 or 80 for pain; at weeks 32, 64, and 96, but not 48 or 80 for fatigue). However, the perception that these symptoms were increasingly problematic gradually increased during the data collection period, reaching statistical significance in all by week 96 (Tables 2 and 3, Figures 1 and 2).

Discussion

An understanding of what are perceived by patients to be the most problematic symptoms should aid in focusing clinical care and in providing direction for future research in clinical management and symptom control in ALS. Although all the symptoms in the ALSSQOL were acknowledged by patients, on average, to be problematic, some clearly had a greater impact than others, and all became more problematic over time.

That strength and the ability to move should be perceived as the greatest problem by patients reinforces the overwhelmingly motor-predominant and progressive nature of ALS. It also serves to reinforce the importance of addressing these concerns by means of a multidisciplinary team, to maximize function, mobility, and independence while preserving safety. And, it complicates the concept of a "response shift," in which patients with life-threatening illnesses alter their expectations and goals to match reality(17–20), and may shift their perception of those activities necessary to maintain QOL from the physical to those that rely more on relationships or satisfaction with their environment. Clearly the loss of the ability to move has great impact.

The prominent attention given by patients to fatigue as a problem supplements our understanding of this symptom. Previous studies have demonstrated a high prevalence of

fatigue in patients with ALS, showing that it affects 44–86% of these patients (21–23). One longitudinal study showed that at baseline, 44% had clinically significant fatigue. Of patients seen 3 months later, 75% of those who were fatigued at baseline remained fatigued, and 22% reported new onset fatigue (21). Fatigue rates were similar at a third visit 3 months later. The combination of the high prevalence and the problematic nature of fatigue suggest that attention to this symptom is of importance in the management of patients with ALS. The etiology of fatigue is multifactorial and not only includes the physical factors such as pain and weakness, but also central and psychological factors, effect of pain medications, and respiratory impairment (24). Poor sleep may also contribute to daytime fatigue(22). Patients with ALS may have difficulty falling asleep due to anxiety or depression, or may experience an inability to sustain sleep because of factors such as muscle cramps, restless legs or nocturia. A multimodality approach targeting these possible etiologies, education regarding energy conservation strategies, and psychostimulant therapy such as modafinil, should be considered(25). Non-invasive ventilation (NIV) also plays a role, as it has been found to improve daytime fatigue and sleepiness and to improve QOL(26–31)

In the context of multiple problematic symptoms in ALS, pain, breathing and bowel and bladder, while increasing in perceived impact of QOL over time, were not perceived to be as problematic as the other physical symptoms. Pain is now understood to be a predominant symptom in ALS, occurring in 50% and perhaps up to 85% of patients with ALS(32–35). There are many possible sources of pain in ALS including muscle atrophy, cramping and spasticity, joint contractors and inability to move (33,36), for which a variety of approaches to symptomatic management are available(1,37,38). The relatively low perception of breathing as a problematic symptom likely relates to the benefits of NIV and to established guidelines for respiratory management in ALS(2,5,26–31). Bowel and bladders symptoms were perceived as the least problematic of the non-bulbar symptoms. Nonetheless, they were perceived as a severe problem by nearly 9% of our patients at week 96, and thus warrant at least an inquiry by the clinical team. This is consistent with literature indicating that urinary incontinence is relatively common in patients with ALS and is associated with a high burden(39).

Speaking was the most problematic of the bulbar symptoms. Dysarthria occurs in more than 80% of ALS patients(40). Loss of communication affects ALS patients' ability to socialize and imposes a significant burden to the individuals QOL(41,42). Early intervention by speech therapists and use of communication devices has been shown to have a positive impact on QOL in ALS patients(41,43) and provides the patients opportunity to improve the skills for later stages of the disease.

Although perceived as less problematic than speaking, eating, excessive saliva and mucus all were reported to become more problematic symptoms over time. Malnutrition, a significant risk for those with ALS, negatively affects prognosis and QOL, making early and frequent nutrition assessment and intervention essential(44). Implementation of an adequate calorie diet, dietary texture modification, use of adaptive eating utensils, and placement of a feeding tube aid in preventing malnutrition(45). Predictive equations have been established as a basis for recommending placement of a feeding gastrostomy in ALS patients who fail to meet their energy requirements by oral intake(46). Patient concerns regarding saliva and mucus

reflect self-reporting of sialorrhea in about half of those with ALS, including 20% who characterized it as moderate to severe (47). Attention to this is important because of the potential for intervention with anticholinergic drugs, and for refractory cases with botulinum toxin injections or radiation therapy to salivary glands(48–54). Thick mucus that patients are unable to clear because of muscle weakness and an ineffective cough may respond to beta blockers or to guaifenesin or nebulized saline or acetylcysteine, often in conjunction with an insufflation-exsufflation (cough-assist) device(37).

We attempted to determine whether specific points in the disease trajectory could be identified at which the perceived severity of individual problems was significant enough to warrant consideration of intervention. However, the variability of the time points at which each of the problems achieved a statistically significant difference from baseline, the inconsistency of some problems in remaining significantly different from baseline throughout the trajectory, and a lack of information as to whether any interventions for these problems were undertaken in these study patients, placed such an analysis beyond the scope of this retrospective review. Also of importance is the fact that mean differences in problem severity rating between data collection points and baseline was often very small (less than one point), raising concerns about whether such changes, while statistically significant, are clinically meaningful. By assessing severity of problems at week 96 and comparing to week 0, differences for all problems were statistically significant and likely to be clinically meaningful. Future studies, conducted prospectively, focusing on a smaller number of problems, and attempting to determine the size of a clinically meaningful difference in problem severity scores, could help guide interventions.

This study has limitations. Patients were part of a clinical trial, and in some respects differed from the general ALS patient population. Those with a forced vital capacity of 60% of predicted or less were excluded, as were those with a symptom duration of 3 years or more and those who completed fewer than 96 weeks in the trial. While the investigational drug was ineffective, the study sample used for this analysis may differ from those of the general ALS population with regard to factors that impact their QOL. Specifically, the decline in QOL over time in this study is in contrast to that of previous studies(55,56), and may reflect a greater emphasis on physical strength and function, with the desire to “get better” as a result of being in a clinical trial. The clinical trial involved the use and care of an intravenous catheter which could have been an added burden. Twice daily infusions combined with frequent visits to the study sites for evaluation may have impacted on patient’s ratings of their problematic symptoms. Patients receiving ceftriaxone experienced significantly more frequent gastrointestinal and hepatobiliary adverse events than did those receiving placebo (14), possibly affecting perception of problematic symptoms, particularly pain, fatigue, and bowel and bladder, in this study population compared to the general ALS patient population. We do not know what interventions were provided to alleviate symptoms, or the extent of compliance with recommended care. This study is a secondary analysis of the finished trial, and the sample size cannot be powered on the primary outcome of this study.

Despite these limitations, this study provides a relatively broad view of the impact of symptoms as perceived by patients with ALS over a long course with the disease. This

should help direct the ALS community in prioritizing research initiatives for symptom management, and hopefully will assist individual clinicians in their approach to patient care.

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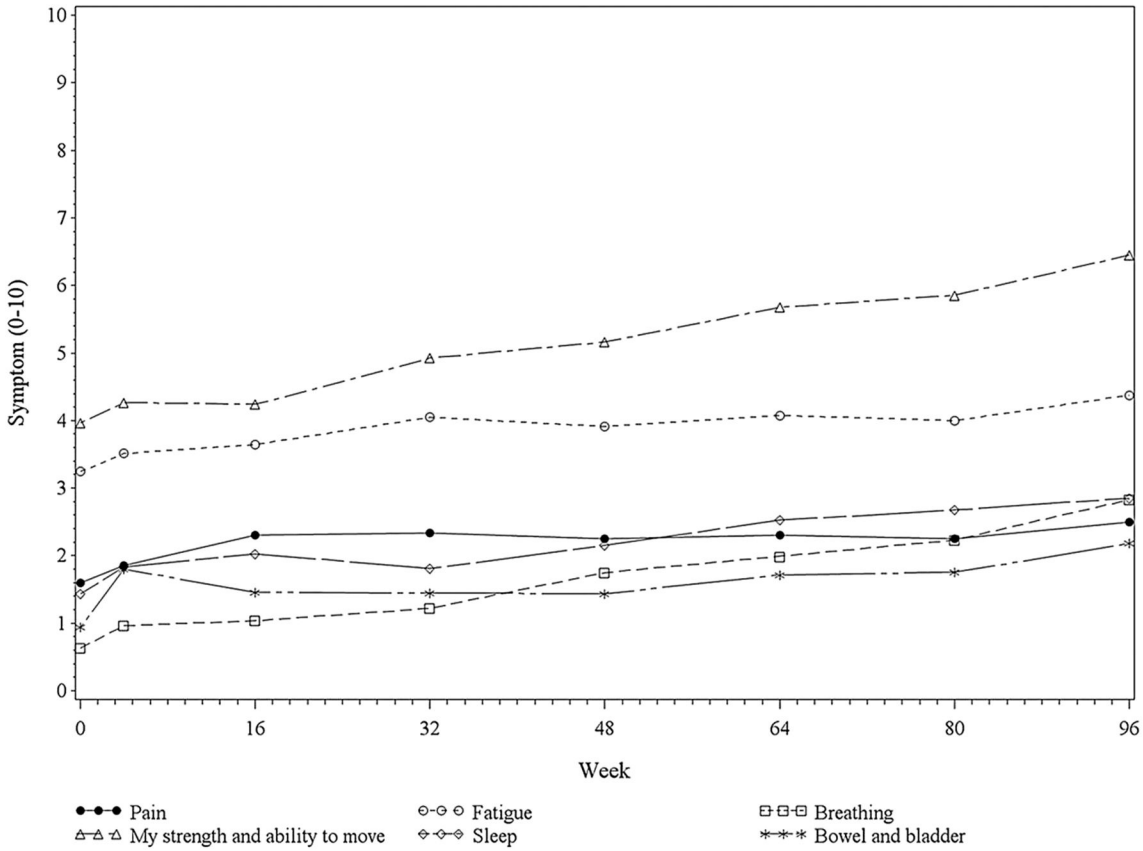

Figure 1.

Mean Non-Bulbar Symptom Scores Over Time. The symptom scores are a subset of the first 10 items of the ALS Specific Quality of Life Instrument, and range from 0 (no problem) to 10 (tremendous problem).

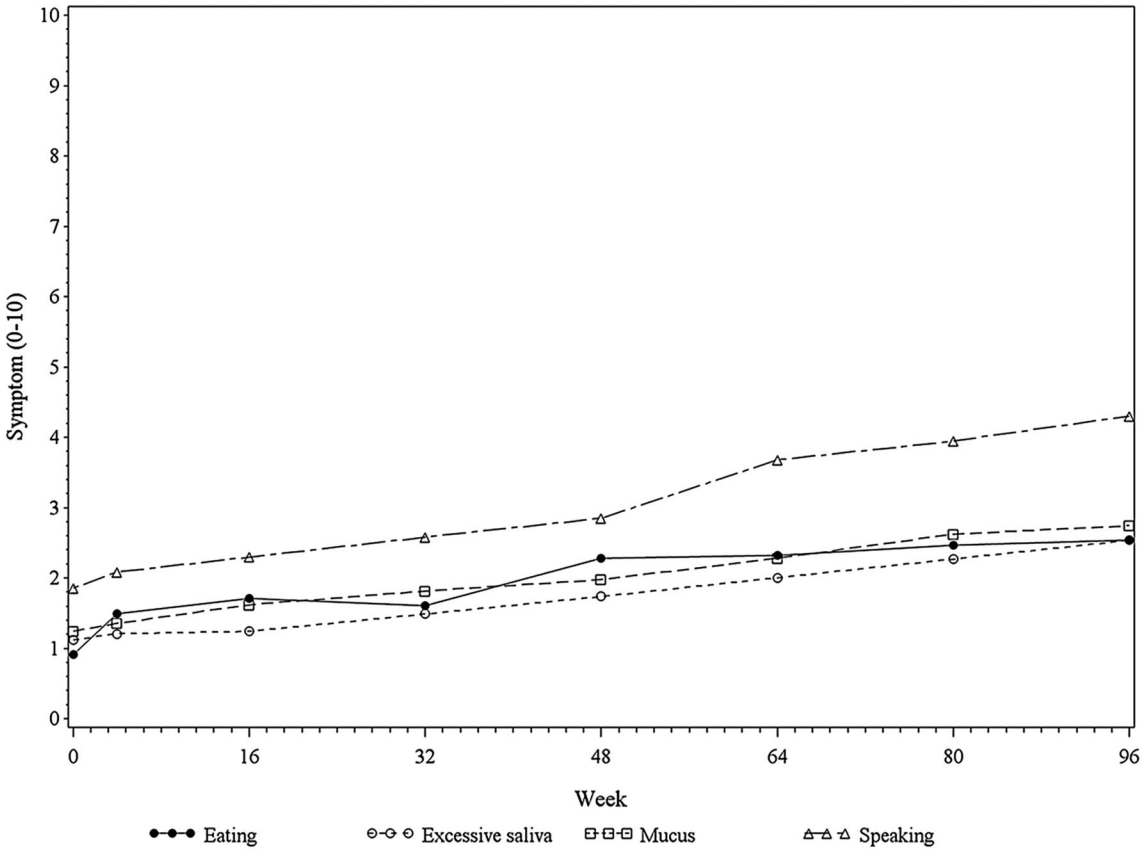

Figure 2.

Mean Bulbar Symptoms Scores Over Time. . The symptom scores are a subset of the first 10 items of the ALS Specific Quality of Life Instrument, and range from 0 (no problem) to 10 (tremendous problem).

Table 1

Physical and Functional Measures

Measure	N	Week 0	Week 96	P-value*
		Mean ± SD (range)	Mean ± SD (range)	
ALSFRSR total score (0–48)	81	38.5 ± 6.0 (20–48)	24.3 ± 9.2 (3–45)	<0.001
% predicted FVC (0–100)	69	89.9 ± 15.5 (62.0–133.3)	57.1 ± 25.5 (6.7–113.0)	<0.001
ALSSQOL average (0–10)	82	7.5 ± 1.1 (4.6–9.3)	6.6 ± 1.3 (3.6–9.8)	<0.001

* Paired t-test

Table 2

Non-Bulbar Symptoms

Symptom	Week 0 N (%) or Mean ± SD	Week 96 N (%) or Mean ± SD	P-value*
Pain score (0–10)	1.60 ± 2.27	2.50 ± 2.37	0.002
Pain severity			
None	38 (46.3)	18 (22.0)	0.001
Mild	32 (39.0)	44 (53.7)	
Moderate	6 (7.3)	12 (14.6)	
Severe	6 (7.3)	8 (9.7)	
Fatigue score (0–10)	3.24 ± 2.24	4.38 ± 2.22	<0.001
Fatigue severity			
None	10 (12.2)	2 (2.4)	0.036
Mild	37 (45.1)	26 (31.7)	
Moderate	28 (34.2)	41 (50.0)	
Severe	7 (8.5)	13 (15.9)	
Breathing score (0–10)	0.67 ± 1.33	2.83 ± 2.77	<0.001
Breathing severity			
None	59 (72.0)	23 (28.1)	<0.001
Mild	19 (23.2)	29 (35.4)	
Moderate	3 (3.7)	18 (22.0)	
Severe	1 (1.2)	12 (14.6)	
Strength/ability to move score (0–10)	3.96 ± 2.57	6.46 ± 2.36	<0.001
Strength/ability to move severity			
None	7 (8.6)	1 (1.2)	<0.001
Mild	32 (39.5)	8 (9.9)	
Moderate	27 (33.3)	29 (35.8)	
Severe	15 (18.5)	43 (53.1)	
Sleep score (0–10)	1.44 ± 1.90	2.85 ± 2.74	<0.001
Sleep severity			
None	37 (45.1)	15 (18.3)	0.002
Mild	32 (39.0)	43 (52.4)	
Moderate	11 (13.4)	13 (15.9)	
Severe	2 (2.4)	11 (13.4)	
Bowel and bladder score (0–10)	0.94 ± 1.79	2.18 ± 2.54	<0.001
Bowel and bladder severity			

Symptom	Week 0 N (%) or Mean ± SD	Week 96 N (%) or Mean ± SD	P-value*
None	53 (64.6)	28 (34.2)	0.006
Mild	22 (26.8)	37 (45.1)	
Moderate	5 (6.1)	10 (12.2)	
Severe	2 (2.4)	7 (8.5)	

*Wilcoxon signed rank test or Bowker's test of symmetry

Table 3

Bulbar Symptoms

Measure	Week 0 N (%) or Mean ± SD	Week 96 N (%) or Mean ± SD	P-value*
Eating score (0–10)	0.91 ± 1.54	2.54 ± 3.09	<0.001
Eating severity			
None	51 (62.2)	30 (36.6)	0.005
Mild	23 (28.1)	34 (41.5)	
Moderate	7 (8.5)	7 (8.5)	
Severe	1 (1.2)	11 (13.4)	
Excessive saliva score (0–10)	1.12 ± 1.92	2.54 ± 2.93	<0.001
Excessive saliva severity			
None	52 (63.4)	27 (32.9)	<0.001
Mild	20 (24.4)	28 (34.2)	
Moderate	7 (8.5)	17 (20.7)	
Severe	3 (3.7)	10 (12.2)	
Mucus score (0–10)	1.24 ± 1.73	2.74 ± 2.84	<0.001
Mucus severity			
None	43 (52.4)	24 (29.3)	0.002
Mild	31 (37.8)	32 (39.0)	
Moderate	6 (7.3)	18 (22.0)	
Severe	2 (2.4)	8 (9.8)	
Speaking score (0–10)	1.85 ± 2.59	4.30 ± 3.77	<0.001
Speaking severity			
None	45 (54.9)	24 (29.3)	<0.001
Mild	18 (22.0)	13 (15.9)	
Moderate	13 (15.9)	17 (20.7)	
Severe	6 (7.3)	28 (34.2)	

*Wilcoxon signed rank test or Bowker's test of symmetry