The Oral Secretion Scale and Prognostic Factors for Survival in Subjects With Amyotrophic Lateral Sclerosis

Pamela A Cazzolli, Benjamin Rix Brooks, Yuki Nakayama, Joseph S Lewarski, Douglas A McKim, Sheryl L Holt, and Robert L Chatburn

BACKGROUND: Noninvasive ventilation (NIV) can be tolerated in patients with amyotrophic lateral sclerosis (ALS), unless bulbar impairment becomes severe. Excessive oral secretions may result in NIV intolerance and insufficient ventilation. OBJECTIVE: To assess the reliability of the Oral Secretion Scale (OSS) for predicting the tolerance of NIV, when to initiate hospice or transition to tracheostomy, and prognostic factors for survival of users of NIV. METHODS: A validated OSS was developed to measure oral secretions in correlation with the ability to swallow saliva and clear the upper airway: OSS score of 4 = normal (automatic swallow); OSS score of 3 = infrequent secretions (automatic swallow decreased); OSS score of 2 = occasional drooling and/or pooling (conscious swallow required); OSS score of 1 = severe, frequent drooling and/or pooling (conscious swallow difficult); OSS score of 0 = most severe, constant drooling/pooling (conscious swallow impossible). A total of 137 subjects were followed up prospectively during ongoing patient visits from NIV initiation until death or tracheostomy. Survival was calculated by using Kaplan-Meier analysis. OSS scores when NIV became intolerable were determined. Uni- and/or multivariate Cox-regression analyses showed prognostic factors that affect survival. RESULTS: The median months of survival from NIV initiation were the following: 11 (95% CI 7.3–14.0), 5 (95% CI 3.1–6.1), and 1 (95% CI 1.1–1.5) stratified by OSS scores of 4, 3–2, and 1, respectively; and 21 (95% CI 8.6–33.2), 8 (95% CI 3.4–11.5), 6 (95% CI 4.2–8.2), and 2 (95% CI 1.5–2.7) stratified by 24, 17–23, 4–16, and <4 h/d of NIV use, respectively. Survival was significantly ($P < .001$) longer with an OSS score of 4 than an OSS score of 1 at NIV initiation; and significantly ($P < .001$) longer when NIV used 24 h/d than <24 h/d. In the subjects unable to tolerate NIV, ≥80% had OSS score of 1 or 0. Univariate and multivariate analyses hazard ratio 4.91, 95% CI 2.98–8.09, $P < .001$, and hazard ratio 4.60, 95% CI 2.66–7.96, $P < .001$), respectively, showed hours per day of NIV use was a significant factor associated with survival. CONCLUSIONS: The subjects with an OSS score of 4 tolerated NIV and survived significantly longer than subjects with an OSS score of <4. An OSS score of 1 signaled NIV intolerance and the need for hospice or transition to planned tracheostomy. Use of OSS can help guide NIV management decisions. *Key words: amyotrophic lateral sclerosis; end-of-life care; hospice; mechanical insufflation-exsufflation; noninvasive ventilation; oral secretions; oropharyngeal suctioning; survival; tracheostomy and invasive ventilation; upper-airway clearance*. [Respir Care 2020;65(8):1063–1076. © 2020 Daedalus Enterprises]

Introduction

Patients with amyotrophic lateral sclerosis (ALS) ultimately die of respiratory failure[1] due to hypoventilation,[2] as respiratory muscle weakness advances, unless adequate ventilation is maintained through use of noninvasive[3-5] or tracheostomy breathing support.[6-8] Unfortunately, excessive oral secretions may affect tolerance of noninvasive ventilation (NIV).[8,9] Since it was first reported that NIV could be used in patients with ALS and without severe bulbar impairment,[8] subsequent studies have shown that subjects with any bulbar involvement are less tolerant of NIV,[10-15] whereas the absence of secretions predicts good tolerance.[9]

In patients without swallow impairment, oral secretions are automatically swallowed.[16-18] As dysphagia progresses,

the spontaneous automatic swallowing that normally clears excessive secretions is reduced.[19] The frequency of swallowing saliva predicts the amount of saliva accumulating in the mouth and throat.[17] Drooling of saliva is a noticeable sign of bulbar ALS.[20] In contrast, accumulation of saliva in the oropharynx is not outwardly visible. Thus, pooling of secretions in the upper airway may be overlooked. As oral secretions increase, eventually, secretion clearance in the mouth and throat can no longer be maintained, nor can continuous use of NIV be tolerated. Therefore, an oral secretion metric is needed to measure secretions and the ability to clear the upper airway for predicting NIV tolerance.

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A simple clinimetric scale was validated[21,22] and developed based on a cohort of subjects with ALS by using NIV in the home setting as a continuation of the early NIV study.[8] The Oral Secretion Scale (OSS) was developed to characterize oral secretions relative to the ability to swallow saliva and clear the upper airway. The purpose of this study was to assess the reliability of the OSS to predict tolerance of NIV, the need for hospice or transition to planned tracheostomy, and prognostic factors for survival in patients with ALS.

QUICK LOOK

Current knowledge

Noninvasive ventilation (NIV) can be tolerated in patients with amyotrophic lateral sclerosis (ALS) unless oral secretions become severe due to bulbar impairment. An oral secretion scale is needed to measure secretions relative to the ability to swallow and clear the upper airway for predicting tolerance of NIV.

What this paper contributes to our knowledge

A validated Oral Secretion Scale was developed to predict tolerance of NIV in patients with ALS. Survival correlated with NIV tolerance and hours per day that NIV was used. The Oral Secretion Scale reliably signaled when to initiate hospice or transition to tracheostomy ventilation. Users with nonbulbar ALS on NIV did not need a tracheostomy when upper-airway clearance was maintained.

Methods

Study Design and Setting

In this observational, longitudinal study, 159 consecutive subjects with ALS were followed prospectively from NIV initiation during subsequent home visits until subjects died or transitioned to tracheostomy and invasive ventilation. Patients, family caregivers, and health-care providers were referred to the ALS Care Project for management in their homes or care facilities, supportive services, and education programs for clinicians on evidenced-based care for ALS. Referrals came from multiple health-care resources throughout Ohio, West Virginia, and western Pennsylvania. Nursing consultation in the tri-state region included assessment of patient problems, planning care interventions, education on choices for breathing and living, and referrals to physicians and multidisciplinary health-care providers in local communities. Data were collected during home visits and follow-up telephone interviews with the subjects and their care providers.

Subjects

All the subjects were diagnosed with ALS according to the El Escorial criteria.[23] Inclusion criteria included

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subjects who (1) were visited at their homes or care facilities; (2) attempted NIV and failed; and (3) tried and continued NIV use (Fig. 1). The subjects were entered into the study at the start of NIV, between 2000 and 2010, and followed up in the subsequent years until the last subject ended NIV.

Ethics

The Ethics Committee for the Protection of Human Subjects (Institutional Review Board ALS Care Project) reviewed and approved the observational study. The approval was based on the federal regulations for human research protections and the methods of assessing subjects and collecting data according to the nursing process[24] and the ALS patient assessment tool of ALS Care Project. All the subjects gave their informed consent.

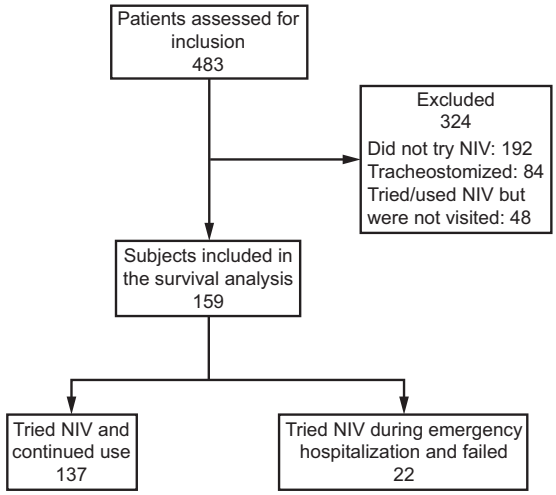

Fig. 1. Flow chart. NIV = noninvasive ventilation.

The OSS

The validated OSS is a simple, 5-point scale for measuring secretions in the mouth and throat, as related to the ability to swallow saliva and clear secretions from the oropharynx.[17,20,25] The OSS was designed to be used in any clinical setting, without testing materials, by minimally trained health-care providers and family caregivers. When using the OSS, clinicians may also assess oral secretions during telephone interviews with the subjects and care providers (Table 1).

The OSS scores correspond to the oral secretion characteristics and the saliva swallow ability (Table 1): OSS score of 4 = normal, no excessive secretions, normal automatic swallow; OSS score of 3 = mild, infrequent secretions in the mouth, automatic swallow decreased; OSS score of 2 = moderate, occasional secretions in the mouth and throat, conscious swallow required; OSS score of 1 = severe, frequent secretions in the mouth and throat, conscious swallow difficult; and OSS score of 0 = most severe, constant secretions in the mouth and throat, conscious swallow impossible (Table 1). The ability to swallow saliva was assessed by using our Saliva Swallow Assessment Tool (Table 2). The OSS also measures the frequency of oropharyngeal suctioning to clear the upper airway in patients with OSS scores 2 and 1–0 (Table 1).

The observer chooses a single score whose criteria most closely match the patient's condition, according to the worst performance. If multiple criteria in multiple score categories are observed, then the observer selects the score with the most criteria that match the patient's worst performance (Table 1). If the observer is uncertain whether the patient has an OSS score of 3 or 2 or an OSS score of 1 or 0, then the observer chooses the worst score by default.

Important factors that may affect the amount of secretions at the time of the secretion assessment were accounted for in the assessment. These include positioning of the

Table 1. Oral Secretion Scale (OSS)

OSS Score	Oral Secretion Characteristics	Saliva Swallow Ability
4, Normal	No excessive secretions	Automatic, normal
3, Mild	Infrequent, small accumulation of secretions in the mouth; infrequent wet lips or drooling; infrequent lip blotting	Automatic, decreased
2, Moderate	Occasional drooling, lip blotting; occasional pooling of secretions in the throat; oropharyngeal suctioning 0–2/h	Conscious, required
1, Severe	Frequent drooling, lip blotting; frequent pooling of secretions in the throat; oropharyngeal suctioning 3–4/h	Conscious, difficult
0, Most severe	Constant drooling, lip blotting; constant pooling of secretions in the throat; oropharyngeal suctioning >4/h	Conscious, impossible

The observer chooses a single score whose criteria most closely match the patient's condition, according to the worst performance; if multiple criteria in multiple score categories are observed, then the observer selects the score with the most criteria that match the patient's worst performance; if the observer is uncertain whether the patient has an OSS score of 3 or 2 or an OSS score of 1 or 0, the observer chooses the worst score as the default.

Table 2. Saliva Swallow Assessment Tool

Saliva Swallow Assessment
OSS score of 4, normal score: Automatic normal swallow, no excessive oral secretions;
Question: Are swallows automatic and spontaneous, without the patient thinking to swallow his or her saliva?
Answer: Saliva swallows are automatic, normal, and occur spontaneously without thinking to swallow.
OSS score of 3, mild OSS score: Automatic swallow is decreased; infrequent secretions in the mouth;
Question: Does the patient notice a delay in swallowing automatically and the patient must "think" to swallow at times?
Answer: Swallows of saliva are not always automatic; spontaneous automatic swallows are decreased, less than normal; infrequently, the patient must think or make an effort to swallow.
OSS score of 2, moderate OSS score: Conscious swallow is required; occasional pooling of secretions in throat;
Question: Does the patient ever need to make a conscious, voluntary effort to swallow his or her saliva? If yes, then how often?
Answer: Making a conscious effort to swallow saliva is usually required; oropharyngeal suctioning may be needed occasionally to clear the upper airway.
OSS score of 1, severe OSS score: Conscious swallow is difficult; frequent pooling of secretions in throat;
Question: Is making a conscious effort to swallow saliva ever difficult, requiring concentration to swallow?
Answer: Swallows are no longer spontaneous; making a conscious effort to swallow saliva is difficult and requires concentration; oropharyngeal suctioning reduces secretions, but it is difficult to maintain upper-airway clearance.
OSS score of 0, most severe OSS score: Conscious swallow is impossible; constant pooling of secretions in the throat;
Question: Is making a conscious effort to swallow saliva impossible most of the time?
Answer: Making a conscious effort to swallow saliva is very difficult or impossible; oropharyngal suctioning reduces secretions, but it is no longer possible to maintain upper-airway clearance.

OSS = Oral Secretion Scale

subject, dehydration or increased fluid intake, pharmacologic agents to treat sialorrhea, the number of times that the subject attempts to make a conscious effort to swallow, if the subject uses a cloth or tissue product to absorb saliva, if a suction pump is used and frequency of oropharyngeal suctioning, and the frequency of NIV use (which may dry secretions).

Assessment of Saliva Management

Management of saliva was also assessed: (1) use of cloths, tissues, or paper towels to blot lips or insert inside the mouth to absorb saliva and frequency of lip blotting; (2) use of pharmacologic agents to treat sialorrhea in subjects with OSS scores of 3–2 or 1–0; and (3) use of oropharyngeal suctioning to clear the throat, the frequency of suctioning, and whether a soft-tip flexible (size 14 French) catheter or a hard-tip nonflexible catheter was used.

Definition of NIV Tolerance and Intolerance

Tolerance of NIV was defined as the ability and willingness to use NIV for as long as necessary, whether continuously or intermittently to maintain adequate ventilation, alleviate respiratory symptoms, and provide breathing comfort. Intolerance of NIV was defined as the inability and unwillingness to use NIV to maintain adequate ventilation, alleviate respiratory symptoms, and provide breathing comfort. The subjects were observed for signs of dyspnea while using NIV. Factors that affected NIV tolerance were also assessed: pooling of secretions that obstructed the upper airway; disrupted use of NIV to suction secretions; inability to maintain upper-airway clearance; disrupted use of NIV to clean secretions from oronasal interfaces; and the inability to tolerate wearing nasal and/or oronasal interfaces.

Tolerance of Mechanical Insufflation-Exsufflation

Tolerance of mechanical insufflation-exsufflation was assessed because of the delivery of the high flow of positive pressure air to inflate the lungs during the insufflation cycle. Thus, we assessed the ability to tolerate the noninvasive delivery of air via a mask in subjects with OSS scores of 4, 3–2, and 1–0. Because mechanical insufflation-exsufflation is indicated for clearing bronchial secretions, not oral secretions, we did not assess the ability of mechanical insufflation-exsufflation to clear the lower airways, nor did we measure the cough force with a testing tool as part of the study.

Hours of NIV Use per Day

The number of hours per day that the subjects used NIV and the number of months after NIV initiation when the subjects began using NIV for the maximum time were determined. The subjects who used NIV continuously, except to withdraw for only a few minutes every 1–2 hours, were defined as using NIV for 24 h/d. Each subject was assigned to the group of maximum hours they used NIV per day: 24, 17–23, 4–16, and <4 h to define the difference between their hours of NIV use and months of survival.

Table 3. Demographic Characteristics of the Subjects With ALS, Grouped by Sex

Characteristic	All Users of NIV	Male Subjects	Female Subjects
Sex, *n* (%)	137 (100)	71 (52)	66 (48)
Age at diagnosis, mean y	58	57.5	58.7
Familial ALS, *n* (%)	10 (7)	5	5
Limb (spinal) onset-nonbulbar	79 (58)	43	36
Respiratory (spinal) onset-nonbulbar	17 (12)	13	4
Bulbar onset	41 (30)	16	25
Age when NIV was initiated, mean y	59.7	59.1	60.3
Time from diagnosis to NIV, mean mo	18.2	17.9	18.6
Ambulatory when NIV began, n (%)	70 (51)	39	31
Ambulatory when died, *n* (%)	40 (29)	24	16
Ambulatory when tracheostomy and invasive ventilation began, *n* (%)	6 (4)	3	3
Lived at home, *n* (%)	123 (90)	67	56
Used home care agency services *n* (%)	18 (13)	10	8
Used hospice services *n* (%)	57 (42)	29	28
Lived at care facility, *n* (%)	14 (10)	3	11

ALS = amyotrophic lateral sclerosis
OSS = Oral Secretion Scale
NIV = noninvasive ventilation

Data Collected

The subjects and caregivers were interviewed through ongoing visits and telephone calls. The data collected included whether the site of onset was bulbar or spinal (limb or respiratory) and the ambulatory status when the usage of NIV began and ended. The subjects with ALS who showed signs of respiratory compromise within 3 months of diagnosis (and without noticeable signs of limb or bulbar weakness) were categorized as having a respiratory onset. The experiences of the subjects before the start of NIV were also determined. These included signs of respiratory compromise, pulmonary function test results, requirement for emergency hospitalizations, how NIV was applied, and the types of ventilators and settings used. Data were also collected on the experiences of the subjects before they died or underwent tracheostomy and invasive ventilation.

Statistical Analysis

Each subject who used NIV was rated with an OSS score at NIV initiation. The subjects were classified into 3 subgroups at the start of NIV: group I, OSS score of 4, group II, OSS scores of 3–2 (mild/moderate); and group III, OSS scores of 1–0 (severe/most severe) to simplify the statistical analysis. Data comparisons among the 3 groups were performed by using the one-way analysis of variance and the chi-square test.

Survival on NIV was defined as the months from NIV initiation to the time NIV ended when the subjects either died or transitioned to tracheostomy. Cumulative survival and the hazard ratio (HR) were determined by using Kaplan-Meier analysis. Log-rank tests were used to determine the differences in survival of subjects with different OSS scores at NIV initiation and hours per day of NIV usage. The frequency of OSS scores when NIV became intolerable was determined.

Uni- and multivariate analyses were performed to identify the effect on months of survival between subjects with nonbulbar (limb or respiratory) and subjects with bulbar onsets, and hours of NIV use from NIV initiation, by using the Cox proportional hazards regression model. Statistical analysis was performed by using predictive analytics software, Statistics version 24.0 (IBM SPSS Statistics, Armonk, NY). The statistical significance was set at $P < .05$.

Results

Subject Demographics

The subjects who met the inclusion criteria ($N = 159$) were included in the analysis (Fig. 1). Of the 159 who attempted NIV, NIV use during emergency hospitalizations failed in 22 subjects (14%) (Fig. 1). Thirteen of the 22 subjects (59%) died of respiratory distress and 9 (41%) commenced emergency tracheostomy and invasive ventilation. A total of 137 subjects (86%) (71 males [52%]) tried and continued NIV use. The mean age at diagnosis was 58.2 years. The mean ± SD time from onset to NIV initiation was 21.1 ± 15.2 months or median 17.3 months. The sites of the disease onset in the 137 subjects were as

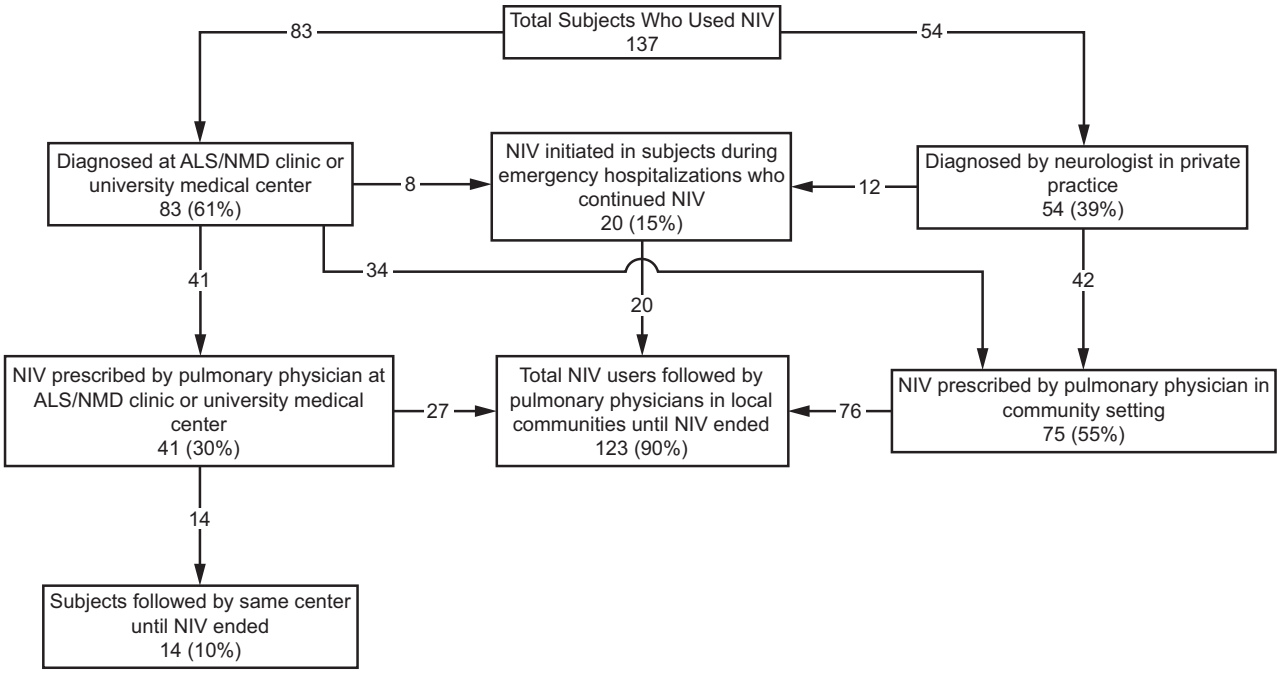

Fig. 2. Flow chart. Physicians who diagnosed the subjects, prescribed noninvasive ventilation (NIV), and followed up the subjects until NIV ended ($N = 137$). ALS = amyotrophic lateral sclerosis, NMD = neuromuscular disease.

follows: 58% limb ($n = 79$), 12% respiratory ($n = 17$), and 30% bulbar ($n = 41$) (Table 3). The OSS scores at limb, respiratory, and bulbar onset were 4, 4, and 3, respectively. Seventy subjects (51%) were either independently ambulatory or walked with minimum or maximum assistance when NIV was initiated. The subjects resided in their homes ($n = 123$ [90%]) or in care facilities ($n = 14$ [10%]) (Table 3).

Before NIV initiation, the subjects were educated on the option of NIV and the need for early pulmonary evaluation. All the subjects made the decision to use NIV. Because the subjects were treated by physicians from multiple clinical settings, there was no uniform protocol for NIV initiation. Although a pulmonary physician initiated NIV in the subjects ($n = 41$ [30%]) at an ALS/neuromuscular or university medical center, 123 subjects (90%) were subsequently followed up by pulmonary physicians in local communities until NIV ended (Fig. 2). OSS scores of the 137 subjects at the start of NIV were the following: group I, 4 ($n = 78$ [56.9%]), group II, 3–2 ($n = 42$ [30.7%]), and group III, 1–0 ($n = 17$ [12.4%]) (Table 4).

Respiratory Status at NIV Initiation

Initial respiratory signs of the 137 subjects, before noticeable signs of dyspnea and pulmonary testing, were a weak cough, reduced voice volume, and the inability to fully inhale and exhale. Commencement of NIV, however, was based on previous pulmonary tests, signs of respiratory compromise, and/or emergency department visits. FVC measurements for groups I, II, and III were 41.2, 43.6, and 31.6% of predicted, respectively (Table 4). At the time of NIV initiation, respiratory symptoms varied among the subjects and included the following: dyspnea, shallow slow breathing, marked fatigue, disrupted sleep, orthopnea, supine and upright dyspnea, respiratory distress, gasping, panic attacks, hypersomnolence, headaches, accessory muscle use, and paradoxical breathing.

Twenty of the 137 subject (15%) began NIV during emergency hospitalizations and survived (Fig. 2). The 20 were previously told that their pulmonary tests "looked good" or that the subjects had acute respiratory failure (ARF) while waiting for pulmonary evaluation. Six of the 20 subjects (30%) (who were nonbulbar, ambulatory, or had a respiratory onset) became nonresponsive during ARF but immediately recovered after emergency NIV initiation and continued its use. The others who tried NIV during ARF and continued its use included 4 subjects with an OSS score of 1 and 4 who had ARF after percutaneous endoscopic gastrostomy placement.

The subjects' pulmonary physicians prescribed the ventilators and settings. The 137 subjects used one of the 4 devices for ventilation: bi-level positive airway pressure (BPAP) with a backup rate (10-12 breaths/min), spontaneous timed mode ($n = 87$ [64%]); BPAP without a backup rate, spontaneous (S) mode ($n = 24$ [18%]), volume-cycled ($n = 21$ [15%]), and CPAP ($n = 5$ [4%]).

Table 4. Clinical Characteristics of Total NIV users

Characteristics	All Subjects	Subjects by Group			*P*
		Group 1: OSS Score of 4	Group II: OSS Scores of 3–2	Group III: OSS Scores of 1–0	
Users of NIV, *n* (%)	137	78 (56.9)	42 (30.7)	17 (12.4)	
Male subjects, *n* (%)	71 (51.8)	51 (65.4)	13 (31.0)	7 (41.2)	.001
Age at diagnosis, y	58.2 (56.0–6.2)	56.7 (54.2–59.8)	58.4 (54.6–62.1)	62.9 (57.7–68.0)	.19
Survival from onset, mo	33.3 (28.8–37.8)	39.3 (32.4–46.2)	28.1 (22.2–33.9)	18.9 (14.4–23.4)	.004
Onset to NIV initiation, mo	21.1 (18.5–23.7)	21.9 (18.1–25.6)	21.2 (16.6–25.7)	17.6 (13.1–22.0)	.58
Mean survival from NIV initiation, mo	12 (9.2–15.2)	18 (12.6–22.4)	7 (4.8–8.8)	1 (0.9–1.7)	<.001
Median survival from NIV initiation, mo	6 (4.2–8.3)	11 (7.3–14.0)	5 (3.1–6.1)	1 (1.1–1.5)	<.001
Subjects on NIV who transitioned to tracheostomy and invasive ventilation, *n* (%)	18 (13.1)	12 (15.4)	4 (9.5)	2 (11.8)	.65
PEG placement, *n* (%)	51 (37.2)	12 (15.4)	30 (71.4)	9 (52.9)	<.001
Ambulatory when NIV began, *n* (%)	70 (51.1)	40 (51.3)	19 (45.2)	11 (64.7)	.40
FVC before NIV initiation, %	41.0 (38.7–43.4)	41.2 (38.4–44.0)	43.6 (38.6–48.6)	31.6 (23.5–39.6)	.03
Maximum hours NIV was used per day, *n* (%)					<.001
24 h/d	37 (27.0)	32 (41.0)	5 (11.9)	0 (0.0)	
17–23 h/d	12 (8.8)	10 (12.8)	1 (2.4)	1 (5.9)	
4–16 h/d	40 (29.2)	26 (33.3)	12 (28.6)	2 (11.8)	
<4 h/d	48 (35.0)	10 (12.8)	24 (57.1)	14 (82.4)	
OSS score when NIV ended, *n* (%)					<.001
4	52 (38.0)	52 (66.7)	NA	NA	
2	16 (11.7)	10 (12.8)	6 (14.3)	NA	
1	45 (32.8)	13 (16.7)	23 (54.8)	9 (52.9)	
0	24 (17.5)	3 (3.8)	13 (31.0)	8 (47.1)	

N = 137
NIV = noninvasive ventilation
OSS = Oral Secretion Scale
PEG = percutaneous endoscopic gastrostomy
NA = not applicable

A respiratory therapist at the home equipment company delivered the ventilator, adjusted the settings (as prescribed by the physician), and helped the subject select the most comfortable and appropriate interfaces. The bulbar subjects used oronasal and/or nasal interfaces with a chin strap. The nonbulbar subjects used nasal interfaces in the day and an oronasal mask at night. Seven subjects who were nonbulbar and with head mobility also used a mouthpiece during the day. All the users who were tolerant of continuous NIV had >2 nasal or oronasal interfaces to promote NIV comfort.

Survival Analysis

Of the 137 subjects who continued NIV, the median survival from NIV initiation (stratified by their OSS scores of 4, 3–2, and 1) were the following: 11 (95% CI 7.3–14.0) months; 5 (95% CI 3.1–6.1) months, and 1 (95% CI 1.1–1.5) months, respectively (Fig. 3). Survival was significantly ($P < .001$) longer in subjects with an OSS score of 4 than an OSS score of 1 at NIV initiation (Table 4). The overall median survival at 6 (ranging 4.2–8.3) months from NIV initiation was significantly lower ($P < .001$) than the survival of subjects with an OSS score of 4.

The 137 users of NIV were grouped by the maximum hours per day that they used NIV: 24 h/d ($n = 37$ [27.0%]), 17–23 h/d ($n = 12$ [8.8%]), 4–16 h/d ($n = 40$ [29.2%]), and <4 h/d ($n = 48$ [35%]) (Table 4). From NIV initiation, the median months of survival (stratified by 24, 17–23, 4–16, and <4 h/d that NIV was used) were the following: 21 (95% CI 8.6–33.2) months, 8 (95% CI 3.4–11.5) months, 6 (95% CI 4.2–8.2) months, and 2 (95% CI 1.5–2.7) months, respectively (Fig. 4). Survival was significantly ($P < .001$) longer in the subjects who used NIV 24/d than <24 h/d (Fig. 4). Overall, the subjects who were NIV tolerant indicated that the use of NIV improved their quality of life.

The Kaplan-Meier survival curves showed a correlation with survival and the hours per day that NIV was used in 78 subjects with an OSS score of 4 (Fig. 5). The median survival of the 78 subjects from NIV initiation, who used NIV for 24, 17–23, 4–16, and <4 h/d, was 22 (95% CI 11.8–31.2) months, 9 (95% CI 0.2–17.4) months, 6 (95% CI 1.3–10.5) months, and 2 (95% CI 1.1–2.6) months,

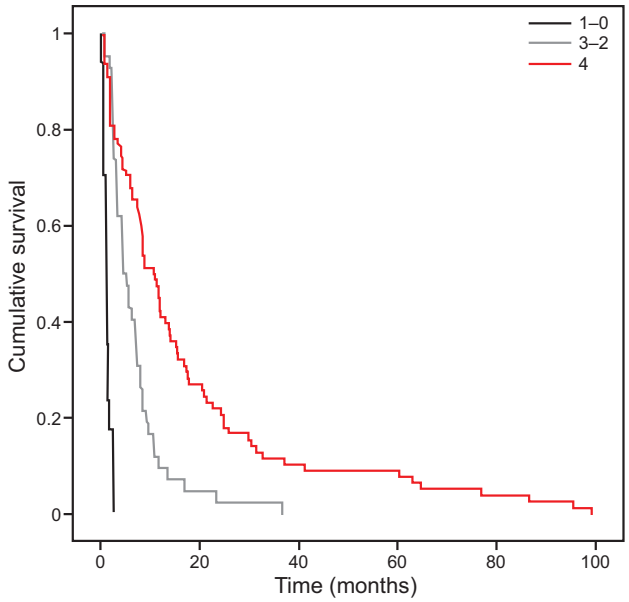

Fig. 3. Kaplan-Meier survival curves of the subjects from noninvasive ventilation (NIV) initiation (N = 137), stratified by an Oral Secretion Scale score of the subjects at NIV initiation.

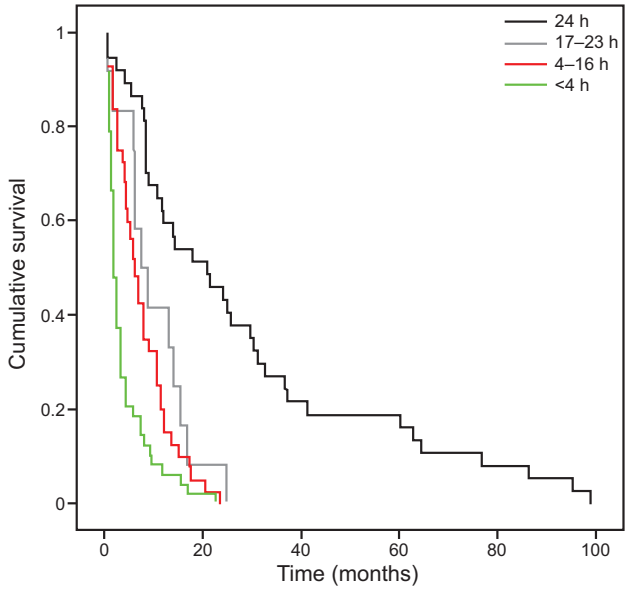

Fig. 4. Kaplan-Meier survival curves of the subjects (N = 137) from noninvasive ventilation (NIV) initiation, stratified by the maximum hours per day the subjects used NIV.

respectively (Fig. 5). Survival was significantly ($P < .001$) longer in the 78 subjects who used NIV 24 h/d than <24 h/d (Fig. 5). Of the 78 subjects at NIV initiation, 32 of 78 (41%) used NIV up to 24 h/d (Table 4), a median of 11 (95% CI 7.3-14.0) months after NIV initiation. This included 16 of 32 subjects with an OSS score of 4, who survived a mean of 52 months; 13 of the 16 long-term

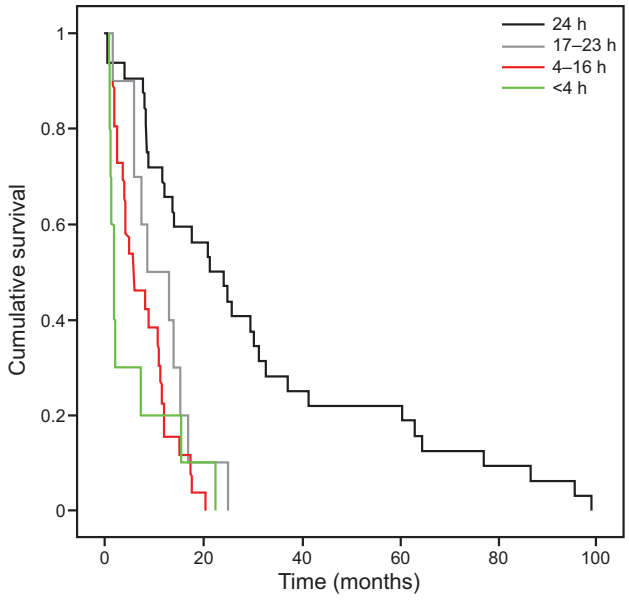

Fig. 5. Kaplan-Meier survival curves of the subjects with Oral Secretion Scale score of 4 from noninvasive ventilation initiation (n = 78), stratified by the maximum hours per day that the subjects used NIV.

survivors used a BPAP spontaneous timed mode ventilator, and 3 used a volume-cycled ventilator.

Compared with the 78 subjects with nonbulbar ALS who used NIV, 42 of the 137 subjects had an OSS score of 3–2 at NIV initiation and used NIV for a median of 5 months. Of these 42, 5 subjects used NIV for up to 24 h, 1 for 17–23 h, 12 for 4–16 h, and 24 for <4 h/d (Table 4). Of the 137 subjects, 17 had an OSS score of 1 at NIV initiation and survived a median of 1 month. One of the 17 subjects used NIV for 17–23 h/d, 2 for 4–16 h/d, and 14 for <4 h/d (Table 4).

Cox Regression Analysis of Survival from NIV Initiation

In the univariate analysis, factors significantly associated with prolonged survival were a nonbulbar onset (HR 1.88, 95% CI 1.53–2.31; $P < .001$) compared with a bulbar onset, and 24 h/d of NIV use (HR 4.91, 95% CI 2.98–8.09; $P < .001$), compared with NIV <24 h/d (Table 5). In contrast, the multivariate analysis showed covariates with a significant prognostic value associated with survival in the subjects with nonbulbar onset (HR 1.47, 95% CI 1.19–1.81; $P < .001$) compared with those with bulbar ALS and also subjects who used NIV 24 h/d (HR 4.60, 95% CI 2.66–7.96; $P < .001$) (Table 5). The subjects who used NIV for 24 h/d survived significantly longer than those who used NIV for fewer hours.

Table 5. Univariate and Multivariate Cox Regression Analysis of Survival of the Subjects from NIV Initiation

Analysis	HR	95% CI	*P*
Univariate analysis			
Sex	1.15	0.97–1.37	.12
Age at diagnosis	1.33	0.94–1.89	.11
Site of onset (limb vs bulbar)	1.88	1.53–2.31	<.001
Diagnosis to NIV initiation, mo	0.71	0.51–1.03	.08
NIV used, h/d	4.91	2.98–8.09	<.001
Ambulatory when NIV began	1.18	0.84–1.65	.35
PEG placement	1.24	0.87–1.76	.24
FVC before NIV	1.07	0.69–1.67	.77
Dyspnea	1.60	0.75–3.44	.23
Shallow breathing slow or rapid	1.33	0.95–1.88	.10
Disrupted sleep	2.72	1.64–4.52	<.001
Orthopnea before NIV	1.83	1.10–3.06	<.05
Upright dyspnea before NIV	1.90	1.33–2.73	<.001
Respiratory distress, gasping	1.30	0.93–1.83	.13
Hypersomnolence	1.11	0.74–1.67	.63
Headaches	1.21	0.73–1.98	.46
Multivariate analysis			
Site of onset (limb vs bulbar)	1.47	1.19–1.81	<.001
NIV used, h/d	4.60	2.66–7.96	<.001
Disrupted sleep	2.25	1.18–4.32	<.01
Orthopnea before NIV	1.24	0.62-2.48	.54
Upright dyspnea before NIV	1.88	1.29-2.74	<.01

N = 137
NIV = noninvasive ventilation
HR = hazard ratio
PEG = percutaneous endoscopic gastrostomy

Secretion Management

Seventy subjects used pharmacologic agents, including glycopyrrolate, scopolamine transdermal patch, atropine, hyoscyamine, and amitriptyline to treat sialorrhea. When 58 of 70 subjects had an OSS score of 3 or 2, they believed that these drugs reduced the amount of drooling; however, when 63 of 70 subjects' OSS scores fell to 1 or 0, they did not report a reduction in drooling.

Oropharyngeal suctioning with a soft-tip catheter was used in 54 subjects to reduce pooling of secretions in the mouth and throat. All the subjects who used a soft-tip, flexible catheter with a narrow lumen (size 14 French) indicated that the catheter reached the back of the throat and cleared secretions more adequately than did a hard-tip, nonflexible catheter with a large lumen and bulb tip (Yankauer or "tonsil tip" catheter). The subjects indicated that a hard-tip catheter was only effective for clearing secretions from the mouth (Table 6).

Of the 54 subjects who required oropharyngeal suctioning, 42 subjects with an OSS score of 3 or 2 were able to maintain upper-airway clearance. However, in subjects with an OSS score of 1 or 0, it was no longer possible to maintain the upper airway, despite frequent suctioning and the ongoing suctioning disrupted NIV use. As a result, failure to maintain clearance of the oropharynx led to NIV intolerance in subjects with an OSS score of 1 or 0.

Use of Mechanical Insufflation-Exsufflation

Twenty-six subjects used mechanical insufflation-exsufflation for secretion clearance. Of the 26 subjects, 13 with an OSS score of 4 and 12 with an OSS score of 3–2 tolerated the delivery of positive pressure air, whereas one subject with an OSS score of 1 did not tolerate mechanical insufflation-exsufflation. When 7 subjects with an OSS score of 4 became an OSS score of 3–2, they continued to be tolerant of mechanical insufflation-exsufflation. However, when subjects' OSS score became 1, with severe pooling of secretions in the upper airway, they no longer tolerated mechanical insufflation-exsufflation (thus, the treatment failed). The subjects with an OSS score of 1–0 indicated that their attempts to use mechanical insufflation-exsufflation caused the sensations of choking and distress.

Intolerance of NIV

In the subjects who were unable to tolerate NIV ≥ 80%, they had an OSS score of 1–0. Of the 137 subjects, 45 (32.8%) and 24 (17.5%) had an OSS score of 1 and 0, respectively, when NIV ended (Table 4). The subjects with an OSS score of 1–0 were also unable to maintain adequate ventilation as respiratory impairment advanced. The subjects often used NIV at intervals for 10–20 min or longer as a palliative measure to alleviate symptoms and provide comfort. Despite frequent oropharyngeal suctioning, the subjects with an OSS score of 1–0 were unable to maintain upper-airway clearance. As a result, 57 subjects opted for hospice and 9 underwent tracheostomy and invasive ventilation. At the end of the study, all the subjects either died or had transitioned to tracheostomy and invasive ventilation.

Independent Causes of NIV Failure in Subjects With an OSS Score of 4

In the subjects who were NIV tolerant and with an OSS score of 4, 15 withdrew from NIV, anticipating death to occur and opting for palliative care. One subject died when the oronasal mask accidently slipped from the face. Unexpected ARF occurred in 3 subjects who were NIV dependent and who withdrew from NIV momentarily for personal care. As a result, 2 died and 1 began unplanned tracheostomy and invasive ventilation. However, 23 subjects with an OSS score of 4 (in which 6 were still ambulatory) had unexpected ARF, which resulted in emergency hospitalizations when they withdrew from NIV to engage

Table 6. Oral Secretions: Definition, Indications for Oropharyngeal Suctioning, and Catheter Selection

Definition: oral secretions consist of saliva and mucus.
Mucus produced by the salivary glands is a normal component of saliva.
Mucus produced in the nose and lungs eventually deposits in the oropharynx, mixes with saliva, and is normally swallowed; impaired saliva swallow ability may cause excessive oral secretions in the mouth and throat.
Thick mucus from the respiratory passages, commonly referred to as "phlegm," is not a normal component of saliva but combines with saliva in the mouth and throat.
Indications for oropharyngeal suctioning: pooling of secretions in the throat (oropharynx) may cause:
Obstruction of the upper airway;
Breathing discomfort;
NIV intolerance, disrupted use of NIV, and the inability to use an oronasal mask;
Risk of aspiration;
Episodes of choking, restlessness, anxiety, and panic attacks;
Emergency hospitalizations, unwanted intubation, and unplanned tracheostomy and invasive ventilation;
Benefits: oropharyngeal suctioning may:
Clear the upper airway for achieving and maintaining adequate ventilation;
Alleviate respiratory distress, and promote breathing comfort;
Improve NIV tolerance;
Minimize the risk of aspiration;
Reduce emergency hospitalizations, unplanned tracheostomy and invasive ventilation, and early mortality;
Oropharyngeal suctioning is a clean and safe technique for clearing the upper airway. Suctioning below the oropharynx is unsafe and must be avoided. Family caregivers should be educated and supervised (initially) by a RN in the home setting on how to safely and effectively suction secretions from the mouth and throat.
Mechanical insufflation-exsufflation is indicated for clearing lower airway secretions, not for clearing the oropharynx.
Evidence-based catheter selection for oropharyngeal suctioning:
A soft-tip, flexible catheter with a narrow lumen (size 14 French) clears secretions from the back of the throat more adequately than using a hard-tip, nonflexible, plastic catheter with a large lumen and bulb tip (Yankauer or "tonsil-tip"catheter) because the narrow lumen catheter produces a significantly higher velocity of suction to clear oral secretions. Also, the soft-tip, flexible catheter reaches the back of the throat more closely. A hard tip catheter may trigger the gag reflex and cause discomfort.
A hard-bulb tip, nonflexible catheter with large lumen is indicated for clearing secretions from the mouth. The large lumen of a Yankauer catheter provides a means for rapidly suctioning secretions, including thick mucus from the mouth. Patients with the ability to self-suction may more easily suction secretions from the mouth by using a catheter with a non-slip grip handle.

NIV = noninvasive ventilation

in activities or leave home. Of the 23 subjects, 20 died and 3 underwent unplanned tracheostomy and invasive ventilation. Four subjects who were NIV tolerant and who desired to live, died unexpectedly after being given morphine and/or oxygen by hospice due to the perception that advanced disability signaled the end of life. Also, 7 of 78 subjects with an OSS score of 4 who used a BPAP (S) mode without a backup rate, up to 24 h/d, suddenly reported the inability to breathe while using NIV. As a result, one subject died and 6 began unwanted tracheostomy and invasive ventilation. In addition, 2 of 78 subjects, intolerant of the intermittent use of CPAP, had ARF and underwent emergency tracheostomy and invasive ventilation after using CPAP < 4 h/d for >1 month.

Discussion

The OSS is a validated reliable tool[21,22] for measuring secretions in the mouth and throat, quantifying the ability to clear secretions from the upper airway, and predicting NIV tolerance in patients with ALS. The ALS Functional Rating Scale-Revised salivation scale[26] measures sialorrhea but not pooling of saliva in the upper airway, and thus, does not predict NIV tolerance.

Health-care providers with appropriate training can use the OSS in any clinical setting and during telephone evaluations with patients with ALS or their caregivers, if necessary. We recommend that care providers of patients with ALS use the OSS as a tool for planning timely NIV initiation and care interventions, while predicting tolerance of NIV.

Our study showed the 2 most important predictors of NIV tolerance and prognostic factors associated with increased survival in subjects with ALS using NIV were (1) an OSS score of 4 at NIV initiation, and (2) the ability to use NIV continuously or for as many hours as required. We found that the absence of excessive oral secretions is the most reliable predictor of NIV tolerance and hours of NIV use. Our observational study indicated that the subjects with ALS and with an OSS score of 4 did not need

tracheostomy and invasive ventilation to maintain adequate ventilation. Use of the OSS during emergency hospitalizations may prevent unplanned tracheostomy and invasive ventilation.

Our observational study indicated that survival correlates with the hours per day that NIV is used. In fact, our subjects with nonbulbar ALS and who used NIV for 24 h/d survived nearly 5 times longer than the subjects who used NIV for <24 h/d. This demonstrates that the hours per day that NIV is used is a significant prognostic factor for survival. Withdrawing from NIV momentarily for personal care (eg, use of restroom or bathing) could lead to ARF in users who are NIV-dependent. The subjects in our study who used NIV continuously began using NIV 24 h/d a median of 11 months after NIV initiation.

A striking observation in our study is that the subjects with nonbulbar ALS survived on NIV for as long as their OSS score remained at 4 (and NIV was used for adequate hours per day with an appropriate ventilator). This observational study shows that maintenance of an OSS score of 4 was associated with prolonged survival and the potential outcome of severe disability in subjects with ALS.

NIV can provide a good survival benefit in mild bulbar ALS.[27,28] Multiple studies have shown a strong association between bulbar impairment and intolerance of NIV,[8-15] and that effectiveness of NIV is related to the severity of bulbar dysfunction.[29] Our results are consistent with those who found that moderate-to-severe bulbar symptoms were associated with twice the risk of death as those with mild or no bulbar symptoms,[30] that the severity of bulbar involvement at NIV initiation was a prognostic factor for survival,[30] and that NIV has a role in ALS-bulbar onset disease.[31]

The OSS can be used as a vital tool for managing the best timing to start NIV. Initiating NIV in patients who have an OSS score of 4 permits time to adapt to NIV before potentially becoming bulbar. Early initiation of NIV also protects against early mortality when signs of pending ARF may be overlooked. Although subjects with an OSS score of 3–2 are NIV tolerant, most of these subjects do not use NIV continuously to maintain long-term survival, as shown by our data. Using NIV before, during,[32] and after percutaneous endoscopic gastrostomy placement might reduce the risk of ARF in patients with severe respiratory compromise.[33] Thus, before subjects with ALS have a percutaneous endoscopic gastrostomy placement, it is important that they have an OSS score of 3–2 and tolerate NIV during the percutaneous endoscopic gastrostomy procedure.

Early NIV initiation for patients with ALS is necessary before respiratory impairment progresses and when OSS scores predict good NIV tolerance. We found that the hallmark signs of early respiratory impairment in ALS are the following: a weak cough, reduced voice volume, and the inability to fully inhale and exhale. We believe that these are indicators for early testing, even if dyspnea is not reported. Late initiation of NIV based on Medicare criteria,[34] <50% FVC or oxygen saturation of ≤88% for 5 consecutive minutes put subjects with ALS at risk for emergency ARF and unwanted tracheostomy. Hence, we believe that NIV should begin as soon as respiratory signs are present, as published in the Guidelines of the European Federation of Neurological Societies,[35] and the NIV guidelines of the National Institute for Health and Clinical Excellence (in the United Kingdom).[36]

Despite the advances in ventilator technology through the years, most of our subjects with an OSS score of 4 who survived the longest used BPAP with a backup rate. In comparison, our subjects with an OSS score of 4 and NIV dependent who used BPAP spontaneous mode without a backup rate, suddenly had ARF while using NIV and died or underwent tracheostomy and invasive ventilation. This demonstrated that patients with ALS may lack the ability to trigger a device in the spontaneous mode, when respiratory impairment progresses.[37] Also, use of CPAP does not treat hypoventilation, and therefore, may be inappropriate for subjects with ALS[38,39] and is why CPAP use failed after 1 month in 2 subjects with an OSS score of 4. Unlike other studies, in which tolerance of NIV was assessed at NIV initiation,[9,30] and 1 month later,[9] we assessed NIV tolerance at initiation, when NIV became intolerable, and when NIV ended. Thus, we found that the least-favorable prognostic factor for survival was an OSS score of 1, when the subjects were no longer able to tolerate NIV.

In addition, we showed that subjects with an OSS score of 1–0 no longer tolerated mechanical insufflation-exsufflation. Perhaps treatment failure with mechanical insufflation-exsufflation in severe bulbar ALS may also be due to the collapse of the upper airway during the insufflation[40] or exsufflation[41] cycle of mechanical insufflation-exsufflation, as shown in these 2 studies of subjects with bulbar ALS. Meanwhile, our subjects with an OSS score of 4 and 3–2 tolerated mechanical insufflation-exsufflation use that is indicated for clearing the lower airways but is not effective in treating sialorrhea or clearing the upper airway.

An OSS score of 1 reliably signals when to initiate hospice care or transition to tracheostomy and invasive ventilation (if desired), if NIV can no longer be tolerated. Patients with ALS with an OSS score of 1 or 0, who are NIV intolerant, are approaching the end of life. A patient with ALS and with an OSS score of 1 or 0 should be offered hospice services and the right to use tracheostomy and invasive ventilation, if desired. ALS treating physicians and hospices should recognize that, even for patients with ALS and with an OSS score of 4 or 3–2, use of oxygen[42-45] and/or morphine[46] may result in respiratory failure and hasten death, as demonstrated in this observational study. If NIV can no longer be tolerated, then tracheostomy and invasive

ventilation is the ultimate alternative for long-term breathing support. Unexpected ARF due to NIV intolerance can result in emergency hospitalizations and unplanned tracheostomy and invasive ventilation.[6,8,47,48] An OSS score of 1 reliably predicts when to initiate planned tracheostomy and invasive ventilation that may prolong survival beyond respiratory failure.[8,47-51]

In addition to severe secretions, there were independent factors that caused NIV failure in our subjects who were NIV tolerant and had an OSS score of 4. Besides planned withdrawals and anticipating death, the most common reasons for unexpected ARF were the following: unawareness of pending ARF; not knowing when to use NIV; not using NIV when withdrawing temporarily for personal care, to walk (if ambulatory), or to leave the home; respiratory onset of ALS; use of a BPAP ventilator without a backup rate; and administering oxygen and/or morphine to NIV tolerant patients.

Guidelines on the best respiratory care interventions and use of NIV for ALS need to be revised.[52-54] Our study showed that most users of NIV who had ALS were followed up in their local health-care community until NIV ended. Therefore, the role of respiratory therapists and nurses is vital for achieving best outcomes of users of NIV and with ALS at their homes or care facilities. Use of the OSS is necessary for predicting NIV tolerance and can help guide ongoing NIV management decisions.

Conclusions

The OSS is a validated, reliable tool for predicting tolerance of NIV. Survival correlates with NIV tolerance and the hours per day that NIV is used. The subjects with ALS and with an OSS score of 4 who could tolerate continuous NIV use, up to 24 h/d, survived significantly longer than the subjects who used NIV $<$ 24 h/d. Patients with ALS and an OSS score of 1, unfortunately, are reliably unable to maintain effective upper-airway clearance, which indicates the need for hospice or transition to planned tracheostomy and invasive ventilation. An OSS score of 4 (no excessive oral secretions) at NIV initiation and the hours per day of NIV use were significant prognostic factors associated with prolonged survival. An OSS score of 1 (severe oral secretions) was a significant prognostic factor associated with decreased survival of users of NIV.

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