Clinical Neurology and Neurosurgery 184 (2019) 105456

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

The prognostic value of spirometric tests in Amyotrophic Lateral Sclerosis patients

Alice Pirola[a,*], Elisa De Mattia[a], Andrea Lizio[a], Giulia Sannicolò[b], Elena Carraro[a], Fabrizio Rao[a], Valeria Sansone[a,c], Christian Lunetta[a]

[a] NEuroMuscular Omnicentre, Fondazione Serena Onlus, Milan, Italy
[b] U.O. Neuropsichiatria Infantile, A.P.S.S, Trento, Italy
[c] Neurorehabilitation Unit, Dept. Biomedical Sciences of Health, University of Milan, Italy

ARTICLE INFO

Keywords:
Amyotrophic Lateral Sclerosis
Forced Vital Capacity
Peak Cough Expiratory Flow
ALSFRS-R
Progression rate

ABSTRACT

Objective: Amyotrophic lateral sclerosis (ALS) patients tend to develop progressive respiratory muscle weakness, leading to ventilatory failure and ineffective cough, principal causes of morbidity and mortality. Since patients are usually unaware of these symptoms, these are generally not noticed until the advanced stages and are associated with poor prognosis. The monitoring of respiratory function on a regular basis is therefore of great importance. Despite the availability of several pulmonary function tests, none of them was found to be the best indicator of the disease progression throughout the course of this condition.

The main aim of our work was to evaluate the prognostic value of these respiratory measures evaluated in a brief period of observation and their correlation with motor functional impairments in an ALS cohort.

Patients and Methods: Patients with ALS who had respiratory assessments performed and functional motor scales administered at baseline and six months later were included. All patients were assessed with forced vital capacity, both in seated and supine position (FVC; sFVC), peak expiratory flow (PEF), peak expiratory cough flow (PCEF), the revised ALS functional rating scale (ALSFRS-R), at baseline and after six months, and their disease progression rate (ΔFS) was obtained.

Results: We included 73 patients with probable or definite ALS according to El-Escorial revised Criteria. At baseline, PCEF and PEF significantly correlated with ALSFRS-R total, bulbar and spinal subscores and ΔFS, while FVC% significantly correlated with ΔFS. After 6 months all the respiratory parameters significantly correlated with ALSFRS-R and all its subscores. Longitudinally, FVC%, sFVC% and PCEF significantly correlated with ΔFS and some of ALSFRS-R subscores. As concerns the survival analysis, monthly declines of FVC% and sFVC%, significantly correlated with the survival. The worse prognosis in terms of survival was finally found in those whose FVC% and sFVC% dropped below their respective cut-offs.

Conclusion: Throughout the course of ALS disease, the monitoring of several respiratory markers, namely FVC, sFVC, PEF and PCEF, plays a critical role in predicting the prognosis of these subjects, both in terms of survival and functional ability. The implementation of monthly cut-offs in the evaluation of FVC and sFVC may allow a faster recognition of those patients with worse prognosis and therefore an optimized tailored clinical care, as well as a better stratification in clinical trials.

1. Introduction

Amyotrophic Lateral Sclerosis (ALS) is an adult-onset, neurodegenerative disease, characterized by the loss of cortical, brain stem, and spinal motor neurons. It is also characterized by a huge heterogeneity in clinical phenotype and disease course [1], probably one of the most important factors influencing the disease progression and the prognosis. In particular, the average survival from symptom onset is approximately 3–5 years, although some patients exhibit a slower disease progression and may survive longer [2]. As a consequence of its natural course, patients suffer progressive respiratory muscle weakness, leading to ventilatory failure and ineffective cough, which are the principal causes of morbidity and mortality in this population [3]. With some exceptions, symptoms of respiratory failure are generally not noticed until the advanced stages: due to this delay and the poor prognosis after their appearance, the monitoring of respiratory

* Corresponding author at: NEuroMuscular Omnicentre, Fondazione Serena Onlus, Piazza dell'Ospedale Maggiore, 3, 20162, Milan, Italy.
E-mail address: alice.pirola@centrocliniconemo.it (A. Pirola).

https://doi.org/10.1016/j.clineuro.2019.105456
Received 21 May 2019; Received in revised form 24 July 2019; Accepted 28 July 2019
Available online 29 July 2019
0303-8467/

functions on regular basis assumes great importance [4]. One of the challenges in ALS research is, therefore, to better determine the differences between patients who progress at different rates of disease, in order to personalize the care, limit the negative consequences of the disease and improve research activities.

The revised ALS functional rating scale (ALSFRS-R) is increasingly used to assess survival outcomes both in ALS clinical and trial settings. Moreover, several works demonstrated that progression rate (ΔFS) appears to be more closely associated with future progression than total ALSFRS-R score alone [5–8].

Spirometry is the most widely used volitional test assessing lung volumes and capacity as a function of time [9,10]; given its role in the diagnosis, as well as in the management, of several conditions affecting the respiratory system it is included in the care recommendations for several neuromuscular disorders [9–12]

The ability of different respiratory function tests to predict survival has already been evaluated [13–15], but the literature trying to define which of them may be more appropriate for describing the ALS disease progression during its natural course is still unestablished [16]. One of the most promising test in a clinical setting is the Forced Vital Capacity (FVC) while the patient is sitting. An FVC drop of 50% of the predicted value correlates with a poor prognosis but there are patients who may already have moderate to severe diaphragmatic weakness before they reach this cut-off [12,17]. FVC obtained while the patient is in a supine position (sFVC) seems to be more sensitive to detect diaphragmatic weakness even in the early stages of the disease [12] and may justify earlier initiation of NIV (non-invasive ventilation). It correlates with the symptoms of dyspnea, orthopnea, and excessive daytime fatigue [18].

The peak expiratory flow (PEF) decreases during the course of neuromuscular diseases and is associated with increased mortality from respiratory causes [19]. In the absence of bronchial obstructions, PEF proved to give a good reflection of expiratory muscle function and can be used to provide a reliable global measure of voluntary cough against the risk of aspiration pneumonia [20].

Finally, the peak cough expiratory flow (PCEF) provides not only a good estimate of cough efficacy and airway clearance capacity, but it also significantly correlates with bulbar impairment [21] and may contribute to discriminate between ALS with “NIV indication” and those with “no NIV indication yet”. [22].

The main aim of our work was to study the relation between different routine PFTs and one of the most commonly used functional scales, the ALSFRS-R during a short, six months followup; their role in affecting ALS subjects’ survival time was also enquired.

2. Patients and methods

2.1. Study population

We performed a retrospective single-center study including subjects with ALS referred to our multidisciplinary center from March 2012 to April 2017. All the data collected for each subject of this study were obtained in the course of a baseline (T0) and a follow-up routine visits, six months later (T1), during the above mentioned period. For the prognosis analysis we followed all patients until death, tracheostomy or data of censoring (November, 20th 2017). All patients signed and personally dated an approved Informed Consent Form after receiving detailed written and verbal information about the reason, the nature, the required procedures, the intended duration, the possible risks and benefits and any discomfort associated with the collection of data for research scope in agreement with the Declaration of Helsinki and the ICH E6 Guideline for Good Clinical Practice.

The study was approved by our Ethics Committee (protocol number: 92-032018).

Specifically, we included data obtained from patients fulfilling the following criteria: a diagnosis of probable or definite ALS, performed according to El-Escorial revised Criteria [23]; a follow-up as close as possible to six months from the baseline, performed according to the standards of care for this disease; age ≥ 18 years.

Exclusion criteria were: prescription and use of mechanical ventilation (invasive or non-invasive) at baseline; baseline assessments performed > 36 months after the ALS onset; inability to perform the required respiratory evaluations; significant concomitant respiratory diseases different to the ALS; significant cognitive impairment; other concomitant conditions which could affect the prognosis and/or the disease evolution.

Time from onset to first evaluation was calculated as the time, in months, between the onset of the disease and the first examination performed at our centre.

2.2. Pulmonary Function Tests (PFTs)

Lung functions were assessed for each patient at both the baseline evaluation (T0) and after 6 months (T1). The following assessments were carried out by the respiratory physiotherapists in compliance with the American Thoracic Society/European Respiratory Society guidelines [9]; the percentages of predicted values (%) were calculated based on the formulas of Goldman and Becklake [24]; age, weight and height were recorded by the respiratory physiotherapist in occasion of every access.

The PFTs were measured using a Cosmed Quark PFT (Cosmed srl Rome – Italy) spirometer and the decision whether to use the mouthpiece with nasal clip or the mask was based on the evaluation of each single patient, specifically on the eventual presence of facial muscle weakness.

The PFTs included were the following tests:

- FVC in seated position and supine (FVC and sFVC, respectively): expressed both as absolute value, in liters, and as a percentage of the predicted value (FVC% and sFVC%, respectively). The patient was guided to inhale deeply and, subsequently, to expire as fast as far he/she could.
- Peak Expiratory Flow (PEF): expressed in liters/minute (L/min) and measured with the patient in seated position.
- Peak Cough Expiratory Flow (PCEF): expressed in L/min, the manoeuvre was performed with a mask of fitting size, having the patient seated and asking him/her to inhale as much air as possible and then to cough it out heavily.

During the procedure, the patient was encouraged to optimize performance. At least three acceptable and repeatable trials were performed, and the best out of these manoeuvre was chosen.

2.3. Motor function evaluation

The ALSFRS-R is a scale that, by measuring an individual’s loss of function in three determined domains (bulbar, spinal and respiratory), provides a physician-generated estimate of the patient’s degree of functional impairment, which can be evaluated serially to objectively assess any response to treatment or progression of disease. It is a simple scale, easy to administer, made up of 12 questions, each with five possible answers (scored from 0 to 4). In 2006, Kimura and coworkers examined the significance of the progression rate (ΔFS) by adding a time axis at diagnosis and conducting comparisons with total ALSFRS-R score alone [5].

ALSFRS-R total score, together with its bulbar (ALSFRS-Rb) and respiratory (RofALSFRS-R) subscores were analyzed. ΔFS was calculated as: 48 - ALSFRS-R at baseline/ Time from onset to evaluation (from onset to baseline) (month). The time of initial onset was determined based on subjective complaints and information (being those weakness, cramps and/or fasciculations) confirmed from family members. In the longitudinal evaluation the ΔFS was calculated as: ALSFRS-R total score or subscores at baseline - ALSFRS-R total score or

subscores at follow-up / Time from follow to baseline to follow-up.

2.4. Statistical analysis

Baseline characteristics were summarized using standard descriptive statistics, such as mean and standard deviation or median and interquartile range for quantitative measures, and number and percentage for dichotomous and categorical variables. For each variable, the Shapiro Wilk test was used to evaluate the normality of the distribution and the Levene test was performed to evaluate the homogeneity of variance. Spearman's correlation coefficient was used to assess the baseline correlations. Monthly decline was calculated as the difference between baseline and last observation, dividing the result by the number of months between baseline and last evaluation. Spearman test was used to evaluate the longitudinal monthly decline correlations between pulmonary function tests and both functional impairment and disease progression rate. Survival analysis for pulmonary function tests' monthly decline was also calculated, considering survival time as the time from onset to either tracheostomy, death or censoring data (November, 20th 2017). Firstly, univariate Cox proportional Hazard models were used to test the relationship with survival using outcomes as continuous variables. Secondly, an outcome-oriented approach based on the log-rank test statistic was used to find the optimal cut-off values of our time to event data [25–27]. Using these cut-offs, survival curves were estimated by the Kaplan-Meier method and the differences between the curves were calculated by the log-rank test. P-value was considered statistically significant at level of 0.05. All statistical analyses were done using SAS software version 9.3.

3. Results

Data from a total of 91 ALS patients were retrieved; 18 of them were excluded, either because one or more of the assessments required were missing or their inter-evaluation time was greater than 6 months. Seventy-three patients (mean age at evaluation: 62.44 ± 9.93 years; M/F ratio: 52/21) were therefore studied. Demographic characteristics of our sample are described in Table 1, while baseline clinical and respiratory features, together with their median monthly declines, are described in Table 2.

At baseline, PCEF moderately correlated with the ALSFRS-R total score (r = 0.49) and bulbar sub-score (r = 0.41), while weakly correlated with spinal sub-score (r = 0.36) and ΔFS (r = −0.39); PEF weakly correlated with the ALSFRS-R total score (r = 0.35), bulbar subscore (r = 0.35), spinal sub-score (r = 0.25) and the ΔFS (r = −0.34). Moreover, FVC% also showed a weak correlation with the ΔFS (r = −0.25) (Table 3).

At the end of the 6-month followup period (mean: 5.55 ± 1.16 months) only one patient (with bulbar onset) required NIV, while none underwent tracheostomy nor invasive ventilation (IMV) or died. Both FVC% and sFVC% were moderately correlated to the ALSFRS-R (r = 0.48 and 0.48 respectively) and weakly to all its subscores (Table 3); as concerns PCEF and PEF values, both moderately correlated with the ALSFRS-R (r = 0.53 and 0.47 respectively) and weakly to moderately with bulbar (r = 0.33 and 0.39 respectively) and spinal (r = 0.46 and 0.33 respectively) subscores (Table 3).

Table 1
Demographic characteristics of our cohort (n = 73).

Site of onset, n (%)	
Bulbar	10 (13.89)
Limb	62 (86.11)
Missing	1
Follow-up period (months), mean ± std	5.55 ± 1.16
Time from onset to first evaluation[a] (months), mean ± std	22.19 ± 15.39
Death, n(%)	
No	49 (67.12)
Yes	24 (32.88)
Time from onset to death (months), mean ± std	38.15 ± 13.64

Abbreviations: n number; std standard deviation.
[a] Time from onset to first evaluation: calculated between the onset of the disease and the first examination.

The analysis of monthly declines showed weak correlations between the FVC% and the ALSFRS-R total score (r = 0.28) and the spinal subscore (r = 0.25), between the sFVC% with the ALSFRS-R total score (r = 0.30) and the bulbar sub-score (r = 0.31), and PCEF with the ALSFRS-R total score (r = 0.27) (Table 3).

All correlations between functional status and respiratory features are listed in Table 3.

As for the results from the survival analysis, considering the monthly decline as a continuous outcome, univariate Cox proportional Hazard model showed that only FVC% and sFVC% revealed significant relations with survival (Table 4). These relations remained significant by using the same variables as dichotomous, with the cut-off, obtained with the log-rank test statistic, of a loss of 3% /month for FVC% and of 1% /month for sFVC% (log rank p < 0.01 for FVC%; log rank p = 0.04 for sFVC%) (Figs. 1 and 2). The relationship with survival of both FVC% and sFVC% suggested a two-ways interaction. Therefore, FVC% and sFVC% were categorized into one hybrid variable with four levels, according to the severity of respiratory decline. The subgroup, composed by patient with only FVC% below its cut-off was not included in the analysis due to the small population included (n = 2; 2.7% of our population).

The survival analysis found that the Severe RP ("respiratory progressors") subgroup (n = 22; 30.1% of our cohort), with both of FVC% and sFVC% below their respective cut-off of 3% monthly decline and 1% monthly decline, showed a significant worst prognosis, compared to those in the Moderate RP subgroup (n = 21; 28.8% of our population), characterized by a decline in only sFVC% below its respective cut-off, and Mild RP subgroup (n = 28; 38.4% of our population), characterized by the absence of decline of values in both parameters below their cut-off (Fig. 3a and b and Table 5). In addition, it was also observed that the longer the time from onset to evaluation, the less severe was the respiratory decline registered (median: 24.43 [11.68–35.68]; 18.67 [14.10–26.06] and 14.93 [10.46–24.70] months for subgroups Mild RP, Moderate RP and Severe RP, respectively).

4. Discussion

One of the challenges in ALS research is the ability to determine clinical parameters which can discriminate between patients with different rates of progression and worst prognosis. Our results showed that, at baseline, only PCEF and PEF, indexes of respiratory muscle strength and cough function [28], in contrast to the other respiratory measures, significantly correlated with patients' functional impairment, expressed by the total, bulbar and spinal scores of ALSFRS-R, as well as by ΔFS. These results emphasize the role of both the respiratory markers to well define, at the first evaluation, the level of disease severity; this could possibly be related to the complex, integrated physiology of cough, which involves a coordinated action of inspiratory, expiratory and bulbar muscles [20,29–31]. Indeed, as reported in the literature [21], our data confirm that PCEF value is strongly associated with bulbar impairment, since generation of effective cough depends on bulbar muscles, which control glottis function. We also confirmed the lack of correlation between the pulmonary variables at baseline and the respiratory ALSFRS-R subscore, as seen in another study [32], thus reinforcing the limits of this domain [33–35], possibly related to the type of questions asked, primarily focusing on the chronicity of the respiratory status, rather than the occurrence of eventual acute episodes, respiratory infections, as well as the ability to comply with the individual respiratory therapy, including NIV [34,36].

The cross-sectional analysis at the end of the follow-up period

Table 2
Descriptive statistics of clinical and respiratory features of our cohort.

	Baseline	Median monthly decline[a]
% FVC	99.00 [86.00 – 108.00]	1.71 [−0.16 – 3.46]
% sFVC	93.00 [83.00 – 103.00]	1.68 [0.23 – 3.95]
PCEF (L/min)	352.50 [318.50 – 446.00]	6.09 [−7.14 – 14.90]
PEF (L/min)	288.90 [207.90 – 360.90]	3.30 [−10.86 – 14.91]
ALSFRS-R total score	39.00 [35.00 – 43.00]	0.51 [0.20 – 1.19]
ALSFRS-R bulbar subscore	11.00 [10.00 – 12.00]	0.00 [0.00 – 0.33]
ALSFRS-R spinal subscore	17.00 [13.00 – 20.00]	0.46 [0.18 - 0.86]
ALSFRS-R respiratory subscore	12.00 [11.00 – 12.00]	0.00 [0.00 – 0.00]
Disease Progression Rate[b]	0.46 [0.28 – 0.70]	.

All values are represented as median and interquartile range.
Abbreviations: FVC, Forced Vital Capacity in seated position; sFVC, Forced Vital Capacity in supine position; PCEF, Peak Cough Expiratory Flow; PEF, Peak Expiratory Flow; L, liters; min, minute; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised.
[a] calculated as (baseline value– follow-up value)/ follow-up period.
[b] calculated between onset and the end of the follow-up period.

confirmed the same significant correlations of PCEF and PEF with the functional impairment of the patients, expressed by the total, bulbar and spinal scores of ALSFRS-R. In addition, further correlations were founded of FVC% and sFVC% with the ALSFRS-R and its subscores. These correlations, although statistically significant, were found to have from weak to moderate strength, in accordance to previous recent results, obtained on a larger ALS patient cohort [32].

In contrast with another work [28], in the longitudinal analysis we found a significant correlation between the PCEF and functional impairment evaluated by ALSFRS-R total score. This difference may be related to several reasons, including their arbitrary use of a surrogate value of PCEF.

We found a significant correlation of different spirometric values with the rate of disease progression. As suggested in a previous work [37], our study showed a significant relation between quantitative respiratory function data (FVC%, sFVC% and PCEF) and ΔFS, thus reinforcing the utility of disease progression rate as a prognostic biomarker.

After performing survival analysis, a univariate Cox proportional hazard model was built to analyze the relations between survival and the different respiratory variables, relations that were found to be significant for FVC% as well as for sFVC%. This confirmed, for our specific population, what had previously been found [12,13,21], that the measure of vital capacity holds significant survival prognostic value.

Table 4
Cox proportional Hazard regression model using monthly decline of respiratory assessments.

	β	p-value	Hazard Ratio	95% confidence limits
FVC %	−0.12	**0.05**	0.89	0.79 – 1.00
sFVC %	−0.11	**0.03**	0.89	0.81 – 0.99
PCEF	< 0.01	**0.89**	1.00	0.98 – 1.02
PEF	< 0.01	**0.44**	1.01	0.99 – 1.03

Abbreviations: FVC, Forced Vital Capacity in seated position; sFVC, Forced Vital Capacity in supine position; PCEF, Peak Cough Expiratory Flow; PEF, Peak Expiratory Flow; β, parameters estimate.
In bold, significant p-values.

FVC has already been broadly investigated in ALS patients and its role in the prediction of survival and hypoventilation has already emerged in several studies [12,13,16]: in fact, a FVC < 50% of the predicted value has already been associated with a weaker prognosis in this disease population. Lastly, our work also confirmed the role and sensitivity of sFVC% in predicting survival in ALS patients, as previous studies on supine FVC highlighted the possibility of it being more sensitive than the seated measurement in detecting respiratory insufficiency in this condition [12,17].

By implementing this analysis with the Log-rank test on FVC% and

Table 3
Correlations between functional status and respiratory assessment at baseline, 6 months and longitudinal monthly decline.

Baseline	FVC %	sFVC %	PCEF	PEF
ALSFRS-R total score	r = 0.20 p = 0.10	r = 0.16 p = 0.17	r = 0.49 **p < 0.01**	r = 0.35 **p < 0.01**
ALSFRS-R bulbar subscore	r = 0.14 p = 0.25	r = 0.07 p = 0.58	r = 0.41 **p < 0.01**	r = 0.35 **p < 0.01**
ALSFRS-R spinal subscore	r = 0.19 p = 0.10	r = 0.18 p = 0.12	r = 0.36 **p < 0.01**	r = 0.25 **p = 0.04**
ALSFRS-R respiratory subscore	r = 0.01 p = 0.99	r = −0.03 p = 0.79	r = 0.22 p = 0.06	r = 0.10 p = 0.42
ΔFS at baseline	r = −0.25 **p = 0.03**	r = −0.19 p = 0.10	r = −0.39 **p < 0.01**	r = −0.34 **p < 0.01**
6th MONTH				
ALSFRS-R total score	r = 0.48 **p < 0.01**	r = 0.48 **p < 0.01**	r = 0.53 **p < 0.01**	r = 0.47 **p < 0.01**
ALSFRS-R bulbar subscore	r = 0.26 **p = 0.03**	r = 0.33 **p < 0.01**	r = 0.33 **p = 0.01**	r = 0.39 **p < 0.01**
ALSFRS-R spinal subscore	r = 0.42 **p < 0.01**	r = 0.39 **p < 0.01**	r = 0.46 **p < 0.01**	r = 0.33 **p < 0.01**
ALSFRS-R respiratory subscore	r = 0.29 **p = 0.01**	r = 0.31 **p = 0.01**	r = 0.21 p = 0.09	r = 0.13 p = 0.26
LONGITUDINAL MONTHLY DECLINE				
ALSFRS-R total score	r = 0.28 **p = 0.02**	r = 0.30 **p = 0.01**	r = 0.27 **p = 0.03**	r = 0.15 p = 0.20
ALSFRS-R bulbar subscore	r = 0.20 p = 0.10	r = 0.31 **p = 0.01**	r = 0.12 p = 0.33	r = 0.22 p = 0.07
ALSFRS-R spinal subscore	r = 0.25 **p = 0.03**	r = 0.22 p = 0.06	r = 0.23 p = 0.07	r = 0.12 p = 0.31
ALSFRS-R respiratory subscore	r = 0.03 p = 0.78	r = 0.09 p = 0.45	r = 0.07 p = 0.60	r=-0.04 p = 0.74

Abbreviations: ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; FVC, Forced Vital Capacity in seated position; sFVC, Forced Vital Capacity in supine position; PCEF, Peak Cough Expiratory Flow; PEF, Peak Expiratory Flow; ΔFS, disease progression rate; r, Spearman Correlation coefficient; p, p-value.
In bold, significant correlations.

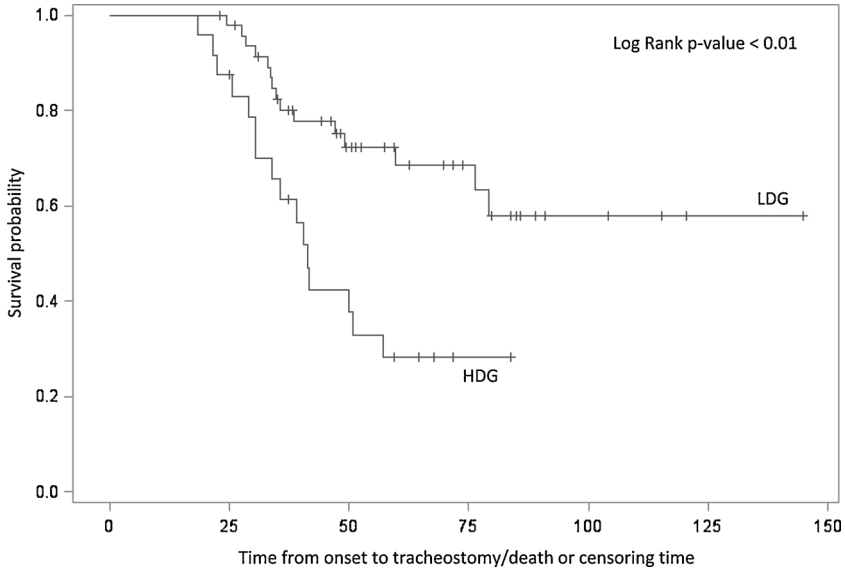

Fig. 1. Cumulative survival from onset by FVC% monthly decline cut-off.

sFVC% we obtained two respectively optimal cut-off values (3% monthly decline and 1% monthly decline, respectively) that were used to define four levels of rate of respiratory decline. We showed that these cut-offs were able to define subgroups with statistically significant differences in terms of survival. In detail, the Cox Model reported a significantly worse prognosis in subjects with both FVC% and sFVC% monthly decline below both cut-off values; this defined a group of patients with rapid respiratory decline, compared to the other patients. Other works already acknowledged the importance of vital capacity decline rate, expressed by FVC, sFVC, FVC% or sFVC%, as a factor impacting on ALS survival [12,38–40]. However, to our knowledge, our work is the first in which the cut-points used for survival analysis were obtained through an outcome-oriented method, rather than a data-oriented one (eg. dichotomization by mean or median values) [26]. This allowed us to individuate two different cut-off values (3% monthly decline and 1% monthly decline, respectively for FVC% and sFVC% monthly declines), which retained the most significant relation with the survival. According to these cut-offs and their combination, when comparing the validity and sensitivity of a combined variable with the decline of only one of the two parameters (FVC% or sFVC%), we obtained three different subgroups of patients with a significant difference in prognosis that we defined as severe, moderate and mild respiratory progressors, respectively. In particular, the Moderate RP subgroup was composed by patients with only a decline in sFVC% that probably in a routine analysis, which generally includes only a FVC% evaluation, would remain unrecognized, limiting the possibility of an early respiratory treatment. Taking into account that an early NIV prescription prolongs the free time from diagnosis to death in ALS patients [41], our study emphasizes the importance to take advantage of all parameters useful in a clinical context, including sFVC%, to early detect a respiratory decline in ALS. Although it may be argued the execution of sFVC can be source of discomfort for the ALS patient, especially in presence of bulbar and/or respiratory symptoms, our work emphasizes the possible role of sFVC%, alongside the more common FVC%, in providing additional information in the ALS population; this seems to be in accordance with previous works, which evidenced a possible higher sensitivity of the decline of sFVC% compared to the decline of FVC% in predicting 2-year survival [12] and, more in general, the value of the sFVC% in individuating the onset of respiratory muscle weakness [17,18] as well as the adequate time of introduction

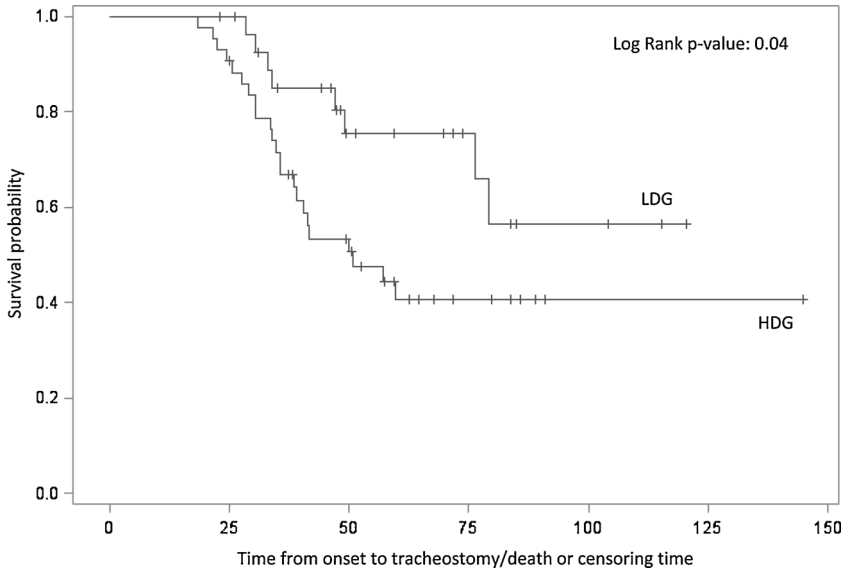

Fig. 2. Cumulative survival from onset by sFVC% monthly decline cut-off.

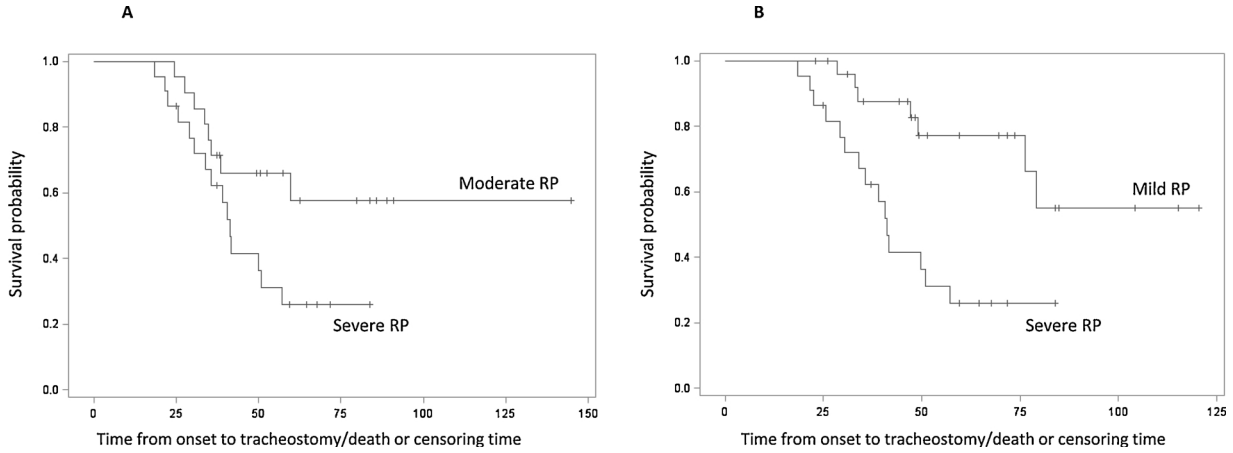

Fig. 3. Cumulative survival from onset by hybrid variable combining FVC% and sFVC%.

Table 5
Cox proportional Hazard regression model using the hybrid variable.

	β	p-value	Hazard Ratio	95% confidence limits
MiRP (n = 28)	−1.32	< 0.01	0.27	0.11 – 0.66
MoRP (n = 21)	−0.91	0.01	0.40	0.17 – 0.96
SRP (n = 22)	.	.	1 [ref]	.

Legend: Severe RP, Severe Respiratory Progressors: patients reported FVC% monthly decline ≥3% and sFVC% monthly decline ≥1%; Moderate RP, Moderate Respiratory Progressors: patients reported FVC% monthly decline < 3% and sFVC% monthly decline ≥1%; Mild RP, Mild Respiratory Progressors: patients reported FVC% monthly decline < 3% and sFVC% monthly decline < 1%.

of any eventual ventilatory support system [42].

As for the difference between FVC% and sFVC% (ΔFVC), the lack of correlation between this value and survival has already been highlighted [12]. According with this finding, our results confirm how normal values of ΔFVC (that is ΔFVC < 20%) may not preclude a respiratory involvement in this population.

Our study includes some limitations, as the small number of patients, the lower percentage of bulbar onset subjects and the higher number of slow progressors. These limitations are related to the retrospective nature of the work. However, this should be considered an explorative study that will help us to better design a new project for a prospective analysis of the respiratory changes in the first 6 months after the diagnosis in patients followed up until death or tracheostomy occurs, in order to better define the more sensitive respiratory parameters for the prognosis of these patients.

In conclusion, our work emphasizes the critical role of spirometry measurements in evaluating the function of respiratory muscles throughout the course of the disease; it also confirms the importance of respiratory markers, namely FVC, sFVC (and their combination), PEF and PCEF, in predicting prognosis of ALS patients, both in terms of survival and functional ability, even in presence of a short follow-up: this, in turn, may grant them the access to a better planned tailored clinical care or, in case of a clinical trial, to better stratify the study population.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Dr Lunetta served as scientific consultant for Neuraltus, Italfarmaco and Mitsubishi Tanabe Pharma, and has received funds from Agenzia Italiana per la Ricerca sulla SLA (ARISLA) and Ministry of Health (CCM2011). The other authors report no conflicts of interest.

Declaration of Competing Interest

Dr Lunetta served as scientific consultant for Neuraltus, Italfarmaco and Mitsubishi Tanabe Pharma, and has received funds from Agenzia Italiana per la Ricerca sulla SLA (ARISLA) and Ministry of Health (CCM2011). The other authors report no conflicts of interest.

References

[1] A. Chio, A. Calvo, C. Moglia, L. Mazzini, G. Mora, PARALS study group, Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study, J. Neurol. Neurosurg. Psychiatry. 82 (2011) 740–746, https://doi.org/10.1136/jnnp.2010.235952.

[2] A.C. Calvo, R. Manzano, D.M.F. Mendonça, M.J. Muñoz, P. Zaragoza, R. Osta, Amyotrophic lateral sclerosis: a focus on disease progression, Biomed Res. Int. 2014 (2014) 925101, , https://doi.org/10.1155/2014/925101.

[3] J. Sancho, E. Servera, P. Banuls, J. Marin, Predictors of need for noninvasive ventilation during respiratory tract infections in medically stable, non-ventilated subjects with amyotrophic lateral sclerosis, Respir. Care 60 (2015) 492–497, https://doi.org/10.4187/respcare.03553.

[4] D. Singh, R. Verma, R.K. Garg, M.K. Singh, R. Shukla, S.K. Verma, Assessment of respiratory functions by spirometry and phrenic nerve studies in patients of amyotrophic lateral sclerosis, J. Neurol. Sci. 306 (2011) 76–81, https://doi.org/10.1016/j.jns.2011.03.039.

[5] F. Kimura, C. Fujimura, S. Ishida, H. Nakajima, D. Furutama, H. Uehara, K. Shinoda, M. Sugino, T. Hanafusa, Progression rate of ALSFRS-R at time of diagnosis predicts survival time in ALS, Neurology. 66 (2006) 265–267, https://doi.org/10.1212/01.wnl.0000194316.91908.8a.

[6] P.H. Gordon, Y.K. Cheung, F. Kimura, Progression rate of ALSFRS-R at time of diagnosis predicts survival time in ALS, Neurology. 67 (2006) 1314–1315, https://doi.org/10.1212/01.wnl.0000243812.25517.87.

[7] M. Proudfoot, A. Jones, K. Talbot, A. Al-Chalabi, M.R. Turner, The ALSFRS as an outcome measure in therapeutic trials and its relationship to symptom onset, Amyotroph. Lateral Scler. Frontotemporal Degener. 17 (2016) 414–425, https://doi.org/10.3109/21678421.2016.1140786.

[8] K. Kollewe, U. Mauss, K. Krampfl, S. Petri, R. Dengler, B. Mohammadi, ALSFRS-R score and its ratio: a useful predictor for ALS-progression, J. Neurol. Sci. 275 (2008) 69–73, https://doi.org/10.1016/j.jns.2008.07.016.

[9] M.R. Miller, J. Hankinson, V. Brusasco, F. Burgos, R. Casaburi, A. Coates, R. Crapo, P. Enright, C.P.M. van der Grinten, P. Gustafsson, R. Jensen, D.C. Johnson, N. MacIntyre, R. McKay, D. Navajas, O.F. Pedersen, R. Pellegrino, G. Viegi, J. Wanger, ATS/ERS task force, standardisation of spirometry, Eur. Respir. J. 26 (2005) 319–338, https://doi.org/10.1183/09031936.05.00034805.

[10] R. Pierce, Spirometry: an essential clinical measurement, Aust. Fam. Physician 34 (2005) 535–539 (Accessed April 29 2019), http://www.ncbi.nlm.nih.gov/pubmed/15999163.

[11] M. Boentert, S. Wenninger, V.A. Sansone, Respiratory involvement in neuromuscular disorders, Curr. Opin. Neurol. 30 (2017) 529–537, https://doi.org/10.1097/WCO.0000000000000470.

[12] F. Baumann, R.D. Henderson, S.C. Morrison, M. Brown, N. Hutchinson, J.A. Douglas, P.J. Robinson, P.A. McCombe, Use of respiratory function tests to predict survival in amyotrophic lateral sclerosis, Amyotroph. Lateral Scler. 11 (2010) 194–202, https://doi.org/10.3109/17482960902991773.

[13] S. Pinto, M. de Carvalho, Comparison of slow and forced vital capacities on ability to predict survival in ALS, Amyotroph. Lateral Scler. Front. Degener. 18 (2017) 528–533, https://doi.org/10.1080/21678421.2017.1354995.

[14] H.-J. Westeneng, T.P.A. Debray, A.E. Visser, R.P.A. van Eijk, J.P.K. Rooney, A. Calvo, et al., Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model, Lancet Neurol. 17

(2018) 423–433, https://doi.org/10.1016/S1474-4422(18)30089-9.
[15] O. Hardiman, A. Al-Chalabi, A. Chio, E.M. Corr, G. Logroscino, W. Robberecht, P.J. Shaw, Z. Simmons, L.H. van den Berg, Amyotrophic lateral sclerosis, Nat. Rev. Dis. Prim. 3 (2017) 17071, https://doi.org/10.1038/nrdp.2017.71.
[16] A. Czaplinski, A.A. Yen, S.H. Appel, Forced vital capacity (FVC) as an indicator of survival and disease progression in an ALS clinic population, J. Neurol. Neurosurg. Psychiatry. 77 (2006) 390–392, https://doi.org/10.1136/jnnp.2005.072660.
[17] N. Lechtzin, C.M. Wiener, D.M. Shade, L. Clawson, G.B. Diette, Spirometry in the supine position improves the detection of diaphragmatic weakness in patients with amyotrophic lateral sclerosis, Chest 121 (2002) 436–442 (Accessed February 4 2019), http://www.ncbi.nlm.nih.gov/pubmed/11834654.
[18] J. Varrato, A. Siderowf, P. Damiano, S. Gregory, D. Feinberg, L. McCluskey, Postural change of forced vital capacity predicts some respiratory symptoms in ALS, Neurology 57 (2001) 357–359 (Accessed March 20 2019), http://www.ncbi.nlm.nih.gov/pubmed/11468332.
[19] S. Yamada, A. Hashizume, Y. Hijikata, T. Inagaki, K. Suzuki, N. Kondo, K. Kawai, S. Noda, H. Nakanishi, H. Banno, A. Hirakawa, H. Koike, K. Halievski, C.L. Jordan, M. Katsuno, G. Sobue, Decreased peak expiratory flow associated with muscle fiber-type switching in spinal and bulbar muscular atrophy, PLoS One 11 (2016) e0168846, , https://doi.org/10.1371/journal.pone.0168846.
[20] A.A. Suárez, F.A. Pessolano, S.G. Monteiro, G. Ferreyra, M.E. Capria, L. Mesa, A. Dubrovsky, E.L. De Vito, Peak flow and peak cough flow in the evaluation of expiratory muscle weakness and bulbar impairment in patients with neuromuscular disease, Am. J. Phys. Med. Rehabil. 81 (2002) 506–511 (Accessed May 3 2019), http://www.ncbi.nlm.nih.gov/pubmed/12131177.
[21] I. Enache, C. Pistea, M. Fleury, M. Schaeffer, M. Oswald-Mammosser, A. Echaniz-Laguna, C. Tranchant, N. Meyer, A. Charloux, Ability of pulmonary function decline to predict death in amyotrophic lateral sclerosis patients, Amyotroph. Lateral Scler. Front. Degener. 18 (2017) 511–518, https://doi.org/10.1080/21678421.2017.1353097.
[22] T.B.M. Tilanus, J.T. Groothuis, J.M.C. TenBroek-Pastoor, T.B. Feuth, Y.F. Heijdra, J.P.L. Slenders, J. Doorduin, B.G. Van Engelen, M.J. Kampelmacher, J. Raaphorst, The predictive value of respiratory function tests for non-invasive ventilation in amyotrophic lateral sclerosis, Respir. Res. 18 (2017) 144, https://doi.org/10.1186/s12931-017-0624-8.
[23] B.R. Brooks, R.G. Miller, M. Swash, T.L. Munsat, World Federation of Neurology Research Group on Motor Neuron Diseases, El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis, Amyotroph. Lateral Scler. Other Motor Neuron Disord. 1 (2000) 293–299 (Accessed February 4 2019), http://www.ncbi.nlm.nih.gov/pubmed/11464847.
[24] H.I. Goldman, M.R. Becklake, Respiratory function tests; normal values at median altitudes and the prediction of normal results, Am. Rev. Tuberc. 79 (1959) 457–467 (Accessed February 4 2019), http://www.ncbi.nlm.nih.gov/pubmed/13650117.
[25] C. Contal, J. O'Quigley, An application of changepoint methods in studying the effect of age on survival in breast cancer, Comput. Stat. Data Anal. 30 (1999) 253–270 (Accessed February 4 2019), https://ideas.repec.org/a/eee/csdana/v30y1999i3p253-270.html.
[26] M.J. N, Cutpoint Determination Methods in Survival Analysis using SAS ®, n.d. https://support.sas.com/resources/papers/proceedings/proceedings/sugi28/261-28.pdf (accessed February 4, 2019).
[27] J.P. Meyers, J.N. Mandrekar, Cutpoint Determination Methods in Survival Analysis Using SAS: Updated %FINDCUT Macro, (2015) (Accessed February 4 2019), https://www.mwsug.org/proceedings/2015/DV/MWSUG-2015-DV-07.pdf.
[28] C. Matsuda, T. Shimizu, Y. Nakayama, M. Haraguchi, Cough peak flow decline rate predicts survival in patients with amyotrophic lateral sclerosis, Muscle Nerve 59 (2019) 168–173, https://doi.org/10.1002/mus.26320.
[29] F. Laghi, V. Maddipati, T. Schnell, W.E. Langbein, M.J. Tobin, Determinants of cough effectiveness in patients with respiratory muscle weakness, Respir. Physiol. Neurobiol. 240 (2017) 17–25, https://doi.org/10.1016/j.resp.2017.02.005.
[30] F.D. McCool, Global physiology and pathophysiology of cough, Chest. 129 (2006) 48S–53S, https://doi.org/10.1378/chest.129.1_suppl.48S.
[31] A.B. Chang, The physiology of cough, Paediatr. Respir. Rev. 7 (2006) 2–8, https://doi.org/10.1016/j.prrv.2005.11.009.
[32] S. Pinto, M. de Carvalho, SVC is a marker of respiratory decline function, similar to FVC, in patients with ALS, Front. Neurol. 10 (2019), https://doi.org/10.3389/fneur.2019.00109.
[33] L. Leonardis, L. Dolenc Grošelj, G. Vidmar, Factors related to respiration influencing survival and respiratory function in patients with amyotrophic lateral sclerosis: a retrospective study, Eur. J. Neurol. 19 (2012) 1518–1524, https://doi.org/10.1111/j.1468-1331.2012.03754.x.
[34] J. Rooney, T. Burke, A. Vajda, M. Heverin, O. Hardiman, What does the ALSFRS-R really measure? A longitudinal and survival analysis of functional dimension subscores in amyotrophic lateral sclerosis, J. Neurol. Neurosurg. Psychiatry. 88 (2017) 381–385, https://doi.org/10.1136/jnnp-2016-314661.
[35] S. Pinto, M. de Carvalho, The R of ALSFRS-R: Does it really mirror functional respiratory involvement in amyotrophic lateral sclerosis? Amyotroph. Lateral Scler. Front. Degener. 16 (2015) 120–123, https://doi.org/10.3109/21678421.2014.952641.
[36] F. Franchignoni, G. Mora, A. Giordano, P. Volanti, A. Chiò, Evidence of multidimensionality in the ALSFRS-R Scale: a critical appraisal on its measurement properties using Rasch analysis, J. Neurol. Neurosurg. Psychiatry. 84 (2013) 1340–1345, https://doi.org/10.1136/jnnp-2012-304701.
[37] J. Labra, P. Menon, K. Byth, S. Morrison, S. Vucic, Rate of disease progression: a prognostic biomarker in ALS, J. Neurol. Neurosurg. Psychiatry. 87 (2016) 628–632, https://doi.org/10.1136/jnnp-2015-310998.
[38] R.L. Vender, D. Mauger, S. Walsh, S. Alam, Z. Simmons, Respiratory systems abnormalities and clinical milestones for patients with amyotrophic lateral sclerosis with emphasis upon survival, Amyotroph. Lateral Scler. 8 (2007) 36–41, https://doi.org/10.1080/17482960600863951.
[39] B.J. Traynor, H. Zhang, J.M. Shefner, D. Schoenfeld, M.E. Cudkowicz, NEALS Consortium, Functional outcome measures as clinical trial endpoints in ALS, Neurology 63 (2004) 1933–1935 (Accessed February 4 2019), http://www.ncbi.nlm.nih.gov/pubmed/15557515.
[40] P.L. Schiffman, J.M. Belsh, Pulmonary function at diagnosis of amyotrophic lateral sclerosis. Rate of deterioration, Chest 103 (1993) 508–513 (Accessed February 4 2019), http://www.ncbi.nlm.nih.gov/pubmed/8432145.
[41] M. Vitacca, A. Montini, C. Lunetta, P. Banfi, E. Bertella, E. De Mattia, A. Lizio, E. Volpato, A. Lax, R. Morini, M. Paneroni, Impact of an early respiratory care programme with non-invasive ventilation adaptation in patients with amyotrophic lateral sclerosis, Eur. J. Neurol. 25 (2018), https://doi.org/10.1111/ene.13547 556-e33.
[42] E.M. Elamin, C.S. Wilson, C. Sriaroon, B. Crudup, S. Pothen, Y.C. Kang, K.T. White, W.M. Anderson, Effects of early introduction of non-invasive positive pressure ventilation based on forced vital capacity rate of change: variation across amyotrophic lateral sclerosis clinical phenotypes, Int. J. Clin. Pract. 73 (2019) e13257, , https://doi.org/10.1111/ijcp.13257.