SHORT REPORT

Forced vital capacity (FVC) as an indicator of survival and disease progression in an ALS clinic population

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In a large cohort of 1034 patients with the diagnosis of definite or probable amyotrophic lateral sclerosis (ALS), the association of forced vital capacity (FVC) at baseline with (*a*) time to progression of 20 points in Appel ALS (AALS) score or (*b*) tracheostomy free survival was investigated. The median survival of ALS patients with baseline FVC <75% was 2.91 years, compared with 4.08 years for patients with baseline FVC >75% (p<0.001). Patients with baseline FVC <75% progressed more rapidly (taking 8.0 months to progress 20 AALS points) compared with patients with baseline FVC >75% (10.0 months, p<0.001). Moreover, FVC at first examination was identified as a significant predictor of survival and disease progression in both univariate and multivariate Cox regression models, after adjustment for age, sex, site of onset, diagnostic delay, riluzole therapy, and use of bilateral positive airway pressure and percutaneous endoscopic gastrostomy (p<0.001). We conclude that a single FVC value obtained at an initial visit may serve as a clinically meaningful predictor of survival and disease progression in ALS.

M ost ALS deaths are due to a decline in pulmonary function resulting from respiratory muscle weakness,[1–3] and the extent of respiratory involvement has been reported as a major prognostic factor.[4] At present, no single test has been shown to reliably detect early respiratory insufficiency and to correlate with respiratory failure in ALS.[5 6] Forced vital capacity (FVC) is one index of respiratory function that may be used to indicate potential respiratory compromise in ALS.[7–11] Because FVC assesses inspiratory muscle strength and does not take into account the important prognostic role of expiratory muscles, additional measures, such as sniff nasal pressure, maximum inspiratory pressure, and maximum expiratory pressure, may be also needed to assess the global respiratory function of ALS patients. The accuracy of FVC measurement is highly dependent on the subject's effort and cooperation and on the coaching of the evaluator. Consequently, there is a clear need for continuous training of evaluators to reduce variability in measurements. However, despite these limitations, FVC measurement has been established as a recommended test for clinical trials and an important standard of ALS management.[8]

The prognostic value of respiratory function measures for survival in ALS has previously been shown in several randomised clinical trials.[1 12–15] Unfortunately, the restrictive inclusion criteria and short follow up time periods may render those data inapplicable to the general ALS population.[16] Studies of clinic based populations have suggested a correlation between tracheostomy free survival and the rate of decline in pulmonary function, defined as either the slope of a pulmonary score [4 9] or the rate of FVC decline.[17 18]

However, other investigators have failed to confirm this or have found no prognostic value after correcting the data for relevant demographic or clinically meaningful covariates.[16]

METHODS

Patients

Data from 1034 patients with the diagnosis of definite or probable ALS according to El Escorial/Airlie House criteria[19 20] who have been regularly followed at our MDA-ALS clinic over the last 21 years were reviewed in this study.

FVC measurement

FVC was performed as recommended for ALS clinical trials using standard techniques in the sitting position and expressed as a percentage of the expected value.[8] FVC was examined at entry and at each follow up visit (in general, every 3 months).

Outcome measurement

Survival and time to progression of 20 points in Appel ALS (AALS) score were selected as outcome parameters. Survival was defined as the number of months from symptom onset to death or tracheostomy. As an alternative to viewing disease progression as a mean rate of change in the given score or the score change from baseline to the study endpoint, we considered time to 20 point increase in AALS total score from baseline examination as failure time, which was determined from patient examination scores. A 20 point change was chosen because it is indicative of a clinically evident change in a patient's clinical status and ability to perform activities of daily living.[4] Moreover, the average time to 20 point change was <1 year for both baseline FVC groups, creating an endpoint that is likely to occur during the time frame of many clinical trials.[21] Details of the AALS score, which is routinely used in our clinic, have been published previously.[4 21–23] Patients who remained alive without tracheostomy and patients who never exceeded a 20 point increase in AALS score over the study period were censored at the time of the last known follow up.

Data analysis

The effects of individual prognostic factors on survival and on disease progression were assessed using the Kaplan-Meier life table methods. Log rank test was used to assess equality of outcome functions. The prognostic value of first FVC measurement was expressed in terms of hazard ratio (HR). Adjusted HRs were estimated by multivariate analyses using the Cox proportional hazards regression model. A p value of <0.05 was considered significant. All statistical analyses were performed using SPSS software (version 11.5.1; SPSS Inc., Chicago, IL, USA).

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Abbreviations: AALS, Appel ALS; ALS, amyotrophic lateral sclerosis; FE, first examination; FS, first symptom; FVC, forced vital capacity; NIV, non-invasive ventilation; PEG, percutaneous endoscopic gastrostomy
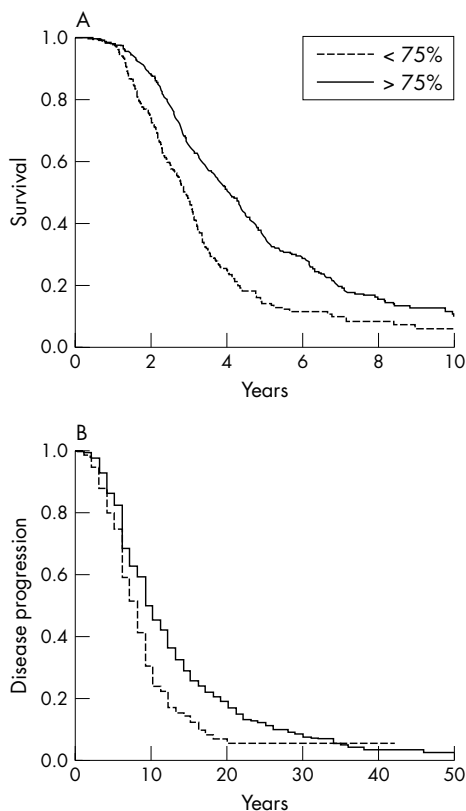
Figure 1 Kaplan-Meier plots of (A) survival and (B) time to 20 point progression probabilities according to the first examination FVC value. Patient population was divided into two groups: FVC >75% and FVC <75%.

RESULTS

Demographic and clinical characteristics

The mean (SD) age at disease onset in our patient population was 54.1 (13.2) years (57.6 for men and 52.4 for women). The male to female ratio was 1.9:1. Time from first symptom to the first examination (FS to FE) was 16.3 (12.3) months. In total, 172 patients (16.6%) exhibited primary bulbar symptoms; 576 (55.7%) of the 1034 analysed patients died (n = 477) or had tracheostomy (n = 99). The median tracheostomy free survival time was 3.45 years (95% confidence interval (CI) 3.27 to 3.74, mean 4.32 years). The median time to 20 AALS point progression was 9.0 months (95% CI 9.00 to 9.00).

Prognostic value of baseline FVC

We investigated the association of the FVC at baseline with (a) tracheostomy free survival or (b) time to 20 point AALS score progression from baseline examination for two subgroups of patients with baseline FVC value above (n = 690) and below 75% (n = 344). This FVC value was not only clinically relevant (mean (SD) baseline FVC 82.9 (20.9)%) but was also the optimum cutoff point, resulting in stratification into two large populations that were significantly different in terms of survival and disease progression. The median survival of ALS patients with baseline FVC <75% was 2.91 years, compared with 4.08 years for patients with baseline FVC >75% (log rank p<0.001) (fig 1A). In addition, patients with baseline FVC value <75% progressed more rapidly (8.0 months to 20 AALS points progression) compared with patients with baseline FVC >75% (10.0 months, p<0.001) (fig 1B). Univariate analyses indicated that lower FVC at baseline was associated with shorter survival (HR 1.68; 95% CI 1.22 to 2.00; p<0.001) and with more rapid disease progression (1.57; 1.29 to 1.91; p<0.001).

Given the importance of well established outcome predictors, the hazard ratio and 95% CI were adjusted for age, sex, and site of symptom onset. In this multivariate model, baseline FVC remained significantly associated with both survival (HR 1.73; 95% CI 1.45 to 2.05; p<0.001) and disease progression (1.49; 1.22 to 1.81; p<0.001). We also analysed the influence of other potential confounding variables on our results. Riluzole (50 mg twice daily) was given to 36% of patients with FVC <75% and to 44% of patients with baseline FVC >75%. Non-invasive ventilation (NIV) was performed in 10.8% of patients in the group with first FVC <75% and 13.2% of patients in the group with FVC >75%. During the disease course, 32% of patients in the FVC <75% group and 24% of those with FVC >75% underwent percutaneous endoscopic gastrostomy (PEG). To explore whether the predictive value of baseline FVC is independent of those factors, we included riluzole, NIV, and PEG use (as time independent variables: "ever" versus "never") in the same multivariate Cox regression model along with age, sex, site of onset, and FS to FE time. In this final model, baseline FVC remained significantly and independently associated with both survival (HR 2.07, p<0.001) and time to 20 point progression (HR 1.56, p<0.001) (table 1). Of note, when dealing with the use of riluzole, NIV, and PEG, our database only allowed an ever versus never analysis and was not designed to analyse the timing of the intervention or to address the compliance issue for those therapies.

DISCUSSION

Our data demonstrate that baseline FVC, easily obtained early in the disease course, and typically at the first clinical visit, may serve as an early predictor of survival and disease

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Table 1 Multivariate analyses, with all factors analysed in the same Cox models

Category	Survival, years (HR (95% CI))	p	Disease progression, years (HR (95% CI))	p
Baseline FVC <75%	2.07 (1.73 to 2.48)	<0.001	1.56 (1.28 to 1.90)	<0.001
Age at onset, years	1.04 (1.03 to 1.05)	<0.001	1.01 (0.99 to 1.01)	0.01
Limb vs. bulbar onset	1.09 (0.87 to 1.37)	0.4	1.34 (1.07 to 1.68)	0.009
FS to FE time, months	0.95 (0.94 to 0.96)	<0.001	0.98 (0.97 to 0.98)	<0.001
Women versus men	1.10 (0.92 to 1.33)	0.3	1.20 (0.99 to 1.43)	0.05
Riluzole (ever versus never)	1.14 (0.94 to 1.38)	0.2	1.12 (0.95 to 1.32)	0.2
NIV (ever versus never)	0.77 (0.62 to 0.95)	0.02	ND	ND
PEG (ever versus never)	0.74 (0.62 to 0.88)	0.001	ND	ND

In most patients who received riluzole, therapy was initiated at the time of the first examination and diagnosis, prior to a documented 20 point progression. In contrast, NIV initiation and PEG placement were generally performed in patients who had reached an advanced degree of disability. Thus, the Cox model for disease progression did not include NIV and PEG use.

progression in an ALS clinic population. Because FVC directly assesses pulmonary function, the decline of which is the most common cause of death or chronic respiratory support in ALS patients,[1] [2] our findings were not surprising. However, to our knowledge, no previous positive data about the predictive value of FVC on disease progression in ALS have been published, and other investigators were unable to confirm a correlation between ALS functional rating scale and FVC.[6]

The interpretation of our data has several potential limitations that should be recognised. Firstly, entry of patients into our database was non-random, because nearly all of the patients were referred by neurologists or primary care physicians. Secondly, because of access to optimum medical treatment at an academic institution, patients seen at a referral centre may have a relatively better prognosis.[24] Thirdly, during the 20 year observation period in this study, different diagnostic criteria have been in use. However, in our experience, the clinical features of patients diagnosed as ''typical ALS'' (this term was in use in our database prior to publication of El Escorial criteria in 1994) correspond very closely to the features of patients diagnosed as definite or probable ALS after 1994.[19]

Our findings may have several consequences for patient management and the planning of symptomatic care in ALS. Moreover, the results of this study also provide a tool for baseline stratification for clinical trials. It is well known that matching patients for established demographic and clinical parameters, such as age, sex, site of symptom onset, and diagnostic delay, is particularly important in planning clinical trials. Because pulmonary function is a critical factor for survival and disease progression, it should be strongly considered during the planning of clinical trials.

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Competing interests: none

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