ABSTRACT: The rapidity of progression of amyotrophic lateral sclerosis (ALS) to death or respiratory failure impacts patients, clinicians, and clinical investigators. This study compared the abilities of various pulmonary function tests to predict tracheostomy-free survival. We evaluated 95 ALS patients by determining upright and supine forced vital capacity (FVC), maximal inspiratory (MIP) and expiratory (MEP) pressures, arterial partial pressure of carbon dioxide ($PaCO_2$), and transdiaphragmatic sniff pressures (Pdi-sniff). Tracheostomy-free survival time was measured from the date of spirometry. Supine FVC, upright FVC, MIP, MEP, and Pdi-sniff were significantly associated with tracheostomy-free survival after controlling for nonpulmonary factors, whereas $PaCO_2$ was not. A normal supine FVC, MIP, or MEP was highly predictive for one-year survival. These tests are well suited to predict survival for trial enrollment and patient counseling. Supine FVC's simplicity of use and availability to ALS investigators makes it a particularly attractive predictor of one-year survival in ALS.

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PULMONARY PREDICTORS OF SURVIVAL IN AMYOTROPHIC LATERAL SCLEROSIS: USE IN CLINICAL TRIAL DESIGN

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Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that ultimately leads to respiratory failure and death. A large degree of interpatient variability exists in the rate of progression, with some patients dying or requiring respiratory support within months and others having relatively prolonged survival.[10,17] The consequent uncertainty in survival is not only difficult for patients and their families, but also frustrates research on ALS, as it may be difficult to assemble a cohort of patients that can be expected to complete a clinical trial.

Certain nonpulmonary factors, including female gender, advanced age, short time from symptom onset to diagnosis, and bulbar onset of disease are associated with shorter survival.[4,5,12,18] However, as ALS overwhelmingly brings death via respiratory compromise, pulmonary function tests should be particularly appropriate predictors of individual survival.[11,14] Upright forced vital capacity (FVC), the best studied of pulmonary tests, correlates with survival in ALS,[12,18] but may not be the best available pulmonary function test for the prediction of death or respiratory failure. Supine FVC and maximal inspiratory pressures (MIP) are more sensitive than upright FVC for the detection of respiratory muscle weakness.[8,9] Unlike upright FVC, maximal expiratory pressure (MEP) and other tests of expiratory function can predict a patient's ability to cough and clear airway secretions,[15] but these tests have not previously been shown to predict survival in ALS. The purpose of this study was to evaluate and compare the ability of the available pulmonary function tests to predict tracheostomy-free survival.

We studied a cohort of ALS patients to evaluate the association between these pulmonary function tests and survival. The findings have relevance to the

Abbreviations: ALS, amyotrophic lateral sclerosis; BiPAP, bilevel positive airway pressure; ΔFVC, change (decline) from upright to supine forced vital capacity; FVC, forced vital capacity; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; $PaCO_2$, arterial partial pressure of carbon dioxide; Pdi-sniff, transdiaphragmatic sniff pressure; ROC, receiver-operating characteristic (curve)

Key words: amyotrophic lateral sclerosis; prognosis; pulmonary function; spirometry; therapeutic trial design

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design of clinical trials and for the care and counseling of patients.

MATERIALS AND METHODS

Study Population. This was a cohort study of consecutively enrolled patients who fulfilled El Escorial criteria for "definite" or "probable" ALS and underwent upright and supine spirometry at a single, tertiary-care academic medical center from 1997 to 2002.[3] Patients were excluded from analysis if they had a prior history of symptomatic pulmonary disease unrelated to ALS. Our institutional Committee on Clinical Investigation approved the study protocol.

Pulmonary Function Testing. All pulmonary function testing was performed at our institution's pulmonary function laboratory, a facility that meets applicable American Thoracic Society standards.[1] Testing included the measurement of upright FVC, supine FVC, the change from upright to supine FVC ("ΔFVC"), maximal expiratory pressure (MEP), maximal inspiratory pressure (MIP), and arterial partial pressure of carbon dioxide ($PaCO_2$). A subset of subjects had transdiaphragmatic sniff pressures (Pdi-sniff) measured using the methods described by Lechtzin et al.[9] Using the formulae of Goldman and Becklake, predicted upright FVC was determined; this standard was used to determine both percent predicted upright FVC as well as (due to the absence of supine standards) percent predicted supine FVC.[7]

Outcome Measurements. The primary outcome measure was tracheostomy-free survival, as defined by the combined end point of death or tracheostomy. The patient's survival, dependence upon mechanical ventilation, and presence of tracheostomy were obtained via telephone interviews with each patient or the patient's surviving family. If contact was unobtainable, the outcome was determined via hospital records, social security records, or a review of local death notices.

Independent Variables. Nonpulmonary characteristics assessed at the time of pulmonary function testing included gender, age, clinical area of disease onset (bulbar vs. extremities), time from symptom onset to diagnosis, and time from symptom onset to spirometry. The prescription of riluzole (Rilutek; Aventis, Strasbourg, France) or noninvasive positive pressure ventilation during the period of observation was recorded.

Statistical Analyses. Descriptive statistics were performed using means and standard deviations, medians and interquartile ranges, and frequencies where appropriate. Baseline categorical variables were compared using chi-square tests; continuous variables were compared using *t*-tests.

Survival was calculated from the time of the patients' spirometry testing. Bivariate, nonparametric survival analyses using the primary end point of tracheostomy-free survival were carried out using the methods of Kaplan and Meier. Statistical significance was tested using Wilcoxon tests.

To adjust for potential confounding by other factors historically associated with survival, Cox proportional hazard modeling was used for the multivariate analysis of each pulmonary predictor with age, area of disease onset, time from symptom onset to diagnosis, and riluzole usage. Continuous variables were grouped into clinically appropriate categories.

Comparing Clinical Utility of the Pulmonary Predictor Variables. After the determination of the significance of each test in predicting death or tracheostomy, attention was shifted to the tests' utility in predicting this outcome at one year of follow-up, a time point applicable to many clinical trials. Sensitivity, specificity, positive predictive value, and negative predictive value of each variable were determined with regard to predicting death or tracheostomy at that time. Clinically relevant cut-points were used for supine and upright FVC; in our pulmonary function laboratory, these corresponded to severe (<50% predicted FVC), moderate (50–64%), mild (65–79%), and no (≥80%) restriction. Cut-points for maximal inspiratory and expiratory pressures were defined in part by the distribution of data points. We refer to MIP < -70 cm H_2O and MEP > 70 cm H_2O as being in a "normal" range. These normal ranges approximate the lower limit of normal used in other studies.[9] Finally, a "normal" value of Pdi-sniff was established at >70 cm H_2O.[9]

Receiver-operating characteristic (ROC) curves, e.g., plots of sensitivity/(1 − specificity) at each potential test cut-point, were determined. The area under the ROC curve, a measurement representative of the overall desirability of a diagnostic test, was determined for each pulmonary test. Statistical tests were performed to compare the areas under the tests' curves.

All statistical analyses were conducted using Stata software version 7.0 or 8.0 (Stata Corp. 2001 and 2003, College Park, Texas).

RESULTS

Ninety-five patients met criteria for inclusion into the study, and 86 were completely accounted for as of the November 30, 2002, study end-date. Seven patients successfully completed several interim clinic visits but were lost to follow up prior to the end-date. Two patients underwent spirometry but had no additional follow-up; they did not contribute to the survival analysis.

Sixty-two percent of patients in the study were male; 77% had limb onset of disease. The mean patient age was 60 years (SD 11.6 years). The median time from symptom onset to ALS diagnosis was 365 days (interquartile range 212–514 days). Spirometry was performed a median of 702 days after symptom onset.

During the period of observation, riluzole was prescribed for 81% of the cohort; noninvasive positive pressure ventilatory support such as bilevel positive airway pressure (BiPAP) ventilation was prescribed for 60%. Individual compliance with either of these interventions was not assessed. No patients used BiPAP at study enrollment. The eventual prescription of BiPAP was more common in subjects with more abnormal pulmonary function, e.g., lower FVC.

The mean upright FVC was 65% of predicted, corresponding to a mild-to-moderate restrictive deficit. FVC decreased in the supine position, with a mean decline of approximately 10%-predicted. Although the mean $PaCO_2$ was normal, there was a wide range (32–72 mm Hg), with some patients displaying hypercapneic ventilatory failure at the time of baseline spirometry. Twenty patients underwent transdiaphragmatic sniff pressure determination; all exhibited diaphragmatic weakness, using a normal reference pressure of >70 cm H_2O. A full list of pulmonary characteristics at study entry is detailed in Table 1.

Table 1. Pulmonary function test results at study entry.

Test	Mean (±SD)	Patients tested
Upright FVC (L)	2.52 ± 1.03	95
Upright FVC (% predicted)	65 ± 19.6	95
Supine FVC (L)	2.12 ± 1.07	95
Supine FVC (% predicted)	54.4 ± 22	95
ΔFVC (change in % predicted)	−10.6 ± 11.4	95
MIP (cm H_2O)	−41.7 ± 23.1	81
MEP (cm H_2O)	53.4 ± 28.9	80
Pdi-sniff (cm H_2O)	31.6 ± 17.5	20
$PaCO_2$ (mm Hg)	43 ± 7.5	69

Outcomes. The median follow-up after spirometry was 369 days (interquartile range: 165–631). Fifty-five patients (57.9%) died during follow-up; only 4 underwent tracheostomy.

Survival Analyses. For each pulmonary function test assessed, survival was significantly longer in the group with values closer to normal (Fig. 1). Pdi-sniff was also predictive of survival, but only 20 patients performed this test. The $PaCO_2$ was not a significant predictor of survival. Controlling for nonpulmonary factors known to predict survival in ALS (age, area of onset, time to diagnosis, and riluzole usage), upright FVC, supine FVC, MIP, MEP, and Pdi-sniff remained significantly associated with tracheostomy-free survival ($p < 0.05$). The ΔFVC lost its significant association with tracheostomy-free survival once controlled for these factors.

Of note, a patient's eventual prescription of BiPAP did not alter the predictive value of pulmonary function testing at study enrollment. In the analysis of the BiPAP-prescribed subgroup of patients, the significance of pulmonary function tests (particularly upright FVC, supine FVC, MIP, and MEP) was identical to that that seen in patients who were not prescribed BiPAP (data not shown).

Clinical Utility of Pulmonary Function Tests. The sensitivities and specificities of each pulmonary function test with regard to tracheostomy or death were calculated at one year of follow-up, a timeline relevant to many clinical trials (Table 2). A test highly sensitive for death/tracheostomy at one year would lead to a high negative predictive value; thus, a negative test would be reassuring for continued patient survival. Using a cut-point of mild restriction or worse (i.e., <80% predicted), supine FVC was 95% sensitive for death/tracheostomy (Fig. 1). Using reference values of >70 cm H_2O (MEP) and <−70 cm H_2O (MIP), the presence of a diminished MIP or MEP was extremely sensitive for death/tracheostomy. Conversely, the negative predictive value of a normal MIP, MEP, or supine FVC was high. Of the pulmonary function tests studied, MEP, MIP, and supine FVC had the largest areas under their respective ROC curves.

DISCUSSION

We found single measures of upright FVC, supine FVC, MIP, MEP, and Pdi-sniff to be significantly associated with tracheostomy-free survival, even after controlling for relevant nonpulmonary patient characteristics.

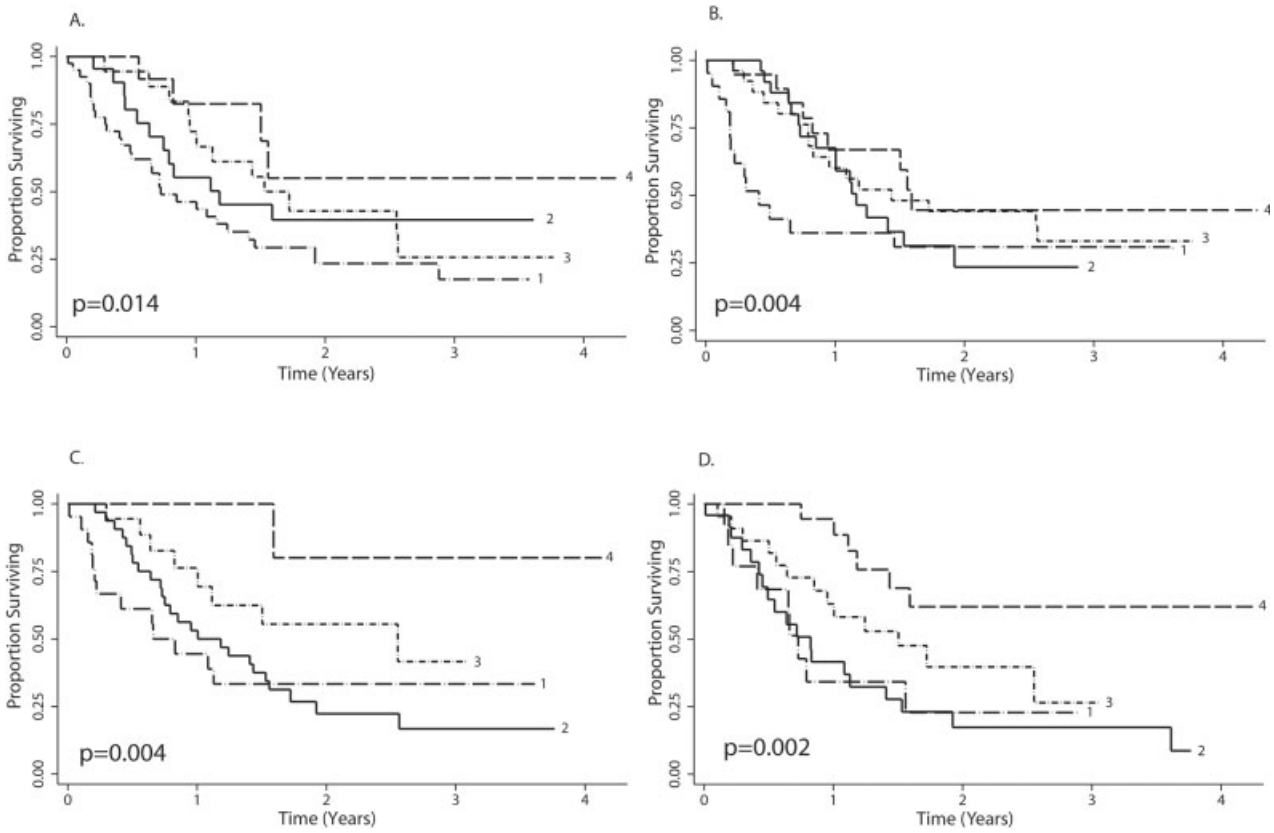

FIGURE 1. Kaplan–Meier curves showing differences in survival based on values of supine FVC **(A)**, upright FVC **(B)**, MIP **(C)**, and MEP **(D)**. The categories of FVC are as follows: FVC ≤ 50% (line 1); FVC = 51–65% (line 2); FVC = 66–80% (line 3); FVC > 80% (line 4). The MIP categories are as follows: MIP > −25 cm H_2O (line 1); MIP = −25 to −50 cm H_2O (line 2); MIP = −51 to −70 cm H_2O (line 3); MIP < −70 cm H_2O (line 4). The MEP categories are as follows: MEP < 25 cm H_2O (line 1); MEP = 25–50 cm H_2O (line 2); MEP = 51–70 cm H_2O (line 3); MEP > 70 cm H_2O (line 4). The *p* values compare differences in survival between the four categories of each pulmonary test by the Wilcoxon test.

Inspiratory Muscle Function. This association between measures of inspiratory muscle function and survival in ALS is reflected in the extensive literature on upright FVC as a predictor of mortality.[12,18] Upright FVC, however, is less sensitive than other measures in the detection of diaphragmatic weakness.[6,8,9,11,15] In our study, we examined FVC in the supine position, a test known to be a better predictor of diaphragmatic weakness than upright FVC.[9] An abnormal supine FVC is 95% sensitive for death or tracheostomy at one year; conversely, a normal supine FVC has a 83% predictive value for survival at this time. A normal upright FVC only has a 70% predictive value.

The MIP is another sensitive measure of inspiratory muscle strength.[8] Although serial measurements of MIP have been studied,[16] few authors have evaluated the prognostic significance of a single measurement. In our study, only one patient with an MIP < −70 cm H_2O died during the follow-up period. Likewise, an MIP more negative than −50 cm H_2O had a high (84%) predictive value for tracheostomy-free survival. The implications of these findings, however, may be confounded by the difficulties often faced by ALS patients in properly performing mouthpiece pressure measurements.[6,14] The production of a normal MIP may be more indicative of a patient's ability to maintain a tight lip seal on a mouthpiece than of the patient's inspiratory muscle strength. Nevertheless, in our study, MIP maintained its strong association with tracheostomy-free survival even after we controlled for bulbar-onset disease. This suggests that though MIP may be difficult to assess in patients with advanced bulbar disease, it does offer useful screening information when employed at a single time, such as a baseline visit or a clinical trial screening visit.

Pdi-sniff is useful in the detection of diaphragmatic weakness; it correlates with hypercapnia.[11] We found a significant association between Pdi-sniff and

Table 2. Sensitivity and specificity of tests in predicting death or tracheostomy at one-year follow-up.

Test	Cut point	Sensitivity (%)	Specificity (%)	Negative predictive value (%)	Area under ROC curve
Upright FVC					
Percent predicted*	FVC < 80%	83.8	25.0	70.0	0.60
	FVC < 65%	56.8	53.6	65.2	
	FVC < 50%	35.1	85.7	66.7	
Supine FVC					
Percent predicted*	FVC < 80%	94.6	17.9	83.3	0.65
	FVC < 65%	81.0	42.9	77.4	
	FVC < 50%	56.8	66.1	69.8	
MEP	MEP < 70 cm H_2O	96.7	35.4	94.4	0.75
	MEP < 50 cm H_2O	70.0	64.6	77.5	
MIP	MIP > −70 cm H_2O	100	14.3	100	0.71
	MIP > −50 cm H_2O	86.7	42.9	84.0	

**Defined at clinically relevant cut-points: i.e., mild, moderate, or severe restriction.*

survival, even though a relatively small number of subjects performed this test. The infrequent use of this test likely reflects its time-consuming and invasive nature, which is undesirable for a screening test. A more attractive alternative to Pdi-sniff is the measurement of sniff nasal pressure, which is known to predict hypoventilation and hypercapnia with a greater sensitivity than upright FVC.[6,11] Only recently, however, has this test been used to predict mortality. Morgan and others noted that sniff nasal pressure < 40 cm H_2O was 97% sensitive for death at 6 months.[13]

Expiratory Muscle Function. Patients with ALS lose their ability to cough effectively and are prone to mucous plugging and pneumonia. Decreased cough gastric pressure predicts the inability to cough,[15] and peak cough flow rates < 270 L/min have been recommended as a threshold below which aggressive airway clearance protocols should begin.[2] However, few studies have fully defined the prognostic implications of decreased expiratory muscle strength.

Our study examined maximal expiratory pressure, a highly available and noninvasive measure of expiratory function. A MEP greater than 60 cm H_2O was shown by Szeinberg and others to predict the ability to cough in patients with muscular dystrophy.[19] Although others have not been able to replicate this association in ALS patients,[15] our study does suggest a protective effect of a normal MEP. In our cohort, a MEP greater than 70 cm H_2O had a 94% predictive value for tracheostomy-free survival. This closely correlates with Szeinberg's values, suggesting an association between MEP and the ability to cough effectively enough to prevent morbidity.

Implications. Our study demonstrated that supine FVC, MIP, and MEP are useful noninvasive measures in the prediction of survival in ALS. A patient with a normal MIP or MEP has a greater than 90% chance of tracheostomy-free survival at one year; a normal supine FVC predicts at least a one-year tracheostomy-free survival in over 80% of cases. We believe that these findings are important and valuable for ALS care, both in clinical trial enrollment and inpatient counseling.

Although the presence of a normal MIP, MEP, or supine FVC is reassuring for survival, these standards may be too stringent for purposes of clinical trial design and may disqualify too many patients from study entry. Normal values were seen in 12 of 95 patients on supine FVC (13%), 8 of 81 patients on MIP (10%), and 18 of 80 patients on MEP (23%). These normal values are uncommon, but they do (particularly MEP) approximate the rate of normal upright FVC (21%), the previous "gold standard" pulmonary function test in ALS. Should these pulmonary function values be too restrictive for trial design, a clinical investigator could liberalize the criteria for trial entry, while still being able to predict outcomes of a patient cohort. Among the patients studied, 33% had supine FVC greater than 65% predicted, and these patients can be expected to have a 77% one-year tracheostomy-free survival; 51% percent of patients had an MEP greater than 50 cm H_2O, indicative of a 77.5% chance of one-year survival. Among the patients studied, 32% had a MIP more negative than −50 cm H_2O; 84% of these patients are expected to survive one-year of follow-up. These tests compare favorably to upright FVC—values greater than 65% predicted were seen in 48%

of patients but only corresponded to a 65% expectation of one-year survival.

Our study has certain limitations. We were not able to quantify patient adherence with noninvasive ventilation and other potential confounders of survival. The majority of subjects were (at some point after study enrollment) prescribed noninvasive ventilation. Any confounding influence, however, is limited by our finding that BiPAP use did not change the predictive value of MIP, MEP, supine FVC, or upright FVC, each of which remained statistically significant regardless of patients' eventual use of noninvasive ventilation. This finding does not contradict the wealth of previous literature supporting BiPAP use (or our own opinions regarding BiPAP's usefulness in the treatment of patients with ALS). Because of limitations of our study design with respect to BiPAP use (indeed, noninvasive ventilation use was more common in subjects with abnormal pulmonary function tests), our study should not be used to draw conclusions about this intervention's utility in the care of the ALS patient.

In summary, we recommend that evaluation of ALS patients for clinical trials should include those tests of pulmonary function most likely to predict survival throughout the designated (usually one-year) trial period: supine FVC, MEP, and MIP. Although MIP and MEP had high negative predictive values in this study, they require equipment and training that may not be available in most ALS clinics. Spirometry is performed routinely for individuals with ALS, but usually only upright FVC is measured. Given the ready availability of supine FVC and the superior sensitivity and negative predictive value over upright FVC, supine FVC should be considered as the single best measure when screening for clinical trial enrollment. These findings have important implications both for design of clinical trials and for patient counseling.

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