Received: 9 January 2023 | Accepted: 27 February 2023

DOI: 10.1111/ene.15765

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Respiratory phenotypes in amyotrophic lateral sclerosis as determined by respiratory questions on the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised and their relation to respiratory tests

Susana Pinto[1,2] | Miguel Oliveira Santos[1,3] | Marta Gromicho[1] | Michael Swash[1,4] | Mamede de Carvalho[1,3]

[1]Institute of Physiology, Instituto de Medicina Molecular João Lobo Antunes, Centro de Estudos Egas Moniz, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

[2]Rehabiliteringsmedicin, Instituten för Medicinska Vetenskaper, Uppsala Universitet—Akademiska Sjukhuset, Uppsala, Sweden

[3]Department of Neurosciences and Mental Health, Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa-Norte, Lisbon, Portugal

[4]Departments of Neurology and Neuroscience, Barts and London School of Medicine, Queen Mary University of London, London, UK

Correspondence
Susana Pinto, Instituto de Medicina Molecular João Lobo Antunes, Av. Professor Egas Moniz, Lisbon 1649-028, Portugal.
Email: susana.c.pinto@gmail.com and susana.c.pinto@neuro.uu.se

Abstract

Background and purpose: Respiratory insufficiency and its complications are the main cause of death in amyotrophic lateral sclerosis (ALS). Respiratory symptoms are scored in questions Q10 (dyspnoea) and Q11 (orthopnoea) of the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R). The association of respiratory test alterations with respiratory symptoms is unclear.

Methods: Patients with ALS and progressive muscular atrophy were included. We retrospectively recorded demographic data, ALSFRS-R, forced vital capacity (FVC), maximal inspiratory (MIP) and expiratory (MEP) pressures, mouth occlusion pressure at 100 ms, nocturnal oximetry (SpO_2mean), arterial blood gases, and phrenic nerve amplitude (PhrenAmpl). Three groups were categorized: G1, normal Q10 and Q11; G2, abnormal Q10; and G3, abnormal Q10 and Q11 or only abnormal Q11. A binary logistic regression model explored independent predictors.

Results: We included 276 patients (153 men, onset age = 62.6 ± 11.0 years, disease duration = 13.0 ± 9.6 months, spinal onset in 182) with mean survival of 40.1 ± 26.0 months. Gender, onset region, and disease duration were similar in G1 (n = 149), G2 (n = 78), and G3 (n = 49). Time to noninvasive ventilation (NIV) was shorter in G3 (p < 0.001), but survival was similar. ALSFRS-R subscores were significantly different (G1 > G2 > G3, p < 0.001), except for lower limb subscore (p = 0.077). G2 and G3 patients were older than G1 (p < 0.001), and had lower FVC, MIP, MEP, PhrenAmpl, and SpO_2mean. Independent predictors for G2 were MIP and SpO_2mean; for G3, the only independent predictor was PhrenAmpl.

Conclusions: These three distinct ALS phenotypic respiratory categories represent progressive stages of ventilatory dysfunction, supporting ALSFRS-R clinical relevance. Orthopnoea is a severe symptom that should prompt NIV, phrenic nerve response being an independent predictor. Early NIV promotes similar survival for G2 and G3.

KEYWORDS
amyotrophic lateral sclerosis, nocturnal pulsed oximetry, phrenic nerve, respiratory function, respiratory tests

INTRODUCTION

Respiratory insufficiency and its complications are the main cause of death in amyotrophic lateral sclerosis (ALS). Respiratory involvement presents initially with subtle symptoms and signs. These symptoms are evaluated in the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R), in questions Q10 (dyspnoea) and Q11 (orthopnoea). The respiratory subscore of the ALSFRS-R (R of ALSFRS-R) includes a third question (Q12), related to the use of noninvasive ventilation (NIV) [1]. Progressive respiratory deterioration is translated from lower Q10 and Q11 scores, the need for respiratory support with lower Q12 values, and an aggravation in the respiratory tests [1].

Different respiratory function tests are used to assess respiratory function in ALS, particularly forced vital capacity (FVC) and slow vital capacity (SVC). These address the same functional deficit [2], are easy to perform and reliable, and have the same significance [3, 4]. Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) are more sensitive to early changes, but more demanding for patients [5]. Peak expiratory flow and peak cough flow are also useful to monitor expiratory muscle weakness and its progression in ALS [6]. Central respiratory drive can be assessed by measuring the mouth occlusion pressure at 100 ms (P0.1) [7]. However, all these tests depend on patient cooperation and motivation, and also require adequate facial and oropharyngeal muscle function to avoid air leakage during test performance [5]. Nonvolitional tests can provide useful complementary information. Percutaneous nocturnal oximetry (PNO) is a sensitive test that has been used to determine the optimum time to initiate NIV [8, 9] and to screening central drive dysfunction [10]. Nocturnal capnography is a sensitive tool for detecting nocturnal hypoventilation and predicting good compliance with NIV in ALS [11], but its abnormality can derive from associated sleep apnoea commonly observed in ALS without respiratory muscle weakness [11]. Arterial blood gas (ABG) analysis is an invasive test that is not regularly applied for monitoring ALS patients. Bicarbonate (HCO_3^-) and standard base excess measurements are indicative of prognosis [12]. Phrenic nerve motor response (PN), representing the functional motor units in the diaphragm, is a simple test that correlates with conventional respiratory tests [5] and predicts hypoventilation and survival [13].

In ALS, dyspnoea is initially described during higher exertion efforts, but the progressive deterioration of the respiratory function leads to its occurrence during activities of daily life such as bathing and even speaking, eventually occurring at rest. Orthopnoea is not initially described but can be seen as a further aggravation of respiratory function, when the diaphragm is unable to respond to ventilatory needs in the supine position. Its emergence does not imply a clear independent deterioration after dyspnoea, as both symptoms coexist at some point of the disease. However, it can occur without dyspnoea, when there is physical impairment and thus reduced respiratory demands [1]. Thereby, a simplification and rationalization of the progressive respiratory deterioration in ALS can be done, from no respiratory symptoms to a progressive aggravation of dyspnoea and the emergence of orthopnoea, ending up in dyspnoea at rest.

In this study, we aim to examine whether dyspnoea and orthopnoea as scored by questions Q10 and Q11 of the ALSFRS-R represent different respiratory phenotypes in ALS and to test their association with volitional and nonvolitional respiratory tests.

MATERIALS AND METHODS

From our clinical database in Lisbon containing 1710 patients with motor neuron disease (from 1995 to 2022), we selected retrospectively those with ALS or progressive muscular atrophy, as supported by the Gold Coast diagnostic criteria [14]. In addition to the ALSFRS-R at baseline (first visit) and during follow-up, the inclusion criteria required full data on respiratory function tests (FVC, MIP, MEP, P0.1, PNO, ABG and PN), all performed within a time frame of 2 months from the clinical assessment. Because several of these tests were not in use in the early years, case selection was limited to more recent patients. We excluded patients with primary lateral sclerosis and monomelic weakness. Patients with concomitant respiratory diseases, anaemia, heart failure, cancer, severe bulbar weakness, and a marked cognitive change unable to cooperate with the volitional tests were also excluded.

The patients were divided into three groups according to the values on the ALSFRS-R Q10 and Q11: Group 1 (G1), normal values in both questions (scored 4); Group 2 (G2), abnormal values in Q10 only; Group 3 (G3), abnormal values in both Q10 and Q11 or abnormal values in Q11 only. We recorded gender, onset age, onset region, baseline body mass index (BMI), disease duration from first symptoms to first visit (baseline), time from first symptoms to NIV, time from NIV to death, and total survival. In addition, we noted the total score on the ALSFRS-R, the bulbar (B), upper limb (UL), lower limb (LL), and respiratory subscores, and the Q10 and Q11 scores. All assessments were made by the same clinicians throughout (M.d.C., S.P., and M.O.S.), who applied the questionnaire similarly.

Respiratory function tests were carried out in a comfortable sitting position, using standard Jäger equipment (Jäger Masterlab and Jäger Masterscreen, Erich Jäger, Wurzburg, Germany). We measured FVC, MIP, MEP, and P0.1 expressed as percentages of individual predictive values derived from the reference values proposed by the European Community for Steel and Coal [15, 16]. An 80% cutoff for normality was used for FVC [15], 60 mmHg for MIP and MEP [17], and for P0.1 a normal value was defined as between 70.95% and 112.34% [7].

ABG analyses were performed in the sitting position, with patients breathing room air for at least 30 min, and before respiratory function tests. Arterial oxygen tension (pO_2), arterial carbon dioxide tension (pCO_2), HCO_3^-, and pH were measured by an automated analyser (ABL 500, Radiometer, Copenhagen, Denmark). Cutoffs were 60 mmHg for pO_2 (moderate hypoxaemia), between 35 and 45 mmHg for pCO_2, between 7.35–7.45 for pH, and between 22 and 26 mEq/L for HCO_3^- [18].

For PN, the mean peak-to-peak amplitude of the diaphragmatic motor responses to stimulation of the phrenic nerve behind the sternocleidomastoid muscle (PhrenAmpl) on each side was calculated. A mean value of 0.4 mV ([right + left] / 2) was considered the cutoff [13].

PNO was studied overnight, for a minimum time of 6 h, using a fingertip infrared pulsed oximeter. The mean value of oxygen saturation (SpO_2mean) was calculated, and a 93% cutoff value was defined [8, 10]. We also recorded the percentage of time oxygen saturation was <90% overnight [8, 10].

Statistical analyses

The demographic characteristics and clinical features were presented as mean ± SD for continuous variables and percentage for discrete variables. Continuous variables were compared between groups using one-way analysis of variance and unpaired *t*-test, with Bonferroni correction. Chi-squared or Fisher exact test was applied for categorical variables, as appropriate. The significant variables were applied to a binary logistic regression model (backward method) for G1 and G3, to assess independent predictors for determining inclusion in one specific group (G1 or G3) and not in the others. SPSS24 (IBM, Armonk, NY, USA) was used for the analyses; $p < 0.05$ was considered as significant.

Ethics

All procedures performed in the study involving human participants were carried out in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The protocol and data analysis were approved by the local ethics committee.

RESULTS

From the total population, 276 patients were included, 153 being men. Mean age at disease onset was 62.6 ± 11.0 years (range = 16–89), and mean disease duration from first symptoms to baseline was 13.0 ± 9.6 months (range = 1.0–63.1). The mean BMI at baseline was 24.7 ± 3.6 kg/m^2 (range = 14.5–33.9), which was significantly lower than before disease onset (26.5 ± 3.5, range = 16–39, $p < 0.001$). The onset region was spinal in 182 and bulbar in 110. Mean total survival was 40.1 ± 26.0 months (range = 7.0–176.7). The demographic characteristics of the whole population, as well as for G1 ($n = 149$), G2 ($n = 78$), and G3 ($n = 49$), are shown in Table 1. In G2, some patients progressed to presenting orthopnoea during the first five evaluations (3–4-month interval in between evaluations). In G3, 7 of 49 patients reported orthopnoea without dyspnoea, but all the others had both symptoms. The three groups presented no significant differences regarding gender, onset region, disease duration, and BMI at baseline ($p > 0.05$), although patients in G3 lost more weight before the first observation ($p = 0.042$). Time to NIV was shorter in G3 (G3 < G2 < G1, $p < 0.001$), but total survival did not differ between groups ($p > 0.05$; Figure 1). Time to gastrostomy was similar between groups.

The respiratory subscore of the ALSFRS-R was different between groups (G1 > G2 > G3, $p < 0.001$). A similar pattern of severity was seen in all other subscores of the ALSFRS-R and in the total score, except for the LL subscore ($p = 0.077$). Compared to G1, patients in G2 and G3 were older (G3 > G2 > G1, $p < 0.001$) and had lower values of SVC, MIP, and MEP, smaller PhrenAmpl values, and lower saturation values on PNO, more severely abnormal in G3. P0.1 was significantly different between groups ($p = 0.005$), but higher in G2 than in G3, which, in turn, had higher values than G1. P0.1 and the bulbar subscore of the ALSFRS-R were not correlated, neither in the entire population nor in the different subgroups. HCO_3^- and partial pressure of carbon dioxide were also significantly higher in G3 ($p < 0.001$).

Independent predictors of being in G1, and not in G2 or G3, were MIP ($p = 0.011$), P0.1 ($p = 0.02$), PhrenAmpl ($p = 0.001$), and SpO_2mean ($p = 0.019$). The odds of a patient being included in G1 and not in G2 or G3 increased by a factor of 15.33 if MIP was above its cutoff value (exp [B] = 15.33 [1.88–124.7]), by a factor of 4.93 if PhenAmp was above its cutoff value (exp [B] = 4.93 [1.96–12.4]), and by a factor of 4.08 if SpO_2mean was above its cutoff value (exp [B] = 4.08 [1.26–13.2]), and the predicted odds of not being in G1 increased by a factor of 2.96 if P0.1 was not in between its cutoff values (exp [B] = 0.338 [0.135–0.846]). The percentage of cases with an observed outcome correctly predicted by the model was 78.3%, with a sensitivity of 83.8% and a specificity of 70.9%.

PhrenAmpl was the only independent predictor of the probability of being in G3 ($p < 0.001$), with predicted odds that increased by a factor of 27.8 if PhrenAmpl was below its cutoff value (exp [B] = 0.036 [0.008–0.17]). The percentage of cases with an observed outcome correctly predicted by the model was 85.5%, with a sensitivity of 34.8% and a specificity of 96.3%.

DISCUSSION

We studied three phenotypic respiratory patterns of ALS patients related to symptom severity as determined by questions Q10 and Q11 on the ALSFRS-R. Patients with no functional respiratory involvement (normal scores on Q10 and Q11 of the ALSFRS-R, G1 group) were significantly younger, had better respiratory tests, and lived longer until they needed NIV. Patients in G3, who had both orthopnoea and dyspnoea or only orthopnoea, were older, had

TABLE 1 Demographic characteristics of the entire population as well as G1 (normal Q10 and Q11), G2 (abnormal Q10), and G3 (abnormal values in Q11 only, or abnormal values in both Q10 and Q11).

Characteristic	All patients, *n* = 276 (100%), mean ± SD (min, max)	G1, *n* = 149 (54%), mean ± SD (min, max)	G2, *n* = 78 (28.3%), mean ± SD (max, min)	G3, *n* = 49 (17.8%), mean ± SD (min, max)	*p*
Male gender, *n*, %	153, 55.4%	89, 59.7%	35, 44.9%	29, 59.2%	0.086
BMI before, kg/m^2	26.5 ± 3.5 (16, 39)	26.6 ± 3.3 (21, 39)	25.4 ± 3.5 (16, 33)	27.74 ± 3.7 (20, 34)	0.042*
BMI first visit, kg/m^2	24.7 ± 3.6 (14.5, 33.9)	24.9 ± 3.4 (18.0, 33.6)	24.4 ± 3.9 (14.5, 33.8)	24.5 ± 3.7 (18.3, 33.9)	0.547
Age at onset, years	62.6 ± 11.0 (16, 89)	60.3 ± 10.8 (27, 89)	64.0 ± 11.8 (16, 84)	67.5 ± 8.3 (38, 83)	<0.001**
Onset form, *n*, %					0.228
Spinal	182, 62.3%	99, 66.4%	43, 55.1%	29, 59.2%	
Bulbar	110, 37.7%	50, 33.6%	35, 44.9%	20, 40.8%	
Disease duration, months	13.0 ± 9.6 (1.0, 63.1)	12.0 ± 9.2 (1.02, 63.1)	14.3 ± 10.6 (2.04, 59.4)	14.0 ± 8.7 (3.2, 47.4)	0.159
Time to NIV, months	7.3 ± 11.5 (−15.28, 78.0)	10.5 ± 13.4 (−0.43, 77.96)	5.34 ± 9.77 (−15.28, 44.7)	2.5 ± 4.12 (−2.92, 23.7)	<0.001**
Survival with NIV, months	20.5 ± 19.4 (−0.3, 112.0)	20.7 ± 19.98 (−0.30, 112.0)	22.3 ± 19.9 (1.68, 94.1)	17.3 ± 17.5 (0.3, 81.9)	0.408
Time to PEG, months	16.4 ± 19.2 (−2.7, 136.0)	15.5 ± 11.3 (0.23, 50.1)	21.6 ± 29.0 (0.30, 136.0)	8.2 ± 11.1 (−2.66, 38.8)	0.144
Total Survival, months	40.1 ± 26.0 (7.0, 176.7)	42.6 ± 28.5 (7.00, 176.7)	39.6 ± 23.8 (8.2, 100.2)	33.1 ± 20.2 (9.1, 108.8)	0.084
ALSFRS-R	39.4 ± 5.7 (19, 47)	41.3 ± 4.7 (19, 47)	38.5 ± 5.5 (20, 47)	34.8 ± 5.7 (25, 46)	<0.001**
ALSFRS-R B	9.8 ± 2.4 (1, 12)	10.2 ± 2.2 (3, 12)	9.4 ± 2.4 (2, 12)	9.1 ± 2.7 (1, 12)	0.003**
ALSFRS-R UL	9.3 ± 2.7 (0, 12)	9.6 ± 2.6 (0, 12)	9.3 ± 2.7 (0, 12)	8.3 ± 2.9 (2, 12)	0.013*
ALSFRS-R LL	9.2 ± 2.6 (0, 12)	9.5 ± 2.5 (0, 12)	9.1 ± 2.8 (1, 12)	8.5 ± 2.6 (3, 12)	0.077
R of ALSFRS-R	11.1 ± 1.3 (5, 12)	12 ± 0 (12)	10.7 ± 0.6 (8, 11)	9.0 ± 1.3 (5, 11)	<0.001**
Q10	3.4 ± 0.83 (1, 4)	4 ± 0 (4)	2.7 ± 0.5 (1, 3)	2.5 ± 0.9 (1, 4)	<0.001**
Q11	3.78 ± 0.54 (1, 4)	4 ± 0 (4)	4 ± 0 (4)	2.7 ± 0.54 (1, 3)	<0.001**
SVC, % predicted	82.9 ± 21.5 (18.0, 132.4)	90.1 ± 20.0 (22, 132.4)	78.5 ± 20.9 (24, 130)	67.5 ± 17.3 (18.0, 104.3)	<0.001**
FVC, % predicted	83.2 ± 21.9 (16.0, 134.0)	90.2 ± 20.5 (21.0, 128.7)	78.9 ± 20.7 (16, 134)	68.8 ± 19.2 (23.0, 127.0)	<0.001**
MIP, mmHg	48.2 ± 27.9 (0, 160.0)	56.4 ± 27.1 (8.6, 157.0)	40.5 ± 27.4 (6.3, 160)	33.1 ± 21.1 (0, 119)	<0.001**
MEP, mmHg	61.2 ± 29.8 (0, 186.6)	68.5 ± 31.7 (7.4, 186.6)	57.1 ± 26.4 (15, 123.4)	43.7 ± 17.9 (0, 76.7)	<0.001**
P0.1, % predicted	96.2 ± 48.4 (8.6, 310.4)	86.6 ± 29.3 (19.1, 167.1)	112.4 ± 60.4 (8.6, 272.1)	104.0 ± 70.4 (30.5, 310.4)	0.005**
pO_2, mmHg	86.0 ± 9.0 (63.9, 113.2)	87.3 ± 8.73 (66.0, 113.2)	85.3 ± 8.5 (65.4, 101.7)	82.5 ± 9.6 (63.9, 100.2)	0.02*
pCO_2, mmHg	40.2 ± 4.8 (28.1, 68.0)	39.2 ± 4.0 (28.1, 56.0)	39.8 ± 4.1 (32, 49.7)	44.1 ± 6.6 (34.9, 68.0)	<0.001**
pH	7.43 ± 0.03 (7.34, 7.52)	7.43 ± 0.03 (7.34, 7.52)	7.44 ± 0.2 (7.41, 7.49)	7.43 ± 0.03 (7.38, 7.48)	0.397
HCO_3^-, mEq/L	26.4 ± 2.9 (21, 42)	26.1 ± 2.7 (21, 38)	26.1 ± 2.4 (22, 33)	28.1 ± 3.9 (22.1, 42)	0.004**
PhrenAmpl, mV	0.48 ± 0.25 (0, 1.28)	0.57 ± 0.24 (0.10, 1.28)	0.43 ± 0.22 (0, 0.99)	0.28 ± 0.18 (0, 0.8)	<0.001**
SpO_2mean, %	94.28 ± 1.9 (86.1, 98.1)	94.7 ± 1.56 (90.9, 98.1)	93.97 ± 1.99 (86.1, 97.95)	93.6 ± 2.4 (87.1, 96.9)	<0.001**
SpO_2 < 90%, %	4.4 ± 10.4 (0, 71)	2.2 ± 4.9 (0, 24)	4.65 ± 9.8 (0, 71)	10.4 ± 18.4 (0, 69)	<0.001**

Abbreviations: ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; B, bulbar subscore; BMI, body mass index; FVC, forced vital capacity; HCO_3^-, bicarbonate; LL, lower limb subscore; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; NIV, noninvasive ventilation; P0.1, mouth occlusion pressure at 100 ms; pCO_2, arterial carbon dioxide tension; PEG, percutaneous endoscopic gastrostomy; PhrenAmpl, mean peak-to-peak amplitude of phrenic nerve motor responses in right- and left-sided recordings; pO_2, arterial oxygen tension; Q10, question 10 of the ALSFRS-R (dyspnoea); Q11, question 11 of the ALSFRS-R; R of ALSFRS-R, respiratory subscore of the ALSFRS-R (orthopnoea); SpO_2 < 90%, mean nocturnal pulsed oxygen saturation below 90%; SpO_2mean, mean nocturnal SpO_2; SVC, slow vital capacity; UL, upper limb subscore.

*p <0.05; **p <0.01.

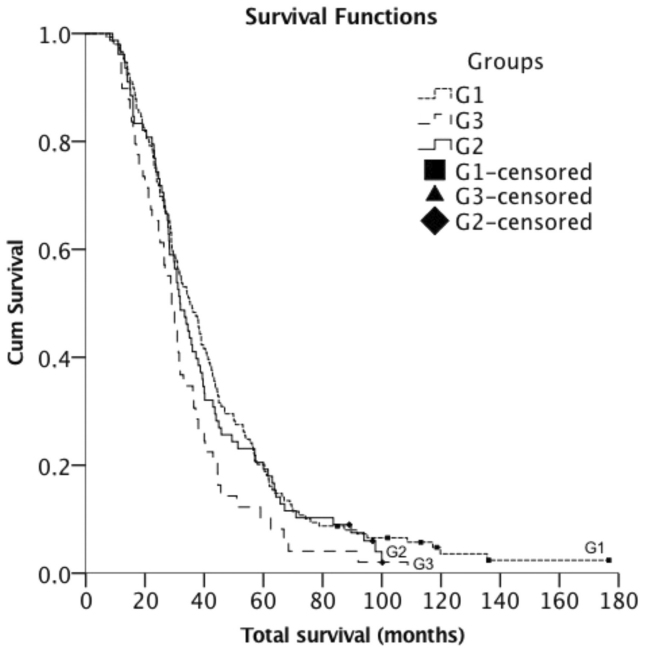

FIGURE 1 Total survival for the three considered groups. Cum, cumulative.

the worst values on respiratory tests, lost more weight before the first visit, and required NIV adaptation earlier after disease onset. Patients who had dyspnoea without orthopnoea (G2) had abnormal respiratory tests but with less severe changes than in G3, and had an intermediate time interval before NIV compared with the other two groups. Although patients in G1 had no respiratory symptoms, MIP was already abnormal, demonstrating a high sensitivity for detecting early changes [5]. These results support that activity-related diurnal dyspnoea antedates orthopnoea, which emerges when the severe weakness of the diaphragm no longer meets the overnight basal metabolic needs in the supine position, despite a possible central respiratory hyperactivation. The clinical differences between the groups indicate specific phenotypic characteristics that can differentiate ALS patients and have different prognostic implications, as determined by the time to NIV. Despite the expected progression of the respiratory dysfunction from no respiratory symptoms to exertional dyspnoea followed, at some point, by orthopnoea, we consider that all our clinical and respiratory results support the existence of different respiratory phenotypes that can be identified at first visit. Although G2 and G3 presented a shorter time to NIV, total survival was similar between the three groups. Our results suggest that NIV was able to increase survival in G3 patients, which is consistent with the known efficacy of NIV in compensating for respiratory failure in ALS, as also happened in G1 and G2 [19]. In our unit, we apply early NIV adaptation, as recommended in the European guidelines [19]. Thus, NIV can be a modifier of the natural course of ALS [20].

Categorization of patients into G1, G2, and G3 based only on Q10 and Q11 of the ALSFRS-R discriminated patients quite well regarding their other motor functions, as shown by the total ALSFRS-R scores, concerning bulbar and upper limbs subscores. Therefore, a relative parallel deterioration in the respiratory and motor functions can be assumed. This approach could be useful in future clinical trials.

We conducted a binomial logistic regression analysis to identify independent predictors of inclusion in G1 and not in the other two groups or in G3 and not in the other two groups. Identifying independent predictors of inclusion in G2 and not in G1 or G3 would be redundant and not clinically relevant, as the other two groups represent the two extremes of the respiratory deterioration spectrum. An ordinal regression analysis, although interesting, would be inadequate, as compensatory mechanisms, such as P0.1, do not show a specific pattern that would allow for it. P0.1 has been shown to compensate for respiratory muscle weakness to a specific extent [6]. Not only MIP ($p = 0.01$) but also P0.1 ($p = 0.02$), PhrenAmpl ($p = 0.001$), and SpO_2mean ($p = 0.02$) were independent predictors of the probability of not having dyspnoea and orthopnoea (G1). Our interpretation is that these tests are sensitive to diaphragm weakness, and that a central drive response as assessed by the P0.1 test is normal in early ALS. With more severe respiratory impairment (G3), only PhrenAmpl was an independent predictor ($p < 0.001$), indicating that this latter test could selectively grade more severe diaphragmatic weakness. In addition, patients in G3 showed a significant HCO_3^- compensatory response, required to pH to be maintained within a normal range. Identifying different respiratory tests that predict the presence of respiratory symptoms in ALS is of relevance. As indicated before, respiratory failure in ALS [5, 21] results from the dysfunction of different respiratory mechanisms. For this reason, it is essential to use various respiratory tests to evaluate specific respiratory mechanisms affected in the disease process [1, 6–8, 11, 22, 23].

Some limitations can be pointed out in this study, namely not having studied other respiratory symptoms such as weak cough and not performing the entire set of respiratory tests longitudinally. Weak cough is particularly relevant, as it is associated with accumulation of secretions and aggravates the risk of respiratory infections. However, MEP, which was included in our study and reflects the strength of the expiratory muscles, did not prove relevant for determining respiratory symptoms (inclusion in G1 or G3), despite being significantly different between groups. Although longitudinal respiratory evaluation was not addressed, this was not relevant to the aim of our study. All patients were followed clinically, without missing data regarding the defined outcomes, and patients with poor respiratory function were not subjected to further evaluations, as they were promptly managed with NIV. Another limitation is the absence of capnography data but we think that the inclusion of nonvolitional tests such as PN and PNO and the evaluation of central respiratory drive (P0.1) powered our findings.

We conclude that three distinct clinical respiratory phenotypes should be considered in ALS, associated with progressive deterioration of the respiratory tests and with different prognostic implications. Orthopnoea is a severe symptom in ALS, associated with a very weak diaphragm, which should prompt rapid NIV intervention. Moreover, early NIV in these patients allows for a similar survival duration compared with ALS patients asymptomatic regarding respiratory dysfunction. According to our study, it is recommended to evaluate ALS patients with different respiratory tests at first visit, including phrenic nerve studies, transcutaneous nocturnal pulsed oximetry, and spirometry.

AUTHOR CONTRIBUTIONS

Susana Pinto: Conceptualization; methodology; clinical follow-up of the patients; investigation; software; data curation; formal analysis; validation; writing–original draft, review & editing. **Miguel Oliveira Santos:** Clinical follow-up of the patients; investigation; writing–review & editing. **Marta Gromicho:** Software; data curation; writing–review & editing. **Michael Swash:** Validation; supervision; resources; writing–review & editing. **Mamede de Carvalho:** Conceptualization; methodology; clinical follow-up of the patients; investigation; validation; supervision; writing–review & editing; funding acquisition; project administration.

FUNDING INFORMATION

Project Brainteaser–Bringing Artificial Intelligence Home for a Better Care of Amyotrophic Lateral Sclerosis and Multiple Sclerosis, funded by the European Union's Horizon 2020 research and innovation program under (grant agreement GA101017598).

CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose. The authors alone are responsible for the content and writing of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Susana Pinto https://orcid.org/0000-0002-0727-5897
Miguel Oliveira Santos https://orcid.org/0000-0002-8290-0410
Marta Gromicho https://orcid.org/0000-0003-2111-4579
Mamede de Carvalho https://orcid.org/0000-0001-7556-0158

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How to cite this article: Pinto S, Oliveira Santos M, Gromicho M, Swash M, de Carvalho M. Respiratory phenotypes in amyotrophic lateral sclerosis as determined by respiratory questions on the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised and their relation to respiratory tests. *Eur J Neurol*. 2023;30:1594-1599. doi:10.1111/ene.15765