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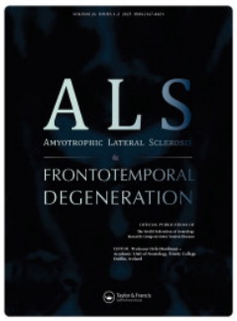

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RESEARCH ARTICLE

Respiratory measurements, respiratory symptoms, and quality of life in ALS: results from the REVEALS study

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Abstract

Objective: Progressing respiratory weakness throughout the course of amyotrophic lateral sclerosis (ALS) is clinically associated with distressing symptoms, including dyspnea, orthopnea, and difficulty clearing secretions. Fatigue, poor sleep, and reduced quality of life are also considered to be associated with declining respiratory function. Respiratory measurements guide prescription of interventions, which aim to alleviate symptoms. The relationships between respiratory measurements and patient reported symptoms are currently unclear. *Method*: The REVEALS study was a longitudinal, observational, multisite study of decline in respiratory function in people with ALS attending six European centers. Respiratory measures (forced and slow vital capacity (F/SVC), sniff nasal inspiratory pressure (SNIP), and peak cough flow) were collected, as were the presence of respiratory symptoms and simple quality of life, fatigue and sleep measures. We used Bayesian's multivariate models to explore the associations of the respiratory measures with outcome variables. *Results*: Two hundred and eighty participants completed in-person assessments over a median of 8 (IQR 2.3, 14.1) months, with 974 data collection timepoints. The probability of reporting symptoms including dyspnea, orthopnea, and difficulty clearing secretions increased with decreasing respiratory measurement scores. The probability of reporting moderately low quality of life and moderate fatigue also increased with decreasing test scores, but reported sleep quality was not associated with respiratory scores. *Conclusion*: Respiratory weakness in people with ALS was associated with symptoms including dyspnea, orthopnea, and difficulty clearing secretions. The probability of reporting symptoms increased incrementally as respiratory weakness increased, supporting the use of both respiratory measurements and the presence of symptoms in making decisions about clinical interventions.

Keywords: *Respiratory measurement, respiratory symptoms, amyotrophic lateral sclerosis*

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Introduction

Sequelae of respiratory weakness, which result from the loss of diaphragmatic, bulbar, and thoracic motor neurons, are the most frequent cause of death in amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND) (1,2). Additionally, progressing respiratory weakness throughout the disease course is clinically associated with a significant symptom burden and morbidity, including dyspnea, orthopnea, difficulty clearing secretions, and respiratory tract infections. Symptoms such as fatigue, poor sleep, and reduced quality of life are also common in ALS and are often considered to be associated with decline in respiratory function. Respiratory impairment and associated symptoms are clinically managed using noninvasive ventilation (NIV), cough augmentation adjuncts, and medications. Clinical guidelines state that initiation of these interventions should be guided by both presenting symptoms and by reaching specified thresholds on respiratory function tests (3–7).

Respiratory function in ALS is commonly monitored objectively using slow and forced vital capacity (S/FVC), which in ALS patients, are primarily used to assess the volume of air that can be in- and exhaled, with decreasing volumes reflecting weakness in the diaphragm and external intercostal musculature. Sniff nasal inspiratory pressure (SNIP) and peak cough flow (PCF) are also widely used assessments of respiratory muscle strength. SNIP measures the pressure produced during a maximal, fast sniff maneuver, while PCF is used to estimate abdominal and internal intercostal expiratory muscle function and efficacy of mucus clearance (8). These tests have demonstrated validity and reliability and are used according to international standards (8,9), as well as assessment guidelines specific to ALS/MND (10). However, while the utility of these objective metrics in tracking respiratory decline has been established, the relationship between decline in these measures and symptom burden and respiratory morbidity in ALS is unclear. There is a need for clarity regarding the impact that decline in respiratory strength, as assessed using these commonly used tests, has on patients. This clarity will aid clinicians in decision making for timely intervention with respiratory interventions and will provide real-world context for improvements in future clinical trials.

The REVEALS study was a longitudinal, observational, multisite study of decline in respiratory function in ALS (11,12). The data was collected between April 2018 and February 2021 and included 280 people with ALS in six European sites (Beaumont Hospital, Dublin; King's College Hospital, London, UK; University Medical Centre, Utrecht, The Netherlands; Azienda Ospedale Università Città della Salute e della Scienza, Turin, Italy; Sheffield Teaching Hospitals, Sheffield and University Hospitals Leuven, Belgium). The study was designed to reflect a real-world clinical population and clinical follow-up cadence. Participants were assessed on a median of three occasions (IQR 2.0, 5.0), over a median of 8 months (IQR 2.3, 14.1). Significant decline was demonstrated in all subgroups (male and female, spinal and bulbar onset), with particularly marked decline in the female subgroup with bulbar onset ALS (12). While FVC and SVC were closely correlated, correlation with SNIP and PCF was moderate, as these tests reflect different aspects of respiratory function (11). The respiratory subscale of the ALSFRS-R correlates poorly with all measures and did not show differences in rates of decline between the onset and sex subgroups compared with the other measures (12).

The aim of this paper is to discuss a series of exploratory hypotheses relating respiratory measures and patient reported symptoms. The probability of the presence of clinically relevant symptoms such as orthopnea, dyspnea, difficulty clearing secretions, and fatigue, in relation to declining scores on respiratory assessments was investigated. In addition, the probability of poor sleep quality and reduced quality of life with declining respiratory scores was explored.

Methods

Study population

The study design and population of the REVEALS study has been described previously (11,12). This was a longitudinal, observational study of patients attending a participating multidisciplinary clinic, with a confirmed diagnosis of spinal or bulbar onset ALS. In addition, participants fulfilled the criteria for ALS King's stage 2 or 3 at recruitment, provided informed consent and were able to complete the necessary respiratory tests and could correspond remotely. Use of NIV at time of recruitment, or the presence of another respiratory condition (asthma, COPD, bronchiectasis, lung cancer, etc.) were exclusion criteria. Follow-up at irregular intervals was acceptable considering the "real world" design of the study. All assessors completed training in standardized outcome measurement procedures and regular site visits, including observation of data collection visits, ensured consistency of the protocol across the sites (11). Ethical approval was in place for the study at each participating site.

Data collection

Demographics including site of ALS onset (spinal/bulbar), date of onset, date of diagnosis, gender, height, weight, and employment were recorded.

The amyotrophic lateral sclerosis rating scale revised (ALSFRS-r) was completed according to the ENCALS standard operating procedure (2015).

Four objective respiratory outcome measurements were recorded at each visit; SNIP (cmH_2O), PCF (L/min), SVC (L and %predicted), and FVC (L and % predicted). The percentage predicted score of FVC was calculated using Global Lung Function Initiative (GLI-2012) reference equations (13,14) and the %predicted for SVC was calculated using the ratio provided by FVC. The procedures for these assessments have been described in detail previously (11,12) and adhered to ENCALS standard operating procedures (10).

In addition, the presence of respiratory symptoms (dyspnea at rest and when active (yes/no) and orthopnea (yes/no)) was recorded. Difficulty with clearing secretions from the chest, from the nose and with managing saliva was documented using a five-point Likert scale anchored by "no difficulty" (0) to "unable to perform" (4). In addition, a specific rating of fatigue associated with clearing secretions was documented (0–10). The McGill Quality of Life Single Item Scale (0–10) (McGill SIS) (15), The EQ-5D-5L (16), the Pittsburgh Sleep Quality Index (Component 1) (17), and a Fatigue Numerical Rating Scale (0–10) (18) were completed.

Exploratory hypotheses

A number of exploratory hypotheses, which were generated based upon clinical experience were identified and are detailed in Table 1, with decline in PCF considered separately to FVC, SVC, and SNIP.

Statistical methods

Our previous analyses (11,12) used Bayesian's multivariate models to explore the correlations of the five respiratory outcomes and ALSFRS-r, and associations of these with demographic factors and clinical presentations of ALS. For this analysis, the outcome variables either have dichotomous (yes/no) values, ordered Likert/ordinal variables, or are continuous variables (Table 1).

For those outcome variables with dichotomous values, we used Bayesian's logistic regression models (i.e. a Bernoulli distribution family was assumed). For the Likert/ordinal outcomes, we used Bayesian's ordinal regression with an assumed cumulative outcome model (19) (i.e. it is assumed the observed ordinal variable originates from the categorization of an unobserved (latent) continuous variable—e.g. a continuous process of disease progression). Explanatory variables were chosen guided by our previous analyses (11), and included random slopes over time from baseline (where the baseline was defined as study enrollment date) and random intercepts by individual, while fixed effects were included for the time from baseline, site of onset by sex subgroups in interaction with time from baseline, study site, and age at diagnosis. Two thousand model iterations were run, and model convergence and fit were assessed by assessing the bulk effective sample size and tail effective sample size.

Software: R statistical software 4.1.3 (R Foundation for Statistical Computing, Vienna,

Table 1. Study hypotheses addressing the probability of patient reported respiratory symptoms with change in respiratory measurements.

	Hypothesis	Variable	Variable type
1	Decline in respiratory function measured using FVC, SVC, and SNIP increases the probability of		
	(a) Dyspnea when active	Yes/no response	Binary
	(b) Dyspnea at rest	Yes/no response	Binary
	(c) Orthopnea	Yes/no response	Binary
	(d) Reduced quality of life	McGill QoL single item 0–10 scale divided into 3 categories: 0–3 = poor, 4–7 = medium, 7–10 = good	Ordinal
		EQ-5D-5L (index score and % rating recorded)	Continuous
	(e) Reduced sleep quality	Pittsburgh Sleep Quality Index 4 point scale: very bad (0) to very good (4)	Ordinal
	(f) Fatigue	0–10 Fatigue Numerical Rating Scale divided into 3 categories: 0–3 = mild, 4–6 = moderate, 7–10 = severe	Ordinal
2	Reduced PCF increases the probability of		
	(a) Difficulty clearing secretions from chest	0–4 Numerical Rating Scale	Ordinal
	(b) Difficulty clearing nose	0–4 Numerical Rating Scale	Ordinal
	(c) Difficulty clearing saliva	0–4 Numerical Rating Scale	Ordinal
	(d) Fatigue clearing secretions	0–10 Numerical Rating Scale	Ordinal
	(e) Having a regular productive cough	Yes/no response	Binary
	(f) Reduced QoL	McGill QoL Single Item Scale 0–10 scale divided into 3 categories: 0–3 = poor, 4–7 = medium, 7–10 = good	Ordinal
		Eq-5D-5L (index score and % rating recorded)	Continuous

Austria) with additional packages were used for data preparation and descriptive analysis (20–24), and R packages brms (25), tidybayes (26), bayesplot (27), and Stan software version 2.29.2 were used to fit and assess Bayesian models. Analysis code is available on Github and archived on Zenodo: https://doi.org/10.5281/zenodo.14029005.

Results

Demographic and clinical baseline data have been described in detail previously (11,12). In summary, 280 participants with ALS (33.2% female, 81.1% with spinal onset ALS), with a mean age at diagnosis of 61.85 ± 11.85 years participated. Median time from disease onset to study entry was 19.42 (IQR 11.65, 35.12) months and median diagnostic delay was 9.99 (IQR 6.67, 16.33) months. Participants completed in-person assessments over a median of 8 (IQR 2.3, 14.1) months, with 974 data collection timepoints (median of 3 (IQR 2, 5) per individual). The baseline respiratory function and selected clinically meaningful symptom variables are described in Table 2.

Results of Bayesian logistic and ordinal models are best summarized graphically. Figure 1 reflects the results related to Hypotheses 1 (a–c) outlined in Table 1 and shows the probability of the presence of dyspnea when active, at rest, and in the lying position (orthopnea) with declining scores in FVC, SVC, and SNIP. For all three outcomes, the probability curves are similar for FVC and SVC, with the mean probability of reporting dyspnea when active increasing below 80% of predicted FVC/SVC scores. For "dyspnea at rest" and "in lying", the probability of reporting the symptoms increases below 50% of predicted SVC/FVC scores. Similarly, the probability of reporting "dyspnea when active" increases below a SNIP score of 80 cmH_2O but the risk of reporting "dyspnea at rest" and "orthopnea" remains low, with some increase below 50 cmH_2O.

Figure 2 shows the probability of reporting a McGill Single Item Scale (SIS) quality of life score within the three defined categories in relation to respiratory function measures (Table 1: Hypotheses 1(d) and 2(f)). The probability of reporting a high McGill SIS score (7–10/10) was greater with higher respiratory test scores. The probability of reporting a medium McGill SIS score (4–6) was higher with lower respiratory test scores and the probability of reporting a low score (0–3) was low at all respiratory test scores. EQ-5D-5L was modeled as a continuous variable, which showed that for each Liter increase in SVC, the EQ-5D-5L index score increased by 0.08 units (95% CrI: 0.06–0.10) and for each liter increase in FVC by 0.09 units (95% CrI: 0.06–0.11).

Supplementary Figure 1 displays the results of Hypothesis 1(e) and shows that the probabilities for reporting Pittsburgh Sleep Scores (0–4) did not change with changes in FVC, SVC, or SNIP. In Supplementary Figure 2, it is apparent that fatigue did not vary significantly with FVC, SVC, or SNIP, although there was a slight trend toward having a higher probability of low fatigue scores with higher FVC and SVC.

The results reflecting the hypotheses related to PCF measurement (Table 2: Hypotheses 2(a)–(e)) are shown in Figures 3–5. There was zero to minimal probability of having any level of difficulty clearing the chest, saliva, and nose for PCF scores above 600 L/min (Figure 3). The probability of having "difficulty clearing the nose" and "chest" increased when PCF fell below 400 L/min, but this trend was less obvious for reporting of "difficulty clearing saliva". Figure 4 shows that the probability of reporting "having a regular productive cough" was higher with lower PCF scores and similarly the probability of reporting "fatigue clearing the chest" increased below 400 L/min PCF (Figure 5).

Discussion

This study aimed to relate respiratory measures, used widely in research and clinical care in ALS to patient reported symptoms, reported sleep quality, and quality of life. We have shown that declining respiratory function, measured using FVC, SVC, SNIP, and PCF, result in increasing probability of distressing patient reported symptoms such as dyspnea, orthopnea, and difficulty clearing secretions. Furthermore, lower respiratory function test scores increase the probability of reporting lower quality of life and fatigue. Surprisingly, patient reported sleep quality was not associated with respiratory scores.

Management of respiratory failure and prescription of interventions including NIV are guided by both clinical symptoms and respiratory test scores (3,5,6). The screening of symptoms such as dyspnea is validated by these data, although conversely the high probability of not reporting dyspnea and orthopnea, even in the presence of significant respiratory weakness emphasizes the importance of regular respiratory testing in addition to symptom screening. The probability of reporting dyspnea at rest and orthopnea began to increase significantly when a marked decline in SVC and FVC has already occurred (approximately 50% predicted S/FVC). By contrast, the probability of reporting "dyspnea when active" started to increase at approximately 80% predicted S/FVC. For example, at 50% predicted FVC and SVC, approximately 25% of participants reported "dyspnea on activity" and less than 10% reported "dyspnea at rest" and "orthopnea". A similar pattern is seen for SNIP. We identified a wide range of credible intervals for probabilities of reporting dyspnea (Figure 1), which increased with increasing respiratory weakness, limiting definition of

Table 2. Descriptive statistics including clinical metrics at baseline.

Variable	Level	Dublin	London	Leuven	Sheffield	Turin	Utrecht	*p* Value
Number of participants		63	22	59	22	56	58	
Number of timepoints per participant, median [IQR]		3.0 [2.0, 4.0]	1.0 [1.0, 2.0]	4.0 [3.0, 7.0]	2.0 [1.0, 2.75]	4.0 [2.0, 4.0]	4.0 [2.0, 6.0]	
Baseline characteristics								
FVC/L (mean (SD))		3.04 (1.08)	3.14 (1.10)	3.06 (1.17)	3.20 (0.81)	3.02 (0.94)	3.55 (1.12)	0.091
SVC/L (mean (SD))		2.93 (1.09)	3.25 (1.36)	2.94 (1.15)	2.74 (0.67)	2.75 (1.00)	3.51 (1.13)	0.005
SNIP/cmH_2O (mean (SD))		66.11 (27.88)	58.57 (24.32)	55.22 (26.99)	58.65 (27.93)	64.12 (31.77)	62.62 (25.81)	0.334
PCF/L/min (mean (SD))		360.24 (128.98)	331.90 (159.99)	341.36 (143.36)	301.10 (88.74)	326.52 (124.16)	363.62 (115.50)	0.316
ALSFRS-R respiratory subscore (mean (SD))		11.41 (1.20)	11.35 (1.14)	10.97 (1.47)	11.35 (1.04)	11.45 (1.17)	11.53 (0.90)	0.157
Clinical metrics								
Dyspnea when active, *N* (%)	'Yes'	10 (17.2)	9 (42.9)	16 (27.1)	8 (36.4)	9 (16.1)	10 (17.5)	0.049
Dyspnea at rest, *N* (%)	'Yes'	2 (3.3)	1 (4.8)	4 (6.8)	0 (0.0)	4 (7.1)	1 (1.7)	0.544
Orthopnea, *N* (%)	'Yes'	5 (8.1)	0 (0.0)	10 (16.9)	3 (13.6)	6 (10.7)	6 (10.3)	0.354
McGill QOL Single Item Scale, *N* (%)	0–3	2 (3.3)	2 (9.5)	1 (1.7)	0 (0.0)	6 (10.7)	1 (1.9)	
	4–6	15 (24.6)	4 (19.0)	14 (23.7)	6 (27.3)	23 (41.1)	3 (5.8)	
	7–10	44 (72.1)	15 (71.4)	44 (74.6)	16 (72.7)	27 (48.2)	48 (92.3)	0.001
Pittsburgh Sleep Quality Index, *N* (%)	Very bad	1 (1.6)	8 (38.1)	2 (3.4)	1 (4.5)	1 (1.8)	0 (0.0)	
	Fairly bad	7 (11.5)	11 (52.4)	10 (16.9)	6 (27.3)	8 (14.3)	14 (24.6)	
	Fairly good	38 (62.3)	2 (9.5)	35 (59.3)	9 (40.9)	32 (57.1)	26 (45.6)	
	Very good	15 (24.6)	0 (0.0)	12 (20.3)	6 (27.3)	15 (26.8)	17 (29.8)	<0.001
Fatigue VAS, *N* (%)	0–3	15 (24.6)	9 (42.9)	14 (23.7)	11 (50.0)	9 (16.1)	20 (35.1)	
	4–6	26 (42.6)	5 (23.8)	32 (54.2)	5 (22.7)	27 (48.2)	27 (47.4)	
	7–10	20 (32.8)	7 (33.3)	13 (22.0)	6 (27.3)	20 (35.7)	10 (17.5)	0.023
Difficulty clearing chest in the past week, *N* (%)	No difficulty	44 (72.1)	15 (75.0)	46 (78.0)	14 (63.6)	47 (83.9)	44 (77.2)	
	Some difficulty	7 (11.5)	3 (15.0)	4 (6.8)	4 (18.2)	5 (8.9)	10 (17.5)	
	Moderate difficulty	6 (9.8)	2 (10.0)	5 (8.5)	2 (9.1)	4 (7.1)	3 (5.3)	
	Significant difficulty	1 (1.6)	0 (0.0)	4 (6.8)	2 (9.1)	0 (0.0)	0 (0.0)	
	Unable	3 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.107
Difficulty clearing nose in past week, *N* (%)	No difficulty	48 (78.7)	17 (85.0)	46 (78.0)	18 (85.7)	50 (89.3)	45 (80.4)	
	Some difficulty	5 (8.2)	1 (5.0)	3 (5.1)	1 (4.8)	3 (5.4)	5 (8.9)	
	Moderate difficulty	7 (11.5)	1 (5.0)	4 (6.8)	2 (9.5)	3 (5.4)	6 (10.7)	
	Significant difficulty	1 (1.6)	0 (0.0)	3 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	
	Unable	0 (0.0)	1 (5.0)	3 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	0.377
Difficulty clearing saliva in past week, *N* (%)	No difficulty	48 (78.7)	19 (95.0)	47 (79.7)	16 (76.2)	33 (58.9)	42 (73.7)	
	Some difficulty	8 (13.1)	0 (0.0)	4 (6.8)	5 (23.8)	14 (25.0)	7 (12.3)	
	Moderate difficulty	4 (6.6)	1 (5.0)	4 (6.8)	0 (0.0)	8 (14.3)	6 (10.5)	
	Significant difficulty	1 (1.6)	0 (0.0)	4 (6.8)	0 (0.0)	1 (1.8)	1 (1.8)	
	Unable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0.081
Regular productive cough, *N* (%)	'Yes'	16 (26.2)	4 (19.0)	23 (39.0)	3 (13.6)	8 (14.3)	45 (77.6)	<0.001
Fatigue clearing secretions, *N* (%)	0–2	47 (78.3)	13 (68.4)	51 (87.9)	18 (81.8)	39 (69.6)	48 (87.3)	
	3–6	13 (21.7)	5 (26.3)	4 (6.9)	1 (4.5)	15 (26.8)	7 (12.7)	
	7–10	0 (0.0)	1 (5.3)	3 (5.2)	3 (13.6)	2 (3.6)	0 (0.0)	0.006

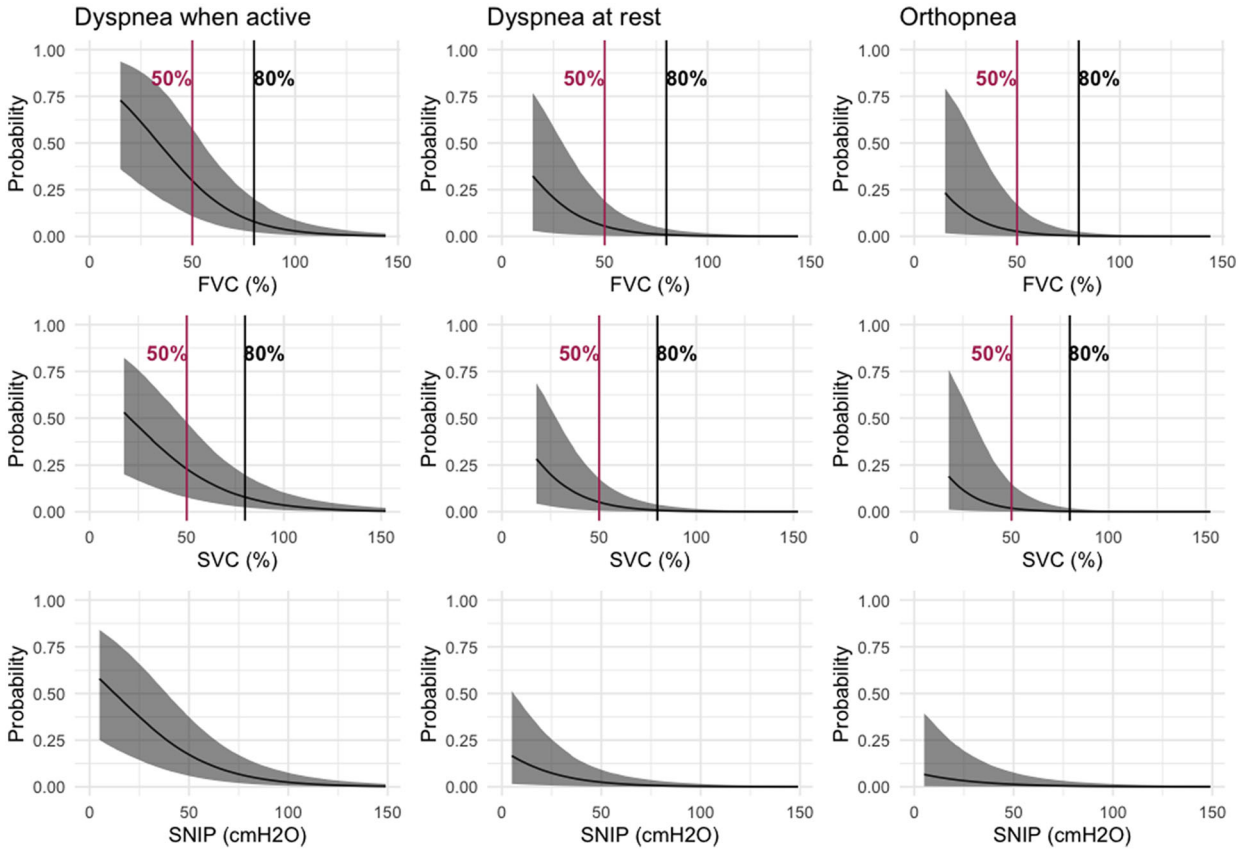

Figure 1. The probability of reporting dyspnea when active, at rest and orthopnea by respiratory function scores (FVC, SVC, and SNIP). These graphs show that as the respiratory measures decrease the probability of reporting each symptom increases. The threshold scores for each measure, commonly used to guide intervention, are shown for reference.

absolute thresholds of respiratory measures to indicate risk of morbidity or requirement for intervention. These findings demonstrate the importance of both objective respiratory testing and of symptom screening, specifically for "dyspnea on activity" as an early sign of decline in respiratory strength. The findings also support use of a combination of clinical signs and symptoms and respiratory measurement in triggering respiratory interventions such as NIV and pharmacological interventions, as symptoms can occur at higher measurement scores or may be absent even with low scores. These findings highlight the complex pathophysiology of dyspnea, which is influenced not only by respiratory muscle weakness, but also factors such as anxiety and support the recommendations of a recent guideline on management of ALS (7) and the requirement for an individualized and multifaceted approach to management (28).

Quality of life is a complex and multifaceted construct, which in ALS is not solely related to the evolving physical disability (29), but is influenced by multiple personal, social, cultural, and environmental factors (30–32). Quality of life is difficult to measure holistically, and it is acknowledged that the chosen measures for this study (McGill 0–10 Numerical Scale and EQ-5D-5L) are limited, but were practical in the context of collection of a significant volume of data in a clinical setting. These data indicate that respiratory function influences quality of life, with an increased probability of reporting lower scores on both quality of life scales with decreasing scores on respiratory function tests. Interestingly, the probability of reporting a McGill score in the very low 0–3 range remained low across all respiratory scores. However, a relationship was apparent at medium and high McGill scoring categories, with decreasing probability of reporting high McGill scores (7–10) as all four respiratory test scores decreased.

Disturbed sleep is clinically associated with respiratory dysfunction, with symptoms such as non-refreshing sleep, nightmares, nocturnal awakenings, and morning headache associated with decline in respiratory function and triggering assessment regarding NIV initiation (3,6). Surprisingly, sleep quality, assessed using item one of the Pittsburgh Sleep Quality Scale, was not associated with respiratory scores (SVC/FVC and SNIP) (Supplementary Figure 1). The probability of reporting "fairly good" sleep quality was high (approximately 75%) at all respiratory test scores. The probability of reporting "very good" sleep was lower but consistent, while the probability of "fairly bad" or "very bad" sleep was low. Sleep is impacted by multiple factors and is likely to be influenced by the use of pharmacological treatments for sleep disturbance. The single Pittsburgh

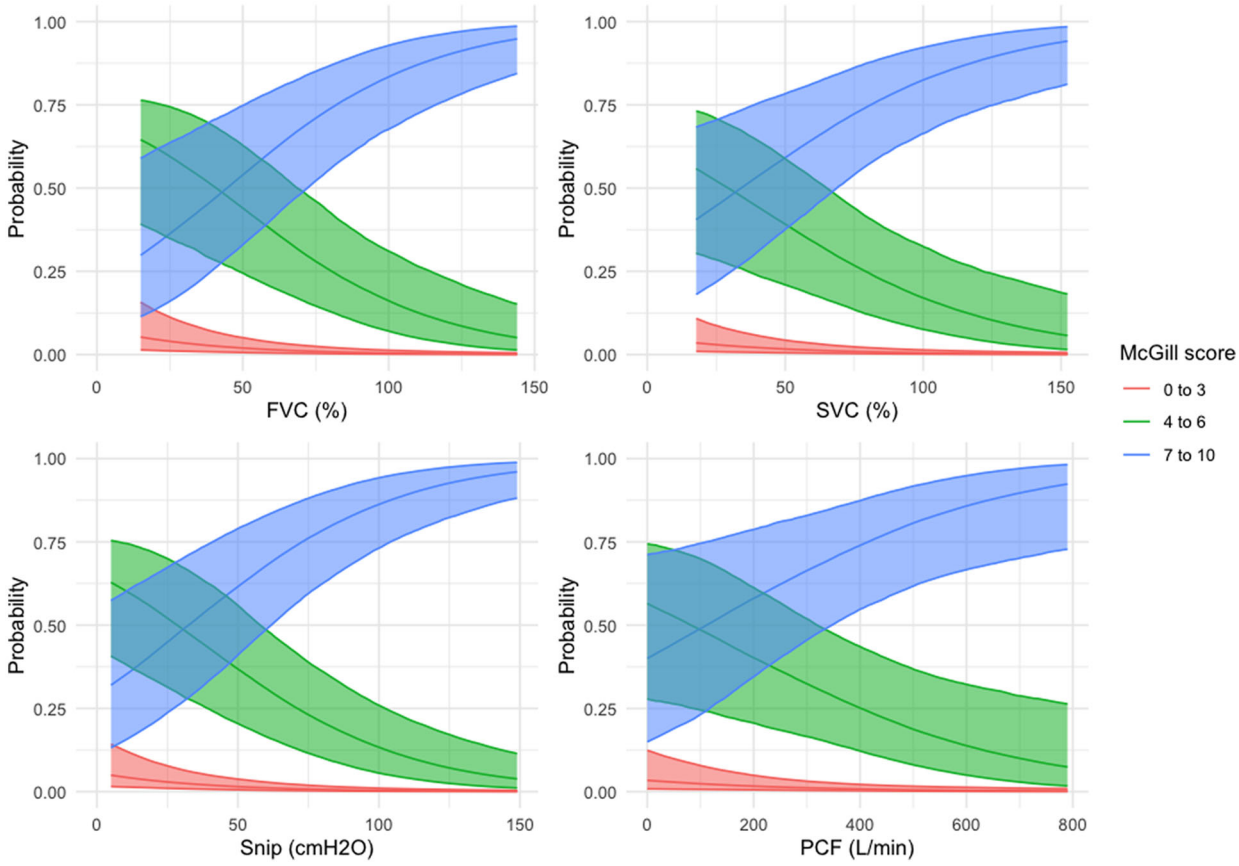

Figure 2. Probability of McGill Quality of Life (QOL) scoring category (0–3: low QOL score, 4–6: medium QOL score, 7–10 high QOL score) by respiratory function scores. The blue slope indicates that as respiratory measures decrease the probability of reporting a high QOL score decreases. This is consistent across all four respiratory measures. The probability of reporting a low QOL score remains low at all respiratory measurements.

item may be inadequate to detect sleep disturbance associated specifically with respiratory dysfunction; however, these data indicate using caution when using a simple assessment of sleep quality to assess respiratory function.

Fatigue is a common symptom in ALS (33), previously associated with worsening respiratory function (34), with some evidence that use of NIV can result in reduced fatigue (35). A simple fatigue 0–10 numerical scale was used to assess fatigue and was divided into three categories (Table 1). We found a that the probability of reporting fatigue within each category did not significantly vary with respiratory scores, although there was a slightly higher probability of reporting severe fatigue (7–10/10) with lower respiratory test scores (approximately 20% probability at 50% predicted FVC) (Supplementary Figure 2). Overall, the probability of reporting moderate fatigue (4–6/10) was highest (>50% probability), which was consistent across respiratory measurements. A relationship between fatigue and dyspnea, with associated impact upon quality of life, has previously been reported (34). There are limited treatment options for fatigue in ALS (36) and the association of fatigue with respiratory function and the utility of interventions such as NIV to ameliorate fatigue (35) requires further investigation.

Difficulty clearing secretions is a frequently reported problem for people with ALS and is associated with progressing respiratory weakness (37). Peak cough flow is used clinically to measure cough efficacy and interpretation is based on often cited threshold scores of 160 L/min for effective secretion clearance and 255–270 L/min used to indicate risk of experiencing difficulty during a respiratory tract infection (38,39). We found an increasing probability of reporting difficulty with "clearing secretions from the nose and chest" as PCF scores decreased. This was less evident for the probability of reporting "difficulty clearing saliva", probably as this is less dependent upon achieving a high expiratory flow. Of note, the probability of reporting "difficulty clearing the nose" was almost zero at above 400 L/min and the probability of reporting "difficulty with clearing the chest" was minimal above 500 L/min. The probability of reporting progressively greater levels of difficulty clearing secretions increased incrementally with lower PCF scores. The clinically meaningful burden of symptoms associated with PCF scores validates its use as a useful clinical measure. However, these data emphasize caution in

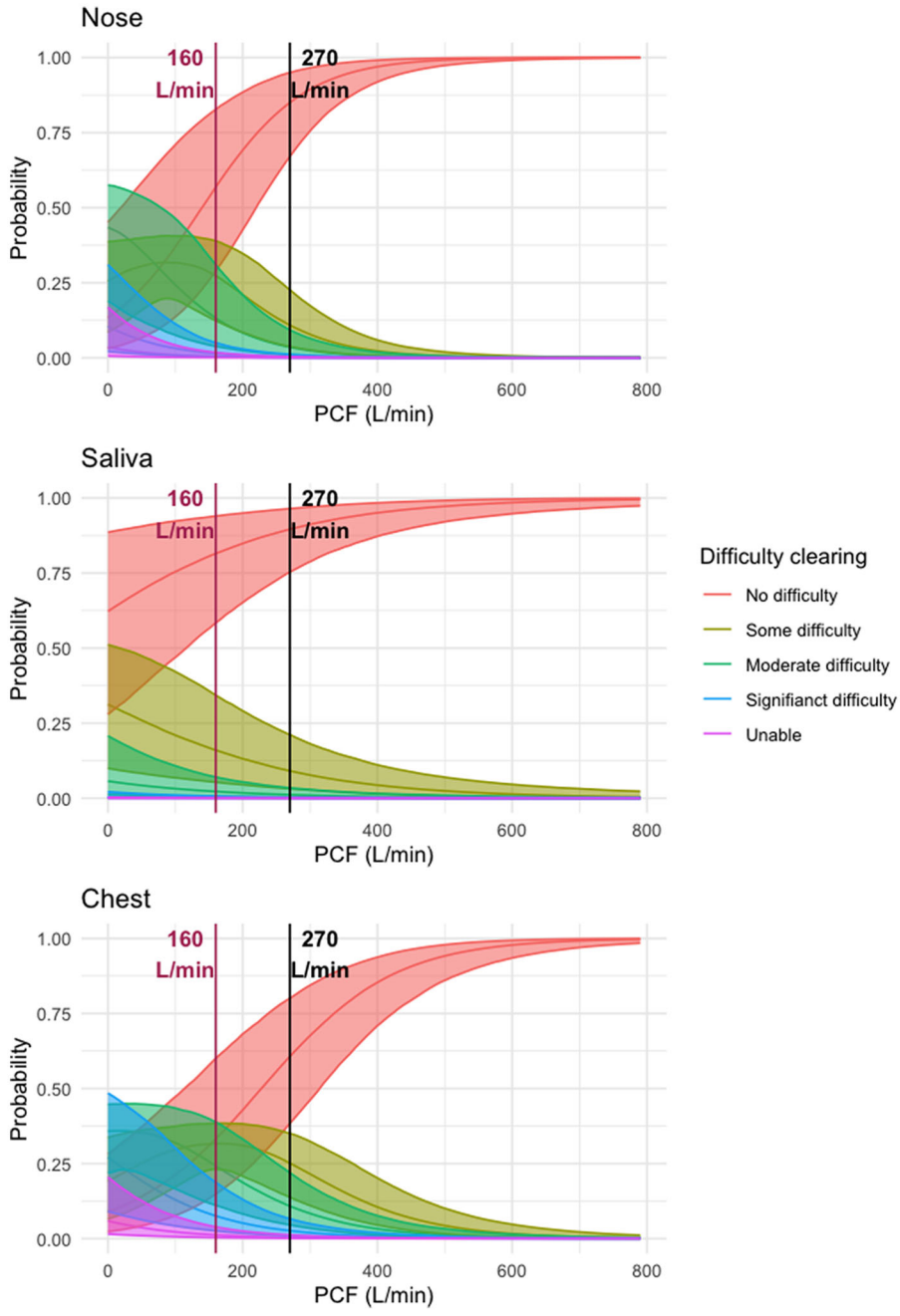

Figure 3. Probability of experiencing difficulty clearing secretions versus peak cough flow. The probability of reporting "no difficulty" with clearing the nose, chest and of clearing saliva decreased with lower PCF scores. The probability of reporting "some" or "moderate difficulty" increased at PCF scores below 400 L/min and the probability of reporting having significant difficulty or of being unable to clear secretions remained low but increased slightly at very low PCF scores.

implementation of arbitrary threshold for implementation of respiratory adjuncts such as lung volume recruitment and mechanical cough assist, as the probability of experiencing difficulty and requiring intervention gradually increases below 400 L/min.

This study had a number of limitations, particularly with regard to the curtailment of the planned follow-up period, due to the Covid-19 pandemic. This particularly affected the UK sites who had commenced data collection later. There are some differences in the presentation of participants at each site which are unexplained; however, the heterogeneity of ALS may have contributed to these. In addition, we did not systematically record the use of medications for this study, which may have impacted on reporting of symptoms such as difficulty managing saliva or sleep issues and would endeavor to include this in future studies.

Conclusion

Progressing respiratory weakness in people with ALS is associated with increasing probability of patient reported symptoms, including dyspnea, orthopnea, and difficulty clearing secretions.

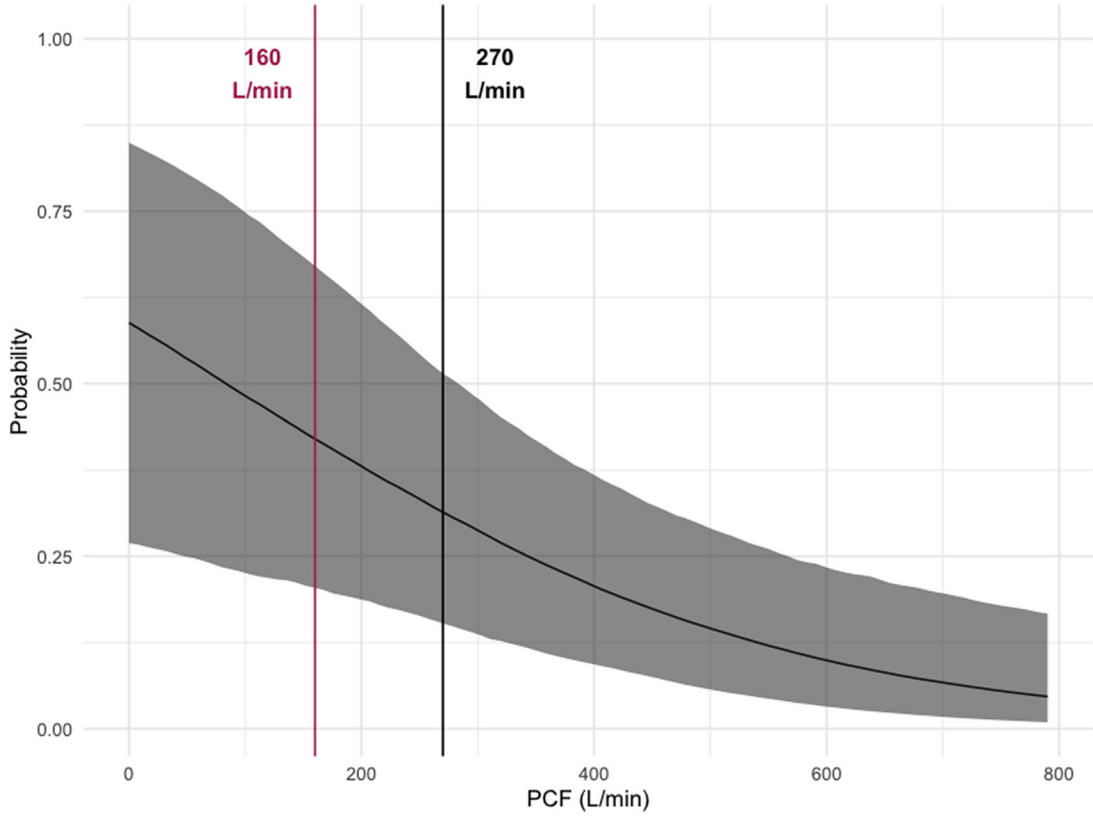

Figure 4. Probability of reporting a regular productive cough versus peak cough flow. The probability of reporting a regular productive cough was recorded as a yes/no response. The probability of recording a yes response was higher at lower PCF scores. The commonly used PCF threshold scores of 160 L/min and 270 L/min are shown for reference.

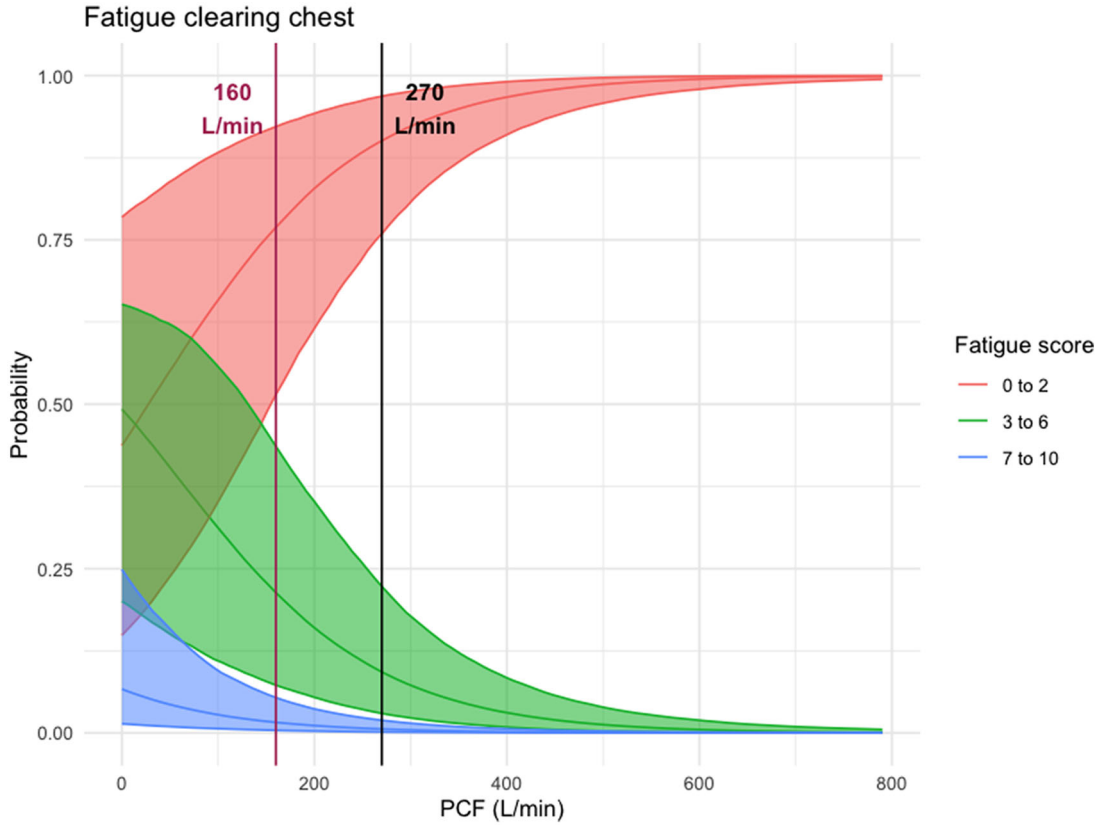

Figure 5. Probability of experiencing fatigue associated with clearing the chest versus peak cough flow. The probability of reporting moderate fatigue (3–6/10 on NRS), specifically associated with clearing the chest increased as the PCF score decreased.

Furthermore, the probability of reporting reduced quality of life and fatigue increases with lower respiratory test scores. The probability of reporting symptoms increased incrementally as respiratory weakness increased, supporting the use of both respiratory measurement scores and the presence of symptoms in making decisions about clinical interventions, rather than defined threshold scores.

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Ethics approval

Dublin: Ethics (Medical Research) Committee Beaumont Hospital, Dublin 9; Study Reference 15/62. Utrecht: Medisch Ethische Toetsings Commissie; Study Reference: MvdL/rgj/18/038367. Leuven: Commissie Medische Ethiek Universitaire, Ziehenhuizen KU Leuven; Study Reference: S60995. Turin: Comitato Etico Interaziendale, A.O.U. Citta'Della Salute e Della Scienza di Torino; Study Reference no. 0029137. Sheffield and London: IRAS 242722; Study reference STH20135.

Declaration of interest

D. Murray and D. Meldrum have served on an advisory board for Cytokinetics. Professor Chiò serves on scientific advisory boards for Mitsubishi Tanabe, Roche, Biogen, and Cytokinetics. PVD holds a senior clinical investigatorship of FWO-Vlaanderen and is supported by the E. von Behring Chair for Neuromuscular and Neurodegenerative Disorders, the ALS Liga België, and the KU Leuven funds "Een Hart voor ALS", "Laeversfonds voor ALS Onderzoek", and the "Valéry Perrier Race against ALS Fund". Several authors of this publication are members of the European Reference Network for Rare Neuromuscular Diseases (ERN-NMD). AAC reports consultancies or advisory boards for Amylyx, Apellis, Biogen, Brainstorm, Clene Therapeutics, Cytokinetics, GenieUs, GSK, Lilly, Mitsubishi Tanabe Pharma, Novartis, OrionPharma, Quralis, Sano, Sanofi, and Wave Pharmaceuticals.

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