Original Article

Dyspnea in Amyotrophic Lateral Sclerosis: Rasch-Based Development and Validation of a Patient-Reported Outcome (DALS-15)

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Abstract

Context. Dyspnea is a cardinal but often underestimated symptom in amyotrophic lateral sclerosis (ALS). The lack of a satisfying assessment tool leads to diagnostic uncertainty and bears the risk that established life-prolonging and symptom-relieving therapeutic options will not be adequately applied.

Objectives. The objective of this study was to develop and validate a German language disease-specific patient-reported outcome measure to assess dyspnea in ALS by combination of a qualitative and quantitative approach using Rasch analysis.

Methods. Based on input from clinical experts and patients, a preliminary 35-item questionnaire was developed and completed by 94 patients with ALS having dyspnea. Data were subjected to Rasch analysis and tested for required measurement issues such as appropriate response categories, the absence of differential item functioning, local independence, and unidimensionality.

Results. After iterative Rasch analyses, the final 15-item Dyspnea-ALS-Scale (DALS-15) was obtained. The scale satisfies the axioms of the Rasch model with good fit statistics, the absence of local dependency, and differential item functioning as well as acceptable unidimensionality. The DALS-15 is optimally targeted and suitable for group and individual use. It shows excellent test-retest reliability and convergent validity.

Conclusion. The DALS-15 satisfies strictest modern measurement criteria and has interval scale properties. It fills an important gap in assessment and could be most helpful to optimize symptom management in patients with ALS. J Pain Symptom Manage 2018;56:736–745.

Key Words

Amyotrophic lateral sclerosis, motor neuron disease, dyspnea, assessment, patient-reported outcome measure, Rasch analysis

Introduction

Amyotrophic lateral sclerosis (ALS) is an incurable neurodegenerative disease with rapidly progressive muscle wasting and paralysis. Most patients die within three to five years of onset because of respiratory complications and ventilatory failure.[1] Dyspnea is a cardinal symptom and occurs in about 80% of patients with ALS[2] causing additional distress.[3,4] Despite its frequency and relevance, dyspnea receives far too little attention by therapists and carers because it is a complex highly subjective sensation[5] and difficult to define by the outsider. In addition, dyspnea cannot be detected by objective clinical measures because the relationship between dyspnea in ALS and

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diagnostic markers of pulmonary function is inconsistent.[3,6–9]

Diagnostic uncertainty and the lack of controlled studies on drug treatment of dyspnea in ALS lead to therapeutic uncertainty and thus insufficient management of dyspnea at the expense of the patients' quality of life. Current guidelines of the European Federation of Neurological Societies can only make recommendations for drug treatment without evidence level.[10]

Underestimation of dyspnea also bears the risk that already established therapeutic options will not be applied, although there is strong evidence that the survival benefit by noninvasive ventilation (NIV) is much greater than the extension of life offered by the only Food and Drug Administration-approved neuroprotective therapies, riluzole and edavarone.[11–14] According to a recently published algorithm regarding initiation of NIV in patients with ALS, NIV is recommended when a patient presents with dyspnea.[15] Therefore, assessment of dyspnea, seen through the patient's eye by a patient-completed rating scale, a so-called patient-reported outcome measure (PROM), could be highly relevant to optimize patient care and symptom management in ALS.[7,16]

Although there is a vast spectrum of assessment tools for dyspnea in general and for specific diseases like malignant or pulmonary diseases (e.g., Refs.[17,18]), most instruments are not readily transferable to patients with ALS because of various reasons. Instruments referring to chronic obstructive pulmonary disease or asthma, for example, include items for obstructive lung diseases; however, ALS as a neuromuscular disease leads to restrictive ventilatory insufficiency. Other instruments are comprehensive tools to measure broader aspects of health[18,19] for which already established ALS-specific instruments exist.[6,20,21] In addition, tools with many items may strain the patients in advanced disease stages of ALS.[18,19] Another important reason is that various dyspnea instruments contain items measuring the impairment of specific activities by dyspnea. For example, the Severe Respiratory Insufficiency (SRI) Questionnaire asks for difficulties concerning housework or climbing stairs and breathing problems when eating.[19] However, such items are confounding with ALS-specific symptoms. In ALS, many activities of daily living are impaired or impossible of being performed independent of the presence of dyspnea, which leads to false-positive test results or missing responses in questionnaires. The merit of an ALS-specific patient-reported assessment tool would be to be adapted to the physical limitations inherent to the motor function loss that characterizes ALS.

ALS-specific assessment instruments are the respiratory subscale of the ALS Functional Rating Scale–Revised[6] and the Motor Neurone Disease Dyspnea Rating Scale (MDRS).[3] A re-evaluation of the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) with Rasch analysis revealed, among other drawbacks, problems with the respiratory subscale.[22] A further study on the respiratory subscale of the ALSFRS-R showed that in about 10% of patients the subscore increased during the course of the disease, despite a confirmed progressive decline in respiratory function, possibly because of decreased mobility and/or implementation or extension of NIV use.[23] In the 16 items comprising MDRS,[3] patients identify five activities that may make them feel breathless. As during the course of the disease not only the extent of dyspnea but also the mobility of the patient and thus the choice of reference activities changes, only limited interpersonal comparisons of dyspnea are possible. In conclusion, there is currently no satisfying disease-specific assessment instrument for dyspnea in patients with ALS.

The aim of our study was to develop and validate a reliable disease-specific PROM to assess dyspnea in ALS, which overcomes the methodological limitations of other instruments. This assessment instrument is intended to meet rigorous psychometric standards using Rasch analysis. The Rasch model is a mathematical measurement model that assumes that the probability of a person to endorse an item is a logistic function of the relative distance between item location and person location on a linear scale that accounts for the latent trait, here dyspnea.[24] Item and person locations are logarithmically transformed into the same unit termed as logit, thereby converting ordinal into interval data. This justifies that individual item scores can be summed to yield a scale score. The new instrument could be used to identify patients with ALS suffering from dyspnea and aid in the early assessment and monitoring of dyspnea for symptom management as an outcome measure.

Methods

The assessment instrument was developed using a combined qualitative and quantitative approach.

Qualitative Methods: Generation of Preliminary Questionnaire

The generation of items was based on the construct of dyspnea in alignment with the definition of the American Thoracic Society.[16,25] Accordingly, dyspnea is a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. Instruments pertaining to dyspnea should be classified as addressing domains of sensory-perceptual experience, affective distress, and symptom impact or burden.[16,25]

The initial item pool of 48 items was developed after an extensive review of the literature including a qualitative study regarding dyspnea in motor neuron disease,[26] available dyspnea assessment instruments, and after explorative interviews with 10 patients with ALS having dyspnea as well as discussion with an expert panel comprising three neurologists and two pulmonologists experienced in ALS. A significant challenge was to create items independent of motor system functioning. The response format was a five-point Likert scale (0 = never, 1 = rarely, 2 = sometimes, 3 = often, and 4 = always), and the items referred to the patient's condition during the past two weeks. The rationale for this time reference period is that dyspnea progression in ALS is gradual, and two weeks might therefore be appropriate for a slow changing symptom like dyspnea. Also, it has been found to be reliable in other instruments such as the Chronic Respiratory Disease questionnaire[27] and its adaptation for patients with ALS, the MDRS.[3] Moreover, this time frame is well established in other ALS-specific instruments,[20,21] and consistency in the reference periods of the different ALS-specific assessment instruments is valuable to avoid confusion of respondents. Items were administered to 10 patients by performing cognitive interviews using the think-aloud technique followed by a debriefing of the questionnaire. After adapting some items, the questionnaire was pretested in 15 patients to ensure comprehensibility and acceptance. This process led to a preliminary questionnaire of 35 items.

Patients

The study was approved by the institutional ethics committees of Hannover Medical School and the University of Magdeburg, and all patients provided written informed consent before enrollment. Between December 2012 and January 2014, 110 patients with ALS diagnosed according to the El Escorial criteria[28] were asked at our outpatient clinic to participate in the study. In the absence of a gold standard to assess dyspnea in ALS, the following were criteria for the inclusion to the study: dyspnea on exertion, dyspnea at rest, or orthopnea without evidence of pulmonary or cardiac causes of dyspnea. Exclusion criteria were insufficient comprehension of the German language and severe cognitive impairment. Patients were staged according to the onset site of the first symptom[29] and clinical milestones of the disease course.[30] Physical functioning was assessed using the patient-rated ALS Functional Rating Scale−Extension (ALSFRS-EX).[9,31]

Interviews

Semistructured exploratory interviews were conducted on a sample of 10 patients with ALS suffering from dyspnea. We selected a heterogeneous sample to capture the views of patients at different phases of ALS and with varying times since diagnosis. All interviews were conducted by a single investigator (S. V.) and took place in a private room within the clinic, either on a one-to-one basis or in the presence of an accompanying relative. During the interview, patients were asked to talk about breathing problems they experienced. A topic guide was loosely followed according to the patient's responses. During each interview, detailed notes were taken, and after each interview, the patients' answers were analyzed for relevant input to identify potential items for the questionnaire. Throughout the analysis, the research group met regularly to discuss the analysis.

Quantitative Methods: Scale Construction Applying Rasch Analysis

Rasch analysis was performed using the RUMM 2030 software (RUMM Laboratory Pty Ltd, Perth, Western Australia)[32] and the recommendations by Tennant and Conaghan.[24] Although the sample size ($n = 94$) is moderately large for a rare disease like ALS, it is relatively small for Rasch analysis. Nevertheless, useful exploratory work using Rasch analysis can be performed.[33] To select the appropriate polytomous version of the Rasch model, likelihood ratio statistic was conducted. The overall fit of the scale to the Rasch model was evaluated after each Rasch analysis by the item-trait interaction Chi-squared statistic (Bonferroni adjusted). A significant result requires further Rasch analyses and consecutive modifications of the scale to improve overall fit. Residual fit statistics are expected to be within a given range of ±2.5 for individual items and persons. For summary statistics, an adequate fit is achieved with a mean fit residual value close to zero and an SD approaching 1.0 (usually <1.4).[34] Misfitting items were analyzed and removed stepwise. Threshold ordering was checked by inspection of the threshold map and the category probability curves of the items. Disordered thresholds may necessitate collapsing of categories to ensure that they progress in a logical order.

Local independence of items is examined through the residual correlation matrix. Residual correlations greater than 0.3 above the average indicate response dependency so that one of a pair of locally dependent items should be removed.[35]

The assumption of unidimensionality was tested by a principal component analysis of the residuals[36] contrasting the person estimates derived from the most strongly positive and negative loading items on the first principal component. If the difference in these estimates does not exceed 5% of cases (or the lower CI for the difference in proportions is less than 5%), the scale is not deemed to be compromised by multidimensionality.[36]

A further source of misfit within the scale could be due to the presence of differential item functioning (DIF) that occurs when two groups of patients with equal levels of dyspnea answer differently to an item. Response should be irrespective of age (two groups based on the median age of 62.5 years), gender, and disease onset (bulbar/spinal).

The targeting of the final scale is evaluated by a targeting plot. For a well-targeted assessment instrument, the mean location for persons would be around the value of zero, which is set for the mean location of the items.[24]

As reliability indices, the Person Separation Index (PSI) and Cronbach's alpha, which are interpreted similarly, were used. In the latter, only persons with complete data sets are included in RUMM software. The minimum accepted value of PSI is 0.7 for group use and 0.85 for individual use.

Once Rasch analysis was finalized, transformation of the raw scores into an interval-scaled score was performed within the same range as the raw score of the scale. This transformation was undertaken to change raw scores consisting of ordinal data to Rasch-transformed interval scores for use in parametric statistical analyses and calculation of change scores.

Assessment of Response Categories and Test-Retest Reliability

Because the initial five response categories of the items were collapsed into three (Fig. 1), the new response format was empirically verified by new data. 34 patients completed the two scales in a randomized order: the final scale with the Rasch model conforming three-point Likert scale as well as the respective items with the original five-point Likert scale. The five categories were again collapsed for analyzing agreement between measurements using the intraclass correlation coefficient (ICC).[37] To estimate test-retest reliability, the 15-item Dyspnea-ALS-Scale (DALS-15) was readministered by phone after one week and evaluated using ICC and Lin's concordance coefficient.[38] The size of the retest sample was sufficient as suggested by Walter et al.[39] In addition, the SEM and minimally detectable change were calculated.[40]

Convergent Validity

Convergent validity investigates how closely a new scale is related to other measures of the same construct. In the absence of a gold standard, patients were asked to complete the following PROMs:

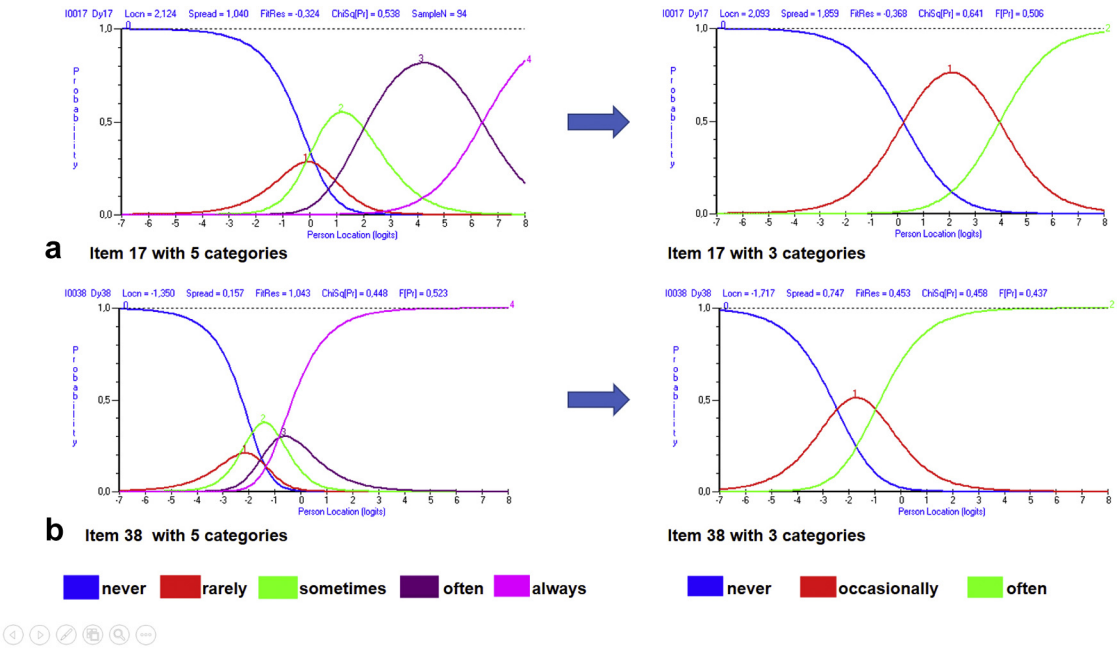

Fig. 1. Category characteristic curves plotting person location in logits across the range of dyspnea (x-axis) against probability of affirming a certain response option (y-axis) for a) Item 17 and b) Item 38. *Left side*: Category characteristic curves with five response categories for Item 17 and Item 38 illustrating disordered thresholds. Category 1 *rarely* (Items 17 and 38) and Category 3 *often* (Item 38) were never the most probable response. Moreover, in many items (e.g., Item 17), Category 4 *always* represented a far too high level of dyspnea, depicted by a very high threshold from Category 3 to 4 (Item 17: 6.4 logits). This was associated with a low frequency in the choice of this answer (e.g., Item 17: 0%, not shown). *Right side*: Category characteristic curves with three response categories for Item 17 and Item 38 showing ordered thresholds.

respiratory subscale of the ALSFRS-EX, Borg Dyspnea Scale in upright and supine positions, and SRI Questionnaire. The Borg scale is a predictor of inspiratory muscle weakness in patients with ALS and quantifies the subjective sensation of dyspnea.[8] The SRI is a specific measure of health-related quality of life, which was validated in patients receiving home mechanical ventilation in different diseases, among others patients with neuromuscular disease.[19]

Statistical Analysis

For statistical analysis, the SPSS software for Windows, Version 23.0 (IBM SPSS Statistics, Armonk, NY) was used. The significance level was set to $\alpha \leq 0.05$, unless stated otherwise, and corrected for multiple comparisons using Bonferroni adjustments, if necessary.

Results

Patient Characteristics

In the study, 94 patients with ALS and dyspnea participated; 16 patients were excluded because of exclusion criteria or because they refused to take part. Patient-referred data are reported in Table 1.

Interviews

The patient interviews lasted 30−50 minutes. The statements of the patients' interviews were classified in a deductive approach with regard to the domains according to the American Thoracic Society.[16,25] Patients with mild to moderate dyspnea described dyspnea mostly in terms of the sensory-perceptual experience and symptom impact and less so in emotional terms. They noticed dyspnea for the first time during physical exertion and when lying flat. This was confirmed retrospectively by patients who already suffered from advanced respiratory impairment. Furthermore, they experienced shortness of breath and felt restricted in their daily routine activities because of dyspnea. Patients with severe dyspnea spoke about shortness of breath while sitting still and about waking up at night because of breathlessness. In contrast to patients with minor symptom burden, they additionally addressed the affective sequelae with descriptions of dyspnea like *highly threatening* or *breathlessness is a real problem for me*. They talked about getting depressed when they have to stop activities because of breathlessness and about feeling isolated because of dyspnea and its consequences. One patient spoke about fear of suffocation and impressively demonstrated that dyspnea overshadowed other ALS-specific symptoms making him realize that breathing is essential for living and that death is approaching.

Table 1
Demographic and Patient-Referred Data in 94 Patients

Patient age; mean, SD (range)	61.8 ± 8.7 (34−81)
Gender, *n* (%)	
Male	57 (60.6)
Female	37 (39.4)
ALSFRS-EX;[a] mean, SD (range)	
Bulbar subscore	11.2 ± 3.9 (2−16)
Fine motor subscore	7.8 ± 4.6 (0−16)
Gross motor subscore	7.8 ± 4.7 (0−16)
Respiratory subscore	8.5 ± 2.6 (1−11)
Sum score	35.2 ± 10.6 (9−55)
Sum score without respiratory subscore	26.7 ± 9.5 (3−47)
Onset site, *n* (%)	
Bulbar	23 (24.5)
Spinal	71 (75.6)
Upper limb	33 (35.1)
Lower limb	34 (36.2)
Axial	1 (1.1)
Respiratory	3 (3.2)
Disease duration from symptom onset in months; mean, SD (range)	48.9 ± 50.4 (9−276)
Disease duration from diagnosis in months; mean, SD (range)	32.7 ± 42.0 (6−240)
Disease progression rate;[b] mean, SD (range)	0.80 ± 0.52 (0.04−2.44)
Progression rate of respiratory impairment;[c] mean, SD (range)	0.12 ± 0.11 (0−0.50)
Clinical staging, *n* (%)	
1: Symptom onset (involvement of first region)	0
2A: Diagnosis	0
2B: Involvement of second region	1 (1.1)
3: Involvement of third region	49 (52.1)
4A: Need for gastrostomy	11 (11.7)
4B: Need for NIV	33 (35.1)

ALSFRS-EX = Amyotrophic Lateral Sclerosis Functional Rating Scale−Extension; NIV = noninvasive ventilation.
[a]Score ranges from 0 to 16 for the bulbar, fine, and gross motor scales and from 0 to 12 for the respiratory subscale. Lower scores represent worse condition.
[b]Disease progression rate was calculated as (60-sum of ALSFRS-EX)/disease duration from symptom onset to investigation date in months.[9]
[c]Progression rate of respiratory impairment was calculated as (12-sum of respiratory subscore of ALSFRS-EX)/disease duration from symptom onset to investigation date in months.

Scale Construction Applying Rasch Analysis

According to the likelihood-ratio test, the unrestricted (partial credit) model was applied ($P < 0.001$).

Initial Rasch analysis of the preliminary scale comprising 35 items showed poor fit to the Rasch model with a significant item-trait interaction ($\chi^2 = 154.22$; degrees of freedom = 70; $P < 0.001$) and relevant misfit of the residual fit statistics (items: mean [M] = 0.36, SD = 1.63; persons: M = 0.04, SD = 1.54).

Before any additional assessment of fit to the Rasch model was made, the ordering of thresholds was inspected in the threshold map revealing disordered thresholds in 19 items. After examination of the category characteristic curves, exemplarily depicted in Fig. 1 (left side), response options were reduced from five to three by collapsing the adjacent categories *rarely* and *sometimes* into *occasionally* as well as *often* and

always into *often* (Fig. 1, right side). Rescoring worked properly in all items with disordered thresholds and was adopted for the whole scale to maintain a consistent response format.

Subsequently, nine items displaying misfit were eliminated stepwise. All persons responded in accordance to the Rasch model.

Local dependence was found among eight pairs of items, indicating that the answer to one item determined the answer to another, for instance for the items *I have fear of suffocation* and *Because of the shortness of breath I get scared*. Eight items were removed to avoid redundancy and improve overall fit.

Regarding the assumption of unidimensionality, a breach was detected, so that three further items were deleted (*I feel tense*, *My breathing costs me a lot of effort*, and *Shortness of breath dominates my everyday life*).

There was no significant DIF for age, gender, and disease onset. The iterative reduction process of Rasch analyses generated the final DALS-15, which satisfies the requirements of the Rasch model indicated by an adequate overall fit with a nonsignificant (Bonferroni adjusted according to the number of items: $P = 0.05/15 = 0.003$) item-trait interaction ($\chi^2 = 43.92$; degrees of freedom = 30; $P = 0.048$) and fit residuals near a perfect fit (items: M = 0.02, SD = 1.01; persons: M = −0.19, SD = 1.16). Final Rasch analysis showed ordered response categories, the absence of local dependency, and DIF as well as acceptable unidimensionality (t-test 7.45%; 95% CI 2.86−11.14). As for each item, a score of 0 (never), 1 (occasionally), or 2 (often) can be reached, the overall score ranges from 0 to a maximum of 30. The DALS-15 should be interpreted on the basis of this sum score: the higher the score the more severe is the patient's dyspnea. A linear transformation of the DALS-15 raw scores into interval-scaled scores is provided in Supplementary Table S1. Item parameters of the German version of the DALS-15 are listed in Table 2; the English translation of the items is preliminary for the reader and has not been formally assessed.

PSI was high with 0.85, and Cronbach's alpha with a value of 0.88 was also good. The comparison of the mean location score obtained for persons with that of the value of zero set for the items (persons: M = −0.36, SD = 1.31; items: M = 0, SD = 1.41) suggests that the DALS-15 is a well-targeted measurement instrument. This is graphically shown in the targeting plot (Fig. 2).

Assessment of Response Categories

A high degree of reliability was found between the two newly completed scales with the initial five, and Rasch model conforming three response category formats (ICC at item level: 0.81−0.95). This justifies further investigations on convergent validity with the data of the original group of 94 patients.

Test-Retest Reliability

For overall test-retest reliability, the ICC was 0.982 (95% CI 0.964−0.991), and Lin's concordance coefficient was ρ_c: 0.981 (95% CI 0.963−0.991), suggesting very good reproducibility of the instrument. On a metric range of 0−30, SEM was 1.16 (3.8%) and minimally detectable change 3.21 (10.7%). Patients completed the scale on average in less than five minutes.

Table 2

Items of the DALS-15 Arranged in Descending Order According to Item Severity (Level of Dyspnea in Logits)

Item	Item Description	Location	Fit Residual	χ^2	*P*
04	I have highly threatening dyspnea	2.45	−1.09	2.41	0.299
07	I am short of breath, while sitting still	2.33	−0.12	3.41	0.182
17	I wake up because of breathlessness at night	2.09	−0.37	0.89	0.641
14	I have fear of suffocation	0.96	0.50	1.21	0.546
25	Because of my breathing difficulty and its consequences, I feel isolated from others	0.80	−0.43	0.76	0.684
28	My breathing is exhausting me	−0.01	1.07	0.29	0.866
13	I feel restless	−0.29	0.81	2.12	0.347
34	It depresses me when I have to stop activities because of my breathlessness	−0.46	−0.70	0.37	0.832
29	Breathlessness is a real problem for me	−0.72	−1.58	9.45	0.009
18	My breathing problems restrict my routine activities in addition	−0.76	−1.68	4.94	0.085
05	I feel short of breath	−0.81	1.61	6.05	0.049
47	Because of shortness of breath, I avoid lying flat	−0.84	1.19	6.55	0.039
02	I suffer from mild breathlessness	−1.43	−0.26	1.08	0.584
10	I have difficulties breathing during physical exertion	−1.50	0.72	1.36	0.506
38	I have difficulties coughing up	−1.82	0.66	3.05	0.218

DALS-15 = 15-Item Dyspnea-Amyotrophic Lateral Sclerosis-Scale.
The item numbers refer to the 35 items comprising preliminary questionnaire.
Bonferroni-adjusted *P*-value according to the number of items: $P = 0.05/15 = 0.003$.
The questionnaire is available in its original German version; the English translation of the items, however, has not been formally assessed.

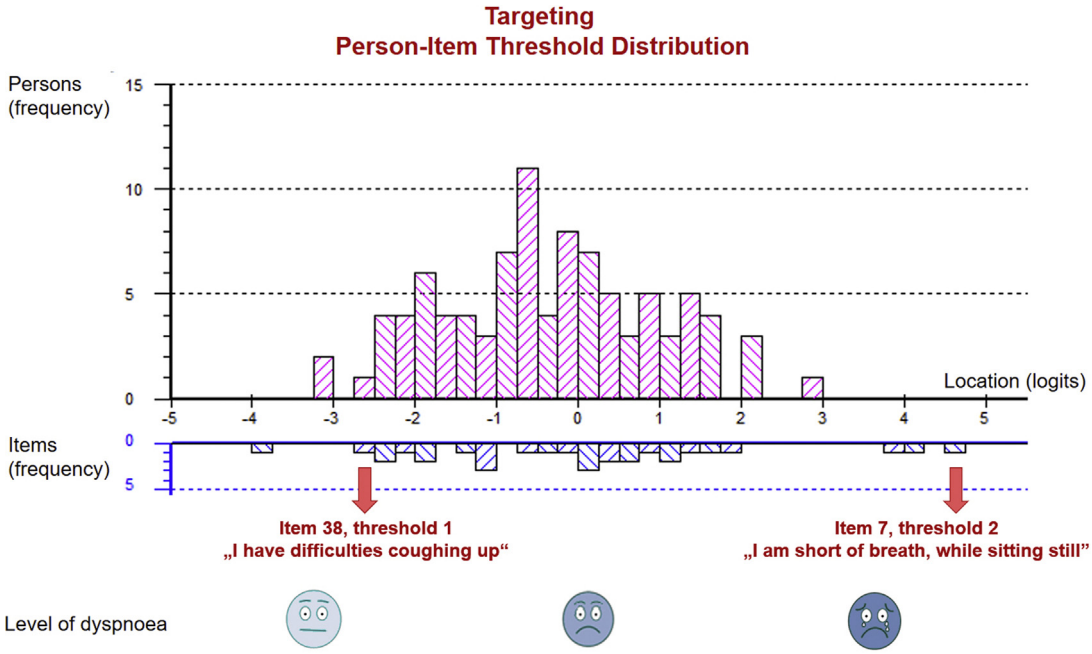

Fig. 2. The targeting plot depicts the person-item threshold distribution and illustrates the ability of the 15-item Dyspnea-ALS-Scale to capture the range of the latent trait, dyspnea, comparing the distribution of person-location estimates (upper part of the graph) and item thresholds (lower part of the graph) on a shared horizontal logit scale. Toward the right side of the logit scale, the level of dyspnea increases—visualized by emoticons with increasing blue discoloration of the skin. The item thresholds are well distributed, and there is no floor or ceiling effect. This is illustrated exemplarily by Items 7 and 38. The first threshold (−2.64 logits) of Item 38 (*I have difficulties coughing up*) preferably captures mild dyspnea, whereas thresholds like the second one (4.62 logits) of Item 7 (*I am short of breath, while sitting still*) measures very severe dyspnea.

Convergent Validity

Results from PROMs used to assess convergent validity are presented in Table 3. The DALS-15 correlated highly with the respiratory subscale of the ALSFRS-EX, the Borg scales, and the SRI subscale *respiratory complaints*.

Further Validation

Based on the newly derived DALS-15, a subgroup analysis was performed in patients with NIV and without NIV to see whether the scale is able to demonstrate significant differences between these patient groups as might be empirically expected. Indeed, patients with NIV suffered from significantly more dyspnea than patients without NIV (mean ± SD of the DALS-15 sum score in patients with NIV 16.75 ± 5.43 and in patients without NIV 12.32 ± 5.46; $P = 0.001$). This may also add to the validity of the scale.

Discussion

This study provides a Rasch-based disease-specific assessment instrument for dyspnea in patients with ALS. The DALS-15 is a reliable and validated PROM that could be particularly helpful for more efficient symptom management in ALS because dyspnea is often not directly apparent, and the relationship to diagnostic markers of pulmonary function is inconsistent in ALS.

The DALS-15 is short, easy, and quick to complete. This is an important aspect in advanced disease stages, in which dyspnea increasingly occurs.

For initial item generation, patient input (explorative and cognitive interviewing) was used to ensure that the patients' perspective was adequately reflected.[41]

The items of the DALS-15 form a unidimensional measure of dyspnea severity. On first sight, this is an apparent paradox with the modern vision of dyspnea according to the American Thoracic Society, underlying the construction of this scale. Accordingly, dyspnea (a sensory-perceptual experience) is not only a physical (symptom impact/burden) but also an emotional burden (affective distress) for the patient.[16] Nevertheless, from a measurement perspective, the unidimensional structure of dyspnea severity is justified because with this approach only items that reflect overall severity of dyspnea—although from different aspects of dyspnea—were selected. Our results are in line with a previous Rasch-based validational study regarding dyspnea in patients with pulmonary and cardiac diseases, which showed that a

Table 3
Pearson's Correlation Coefficients Between DALS-15 and Respiratory Subscale of the ALSFRS-EX, SRI Subscales, and Borg Scale in Patients With ALS and Dyspnea

Assessment Instruments to Evaluate Convergent Validity	DALS-15 Sum Score	
	r	*P*
SRI		
Respiratory complaints	−0.75	<**0.001**
Physical functioning	−0.41	<**0.001**
Attendant symptoms and sleep	−0.29	**0.005**
Social relationships	−0.25	0.015
Anxiety	−0.58	<**0.001**
Psychological well-being	−0.45	<**0.001**
Social functioning	−0.45	<**0.001**
Borg Dyspnea Scale		
Upright position	0.52	<**0.001**
Supine position	0.50	<**0.001**
ALSFRS-EX		
Respiratory subscore	−0.56	<**0.001**

DALS-15 = 15-Item Dyspnea-Amyotrophic Lateral Sclerosis-Scale; SRI = Severe Respiratory Insufficiency; ALSFRS-EX = Amyotrophic Lateral Sclerosis Functional Rating Scale−Extension.
Boldfaced: correlation is significant after Bonferroni correction ($P = 0.05/10 = 0.005$).
Negative correlations mean that higher scores of the DALS-15 (increased dyspnea) correlate with lower scores (increased impairment) of the respective assessment instruments.

range of different descriptors from physical to affective components of dyspnea could be combined to form a single overall unidimensional scale.[5] Similar to Yorke et al.,[5] we observed that items reflecting the affective component of dyspnea (e.g., Items 14, 25, and 34) tended to be associated with more severe breathlessness. From a therapeutic point of view, it can be assumed that effective approaches to help patients with ALS live with their dyspnea will target the affective dimension of the symptom.

One of the strengths of the DALS-15 is its optimal targeting. Item thresholds are excellently distributed across the entire spectrum of dyspnea and not clustered, so dyspnea can be estimated with good accuracy over a wide range without a ceiling or floor effect. The DALS-15 sum score can be easily computed by summing up the individual item scores (from 0 to 2) to obtain an overall score ranging from 0 to a maximum of 30 points. Conforming to the Rasch model, the scale satisfies strictest modern measurement criteria and allows to quantify dyspnea by a linear transformation of the raw ordinal score to an interval-scaled score. We recommend to use the transformed interval-scaled score when change scores and other parametric procedures are required.

PSI was high enough to allow individual use and reliably distinguish between up to three different levels of dyspnea by the overall score (e.g., mild, moderate, and severe).[24] Future studies should determine respective cutoff scores of clinical relevance, for example, with regard to treatment need.

There was no diagnostic bias regarding age and gender. Also, the onset of the disease, another relevant criterion for DIF in patients with ALS, did not influence the probabilities of endorsing the items of the scale. During the development phase of the items, special attention was therefore paid to their wording. For instance, Item 25 "Because of my breathing difficulty and its consequences I feel isolated from others" refers to dyspnea-related isolation because of, for example, impaired speech by shortness of breath or frequently used NIV, whereas isolation because of bulbar symptoms (dysarthria, sense of shame because of pseudohypersalivation) is not the subject of the item.

Construct validity of the scale is supported by the consistency of the hierarchical order of the items within the scale with the anticipated dyspnea severity of the items. Thus, items that are most likely to be affirmed in the presence of dyspnea are located at the bottom of the logit scale, whereas items representing severe dyspnea are at the top. From measurement perspective, construct validity can be considered as given because of conformity of the measure to the Rasch model. The scale possesses robust psychometric properties with excellent test-retest reliability and convergent validity.

One limitation of the study is the application of the SRI for convergent validity because the questionnaire measures health-related quality of life in patients with home mechanical ventilation, not only dyspnea. In the present study, only one-third of the patients received NIV. However, the development and validation of the SRI in German language included, among others, patients with ALS.

As another potential limitation of the study, the sample size is moderately large for a rare disease like ALS but relatively small for Rasch analysis. However, a sample size of about 100 persons will estimate item difficulty with an alpha of 0.05 within ±0.5 logits.[33] However, beside optimal targeting between the sample and items, the sample should be heterogeneous reflecting the typical patient characteristics of the disease. The underlying sample originates from two ALS outpatient clinics with a large catchment area covering Northern, Central, and Eastern Germany, and patients' clinical characteristics are similar to previous studies with regard to onset site and progression rate,[9,42,43] ranging from patients with mild to very severe physical impairment as well as dyspnea. Thus, precision of the estimates of the Rasch model can be assumed as appropriate. Nevertheless, further validation on a larger sample is needed because response categories were corrected post hoc—a common procedure in Rasch analysis. Hence, this study should be regarded as a pilot study. Another limitation is the critical value used to indicate local response dependency. According to a recent

methodological research article, a stricter criterion has been proposed (residual correlations 0.2 above the average).[44]

Future work will focus on longitudinal assessment of dyspnea in ALS using the DALS-15, including determination of the minimal clinically important difference and evaluation of longitudinal DIF. This is an interaction with time, which could occur in case of a change in perception or development of tolerance to symptoms. In addition, translations of the measure into other languages with transcultural adaptation are necessary to enable the use of the DALS-15 beyond German-speaking countries.

The results of the present study suggest that the DALS-15 is able to fill an important gap in the assessment of patients with ALS. As long as ALS cannot be cured, evaluation and treatment of symptoms, in particular respiratory complaints, is of fundamental importance, as symptomatic treatment with NIV has so far the greatest impact on survival and improves quality of life.[12,13,45]

The administration of the DALS-15 could also be of great interest as an outcome measure to capture the patients' perspective in clinical trials of neuroprotective therapies in general and in particular for pharmacological management of dyspnea as well as in intervention studies evaluating symptom management in the field of ventilation and airway secretion. The DALS-15 is free for use and is shown in the supplementary material provided online.

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Supplementary Material

Dyspnoe bei Amyotropher Lateralsklerose

DALS-15

Die Amyotrophe Lateralsklerose (ALS) kann zu einer Schwäche der Atemmuskulatur führen. Dieser Fragebogen dient dazu, mögliche Atembeschwerden zu erkennen und deren Ausmaß einzuschätzen.

Die folgenden Aussagen beziehen sich auf den Zeitraum der letzten 2 Wochen. Bitte beantworten Sie jede Frage mit einem Kreuz.

Wie oft trafen die folgenden Aussagen in den letzten 2 Wochen auf Sie zu?

		nie	gelegentlich	oft
01	**Ich habe leichte Luftnot**	❍	❍	❍
02	**Ich habe bedrohliche Luftnot**	❍	❍	❍
03	**Ich bin kurzatmig**	❍	❍	❍
04	**Ich habe Luftnot, wenn ich ruhig sitze**	❍	❍	❍
05	**Ich habe Luftnot bei körperlicher Belastung**	❍	❍	❍
06	**Ich bin unruhig**	❍	❍	❍
07	**Ich habe Erstickungsängste**	❍	❍	❍
08	**Ich wache nachts mit Luftnot auf**	❍	❍	❍
09	**Meine Atembeschwerden schränken mich bei meinen Alltagsanforderungen zusätzlich ein**	❍	❍	❍
10	**Durch die Luftnot und ihre Folgen fühle ich mich von meinen Mitmenschen isoliert**	❍	❍	❍
11	**Meine Atmung erschöpft mich**	❍	❍	❍
12	**Die Luftnot ist für mich ein Problem**	❍	❍	❍
13	**Es deprimiert mich, Aktivitäten aufgrund meiner Luftnot abbrechen zu müssen**	❍	❍	❍
14	**Das Abhusten fällt mir schwer**	❍	❍	❍
15	**Aufgrund meiner Luftnot vermeide ich es flach zu liegen**	❍	❍	❍

Table S1

Transformation Table to Convert Raw Ordinal Scores of the DALS-15 to Interval Scores

DALS-15 Raw Score	DALS-15 Interval Score
0	0.00
1	2.53
2	4.34
3	5.62
4	6.64
5	7.52
6	8.29
7	9.00
8	9.65
9	10.27
10	10.87
11	11.44
12	12.00
13	12.55
14	13.09
15	13.63
16	14.18
17	14.72
18	15.28
19	15.86
20	16.46
21	17.09
22	17.76
23	18.50
24	19.33
25	20.31
26	21.50
27	23.03
28	24.92
29	27.22
30	30.00

DALS-15 = 15-Item Dyspnea-Amyotrophic Lateral Sclerosis-Scale.
This transformation table can only be used for respondents with no missing data.