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ORIGINAL ARTICLE

Predictive parameters of early respiratory decline in amyotrophic lateral sclerosis

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Abstract

Background and purpose: Respiratory insufficiency is a common symptom during the course of amyotrophic lateral sclerosis (ALS). The diagnostic workup may be challenging and includes a wide array of diagnostic measures. In this study, the aim was to analyze the relationship between hypercapnia-associated symptoms, blood gas parameters and pulmonary function tests.

Methods: In total, 109 patients (56 women, 53 men, 62.4 ± 11.9 years) with definite, possible or probable ALS according to El Escorial criteria were included. All patients received either arterial blood gas analysis, nocturnal capnometry or both. Pulmonary function was assessed by spirometry and peak cough flow. Clinical symptoms potentially indicating hypercapnia were assessed using 17 dichotomous (yes/no) items.

Results: Of 109 ALS patients, 40 had hypercapnia. The highest accuracy and specificity for predicting hypercapnia was observed for dyspnea at rest (Youden's index 17%, 95% confidence interval [CI] 2%–34%; sensitivity 23%, 95% CI 9%–38%; specificity 95%, 95% CI 88%–100%). Daytime fatigue yielded the highest sensitivity of 58% (95% CI 40%–76%). Logistic regression for all assessed symptoms combined yielded an area under the receiver operating charteristic curve of 0.8 (95% CI 0.7–0.9). Compared to the clinical symptoms, forced vital capacity and peak cough flow showed higher sensitivity (70% and 87%, respectively) but lacked specificity (33% and 20%).

Conclusion: Evaluation of the presence of hypercapnic symptoms can be utilized to predict incipient respiratory insufficiency and should complement pulmonary function tests. Further studies are needed to validate specific questionnaires in this regard. No single hypercapnia-associated symptom or pulmonary function test on its own seems sufficient to safely predict hypercapnia.

KEYWORDS
amyotrophic lateral sclerosis, hypercapnia, respiratory function

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease characterized by a loss of upper and lower motor neurons [1]. During the course of the disease, patients develop progressive weakness of respiratory muscles causing a decrease of oxygen and a rise of carbon dioxide levels in the blood. Early clinical symptoms of respiratory insufficiency are variable, including sleep disturbances (difficulty falling asleep and/or staying asleep), fatigue, apathy, cognitive impairment, poor appetite, depression and morning headaches [2, 3]. Rapid shallow breathing, shortness of breath on exertion, during speech or at rest, orthopnea, and the use of accessory respiratory muscles are frequently observed [4]. As the disease progresses, respiratory failure is the most common cause of death in ALS patients [5].

Diagnostic instruments for respiratory failure include, amongst others, forced vital capacity (FVC), slow vital capacity, peak cough flow (PCF), maximum inspiratory and expiratory pressure, invasive arterial blood gas analysis (ABGA) as well as non-invasive oximetry and capnometry [4, 6].

Early detection and management of respiratory decline in ALS is essential as adequate therapy improves survival and quality of life [2, 7, 8]. Treatment includes, most importantly, the use of non-invasive ventilation (NIV), that is, providing positive pressure via a facial or nasal mask through the upper airways. Usually, breathing support is initially started during the night to ameliorate nocturnal hypoventilation [4]. There is a lack of consensus regarding the timing and indication criteria of NIV. Most guidelines recommend the use of spirometry to diagnose respiratory insufficiency [4, 9]. In addition, PCF is often used to measure expiratory muscle strength as it reflects the ability of coughing and airway clearance and may point towards the risk for atelectasis and pneumonia [10]. However, results of pulmonary function tests are generally difficult to interpret as they can fluctuate for a variety of reasons [11–13]. Specifically, patients with bulbar dysfunction may have difficulties in forming a tight lip-seal around the tube [13] and spasticity can impact coordinating the upper respiratory muscles resulting in lower spirometry measurements [11].

Since arterial ABGA [14] and capnometry do not require the same extent of compliance compared to pulmonary function tests, they provide more reliable measures of the respiratory status. First signs of respiratory decline with hypercapnic peaks are usually observed during sleep due to sleep-disordered breathing, hypotonia of the accessory respiratory muscles and possible central respiratory drive dysfunction [15–17]. Therefore, pulmonary function tests can overlook nightly hypoventilation. For this reason, nightly or morning ABGA and ideally continuous nocturnal capnometry are considered to provide more conclusive information about the onset of early respiratory decline. However, ABGA only displays the respiratory situation at a given time and arterial puncture is an invasive and painful technique. While capnometry is a non-invasive tool that provides constant measurements of the respiratory status [16], it requires a long examination period and therefore cannot be routinely performed as a screening instrument in an outpatient setting.

Therefore, in clinical practice, the evaluation of hypercapnia-associated clinical symptoms still represents one of the most important screening instruments for mechanical ventilation as these directly indicate the patient's burden. However, in this context, it can be challenging to determine whether the aforementioned, mostly nonspecific, clinical symptoms are due to respiratory decline or other causes. For example, daytime fatigue may be caused by hypercapnia, but also by an increased energy expenditure due to progressive muscle weakness.

For this reason, this study aimed to evaluate whether specific pulmonary function tests or the presence of specific hypercapnia-associated clinical symptoms yield sufficient sensitivity and specificity to safely predict hypercapnia as a marker for early respiratory decline in ALS. In order to represent a real-life clinic setting, ALS patients in various disease stages and independent from their respiratory status were deliberately included. However, it was decided to exclude patients with pre-existing mechanical ventilation support as these measures heavily affect the collected outcome data.

METHODS

In all, 109 inpatients admitted to the Department of Neurology at Ulm University between September 2017 and August 2019 were enrolled. All participants were diagnosed with ALS (definite, probable or possible ALS) according to El Escorial criteria [18]. Each participant provided written informed consent before enrollment. Exclusion criteria were the use of NIV or invasive ventilation, and severe cognitive impairment. Ethical approval was obtained from the ethics committee of the University of Ulm (reference number 344/21).

Upon enrollment, patients underwent non-invasive capnometry (transcutaneous monitor 4 and transcutaneous monitor 5, Radiometer, Copenhagen, Denmark) at night, invasive ABGA (radial artery) the next morning, spirometry, and measurement of PCF by a hand-held flow meter. In addition, potential hypercapnia-associated symptoms were retrieved by 17 dichotomous (yes/no) items.

Clinical data including age, sex, ALS Functional Rating Scale Revised (ALSFRS-R), disease duration (time since onset of first paresis), site of onset (spinal vs. bulbar) and body mass index were collected.

Hypercapnia was defined by fulfilling at least one of the following criteria: pCO_2 of ≥45 mmHg in ABGA, mean pCO_2 of ≥47 mmHg or maximum pCO_2 of ≥50 mmHg in nocturnal capnometry. A pathological PCF was defined as <500 l/min in men and <360 l/min in women; with regard to FVC and forced expiratory volume in 1 s (FEV1), values of less than 80% were classified as abnormal [4, 19].

Data were analyzed using R software (version 3.6.2). Median (interquartile range) was used for description of continuous variables and *n* (%) for categorical variables. Sensitivity, specificity and

Youden's index for prediction of hypercapnia were calculated for each clinical symptom. Youden's index (in percent) was calculated as (sensitivity + specificity − 1) × 100. All 95% confidence intervals (CIs) for sensitivity, specificity and Youden's index were bootstrapped using package boot and 10,000 bootstrap samples. Multiple logistic regression and receiver operating characteristic (ROC) curves were used to evaluate the overall accuracy. To determine the combination of symptoms with the best predictive value, an explorative multiple analysis was performed using a logistic regression model and stepwise variable selection based on the Akaike information criterion. Statistical significance was assumed for p values <0.05. No adjustment was performed for multiple testing due to the explorative nature of this study.

RESULTS

In total, 109 patients (56 female, 53 male) with a mean age of 62.4 ± 11.9 years were enrolled in this study. Thirty-two patients (28.6%) had bulbar onset. Bulbar patients were 4.8 ± 5.0 years older at symptom onset and had a lower body mass index (23.1 kg/m^2 vs. 24.4 kg/m^2) (see Table S1). Ninety-nine patients (90.8%) received nightly capnometry, 75 patients (68.8%) received ABGA in the morning and 65 patients (59.6%) received both. The characteristics of the study cohort are presented in Table 1.

Capnometry, blood gas analysis and respiratory function tests

Of 109 capnometries recorded during the nights, 40 patients (35.7%) were hypercapnic. A total of 75 patients (56 with spinal onset and 19 with bulbar onset) received a ABGA in the morning. Of 26 patients who received both capnometry and ABGA, capnometry detected hypercapnia in 25/26 (96%) patients and arterial BGA detected hypercapnia in 10/26 (38%) patients.

Hypercapnia was more frequently observed in patients with bulbar onset, although not statistically significant (46.9% vs. 32.5%; p = 0.23). Accordingly, median pCO_2 was 0.9 mmHg (interquartile range 41.0–46.4; p = 0.22) higher amongst patients with bulbar onset compared to patients with spinal onset. ABGA revealed higher pCO_2 (p = 0.03) and a trend towards lower pH (p = 0.09) in patients with bulbar compared to spinal onset. Furthermore, bulbar patients showed lower FVC (p < 0.001), FEV1 (p < 0.001) and PCF (p < 0.001) compared to spinal patients. The overall share of pathological values was higher in bulbar patients (see Table S1). Sensitivity, specificity and Youden index for FVC, FEV1 and PCF for predicting hypercapnia are presented in Table 2. PCF yielded the highest sensitivity of 87% (95% CI 74%–97%) and the lowest specificity of 20% (95% CI 10%–31%). FEV1 had the highest specificity of 65% (95% CI 45%–84%) and a sensitivity of 65% (95% CI 45%–80%).

Clinical symptoms of hypercapnia

Potential clinical symptoms of respiratory decline were evaluated in 87 subjects. The items "dyspnea at rest" and "dyspnea while talking" had a high specificity of 95% (95% CI 88%–100%) and 75% (95% CI 9%–38%), respectively, to detect hypercapnia. The odds of having dyspnea at rest were nine-fold amongst patients with hypercapnia (OR 9.0, 95% CI 1.3–88.0) in the multiple logistic regression. Daytime fatigue yielded the highest sensitivity of 58% (95% CI 40%–76%) to predict hypercapnia. The area under the ROC for all recorded items combined to detect hypercapnia was 0.77 (95% CI 0.67–0.83, Figure 1). Sensitivity, specificity and the Youden index for all items are presented in Table 2, and multiple logistic regression is shown in Table 3. An explorative multiple logistic regression model identified "dyspnea at rest", "use of sleeping drugs" and "dyspnea while talking" as the best combination of three items. The predicted probabilities for hypercapnia based on this model were 82% if all three items were answered with "yes" and 26% if all three items were answered with "no" (see Table S1). The ROC curve for the combination of three items to predict hypercapnia is presented in Figure S1.

DISCUSSION

Respiratory failure is the most common cause of death in ALS patients. Therefore, the present study examined the utility of respiratory symptoms and pulmonary function tests as easily applicable screening tools to predict hypercapnia defined by nocturnal capnometry and ABGA in ALS patients.

Nocturnal hypercapnia was observed in 36.7% of all patients with a higher prevalence in male patients. Similar results were reported by Boentert et al. with a percentage of 40.0% amongst all patients [20]. The instrumental respiratory parameters (FVC, FEV1 and PCF) showed a higher sensitivity (70%, 65% and 87%) but lacked specificity (33%, 65% and 20%) compared to the evaluation of respiratory clinical symptoms. Of note, PCF as a marker for expiratory force yielded the highest sensitivity for detecting hypercapnia. As the best overall indicator of hypercapnia, FEV1 showed a reasonable estimate with a sensitivity and specificity around 65%. The poor specificity of spirometry is in line with previous data from Tilanus et al., who found a specificity of only 22% for FVC to predict NIV indication [9]. This is also in accordance with previous studies indicating that the association between respiratory symptoms and spirometry measurements was weak [11, 21, 22].

Of note, bulbar patients had a significantly lower spirometric performance compared to spinal patients. This might be contributed to bulbar dysfunction causing involuntary glottic closure during forced expiration and difficulties in forming a tight lip-seal around the tube. In summary, it is concluded that pulmonary function tests are not able to provide valid information for bulbar patients (see Table S1).

TABLE 1 Characteristics of the study cohort

	Normocapnia	Hypercapnia	Total	
	N = 69*	*N* = 40*	*N* = 109	*p* value
Sex				
Female	39 (56.5%)	17 (42.5%)	56 (100%)	0.23
Male	30 (43.5%)	23 (57.5%)	53 (100%)	
Age at onset (years)	61.1 (53.2–71.6)	61.7 (53.7–67.2)	61.6 (53.2–70.8)	0.79
Age at visit (years)	62.3 (55.1–73.1)	64.5 (55.9–69.2)	63.7 (55.0–72.7)	0.84
Disease duration (months)	14.7 (9.4–24.6)	17.2 (11.8–29.5)	15.4 (10.2–24.9)	0.19
ALSFRS-R score	39.5 (34.0–42.0)	36.0 (31.5–42.5)	38.0 (33.0–42.0)	0.45
BMI (kg/m^2)	24.4 (21.5–26.4)	22.9 (21.6–24.9)	24.0 (21.6–26.1)	0.23
Site of onset				
Bulbar	17 (53.1%)	15 (46.9%)	32 (100%)	0.23
Spinal	52 (67.6%)	25 (32.4%)	77 (100%)	
ABGA				
pO_2 (mmHg)	87.0 (79.0–94.8)	86.0 (74.5–91.8)	86.2 (77.5–94.8)	0.26
pCO_2 (mmHg)	37.0 (32.5–39.0)	42.5 (35.8–46.0)	37.0 (34.0–42.0)	**0.002**
pH	7.45 (7.43–7.47)	7.45 (7.43–7.46)	7.45 (7.43–7.47)	0.31
HCO_3^- (mmol/l)	25.4 (23.1–26.9)	27.6 (24.9–31.1)	25.9 (23.5–28.5)	**0.002**
Spirometry				
FVC (%)	71.0 (58.5–89.8)	59.0 (47.5–84.0)	68.5 (55.5–86.0)	0.06
FEV1/FVC	99 (74.8–112)	104 (81.2–117)	103 (79.0–114.0)	0.54
FEV1 (%)	64.0 (45.5–83.2)	61.0 (43.5–85.5)	62.5 (44.5–85.0)	0.53
Capnometry at night				
Capnometry mean (mmHg)	40.8 (38.6–43.0)	47.0 (45.8–50.2)	43.0 (40.0–46.2)	**<0.001**
Capnometry max. (mmHg)	45.0 (42.0–47.0)	53.0 (51.0–56.0)	47.0 (44.0–51.0)	**<0.001**
PCF (l/min)	220 (140–370)	230 (90–360)	225 (120–370)	0.84

Abbreviations: ABGA, arterial blood gas analysis; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale Revised; BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; PCF, peak cough flow.

t-test was used to compare continuous variables between two groups, p value < 0.05 was considered significant and significant values are written in bold.

Out of 17 evaluated respiratory symptoms, only dyspnea at rest showed a significant association with hypercapnia as well as the highest specificity (95%). Daytime fatigue had the highest sensitivity (58%). All evaluated items combined showed a good predictive power to screen for hypercapnia (ROC 0.77). The highest prediction of hypercapnia for a combination of three clinical symptoms was achieved by using the items "dyspnea at rest", "use of sleeping drugs" and "dyspnea while talking". If all three items were answered in the affirmative, the probability of hypercapnia was 82%. If none of the three symptoms was present, the probability of hypercapnia was 26%. The correlation between respiratory clinical symptoms, respiratory function tests and hypercapnia has rarely been investigated. In previous studies, the association between clinical symptoms and hypercapnia showed a high degree of variability. A capnography study from Kim et al. showed a strong correlation between clinical symptoms and nocturnal hypercapnia [16]. The results of two dyspnea scores (Borg dyspnea score and the DALS-15) showed mixed results [22, 23]. While the Borg score showed significantly higher values in hypercapnic patients [23], the DALS-15 revealed no correlation with FVC or partial pressure of carbon dioxide [22].

In summary, our data indicate that the presence of a single potentially hypercapnia-associated symptom insufficiently predicts hypercapnia. However, the simultaneous presence of several symptoms yields a significantly higher predictive power. Therefore, in order to facilitate early and reliable detection of patients with respiratory insufficiency, a careful evaluation of respiratory symptoms and spirometry parameters must be applied based on our results. The European Federation of the Neurological Societies (EFNS) and American Academy of Neurology (AAN) guidelines suggest initiation of NIV when at least one respiratory symptom or one of the following criteria is present: reduced FVC (EFNS <80%, AAN <50%), sniff nasal inspiratory pressure <40 cmH_2O, abnormal nocturnal oximetry, maximum inspiratory pressure <60 cm (AAN only), pCO_2 >45 mmHg in morning ABGA (EFNS only) [4, 24]. In ALS, however, respiratory

TABLE 2 Sensitivity, specificity and Youden index to detect hypercapnia for each potentially hypercapnia-associated symptom

	Sensitivity 95% CI	Specificity 95% CI	Youden index 95% CI
Spirometry			
FVC (*N* = 69)	70% (50%–88%)	33% (19%–47%)	0.02 (−0.21–0.26)
FEV1 (*N* = 69)	65% (45%–80%)	65% (45%–84%)	−0.02 (−0.27–0.22)
PCF (*N* = 87)	87% (74%–97%)	20% (10%–31%)	0.07 (−0.09–0.22)
Clinical symptoms (N = 87)			
Tired at daytime	**58% (40%–76%)**	**45% (32%–58%)**	**0.03 (−0.19–0.25)**
Falling asleep during daytime	19% (6%–34%)	80% (69%–90%)	0.00 (−0.17–0.18)
Falling asleep late at night	32% (17%–50%)	68% (55%–80%)	0.00 (−0.21–0.21)
Use of sleeping drugs	26% (11%–42%)	86% (76%–94%)	0.12 (−0.06–0.30)
Awake at night	52% (34%–70%)	45% (32%–58%)	−0.04 (−0.26–0.19)
Waking up earlier than usual	29% (13%–46%)	86% (76%–94%)	0.15 (−0.03–0.34)
Difficulties with breathing at night	13% (3%–26%)	91% (83%–98%)	0.04 (−0.09–0.19)
Exhausted in the morning	52% (33%–69%)	64% (52%–76%)	0.16 (−0.06–0.38)
Sweating at night	19% (6%–34%)	91% (83%–98%)	0.10 (−0.05–0.27)
Headaches in the morning	16% (4%–30%)	82% (71%–92%)	−0.02 (−0.18–0.16)
Dyspnea at rest	**23% (9%–38%)**	**95% (88%–100%)**	**0.17 (0.02–0.34)**
Concentration difficulties	13% (3%–26%)	79% (67%–89%)	−0.09 (−0.24–0.08)
Dyspnea while talking	**42% (25%–59%)**	**75% (63%–86%)**	**0.17 (−0.03–0.37)**
Depression	35% (19%–53%)	71% (59%–83%)	0.07 (−0.13–0.28)
Dyspnea while walking	32% (17%–48%)	73% (61%–84%)	0.05 (−0.15–0.26)
Dyspnea while eating or showering	23% (9%–38%)	91% (83%–98%)	0.14 (−0.02–0.31)
Sleeping with elevated head	26% (11%–42%)	80% (69%–90%)	0.06 (−0.12–0.25)

Abbreviations: CI, confidence interval; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; PCF, peak cough flow.

The items with the highest sensitivity, highest specificity, and highest Youden-Index are written in bold.

insufficiency is not caused by impaired oxygen exchange but by hypoventilation due to progressive respiratory muscle weakness. Therefore the measurement of partial carbon dioxide for incipient respiratory insufficiency is suggested.

Based on our results, the sole measurement of pulmonary function tests (e.g., FVC, FEV1), especially in bulbar patients, is not reliable as a screening tool and therefore cannot be recommended. If the combination of respiratory symptoms and spirometry points

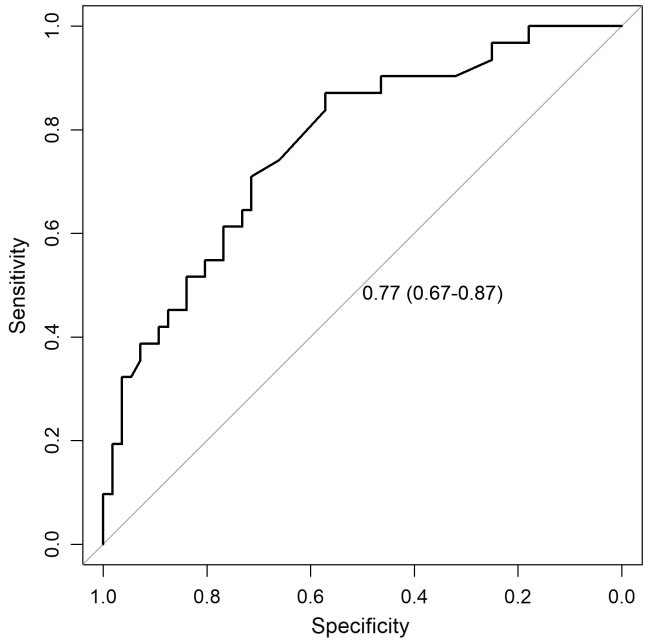

FIGURE 1 Receiver operating characteristic (ROC) curve for all questions combined to detect hypercapnia

TABLE 3 Multiple logistic regression using clinical symptoms as independent variables and hypercapnia (yes/no) as dependent variable

Item	Odds ratio (95% CI)	*p* value
Tired in daytime	**1.0 (0.3–3.6)**	**0.99**
Falling asleep during daytime	0.5 (0.0–3.7)	0.47
Falling asleep late at night	0.5 (0.1–2.2)	0.35
Use of sleeping drugs	2.4 (0.4–15.4)	0.33
Awake at night	0.5 (0.1–1.5)	0.22
Waking up earlier than usual	3.5 (0.7–22.2)	0.15
Difficulties with breathing at night	0.6 (0.0–5.7)	0.65
Exhausted in the morning	2.3 (0.6–9.6)	0.24
Sweating at night	5.3 (0.5–75.1)	0.18
Headaches in the morning	0.5 (0.1–2.9)	0.44
Dyspnea at rest	**9.0 (1.3–88.0)**	**0.03**
Concentration difficulties	0.2 (0.0–1.2)	0.12
Dyspnea while talking	**2.0 (0.5–7.7)**	**0.29**
Depression	1.3 (0.4–5.1)	0.67
Dyspnea while walking	0.6 (0.1–2.9)	0.52
Dyspnea while eating or showering	1.5 (0.1–20.5)	0.76
Sleeping with elevated head	0.8 (0.2–3.1)	0.73

Abbreviation: CI, confidence interval.

Items with the highest specificity to dectect hypercapnia ("dyspnea at rest" and "dyspnea while talking") and the item with the highest sensitivity ("tired in daytime") were written in bold.

towards hypoventilation, arterial blood gas analysis or preferably nocturnal capnometry should be applied to confirm hypercapnia and subsequent NIV should be initiated.

AUTHOR CONTRIBUTIONS

Sebastian Michels: Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); writing – original draft (lead). **Paul Widmann:** Data curation (equal); investigation (equal); writing – review and editing (equal). **Daniel Rapp:** Data curation (equal); formal analysis (equal); methodology (equal); visualization (equal); writing – review and editing (equal). **Frank Willkomm:** Investigation (supporting); methodology (supporting); writing – review and editing (equal). **Albert Christian Ludolph:** Supervision (equal); writing – review and editing (equal). **Johannes Dorst:** Conceptualization (equal); formal analysis (equal); methodology (equal); project administration (lead); writing – review and editing (lead).

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data presented in this study are included in this published article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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