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# Prediction of cough effectiveness in amyotrophic lateral sclerosis patients assessed by ultrasuond of the diaphragm during the cough expiration phase

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ABSTRACT

Assessing cough effectiveness, using Cough Peak Flow, is crucial for patients with Neuromuscular Diseases, such as Amyotrophic Lateral Sclerosis. Impaired cough function can contribute to respiratory decline and failure. The goal of the study is to determine the correlation between diaphragmatic excursion and cough expiratory phase, potentially utilizing ultrasonographic indices to estimate Cough Peak Flow in these patients. Twenty-two patients were enrolled in this study. The upward displacement of the diaphragm was measured with ultrasonography during voluntary cough expiration and Cough Peak Flow was simultaneously measured. A multivariable linear regression model was built to quantify the association between Cough Peak Flow and diaphragm expiratory excursion. There is significative relationship between Cough Peak Flow and diaphragm excursion with a Pearson's r coefficient of 0.86 observed in the patients group. Multiple linear regression analysis for Cough Peak Flow (Adjusted $R^2 = 0.86$) revealed significant associations between Cough Peak Flow and expiratory excursion (adjusted $\beta$-coefficient: 64.78, 95 %, CI: 51.50–78.07, $p<0.001$) and sex (adjusted $\beta$-coefficient: −69.06; 95 % CI: −109.98 to −28.15, $p=0.001$). Our results predict the cough effectiveness by using M-mode diaphragmatic sonography with a potentially significant impact on therapeutic choices.

## 1. Introduction

A cough is a physiological reflex that plays a central role in the airways protection by preventing the accumulation of endogenous materials, such as mucus or inflammatory substances, and the aspiration of extraneous materials such as particulate matter, pathogens or post-nasal drip (Tabor-Gray et al., 2019; Sancho et al., 2017). Cough is a complex mechanism, whose effectiveness depends on the integrity of different muscle: inspiratory muscles ensure inhalation from 50 % of Tidal Volume (TV) to 50 % of Vital Capacity (VC), contraction of the adductor muscles of the arytenoid cartilages leads to tight glottis closure, and contraction of the expiratory muscles causes a quick rise of intra-abdominal and intrathoracic pressure to reach around 400 $cmH_2O$ (Canning et al., 2006; Matsumoto, 1988). Then, the glottis reopens and generates a biphasic turbulent air blast with an initial peak, named Cough Peak Flow (CPF) occurring within 30–50 ms, followed by a flow-plateau phase of 200–500 ms (McCool and Tzelepis, 2012; Hadjikoutis et al., 1999). Amyotrophic Lateral Sclerosis (ALS) is a progressive degenerative motor neuron disease (MND), which causes weakness, wasting and fatigue of skeletal muscles (Chaudri et al., 2002). Various combinations of inspiratory, expiratory and bulbar muscle weakness, among other deficiencies, leads to a decrease cough effectiveness. The deficit of expiratory muscles causes an inability to generate high expiratory pressures and, therefore, a reduction in flow, loss of dynamic compression of the airways and, finally, paradoxical abdominal motion (Sarmento et al., 2019). Impairment of cough results into retention of

*Abbreviations:* Aβ, Adjusted β-Coefficient; ALS, Amyotrophic Lateral Sclerosis; BMI, Body Mass Index; CI, Confidence Interval; CPF, Cough Peak Flow; DCEE, Diaphragm Cough Expiratory Excursion; DUS, Diaphragm Ultrasound; IQR, Interquartile Range; MND, Motor Neuron Disease; NIV, Non-Invasive Ventilation; NMDs, Neuromuscular Diseases; PFTs, Pulmonary Function Tests; POCUS, Point of Care Ultrasound; RV, Residual Volume; SD, Standard Deviation; TLC, Total Lung Capacity; TV, Tidal Volume; VC, Vital Capacity.

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bronchial secretions, atelectasis and respiratory infections that leads to a rapid decline in respiratory function and respiratory failure, the main cause of death for ALS patients (Morelot-Panzini et al., 2019). Thus, assessing voluntary cough function is essential for achieving accurate evaluations and making therapeutic choices (Plowman et al., 2016). The adequacy of mucus clearance relies on having an appropriate CPF.

We investigated the possible association between PCF and sex, age, and height with the aim of determining whether these anthropometric parameters can have a significant effect on the volumes generated with maximal effort by subjects with very different physical characteristics.

While specific threshold values for CPF remain unspecified, elevated CPF levels are linked to a more favourable prognosis in ALS patients (Matsuda et al., 2019; Miller et al., 2009). A CPF below 270 L/min has been correlated with a higher incidence of pulmonary complications during respiratory infections in individuals with Neuromuscular Disorders (NMDs), possibly necessitating the use of assisted cough devices (Chatwin and Simonds, 2020). Additionally, a CPF of 160 L/min is noted as the minimum threshold necessary for effectively clearing secretions in individuals with NMDs, and values below this indicate a potential requirement for a tracheostomy. A CPF of 160 L/min has been reported as the minimum required to effectively clear secretions in patients with NMDs and lower values indicate the need of tracheostomy (Bach, 1995; Sahni and Wolfe, 2018). Furthermore, CPF is found to have the best predictive value for non-invasive ventilation (NIV) indication and tolerance in patients with ALS and for the identification of an increased risk of aspiration (Tilanus et al., 2017; Martínez et al., 2015). ALS patients, especially those with bulbar impairment and severe weakness of the facial and masticatory muscles, are often unable to perform all volitional respiratory function tests. In these cases, the choice of starting ventilator or coughing support is based only on oximetry, arterial blood gas sampling or, if sleep-related symptoms are present, nocturnal studies, often leading to significant delays in support treatment prescription (O'Neill et al., 2012; Benditt, 2019). Diaphragm Ultrasound (DUS) is now an accepted method of assessing the diaphragmatic motion in normal and pathological conditions (Fayssoil et al., 2018). Moreover, the specificity of DUS to predict the risk of extubation failure, in critically ill patients, appears to be moderate-to-high (Le Neindre et al., 2021). We hypothesized that the diaphragmatic excursion assessed during the cough expiratory phase might predict CPF. No previous study has investigated the relationship between diaphragmatic movement and simultaneously measured CPF in ALS patients. The outcome of this study is to quantify the association between diaphragmatic excursion and the expiratory phase of cough, in order to investigate if the ultrasonographic index can be used to ascertain CPF in ALS.

## 2. Methods

### 2.1. Study design

The study was conducted in the Respiratory Disease Day Hospital for Neuromuscular Diseases of the Policlinico Umberto I Hospital in Rome, Italy. During a six months run-in period from November 2022 to April 2023, twenty-two ALS patients were recruited based on El Escorial-Revised Diagnostic Criteria (Brooks et al., 2000). The inclusion criteria were as follows: (1) a diagnosis of ALS following the El Escorial-Revised Diagnostic Criteria; (2) age > 18 years old; (3) the ability to perform a cough. Exclusion criteria included: (1) inability to perform pulmonary function tests; (2) tracheostomy; (3) pregnancy; (4) breastfeeding (5) current or previous lung diseases. This study was conducted following the Declaration of Helsinki and Good Clinical Practice guidelines. Ethical committee approval was obtained with protocol number: 0509/2023 and written informed consent was signed by all the subjects enrolled.

### 2.2. Measurements

Demographic and anthropometric variables, including age, weight, height, and sex, were recorded. All subjects underwent Pulmonary Function Tests (PFTs) and CPF measurements, along with a simultaneous assessment of the diaphragm passive displacement. Since PFTs and CPF cannot be measured simultaneously, diaphragm excursion evaluations were recorded three times for each expiratory maneuver. Specifically, the same observer, while subjects were in a lying 30° supine position, measured the upward displacement of the diaphragm using M mode 3.5 MHz convex transducer *(Esaote Medica AU5 Harmonic.* PFTs and CPF were measured using a peak flow meter and *Quark-PTF Cosmed spirometer*, respectively. Each participant was instructed to perform a maximal inspiration manoeuvre followed by a coughing act with maximum effort. The probe was positioned on the abdominal wall with a right anterior subxiphoid approach, using the liver as an acoustic window. The ultrasound beam was directed to the posterior third of the right hemidiaphragm. The passive Diaphragm Cough Expiratory Excursion (DCEE) was assessed during all expiratory manoeuvres, specifically recorded from Total Lung Capacity (TLC) to Residual Volume (RV). These measurements were repeated until obtaining at least three reliable values of all indices, with a maximum variability of 5 % between each measurement. Only the best value of the three measurements was recorded for each index.

### 2.3. Statistical analysis

Descriptive statistics were obtained using mean and standard deviation (SD), and median and interquartile range (IQR), for continuous variables, and proportions for dichotomous and categorical variables. Pearson's r coefficient was used to estimate the correlation between CPF (L/min) and diaphragm expiratory excursion (cm). Then, a multivariable linear regression model was built to quantify the association between CPF and diaphragm expiratory excursion. Age (years), height (cm), and sex (female vs. male) were used as adjustment variables. A two-sided p-value $< 0.05$ was considered statistically significant. All analyses were performed using Stata (StataCorp LLC, 4905 Lakeway Drive, College Station, TX 322, USA), version 17.0.

## 3. Results

The demographic and anthropometric characteristics of the group, along with the respiratory and ultrasonographic measurements, are summarized in Table 1.

The relationship between CPF and diaphragm excursion is illustrated

**Table 1**
ALS patients' general characteristics (N = 22).

| **Sex** | | |
|---|---|---|
| **Male** | 15 (68.2 %) | |
| **Female** | 7 (31.8 %) | |
| **Smoke** | | |
| **Non-smoker** | 10 (45.5 %) | |
| **Former smoker** | 8 (36.4 %) | |
| **Smoker** | 4 (18.2 %) | |
| | **Mean (SD)** | **Median (IQR)** |
| **Age** | 61.0 (14.4) | 58.0 (51.0–70.0) |
| **Weight (kg)** | 64.5 (11.6) | 63.0 (55.0–72.0) |
| **Height (cm)** | 170.7 (7.4) | 170.0 (165.0–176.0) |
| **BMI** | 22.1 (3.5) | 21.6 (19.7–24.2) |
| **FVC (%)** | 61.7 (26.2) | 56.0 (43.0–86.0) |
| **VC (%)** | 71.8 (23.2) | 70.0 (60.0–86.0) |
| **CPF (L/min)** | 243.8 (115.3) | 223.0 (168.0–298.0) |
| **DCEE (cm)** | 3.8 (1.4) | 3.5 (3.0–4.6) |

ALS: Amyotrophic Lateral Sclerosis; BMI: Body Mass Index; CPF: Cough Peak Flow; DCEE: Diaphragm Cough Expiratory Excursion; FVC: Forced Vital Capacity; VC: Vital Capacity; SD: standard deviation, IQR: interquartile range.

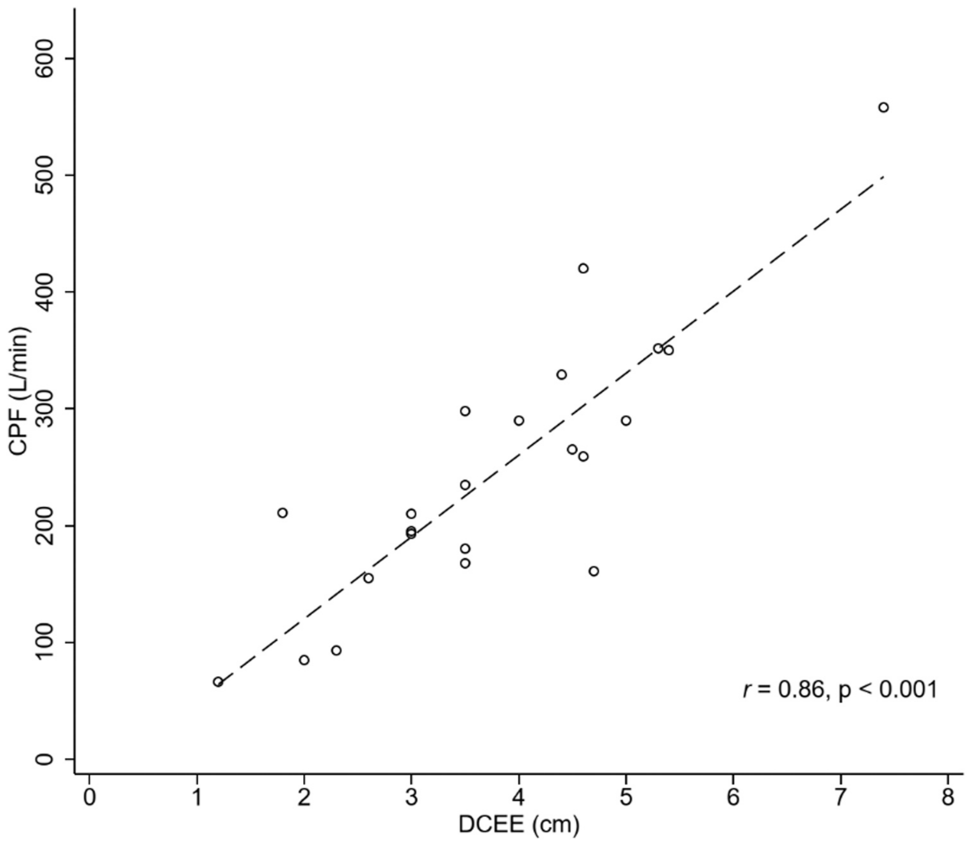


**Fig. 1.** Correlation of CPF (L/min) and DCEE (cm) in ALS patients (N = 22). ALS: Amyotrophic Lateral Sclerosis; CPF: Cough Peak Flow; DCEE: Diaphragm Cough Expiratory Excursion.

**Table 2**
Multiple linear regression models for Cough Peak Flow (L/Min) in ALS patients (N = 22).

| | aβ | 95 % CI | *P* value |
|---|---|---|---|
| **Expiratory excursion (cm)** | 76.13 | 58.04–94.22 | <0.001 |
| **Age** | -0.51 | -2.24–1.21 | 0.541 |
| **Height (cm)** | 2.21 | -1.26–5.67 | 0.197 |
| **Sex** | -55.09 | -109.42 to −0.76 | 0.047 |
| **Intercept** | -370.74 | -1002.07–260.58 | 0.232 |

Adjusted R2 = 0.79; p-value <0.001
ALS: Amyotrophic Lateral Sclerosis; aβ: adjusted β-coefficient

in Fig. 1, with a Pearson's r coefficient of 0.86 observed in the ALS group.

Multiple linear regression analysis for CPF (Adjusted $R^2$ = 0.86) (Table 2) revealed significant associations between CPF and expiratory excursion (adjusted $\beta$-coefficient: 64.78, 95 % CI: 51.50–78.07, p<0.001) and sex (adjusted $\beta$-coefficient: −69.06; 95 % CI: −109.98 to −28.15, p=0.001). However, no relationship was found for age (adjusted $\beta$-coefficient: −0.81, 95 %, confidence interval (CI): −2.45–0.84, p=0.328) and height (adjusted $\beta$-coefficient: 0.07, 95 % CI: −2.46–2.59, p=0.959).

As a result, the **multiple linear regression equation** to predict CPF is as follows:

CPF (L/min) = 76.13 × Expiratory excursion -0.51 × Age +2.21 × Height -55.09 × Sex (ref. Male) -370.74

## 4. Discussion

This is the first study to analyse the association between CPF, assessed during the cough expiration phase, and diaphragm expiratory excursion in ALS subjects. Since we needed the patients to be able to perfectly perform the respiratory function tests, we enrolled patients with newly diagnosed ALS, in a disease state that could be classified as mild-symptomatic. Performing a correct CPF maneuver in ALS patients with bulbar impairment is challenging, highlighting the importance of assessing cough efficiency using an alternative method to ensure the correct timing of therapeutic choices. Our findings enable the prediction of cough efficacy in patients with neuromuscular deficits, often faced with difficulty in performing PFTs. As indicated by several studies (Boussuges et al., 2009; Vieira Santana et al., 2020; Scarlata et al., 2018) M-mode ultrasound assessment emerges as an alternative method for evaluating diaphragm function. It is considered a valid, radiation-free, bedside approach, particularly beneficial for individuals with disabilities demonstrating good interobserver and intraobserver reproducibility (Noh et al., 2016; Testa et al., 2011). Given that the diaphragm is the principal inspiratory muscle, diaphragmatic excursion is directly correlated with inspiratory volume (Ayoub et al., 2002; Yamada et al., 2017). Thus, a correct inspiratory volume is fundamental to guarantee an adequate expiratory cough phase, a crucial component of the process.

During the coughing expiratory phase, when the glottis opens, the diaphragm moves cranially driven by the high-pressure gradient between abdominal and chest cavity. In this study we measure diaphragmatic cough expiratory excursion and CPF simultaneously, revealing a direct relationship. Our results suggest a strong connection between the performance of passive cephalic movement of the diaphragm and the CPF. This finding aligns with a previous study by Norisue et al. (2019), demonstrating that diaphragmatic excursion during the cough expiratory phase significantly predicted CPF with maximum cough effort in a cohort of 56 healthy adults. The effectiveness of mucus clearance depends on an adequate CPF. Although precise threshold values for CPF are not available, higher CPF values are associated with a better prognosis in patients with ALS. Conversely, a CPF < 270 L/min has been associated with an increased rate of pulmonary complications during respiratory infections and cough deficiency, leading to ineffective secretion clearance. Assessing inadequate airway clearance, defined as CPF values lower than 160 L/min, prevents pulmonary complications and ensures the correct timing of therapeutic choices (Matsuda et al., 2019; Miller et al., 2009; Bach, 1995; Sahni and Wolfe, 2018).

The lack of significant association with age and height suggests that, within the range of the study, these variables do not independently affect CPF. This might imply that respiratory function, as measured by CPF, is more directly influenced by factors like muscle strength (reflected in expiratory excursion) rather than general physical characteristics like age or height. The difference in CPF between sexes might necessitate sex-specific reference values in clinical practice, however, to date, the cutoff used in clinical practice to determine cough inefficiency is the same for both sexes.

The authors of this study chose not to investigate the possible association between PCF and FVC because the latter could be reduced due to causes unrelated to the disease under examination, such as bronchial obstruction, and thus be a confounding factor in the data analysis (Chatwin and Simonds, 2020).

The clinical worthiness of ultrasound assessment of cough stretch lies in its simplicity, non-invasiveness, and bedside applicability. In the recent past, it was thought that ultrasound had no role in the study of lung diseases, but the increasing use of ultrasound, especially Point of Care Ultrasound (POCUS), for lung pathologies has the potential to improve patient care by enabling earlier and more accurate diagnoses, facilitating interventions, and reducing the need for more invasive procedures.

Using the hepatic window for measurements on the right hemidiaphragm is a standardized and easy-to-approach method (Wilches-Luna et al., 2022). Moreover, our findings have potential application to predict cough efficacy in neuromuscular patients with bulbar impairment, evaluate cough in neuromuscular patients at risk for respiratory failure, assess pre-extubation weaning outcome, and reduce the time to extubation (Thille et al., 2015).

An important limitation of this study is the small sample size of ALS patients, challenging to recruit due to their physical vulnerability and emotional frailty. Another limitation worth mentioning is that diaphragm excursion is influenced by respiratory system mechanics such as lung and chest wall compliance and airway resistance. At last, further studies are needed to confirm and validate our findings.

## 5. Conclusion

In conclusion, this is the first study that analyses the relationship between diaphragm cough expiratory excursion and CPF during the expiratory phase of cough, detected by ultrasound in ALS patients, demonstrating a strong relationship. Moreover, our results predict the cough effectiveness by using M-mode diaphragmatic sonography in subjects affected by ALS, with a potentially significant impact on therapeutic choices, preventing pulmonary complication in patient at high risk of respiratory failure.

## Declarations of interest

None.

## CRediT authorship contribution statement

**Daniel Piamonti:** Writing – review & editing, Writing – original draft, Visualization. **Antonio Sciurti:** Writing – original draft, Formal analysis, Data curation. **Maurizio Inghilleri:** Visualization, Resources, Investigation. **Paolo Palange:** Visualization, Validation, Supervision. **Letizia D′Antoni:** Visualization, Validation, Supervision, Data curation, Conceptualization. **Fausta Viccaro:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Conceptualization. **Valentina Baccolini:** Writing – original draft, Formal analysis, Data curation. **Altea Lecci:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization.

## Data Availability

Data will be made available on request.

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