Health status can predict diaphragmatic muscle thickness in COPD: pilot study

O estado de saúde pode prever a espessura muscular diafragmática na DPOC: estudo-piloto

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Abstract

Introduction: Among the systemic implications of chronic obstructive pulmonary disease (COPD) there are changes in the diaphragm and impact on health status. However, there are few studies on the possible relationship between these variables, and whether health status could predict diaphragmatic muscle thickness (DMT). **Objective:** To investigate whether there is a relationship between DMT and the prognostic mortality index Body Mass-Index, Airway Obstruction, Dyspnea and Exercise Capacity (BODE), dyspnea and health status, and to investigate whether health status can predict DMT in patients with COPD entering a pulmonary rehabilitation program. **Methods:** This is a pilot study with a cross-sectional design. Diaphragmatic muscle thickness was evaluated using ultrasound; health status through the COPD Assessment Test (CAT); the sensation of dyspnea by the modified Medical Research Council scale; and mortality, using the BODE index. **Results:** The sample consisted of 13 patients (68.69 ± 9.3 years) classified as having moderate to severe COPD. There was a strong and inverse correlation between diaphragmatic muscle thickness and health status ($r = -0.735$; $p = 0.004$). Simple regression analysis demonstrated that health status influenced diaphragmatic muscle thickness ($\beta = -0.002$; IC 95% - 0.004 to -0.001; $p = 0.004$), explaining 49% of the variance. However, no correlations were observed between diaphragmatic muscle thickness with dyspnea ($r = 0.005$; $p = 0.985$) or with the BODE mortality index ($r = -0.219$; $p = 0.472$). **Conclusion:** This pilot study demonstrated a strong inverse correlation between health status and DMT. In addition, health status was able to predict DMT in patients with COPD.

Keywords: Chronic obstructive pulmonary disease. Diaphragm. Dyspnea. Health evaluation. Ultrasonography.

Resumo

Introdução: *Dentre as implicações sistêmicas da doença pulmonar obstrutiva crônica (DPOC), há modificações no diafragma e impacto no estado de saúde; entretanto, são escassos os estudos sobre a possível relação entre essas variáveis e sobre a possibilidade de o estado de saúde prever a espessura muscular diafragmática (EMD).* ***Objetivo:*** *Investigar se há relação entre a EMD com o índice prognóstico de mortalidade Body Mass-Index, Airway Obstruction, Dyspnea and Exercise Capacity (BODE), dispneia e estado de saúde, e investigar se o estado de saúde pode prever a EMD em pacientes com DPOC ingressantes em um programa de reabilitação pulmonar.* ***Métodos:*** *Estudo piloto com delineamento transversal. A EMD foi avaliada através de ultrassonografia; o estado de saúde, através do COPD Assessment Test (CAT); a sensação de dispneia, pela escala modified Medical Research Council; e a mortalidade, por meio do índice BODE.* ***Resultados:*** *A amostra foi composta por 13 pacientes (68,69 ± 9,3 anos) classificados como portadores de DPOC moderada a grave. Houve uma correlação inversa e forte entre a EMD e o estado de saúde (r = -0,735; p = 0,004). A análise de regressão simples demonstrou que o estado de saúde influenciou a EMD (β = -0,002; IC 95% -0,004 a -0,001; p = 0,004), explicando 49% da variância. Entretanto não foram observadas correlações entre EMD e dispneia (r = 0,005; p = 0,985) ou com o índice BODE (r = -0,219; p = 0,472).* ***Conclusão:*** *Esse estudo piloto demonstrou uma forte correlação inversa entre estado de saúde e EMD. Ademais, o estado de saúde foi capaz de prever a EMD em pacientes com DPOC.*

Palavras-chave: *Doença pulmonar obstrutiva crônica. Diafragma. Dispneia. Avaliação em Saúde. Ultrassonografia.*

Introduction

Chronic obstructive pulmonary disease (COPD) has increased worldwide and is currently the third most frequent cause of death, thereby being a significant public health concern.[1] In 2020, 37,686 deaths were directly related to COPD in Brazil,[2] and various factors contribute to the high mortality rate of these patients, more notably lower health status.[3,4]

Moreover, COPD is mainly characterized by pulmonary impairment due to factors inherent to the respiratory condition, including altered ventilatory mechanics (restricted airflow, pulmonary hyperinflation, and increased compliance and imposed loads) or even systemic components (oxidative stress and systemic inflammation) that can exacerbate metabolic disorders.[5,6] Nonetheless, as COPD progresses, numerous systemic changes occur that affect the skeletal muscle system.[7] More specifically in the diaphragm muscle, these changes include diaphragm shortening, reduced curvature, apposition and cross-sectional muscle fiber areas, decreased ability to generate tension,[8] lower efficacy of contraction in lifting and expanding the rib cage, fewer sarcomeres,[9] rreduced mobility,[10] and impaired phrenic nerve conduction velocity,[11] resulting in relevant clinical implications.

Given the theoretical assumptions presented above, studying the diaphragm of COPD patients is crucial, and many methods have been employed.[12,13] Ultrasonography is widely used because it is safe, non-invasive, relatively inexpensive, portable, and free of ionizing radiation.[12] This method allows the diaphragm muscle thickness to be measured and is considered an indirect measure of contractility, with clinical implications in inspiratory muscle strength and dysfunction diagnosis.[12-14]

In addition to the systemic implications of COPD, research has shown an important impact of the symptoms of the disease on the health status of patients.[15,16] Based on this premise, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines suggest the use of the COPD Assessment Test (CAT) as a complementary tool in the clinical evaluation; this tool is considered a predictor of exacerbation, deterioration of health status, depression, and mortality.[17-19] Nevertheless, the lack of data on the potential relationship between the CAT and diaphragm muscle thickness makes it paramount to consider data correlating this instrument with other important clinical outcomes. Singh et al.[20] demonstrated that CAT was inversely correlated with forced expiratory volume in 1 second (FEV_1) and positively correlated with the BODE index (body mass index, airway obstruction, dyspnea, and exercise capacity), which is considered the main predictor of disease severity, number of exacerbations, and mortality,[21] being characterized as a useful tool in clinical practice and patient treatment planning.[20] As a result of this gap in the literature and considering that CAT is a reliable and easily and quickly applied method, investigating whether this instrument can predict diaphragm thickness is relevant for the clinical practice of physiotherapists since ultrasound is not widely available in pulmonary rehabilitation programs (PRP).

Given this scenario, this study aimed to investigate whether there is a relationship between diaphragmatic muscle thickness with the BODE index, dyspnea, and health status and investigate whether the health status can predict diaphragmatic muscle thickness in COPD patients entering a PRP.

Methods

Study design

This cross-sectional study was developed at the University Hospital of Santa Maria (HUSM) of the Federal University of Santa Maria (UFSM) from June 2019 to February 2020.

Participants

Patients referred by the HUSM pulmonology department to enter the PRP and clinically diagnosed with COPD according to the GOLD criteria (forced expiratory volume in 1 second/forced vital capacity; $FEV_1/FVC < 70$ and predicted $FEV_1 < 80\%$)[17] were considered eligible for the study. The inclusion criteria included clinically stable patients (i.e., absence of infections or exacerbations in the last three months), medical team consent for physical exercise, and willingness to attend the rehabilitation program.[17] The exclusion criteria included active smokers, active drinkers, hemiparalysis or diaphragmatic paresis, neurological impairment diagnosis, severe self-reported hearing or visual impairments, symptomatic heart disease, hemodynamically unstable patients, liver disease, obesity (body mass index > 30 kg/m^2), history of abdominal or thoracic surgery, uncontrolled diabetes mellitus, and neuromuscular, musculoskeletal, or joint disorder that could prevent the assessments from being carried out.

This study was approved by the Research Ethics Committee of UFSM (process no. 3.208.982). All participants provided written informed consent before participation.

Evaluations

All patients were submitted to the same evaluations, with a minimum interval of 48 h between them. On the first day, the patients underwent a physical examination, anamnesis, anthropometric data measurement, and health status and dyspnea evaluations. On the second day, the diaphragmatic muscle thickness was evaluated. Lastly, the six-minute walk test (6MWT) was performed on the third day.

Health status assessment

The Portuguese version of the CAT, which was validated for the Brazilian population, was applied in the form of an interview to evaluate the health status of COPD patients by quantifying the impact of frequent symptoms resulting from the disease (cough, catarrh, chest tightness, shortness of breath when climbing hills/steps, limited household activities, confidence when leaving home, sleep, and energy).[22] The CAT score ranges from 0 to 5 points for each of the eight items, reaching a total of 40 points.[23] The sum of the instrument can be stratified into four categories that reflect the clinical impact of COPD symptoms on patients' lives: mild (1 - 10), moderate (11 - 20), severe (21 - 30), and very severe (31 - 40).[23] Notably, the higher the CAT score, the worse the health status (i.e., a more significant clinical impact of the disease).[23]

Evaluation of diaphragmatic muscle thickness

Diaphragm muscle thickness was evaluated using a high-resolution ultrasound device (DP-2200, Mindray, China) in B mode with a micro-convex transducer (65C15EA; 5.0-9.0, MHz, 4W). Diaphragmatic muscle thickness was determined with the patient in dorsal decubitus in the right upper limb above the head and the transducer perpendicularly positioned between the eighth and ninth intercostal spaces at the mid-axillary line at the end of expiration.[24] Diaphragm muscle thickness was defined as the distance from the pleural surface to the peritoneal surface. Three measurements were taken with a maximum difference of 0.1 cm between them.[24]

Predictor of mortality

Mortality was assessed using the BODE index, which is composed of the following variables: BMI, predicted forced expiratory volume in 1 second as a percentage (FEV_1% predicted), modified Medical Research Council Dyspnea Scale (mMRC), and distance walked on the 6MWT.[19]

The BMI was calculated as recommended by the International Society for the Advancement of

Kinanthropometry (ISAK),[25] and the FEV_1 was measured through the pulmonary function evaluation performed prior to the admission to the PRP by the Pulmonology Outpatient Clinic of the HUSM using a calibrated portable spirometer (microQuark, Cosmed, Rome, Italy) following the technical procedures of the Guidelines of the Brazilian Society of Pulmonology and Phthisiology.[26] Dyspnea symptoms were evaluated using the mMRC method, being composed of five items and scores ranging from 0 to 4, in which patients refer to the description that best corresponds to the limitation caused by dyspnea in their daily life.[27]

The 6MWT was performed according to international guidelines by trained evaluators, obtaining the distance walked in the six-minute walk test (DW6T).[28] The patients were instructed to walk a 30-meter distance for 6 minutes, and the test was performed twice, with a 30-minute rest interval between each round to reduce the learning effect. For analysis, the best result obtained in the test was considered, and the equation of Britto et al.[29] was used to calculate the predicted distance.

The BODE index was calculated as described by Celli et al.,[30] in which patients received scores according to the values obtained in the evaluations of FEV_1, 6MWT, and mMRC dyspnea scale, with points ranging from 0 (minimum value) to 3 (maximum value); for the BMI, the values were 0 or 1.[30] After the score obtained in each variable, the patients were grouped into quartiles according to the following classification: I (0 - 2 points), II (3 - 4 points), III (5 - 6 points), and IV (7 - 10 points).[20,30]

Sample size calculation

The sample size calculation was performed in the BioEstat software (version 5.0) based on the first seven patients included in this pilot study. A minimum sample size of ten patients was calculated to detect a correlation coefficient of r = -0.807 between diaphragm muscle thickness and CAT with a significance level of 5% ($p < 0.05$) and statistical power of 80%.

Statistical analysis

Data were analyzed in GraphPad Prism 5 statistical software (GraphPad Software Inc., San Diego, CA, USA). The Shapiro-Wilk test was employed to assess the normality of the variables, and continuous variables are presented as mean ± standard deviation. Categorical variables are described as absolute frequencies and percentages. Pearson's correlation test assessed the relationships among the variables (diaphragm muscle thickness, dyspnea, BODE index, and health status). Correlations were classified as weak (r values between 0.10 and 0.39), moderate (r values between 0.40 and 0.69), and strong (r values between 0.70 and 1.00). A simple linear regression analysis was performed between diaphragm muscle thickness (dependent variable) and health status (independent variable). The 95% confidence interval (95% CI) was also presented in this regression. Additionally, the GPower software (version 3.1.9.4) was used to measure the power of the test in relation to the correlation found, and a large effect size was considered for analysis. The established significance level was 5% ($p < 0.05$).

Results

Thirteen patients with COPD (68.69 ± 9.3 years, eight female, GOLD II) entering a PRP were included in this study. The general characteristics of the sample and values for the outcome variables of the subjects with COPD upon entering the PRP are listed in Tables 1 and 2, respectively.

Table 1 - General characteristics of the sample (n = 13)

Characteristics	Subjects with COPD
Sex M/F	5/8
Age (years)	68.69 ± 9.30
BMI (kg/m²)	27.38 ± 2.19
FEV_1/FVC (%)	50.02 ± 14.75
FEV_1 (%)	48.95 ± 18.11
GOLD (I/II)	2/6
GOLD (III/IV)	2/3
Ex-smokers	12 (92.31)
HTN	12 (92.31)
Diabetes mellitus	2 (15.38)
Dyslipidemia	2 (15.38)
Family history of respiratory diseases	13 (100)

Nota: COPD = Chronic obstructive pulmonary disease; BMI = Body mass index; FEV_1/FVC = Ratio between forced expiratory volume in the first second and forced vital capacity; FEV_1 = Forced expiratory volume in the first second; GOLD = Global Initiative for Chronic Obstructive Lung Disease, HTN = hypertension. Data are expressed as mean (SD) or frequency (%).

Table 2 - Sample outcome variables

Outcome variables	n = 13
BODE index (total score), mean ± SD	5 ± 1.87
Quartile 1, n (%)	1 (7.69)
Quartile 2, n (%)	3 (23.08)
Quartile 3, n (%)	6 (46.15)
Quartile 4, n (%)	3 (23.08)
mMRC, mean ± SD	2.85 ± 0.80
6MWT (m)	275.38 ± 102.34
Percentage of expected value 6MWT (%)	55.74 ± 20.73
DMT (cm), mean ± SD	0.15 ± 0.02
CAT (total score)	17.85 ± 6.78
Classification, n (%)	
Mild	2 (15.38)
Moderate	7 (53.85)
Severe	4 (30.77)

Note: BODE = Body Mass-Index, Airflow Obstruction, Dyspnea and Exercise Capacity; mMRC = modificada Medical Research Council; 6MWT: six-minute walk test; DMT: Diaphragmatic muscle thickness; CAT = COPD Assessment Test. Data are expressed as mean (SD) or frequency (%).

According to the CAT questionnaire, diaphragm muscle thickness showed an inverse and strong correlation with health status (r = -0.735; p = 0.004; Figure 1A), corresponding to a power of 0.435. However, no correlations were observed between diaphragm muscle thickness with dyspnea (r = 0.005; p = 0.985) or the BODE index (r = -0.219; p = 0.472; Figures 1B and 1C). A simple regression analysis showed that health status influenced diaphragm muscle thickness (β = -0.002; 95% CI = -0.004 to -0.001; p = 0.004; F of significance = 0.004), explaining 49% of the variance (Table 3).

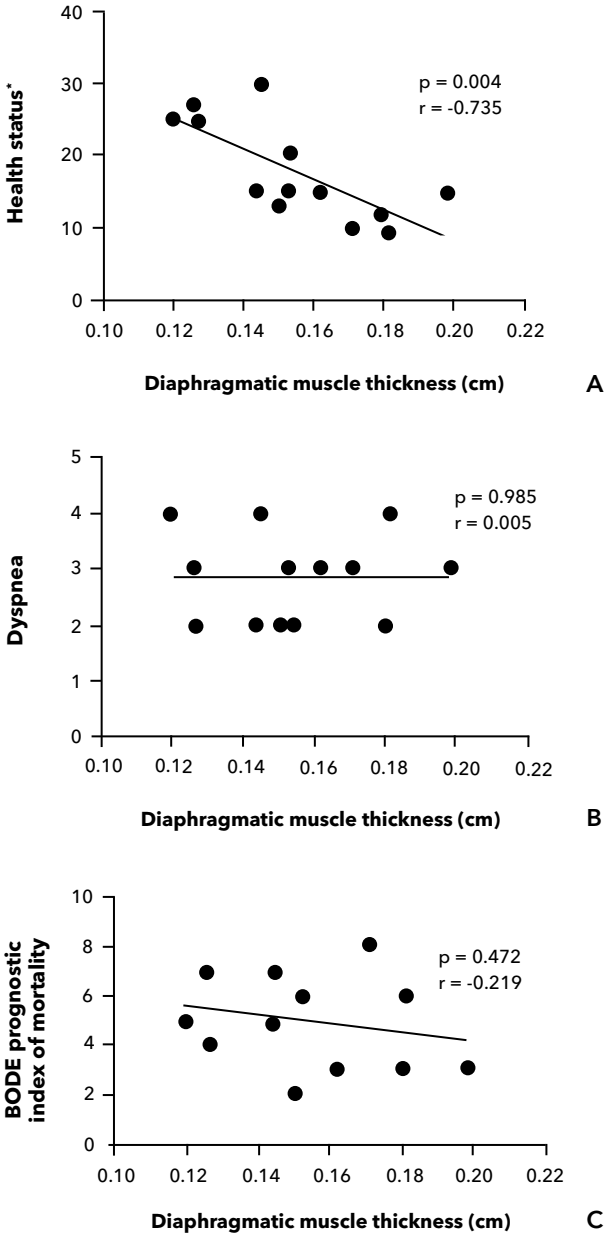

Figure 1 - Relationship between diaphragmatic muscle thickness and health status, dyspnea and the BODE prognostic index of mortality.*Total CAT score.

Table 3 - Linear regression analysis between diaphragmatic muscle thickness and health status in patients with chronic obstructive pulmonary disease (COPD) entering a pulmonary rehabilitation program

Dependent variable	Independent variable	R^2	R^2 adjusted	Coefficient β	95% CI	p
DMT	Health status through CAT	0.54	0.49	-0.002	-0.004 a -0.001	0.004

Note: DMT = diaphragmatic muscle thickness; CAT = COPD Assesment Test; 95% CI: 95% confidence interval. Significant difference p < 0.05.

Discussion

The results showed a strong inverse correlation between diaphragm muscle thickness and health status; however, no correlation was observed between diaphragm muscle thickness and dyspnea or BODE index. Furthermore, as measured by CAT, health status could predict diaphragm muscle thickness in COPD patients. These findings are clinically relevant since the evaluation of the diaphragm by ultrasonography is a useful prognostic marker of pulmonary rehabilitation outcomes in COPD patients,[31] although it is not always available in rehabilitation centers. Thus, applying the CAT may reflect diaphragmatic thickness in COPD patients.

GOLD guideliens proposes using the CAT and mMRC dyspnea scale for symptom assessment in COPD patients.[17] In this regard, Cheng et al.[32] compared the CAT and mMRC to assess clinical symptoms, comorbidities, and health care resource utilization. The authors reported that the CAT was more sensitive in identifying patients with comorbidities and assessing the severity of disease symptoms. Nonetheless, when comparing the CAT and mMRC on health resource utilization, both were equally effective. Hence, the authors suggested that the CAT is better for assessing the multiple dimensions of health negatively impacted by COPD.[32] Given the above, assessing the health status by employing the total score obtained in the CAT was investigated, albeit its possible relationship with modifications in the diaphragm in COPD requires further elucidation.

AThe assessment of diaphragm muscle thickness has been reported to be useful in determining pulmonary hyperinflation in subjects with COPD and used to predict the outcome of weaning and extubation in critically ill patients and determine the patient's respiratory effort and diaphragm contractile activity.[30] PBased on this premise, Baria et al.[33] compared the diaphragm muscle thickness in COPD and healthy subjects and found no significant difference between the groups. Therefore, the authors suggested that a diaphragmatic muscle thickness of 0.15 cm can be applied to COPD patients for diaphragmatic evaluation, with lower values indicating decreased thickness.[33] In view of the above, the patients in this pilot study had mean diaphragmatic muscle thickness values within the normal range.

The literature lacks studies investigating relationships between diaphragm muscle thickness with variables of clinical relevance in COPD. Among the few studies that do, Jain et al.,[12] evaluated a correlation between diaphragm muscle thickness and COPD staging and found that muscle thickness, mobility, and diaphragmatic apposition zones were significantly reduced in mild to moderate COPD and higher in severe COPD and that the variation in diaphragm thickness was not directly related to disease severity. Furthermore, the authors evidenced that the diaphragm muscle thickness in patients with severe COPD was not reduced compared with healthy subjects. A possible explanation attributed to this finding includes the remodeling of diaphragm muscle fibers due to chronic overload.[12] Differently, in the present study, we observed that the greater the diaphragmatic muscle thickness, the lower the CAT score (i.e., the better the patient's health status). The search to explain these conflicting data is difficult since, in the study by Jain et al.,[12] there was no clarity regarding the ultrasonography method used, such as patient position, anatomic reference to position the equipment, ultrasound equipment used, number of measurements employed, the experience of the professional who performed the measurement, and information related to anthropometric characteristics and demographic factors of the patients, which can also influence ultrasonographic data.

Ogan et al.[34] found no relationship between diaphragm muscle thickness, disease severity, respiratory function, exacerbation frequency, and symptoms (mMRC), as well as no significant difference between the diaphragm muscle thickness of healthy subjects and COPD patients. Thus, the authors in question related diaphragmatic dysfunction in COPD to mobility restriction,[34] and in this pilot study, in which the sample was composed predominantly of patients with moderate COPD and moderate clinical impact of the disease, diaphragm muscle thickness correlated strongly and negatively with health status through the total score obtained by the CAT. Furthermore, health status could predict diaphragm muscle thickness, and the clinical importance of this finding lies in the fact that the CAT is an easy and rapidly applied tool capable of reflecting muscular implications resulting from COPD, corroborating its use in the clinical practice of the physiotherapist when ultrasonography is not possible.

There was no significant correlation between diaphragm muscle thickness and dyspnea assessed using the mMRC scale in the present study. Similarly, Eryüksel et al.[35] found no association between diaphragm muscle thickness and dyspnea score (mMRC)

and the number of exacerbations in COPD patients, and Cimsit et al.[36] reported that diaphragm muscle thickness was only related to FEV_1, with no correlation with dyspnea symptoms (mMRC), BMI, age, or gender in patients with mild COPD. Notably, possible explanations for the absence of correlation in our study may be related to the fact that the scores obtained in the mMRC comprised subjects with dyspnea symptoms predominantly classified as moderate to severe or also because the predominance of disease severity contemplates patients classified from moderate to very severe, in whom chronic overload to the diaphragm may culminate in remodeling.[12] Another probable explanation that should be considered comprises the small sample size of this study.

Initially, only FEV_1 was considered for the staging of COPD severity.[37] In recent years, however, given its complexity, heterogeneity, and multicomponent aspects, different indices and scores have been developed to estimate several important clinical outcomes such as mortality.[37] Among these, the BODE index proves to be ahead of other parameters associated with COPD severity[38] due to being a simple multidimensional classification system used to predict the risk of mortality among patients with COPD[30] and related to the use of hospital resources, number and days of hospitalization, and total medical and hospitalization costs.[20] In the sample of the present study, patients with COPD were mostly grouped to quartile 3 of the BODE index, representing an annual mortality of 40%.

Moreover, there was no correlation between diaphragm muscle thickness and the BODE index. Given the scarcity of studies that have investigated the possible relationship between respiratory muscle variables and mortality rates, it is crucial to mention the studies by Formiga et al.,[38] which demonstrated an inverse correlation between inspiratory variables (maximal inspiratory pressure, maximal sustained inspiratory pressure, and inspiratory duration) with the BODE index and Smargiassi et al.,[39] who found a strong correlation between inspiratory capacity and total lung capacity with the BODE index. To the best of our knowledge, this is the first study investigating the possible relationship between diaphragm muscle thickness and the BODE index. We speculate that the lack of correlation between diaphragm muscle thickness and the BODE index may be related to the mean values of diaphragm muscle thickness being within normal values. Hence, further research must explore the relationship between diaphragm muscle thickness and diaphragmatic mobility, as this has been attributed to respiratory muscle dysfunction in COPD.[34]

Despite the promising data presented herein, this study poses several limitations that must be considered. As a result of its cross-sectional design, the relationships observed herein are restricted to the moment evaluated (i.e., pulmonary pre-rehabilitation). In addition, the sonographic analysis of the diaphragm was only performed by quantitative variables, and no qualitative analysis (echogenicity) was performed, and it was not possible to evaluate diaphragmatic mobility.

Conclusion

To date, the results of this pilot study suggest that health status, as assessed through CAT, can predict diaphragm muscle thickness, and these variables correlated inversely in COPD patients entering a PRP. Nonetheless, no correlation was observed between diaphragm muscle thickness and dyspnea and the BODE index. Thus, our findings demonstrated that the health status assessment, through the CAT, which correlated with other parameters and evaluative instruments of COPD patients, may also reflect implications for diaphragm thickness. Studies with a larger sample size are necessary to corroborate the findings presented herein.

Authors´ contributions

All authors contributed to the conception and design of the study, analysis and interpretation of results, writing and critical review of the manuscript, and approval of the final version, being responsible for all aspects of the study, including its accuracy and completeness.

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