Northwestern Med J. 2022;2(2):84-93
doi: 10.54307/NWMJ.2022.09719

Original Article

Sonographic examination of respiratory muscles in chronic obstructive lung disease and evaluation of the relationship with clinical severity of exacerbation

Kronik akciğer hastalığında solunum kaslarının sonografik incelenmesi ve klinik alevlenme şiddeti ile ilişkisinin değerlendirilmesi

Semiha Akbulut, Zeliha Coşgun, Emine Özsarı, Oya Kalaycıoğlu

Atıf/Cite as: Akbulut S, Coşgun Z, Özsarı E, Kalaycioglu O. Sonographic examination of respiratory muscles in chronic obstructive lung disease exacerbation and evaluation of the relationship with clinical severity of exacerbation. Northwestern Med J. 2022;2(2):84-93.

ABSTRACT

Introduction: This study aimed to sonographically examine the fraction of thickening in the respiratory muscles during the acute exacerbation of chronic obstructive pulmonary disease (COPD) and to determine its relationship with the clinical severity of the exacerbation.
Methods: This prospective study looked at 159 people over the age of 50 who were diagnosed with COPD using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria and were admitted to the hospital because they were having an acute COPD flare-up. Ultrasonography was used to measure how thick the parasternal intercostals, pectoralis major, and diaphragm muscles were in each patient.
Results: Of the patients, 63 had mild, 63 had moderate, and 33 had severe exacerbations. Parasternal intercostal and pectoralis major muscle thickening fractions were significantly higher in moderate and severe exacerbations compared to mild exacerbations, while the diaphragm muscle thickening fraction was significantly lower ($p<0.001$). In the severe and moderate exacerbation groups, the thickening percentages of parasternal intercostal and pectoralis major muscle were significantly higher in severe exacerbation than in moderate exacerbation ($p<0.001$). There was no significant difference in the diaphragm muscle thickening fraction between the two groups.
Discussion and Conclusion: Ultrasonography of the respiratory muscles may provide useful information in identifying COPD patients at risk of severe exacerbation, as well as a reliable and repeatable biomarker in patient follow-up.

Keywords: COPD exacerbation, parasternal muscle, respiratory muscle ultrasonography, thickening fraction

ÖZ

Giriş ve Amaç: Bu çalışmada, kronik obstrüktif akciğer hastalığının (KOAH) akut alevlenmesi sırasında solunum kaslarındaki kalınlaşma fraksiyonunun sonografik olarak incelenmesi ve alevlenmenin klinik şiddeti ile ilişkisinin belirlenmesi amaçlanmıştır.
Yöntem ve Gereçler: Bu prospektif çalışmaya, Global Initiative for Chronic Obstructive Lung Disease (GOLD) kriterlerine göre KOAH tanısı alan ve KOAH'ın akut alevlenmesi ile başvuran 50 yaş üstü toplam 159 hasta dahil edildi. Hastaların parasternal interkostal, pektoralis major ve diyafram kaslarının kalınlıkları ultrasonografik olarak ölçüldü.
Bulgular: Hastaların 63'ünde hafif, 63'ünde orta ve 33'ünde şiddetli alevlenme vardı. Parasternal interkostal ve pektoralis majör kas kalınlaşma fraksiyonları orta ve şiddetli alevlenmelerde hafif alevlenmelere göre anlamlı olarak yüksek, diyafram kası kalınlaşma fraksiyonu ise anlamlı olarak daha düşüktü ($p<0.001$). Şiddetli ve orta şiddette alevlenme gruplarında, parasternal interkostal ve pektoralis majör kas kalınlaşma fraksiyonları

Received: 27.03.2022
Accepted: 17.05.2022
Publication date: 30.06.2022

Corresponding Author:
Z. Coşgun
ORCID: 0000-0003-1996-1568
Bolu Abant İzzet Baysal University, Faculty of Medicine, Department of Radiology, Bolu, Turkey
✉ zeliha44@gmail.com

S. Akbulut
ORCID: 0000-0001-8910-9333
Bolu Abant İzzet Baysal University, Faculty of Medicine, Department of Radiology, Bolu, Turkey

E. Özsarı
ORCID: 0000-0001-5842-7849
Bolu Abant İzzet Baysal University, Faculty of Medicine, Department of Chest Diseases, Bolu, Turkey

O. Kalaycıoğlu
ORCID: 0000-0003-2183-7080
Bolu Abant İzzet Baysal University, Faculty of Medicine, Department of Biostatistics and Medical Informatics, Bolu, Turkey

şiddetli alevlenmelerde orta alevlenmelere göre anlamlı olarak daha yüksekti (p<0.001). Diyafram kası kalınlaşma fraksiyonu açısından iki grup arasında anlamlı bir fark yoktu.
Tartışma ve Sonuç: Solunum kaslarının ultrasonografi ile değerlendirilmesi, şiddetli alevlenme riski olan KOAH hasta grubunu karakterize etmede faydalı bilgiler sağlayabilir ve hasta takibinde belki de güvenilir ve tekrarlanabilir bir biyobelirteç sağlayabilir.

Anahtar kelimeler: Kalınlaşma fraksiyonu, KOAH alevlenmesi, parasternal kas, solunum kası ultrasonografisi

INTRODUCTION

COPD (chronic obstructive pulmonary disease) is a common disease globally that is not fully reversible and results in progressive airflow limitation, in other words, hyperinflation (1). It progresses with exacerbations, the most important cause of mortality, which requires different treatment from the stable period, which accelerate the progression of the disease. The severity of exacerbation is evaluated according to the clinical and laboratory findings of the patient (1).

Intercostal muscle quality and quantity were linked to the spirometric severity of COPD, and there was a positive correlation between FEV1 and intercostal muscle thickness in studies looking into the relationship between COPD and respiratory muscles (2). In addition, it has been found that the diaphragm thickening fraction was associated with functions determined by lung volume (3). As far as we know, there are no studies that look at the relationship between muscle thickening and changes in the muscles as a sign of more hyperinflation during the exacerbation period.
The goal of this study is to see if there's a link between the thickening fraction in the parasternal intercostal and diaphragm respiratory muscles, which acts as an indirect indicator of increased load on the respiratory muscles, and the clinical severity of the exacerbation in COPD patients who were admitted to an exacerbation clinic.

MATERIALS AND METHOD

The study was conducted prospectively between September 2019 and March 2020 in the Department of Chest Diseases and Radiology after obtaining the approval of Bolu Abant Izzet Baysal University Ethics Committee (2019/84).

Patient selection

The study comprised 159 COPD patients over the age of 50 who were diagnosed at the Chest Diseases department and admitted to the hospital with an exacerbation complaint, according to the GOLD criteria. The patients were informed about the study, and their consent was obtained. Inclusion and exclusion criteria are given in Table 1.

Collection of clinical and demographic information and determination of COPD exacerbation severity

The patients' gender, height, weight, recent spirometric measurements, diabetes mellitus, hypertension history, smoking history, number of attacks in the last year, and history of O_2 concentrator use at home were questioned and recorded in the patient evaluation form. Also, the spirometry values obtained in the patient's last six months were noted.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	**• >50 years** **• Known COPD diagnosis according to GOLD criteria** **• Informed consent to participate in the study** **• Having applied to the hospital with the complaint of exacerbation of COPD** **• Had a spirometry performed in the last 6 months**
Exclusion criteria	**• ≤ 50 years** **• No diagnosis of COPD** **• No complaints of exacerbation** **• Absence of spirometry in the last 6 months** **• Failure to give informed consent to participate in the study** **• Diagnosis of pulmonary interstitial lung disease, pleural effusion, previous thoracic surgery, chest wall deformity, neuromuscular disease, and malignancy**

The clinical severity of COPD exacerbation was determined by the Chest Diseases Department as mild (sufficient short-acting bronchodilators alone in treatment), moderate (in addition to short-acting bronchodilators, antibiotics and/or oral corticosteroids are required in the treatment), or severe (hospitalization or emergency admission need) according to the patient's response to treatment and recorded in the patient form (1).

Radiological evaluation

Two radiologists performed the study with 3 and 10 years of experience together to provide a common view and technique. Logiq S8 US (GE Healthcare, Milwaukee, WI, USA) device was used for the examination. Before starting treatment, the examination was performed with 6-15 Hz and 9 Hz linear ultrasound probes in the B-mode examination, with patients in the 45 degrees supine position. A 6-15 Hz ultrasound probe was used to evaluate the thickness of the parasternal intercostal muscles and pectoralis major muscles, while a 9 Hz linear ultrasound probe was used to evaluate the diaphragm muscle. During normal inspiration and expiration, parasternal intercostal muscle thicknesses were measured in the sagittal plane from the second and third intercostal space on both the right and left sides, 2-3 cm lateral to the sternum. In contrast, pectoralis major muscle thicknesses were measured in the midclavicular third costa level on the sagittal plane from both the right and left sides. Diaphragm muscle thicknesses was measured in the coronal plane on the anterior axillary line between the right 8th and 9th costa (Figure 1). All measurements were recorded in the patient form. Forced inspiration and expiration were not performed.

Muscle thickening fractions of parasternal intercostal muscles and pectoralis muscles measured in inspiration and expiration were determined according to the $\frac{muscle\ thickness\ in\ expiration - muscle\ thickness\ in\ inspiration}{muscle\ thickness\ on\ inspiration} * 100$ formula and the diaphragm muscle thickening fraction was determined according to the $\frac{muscle\ thickness\ in\ inspiration - muscle\ thickness\ in\ expiration}{muscle\ thickness\ on\ expiration} * 100$ formula. These change values were compared with COPD exacerbation classifications (4).

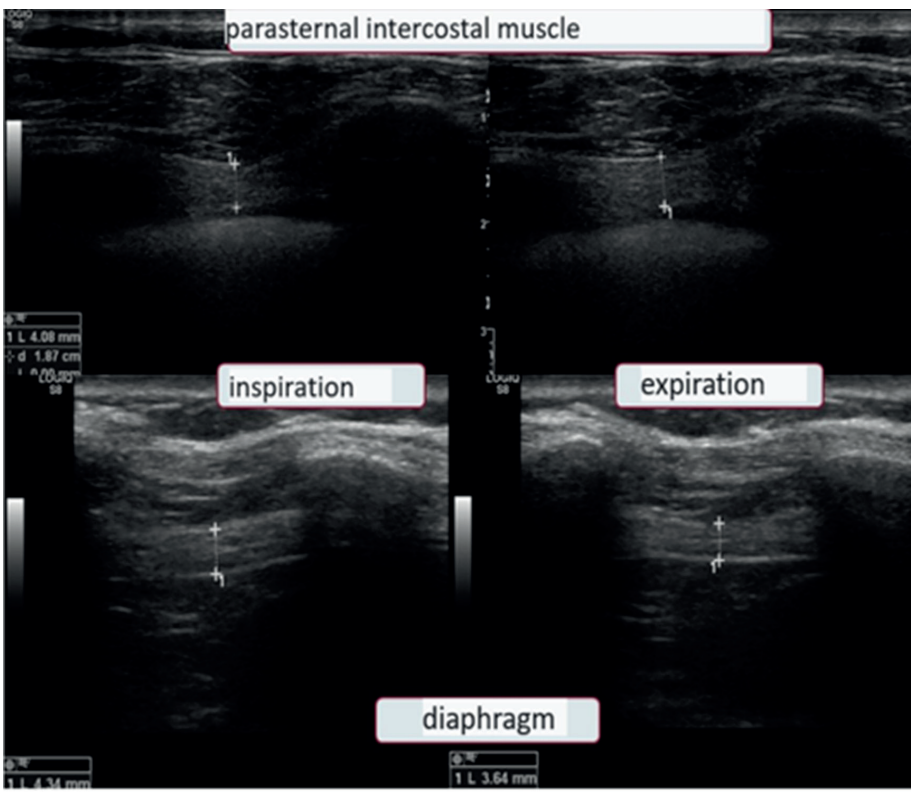

Figure 1. Diaphragm and parasternal muscle thickness measurements in inspiration and expiration.

Statistical analysis

Numerical variables were summarized as mean ±standard deviation, and categorical variables were summarized as frequency (percentage). The conformity of numerical variables to the normal distribution was examined using Shapiro Wilk tests and histogram graphs. Variables conforming to the normal distribution were first compared with a one-way ANOVA test. Afterward, Bonferroni post-hoc tests and pairwise group comparisons were made. Kruskal Wallis and post-hoc Dunn's tests were applied for the variables that did not have a normal distribution. Pearson's chi-square analysis and Fisher's exact test were used to analyze categorical variables. Pearson's correlation analysis analyzed pairwise relations between numerical variables. SPSS v.25.0 program (SPSS Inc., Chicago, Illinois, USA) was used for data analysis; statistical tests were interpreted at p=0.05 significance level.

RESULTS

According to the criteria previously stated, 159 patients participated in the study, and 3.1% (n=5) of the patients were female, and 96.9% (n=154) were male. 39.6% (n=63) of the patients were classified as mild, 39.6% (n=63) moderate, and 20.7% (n=33) severe according to COPD exacerbation classification.

The comparison of patients' demographic characteristics and clinical data is summarized in Table 2 and Table 3 according to the COPD exacerbation classification.

Parasternal intercostal muscle thickness measurements during normal inspiration and expiration differed significantly between mild-moderate and severe COPD exacerbation groups (p<0.001). It was found that cases in the mild exacerbation group had statistically significantly

Table 2. Comparison of demographic characteristics by COPD exacerbation class.

Variables	COPD Exacerbation Class			P
	MILD (n=63)	MODERATE (n=63)	SEVERE (n=33)	
Gender[a]				0.634
Female	3 (4.8%)	2 (3.2%)	0 (0%)	
Male	60 (95.2%)	61 (96.8%)	33 (100%)	
Height (cm)[b]	170.84±5.85	170.16±5.83	171.48±5.65	0.553
Weight (kg)[b]	70.25±7.9	64.59±9.83	67.3±13.09	**0.007**
BMI (kg/m^2)[b]	24.04±2.18	22.31±3.14	22.89±4.28	**0.008**

Numerical data were summarized as mean±SD and categorical data as n (%).
Bold p-values indicate statistical significance at the α=0.05 level.
[a]Fisher's definitive test
[b]One-way ANOVA
BMI: body mass index

Table 3. Comparison of clinical features of patients according to COPD exacerbation class.

Variables	COPD Exacerbation Class			P
	MILD (n=63)	MODERATE (n=63)	SEVERE (n=33)	
Diabetes[a]	16 (25.4%)	11 (17.5%)	14 (42.9%)	**0.029**
Hypertension[a]	12 (19.0%)	15 (23.8%)	22 (66.7%)	**<0.001**
Smoking[a]	18 (28.6%)	8 (12.7%)	6 (18.2%)	0.081
Years without smoking[b]	0.7±1.2	1.7±2.0	3.4±2.6	0.325
Packs/Year[b]	37.0±18.1	38.5±20.8	41.8±14.4	0.422
Number of attacks in the last 1 year[b]	0.7±1.2	1.7±2.0	3.4±2.6	**<0.001**
O2 concentrator use at home[a]	5 (7.9%)	15 (23.8%)	19 (57.6%)	**<0.001**
How many years of COPD[b]	4.8±3.9	8.4±7.3	9.5±6.5	**<0.001**

Numerical data were summarized as mean±SD, and categorical data as n (%).
Bold p-values indicate statistical significance at the α=0.05 level.
[a]Pearson's chi-square test
[b]Kruskal Wallis test

Table 4. Comparison of parasternal intercostal muscle thicknesses in inspiration and expiration according to COPD exacerbation.

Variables	COPD Exacerbation Class			p[a]
	MILD (n=63)	MODERATE (n=63)	SEVERE (n=33)	
R2.PRS-inspiration	4.13±0.64	3.37±0.52	3.08±0.84	<**0.001**
R2.PRS-expiration	4.45±0.64	3.94±0.52	3.79±0.89	<**0.001**
R3.PRS-inspiration	4.53±0.70	3.75±0.56	3.37±0.93	<**0.001**
R3.PRS-expiration	4.76±0.72	4.31±0.57	4.05±0.86	<**0.001**
L2.PRS-inspiration	4.21±0.64	3.43±0.53	3.11±0.84	<**0.001**
L2.PRS-expiration	4.49±0.66	4.00±0.54	3.82±0.86	<**0.001**
L3.PRS-inspiration	4.58±0.70	3.87±0.55	3.44±0.86	<**0.001**

mean±sd. [a]One-way ANOVA test
PRS: parasternal intercostal muscle
R: right
L: left

Table 5. Comparison of pectoralis major muscle thickness in inspiration and expiration according to COPD exacerbation class.

Variables	COPD Exacerbation Class			P
	MILD (n=63)	MODERATE (n=63)	SEVERE (n=33)	
Pectoralis major-inspiration	8.02±1.30	6.84±1.05	6.62±1.58	<**0.001**
Pectoralis major-expiration	8.50±1.36	7.50±1.16	7.42±1.71	<**0.001**

mean±sd. [a]One-way ANOVA test

Table 6. Comparison of diaphragm muscle thickness in inspiration and expiration according to COPD exacerbation class.

Variables	COPD Exacerbation Class			P
	MILD (n=63)	MODERATE (n=63)	SEVERE (n=33)	
Diaphragm muscle thickness - inspiration	2.15±0.48	1.69±0.30	1.68±0.35	<**0.001**
Diaphragm muscle thickness – expiration	1.50±1.75	1.18±0.23	1.21±0.31	0.224

mean±sd. [a]One-way ANOVA test

higher values of parasternal intercostal muscle thickness (R2. PRS, R3. PRS, L2. PRS, L3. PRS) than cases in the moderate and severe exacerbation groups (Table 4) (p<0.001).When the values of the right third parasternal intercostal muscle (R3 PRS-inspiration) (p=0.039) and the left third parasternal intercostal muscle thickness (L3 PRS-inspiration) (p=0.013) during inspiration were compared between the moderate and severe exacerbation groups, it was found that the moderate exacerbation group had significantly higher values than the severe exacerbation group. However, there was no statistically significant difference between the moderate and severe exacerbation groups regarding other variables presented in Table 4.

Pectoralis major muscle thickness was also significantly different between the groups (p<0.001) (Table 5). The thickness of the pectoralis major muscle was found to be statistically significantly higher in cases of mild exacerbation than in cases in moderate and severe exacerbation (p<0.001). While there was a significant difference between the groups regarding the diaphragm muscle thickness during inspiration (p<0.001) (Table 6), there was no significant difference between the groups during expiration (p=0.224). When comparing the cases in the mild exacerbation group to the cases in the moderate and severe exacerbation groups, it was discovered that the mild exacerbation group had significantly higher values of diaphragm muscle thickness during inspiration (p<0.001).

The results of the correlation analysis examining the relationships between FEV_1 values (predicted percentage) and parasternal intercostal muscle measurements during inspiration and expiration are shown in figures 2 and 3. A strong positive

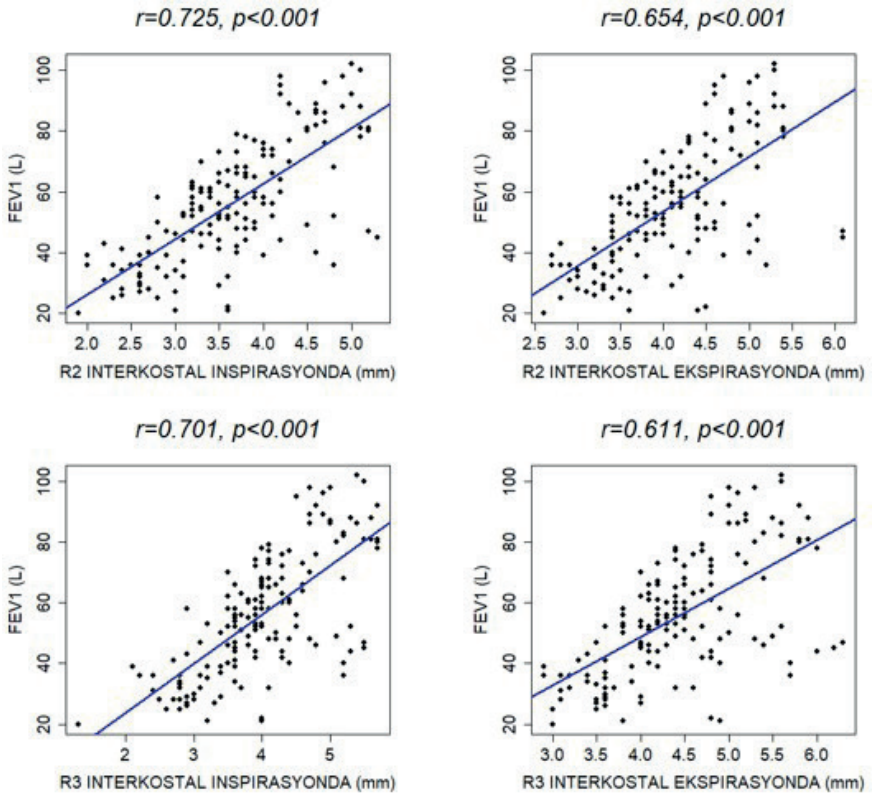

Figure 2. Investigation of the relationship between FEV1 (% expected) and R2, R3 (2nd and 3rd right) parasternal intercostal muscle measurements (Pearson's correlation analysis).

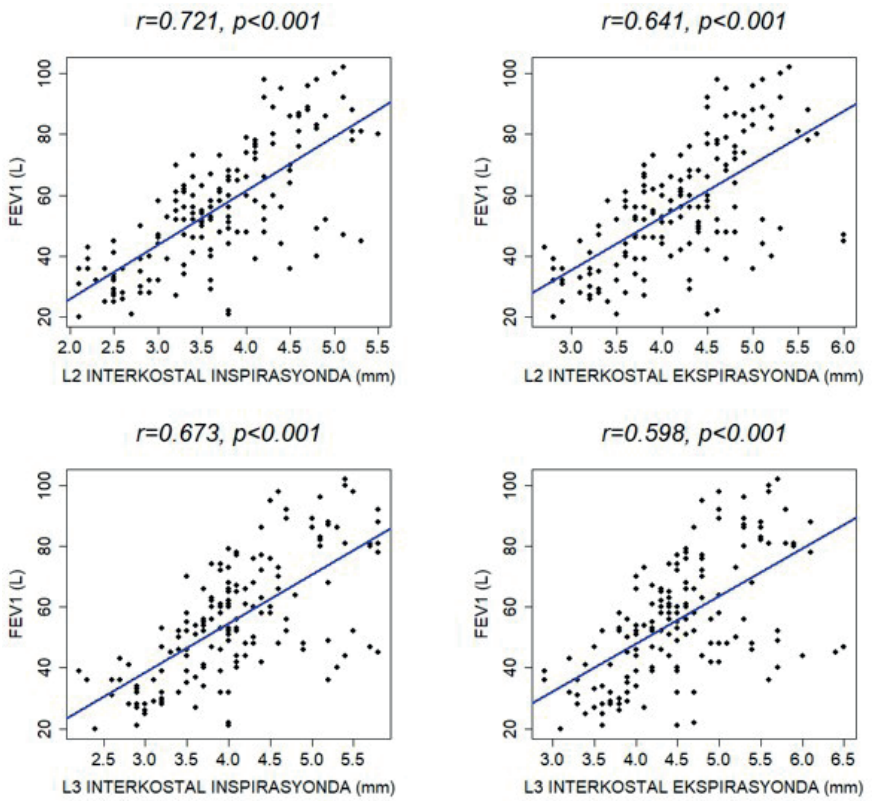

Figure 3. Examining the relationship between FEV1 (% expected) and L2, L3 (2nd and 3rd left) parasternal intercostal muscle measurements (Pearson's correlation analysis).

and statistically significant correlation was found between measurements of parasternal intercostal muscle thickness (mm) and FEV_1 values (predicted percentage) (p<0.001). Correlation analysis results examining the relationship between the number of attacks in the last year and FEV1 (predicted %) values and respiratory muscle thicknesses revealed a significant negative correlation (p<0.001) (Table 7).

Muscle fractions in mild, moderate, and severe exacerbations are given in Table 8. Accordingly, it was observed that the change in all muscles during inspiration and expiration was significantly different between the groups (p<0.001).

Mild exacerbations were shown to have lower parasternal intercostal and pectoralis major muscle fraction values, as well as higher diaphragm muscle fraction values, than moderate and severe exacerbations (p<0.001). When severe and moderate exacerbations were compared, muscle thickening fractions of the cases in the severe group were significantly higher than the moderate group, except for the thickening fraction in the diaphragm muscle (p<0.001). It was observed that the diaphragm muscle fraction had lower values in severe exacerbations than in moderate exacerbations, but this difference was not statistically significant (Table 7).

Table 7. The relationship between the number of exacerbations and FEV1(% expected) and muscle thickness.

Number of exacerbations in the last 1 year	rho	p
FEV1 (% expected)	-0.437	<**0.001**
R2. in intercostal inspiration	-0.427	<**0.001**
R2. in intercostal expiration	-0.356	<**0.001**
R3. in intercostal inspiration	-0.420	<**0.001**
R3. in intercostal expiration	-0.357	<**0.001**
L2. in intercostal inspiration	-0.453	<**0.001**
L2. in intercostal expiration	-0.367	<**0.001**
L3. in intercostal inspiration	-0.438	<**0.001**
L3. in intercostal expiration	-0.374	<**0.001**
Diaphragm muscle on inspiration	-0.362	<**0.001**
Diaphragm muscle on inspiration	-0.184	<**0.001**

Spearman's correlation analysis.
R: right
L: left

DISCUSSION

It was determined that the percentage of change in the thickness of the respiratory muscles other than the diaphragm during inspiration and expiration was positively correlated with the severity of COPD exacerbation, which supports our hypothesis. Also, parasternal intercostal, pectoralis major, and diaphragm muscle thicknesses were significantly correlated with the clinical severity of COPD exacerbation and the patient's FEV1 (predicted %) values in the last 6 (six) months (p<0.001).

It is known that the respiratory muscles are overloaded during an exacerbation. Due to the further increase in hyperinflation, mechanical ventilatory limitation develops, and the functional capacity of the inspiratory muscles decreases. In COPD patients, the function of the intercostal muscles is required to maintain alveolar ventilation when diaphragm function deteriorates or is

Table 8. Comparison of thickening fractions in muscle groups with exacerbation classes.

Variables	COPD Exacerbation Class			p
	MILD (n=63)	MODERATE (n=63)	SEVERE (n=33)	
ΔT R2.prs	7.92±3.00	17.43±4.71	24.19±6.86	<**0.001**
ΔT R3.prs	5.18±2.64	15.34±6.75	20.67±7.32	<**0.001**
ΔT L2.prs	6.83±2.30	17.02±4.44	24.39±7.71	<**0.001**
ΔT L3.prs	5.59±2.95	13.32±3.70	20.05±6.04	<**0.001**
ΔT pectoralis major	6.05±1.75	9.78±3.28	13.40±4.41	<**0.001**
ΔT diaphragm	67.56±19.09	45.89±21.42	41.76±20.67	<**0.001**

mean±sd. [a]One-way ANOVA test
ΔT: thickening fraction
PRS: parasternal intercostal muscle
R: right
L: left

insufficient to cope with the increased workload (5). According to Kisner and Colby, as the severity of COPD increases, the activity of the diaphragm decreases, and involuntary muscles engage to facilitate breathing (6). The study by Jeong-il Kang et al.[7] showed that the intercostal muscles were more active in people with advanced COPD than in people with mild COPD. The study also suggested that the abnormality in the respiratory system was caused by the increased movement of the respiratory synergistic muscles rather than the diaphragm. We hypothesized in our study that during an exacerbation, the respiratory muscles would contract in direct proportion to the load, and that this would be directly proportional to the clinical severity of the exacerbation. The thickening fractions of the parasternal intercostal and pectoralis major muscle groups during inspiration and expiration were significantly correlated with the clinical severity of exacerbation ($p<0.001$), according to the available data.

In COPD patients, the diaphragm tends to shorten by 40% due to pulmonary hyperinflation, which leads to ineffective contractions of the diaphragm due to reduced piston-like movements (8). According to Calverley et al.[9], hyperinflation causes the diaphragm to malfunction due to the shortening of the contractile fibers. These abnormalities in the diaphragm lead to inhalation difficulties that can be alleviated by the use of synergist muscles. In our study, the diaphragm muscle thickening fraction in inspiration and expiration was higher in mild exacerbations. However, no significant difference was found between severe and moderate exacerbation groups, suggesting that the diaphragm muscle thickening fraction decreases in mild and moderate exacerbations, inversely proportional to the exacerbation severity. However, after a certain value, in cases of extreme hyperinflation such as severe exacerbation, this decrease may not occur due to the muscle dysfunction development. In other words, we think that diaphragm dysfunction develops after a certain loading limit is exceeded, and no significant difference is observed in the thickening fraction after this loading limit.

The pathogenesis of intercostal muscle weakness in a patient with COPD is unclear; however, atrophy of muscle fibers is an important factor associated with skeletal muscle mass. A study by Campbell John et al.[10] showed that atrophy of intercostal muscle fibers in patients with COPD was associated with airflow limitation. In the study of Park Mi Jung et al.[11], it was found that muscle cross-sectional area was associated with the severity of COPD. Similarly, in the study by Ju Sunmi et al.[12], it was reported that intercostal muscle atrophy seen in COPD patients was related to the severity of airway obstruction, BMI, and increasing age. Similar to the literature, our study also found a significant correlation between FEV1 values and muscle thickness. In our study, it was found that the thickness of the parasternal intercostal muscle was significantly higher in the patients in the mild exacerbation group than in the moderate and severe exacerbation groups. No significant difference was found between the moderate and severe groups. These results indicate that the weakening of respiratory muscles predisposes to severe exacerbations. As a result, it may be a predictive variable in the probability of hospitalization for COPD patients or help better evaluation and follow-up of outpatients.

Although the mechanism of intramuscular fat infiltration and muscle weakening in COPD patients is not well understood, it is thought that inflammatory factors released from intramuscular adipose tissue may induce skeletal muscle dysfunction. Systemic inflammation characterized by elevated proinflammatory cytokines (e.g., interleukin [IL] -6, tumor necrosis factor-alpha [TNF-α], IL-1ß, and chemokines), acute phase proteins (e.g., C-Reactive Protein (CRP), fibrinogen, and serum amyloid A), and leukocytes are observed in COPD patients, especially during exacerbations (13). Furthermore, systemic inflammation causes sarcomeric injury and protein modification, leading to further deterioration of respiratory muscles (14). In conclusion, it can be argued that as the frequency and number of exacerbations increase, the deterioration of respiratory muscles may increase, and there may

be more thinning of the muscles. Patients who were admitted to the hospital due to four or more exacerbations within a year were defined as COPD susceptible to severe exacerbations in a study by Güerri Roberto et al.[15], and it was discovered that patients who were susceptible to multiple exacerbations had a decrease in intercostal muscle mass. In the same way, our study found a statistically significant negative correlation between FEV1 and the thickness of the respiratory muscles as the number of exacerbations increased within one year. This supports the idea that multiple exacerbations are linked to respiratory muscle atrophy. The main limitation of our study is the lack of a control group. Another limitation is the low proportion of women in our study. Whether these dynamic changes in muscles in COPD exacerbations are also observed in stable COPD patients must be confirmed. Evaluation of these dynamic changes in the prospectively stable periods of the same patients will also define the role of acute hyperinflation observed during exacerbations (15). One of the other important limitations of the study is the inability to evaluate other parameters affecting muscle strength. The strength and durability of the intercostal muscles may be important in assessing the function of the respiratory muscles. Muscle strength depends on muscle mass, composition, and microarchitecture. However, in our study, we only evaluated muscle section thickness as an indicator of muscle mass. However, it is unclear whether these data accurately reflect the intercostal muscles' overall volume and muscle mass (15). Therefore, more studies are needed to evaluate these relationships between respiratory muscle mass and function. Besides, muscle composition is an important parameter that affects muscle strength and function. Park, Mi Jung, et al.[11] used CT attenuation values to evaluate fat infiltration and showed that CT attenuation values were moderately correlated with COPD severity.

Consequently, as the severity of COPD exacerbation increases, diaphragmatic dysfunction develops and accessory respiratory muscle function increases to compensate. In our study, as an indirect indicator of this finding, the thickness of the parasternal intercostal and pectoralis major muscles increased with increasing severity of the exacerbation. However, on the contrary, in the diaphragm, the change in muscle thickness decreased as the severity of exacerbation increased. Also, intercostal muscle thickness was negatively correlated with severe exacerbations in COPD patients. These results suggest that ultrasonography may help characterize the cohort of COPD patients at risk for severe exacerbations, which could be an additional predictive variable. Evaluation of COPD exacerbation, an important step in COPD management, is subjective and is mostly based on the patient's pre-exacerbation clinical condition and treatment response. Our results predict that the evaluation of respiratory muscles by ultrasonography may provide useful information in evaluating COPD exacerbation and may be a promising, reliable, and reproducible biomarker for muscle evaluation without the risk of ionizing radiation. It also promises that it may create new opportunities to evaluate function and response to treatments in COPD patients and may be an important biomarker in patient follow-up.

Ethics Committee Approval: The study protocol was approved by the Bolu Abant Izzet Baysal University Clinical Researches Ethics Committee (Ethics committee registration number: 2019/84).

Conflict of Interest: The authors have declared that they have no conflict of interest.

Funding: The authors have declared that they have not received any financial support.

REFERENCES

1. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020. Available from: http://www.goldcopd.org/
2. Wallbridge P, Parry SM, Das S, Law C, Hammerschlag G, Irving L, et al. Parasternal intercostal muscle ultrasound in chronic obstructive pulmonary disease correlates with spirometric severity. Scientific reports. 2018; 8 (1): 1-9. https://doi.org/10.1038/s41598-018-33666-7

3. Wait JL, Nahormek PA, Yost WT, Rochester DP. Diaphragmatic thickness-lung volume relationship in vivo. J Appl Physiol. 1989; 67 (4): 1560-68. https://doi.org/10.1152/jappl.1989.67.4.1560
4. Formenti P, Umbrello M, Dres M, Chiumello D. Ultrasonographic assessment of parasternal intercostal muscles during mechanical ventilation. Ann of Intensive Care. 10.1 2020; 10 (1): 1-9. https://doi.org/10.1186/s13613-020-00735-y
5. DiMarco AF, Connors Jr AF, Kowalski KE. Gas exchange during separate diaphragm and intercostal muscle breathing. J App Physiol. 2004; 96 (6): 2120-24. https://doi.org/10.1152/japplphysiol.00628.2003
6. Kisner C, Colby LA. Therapeutic Exercise: Foundations and Techniques, 6th ed. Philadelphia: FA Davis, 2012. P. 993-1031.
7. Kang JI, Jeong DK, Choi H. Correlation between diaphragm thickness and respiratory synergist muscle activity according to severity of chronic obstructive pulmonary disease. J Phys Ther Sci. 2018;30 (1): 150-3. https://doi.org/10.1589/jpts.30.150
8. Rochester DF, Braun NM: Determinants of maximal inspiratory pressure in chronic obstructive pulmonary disease. Am Rev Respir Dis, 1985, 132: 42-47.
9. Calverley PM, Koulouris NG. Flow limitation and dynamic hyperinflation: key concepts in modern respiratory physiology. Eur Respir J. 2005; 25 (1): 186-99. https://doi.org/10.1183/09031936.04.00113204
10. Campbell JA., Hughes RL, Sahgal V, Frederiksen J, Shields TW. Alterations in intercostal muscle morphology and biochemistry in patients with obstructive lung disease. American Review of Respiratory Disease. 1980; 122 (5): 679-86. https://doi.org/10.1164/arrd.1980.122.5.679
11. Park MJ, Cho JM, Jeon KN, Bae KS, Kim HC, Choi DS, et al. Mass and fat infiltration of intercostal muscles measured by CT histogram analysis and their correlations with COPD severity. Acad Radiol. 2014; 21 (6): 711-7. https://doi.org/10.1016/j.acra.2014.02.003
12. Ju S, Lee SJ, Park MJ, Cho YJ, Jeong YY, Jeon KN, et al. Clinical importance of cross-sectional area of intercostal muscles in patients with chronic obstructive pulmonary disease. Clin Respir J. 2018; 12 (3): 939-47. https://doi.org/10.1111/crj.12609
13. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax. 2004; 59 (7): 574-80. https://doi.org/10.1136/thx.2003.019588
14. Ottenheijm CA, Heunks LM, Dekhuijzen PN. Diaphragm muscle fiber dysfunction in chronic obstructive pulmonary disease: toward a pathophysiological concept. Am J Respir Crit Care Med. 2007; 175 (12): 1233-40. https://doi.org/10.1164/rccm.200701-020PP
15. Güerri R, Gayete A, Balcells E, Ramirez-Sarmiento A, Vollmer I, Garcia-Aymerich J, et al. Mass of intercostal muscles associates with risk of multiple exacerbations in COPD. Respiratory medicine. 2010; 104 (3): 378-88. https://doi.org/10.1016/j.rmed.2009.10.015