BEYOND DYSPNEA: FRAILTY, KINESIOPHOBIA, FATIGUE, MUSCLE WEAKNESS AND FUNCTIONNAL DECLINE IN GERIATRIC COPD PATIENTS

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(Received 29th October 2025; revised 02nd February 2026; accepted 27th February 2026)

Abstract. This study aims to comprehensively evaluate and compare frailty, handgrip strength, physical activity, kinesiophobia, and fatigue in geriatric individuals with COPD and asymptomatic counterparts, and to investigate the specific impact of COPD on these clinical parameters. This study was completed with 25 older adults diagnosed with COPD and 25 asymptomatic elderly without a COPD diagnosis, selected from a total of 87 individuals who visited the Chest Diseases Clinic, were diagnosed with COPD, and agreed to participate in the study. The Fatigue Severity Scale was used to assess the fatigue levels of individuals, the TAMPA Scale of Kinesiophobia to evaluate kinesiophobia, the PRISMA-7 Frailty Test to determine frailty, the Physical Activity Scale for the Elderly (PASE) to assess physical activity levels, and the Handgrip Test to measure handgrip strength. A statistically significant difference was found between individuals with COPD and asymptomatic individuals in terms of fatigue severity level ($t=7.157$; $p=0.000$), TAMPA kinesiophobia level ($t=6.506$; $p=0.000$), PASE Physical Activity test ($t=-4.199$; $p=0.000$), Jamar Right Hand Strength test ($t=-2.812$; $p=0.007$), Jamar Left Hand Strength test ($t=-2.419$; $p=0.019$), and PRISMA-7 frailty test scores ($\chi^2=10.27$; $p=0.001$). Screening for frailty and kinesiophobia should be included in physiotherapy planning for geriatric COPD patients. Early and comprehensive evaluation of these domains is essential to guide targeted interventions, prevent functional decline, and improve overall quality of life in this population.
Keywords: *chronic obstructive pulmonary disease, fatigue, frailty, handgrip strength, kinesiophobia, physical activity*

Introduction

Chronic Obstructive Pulmonary Disease (COPD) has increasingly become a public health problem in the 21st century and will continue to maintain its importance in the future. Due to its high prevalence, potential to cause serious health issues, and increased risk of death, it poses a significant challenge to healthcare systems worldwide. The importance of this disease is expected to increase, especially as an aging global population will further demonstrate the long-term effects of COPD risk factors. Chronic obstructive pulmonary disease (COPD) is characterized not only by dyspnea, its most recognized symptom, but also by fatigue, which substantially impairs daily functioning and quality of life. Kinesiophobia, defined as fear of movement stemming from perceived risk of injury or pain, has been increasingly reported in COPD and is associated with avoidance of physical activity, thereby exacerbating functional decline. Among older adults, COPD has been linked to a heightened risk of frailty, driven by a combination of fatigue, kinesiophobia, reduced physical activity, comorbidities, and the restrictive effects of dyspnea on daily living (Zhao et al., 2018). Although regular physical activity is a cornerstone in preventing chronic disease progression, individuals

with COPD often experience exercise intolerance that promotes sedentary behavior from the early stages of the disease. This decline in activity levels accelerates over time, increasing the risk of hospitalization and mortality while diminishing quality of life (Meriam Syed Akil and Abdullah, 2014; The et al., 2014). Despite the well-documented impact of these factors individually, few studies have examined their combined effect in the geriatric COPD population. This study addresses that gap by providing a multidimensional evaluation of physical and psychological parameters, offering insights that may inform rehabilitation strategies and clinical practice.

A review of the literature reveals that there is insufficient research examining the combined assessment of frailty, handgrip strength, physical activity, kinesiophobia, and fatigue in individuals with COPD and asymptomatic geriatric individuals, as well as studies investigating the impact of COPD on these parameters in geriatric patients diagnosed with the disease. This is the first study in a purely geriatric sample simultaneously evaluating five parameters and comparing them with age-matched asymptomatic controls. The novelty and contribution of this study lie in the multidimensional assessment of physical and psychological parameters in geriatric COPD patients, providing insights that can guide rehabilitation and clinical practice. This study aims to conduct a multidimensional evaluation of frailty, handgrip strength, physical activity, kinesiophobia, and fatigue in geriatric individuals with and without COPD, and to determine the impact of COPD on these parameters.

Materials and Methods

Participant

The population of this descriptive study consisted of geriatric individuals diagnosed with COPD who presented to the Hospital outpatient clinic between June 2023 and December 2023. COPD participants were recruited from a clinical setting to ensure accurate diagnosis based on established clinical and spirometric criteria, while asymptomatic individuals were identified through snowball sampling to facilitate access to community-dwelling older adults without respiratory disease. This approach was selected to optimize feasibility and ensure an adequate sample size within the study period. G*Power (version 3.1.9.7, Universität Düsseldorf, Düsseldorf, Germany) was used for post-hoc power analysis, and the effect size was calculated based on the Fatigue Severity Scale scores between individuals diagnosed with COPD and asymptomatic geriatric individuals. Assuming that the effect size between the two groups would be large (f = 1.26(EFFECT SIZE)), the power analysis determined that including at least 36 participants in the study (at least 18 per group) would achieve 95% power at a 95% confidence level (with a 0.05 error rate).

A total of 87 individuals were initially contacted for participation in the study. Of these, 20 individuals were excluded for being under the age of 65 years, and 7 individuals declined to participate, resulting in 57 participants who met the initial inclusion criteria. Participants were allocated into two groups: 29 individuals diagnosed with COPD, recruited from a clinical setting, and 28 asymptomatic individuals, identified through snowball sampling from the community. Cognitive function was screened using the Mini Mental Test (MMT), and individuals with scores below the cutoff were excluded. Based on this criterion, 4 participants from the COPD group and 3 participants from the asymptomatic group were excluded. Consequently, 25 individuals with COPD and 25 asymptomatic individuals were included in the final

analysis. (*Figure 1*). In the COPD group, inclusion criteria for the study were defined as follows: having a diagnosis of stage 1 or stage 2 COPD according to GOLD criteria (COPD stages 1–2: FEV1/FVC <0.70; Stage 1: FEV1 ≥80% predicted, Stage 2: FEV1 50–79% predicted (GOLD, 2023), being over 65 years of age, volunteering to participate, having no mental or communication issues that would prevent responding to the study questionnaires, and having a Mini-Mental Test score of 24 or above. In the asymptomatic group, inclusion criteria were defined as follows: being over 65 years of age, volunteering to participate, having no mental or communication issues that would prevent responding to the study questionnaires, and having a Mini-Mental Test score of 24 or above. Exclusion criteria for the study were defined as having a diagnosis of physical or mental illness, unstable COPD, unstable angina, a history of myocardial infarction, uncontrolled hypertension, cancer, any orthopedic or neurological condition causing functional limitations, current alcohol or substance dependency, severe visual or hearing impairment, having undergone major surgery (such as cardiac surgery) in the past few months, and a history of recurrent significant clinical infections.

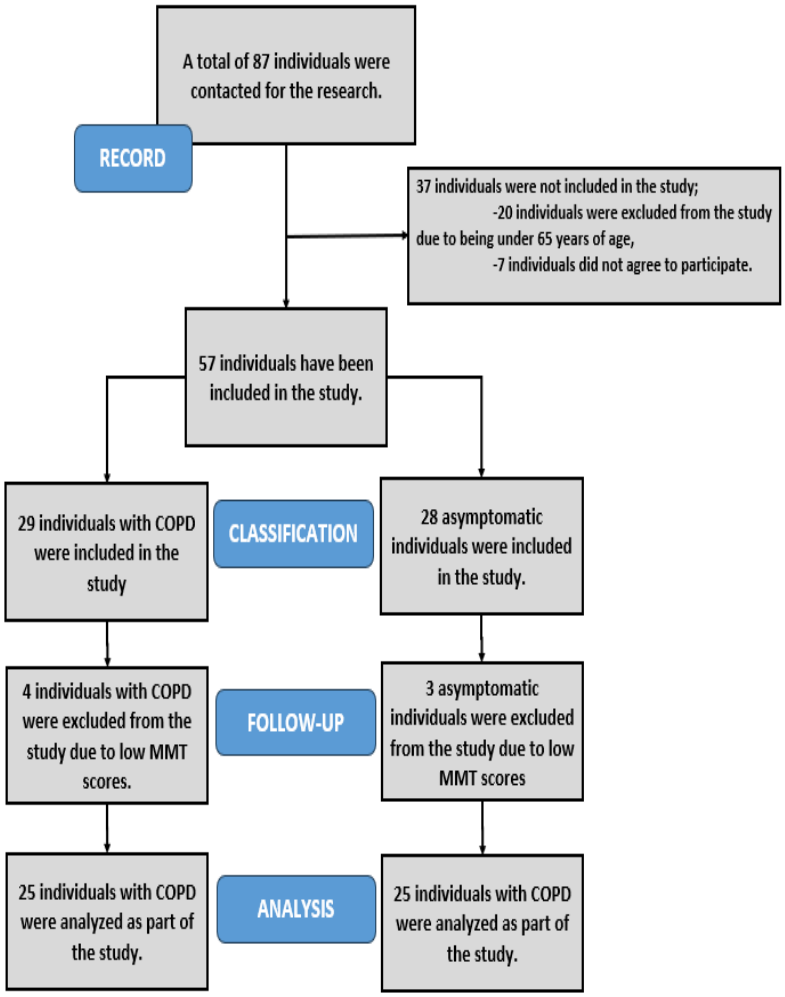

Figure 1. *Flowchart of individuals included in the study.*

Assessment tools

Pulmonary function tests, including FEV1, FVC, PEF, and FEV1/FVC ratio, were performed using a calibrated spirometer (device brand/model specified). Each participant performed at least three acceptable maneuvers, in accordance with ATS/ERS guidelines, and the highest values were recorded. Calibration of the device was conducted daily to ensure accuracy, and reproducibility criteria were applied to confirm that repeated measurements were consistent. All testing procedures followed standardized protocols to maintain reliability and comparability of results. In the COPD group, respiratory function test results indicated a mean FEV1 of 52.68±27.18 % predicted, a mean FVC of 52.96±22.62 % predicted, and a mean PEF of 41.08±19.13 % predicted. Consistent with the inclusion criteria based on GOLD stage 1–2 definitions, all participants had an FEV1/FVC ratio <0.70. To assess each individual included in the study, the Fatigue Severity Scale (FSS) was used to evaluate fatigue levels, and the TAMPA Scale (TKS). for Kinesiophobia to assess kinesiophobia, the PRISMA-7 Frailty Test (Akhter-Khan et al., 2022; Alhalaseh et al., 2022; Awang et al., 2022; Jaafar et al., 2022) to determine frailty, the Physical Activity Scale for the Elderly (PASE) to measure physical activity levels, and the Handgrip Strength Test to assess handgrip strength with JAMAR. Cognitive status was assessed with the Mini-Mental Test (MMSE). The Modified Medical Research Council Dyspnea Scale (MMRC) is used to evaluate the perception of shortness of breath in daily living activities.

Statistical analysis

Data were analyzed using IBM SPSS version 22 software. Descriptive statistics (mean, median, standard deviation, count, percentage, etc.) were calculated using the study participants' data. The suitability of quantitative variables for normal distribution was assessed using the Shapiro-Wilk test. For comparing differences between two groups regarding quantitative variables, an independent samples t-test was used for those showing normal distribution. In contrast, the Mann-Whitney U test was used for those not normally distributed. Differences between the two groups regarding qualitative variables were analyzed using the Chi-square test. Effect sizes were calculated and interpreted according to Cohen's conventional thresholds (0.20 = small, 0.50 = medium, 0.80 = large). In all analyses, a p-value of <0.05 was considered statistically significant.

Results and Discussion

Table 1 shows the distribution of physical characteristics. The demographic and clinical characteristics of the COPD and asymptomatic groups are presented in *Table 2*. Gender distribution was identical in both groups, with 52% female and 48% male participants (p=1.000). A family history of COPD was reported in 36% of the COPD group and 24% of the asymptomatic group, but the difference was not statistically significant (p=0.354). The presence of chronic disease was similar between groups (52% vs. 56%, p=0.777) (*Table 2*).Regarding the types of chronic diseases, diabetes mellitus (DM) and hypertension (HT) were the most common comorbidities in both groups, while osteoporosis (OP) and coronary artery disease (CAD) were only observed in the COPD group; however, no statistically significant differences were found (p=0.430) (Table 2). Smoking status differed significantly between groups (p=0.012). In the COPD group, 28% were current smokers and 48% were former smokers, while in the asymptomatic group, 20% were current smokers and only 16% were former

smokers. The number of cigarettes smoked per day and the duration of smoking did not differ significantly between the groups (p=0.416 and p=0.208, respectively) (*Table 2*). The results of the PRISMA-7 Test for frailty, hand grip strength, MMRC, PASE, fatigue, TAMPA Kinesiophobia Scale, and Mini Mental Test for individuals with COPD and asymptomatic individuals are presented in *Table 3*.

***Table 1**. Physical characteristics of individuals.*

Category	COPD (Mean±SD)	Asymptomatic (Mean±SD)	t	p
Age(year)	72,2 ± 7	72,64 ± 6,05	-0,238	0,813
Height(cm)	160,52 ± 7,05	162,44 ± 4,27	-1,164	0,250
Weight (kg)	72,72 ± 12,22	73,48 ± 11,02	-0,231	0,818
BMI(kg/m^2)	28,44 ± 4,46	27,86 ± 4,2	0,467	0,642

Note: P < 0.05; t=Independent Simple T-Test; SD=Standard Deviation; BMI=Body Mass Index; COPD=Chronic Obstrictive Pulmonary Disease.

***Table 2**. Sociodemographic characteristics of individuals.*

Category		COPD (N;%)		Asymptomatic (N;%)		X^2	P
Gender	Famale	13	52 %	13	52 %	0	1
	Male	12	48 %	12	48%		
Presence of COPD in family	Yes	9	36 %	6	24%	0.857	0.354
	No	16	64%	19	76%		
Presence of Chronic Disease	Yes	13	52%	14	56%	0.081	0.777
	No	12	42%	11	44%		
Education	Illiterate	4	16%	6	20%	16.47	0.006*
	Literate	1	4%	10	40%		
	Primary School	18	72%	6	24%		
	Secondary School	1	4%	3	12%		
	University	1	4%	1	4%		
Chronic Disease	No	12	48%	11	44%	3.827[a]	0.43
	DM	5	20%	6	24%		
	HT	5	20%	8	32%		
	OP	1	4%	0	0%		
	CAD	2	8%	0	0%		
Smoking Status	Yes	7	28%	5	20%	8.878	0.012*
	Quit	12	48%	4	16%		
	No	18	72%	20	80%		
Cigarettes (Quantity)	1-5 Per Day	2	8%	0	0%	2.844[a]	0.416
	6-10 Per Day	1	4%	1	4%		
	10 and more	4	16%	4	16%		
Duration of Smoking (Year)	Never	16	64%	20	80%	1.587[a]	0.208
	Less than year	0	0%	0	0%		
	1-5 Year	0	0%	0	0%		
	6-10 More Year	9	36%	5	20%		

*Note: *p<0,00; a=x^2; DM=Diabetes Mellutus; HT=Hypertension; OP=Osteoporosis; CAD=Coronary Artery Disease.*

***Table 3**. Results of the PRISMA-7 Test for Frailty, Grip Strength, MMRC, PASE, Fatigue, TAMPA Kinesiophobia Scale, and Mini Mental Test in Geriatric Individuals with COPD and Asymptomatic Individuals.*

PRISMA 7	COPD	Asymptomatic	x^2/t	P	d
Frailty (n/%)	15 (60%)	4 (16%)	10,27[a]	0,001*	-
Non Frailty (n/%)	10 (40%)	21 (84%)	10,27[a]	0,001*	-
MMRC (Mean±SD)	3,68±0,8	0,56±0,51	16,4[b]	0,000*	4,65
PASE Leisure Activities (Mean±SD)	57,11±39,56	75,71±31,74	-1,83[b]	0,073	-0,52
PASE Household Activites (Mean±SD)	16,08±30,85	59,65±45,78	-3,94[b]	0,000*	-1,12
PASE Work Activites (Mean±SD)	0±0,000	59,65±45,78	FE	FE	FE
PASE Total (Mean±SD)	73,19±52,33	131,31±45,29	-4,19[b]	0,000*	-1,18
Fatigue (Mean±SD)	3,82±1,05	1,63±1,12	7,15[b]	0,000*	2,03
TAMPA Kinesiophobia Scale (Mean±SD)	49,84±9,42	36,2±4,6	6,50	0,000*	1,84
Mini-Mental State Examination (Mean±SD)	26,92± 2	24,92±0,76	4,67[b]	0,000*	1,32
Right Hand Grip Strength (Mean±SD)	15,34±7,95	20,93±5,97	-2,81[b]	0,007*	-0,79
Left Hand Grip Strength (Mean±SD)	16,21±7,81	20,69±4,98	-2,41[b]	0,019*	-0,69

*Note: *P<0.05; a=x^2 test, d=Chon's d; b=Independent Samples T-Test; SD=Standard Deviation; MMRC=Modified Medical Research Council Dyspnea Scale; PASE=Physical Activity Scale for the Elderly; FE=Floor Effect.*

In the comparison of groups, the prevalence of frailty was significantly higher in the COPD group (60%) compared to the asymptomatic group (16%) (p=0.001). Physical activity levels assessed by PASE revealed that COPD participants had markedly lower scores in household activities (p=0.000, d=-1.12) and total activity (p=0.000, d=-1.18), while leisure activity scores were lower but not statistically significant between groups (p=0.073, d=-0.52). In the PASE "work activity" domain, all participants scored 0 (0±0.00), indicating a clear floor effect. Therefore, no comparative statistical analysis was performed for this domain. Fatigue severity was significantly higher in the COPD group compared to the asymptomatic group, (p=0.000, d=2.03). Similarly, kinesiophobia scores were elevated among COPD participants relative to the asymptomatic group (p=0.001, d=1.84). Regarding muscle strength, the COPD group demonstrated significantly lower grip strength both in the right hand (p=0.007, d=-0,79) and the left hand (p=0.019, d=-0,69) (*Table 3*).

As a result of the study, it was determined that geriatric individuals with COPD had lower hand grip strength and physical activity levels compared to asymptomatic individuals, while their levels of kinesiophobia, frailty, and fatigue were found to be higher. The finding that MMSE scores were higher in the COPD group than in the asymptomatic controls is unexpected and requires explanation. A plausible reason may be differences in educational attainment, which is a well-established determinant of MMSE performance. Previous research has shown that longer years of education are strongly associated with higher MMSE scores (Banerjee et al., 2023; Granet et al., 2023; Pengpid and Peltzer, 2023). Studies show that low education can result in lower MMSE scores and may lead to false identification of cognitive impairment. Educational level influences MMSE more than age in some populations, and cultural factors related to schooling contribute to these effects Higher educational attainment is also linked to greater cognitive reserve, allowing individuals to compensate for neuropathology and achieve better scores despite underlying impairments (Singh and Misra, 2009).

Fatigue in COPD, typically described as physical fatigue, is a critical determinant of quality of life and requires accurate assessment to guide coping strategies. Previous studies have reported clinically significant fatigue in a majority of COPD patients, with associations to reduced health-related quality of life and increased psychological burden. In the current study, the results of the FSS applied to individuals with COPD and asymptomatic individuals indicated that the fatigue severity was higher in the COPD group. In our study, which yielded results similar to those in the literature, fatigue was identified as a significant issue in individuals with COPD. The respiratory difficulties, shortness of breath, and coughing symptoms experienced by patients can lead individuals with COPD to exert more effort when breathing. Consequently, many COPD patients may avoid physical activity, resulting in decreased physical capacity and, in turn, reduced respiratory capacity. Fatigue, physical capacity, and fatigue parameters can create a cyclical pattern, where each aspect reinforces the others. This cycle can increasingly contribute to chronic fatigue in individuals with COPD, leading to a deterioration in COPD severity levels. Conversely, it may result in a decline in physical capacity and muscle strength over time. Therefore, we believe that accurately

assessing fatigue is a critical step in enhancing patients' quality of life and helping them manage their symptoms effectively.

Severe dyspnea in COPD patients negatively affects sleep quality and recovery, often leading to fatigue, which is the second most common symptom after dyspnea but frequently overlooked. Fatigue contributes to reduced quality of life, lower physical activity, higher hospitalization rates, and psychological complications such as anxiety and depression, which may in turn promote kinesiophobia and reduce treatment adherence (Fakoya et al., 2020). Consistently, studies have shown that increasing respiratory distress is associated with higher kinesiophobia, and that 90.3% of COPD patients exhibit high kinesiophobia, which is significantly correlated with fatigue severity (Tricco et al., 2018). The results of the current study indicate that individuals with COPD have higher kinesiophobia scores compared to asymptomatic controls. Decreased muscle strength and symptoms such as coughing, sputum production, shortness of breath, and pain may exacerbate fear of movement, affecting daily activities. These findings highlight the importance of targeted education and exercise programs, including pulmonary rehabilitation and strength training, to improve muscle function, reduce kinesiophobia, and enhance functional independence and quality of life in geriatric patients with COPD.

In geriatric individuals with COPD, frailty is influenced by factors such as age, disease stage, ineffective management, high CAT and MMRC scores, frequent exacerbations, smoking, and comorbidities. Advancing age and disease progression reduce physiological reserves and increase frailty risk, while poor disease control and frequent exacerbations further exacerbate vulnerability. A meta-analysis of 27 studies demonstrated that COPD doubles the risk of frailty in older adults. Furthermore, frailty has been linked to worse outcomes; for example, 45% of COPD patients with severe frailty were rehospitalized within 90 days after an acute exacerbation, compared to 18% of non-frail patients. In the present study, when examining the PRISMA-7 frailty test results of individuals with COPD, frailty was found in 60% of the COPD group, while this rate was only 16% in the asymptomatic geriatric group. The frailty status of the COPD participants in the study was determined to be frail compared to the asymptomatic individuals. An increase in the degree of frailty can negatively affect patients' quality of life and lead to various complications. In line with these results, assessing the frailty status of COPD patients and implementing appropriate interventions suggests that it is crucial for improving patients' quality of life and health outcomes. Therefore, taking action to detect frailty symptoms at an early stage and implementing preventive measures is an important issue that concerns all healthcare personnel working with geriatric COPD patients. Patients should be relieved of their kinesophobia and gradually re-engaged in movement with the safest exercises. Additionally, identifying frailty COPD patients can reduce the rates of early hospital admissions and shorten the length of stay.

Individuals with COPD had lower PASE household chores, work activities, and total scores compared to asymptomatic individuals. These results suggest that a combination of factors such as reduced lung function and capacity, dyspnea, low motivation, unawareness of the benefits of physical activity, socio-environmental factors, exacerbations, and comorbidities may be associated with low physical activity levels. For instance, dyspnea, inability to breathe, sudden coughing, and sputum production can lead to low motivation. In such cases, patients may reduce their participation in physical activity due to anxiety caused by unmanageable respiratory distress. The tendency to

think about the potential risks of being physically active and avoid incidents like falls can also diminish individuals' willingness to engage in physical activity. The combination of these factors may lead to decreased physical activity among COPD patients, consequently reducing their quality of life. Encouraging individuals to develop a more positive attitude towards physical activity can enhance their quality of life. Changing physical activity behavior in patients with COPD requires multidisciplinary collaboration. Different types, timing, and intensity levels of physical activity should be well-defined for geriatric individuals with COPD, and encouragement for movement should be increased.

Handgrip strength is a widely used marker of overall muscle strength, functional capacity, and disease progression in COPD, providing valuable information for treatment monitoring and management. Peripheral muscle dysfunction and respiratory muscle weakness are common in COPD. COPD patients with clinically significant fatigue had lower grip strength compared to those without fatigue. Similarly, although grip strength did not differ significantly between COPD and asymptomatic groups, it was associated with quality-of-life domains such as physical functioning, pain, anxiety, and depression. Moreover, significant sex-related differences in grip strength among COPD patients, highlighting the importance of muscle function in disease outcomes. The current study found that both right and left handgrip strength were lower in geriatric COPD patients compared to asymptomatic controls, reflecting the impact of prolonged immobility and sedentary lifestyle on major and peripheral muscle groups. These findings highlight the importance of targeted exercise interventions, including resistance and functional strength training, within pulmonary rehabilitation programs to preserve muscle function, enhance daily activity performance, and improve overall quality of life in this population.

In the current study, effect size analysis demonstrated clinically meaningful differences between geriatric individuals with COPD and asymptomatic controls across multiple parameters. The largest effects were observed in dyspnea severity (MMRC, d = 4.65), fatigue (d = 2.03), and kinesiophobia (d = 1.84), underscoring the profound impact of COPD on respiratory function, perceived exertion, and fear of movement. Physical activity showed large negative effects, particularly in household (d = -1.12), work-related (d = -1.84), and total activity scores (d = -1.18), reflecting significant functional limitations in daily life. Handgrip strength (right d = -0.79, left d = -0.69) also revealed moderate-to-large differences, indicating that COPD extends beyond respiratory impairment to influence musculoskeletal health. Collectively, these findings highlight the multidimensional burden of COPD in older adults and reinforce the need for comprehensive management strategies, including pulmonary rehabilitation, resistance training, and targeted educational programs to address both physical and psychological domains.

Limitations of the study

This study was conducted in only one province, Kırıkkale, and at a single hospital. Research conducted in a single hospital may not encompass individuals with diverse demographic and socioeconomic characteristics, which can limit the validity of the results. In addition, the recruitment of COPD participants from a clinical setting and asymptomatic individuals through snowball sampling may have introduced selection bias and limited the comparability between groups. COPD participants may represent individuals with more severe or clinically recognized disease, while asymptomatic

participants may differ in unmeasured sociodemographic or health-related characteristics. Future studies should consider employing matched sampling strategies or recruiting both groups from similar settings to enhance comparability. Assessors were not blinded to group allocation, which may have introduced measurement bias, particularly for subjective outcomes such as fatigue and kinesiophobia. To minimize potential bias in future studies, assessors should be blinded to participants' group allocation. If blinding is not feasible, objective outcome measures or standardized assessment protocols should be emphasized to reduce subjective influence on the results. One of the other limitations of the current study is its cross-sectional design, which precludes establishing causal relationships between COPD and the observed outcomes. While significant associations were identified across physical and psychological domains, the temporal order of these findings cannot be determined. Therefore, longitudinal or interventional studies are needed to confirm these associations and better understand the causal mechanisms underlying the impairments observed in older individuals with COPD. PASE 'work activity' domain, all participants scored 0, indicating a floor effect; therefore, comparative statistical analysis could not be performed for this domain, which may be considered a limitation of the study.

Conclusion

In geriatric COPD patients, physiotherapy planning should not only target dyspnea but also assess frailty, kinesiophobia, handgrip strength, and physical activity. The simultaneous deterioration in these domains highlights the need for integrated pulmonary rehabilitation. Although fatigue, kinesiophobia, muscle weakness, and reduced physical activity are well-established features of COPD, this study provides novel insight by examining these parameters specifically in geriatric patients and comparing them with asymptomatic age-matched controls. By simultaneously evaluating frailty, handgrip strength, and different domains of physical activity, our findings highlight the combined functional and psychological burden of COPD in older adults, offering a more comprehensive perspective than previous studies that assessed these outcomes separately or in younger populations. In addition, the relationship between these parameters can be examined in future studies.

Acknowledgement

This research is self-funded.

Conflict of interest

The authors confirm that there is no conflict of interest involve with any parties in this research study.

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