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RESEARCH ARTICLE

The effect of health-related quality of life and physical activity on time to first exacerbation in chronic obstructive pulmonary disease patients

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ABSTRACT

The effect of health-related quality of life and physical activity on time to first exacerbation in chronic obstructive pulmonary disease patients

Introduction: *It is known that there is a relationship between severe exacerbations of chronic obstructive pulmonary disease(COPD) requiring hospitalization with loss of forced expiratory volume in one second (FEV_1), impaired quality of life, and increased mortality. The aim of this study was to investigate factors [health-related quality of life with COPD Assessment Test (CAT), physical activity, FEV_1, PaO_2] affecting the time to first exacerbation (TTFE) after discharge in patients hospitalized with exacerbation.*

Materials and Methods: *Seventy-five patients who were hospitalized due to COPD acute exacerbation were included in the study and were prospectively monitored. First exacerbation after discharge was recorded. During the first three days of hospitalization, patients were fitted with a pedometer on any of these days; 24-hour step counts were recorded and CAT was administered through face-to-face interviews. Data on age, sex, PaO_2, FEV_1, and comorbidities were recorded. The median value of the CAT scores of the participants were taken as the cut-off point. High scores were considered as an indicator of poor quality of life. Cox regression models were created for multivariate analyses and hazard ratios (HR) with 95% confidence interval (95% CI) provided.*

Results: *There was a statistically significant relationship between the TTFE and CAT score (p= 0.001), FEV_1 (pred %) (p= 0.02) and PaO_2 (p= 0.02). No statistically significant relationship was found between TTFE and the number of steps used as an indicator of physical activity (p= 0.3). In multivariate analysis, age and sex adjusted CAT and PaO_2 significantly affected the TTFE*

(HR= 2.06 CI 95%= 1.17-3.65 and HR= 5.50 CI 95%= 2.09-14.49, respectively) while adjusted FEV_1 (pred %) was not significantly affected the TTFE (HR= 1.54 CI 95%= 0.88-2.70).

Conclusion: *The results of this study suggest that using CAT may be an easy-to-apply and practical tool to help identify patients with an increased risk of exacerbation. No significant correlation was found with the daily number of steps, which is an easily measurable indicator of physical activity.*

Key words: *Exacerbation; COPD; COPD Assessment Test (CAT); health-related quality of life; pedometer*

ÖZ

KOAH'lı hastalarda sağlıkla ilişkili yaşam kalitesi ve fiziksel aktivitenin taburculuk sonrası ilk alevlenmeye kadar geçen süre üzerine etkisi

Giriş: *Hastaneye yatış gerektiren ağır kronik obstrüktif akciğer hastalığı (KOAH) akut alevlenmeleri ile zorlu ekspirasyonun birinci saniyesindeki volüm (FEV_1) kaybı, yaşam kalitesinde kötüleşme ve mortalite artışı arasında ilişki olduğu gösterilmiştir. Bu çalışmanın amacı ağır KOAH alevlenmelerinde taburculuk sonrası yeniden alevlenmeye kadar geçen süre üzerine etki eden faktörleri [yaşam kalitesi anketi olarak KOAH Değerlendirme Testi (CAT), fiziksel aktivite, FEV_1 ve PaO_2] araştırmaktır.*

Materyal ve Metod: *KOAH akut alevlenme sebebi ile hastaneye yatırılan 75 hasta çalışmaya alındı ve prospektif olarak izlendi. Taburculuk sonrası ilk alevlenme zamanı kaydedildi. Hastalara yatışlarının ilk üç günü içerisinde herhangi bir gün pedometre takılarak 24 saatlik adım sayıları kaydedildi ve CAT yüz yüze görüşme yöntemiyle uygulandı. Yaş, cinsiyet, PaO_2, FEV_1 ve komorbidite varlığı verileri kaydedildi. Çalışmaya katılanların CAT skorlarının ortanca değerleri kesim noktası olarak alındı. Yüksek skor kötü yaşam kalitesi göstergesi olarak kabul edildi. Çok değişkenli analizler için cox regresyon modelleri oluşturuldu ve zarar oranı (HR) %95 güven aralığı ile sunuldu.*

Bulgular: *Taburculuk sonrası ilk alevlenmeye kadar geçen süre (İAGS) ile CAT skoru(p= 0,001), FEV_1 (pred %) (p= 0,02) ve PaO_2 (p= 0,02) arasında istatistiksel anlamlı ilişki saptandı. İAGS ile fiziksel aktivite göstergesi olarak kullanılan adım sayısı arasında istatistiksel olarak anlamlı ilişki yoktu (p= 0,3). Çok değişkenli analizlerde yaş ve cinsiyet kontrol edildiğinde CAT ve PaO_2 İAGS'yi etkilerken (sırasıyla, HR= 2,06 CI 95%= 1,17-3,65 ve HR= 5,50 CI 95%= 2,09-14,49) FEV_1'in böyle bir etkisi gözlenmedi (HR= 1,54 CI 95%= 0,88-2,70).*

Sonuç: *Taburculuk sonrası ilk alevlenmeye kadar geçen süre (İAGS) ile CAT skoru(p= 0,001), FEV_1 (pred %) (p= 0,02) ve PaO_2 (p= 0,02) arasında istatistiksel anlamlı ilişki saptandı. İAGS ile fiziksel aktivite göstergesi olarak kullanılan adım sayısı arasında istatistiksel olarak anlamlı ilişki yoktu (p= 0,3). Çok değişkenli analizlerde yaş ve cinsiyet kontrol edildiğinde CAT ve PaO_2 İAGS'yi etkilerken (sırasıyla, HR= 2,06 CI 95%= 1,17-3,65 ve HR= 5,50 CI 95%= 2,09-14,49) FEV_1'in böyle bir etkisi gözlenmedi (HR= 1,54 CI 95%= 0,88-2,70).*

Anahtar kelimeler: *Alevlenme; KOAH; KOAH Değerlendirme Testi (CAT); sağlıkla ilişkili yaşam kalitesi; pedometre*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation that is not fully reversible and occurs as a result of an inflammatory response to harmful gases and particles, particularly cigarette smoke. The inflammation is not limited to the lungs and has systemic features. It is a preventable and treatable disease that progresses with acute exacerbations with increasing severity and frequency.

COPD is becoming a significant socioeconomic issue in both developed and developing countries. It is a major public health issue all over the world, and in our country, its mortality, morbidity, and prevalence are all high and rising. In 2020, it is expected to rank third among all causes of death worldwide (1).

Acute COPD exacerbation goes beyond the normal changes that occur during the course of the disease. It is defined as acute events that are severe enough to necessitate treatment modifications and are characterized by dyspnea, cough, and/or a change in sputum (2).

In previous studies, a relationship has been found between the frequency of acute exacerbations of COPD and loss of forced expiratory volume in one second (FEV_1), poor health-related quality of life, and increased mortality. As a result, it is now widely accepted that acute exacerbations are a significant complication of COPD, and identifying risk factors that increase the frequency of exacerbations is beneficial for improving treatment and disease outcomes (3).

Patients with moderate to severe COPD have one or two exacerbations per year that require hospitalization. However, annual exacerbation frequency varies among individuals, some individuals are more prone to frequent exacerbations (4). In acute exacerbations, the ventilation/perfusion balance is further disturbed, and alveolar hypoventilation and carbon dioxide retention may develop as a result of hypoxia and res-

piratory muscle dysfunction. Exacerbations increase the annual decline in FEV_1 and accelerate disease progression (5,6).

Respiratory questionnaires and dyspnea scales have been designed to assess the level of respiratory distress, to distinguish between patients who have less or more dyspnea, to assess change in the level of dyspnea as the disease progresses, and to quantify the degree of respiratory distress (7,8). Quality of life questionnaires and dyspnea scales have a wide range of uses for measuring dyspnea.

The most important clinical problems reported by patients are dyspnea and impaired quality of life. As suggested by Jones, "Health-related quality of life is the formal and standardized measurement of the effect of the disease on a person's daily life and well-being, it is a structured clinical history" (9).

The COPD Assessment Test (CAT) is an eight-question scale that measures health status in COPD and is used in many languages with validity and reliability. This test examines the impact of COPD on a broad scale, including cough, sputum, respiratory symptoms, fatigue, and confidence in leaving the house. Its validity and reliability in Türkiye have been demonstrated by Yorgancıoğlu et al (10). It is suitable for routine clinical use, is easily accessible, and simple to understand and interpret (11). It also provides a good understanding of the impact on health in COPD patients (12). A previous study found that CAT scores differed significantly between patients with stable and exacerbated COPD (9). In addition, longitudinal studies have shown that CAT scores are associated with the severity of exacerbation and respond to changes in health status during and after exacerbations (13-15).

Because of the close relationship between physical activity levels, health, disability, and mortality, it is widely accepted that determining the amount and degree of physical activity in daily life is critical. As a result, in recent years, there has been an increased interest in determining physical activity in sedentary populations, particularly patients with COPD (16). Physical activity levels in patients decrease during an exacerbation, and it takes time to return to pre-exacerbation levels (17).

Anticipating exacerbations is important for regulating the post-discharge treatment of patients and developing preventive measures for risk factors. In patients with COPD admitted to the hospital with exacerbation, CAT scores of 31 and above were found to be a risk factor for re-admission to the hospital within three months (18). This study aimed to investigate factors affecting the time to re-exacerbation after discharge in patients hospitalized with exacerbations. To that end, we assess the utility of the COPD Assessment Test (CAT), a practical and easy-to-understand quality of life questionnaire used in clinical practice, and the number of steps providing objective data measured with a pedometer in predicting TTFE.

MATERIALS and METHODS

Seventy-five patients who were hospitalized with a diagnosis of acute exacerbation [according to Anthonisen criteria: (1) increased dyspnea, (2) increased amount of sputum, (3) increased sputum purulence] and were compatible with COPD diagnosis criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines with chronic dyspnea, cough and sputum, and airflow limitation (FEV_1/FVC rate 70% or less in respiratory function test) between October 2013 and August 2015 in a pulmonary diseases department were included in the study. Patients included in the study were prospectively followed up. Seventy patients were called by phone if they did not attend follow-up assessments. The first exacerbation after discharge was defined according to the Anthonisen criteria and its time was recorded. The demographic data of the patients were recorded during hospitalization, and pulmonary function tests were performed.

Patients with bronchiectasis, asthma, interstitial fibrosis, or physical impairment (e.g., cerebrovascular disease, rheumatoid arthritis) were unable to comply with the pulmonary function tests and were excluded from the study. Patients who had problems with consciousness and cooperation in understanding and completing questionnaires were also excluded from the study.

A detailed history of the patients was taken. Clinical symptoms and findings, duration of illness and treatment, concomitant diseases, smoking history, number of exacerbations in the previous year, and hospitalization history due to exacerbation were inquired. A history of two or more exacerbations per year was considered frequent exacerbations. Height (m), weight (kg), and body mass index (kg/m^2) were recorded. Respiratory function tests were performed. Four patients could not comply with the respiratory

function tests. On any of the first three days of hospitalization, patients were fitted with a pedometer; 24-hour step counts were recorded and CAT was administered through face-to-face interviews

Statistical Analysis

The analysis of the data was performed using the SPSS Windows 15 software. Descriptive statistics were given as mean ± standard deviation and median (minimum-maximum) for continuous variables, and categorical variables were shown as numbers and percentages.

The median value of the CAT score was taken as the cut-off point. twenty five or above was considered an indication of poor quality of life. For physical activity level, the median of step numbers was taken as the cut-off point. FEV_1 (pred %) value was dichotomized by %30 as the indicator for severe obstruction (19). Similarly, PaO_2 of <40 mm Hg was the indicator for severe hypoxemia (20). In univariate analysis, the student's t-test and the Mann-Whitney U test were used. The Cox regression model was used for multivariate analyses. The model included variables that were significant in the univariate analysis as well as variables that were considered confounding factors. The results of multivariate analyses are presented with hazard ratios (HR) and 95% confidence intervals (CI).

RESULTS

The study included 75 patients (eight females and 67 males) who were hospitalized due to an acute exacerbation of COPD between October 2013 and March 2015. The mean age of the patients was 67.1 ± 8.8 years. The median CAT score was 25 (minimum 6-maximum 40).

The median number of steps as measured using a pedometer to evaluate the physical activities of the patients was 933 (min-max= 122-3609). The time to first exacerbation (TTFE) after discharge was 60 ± 34 days. Table 1 shows the demographics and characteristics of all patients at baseline.

The relationship between TTFE after discharge and other parameters is shown in Table 2. There was a statistically significant relationship between CAT scores (p= 0.001), FEV_1 (pred %) (p= 0.02), and PaO_2 (p= 0.02). There was no relationship between TTFE (p= 0.72) with age (p= 0.72), sex (p= 0.21), presence of comorbidities (p= 0.23), and the number of steps

Table 1. Demographics and other baseline characteristics

Variables	n= 75*
Age	67.1 ± 8.8
Sex	
Female	8 (10.7)
Male	67 (89.3)
Smoking History	
Never smoking	4 (5.3)
Quit	60 (80)
Smoking	11 (14.7)
Pack years [median (min-max)]	55 (10-150)
Laboratory parameters	
PaO_2 (mmHg)	54.8 (±12)
FEV_1 (pred%)†	38.8 (±15.8)
Pedometer	
Number of steps	933 (122-3609)
CAT score	25 (6-40)
Comorbidity	
Yes	38 (50.7)
No	37 (49.3)
Frequent exacerbation history (≥2 exacerbation/year)	
Yes	60 (80)
No	15 (20)

* Data are presented as mean ± SD, n (%) or median (min-max).
† FEV_1% is presented for over 71 people.
mMRC: Modified medical research council.
FEV_1: Forced expiratory volume in 1 second.
CAT: COPD assessment test.

(p= 0.3). It was found that the mean TTFE (72 ± 39 days) of patients with CAT scores below 25 was longer than the mean TTFE (47 ± 18 days) for those with CAT scores above 25 (p= 0.001). in patients with severe airway obstruction with FEV_1 below 30%, the mean TTFE was 52 ± 18 days, whereas it was 68 ± 40 days for those with FEV_1 above 30% (p= 002). Patients with low PaO_2 had similar exacerbations after a shorter time (p= 0.02). (Table 2).

In multivariate analysis, age and sex-adjusted CAT and PaO_2 significantly affected the TTFE (HR= 2.06 CI 95%= 1.17-3.65 and HR= 5.50 CI 95%= 2.09-14.49, respectively) whereas adjusted FEV_1 (% pred) did not (HR= 1.54 CI 95%= 0.88-2.70) (Table 3). Figure 1 shows the TTFE hazard graph according to low and high CAT scores.

Table 2. Relationship between TTFE with demographic characteristics, laboratory findings, and quality of life

Parameters		TTFE (day) (mean ± SD)	p
Age	<60 (n= 13)	66 ± 40	0.72
	≥60 (n= 57)	59 ± 32	
Sex	Female (n= 8)	74 ± 42	0.21
	Male (n= 62)	59 ± 32	
Comorbidities	Yes (n= 36)	58 ± 19	0.23
	No (n= 34)	63 ± 44	
CAT	<25 (n= 37)	72 ± 39	0.001
	≥25 (n= 33)	47 ± 18	
Number of steps	<933 (n= 35)	56 ± 31	0.3
	≥933 (n= 35)	65 ± 35	
FEV_1 (pred%)	<30% (n= 27)	52 ± 18	0.02
	≥30% (n= 40)	68 ± 40	
PaO_2	<40 (n= 8)	35 ± 8	0.02
	≥40 (n= 61)	64 ± 34	

FEV_1: Forced expiratory volume in 1 second, CAT: COPD assessment test, TTFE: Time to first exacerbation.

Table 3. Risk factors affecting TTFE (Cox regression)

Risk factors	HR (95% CI)	p
Sex Female (R)	0.63 (0.27-1.48)	0.29
Age	1.01 (0.98-1.04)	0.47
FEV_1 (%) <30% (R)	1.54 (0.88-2.70)	0.12
CAT ≥25 (R)	2.06 (1.17-3.65)	**0.01**
PaO_2 <40 (R)	5.50 (2.09-14.49)	**0.001**

FEV_1: Forced expiratory volume in 1 second, CAT: COPD assessment test, TTFE: Time to first exacerbation, (R): Reference group.

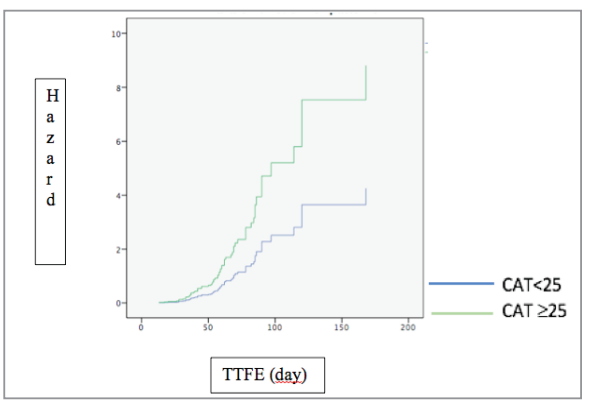

Figure 1. TTFE hazard graph based on low and high CAT scores. CAT: COPD assessment test, TTFE: Time to first exacerbation.

DISCUSSION

Chronic obstructive pulmonary disease is a treatable and preventable disease and is one of the leading causes of morbidity and mortality worldwide. The current method of evaluating COPD patients based solely on spirometry results is insufficient. COPD is a disease that must be assessed in a variety of ways, including its effects on daily life activities, respiratory functions, symptoms, health status, daily physical activity level, exercise capacity, body mass index, complications, comorbidities, exacerbations, and social determinants of the disease (3).

Studies have shown that acute exacerbations of COPD have negative effects on health-related quality of life, lung function, use of health resources, and mortality (5,6). Therefore, appropriate treatment of exacerbations is considered to have an important role in the management of the disease (21).

There are studies comparing the activity levels of COPD patients and healthy groups, as well as evaluating the physical activity and health-related quality of life of COPD patients when stable (22-24). However, studies evaluating patients during exacerbations are limited (4,6,25). The purpose of this study was to assess the effects of physical activity and health-related quality of life on TTFE and to interpret the findings in a way that would help with the approach to acute exacerbations and treatment.

The utility of CAT was investigated. In the study, patients with low CAT scores had a significantly longer time until their first exacerbation after discharge. When CAT scores were adjusted for frequent exacerbation history, age, sex, presence of comorbidities, and FEV_1, good quality of life was shown to significantly increase the time to hospitalization with re-exacerbation. In a study by Lee et al., patients were divided into four groups according to CAT scores, and a strong relationship was found between CAT scores and TTFE. Similarly, in the same study, higher CAT score categories were found to be associated with shorter TTFE and higher exacerbation risk when compared to the lowest CAT score category (26).

Suetemo et al. discovered that high CAT scores and low FEV_1 predicted moderate or severe COPD exacerbations independently when they compared the frequency of moderate or severe exacerbation and hospitalization in two groups of 64 people with high CAT scores and 59 people with low CAT scores. In our study, patients with low FEV_1 presented to hospital with exacerbation after a significantly shorter time, but this effect disappeared when taken into the model (27).

Rivero et al. evaluated 106 patients who presented to the hospital with exacerbations and again three months later to investigate poor outcomes of patients with COPD. They accepted poor outcomes as death, readmission, and new exacerbations. A stepwise logistic regression model revealed that low FEV_1, low Hb, PCO_2, fibrinogen, CRP, high leukocyte, purulent sputum, and long-term oxygen therapy (LTOT) increased the probability of poor outcomes by up to 82.4%. When CAT scores were higher than 31, the probability of poor outcomes increased to 91.6% (18).

There is limited data on the impact of hospitalization on typical daily activities during an exacerbation (25,28). In our study, the median step count of 75 patients admitted to the hospital due to exacerbation was 933 based on objective measurements of daily physical activities (min-max= 122-3609). In a study by Schönhofer et al., the mean number of steps per day in 25 healthy adults was 8590, whereas the mean number of steps in patients with non-hypercapnic COPD was 3781, and 1413 in patients with COPD who needed non-invasive ventilation (22). In a recent longitudinal study by Oliveira et al., the physical activities of 24 patients who were hospitalized due to COPD exacerbation were evaluated by measuring the number of steps with an accelerometer and quadriceps muscle strength during hospitalization and 30 days later. In this study, it was determined that the number of steps during exacerbation and after discharge was significantly lower in the exacerbation period, and there was no significant difference in quadriceps muscle strength (25). According to our findings, acute COPD exacerbations severely limit daily physical activity in patients. In this case, we believe that hospitalization may be a contributing factor to the decrease in daily steps (29). In our study, step count measurements were made in the hospital. As a result, there is a possibility that the number of steps was measured lower than its true value. Despite the low measurement, the absence of a relationship with re-admission may lead to a bias away from the null hypothesis.

There was no relationship between the number of steps and TTFE in our study. Lin et al. evaluated the post-discharge activities of patients with COPD and calculated the risk of re-admission to the hospital within 30 days. They discovered that an activity quality model based on the number of daily steps had a sensitivity of 63% and a positive predictive value of 37.8% in predicting the risk of re-admission (30). These findings show that there is a weak relationship between the number of steps and re-admission to the hospital. In our study, the rate of patients admitted within 30 days was only 13%. Lin's sensitivity rate of 63% may not be valid for long-term follow-up studies. When Crook et al. examined the link between daily exacerbation symptoms and daily step number

in COPD patients, they discovered that a 653.3-unit decrease in the number of steps was significantly associated with the occurrence of exacerbation symptoms (31). This difference may be due to our study's evaluation of the time to re-admission to the hospital, rather than the symptoms. Similar to our findings, Sievi et al. used an accelerometer to measure the annual number of steps in COPD patients for one week; neither the frequency nor severity of exacerbations were related to the decline in the annual number of steps (32). Ngyan et al. evaluated the self-reported daily living activities of patients with COPD and found that active COPD patients had a 34% lower risk of 30-day readmission compared to inactive patients (33). In another study conducted by the same researchers, no significant difference was found in the frequency of exacerbations between active and inactive patients in daily life (34). However, unlike our research, these studies evaluated the physical activities of patients during stable periods and some of them measured the activity based on patients' self-reports. Although physician-controlled pedometer measurement seems to be more reliable in this study, stronger evidence is needed regarding the reliability, validity, and responsiveness of pedometers in the COPD population. With the rapid advancement of technology, adding features to these devices that measure other parameters such as heart rate, temperature, and upper extremity movement may increase the value of our daily physical activity prediction. Although the use of pedometers in patients with slow walking is limited, they can provide information about the number of movements (16). Despite their limitations, self-reporting methods (surveys) have practical value, especially in the daily life activities of patients, their independence, and in evaluating the performance of their functional status. Activity meters can be used complementarily to show exercise restriction when using quality of life questionnaires (22).

The strengths of this study are that arterial blood gases, PFT, CAT, step numbers, and many parameters of patients hospitalized with exacerbation were collected. This is an important study in terms of evaluating patients with COPD during exacerbation. However, the study has some limitations. One of the limitations of the study is that exacerbations in COPD can be seasonal, which can change the time to admission to the hospital with exacerbation. In addition, when evaluating step numbers with a pedometer, it may not reflect the real value because they are sensitive to vertical acceleration and measure on a single day.

CONCLUSION

The results of this study support the use of CAT as an easy-to-apply and practical tool to help identify patients with an increased risk of exacerbation. This can facilitate timely and proper prevention of preventive interventions and contribute to improving disease management. No significant correlation was found with the daily step count, which is an easily measurable indicator of physical activity.

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Ethical Committee Approval: Ethics Committee approval (Date: 11.11.2013, Number: 16-623-13) was obtained for the study. Written informed consent was obtained from all patients. There was no financial support and no conflict of interest in the study.

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: EŞ, GAD

Analysis/Interpretation: GAD, EŞ

Data acqusition: GAD, EŞ

Writing: GAD

Clinical Revision: EŞ

Final Approval: GAD, EŞ

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