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ORIGINAL ARTICLE

The Factors Related to the 6 Minute Walk Test: The Experience of a Referral Lung Transplantation Center

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ABSTRACT

Objectives: The 6-minute-walk test is a practical and widely used test, which indicates the exercise capacity in patients with a severe pulmonary disease. The study aims to investigate the related factors with the 6-minute-walk test in lung transplantation candidates.

Materials and Method: The data were collected retrospectively from 349 patients, between January 2012 and September 2020. The patients were grouped according to their underlying lung disease as obstructive lung diseases, interstitial lung diseases, and infective lung diseases. The data collected included patient demographics, gender, body mass index, artery blood gas, the results of the respiratory function test, six-minute walk test, long-term oxygen therapy, and the need for non-invasive mechanical ventilation [such as group 1 (6MWD<200) and group 2(6MWD≥200)]. All of the collected data were analyzed and compared between the groups.

Results: Overall, 349 patients were included in the study, and there were 123 females and 226 males (35.2% and 64.8% respectively) with a mean age of 46.92 ± 14.1 years. Their mean body mass index was 23.58 ± 12.52 kg/m2, the median FEV1(%) was 35.3 (33.4-37.2), the median six-minute walk distance was 222 m (125-335 m), and the mean PaO2/FiO2 (P/F) was 250.32% ± 74.81, the mean PCO2 was 45.71 mmHg ± 11.97. Furthermore, the patients using long-term oxygen therapy were (n=274, 78.5%) and non-invasive mechanical ventilation were (n=125, 35.8%). The mortality status, P/F, long-term oxygen therapy usage, and non-invasive mechanical ventilation usage were different between Group 1 and Group 2 (p=0.001, p=0.001, p<0.001, and p<0.001, respectively). There was no difference between the groups in patients with and without IPF between underlying diseases. The 6-minute walk test was found to have moderate correlation with FEV1 and P/F; and a negative correlation with age and PCO2 (p<0.01, r=0.33.8, p<0.001, r= 38.1 and p=0.17, r=12,7, p<0.001, r=-0.30.6, respectively). There was no correlation between P/F, FEV1, and body mass index; and also, between PCO2, age, and body mass index. Age had a weak correlation with FEV1(p<0.001, r=19.3). There was no correlation between the age and 6MWD, as well as P/F, PCO2, and the body mass index. The factors affecting survival in multivariate analysis were investigated by using the Cox regression model. It was observed that gender (OR, 0.001; 95% CI, 0.246-0.716; p=0.42), FEV1(OR, 1.02; 95% CI, 1.00-1.04; p<0.001), P/F (OR, 1.00; 95% CI, 1.00-1.01; p<0.001), and LTOT (OR, 9.83; 95% CI, 3.70-26.14; p<0.001) were independent factors associated with 6MWD<200 m.

Conclusion: The 6-minute walk test is associated with mortality, gender, poor oxygenation, and with the utilization of domiciliary non-invasive mechanical ventilation or long-term oxygen therapy. Furthermore, it is an independent risk factor for mortality in lung transplant candidates and in providing a valuable method for the management of patients.

Keywords: Lung transplant candidates, six minute walk test, end stage lung diseases

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INTRODUCTION

The 6-minute walk test (6MWT) is a useful measure of functional capacity. Furthermore, for patients with pulmonary and cardiac disease, it can be widely used for measuring the outcomes before and after treatment, their functional status evaluation, as well as for predicting mortality and hospitalization [1]. This test is performed by monitoring the patient's heart rate and oxygen saturation with a pulse oximeter device, accompanied by a trained respiratory physiotherapist. The test is based on the principle of walking a 50-meter corridor for a duration of six minutes. It is also a practical test that the patient can easily apply. In order to standardize the performance of the patient, encouraging expressions should be used in one minute intervals, as per the recommendations in the ATS Guidelines, since the patient's performance is affected by these encouraging phrases [1].

The previous studies have shown that 6MWT results predict complications, prolonged hospital stays, and mortality after cardiothoracic surgery [2-4]. In the study by Chaikriangkrai et al. conducted with lung transplant patients, they showed that the 6-minute walking distance (6MWD) is an independent predictor for postoperative mortality [5]. However, it has been observed that the data from the studies, which have been conducted to identify optimal thresholds for recognizing and distinguishing high-risk lung transplant candidates based on exercise tolerance, have been found to be insufficient [6]. Accordingly, the objectives of this study were to investigate the association of 6MWD with clinical characteristics and mortality, thus investigating its role in identifying the lung transplant candidates under risk.

MATERIALS AND METHODS

Overall, 349 patients with end-stage lung disease were selected for this single-center retrospective cohort study, which was conducted in a tertiary hospital that is also the main referral lung transplantation center in the country, from January 2012 to October 2020.

This study was approved by the local ethics committee of the Kosuyolu Specialty Training and Research Hospital Istanbul- 24.08.2021 No: 2021/10/521). The ethical approval was given in accordance with the Declaration of Helsinki.

Patients

The patient group included in the study were those who were older than 18 years of age, had end-stage lung disease, and were referred to a lung transplant center for treatment. Patients with a physical or orthopedic disability that would prevent walking, recent MI or acute coronary disease, systolic heart pressure above 180 mmHg, insufficient data, and seventy-four transplants were excluded from the study.

Data collection

The data were collected from the files of the patients and the operating systems of the hospital and subsequently analyzed using IBM SPSS Statistics for Windows v.23.0 IBM Corp. Released 2015. The patient demographics, gender, body mass index (BMI), artery blood gas, respiratory function test, 6MWD (Group 1≥200 m, Group 2<200 m), long term oxygen therapy (LTOT), NIMV (non-invasive mechanical ventilation) need, as well as the time since diagnosis results were recorded. The values were calculated by using mean and standard deviation values, and the median and inter-quartile ratios according to their distribution. Accordingly, while the median and inter-quartile ratios were used for non-parametric variables; mean and standard deviation were used for the parametric variables. The categorical variables were compared with the Chi-Square test. The correlations of the collected parameters were determined using Pearson's correlation coefficient(r). Receiver operating characteristics (ROC) analysis was performed to calculate the cut-off value of the six-minute walking test distance. The candidate variables were chosen based on a p-value<0.25 from the univariate logistic regression. Backward elimination was performed with those variables. The results of the final logistic regression models were represented with the odds ratio (OR), a confidence interval of 95%, and the p-value. The level of statistical significance was set at a p-value < 0.05. All reported p-values were 2-sided.

These patients were categorized as per their disease type into OLD (obstructive lung diseases), ILD

(interstitial lung diseases), and SLD (Suppurative Lung diseases). Their demographic profile was noted; 6MWT and spirometry were conducted as per the ATS guidelines at the initiation of the study [1].

Six-minute walk and pulmonary function tests

The 6MWT was performed indoors, along a flat and straight 50 m corridor supervised by a trained researcher, according to the ATS guidelines. A prior practice 6MWT was not performed. All 6MWT were performed with pulse oximetry for continuous recording of the oxygen saturation (SpO2) level. Dyspnea was assessed using the Borg scale for each minute during the 6MWT and the maximum dyspnea level was recorded. Patients were encouraged every minute using the standardized recommended sentences: "you are doing well" or "keep up the good work". The patients were allowed to stop during the test; but were instructed to resume the walking as soon as they felt able to do so. All the pulmonary function data were obtained as absolute values and expressed as % predicted of reference values according to the ATS/ERS consensus guidelines [1,7].

RESULTS

Overall, 349 patients were included in the study, there were 123 females and 226 males (35.2% and 64.8%; respectively) with a mean age of 46.92 ± 14.15 years. Their mean BMI was 23.58 ± 12.52 kg/m2, median FEV1 was 35.3 (IQR, 33.4-37.2%), median 6MWD was 222 m (IQR, 125-335 m). The (arterial blood oxygen tension (PaO2)/fraction of inspired oxygen (Fio2) ratio) P/F was 250.32% ± 74.81, mean PCO2 was 45.71 mmHg ± 11.97, patient using LTOT (n=274, 78.5%) and NIMV (n=125, 35.8%). The median time since diagnosis was 6 years (IQR, 3-10 years). The demographic characteristics and clinical parameters of the patients have been summarized in Table 1. The underlying diseases of the patients, who applied as lung transplant candidates, were idiopathic pulmonary fibrosis (n = 123, 35.2%), chronic obstructive pulmonary disease (n = 71, 20.3%), bronchiectasis (n = 64, 18.3%), cystic fibrosis (n = 27, 7.7%), interstitial lung disease (n = 16, 4.6%), sarcoidosis (n=10, 2.9%), silicosis (n = 18, 5.2%), retransplant (n=2, 0.6%), bronchiolitis obliterans (n = 4, 1.1%), histiocytosis X (n = 3, 0.9%), idiopathic pleuroparenchymal fibroelastosis (n = 3, 0.9%), interstitial pneumonia due to bleomycin (n = 2, 0.6%), lymphangioleiomyomatosis (n = 2, 0.6%), hypersensitivity pneumonia (n = 2, 0.6%), and alveolar microelastosis (n = 2, 0.6%). The patients' demographics such as gender were found to have a significant difference between the groups (p=0.04). Other demographics were similar in both groups.

The mortality status, P/F, LTOT usage, and NIMV usage were different between Group 1 and Group 2 (p=0.001, p=0.001, p<0.001, and p<0.001, respectively) There was a difference between the groups in patients with and without OLD (Table 2).

Cut-off Value of Six-minute Walk Distance

In the evaluation of lung transplantation candidates in end-stage lung patients, the appropriate cut-off

Table 1. Demographic and Clinical Parameters of the Study Groups.

	All patients (n=349)	OLD (n:74)	ILD (n:185)	SLD (n:90)	P value
Age, mean ± SD	46.92±14.15	55.15 ± 10.6	48.5 ± 13.4	36.9 ± 12.3	<0.001
Sex, female, n (%)	123(35.2%)	15(20.2%)	66(35.6%)	42(39.5%)	0.002
Time since disease, median (IQR, 25-75%)	8.10(7.36-8.84)	7.66(6.35-8.96)	5.19 (4.55-5.84)	14.43(12.68-16.18)	<0.001
BMI, mean ± SD	23.58± 12.52	23.6 ± 4.1	23.5± 4.6	23.6 ± 4.8	0.997
$PaCO_2$, mean ± SD	45.71 ± 11.97	50.4±11.7	45.8±13.1	42.5±10.4	<0.001
PaO_2 /FiO_2, mean± SD	250.32 ± 74.81	250.4±74.3	253.2±76.6	244.2±71.7	0.648
6MWD, meters, median (IQR, 25-75%)	222 (125-335	226(196-255)	219(197-241)	211(176-247)	0.230
FEV_1, %, median (IQR, 25-75%)	35.3 (33.4-37.2)	27.2(24.1-30.2)	42.2(39.9-45.0)	27.7(25.3-30.1)	<0.001
NIMV,n,%	125(79.1%)	46(62.1%)	21(54.5%)	58(64.4%)	<0.001
LTOT, n, %(>12 hours)	274(78.5%)	63(85.1%)	141(76.2%)	70(77.7%)	0.284

Abbreviations: OLD: Obstructive lung disease; ILD: Interstitial lung disease; SLD: Suppurative Lung diseases; PaCO2:partial arterial pressure of carbon dioxide; PaO2:partial arterial pressure of oxygen; FiO2: fraction of inspired oxygen; BMI: body mass index; 6MWD:6-minute walking distance; FEV1: Forced Expiratory Volume in the First Second, LTOT: Long term oxygen treatment; NIMV: Non-invasive mechanical ventilation; SD: standard deviation, IQR:Interquartile ratio

Table 2. Comparison of Age, Gender, BMI, Underlying diseases, Mortality, P/F, LTOT, NIMV in patients with Group 1 and Group 2.

	≥200 m (Group1)	<200 m (Group 2)	P value
Age, IQR (25-75%)	52 (37-61)	48 (34-58)	0.114
Gender, (n, %)			
Female	59 (29.1)	64 (43.8)	**0.004**
BMI, (n, %)			
≤18	29 (45.3)	35 (54.7)	0.592
>18	117 (41.1)	168 (58.9)	
ILD (n,%)	70 (37.8)	115(62.2)	0.108
SLD (n,%)	53 (58.9)	37 (41.1)	0.902
OLD (n,%)	35 (47.3)	39 (47.3)	**0.035**
Mortality, (n, %)	83 (40.9)	85 (58.2)	**0.001**
P/F, (n, %)			
≥237	86 (42.4)	88 (60.3)	**0.001**
>237	117 (57.6)	58 (39.7)	
LTOT, (n, %)	133 (65.5)	141 (96.6)	**<0.001**
NIMV, (n, %)	56 (27.6)	69 (47.3)	**<0.001**

Abbreviations: OLD: Obstructive lung disease; ILD: Interstitial lung disease; SLD: Suppurative lung diseases; (P/F) PaO_2:partial arterial pressure of oxygen; FiO_2: fraction of inspired oxygen; BMI: body mass index; 6MWD: 6-minute walking distance; LTOT: Long term oxygen treatment; NIMV: Non-invasive mechanical ventilation; LTOT: Long term oxygen treatment; NIMV: Non-invasive mechanical ventilation, IQR:Interquartile ratio; m: meter

Table 3. Logistic regression analysis for Mortality.

	Univariate logistic regression			Multivariate logistic regression		
	Odds Ratio	Confidence Interval (95%)	P value	Odds Ratio	Confidence Interval (95%)	P value
Age	1.01	0.99-1.02	0.087	1.02	1.00-1.03	0.024
Gender	1.33	0.86-2.07	0.195	1.41	0.88-2.26	0.145
BMI	0.97	0.93-1.01	0.224	0.95	0.91-1.00	0.099
FEV_1, %	0.99	0.98-1.01	0.906	1.01	0.99-1.02	0.063
6MWD(<200m)	2.01	1.30-3.10	0.001	1.64	1.01-2.64	0.042
LTOT	0.53	0.31-0.89	0.019	0.86	4.89-35.09	0.649
NIMV	0.61	0.39-0.95	0.029	0.70	0.42-1.14	0.155

Abbreviations: BMI: body mass index; 6MWD: 6-minute walking distance; FEV_1: Forced Expiratory Volume in the First Second, LTOT: Long term oxygen treatment; NIMV: Non-invasive mechanical ventilation.

value for the 6MWD was 200 m in the prognosis. The sensitivity of this cut-off value was 53.6% and specificity was 64.9%, and the area under the curve was (AUC) 0.610 (95% CI, 0.551-0.669, p<0.001) (Figure 1).

The distribution of 6MWD values according to the 200-threshold value in the underlying disease groups has been shown in Figure 2.

6MWD value was found to have a moderate correlation with FEV1 and P/F; and a negative correlation with age and PCO2 (p<0.01, r=0.33.8, p<0.001, r= 38.1 and p=0.17, r=12,7, p<0.001, r=-0.30.6, respectively). There was no correlation between P/F and FEV1, BMI; as well as between PCO2 and age, BMI. The relationship between FEV1 and baseline values of 6MWD has been shown in Figure 3.

In the logistic regression analysis, the univariate predictors were age, gender, BMI, 6MWD (<200m), patients receiving long-term oxygen therapy, and patients using NIMV. The multivariate analysis identified age (OR, 1.02; 95% CI, 1.00-1.03; p=0.024), and 6MWD(<200m) (OR, 1.64; 95% CI, 1.01-2.64; p=0.042) as the independent predictors of mortality (Table 3).

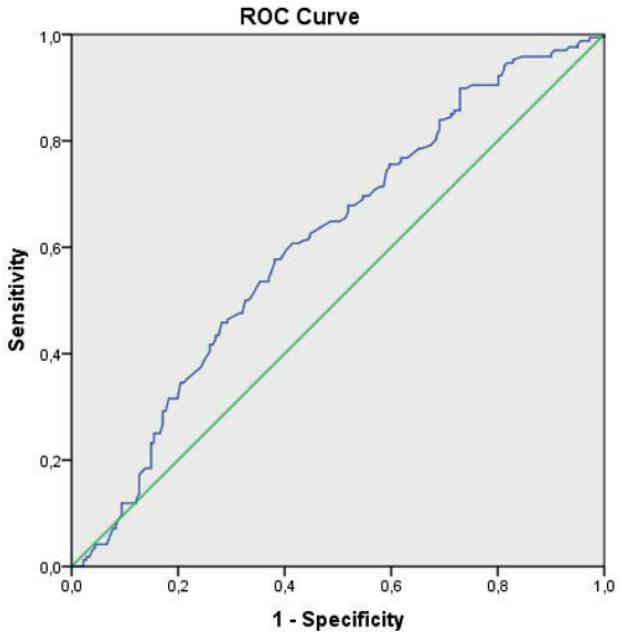

Figure 1. ROC curve analysis of six minute walk distance for predicting of prognosis in lung transplant candidates.

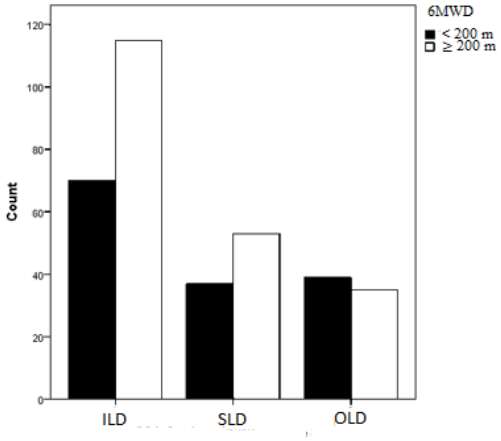

Figure 2. The proportion of underlying disease groups for six minute walk distance by 200 m threshold.

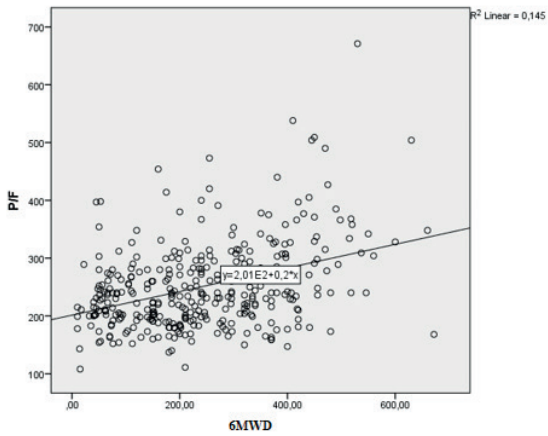

Figure 3. Correlation between baseline values of six minute walk distance and Pa02/FiO2 ratios'.

DISCUSSION

The study found that a low 6MWD value in lung transplant patients was associated with mortality, female gender, OLD as the underlying disease, poor oxygenation, and the use of respiratory failure devices (NIMV and LTOT). The results also demonstrated that age and low 6MWD are independent predictors of mortality. Therefore, our primary results reveal that the 6MWT is a practical and beneficial method that can guide the clinician in distinguishing critical lung transplant candidates and in assisting patient management. The previous studies have shown that 6MWT is a good indicator of exercise capacity, which can predict postoperative survival in lung transplant patients. Thus, this test has been included in pretransplant scoring systems and in the pretransplant evaluation process [8].

With this measurement, the survival prediction has been shown in chronic lung diseases such as chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), and pulmonary hypertension (PHT) [9,10]. In addition, 6MWD was found to be associated with waiting-list mortality in lung transplant candidates with end-stage lung disease [11].

Lederer et al. found that a 6MWD of less than 350 meters in patients with IPF, who were evaluated for lung transplantation, was associated with a shorter survival time. On the other hand, in a cohort study conducted in patients with newly diagnosed IPF, no relationship was found between the 6MWD and survival [12-14]. In addition, another study with 9525 lung transplant candidates reported that 6MWD was strongly associated with postoperative survival [6]. In the study conducted by Chaikriangkrai et al. with 324 lung transplant patients, it was shown that the preoperative 6MWD is an independent predictor for postoperative mortality, similar to the results of our study [5]. In the same study, it was shown that a low 6MWD (<237 feet) was associated with underlying OLD disease, the need for preoperative oxygen or ECMO, double lung transplantation, high LAS score, postoperative vasopressor requirement, and mortality [5].

Similarly, in our study, we found that transplant candidates with underlying OLD disease and patients with poor oxygenation (P/F ratio below 237) had a lower 6MWD. OLD patients in our study were observed to be the group of patients

who were treated more frequently with LTOT and had the highest mean PCO2 value in blood gas disorders. Therefore, a significant portion of the use of NIMV consisted of OLD patients. The low 6MWD associated with NIMV, LTOT, and low oxygenation can be explained by this situation.

We found 6MWD(<200m) and age to be the predictors of mortality. In our study, in the multivariate analysis; while the 6MWD was found to be a predictor of mortality, FEV1 was found to have no effect. The 6MWT result aids in planning such as estimating mortality, management of end-stage lung disease, and deciding referral for lung transplantation. Similarly, in the study by Karanth et al. on 139 patients with chronic lung diseases, 6MWD was found to be a better predictor of mortality than FEV1 [15]. Pinto-Plata VM concluded in his study that 6MWD is an independent predictor for mortality in COPD [16].

Dajczman E et al. found that the survival rate in COPD patients with a 6MWD value less than 150 meters at baseline was 58% [17]. Du Bois RM et al. reported that a 50 m per year decrease in 6MWD was associated with a four-fold increase in one-year mortality in IPF [18]. As a mortality predictor, Karanth et al. determined a cut-off value of 240 m in 6MWD, while we found a cut-off value of 200 m in our study [15]. Tuppin et al. showed that patients with a six-minute walking distance below 315 meters had a higher risk of mortality [19].

Pulmonary function test may be a relatively inadequate tool to measure the functional status in patients, especially since our patient population, which have been accepted for evaluation for lung transplantation in our clinic, consists of patients with end-stage lung disease accompanied by severe respiratory failure and difficulties in performing spirometry. In addition, 6MWT can be easily applied even in patients with advanced respiratory failure.

Our study shows that 6MWT is an important tool in addition to spirometry in evaluating end-stage lung patients as lung transplant candidates. This study supports the use of the 6MWT as a guide to assess the mortality in patients with end-stage lung disease.

In conclusion, this study found that the 6MWD was associated with mortality, gender, underlying lung disease, oxygenation status, and the use of home-type chronic respiratory failure devices (NIMV and LTOT) in lung transplant candidates. Furthermore, the study has demonstrated that age and a short 6MWD are independent risk factors for mortality. In lung transplant candidates, the 6MWT is a practical and useful test that can guide the clinician in distinguishing critically ill patients; therefore, it constitutes an important component of patient management.

Author contribution

Study conception and design: PAG; data collection: PAG; analysis and interpretation of results: PAG; draft manuscript preparation: PAG. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Koşuyolu Higher Specialized Educational and Research Hospital Clinical Research Ethics Committee (Protocol no. 2021/10/521/24.08.2021).

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Conflict of interest

The authors declare that there is no conflict of interest.

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