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ORIGINAL ARTICLE

Factors Related to 6-Minute Walk Distance in Pulmonary Arterial Hypertension

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What is already known on this topic?

- *Pulmonary arterial hypertension (PAH) is associated with poor prognosis, making accurate prognosis assessment crucial for guiding treatment decisions.*
- *The 6-minute walk test is the most commonly used exercise test to evaluate exercise capacity in PAH, and 6-minute walk distance (6MWD) is closely linked to prognosis.*
- *Since changes in 6MWD are the most commonly used endpoint in clinical trials, it is essential to understand which parameters are associated with 6MWD and its changes.*

What this study adds on this topic?

- *The study highlights the parameters associated with 6MWD in PAH, including variations across different PAH etiologies.*
- *The diffusing capacity of the lungs for carbon monoxide (DLCO) is an independent predictor of 6MWD in PAH.*
- *The DLCO is also associated with changes in walking distance during follow-up.*
- *In idiopathic PAH, 6MWD is more closely associated with DLCO and arterial oxygen pressure (PaO_2), whereas in systemic sclerosis-associated PAH, pulmonary arterial pressures play a more significant role.*

Abstract

Objective: The 6-minute walk test is the most commonly used tool for evaluating prognosis in patients with pulmonary arterial hypertension (PAH). This study aims to identify the parameters associated with 6-minute walk distance (6MWD) and its changes over time.

Methods: Sixty-three patients diagnosed with PAH or chronic thromboembolic pulmonary hypertension between January 2005 and January 2013 were included in the study. Demographic, clinical, echocardiographic, hemodynamic data, and initial and follow-up 6MWD were recorded. The 6MWD cut-off was determined based on previous studies. Patients were then categorized into groups based on their initial 6MWD: ≥ 332 m or < 332 m.

Results: Patients were followed up for 31.56 ± 15.07 months. In those with a 6MWD < 332m, diffusing capacity of the lungs for carbon monoxide (DLCO) (P = .040), estimated glomerular filtration rate (P = .018), and partial arterial oxygen pressure (PaO_2) (P = .024) were significantly lower, whereas age (P = .016), right atrial pressure (P = .034), the frequency of pericardial effusion (P = .004), and mortality (P = .020) were significantly higher. Low DLCO was identified as an independent predictor of walking less than 332 meters (P = .048). In the subgroup analysis, among idiopathic PAH (IPAH) patients, DLCO (P = .024) was lower in those with 6MWD < 332 m. In patients with scleroderma-associated PAH (SSc-PAH), systolic pulmonary artery pressure (sPAP) (P = .018), and mean PAP (p = 0.034) were higher in patients with 6MWD < 332 m. When the change in 6MWD (Δ6MWD) was evaluated based on the difference between the initial 6MWD and at the end of the follow-up period, DLCO was lower in the group with a decreased 6MWD (P < .001).

Conclusion: The study identified higher DLCO as an independent predictor of 6MWD ≥ 332 m and its improvement over time. In IPAH, 6MWD is more closely associated with DLCO and PaO_2, whereas in SSc-PAH, PAPs play a more significant role.

Keywords: Diffusing capacity of the lungs for carbon monoxide, idiopathic pulmonary arterial hypertension, pulmonary arterial hypertension, six-minute walk distance, systemic sclerosis

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by increased pulmonary vascular resistance (PVR) and pulmonary arterial pressure (PAP), with a prevalence of 45-55 per million in developed countries.[1] It is associated with poor prognosis, leading to right heart failure and death. Despite advancements in management, a recent registry reported 1-, 2-, and 3-year mortality rates of 8%, 16%, and 21%, respectively, in patients with PAH.[2]

Evaluating prognosis and clinical status in PAH patients plays a pivotal role in selecting initial treatments, assessing therapeutic responses, and determining the need for advanced therapies.[3] With the widespread use of specific PAH treatments, identifying the most appropriate diagnostic tests and parameters to monitor treatment efficacy and prognosis has become a key research focus.

The 6-minute walk test (6MWT) is the most commonly used method to assess exercise capacity in PAH.[4] The 6-minute walk distance (6MWD) has prognostic value and serves as an essential

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parameter for risk stratification.[3] Many PAH-specific clinical trials have used 6MWD as a primary endpoint.

Despite its widespread use, few studies have investigated the relationship between the 6MWT and other prognostic parameters, and even fewer have investigated the factors influencing 6MWD in specific PAH etiologies.[5,6] In addition, there are conflicting data regarding the relationship between changes in 6MWD and improvements in prognosis.[7]

This study aims to investigate the relationship between clinical, hemodynamic, and echocardiographic parameters in determining 6MWD and their impact on treatment response by analyzing changes in 6MWD during follow-up in PAH patients.

Additionally, it explores etiology-specific associations between 6MWD and other characteristics through subgroup analysis.

Methods

This retrospective, single-center study included 63 patients diagnosed with PAH or chronic thromboembolic pulmonary hypertension (CTEPH) who were followed at the pulmonary hypertension (PH) outpatient clinic of a tertiary university hospital between January 2005 and January 2013. The study was approved by the local ethics comitee of Istanbul University Cerrahpaşa Medical Faculty on 04 December 2012 with an approval number 35435, and informed consent was obtained from all included patients. Patients classified under groups 2, 3, or 5 according to the PH classification, patients with primary cardiac and pulmonary diseases, such as left heart dysfunction, valvular heart disease, obstructive lung diseases (e.g., asthma, COPD), and interstitial lung disease, who had a pulmonary capillary wedge pressure above 15 mmHg, those with a follow-up period of less than a year, and those whose PAH diagnosis was not confirmed by right heart catheterization (RHC) were excluded from the study.

The standard diagnostic protocol for patients referred to the PH Outpatient Clinic with a preliminary diagnosis of PAH or CTEPH during this time period included a thorough history and physical examination, renal and liver function tests, echocardiography, pulmonary function testing (PFT), diffusing capacity of the lungs for carbon monoxide (DLCO), arterial blood gas analysis, high-resolution computed tomography (CT) and CT-pulmonary angiogram, abdominal ultrasound, the 6MWT, and RHC. The RHCs were performed by 2 experienced cardiologists, and in cases of complex hemodynamic data, decisions were made by consensus. The follow-up protocol included echocardiography, 6MWT, and PFTs, repeated every 3 months. If the therapeutic response was inadequate, symptoms worsened, or treatment changes such as switching drugs or initiating combination therapy were considered, RHC was repeated. All data obtained from these tests were reviewed retrospectively.

The following variables were included in the analysis: demographic characteristics (age, sex, height, weight, and comorbidities); echocardiographic parameters, including systolic pulmonary artery pressure (sPAP), and the presence of pericardial effusion. The RHC parameters, including PAPs (systolic, diastolic, and mean), right atrial pressure (RAP), PVR, cardiac output (CO), and cardiac index (CI). Additional data included DLCO, arterial blood gas analysis with partial pressure of oxygen (PaO_2), and 6MWT results. Baseline resting heart rate, systolic blood pressure, biochemistry parameters (urea, creatinine levels, and estimated glomerular filtration rate [eGFR, calculated using the Cockcroft–Gault formula]), and the use of either combination therapy with an endothelin receptor antagonist and phosphodiesterase-5 inhibitors or monotherapy with one of these PAH-specific medications were also recorded.

Initial and final follow-up (corresponding to the last visit before data collection) 6MWD results were recorded. Patients were categorized into 2 groups based on their initial 6MWD, following previously published studies: those who walked ≥ 332 m (n = 26) and those who walked < 332 m (n = 37).[8] Change in Δ6MWD was calculated as the difference between the final and initial 6MWD and could be assessed in 49 patients due to the unavailability of the final 6MWT in others. Patients were then categorized into 2 groups based on whether their walking distance increased or remained unchanged/decreased.

Statistical Analysis

Statistical tests were conducted using the Statistical Package for the Social Sciences 26.0 for Windows (IBM SPSS Corp.; Armonk, NY, USA). The normal distribution of the data was evaluated by the Kolmogorov–Smirnov test. Continuous data were expressed as mean ± SD and categorical data were expressed as percentages. Categorical variables were analyzed using the Chi-square test, while Student's *t*-test and the Mann–Whitney *U* test were employed for normally distributed and non-normally distributed continuous variables, respectively. Multivariate analysis was performed using binary logistic regression. Pearson correlation was used for correlation analyses. A P value < .05 was considered statistically significant for all tests.

Results

The mean age of the study group was 56.32 ± 13.63 years, with a predominance of female patients (66.7%). The mean follow-up duration was 31.6 ± 15.1 months. During this period, 29 patients (46%) died.

At the initial 6MWT, 37 patients walked < 332 m, while 26 walked ≥ 332 m. Table 1 presents the differences between these groups. Patients with 6MWD < 332 m were older, had lower DLCO and eGFR values, and exhibited higher RAP. Pericardial effusion was observed in one-third of patients with 6MWD < 332 m, compared to only 5.4% in those with 6MWD ≥ 332 m. Combination therapy usage was similar between groups. However, mortality was significantly higher in the <332 m group (51.35% vs. 24.4%, $P = .046$). In multivariate analysis, low DLCO was identified as the only independent predictor of 6MWD < 332 m (OR: 1.042, $P = .048$, 95% CI: 1-1.076).

Correlation analysis showed that 6MWD was negatively correlated with age ($r = -0.319$, $P = .015$) and RAP ($r = -0.377$, $P = .006$), while it was positively correlated with PaO_2 ($r = 0.457$, $P < .001$) and DLCO ($r = 0.303$, $P = .007$) (Figure 1). No significant correlation was found between 6MWD and other parameters.

Subgroup Analyses According to Etiology

Subgroup analyses were conducted for patients with IPAH and systemic sclerosis (SSc). The mean baseline 6MWD was 291.33 ± 109.89 m for IPAH patients and 280.50 ± 125.47 m for SSc patients ($P = .770$). The mean final 6MWD was 336.16 ± 155.06 m for IPAH patients and 277.42 ± 130.27 m for SSc patients ($P = .195$) and the change in the 6MWD from the beginning to the end of follow-up was 128.49 ± 30.28 in IPAH and 104.80 ± 22.87 in SSc patients ($P = .065$).

In both subgroups, analyses were performed based on a baseline 6MWD cutoff of 332 m. (Supplementary Tables 1 and 2). Among IPAH patients, those with a 6MWD < 332 m had significantly lower DLCO (41.42 ± 15.18 vs. 58.75 ± 16.38, $P = .024$) and SBP (103.92 ± 13.22 vs. 120.00 ± 16.90, $P = .028$) and mortality was significantly higher (0% vs. 66%, $P = .005$). Additionally, 6MWD was positively correlated with PaO_2 ($r = 0.664$, $P = .003$).

Table 1. Characteristics of Study Group

Characteristic	6MWD ≥ 332 (n = 26)	6MWD < 332 (n = 37)	*P*
Age years (Mean ± SD)	51.42 ± 16.772	59.76 ± 9.77	**.016**
Female n (%)	16 (61.5)	26 (70.3)	
Etiology			.422
IPAH	8 (30.8)	12 (32.4)	
Systemic sclerosis—PAH	10 (38.5)	16 (43.2)	
Congenital heart disease—PAH	5 (19.2)	3 (8.1)	
Portopulmonary hypertension	1 (3.8)	-	
CTEPH	2 (7.7)	6 (16.2)	
Hypertension n (%)	9 (34.6)	13 (35.1)	1.00
Diabetes n (%)	3 (4.8)	4 (6.3)	1.00
PaO_2	73.04 ± 23.045	60.81 ± 17.17	**.024**
DLCO % (mean ± SD)	56.73 ± 20.18	38.29 ±22.44	**.001**
sPAP in TTE, mmHg (mean ± SD)	64.19 ± 36.23	74.03 ± 23.24	.202
Pericardial effusion, n (%)	1 (3.8)	13 (36.1)	**.004**
Hemodynamics			
Systolic PAP, mmHg (mean ± SD)	74.0 ± 22.6	75.64 ± 44.2	.852
Diastolic PAP, mmHg (mean ± SD)	30.4 ± 11.3	33.04 ± 19.6	.507
Mean PAP, mmHg (mean ± SD)	45.5 ± 14.9	48.48 ± 26.5	.573
RAP mmHg (mean ± SD)	7.7 ± 4.6	10.4 ± 4.6	**.034**
Cardiac index, L /min/m^2 (mean ± SD)	2.3 ± 1.7	2.3 ± 0.9	.989
PVR WU (mean ± SD)	8.15 ± 5.3	9.9 ± 8.6	.455
Systolic blood pressure, mmHg (mean ± SD)	116.2 ± 19.6	107.2 ± 18.5	.070
Heart rate, bpm (mean ± SD)	86.0 ± 11.5	91.0 ± 14.2	.141
Hemoglobin, g/dL (mean ± SD)	12.94 ± 3.11	12.4342 ± 3.19	.535
Creatinine, mg/dL (mean ± SD)	0.87 ± 0.24	1.22 ± 1.63	.289
eGFR, mL/min/1.73m^2 (mean ± SD)	92.2 ± 25.5	74.2 ± 31.0	**.018**
Baseline 6MWD m (mean ± SD)	405.4 ± 68.91	192.2± 90.9	<.001
Final 6MWD m (mean ± SD)	394.4 ± 103.2	247.7 ± 135.4	<.001
Combination therapy, n (%)	11 (42.3)	18 (48.6)	.798
Mortality, n (%)	7 (24.1)	22 (75.9)	**.020**

6MWD, six-minute walk distance; CTEPH, chronic thromboembolic pulmonary hypertension; DLCO, diffusing capacity of the lung for carbon monoxide; eGFR, estimated glomerular filtration rate; IPAH, idiopathic pulmonary arterial hypertension; PaO_2, partial pressure of oxygen in arterial blood; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

In SSc patients, those with a 6MWD < 332 m had significantly higher systolic PAP (68.93 ± 26.16 vs. 45.44 ± 10.32, *P* = .018) and mean PAP (42.60 ± 17.49 vs. 28.89 ± 5.66, *P* = .034), while SBP was significantly lower (105 ± 18.16 vs. 123 ± 19.46, *P* = .025). Additionally, 6MWD was negatively correlated with PASP (*r* = −0.578, *P* = .004).

The Parameters Associated with Changes in 6-Minute Walk Distance

The mean Δ6MWD was 24.14 ± 109.67 m, with a range of −290 m to 462 m. Among the 49 patients, walking distance increased in 30 patients (61.22%), while it decreased or remained unchanged in 19 patients (38.77%). The mean Δ6MWD was −62.19 ± 74.13 m in the group with non-increased walking distance and 84.56 ± 88.16 m in the group with increased walking distance. In patients with increased walking distance, DLCO was higher, whereas in those with non-increased walking distance, mortality and the rate of receiving combination therapy were higher. (Table 2). In the multivariate regression model adjusted for therapy, DLCO remained an independent predictor of an increase in 6MWD (OR: 1.048, 95% CI: 1.015–1.082, *P* = .004).

Correlation analysis showed a positive correlation between Δ6MWD and DLCO (*r* = 0.327, *P* = .030) as well as hemoglobin levels (*r* = 0.358, *P* = .010) (Figure 2).

Discussion

In this study, it was found that PAH patients with a shorter walking distance were older, had lower DLCO and eGFR, and exhibited higher RAP, a greater prevalence of pericardial effusion, and higher mortality. Low DLCO was identified as an independent predictor of walking <332 m. Additionally, 6MWD was negatively correlated with age and RAP and positively correlated with DLCO and PaO_2. In the subgroup analysis, among IPAH patients, those with a shorter walking distance had lower DLCO and higher mortality,

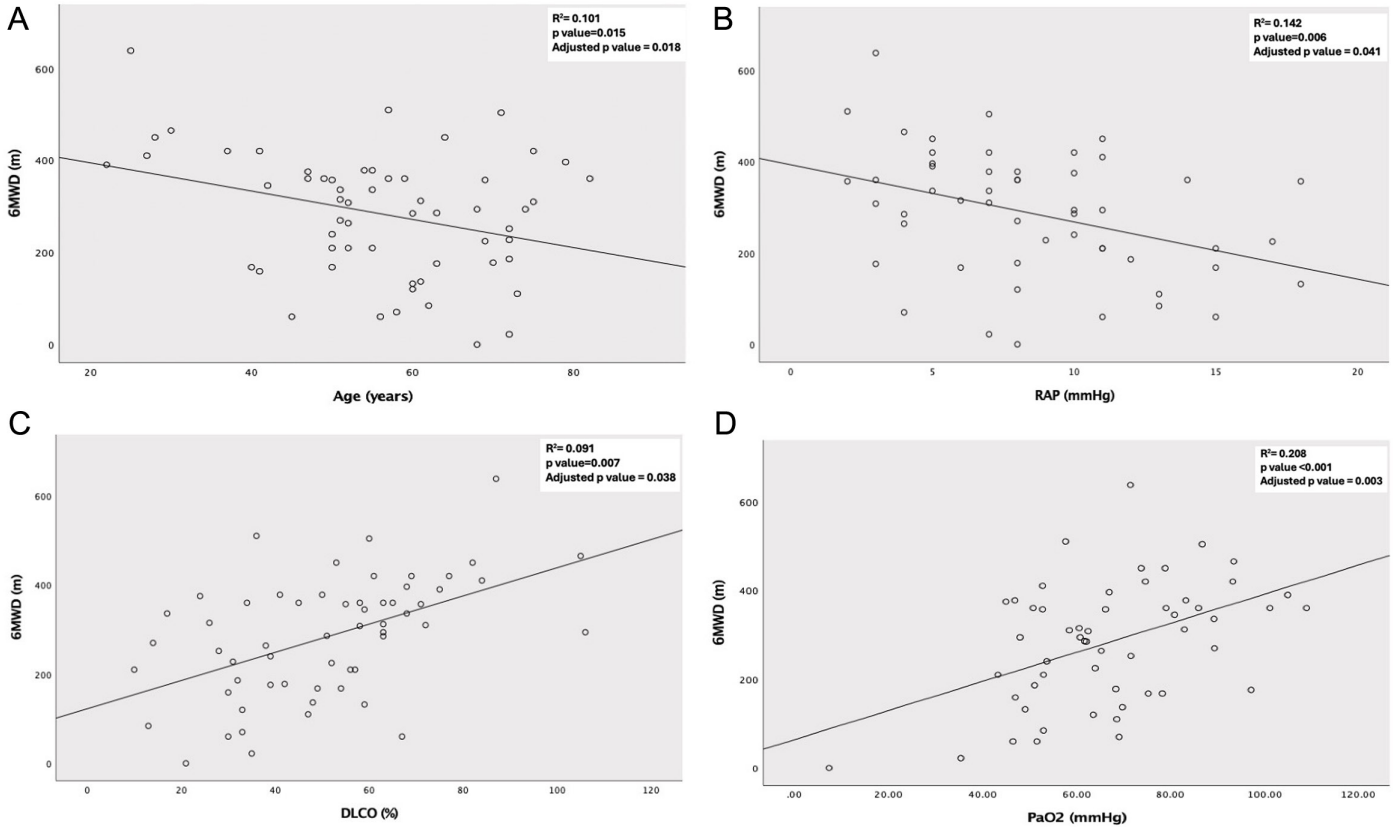

Figure 1. Correlation graphs of 6MWD. A. Correlation between 6MWD and age ($r = -0.319$, $P = .015$) B. Correlation between 6MWD and RAP ($r = -0.377$, $P = .006$) C. Correlation between 6MWD and DLCO ($r = 0.303$, $P = .007$) D. Correlation between 6MWD and PaO_2 ($r = 0.457$, $P < .001$).

whereas in SSc patients, a shorter walking distance was associated with higher mean and sPAP. Systolic blood pressure was lower in both groups among patients with a shorter walking distance. When Δ6MWD was evaluated for all patients, DLCO was higher in the group with increased walking distance, while mortality was significantly higher in the group with non-increased 6MWD. Additionally, Δ6MWD was positively correlated with DLCO and hemoglobin.

The 6MWT is the most commonly used test to assess exercise capacity in patients with PAH. A shorter 6MWD is confirmed to be related to poor prognosis in PAH.[9] Various 6MWD cut-offs have been proposed for prognosis prediction in PAH studies. In the study by Batal et al,[10] a 6MWD below 250 m was associated with poor prognosis, while Miyamoto et al[8] demonstrated that a 6MWD below 332 m was linked to worse outcomes. The REVEAL study identified a 6MWD below 165 meters as a marker of poor prognosis, while distances above 440 meters were associated with better outcomes. These thresholds are currently recommended for risk prediction in the European Society of Cardiology (ESC) guidelines for PH. In the 4-strata risk model, a 6MWD of 320 meters has been suggested as the threshold for intermediate–low risk.[3,11,12] In this study, a cut-off of 332 m was used, similar to Miyamoto et al,[8] as it aligned well with the dataset, where the mean 6MWD was 312.8 m and the median 6MWD was 346 m.

Although 6MWD is strongly associated with prognosis in PAH, studies investigating its relationship with clinical and hemodynamic parameters remain limited. While it is well established that a reduced 6MWD correlates with poor prognosis, the recent ESC guideline did not include DLCO and eGFR in its risk assessment model.[3] However, previous studies have demonstrated that low DLCO, reduced eGFR, and a shorter walking distance are related to poor prognosis.[3] In this cohort, DLCO was significantly lower in patients walking less than 332 m and in those with non-increased Δ6MWD. The DLCO also positively correlated with both 6MWD and Δ6MWD. Importantly, DLCO was the only independent predictor of 6MWD < 332 m in multivariate analysis. The DLCO reflects the diffusion capacity of the alveolar-capillary membrane and hemoglobin's ability to bind carbon monoxide.[13] Its association with prognosis and exercise capacity has been confirmed in large registries, including COMPERA and REVEAL.[14-17] The findings are consistent with these results.

Elevated RAP has been widely recognized as a poor prognostic indicator.[3] In Miyamoto's study, mean RAP was significantly higher in patients walking less than 332 m, a finding that was also observed in the study.[8] Additionally, pericardial effusion has been associated with poor prognosis in PAH patients.[18] Consistent with these findings, this study demonstrated a higher prevalence of pericardial effusion among patients with shorter walking distances, further supporting its role as a poor prognostic marker. Pericardial effusion likely reflects elevated right-sided filling pressures and impaired right ventricular function. It may result from increased pericardial venous pressure and impaired venous and lymphatic drainage, which are markers of advanced disease and potential contributors to reduced exercise capacity.[19]

Subgroups were analyzed based on etiology. Due to the low number of patients in other groups, subgroup analysis was only performed for IPAH and SSc-associated PAH. In IPAH patients, mortality was significantly higher in those with a shorter 6MWD, highlighting its prognostic importance in this subgroup. In contrast, in SSc-PAH patients, mortality rates remained similarly high

Table 2. Comparison of Patient Characteristics by Change in 6MWD

Characteristics	Patients with Increased Walk Distance (n = 30)	Patients with Non-increased Walk Distance (n = 19)	*P*
Age years (Mean ± SD)	56.68 ± 12.20	55.71 ± 15.25	.784
Female n (%)	64.5	71	.786
Etiology			.500
IPAH n (%)	11 (35.5)	8 (12.9)	
Systemic sclerosis—PAH n (%)	10 (32.3)	16 (51.6)	
Congenital Heart Disease—PAH n (%)	4 (12.9)	4 (12.9)	
Portopulmonary Hypertension n (%)	1 (3.2)	0	
CTEPH n (%)	5 (16.1)	3(9.7)	
Hypertension n (%)	12 (38.7)	9 (29)	.592
Diabetes n (%)	3 (9.7)	3 (9.7)	1
PaO_2	70.31 ± 16.70	63.35 ± 21.14	.172
DLCO % (Mean ± SD)	55.88 ± 24.00	33.07 ± 20.11	**<.001**
sPAP in TTE, mmHg (Mean ± SD)	65.17 ± 25.57	72.83 ± 32.28	.312
Pericardial effusion, n (%)	6 (19.4)	8 (26.7)	.554
Hemodynamics			
Systolic PAP, mmHg (Mean ± SD)	72 ± 30.70	75.07 ± 33.22	.712
Diastolic PAP, mmHg (Mean ± SD)	30.03 ± 14.82	32.93 ± 15.91	.468
Mean PAP, mmHg (Mean ± SD)	44.37 ± 17.83	48.03 ± 2.22	.484
RAP mmHg (Mean ± SD)	8.64 ± 4.44	9.50 ± 4.71	.487
Cardiac index,L /min/m^2 (Mean ± SD)	2.51 ± 1.03	2.12 ± 0.90	.209
PVR WU (Mean ± SD)	7.14 ± 4.60	10.63 ± 8.56	.120
Systolic Blood Pressure mmHg (Mean ± SD)	116.03 ± 20.68	105.81 ± 17.03	.312
Heart Rate mmHg (Mean ± SD)	89.45 ± 10.25	93.38 ± 14.71	.447
Hemoglobin g/dL (Mean ± SD)	12.67 ± 3.12	12.68 ± 3.25	.986
Creatinine mg/dL (Mean ± SD)	0.94 ± 0.46	1.10 ± 0.54	.427
eGFR ml/min/1.73m^2 (Mean ± SD)	83.97 ± 24.32	79.91 ± 35.29	.599
Baseline 6MWD m (Mean ± SD)	297.77 ± 108.90	268.39 ± 158.90	.205
Final 6MWD m (Mean ± SD)	374.45 ± 113.77	229.89 ± 134.65	<.001
Combination therapy n (%)	10 (32.3)	19 (61.3)	**.041**
Mortality n (%)	7 (22.6)	22 (71)	**<.001**

6MWD, six-minute walk distance; CTEPH, chronic thromboembolic pulmonary hypertension; DLCO, diffusing capacity of the lung for carbon monoxide; eGFR, estimated glomerular filtration rate; IPAH, idiopathic pulmonary arterial hypertension; PaO_2, partial pressure of oxygen in arterial blood; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

regardless of walking distance (60% vs. 62.5%), suggesting that factors beyond exercise capacity influence survival outcomes in this population.[20] While baseline 6MWD was similar between IPAH and SSc-PAH patients, the final 6MWD and Δ6MWD were lower in SSc-PAH patients; however, these differences did not reach statistical significance. This trend may reflect the broader impact of SSc on exercise capacity, where vascular dysfunction, impaired systemic circulatory response to exertion, and reduced joint and skin mobility contribute to physical limitations independent of pulmonary hemodynamics.[21] In both etiology subgroups, all parameters were analyzed based on 6MWD. While DLCO and PaO_2 differed between the 6MWD groups in IPAH, systolic PAP and mean PAP differed between the 6MWD groups in SSc-PAH. Furthermore, while PaO_2 was positively correlated with 6MWD in IPAH, systolic PAP and mean PAP were negatively correlated with 6MWD in SSc-PAH. Consistent with these findings, Hoeper et al[22] reported a positive correlation between PaO_2 and 6MWD in IPAH patients. Sanges et al[5] conducted a study to identify parameters influencing 6MWD in SSc and found that DLCO significantly affected exercise capacity; however, hemodynamic parameters were not included in their analysis. In SSc patients, DLCO was low in both 6MWD groups, but the difference was not statistically significant. The relationship between PAP and 6MWD in SSc was also suggested by Villalba et al,[6] who reported an association between PASP > 30 mmHg and 6MWD < 400 m in SSc patients. Despite these studies, the exact reason for the differences in 6MWD-related parameters between IPAH and SSc-PAH could not be determined due to limited data in the current literature. Pulmonary vascular pathology and lung fibrosis are more prominent in SSc-PAH, which may explain the more significant influence of hemodynamic parameters on exercise capacity in these patients.[23] Considering the low number of

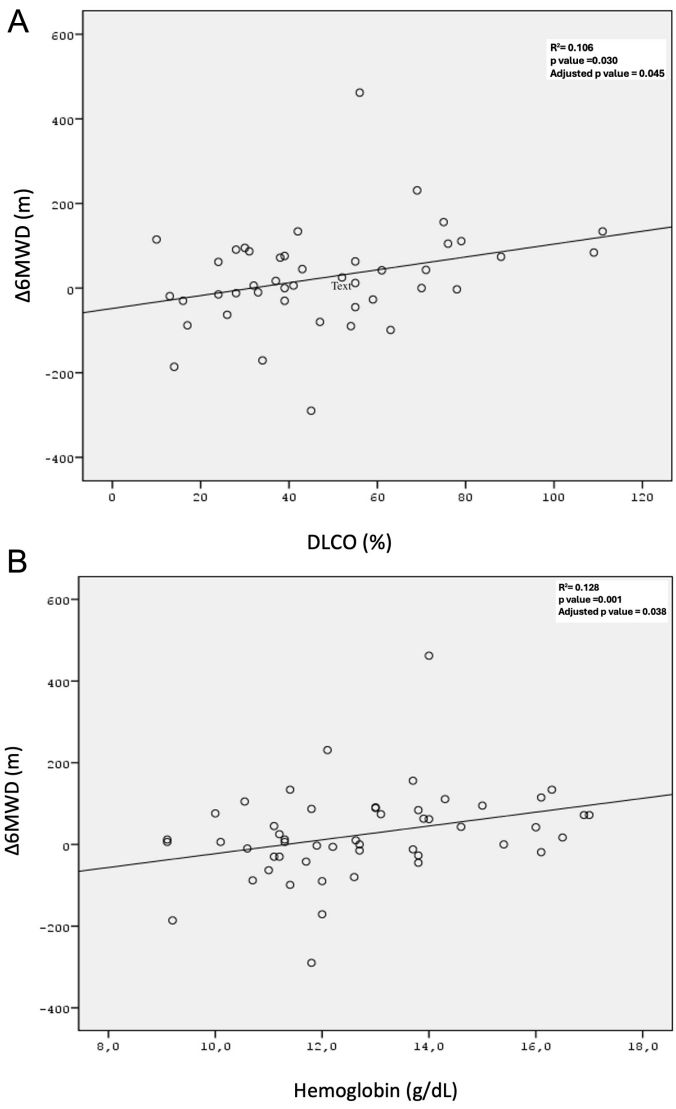

Figure 2. Correlation graphs of Δ6MWD. A. Correlation between Δ6MWD and DLCO ($r = 0.327$, $P = .030$). B. Correlation between Δ6MWD and Hemoglobin ($r = 0.358$, $P = .01$).

patients in subgroups, further studies are needed to confirm these subgroup results.

The relationship between Δ6MWD and clinical and hemodynamic parameters was alsoevaluated. Since walking distance is associated with prognosis, changes in walking distance have been used as an endpoint in studies analyzing PAH-specific treatments. While an increase in walking distance is associated with a better prognosis, a decrease in walking distance is linked to poorer outcomes. However, the relationship between Δ6MWD and mortality was not demonstrated in the meta-analyses conducted by Savarese et al.[7] In this study, when patients were categorized based on changes in walking distance, mortality was higher in the group with non-increased walking distance ($P = .036$). This discrepancy may be attributed to the longer follow-up period in the study compared to the studies included in the mentioned meta-analyses, suggesting that long-term changes in walking distance may have a stronger association with prognosis. Consistent with these findings, the COMPERA registry suggested that a deterioration in 6MWD is a stronger predictor of prognosis than an improvement.[4] A positive correlation was found between Δ6MWD and both DLCO and hemoglobin. Numerous studies have identified anemia as a factor associated with reduced exercise capacity and poor prognosis in PAH.[24] Given the known negative impact of anemia on exercise capacity, the findings suggest that elevated hemoglobin levels and higher DLCO may be indicators of increased exercise capacity.

As a result, DLCO, eGFR, elevated RAP, anemia, and pericardial effusion are well-established prognostic factors in PAH, as identified in large-scale registries and risk models including COMPERA, REVEAL, and the ESC/ERS guidelines. However, the direct effect of these markers on exercise capacity—particularly on 6MWD—has not been specifically analyzed in these models. This study's findings suggest that, among all recognized prognostic indicators, these parameters exert the most pronounced influence on functional capacity.

The study has certain limitations. The primary limitation is its retrospective design. As the analysis relies on medical records collected over an extended period, variations in patient follow-up protocols and limited data availability in earlier years restricted certain analyses and resulted in missing data for key markers, such as NT-proBNP. The continuous evolution in PAH-specific treatment regimens during and after the study period may have influenced the 6MWD outcomes and the interpretation of the findings. The limited sample size is another acknowledged limitation. Despite these constraints, the extended follow-up period of the study represents a significant strength compared to other studies on PAH.

In summary, the study identified DLCO as an independent determinant of longer 6MWD, demonstrating its association with both 6MWD and its increase over time. While PaO_2 appeared to be more closely related to 6MWD in IPAH patients, systolic and mean pulmonary arterial pressures were more prominently associated with 6MWD in SSc-PAH patients. Further prospective studies with a larger patient population are needed to confirm the findings.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University Cerrahpaşa Medical Faculty (Date: December 04, 2012; Approval No: 35435).

Informed Consent: Written informed consent was obtained from the patients who participated in this study, or from their relatives if the patients were unable to provide it themselves.

Peer-review: Externally peer-reviewed.

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Supplementary Table 1. Characteristics of Patients with IPAH

Characteristic	**6MWD ≥332 (n=8)**	**6MWD <332 (n=12)**	**p**
Age years (Mean ± SD)	54.88±15.65	56.33±8.25	0.788
Female n (%)	5 (62.5)	8 (66.7)	1
Hypertension n(%)	5 (62.5)	6 (50)	0.670
Diabetes n(%)	5 (62.5)	3 (37.5)	0.347
PaO2	77.52±31.11	61.25±12.06	0.116
DLCO % (Mean ± SD)	58.75 ± 16.38	41.42 ± 15.18	**0.024**
sPAP in TTE, mmHg (Mean ± SD)	63.63±24.24	73.18±22.83	0.392
Pericardial effusion, n (%)	0	2 (16.7)	0.495
Hemodynamics			
Systolic PAP, mmHg (Mean ± SD)	67.13±38.35	75.42±14.43	0.501
Diastolic PAP, mmHg (Mean ± SD)	30.25±15.90	35.83±9.00	0.328
Mean PAP, mmHg (Mean ± SD)	43.13±17.48	49.75±13.15	0.346
RAP mmHg (Mean ± SD)	10.25±6.18	11.08±5.21	0.749
Cardiac index,L /min/m²(Mean ± SD)	2.65±0.90	2.07±0.93	0.265
PVR WU (Mean ± SD)	7.12±5.38	11.01±5.42	0.222
Systolic Blood Pressure mmHg *(Mean ± SD)*	120±16.90	103.92±13.22	0.028
Heart Rate bpm *(Mean ± SD)*	87.25±13.37	93.17±14.39	0.367
Hemoglobin g/dL *(Mean ± SD)*	11.92±4.46	12.57±4.39	0.376
Creatinine mg/dL *(Mean ± SD)*	0.80±0.13	1.73±0.79	0.363
eGFR ml/min/1.73m²*(Mean ± SD)*	96.96±26.23	79.61±29.87	0.100
Baseline 6MWD m *(Mean ± SD)*	408.86±61.69	198.82±73.95	<0.001
Final 6MWD m *(Mean ± SD)*	430±45.60	276.45±171.88	**0.018**
Combination therapy n (%)	6 (75)	6 (50)	0.373
Mortality n (%)	0	8 (66.7)	**0.005**

6MWD, Six-Minute Walk Distance; CTEPH, Chronic Thromboembolic Pulmonary Hypertension; DLCO, Diffusing Capacity of the Lung for Carbon Monoxide; eGFR, Estimated Glomerular Filtration Rate; IPAH, Idiopathic Pulmonary Arterial Hypertension; Pa02: Partial Pressure of Oxygen in Arterial Blood; PAH, Pulmonary Arterial Hypertension; PAP, Pulmonary Arterial Pressure;; PVR, Pulmonary Vascular Resistance; RAP, Right Atrial Pressure.

Supplementary Table 2. Characteristics of Patients with SSc Associated PAH

Characteristic	**6MWD ≥332 (n=16)**	**6MWD <332 (n=10)**	**p**
Age years (Mean ± SD)	59±12.58	61.63±9.24	0.546
Female n (%)	7 (70)	14 (87.5)	0.340
Hypertension n(%)	3 (30)	5 (31.3)	1
Diabetes n(%)	0	2 (12.5)	0.508
PaO2	72.11±18.31	69.57±14.91	0.720
DLCO % (Mean ± SD)	30.88±15.15	29.07±12.93	0.770
sPAP in TTE, mmHg (Mean ± SD)	37.40±5.35	68.13±23.92	**<0.001**
Pericardial effusion, n (%)	1 (10)	0 (56.3)	**0.037**
Hemodynamics			
***Systolic PAP, mmHg* (Mean ± SD)**	45.44±10.32	68.93±26.16	**0.018**
Diastolic PAP, mmHg (Mean ± SD)	19.56±6.50	27.80±12.56	0.083
***Mean PAP, mmHg* (Mean ± SD)**	28.89±5.66	42.60±17.49	**0.034**
RAP mmHg (Mean ± SD)	5.89±2.57	9.46±4.66	0.051
Cardiac index,L /min/m²(Mean ± SD)	2.30±0.67	1.97±0.88	0.433
PVR WU (Mean ± SD)	5.63±1.15	7.38±5.38	0.490
Systolic Blood Pressure mmHg *(Mean ± SD)*	123±19.46	105±18.16	**0.025**
Heart Rate bpm *(Mean ± SD)*	86.4±11.24	89.63±14.33	0.552
Hemoglobin g/dL *(Mean ± SD)*	12.48±2.55	12.11±2.76	0.737
Creatinine mg/dL *(Mean ± SD)*	0.92±0.35	0.97±0.59	0.819
eGFR ml/min/1.73m²*(Mean ± SD)*	78.65±27.14	74.45±33.99	0.745
Baseline 6MWD m *(Mean ± SD)*	388.50±52.59	216.58±78.37	<0.001
Final 6MWD m *(Mean ± SD)*	338.10±130.36	230.731±113.74	**0.047**
Combination therapy n (%)	9(56.3)	5(50)	1
Mortality n (%)	6 (60)	10 (62.5)	1

6MWD, Six-Minute Walk Distance; CTEPH, Chronic Thromboembolic Pulmonary Hypertension; DLCO, Diffusing Capacity of the Lung for Carbon Monoxide; eGFR, Estimated Glomerular Filtration Rate; IPAH, Idiopathic Pulmonary Arterial Hypertension; Pa02: Partial Pressure of Oxygen in Arterial Blood; PAH, Pulmonary Arterial Hypertension; PAP, Pulmonary Arterial Pressure;; PVR, Pulmonary Vascular Resistance; RAP, Right Atrial Pressure.