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# Oxygen saturation recovery after 6-minute walk test in patients with idiopathic pulmonary fibrosis

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## Abstract

**Background** The six-minute walk test (6MWT) is widely used to assess functional capacity and prognosis in patients with idiopathic pulmonary fibrosis (IPF). However, studies on oxygen saturation recovery after the 6MWT in patients with IPF are rare. In our study, we investigated the relationship between oxygen saturation recovery time and dyspnea, fatigue, quality of life, prognostic markers and pulmonary hypertension (PH).

**Methods** In this cross-sectional study, IPF patients diagnosed according to current guidelines and followed up in our Interstitial Lung Disease Outpatient Clinic between 2021 and 2022 were included. Demographics, data from spirometry, diffusion capacity measurement, arterial blood gas analysis, transthoracic echocardiography and the 6MWT were recorded. The oxygen saturation recovery time, distance saturation product (DSP), gender-age-physiology (GAP) index and composite physiological index (CPI) scores were calculated. Dyspnea severity was assessed by the modified Medical Research Council (mMRC) and Dyspnoea-12 (D-12) scales, fatigue severity by the Multidimensional Fatigue Inventory (MFI-20) and quality of life by the St George's Respiratory Questionnaire (SGRQ).

**Results** Fifty IPF patients (34 men, 16 women, age: 66.8 ± 7.3 years) were included in the study. The mean FVC was 77.8 ± 19.3%, the DLCO was 52.9 ± 17.1%, the 6-minute walk distance (6MWD) was 385.7 ± 90.6 m, the GAP index was 3.5 ± 1.5, and the CPI was 43.7 ± 14.1. Oxygen saturation after the 6MWT reached pretest values at an average of 135.6 ± 73.5 s. The oxygen saturation recovery time was longer in patients with higher GAP index scores (Rs = 0.870, $p < 0.001$), CPI scores (Rs = 0.906, $p < 0.001$), desaturation (Rs = 0.801, $p < 0.001$), FVC%/DLCO% (Rs = 0.432, $p = 0.002$), sPAP (Rs = 0.492, $p = 0.001$), TRV (Rs = 0.504, $p = 0.001$), mMRC (Rs = 0.913, $p < 0.001$), MFI-20 (Rs = 0.944, $p < 0.001$), D-12 scale (Rs = 0.915, $p < 0.001$) and SGRQ scores (Rs = 0.927, $p < 0.001$); lower FVC (%) (Rs=-0.627, $p < 0.001$), DLCO (%) (Rs=-0.892, $p < 0.001$), $PaO_2$ (Rs=-0.779, $p < 0.001$), DSP (Rs=-0.835, $p < 0.001$), and 6MWD (Rs=-0.763, $p < 0.001$). A total of twenty patients (40%) exhibited an increased risk of PH. According to our multiple regression analysis, oxygen saturation recovery time was independently associated with the GAP index ($p = 0.036$), the lowest oxygen saturation occurring during the 6MWT ($p = 0.011$) and the SGRQ score ($p < 0.001$).

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**Conclusions** Our results showed that oxygen saturation recovery time is associated with dyspnea, fatigue, quality of life, increased risk of PH and prognostic markers in IPF. Therefore, we recommend continuous measurement of oxygen saturation after 6MWT until pretest values are reached.

**Keywords** Idiopathic pulmonary fibrosis, Pulmonary hypertension, Six minute walk test, Oxygen saturation recovery time

## Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive fibrotic lung disease that mainly affects older individuals [1]. The average life expectancy after diagnosis is 3 to 5 years [2]. Markers associated with prognosis and mortality have been defined for the follow-up and treatment of patients with IPF [3]. The physiological markers included low baseline values of forced vital capacity (FVC), low diffusing capacity of the lung for carbon monoxide (DLCO), the composite physiological index (CPI) and the gender, age and physiology (GAP) staging system was shown to be associated with survival [4–10].

The six-minute walk test (6MWT) is widely used to assess the functional status and prognosis of patients with IPF [11, 12]. The six-minute walk distance (6MWD) at diagnosis and/or the decline in 6MWD at follow-up have been identified as an independent predictor of mortality [11]. In addition, the presence of desaturation during the 6MWT was associated with patient prognosis and mortality [13]. The distance-saturation product (DSP) is the product of the distance walked and the lowest oxygen saturation during the 6MWT and has been correlated with survival in IPF patients [14]. However, there are limited data, and further studies are needed to confirm this claim.

On the other hand, the presence of pulmonary hypertension (PH) is also associated with poor prognosis and increased mortality in IPF patients [15]. A study revealed an association between patients with IPF and PH who walked significantly shorter 6MWD and had significantly lower peripheral capillary oxygen saturation ($SpO_2$) levels measured by pulse oximetry at rest and at the end of exercise [16]. The present study demonstrated that $SpO_2$ at the end of exercise could independently predict the presence of PH in patients with IPF through multivariate logistic regression analysis. In this study, PH was defined as a pulmonary artery systolic pressure (sPAP) greater than 36 mmHg, estimated by echocardiography. Existing a few studies have shown that the efficiency of the DSP in detecting PH in patients with IPF is variable [17, 18]. It has also been shown that a change in heart rate of less than 13 beats per minute within 1 min of a 6MWT is predictive of PH in patients with IPF [19]. Additionally, impaired heart rate recovery following the 6MWT is associated with an increased risk of mortality in IPF patients [19, 20]. However, there is insufficient research on the relationship between $SpO_2$ recovery time and prognosis, mortality, and PH [21, 22].

The aim of this study was to investigate the relationship between 6MWT results, in particular $SpO_2$ recovery time and DSP, with prognostic factors, PH, dyspnoea severity, quality of life and fatigue severity in patients with IPF.

## Method

Our study included IPF patients who were followed up between 2021 and 2022 at the Interstitial Lung Diseases Outpatient Clinic, Department of Chest Diseases, Istanbul University, Istanbul Faculty of Medicine. Patients who were diagnosed IPF in with a multidisciplinary council in accordance with the 2022 American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society, and Latin American Thoracic Association IPF diagnosis guidelines, and who were able to speak and read Turkish, were included in the study. If the diagnosis could not be confirmed through on high-resolution computed tomography, and clinical evaluation alone, a pathological diagnosis via surgical biopsy was performed to ensure the accuracy of the IPF diagnosis.

The exclusion criteria were having IPF exacerbation in the last 1 month; any extrapulmonary impairment that could interfere with physical activity, such as significant comorbid conditions or orthopedic problems that prevent physical activity; a diagnosis of psychiatric or cognitive disorders; or progressive neurological or neuromuscular disorders; receiving any medical treatment that may affect heart rate; or having a rhythm disorder.

Clinical and laboratory parameters, including age, sex, body mass index (BMI), environmental and occupational exposures, comorbidities, active symptoms, physical examination findings, use of antifibrotic therapy, N-terminal pro-B-type natriuretic peptide (proBNP) levels, and long-term oxygen therapy requirements, were recorded. All patients underwent spirometry, diffusion capacity measurement, arterial blood gas analysis in room air and a 6MWT. The 6MWT was performed by an experienced physiotherapist using an Edan-IT-20 model telemetry system to continuously measure and record $SpO_2$ in a 30-meter corridor according to established guidelines [23, 24]. Patients with a resting $SpO_2$ of 88% or higher underwent the 6MWT in room air, while patients with a resting $SpO_2$ of less than 88% underwent the test with supplemental oxygen support titrated to achieve a resting $SpO_2$ of 92% [25]. We recorded $SpO_2$,

pulse rate, blood pressure, Borg scale dyspnoea and fatigue scores and total walking distance at the beginning and end of the test. We calculated the lowest $SpO_2$ during the 6MWT and the time to return to resting. Desaturation during the 6MWT was defined as the lowest $SpO_2$ of 88% or less [12, 13, 21]. DSP was defined as the product of the final 6MWD in metres and the lowest $SpO_2$ during the 6MWT [14]. The CPI was calculated according to the CPI formula: CPI=91.0- (0.65 expected DLCO%) -(0.53 expected FVC%) + (0.34 expected forced expiratory volume in 1 s [FEV1]%) [7]. The GAP index was calculated based on gender (0–1 points), age (0–2 points), %FVC (0–2 points) and %DLCO (0–3 points) [9]. Dyspnoea severity was assessed according to the modified Medical Research Council (mMRC) and Dyspnoea-12 (D-12) scales, fatigue severity according to the Multidimensional Fatigue Inventory (MFI-20) and quality of life according to the St George's Respiratory Questionnaire (SGRQ) [26–29].

Transthoracic echocardiography was performed in all patients by an experienced cardiologist. sPAP was determined using the formula: sPAP=4 x tricuspid regurgitant velocity $(TRV)^2$ + right atrial pressure. According to the 2022 European Society of Cardiology/ERS guidelines for the diagnosis and management of pulmonary hypertension, echocardiographic findings suggestive of PH include peak tricuspid regurgitation velocity (TRV), right ventricular/left ventricular basal diameter ratio, interventricular septal flattening, right ventricular outflow Doppler acceleration time, mid-systolic notching, early diastolic pulmonary regurgitation velocity, pulmonary artery diameter, inferior vena cava diameter with reduced inspiratory collapse, and right atrial area. A TRV≥2.9 m/s or a TRV≤2.8 m/s with at least two additional echocardiographic signs from different categories were considered to indicate a risk of PH [30].

**Table 1** Demographic parameters of idiopathic pulmonary fibrosis patients

| ***N*=50** | | **Mean±SD, %** | **Min.-Max.** |
|---|---|---|---|
| Age (years) | | 66.8±7.3 | 51–80 |
| Male (n, %) | | 34, %68 | |
| BMI (kg/m2) | | 27.8±3.2 | 20.9–35 |
| Cough n, % | | 43, %86 | - |
| Dyspnoea upon exertion n, % | | 41, %82 | |
| Dyspnoea at rest n, % | | 23, %46 | - |
| Smoking status (n, %) | Past-smoker | 30, %60 | |
| | Current smoker | 10, %20 | |
| | Non-smoker | 10, %20 | |
| Past smoking history (pack-year) | | 30.6±22.6 | 5–150 |
| Comorbidities n, % | | 41, %82 | |
| | Hypertension | 24, %48 | |
| | GERD | 14, %28 | |
| | OSA | 10, %20 | |
| | Depression | 10, %20 | |
| | COPD | 6, %12 | |
| Antifibrotic treatment n, % | | 45, %90 | |
| LTOT n, % | | 3, %6 | |

BMI: Body mass index, COPD: Chronic Obstructive Pulmonary Disease, GERD: Gastroesophageal reflux disease, LTOT: Long-Term Oxygen Therapy, OSA: Obstructive sleep apnoea, N: Number, %: percent

### Statistical analysis

The data was analysed using the IBM SPSS 29.0.2.0 package program (AIMS, Istanbul, Turkey). Descriptive statistics were reported as mean±standard deviation for continuous variables and as number (%) for categorical variables. The normality of the distribution of the data was assessed using a histogram, q-q plots, and the Shapiro–Wilk test. The homogeneity of variance was tested using Levene's test. The Mann–Whitney U test was used to compare independent groups. The chi-square test was used to compare categorical variables, while the Spearman correlation test was used to analyze the relationship between two variables. Multiple regression analysis was used to evaluate the independent variables associated with the $SpO_2$ recovery time.

## Results

The study included 50 patients, 34 (68%) of whom were male and 16 (32%) of whom were female. The mean age of the patients was 66.8±7.3 years (range: 51–80 years), and the mean BMI was 27.8±3.2 kg/m² (range: 20.9–35 kg/m²). A smoking history was present in 80% of the patients ($n$=40), with a mean of 30.6±22.6 pack-years. Ten patients (20%) were current smokers. Comorbidities were present in 41 patients (82%). The most common comorbidities were hypertension ($n$=24, 48%) and gastroesophageal reflux ($n$=14, 28%). Six (12%) patients had concomitant chronic obstructive pulmonary disease. The most common IPF-related symptoms were cough ($n$=43, 86%) and dyspnea upon exertion ($n$=41, 82%). In addition, 90% of patients received antifibrotic therapy, 25 patients received pirfenidone, and 20 patients received nintedanib. Three patients (6%) were on long-term oxygen support. A surgical biopsy was performed in eight patients (16%), while 42 patients (84%) were diagnosed with IPF based on clinical and radiological criteria. Patient demographics and clinical parameters are shown in Table 1.

The results of the functional evaluation showed a mean FVC (%) of 77.8±19.3, $FEV_1$ (%) of 83.4±20.1 and DLCO (%) of 52.9±17.1. The arterial blood gas concentrations in room air were as follows: partial pressure of oxygen ($PaO_2$): 76±10.2 mmHg, partial pressure of carbon dioxide: 38.2±3.4 mmHg, and oxygen saturation: 94.3±2.9%. The mean GAP index was 3.5±1.5 (range: 1–7) and the CPI was 43.7±14.1 (range: 6.7–71.6) values. According to the GAP index, 28 (56%) patients were in stage 1, 18

(36%) were in stage 2 and 4 (8%) were in stage 3. Only three patients (6%) received supplemental oxygen support during the 6MWT. The mean baseline $SpO_2$ was 96.0±2.1%, while the mean end-test $SpO_2$ was 88.4±6.6%. The minimum $SpO_2$ was 85.8±7.3%, and the 6MWD was 385.7±90.6 m. The mean DSP was 334.8±97.7 m%, and the $SpO_2$ recovery time was 135.6±73.5 s. Tables 2 and 3 show the functional parameters and questionnaire results of the IPF patients included in the study.

In the 6MWT, 21 patients (42%) exhibited exertional desaturation as evidenced by end-test $SpO_2$ values, while 31 patients (62%) demonstrated desaturation when the lowest $SpO_2$ was continuously monitored during the test. Patients who desaturated during the 6MWT had significantly greater GAP (4.2±1.2 vs. 2.2±0.9, $p<0.001$) and CPI (51.6±8.5 vs. 30.9±12, $p<0.001$) scores than did those who did not. In addition, the FVC (69.9±17.4% vs. 90.7±15.1%, $p<0.001$), DLCO (43.3±10.7% vs. 68.4±14%, $p<0.001$) and 6MWD (342.6±80.8 m vs. 456.1±55 m, $p<0.001$) were significantly lower in the exercise-induced desaturation group.

In 14% of the patients ($n=7$), the DSP was less than 200 m. No patient in the DSP less than 200 m% group had GAP stage 1 disease. The group with a DSP less than 200 m had higher sPAP ($p=0.021$), GAP index ($p<0.001$), CPI ($p<0.001$), MFI-20 ($p<0.001$), D-12 scale ($p=0.001$), mMRC ($p<0.001$) and SGRQ scores ($p<0.001$). The group with DSP less than 200 m% exhibited lower FVC (%), DLCO (%) and room air $PaO_2$ values ($p=0.001$, $p<0.001$, $p=0.004$, respectively). Table 4 shows the comparative data between patients with a DSP less than 200 m% and those with a DSP greater than or equal to 200 m%.

The mean sPAP was 33.4±9.1 mmHg, and the mean TRV was 2.7±0.7 m/s. Twenty patients (40%) were identified as being at risk of PH based on the echocardiographic findings. The mean sPAP was 41.6±6.3 mmHg, and the mean TRV was 3.1±0.7 m/s. Of these patients, 13 had TRV≥2.9 m/s. Among those at risk of PH, 70% ($n=14$) exhibited a FVC%/DLCO% ratio of >1.6. No statistically significant differences were observed in sex, age, BMI, ProBNP (pg/ml), and FVC (%) between patients with and without an increased risk of PH. The FVC%/DLCO%, the presence of desaturation on the 6MWT, the GAP index, the CPI score, the MFI-20, the mMRC, the D-12 scale and the SGRQ total scores were found to be significantly higher in patients with an increased risk of PH than in those without a risk of PH ($p=0.001$, $p=0.001$, $p=0.001$, $p=0.005$, $p<0.001$, $p=0.006$, $p=0.003$, $p=0.003$, respectively). In addition, the 6MWD, DSP, DLCO (%) and $PaO_2$ values were significantly lower in patients at risk of PH than in those without such risk ($p=0.047$, $p=0.01$, $p=0.001$, $p=0.038$, respectively). The group at increased risk of PH exhibited a significantly longer $SpO_2$ recovery time than the group without an increased risk of PH ($p=0.001$). Table 5 shows the data for patients with and without an increased risk of PH.

In patients with IPF, longer $SpO_2$ recovery time was correlated with a greater GAP index (Rs=0.870, $p<0.001$), CPI (Rs=0.906, $p<0.001$), presence of desaturation in the 6MWT (Rs=0.801, $p<0.001$), FVC/DLCO% (Rs=0.432, $p=0.002$), sPAP (Rs=0.492, $p=0.001$), TRV (Rs=0.504, $p=0.001$), mMRC (Rs=0.913, $p<0.001$), MFI-20 score (Rs=0.944, $p<0.001$), D-12 scale score (Rs=0.915, $p<0.001$), and SGRQ score (Rs=0.927, $p<0.001$). In addition, longer recovery times were also associated with lower FVC (%) (Rs=-0.627, $p<0.001$), DLCO (%) (Rs=-0.892, $p<0.001$), room air PaO2 (Rs=-0.779, $p<0.001$), DSP (Rs=-0.835, $p<0.001$) and 6MWD (m) (Rs=-0.763, $p<0.001$). The $SpO_2$ recovery time was not significantly associated with age, sex, BMI or comorbidities (Table 6).

**Table 2** Functional parameters of patients with idiopathic pulmonary fibrosis

| *N*=50 | Mean±SD, % | Min. - Max. |
|---|---|---|
| FVC (%) | 77.8±19.3 | 32–126 |
| FVC (mL) | 2518±854 | 970–4540 |
| DLCO (%) | 52.9±17.1 | 20–94 |
| $PaO_2$ (mmHg) | 76±10.2 | 53.9–94.6 |
| GAP index | 3.5±1.5 | 1–7 |
| CPI score | 43.7±14.1 | 6.7–71.6 |
| 6MWD (m) | 385.7±90.6 | 230–560 |
| Desaturation at the end of 6MWT n, % | 21, %42 | |
| Desaturation during 6MWT n, % | 31, %62 | |
| DSP | 334.8±97.7 | 186.2-520.8 |
| Saturation recovery time (s) | 135.6±73.5 | 12–308 |

6MWD: 6-Minute Walk Distance, 6MWT: 6-Minute Walk Test, CPI: Composite Physiological Index, DLCO: Diffusion Capacity of the Lung for Carbon Monoxide, DSP: Distance-Saturation Product, GAP: Gender-Age- Physiology $PaO_2$: Partial Pressure of Oxygen, N: Number, %: Percent

**Table 3** Results of symptom and quality of Life Questionnaire (SGRQ Questionnaire, MFI-20, mMRC and D-12 scale)

| *N*=50 | | Mean±SD, % | Min. -Max. |
|---|---|---|---|
| SGRQ total score | | 45.2±16.6 | 11.8–71.1 |
| SGRQ symptom score | | 45.2±17.6 | 7.8–77.6 |
| SGRQ activity score | | 47.4±19.5 | 5.9–93.4 |
| SGRQ sensation score | | 43.9±15.9 | 10.5–69.8 |
| MFI-20 score | | 55.8±17.2 | 24–88 |
| mMRC n, % | 0 | 9, %18 | |
| | 1 | 15, %30 | |
| | 2 | 19, %38 | |
| | 3 | 5, %10 | |
| | 4 | 2, %4 | |
| D-12 scale | Emotional | 5.9±3.3 | 0–15 |
| | Physical | 10.3±5.2 | 0–20 |

D-12 Scale: Dyspnea-12 Scale, MFI-20: Multidimensional Fatigue Inventory-20,mMRC: Modified Medical Research Council, SGRQ: St George's Respiratory Questionnaire, N: Number, %: Percent

**Table 4** Comparison of patients with DSP < 200 and DSP ≥ 200

| Parameter | DSP < 200 | DSP ≥ 200 | *p* Value |
|---|---|---|---|
| Age (Year) | 70.6 ± 4.4 | 66.2 ± 7.5 | 0.141 |
| BMI (kg/m2) | 28.6 ± 3.4 | 27.7 ± 3.2 | 0.522 |
| TRV (m/s) | 3.3 ± 1.3 | 2.6 ± 0.4 | 0.178 |
| sPAP (mmHg) | 40.6 ± 12.1 | 32 ± 7.9 | 0.021 |
| FVC (%) | 57 ± 18 | 81.2 ± 17.4 | 0.001 |
| DLCO (%) | 31.7 ± 6.3 | 56.3 ± 15.8 | < 0.001 |
| Room Air $PaO_2$ (mmHg) | 66 ± 5.9 | 77.6 ± 9.8 | 0.004 |
| GAP Index | 5.6 ± 1.3 | 3.1 ± 1.2 | < 0.001 |
| CPI Score | 62.3 ± 6 | 40.7 ± 12.7 | < 0.001 |
| SGRQ Total Score | 63.4 ± 5.7 | 42.2 ± 15.9 | < 0.001 |
| MFI-20 | 78.0 ± 8.3 | 52.2 ± 15.5 | < 0.001 |
| mMRC | 2.9 ± 0.7 | 1.3 ± 0.9 | < 0.001 |
| D-12 Scale | 25.6 ± 5.3 | 14.7 ± 7.5 | 0.001 |

DSP: Distance-Saturation Product, BMI: Body Mass Index, TRV: Tricuspid Regurgitation Velocity, sPAP: Systolic Pulmonary Arterial Pressure, FVC: Forced Vital Capacity, DLCO: Diffusing Capacity of the Lungs for Carbon Monoxide, $PaO_2$: Partial Pressure of Arterial Oxygen, GAP: Gender-Age-Physiology, CPI: Composite Physiologic Index, SGRQ: St. George's Respiratory Questionnaire, Test, MFI-20: Multidimensional Fatigue Inventory-20, mMRC: Modified Medical Research Council, D-12 Scale : Dyspnea-12 Scale

**Table 5** Comparison of patients with and without an increased risk of pulmonary hypertension

| Parameter | PH (+) cases | PH (-) cases | *p* Value |
|---|---|---|---|
| Age (Year) | 69.1 ± 6.6 | 65.3 ± 7.4 | 0.068 |
| Sex (Female / Male) | 6 / 14 | 10 / 20 | 0.804 |
| BMI (kg/m2) | 28.7 ± 3.2 | 27.3 ± 3.1 | 0.117 |
| GAP index | 4.3 ± 1.3 | 2.9 ± 1.2 | 0.001 |
| CPI score | 50.4 ± 9.9 | 39.3 ± 14.9 | 0.005 |
| CPI score > 41 n, % | 17, %85 | 16, %53 | 0.021 |
| FVC (%) | 75.8 ± 19.8 | 79.1 ± 19.2 | 0.555 |
| DLCO (%) | 43.4 ± 11.4 | 59.2 ± 17.5 | 0.001 |
| Room Air $PaO_2$ (mmHg) | 72.3 ± 10.1 | 78.4 ± 9.7 | 0.038 |
| FVC % / DLCO % | 1.8 ± 0.6 | 1.3 ± 0.3 | 0.001 |
| ProBNP (pg/ml) | 385.7 ± 708.7 | 132.5 ± 90.6 | 0.128 |
| 6MWD (m) | 354.8 ± 84.6 | 406.3 ± 89.9 | 0.047 |
| DSP (m%) | 291.8 ± 86.9 | 363.5 ± 95 | 0.01 |
| Desaturation in 6MWT n, % | 18, %90 | 13, % 43 | 0.001 |
| Saturation recovery time (s) | 174.7 ± 58.8 | 109.5 ± 71.4 | 0.001 |
| MFI-20 | 66 ± 14.9 | 49 ± 15.4 | < 0.001 |
| mMRC | 2 ± 1.1 | 1.2 ± 0.9 | 0.006 |
| D-12 Scale | 20.3 ± 8.5 | 13.5 ± 6.8 | 0.003 |
| SGRQ Total Score | 53.4 ± 15.7 | 39.7 ± 15.1 | 0.003 |
| SGRQ Symptom Score | 54.8 ± 14.5 | 38.8 ± 15.1 | 0.001 |
| SGRQ Activity Score | 56.9 ± 19.5 | 41 ± 17.1 | 0.004 |
| SGRQ Sensation Score | 50.9 ± 15.8 | 39.2 ± 14.5 | 0.01 |

PH: Pulmonary Hypertension, BMI: Body Mass Index, GAP: Gender-Age-Physiology, CPI: Composite Physiologic Index, FVC: Forced Vital Capacity, DLCO: Diffusing Capacity of the Lungs for Carbon Monoxide, $PaO_2$: Partial Pressure of Arterial Oxygen, ProBNP: Pro-Brain Natriuretic Peptide, 6MWD: 6-Minute Walk Distance, DSP: Distance-Saturation Product, 6MWT: 6-Minute Walk Test, MFI-20: Multidimensional Fatigue Inventory-20, mMRC: Modified Medical Research Council, D-12 Scale : Dyspnea-12 Scale, SGRQ: St. George's Respiratory Questionnairre

**Table 6** Variables correlated with saturation recovery time

| Variable | Rs | *p* Value |
|---|---|---|
| GAP index | 0.870 | < 0.001 |
| GAP stage | 0.826 | < 0.001 |
| CPI score | 0.906 | < 0.001 |
| FVC (%) | -0,627 | < 0.001 |
| DLCO (%) | -0.892 | < 0.001 |
| FVC % / DLCO % | 0.432 | 0.002 |
| Room Air $PaO_2$ (mmHg) | -0.779 | < 0.001 |
| 6MWD (m) | -0.763 | < 0.001 |
| DSP (m%) | -0.835 | < 0.001 |
| Lowest $SpO_2$ during 6MWT (%) | -0,931 | < 0.001 |
| Presence of Desaturation in 6MWT | 0.801 | < 0.001 |
| sPAP(mmHg) | 0.492 | 0.001 |
| TRV (m/s) | 0.504 | 0.001 |
| mMRC | 0.913 | < 0.001 |
| MFI-20 | 0.944 | < 0.001 |
| D-12 Scale | 0.915 | < 0.001 |
| SGRQ total score | 0.927 | < 0.001 |
| SGRQ symptom score | 0.950 | < 0.001 |
| SGRQ activity score | 0.882 | < 0.001 |
| SGRQ sensation score | 0.884 | < 0.001 |

GAP: Gender-Age-Physiology, CPI: Composite Physiologic Index, FVC: Forced Vital Capacity, DLCO: Diffusing Capacity of the Lungs for Carbon Monoxide, $PaO_2$: Partial Pressure of Arterial Oxygen, 6MWD: 6-Minute Walk Distance, DSP: Distance-Saturation Product, $SpO_2$: Peripheral Capillary Oxygen Saturation, 6MWT: 6-Minute Walk Test, sPAP: Systolic Pulmonary Arterial Pressure, TRV: Tricuspid Regurgitation Velocity, mMRC: Modified Medical Research Council, MFI-20: Multidimensional Fatigue Inventory-20, D-12 Scale : Dyspnea-12 Scale, SGRQ: St. George's Respiratory Questionnaire

The regression model included the GAP index, 6MWD, lowest $SpO_2$ during the 6MWT, $PaO_2$, BMI, TRV and SGRQ total score, and 92% of the $SpO_2$ recovery time (adjusted R2 = 0.917). These variables were explained by the independent variables. The $SpO_2$ recovery time was found to be independently associated with the GAP index, lowest $SpO_2$ and total SGRQ score ($p = 0.036$, $p = 0.011$, and $p < 0.001$, respectively).

## Discussion

Our study showed that $SpO_2$ recovery time after the 6MWT was significantly associated with an increased risk of PH and prognostic markers in patients with IPF. A prolonged $SpO_2$ recovery time was associated with a decrease in quality of life and an increase in symptoms such as fatigue and shortness of breath. The group with DSP < 200 m% had lower functional capacity and experienced a decrease in quality of life as well as an increase in the severity of fatigue and shortness of breath. According to the transthoracic echocardiography, PH was detected in 40% of patients. The 6MWD, DSP, DLCO (%) and room air $PaO_2$ values of patients with an increased risk of PH were significantly lower than those of patients without a risk of PH. In addition, $SpO_2$ recovery time was longer in IPF patients with an increased risk of PH.

The negative impact of PH on quality of life, dyspnea and fatigue symptoms in IPF patients was demonstrated.

According to national and international registries, approximately 70% of patients diagnosed with IPF are male, with a mean age at diagnosis of 65 years [31, 32]. In our study, the majority of patients were male (68%), and the mean age was 66.8±7.3 years. The demographic data of our patients are compatible with the literature, which increases the power of our study by ensuring that they are representative of the general population and that more reliable results are obtained.

Desaturation ($SpO_2 \leq 88\%$) during or at the end of the 6MWT has been found to be a significant predictor of mortality in some, but not all, studies of patients with IPF [13, 33, 34]. Furthermore, PH in IPF is associated with exercise-induced desaturation [35]. In clinical researches, there is considerable variability in how desaturation is defined during the 6MWT. For example, some studies identify oxygen desaturation as a decrease in $SpO_2$ of more than 4% from rest to end of test, accompanied by an end-test $SpO_2$ of less than 90% or 88% [12, 13, 34, 36–38]. In our study, we used a threshold of $SpO_2 \leq 88\%$ to define desaturation, as this threshold is considered to be a more accurate predictor of poor prognosis and mortality [21, 22, 34]. There are different studies that define the presence of desaturation in the 6MWT according to the lowest $SpO_2$ or the end-test $SpO_2$ [13, 23, 24, 38–40]. In a study focusing on patients with interstitial lung disease, primarily those diagnosed with IPF, end-test $SpO_2$ measurements failed to detect desaturation events during testing in 20% of patients [39]. In our study, 31 (62%) patients experienced desaturation during testing according to the lowest $SpO_2$ values recorded on the 6MWT. However, end-test $SpO_2$ values indicated the presence of desaturation in only 21 (42%) of these patients. This finding is consistent with the literature showing that end-test $SpO_2$ did not accurately reflect desaturation during testing in 20% of our subjects. To correctly detect desaturation during the 6MWT, we support continuous saturation monitoring throughout the test, as recommended by the 2014 ERS/ATS technical standard [24]. In our study, similar to the literature, the presence of desaturation during the 6MWT was associated with an increase in GAP index and CPI score, whereas the FVC (%), DLCO (%) and 6MWD decreased.

The incidence of desaturation during the 6MWT was significantly greater in patients with detected PH than in those without PH. The presence of PH in IPF is associated with an unfavorable prognosis and a high mortality rate [35, 41, 42]. Across studies, the prevalence of PH in IPF patients ranged from 3 to 86%, with most estimates tending to be between 30% and 50% [16, 30, 43]. This wide range may be due to differences in patient populations, disease severity, diagnostic methods and criteria for PH. As there is currently no proven effective treatment for PH in patients with IPF, routine right heart catheterization (RHC) is not recommended for these patients [30]. Studies of IPF primarily assess PH using transthoracic echocardiography, which has shown a higher incidence of PH in this patient population [41].

The presence of PH adversely affects the functional status and quality of life of patients with IPF [44, 45]. Similarly, our study demonstrated that an increased risk of PH has a negative impact on the quality of life, dyspnea, and fatigue symptoms in patients with IPF. Studies have investigated the usefulness of noninvasive diagnostic tests, such as the 6MWT and oxygen saturation level measured by pulse oximetry, for detecting the presence of PH in IPF patients. In a clinical trial of 488 IPF patients, the lowest $SpO_2$ and baseline $SpO_2$ values at the 6MWT and 6MWD were found to be significantly lower in patients with PH than in those without PH [15]. One study defined abnormal heart rate recovery as a decrease of less than 13 beats per minute one minute after the 6MWT and found it to be a predictor of PH in patients with IPF [19]. In a related study, a significant correlation was observed between saturation recovery time and sPAP [46]. However, smaller retrospective studies have shown inconsistent results regarding whether the coexistence of PH in patients with IPF leads to a reduction in the 6MWD [18, 47]. In our study, we found that patients with echocardiographic findings indicative of increased PH had a significant increase in desaturation during the 6MWT, along with increased GAP index and CPI score, known prognostic markers in IPF. In addition, these patients had significantly lower 6MWD, DSP and room air $PaO_2$. A significant correlation was found between prolonged saturation recovery time and PH. In line with our study results, we suggest that the assessment of PH risk in IPF patients should include a comprehensive evaluation of the 6MWD, the presence of desaturation during the 6MWT, impaired chronotropic response, and $SpO_2$ recovery time.

There are conflicting results regarding the impact of 6MWT results in predicting prognosis and mortality [11, 33, 48]. The main reason for this situation is the inadequate standardization of the 6MWT in patients with IPF, as well as the complexities in interpreting the test due to variability in patient effort, oxygen supplementation, and the presence of comorbid conditions [21, 22, 49]. The 2002 ATS guidelines for the 6MWT and the 2014 ERS/ATS technical standard on field walking tests in chronic respiratory disease, together with the work of Lancaster L et al. on standardizing the 6MWT in patients with IPF, provide a comprehensive framework for the performance and interpretation of the 6MWT in clinical practice [23, 24, 49] These recommendations include the recommendation to assess a wider range of 6MWT outcomes, to

include factors such as saturation recovery time and lowest $SpO_2$ and to develop indices that include more than one 6MWT outcome. The DSP is a robust and multidimensional index that combines two important measures, the 6MWD and minimum $SpO_2$ [14, 50]. In IPF, the DSP index is a stronger predictor of mortality than its individual components. A related study showed that those with a DSP of less than 200 m% had a 6.5-fold increased annual risk of mortality compared to with those with a DSP of 200 m% or more [14]. In addition, median survival was 18% shorter [14]. Consistent with the literature, the GAP index and CPI score were significantly greater, and the FVC (%) and DLCO (%) were significantly lower in the DSP < 200 m% group. The mean SGRQ score, MFI-20 score, mMRC and D-12 scale score were significantly greater in the group with a DSP < 200 m. In line with the findings in the literature and the results of our study, we recommend the use of DSP in the evaluation of follow-up and treatment response in IPF patients. We recommend the development of indices that include more than one outcome in the 6MWT (e.g., presence of desaturation, time to return to baseline saturation, baseline $SpO_2$- minimum $SpO_2$, etc.).

One of the strengths of our study is that it is prospective and examines the relationship between 6MWT results and quality of life, fatigue and dyspnea severity in addition to functional parameters. The main limitation of our study is the inadequate standardization of the 6MWT in IPF patients, as well as the difficulties associated with interpreting the test results [21, 22, 49]. Supplemental oxygen support, especially during testing, may alter the results of the 6MWT. However, only three of our patients received supplemental oxygen support during the 6MWT, which did not significantly change our results. PH was not defined according to the RHC, which is the gold standard. Current guidelines do not recommend routine RHC in patients with IPF. Therefore, the study protocol avoided invasive intervention. In our study, transthoracic echocardiography was performed by a single experienced cardiologist.

## Conclusion

In conclusion, we suggest that saturation recovery time and DSP are inexpensive, easily applicable, and noninvasive new markers that can be used to predict the clinical course of the disease and concomitant PH. Based on the results of our study, we recommend continuous saturation monitoring during and after the 6MWT until the patient returns to baseline.

### Abbreviations

| | |
|---|---|
| IPF | Idiopathic Pulmonary Fibrosis |
| FVC | Forced Vital Capacity |
| DLCO | Diffusing Capacity of the Lung for Carbon Monoxide |
| CPI | Composite Physiological İndex |
| GAP | Gender-Age-Physiology |
| 6MWT | 6-Minute Walk Test |
| 6MWD | 6-Minute Walk Distance |
| DSP | Distance-Saturation Product |
| EHRA | European Heart Rhythm Association |
| PH | Pulmonary Hypertension |
| $SpO_2$ | Saturation of Peripheral Oxygen |
| sPAP | Pulmonary Artery Systolic Pressure |
| ATS | American Thoracic Society |
| ERS | European Respiratory Society |
| BMI | Body Mass Index |
| proBNP | N-terminal pro-B-type Natriuretic Peptide |
| FEV1 | Forced Expiratory Volume in 1 second |
| SGRQ | St. George's Respiratory Questionnaire, Test |
| MFI-20 | Multidimensional Fatigue Inventory-20 |
| mMRC | Modified Medical Research Council |
| D-12 | Dyspnea-12 |
| $PaO_2$ | Partial Pressure of Oxygen |

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### Author contributions

MSO, ZB, and GO designed the study protocol. AP, ZB, and MSO analyzed the data and wrote the manuscript. PK, EK and MSAK collected the data. ZK, EK, AKB, and GO substantively revised it. All authors contributed to the article and approved the submitted version.

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### Data availability

The datasets used in the present study are available from the first author and corresponding authors on reasonable request.

## Declarations

### Ethics approval and consent to participate

The present study protocol was approved by the İstanbul Faculty of Medicine Ethics Committee approval was obtained. The study was approved by the with the number 2021/227450 and was conducted in accordance with the standards specified in the World Medical Association Helsinki Declaration. All participants were provided with verbal and written information and written informed consent was obtained from all. As this study involved standard clinical procedures and assessments without an experimental treatment protocol, it did not require registration with a public clinical trials registry.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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### References

1. Cancellieri A, Maffessanti M, Dalpiaz G. Diffuse lung diseases: clinical features, pathology, HRCT. 1st ed. Milan; New York: Springer Milan; 2006.
2. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An Official ATS/ERS/JRS/ALAT Statement: idiopathic pulmonary fibrosis: evidence-based

guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788–824.
3. King TE, Pardo A, Selman M. Idiopathic pulmonary fibrosis. Lancet. 2011;378:1949–61.
4. Ley B, Collard HR, King TE. Clinical course and prediction of Survival in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2011;183:431–40.
5. Sgalla G, Biffi A, Richeldi L. Idiopathic pulmonary fibrosis: diagnosis, epidemiology and natural history. Respirology. 2016;21:427–37.
6. Kim HJ, Perlman D, Tomic R. Natural history of idiopathic pulmonary fibrosis. Respir Med. 2015;109:661–70.
7. Wells AU, Desai SR, Rubens MB, Goh NSL, Cramer D, Nicholson AG, et al. Idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2003;167:962–9.
8. Mura M, Porretta MA, Bargagli E, Sergiacomi G, Zompatori M, Sverzellati N, et al. Predicting survival in newly diagnosed idiopathic pulmonary fibrosis: a 3-year prospective study. Eur Respir J. 2012;40:101–9.
9. Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, et al. A Multidimensional Index and Staging System for Idiopathic Pulmonary Fibrosis. Ann Intern Med. 2012;156:684.
10. Lee SH, Kim SY, Kim DS, Kim YW, Chung MP, Uh ST, et al. Predicting survival of patients with idiopathic pulmonary fibrosis using GAP score: a nationwide cohort study. Respir Res. 2016;17:131.
11. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Six-minute-walk test in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;183:1231–7.
12. Flaherty KR, Andrei A-C, Murray S, Fraley C, Colby TV, Travis WD, et al. Idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2006;174:803–9.
13. Lama VN, Flaherty KR, Toews GB, Colby TV, Travis WD, Long Q, et al. Prognostic Value of Desaturation during a 6-Minute walk test in idiopathic interstitial pneumonia. Am J Respir Crit Care Med. 2003;168:1084–90.
14. Lettieri CJ, Nathan SD, Browning RF, Barnett SD, Ahmad S, Shorr AF. The distance-saturation product predicts mortality in idiopathic pulmonary fibrosis. Respir Med. 2006;100:1734–41.
15. Raghu G, Nathan SD, Behr J, Brown KK, Egan JJ, Kawut SM, et al. Pulmonary hypertension in idiopathic pulmonary fibrosis with mild-to-moderate restriction. Eur Respir J. 2015;46:1370–7.
16. Papakosta D, Pitsiou G, Daniil Z, Dimadi M, Stagaki E, Rapti A, et al. Prevalence of pulmonary hypertension in patients with idiopathic pulmonary fibrosis: correlation with physiological parameters. Lung. 2011;189:391–9.
17. Modrykamien AM, Gudavalli R, McCarthy K, Parambil J, Echocardiography. 6-minute walk distance, and distance-saturation product as predictors of pulmonary arterial hypertension in idiopathic pulmonary fibrosis. Respir Care. 2010;55:584–8.
18. Minai OA, Santacruz JF, Alster JM, Budev MM, McCarthy K. Impact of pulmonary hemodynamics on 6-min walk test in idiopathic pulmonary fibrosis. Respir Med. 2012;106:1613–21.
19. Swigris JJ, Olson AL, Shlobin OA, Ahmad S, Brown KK, Nathan SD. Heart rate recovery after six-minute walk test predicts pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Respirology. 2011;16(3):439–45.
20. Swigris JJ, Olson AL, Shlobin OA, Ahmad S, Brown KK, Nathan SD. Heart rate recovery after six-minute walk test predicts pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Respirology. 2011;16(3):439–45. https://doi.org/10.1111/j.1440-1843.2010.01877.x-52.
21. Lancaster LH. Utility of the six-minute walk test in patients with idiopathic pulmonary fibrosis. Multidiscip Respir Med. 2018;13:45.
22. Harari S, Wells AU, Wuyts WA, Nathan SD, Kirchgaessler K-U, Bengus M, et al. The 6-min walk test as a primary end-point in interstitial lung disease. Eur Respir Rev. 2022;31:220087.
23. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166:111.
24. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44:1428–46.
25. A Controlled Trial of Sildenafil in Advanced Idiopathic Pulmonary Fibrosis. N Engl J Med. 2010;363:620–8.
26. Swigris JJ, Brown KK, Behr J, du Bois RM, King TE, Raghu G, et al. The SF-36 and SGRQ: validity and first look at minimum important differences in IPF. Respir Med. 2010;104:296–304.
27. Bahmer T, Kirsten A-M, Waschki B, Rabe KF, Magnussen H, Kirsten D, et al. Clinical correlates of reduced physical activity in idiopathic pulmonary fibrosis. Respiration. 2016;91:497–502.
28. Yorke J, Swigris J, Russell A-M, Moosavi SH, Ng Man Kwong G, Longshaw M, et al. Dyspnea-12 is a Valid and Reliable measure of breathlessness in patients with interstitial lung disease. Chest. 2011;139:159–64.
29. Touil I, Keskes Boudawara N, Bouchareb S, Ben Saad A, Migaou A, Cheikh Mhamed S, et al. Facteurs pronostiques Au cours de la fibrose pulmonaire idiopathique: étude d'une cohorte tunisienne. Rev Mal Respir. 2021;38:681–8.
30. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43:3618–731.
31. Nalysnyk L, Cid-Ruzafa J, Rotella P, Esser D. Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature. Eur Respir Rev. 2012;21:355–61.
32. Tran T, Šterclová M, Mogulkoc N, Lewandowska K, Müller V, Hájková M, et al. The European MultiPartner IPF registry (EMPIRE): validating long-term prognostic factors in idiopathic pulmonary fibrosis. Respir Res. 2020;21:11.
33. Caminati A, Bianchi A, Cassandro R, Rosa Mirenda M, Harari S. Walking distance on 6-MWT is a prognostic factor in idiopathic pulmonary fibrosis. Respir Med. 2009;103:117–23.
34. Eaton T, Young P, Milne D, Wells AU. Six-Minute Walk, maximal Exercise tests. Am J Respir Crit Care Med. 2005;171:1150–7.
35. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in Advanced Idiopathic Pulmonary Fibrosis. Chest. 2006;129:746.
36. Gupta R, Ruppel GL, Espiritu JRD. Exercise-Induced Oxygen Desaturation during the 6-Minute Walk Test. Med Sci. 2020;8:8.
37. Waatevik M, Johannessen A, Gomez Real F, Aanerud M, Hardie JA, Bakke PS, et al. Oxygen desaturation in 6-min walk test is a risk factor for adverse outcomes in COPD. Eur Respir J. 2016;48:82–91.
38. Khor YH, Goh NS, Glaspole I, Holland AE, McDonald CF. Exertional desaturation and prescription of ambulatory oxygen therapy in interstitial lung disease. Respir Care. 2019;64:299–306.
39. Fiore C, Lee A, McDonald C, Hill C, Holland A. Should oxyhaemoglobin saturation be monitored continuously during the 6-minute walk test? Chron Respir Dis. 2011;8:181–4.
40. Chuang M-L, Lin I-F, Chen S-P. Kinetics of changes in Oxyhemoglobin Saturation during walking and Cycling tests in COPD. Respir Care. 2014;59:353–62.
41. Nadrous HF, Pellikka PA, Krowka MJ, Swanson KL, Chaowalit N, Decker PA, et al. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Chest. 2005;128:2393–9.
42. King CS, Shlobin OA. The trouble with Group 3 pulmonary hypertension in interstitial lung disease. Chest. 2020;158:1651–64.
43. Raghu G, Amatto VC, Behr J, Stowasser S. Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. Eur Respir J. 2015;46:1113–30.
44. Pitsiou G, Papakosta D, Bouros D. Pulmonary hypertension in idiopathic pulmonary fibrosis: a review. Respiration. 2011;82:294–304.
45. Boutou AK, Pitsiou GG, Trigonis I, Papakosta D, Kontou PK, Chavouzis N, et al. Exercise capacity in idiopathic pulmonary fibrosis: the effect of pulmonary hypertension. Respirology. 2011;16:451–8.
46. Pitsiou G, Bagalas V, Boutou A, Stanopoulos I, Argyropoulou-Pataka P. Should we routinely screen patients with idiopathic pulmonary fibrosis for nocturnal hypoxemia? Sleep Breath. 2013;17:447–8.
47. Harari S, Caminati A, Cassandro R, Conti S, Madotto F, Luisi F et al. Pulmonary hypertension in idiopathic pulmonary fibrosis does not influence six-minute walk distance: results from a retrospective study. Sarcoidosis, Vasc Diffus lung Dis Off J WASOG. 2015;31:297–305.
48. Ley B, Bradford WZ, Vittinghoff E, Weycker D, du Bois RM, Collard HR. Predictors of Mortality poorly predict common measures of Disease Progression in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2016;194:711–8.
49. Lancaster L, Fieuw A, Meulemans J, Ford P, Nathan SD. Standardization of the 6-min walk test in clinical trials of idiopathic pulmonary fibrosis. Contemp Clin Trials. 2021;100:106227.
50. Bourbonnais JM, Malaisamy S, Dalal BD, Samarakoon PC, Parikh SR, Samavati L. Distance saturation product predicts health–related quality of life among sarcoidosis patients. Health Qual Life Outcomes. 2012;10:67.

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