Research Paper

# Pulmonary Rehabilitation in Idiopathic Pulmonary Fibrosis: A Chance for a Multidisciplinary Treatment Approach

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## ABSTRACT

**Objectives:** Idiopathic pulmonary fibrosis (IPF) is characterized by progressively worsening lung function, ventilation capacity, dyspnea, and finally reduced exercise intolerance. All of these have a significant negative impact on functional capacity and quality of life. In this study, we aim to evaluate the effects of pulmonary rehabilitation (PR) in IPF and assess the predictors of success.

**Methods:** Data from 17 IPF patients who completed the program from the total of 27 patients who applied to PR were used in our study. We evaluated their pulmonary function tests, exercise capacity, peripheral-respiratory muscle strength, body composition, quality of life, and psychological states before and after PR.

**Results:** Following the PR program, improvements over the minimal clinically important differences were observed in almost all parameters compared to the baseline; however, statistically significant improvements were only observed in the medical research council (P=0.020), the St. George respiratory questionnaire (P=0.002), the maximal inspiratory pressure (P=0.024), the anxiety score (P=0.001), the depression score (P=0.002), and the right quadriceps muscle strength (P=0.046). There was only a statistically significant negative correlation between the initial forced vital capacity and the forced expiratory volume in one-second value with the increase in patients' maximal inspiratory pressure values after PR.

**Discussion:** After a multidisciplinary, comprehensive PR program, dyspnea sensation, exercise capacity, endurance time, quality of life, respiratory and peripheral muscle strengths, and psychological status were improved regardless of age, gender, antifibrotic treatment, and comorbidities. Therefore, patients should be referred to PR units before the deterioration in the quality of life in the early stages of the disease.

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## Highlights

• After a multidisciplinary, comprehensive pulmonary rehabilitation (PR) program in idiopathic pulmonary fibrosis, dyspnea sensation, exercise capacity, endurance time, quality of life, respiratory and peripheral muscle strengths, and psychological status were improved.

• Age, gender, antifibrotic medication, and comorbidities did not affect the provided benefits.

• Patients should be referred to PR units in the early stages of the disease, before their quality of life starts to deteriorate.

## Plain Language Summary

Idiopathic pulmonary fibrosis is a disease that does not respond to medication. As a result of alterations in the lung tissue, this condition is characterized by difficulty in breathing during movement, movement limitations, and worsening of quality of life. Lung transplantation, the only therapy option, is merely available to a limited percentage of patients. This study aimed to see how the pulmonary rehabilitation program affects patients with this condition. Accordingly, we discovered that patients who received pulmonary rehabilitation program had improved shortness of breath, range of motion, endurance time, quality of life, muscle strength, and psychological status.

## 1. Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common disorder among all types of interstitial lung diseases. It is characterized by irreversible inflammation and fibrosis of the lung parenchyma and it occurs primarily in the elderly. The clinical course of IPF continues with rapid loss of lung function in some patients while it is slower in others; however, the average life expectancy of the disease is 2 to 5 years [1]. Comorbidities are common and several that are associated with survival. The most notable examples include lung cancer, pulmonary hypertension, cardiovascular diseases, obstructive sleep apnea, emphysema, and or chronic obstructive pulmonary disease (COPD) [2]. Body composition abnormalities, especially having a low body mass index (BMI), are related to worse survival [3]. Psychosocial problems, such as anxiety and depression are also reported. Several studies have indicated that the prevalence of depression ranges from 24.3% to 49.2%, while the prevalence of anxiety may be as high as 60% in patients with IPF [4].

While many pharmacological agents have been developed, they can only slow the disease progression and physical impairment. Lung transplantation is the only treatment but it can be applied to a minority with IPF due to advanced age and comorbidities.

Pulmonary rehabilitation (PR) has provided a chance as a holistic approach to chronic respiratory disease because of its effectiveness in alleviating symptoms, reducing the duration of hospital stay, increasing exercise tolerance, and maximizing functional ability [5]. In this context, PR is important in the palliative treatment of IPF patients as it is a multidisciplinary approach and can also act as a bridge for patients waiting on the transplant list. Accordingly, this study aims to examine the impact of PR and the factors that influence success in IPF patients.

## 2. Materials and Methods

### Study population

Considering that the beginning of our study was old and there was limited information about the effectiveness of PR, very few patients were referred to our center with the diagnosis of IPF, and since we included the years 2008-2017 in our study, we conducted our research with 27 patients referred to our PR center with the diagnosis of IPF. Of this population, 10 patients who were evaluated at the beginning were not included in the study as they could not complete the program (due to active working, transportation problems, disease attack, or compatibility problems). Therefore, the parameters of 17 patients diagnosed with IPF who referred to our PR center were included in the study, and then pre- and post-PR parameters were evaluated in the same group of patients. The results were statistically analyzed for PR efficiency, retrospectively. Meanwhile, informed consent was obtained from the patients.

## Outcome parameters

We recorded the pulmonary function, dyspnea sensation, exercise capacity, peripheral and respiratory muscle strengths, quality of life, body composition, and psychological status before and after the PR program. The comorbidity and pharmacological treatment data were obtained retrospectively from medical records. Spirometry was performed to determine forced vital capacity (FVC), forced expiratory volume in one second ($FEV_1$), and $FEV_1$/FVC using a spirometer (AS-507, Minato Medical Science, Tokyo, Japan), following the American Thoracic Society-European Respiratory Society (ATS-ERS) guidelines [6]. Respiratory muscle strength was evaluated by measuring the maximal inspiratory and expiratory pressure (MIP and MEP, respectively) using a Micro-RPM respiratory pressure meter (Care Fusion, Hoech-berg, Germany). MIP and MEP were measured starting from the residual volume and total lung capacity, respectively. Exercise capacity was evaluated using the Incremental Shuttle Walking Test (ISWT) and Endurance Shuttle Walking Test (ESWT) according to field walking test guidelines [7]. A value of the minimal clinically important difference (MCID) has been identified for the ISWT as 47.5 m (~5 shuttle) [7]. Health-related quality of life (QoL) was assessed using the St. George Respiratory Questionnaire (SGRQ) [8] and dyspnea was assessed using the Medical Research Council (MRC) scale [9]. Bioelectrical impedance was performed to assess body composition (BMI and fat-free mass index [FFMI]) using a TANITA (TBF-300A Total Body Composition Analyzer, Tokyo, Japan). The hospital anxiety and depression (HAD) scores were used to assess psychological status [10].

## Pulmonary rehabilitation

Before the PR program, all patients were consulted by a cardiologist on whether there was any cardiac contraindication. After examining the routine laboratory tests, basic posteroanterior chest radiographs were taken and respiratory function tests were performed. Patients were also evaluated by a psychologist, physiotherapist, dietician, and nurses who were a part of the multidisciplinary team after the detailed medical history information was obtained by the chest physicians. Patients underwent an 8-week hospital-based outpatient comprehensive PR program on 2 half-days per week. The PR program consisted of exercise training, education, nutritional and psychosocial counseling, and, if necessary, supportive therapy.

The exercise training program consisted of endurance and resistance training for the upper and lower limbs with inspiratory and expiratory muscle training. In individuals with a low BMI and FFMI, oral nutritional supplementation was provided. In the PR program for patients with low peripheral muscle strength, neuromuscular electrical muscle stimulation was included. Individuals with poor HAD scores received psychosocial counseling and psychiatric assistance to meet their medical treatment needs. As a result, when establishing a PR program for all patients, individual needs were considered based on prior and continuing evaluations, exercise tolerance, and disease severity.

The endurance training included 30 min of endurance exercise (15 min on a treadmill and 15 min on a stationary bicycle) at 85% of each patient's peak oxygen consumption ($VO_2$ peak) calculated from the ISWT. A 15-min warm-up and cool-down period were also included. Quadriceps resistance training entailed leg extension using free weights according to a 1-repetition maximum, starting at 45% for two sets (10 repetitions per set) followed by 70% for 3 sets. Resistance training of the shoulder girdle and elbow muscles consisted of 1 set at 10 repetitions per set starting at 0.5 kg before being increased to 1 to 1.5 kg. Strengthening the inspiratory muscles was applied initially through devices with inspiratory flow targets or threshold loading, with a gradual increase in workload to the extent that MIP ≥ %30 and to the extent that they can tolerate. The program was based on the recommendations of current guidelines, the most widely used "Official American Thoracic Society/European Respiratory Society Statement", published by Spruit et al. in 2013, which consists of the updated 2006 statement with new information [11]. During the PR sessions, the vital signs were monitored by physiotherapists. Oxygen support was provided where necessary, with an oxygen level above 90%.

## Statistical analysis

The statistical analysis was performed using the SPSS software, v. 18.0 (SSPS, Chicago, IL, USA). The data are given as SD and median (minimum: maximum). A minimum of 17 patients were required, with an 80% confidence interval (CI), a 5% margin of error, and an effect size of 0.73. At first, the variables were analyzed using the Shapiro-Wilks test for normal distribution. The paired t test was then used for variables with normal distribution and the Wilcoxon signed-rank test was used for variables without normal distribution. The Mann-Whitney U test was used to compare the

groups. The Spearman correlation analyses were also performed. Statistical significance was determined as a probability value of <0.05.

## 3. Results

Of the study population, 13 patients were male and 4 were female. The mean age of all patients was 60±10 years. Detailed demographic characteristics and initial assessment parameters of the patients are given in Table 1. A total of 11 patients had been receiving antifibrotic therapy, while 6 of our patients were not receiving antifibrotic treatment as the beginning of our study was in 2007 and antifibrotic treatment was not yet available in our country. The comorbidities can be listed as coronary artery disease 7(41%), pulmonary hypertension 7(41%), gastroesophageal reflux 15(88%), hiatal hernia 3(18%), diabetes mellitus 3(18%), arterial hypertension 12(70%), hyperlipidemia 4(23%), obstructive sleep apnea 2(12%), emphysema 5(29%), hypothyroidism 2(12%), osteoporosis 2(12%), and renal failure 1(6%). One patient had no comorbidities, 6 had 1 to 3 comorbidities, and 10 had 4 to 7 comorbidities. Two of the patients underwent bilateral lung transplantation, and one of them died in the second year of transplantation.

Improvements in dyspnea sensation, health-related QoL (HRQL), inspiratory muscle strength, right quadriceps muscle strength, and HAD scores were found statistically significant. Even the improvements in both ISWT and ESWT were over the MCID (Δ:60m, Δ:2.9min, respectively), and they were not statistically significant (P=0.070, P=0.109, respectively). Although not statistically significant, the mean values in both the right and left handgrip tests increased after PR when compared to the baseline (right hand 27.4±9.1 kg to 28±6.6 kg; P=0.590, and left hand 26.7±8.2 kg to 27±7.0 kg; P=0.810, respectively). In addition, both right and left quadriceps muscle strengths were increased after PR, but only the improvement in the right quadriceps was statistically significant (P=0.046). Furthermore, no statistically significant difference was observed in BMI and FFMI (P=0.326 and P=0.060, respectively) (Table 2).

When patients were grouped according to antifibrotic usage, the gainings for all outcome measures were similar between the two groups.

There were correlations between the initial FVC% predicted and $FEV_1$% predicted levels with increases in MIP levels. The improvements in inspiratory muscle function were much more relevant in patients with lower pulmonary function. In this study, the other predictor of success was basal HRQL. There was a negative correlation between the initial SGRQ total score with the increases in this parameter (P=0.015, r=-0.594). No other indicative result was found as a predictor of success (Table 3).

## 4. Discussion

This study demonstrated that dyspnea sensation, QoL, respiratory and peripheral muscle strength, and psychological status improved in IPF patients after a hospital-based outpatient, multidisciplinary, comprehensive supervised PR program regardless of age, gender, antifibrotic treatment, and comorbidity. In addition, we found that in patients with poor initial respiratory function, respiratory muscle strength improved more; meanwhile, in patients who have fewer SGRQ scores, there was a further increase in QoL.

The data based on a cohort study of more than 1600 IPF patients enrolled in the EMPIRE system found that only 46% of patients survived up to 5 years after diagnosis [1]. There is still no curative medical treatment and current antifibrotic drugs are only partially effective at disease progression. However, the symptoms limit the daily activities of patients with IPF. Since there is no effective pharmacotherapy for IPF, all methods that will improve the QoL are eagerly awaited by patients. Dyspnea is the cardinal symptom and is responsible for physical restraint. Weakness, possibly because of skeletal muscle dysfunction, may also limit the ability of IPF patients to perform their physical activities. That is why alleviating such symptoms improves patients' QoL and physical activity [12].

PR is recognized as an integral and essential component of the management of patients with IPF and is recommended in guidelines. PR is defined by the ATS and the ERS as a "comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors" [12].

**Table 1.** Demographic features and initial assessment parameters

| Demographic Variables | | Mean±SD | Median (Min:Max) | No. (%) |
|---|---|---|---|---|
| Age (y) | | 60±10 | 60 (50:78) | - |
| Gender | Male | - | - | 13(77) |
| | Female | - | - | 4(23) |
| Smoking | Never | - | - | 3(18) |
| | Current | - | - | 1(6) |
| | Ex-smoker | - | - | 13(77) |
| Smoking (p/y) | | 26±22 | 20(0:80) | - |
| Antifibrotic treatment | Positive | - | - | 6(35) |
| | Negative | - | - | 11(65) |
| The number of comorbidities | | - | (0:7) | 4(23.5) |
| Long-term oxygen use | | - | - | 7(41) |
| $FEV_1$ predicted (%) | | 73±25 | 66(40:137) | - |
| FVC predicted (%) | | 68±32 | 69(40:140) | - |
| MRC score | | 2.8±0.9 | 3(2:5) | - |
| BMI ($kg/m^2$) | | 28±5 | 27(19:37) | - |
| FFMI ($kg/m^2$) | | 20±3 | 20(15:24) | - |
| SGRQ total score | | 64±19 | 67(36:98) | - |
| ISWT (m) | | 230±154 | 160(50:520) | - |
| ESWT (min) | | 6.6±5.1 | 4.1(2:16) | - |
| MIP ($cmH_2O$) | | 97±29/ | 106(48:142) | - |
| MEP ($cmH_2O$) | | 118±41/ | 109(63:181) | - |
| HAD scores | Anxiety | 11±2 | 12(8:14) | - |
| | Depression | 10±2 | 10(7:14) | - |
| Handgrip test | Right | 27.4±9.1 | 29(10:44) | - |
| | Left | 26.7±8.2 | 28(12:42) | - |
| Quadriceps muscle strength | Right | 4.2±0.7 | 4(3:5) | - |
| | Left | 4.1±0.6 | 4(3:5) | - |

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SD: standard deviation; min:minimum; max:maximum; m/f: male/female; n: number; p/y: per year; $FEV_1$: forced expiratory volume in one second; FVC: forced vital capacity; MRC: medical research council; BMI: body mass index; FFMI: fat free mass index; SGRQ: St. George respiratory questionnaire; ISWT: incremental shuttle walk test; ESWT: endurance shuttle walk test; MIP: maximal inspiratory presssure; MEP: maximal expiratory pressure; HAD: hospital anxiety depression; R: right; L: left

**Table 2.** Outcome measures before and after the PR program

| Parameters | | Mean±SD | Median(Min:Max) | Mean±SD | Median(Min:Max) | P |
|---|---|---|---|---|---|---|
| | | Before PR | | After PR | | |
| $FEV_1$ predicted (%) | | 73±25 | 66(40:137) | 73±25 | 70(40:140) | 0.925 |
| FVC predicted (%) | | 68±32 | 69(40:140) | 72±24 | 70(40:137) | 0.574 |
| MRC score | | 2.8±0.9 | 3(2:5) | 2.4±0.8 | 2(1:5) | 0.020 |
| BMI ($kg/m^2$) | | 28±5 | 27(19:37) | 28±5 | 28(19:37) | 0.326 |
| FFMI ($kg/m^2$) | | 20±3 | 20(15:24) | 20±3 | 20(15:22) | 0.060 |
| SGRQ score | | 64±19 | 67(36:98) | 41±21 | 35(19:94) | 0.002 |
| ISWT (meters) | | 230±154 | 160(50:520) | 260±146 | 280(25:530) | 0.070 |
| ESWT (min) | | 6.6±5.1 | 4.1(2:16) | 9.0±7.6 | 7.0(2:20) | 0.109 |
| MIP (cm $H_2O$) | | 97±29 | 106(48:142) | 102±36 | 112(52:165) | 0.024 |
| MEP (cm $H_2O$) | | 118±41 | 109(63:181) | 124±36 | 122(63:186) | 0.245 |
| HAD | anxiety | 11±2 | 12(8:14) | 9±2 | 8(3:14) | 0.001 |
| | depression | 10±2 | 10(7:14) | 8±2 | 7(4:13) | 0.002 |
| Handgrip test (kg) | Right | 27.4±9.1 | 29(10:44) | 28±6.6 | 28(16:36) | 0.590 |
| | Left | 26.7±8.2 | 28(12:42) | 27±7 | 30(12:36) | 0.810 |
| Quadriceps MS | Right | 4.2±0.7 | 4(3:5) | 4.5±0.5 | 4(4:5) | 0.046 |
| | Left | 4.1±0.6 | 4(3:5) | 4.4±0.6 | 4(3:5) | 0.102 |

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PR: pulmonary rehabilitation; SD: standard deviation; min: minimum; max: maximum; $FEV_1$: forced expiratory volume in one second; FVC: forced vital capacity; MRC: medical research council; BMI: body mass index; FFMI: fat free mass index; SGRQ: St. George respiratory questionnaire; ISWT: incremental shuttle walk test; ESWT: endurance shuttle walk test; min: minute; MIP: maximal inspiratory presssure; MEP: maximal expiratory pressure; HAD: hospital anxiety depression; R: right; L: left; MS: muscle strength.

Comorbidities that are the cause or consequence of the disease affect IPF symptomatically, and negatively affect survival; therefore, a comprehensive and holistic approach is necessary. Thus, in addition to the function of increasing exercise capacity, PR should include non-exercise components, such as nutritional support, training of patients and relatives, psychological support, and symptom management, which are of great importance in IPF [12].

One of the most important rationales for PR in IPF is an increase in dyspnea sensation. A study by Holland et al. aimed to determine the safety and effects of exercise training in interstitial lung diseases and to investigate whether patients with IPF have similar responses to other types of interstitial lung diseases. In this study, a significant reduction in MRC scores was observed along with improvements in dyspnea and fatigue on the chronic respiratory disease questionnaire [13]. In our study, we used MRC for the perception of dyspnea and the improvement was statistically and clinically significant.

Patients with IPF have severely limited exercise capacity because of dyspnea, hypoxemia, and abnormal lung mechanics. In our study, ISWT and ESWT were used to evaluate exercise capacity. The basal ISWT distance revealed an impairment in the exercise capacity of our patients, in which the median distance was found at 160 m. After PR, both the walking distance

**Table 3.** Correlation of the gains with the initial assessment parameters

| Variable | ΔMRC | ΔSGRQ | ΔISWT | ΔMIP | ΔAnx | ΔDep | ΔQuadMS (R//L) |
|---|---|---|---|---|---|---|---|
| Age (y) | P=0.331 r=0.151 | P=0.707 r=0.050 | P=0.587 r=-0.257 | P=0.245 r=-0.263 | P=0.417 r=-0.162 | P=0.548 r=-0.157 | P=0.346, r=-0.252 // P=0.330, r=0.270 |
| Gender | P=0.394 | P=0.433 | P=0.114 | P=0.193 | P=0.216 | P = 0.423 | P=0.283 // P=0.433 |
| Smoking (p/y) | P=0.377, r = 0.237 | P=0.505, r=0.187 | P=0.459, r=0.200 | P=0.889, r=-0.040 | P=0.726, r=-0.095 | P=0.716, r=-0.099 | P=0.261, r=-0.299 // P=0.298, r=0.288 |
| $FEV_1$ | P=0.644, r=0.130 | P=0.691, r=-0.117 | P=0.527, r=-0.177 | P=0.004, r=-0.675 | P=0.453, r=-0.210 | P=0.387, r=-0.241 | P=0.380, r=-0.244 // P=0.112, r=-0.443 |
| FVC | P=0.994, r=0.002 | P=0.686, r=0.119 | P=0.394, r=-0.237 | P=0.012, r=-0.632 | P=0.266, r=-0.307 | P=0.174, r=-0.371 | P=0.064, r=-0.489 // P=0.078, r=-0.486 |
| MRC | P=0.064, r=-0.473 | P=0.910, r=-0.032 | P=0.336, r=-0.257 | P=0.951, r=-0.017 | P=0.333, r=0.259 | P=0.229, r=0.319 | P=0.222, r=-0.323 // P=1, r=0 |
| SGRQ total score | P=0.726, r=0.099 | P=0.015, r= -0.594 | P=0.336, r=-0.267 | P=0.551, r=0.174 | P=0.420, r=0.225 | P=0.985, r=0.005 | P=0.891, r=0.039 // P=0.671, r=0.125 |
| ISWT | P=0.436, r=-0.210 | P=0.904, r=0.034 | P=0.342, r=-0.254 | P=0.904, r=-0.034 | P=0.914, r=0.029 | P=0.695, r=0.106 | P=0.486, r=-0.188 // P=0.985, r=-0.012 |
| MIP | P=1.0, r=0 | P=0.350, r=0.270 | P=0.718, r=0.102 | P=0.800, r=-0.072 | P=0.174, r=0.370 | P=0.990, r=0.004 | P=0.449, r=-0.204 // P=0.512, r=-0.184 |
| Anxiety | P=0.746, r=0.088 | P=0.146, r=-0.394 | P=0.212, r=0.330 | P=0.396, r=-0.236 | P=0.586, r=-0.147 | P=0.410, r=-0.221 | P=0.435, r=-0.210 // P=0.988, r=-0.004 |
| Depression | P=0.171, r=-0.373 | P=0.712, r=0.100 | P=0.367, r=0.242 | P=0.360, r=-0.255 | P=0.630, r=-0.130 | P=0.079, r=-0.452 | P=0.555, r=-0.162 // P=0.731, r=-0.097 |

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p/y: per year; $FEV_1$: forced expiratory volume in one second; FVC: forced vital capacity; MRC: medical research council; SGRQ: St. George respiratory questionnaire; ISWT: incremental shuttle walk test; MIP: maximal inspiratory presssure; Anx: anxiety; Dep: depression; Quad MS: quadriceps muscle strength; R//L: right//left

and endurance capacity of our patients improved, even though they did not reach statistically significant levels. In a prospective study searching validity, responsiveness, and MCID of the ISWT in IPF, MCID ranged from 31 to 46 m [14]. Tonelli et al. also observed substantial improvements in symptom severity, HRQL, and physical functioning in interstitial lung disease patients after 30 rehabilitation sessions [15]. In a study by Huppmann et al., a total of 202 out of 402 patients were diagnosed with IPF and had an average of 53% FVC. They presented a median 45 m improvement in the 6-Minute-Walk Test (MWT) [16]. In both of these studies, the group of patients who showed the best improvement was the ones with the worst walking distance at the beginning. In our study, we did not see any relation between the baseline walking distance with the gainings in exercise capacity, but the increase in our patients' walking distance was also in this range.

There is an improvement in inspiratory muscle strength, functional capacity, and perception of dyspnea by inspiratory muscle training (IMT). In a study investigating the effectiveness of PR, including IMT in 30 patients diagnosed with IPF, patients were divided into 2 groups before the PR program [17]. In the study group consisting of 16 patients, IMT was added and only general body conditioning was performed in the control group. As a result, it was found that there was an improvement in dyspnea, 6-MWT, QoL, and MIP values in the study group. In our study, we also administered IMT for the treatment of dyspnea sensations, and even though our patients' MIP levels were within normal reference ranges, there was a statistically significant increase in their MIP levels after PR.

As for another parameter, handgrip strength is a simple measurement of the upper limb muscle function that is associated with mortality in the general population and patients with COPD. Moreover, measures of interstitial lung disease severity were associated with grip strength and gait speed independent of body composition [18]. The severity of the disease is strongly associated with body composition, with significantly lower muscle mass and higher fat mass in individuals

with more impaired pulmonary function, according to a prospective cohort study of 115 fibrotic interstitial lung disease patients, including 40 IPF patients. This study also revealed that the severity of the disease is associated with upper limb muscle dysfunction and worse physical performance, regardless of muscle mass or fat mass [18]. Kozu R.et al. investigated the relationships between MRC and peripheral muscle force, activities of a daily living performance, health status, lung function, and exercise capacity in 65 patients diagnosed with IPF. Handgrip force and 6-MWT scores decreased with increasing MRC grade (all P<0.001) [19]. In our study, we observed that handgrip strength after the PR program increased, however not statistically significant.

Improving the QoL is also of great importance in IPF treatment. Nishiyama et al. used the SGRQ to evaluate HRQL during a 10-week outpatient PR in 30 IPF patients. Only the change in the total SGRQ score made a significant difference in favor of the PR group against those who did not receive PR [20]. In line with the literature, in our study, there was a statistically significant improvement in the SGRQ values. The improvement was much more evident in patients who had a good QoL at the beginning of the program.

Anxiety and depression are also two of the common comorbidities of IPF. In this group of patients, the prevalence of anxiety ranged from 30% to 50%, while the prevalence of depression was found to be 20% to 30% [21]. Anxiety and depression are not directly related to physiological parameters, however, it is well-known that dyspnea and disease progression are aggravating factors. In addition, they are known to have a major impact on the QoL. Similarly, there was a significant improvement in the HAD scores of our patients after completing the PR. Basal HAD scores did not find relevant to any outcome measure in this study.

Another benefit of PR is its positive contribution to nutritional status. Relationships between BMI and prognosis have been reported between patients with COPD and other disorders. Recent studies have also associated BMI with survival in IPF, even though the mechanisms of the association have not been investigated adequately [22]. In the study in which 44 IPF patients were included, Nishiyama et al. found a significant positive correlation between FFMI and FVC, DLCO, and 6-MWT and a significant negative correlation with age. And consequently, they argue that FFMI is an important independent predictor for survival in IPF [22]. Accordingly, monitoring the BMI and FFMI in IPF, and providing the necessary support in the early period positively contribute to the situation. In our study, there was no significant change in patients' BMI and FFMI values, which we associated with patients being overweight at the beginning of PR.

In addition, PR is beneficial in patients referred for lung transplantation [23]. A recent study also revealed that a multidisciplinary PR program is beneficial for patients on the waiting list for lung transplantation and leads to improvements in QoL with 6-MWT [23]. While 3 of our patients were on the transplantation list, 2 patients were transplanted and 1 patient died before the operation.

Questions such as which patients would benefit the most and when should be referred to PR have been still not answered. Some studies show that those with higher basic FVC and less baseline 6-MWT desaturation have larger and sustained improvements at the end of exercise training [24]. This supports that the earlier patients start PR, the more they will benefit. On the other hand, in a study by Dowman et al., 142 interstitial lung disease patients, 61 of whom were diagnosed with IPF, were evaluated. They found that patients with high baseline 6-MWT results received less benefit following an 8-week PR [25]. The differences between the results of these studies can be explained by the diversity of patients including the presence of comorbidities or the design of the studies. In our study, no significant correlation was found between the initial FVC value and the gainings in MRC, HAD, SGRQ, and ISWT after the PR program. A correlation was found between the FVC% predicted and $FEV_1$% predicted levels and the gains in MIP levels. The improvements in inspiratory muscle function were much more relevant in patients with lower pulmonary function. Also, we found that the other predictor of success was basal HRQL. There was a positive correlation between the initial SGRQ total score with the gainings in this parameter. The improvements in SGRQ, MRC, ISWT, MIP, and HAD were not related to age, gender, antifibrotic treatment, baseline exercise capacity, or psychological status.

## 5. Conclusion

This study shows that the comprehensive multidisciplinary hospital-based outpatient PR program in patients diagnosed with IPF improved dyspnea perception, respiratory muscle strength, exercise capacity with endurance time, HRQL, and HAD scores regardless of age, gender, antifibrotic treatment, baseline exercise capacity, and psychological status. IMT should be imple-

mented in patients who have lower values of FVC and $FEV_1$. As the improvement in quality of life is a major target, patients should be referred before deterioration.

### Study limitations

The limitations of this study can be evaluated as the few patients. Other limitations are that the study was not a randomized controlled trial and that some patients were included in the study before the use of antifibrotic drugs in our country.

## Ethical Considerations

### Compliance with ethical guidelines

The Committee of Medical Specialty Education Board checked and approved the appropriateness of the planned studies as an Ethics Committee (No.: 697-6).

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### Authors' contributions

All authors equally contributed to preparing this article.

### Conflict of interest

The authors declared no conflict of interest.

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### References

[1] 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. Respiratory Research. 2020; 21(1):11. [PMID] [PMCID]

[2] Raghu G, Amatto VC, Behr J, Stowasser S. Comorbidities in idiopathic pulmonary fibrosis patients: A systematic literature review. The European Respiratory Journal. 2015; 46(4):1113-30. [PMID]

[3] Mogulkoc N, Sterclova M, Müller V. Kus J, Hajkova M, Jovanovic D, et al. Does body mass index have prognostic significance for patients with idiopathic pulmonary fibrosis? European Respiratory Journal. 2018; 52:PA2210. [DOI:10.1183/13993003.congress-2018.PA2210]

[4] Ryerson CJ, Arean PA, Berkeley J, Carrieri-Kohlman VL, Pantilat SZ, Landefeld CS, et al. Depression is a common and chronic comorbidity in patients with interstitial lung disease. Respirology. 2012; 17(3):525-32. [PMID]

[5] Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: A randomised controlled trial. The Lancet. 2000; 355(9201):362-8. [DOI:10.1016/S0140-6736(99)07042-7]

[6] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. ATS/ERS Task Force. Standardisation of spirometry. The European Respiratory Journal. 2005; 26(2):319-38. [PMID]

[7] Singh SJ, Jones PW, Evans R, Morgan MD. Minimum clinically important improvement for the incremental shuttle walking test. Thorax. 2008; 63(9):775-7. [PMID]

[8] Jones PW, Quirk FH, Baveystock CM, Littlejohns P. Self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. The American Review of Respiratory Disease. 1992; 145(6):1321-7. [PMID]

[9] Fletcher CM (Chairman). Standardised questionnaire on respiratory symptoms: A statement prepared and approved by the MRC Committee on the Aetiology of Chronic Bronchitis (MRC breathlessness score). BMJ. 1960; 2:1665.

[10] Zigmond AS, Snaith PR. The hospital anxiety and depression scale. Acta Psychiatrica Scandinavica. 1983; 67(6):361-70. [PMID]

[11] Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: Key concepts and advances in pulmonary rehabilitation. American Journal of Respiratory and Critical Care Medicine. 2013; 188(8):e13-64. [PMID]

[12] Rochester CL, Vogiatzis I, Holland AE, Lareau SC, Marciniuk DD, Puhan MA, et al. An official American Thoracic Society/European Respiratory Society policy statement: Enhancing implementation, use, and delivery of pulmonary rehabilitation. American Journal of Respiratory and Critical Care Medicine. 2015; 192(11):1373-86. [PMID]

[13] Holland AE, Fiore JF Jr, Goh N, Symons K, Dowman L, Westall G, et al. Be honest and help me prepare for the future: what people with interstitial lung disease want from education in pulmonary rehabilitation. Chronic Respiratory Disease. 2015; 12(2):93-101. [PMID]

[14] Nolan CM, Delogu V, Maddocks M, Patel S, Barker RE, Jones SE, et al. Validity, responsiveness and minimum clinically important difference of the incremental shuttle walk in idiopathic pulmonary fibrosis: A prospective study. Thorax, thoraxjnl-2017-210589. Advance online publication. [PMID]

[15] Tonelli R, Cocconcelli E, Lanini B, Romagnoli I, Florini F, Castaniere I, et al. Effectiveness of pulmonary rehabilitation in patients with interstitial lung disease of different etiology: A multicenter prospective study. BMC Pulmonary Medicine. 2017; 17(1):130. [PMID] [PMCID]

[16] Huppmann P, Sczepanski B, Boensch M, Winterkamp S, Schönheit-Kenn U, Neurohr C, et al. Effects of inpatient pulmonary rehabilitation in patients with interstitial lung disease. The European Respiratory Journal. 2013; 42(2):444-53. [PMID]

[17] Jastrzebski D, Kozielski J, Zebrowska A. [Pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis with inspiratory muscle training (Polish)]. Pneumonologia i Alergologia Polska. 2008; 76(3):131-41. [PMID]

[18] Guler SA, Hur SA, Lear SA, Camp PG, Ryerson CJ. Body composition, muscle function, and physical performance in fibrotic interstitial lung disease: A prospective cohort study. Respiratory Research. 2019; 20(1):56. [PMID] [PMCID]

[19] Kozu R, Jenkins S, Senjyu H. Evaluation of activity limitation in patients with idiopathic pulmonary fibrosis grouped according to Medical Research Council dyspnea grade. Archives of Physical Medicine and Rehabilitation. 2014; 95(5):950-5. [PMID]

[20] Nishiyama O, Kondoh Y, Kimura T, Kato K, Kataoka K, Ogawa T, et al. Effects of pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Respirology. 2008; 13(3):394-9. [PMID]

[21] Ryerson CJ, Berkeley J, Carrieri-Kohlman VL, Pantilat SZ, Landefeld CS, Collard HR. Depression and functional status are strongly associated with dyspnea in interstitial lung disease. Chest. 2011; 139(3):609-16. [PMID]

[22] Nishiyama O, Yamazaki R, Sano H, Iwanaga T, Higashimoto Y, Kume H, et al. Fat-free mass ındex predicts survival in patients with ıdiopathic pulmonary fibrosis. Respirology. 2017; 22(3):480-5. [PMID]

[23] Florian J, Watte G, Teixeira PJZ, Altmayer S, Schio SM, Sanchez LB, et al. Pulmonary rehabilitation improves survival in patients with idiopathic pulmonary fibrosis undergoing lung transplantation. Scientific Reports. 2019; 9(1):9347. [PMID] [PMCID]

[24] Kozu R, Jenkins S, Senjyu H. Effect of disability level on response to pulmonary rehabilitation in patients with idiopathic pulmonary fibrosis. Respirology. 2011; 16(8):1196-202. [PMID]

[25] Dowman LM, McDonald CF, Hill CJ, Lee AL, Barker K, Boote C, et al. The evidence of benefits of exercise training in interstitial lung disease: A randomised controlled trial. Thorax. 2017; 72(7):610-9. [PMID]