Efficacy of lower dose Pirfenidone for idiopathic pulmonary fibrosis in real practice: a retrospective cohort study

Hyeontaek Hwang
Seoul National University College of Medicine
Jung-Kyu Lee
Seoul National University Seoul Metropolitan Government Boramae Medical Center
Sun Mi Choi
Seoul National University College of Medicine
Yeon Joo Lee
Seoul National University Bundang Hospital
Young-Jae Cho
Seoul National University Bundang Hospital
Ho Il Yoon
Seoul National University Bundang Hospital
Jae Ho Lee
Seoul National University Bundang Hospital
Choon-Taek Lee
Seoul National University Bundang Hospital
Young Whan Kim
Seoul National University College of Medicine
Jong Sun Park (jspark.im@gmail.com)
Seoul National University Bundang Hospital https://orcid.org/0000-0003-3707-3636

Research

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Abstract

Background Pirfenidone slows the progression of idiopathic pulmonary fibrosis. We investigated the efficacy and safety of pirfenidone by dose and disease severity in real-world patients with idiopathic pulmonary fibrosis.

Methods This multi-centre retrospective cohort study investigated 338 patients treated with pirfenidone between July 2012 and March 2018. Demographics, pulmonary function, mortality, and pirfenidone-related adverse events were recorded. Efficacy was analysed according to pirfenidone dose and disease severity using linear mixed-effects models to assess the annual decline rate of forced vital capacity (FVC) and diffusing capacity (DL CO) of the lungs for carbon monoxide.

Results The mean %FVC predicted and %DL COpredicted were 72.6±13.1% and 61.4±17.9%, respectively. Pirfenidone treatment lasted 16.1±9.0 months. In the standard-dose (1800 mg/day) group, the mean %FVC predicted was -6.56% (95% CI -9.26, -3.87) per year pre-pirfenidone treatment, but -4.43% (95% CI -5.87, -3.00) per year post-treatment. In the lower-dose group, the mean %FVC predicted was -4.96% (95% CI -6.82, -3.09) per year pre-pirfenidone treatment, but -1.79% (95% CI -2.75, -0.83) per year post-treatment. The FVC decline rate was significantly reduced regardless of GAP stage. However, the DL CO decline rate was significantly reduced in the GAP stage II–III group, but not stage I group. Adverse events and mortality were similar across dose groups, but were more frequent in the GAP stage II–III group than in the stage I group.

Conclusions The effect of pirfenidone on reducing disease progression persisted even with a consistent lower dose of pirfenidone.

Trial registration Retrospectively registered

Background

Idiopathic pulmonary fibrosis (IPF) is a fibrotic interstitial pneumonia of unknown cause. It is a chronic, progressive disease with very poor prognosis, of which median survival is about 3 years from the time of diagnosis (1). Pirfenidone, an antifibrotic drug, could reduce the rate of decline in forced vital capacity (FVC) and prolong progression-free survival in large-scale randomized controlled trials. Although it has been shown to be effective in the treatment of IPF, it is also associated with adverse events (2, 3).

Because there may be differences between clinical trials and real-world situations, some studies have investigated the efficacy and adverse events of pirfenidone in real clinical settings. In these studies, pirfenidone was effective and well-tolerated. In most of these studies, patients were treated with a standard dose (2400 mg) of pirfenidone, except in Japan, where the standard dose was 1800 mg (4–7). In the CAPACITY 004 study, the pirfenidone-associated attenuation of decline in FVC at 1197 mg pirfenidone per day was intermediate to that with 2403 mg pirfenidone per day and placebo (2). However, few studies have investigated the effect of a lower dose of pirfenidone in a real-world situation (8).

Additionally, in real-world studies of the efficacy and safety of pirfenidone according to disease severity (9–11), similar results in terms of the safety of pirfenidone were obtained in both patients with severe and with less-severe IPF. However, the efficacy of pirfenidone according to disease severity varied. It was similar in advanced IPF and non-advanced IPF in one study, but another study showed that it was more beneficial for advanced IPF patients (10, 11).

We considered whether a lower dose of pirfenidone would also be effective in real-world settings and whether there would be differences in the efficacy and safety of pirfenidone according to disease severity. This study thus investigated the efficacy and safety of pirfenidone according to the pirfenidone dose and disease severity in patients with IPF, in real-world conditions.

Materials And Methods

This was a multi-centre retrospective cohort study of patients with IPF from three referral centres in Korea, i.e., Seoul National University Hospital, Seoul National University Bundang Hospital, and Seoul Metropolitan Government-Seoul National University Boramae Medical Centre.

The study included patients who were diagnosed with IPF according to the consensus statement of the ATS/ERS/JRS/ALAT (1) and who were treated with pirfenidone between July 2012 and March 2018. To improve the reliability of results, patients with at least two follow-up pulmonary function tests (PFTs) performed after commencing pirfenidone treatment were included. Patients for whom the start date of pirfenidone treatment was unclear due to referral from other hospitals were excluded.

Baseline demographic characteristics, information on diagnosis of IPF, comorbidities, and previous and combined treatments with pirfenidone were recorded for each patient.

Pirfenidone treatment was started with 800 mg, as three divided doses, and was increased to 1800 mg, as three divided doses. Titration was performed every 2 weeks, at the discretion of the attending physician. Before the first administration of the drug, the patient's PFT, 6-minute walk test, and use of supplemental oxygen were checked. PFT was performed at least every 6 months before and after treatment with pirfenidone. As clinical outcomes, overall death and IPF-related death were recorded.

When the patients were divided into two groups according to the dose of pirfenidone, those who had received the standard full dose of 1800 mg pirfenidone per day for more than 6 months were assigned to the standard-dose group. Patients who had received less than 1800 mg of pirfenidone per day for more than 6 months were assigned to the non-standard group. Disease severity was classified according to the GAP stage and patients were divided into GAP stage I and GAP stage II–III groups.

Statistical analysis

For efficacy analysis, collected PFT data from patients were used. A mixed-effects linear regression model was used to analyse repeated-measurement data and to correct missing data. First, forced vital

capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DL_{CO}) data from patients who underwent at least two PFT measurements from commencing pirfenidone treatment were used to estimate the annual FVC and DL_{CO} decrease rate after treatment with pirfenidone. In order to evaluate the efficacy of pirfenidone, the annual FVC and DL_{CO} decrease rate before and after treatment were compared using the paired *t* test. Finally, it was examined whether there was a difference in the annual rate of decline of FVC and DL_{CO} between before and after treatment in each group, according to dose and disease severity. Differences between groups were examined by unpaired *t*-test.

For safety analysis, adverse events related to treatment were analysed and the rate of discontinuation of treatment due to adverse events was calculated.

Statistical analysis was performed with StataSE version 12 and SPSS statistics version 19. P-value < 0.05 was considered to indicate statistical significance.

Results

Characteristics of the study patients

Of the 565 patients who were prescribed pirfenidone in the three participating hospitals, 338 patients were enrolled in the study, after excluding 17 patients with unclear date of onset of pirfenidone treatment and 210 patients without at least two follow-up PFTs. Among the enrolled patients, efficacy analysis was performed in 174 patients who had at least two PFTs before treatment with pirfenidone (Figure 1).

Of the included patients, 75.1% were male and the mean age was 71.0 years. Most were former smokers (55.0%); 9.2% were current smokers. Most patients did not receive other treatments before (82.2%) or during treatment with pirfenidone (76.6%). More than half of the patients (67.2%) started treatment with pirfenidone within 1 year of IPF diagnosis. Patients in the standard dose group had a higher percentage of males, younger age, and higher body mass index and body surface area than those in the non-standard dose group. Higher distances in the 6-minute walk test and lower modified Medical Research Council (mMRC) grades were seen in patients treated with a standard dose of pirfenidone (Table 1). These results were similar in patients included in efficacy analysis (see Additional file 1).

Of the patient cohort, 46.2% received 1800 mg (standard dose) of pirfenidone per day as the maximum dose during the whole period of pirfenidone treatment, but 21.3% of patients were eventually maintained on 1800 mg of pirfenidone. About half of the patients were maintained on a pirfenidone dose lower than 1800 mg. The rate of pirfenidone discontinuation for any cause was 26.3%. The overall mean duration of treatment with pirfenidone was 16.1 ± 9.0 months, and 68 patients (20.1%) received pirfenidone at the standard dose (1800 mg) for more than 6 months. In these patients, the overall mean duration of pirfenidone treatment was 18.2 ± 7.8 months (Table 2).

Changes in lung function

The annual FVC and DL_{CO} changes were estimated in patients who underwent at least two PFTs during pirfenidone treatment. The mean percentage predicted FVC ($\%FVC_{predicted}$) change after pirfenidone treatment was -1.78% (95% CI -2.37, -1.20) per year, and the mean change in percentage predicted DL_{CO} ($\%DL_{COpredicted}$) after pirfenidone treatment was -3.11% (95% CI -3.92, -2.30) per year (Figure 2).

FVC and DL_{CO} changes before and after treatment were investigated in patients with data for at least two PFTs before and after treatment (Table 3, Figure 3). The $\%FVC_{predicted}$ and $\%DL_{COpredicted}$ decline rates were significantly reduced after treatment with pirfenidone ($p < 0.001$).

Differences in FVC and DL_{CO} changes before and after the administration of pirfenidone were compared in the standard dose group; the mean $\%FVC_{predicted}$ was -6.56% (95% CI -9.26, -3.87) per year before treatment with pirfenidone, but -4.43% (95% CI -5.87, -3.00) per year after treatment. In the non-standard, lower-dose group, the mean $\%FVC_{predicted}$ was -4.96% (95% CI -6.82, -3.09) per year before treatment with pirfenidone, but was -1.79% (95% CI -2.75, -0.83) per year after treatment. The decline rate of $\%FVC_{predicted}$ was significantly attenuated by pirfenidone treatment in both groups ($p < 0.05$). There was no significant difference in decline rates between groups according to dose. Similar findings were obtained for DL_{CO} changes, and there was no significant difference between the groups (Table 4).

In efficacy analysis according to baseline GAP stage, the $\%FVC_{predicted}$ decline rates were significantly reduced in both GAP stage I and GAP stage II–III groups ($p < 0.001$) (Table 5). There was no difference in decline in FVC between the two groups. However, there was a significant reduction in the decline rate of DL_{CO} in the GAP stage II–III group before and after treatment, but not in the GAP stage I group.

Adverse events

Adverse events occurred in 276 (81.7%) of the patients. Among these effects, anorexia was the most common, followed by skin rash and dyspepsia. Eighty-three (24.6%) patients discontinued treatment due to adverse events. Overall, death occurred in 36 (10.7%) patients, and IPF-related death occurred in 31 (9.2%) patients (Table 6). There was no significant difference in adverse events between the groups (Table 7). Compared with adverse events and mortality according to disease severity, anorexia, nausea, and general weakness occurred more frequently in the GAP stage II–III group than in the GAP stage I group. (Table 8).

Discussion

This real-world study showed that pirfenidone attenuated the rate of decline of FVC and DL_{CO} in both the standard-dose and the non-standard, lower-dose group, with similar adverse events. The effect of reducing DL_{CO} was prominent in patients with moderate to severe IPF, but more adverse events occurred in patients with moderate to severe IPF.

In this study, the reduction in the rate of FVC decline after treatment with pirfenidone was similar to the results of previous real-world studies in other countries (4, 6, 12). In the case of DL_{CO}, some clinical trials and real-world studies suggested that there was no significant reduction in the rate of decline before and after treatment (2, 6, 13). However, our study found that the rate of decline of DL_{CO} was reduced after treatment with pirfenidone, in agreement with reports of some other real-world studies (4, 12). This indicates that pirfenidone may be effective in reducing the decline of DL_{CO} as well as the decline of FVC.

In efficacy analysis, treatment with both standard (1800 mg/day) and non-standard, lower doses (< 1800 mg/day) reduced the rate of decline of FVC and DL_{CO} before and after treatment. There was no significant difference in homogeneity between the groups. These results suggest that taking doses with tolerable side effects, even if these doses are lower than the standard full dose, may help to prevent disease progression. This finding is similar to that of a recent post-hoc analysis of multinational phase III trials, which revealed that patients receiving pirfenidone at ≤ 90% of the standard dose intensity also showed treatment benefit as compared to placebo (14). Most patients in our non-standard, lower-dose group were maintained at 1200 mg of pirfenidone per day. In a study from Japan, changes in %FVC (Δ%FVC) at 12 months were not significantly different between patients taking 1200 mg and those taking 1800 mg of pirfenidone. However, when patients were divided into groups based on body surface area-adjusted dose of pirfenidone (876 mg/m^2), the Δ%FVC of patients taking higher doses was significantly greater than that of patients taking lower doses (8). In this study, patients in the standard dose group received 1017 mg/m^2 of pirfenidone, a body surface-adjusted dose, and patients in the non-standard dose group received 719 mg/m^2 or less. Nevertheless, patients receiving lower dose pirfenidone have been shown to reduce FVC and DLCO, suggesting that lower dose pirfenidone may be helpful in patients who are unable to withstand the side effects of the drug due to their age, low body surface area, or poor performance.

The minimum dose of pirfenidone that can maintain efficacy without causing adverse effects should be further investigated. According to the baseline GAP stage, the FVC decline rate was significantly reduced by pirfenidone, regardless of GAP group. One study showed that the effect of pirfenidone on reducing the rate of decline of FVC was greater in advanced IPF patients (6). Another study concluded that pirfenidone significantly reduced disease progression (≥ 10% decline in FVC or death) at 12 months, regardless of the baseline GAP stage (15). In terms of attenuating the decline rate of FVC, the present study showed similar results.

Our study further demonstrated that the decline rate of DL_{CO} was significantly reduced in the GAP stage II-III group. A real-world study conducted in Italy showed that pirfenidone did not diminish the rate of decline rate of DL_{CO}, regardless of the baseline GAP stage (6). This may be due to differences of ethnicity of the study populations. A recent study showed that the decline rate of DL_{CO} decreased 6 months after commencing pirfenidone treatment in IPF patients with a mean GAP score of 5 at baseline (stage II) (10). Thus, pirfenidone should be used for treatment of even patients with severe IPF.

Although there have been several real-world studies of pirfenidone use in IPF (4, 10, 11, 16, 17), those studies did not focus on the dose of pirfenidone. Our study comprehensively investigated the effect of the dose of pirfenidone on the pulmonary function of IPF patients from three tertiary referral hospitals in real-world conditions. Therefore, these results would be useful to clinicians during their daily practice of IPF treatment.

The standard dose of pirfenidone in Asian countries is 1800 mg according to the clinical trial from Japan, which is lower than the standard dose of 2400 mg used in western countries. Despite the use of lower doses, only 20.1% of our patients maintained the standard dose over a period of 6 months. These results are quite different from those of other countries, including Japan, in which most patients received standard doses (6, 7, 18), and from those of a recent study in which most patients with IPF maintained a relatively high dose intensity of pirfenidone (14). In real-world conditions, pirfenidone could be less tolerable than that in a clinical trial setting. In Korea, government insurance reimbursement for pirfenidone use has been applied since October 2015. Some patients who were prescribed before this insurance period could not continue use of pirfenidone due to its high cost. Although the proportion of patients who maintained the standard dose was low, the rate of complete discontinuation due to adverse events was 24.6%, which is similar to the rate found in other studies (4, 7, 10, 11, 19).

This study has several limitations. First, because it was a retrospective cohort study, selection bias and missing data were inevitable. A mixed linear regression model was used to calibrate the missing data as much as possible and to adjust for age, sex, and body mass index, which may affect the PFT results. Second, the follow-up period of the patients was short. Therefore, further long-term follow-up studies will be needed in future. Third, this was not a multi-national study, which may make it difficult to generalize this result to other countries.

Conclusions

The effect of pirfenidone on reducing disease progression persisted even with a consistent lower dose of pirfenidone. Thus, use of doses with tolerable side effects, even if these doses are lower than the standard full dose of pirfenidone, may help to prevent IPF progression.

Abbreviations

DLCO = diffusing capacity of the lungs for carbon monoxide; FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; %DLCOpredicted = percentage predicted DLCO; %FVCpredicted = percentage predicted FVC; PFT = pulmonary function test

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the amended Declaration of Helsinki. The study protocol was approved by the institutional review board or ethics committee in each hospital. (IRB no.: J-1803-006-924 (Seoul National University Hospital), B-1801/442-104 (Seoul National University Bundang Hospital), 20180129/30-2018-5/023 (Seoul Metropolitan Government-Seoul National University Boramae Medical Center). The need to obtain informed consent was waived due to the retrospective nature of the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors contributed substantially to the study design. HH and JSP collected and analyzed the data. HH and JSP wrote the first draft of the manuscript. JKL, SMC, YJL, YJC, HIY, JHL, CTL, YWK critically reviewed and approved the final manuscript.

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Tables

Table 1. Baseline characteristics of enrolled patients*

Demographic characteristics	N = 338	Standard dose (n = 68)	Non-standard dose (n = 160)	*p*-value
Male	254 (75.1)	58 (85.3)	112 (70.0)	0.015
Age (years)	71.0 ± 8.0	69.3 ± 7.6	72.3 ± 8.4	0.012
Body mass index (kg/m^2)	24.3 ± 2.9	25.0 ± 2.9	24.0 ± 3.0	0.032
Body surface area (m^2)	1.71 ± 0.17	1.77 ± 0.15	1.67 ± 0.16	<0.001
Smoking history				0.460
Current smoker	31 (9.2)	3 (4.5)	14 (9.2)	
Former smoker	186 (55.0)	42 (63.6)	88 (57.9)	
Never smoker	107 (31.7)	21 (31.8)	50 (32.9)	
Comorbidity				
Diabetes	76 (22.5)	17 (25.0)	33 (20.6)	0.465
Hypertension	92 (27.2)	14 (20.6)	43 (26.9)	0.316
Coronary arterial disease	34 (10.1)	4 (5.9)	19 (11.9)	0.169
Chronic obstructive pulmonary disease	16 (4.7)	3 (4.4)	9 (5.6)	1.000
Surgical lung biopsy	46 (13.6)	7 (10.3)	22 (13.8)	0.474
Definite UIP pattern on CT	283 (83.7)	58 (85.3)	134 (83.8)	0.770
Diagnosis (≤ 1 year) of IPF	227 (67.2)	48 (70.6)	100 (62.5)	0.242
Pulmonary function test				
$\%FVC_{predicted}$	72.6 ± 13.1	71.1 ± 10.2	72.9 ± 13.4	0.263
FVC (L)	2.45 ± 0.62	2.59 ± 0.57	2.37 ± 0.62	0.012
$\%DL_{COpredicted}$	61.4 ± 17.9	64.6 ± 19.4	60.9 ± 17.1	0.153
Use of supplemental oxygen	7 (2.1)	1 (1.5)	5 (3.1)	0.672
6-minute walk test distance (m)	416.7 ± 92.4	448.1 ± 90.1	401.0 ± 92.3	<0.001
mMRC grade	1.3 ± 0.6	1.1 ± 0.6	1.4 ± 0.6	0.002
GAP stage				0.453
GAP I	171 (50.6)	33 (49.3)	84 (55.3)	
GAP II	160 (47.3)	34 (50.7)	65 (42.8)	
GAP III	7 (2.1)	0 (0)	3 (2.0)	
Previous treatment				0.825
No	278 (82.2)	57 (85,1)	128 (80.5)	
Steroid only	45 (13.3)	8 (11.9)	23 (14.5)	
Steroid + immunosuppressant	10 (3.0)	1 (1.5)	6 (3.8)	
Immunosuppressant only	3 (0.9)	1 (1.5)	2 (1.3)	
Combined treatment with pirfenidone				0.731
No	259 (76.6)	53 (77.9)	117 (73.1)	
Steroid only	78 (23.1)	15 (22.1)	42 (26.3)	
Steroid + immunosuppressant	1 (0.3)	0 (0)	1 (0.6)	

UIP = Usual interstitial pneumonia

* Data are presented as n (%) or mean ± SD

Table 2. Treatment duration and dose of pirfenidone in study patients*

All patients	N = 338
Duration of total pirfenidone treatment (month)	16.1 ± 9.0
Maximum dose of pirfenidone, n (%)	
1800 mg	156 (46.2)
1200–1500 mg	169 (50.0)
≤ 600 mg	13 (3.8)
Final dose of pirfenidone, n (%)	
1800 mg	72 (21.3)
1200–1600 mg	145 (42.9)
800–1000 mg	9 (2.7)
≤ 600 mg	23 (6.8)
Discontinuation	89 (26.3)
Patients receiving standard dose (n = 68)	
Duration of total pirfenidone treatment (month)	18.2 ± 7.8

*Data are presented as n (%) or mean ± SD

Table 3. Comparison of FVC and DLCO changes before and after treatment with pirfenidone

Parameter	Before treatment		After treatment		Mean difference	*p*-value
	Mean	95% C.I.	Mean	95% C.I.		
Δ FVC/year* (n = 174)	-5.34	(-6.56, -4.12)	-2.89	(-3.64, -2.14)	+2.45	< 0.001
Δ DL_{CO}/year* (n = 164)	-7.55	(-9.42, -5.68)	-3.76	(-4.69, -2.82)	+3.79	< 0.001

* Change in % predicted per year

Table 4. Comparison of FVC and DLCO decline rate before and after treatment according to the dose of pirfenidone

Parameter	Time	Standard dose (n = 32)			Non-standard dose (n = 82)		
		Mean	95% CI	*p*-value	Mean	95% CI	*p*-value
Δ FVC/year* (n = 114)	Pre-Treatment	-6.56	(-9.26, -3.87)		-4.96	(-6.82, -3.09)	
	Post-Treatment	-4.43	(-5.87, -3.00)		-1.79	(-2.75, -0.83)	
	Difference	+2.13		0.010	+3.17		< 0.001
p-value for homogeneity of difference in parameter between two groups: 0.307							
Parameter	Time	Standard dose (n = 32)			Non-standard dose (n = 75)		
		Mean	95% CI	*p*-value	Mean	95% CI	*p*-value
Δ DL_{CO}/year* (n = 107)	Pre-Treatment	-8.03	(-11.93, -4.13)		-7.69	(-10.68, -4.70)	
	Post-Treatment	-4.38	(-6.44, -2.31)		-3.12	(-4.34, -1.90)	
	Difference	+3.65		0.008	+4.57		< 0.001
p-value for homogeneity of difference in parameters between two groups: 0.536							

* Change in % predicted per year

Table 5. Comparison of FVC and DLCO decline rate before and after treatment according to baseline GAP stage

Parameter	Time	Baseline GAP I (n = 95)			Baseline GAP II–III (n = 76)		
		Mean	95% CI	*p*-value	Mean	95% CI	*p*-value
Δ FVC/year* (n = 171)	Pre-Treatment	-4.56	(-6.10, -3.02)		-6.40	(-8.38, -4.42)	
	Post-Treatment	-2.28	(-3.21, -1.35)		-3.72	(-4.97, -2.48)	
	Difference	+2.28		<0.001	+2.68		< 0.001
p-value for homogeneity of difference in parameter between two groups: 0.626							
Parameter	**Time**	**Baseline GAP I (n = 90)**			**Baseline GAP II–III (n = 72)**		
		Mean	**95% CI**	***p*-value**	**Mean**	**95% CI**	***p*-value**
Δ DL_{CO}/year* (n = 162)	Pre-Treatment	-4.84	(-7.34, -2.34)		-11.09	(-13.84, -8.34)	
	Post-Treatment	-3.80	(-5.03, -2.57)		-3.46	(-4.89, -2.02)	
	Difference	+1.04		0.153	+7.63		< 0.001
p-value for homogeneity of difference in parameter between two groups: < 0.001							

* Change in % predicted per year

Table 6. Adverse events and mortality of enrolled patients

Adverse event, n (%)	N = 338
Total	276 (81.7)
Anorexia	123 (36.4)
Skin rash	97 (28.7)
Dyspepsia	89 (26.3)
Nausea	65 (19.2)
General weakness	51 (15.1)
Liver function test abnormality	43 (12.7)
Photosensitivity	34 (10.1)
Fatigue	22 (6.5)
Diarrhoea	19 (5.6)
Others	57 (16.9)
Discontinuation of treatment due to adverse event, n (%)	83 (24.6)
Overall death, n (%)	36 (10.7)
IPF related death, n (%)	31 (9.2)

Table 7. Adverse events and mortality according to dose of pirfenidone

Adverse event, n (%)	Standard dose (n = 68)	Non-standard dose (n = 160)	*p*-value
Total	56 (82.4)	124 (77.5)	0.411
Anorexia	26 (38.2)	54 (33.8)	0.516
Skin rash	16 (23.5)	45 (28.1)	0.473
Dyspepsia	18 (26.5)	37 (23.1)	0.589
Nausea	13 (19.1)	23 (14.4)	0.369
General weakness	12 (17.6)	22 (13.8)	0.450
Liver function test abnormality	7 (10.3)	20 (12.5)	0.637
Photosensitivity	5 (7.4)	18 (11.3)	0.371
Fatigue	8 (11.8)	7 (4.4)	0.075
Diarrhoea	5 (7.4)	8 (5.0)	0.536
Others	11 (16.2)	22 (13.8)	0.634
Discontinuation of treatment due to adverse event, n (%)	10 (14.7)	38 (23.8)	0.125
Overall death, n (%)	5 (7.4)	13 (8.1)	0.843
IPF-related death, n (%)	5 (7.4)	11 (6.9)	1.000

Table 8. Adverse events and mortality according to disease severity

Adverse event, n (%)	GAP I (n = 168)	GAP II–III (n = 159)	*p*-value
Total	133 (79.2)	134 (84.3)	0.233
Anorexia	50 (29.8)	69 (43.4)	0.010
Skin rash	55 (32.7)	38 (23.9)	0.077
Dyspepsia	41 (24.4)	46 (28.9)	0.355
Nausea	25 (14.9)	38 (23.9)	0.039
General weakness	17 (10.1)	34 (21.4)	0.005
Liver function test abnormality	21 (12.5)	21 (13.2)	0.848
Photosensitivity	19 (11.3)	13 (8.2)	0.341
Fatigue	11 (6.5)	11 (6.9)	0.894
Diarrhoea	9 (5.4)	9 (5.7)	0.904
Others	27 (16.1)	29 (18.2)	0.603
Discontinuation of treatment due to adverse event, n (%)	37 (22.0)	45 (28.3)	0.191
Overall death, n (%)	9 (5.4)	26 (16.4)	0.001
IPF-related death, n (%)	7 (4.2)	23 (14.5)	0.001

Figures

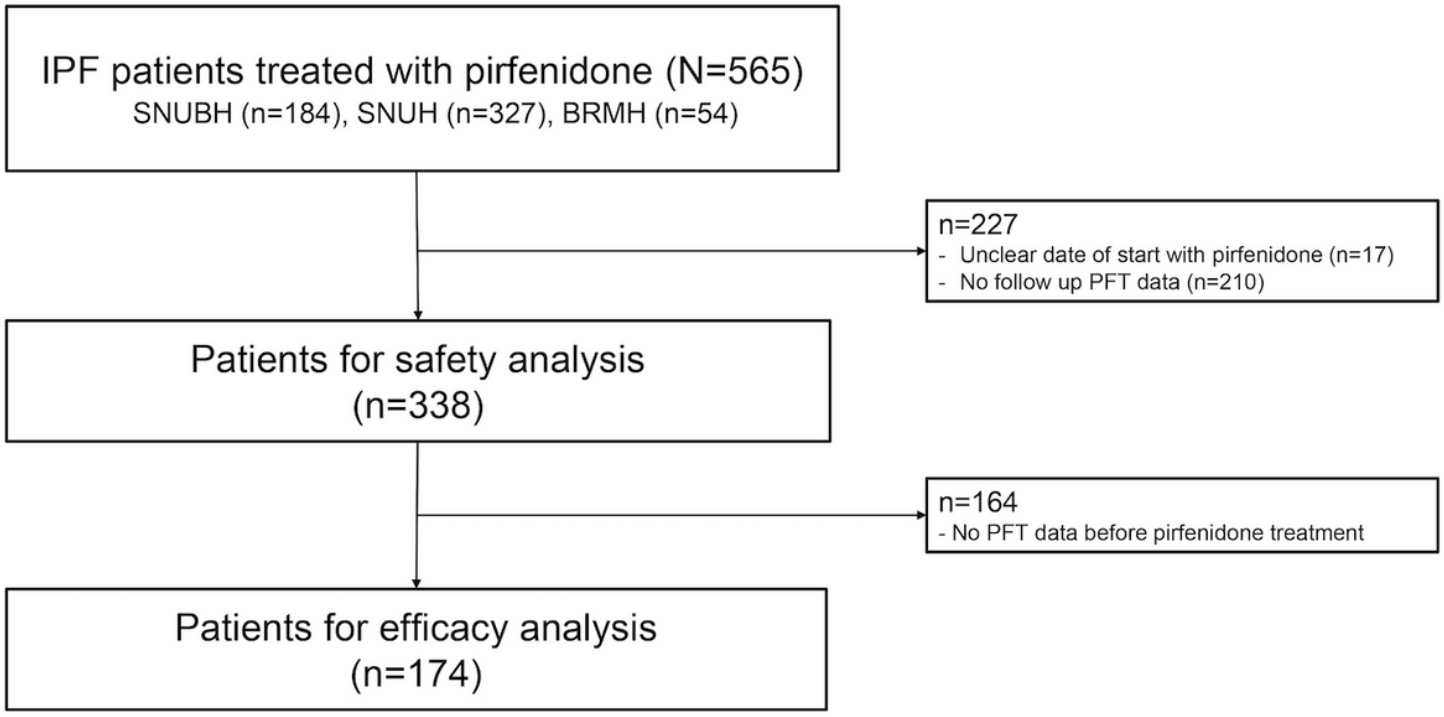

Figure 1

Flow diagram of the study

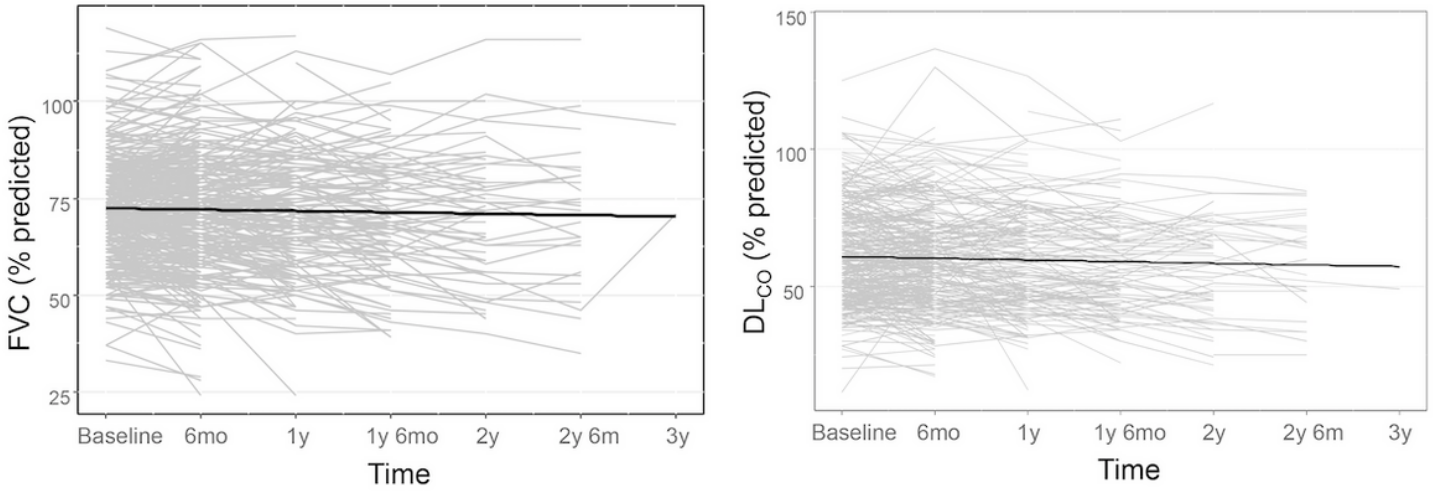

Figure 2

Decline of FVC and DLCO during pirfenidone treatment

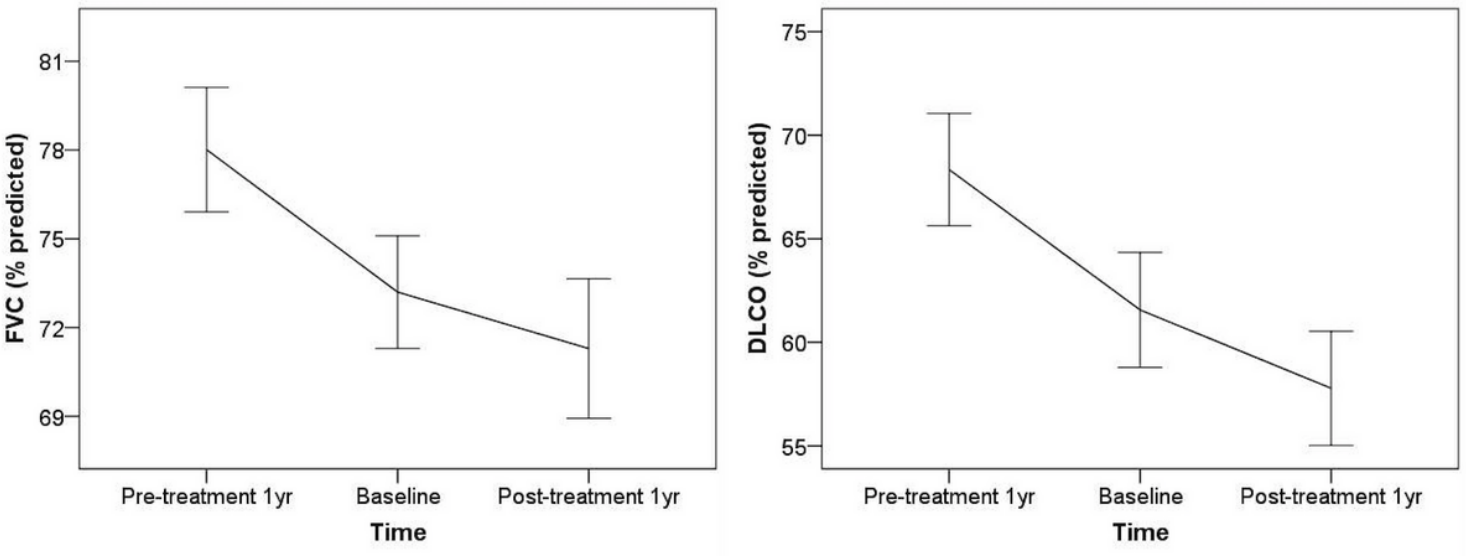

Figure 3

Annual decline of FVC and DLCO before and after treatment with pirfenidone

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1.docx
- STROBEchecklistv4combinedpirfenidone.doc