

1 **Deterioration of high-resolution computed tomography findings**
2 **predicts disease progression after initial decline in forced vital capacity**
3 **in idiopathic pulmonary fibrosis patients treated with pirfenidone**

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3

4 **Short Title:** Computed tomography findings predict disease progression in idiopathic
5 pulmonary fibrosis

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11 **Abbreviations**

12 IPF, idiopathic pulmonary fibrosis; FVC, forced vital capacity; ATS, American Thoracic

13 Society; ERS, European Respiratory Society; JRS, Japanese Respiratory Society; ATRA,

14 Latin American Thoracic Association; PFT, pulmonary function test; HRCT,

15 high-resolution computed tomography; UIP, usual interstitial pneumonia; KL-6,

16 Krebs-von-Lungen-6.

17

1 **Abstract**

2 **Background:** Pirfenidone suppresses the decline of forced vital capacity (FVC) in
3 patients with idiopathic pulmonary fibrosis (IPF). However, IPF progresses in some
4 patients despite treatment. We analyzed patients with meaningful FVC declines during
5 pirfenidone treatment and explored the factors predictive of disease progression after
6 FVC decline.

7 **Methods:** This study was a retrospective, multicenter, observational study conducted by
8 the Okayama Respiratory Disease Study Group. We defined initial decline in %FVC as
9 $\geq 5\%$ per 6-month period during pirfenidone treatment. IPF patients who were treated
10 with pirfenidone and experienced an initial decline from December 2008 to September
11 2017 were enrolled.

12 **Results:** We analyzed 21 patients with IPF. After the initial decline, 4 (19.0%), 11
13 (52.4%), and 6 (28.6%) patients showed improved, stable, and progressive disease,
14 respectively. There was no significant correlation between %FVC reduction on initial
15 decline and the subsequent %FVC change ($p = 0.475$). A deterioration of
16 high-resolution computed tomography (HRCT) findings at the initial decline was
17 observed significantly more often in the progressive *versus* improved/stable disease
18 groups (100% *vs.* 20.0%, $p = 0.009$).

19 **Conclusions:** We revealed that deteriorating HRCT findings may predict disease

1 progression after the initial decline in %FVC in IPF patients treated with pirfenidone.

2

3 **Key words:** idiopathic pulmonary fibrosis, high-resolution computed tomography,

4 pirfenidone, forced vital capacity

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1 **1. Introduction**

2 Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and fatal lung disease.
3 The survival time for IPF is reported to be 2–3 years from diagnosis [1,2]. Recently, the
4 antifibrotic drugs, pirfenidone and nintedanib, have become available to suppress
5 disease progression [3-7]. Pirfenidone significantly suppresses the decline of forced
6 vital capacity (FVC) and is a standard therapy for IPF. However, IPF progresses in some
7 patients despite treatment. At 52 weeks after pirfenidone administration, a decline of
8 10% or more in the percentage of predicted FVC (%FVC) or death was observed in
9 16.5% of patients in the ASCEND study [4].

10 It remains unclear whether treatment should be changed when disease progression is
11 observed. It can be difficult to determine the appropriate treatment course because there
12 are a variety of ways in which the disease can develop. Previous reports have shown
13 that prior FVC decline does not predict subsequent decline [8,9]. Therefore, IPF may
14 stabilize or improve even after an initial decline. In addition, Nathan, *et al.* reported that
15 continued treatment with pirfenidone resulted in a lower risk of subsequent FVC decline
16 or death, even in patients showing disease progression during treatment [9]. The ability
17 to predict continuous disease progression during treatment could be informative in
18 deciding whether a treatment change should be considered.

19 Therefore, we analyzed patients with a meaningful FVC decline during pirfenidone

1 treatment and explored the predictive factors of disease progression after the initial FVC
2 decline.

3

4 **2. Patients and Methods**

5 2.1 Study design

6 This study was a retrospective, multicenter, observational study conducted by the
7 Okayama Respiratory Disease Study Group. Okayama University Hospital, KKR
8 Takamatsu Hospital, National Hospital Organization Minami-Okayama Medical Center,
9 National Hospital Organization Okayama Medical Center, and Kobe Red Cross Hospital
10 all participated. This study was approved by the Institutional Review Boards of
11 Okayama University Hospital (No. 1711-028) and all other participating hospitals. The
12 requirement for written informed consent was waived because this study was based on a
13 retrospective analysis.

14 We defined initial decline as an absolute reduction in %FVC of $\geq 5\%$ per 6-month
15 period during pirfenidone treatment. IPF patients who were treated with pirfenidone
16 from December 2008 to September 2017 and showed an initial decline were enrolled.
17 The diagnosis of IPF was based on the official ATS/ERS/JRS/ALAT statement [10]. We
18 excluded patients whose subsequent pulmonary function test (PFT) data were not
19 available. Patients who discontinued pirfenidone after the initial decline were also

1 excluded. Clinical data were collected from medical records. The enrolled patients were
2 categorized into the following three groups based on the absolute change of %FVC per
3 6-month period after the initial decline: 1) improved disease: $5\% \leq$ %FVC change, 2)
4 stable disease: $-5\% <$ %FVC change $< 5\%$, and 3) progressive disease: $-5\% \geq$ %FVC
5 change. Patients who died or had acute exacerbation within 6 months after the initial
6 decline were included in the progressive disease group.

7 We evaluated high-resolution computed tomography (HRCT) images at the time of the
8 initial decline and approximately 6 months before the initial decline. Deterioration on
9 HRCT was defined as an increase of $\geq 10\%$ in the area affected by fibrosis per unit area
10 of the lung on any axial slice. The images were checked for reticular abnormalities,
11 honeycombing, traction bronchiectasis, and ground glass abnormalities; they were
12 acquired, and the affected area quantified, using the SYNAPSE VINCENT image
13 analysis system (FUJIFILM, Tokyo, Japan). Worsening symptoms of dyspnea or cough
14 at the initial decline compared with that 6 months earlier was also defined as a
15 deterioration of the respective symptom.

16

17 2.2 Statistical analyses

18 Statistical analyses were performed using STATA software (ver. 11.0; StataCorp,

1 College Station, TX, USA). Patient characteristics were compared using Fisher's exact
2 test for binary variables and Student's t-test for continuous variables. The correlations
3 between %FVC reduction on initial decline and subsequent %FVC change were
4 analyzed using Spearman's rank correlation coefficient. P values <0.05 were considered
5 statistically significant.

6

7

1 **3. Results**

2 3.1 Patient characteristics

3 We enrolled 34 patients with IPF who experienced an initial decline and excluded 13
4 patients due to an absence of subsequent PFT data or cessation of pirfenidone. Finally,
5 we analyzed 21 patients (Figure 1). The median period from starting pirfenidone to the
6 initial decline was 385 days (range: 145–730 days).

7 The clinical characteristics of the patients at the initial decline in %FVC are shown in
8 Table 1. Mean age was 72.4 ± 3.9 years, and 17 patients (81.0%) were male. Eighteen
9 patients (85.7%) had a history of smoking, and the mean smoking exposure was 47.1
10 pack-years. The mean Modified Medical Research Council dyspnea score was 2.1 ± 1.0 .
11 Long-term oxygen therapy was used by 38.1% of patients. Twenty patients (95.0%) had
12 a usual interstitial pneumonia (UIP) pattern on HRCT. Surgical lung biopsy was
13 performed in 3 out of 21 cases (14.3%). The diagnosis of IPF in other cases was based
14 on a UIP pattern on HRCT. The mean FVC, %FVC, and percentage of predicted
15 diffusing capacity of lung carbon monoxide were $2,118 \pm 630$ mL, $67.8 \pm 16.3\%$, and
16 $40.6 \pm 22.9\%$, respectively.

17

18 3.2 Longitudinal change in FVC around the time of initial decline

19 Figure 2 shows the longitudinal change in FVC around the time of initial decline in

1 each patient. After the initial decline, we observed 4 (19.0%), 11 (52.4%), and 6
2 (28.6%) cases of disease improvement, stable disease, and progressive disease,
3 respectively. The progressive disease group included one case of death and one case of
4 acute exacerbation within 6 months after the initial decline. There was no significant
5 correlation between %FVC reduction on initial decline and subsequent %FVC change
6 (Figure 3; $r_s = 0.174$, $p = 0.475$).

7

8 3.3 Predictive factors of disease progression

9 We compared the progressive and improved/stable disease groups to explore the
10 factors of disease progression after the initial decline (Table 2). Deterioration of HRCT
11 findings at the initial decline was seen significantly more frequently in the progressive
12 disease group compared with improved/stable disease groups (100% vs. 20.0%, $p =$
13 0.009). Serum Krebs-von-Lungen-6 (KL-6) levels were relatively higher in the
14 progressive disease group than in the improved/stable disease groups (1,496 U/ml vs.
15 811 U/ml), but the difference was not significant ($p = 0.06$).

16

17

1 **4. Discussion**

2 In IPF patients, a decline in %FVC of $\geq 10\%$ over a span of 6–12 months predicts an
3 increased risk of mortality [11-16]. This magnitude of FVC decline is considered as a
4 significant decline, indicating disease progression. Based on the results of these
5 previous studies, we defined initial decline as an absolute reduction in the initial %FVC
6 of $\geq 5\%$ over 6 months during pirfenidone treatment. In addition, it has been reported
7 that the clinical course of IPF is relatively variable; the change of FVC in 1 year does
8 not predict the change of FVC in the subsequent year [8]. Nathan *et al.* reported a weak
9 inverse correlation between changes in FVC during 2 consecutive 6-month intervals [9].
10 In this study, continuous FVC decline was observed in only 28.6% of patients. In
11 addition, in line with previous reports, there was no significant correlation
12 between %FVC reduction on initial decline and subsequent %FVC change. Clinicians
13 can be unsure regarding treatment change when a significant FVC decline occurs;
14 therefore, we analyzed the patients who experienced an initial decline during
15 pirfenidone treatment. This study showed that deterioration of HRCT findings at initial
16 decline occurred significantly more often in the progressive disease group, which
17 indicates that HRCT findings may predict disease progression.

18 The pulmonary function test showed a large measurement error because the results
19 depend on the exhalation effort of the patient; therefore, the decline in FVC may not be

1 a true decline. We believe that measurement error is one of the reasons why changes in
2 FVC within 1 year do not predict the changes in FVC in the subsequent year. Elsewhere,
3 it was reported that HRCT findings are related to prognosis [17-20]. Lynch *et al.*
4 determined that the overall degree of lung fibrosis on HRCT was a strong independent
5 predictor of mortality in patients with IPF [17]. Therefore, FVC decline accompanied by
6 deterioration of HRCT findings may indicate the true decline in FVC, which in turn
7 may predict the subsequent decline in FVC.

8 Serum KL-6 levels showed a higher trend in the progressive disease group compared
9 with that in the improved/stable groups; however, this did not reach significance.
10 Several studies have reported that higher KL-6 is associated with poor prognosis in IPF
11 [21,22]. Therefore, large-scale studies may reveal the association between serum KL-6
12 at the initial decline and disease progression after the initial decline.

13 When a significant decline in FVC is observed, we suggest performing HRCT to
14 predict whether the decline is likely to continue. However, it remains unclear whether
15 pirfenidone should be used instead of other drugs such as nintedanib in cases showing
16 FVC decline accompanied by a deterioration of HRCT findings. In a previous study,
17 continuous treatment with pirfenidone resulted in a lower risk of FVC decline or death,
18 even in patients with disease progression [9]. The efficacy of pirfenidone for patients

1 with FVC decline and deterioration of HRCT findings must be determined.

2 Our study had several limitations. First, it was retrospective and the sample size was
3 relatively small. Second, the observation period was relatively short and the clinical
4 course before the initial decline was not assessed. Third, there may have been a
5 selection bias due to the exclusion of approximately one third of the patients. Fourth,
6 surgical lung biopsy was performed in only 3 of 21 patients (14.3%). This biopsy
7 percentage is relatively low compared with those of clinical trials [3,4] but similar to a
8 previous real-world report [23]. Larger-scale prospective studies are required to confirm
9 our results.

10

11 **5. Conclusion**

12 We revealed that deterioration of HRCT findings may predict disease progression after
13 an initial decline in FVC in patients with IPF treated with pirfenidone. When a
14 significant decline in FVC is observed, we suggest performing HRCT to predict
15 whether the decline is likely to persist.

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2

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2

1 **Table 1: Patient characteristics at the initial decline in %FVC**

2

Characteristics	n = 21
Age — yr	72.4 ± 3.9
Male sex — no. (%)	17 (81.0)
Body-mass index	22.9 ± 2.7
Smoking status	
Never smoker — no. (%)	3 (14.3)
Former smoker — no. (%)	18 (85.7)
Pack-years	47.1 ± 30.9
mMRC dyspnea scale	2.1 ± 1.0
Long-term oxygen therapy — no. (%)	8 (38.1)
Dose of pirfenidone — mg	1390 ± 387
UIP pattern on HRCT — no. (%)	20 (95.0)
Surgical lung biopsy — no. (%)	3 (14.3)
FVC — ml	2118 ± 630
FVC — % of predicted value	67.8 ± 16.3
D _{LCO} — % of predicted value	40.6 ± 22.9*
KL-6 — U/ml	982 ± 714
LDH — mg/dl	236 ± 47

3

4 Abbreviations: mMRC, Modified Medical Research Council; UIP, usual interstitial

5 pneumonia; HRCT, high-resolution computed tomography; FVC, forced vital capacity;

6 D_{LCO}, diffusing capacity of lung carbon monoxide; KL-6, Krebs-von-Lungen-6; LDH,

7 lactate dehydrogenase. *n = 13

8

9

1 **Table 2: Comparison between progressive disease group and improved/stable**

2 **disease group**

Characteristics	Progressive disease (n = 6)	Improved/stable disease (n = 15)	P value
Age, yr	73.2 ± 3.3	72.1 ± 4.2	0.60
Male sex, no. (%)	5 (83.3)	12 (80.0)	1.00
Body-mass index	22.3 ± 2.7	23.2 ± 2.8	0.50
Smoking status			
Never smoker — no. (%)	0 (0)	3 (20.0)	0.53
Former smoker — no. (%)	6 (100)	12 (80.0)	
Pack-years	44.9 ± 34.2	48.0 ± 31.0	0.84
mMRC dyspnea scale	2.0	2.1	0.87
Long-term oxygen therapy — no. (%)	1 (16.7)	7 (46.7)	0.34
Dose of pirfenidone — mg	1200 ± 379	1467 ± 375	0.16
FVC — ml	2050 ± 548	2145 ± 675	0.76
FVC — % of predicted value	63.7 ± 10.4	69.4 ± 18.2	0.48
D _{LCO} — % of predicted value	38.1 ± 2.9*	41.4 ± 26.3‡	0.84
KL-6 — U/ml	1496 ± 968	811 ± 545	0.06
LDH — mg/dl	231 ± 37	238 ± 51	0.77
Decline in FVC > 10% at initial decline	0 (0)	4 (26.7)	0.28
Deterioration of dyspnea	3 (50.0)	6 (40.0)	1.00
Deterioration of cough	2 (33.3)	4 (26.7)	1.00
Deterioration of HRCT findings	6 (100.0)	3 (20.0)	0.009

3 Abbreviations: mMRC, Modified Medical Research Council; UIP, usual interstitial

4 pneumonia; FVC, forced vital capacity; D_{LCO}, diffusing capacity of lung carbon

5 monoxide; KL-6, Krebs-von-Lungen-6; LDH, lactate dehydrogenase; HRCT,

6 high-resolution computed tomography. *n = 3, ‡n = 10

1 **Figure legends**

2 **Figure 1: The study population**

3 Abbreviation: PFT, pulmonary function test.

4

5 **Figure 2: Longitudinal changes in %FVC and FVC in each patient**

6 Absolute changes in %FVC in each patient 6 months before (−6 months) the initial
7 decline in %FVC, at the initial decline, and 6 months after the initial decline (+6
8 months) are shown relative to the initial decline (A). Changes in FVC values in each
9 patient are also shown relative to the initial decline (B).

10 Based on the subsequent %FVC change at 6 months after the initial decline, the enrolled
11 patients were categorized into the following three groups: 1) improved disease (blue
12 line): $5\% \leq \text{\%FVC change}$, 2) stable disease (yellow line): $-5\% < \text{\%FVC change} < 5\%$,
13 and 3) progressive disease (red line): $-5\% \geq \text{\%FVC change}$.

14 Abbreviation: FVC, forced vital capacity; %FVC, percentage of predicted FVC.

15

16 **Figure 3: Relationship between changes in %FVC during two consecutive 6-month**
17 **periods around the time of the initial decline**

18 Abbreviation: %FVC, percentage of predicted forced vital capacity.