# Association of antifibrotics with slower forced vital capacity and diffusing capacity of the lungs for carbon monoxide decline in progressive pulmonary fibrosis: a real-world study

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## Abstract

**Introduction:** A few real-world studies have investigated the effectiveness of antifibrotics in patients with progressive pulmonary fibrosis (PPF). The aim of this study was to evaluate the real-life efficacy of antifibrotics in PPF.
**Material and methods:** In this real-world study, medical records of patients with non-idiopathic pulmonary fibrosis (IPF) fibrosing interstitial lung disease (ILD) between January 2013 and December 2023 were examined retrospectively. Patients with PPF were included and classified into two groups: the antifibrotic group (pirfenidone or nintedanib) and the non-antifibrotic group. Forced vital capacity (FVC), diffusing capacity of the lungs for carbon monoxide ($DL_{CO}$) decline, exacerbations, and mortality were compared between the groups.
**Results:** A total of 406 patients with ILD were examined. Of these, 262 patients had fibrotic ILD other than IPF, of whom 126 with a progressive phenotype were included. Among these, 41 (32.5%) had a connective tissue disease-associated ILD, 38 (30.2%) chronic fibrosing hypersensitivity pneumonitis, 21 (16.7%) unclassifiable idiopathic interstitial pneumonia, 16 (12.7%) idiopathic fibrosing non-specific interstitial pneumonia, and 10 (7.9%) other ILDs. At 36 months, FVC % predicted declined by 13% in the antifibrotic group vs. 25% in the non-antifibrotic group ($p < 0.001$); $DL_{CO}$ declined by 10% vs. 26%, respectively ($p < 0.001$). Exacerbations and mortality were lower in patients receiving antifibrotics (29% vs. 6%, OR = 6.38, $p < 0.001$; 21% vs. 5%, OR = 5.59, $p = 0.006$; respectively). The rate of adverse events leading to treatment discontinuation was 9% in patients receiving pirfenidone and 25.6% with nintedanib ($p = 0.19$).
**Conclusions:** Our real-world results showed an association between antifibrotic treatment and slower $DL_{CO}$ and FVC decline, fewer exacerbations, and lower mortality in PPF. Adverse events that should not be neglected were associated with a considerable rate of discontinuation.

**Key words:** antifibrotics, diffusion capacity, forced vital capacity, interstitial lung disease, pulmonary fibrosis.

## Introduction

Progressive fibrosing interstitial lung disease (ILD) is an umbrella term comprising ILDs characterized by a deterioration of symptoms, decline in



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lung function, and worsening of fibrosis on thoracic high-resolution computed tomography (HRCT) [1]. In 2022, the term 'progressive pulmonary fibrosis (PPF)' was defined for progressive fibrosing ILDs other than idiopathic pulmonary fibrosis (IPF) [2]. PPF encompasses a group of ILDs that exhibit a progressive fibrotic phenotype, independent of the underlying cause, including connective tissue disease-associated ILD (CTD-ILD), chronic hypersensitivity pneumonitis (HP), fibrotic nonspecific interstitial pneumonia (NSIP), and fibrotic sarcoidosis. In Türkiye, nationwide multicenter data have shown that ILDs have a considerable prevalence of approximately 25.8 per 100,000 population, with IPF accounting for nearly one-fifth of cases [3]; although specific epidemiological data for PPF are lacking, this highlights the importance of real-world studies in this patient group. Unlike self-limiting or stable forms of ILD, PPF continues to worsen over time, often leading to respiratory failure.

Current treatment strategies focus on antifibrotic therapies. The INBUILD trial demonstrated that nintedanib significantly slowed forced vital capacity (FVC) decline in progressive fibrosing ILDs [1]. In the SENSCIS trial, conducted in patients with systemic sclerosis and PPF, the annual rate of decline in FVC over a 52-week period was found to be significantly lower in the nintedanib group compared to the placebo group [4]. Nintedanib is recommended for the treatment of PPF based on its statistically significant effect in reducing disease progression. However, clinical trials investigating pirfenidone in patients with progressive fibrosing ILDs did not demonstrate a significant benefit over placebo in terms of FVC decline [5, 6]. Only a few real-world studies have examined the effectiveness and tolerability of antifibrotic agents and have shown that antifibrotic therapy slows the FVC decline in PPF, including disease-specific cohorts such as RA-ILD, with findings broadly consistent with clinical trial results [7–10]. All the above-mentioned studies contribute to the growing body of evidence supporting the use of antifibrotic therapies in various forms of PPF. However, they also underscore the need for further research to better understand the impact of these treatments on different patient populations and confirm these results in real-life experience.

Regrettably, the existing antifibrotic medications, nintedanib and pirfenidone, are associated with several adverse effects that could impact adherence to treatment and potentially result in the discontinuation of therapy. Consequently, it is crucial to evaluate the effects of these antifibrotic drugs on functional decline, survival, and their tolerability in practical terms.

The objective of this study was to examine the real-world impact of antifibrotics on the decline of FVC and diffusing capacity of the lungs for carbon monoxide ($DL_{CO}$) in patients with progressive pulmonary fibrosis.

## Material and methods

### Study design and participants

This retrospective, longitudinal, observational study included patients with progressive pulmonary fibrosis. All consecutive patients with ILD at a tertiary center between January 1, 2013 and December 31, 2023 were identified using hospital medical records and assessed for eligibility. Patients meeting the criteria for PPF were defined according to the 2022 ERS/ATS/JRS/ALAT IPF and PPF Clinical Practice Guideline [2]. Progressive pulmonary fibrosis was defined as at least two of the following three criteria within the previous year: 1) an absolute decline in FVC of ≥ 5% predicted or an absolute decline in $DL_{CO}$ ≥ 10% predicted; 2) worsening respiratory symptoms; 3) radiological progression as assessed by thoracic HRCT. All cases were systematically re-evaluated in collaboration with our multidisciplinary ILD team (pulmonologists, radiologists, and rheumatologists). To further ensure diagnostic accuracy and minimize selection bias, the categorization of patients after ILD board review was independently verified by an external committee. To further ensure data completeness and reliability, patients were required to have undergone regular semiannual (every 6 months) pulmonary function tests (PFTs) and at least two thoracic HRCT scans during the subsequent 2 years of follow-up. Individuals who did not meet the definition of PPF according to the 2022 ERS/ATS/JRS/ALAT criteria, those with IPF, and those without regular PFT records or without serial HRCT imaging ($n$ = 12) were excluded, as illustrated in Figure 1. This two-step evaluation process – initial re-assessment by the ILD board and subsequent independent committee verification – was designed to strengthen diagnostic accuracy, minimize missing data, and ensure comparability between study groups, thereby increasing the robustness of our retrospective analysis.

Eligible PPF patients were divided into two groups: the antifibrotic group, consisting of those who had undergone antifibrotic therapy (pirfenidone or nintedanib) for at least 3 months; and the non-antifibrotic group, consisting of patients diagnosed with progressive fibrosing ILD before antifibrotic drugs were included in the national reimbursement system by the Ministry of Health for PPF in our country, and therefore not receiving antifibrotic treatment. For these patients, only pulmonary function test parameters and other clinical outcomes obtained during the period before antifibrotics became reimbursable were included

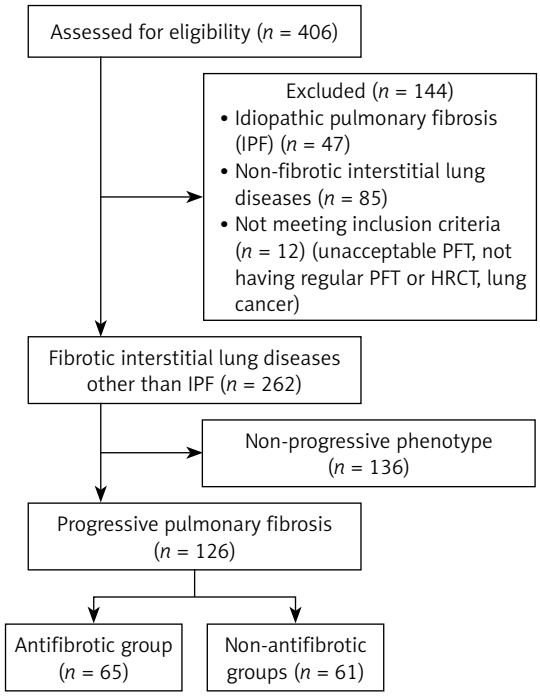


**Figure 1.** Patient flow diagram

in the analysis. Baseline characteristics were determined based on the date of PPF diagnosis. Pulmonary function parameters, including $DL_{CO}$ and FVC, as well as HRCT findings, were defined using the assessments performed closest to the diagnosis date. Follow-up PFT measurements were assigned to time points at 6-month intervals, using a ±3-month window. The measurement closest to each designated time point within this window was selected for analysis. For HRCT follow-up, annual scans were evaluated throughout the study period.

### Outcomes

The primary outcomes of the study were the decline in FVC and $DL_{CO}$ over time. Secondary outcomes included radiological progression, acute exacerbations, and all-cause mortality. The outcomes were compared between patients receiving antifibrotic therapy and those not receiving any antifibrotics. Additionally, within the antifibrotic therapy group, adverse events were evaluated and compared between patients treated with pirfenidone and those treated with nintedanib.

### Statistical analysis

The study conducted descriptive analyses on quantitative variables, including mean and standard deviation calculations. The significance of the difference in functional tests (FVC and $DL_{CO}$) between the groups was investigated after the normal distribution of continuous variables was checked. Parametric tests were used when distributions were normal, whereas non-parametric (Mann-Whitney *U*) tests were used when data were not normally distributed. For categorical variables including secondary outcomes (radiologic progression, exacerbations, and mortality) and adverse events, proportions were compared between the groups using $\chi^2$ and Fisher's exact tests. Statistical significance was set at $p < 0.05$.

## Results

### Baseline characteristics

Out of 406 ILD patients, 126 had progressive pulmonary fibrosis other than IPF (Figure 1). The baseline characteristics of the patients are summarized in Table I. The mean ± SD age was 70 ±12 years, and 43% of patients were female. Of 126, 41 (32.5%) had a connective tissue disease (CTD)-associated ILD, 38 (30.2%) chronic fibrosing hypersensitivity pneumonitis, 21 (16.7%) unclassifiable idiopathic interstitial pneumonia, 16 (12.7%) idiopathic fibrosing non-specific interstitial pneumonia, and 10 (7.9%) other ILDs (Table I). The ratio of concomitant immunosuppressive use was 75.4% (*n* = 95); glucocorticoids were the most frequently used immunosuppressive agents in the overall cohort (*n* = 76, 80%), followed by mycophenolate mofetil as the second most prescribed (*n* = 39, 41%). Pulmonary function tests (mean percentage of predicted value ± SD) were as follows: forced expiratory volume in 1 s (FEV1) was 69 ±19%, FVC was 73 ±19%, and the $DL_{CO}$ was 60 ±21%. Radiological characteristics of the patients are shown in Table II. Nonspecific interstitial pneumonia (NSIP) was the most frequent radiological pattern (*n* = 42, 33.3%); 31.7% (40 out of 126) of patients had a usual interstitial pneumonia (UIP)-like fibrotic pattern on HRCT at baseline. Baseline pulmonary function tests and radiological features were not significantly different between the antifibrotic and the non-antifibrotic groups (Tables I and II).

### Decline in pulmonary function tests

FVC and $DL_{CO}$ decline over the 36-month follow-up period is shown in Figure 2. In the antifibrotic and the non-antifibrotic groups, the mean absolute FVC decline from baseline was –90 ml vs. –160 ml at 12 months, –180 ml vs. –490 ml at 24 months, and –330 ml vs. –660 ml at 36 months of follow-up (Figure 2 A). The mean FVC (% predicted) decline from baseline was –3% vs. –6% at 12 months, –7% vs. –18% at 24 months, and –13% vs. –25% at 36 months of follow-up. The mean $DL_{CO}$ (% predicted) decline was –3% vs. –16% at 12 months, –7% vs. –18% at 24 months, and –10% vs. –26% at 36 months of follow-up (Figure 2 B).

**Table I.** Baseline characteristics of patients with progressive pulmonary fibrosis

| Parameter | Overall (*n* = 126) | Non-antifibrotic group (*n* = 61) | Antifibrotic group (*n* = 65) | *P*-value |
|---|---|---|---|---|
| Age [years] | 70 ±12 | 70 ±12 | 69 ±11 | 0.626 |
| Sex | | | | |
| Male | 72 (57%) | 33 (54%) | 39 (60%) | 0.557 |
| Female | 54 (43%) | 28 (46%) | 26 (40%) | 0.794 |
| Smoking status | | | | |
| Never smoker | 77 (61.1%) | 38 (62.3%) | 39 (60%) | 0.927 |
| Active smoker | 8 (6.5%) | 2 (3.3%) | 6 (10%) | 0.003* |
| Ex-smoker | 41 (32.5%) | 21 (34.4%) | 20 (30.8%) | 0.863 |
| Cigarettes [pack-years] | 25 ±21 | 27 ±24 | 24 ±19 | 0.63 |
| Body mass index [kg/m$^2$] | 27.5 ±6.4 | 27.4 ±4.8 | 27.6 ±7.6 | 0.861 |
| Underlying ILD diagnosis | | | | |
| CTD-ILD | 41 (32.5%) | 19 (31.1%) | 22 (33.8%) | 0.605 |
| Fibrosing HP | 38 (30.2%) | 17 (27.9%) | 21 (32.3%) | 0.459 |
| Unclassifiable IIP | 21 (16.7%) | 9 (14.7%) | 12 (18.5%) | 0.317 |
| Fibrosing iNSIP | 16 (12.7%) | 9 (14.7%) | 7 (10.8%) | 0.383 |
| Other ILDs | 10 (7.9%) | 7 (11.5%) | 3 (4.6%) | 0.01* |
| Concomitant immunosuppressive use | 95 (75.4%) | 47 (77%) | 48 (73.9%) | 0.94 |
| $FEV_1$ at baseline [l] | 2.28 ±0.75 | 2.36 ±0.82 | 2.2 ±0.66 | 0.106 |
| $FEV_1$% at baseline | 69 ±19 | 72 ±19 | 66 ±18 | 0.071 |
| FVC at baseline [l] | 2.6 (0.88) | 2.64 (0.97) | 2.57 (0.76) | 0.274 |
| FVC% at baseline | 73 ±19 | 73 ±19 | 74 ±19 | 0.78 |
| $FEV_1$/FVC% at baseline | 87 ±9 | 87 ±8 | 87 ±10 | 0.998 |
| $DL_{CO}$% at baseline | 60 ±21 | 63 ±20 | 58 ±21 | 0.16 |
| 6MWD | 374 ±146 | 388 ±151 | 360 ±140 | 0.282 |

*Data are mean ± SD or n (%). *Results are significantly different between the antifibrotic and the non-antifibrotic groups (p < 0.05). CTD-ILD – connective tissue disease-related interstitial lung disease. $DL_{CO}$ – diffusing capacity of the lungs for carbon monoxide. $FEV_1$ – forced expiratory volume in one second. FVC – forced vital capacity. HP – hypersensitivity pneumonitis. ILD – interstitial lung disease. IIP – idiopathic interstitial pneumonia. iNSIP – idiopathic nonspecific interstitial pneumonia. MRC – Medical Research Council. 6MWD – 6-minute walk distance.*

**Table II.** Radiological characteristics of the patients with progressive pulmonary fibrosis

| Radiological features | Overall population (*n* = 126) | Non-antifibrotic group (*n* = 61) | Antifibrotic group (*n* = 65) | *P*-value |
|---|---|---|---|---|
| Radiological pattern type | | | | |
| NSIP | 42 (33.3%) | 22 (36%) | 20 (30.8%) | |
| UIP-like | 40 (31.7%) | 21 (34.4%) | 19 (29.2%) | 0.78 |
| HP | 39 (31%) | 16 (26.2%) | 23 (35.3%) | |
| Other patterns | 5 (4%) | 2 (3.3%) | 3 (4.6%) | |
| Distribution of the lesions | | | | |
| Peripheral | 60 (47.6%) | 32 (52.4%) | 28 (43%) | 0.62 |
| Peripheral + central | 66 (52.4%) | 29 (47.5%) | 37 (57%) | |
| Septal thickening | 81 (64.3%) | 38 (62.3%) | 43 (66.1%) | 0.72 |
| Traction bronchiectasis/ bronchioloectasis | 77 (61.1%) | 37 (60.6%) | 40 (61.5%) | 0.89 |
| Honeycomb cysts | 62 (49.2%) | 29 (47.5%) | 33 (50.8%) | 0.68 |
| Ground glass opacities | 49 (38.9%) | 23 (37.7%) | 26 (40%) | 0.85 |
| 3-density sign | 35 (27.8%) | 14 (23%) | 21 (32.3%) | 0.23 |
| Four-edge sign | 22 (17.4%) | 10 (16.4%) | 12 (18.4%) | 0.82 |

*Data are n (%). HP – hypersensitivity pneumonitis, NSIP – nonspecific interstitial pneumonia, UIP – usual interstitial pneumonia. *Results are significantly different between the antifibrotic and the non-antifibrotic groups (p < 0.05).*

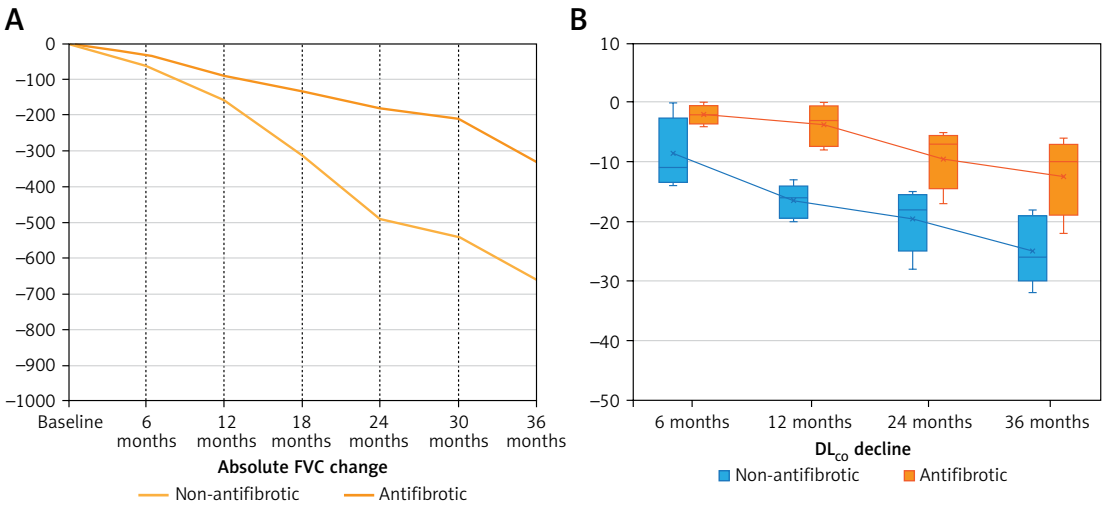


**Figure 2.** Functional decline in patients with progressive pulmonary fibrosis. **A** – FVC decline over 36-month follow-up period between the antifibrotic and non-antifibrotic groups. Group differences in FVC decline became statistically significant at 12 months ($p < 0.05$) and remained significant throughout the 36-month follow-up period ($p < 0.001$). **B** – $DL_{CO}$ decline over 36-month follow-up period between the antifibrotic and non-antifibrotic groups. Group differences in DLCO decline became statistically significant at 6 months ($p < 0.05$) and remained significant throughout the 36-month follow-up period ($p < 0.001$)

## Radiological progression, exacerbations, and survival

Radiological progression at 36 months was significantly higher in the patients who did not receive antifibrotic treatment compared to those in the antifibrotic group (83.6% vs. 58.5%, OR = 3.623, 95% CI: 1.566–8.38, $p = 0.003$). Antifibrotic treatment significantly reduced the exacerbations (OR = 6.383, 95% CI: 2.018–20.192, $p < 0.001$); 18 (29.5%) patients had at least one acute exacerbation in the non-antifibrotic group, while 4 (6.1%) patients had exacerbations in the antifibrotic group (Table III). Overall survival at 36 months was 95.4% in the antifibrotic group and 78.7% in the non-antifibrotic group (OR = 5.597, 95% CI 1.509–20.759, $p = 0.006$).

**Table III.** Secondary outcomes in the antifibrotic and the non-antifibrotic groups

| Parameter | Non-antifibrotic group ($n = 61$) | Antifibrotic group ($n = 65$) | Odds ratio [95% CI] | *P*-value |
|---|---|---|---|---|
| Exacerbations | 18 (29.5%) | 4 (6.1%) | 6.383 [2.018–20.192] | < 0.001* |
| Mortality | 13 (21.3%) | 3 (4.6%) | 5.597 [1.509–20.759] | 0.006* |
| Radiological progression | 51 (83.6%) | 38 (58.5%) | 3.623 [1.566–8.38] | 0.003* |

*Data are n (%). *Results are significantly different between the antifibrotic and the non-antifibrotic groups ($p < 0.05$).*

**Table IV.** Treatment-related adverse events in patients who received pirfenidone or nintedanib

| Adverse effects | Pirfenidone ($n = 22$) | Nintedanib ($n = 43$) | *P*-value |
|---|---|---|---|
| Nausea/vomiting | 13 (59%) | 33 (76.7%) | 0.159 |
| Diarrhea | 1 (4.5%) | 38 (88.4%) | < 0.001* |
| Decreased appetite/weight loss | 4 (18.2%) | 16 (37.2%) | 0.158 |
| Abdominal pain | 2 (9%) | 8 (18.6%) | 0.473 |
| Photosensitivity | 8 (36.4%) | 0 | < 0.001* |
| Skin rash | 3 (13.6%) | 0 | 0.035* |
| Elevation of liver transaminases (ALT and/or AST) | 2 (9%) | 3 (7%) | 0.987 |
| Adverse event leading to permanent dose reduction | 7 (31.8%) | 10 (23.2%) | 0.553 |
| Adverse event leading to treatment discontinuation | 2 (9%) | 11 (25.6%) | 0.19 |

*Results are given as n (%). *Results are significantly different between pirfenidone and nintedanib groups ($p < 0.05$).*

### Adverse events

Treatment related adverse events in the patients who received antifibrotic agents are summarized in Table IV. The most frequent pirfenidone related adverse events were nausea (13/22, 59%), photosensitivity (8/22, 36.4%), and appetite loss (4/22, 18.2%). In the patients who received nintedanib, the most common side effects were diarrhea (38/43, 88.4%), nausea (33/43,76.7%), and appetite loss (16/43, 37.2%). The rate of adverse events which led to permanent treatment discontinuation was 25.6% with nintedanib and 9% with pirfenidone (Table IV).

## Discussion

The results of this real-world, retrospective, longitudinal, cohort study demonstrated that antifibrotic therapy significantly attenuates the decline in lung functions, reduces acute exacerbations, and improves survival in patients with PPF. Moreover, fibrosis progression on HRCT was significantly lower with antifibrotic use. Findings of the current study supported the real-world efficacy of antifibrotic treatment in patients with PPF by means of functional, radiological, and clinical stability. When compared to patients receiving antifibrotic therapy, those who did not receive antifibrotic treatment exhibited a more pronounced decline in FVC after a year and a more significant decrease in $DL_{CO}$ as early as 6 months.

The study demonstrated that antifibrotic therapy was associated with a significantly lower rate of decline in both FVC and $DL_{CO}$. The difference in FVC decline between treated and untreated patients became more pronounced over time, with a notable divergence at 12 months (–90 ml vs. –160 ml) and a substantial gap by 36 months (–330 ml vs. –660 ml). This suggests that antifibrotics may have a sustained association with preservation of lung function, consistent with findings from trials [1, 11]. INBUILD demonstrated that nintedanib significantly slowed the rate of lung function decline across various types of PF-ILDs [1]. The INBUILD extension study (INBUILD-ON) reported that similar rates of FVC decline attenuation were maintained during the second year in patients who continued treatment [11]. In SENSCIS, conducted in systemic sclerosis-associated ILD, FVC decline trajectories began to diverge between the nintedanib and placebo groups from the early months of the study [4]. Outside the conditions of clinical trials, real-world data also suggest that nintedanib provides similar benefits in patients with PF-ILD. According to the results of a UK real-world study, the average FVC decline was –239 ml/year in the year prior to initiation of nintedanib treatment, whereas it was –89 ml/year in the year following treatment initiation [9]. A multicenter study investigated the outcomes of nintedanib in patients with rheumatoid arthritis-associated ILD (RA-ILD); most patients were also receiving concurrent immunosuppressive therapy. The results demonstrated that nintedanib was associated with slower lung function decline in RA-ILD [12]. In line with our findings, a recent nationwide multicenter registry study from the Netherlands, including 538 patients (142 with PPF and 396 with IPF), demonstrated that antifibrotic therapy was associated with markedly slower lung function decline in both PPF and IPF. In this cohort, the mean annual FVC decline in PPF decreased from 412 ml before treatment to 18 ml after initiation of antifibrotics, while in IPF it decreased from 158 to 38 ml. Importantly, $DL_{CO}$ decline was also significantly reduced in both groups following treatment [13].

For pirfenidone, randomized controlled trials (RCTs) such as RELIEF (127 patients, 48 weeks) and a multicenter phase 2 (u-ILD) trial (253 patients, 24 weeks) have also been conducted [5, 6]. Although no statistically significant differences were found between pirfenidone and placebo in terms of endpoints such as mortality or the FVC decline, a systematic review and meta-analysis of the outcomes of these two RCTs found that, compared to placebo, pirfenidone was associated with an approximate absolute improvement of ~2.3% in FVC over 6–12 months of follow-up, translating to about 100 ml less volume loss [14]. In a multicenter, real-world, retrospective cohort study evaluating the 6-month outcomes of adding pirfenidone to immunosuppressive therapy in patients with CTD-ILD, an improvement in lung functions was observed in the pirfenidone group, whereas the control group showed either stability or slight deterioration [15]. In small patient series with chronic HP, pirfenidone has been reported to slow the decline in FVC [16]. Similarly, the TRAIL-1 pilot study conducted in RA-ILD showed that FVC decline was reduced with pirfenidone [17]. In our study, 34% of patients receiving antifibrotic therapy were treated with pirfenidone. Accordingly, our findings support the efficacy of pirfenidone in slowing both FVC and $DL_{CO}$ decline in patients with PPF. Overall evidence suggests that pirfenidone is effective across different fibrotic ILD phenotypes.

The findings of our study suggest that a minimum follow-up duration of 12 months may be required to detect significant improvements in FVC. Conversely, favorable effects on $DL_{CO}$ were observed at an earlier stage, emerging within the first 6 months of treatment. Use of $DL_{CO}$ decline as a primary outcome in clinical trials of progressive fibrotic ILDs is not as common as that of FVC. The current study demonstrated a remarkable attenuation in $DL_{CO}$ decline among patients receiving antifibrot-

ics. Our results regarding the association between antifibrotic treatment and slower $DL_{CO}$ decline are also supported by recent real-world data. In a large multicenter registry study, antifibrotic treatment significantly slowed the $DL_{CO}$ decline in both PPF and IPF, decreasing from an annual loss of 8.7% to 0.9% predicted in PPF and from 9.4% to 2.6% predicted in IPF after antifibrotic initiation [13]. In both the RELIEF and uILD studies, the slowing of $DL_{CO}$ decline in favor of pirfenidone was found to be statistically significant [5, 6]. Even when changes in FVC are not clear within 6–12 months, differences in $DL_{CO}$ may provide early signals of treatment response. Although pirfenidone has not yet been approved for non-IPF indications, these data have supported consideration of its use in patients with progressive fibrotic ILD. In a study investigating the effect of nintedanib in patients with RA-ILD, the $DL_{CO}$ trajectory during treatment was significantly improved compared to the pretreatment course [12]. These findings may suggest that $DL_{CO}$ reflects involvement of the alveolar-capillary unit, which may be affected early in the fibrotic process; damage to this membrane may lead to an early decline in $DL_{CO}$. Antifibrotics may slow this process, resulting in a more favorable $DL_{CO}$ trajectory.

Antifibrotic therapy not only slows the decline in lung function, but is also associated with less clinical worsening, and may improve survival. In a comprehensive meta-analysis encompassing nine studies with 1,990 participants, antifibrotic therapy was associated with a statistically significant reduction in all-cause mortality [18]. In our study, patients receiving antifibrotics had significantly fewer acute exacerbations and better survival rates compared to untreated patients. Our findings suggest that antifibrotic therapy may be associated with a lower risk of these catastrophic events. Antifibrotic therapy was also associated with a significant reduction in radiological progression, consistent with the results of a meta-analysis which revealed that the proportion of patients with a worsening fibrotic extent on imaging was significantly lower with treatment [18].

Despite these favorable effects, adverse events leading to permanent treatment discontinuation were not negligible, particularly in patients treated with nintedanib. Gastrointestinal side effects such as diarrhea and nausea were the most frequently reported adverse events, with much higher rates than previous reports [1, 19–21]. Although the rate of treatment discontinuation was higher with nintedanib compared to pirfenidone (25.6% vs. 9%), this difference did not reach statistical significance in our cohort. The treatment discontinuation rate was found to be higher in the current study compared to clinical trials [1, 19], but was similar to rates reported in real-world studies [22]. These findings highlight the need for close monitoring and proactive management of side effects to optimize treatment adherence and outcomes in clinical practice.

While antifibrotic therapy has become a standard option for patients with PPF based largely on the INBUILD and SENSCIS trials with nintedanib, the overall body of evidence remains limited, particularly regarding pirfenidone and outcomes beyond FVC decline. Our study makes several potentially important contributions: it demonstrates, in a real-world long-term cohort, that both nintedanib and pirfenidone were associated with slower disease progression; it provides real-life evidence of a favorable association with $DL_{CO}$ decline, which emerged as early as 6 months and preceded the attenuation of FVC decline; it shows that antifibrotics are associated with a lower rate of radiological progression, which has not been adequately addressed in previous studies; and it documents the frequency of adverse events and treatment discontinuation in daily practice. Collectively, these findings complement existing RCT evidence, highlight previously underexplored aspects of disease progression, and add to real-world evidence supporting antifibrotic use in progressive pulmonary fibrosis.

The potential influence of concomitant immunosuppressive therapies on the attenuation of FVC and $DL_{CO}$ decline cannot be fully excluded. However, the use of immunosuppressive agents was comparable between patients who received antifibrotic treatment and those who did not, suggesting that the observed differences in FVC and $DL_{CO}$ decline may be partly attributable to differences in antifibrotic therapy. Some real-world studies comparing the outcomes associated with antifibrotic therapies in patients with IPF and PPF have demonstrated a lower benefit in the PPF group [7, 23]. This may be attributed to the fact that PPF represents an umbrella term encompassing a heterogeneous group of diseases. In addition to these studies, there remains a need for prospective randomized controlled trials aimed at investigating inadequate treatment responses within PPF subgroups and elucidating the factors underlying insufficient or poor therapeutic outcomes.

Some limitations of our study should be acknowledged. First, the retrospective, single-center design may introduce selection bias and limit the generalizability of the findings. Second, the relatively small sample size may have limited the statistical power to detect differences in some secondary outcomes, particularly within subgroup analyses. The effect of antifibrotics could not be examined individually for each subgroup (fibrotic HP, CTD-ILD, etc.) in our cohort due to their limited number. Third, although efforts were made

to adjust for baseline characteristics, potential confounders related to disease severity and treatment decisions cannot be entirely excluded. Lastly, the non-antifibrotic group included patients diagnosed before the availability of antifibrotic therapy for PPF in our country, which may have influenced treatment allocation and outcomes.

In conclusion, this real-world study demonstrated that antifibrotic therapy was associated with slower decline in lung functions, fewer exacerbations, and improved survival in patients with PPF. While both the antifibrotic and non-antifibrotic groups exhibited similar FVC decline within the first 6 months, the association with slower FVC decline became more apparent during long-term follow-up. Moreover, our study demonstrated a marked attenuation of $DL_{CO}$ decline among patients receiving antifibrotics. This result suggests that $DL_{CO}$ may provide an early indicator of treatment response in PPF. The tolerability profile of antifibrotics remains a challenge in clinical practice, underscoring the need for individualized treatment strategies and supportive care to manage adverse events. Future prospective, multicenter studies are warranted to validate these findings and to further explore optimal treatment strategies in diverse PPF populations.

## Funding

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## Ethical approval

This study was approved by Başkent University Institutional Review Board (Approval Date: 02.07.2024, Number: E-94603339-604.01-355831).

## Conflict of interest

The authors declare no conflict of interest.

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