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Original Article

# Comparative Long-term Effects of Nintedanib and Pirfenidone in Idiopathic Pulmonary Fibrosis: A Real-life Study with Five-year Follow-up

Ayça Yanalak[1], Onur Yazıcı[2]

[1]Clinic of Pulmonary Diseases, Kahta State Hospital, Adıyaman, Türkiye
[2]Department of Chest Diseases, Aydın Adnan Menderes University Faculty of Medicine, Aydın, Türkiye

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## Abstract

**OBJECTIVE:** This study aimed to compare the clinical, radiological, and functional outcomes of idiopathic pulmonary fibrosis (IPF) patients treated with nintedanib or pirfenidone, focusing on long-term efficacy, safety, and survival.

**MATERIAL AND METHODS:** A retrospective cross-sectional real-life study was conducted at a tertiary healthcare center between 2016 and 2021, including 93 IPF patients treated with either nintedanib (n = 41) or pirfenidone (n = 52). Data on demographics, pulmonary function tests [forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and diffusing capacity for carbon monoxide], radiological assessments, exacerbations, mortality, and side effects were analyzed using appropriate statistical methods.

**RESULTS:** Both groups were comparable in age (nintedanib: 68.6 years; pirfenidone: 71.3 years) and gender distribution. Patients on pirfenidone had a higher body mass index (27.7 vs. 26.0 kg/m$^2$, $P$ = 0.049) and more radiological involvement ($P$ = 0.034). Baseline: Gender, Age, Physiology scores were lower in the nintedanib group (3.39 vs. 4.21, $P$ = 0.007). Lung function (FVC, FEV1) was significantly better in the nintedanib group at two years; though differences were not sustained over five years. Side effects were more frequent with nintedanib (73.2% vs. 46.2%, $P$ = 0.009), particularly affecting the gastrointestinal system. At five years after follow-up, mortality was higher in the pirfenidone group (53.4% vs. 17.5%, $P$ = 0.02), although time from diagnosis to death was longer (33.8 vs. 19.0 months, $P$ = 0.020).

**CONCLUSION:** Pirfenidone may prolong survival in patients with severe disease and greater radiological involvement, while nintedanib showed lower mortality in milder disease. Treatment outcomes appear influenced by baseline characteristics, highlighting the need for individualized therapeutic strategies. Comprehensive studies involving more homogeneous patient groups are needed to clarify the comparative efficacy of these treatments.

**KEYWORDS:** Idiopathic pulmonary fibrosis, nintedanib, pirfenidone, lung function, long-term outcomes, real-life data

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## INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a severe and progressive interstitial lung disease characterized by irreversible scarring of lung tissue, leading to significant impairment in respiratory function and quality of life.[1] It primarily affects older adults, presenting with symptoms such as progressive dyspnea and chronic cough. Although the exact etiology remains unclear, genetic predisposition and environmental factors, including smoking and potential viral infections, are considered key contributors. IPF is relatively rare, with a global incidence of 2.8 to 9.3 per 100,000, but it carries a high burden of morbidity and mortality. Without treatment, the median survival is 3-5 years post-diagnosis.[2,3] Over the past decade, the introduction of antifibrotic therapies has significantly advanced IPF management, offering hope for slowing disease progression.

**Corresponding author:** Onur Yazıcı MD, dronur_yazici@hotmail.com

Two key antifibrotic agents, nintedanib and pirfenidone, have become central in IPF treatment. Nintedanib, a tyrosine kinase inhibitor, targets fibrosis-related pathways activated by growth factors such as platelet-derived growth factor and transforming growth factor-beta (TGF-β).[2] The INPULSIS trials demonstrated its efficacy in significantly reducing forced vital capacity (FVC) decline over one year.[4] Pirfenidone, on the other hand, has both anti-inflammatory and antifibrotic properties, primarily through its inhibition of TGF-β-induced collagen production and fibroblast proliferation. Clinical trials like CAPACITY and ASCEND have shown that pirfenidone slows FVC decline and may improve progression-free survival.[2,5-8] Both drugs have been shown to reduce acute exacerbations and prolong survival, though side effect profiles often guide treatment selection.[9,10]

This study aimed to directly compare the clinical, radiological, and functional outcomes of nintedanib and pirfenidone in patients with IPF. By evaluating long-term efficacy, safety, and survival outcomes, the study seeks to provide valuable insights into optimizing therapeutic strategies for IPF management.

## MATERIAL AND METHODS

Patients with IPF followed at the pulmonology clinics of a tertiary healthcare center between 2016 and 2021 were included in this retrospective study. A total of 118 patients with a confirmed diagnosis of IPF were initially screened. Of these, 25 were excluded due to either a disease duration of less than one year at the time of data collection or incomplete medical records, in accordance with the study's exclusion criteria. Consequently, 93 patients were included in the final analysis. The inclusion criteria were adults aged 18 years or older with an IPF diagnosis confirmed by radiological or histopathological criteria. The patient selection process and follow-up scheme are summarized in Figure 1. Data were collected using a standardized case report form designed by the researchers. This form included demographic information, clinical symptoms, physical examination findings, radiological features, treatment details, observed side effects, and outcomes, such as acute exacerbations and mortality.

**Main Points**

- This five-year, real-life retrospective study compared the clinical, radiological, and functional outcomes of idiopathic pulmonary fibrosis (IPF) patients treated with nintedanib or pirfenidone.
- Despite similar functional outcomes, long-term mortality was significantly lower in the nintedanib group, which included patients with lower baseline the Gender, Age, Physiology scores and milder disease severity.
- Gastrointestinal side effects were more common with nintedanib, while photosensitivity occurred in both groups with similar frequency.
- Patients treated with pirfenidone, despite having more severe baseline radiological involvement, experienced a longer time from diagnosis to death, suggesting a potential survival benefit in advanced disease.
- The findings emphasize the influence of baseline disease severity on treatment outcomes and support the need for personalized antifibrotic therapy decisions in IPF management.

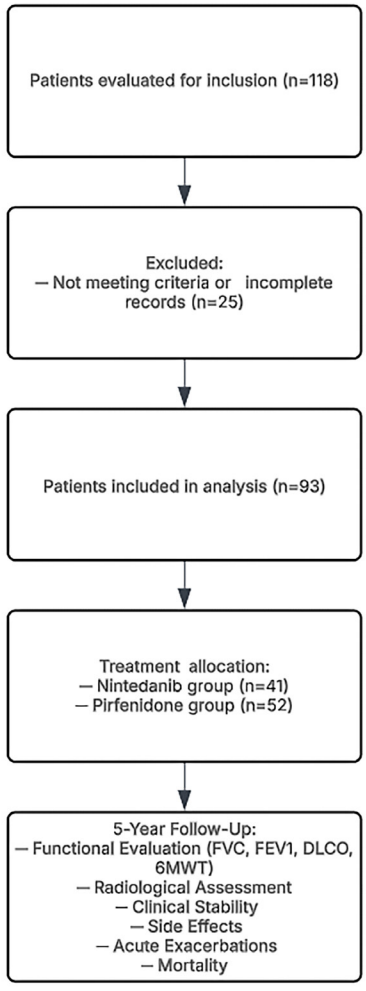


**Figure 1.** Flowchart of patient inclusion, treatment allocation, follow-up, and outcome assessment in the study

*FVC: Forced vital capacity, FEV1: Ratio of forced expiratory volume in the first second, DLCO: Diffusing capacity for carbon monoxide, 6MWT: 6 minute walk test*

Radiological disease extent was evaluated based on the anatomical lobe distribution of fibrotic changes observed in high-resolution computed tomography scans, categorized as involvement of lower lobes only, middle and lower lobes, or upper, middle, and lower lobes. The categorization was performed by experienced radiologists as part of routine clinical reporting at the time of diagnosis.

The Gender, Age, Physiology (GAP) index was recorded at diagnosis, while clinical, radiological, and functional parameters were evaluated both at baseline and during follow-up (at 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years). Patients were categorized based on the antifibrotic treatment regimen received: either nintedanib or pirfenidone. Detailed records of treatment dosage, duration, and any adjustments due to side effects or disease progression were maintained. Pulmonary function tests were conducted in the pulmonary laboratory of the healthcare center, using a Jaeger Master Scope spirometer. Tests were performed with the patient in a seated position and followed the American Thoracic Society/European Respiratory Society criteria.[11] A certified technician conducted all tests. Forced expiratory volume in 1 second (FEV1), FVC,

and the FEV1/FVC ratio were measured. Bronchodilation tests were performed 15 minutes after salbutamol inhalation (4 puffs, 400 µg). Results were recorded as percentages of the predicted values. The 6 minute walk test (6MWT) was utilized to evaluate the functional capacity of the patients. Each test was conducted on a flat surface, and patients were instructed to walk at their maximum speed for 6 minutes. Oxygen saturation ($SpO_2$) was measured using pulse oximetry before and after the test. Dyspnea and fatigue levels were assessed and recorded pretest and posttest. The primary outcome measures were changes in FVC, radiological progression, and survival rates. Secondary outcomes included the incidence of acute exacerbations and an assessment of treatment-related side effects. The study was approved by the Aydın Adnan Menderes University Local Ethics Committee and conducted, following the principles of the 1964 Declaration of Helsinki and its later amendments (approval no: 2022/108, date: 04.08.2022).

### Patient Follow-up and Missing Data Handling

During the five-year follow-up period, some patients missed scheduled visits or discontinued regular clinical follow-up. However, vital status, (alive or deceased) of all patients was verified through the national electronic health record system, allowing complete and accurate mortality data collection for all patients regardless of clinic attendance.

For other outcome variables [e.g., pulmonary function tests, diffusing capacity for carbon monoxide (DLCO), 6MWT, radiological and clinical assessments], only data from patients who attended follow-up visits at each timepoint were included in the analyses. Missing data were not imputed, and an available-case analysis was used for each parameter at each timepoint.

A total of 10 patients (24.4%) in the nintedanib group switched to pirfenidone, and 9 patients (17.3%) in the pirfenidone group switched to nintedanib. Patients who were lost to follow-up or switched treatments, did not significantly differ in baseline characteristics [age, sex, body mass index (BMI), GAP index, and extent of radiologic involvement] compared to those who remained on their original treatment.

### Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 22.0 (IBM SPSS, Chicago, IL). The normality of continuous variables was assessed with the Kolmogorov-Smirnov test. Descriptive statistics, including means, standard deviations, and percentages, were used to summarize the data. Chi-square tests were applied to categorical variables, while t-tests or Mann-Whitney U tests were used for continuous variables based on their distribution. Statistical significance was defined as $P < 0.05$.

## RESULTS

The study included 41 patients in the nintedanib group and 52 patients in the pirfenidone group. In the comparative analysis of demographic and clinical characteristics between the two treatment groups, both groups had similar age distributions, with nintedanib-treated patients having a mean age of 68.67±7.98 years and pirfenidone-treated patients having a mean age of 71.33±7.63 years ($P = 0.098$). The sex distribution was also comparable, with no statistically significant difference ($P = 0.061$). However, a significant difference was observed in BMI between the treatments, with Pirfenidone-treated patients having a higher mean BMI (27.65±3.68 kg/m) compared to nintedanib-treated patients (26.00±4.30 kg/m, $P = 0.049$). No significant differences were found between the groups regarding education level, residence, smoking history, or the presence of comorbidities, indicating similar demographic and clinical profiles across treatments. The follow-up duration was also comparable between the nintedanib and pirfenidone groups (35.48±20.22 vs. 35.19±19.90 months, $P = 0.814$). In terms of diagnostic methods, clinical and radiological diagnosis was predominant in both groups, though histopathological diagnosis was more frequently observed in the pirfenidone group (13.5%) compared to the nintedanib group (2.4%, $P = 0.074$). In the analysis of radiological findings, lower lobe involvement was significantly higher in nintedanib-treated patients (41.5%) compared to those treated with pirfenidone (25.0%), whereas combined middle and lower lobe involvement was more pronounced in the pirfenidone group. Detailed results of this comparison are presented in Table 1.

In the comparative analysis of laboratory and functional parameters between the nintedanib and pirfenidone groups, no significant differences were observed in arterial blood gas measurements, including pH, $pO_2$, and $pCO_2$ levels ($P > 0.05$). Pulmonary function tests also showed comparable results between the groups, with no statistically significant differences in FVC, FEV1, FEV1/FVC ratio, or DLCO levels ($P > 0.05$). Similarly, functional capacity as assessed by the 6MWT revealed no significant differences, with both groups achieving comparable distances ($P = 0.565$). However, GAP scores, a composite measure of disease severity, were significantly lower in the nintedanib group (3.39±1.61) compared to the pirfenidone group (4.21±1.14, $P = 0.007$), indicating that patients in the nintedanib group had less severe disease at baseline. Detailed results are presented in Table 2.

In the analysis of treatment characteristics between the nintedanib and pirfenidone groups, significantly, more patients in the nintedanib group reported experiencing side effects compared to the pirfenidone group (73.2% vs. 46.2%, $P = 0.009$). Among those with reported side effects, skin-related issues were observed in 14.6% of nintedanib patients and 11.5% of pirfenidone patients, while gastrointestinal side effects were more common in the nintedanib group (58.5%) compared to the pirfenidone group (30.8%). Additionally, other side effects were only observed in the pirfenidone group (3.9%). Detailed results of the comparison of treatment side effects are presented in Table 3.

This study involves a five-year longitudinal evaluation of functional, clinical, and radiological outcomes in patients with IPF with nintedanib or pirfenidone. Throughout the follow-up period, radiological and clinical progression rates were comparable between the two treatment groups, with no significant differences observed overall. Notably, during the second year of follow-up, patients receiving nintedanib showed significantly better lung function outcomes, with

higher FVC (88.95±26.99 vs. 73.45±20.37, $P$ = 0.026) and FEV1 (94.05±28.21 vs. 79.32±20.93, $P$ = 0.040) compared to those treated with pirfenidone. However, this difference in lung function parameters did not persist in subsequent years, as no significant variations were observed between the groups in later follow-ups (Table 4).

In the comprehensive five-year evaluation of treatment dynamics and outcomes between the nintedanib and pirfenidone groups, the mean follow-up duration was comparable at 35.48±20.22 months for nintedanib and 35.19±19.90 months for pirfenidone ($P$ = 0.814). Radiological stability was observed in 48.0% of nintedanib-treated patients compared to 38.7% in the pirfenidone group, though this difference was not statistically significant ($P$ = 0.368). Similarly, clinical stability was reported in 48.0% of nintedanib patients and 38.7% of pirfenidone patients ($P$ = 0.401). Acute exacerbations were slightly more frequent in the nintedanib group (44.0%) than in the pirfenidone group (40.9%), but this difference was not statistically significant ($P$ = 0.777). Most exacerbations were due to infections, with a smaller proportion being idiopathic, again with no significant difference between the groups. Lung cancer incidence was low and similar across both groups, at 2.4% for nintedanib and 1.9% for pirfenidone ($P$ = 1.000). In terms of clinical endpoints, mortality was significantly higher in the pirfenidone group (53.4%) compared to the nintedanib group (17.5%) ($P$ = 0.002) (Table 5).

**Table 1.** Comparison of demographic, clinical, and diagnostic characteristics between nintedanib and pirfenidone treatment groups in IPF patients

| Parameter | Nintedanib (n = 41) | Pirfenidone (n = 52) | *P* |
|---|---|---|---|
| Age, (years) | 68.67±9.78 | 71.33±7.65 | 0.098 |
| Gender, n (%) | | | 0.061 |
| - Male | 29 (70.7%) | 45 (86.5%) | |
| - Female | 12 (29.3%) | 7 (13.5%) | |
| BMI, (kg/m²) | 26.00±4.30 | 27.65±3.68 | 0.049 |
| Education level, n (%) | | | 0.103 |
| - Less than high school | 19 (22.6%) | 10 (19.2%) | |
| - High school | 36 (42.9%) | 20 (38.5%) | |
| - University or higher | 29 (34.5%) | 22 (42.3%) | |
| Residence, n (%) | | | 0.099 |
| - Urban | 19 (46.3%) | 33 (63.5%) | |
| - Rural | 22 (53.7%) | 19 (36.5%) | |
| Smoking history, n (%) | | | 0.335 |
| - Yes | 27 (65.9%) | 39 (75.0%) | |
| - No | 14 (34.1%) | 13 (25.0%) | |
| Average smoking duration (years) | 37.26±15.76 | 30.71±12.90 | 0.069 |
| Comorbidities, n (%) | | | |
| - Yes | 32 (78) | 38 (73.1) | 0.581 |
| - No | 9 (22) | 14 (26.9) | |
| sPAP, (mmHg) | 33.65±8.46 | 38.64±19.17 | 0.781 |
| Radiological involvement, n (%) | | | 0.034 |
| - Lower lobe | 41.5% | 25.0% | |
| - Middle and lower lobes | 48.8% | 44.2% | |
| - Upper, middle, and lower lobes | 9.08% | 30.08% | |
| PA/Ao | 0.90±0.13 | 0.87±0.15 | 0.304 |
| Follow-up duration, (months) | 35.48±20.22 | 35.19±19.90 | 0.814 |
| Diagnosis method, n (%) | | | 0.074 |
| - Histopathological | 1 (2.4%) | 7 (13.5%) | |
| - Clinical and radiological | 40 (97.6%) | 45 (86.5%) | |

IPF: idiopathic pulmonary fibrosis, SPAP: systolic pulmonary artery pressure, PA/Ao: pulmonary artery/aorta ratio, BMI: body mass index

**Table 2.** Comparison of laboratory and functional parameters between nintedanib and pirfenidone treatment groups in IPF patients

| Parameter | Nintedanib (n = 41) | Pirfenidone (n = 52) | *P* |
|---|---|---|---|
| **Arterial blood gas measurements** | | | |
| - pH | 7.41±0.04 | 7.42±0.04 | 0.361 |
| - $pO_2$ (mmHg) | 71.65±5.85 | 75.47±6.15 | 0.734 |
| - $pCO_2$ (mmHg) | 34.85±3.94 | 36.13±3.92 | 0.391 |
| **Pulmonary function tests** | | | |
| - FVC (%) | 77.37±18.68 | 72.00±17.67 | 0.160 |
| - FEV1 (%) | 82.63±19.46 | 77.15±16.93 | 0.150 |
| - FEV1/FVC (%) | 86.02±7.98 | 83.54±11.84 | 0.219 |
| - DLCO (%) | 55.21±16.64 | 54.06±16.70 | 0.493 |
| 6 minute walk test, (m) | 359.89±42.23 | 347.91±41.47 | 0.565 |
| 6 minute walk test, % | 65.92±14.60 | 65.08±15.20 | 0.805 |
| GAP score | 3.39±1.61 | 4.21±1.14 | 0.007 |

IPF: idiopathic pulmonary fibrosis, PFT: pulmonary function tests, FVC: forced vital capacity, FEV1/FVC: ratio of forced expiratory volume in the first second to forced vital capacity, DLCO: diffusing capacity for carbon monoxide, m: meter

**Table 3.** Comparison of treatment characteristics between nintedanib and pirfenidone groups

| Parameter | Nintedanib (n = 41) | Pirfenidone (n = 52) | *P* |
|---|---|---|---|
| **Antifibrotic drug side effects** | | | |
| - Yes | 30 (73.2%) | 24 (46.2%) | 0.009 |
| - No | 11 (26.8%) | 28 (53.8%) | |
| **Side effects type** | | | |
| - Skin | 6 (14.63%) | 6 (11.54%) | |
| - GIS | 24 (58.54%) | 16 (30.77%) | 0.227 |
| - Other | 0 (0%) | 2 (3.85%) | |

GIS: gastrointestinal

**Table 4.** Longitudinal comparison of functional, clinical, and radiological outcomes between nintedanib and pirfenidone treatment groups over five years

| Year | Parameter | Nintedanib (n = 41) | Pirfenidone (n = 52) | *P* |
|---|---|---|---|---|
| 6 months | Mortality (%) | 7.89% (3/38) | 0% (0/50) | 0.077 |
| | FVC (%) | 79.97±20.86 | 75.00±15.71 | 0.179 |
| | FEV1 (%) | 84.64±20.64 | 80.92±17.85 | 0.375 |
| | FEV1/FVC (%) | 86.75±9.14 | 83.86±10.01 | 0.163 |
| | DLCO (%) | 61.88±51.40 | 54.70±14.37 | 0.972 |
| | 6MWT (m) | 363.82±97.78 | 372.68±132.17 | 0.803 |
| | Radiology, n (%) | | | |
| | Stable | 35 (94.6) | 49 (98.0) | |
| | Progression | 2 (5.4) | 1 (2.0) | 0.572 |
| | Clinical n (%) | | | |
| | Stable | 34 (91.9%) | 49 (98.0%) | |
| | Progression | 3 (8.1%) | 1 (2.0%) | 0.308 |

**Table 4.** Continued

| Year | Parameter | Nintedanib (n = 41) | Pirfenidone (n = 52) | *P* |
|---|---|---|---|---|
| 1 year | Mortality (%) | 0% (0/32) | 0% (0/47) | - |
| | $SpO_2$ | 95.59±2.30 | 93.81±4.56 | 0.155 |
| | FVC (%) | 82.06±26.64 | 72.53±16.52 | 0.061 |
| | FEV1 (%) | 86.03±24.47 | 78.02±16.87 | 0.114 |
| | FEV1/FVC (%) | 86.56±10.31 | 84.98±10.73 | 0.656 |
| | DLCO (%) | 52.55±17.22 | 51.40±14.24 | 0.755 |
| | 6MWT (m) | 369.83±103.27 | 362.17±108.03 | 0.788 |
| | sPAP | 41.60±17.90 | 55.80±22.54 | 0.353 |
| | Radiology, n (%) | | | |
| | Stable | 24 (75.0%) | 36 (76.6%) | |
| | Progression | 8 (25.0%) | 11 (23.4%) | 0.871 |
| | Clinical, n (%) | | | |
| | Stable | 22 (68.8%) | 34 (72.3%) | |
| | Progression | 10 (31.3%) | 13 (27.7%) | 0.730 |
| 2 year | Mortality (%) | 7.1% (2/28) | 20.5% (9/44) | 0.183 |
| | $SpO_2$ | 95.16±2.17 | 92.68±5.55 | 0.266 |
| | FVC (%) | 88.95±26.99 | 73.45±20.37 | 0.026 |
| | FEV1 (%) | 94.05±28.21 | 79.32±20.93 | 0.040 |
| | FEV1/FVC (%) | 86.11±8.24 | 85.46±9.65 | 0.920 |
| | DLCO (%) | 46.92±15.75 | 55.08±13.06 | 0.257 |
| | 6MWT (m) | 368.44±69.69 | 353.75±114.94 | 0.479 |
| | Radiology, n (%) | | | |
| | Stable | 13 (68.4%) | 17 (54.8%) | |
| | Progression | 6 (31.6%) | 14 (45.2%) | 0.341 |
| | Clinical, n (%) | | | |
| | Stable | 14 (73.7%) | 16 (51.6%) | |
| | Progression | 5 (26.3%) | 15 (48.4%) | 0.122 |
| 3 year | Mortality (%) | 3.85% (1/26) | 14.71% (5/34) | 0.377 |
| | $SpO_2$ | 95.00±2.55 | 93.81±5.24 | 0.857 |
| | FVC (%) | 96.11±28.03 | 78.44±21.58 | 0.074 |
| | FEV1 (%) | 97.89±26.83 | 83.94±20.80 | 0.165 |
| | FEV1/FVC (%) | 84.56±12.22 | 85.25±8.55 | 0.609 |
| | DLCO (%) | 50.29±8.67 | 53.36±12.31 | 0.765 |
| | 6MWT (m) | 406.67±20.82 | 381.36±121.32 | 0.696 |
| | Radiology n (%) | | | |
| | Stable | 7 (77.8%) | 10 (62.5%) | |
| | Progression | 2 (22.2%) | 6 (37.5%) | 0.661 |
| | Clinical n (%) | | | |
| | Stable | 7 (77.8%) | 10 (62.5%) | |
| | Progression | 2 (22.2%) | 6 (37.5%) | 0.661 |

**Table 4.** Continued

| Year | Parameter | Nintedanib (n = 41) | Pirfenidone (n = 52) | *P* |
|---|---|---|---|---|
| 4 year | Mortality (%) | 0% (0/25) | 20.69% (6/29) | 0.129 |
| | $SpO_2$ (%) | 95.8±0.84 | 95.5±2.07 | 0.747 |
| | FVC (%) | 107.0±15.22 | 85.2±33.30 | 0.111 |
| | FEV1 (%) | 107.0±19.84 | 93.2±35.67 | 0.220 |
| | FEV1/FVC (%) | 79.2±9.83 | 87.3±6.04 | 0.121 |
| | DLCO (%) | 45.5±3.54 | 48.5±14.83 | 1.000 |
| | 6MWT (m) | Not provided | Not provided | |
| | Radiology n (%) | | | |
| | Stable | 3 (60.0%) | 7 (70.0%) | |
| | Progression | 2 (40.0%) | 3 (30.0%) | 1.000 |
| | Clinical n (%) | | | |
| | Stable | 3 (60.0%) | 8 (80.0%) | |
| | Progression | 2 (40.0%) | 2 (20.0%) | 0.560 |
| 5 year | Mortality (%) | 4% (1/25) | 13.04% (3/23) | 1.000 |
| | Radiology n (%) | | | |
| | Stable | 1 (100.0%) | 1 (25.0%) | |
| | Progression | 0 (0.0%) | 3 (75.0%) | 0.400 |
| | Clinical n (%) | | | |
| | Stable | 1 (100.0%) | 2 (50.0%) | |
| | Progression | 1 (0.0%) | 2 (50.0%) | 1.000 |

SpO2: peripheral oxygen saturation, FVC: forced vital capacity, FEV1/FVC: ratio of forced expiratory volume in the first second to forced vital capacity, DLCO: diffusing capacity for carbon monoxide, GAP: Gender, Age, Physiology Score, sPAP: systolic pulmonary artery pressure

**Table 5.** Outcomes and treatment dynamics between nintedanib and pirfenidone treatment groups over a five-year period

| Parameter | Nintedanib (n = 41) | Pirfenidone (n = 52) | *P* |
|---|---|---|---|
| Follow-up duration, (months) | 35.48±20.22 | 35.19±19.90 | 0.814 |
| Radiological stability rate, % (rate) | 51.6% (16/31) | 37.2% (16/43) | 0.217 |
| Clinical stability rate, % (rate) | 48.4% (15/31) | 34.9% (15/43) | 0.243 |
| Incidence of acute exacerbations, % (rate) | 44.1% (15/34) | 61.2% (30/49) | 0.124 |
| Idiopathic cause | 13.3% (2/15) | 10.0% (3/30) | 1.000 |
| Infection-related | 100% (13/13) | 96.3% (26/27) | 1.000 |
| Lung cancer development rate, % (rate) | 2.4% (1/41) | 1.9% (1/52) | 1.000 |
| Mortality rate, % (rate) | 17.5% (7/31) | 53.4.0% (23/43) | 0.002 |
| Time from diagnosis to mortality (month) | 19.00±16.15 | 33.83±12.69 | 0.020 |
| **Cause of death % (rate)** | | | |
| IPF-associated causes | 71.4% (5/7) | 58.3% (14/24) | |
| Non-IPF causes | 28.6% (2/7) | 41.7% (10/24) | 0.676 |
| **Switched treatments (%)** | | | |
| From pirfenidone to nintedanib | - | 17.3% (9/52) | |
| From nintedanib to pirfenidone | 24.4% (10/41) | - | |

IPF: idiopathic pulmonary fibrosis

## DISCUSSION

This study provides valuable insights into the comparative efficacy and safety profiles of nintedanib and pirfenidone in the management of IPF. Below, the key findings and their implications are discussed:

The baseline characteristics of the two treatment groups, including age, sex, smoking history, comorbidities, $SpO_2$ levels, mean pulmonary artery pressure, and pulmonary function parameters (FVC and DLCO), were comparable, enhancing the reliability of the study outcomes. However, a notable difference was BMI, which was higher in the pirfenidone group. This difference may reflect potential disparities in the metabolic processing or side effect profiles of the drugs, given the influence of BMI on drug pharmacokinetics and pharmacodynamics.[12] Further studies are needed to explore the clinical implications of this finding, particularly in antifibrotic therapies, where data remain limited.

The side effect profiles differed between the two groups. Drug-related side effects were more frequently observed in the nintedanib group (73.2% vs. 46.2%; $P = 0.009$). Gastrointestinal side effects, particularly diarrhea, were significantly more common in patients treated with nintedanib, consistent with previous studies, including those by Bargagli et al.[13] and Hughes et al.[14] On the other hand, photosensitivity and rash were more frequent in the pirfenidone group in earlier studies, such as the CAPACITY and ASCEND studies.[7,8] However, our study found a lower incidence of skin-related side effects in pirfenidone-treated patients, which may be attributed to lifestyle factors and patient adherence to preventive measures such as sunscreen use and sun avoidance. In the literature, the incidence of photosensitivity associated with nintedanib use has generally been reported as low.[15-17] However, in our study, the incidence of photosensitivity in patients treated with nintedanib (14.63%) was higher compared to those treated with pirfenidone (11.54%). We believe this may be related to factors specific to our patient population, such as genetic predisposition, comorbid conditions, or concomitant medications. Although the mechanisms underlying the development of photosensitivity in patients treated with nintedanib are not fully understood, this finding warrants further investigation in future studies. In this context, careful monitoring of dermatological side effects during nintedanib treatment and providing patients with appropriate information on this matter appears to be crucial.

Functional parameters, including FVC, FEV1, DLCO, 6MWT, and $SpO_2$, showed similar trends in both groups during the 5-year follow-up. However, at the 2-year mark, significantly lower FVC and FEV1 values were observed in the pirfenidone group, which could be due to the exclusion of some patients for reasons such as treatment changes or mortality. Despite this, the long-term trends were consistent between the two groups, aligning with previous studies showing comparable efficacy of both drugs in maintaining pulmonary function.[6,10,18]

At the end of the 5-year follow-up in our study, both groups demonstrated similar clinical and radiological courses. These findings align with broader clinical studies, such as INPULSIS and ASCEND, which have shown that both treatments effectively slow radiological progression.[4,8] The lack of a significant difference in clinical stability and progression rates supports the notion that both drugs exhibit comparable long-term efficacy in the management of IPF.

In our study, the rates of acute exacerbations were similar between the two treatment groups, supporting the efficacy of both antifibrotic agents in reducing exacerbation risk. This finding aligns with previous studies evaluating antifibrotic therapies in IPF. Notably, the TOMORROW and INPULSIS trials demonstrated that nintedanib significantly reduces the frequency of acute exacerbations.[19,20] However, in the INSTAGE trial, this effect was not observed in patients with more advanced disease.[21] For pirfenidone, the CAPACITY and ASCEND trials reported a reduction in exacerbation rates among patients treated with pirfenidone, but these reductions did not reach statistical significance.[7,8] A meta-analysis by Petnak et al.[22] compared the risk of acute exacerbations between IPF patients receiving antifibrotic therapy and those who did not. The analysis, which included 26 studies (8 randomized controlled trials and 18 cohort studies) and a total of 12,956 patients, found that antifibrotic therapies effectively reduce exacerbation risk. The effect was more consistent with nintedanib than with pirfenidone, which showed less consistency. Furthermore, real-world data from the Belgian Health System records indicated a trend toward fewer acute exacerbations in the nintedanib group compared to the pirfenidone group, although this difference was not statistically significant.[23] A 2019 meta-analysis of 10 randomized controlled trials also reported no significant difference between nintedanib and pirfenidone in their effects on acute exacerbations.[24] Increased radiological extent is a well-established risk factor for acute exacerbations in IPF.[25] Despite the pirfenidone group in our study showing more extensive radiological involvement at baseline, the frequency of acute exacerbations remained comparable between the two groups. This observation suggests that pirfenidone may provide additional protection against exacerbations. However, further studies involving patient groups with similar baseline radiological characteristics are required to validate this finding.

Mortality outcomes in our study revealed notable patterns. A higher mortality rate was observed in patients treated with pirfenidone. However, previous studies comparing the effects of pirfenidone and nintedanib on mortality have generally reported similar all-cause mortality rates for both drugs.[10,26,27] This discrepancy in our findings may be attributed to differences in baseline characteristics, particularly the more extensive radiological involvement in the pirfenidone group, which is a well-established risk factor for mortality in IPF.[25,28]

In our study, the GAP index, a multidimensional tool integrating factors such as sex, age, and pulmonary function, was significantly higher in the pirfenidone group compared to the nintedanib group ($P = 0.007$). While the two groups were comparable in terms of baseline age, sex, and pulmonary function parameters, the higher GAP index in the pirfenidone group correlates with the increased mortality rate observed in this cohort. These findings highlight the critical importance of using integrated assessment methods like the GAP index in predicting mortality, as they provide a more comprehensive evaluation than individual parameters alone.

Studies in the literature have shown that in patients with IPF treated with pirfenidone or nintedanib, the time from diagnosis to mortality is generally similar for both drugs.[29,30] However, in our study, this duration was significantly longer in the pirfenidone group than the nintedanib group. Interestingly, despite the more extensive baseline radiological involvement in the pirfenidone group - a known risk factor for mortality - the longer time from diagnosis to mortality suggests that pirfenidone may have a more pronounced effect on prolonging survival, despite this risk factor. Further studies with patient groups matched for radiological involvement are needed to validate these findings and clarify the comparative impacts of these antifibrotic agents.

The limitations of our study include its retrospective design, which relies on the accuracy and completeness of patient records, potentially limiting the generalizability of the findings. Additionally, significant baseline differences between the nintedanib and pirfenidone groups, such as GAP index and radiological involvement, may reduce the reliability of conclusions regarding treatment efficacy. Furthermore, the exclusion of some patients during the 5-year follow-up due to treatment changes or mortality limits the ability to comprehensively assess long-term outcomes. In addition, due to incomplete longitudinal FVC data in absolute values, we were unable to calculate yearly FVC change in milliliters or percentage from baseline, which limits the precision of treatment effect comparisons.

## CONCLUSION

In this study, we evaluated the comparative efficacy and safety of nintedanib and pirfenidone in IPF, providing insights that contribute to clinical decision-making. We believe that antifibrotic therapies have a positive impact on mortality. The incidence of mortality was found to be higher in patients treated with pirfenidone compared to those treated with nintedanib, a finding that aligns with the lower GAP index observed in the nintedanib group. However, this finding should be interpreted cautiously due to the more extensive baseline radiological involvement in the pirfenidone group. Despite the higher baseline radiological involvement in the pirfenidone group, the longer time from diagnosis to mortality, compared to the nintedanib group, suggests that pirfenidone may have the potential to extend this period. Furthermore, the similar frequency of acute exacerbations between the two groups, despite the greater radiological burden in the pirfenidone group, suggests a potential protective effect of pirfenidone. To better understand the efficacy of antifibrotic agents in the treatment of IPF and to compare these therapies, more comprehensive studies are needed that include patients with similar demographic and functional characteristics and comparable radiological involvement.

### Ethics

**Ethics Committee Approval:** The study protocol was approved by the Aydın Adnan Menderes University Local Ethics Committee (approval no: 2022/108, date: 04.08.2022).

**Informed Consent:** Retrospective study.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: A.Y., O.Y., Concept: A.Y., O.Y., Design: A.Y., O.Y., Data Collection or Processing: A.Y., O.Y., Analysis or Interpretation: O.Y., Literature Search: A.Y., O.Y., Writing: A.Y., O.Y.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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