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Comparison of the effectiveness of pirfenidone and nintedanib in patients with advanced stage idiopathic pulmonary fibrosis

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Abstract. *Background and aim:* Idiopathic Pulmonary Fibrosis (IPF) is a progressive, fatal lung disease with high mortality, especially in advanced stages, defined as forced vital capacity (FVC) ≤50% and/or diffusing capacity of the lungs for carbon monoxide (DLCO) ≤30% of predicted values. While antifibrotic therapies, such as nintedanib and pirfenidone, are effective in mild to moderate IPF, their efficacy in advanced-stage IPF remains unclear due to the exclusion of these patients from major clinical trials. This study aimed to compare the effectiveness of nintedanib and pirfenidone on mortality and to identify predictors of mortality in patients with advanced-stage IPF. *Methods:* This retrospective cohort study included 198 advanced-stage IPF patients treated with nintedanib (n=91) or pirfenidone (n=107) between 2017 and 2023. Demographic, clinical, and radiological data were collected. Mortality predictors were analyzed using multivariate Cox regression, and survival outcomes were compared using adjusted Kaplan-Meier curves. *Results:* Independent predictors of mortality were found to be six-minute walk distance (HR=0.99, 95% CI: 0.996–0.999, p=0.049), pulmonary fibrosis score ≥150 (HR=1.86, 95% CI: 1.07–3.22, p=0.026), and heart failure (HR=2.24, 95% CI: 1.18–4.26, p=0.014). After adjusting for these factors, no significant differences in mortality were observed between the nintedanib and pirfenidone groups. *Conclusions:* Nintedanib and pirfenidone showed comparable effectiveness in reducing mortality among advanced-stage IPF patients. Future clinical trials should include advanced-stage patients to better evaluate treatment efficacy in this population.

Key words: idiopathic pulmonary fibrosis, advanced stage, nintedanib, pirfenidone, mortality, antifibrotic therapy

Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a progressive and fatal lung disease characterized by fibrosis of the lung parenchyma with an unknown etiology. This condition leads to a marked reduction in respiratory capacity and rapid clinical deterioration, culminating in high mortality rates (1). Mortality is particularly elevated in patients with advanced-stage IPF, defined by a forced vital capacity (FVC) ≤ 50% of predicted and/or a diffusing capacity for carbon monoxide (DLCO) ≤ 30% of predicted. Clinical trials have shown that antifibrotic therapies, such as nintedanib and pirfenidone, are effective in preserving FVC and DLCO, and in reducing mortality in IPF patients, especially those with mild to moderate disease (2-4). Recent studies comparing pirfenidone and nintedanib have not revealed any significant differences in efficacy between these two

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treatments (5,6). The efficacy of antifibrotic drugs in patients with advanced-stage IPF remains unclear, as major studies like ASCEND and CAPACITY excluded this patient population (7,8). There are only several studies evaluating the efficacy of nintedanib and pirfenidone in patients with advanced-stage IPF. The INPULSIS-ON study demonstrated that nintedanib had similar effects in slowing disease progression in both FVC ≥ 50% and FVC < 50% predicted groups (9). Similarly, a real-world study with pirfenidone showed a favourable effect in the advanced group (10). However, there is a lack of data directly comparing the effects of these two drugs in advanced-stage IPF patients. In response to this gap, we aimed to evaluate the compare the impact of nintedanib and pirfenidone on mortality and to identify predictors of mortality in patients diagnosed with a large cohort of advanced-stage idiopathic pulmonary fibrosis.

Material and Methods

Study design and setting

We performed a retrospective cohort study at Yedikule Chest Disease and Chest Surgery Training and Research Hospital, University of Health Sciences, Istanbul, Turkey. Our study was conducted in line with the Declaration of Helsinki tenets and our institutional ethics committee approved it (Approvement protocol number: 24/596)

Study population

Our inclusion criterias for the study are as following: patients aged 18-85 with a diagnosis of advanced-stage IPF, currently receiving treatment with either nintedanib or pirfenidone, and able to perform pulmonary function tests. Between 2017 and 2023, a total of 846 patients with idiopathic pulmonary fibrosis undergoing antifibrotic treatment were consecutively included in the study, ensuring that all patients were followed for at least one year. For advanced-stage IPF patients, antifibrotic therapy was initiated under an off-label use authorization granted by the Ministry of Health, following clinical and radiological assessment. Among these, 283 patients were diagnosed with advanced-stage IPF, defined as severe physiological impairment with an FVC ≤ 50% of the predicted value and/or a DLCO ≤ 30% of the predicted value. After excluding 44 patients due to unacceptable pulmonary function test (PFT), 43 patients who discontinued antifibrotic treatment, and 42 patients lacking follow-up data, 198 patients remained in the study cohort (Figure 1).

Data collection

Demographic features and comorbidities, including heart failure (EF ≤ 40%, classified as HFrEF according to the 2022 ACC/AHA guideline) (22), hypertension, diabetes mellitus, ischemic heart disease, malignancy and pulmonary hypertension were retrieved from electronic medical records. Additionally, smoking status, spirometric parameters, diffusion capacity, high-resolution computed tomography findings, six-minute walking distance, ejection fraction (%), and systolic pulmonary artery pressure were also obtained from the electronic medical records.

Definitions and measurements

In our clinic, the diagnosis of idiopathic pulmonary fibrosis (IPF) is established based on the criteria outlined in the latest guidelines of the American Thoracic Society (ATS) through multidisciplinary council evaluations. Treatment is initiated following the recommendations of these councils.(1) Patients were considered to have advanced-stage IPF if they demonstrated severe physiological impairment, defined by an FVC ≤ 50% of the predicted value and/or a DLCO ≤ 30% of the predicted value (11). Pulmonary function tests (PFTs) were conducted by multiple trained technicians using a single device, with daily calibrations performed to ensure accuracy. Spirometry acceptability criteria were met according to the ATS/ERS standards (12). The six-minute walk test (6MWT) was administered following ATS guidelines, with participants instructed to walk as far as possible in six minutes using standard verbal prompts (13). The GAP (Gender-Age-Physiology) score, used to predict survival in idiopathic pulmonary fibrosis, includes gender, age, and physiological parameters such as forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO). The GAP score is categorized into three stages: Stage I (score of 0-3), Stage II (score of 4-5), and Stage III (score of 6-8) (14).

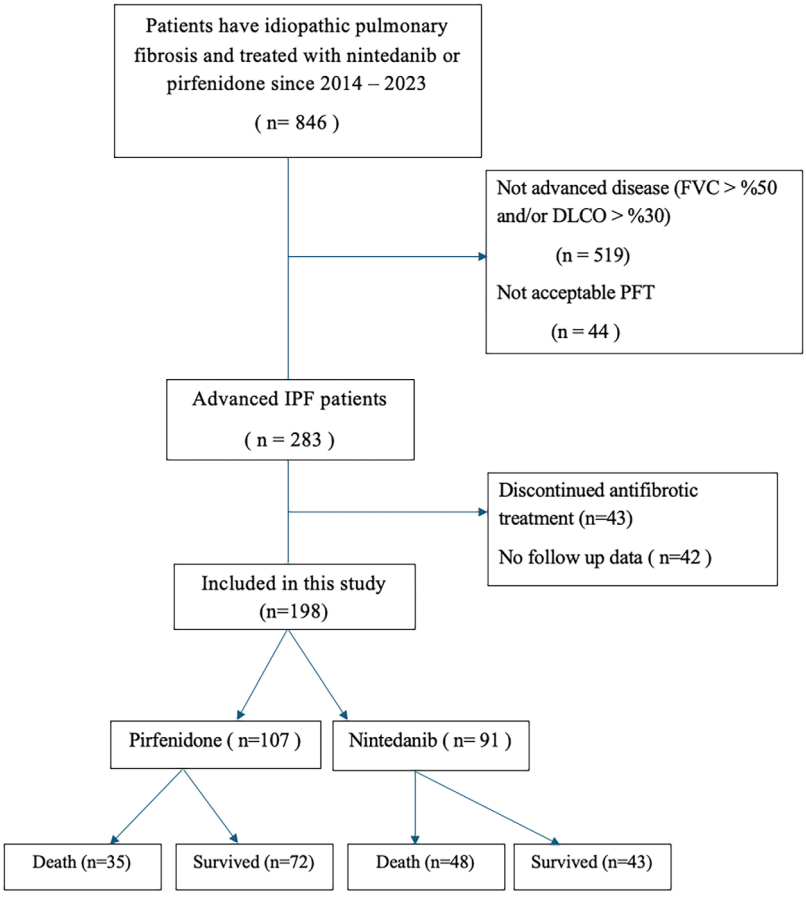

Figure 1. Flow diagram.

Imaging analysis

High-resolution computed tomography (HRCT) scans were performed following established guidelines (15). All HRCT images were independently reviewed by two thoracic radiologists with 11 and 12 years of experience, respectively, in chest CT interpretation. The radiologists were blinded to the patients' demographic data, clinical information, vital signs, and laboratory results. The interobserver reliability for the pulmonary fibrosis score was excellent, with an intraclass correlation coefficient (ICC) of 0.95. Any discrepancies between the radiologists were resolved through consensus discussion. Fibrosis was assessed visually using a standardized scoring system in thoracic tomography images. In this system, normal lung parenchyma was assigned a score of 1, reticular abnormalities a score of 2, traction bronchiectasis a score of 3, and honeycombing a score of 4. Each lung was divided into three distinct zones: the upper zone (above the tracheal carina), the middle zone (between the upper and lower zones), and the lower zone (below the level of the inferior pulmonary vein). The extent of involvement in each region (%) was multiplied by the assigned grading score (1–4) to calculate a score for each zone. The total HRCT score for each patient was obtained by averaging the scores from all six zones, resulting in a possible score range of 100 to 400, with higher scores indicating more severe fibrosis. This score is referred to as the "Pulmonary fibrosis score" (16) .

Treatment, follow-up and outcome

Treatment of mild to moderate IPF with pirfenidone in adults begins with 800 mg/day and is increased up to 2400 mg/day over the course of 3 weeks. Treatment with nintedanib begins with

300 mg/day. During the treatment, patients using pirfenidone were monitored monthly for the first 6 months and then every 3 months, while those using nintedanib were monitored monthly for the first 3 months and then every 3 months. Liver function enzymes were checked during follow-ups, and other side effects were monitored. Symptom follow-ups were conducted every 3 months, spirometry and diffusion capacity every 6 months, and annual HRCT checks were performed. The primary outcome was defined to be all-cause mortality.

Statistical analyses

All statistical analyses were performed with usign IBM SPSS Software version 28.0. Categorical data were presented as counts and percentages. Continuous variables were presented as mean and standard deviation if normally distributed, and as median values and interquartile ranges if not. Intraclass correlation coefficient was used to assess the consistency of the radiological scores measured by two radiologists. A Youden index was used to indicate an optimal cut-off value with using ROC curve analysis. To evaluate factors affecting mortality, a univariate Cox regression analysis was initially performed, followed by a multivariate Cox regression analysis with significant parameters ($p<0.2$). Among highly correlated parameters ($r > 0.7$), the clinically more meaningful parameters were included in the multivariate analysis. After identifying the independent predictors of mortality among advanced IPF patients, adjusted survival curves of nintedanib and pirfenidone groups were compared using log-rank test. A p-value of less than 0.05 was considered statistically significant.

Results

This study included 198 patients with advanced idiopathic pulmonary fibrosis (IPF), with a mean age of 66 ± 10 years. Among these participants, 143 (72.2%) were male. A total of 113 patients (66.1%) had a history of cigarette smoking, while 58 patients (33.9%) were non-smokers. Comorbidities were present in 72% of the patients. The most common comorbidity was hypertension, observed in 34.7% of patients, followed by diabetes mellitus in 28.5% and ischemic heart disease in 24.4%. Using the Youden index with ROC curve analysis, an optimal cut-off value of 150 for the Pulmonary Fibrosis Score was identified. In the cohort, 58.1% of patients had a Pulmonary Fibrosis Score of ≥150.

Regarding pulmonary function, the median [IQR] values were as follows: forced vital capacity (FVC) was 1.67 liters [1.26–2.14], FVC percentage was 46% [41–53.6], diffusing capacity of the lungs for carbon monoxide (DLCO) was 4.41 ml/min/mmHg [2.18–7.31], DLCO percentage was 30% [26–36], forced expiratory volume in 1 second (FEV1) was 1.53 liters [1.13–1.92], FEV1 percentage was 51% [43–61.4], and FEV1/FVC ratio was 90% [83–95.02]. The mean six-minute walk distance was 296.2 ± 121.0 meters. The median systolic pulmonary artery pressure, as measured by transthoracic echocardiography, was 43.5 mmHg [30–60]. All patients had a median GAP score of 5 [5–6]. Risk stratification revealed that 103 patients (52%) were classified as high risk, 90 patients (45.5%) as intermediate risk, and 5 patients (2.5%) as low risk (Table 1). A total of 107 patients were treated with pirfenidone, and 91 patients were treated with nintedanib. Comparative analysis of these two treatment groups showed no significant differences in demographics, smoking status, comorbidities (with the exception of ischemic heart disease), systolic pulmonary artery pressure, or GAP score ($p > 0.05$). However, patients treated with nintedanib had a significantly higher pulmonary fibrosis score and six-minute walk distance compared to those receiving pirfenidone ($p = 0.04$ and $p = 0.03$, respectively). In terms of pulmonary function test results, patients on pirfenidone had a higher FVC percentage ($p = 0.027$), while those on nintedanib had significantly higher DLCO percentage and FEV1/FVC ratio ($p = 0.02$ for both). Of the 198 patients, 39 (19.6%) switched treatment within the first month. Among them, 12 patients discontinued nintedanib due to gastrointestinal side effects (diarrhea, vomiting, deterioration of liver function tests), and 3 patients stopped nintedanib due to non-adherence, switching to pirfenidone. These patients were classified in the pirfenidone group as they transitioned to pirfenidone treatment within a short period. Conversely, 9 patients discontinued pirfenidone due to skin lesions, and 15 patients discontinued it due to non-adherence, leading them to switch to nintedanib. Similarly, these patients were classified in the nintedanib group as they transitioned to nintedanib treatment within a short period.

Univariate cox regression analysis was performed to determine independent mortality predictors.

Table 1. Demographic and clinical characteristics of the patients with IPF

Parameter	All patients (n=198)	Pirfenidone (n=107)	Nintedanib (n=91)	P-value
Male gender, n(%)	143 (72.2)	83 (77.6)	60 (65.9)	0.07
Age(years), mean ± SD	66 ± 10.0	66.8 ± 9.5	65.1 ± 10.5	0.23
Comorbidities, n(%)	136 (71.5)	75 (70.1)	61 (67.0)	0.96
Heart Failure	42 (22.3)	26 (24.3)	16 (17.6)	0.29
Hypertension	65 (34.7)	39 (36.4)	26 (28.6)	0.27
Diabetes Mellitus	53 (28.5)	33 (30.8)	20 (22.0)	0.2
Ischemic Heart Disease	46 (24.4)	31 (30.1)	15 (17.6)	**0,048**
Malignancy	14 (8.04)	8 (7.7)	6 (7)	0.85
Pulmonary Hypertension	62 (43)	32 (44.4)	30 (41.6)	0.73
Smoking status, n(%)				0.11
Smoking history (+)	113 (66.1)	69 (40.4)	44 (25.7)	
Smoking history (-)	58 (33.9)	28 (16.4)	30 (17.5)	
Pulmonary Fibrosis Score, median[IQR]	160 [140-180]	155 [140-175]	165 [140-200]	**0.005**
Pulmonary Fibrosis Score ≥ 150, n(%)	115 (58.1)	55(47.8)	60(52.1)	**0.039**
Pulmonary Function Test, median[IQR]				
FEV1 (lt)	1.53 [1.13 – 1.92]	1.56 [1.24-1.96]	1.40 [1.04-1.92]	0.35
FEV1 (%)	51 [43 – 61.4]	53 [46 – 63]	50 [42 – 60]	0.12
FVC (lt)	1.67 [1.26 – 2.14]	1.69 [1.39-2.17]	1.51 [1.17-2.12]	0.16
FVC (%)	46 [41 - 53.6]	47 [42 – 58]	44.5 [39 – 50]	**0.027**
DLCO (ml/min/mmHg)	4.41 [2.18 – 7.31]	3.49 [2.11 – 6.92]	5.72 [2.52–8.01]	0.21
DLCO (%)	30 [26 – 36]	29 [24 – 33]	30 [27.5 – 40]	**0.028**
FEV1 / FVC	90 [83 – 95.02]	88 [81 – 94]	91 [85 – 102]	**0.019**
Six minutes walking distance (meter), mean ± SD	296.21 ± 121.07	277.36 ± 114.77	329.07 ± 126.16	**0.033**
Systolic Pulmonary Artery Pressure (mmHg), median[IQR]	43.5 [30 – 60]	44 [30 – 60]	42 [30 – 59]	0.96
GAP Score, median [IQR]	5 [5 – 6]	5 [5 – 6]	5.5 [5 – 6]	0.55
Low risk, n(%)	5 (2.5)	2 (1.9)	3 (3.3)	
Intermediate risk, n(%)	90 (45.5)	52 (48.6)	38 (41.8)	
High risk, n(%)	103 (52)	53(49.5)	50 (54.9)	

Abbreviations: FVC: Forced vital capacity, FEV1: Forced expiratory voume in 1st second, DLCO: Diffusing capacity of the lungs for carbon monoxide.

Male gender, having ishemic heart disease, having heart failure, low six minute walking distance, along with low FVC (%), DLCO (lt) and DLCO (%) were found to be associated with increased mortality ($p<0.05$). In the multivariate analysis, the GAP score was included to account for multiple pulmonary function parameters and gender simultaneously. Among variables with a significance level of $p < 0.2$, age (a component of the GAP score) and FEV1 (%) (which shows high correlation with FVC (%)) were excluded from the multivariate model to mitigate multicollinearity (Table 2).

In the multivariate analysis, the six-minute walk distance, Pulmonary Fibrosis Score (≥150), presence of heart failure, and GAP Score were included. The analysis identified the six-minute walk distance

Table 2. Univariate cox regression analyses for variables predicting mortality

Variable	HR	CI (95%)	p value
Male gender	1.64	1.03 – 2.61	**0.037**
Age (years)	0.98	0.96 – 1.004	0.12
Current Smoking	1.33	0.85 – 2.06	0.20
Any comorbidity	1.08	0.71 – 1.64	0.71
Diabetes Mellitus	0.91	0.60 – 1.38	0.68
Hypertension	1.04	0.69 – 1.56	0.84
Ischemic Heart Disease	1.72	1.12 – 2.65	**0.013**
Heart Failure	1.62	1.05 – 2.50	**0.027**
Malignancy	1.30	0.66 – 2.59	0.44
Pulmonary Hypertension	0.91	0.58 – 1.42	0.69
Systolic Pulmonary Artery Pressure (mmHg)	1.00	0.98 – 1.01	0.97
Ejection Fraction (%)	0.99	0.95 – 1.04	0.87
Six minutes walking distance (meter)	0.99	0.99 – 1.000	**0.025**
Pulmonary function test			
FVC (lt)	0.86	0.62 – 1.19	0.36
FVC (%)	0.98	0.96 – 0.99	**0.031**
FEV1 (lt)	0.90	0.68 – 1.18	0.46
FEV1 (%)	0.99	0.97 – 1.003	0.14
DLCO (ml/min/mmHg)	0.91	0.85 – 0.98	**0.015**
DLCO (%)	0.97	0.94 – 0.99	**0.013**
Nintedanib (vs. pirfenidone)	1.22	0.79 – 1.88	0.35
GAP Score			
Low risk	1.00	Ref	
Intermediate risk	3.93	0.54 – 28.60	0.17
High risk	4.98	0.69 – 35.95	0.11
Pulmonary Fibrosis Score ≥ 150	1.54	1.50 – 2.27	**0.027**

(HR = 0.99, 95% CI: 0.996–0.999, p = 0.049), a Pulmonary Fibrosis Score ≥150 (HR = 1.86, 95% CI: 1.07–3.22, p = 0.026), and the presence of heart failure (HR = 2.24, 95% CI: 1.18–4.26, p = 0.014) as independent predictors of mortality (Table 3).

Patients who were treated with nintedanib and pirfenidone were compared with Kaplan-Meier survival curves after adjusting for these independent predictors. No significant difference was detected between adjusted survival curves of nintedanib and pirfenidone group (p=0.4) (Figure 2).

Table 3. Multivariate Cox regression analyses for independent predictors of mortality

Variable	HR	CI (95%)	p value
Six minutes walking test (meter)	0.99	0.996 – 0999	**0.049**
Pulmonary Fibrosis Score ≥ 150	1.86	1.07 – 3.22	**0.026**
Heart Failure	2.24	1.18 – 4.26	**0.014**
GAP Score			
Low risk	1.00	Ref	0.75
Intermediate risk	0.45	0.60 – 3.53	0.455
High risk	0.45	0.59 – 3.56	0.456

Discussion

In this study, we aimed to compare the impacts of nintedanib and pirfenidone on mortality and to identify predictors of mortality in a large cohort of patients diagnosed with advanced-stage idiopathic pulmonary fibrosis. Our analysis revealed that the factors associated with an increased mortality were found to be shorter six-minute walking test distance, a pulmonary fibrosis score ≥150, and the presence of

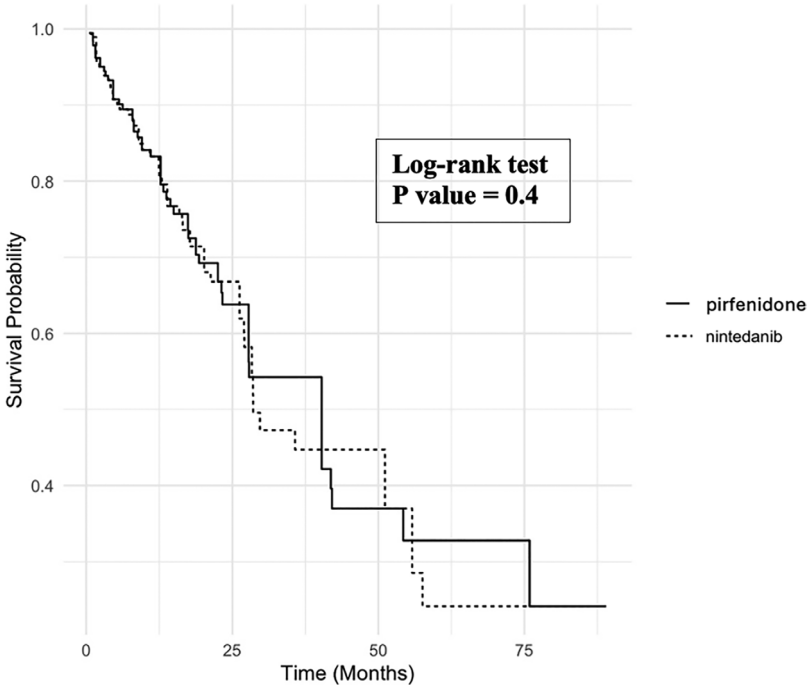

Figure 2. Comparing adjusted survival curves of patients using pirfenidone and nintedanib using log rank analysis.

heart failure. Kaplan-Meier survival curves, adjusted for the identified independent predictors, demonstrated no significant survival advantage between patients treated with pirfenidone and those treated with nintedanib. The GAP score is a commonly used prognostic tool in patients with idiopathic pulmonary fibrosis; however, its predictive role may be diminished in advanced-stage patients. This is because patients with low FVC and DLCO values are grouped similarly in the GAP score's physiological parameters, while the predictive power of the remaining parameters (gender, age) is reduced (17). Therefore, instead of comparing drugs by adjusting for GAP score, our study aimed to adjust for predictors specifically identified in advanced-stage IPF patients. Independent predictors including pulmonary fibrosis score ≥ 150, six-minute walking test and heart failure were used to adjust the groups. When adjusted curve analysis was planned based on these values, the efficacy of nintedanib and pirfenidone was found to be similar. Existing studies generally exclude patients with advanced disease (7,8). However, a few studies have included these patients. The INPULSIS-ON study, conducted on patients who participated in the INPULSIS trial, found that the efficacy of nintedanib, as measured by the absolute change in FVC at week 48, was similar in both advanced-stage (FVC <50%) and non-advanced stage IPF. However, the cohort of patients in the advanced group (n=41) was relatively small (9). In a 2020 study conducted on Korean patients to evaluate the efficacy of pirfenidone compared to placebo, the drug's effectiveness was found to be similar in both advanced-stage (FVC <50% and DLCO <35%) and non-advanced-stage IPF (10). However, the study's interpretation was limited due to the absence of a control group and a relatively small number of advanced-stage patients (n=39). Additionally, the study utilized a relatively lower dosage of pirfenidone (1800 mg/day) and reported a high proportion of patients who discontinued treatment, which further limits the clinical outcome assessment. When evaluating the data of patients referred to the transplant center, antifibrotic treatment in patients with severe physiologic impairment was reported to be associated with improved outcomes (11). However, the generalizability of this data is limited because the patients referred to the transplant center were more severe cases. While these studies do not provide strong evidence, they suggest that antifibrotic treatments may be effective in severe patient populations. Studies comparing pirfenidone and nintedanib, irrespective of disease severity, have

shown similar efficacy for these treatments (5,21). Given that advanced-stage patients are more likely to experience potential drug side effects, the choice of medication becomes increasingly critical (10). Our study, which found similar rates of drug discontinuation due to side effects, contributes valuable insights to the literature by demonstrating comparable efficacy of antifibrotic treatments in advanced-stage patients. Our study was limited by its single-center and retrospective nature. Despite the patients having switched medications due to various side effects, since these side effects emerged rapidly, the initial medication was used for a very short period. Consequently, only patients who had used the altered medications for at least one year were included in the study. Additionally, the fact that not all advanced-stage patients in our country receive treatment approval from the Health Ministry may have introduced selection bias. On the other hand, the fibrosis scores of the patients were evaluated by two radiologists with expertise in this field, and a high level of agreement (intraclass correlation) was found between them. To the best of our knowledge, our study is the first to compare antifibrotic therapies in a large cohort of patients with advanced-stage IPF.

Conclusion

In our study, we found that there was no significant difference in mortality between advanced-stage idiopathic pulmonary fibrosis patients treated with nintedanib and those treated with pirfenidone. Given the high mortality in this group, it is important to include them in clinical trials to better understand treatment effects.

Ethical Approval: We performed a retrospective cohort study at Yedikule Chest Disease and Chest Surgery Training and Research Hospital, University of Health Sciences, Istanbul, Turkey. Our study was conducted in line with the Declaration of Helsinki tenets, and our institutional ethics committee approved it (approval protocol number: 24/596).

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article.

Authors' Contributions: G.D. conceptualized the study and drafted the manuscript. D.A.Y. and C.S. contributed to data analysis. N.C. and U.E. supported imaging evaluations as radiologists. B.D. and A.E. assisted in data collection. C.S. supervised the overall project and provided final approval. All authors read and approved the final manuscript.

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