An Investigation on Administration of Medicines and Survival in Patients with Idiopathic Pulmonary Fibrosis Treated with Nintedanib or Pirfenidone

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Research Article

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Abstract

**Background:** Idiopathic pulmonary fibrosis is a progressive and fatal lung disease that lacks effective therapeutics. Treatment with pirfenidone or nintedanib is recommended for patients to delay the progression of the disease. Anti-fibrosis drugs may cause adverse reactions, even interrupt the treatment, affecting the disease's progress.

**Objective:** To investigate the current situation and adverse reactions of using pirfenidone and nintedanib in patients with idiopathic pulmonary fibrosis.

**Methods:** We recruited patients with idiopathic pulmonary fibrosis who were treated with pirfenidone or nintedanib in China-Japan Friendship Hospital from February 2017 to February 2022. Conduct an investigation of the medication situation, adverse reactions and survival of patients while taking medications.

**Results:** A total of 303 patients with idiopathic pulmonary fibrosis were enrolled in the study, including 205 patients received pirfenidone and 98 patients received nintedanib. Baseline data between the two groups were not significantly different. Patients treated with nintedanib had a higher overall discontinuation rate than those treated with pirfenidone (61.22 vs 32.68%, \( P<0.001 \)). The primary reason of patients discontinued treatment across all patient groups is medication-related adverse effects. Compared to pirfenidone, nintedanib had a significantly higher rate of treatment discontinuation due to adverse events (48.98% vs 27.80%, \( P<0.001 \)). Both drugs have digestive system side effects, diarrhea is the most common. Pirfenidone was associated with a higher rate of extra-digestive adverse effects than nintedanib. Survival was not significantly different between the two drugs, and the use of pirfenidone above 1200 mg/day did not confer significant survival benefits.

**Conclusion:** Gastrointestinal adverse effects are the main adverse effects that arise from performing antifibrotic therapy. Patients taking nintedanib were more likely to interrupt their treatment due to gastrointestinal side effects, while patients taking pirfenidone had more extra gastrointestinal side effects. It is possible that patients might benefit from modifying dosages of antifibrotic drugs according to their own tolerance, but taking more than 1200 mg/day of pirfenidone did not seem to produce any significant improvements in patient survival time.

1. **Introduction**

The idiopathic pulmonary fibrosis (IPF) is a severe and lethal interstitial lung disease (ILD) characterized by progressive dyspnea and distorted lung function (1, 2). The prognosis for patients diagnosed with IPF is poor, with a median survival time of 3–5 years (3). In spite of some breakthroughs in treatment in recent years, most patients with IPF eventually succumb to respiratory failure. Pirfenidone and nintedanib are currently the only FDA-approved drugs for the treatment of IPF, which may slow its progression (4). In 2018 and 2022, the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and the Latin American Thoracic Society (ALAT) updated their
diagnostic guidelines for IPF, both guidelines recommend using antifibrotic agents for IPF patients (5, 6). In China, pirfenidone and nintedanib were approved for marketing by the Chinese National Drug Administration in 2013 and 2017, respectively, and are gradually being included in the reimbursement of basic medical insurance in recent years.

Pirfenidone, an inhibitor of multiple cytokines including transforming growth factor-beta (TGF-β), platelet derived growth factor receptor (PDGFR), and Tumor necrosis factor-β (TNF-β), which has several anti-inflammatory and anti-fibrotic effects, including inhibition of collagen synthesis, downregulation of TGF-β, and reduction in fibroblast proliferation (7, 8). Pirfenidone has shown excellent efficacy in alleviating disease progression, improving lung function, and prolonging progression-free survival in patients with fibrotic interstitial lung diseases, including idiopathic pulmonary fibrosis, according to numerous clinical trials (9, 10, 11). Pirfenidone has a high level of safety concerns as one of the few clinical antifibrotic drugs. It is common to experience nausea, rash, fatigue, diarrhea, and abnormal liver function after taking medication. Although most side effects are usually mild to moderate and reversible with no clinically significant consequences, they often lead to dose reduction or interruption of therapy in patients, or even permanent discontinuation in some cases (12, 13). In addition, these conclusions are backed up by studies conducted in the real world (14, 15, 16).

As a small molecule tyrosine kinase inhibitor, nintedanib targets the receptors of fibrosis-related kinases, including PDGFR, fibroblast growth factor receptor (FGFR), vascular endothelial growth factor receptor (VEGFR), and TGF-β, thus inhibiting fibroblast proliferation, migration, myofibroblast transformation, and extracellular matrix (ECM) synthesis (17, 18). There have been multiple clinical trials showing that nintedanib is effective against many types of fibrotic interstitial lung diseases (19, 20, 21, 22). There are many potential side effects associated with medications, including diarrhea, nausea, vomiting, and abnormal liver function. It is important to note that due to the increased bleeding risk associated with VEGFR inhibitors, patients with anticoagulation or cardiovascular disease should use nintedanib with caution, even if there is no clear evidence that this would greatly affect the patient [17, 18]. Additionally, nintedanib should not be used in patients with moderate or severe liver disease (Child-Pugh B and C), and the dose should be adjusted accordingly in patients with mild hepatic dysfunction (Child-Pugh A), also, liver enzymes should be monitored regularly during medication administration (23). Similarly, these conclusions are proved by studies conducted in the real world (24, 25, 26).

As pirfenidone and nintedanib began to be widely used in patients with various fibrotic interstitial lung diseases including IPF, it is highly necessary to evaluate drug administration and drug-related adverse effects in the real world. Although pirfenidone and nintedanib are widely used in China as the main antifibrotic drugs, there is still a lack of data on the use and discontinuation of the two antifibrotic drugs in Chinese patients, and their impact on patient outcomes. Our study evaluated the clinical usage of the two drugs by comparing the clinical background, drug use, adverse effects in IPF patients.

2. Materials And Methods
2.1 Study population

Our study recruited patients with IPF who were treated with pirfenidone or nintedanib between February 2017 and February 2022 in China-Japan Friendship Hospital, Chaoyang District, China. Inclusion criteria were as follows: (1) adult patients (Over 18 years old) with the diagnosis of IPF, which was diagnosed after multidisciplinary team discussion, according to the IPF consensus criteria of the ATS/ERS/JRS/LATA (5). (2) Patients were treated with antifibrotic drugs. Under the guidance of a physician, the patient agreed to normative antifibrotic treatment with nintedanib and pirfenidone as well as regular follow-up. In total, 338 patients were initially recruited, and 35 patients were excluded due to these reasons. 9 patients withdrew from the study for personal reasons. 4 patients were excluded because of the combination of pirfenidone with nintedanib or change drugs during the observation period. 22 patients were excluded for missing baseline data such as lung function or blood gas analysis. Finally, our study included 205 patients with idiopathic pulmonary fibrosis treated with pirfenidone and 98 patients treated with nintedanib, respectively. The flow diagram illustrates recruitment into the study (Fig. 1). In accordance with the Declaration of Helsinki, the study protocol was approved by the China Japan Friendship Hospital Ethics Committee.

2.2 Drug dose

Initially, patients are advised to take 600 mg/d of pirfenidone, which should be increased by 300-600mg per 1–2 weeks until 1800 mg/d. For nintedanib, patients are advised to take 300 mg/d of the drug. Antifibrotic drugs were allowed to be adjusted according to patient tolerance, since patients have variable tolerance and even low doses antifibrotic drugs can still be beneficial.

2.3 Follow-up and data collection

Until July 2022, the clinic followed up with patients through regular clinical visits every three to six months or according to clinical requirements. Patients who were unable to attend the clinic were contacted by telephone. During the face-to-face visit, clinical symptoms, laboratory examination, HRCT, and pulmonary function were monitored depending on the follow-up protocol. In order to calculate the severity of IPF, a multidimensional index and staging system were used: the Gender-Age-Physiology index (GAP) (27). Meanwhile, disease severity was assessed using the composite physiologic index (CPI), a simple clinical prediction model integrating lung function with HRCT imaging features, which corrects for the possible presence of emphysema, in order to reflects a patient’s true degree of lung fibrosis (28). CPI was calculated using the formula: CPI = 91 - (0.65*DLCO % predicted) - (0.53*FVC % predicted) + (0.34*FEV1% predicted).

2.4 Statistical analysis

Analysis of the data was performed with SPSS version 26.0 (SPSS, Chicago, IL, USA). Statistical analyses were performed using Chi square or Fisher exact tests for categorical data, and Mann-Whitney U tests for continuous data. Survival was estimated using the Kaplan-Meier method, and comparison was
conducted using the log-rank test or Gehan-Breslow-Wilcoxon test. P > 0.05 was considered statistically significant for all comparisons.

3. Results

From 2017 to 2022, a total of 303 IPF patients used antifibrotic drugs were included in our study. As shown in Table 1, the demographics, clinical characteristics, and laboratory results of the participants were summarized. Of the 303 patients, 205 (67.7%) took pirfenidone and 98 (32.3%) took nintedanib. 276 (91.1%) were male. The mean (SD) age was 65.2 (8.6) years. The mean of the percent predicted forced vital capacity (%FVC) were 82.33% and the percent predicted diffusing capacity of carbon monoxide (%DLCO) were 54.65%. No significant differences were found between patients taking pirfenidone or nintedanib as far as oxygenation index, 6-minute walk distance, or serum KL-6. In terms of GAP stage and CPI score, there were no significant differences between the two groups.

The dosage and frequency of pirfenidone and nintedanib are different. For pirfenidone, a therapeutic dose of 600 mg per day is generally recommended within the first two weeks, increased 300–600 mg per 1-2 weeks if intolerable side effects did not occur, and so on, until increased to 1800 mg per day and taken chronically. The initial administered dose of nintedanib is 300 mg daily, and this dose is recommended as a long-term oral dose. In our study, the mean initial doses of pirfenidone and nintedanib were 766.83 mg and 290.82 mg, the mean doses at which side effects occurred while taking drugs were 1476.59 mg and 298.47 mg, and the mean final doses of two drugs were 1239.5 mg and 278.57 mg, respectively.

3.1 Treatment discontinuation

According to our study, patients treated with nintedanib had a higher overall discontinuation rate than those treated with pirfenidone (61.22 vs 32.68%, P < 0.001). We analyzed the reasons why patients interrupt antifibrotic treatment. Medication-related adverse effects were the primary reason patients discontinued treatment across all patient groups, and compared to pirfenidone, nintedanib had a higher rate of treatment discontinuation due to adverse events (48.98% vs 27.80%, P < 0.001). Gastrointestinal adverse events were responsible for nearly half of patients taking nintedanib (46.94%) and a quarter of patients taking pirfenidone (24.88%) who interrupted medication. Financial reasons were common reason for discontinuation of patients using nintedanib rather than pirfenidone (9.18% vs 2.93%, P < 0.05). There was no significant difference between the two drugs in the percentage of patients who discontinued because of other factors (Fig. 2).

In order to further analyze the factors that affect the continuity of medication, we counted the duration of the discontinuation of the two different medications. More than half of discontinuation behaviors occurred within 1 year of treatment initiation, accounting for 74.63% versus 68.33% of the total number of discontinuations for the pirfenidone and nintedanib, respectively (Fig. 3). In patients taking pirfenidone, over one-third of discontinuation behaviors occurred during 30–90 days after starting the medication.
Patients on nintedanib demonstrated a more diffuse distribution of time to discontinuation, and their discontinuation rate steadily increased over time. (Fig. 4).

Considering that more than half of patients discontinued both medications within one year of starting them, we compared the reasons for discontinuation within the first year. There was a greater number of patients discontinuing treatment due to gastrointestinal adverse effects in nintedanib group than in pirfenidone group, but no statistically significant differences were found between the two groups (85.37% vs 68.0%, P = 0.310). There was no significant difference in the proportion of discontinuations due to other reasons between the two drugs (Fig. 5).

### 3.2 Adverse effects

In most cases, antifibrotic therapy is associated with multiple adverse effects, the majority of which are gastrointestinal. Diarrhea (21.95%), rash (17.56%), acid reflux (13.66%), anorexia (12.68%), and nausea (11.71%) were the most frequently reported adverse effects of pirfenidone. Meanwhile, the most common side effects of nintedanib were anorexia (39.80%), diarrhea (36.73%), nausea (32.66%), abnormal liver function tests (15.31%), and acid reflux (14.29%). The presence of adverse effects, particularly gastrointestinal ones, is main reasons for patients discontinuing their medication. Patients who discontinued because of diarrhea were significantly more likely to take nintedanib (27.55% vs 12.20%, P = 0.002). As compared to pirfenidone, patients using nintedanib discontinued more frequently as a result of abnormal liver function (9.18% vs 2.44%, P = 0.016). Pirfenidone users were more likely to experience skin rash / itching, but there was no statistically significant difference in the rate of discontinuations due to this side effect. The loss of appetite and fatigue are common side effects, but few patients discontinue their medication because of these side effects (Table 2).

### 3.3 Survival time

The survival time was determined with Kaplan-Meier analysis unless otherwise indicated. As most patients starting taking nintedanib after 2019, we conducted a Kaplan-Meier analysis on patients within the last three years. It did not appear that the survival of patients with idiopathic pulmonary fibrosis treated with pirfenidone and those treated with nintedanib differed significantly (Fig. 6). Median survival is not shown because survival was greater than 50% in both groups. Even after Kaplan-Meier analysis was applied to all included patients, no significant difference in survival could be found between the two groups (Fig. 7). As pirfenidone was commonly taken at doses between 1200 mg / day, 1500 mg / day, or 1800 mg / day by the majority of patients, survival analyses were performed on patients taking these doses. The Kaplan-Meier analysis showed no significant difference between patients taking 1200 mg/d and those taking more doses. (Fig. 8)

To determine whether medication length affects patient outcomes, survival analyses were conducted in patients receiving different medication lengths. Among patients who adhered to medication for more than 1 month, nintedanib had a weak survival advantage (Gehan-Breslow-Wilcoxon test, p = 0.039) (Fig. 9). The two drugs, however, did not appear to differ significantly in survival among patients who had taken them for at least 3, 6, and 12 months (Fig. 10–12).
4. Discussion

In our current study, the discontinuation rate of pirfenidone and nintedanib was 61% and 32%, respectively. Antifibrotic treatment is associated with multiple adverse reactions, of which gastrointestinal problems are the most common and significant reasons for discontinuing treatment.

4.1 Pirfenidone

In general, pirfenidone should be taken at 600 mg per day for the first few weeks, and then gradually increased to 1800 mg. Based on our findings, patients with pirfenidone used a dose of around 600mg as a starting dose. When the dose was increased above 1500mg daily, most patients experienced significant side effects (digestive tract reactions, rash, light allergies), and patients were maintained on a dose of around 1200mg at the end. Despite the fact that co-administration of drugs with food and anti-acid treatment can relieve the patients' post-medication discomfort to some extent, about half of the patients still interrupt the treatment due to intolerable side effects, which is consistent with the results of a post-marketing surveillance study in Japanese (29).

Death / lung transplantation was an important cause for withdrawal from our study in patients taking pirfenidone, we believe is related to the inclusion of a larger number of patients taking pirfenidone in the early phase of the study. Due to the fact that pirfenidone was included in basic medical insurance earlier than nintedanib in most regions of China, most patients could only be able to choose pirfenidone before 2019, including many patients who were in the end stage of the disease. Furthermore, this explains why patients using nintedanib was discontinued more frequently for economic reasons.

Pirfenidone's flexibility in dosing is an important advantage over nintedanib. When patients take pirfenidone at doses up to 1500 mg (500 mg, three times a day), they often experience significant adverse effects. To maximize therapeutic effect, tapering from intolerable dose to about 1200 mg (400 mg, three times daily) is an effective method of extending treatment. At this stage, many patients who are unable to tolerate doses below 1200 mg/d will usually discontinue medication, which explains why one-third of discontinuation behaviors occurred within three months of first dosing pirfenidone in our study. Based on Kaplan Meier analysis, there were no significant differences between 1200 mg per day and 1500 mg per day or 1800 mg per day in our study. Previous studies have proved that low-dose pirfenidone still improves patient survival and lung function measures with fewer side effects than higher doses, which explains patients taking pirfenidone are less likely to discontinue due to adverse effects (16, 30, 31). To maximize drug effects, patients can adjust their drug dosage according to their circumstances to find a balance between therapeutic efficacy and side effects.

4.2 Nintedanib

The recommended dose of nintedanib is 300 mg daily. In our study, patients' starting dosages averaged 289.53 mg/day, and final dosages averaged 282.56 mg/day. The rate of discontinuations for nintedanib due to adverse reactions has been reported as less than 15% in the INPULSIS trial (20), however, this data
may differ according to race. Based on the study from INPULSIS-ON, nintedanib discontinuations among Asians were as high as 50% (32). Furthermore, Japanese studies have shown that almost half of patients treated with nintedanib stopped their usual dose within six months (33). The results confirm our findings that Asian populations were more likely to discontinue nintedanib than pirfenidone due to side effects.

Based on the present study, side effects caused by nintedanib, especially digestive system side effects, should be seriously considered. The most frequent side effect is diarrhea, which may be relieved by reducing the drug dosage, by using antidiarrheal medications, or by using gut modifiers, in order to prolong antifibrotic therapy (34, 35). Additionally, patients treated with nintedanib whose body mass index was below 21.6 were more likely to suffer gastrointestinal side effects (36). The possibility of reversible hepatic dysfunction is also common, and those with a lower surface area and BMI are more likely to experience it. Fortunately, the abnormal liver function recovered spontaneously once the medication was discontinued (37). According to results from the INPULSIS-ON trial, taking a lower dose of nintedanib had no significant impact on patients' annual decline rates in FVC, therefore, it is feasible to reduce the dose of medication taken in order to ensure continuity of treatment (38). Regrettably, due to the drug specification, tapering nintedanib was more difficult than pirfenidone, many patients might have therefore decided not to try a step-by-step reduction but to discontinue their medications directly. In summary, to provide long-term sustained anti-fibrosis treatment, drugs must be used in combination with individual differences like race and weight. It is paradoxical, but very important, to balance the doses of antifibrotic drugs used while maintaining therapeutic continuity.

4.3 Limitations

This study suffers from several limitations. As a first point, this is an observational study. With the limited number of antifibrotic drugs currently available and the noticeable side effects associated with these drugs, a large-scale, multicenter, prospective study is highly necessary to evaluate and manage adverse effects of antifibrotic drugs in order to reduce discontinuation of treatment. Secondly, the present study was conducted in a single center, and the participants all came from the Chinese national respiratory center (China-Japan Friendship Hospital). In spite of the fact that patients from a nationwide cohort were included in the study, we believe a rigorous multicenter study would provide more accurate results. A notable feature of this study is that the baseline characteristics of the patients were similar to those reported in previous studies, which to some extent indicates its high representativeness (32, 39, 40). Also, other real-world studies have shown similar outcomes for both drugs in terms of lung function data and survival times for patients [29–31]. A third problem with this study was that fewer patients were using nintedanib than pirfenidone, and the observation duration was not the same for both drugs. The reason for this is that nintedanib is covered by national basic medical insurance later than pirfenidone, and nintedanib was released later to market in China. A larger number of patients using nintedanib should be included in future studies in order to refine the findings.

5. Conclusion
In general, multiple adverse effects occur during antifibrotic therapy, which is an important reason why patients discontinue treatment. In patients taking nintedanib, gastrointestinal side effects caused them to interrupt their treatment more often, while in patients taking pirfenidone, extra gastrointestinal side effects were more common. Patients may benefit from adjusting their antifibrotic medications, dosage, and active management of side effects in accordance with their own tolerance, but taking more than 1200 mg/day of pirfenidone did not confer a significant benefit on patient survival time, and the survival benefits of the two drugs were not significantly different for patients on long-term medication.

Declarations

Ethics statements

In accordance with the Declaration of Helsinki, the study protocol was approved by the China Japan Friendship Hospital Ethics Committee. Written informed consent was obtained from all participants prior to the enrollment of this study.

Availability of data and materials

The raw data required to reproduce the above findings will be shared on reasonable request to the corresponding author.

Competing interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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CRediT authorship contribution statement

Ruiming Zhao Contribute to the design, data collection and analysis, the writing and revision of the manuscript. Bingbing Xie Contribute to design, data collection and analysis, and revision of the manuscript. Xin Wang Contribute to the data collection and analysis. Yanhong Ren contributed to the data collection and analysis. Validation. Huaping Dai and Chen Wang contributed to the conception, design of the study, the data collection and analysis, the revision of the manuscript, and the final approval of the version to be published. All authors have read and approved the final manuscript prior to submission.

Acknowledgements
References


Table 1. Clinical characteristics of idiopathic pulmonary fibrosis patients treated with pirfenidone or nintedanib

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients (n=303)</th>
<th>Pirfenidone (n=205)</th>
<th>Nintedanib (n=98)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>276 (91.1)</td>
<td>190 (92.7)</td>
<td>86 (87.8)</td>
<td>0.159</td>
</tr>
<tr>
<td>Women</td>
<td>27 (8.9)</td>
<td>15 (7.3)</td>
<td>12 (12.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>65.2 (8.60)</td>
<td>65.3 (8.38)</td>
<td>65.0 (9.07)</td>
<td>0.775</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>21.33 (3.10)</td>
<td>21.41 (3.20)</td>
<td>21.18 (2.87)</td>
<td>0.544</td>
</tr>
<tr>
<td><strong>BSA, m²</strong></td>
<td>1.79 (0.16)</td>
<td>1.79 (0.16)</td>
<td>1.80 (0.16)</td>
<td>0.512</td>
</tr>
<tr>
<td><strong>Physiological Function and Laboratory Tests</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>FVC, L</strong></td>
<td>2.92 (0.89)</td>
<td>2.87 (0.91)</td>
<td>3.03 (0.87)</td>
<td>0.148</td>
</tr>
<tr>
<td><strong>FVC%pred, %</strong></td>
<td>82.33 (20.80)</td>
<td>80.82 (21.03)</td>
<td>85.5 (20.06)</td>
<td>0.067</td>
</tr>
<tr>
<td><strong>FEV₁%pred, %</strong></td>
<td>84.62 (20.46)</td>
<td>83.17 (20.81)</td>
<td>87.67 (19.46)</td>
<td>0.073</td>
</tr>
<tr>
<td><strong>FEV₁/FVC, %</strong></td>
<td>81.51 (7.68)</td>
<td>81.36 (8.21)</td>
<td>81.84 (6.45)</td>
<td>0.606</td>
</tr>
<tr>
<td><strong>DLCOSB%pred, %</strong></td>
<td>54.65 (17.56)</td>
<td>53.20 (17.21)</td>
<td>56.09 (18.32)</td>
<td>0.208</td>
</tr>
<tr>
<td><strong>PaO₂/FiO₂</strong></td>
<td>407.55 (68.49)</td>
<td>409.18 (71.38)</td>
<td>404.14 (62.24)</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>6MWD, m</strong></td>
<td>485.53 (105.88)</td>
<td>476.81 (94.10)</td>
<td>501.58 (123.71)</td>
<td>0.118</td>
</tr>
<tr>
<td><strong>KL-6, U/ml</strong></td>
<td>1361.69 (1252.91)</td>
<td>1514.98 (1461.54)</td>
<td>1102.27 (739.71)</td>
<td>0.185</td>
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<tr>
<td><strong>Stage Evaluation</strong></td>
<td></td>
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<tr>
<td>GAP staging system</td>
<td></td>
<td></td>
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<td>0.547</td>
</tr>
<tr>
<td>I</td>
<td>173 (57.10)</td>
<td>113 (55.12)</td>
<td>60 (61.22)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>106 (34.98)</td>
<td>76 (37.07)</td>
<td>30 (30.62)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>24 (7.92)</td>
<td>16 (7.81)</td>
<td>8 (8.16)</td>
<td></td>
</tr>
<tr>
<td>CPI</td>
<td>40.95 (14.14)</td>
<td>41.53 (14.07)</td>
<td>39.72 (14.27)</td>
<td>0.296</td>
</tr>
<tr>
<td>CPI score</td>
<td></td>
<td></td>
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<td>0.274</td>
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<tr>
<td></td>
<td>≥41</td>
<td>41</td>
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<tr>
<td></td>
<td>147 (48.51)</td>
<td>95 (46.34)</td>
<td>52 (53.06)</td>
<td></td>
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<tr>
<td></td>
<td>156 (51.49)</td>
<td>110 (53.66)</td>
<td>46 (46.94)</td>
<td></td>
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</table>

**Medication Use**

<table>
<thead>
<tr>
<th></th>
<th>Pirfenidone (n=205)</th>
<th>Nintedanib (n=98)</th>
<th>p Value</th>
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</thead>
<tbody>
<tr>
<td>Initial amount, mg</td>
<td>766.83 (292.29)</td>
<td>290.82 (35.96)</td>
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<tr>
<td>Amount with side effects, mg</td>
<td>1476.59 (366.98)</td>
<td>298.47 (15.07)</td>
<td></td>
</tr>
<tr>
<td>Final amount, mg</td>
<td>1239.51 (321.51)</td>
<td>278.57 (52.49)</td>
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<tr>
<td>Medication periods, days</td>
<td>593 (478)</td>
<td>357 (259)</td>
<td></td>
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</tbody>
</table>

Note: Data are expressed as mean (SD) or count (percentage) where appropriate.

**Table 2** Impact of adverse event on patient treated with pirfenidone or nintedanib

<table>
<thead>
<tr>
<th></th>
<th>Pirfenidone (n=205)</th>
<th>Nintedanib (n=98)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrhea</strong></td>
<td>45 (21.95)</td>
<td>25 (12.20)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>36 (36.73)</td>
<td>27 (27.55)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25 (12.20)</td>
<td>27 (27.55)</td>
<td></td>
</tr>
<tr>
<td><strong>Anorexia</strong></td>
<td>26 (12.68)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>39 (39.80)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td><strong>Acid reflux/Stomach discomfort</strong></td>
<td>28 (13.66)</td>
<td>12 (5.85)</td>
<td>0.596</td>
</tr>
<tr>
<td></td>
<td>14 (14.29)</td>
<td>4 (4.08)</td>
<td></td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>24 (11.71)</td>
<td>9 (4.39)</td>
<td>0.576</td>
</tr>
<tr>
<td></td>
<td>32 (32.66)</td>
<td>6 (6.12)</td>
<td></td>
</tr>
<tr>
<td><strong>Liver disorder</strong></td>
<td>5 (2.44)</td>
<td>5 (2.44)</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>15 (15.31)</td>
<td>9 (9.18)</td>
<td></td>
</tr>
<tr>
<td><strong>Rash/Pruritus</strong></td>
<td>36 (17.56)</td>
<td>4 (1.95)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>8 (8.16)</td>
<td>1 (1.02)</td>
<td></td>
</tr>
<tr>
<td><strong>Fatigue and lassitude</strong></td>
<td>16 (7.80)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>8 (8.16)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>4 (1.96)</td>
<td>2 (0.98)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>6 (6.12)</td>
<td>1 (1.02)</td>
<td></td>
</tr>
</tbody>
</table>

**Figures**
Figure 1

Flow diagram to show recruitment into the study.
Figure 2

Percentage of drug discontinuation caused by different reasons in total patients. abbreviations: GI-AE=gastrointestinal adverse events; EGI-AE=extra gastrointestinal adverse events; FR=financial reasons; Others: two patients taking pirfenidone and one taking nintedanib, respectively, discontinued for personal reasons, and two patients each taking two medications discontinued for reasons that could not purchase medicine locally.
Figure 3

Comparison of discontinuation rates over time.
Figure 4

Comparison of discontinuation rates over time within one year.
Figure 5

Percentage of patients discontinuing for different reasons within the first year.

abbreviations: GI-AE=gastrointestinal adverse events; EGI-AE=extra gastrointestinal adverse events; FR=financial reasons; Others: two patients taking pirfenidone and one taking nintedanib, respectively, discontinued for personal reasons, and two patients taking pirfenidone discontinued for reasons that could not purchase medicine locally.

![Graph showing survival rates and P value](image)

**P value (log-rank) = 0.064**

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pirfenidone</td>
<td>109 77 54 36 31 24 12</td>
</tr>
<tr>
<td>Nintedanib</td>
<td>91 70 37 15 6 3 1</td>
</tr>
</tbody>
</table>

Figure 6

Kaplan–Meier survival analysis of patients received treatment of pirfenidone and nintedanib during 2019 to 2022.
Figure 7

Kaplan–Meier survival analysis of patients received treatment of pirfenidone and nintedanib

<table>
<thead>
<tr>
<th>Months</th>
<th>Pirfenidone</th>
<th>Nintedanib</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>205</td>
<td>98</td>
</tr>
<tr>
<td>12</td>
<td>163</td>
<td>65</td>
</tr>
<tr>
<td>24</td>
<td>108</td>
<td>15</td>
</tr>
<tr>
<td>36</td>
<td>53</td>
<td>3</td>
</tr>
<tr>
<td>48</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>60</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

P value (log-rank) = 0.102
Figure 8

Kaplan–Meier survival analysis of patients treated with different doses of pirfenidone
Figure 9

Kaplan–Meier survival analysis of patients received treatment of pirfenidone and nintedanib over 1 month.
Figure 10

Kaplan–Meier survival analysis of patients received treatment of pirfenidone and nintedanib over 3 months.
Figure 11

Kaplan-Meier survival analysis of patients received treatment of pirfenidone and nintedanib over 6 months.
Figure 12

Kaplan–Meier survival analysis of patients received treatment of pirfenidone and nintedanib over 12 months.