The role of Pirfenidone in the treatment of interstitial pneumonia with autoimmune features

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Research

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Abstract

Rationale: No study indicated whether pirfenidone is appropriate for treatment of Interstitial pneumonia with autoimmune features (IPAF) patients.

Objective: To evaluate the efficacy and safety of pirfenidone in the treatment of IPAF.

Methods: The clinical data of 184 patients who met the diagnostic criteria of IPAF was selected. Those patients were assigned to pirfenidone treatment group (n=81) and control group (n=103). The baseline data and diagnostic characteristics of patients were retrospectively collected. Pulmonary function and prednisone dose were analyzed by mix-effect model.

Results: 1. Baseline data: Forced vital capacity (FVC%, $P< 0.001$) and diffusion capacity of the lung for carbon monoxide (DLCO%, $P= 0.003$) of predicted values in the pirfenidone group were lower than those in the control group. 2. Diagnostic characteristics: There was no significant difference of diagnostic characteristics between two groups. 3. Therapeutic evaluation: The volume of FVC in pirfenidone group was increased by 0.0390 L/year, while that was decreased by 0.0769 L/year in the control group ($P=0.038$). 4. Subgroup analysis: Pirfenidone with dosage > 600 mg/day ($P = 0.010$) and medication course of treatment longer than 12 months ($P = 0.007$) showed superior therapeutic effects. 5. Dose of prednisone: During the period of 12-40 months, prednisone dose was reduced by 6.27 mg per day in pirfenidone group, compared with control group. 6. Side effects: A total of 17 patients (19.32%) experienced side effects after taking pirfenidone.

Conclusion: Pirfenidone (600-1800 mg/day) can improve FVC of pulmonary function and help to reduce prednisone dose in IPAF patients. It contains controllable side effects.

Introduction

Interstitial lung disease (ILD) includes a heterogeneous collection of uncommon disorders that are frequently characterized by progressive decline in lung function and respiratory failure. A significant subset of patients with ILD demonstrates clinical or serological features suggestive of a CTD, but fails to meet established CTD diagnostic criteria. These patients have been labelled interstitial pneumonia with autoimmune features (IPAF), according to a European Respiratory Society/American Thoracic Society research statement [1-2]. This new classification system incorporates not only clinical and serological manifestations of CTD, but also morphological features suggestive of a CTD encountered on high-resolution computed tomography (HRCT), surgical lung biopsy (SLB) and pulmonary function testing (PFTs). IPAF criteria are not diagnostic but criteria useful for classification. Validated classification criteria are considered critical to the interpretation of study findings and comparisons of results between studies [3]. According to previous publications majority of IPAF patients were shown to be female [4], and mean age of its onset is 58-63 years old. Among IPAF patients, 5-12% may develop to definite CTD-ILD [1, 5]. Raynaud's phenomenon and inflammatory arthritis or polyarticular morning stiffness >60 minutes were the most prevalent systemic symptoms [6]. Non-specific interstitial pneumonia (NSIP) is the most

common morphological and pathological pattern of IPAF [7]. Antinuclear antibody (ANA) and rheumatoid factor (RF) are the most frequent autoantibodies in serum of IPAF patients [8]. A number of studies indicated that the prognosis of IPAF outperforms IPF, while that is worse than CTD-ILD [9]. Another study showed that IPAF has a similar prognosis to CTD-ILD [1]. Honeycombing and pulmonary artery enlargement on computed tomography (CT) are independent predictors of poor survival in IPAF [10]. Clinical treatments for patients with IPAF are similar to CTD-ILD [1]. Glucocorticoid is the most important therapeutic drug. Some patients were treated with immunosuppressive agents. Whether IPF-recommended anti-fibrosis drugs are effective for IPAF patients has still remained elusive. The most recent multi-center clinical trials demonstrated that both pirfenidone and Nintedanib can prevent decline of FVC in patients with progressive fibrosing unclassifiable ILD (PF-ILD) [11,12]. Besides, a study found that Nintedanib can slow down the annual rate of FVC decline in patients with systemic sclerosis-associated ILD [13], and some patients with amyopathic dermatomyositis could benefit from pirfenidone [14]. The above-mentioned studies indicated that IPAF patients might benefit from the anti-fibrosis drugs. To verify whether pirfenidone is effective for IPAF, the present study was conducted to explore the efficacy and safety of pirfenidone capsules for the treatment of IPAF, and it was registered in the Chinese Clinical Trial Registry (ChiCTR-IPR-17010813) as well. For this purpose, clinical data of 184 cases with IPAF were collected and retrospectively analyzed. The efficacy and side effects of pirfenidone in the treatment of IPAF were preliminarily evaluated.

Patients And Methods

1. Patients' screening process

A total of 1070 cases of ILD patients diagnosed at Shanghai Pulmonary Hospital (Shanghai, China) from January 2014 to January 2019 were reviewed the electronic medical record data, and made diagnosis by pertinent data retrospectively. The screening process is illustrated in Figure 1. There were totally 242 patients who met IPAF diagnostic criteria [2]. Of the 242 patients, there were 172 with UCTD-ILD, and 70 with idiopathic interstitial pneumonia (IIP) including 4 with biopsy-proven cryptogenic organic pneumonia (COP), 8 with IPF, and 58 with unclassifiable IIP. Following situations were excluded: (1) without follow-up data(n=30); (2) Other complications (n = 15 including any active infection, heart or hepatic or renal impairment); (3) Administration of pirfenidone would be shorter than 3 months (n = 7); (4) The follow-up interval would be longer than 40 months (n = 6). Eventually, 184 cases of IPAF patients were included in the analysis, and those patients were assigned to pirfenidone group (n = 81) and control group (n = 103). The follow-up deadline was January 1, 2019. This study was approved by the Ethics Committee of Shanghai Pulmonary Hospital (Approval No. K17-H1).

2. Diagnostic criteria

The diagnosis of ILD was carried out according to the diagnostic criteria described previously [15, 16]. All patients with CTD-ILD or UCTD-ILD were confirmed by a rheumatologist. The diagnostic criteria for CTD in this study followed the recommendations by the American Rheumatism Association and the American

College of Rheumatology [17-22]. The diagnosis of UCTD was performed according to the diagnostic criteria based on previous reports [1]. All of the patients' data were reviewed retrospectively and the final diagnosis was made by multidisciplinary discussion (MTD) (the group included 3 experienced pulmonologists, 2 rheumatologists, 2 chest radiologists, and 2 pathologists).

3. Data collection

Data were collected by outpatient consulting and inpatient records, including demographic characteristics, body mass index(BMI), past medical history, medication history, smoking history, RFs and autoantibodies (ANA anti-CCP, anti-double stranded DNA, anti-SSA, anti-SSB, anti-RNP, anti-smith, anti-Scl-70, anti-tRNA synthetase), arterial oxygen saturation, pulmonary function, side effects of drugs, etc. Medication history included glucocorticoids, immunosuppressive agents, and pirfenidone (dosage and duration of therapy).

4. High-resolution CT (HRCT) of chest

HRCT image was assessed by two chest imaging specialists, individually, and HRCT diagnosis was carried out according to IPAF imaging characteristics proposed by ERS/ATS guidelines [2], including NSIP, organic pneumonia (OP), and NSIP combined with OP (Figure S1). HRCT image before pirfenidone treatment was compared with that after 3, 6 and 12 months of pirfenidone treatment. The evaluation of HRCT was performed by two chest radiologists separately and gave their evaluation outcomes in four levels (complete remission, partial remission, stabilization and progression). Different outcomes between two chest radiologists were discussed by MTD group until reaching consistent opinion. Evaluation criteria for changes of lesions on CT were as follows: **complete remission**: pulmonary lesions were mainly resolved, leaving only a limited number of fibrotic streaks; **partial remission**: pulmonary lesion were partially resolved, leaving tractive bronchiectasis and fibrotic streaks; **stabilization**: no significant changes in the scope and shape of pulmonary lesions on CT scan of chest; **progression**: fibrotic and exudative lesions were notably increased, including honeycomb, reticular, ground-glass and consolidation lesions.

5. Data Processing

Continuous variables were presented in the form of mean (standard deviation), and categorized variables were expressed in form of frequency (percentage). The difference between the two groups was analyzed by independent sample t-test, chi-square test, and Wilcoxon rank-sum test. All analyses were performed by GraphPad Prism 6 and SPSS 24 software (IBM, Armonk, NY, USA).

FVC% and DLCO% before the pirfenidone treatment were recorded as baseline value, and followed up for 40 months with pirfenidone treatment. The difference between the follow-up value and the baseline value at each time point was further calculated (difference = follow-up value - baseline value), then the differences in FVC absolute value, FVC% and DLCO% between the two groups were compared in a mixed-effect model. Fixed effects included gender, age, baseline FVC% and DLCO%. This method had been

proved reliable in other retrospective studies [23-25]. The prednisone dose and sub-groups analysis were analyzed by the same method. The above-mentioned analysis was carried out by R software.

Results

1. Baseline characteristics of patients

As presented in Table 1, a total of 184 patients with IPAF were enrolled from January 2014 to January 2019. Among them, 81 (44.0%) patients were in the pirfenidone group and 103 (56.0%) patients were in the control group. There were no significant differences in gender, BMI, smoking history, arterial oxygen partial pressure and oxygen saturation. Both FVC% and DLCO% in the pirfenidone group were lower than those in the control group ($P < 0.001$ and $P = 0.003$). 151 (82.1%) patients were treated with oral glucocorticoid, and 13 (7.1%) patients were treated with immunosuppressants. There were no differences in the treatment of glucocorticoid and immunosuppressants between pirfenidone and control group. The mean duration of follow-up was 15.0 months, and no significant difference was observed between the pirfenidone group (14.6 months) and the control group (15.4 months). The range of pirfenidone dose was 600-1800 mg/day, with a median dose of 1492 mg/day. The duration of pirfenidone treatment was 3-44 months, with a mean duration of 14.4 months.

2. Diagnostic characteristics of IPAF patients

The diagnostic characteristics of all the IPAF patients were shown in Table 2. Overall, 66(35.9%) patients met IPAF criteria through a combination of serological and morphological domains, 53 (28.8%) by clinical and morphological domains, 34 (18.5%) by clinical and serological domains and 26 (14.1%) by all the three diagnostic domains.

A breakdown of features within each IPAF domain showed that the most common clinical findings were Raynaund's phenomenon (49, 26.6%) and inflammatory arthritis or polyarticular morning joint stiffness lasting >60min (45, 24.5%). 131 patients had positive serum autoantibody (71.2%), of which, 51 cases had two or more positive antibodies. An ANA $\geq$ 1:320 (or nucleolar or centromere pattern of any titer) was the most common serological finding (81, 44.0%). Morphological features were all obtained from HRCT. Within the morphological domain (150 81.5%), NSIP pattern by HRCT was found in 62.0% (114), while organizing pneumonia (OP) pattern was found in 14.1% (26). There were no significant differences in any of the diagnostic characteristics between the pirfenidone group and control group.

3. Arterial oxygen saturation and CT scan of chest

The differences after the treatment in chest CT scan and arterial oxygen saturation (SaO_2% Figure 2) were analyzed. Although SaO_2% of pirfenidone group tend to improve in 12 months (month 0 (95.48% ±2.43%) vs. month 12 (96.51%±1.49%), P=0.098), no statistical significance was observed (Figure 2C). The SaO_2% at other follow-up time points had no significant differences, when compared with the

baseline SaO_2% (m0). In addition, the changed SaO_2% between two groups had no differences (Figure 2D).

According to the evaluation criteria, the changes in CT scan of chest were divided into four groups: complete remission, partial remission, stabilization, and progression. The representative CT images are shown in Figure 3A. There were no significant differences in changes of chest CT scan between the two groups (Figure 3B).

4. Changes in pulmonary function

The differences in FVC% (Figure 4A) and DLCO% (Figure 4B) between the two groups were compared at the time of 3, 6, 12, 18, and 24 months with or without pirfenidone treatment. We found that after 12 months of treatment, FVC% in pirfenidone group was improved by 10.44%±18.83%, while that was decreased in the control group by 1.18%±6.96%, and the difference was statistically significant (P=0.016). In addition, FVC% was significantly increased in pirfenidone group after 6 (P=0.047) and 24 months (P=0.040) of treatment, compared with that of control group. The improvement of DLCO% in pirfenidone group was higher than that in the control group at 6 months (P=0.043).

Considering the bias in the retrospective research, we used mixed-effect model to estimates the differences of FVC% (Figure 4C) and DLCO% (Figure 4D) in the two groups. After adjusted by the sex, age, baseline FVC% and DLCO%, we found that compared with the control group, changed FVC% in pirfenidone group tend to improve by 1.49% (95% CI (0.14%, 2.84%)) within 40 months ($\chi2$ (1) =4.59, P=0.032), however there was no difference in the change of DLCO% ($\chi2$ (1) =0.49, P=0.48).

5. Subgroup analysis of pulmonary function

Patients in the two groups were subdivided according to different conditions. The average annual changes in absolute value of FVC within 40 months are presented in **Table 4.** The volume of FVC (liters) in the pirfenidone group increased by 0.0390 L/year on average, while that decreased by 0.0769 L/year on average in the control group (P=0.038). In patients with FVC < 70%, the improvement of FVC in the pirfenidone group significantly increased, compared with the control group (P=0.021). In patients with FVC > 70%, there was no significant difference in changes of FVC between the two groups. Patients in the pirfenidone group were subdivided according to the dosage and length of pirfenidone treatment. The results showed that the improvement of FVC significantly increased in patients with dose of pirfenidone > 600 mg/day (P=0.010) and total medication time > 12 months (P=0.007) compared with patients in control group. In addition, for patients with dose of prednisone > 20 mg combined with the medication of pirfenidone, the improvement of FVC was higher than that of the control group (P=0.031). According to the diagnostic characteristics, the changes of FVC increased in the pirfenidone group, who were diagnosed on the basis of morphological and serological domains (P=0.033), whereas there were no significant differences among the other three groups analysis in terms of the diagnostic characteristics.

6. Administration of pirfenidone with IPAF patients can reduce the dose of prednisone after 12 months.

We compared total dose (Figure 5A) and average daily dose (Figure 5B) of prednisone in the two groups. There was no significant difference of total dose and daily dose in two groups during the whole follow-up of 40 months. But we found that both total dose (P=0.012) and daily dose (P=0.032) of prednisone were less in pirfenidone group than those of control group after 12 months of treatment. Then, mixed-effect model was used to analyze differences of the prednisone dose. We found that during the whole follow-up of 40 months ($\chi2$ (1) =0.7318, P=0.392, pirfenidone n=53, control n= 47) and initial 12 months ($\chi2$ (1) =0.1396, P=0.709, pirfenidone n=53, control n= 47), there was no significant difference in dose of prednisone (Figure 5C&D) between two groups. However, prednisone dose was reduced by 6.27 mg per day in pirfenidone group in 12-40 months (Figure 5E), compared with control group ($\chi2$ (1) =9.8385, P=0.002, pirfenidone n=34, control n= 27).

7. Side effects of pirfenidone

Analysis of side effects showed that 17 (19.32%) patients had side effects after taking pirfenidone (Figure 6A). Among them, 7 (7.95%) patients stopped medication due to side effects and 1 patient had anaphylactic shock. Skin rash (10.23%) and liver damage (5.68%) were the most common side effects, which were similar to those of IPF patients who were treated with pirfenidone [12]. Additionally, 14 (14/17, 82.35%) patients experienced side effects at the initial dose (600 mg Figure 6B), and 3 (17.65%) patients experienced side effects during the increasing dose of pirfenidone (Figure 6B).

Discussion

The efficacy of pirfenidone in the treatment of IPF has been confirmed by several clinical trials, which could delay the decline of FVC in IPF patients and increase the progression-free survival rate [26-28]. However, the clinical indication of pirfenidone is limited to IPF patients at present, and to date, no research explored therapeutic effects of pirfenidone in patients of IPAF. In the present study, the therapeutic effects of pirfenidone on each clinical indicator of IPAF patients were retrospectively analyzed. It was found that FVC was improved in pirfenidone group compared with control group within 40 months, especially after 12 months of treatment. Follow-up data of CT scan showed a tendency for more patients with complete remission in the pirfenidone group, compared with control group (9 vs. 2). Moreover, pirfenidone was also associated with significantly lower corticosteroid dose.

In our study, following situations were recommended to pirfenidone treatment: 1) patients had more than 10% fibrosis on HRCT; 2) patients had a more than 5% absolute decline in percent predicted FVC within the previous 6 months. All the patients started pirfenidone therapy with a dose of 600 mg/day, and added to 1800 mg/day in six months, unless the patients experienced the serious side effects. We began with low dose(600mg/day) for the following considerations:1) we observed that low dose can achieve certain effect in IPAF patients; 2) Beginning with low dose can prevent side effects; 3) There is heavier financial burden for some patients in China if they take high dose of pirfenidone. The average dosage of pirfenidone was 1492 mg/day, which already showed clinical effect. This suggested that pirfenidone for IPAF may not need as much dose as IPF. Reasons might be: 1) relatively younger for IPAF patients, 2)

more inflammatory exudative lesions on chest CT scan, such as NSIP and OP, 3) pirfenidone was mainly used in combination with glucocorticoid therapy. In a phase III clinical trial in Japan [28], the effective dose of pirfenidone was 1800 mg/day or 1200 mg/day for IPF patients, which was also lower than that of clinical trials (CAPACITY and ASCEND) in Caucasians (2400 mg/day) [26, 27].

The course of pirfenidone treatment in IPAF patients ranged from 3 to 44 months in this study, and the improvement of FVC was more significant in patients with medication course longer than 12 months. This was similar to the clinical trial of pirfenidone for IPF patients [26-28]. These researches indicated that significant therapeutic effects for IPF patients could be observed after 12 months of treatment as well.

Corticosteroids are widely used among IPAF patients in clinical practice. In this study, the baseline prednisone doses in the two groups had no significant differences. Furthermore, we underwent subgroup analysis by dose of prednisone, and we observed more significant improvement of FVC in patients with prednisone ≥ 20 mg. It was suggested that pirfenidone combined with high-dose glucocorticoid (prednisone ≥ 20 mg) may contain superior effects, while it still requires further confirmation by prospective clinical studies with large samples. Recent study indicates that use of immunosuppressants (azathioprine and mycophenolate) is associated with reduction of prednisone dose in CTD-ILD [29]. Our results demonstrated that therapy with pirfenidone had similar results when used for initial steroid-sparing therapy with a significant steroid dose reduction, especially after 12 months (6.27 mg per day). We believe that will significantly reduce the side-effect of corticoids and improve the medication compliance and treatment outcomes in IPAF patients.

The overall incidence of side effects was low in the pirfenidone group (19.32%). Only 10.23% of the patients had skin rash in this study, while the incidence of skin rash in IPF clinical trial was 28.1-32% [26, 27]. This might be related to the lower dosage of pirfenidone (average, 792 mg/day) in this study than that in IPF clinical trial (2400 mg/day) [26, 27]. The incidence of side effects also increased with the increasing dosage of pirfenidone. In the pirfenidone group, 3 (3.4%) patients had no side effects when the dosage was 600 mg/day, while skin rash and liver damage were noted after increasing pirfenidone dose.

Conclusions

In conclusion, our study indicated that the use of low-dose pirfenidone (1492 mg/day) is associated with improvement of FVC and reduction of prednisone dose, with an acceptable safety and tolerability profile.

Abbreviations

IPAF=Interstitial pneumonia with autoimmune features; FVC= Forced vital capacity; DLCO= diffusion capacity of the lung for carbon monoxide; ILD= Interstitial lung disease; CTD-ILD= Connective tissue disease-associated ILD; IPF= idiopathic pulmonary fibrosis; NSIP= Non-specific interstitial pneumonia; HRCT=high-resolution computed tomography; IIP= idiopathic interstitial pneumonia; COP= cryptogenic organic pneumonia; MTD= multidisciplinary discussion; BMI= body mass index

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Shanghai Pulmonary Hospital (Approval No. K17-H1). Informed consent was obtained from all patients before.

enrollment in this study.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this article.

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Competing interests

The authors declare that they have no competing interests.

Authors' Contributions

HP Li, T Chen, QH Li, and Y Zhang participated in the conception, hypothesis, and design of the study. T Chen, CS Yin, and QH Li collected data. T Chen, CS Yin, and Y Zhou carried out the statistical analyses. All authors contributed to interpretation of the data. T Chen and HP Li drafted the manuscript, and all authors made critical revisions. All authors studied and approved the final version of the manuscript.

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Tables

Table 1. Baseline characteristics of patients.

Characteristics	Total	Pirfenidone	Control	P-value
	N=184	N=81	N=103	
Age (year)	59.4±9.5	58.0±10.3	60.5±8.7	0.077
Sex				
Male, n (%)	84(45.7)	32(39.5)	52(50.5)	0.176
Female, n (%)	100(54.3)	49(60.5)	51(49.5)	
BMI	24.8±2.9	25.0±3.1	24.7±2.8	0.521
Smoking status				
Never, n (%)	131(71.2)	61(75.3)	70(68.0)	0.326
Ever, n (%)	53(28.8)	20(24.7)	33(32.0)	
Current, n (%)	30(16.3)	9(11.1)	21(20.4)	0.109
Observation periods(months)	15.0±11.4	14.6±10.3	15.4±12.4	0.649
Pulmonary function				
FVC (Liters)	2.00±0.67	1.86±0.67	2.10±0.65	0.013*
FVC, %predicted	64.7±16.6	59.7±15.8	68.6±16.3	<0.001*
DLCO, %predicted	59.3±18.7	54.3±17.9	63.0±18.6	0.003*
PaO_2	83.0±17.9	81.4 ± 1.9	84.3 ± 1.7	0.266
SaO_2%	95.5±4.0	95.5 ± 2.5	95.6 ± 4.8	0.881
Treatment on clinical course				
Corticosteroids n (%)	151(82.1)	69(85.2)	82(79.6)	0.342
Immunosuppressant n (%)	13(7.1)	7(8.6)	6(5.8)	0.459

Abbreviations: BMI, body mass index; FVC, forced vital capacity; DLCO, carbon monoxide diffusing capacity. * $P<0.05$

Table 2. Proportion of each domain of IPAF

	Total n (%)	Pirfenidone n (%)	Control n (%)	*P* value
Subjects	184	81	103	
Clinical and serological	34(18.5)	11(13.6)	23(22.3)	0.180
Clinical and morphological	53(28.8)	25(30.9)	28(27.2)	0.625
Serological and morphological	66(35.9)	31(38.3)	35(34.0)	0.547
All three domains	31(16.8)	14(17.3)	17(16.5)	1.000
Clinical domain	118(64.1)	50(61.7)	68(66.0)	0.643
Mechanical hands	14(7.6)	5(6.0)	9(8.7)	0.472
Distal digital tip ulceration	3(1.6)	1(1.2)	2(1.9)	0.684
Inflammatory arthritis or polyarticular morning joint stiffness≥60min	45(24.5)	20(24.7)	25(24.3)	0.948
Palmer telangiectasia	8(4.3)	5(6.0)	3(2.9)	0.307
Raynaund’s phenomenon	49(26.6)	23(28.4)	26(25.2)	0.737
Unexplained digital edema	7(3.8)	3(3.7)	4(3.9)	0.950
Gottron’s sign	2(1.1)	1(1.2)	1(1.0)	0.864
Serological domain※	131(71.2)	56(69.1)	75(72.8)	0.625
□	80(43.5)	31(38.3)	49(47.6)	0.240
□	26(14.1)	12(14.8)	14 (13.6)	
□	18(9.8)	10(12.3)	8(7.8)	
□	7(3.8)	3(3.7)	4(3.9)	
Antinuclear antibody ♯	81(44.0)	38(46.9)	43(41.7)	0.550
Rheumatoid factor ≥2 upper limit normal	49(26.6)	17(21.0)	32(31.1)	0.125
Anti- CCP	1(0.5)	1(1.2)	0(0)	0.258
Anti-double stranded DNA	6(3.3)	2(2.5)	4(3.9)	0.592
Anti-SSA	27(14.7)	14(17.3)	13(12.6)	0.375
Anti-SSB	15(8.2)	8(9.9)	7(6.8)	0.448
Anti-ribonucleoprotein (RNP)	3(1.6)	2(2.5)	1(1.0)	0.426
Anti-smith	11(6.0)	5(6.2)	6(5.8)	0.921
Anti-topoisomerase (Scl-70)	4(2.2)	3(3.7)	1(1.0)	0.207
Anti-tRNA synthetase	17(9.2)	7(8.6)	10(9.7)	0.804
Morphological domain	150(81.5)	70(86.4)	80(77.7)	0.180
NSIP	114(62.0)	51(63.0)	63(61.2)	0.879
OP	26(14.1)	13(16.0)	13(12.6)	0.508
NSIP+OP	10(5.4)	6(7.4)	4(3.9)	0.295

FVC%- forced vital capacity% predicted. ♯Adjusted for age, sex, baseline forced vital capacity% predicted and baseline carbon monoxide diffusing capacity% predicted. ♢Grouped by the time of pirfenidone therapy. △Grouped according to the diagnostic domain. M-morphological domain, C-clinical domain, S-serological domain. * $P<0.05$

Table 3. Analysis of change in Forced Vital Capacity(liters) Outcome♯

	Pirfenidone		Control		Pirfenidone *vs* control
	n	Estimated FVC change in 1 year (95%)	n	Estimated FVC change in 1 year (95%)	*P* value
Total	81	0.0390 (-0.0545,0.1326)	103	-0.0769 (-0.1250,-0.0288)	0.038*
FVC%<70%	58	0.0697 (-0.0541,0.1935)	56	-0.0574 (-0.1416,0.0269)	0.021*
FVC%>70%	23	-0.0533 (-0.1550,0.0483)	47	-0.1001 (-0.1550,-0.0453)	0.745
Pirfenidone= 600mg	33	-0.0369 (-0.1379,0.040)	103	-0.0848 (-0.1307,-0.0390)	0.125
Pirfenidone> 600mg	48	0.1251 (-0.0440,0.2942)	103	-0.0848 (-0.1307,-0.0390)	0.010*
Time≤12 month♢	37	-0.0164 (-0.1435,0.2307)	103	-0.0848 (-0.1307,-0.0390)	0.224
Time>12 month	44	0.0960 (-0.0388,0.2307)	103	-0.0848 (-0.1307,-0.0390)	0.007*
Prednisone≤20 mg	19	-0.0869 (-0.2307,0.0569)	50	-0.0590 (-0.0100,-0.2180)	0.100
Prednisone>20 mg	62	0.0777 (-0.0403,0.1956)	53	-0.0877 (-0.1550,-0.0205)	0.031*
M+C+S△	14	0.0612 (-0.0959,0.2183)	17	-0.1669 (-0.3340,0.0003)	0.407
C+S	11	-0.1957 (-0.3643,-0.0270)	23	-0.1174 (-0.1711,-0.0637)	0.149
M+C	25	0.2075 (-0.0471,0.4621)	28	-0.0051 (-0.1747,0.1646)	0.246
M+S	31	0.0229 (-0.1368,0.1826)	35	0.0005 (-0.0673,0.0684)	0.033*

Abbreviations: NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia. ※□, □, □, □ respectively represent one, two, three or four different kinds of auto-antibodies are positive with the patients. ♯ ANA ⩾ 1:320 titer, diffuse, speckled, homogeneous patterns or a. ANA nucleolar pattern (any titer) or b. ANA centromere pattern (any titer). * $P<0.05$

Figures

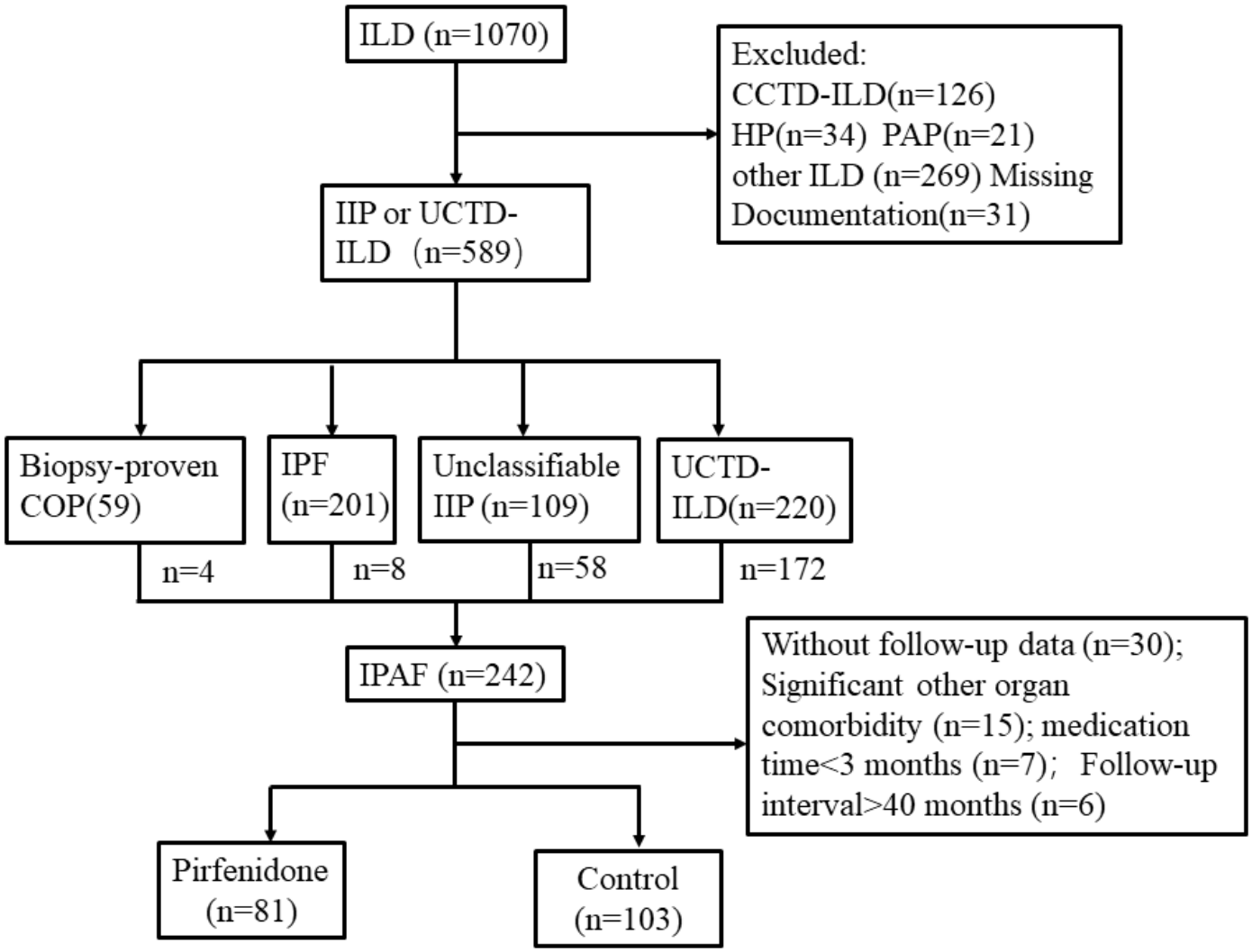


Figure 1

Flowchart of patients' selection process. Of 1070 patients diagnosed with ILD, 184 patients with IPAF (81 received pirfenidone therapy, while 103 didn't receive) were enrolled in this study.

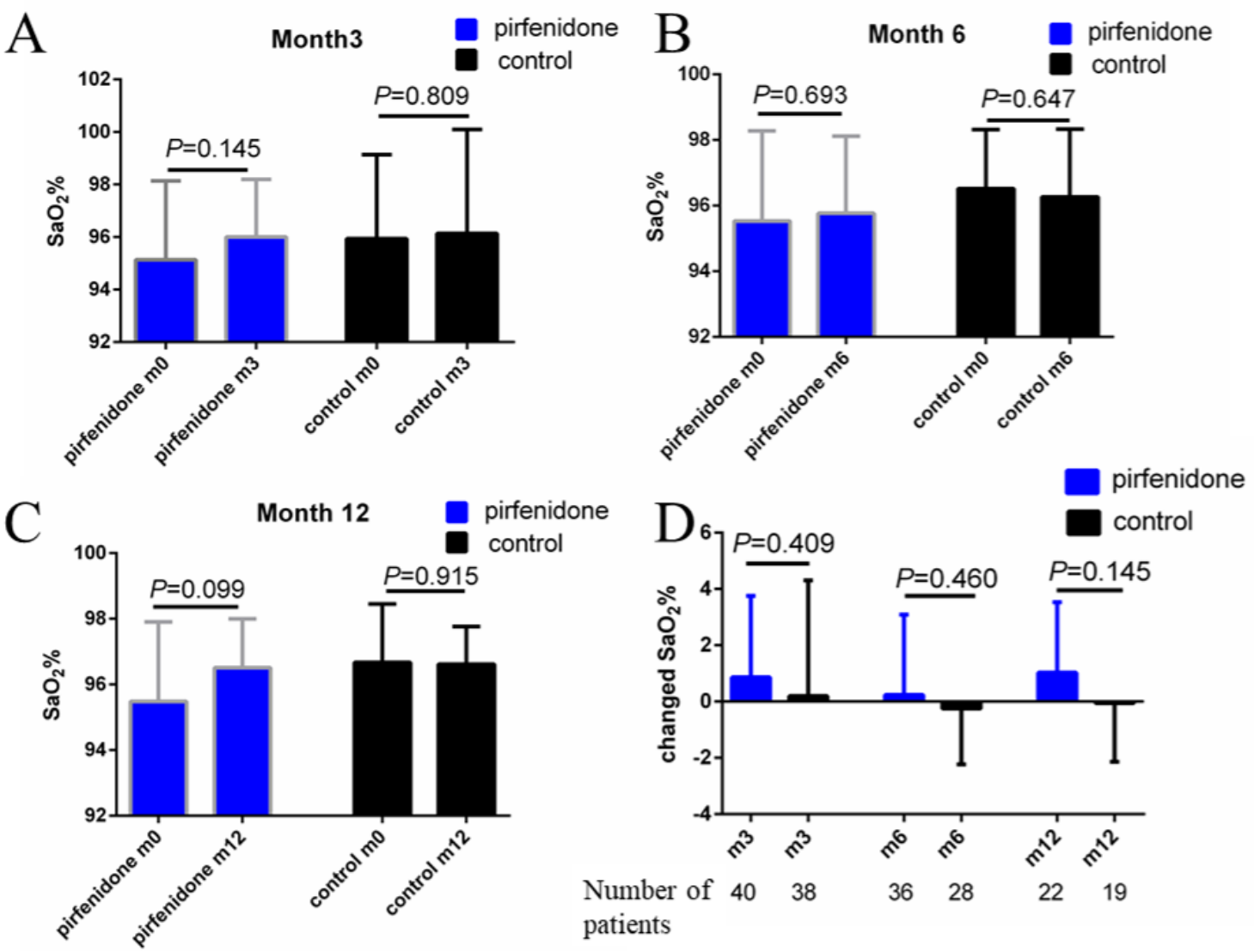
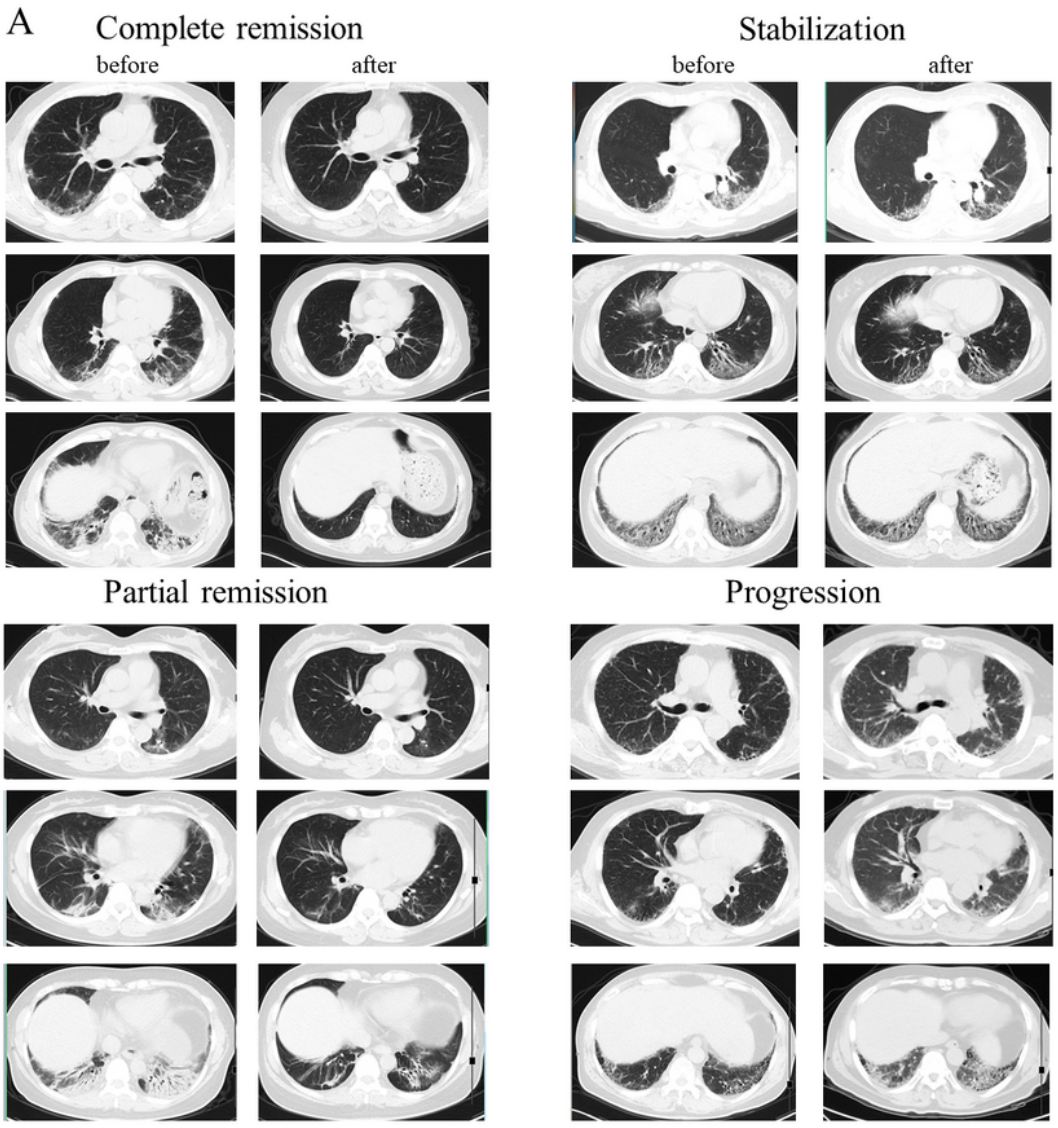


Figure 2

Change of SaO2% in two groups of patients A&B&C. SaO2% in two groups of patients at the initial time point and 3 months (A), 6 months (B), and 12 months (C) after diagnosis. D. Change of SaO2% in the two groups of patients.



B

Follow-up of chest CT within one year

	Month 3			Month 6			Month 12		
	Pirfenidone n (%)	Control n (%)	*P*	Pirfenidone n (%)	Control n (%)	*P*	Pirfenidone n (%)	Control n (%)	*P*
Total	62	68		56	61		57	60	
Complete remission#	0(0.0)	0(0.0)		3(5.4)	0(0.0)		9(15.8)	2(3.3)	
Partial remission	23(37.1)	26(38.2)		17(3.0)	22(36.1)		11(19.3)	14(23.3)	
Stabilization	35(56.5)	34(50.0)	0.802	27(48.2)	34(55.7)	0.724	26(45.6)	35(58.3)	0.474
Progression	4(6.5)	8(11.8)		9(16.1)	5(8.2)		11(19.3)	9(15.0)	
Mean Rank	64.73	66.21		60.04	58.04		56.89	61.01	

#definition of rank: Complete remission 1, Partial remission 2, Stabilization 3, Progression 4.

Figure 3

Assessment of lesions by CT of chest. A. The typical morphological changes of complete remission, partial remission, stabilization, and progression. B. Results of statistical analysis of morphological changes.

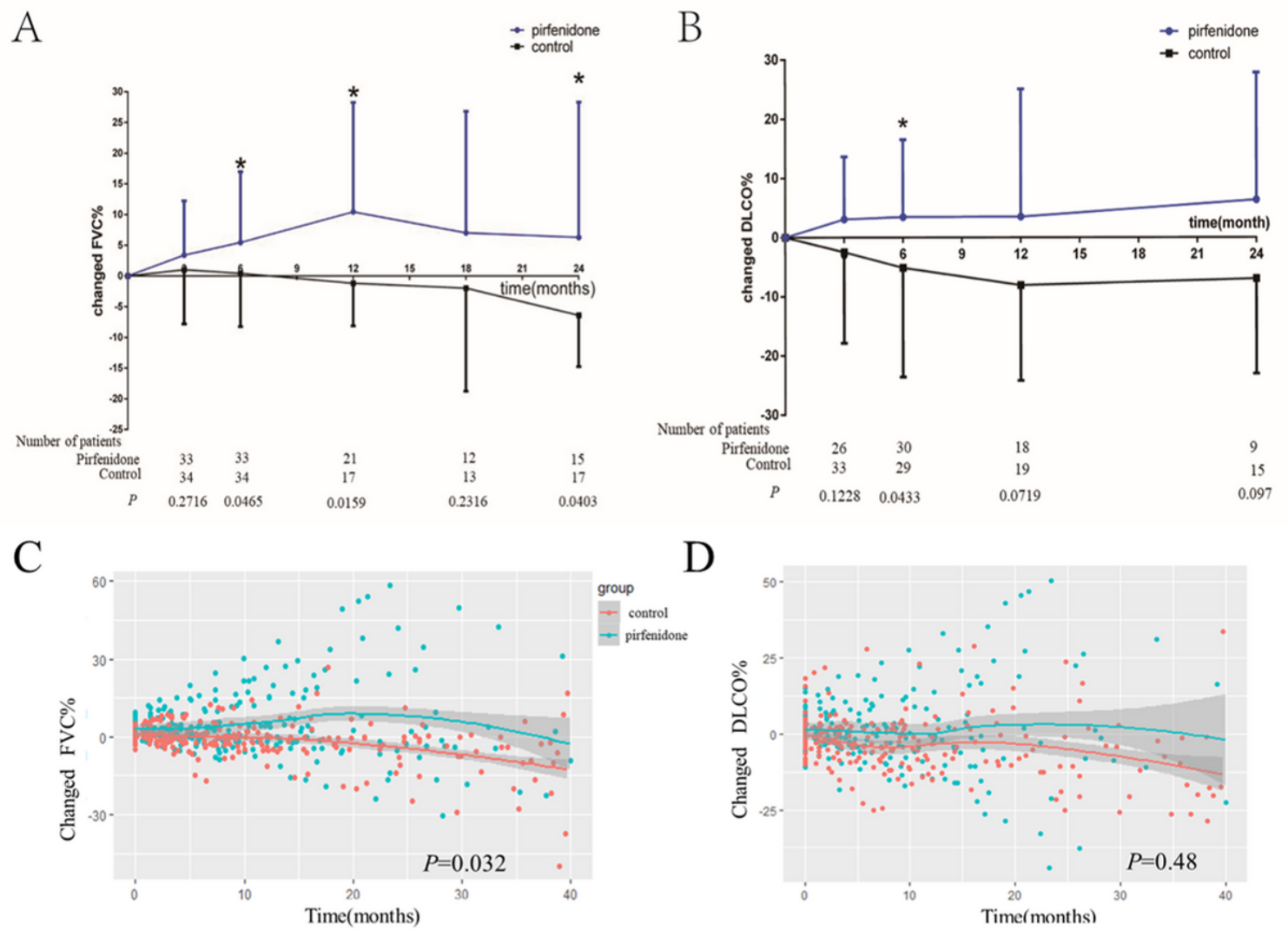


Figure 4

Changes of FVC% and DLCO% for two groups of IPAF patients. A&B. Changes of FVC% (A) and DLCO% (B) in the corresponding time point for two groups of IPAF patients. C&D. Difference in FVC% (C) and DLCO% (D) in two groups of patients. The adjustment was performed by mix-effect model for gender, age, baseline FVC% and DLCO%.

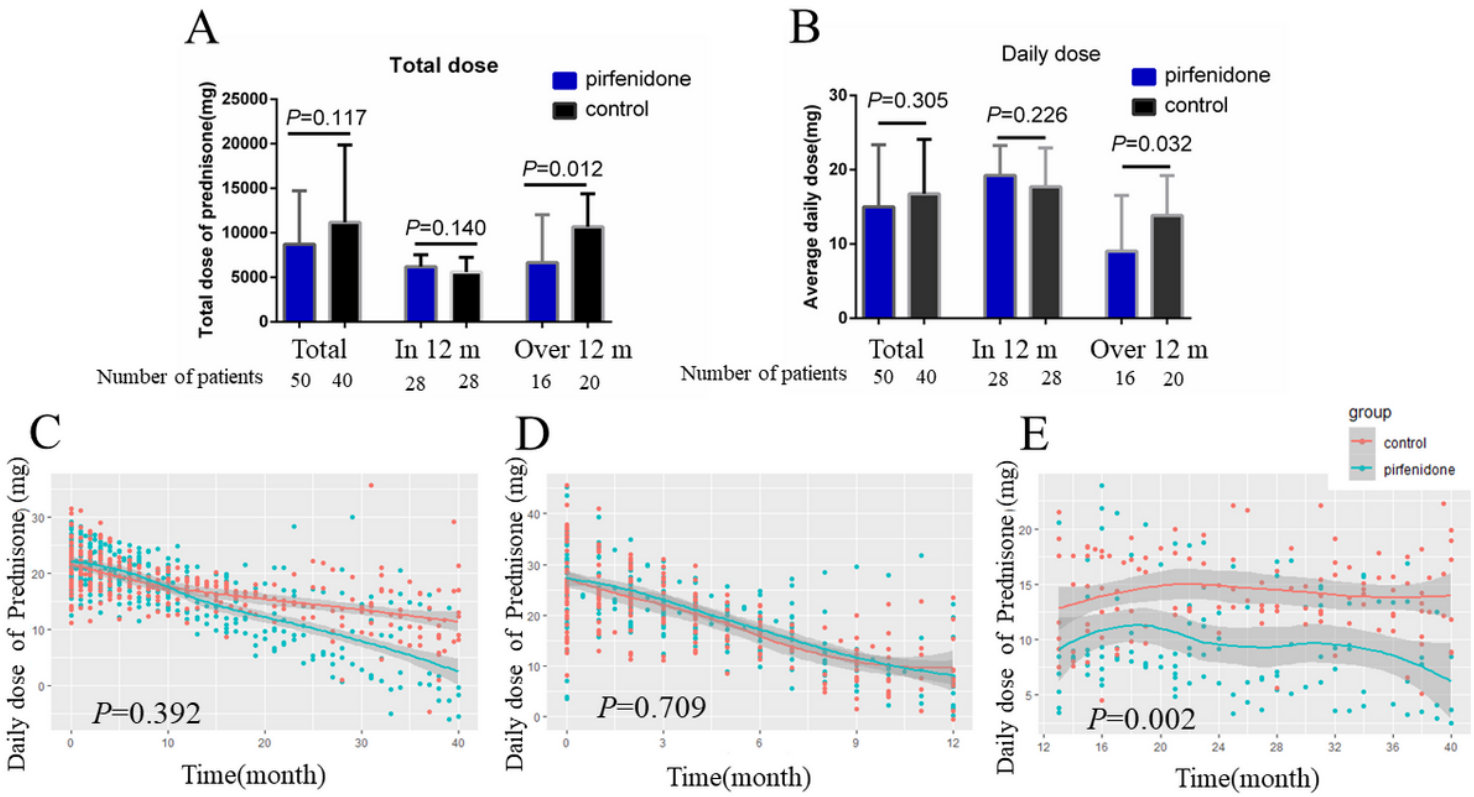


Figure 5

Prednisone dose over time for IPAF patients treated with or without pirfenidone A&B. Total dose(A) and average daily dose(B) of prednisone in two groups of patients. C&D&E. The fitting chart of prednisone dose changed through overall observation time (C), in the initiate 12 month (D), and during month 12-40 (E). The adjustment was performed by mix-effect model for time interval, baseline FVC%, and baseline DLCO%.

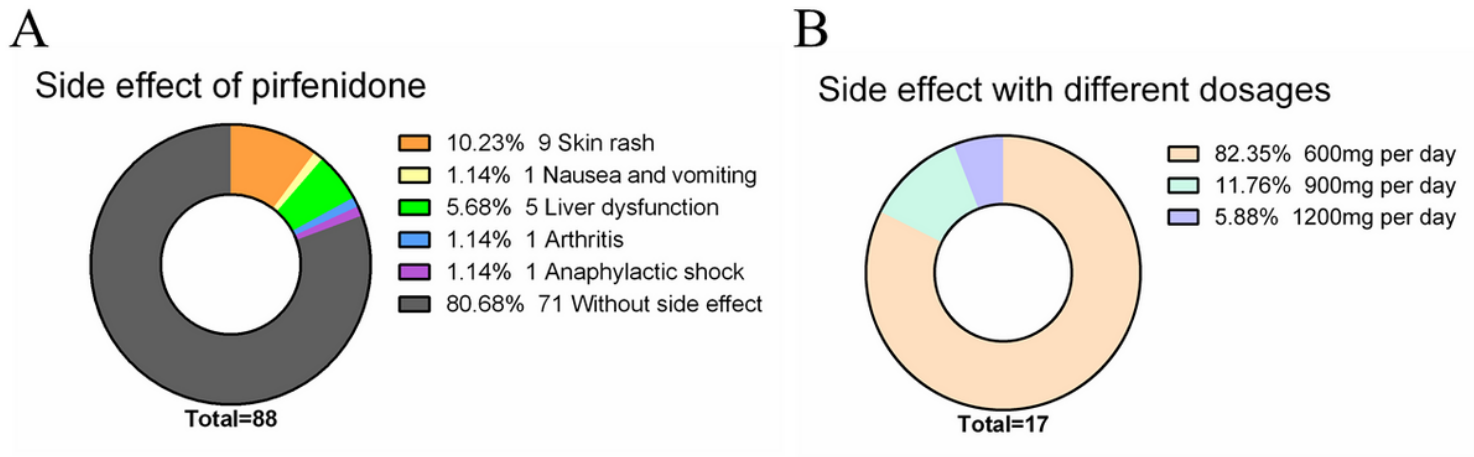


Figure 6

Side effects of pirfenidone. A. 17 (19.32%) patients, who received pirfenidone therapy, suffered from side effects, and 7 (7.95%) patients stopped the pirfenidone therapy due to side effects. B. Side effects

occurred in 14 patients (82.35%) with initial dosage (600 mg/day). Besides, 3 patients experienced side effects, while increasing pirfenidone dose.

Supplementary Files

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