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Original Article

Effect of Qingfei Huaxian Decoction combined with prednisone acetate on serum inflammatory factors and pulmonary function of patients with idiopathic pulmonary fibrosis

Lei Zhou[1], Hui Tian[2], Qiong Wang[3], Wuzhong Xiong[3], Xiang Zhou[4], Jingjing Yan[5]

[1]Nephrology Department, Wuhan Hospital of Traditional Chinese Medicine, No. 303 Sixin Avenue, Hanyang District, Wuhan 430050, Hubei, China; [2]Department of Pulmonary Diseases, Wuhan Hospital of Traditional Chinese Medicine, Wuhan 430050, Hubei, China; [3]Endocrine Department, Wuhan Hospital of Traditional Chinese Medicine, Wuhan 430050, Hubei, China; [4]Clinical Laboratory, Wuhan Hospital of Traditional Chinese Medicine, Wuhan 430050, Hubei, China; [5]Department of Pulmonary Diseases, Wuhan Hospital of Traditional Chinese Medicine, Wuhan 430050, Hubei, China

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Abstract: Objective: To determine the effect of Qingfei Huaxian Decoction combined with prednisone acetate on serum inflammatory factors and pulmonary function in patients with idiopathic pulmonary fibrosis (IPF). Methods: The clinical data of 118 patients with IPF treated in Wuhan Hospital of Traditional Chinese Medicine from June 2019 to August 2021 were retrospectively analyzed. Among the patients, 56 patients treated with prednisone acetate were assigned to the control group, and the remaining 62 patients treated with Qingfei Huaxian Decoction combined with prednisone acetate were assigned to the observation group. The efficacy and incidence of adverse reactions were compared between the two groups, and forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC, interleukin-6 (IL-6), interleukin-12 (IL-12), interleukin-18 (IL-18), hyaluronic acid (HA) and laminin (LN) in the two groups were evaluated before and after therapy. Logistic regression was conducted to analyze the risk factors impacting the treatment efficacy in patients. Results: After therapy, the observation group showed significantly higher efficacy than the control group. Compared with the control group, the observation group showed significantly higher levels of FEV1, FVC and FEV1/FVC, significantly lower levels of HA and LN, and a significantly higher IL-12 level (all $P < 0.05$). Therapeutic regimen, IL-6, IL-12, IL-18 and HA were independent risk factors impacting the efficacy of treatment in patients ($P < 0.05$). Conclusion: Qingfei Huaxian Decoction combined with prednisone acetate has greater treatmetn efficacy in patients with IPF by improving the serum inflammatory factors and pulmonary function.

Keywords: Qingfei Huaxian Decoction, prednisone acetate, idiopathic pulmonary fibrosis, inflammatory factors, pulmonary function

Introduction

Idiopathic pulmonary fibrosis (IPF) is a disease characterized by pulmonary interstitial fibrosis of unknown etiology, resulting from alveolar structural disorder and diffuse alveolitis [1]. The most common clinical symptoms of IPF include progressive labored dyspnea, hypoxemia and cough, and other symptoms and signs that include emaciation, fatigue, acropachy, and a double lower lung popping sound. The end-stage patients often die from respiratory failure [2]. Although pirfenidone and nintedanib (anti-fibrosis drugs) have been conditionally recommended in the latest guidelines issued by major thoracic science societies around the world, these two drugs still cannot reverse pulmonary fibrosis or change the final outcome of patients [3]. In addition, according to research, the efficacy of glucocorticoids alone in the treatment of IPF is not satisfactory, because they are unable to effectively inhibit the disease process, and some patients still have persistent symptoms after therapy [4]. Therefore, it is urgent to find novel therapeutic drugs for IPF.

However, due to the insufficient understanding of etiology and pathogenesis, IPF lacks definite and effective drugs for it's therapy [4]. According to clinical studies at home and abroad with more than 30 years of research, there are not satisfactory anti-inflammatory or cytotoxic drugs and IPF is accompanied with serious side effects after drug therapy [5]. So far, no drug can significantly change or reverse the inflammatory process of IPF. Clinically, the comprehensive therapy of traditional Chinese medicine (TCM) combined with conventional western medicine is found to be an ideal treatment method for patients with non-acute exacerbation of IPF [6]. Qingfei Huaxian Decoction is composed of scutellaria, polygonum cuspidatum, and bulbus iphigeniae, with a favorable clinical effect on chronic cough. Previous research has pointed out that Qingfei Huaxian Decoction has considerable efficacy on pneumoconiosis [7], but there is limited relevant research on whether it has clinical significance in IPF treatment.

The present study adopted Qingfei Huaxian Decoction to treat patients and then evaluated its therapeutic efficacy on IPF to provide a novel scheme for clinical therapy.

Methods and data

Clinical data

A total of 118 patients with IPF admitted to Wuhan Hospital of Traditional Chinese Medicine from June 2019 to August 2021 were retrospectively enrolled. Among them, 56 patients treated with prednisone acetate were assigned to the control group, and the remaining 62 patients treated with Qingfei Huaxian Decoction combined with prednisone acetate were assigned to the observation group. This study was performed with permission from the Medical Ethics Committee of Wuhan Hospital of Traditional Chinese Medicine, with approval number of 2019(A)015.

Inclusion and exclusion criteria

The inclusive criteria: Patients diagnosed with IPF according to the diagnostic criteria of American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) in 2011 [8]; patients with detailed clinical data; patients > 18 years old; and patients who received anti-fibrosis therapy for the first time after diagnosis.

The exclusion criteria: Patients with severe infection (sepsis) or acute exacerbation of IPF; pregnant women; lactating women; patients with malignant tumour or allergic constitution; patients with mental illness; patients with severe hysteria, severe heart, liver or kidney dysfunction; or those allergic to drug therapy in this study.

Therapeutic regimen

For the control group: Each patient was orally given Pirfenidone tablets (Beijing Kaiwin Technology Co., Ltd., State Food and Drug Administration (SFDA) approval no.: H20193259), 200 mg/time and 3 times/d in the first week, and 400 mg/time and 3 times/d in the 2-5 weeks. From the 6th week, the treatment was maintained at 600 mg/time and 3 times/d. In addition, the patient was given prednisone acetate tablets (Taosheng Pharmaceutical Co., Ltd., SFDA no.: H34020009) at 0.5 mg/(kg d) in the first 4 weeks and 0.25 mg/(kg d) after 4 weeks. The patient was treated consecutively for 8 weeks.

For the observation group: The patients were given Qingfei Huaxian Decoction based on the therapy given to the control group. Qingfei Huaxian Decoction was composed of codonopsis pilosula (15 g), ophiopogon japonicas (15 g), adenophora tetraphylla (15 g), tuckahoe (15 g), radix astragali (15 g), and salvia miltiorrhiza (15 g), polygonum cuspidatum (10 g), rhizoma pinelliae preparatum (10 g), polygonatum odoratum (10 g), malaytea scurfpea fruit (10 g), root of chinese trichosanthes (10 g), rhizoma chuanxiong (10 g), radix curcumae longae (10 g), and peach kernel (10 g),scutellaria (9 g), and liquorice (5 g). The herbs were decocted in water to 300 ml, which was heated to a warm temperature and taken orally in the morning and evening. The patient was treated consecutively for 8 weeks.

Enzyme-linked immunosorbent assay (ELISA)

Serum levels of interleukin-6 (IL-6), interleukin-12 (IL-12) and interleukin-18 (IL-18) were

quantified before therapy and after 8 weeks of treatment (after therapy) using kits from Shanghai Mlbio (IL-6: ml058097; IL-12: ml05-8044; IL-18: ml058055). Peripheral blood (5 mL) was collected from each patient before and after treatment and subjected to centrifugation for 10 min at 1500 rpm to collect serum by strictly following the instructions of the manufacturer's kit.

Pulmonary function test

The forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and FEV1/FVC of all patients were determined using CUSTO Vitm pulmonary function instrument from Germany.

Outcome measures

Primary outcome measures: The clinical treatment efficacy and the FEV1%, FVC and FEV1/FVC before and after therapy were compared between the two groups. The IL-6, IL-12 and IL-18 levels in the patients were compared before and after therapy. The TCM symptom score [9] of the two groups were compared, and the patients' primary syndrome and secondary syndrome were scored with 3 points, 2 points and 1 point according to the severe, medium and light conditions, respectively, and the sum of all symptom scores was the TCM syndrome score.

Secondary outcome measures: The clinical data of the two groups were compared. The serum laminin (LN) and hyaluronic acid (HA) were quantified through radioimmunoassay before and after therapy. Patients were assigned to the improved group (markedly effective + effective) and the non-improved group (ineffective), and the logistic regression was conducted to analyze the risk factors of efficacy.

Evaluation of efficacy

Markedly effective: The clinical symptoms disappeared, and the TCM syndrome score decreased by 90% or more after therapy; Effective: The clinical symptoms were obviously alleviated, and the TCM syndrome score was reduced by 50%-89% after therapy; Ineffective: The above criteria were not met, or the condition was even aggravated. Total effective rate = (number of markedly effective cases + number of effective cases)/total number of cases ×100%.

Statistical analysis

SPSS 20.0 was adapted for data analysis, and GraphPad Prism 8 was used for visualization of the processed data. Independent-samples t test and paired t test were adopted for inter-group comparison and intro-group comparison (presented by t), respectively, and the rank sum test and chi-square test were utilized to analyze ranked data (presented by Z) and counting data, respectively. Logistic regression analysis was used to analyze the risk factors affecting the tretmetn efficacy in patients. Receiver operating characteristic (ROC) curves were drawn to analyze the value of risk factors in forecasting the clinical efficacy on patients. $P < 0.05$ implies a statistically significant difference.

Results

Comparison of clinical data

According to the comparison, the two groups showed no significant differences in age, gender, body mass index (BMI), course of disease, hypertension, diabetes mellitus, smoking history and alcoholism history (all $P > 0.05$, **Table 1**).

Evaluation of clinical efficacy

According to the comparison of clinical efficacy between the two groups, the control group showed significantly lower clinical efficacy than the observation group (**Table 2**, $P < 0.05$).

Comparison of TCM symptom scores before and after therapy

Comparison of TCM symptom scores between the two groups revealed that before therapy, the TCM symptom scores of the two groups were not greatly different ($P > 0.05$), while after therapy, TCM symptom scores of both groups decreased significantly ($P < 0.05$), with significantly higher TCM symptom scores in the control group than those in the observation group ($P < 0.05$, **Table 3**).

Table 1. Clinical data analysis

Factor	Control group (n=56)	Observation group (n=62)	*P* value
Age			0.320
≥ 65 years old	22	30	
< 65 years old	34	32	
Gender			0.573
Male	30	30	
Female	26	32	
BMI (kg/m^2)	21.91±2.37	22.20±2.12	0.479
Course of disease (month)	12.79±2.30	12.95±2.48	0.723
Hypertension			0.483
Yes	28	35	
No	28	27	
Diabetes mellitus			0.606
Yes	20	25	
No	36	37	
Smoking history			0.361
Yes	30	28	
No	26	34	
Alcoholism history			0.454
Yes	10	8	
No	46	54	

Body Mass Index (BMI).

Table 2. Efficacy evaluation

Group	Markedly effective	Effective	Ineffective	Total effective rate
Control group (n=56)	25	16	15	41 (73.21)
Observation group (n=62)	40	16	6	56 (90.32)
χ^2/Z value		-5.632		5.887
P-value		< 0.001		0.015

Table 3. Comparison of TCM symptom scores

Group	Before therapy	After therapy
Control group (n=56)	18.12±2.96	7.44±2.09
The observation group (n=62)	17.96±3.39	4.95±1.60
T value	0.266	7.300
P-value	0.790	< 0.001

Traditional Chinese medicine (TCM).

Changes of pulmonary function before and after therapy

Before therapy, the FEV1%, FVC and FEV1/FVC of the two groups were not greatly different (all P > 0.05); however, after therapy, FEV1%, FVC and FEV1/FVC of both groups increased significantly (all P < 0.05), with more significant increases in the observation group (all P < 0.05, **Figure 1**).

Changes of inflammatory factors before and after therapy

Before therapy, there were no significant difference in IL-6, IL-18 and IL-12 levels between the two groups. However, after therapy, the IL-6 and IL-18 levels decreased significantly, while the IL-12 level increased significantly (P > 0.05) in both groups, and the decrease/increase was more obvious in the observation group as compared with the control group (all P < 0.05, **Figure 2**).

Comparison of pulmonary fibrosis indexes before and after therapy

Before therapy, the two groups were not greatly different in LN and HA levels (all P > 0.05), while after therapy, the levels of LN and HA in the two groups decreased significantly (P < 0.05), with more significant decrease in the observation group than the control group (P < 0.05, **Figure 3**).

Analysis of risk factors influencing efficacy

Patients were grouped according to the clinical efficacy after therapy, including 97 patients in the improved group and 21 patients in the non-improved group. According to univariate analysis, therapeutic regimen, IL-6, IL-12, IL-18 and HA differed significantly between the two groups (**Table 4**, P < 0.05), which were then assigned (**Table 5**) and included into logistics regression analysis. The Results showed that IL-6, IL-12, IL-18 and HA were the independent risk factors impacting the treatment efficacy in patients (**Table 6**, P <

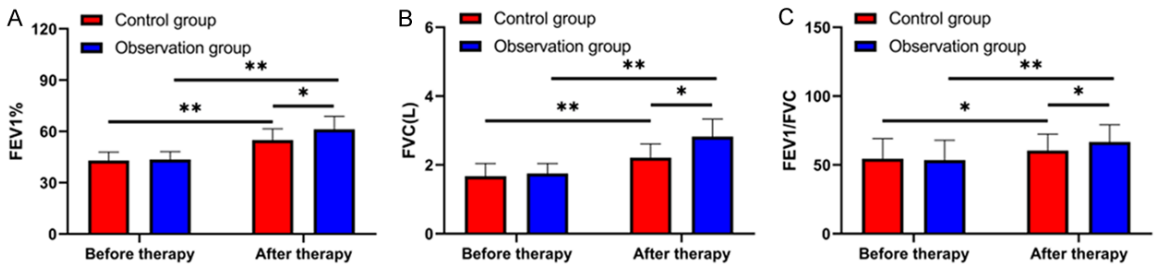

Figure 1. Changes of pulmonary function in patients before and after therapy. A. Changes of FEV1% level before and after therapy. B. Changes of FVC level before and after therapy. C. Changes of FEV1/FVC level before and after therapy. *P < 0.05, **P < 0.01, Forced expiratory volume in 1 second (FEV1).

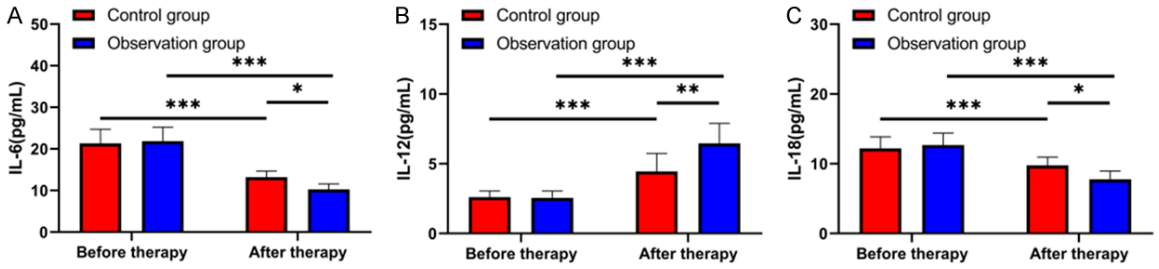

Figure 2. Changes of inflammatory factors in patients before and after therapy. A. Changes of IL-6 level in patients before and after therapy. B. Changes of IL-12 level in patients before and after therapy. C. Changes of IL-18 level in patients before and after therapy. *P < 0.05, **P < 0.01, ***P < 0.001, interleukin (IL).

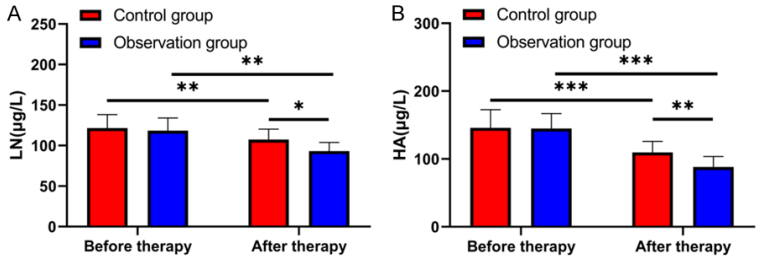

Figure 3. Changes of pulmonary fibrosis indexes in patients before and after therapy. A. Changes of LN level in patients before and after therapy. B. Changes of HA level in patients before and after therapy. *P < 0.05, **P < 0.01, ***P < 0.001, hyaluronic acid (HA) and laminin (LN).

0.05). In addition, according to ROC curve-based analysis, each index demonstrated certain clinical value in predicting treatment efficacy, among which IL-12 with the area under the curve (AUC) > 0.8 showed the highest predictive value (**Figure 4**).

Discussion

Currently, the inducing factors of IPF are still under investigation, which might be related with smoking, genetic factors, environmental exposure, virus infection, gastroesophageal reflux, etc. [10]. If IPF patients are not well given timely intervention, the lung lesions will progress rapidly and may result in 'honeycomb lung' in severe cases; seriously impacting the physiological function of patients. IPF has the characteristics of rapid disease progress, poor prognosis, short survival time, and high mortality [11-13]. In Western medicine, IPF is mainly treated with cytotoxic drugs or glucocorticoids, with a long therapy cycle, limited effect, high cost, severe side effects, and low compliance of patients, all of which will form a vicious cycle and accelerate the deterioration of the disease condition [14, 15].

According to the research on the pathogenesis of IPF, Chinese medicine scholars mostly think that the disease belongs to the categories of "lung flaccidity" and "lung distension". Its occurrence is correlated with an invasion of external evil, physical weakness, acquired dystrophy, internal emotional injury, and chronic ill-

Table 4. Multivariate analysis

Items	Improved group (n=97)	Non-improved group (n=21)	*P* value
Age			0.850
≥ 65 years old	44	10	
< 65 years old	53	11	
Gender			0.524
Male	48	12	
Female	49	9	
BMI (kg/m^2)	22.18±2.19	21.55±2.44	0.244
Course of disease (month)	12.73±2.45	13.57±2.05	0.146
History of hypertension			0.121
Yes	55	8	
No	42	13	
Diabetes mellitus			0.323
Yes	35	10	
No	62	11	
Smoking history			0.876
Yes	48	10	
No	49	11	
Alcoholism history			0.593
Yes	14	4	
No	83	17	
Therapeutic regimen			0.015
Single	41	15	
Combined	56	6	
FEV1%	43.30±4.68	43.47±5.03	0.881
FVC (L)	1.64±0.27	1.73±0.35	0.192
FEV1/FVC	53.36±14.33	56.78±14.86	0.326
IL-6 (pg/mL)	21.29±3.46	23.06±2.64	0.029
IL-12 (pg/mL)	2.67±0.44	2.19±0.37	<0.001
IL-18 (pg/mL)	12.26±1.71	13.50±1.14	0.002
LN (μg/L)	118.76±16.28	125.26±14.80	0.094
HA (μg/L)	143.05±24.11	155.70±22.91	0.029

Body Mass Index (BMI), Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), interleukin (IL), hyaluronic acid (HA) and laminin (LN).

ness [16, 17]. Therefore, the therapy should focus on warming the spleen and kidney, activating Qi, promoting blood circulation and removing blood stasis. Previously, in the study of Shen et al. [18], it was found that Maimendong Decotion improved the pulmonary function of rats with idiopathic pulmonary fibrosis by inhibiting the stress of the aeciis endoplasmic reticulum. The research of Guo et al. [19] found that Qizhukangxian granules can effectively improve the lung function of IPF patients, improve the quality of life and reduce the acute attack rate. This suggests that traditional Chinese medicine has considerable curative effects in the treatment of IPF. In this study, the observation group showed a significantly higher total effective rate and significantly higher levels of FEV1%, FVC, FEV1/FVC than the control group, while it showed significantly lower TCM syndrome scores, as well as LH and HA levels than the control group. Our results are similar to those of Guo et al. [19]. Additionally, after therapy, serum IL-6 and IL-18 in the patients decreased significantly, while the serum IL-12 increased, suggesting that the combined treatment with Qingfei Huaxian Decoction delivered better efficacy. Ligustrazine is the main effective component of TCM rhizoma chuanxiong. According to prior research, ligustrazine can improve microcirculation, resist lipid peroxidation, regulate immunity, antagonize calcium, and inhibit the proliferation of fibroblasts and the transcription of type I collagen gene [20, 21]. Reportedly, ligustrazine can reduce bleomycin-induced pulmonary fibrosis in rats by regulating TNF-α and TGF-β [22]. Polygonum cuspidatum has the effects of clearing away heat and toxic materials, promoting blood circulation, removing blood stasis, eliminating phlegm, relieving cough, expelling wind and promoting diuresis [23]. According to modern pharmacological study, polygonum cuspidatum has antibacterial, anti-inflammatory, antitussive and antiasthmatic effects [24]. Song et al. [25] have found that polygonum cuspidatum has a good preventive and therapeutic effect on the development of alveolitis and the formation of pulmonary fibrosis and is able to delay the process of pulmonary fibrosis. The integration of these herbs in the prescription used in this study could exert effects in clearing lung-heat and eliminating phlegm, invigorating Qi and nourishing Yin, promoting blood circulation and removing blood stasis, dredging collaterals and relieving pain,

Table 5. Assignment

Items	Assignment
IL-6 (pg/mL)	Data belonging to continuous variables were analyzed with their raw data.
IL-12 (pg/mL)	Data belonging to continuous variables were analyzed with their raw data.
IL-18 (pg/mL)	Data belonging to continuous variables were analyzed with their raw data.
HA (μg/L)	Data belonging to continuous variables were analyzed with their raw data.
Therapeutic regimen	Single =1, combined =0.
Efficacy-based grouping	Non-improved group =1, improved group =0.

Interleukin (IL), hyaluronic acid (HA) and laminin (LN).

Table 6. Multivariate analysis

Factor	β	S.E	Wals	Sig.	OR value	95% CI	
						Lower limit	Upper limit
IL-6 (pg/mL)	0.251	0.11	5.209	0.022	1.285	1.036	1.594
IL-12 (pg/mL)	-3.456	0.934	13.697	0	0.032	0.005	0.197
IL-18 (pg/mL)	0.757	0.268	8.006	0.005	2.133	1.262	3.604
HA (μg/L)	0.03	0.015	4.218	0.04	1.031	1.001	1.061
Therapeutic regimen	2.297	0.807	8.092	0.004	9.942	2.043	48.383

Interleukin (IL), hyaluronic acid (HA).

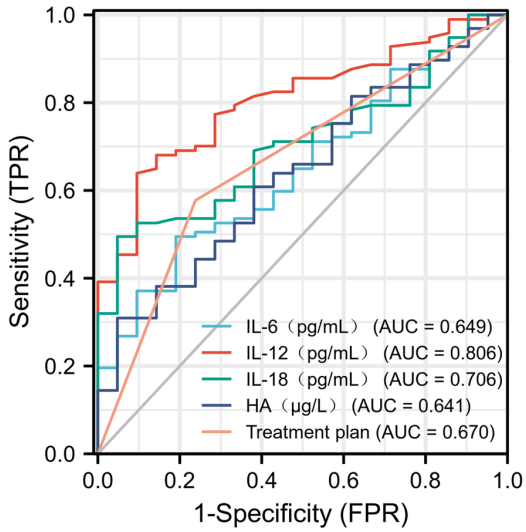

Figure 4. ROC curve of risk factors in predicting the efficacy on patients. Interleukin (IL), hyaluronic acid (HA).

thus achieving the purpose of treating dryness, Qi deficiency, phlegm obstruction and blood stasis.

IPF has an unfavorable prognosis. Once diagnosed, IPF patients have an expected survival time of 2-5 years. However, as we know, there are notable individual differences in the progression of IPF [26]. The pulmonary function in some patients decline very quickly, with unsatisfactory efficacy [27].

At the end of this study, the factors influencing the efficacy in patients were analyzed. As a result, therapeutic regimen, IL-6, IL-12, IL-18 and HA were found to be the risk factors affecting the treatment efficacy in patients. This study found for the first time that Qingfei Huaxian Decoction combined with prednisone acetate could deliver good treatment efficacy in patients. IL-6 is a frequently seen inflammatory factor, with abilities to promote collagen aggregation, inhibit extracellular matrix decomposition and promote fibroblast proliferation [28]. In addition, its increase in the process of pulmonary fibrosis promotes the proliferation of fibroblasts, leading to the replacement of normal lung tissue by fibrous connective tissues and finally triggering the occurrence of IPF [29]. IL-12, as a pleiotropic cytokine, plays a crucial role in enhancing cellular immunity and regulating immune responses [30]. Prior research has revealed that early intervention of IL-12 in animal models of pulmonary fibrosis can contribute to anti-inflammation, immune regulation and anti-fibrosis results [31]. As a pro-inflammatory factor, IL-18 mainly induces Th1 cells and NK cells to produce IFN-γ, thus promoting an inflammatory reaction. Its elevation is also correlated with many autoimmune diseases,

tumors and other diseases [32]. Reportedly, IL-18-binding protein can serve as a prognostic biomarker of IPF [33]. HA is a major macromolecular glycosaminoglycan that can be secreted by type II lung epithelial cells, endothelial cells and lung fibroblasts, among which fibroblasts can be stimulated by pathogenic factors (such as oxygen free radicals) to synthesize a large amount of HA [34]. Prior research has revealed that HA has a positive association with the severity and prognosis of IPF, and patients with increased HA expression generally have an unfavorable prognosis [35]. All these can explain that IL-6, IL-12, IL-18 and HA are associated with the severity of IPF, but whether they can predict the treatment efficacy in patients is still under investigation. Therefore, ROC curve-based analysis was carried out, and IL-12 with AUC > 0.8 in predicting the treatment efficacy in patients was found to be a promising efficacy predictor.

This study has confirmed that Qingfei Huaxian Decoction combined with prednisone acetate can substantially improve the patient's condition and reduce the inflammatory reaction in the body. However, it still has some limitations. First of all, the patients have not been followed up in this study, so whether Qingfei Huaxian Decoction combined with prednisone acetate can improve the survival of patients still needs investigation. Secondly, the samples of this study were acquired by querying electronic medical records, so in such a retrospective study, the analysis of this data may be biased. Therefore, we hope to carry out study with randomized controlled samples and follow up patients to solidify the conclusions.

To sum up, Qingfei Huaxian Decoction combined with prednisone acetate can exert better therapeutic efficacy in IPF patients by improving the serum inflammatory factors and pulmonary function.

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Disclosure of conflict of interest

None.

Address correspondence to: Jingjing Yan, Department of Pulmonary Diseases, Wuhan Hospital of Traditional Chinese Medicine, No. 303 Sixin Avenue, Hanyang District, Wuhan 430050, Hubei, China. Tel: +86-13554328457; E-mail: yanxu2005@163.com

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