Review

Idiopathic pulmonary fibrosis: The current status of its epidemiology, diagnosis, and treatment in China

Haibo Huang, Xiaonu Peng*, Chongwen Zhong

Department of Thoracic Surgery, Yantai Yuhuangding Hospital, Medical College of Qingdao University, Yantai, Shandong, China.

Summary	Idiopathic pulmonary fibrosis (IPF) is a type of intractable and rare disease, and its epidemiology in China is still unclear. The diagnosis and treatment of IPF has received considerable attention and two editions of guidelines on IPF diagnosis and treatment have been published by the Chinese Society of Respiratory Diseases. Treatment of IPF with Traditional Chinese Medicine (TCM) has been widely investigated in China and several types of TCM extracts are reported to be effective in animal models. One effective treatment is lung transplantation; this treatment has been successfully performed in China, yielding satisfactory long-term survival.

Keywords: Prevalence, guideline, therapy, Traditional Chinese Medicine, lung transplantation

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a rare disease characterized by chronic, progressive fibrosing interstitial pneumonia of unknown etiology. Although the exact morbidity is still unclear due to the lack of large-scale studies, IPF is reported to have no distinct geographical or ethnical distribution (*1*). Because of China's huge population, the country is estimated to have the largest number of patients with IPF. IPF is a type of intractable disease. No specific pharmacologic therapies to treat IPF have been found to date. IPF is progressive, irreversible, and associated with an extremely poor prognosis. The pulmonary function of patients with IPF will progressively deteriorate as the disease progresses, and patients have a median survival time of 2 to 3 years (*2*). The current article briefly reviews the current status of IPF epidemiology, diagnosis, and treatment in China.

2. Search strategy

Wanfang Database, an electronic database of Chinese medicine, was searched using the keyword "idiopathic

pulmonary fibrosis" combined with "diagnosis" or "treatment" or "epidemiology" to identify all relevant literature published in Chinese journals since January 1980. The full text of each article was reviewed and the article was selected if pertinent.

## 3. General condition and epidemiology

The first article about IPF in Chinese academic journals was a description of the condition in Japan in 1980 (*3*). The first Chinese case was reported in 1981 (*4*). IPF was first known as Hamman-Rich syndrome and then later known as cryptogenic fibrosing alveolitis (CFA) before its current appellation of IPF. The terms CFA and IPF have both been used in China but IPF is now preferred.

Different studies have reported a varying prevalence of IPF from 1.25 to 27.9 cases per 100,000 (*5-12*), as shown in Figure 1. A study in the United Kingdom estimated that the incidence of IPF increased by 11% annually from 1991 to 2003 (*13*).

Most data on IPF were from North America, Europe, and Japan. To date, no epidemiological studies of IPF have been conducted in China and the exact prevalence of IPF in China is still unknown. There is very little documentation on the epidemiology of rare diseases in China because there are no systems to register rare diseases (*14*). This is partly because of the delays in Chinese epidemiology, unbalanced economic development, and China's large population. Another key reason for the lack of information on IPF in China is

*Address correspondence to:
Dr. Xiaonu Peng, Department of Thoracic Surgery, Yantai Yuhuangding Hospital, No. 20, Yuhuangding Donglu, Yantai, Shandong, China.
E-mail: doctorhuanghaibo@outlook.com
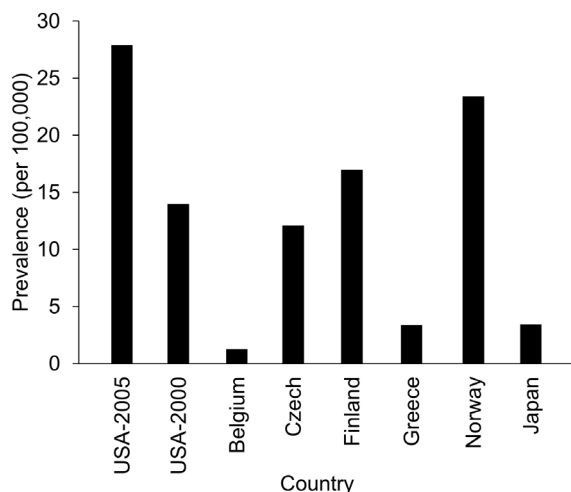
Figure 1. Prevalence of idiopathic pulmonary fibrosis in different countries and according to different studies.

because the former gold standard for IPF diagnosis (*15*), a surgical biopsy, is not readily accepted in China. To Chinese patients, the risk of diminished health caused by a diagnostic procedure is greater than the benefit of a surgical biopsy. Because of the absence of effective treatments, Chinese patients prefer experimental therapy to a diagnostic procedure.

Some epidemiological characteristics of IPF can be ascertained indirectly from several studies in China. A study (*16*) conducted by the Chinese Society of Respiratory Diseases at ten hospitals found that those hospitals treated 697 cases of IPF from 1990 to 2003; these cases accounted for about 25.5% of all cases of diffuse interstitial lung disease (DILD). In another multicenter study in Tianjin (*17*), patients with DILD accounted for about 39.5% of patients in Respiratory Medicine and 1.51% of all inpatients in 2009. Some epidemiologic characteristics of IPF in China have been noted, such as one diagnostic criterion listed in the 2002 guidelines for the diagnosis and treatment of IPF from the Chinese Society of Respiratory Diseases (*18*). IPF usually develops past middle age and males are more susceptible than females at a rate of about 2 to 1. IPF is rarely seen in children. Smoking (*19*) and environmental factors, like metal and wood dust exposure (*20*), have been reported to be major risk factors for IPF. Smoking is strongly associated with IPF, particularly for individuals with a history of smoking more than 20 cigarettes a day over 20 years (20 pack-years). China is known to have the largest population of smokers. According to one study in 2002, the prevalence of smoking among males was 66% and the prevalence of smoking among females was 3.08% (*21*). As the largest developing country, labor protections are still developing in China and the risk of metal and wood dust exposure remains high. Thus, China will have a higher incidence of IPF compared to developed countries, and further large-scale epidemiologic studies are needed.

4. Diagnosis

Usual interstitial pneumonia (UIP) is the characteristic pattern of IPF. UIP has distinctive findings in both pathological and radiological examinations. However, a number of other conditions can also cause the changes associated with UIP. The most common are connective tissue disease and certain drug toxicities. Before a diagnosis of IPF is made, these conditions should be ruled out.

For a long time, there was debate about whether evidence of UIP in a radiological examination could be used to diagnose IPF without pathological confirmation. In China, the first paper on the diagnosis of IPF was published in 1984 (*22*). In this paper, the author posited that a surgical lung biopsy was not necessarily needed for patients suspected of having IPF. In a trial version of IPF guidelines drafted by the Chinese Society of Respiratory Diseases in 1994 (*23*), both pathological and radiological evidence of UIP were considered diagnostic criteria. The guidelines deemed pathological evidence of UIP to be confirmed IPF and they deemed radiological evidence of UIP to be clinically diagnosed IPF. The guidelines recommended that both be treated for IPF.

In 2002, the Chinese Society of Respiratory Diseases revised its guidelines. In the new guidelines (*18*), the criteria for pathologically diagnosed IPF did not change but the criteria for clinical diagnosis of IPF did change. Four major diagnostic criteria and four minor diagnostic criteria were listed. The major criteria included ruling out of other possible diseases based on the patient's medical history, restrictive ventilatory functional disturbance or gas interchange disturbance, radiological evidence of UIP and ruling out of other diseases based on bronchoalveolar lavage fluid (BALF) or a transbronchial lung biopsy (TBLB). The minor criteria included being over 50 years of age, a history of symptoms for three months or longer, insidious onset of unexplained dyspnea on exertion, and bibasilar inspiratory ("Velcro") crackles. All four major diagnostic criteria and at least 3 minor criteria should be met.

Performing a lung biopsy when IPF is suspected has not been readily accepted in China because of the potential for IPF to worsen, the invasiveness of the procedure, and its cost. Although the exact rate of lung biopsies in China has not been reported, it is estimated to be lower than 10%. Nearly all reports of IPF involved the clinical diagnostic criteria in the guidelines drafted by the Chinese Society of Respiratory Diseases. Only a few reports of surgically diagnosed IPF described a pathological diagnosis reached incidentally as a result of surgery to treat another disease, such as spontaneous pneumothorax. One study reviewed the ability of high-resolution computed tomography (HRCT)-guided lung needle biopsy to diagnose IPF. The technique had an accuracy of 76.2% (*24*). Another

study (*25*) retrospectively analyzed 39 cases of IPF and compared the 2002 guidelines of the Chinese Society of Respiratory Diseases and 2000 guidelines of the American Thoracic Society (ATS); the study noted that the guidelines coincided at a rate of 84.6%.

In the West, the first guidelines for IPF were drafted by the ATS, European Respiratory Society (ERS), and the American College of Chest Physicians (ACCP) in 2000 (*15*). These guidelines recommended a surgical lung biopsy for most patients to reach a correct diagnosis. However, one study (*26*) found that the radiological pattern of UIP was nearly always consistent with pathological evidence of UIP. Thus, the guidelines on IPF drafted by the ATS, ERS, the Japanese Respiratory Society (JRS), and the Latin American Thoracic Association (ALAT) in 2011 no longer recommend a surgical lung biopsy for patients with a UIP pattern on HRCT (*27*).

5. Treatment

5.1. *Pharmacological therapies*

Because of its unknown pathogenesis, most pharmacologic treatments of IPF assume that IPF is caused by inappropriate inflammation and subsequent injury and fibrosis of pulmonary alveoli. Thus, corticosteroids, immunosuppressive or cytotoxic agents, and antifibrotic agents have long been used to treat IPF. To date, however, pharmacologic therapies to treat IPF have failed to offer promise.

The 1994 trial guidelines for the diagnosis and treatment of IPF (*23*) recommended corticosteroids as a first-line therapy and immunosuppressive or cytotoxic agents were recommended as a second-line therapy. Because of the possible side effects of these drugs, personalized therapy and timely dose adjustment according to test results were also recommended. After several years of clinical use, these regimens were found to temporarily improve symptoms but not improve long-time survival. The 2002 guidelines of the Chinese Society of Respiratory Diseases (*18*) recommended a combination of corticosteroids with immunosuppressive or cytotoxic agents. Courses of treatment and indices of their effectiveness were also described. The revised guidelines also mentioned many types of new drugs, like N acetylcysteine, γ interferon, colchicine, erythromycin, and pirfenidone. Because of the lack of clinical evidence, however, they were not recommended.

After years of clinical experience and advances in evidence-based medicine, the 2011 guidelines on IPF diagnosis and treatment from the ATS (*27*) indicated that corticosteroid monotherapy, colchicine, acetylcysteine, γ interferon, bosentan, etanercept, and the combination of corticosteroids with immunosuppressive agents were not recommended. Only acetylcysteine combined with corticosteroids and azathioprine, acetylcysteine monotherapy, anticoagulant monotherapy, and pirfenidone monotherapy were recommended in a minority of IPF cases.

Traditional Chinese Medicine (TCM) in the form of both herbal compounds and single herb extracts has been reported to have some effect on IPF (*28*). The 1994 trial guidelines for the diagnosis and treatment of IPF recommended TCM therapy as an experimental therapy (*23*). TCM is a reflection of the Chinese people's long struggle against disease. TCM is readily accepted in China and nearly all patients with IPF had received TCM therapy at one point. Because there are no large-scale, multicenter, randomized, double-blind, parallel-treatment, placebo-controlled studies of the effects of TCM, its exact effects are still debated. TCM has not been readily accepted in the West because clear evidence of its pharmacological mechanisms is lacking. That said, the development of TCM extraction and purification techniques has resulted in several studies (*29-41*) reporting that some single herb extracts of TCM had some effect in animal models of IPF (Table 1).

5.2. *Oxygen therapy and palliative therapy*

The patient's pulmonary function will deteriorate rapidly as IPF progresses. In the end stages, severe hypoxia will develop even when at rest. The 1994 trial guidelines for the diagnosis and treatment of IPF (*23*) recommended that patients with end-stage IPF not receive drug therapy but only oxygen therapy and palliative therapy. The 2011 guidelines of the ATS recommended long-term oxygen therapy for patients with IPF and clinically significant resting hypoxemia (*27*).

Because nearly all patients will develop severe hypoxia in the end stages of IPF, oxygen therapy and palliative therapy are crucial. However, there are still no Chinese guidelines on the indications for oxygen therapy, inhaled oxygen flow, and the duration of oxygen therapy. One study (*42*) retrospectively analyzed 5 patients with end-stage IPF who received oxygen therapy. The study found that high-flow oxygen therapy was not suitable and the oxygen flow needed to be adjusted depending on blood oxygen saturation. In China, however, most patients with end-stage IPF receive oxygen therapy at home. They would have difficulty monitoring their blood oxygen saturation. Thus, instructing patients with end-stage IPF in use of home oxygen therapy is still a major problem.
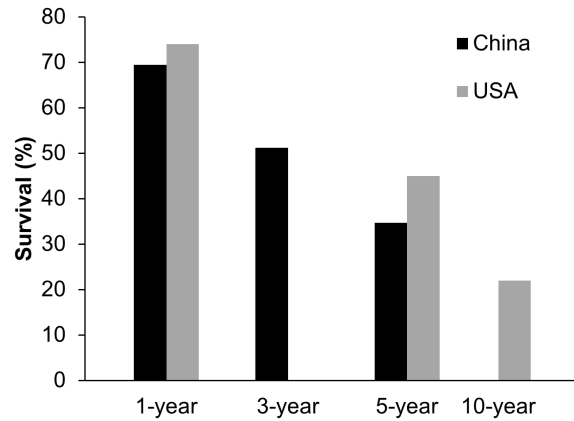
5.3. *Lung transplantation*

Lung transplantation is one form of highly effective treatment for many types of end-stage lung disease. Lung transplantation has made great advances in recent years. Lung transplantation to treat IPF first resulted in successful long-term survival in 1983 (*43*). Since then, IPF has become the primary indication for lung

Table 1. Single-herb TCM reported to be effective in treating IPF in animal models

Common name	Latin name	Major active ingredients	Main pharmacologic function	Ref.
Danshen root	*Radix salvia miltiorrhiza*	Salvianolic acid A and B, polysaccharide	Scavenges oxygen radicals, anti-lipid peroxidation	29
Chuanxiongzine	*Ligustrazine*	Tetramethylpyrazine	Inhibits fibroblast cell proliferation, down-regulates CTGF expression	30
Chinese angelica	*Angelica sinensis*	5-Hydroxymethyl-furfural, polysaccharides	Scavenges oxygen free radicals, down-regulates CTGF expression	31,32
Huangqi, Radix astragali	*Astragalus membranaceus*	Polysaccharides, saponins, and flavonoids	Down-regulates the expression of MMP-2 and TIMP-1	33
Sanqi, pseudo-ginseng	*Panax notoginseng*	Panax notoginseng saponins	Down-regulates the expression of hydroxyproline and CTGF	34
Ginkgo Leaf	*Folium Ginkgo*	Flavonoid, terpenoid	Down-regulates the expression of CTGF, inhibit AT II epithelial cell apoptosis	35,36
Fourstamen Stephania root/radix	*Stephania tetrandra*	Tetrandrine	Blocks calcium channels and calmodulin	37
Common three-wingnut root/radix	*Tripterygium wilfordii*	Triptolide and diterpenoids	Anti-inflammatory and anti-oxidant	38
Sha shen, root of straight ladybell	*Adenophora stricta*	Triterpenoids and β-sitosterol	Down-regulates the expression of TGF-β1 and TNF-α	39
Chinese caterpillar fungus	*Cordyceps sinensis*	Cordyceps polysaccharide, cordycepin, ergosterol	Reduces inflammatory cell infiltration and fibroblast deposition, regulates the balance of MMP-9/TIMP-1	40
Turmeric, Jianghuang	*Curcuma longa*	Curcumin, demethoxycurcumin, and bisdemethoxycurcumin	Induces the apoptosis of abnormal lung fibroblasts	41

Abbreviations: AT, alveolar type; CTGF, connective tissue growth factor; MMP-2, matrix metalloproteinases-2; MMP-9, matrix metalloproteinases-9; TIMP-1, tissue inhibitor of metalloproteinases-1; TGF-β1, transforming growth factor; TNF-α, tumor necrosis factor-α.

Figure 2. Long-term survival after lung transplantation.

transplantation and about 37% of lung transplants prior to 2009 were to treat IPF (*44*). Lung transplantation to treat IPF was recommended by both the 1994 trial guidelines for the diagnosis and treatment of IPF and the 2011 guidelines of the ATS.

The largest lung transplantation center in China is in Jiangsu Province. There, 131 patients underwent lung transplantation from September 2002 to December 2011. Of these patients, 59 (45%) were diagnosed as having end-stage IPF (*45*). Patients had a 1-year survival rate of 69.5%, a 3-year survival rate of 51.2%, and a 5-year survival rate of 34.7%, with a median survival time of 42 months. In the West, lung transplantation to treat IPF (*46*) has yielded significant benefits in terms of survival. Currently, patients have a 1-year survival rate of 74%, a 5-year survival rate of 45%, and a 10-year survival rate of 22%. A comparison of survival rates is shown in Figure 2.

Therapies to treat IPF are rarely effective and disease progression is inevitable. To date, lung transplant remains the only viable treatment option offering long-term survival, with a 5-year survival rate of 45% and a 10-year survival rate of 22% (*46*). This is very encouraging for patients with IPF. However, only a few patients with IPF in China have the opportunity to receive a lung transplant to improve their quality of life and prolong their survival due to the expense of the procedure and lack of donors. From 1978 to 2010, only about 244 lung transplants were performed at about 20 facilities in China (*47*). This cannot meet the demands of the large estimated population of patients with IPF. In addition, progression of fibrosis in the native lungs after lung transplantation is also a major challenge (*46*).

6. Conclusion

IPF is a type of rare disease, and little is known about its epidemiologic characteristics in China. Because of China's huge population, the country is estimated to have the largest population of patients with IPF.

Doctors in China have continually focused on this intractable disease and they have drafted two editions of guidelines for IPF diagnosis and treatment. However, the current state of IPF diagnosis and treatment remains unsatisfactory. To date, there are no specific pharmacological therapies for IPF. CTM is widely used in China and is reported to have some effect on IPF, but more large-scale studies and randomized, placebo-controlled studies are needed, as are studies of the pharmacological mechanisms of TCM. Home oxygen therapy is widely accepted in China. Lung transplantation to treat IPF has been successfully performed in China, resulting in long-term survival.

References

1. Mannino DM, Etzel RA, Parrish RG. PPulmonary fibrosis deaths in the United States, 1979-1991. An analysis of multiple-cause mortality data. Am J Respir Crit Care Med. 1996; 153:1548-1552.
2. Rudd RM, Prescott RJ, Chalmers JC, Johnston ID; Fibrosing Alveolitis Subcommittee of the Research Committee of the British Thoracic Society. British Thoracic Society Study on cryptogenic fibrosing alveolitis: Response to treatment and survival. Thorax. 2007; 62:62-66.
3. Zhu GG. Idiopathic pulmonary fibrosis. Progress in Japanese Medicine. 1980; 1:9-11. (in Chinese)
4. Peng DH, Xu HY. Idiopathic pulmonary fibrosis (Hamman-Rich syndrome): A case report and review of the data. Medicine and Pharmacology of YunNan. 1981; 10-12. (in Chinese)
5. Fernández Pérez ER, Daniels CE, Schroeder DR, St Sauver J, Hartman TE, Bartholmai BJ, Yi ES, Ryu JH. Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis: A population-based study. Chest. 2010; 137:129-137.
6. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2006; 174:810-816.
7. Thomeer MJ, Costabe U, Rizzato G, Poletti V, Demedts M. Comparison of registries of interstitial lung diseases in three European countries. Eur Respir J. 2001; 32(suppl):114-118.
8. Kolek V. Epidemiology of cryptogenic fibrosing alveolitis in Moravia and Silesia. Acta Univ Palacki Olomuc Fac Med. 1994;137:49-50.
9. Hodgson U, Laitinen T, Tukiainen P. Nationwide prevalence of sporadic and familial idiopathic pulmonary fibrosis: Evidence of founder effect among multiplex families in Finland. Thorax. 2002; 57:338-342.
10. Karakatsani A, Papakosta D, Rapti A, Antoniou KM, Dimadi M, Markopoulou A, Latsi P, Polychronopoulos V, Birba G, Ch L, Bouros D; Hellenic Interstitial Lung Diseases Group. Epidemiology of interstitial lung diseases in Greece. Respir Med. 2009; 103:1122-1129.
11. Von Plessen C, Grinde O, Gulsvik A. Incidence and prevalence of cryptogenic fibrosing alveolitis in a Norwegian community. Respir Med. 2003; 97:428-435.
12. Ohno S, Nakaya T, Bando M, Sugiyama Y. Idiopathic pulmonary fibrosis – results from a Japanese nationwide epidemiological survey using individual clinical records.

13. Gribbin J, Hubbard RB, Le Jeune I, Smith CJ, West J, Tata LJ. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. Thorax. 2006; 61:980-985.
14. Zhao H, Cui YZ, Zhou XY, Pang JX, Zhang XM, Xu SQ, Han JX. Study and analysis of the state of rare disease research in Shandong Province, China. Intractable Rare Dis Res. 2012; 1:161-166.
15. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med. 2000; 161:646-664.
16. Kang J, Kong LF. Proceedings of the 6th National Conference on Respiratory Diseases of the Chinese Medical Association. Chinese Journal of Internal Medicine. 2005; 44:154-156. (in Chinese)
17. Wei LQ, Peng SC, Cao J, Liu GY, Lai YP, Jia W, Zheng H, Li LY, Xiao YY, Li N, Zhang NX. A multicenter study of the clinical characteristics of diffuse interstitial lung diseases and their diagnosis and treatment. Chinese Journal of General Practice. 2012; 15:2521-2524. (in Chinese)
18. Chinese Society of Respiratory Diseases. Draft guidelines for the diagnosis and treatment of IPF. Chinese Journal of Internal Medicine. 2002; 41:498-500. (in Chinese)
19. Hubbard R, Lewis S, Richards K, Johnston I, Britton J. Occupational exposure to metal or wood dust and aetiology of cryptogenic fibrosing alveolitis. Lancet. 1996; 347:284-289.
20. Iwai K, Mori T, Yamada N, Yamaguchi M, Hosoda Y. Idiopathic pulmonary fibrosis. Epidemiologic approaches to occupational exposure. Am J Respir Crit Care Med. 1994; 150:670-675.
21. Yang GH, Ma JM, Liu N, Zhou LN. Smoking and passive smoking of Chinese, 2002. Chin J Epidemiol. 2005; 26:77-83. (in Chinese)
22. Lei ZZ. The diagnosis of idiopathic pulmonary disease. Chinese Journal of Postgraduates of Medicine. 1984; 5:6-7. (in Chinese)
23. Chinese Society of Respiratory Diseases. Trial guidelines for the diagnosis and treatment of idiopathic pulmonary fibrosis. Chin J Tuberc Respir Dis. 1994; 17:8-8. (in Chinese)
24. Liu JH, Bao YW. The diagnostic value of HRCT-guided lung needle biopsy for 21 cases of Idiopathic pulmonary fibrosis. Fujian Medical Journal. 2005; 27:68-69. (in Chinese)
25. Zhao YB, Tong ZY, Ao R, Li ZH, Hou XM. Retrospective analysis of 39 cases of idiopathic pulmonary fibrosis. Journal of China Medical University. 2003; 32:77-78. (in Chinese)
26. FFlaherty KR, King TE Jr, Raghu G, Lynch JP 3rd, Colby TV, Travis WD, Gross BH, Kazerooni EA, Toews GB, Long Q, Murray S, Lama VN, Gay SE, Martinez FJ. Idiopathic interstitial pneumonia: What is the effect of a multidisciplinary approach to diagnosis? Am J Respir Crit Care Med. 2004; 170:904-910.
27. Raghu G, Collard HR, Egan JJ, *et al*. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. Am J Respir Crit Care Med. 2011; 183:788-824.
28. Chen YY, Fan XM. Advances in the treatment of IPF

with Traditional Chinese Medicine. Chinese Journal of Clinicians (Electronic Edition). 2010; 4:130-132. (in Chinese)

29. Lu SJ, Liu YN, Wang HZ. Study of the protective function of salvia miltiorrhiza on bleomycin-induced pulmonary fibrosis in a rat model. Chinese Journal of Clinical Pharmacology and Therapeutics. 2005; 10:514-517. (in Chinese)

30. Jiang Y, Li W, Chen M. Effect of ligustrazine on CTGF expression and collagen deposition in rats with pulmonary fibrosis. Chinese Journal of General Practice. 2008; 6:1215-1216. (in Chinese)

31. Chai WS, Li YC, Wang HX, Guo M, Li YQ. The effects of Angelica sinensis on pulmonary fibrosis in rats. Chinese Pharmacological Bulletin. 2003; 19: 819-822. (in Chinese)

32. Guo GS, Wang H. Effects of Angelica sinensis on fibrosis in rats with bleomycin-induced pulmonary fibrosis. Medical Journal of Wuhan University. 2007; 28:560-563. (in Chinese)

33. Peng Q, Xin JB, Su LP, Xiang F, Ma WL, Wang F. Effect of Radix astragali on expression of MMP-2 and TIMP-1 in rats with pulmonary fibrosis. ACTA MED Univ Sci Technol Huazhong. 2007; 36:35-37. (in Chinese)

34. Quan Y, Xia QM, Li FX, Li HY, Zhang DT. Effects of Panax notoginseng on pulmonary fibrosis and CTGF expression in rats. Medical Journal of National Defending Forces in Southwest China. 2009; 19:23-25. (in Chinese)

35. Huang YM, Chen XL, Xu N, Liu W, Qi J, Liu JH, Ai J. Effects of Ginkgo biloba extract on the expression of connective tissue growth factor in the initial stage of fibrosis in lungs of rats. Chinese Journal of Pathophysiology. 2007; 23:1130-1132. (in Chinese)

36. Xu ZX, Ding MQ, Chen R, Wang P, Fei Y, Liu X. Effects of Ginkgo biloba extract on apoptotic changes in AT-II cells in rats with bleomycin-induced pulmonary fibrosis. Liaoning Journal of Traditional Chinese Medicine. 2008; 35:1312-1314. (in Chinese)

37. Chen YF, Xi JZ, Gao CY, Liu JY. The effects of tetrandrine on the calmodulin system in rats with pulmonary fibrosis. Journal of Xinxiang Medical College. 2003; 20:83-85. (in Chinese)

38. Ren YX, Zhou R, Tang W, Wang WH, Li YC, Yang YF, Zuo JP. (5R)-5-hydroxytriptolide (LLDT-8) protects against bleomycin-induced lung fibrosis in mice. Acta Pharmacol Sin. 2007; 28:518-525.

39. Yao L, Sheng L, Li DS, Ma Z. The effects of adenophora stricta on the expression of TGF-β1 and TNF-α in pulmonary fibrosis of rats. Traditional Chinese Medicinal Research. 2007; 20:20-22. (in Chinese)

40. Chen M, Cheung FW, Chan MH, Hui PK, Ip SP, Ling YH, Che CT, Liu WK. Protective roles of Cordyceps on lung fibrosis in cellular and rat models. J Ethnopharmacol. 2012; 143:448-454.

41. Gao W, Zhang DP, Hua YF. Effect of curcumin on proliferation and apoptosis of pulmonary fibroblasts. The Journal of Practical Medicine. 2008; 24:2393-2396. (in Chinese)

42. Chen XY. Oxygen therapy and care for 5 patients with idiopathic pulmonary fibrosis. Journal of Clinical Pulmonary Medicine. 2010; 15:1213-1213. (in Chinese)

43. Toronto Lung Transplant Group. Unilateral lung transplantation for pulmonary fibrosis. N Engl J Med. 1986; 314:1140-1145.

44. Christie JD, Edwards LB, Aurora P, Dobbels F, Kirk R, Rahmel AO, Stehlik J, Taylor DO, Kucheryavaya AY, Hertz MI. The Registry of the International Society for Heart and Lung Transplantation: Twenty-sixth Official Adult Lung and Heart-Lung Transplantation Report-2009. J Heart Lung Transplant. 2009; 28:1031-1049.

45. Liu D, Mao WJ, Chen JY. A single center's experience with lung transplantation for idiopathic pulmonary fibrosis. Chinese Academic Conference on Organ Transplantation. 2012; 25:213-213. (in Chinese)

46. Elicker BM, Golden JA, Ordovas KG, Leard L, Golden TR, Hays SR. Progression of native lung fibrosis in lung transplant recipients with idiopathic pulmonary fibrosis. Respir Med. 2010; 104:426-433.

47. Mao W, Chen J, Zheng M, Wu B, Zhu Y. Initial experience of lung transplantation at a single center in China. Transplant Proc. 2013; 45:349-355.