Review

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Idiopathic pulmonary fibrosis in East Asian

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Summary **Idiopathic pulmonary fibrosis (IPF) is a rare lung disease with a prognosis that can be worse than that of many cancers. Recent studies have improved our understanding of IPF and new treatment options have become available. However, most studies are conducted predominantly in Western countries while few are conducted in East Asian countries. The distribution, effectiveness of treatment, and prognosis for IPF differ among Westerners and East Asians, but whether the heterogeneity of IPF in East Asians is the result of ethnic differences and geographic variability is unclear. This study highlights the current prevalence of IPF and its characteristics in the East Asian population and it provides valuable information to understand the current clinical status of patients with IPF in light of recent advances in its diagnosis and treatment.**

Keywords: Idiopathic pulmonary fibrosis, East Asian population, heterogeneity, diagnosis, treatment

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a rare, chronic, progressive, and irreversible lung disease with no specific cause and pathophysiological mechanism. Most patients are males over the age of 60 and most patients have a history of smoking. IPF is the most common and severe form of usual interstitial pneumonia (UIP). Median survival is estimated to be 3 to 5 years from the time of diagnosis (*1*). Over the past few years, several medications have demonstrated the ability to slow the progression of this devastating disease, but there is no effective treatment for the disease itself (*2*). For now, lung transplantation seems to be the sole option for selected patients with advanced IPF (*3*).

Since the ATS/ERS/JRS/ALAT guidelines on the diagnosis and management of IPF were published in 2011, new data from major clinical studies, particularly with regard to epidemiology, and from clinical trials have been released from several Western countries. Only a few recent studies focused on East Asians. The distribution, effectiveness of treatment, and prognosis for IPF differ among Westerners and East Asians, but whether the heterogeneity of IPF in East Asians is the result of ethnic differences and geographic variability is unclear. To date, no systematic study has reviewed the prevalence and clinical course of IPF in the East Asian population. The current study has discussed the features and management of IPF in Chinese, Japanese, and Korean patients as a whole since those populations have a similar ethnicity. The aim of this study was to describe the current state of IPF in East Asia as well as recent advances in its diagnosis and treatment.

2. Epidemiology

IPF is a disease that affects the elderly and is more prevalent in males. The true incidence and prevalence of IPF have not been accurately determined because of the lack of a uniform definition, diagnostic criteria, and differences in methodologies and populations in previous studies (*4*). However, the 2001 ATS/ERS consensus statement offers an opportunity for more precise epidemiologic studies. Generally, the prevalence and incidence of IPF are higher in American studies than in European and Asian studies (*5,6*). Whether this is due to true differences in geography and ethnicity or simply due to methodological differences in the way the studies were conducted is unclear.

Data from the US indicate that IPF has a prevalence

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between 14 and 28 cases per 100,000 population. The annual estimated incidence in the US is between 6.8 and 8.8 cases per 100,000 population. IPF-related morbidity and mortality is higher in men and increases progressively with age (*5*). A study from South Korea in 2011-2012 indicated that the incidence of IPF was 1.7/100,000, based on the new ATS/ERS/JRS/ALAT statement published in 2011. There was an overall increase in morbidity and mortality in those years. Longevity, regular medical examinations, and increasing use of CT might contribute to changes in the epidemiology of IPF (*7*). An epidemiological survey in Japan from 2003 to 2007 indicated that the prevalence and cumulative incidence of IPF was 10.0 and 2.23 per 100,000 population, respectively, with 72.7% of cases involving males and an increase in frequency with age (*8*).

3. Risk factors

Although IPF is a condition of unknown origin. Exposure to risk factors such as cigarette smoking, environmental factors, and microbial agents as well as genetic factors and gastroesophageal reflux have been found to increase the risk of developing the disease according to different studies (*9*).

4. Diagnosis

4.1. *Clinical Presentation*

IPF primarily occurs between 60 and 70 years of age and the clinical symptoms of IPF are nonspecific. In the early stages, IPF clinically presents as progressive exertional dyspnea with a dry cough. In lung auscultation, bilateral inspiratory crackles ("Velcro crackles") at the lung base are characteristic and appear early in the disease. Finger clubbing is present in less than 50% of cases. Cyanosis and signs of right ventricular failure occur in the advanced stage with respiratory insufficiency, and precapillary pulmonary hypertension is often present, particularly if emphysema is associated with IPF. The disease progresses towards chronic restrictive respiratory failure and death (*1*).

4.2. *Pulmonary function tests*

Pulmonary function is usually evaluated with systematic tests when diagnosing IPF. The index of spirometry typically reveals restrictive ventilatory dysfunction with a reduced forced vital capacity (FVC) and total lung capacity (TLC) reflecting reduced lung function; the extent of the decrease is useful in quantifying the severity of disease and predicting outcome. Diffusing capacity for carbon monoxide (DLCO) almost invariably decreases due to both a contraction of the pulmonary capillary volume and ventilation and perfusion mismatching. The decline in DLCO may appear in the early or middle stages of IPF as the only functional abnormality. Resting arterial oxygen saturation is usually normal, but pulmonary function tests performed during exercise, such as a 6-min walk test (6MWT), reveal a reduced exercise capacity with increased alveolar-arterial oxygen tension difference and oxygen desaturation.

4.3. *Biomarkers*

There are no specific laboratory abnormalities in patients with IPF. Lung diseases with a specific etiology need to be systematically ruled out and extra-pulmonary signs and biomarkers need to be examined to eliminate connective tissue diseases (CTD) before IPF is diagnosed. Inflammatory and potential disease–associated biomarkers such as blood cell count, C-reactive protein, antinuclear antibodies, rheumatoid factor, and precipitin should be measured. Bronchoalveolar lavage is non-specific in patients with IPF and is characterized by the presence of macrophages and neutrophils with or without eosinophils. A bronchoalveolar lavage may be warranted and crucial to ruling out other diseases. Ohshimo *et al*. found that a high proportion of lymphocytes in the lavage fluid (more than 30%) tends not to indicate IPF (*10*).

4.4. *Radiology*

HRCT is an essential component to the diagnosis of IPF. The ATS/ERS/JRS/ALAT 2011 guidelines have assigned a primary diagnostic role to high-resolution computed tomography (HRCT) (*1*). Radiological criteria for IPF are classified into three categories: a UIP pattern, a possible UIP pattern, and a pattern inconsistent with UIP. On HRCT, UIP is characterized by the presence of reticular opacities, which are often associated with traction bronchiectasis. Honeycombing is a sufficient and persuasive sign of a definite UIP pattern on HRCT. Honeycombing on HRCT appears as clustered cystic airspaces 3-10 mm in diameter and is located below the pleura with well-defined walls (Figure 1). The distribution of UIP on HRCT is characteristically basal and peripheral, although it is often patchy (*11*).

4.5. *Surgical lung biopsy*

An HRCT and histopathologic correlate for IPF is UIP. If UIP is definitively diagnosed based on typical manifestations on HRCT, a surgical lung biopsy is not necessary. A video-assisted surgical lung biopsy after careful evaluation of the operative risk is required to confirm the diagnosis if the imaging features are not characteristic. In some cases, multidisciplinary team must consult to reach a definite diagnosis when HRCT findings are inconsistent with findings from a surgical

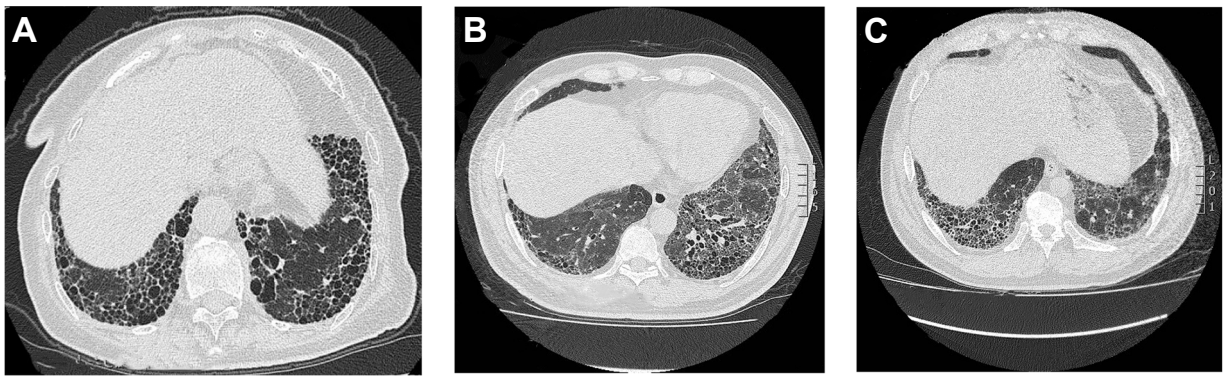

Figure 1. Chest computed tomography (CT) scans from patients with idiopathic pulmonary fibrosis (IPF). (A) A typical radiological pattern of usual interstitial pneumonia with subpleural honeycombing in the costophrenic angle in Patient A. Based on CT images from Patient B **(B)** and Patient C **(C)**, there is a familial cluster of IPF in two brothers age 50 and age 52, respectively.

lung biopsy (*1*).

5. Treatment

5.1. *Pharmacological treatment*

For many years, there were no effective treatments of IPF until two agents, pirfenidone and nintedanib, demonstrated the ability to slow the progression of the disease according to recent clinical trials.

Pirfenidone is an oral antifibrotic agent that inhibits the TGF-β pathway. The first multicenter, double-blind, placebo-controlled phase III randomized controlled trial of pirfenidone in IPF, which was conducted in 275 Japanese patients with well-defined IPF over 52 weeks, indicated that pirfenidone 1,800 mg/day slowed the decline in vital capacity (70 mL) and it may increase the PFS time. Photosensitivity was a major adverse event in that trial, though it was mild in most of the patients (*12*).

Nintedanib is an intracellular inhibitor that targets multiple tyrosine kinases, including PDGF, VEGF, and FGF. A randomized, double-blind, phase 3 trial to evaluate the efficacy and safety of 150 mg of nintedanib twice daily in comparison to a placebo was conducted over 52 weeks in a total of 1,066 patients with IPF. Nintedanib reduced the decline in FVC (125 ml FVC decline), which is consistent with slowing of the disease progression. There were no differences in DLCO measurements or in the distance walked in 6 minutes. Nintedanib use was frequently associated with diarrhea, which led to discontinuation of the study medication in less than 5% of patients (*13*). Patients who completed the trial were able to receive nintedanib in an open-label extension trial. In patients with a baseline FVC ≤ 50% and > 50% predicted at the start of the extension trial, the absolute mean change in FVC from the baseline to week 48 was –62.3 and –87.9 mL, respectively (n = 24 and n = 558, respectively). The decline in FVC in both subgroups by baseline FVC % predicted was similar to that in an earlier trial, suggesting that nintedanib may have a similar effect on disease progression in patients with advanced disease as in less advanced disease (*14*).

The decline in FVC was significantly slower in patients treated with pirfenidone or nintedanib compared to a placebo. Both pirfenidone and nintedanib were recommended for treatment of IPF in an update of an Official ATS/ERS/JRS/ALAT Clinical Practice Guideline in 2015 after a comprehensive analysis of a series of clinical trials involving these two medications (*2*). Furthermore, the FDA also has approved both pirfenidone and nintedanib for the treatment of IPF.

However, which drug is superior as the first-line therapy for IPF is still unclear. A recent systematic review that indirectly compared both treatments based on network meta-analysis reported that the two treatments had a beneficial effect; nintedanib appears to have superior benefit on FVC, but mortality did not differ significantly with nintedanib and pirfenidone (*15*). A superior first-line therapy for IPF has yet to be determined based on clinical efficacy. Furthermore, the two drugs cause slightly different adverse reactions. Gastrointestinal and skin-related events were more common in the pirfenidone group, whereas diarrhea and liver dysfunction were more common in the nintedanib group. The choice of pirfenidone or nintedanib for IPF should be individualized based on these results.

5.2. *Lung transplantation*

Lung transplantation is now a widely accepted treatment option for the management of a wide range of chronic end-stage lung disorders. Given the progressive and incurable nature of IPF, lung transplantation is commonly suggested as the most effective treatment for patients with moderate to severe IPF (*16*).

IPF accounts for the largest group of patients on the transplant list and median survival post-transplantation among patients with IPF is estimated to be 4.5 years.

Post-transplant survival is lower for patients with IPF than for patients with other pre-transplant conditions, with a 5-year survival rate of about 50% internationally (*17*). According to data from the International Society for Heart and Lung Transplantation (ISHLT) on lung transplants received by patients with IPF, bilateral lung transplantation has been increasingly performed at most facilities because it provided a better long-term survival than single lung transplantation (*18*). A pooled survival analysis of three observational studies revealed no differences between patients who received single versus bilateral lung transplantation. The improved survival of bilateral lung transplantation over single lung transplantation may be the result of selection bias (*1*).

In East Asia, a shortage of lung donors is a key problem that has yet to be resolved because of the difficulty in accepting the concept of brain death and strict laws.

A systematic review in Japan reported that lung transplantation was performed in 464 patients at 9 lung transplant centers in Japan between 1998 and 2015. Cadaveric lung transplantation was performed in 283 patients (61%) and living-donor lobar lung transplantation was performed in 181 patients (39%). The upper age limit in Japan is stricter due to the severe shortage of cadaveric donors. Candidates should be under the age of 55 for bilateral lung transplantation and under the age of 60 for single lung transplantation when registered with the Japan Organ Transplant Network waiting list. Single lung transplantation has been chosen more often than bilateral lung transplantation to maximize the number of transplants by sharing scarce donors, with a donor/recipient ratio approaching 80%. Over the past several years, living-donor lobar lung transplantation has been performed extensively as a life-saving procedure for critically ill patients in Japan because of the long average waiting time, which is more than 800 days for a cadaveric lung. There was no significant difference in survival between patients who underwent single lung transplantation and those who underwent bilateral lung transplantation (*19*).

A retrospective review of a total lung transplant database from a medical facility in China indicated that IPF accounts for 47% of all lung transplants. Single lung transplantation accounted for 72% of transplants. The proportion of bilateral lung transplants is consistently low (less than 30% of all procedures), and this proportion is much lower than that noted in the ISHLT Registry (*20*).

Based on evidence of favorable long-term survival in patients with IPF who have received a lung transplant, current statements recommend that patients with progressive IPF and limited diffusion capacity should be evaluated early for lung transplantation (*1*). International recommendations specify that transplantation should be considered in patients younger than age 65 if their DLCO is less than 39% predicted and FVC has decreased by more than 10% over 6 months of follow-up (*21*).

6. Complications and comorbidities

6.1. *Acute exacerbation*

Acute exacerbation of IPF (AE-IPF) is a life-threatening event with no identified cause. In a large retrospective study, the 1-year and 3-year incidence of AE-IPF was as high as 14.2% and 20.7%, respectively. The presence of AE-IPF results in a poor prognosis, with mortality exceeding 60% during hospitalization and 90% within 6 months of discharge (*22*). A study in Japan reported that acute exacerbation is the most frequent cause of death in up to 40% of patients with IPF (*8*).

AE-IPF is characterized by acute (less than 30 days) worsening of dyspnea with new opacities, and ground-glass opacities in particular, on HRCT after ruling out specific causes such as infection, pulmonary embolism, and left heart failure. High-dose steroid treatment is recommended for AE-IPF, but evidence of its efficacy is lacking. Bronchoalveolar lavage may be warranted to rule out pulmonary infection before starting steroid therapy if the patient's condition allows it. Antibiotic treatment depends on the clinical status of the patient or the results of a bronchoalveolar lavage. Mechanical ventilation may be needed in spite of the difficulty of weaning from patients (*1,3*).

6.2. *Pulmonary hypertension*

Pulmonary hypertension is present in less than 10% of patients with IPF at the time of diagnosis and in 30-45% during evaluation prior to lung transplantation. Pulmonary hypertension is associated with increased mortality, dyspnea and hypoxemia, decreased exercise capacity and DLCO, and a risk of acute exacerbation. Doppler echocardiography is the first-line noninvasive examination to diagnose pulmonary hypertension, but it has low positive and negative predictive values. Whether right heart catheterization is indicated for a patient with IPF patient should be decided at specialized facilities (*3*). Currently, there is no specific treatment recommended for pulmonary hypertension in patients with IPF. Further evidence is needed to make a clinical decision (*2*).

6.3. *Gastro-esophageal reflux*

Abnormal gastroesophageal reflux (GER), either symptomatic or asymptomatic, has been noted in more than 90% of patients with IPF (*23*). GER is a risk factor for aspiration and microaspiration, which may play a significant role in the pathogenesis of IPF (*24*). Antiacid treatments such as proton pump inhibitors (PPIs) or histamine-2 blocker receptor antagonists (H2RAs) may decrease the risk of microaspiration-associated lung injury or damage. Two retrospective studies have indicated that pulmonary function and oxygen requirements stabilized with medical and surgical

management of GER (*25,26*). The updated Official ATS/ERS/JRS/ALAT Clinical Practice Guideline recommends regular antiacid treatment for patients with IPF (*2*).

6.4. *Lung cancer*

The risk of lung cancer increases in patients with IPF. Compared to the risk of lung cancer in the general population, patients with IPF have a 7-fold higher incidence of lung cancer (*27*). The prevalence of lung cancer in patients with IPF is between 4.4% and 9.8% (*28*), and a retrospective study reported that the 10-year risk of developing lung cancer was 55% (*29*). A prospective study of complications among patients with IPF in Japan reported that the prevalence of lung cancer was 3.1% (*30*). The physician in charge of follow-up should be made aware of the frequent occurrence of lung cancer in patients definitively diagnosed with IPF (*3*). Management of lung cancer including surgical resection, radiation therapy, and chemotherapy is hampered by IPF and by the risk of acute respiratory failure and/or acute exacerbation associated with treatment of cancer.

7. Pulmonary rehabilitation and palliative treatment

Pulmonary rehabilitation consists of aerobic conditioning, strength and flexibility training, educational lectures, nutritional advice, and psychosocial support. In a study in Japan, a rehabilitation group had marked improvement in their 6-minute walking distance and their total score for health-related quality of life (*31*). Although only a few studies have investigated the effects of pulmonary rehabilitation on patients with IPF, pulmonary rehabilitation seems to be beneficial with respect to exercise capacity and quality of life in patients with IPF (*32*).

Dyspnea and coughing are the main symptoms of progressive disease, reducing the quality of life for patients and hampering treatment. Supplemental oxygen alleviates symptoms, and particularly dyspnea on exertion. Despite the lack of properly designed studies, oxygen supplementation is currently recommended by international guidelines (*1*). Treatment of coughing in IPF is problematic, and particularly so in the later stages of the disease. For the patients with a dry cough that is not alleviated by codeine, transient, low-dose oral corticosteroid therapy is an option for patients with IPF, but the efficacy and tolerance of this therapy should be monitored (*3*).

8. Prognosis

Currently, IPF remains an incurable disease with varying rates of progression and a poor prognosis. Several clinical phenotypes of IPF have been described, including slow progression in patients with a history of worsening dyspnea and/or a dry cough lasting for months to years and rapid progression (referred to accelerated IPF) characterized by shortened survival (Figure 2) (*33,34*). Indices such as symptoms, respiratory function, and imaging are used to evaluate the clinical progression and outcome of IPF. Studies are underway to determine the heterogeneity of the disease (*35*). A prognostic staging system named after the GAP score

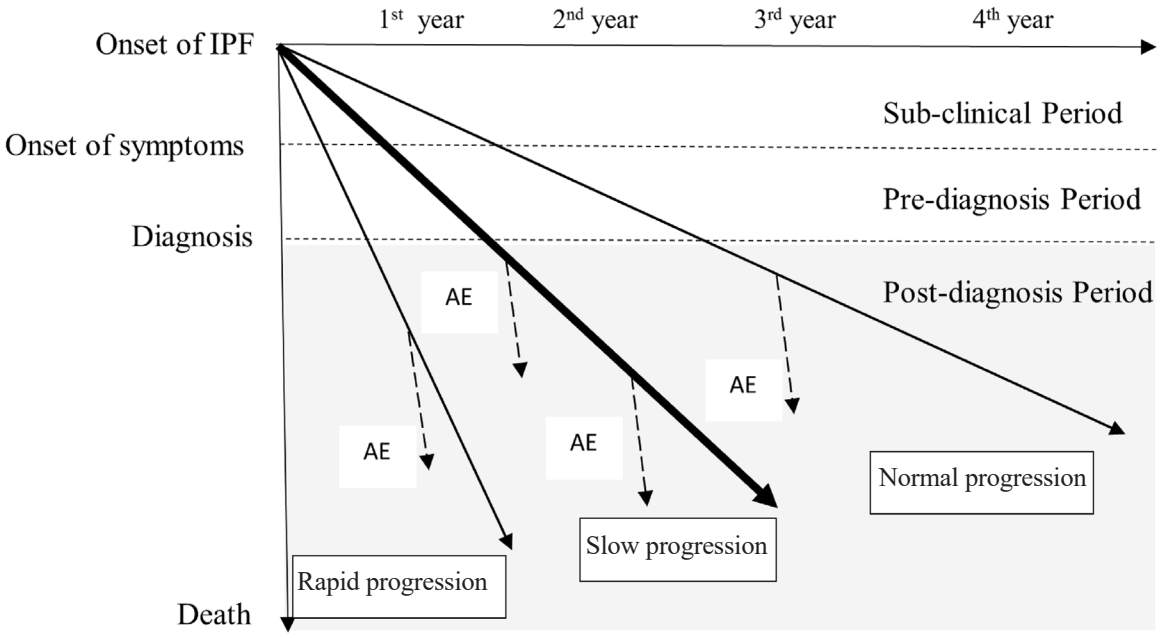

Figure 2. The disease course of idiopathic pulmonary fibrosis (IPF) varies. Predicting the exact phenotype in individuals is difficult. The disease progresses rapidly in some patients, slowly in some patients, and normally in other patients experience. Some patients may experience acute exacerbation (AE) of IPF in an unpredictable stage.

risk prediction model has been developed for IPF and it has been validated in three large, geographically distinct cohorts of patients (*36*). The GAP score risk prediction model is a feasible and useful marker that includes four factors: gender (G), age (A), and two lung physiologic (P) variables (FVC and DLCO). Improvement in pulmonary function as a result of pharmacologic and non-pharmacologic therapies is crucial to improving the prognosis for patients with IPF because gender and age are non-modifiable variables.

The clinical course of IPF is highly variable and unpredictable in individuals. Different patterns of IPF progression may determine survival time and the cause of death. In a Japanese study, a total of 328 patients (59.3% of those patients had IPF) died from various causes. Among patients with IPF, the most common cause of death was an acute exacerbation of the disease (40% of events), followed by lung cancer (11%), pneumonia (7%), and cardiovascular diseases (3%). The percentage of patients with acute exacerbation was higher than that in American studies, which may suggest an ethnic difference between East Asian and Western populations (*8*).

9. Conclusion

IPF is a rare and intractable respiratory disease with a poor prognosis. The incidence of that disease, the rate of lung transplants, and mortality rates and causes of death differ between East Asians and Westerners. These differences may be the result of ethnic and geographical factors. Regional studies and trials should be conducted to accurately diagnose and treat IPF. Since the East Asian population is rapidly aging, the prevalence and incidence of IPF will presumably increase in the near future. Thus, more effective therapies need to be developed to improve survival from this devastating disease. This development must come from advanced and collaborative clinical and basic scientific research. Although East Asians accounts for 1/4 of the world's population, patients with IPF are less likely to receive a lung transplant due to national shortages in lung donors. As in European countries, coordination and collaboration among networks should be promoted in East Asia to facilitate more lung transplants.

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