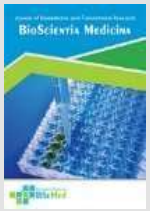
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Idiopathic Pulmonary Fibrosis: A Narrative Literature Review

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ARTICLE INFO

Keywords:
Antifibrosis
Idiopathic pulmonary fibrosis
Usual interstitial pneumonia

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v8i8.1052

A B S T R A C T

Idiopathic pulmonary fibrosis is a chronic progressive interstitial lung disease (ILD) with unknown causes. Male gender, age > 60 years, history of smoking with symptoms of dry cough and progressive chronic shortness of breath are typical clinical findings in this patient. The diagnosis is made based on a combination of radiological findings in the form of a pattern consistent with usual interstitial pneumonia (UIP) and/or histopathology with the exclusion of other causes of ILD. Treatment includes pharmacological and non-pharmacological therapy in the form of pulmonary rehabilitation, psychosocial support, and lung transplantation. Anti-fibrosis pharmacological therapy, namely nintedanib and pirfenidone, has been proven to slow the progression of pulmonary fibrosis and reduce mortality. The relatively low average survival rate of 3-4 years after the diagnosis is made makes this disease have a poor prognosis and requires adequate identification and treatment in order to reduce morbidity, mortality and improve the quality of life of sufferers.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a part of interstitial lung disease (ILD) with unknown causes. Interstitial lung diseases are a large group of diseases that cause inflammation and fibrosis in the lung parenchyma. Some of these diseases occur secondary to known causes and can also occur due to unknown causes which are referred to as idiopathic interstitial pneumonias (IIPs). Idiopathic pulmonary fibrosis is one of the most common and aggressive forms of IIPs with characteristics of chronic and progressive fibrosis of the lung parenchyma accompanied by irreversible reduction in lung function. Recent years have seen a number of advances in the understanding of the pathogenesis, diagnosis and management of idiopathic pulmonary fibrosis. The characteristics of irreversible decline in lung function due to fibrosis manifest as chronic and progressive respiratory complaints, namely coughing and shortness of breath followed by a decrease in quality of life. This disease occurs in older adults, especially men, with a prevalence that continues to increase in the last decade. Apart from the unknown cause, several genetic and environmental factors are said to be involved in the incidence of IPF.[1-3]

Idiopathic pulmonary fibrosis has a poor prognosis with a median survival of 3-5 years after diagnosis. Disease progression varies between individuals related to the extent of lesions and comorbidities so that progression varies and is difficult to predict. The main morphological characteristic is the finding of a usual interstitial pneumonia pattern or usual interstitial pneumonia (UIP) on high-resolution computed tomography (HRCT) and/or lung biopsy histopathology. It is important to differentiate this disease from other interstitial lung disease entities

because they have different prognoses and management such as chronic extrinsic allergic alveolitis, non-specific interstitial pneumonia, and interstitial pneumonia with autoimmune features. Disease prognosis is influenced by early detection and appropriate management, especially in at-risk populations. There are several guidelines for the management of idiopathic pulmonary fibrosis, but definitive management of patients with probable or susceptible IPF versus definite IPF has not been established. Two anti-fibrosis therapies, namely pirfenidone, and nintendanib, are currently recommended as therapeutic options for idiopathic pulmonary fibrosis which have been proven to slow the progression of pulmonary fibrosis. This study aims to determine and understand the pathogenesis, diagnosis, and management of idiopathic pulmonary fibrosis patients.[4-7]

Definition

Idiopathic pulmonary fibrosis is a specific form of chronic interstitial pneumonia of unknown etiology that is associated with the histopathological and radiological pattern of UIP. Idiopathic pulmonary fibrosis occurs primarily in adults and is characterized by progressive worsening of symptoms of shortness of breath and lung function. Common interstitial pneumonia refers to a morphological entity defined as a combination of patchy interstitial fibrosis with alternating areas of normal lung, temporal fibrosis heterogeneity with scattered foci of fibroblasts accompanied by a dense acellular collagen background and altered alveolar architecture due to chronic scarring with or without the appearance of cystic nests. bees (honeycomb appearance).[8-10]

Epidemiology

Idiopathic pulmonary fibrosis is a severe interstitial lung disease and accounts for around 20-50% of all cases of interstitial lung disease. This disease is considered a rare disease, but the incidence rate is increasing every year. The increasing incidence of this disease is due to an increasing aging population, higher levels of disease awareness, and better diagnostic procedures and tools. Determining the epidemiology of idiopathic pulmonary fibrosis has its own difficulties due to limitations in diagnostic procedures, changes in guidelines, and regional variations in environmental exposures and risk factors that cause pulmonary fibrosis. The average age of patients with idiopathic pulmonary fibrosis is 65 – 70 years with the incidence increasing with age. Idiopathic pulmonary fibrosis is more common in men, which is thought to be due to exposure to risk factors, namely smoking, metal or wood dust and genetics. Globally, idiopathic pulmonary fibrosis affects 0.09–0.13 per 10,000 individuals. The incidence ratio for each country globally in 2021 per 10,000 population ranges from 0.35-1.30 in Asia-Pacific countries, 0.09-0.49 in Europe, and 0.75-0.93 in North America. According to epidemiological data, South Korea occupies the highest position followed by Canada and the United States.[11-15]

Risk factors and clinical manifestations

The main risk factors for idiopathic pulmonary fibrosis according to the American Thoracic Society (ATS) are a history of smoking at least more than 20 packs per year, gastroesophageal reflux associated with microaspiration, age of more than 60 years, and male gender. Although the disease is known to be limited to the lung, there are other risk factors that may independently increase susceptibility to IPF or act synergistically to increase the risk of disease progression. These risk factors include intrinsic risk factors, namely genetic factors in the form of genetic variants with shortened telomeres, aging, gender and lung microbiome, comorbid factors such as cardiovascular disease, gastroesophageal reflux, obstructive sleep apnea (OSA), diabetes mellitus, herpes virus infection, as well as extrinsic risk factors, namely smoking, environmental exposure, and air pollution. Aging is defined as a progressive decline in the body's physiological functions that can increase mortality with increasing age. This process includes various mechanisms at different cellular levels.

Several studies state that as we age, cells tend to experience random accumulation of damage which is compensated by genetic repair mechanisms and this has a reciprocal relationship with comorbidities or accompanying diseases. The accumulation of cell damage has an impact on the body as a whole related to age vulnerability, morbidity, disability, and comorbidities which can be seen in Table 1.

Table 1. Comorbidities that are often found in patients with idiopathic pulmonary fibrosis.

Pulmonary	Extrapulmonary
Pulmonary arterial hypertension	Coronary artery disease
Emphysema	Anxiety and depression
Obstructive sleep apnea (OSA)	Sarcopenia
Lung cancer	Osteoporosis and bone fractures
Venous thromboembolism	Diabetes mellitus and hyperthyroidism
Chronic obstructive pulmonary disease	Gastroesophageal reflux

Idiopathic pulmonary fibrosis has a variable clinical course. Some patients experience rapid progression, whereas others experience a gradual decline in lung function. Typical clinical findings in patients with idiopathic pulmonary fibrosis are men, aged more than 60 years and have a history of smoking accompanied by clinical manifestations of cough without phlegm accompanied by chronic progressive shortness of breath.[6,9,10] Shortness of breath is a common symptom and is related to quality of life and disease progression.[13] Acute onset or exacerbation can be found in patients with clinical worsening of unexplained shortness of breath accompanied by ground glass opacity (GGO) new on HRCT imaging with a background of fibrosis in the lower lobes of the lung.[12,14] Velcro crackles can be found and is a typical finding on physical examination of IPF lungs. This sound is heard in mid to late inspiration with a breathing sound that sounds like rubbing hair between the fingers.[22] Velcro crackles this was independently associated with HRCT pattern findings and/or UIP histopathology in 132 ILD patients undergoing a multivariate clinical trial.[23] Clubbing finger reportedly found in 30-50% of idiopathic pulmonary fibrosis patients. Pulmonary function examination with spirometry and examination diffusing capacity of the lung for carbon monoxide (DLCO) shows a decrease in diffusion capacity with persistent restriction disorders.[10,13]

Pathogenesis

Genetic and epigenetic phenomena contribute to the development of epithelial dysfunction that is susceptible to repetitive microinjury due to environmental exposures such as cigarette smoke, inhaled dust, infections, and gastroesophageal reflux. Epithelial damage disrupts the basement membrane and capillary-alveolar support. This causes leakage of capillary proteins (including fibrin and fibronectin) into the interstitial and alveolar spaces accompanied by activation of the coagulation cascade and extracellular matrix deposition and remodelling of abnormal vasculature. This activation of epithelial and endothelial cells creates aberrant epithelial-mesenchymal interactions, fibroblast recruitment, migration, proliferation, and differentiation of pro-fibrotic mediators namely transforming growth factor-1 (TGF-1), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF).[1] Genetic predisposition is closely related to cellular aging and abnormal tissue repair in lung epithelial cells. Mutations in the TERT and TERC genes, which are telomerase catalysts for maintaining telomere length, cause accelerated telomere shortening. Short telomeres have been studied and found in both familial and sporadic IPF. In addition, mutations in the MUC5B gene cause abnormalities in mucociliary function in the peripheral airways. This mutation causes overexpression of

MUC5B, thereby increasing chronic mucus secretion, disrupting bronchoalveolar mucociliary clearance, and triggering infection, injury, and chronic inflammation.[8] The importance of the immune response in idiopathic pulmonary fibrosis is explained by genetic studies showing increased risk or severity of the disease associated with polymorphisms of the genes encoding toll-like receptor-3 (TLR-3), toll-interacting protein (TOLLIP) and interleukin-1 receptor antagonist (IL-1RA). Research on individuals and mice with IPF supports the role of immune dysregulation in the development of pulmonary fibrosis through the profibrotic cytokines M2 macrophages, Th17 cells, CD8+ T cells, Tregs, as well as antifibrotic cytokines, namely CD4+, Th1, and T cells. Tissue Resident Memory (TRM) which is protective.[16-19]

Mechanical interactions between fibroblasts and the stiffness of the extracellular matrix are the main factors in the occurrence of pulmonary fibrosis. Collagen, proteoglycans, and extracellular matrix glycoproteins in idiopathic pulmonary fibrosis are increased, but specific basement membrane proteins such as laminin and type IV collagen are decreased. Type IV collagen is the main component of the basement membrane and functions as a tissue support. This dysregulation of collagen cross-linking causes increased stiffness of the extracellular matrix which triggers myofibroblast invasion of the basement membrane by increasing the expression of α6 protein and MMP-2-dependent pericellular proteolysis from collagen IV and inhibits the synthesis of the anti-fibrosis mediator prostaglandin E2 (PGE2).[18] Autophagy is involved in the regulation of extracellular matrix formation. Autophagy is a basic intracellular process in maintaining cellular homeostasis and regulating cell survival. Autophagy carries out various normal physiological processes in response to stress such as nutritional deficiencies, radiation exposure, and infections. Recent research has found that in pulmonary fibrosis there is insufficiency in the autophagy process. This is in line with a literature review by Liang Yue et al which states that inhibition of the autophagy pathway and function in the lung tissue of IPF patients is caused by a decrease in autophagosomes, inability to fuse autophagosomes with lysosomes, increased intracellular p62 expression and excessive protein accumulation.[18,20]

Various molecular mechanisms under the influence of various factors, namely internal and external, form the basis of the pathogenesis of idiopathic pulmonary fibrosis. The combined action of three factors, namely genetic factors that influence epithelial cell integrity, as well as aging and environmental factors that trigger epigenetic changes, causes epithelial cell damage and triggers activation of abnormal epithelial cells. Activation of these abnormal epithelial cells secretes pro-fibrotic cytokines such as TGF-β in large amounts and causes migration, proliferation, and differentiation of fibroblasts into myofibroblasts. Furthermore, myofibroblasts secrete extracellular matrix excessively accompanied by the autophagy process as a response to tissue damage. Next, there is abnormal deposition and stiffness of the extracellular matrix which plays an important role in changes in lung structure.[20-22]

Classification

The approach to diagnosis of idiopathic pulmonary fibrosis relies heavily on lung volumetric imaging and lung tissue histopathology. Volumetric imaging with HRCT can essentially replace traditional computed tomography scans and improve the detection of previously unseen focal abnormalities to support in-depth analysis of lesion characteristics and distribution.[8] Based on radiological imaging, IPF is divided into 4 diagnostic categories, namely UIP, probable UIP, indeterminate UIP and alternative diagnoses with the findings and distribution of lesions which can be seen in Table 2.[5,9,10]

Table 2. Volumetric imaging patterns with HRCT in UIP.

UIP	Probable UIP	Indeterminate UIP	Alternative diagnosis
Predominantly subpleural and basal. The distribution is often heterogeneous (areas of normal lung interspersed with fibrosis). Sometimes diffuse. Can be asymmetrical.	Predominantly subpleural and basal. The distribution is often heterogeneous (areas of normal lung interspersed with reticulation and; traction bronchiectasis or bronchiectasis).	Diffuse distribution without subpleural predominance.	Predominantly peribronchovascular with subpleural sparing (consider NSIP). Perilymphatic distribution (consider sarcoidosis). Upper or lower lung (consider fibrosis, pulmonary hypertension, sarcoidosis and interstitial lung connective tissue disease). Subpleural sparing (consider NSIP or smoking-related interstitial pneumonia.
Honeycombing with or without traction bronchiectasis or bronchiectasis. Irregular thickening of the interlobular septum. Often accompanied by a reticular pattern, mild GGO. May be accompanied by pulmonary ossification.	Reticular pattern with traction bronchiectasis or bronchiectasis. Light GGO can be found. There is no subpleural sparing.	Lung CT features fibrosis that does not reflect other specific etiologies.	Lung imaging findings: Cysts (consider LAM, PLCH, LIP and DIP). Mosaic attenuation or three signs of attenuation (pulmonary hypertension). GGO predominance (consider pulmonary hypertension, smoking-related diseases, drug toxicity and acute exacerbation of fibrosis). Centrilobular micronodules (consider pulmonary hypertension or cigarette exposure). Nodules (consider sarcoidosis). Consolidation (consider organizing pneumonia). Mediastinal imaging findings: Pleural plaque (asbestosis). Esophageal dilatation (connective tissue disease).

Honeycomb appearance is a UIP feature that must be included to establish a definitive diagnosis of idiopathic pulmonary fibrosis based on the HRCT pattern seen in Figure 4.[9,10] Pulmonary fibrosis is recognized if traction bronchiectasis or bronchiectasis and/or are found honeycomb appearance, although the finding of a honeycomb cyst must be differentiated from paraseptal emphysema and air space dilation. Honeycomb appearance is associated with bronchiolar cysts that develop after the fibrosis of the alveolar septum collapses and the terminal airways are dilated so that the finding of a honeycomb cyst accompanied by peripheral dilatation of the airways surrounding the fibrosis of the alveolar septum appears as traction bronchiolectasis.[5]

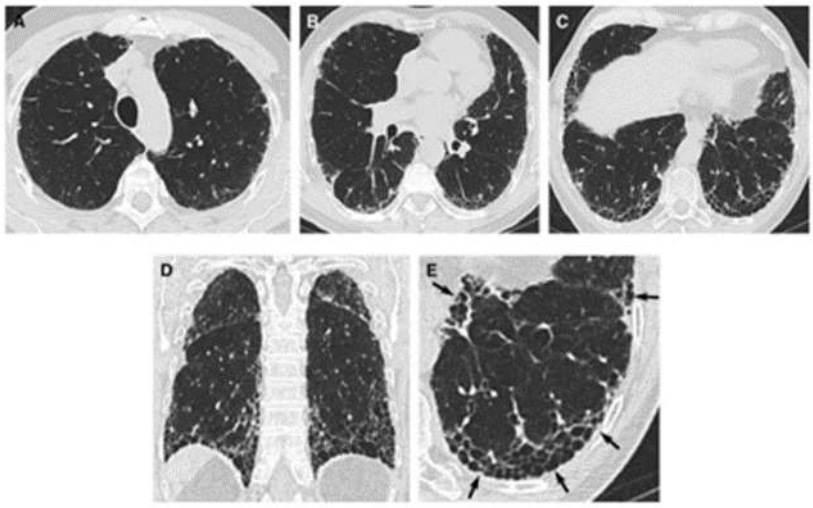

Figure 1. HRCT radiological pattern of UIP. (A–C) Transverse and (D) coronal CT images honeycombing with subpleural and basal predominance. (E) A magnified view of the left lower lobe shows typical characteristics honeycomb, consisting of clustered cystic air spaces with clear walls and variable diameter accompanied by opacity ground glass light.

The 2022 idiopathic pulmonary fibrosis guidelines by ATS/ERS/JRS/ALAT state the level of confidence in the diagnosis of UIP, probable UIP, indeterminate UIP and alternative diagnoses based on histopathology were >90%, 70-89%, 51-69% and ≤50% respectively.[10,5] Subpleural and basal predominance accompanied by reticular abnormalities with peripheral traction bronchiectasis or bronchiectasis without honeycomb appearance should be considered as probable UIP. Indeterminate UIP based on HRCT showing fibrosis but without UIP criteria or probable and does not refer to an alternative diagnosis with limited or reticulated subpleural GGO without obvious fibrosis which can be seen in figures 2 and 3 below.[10]

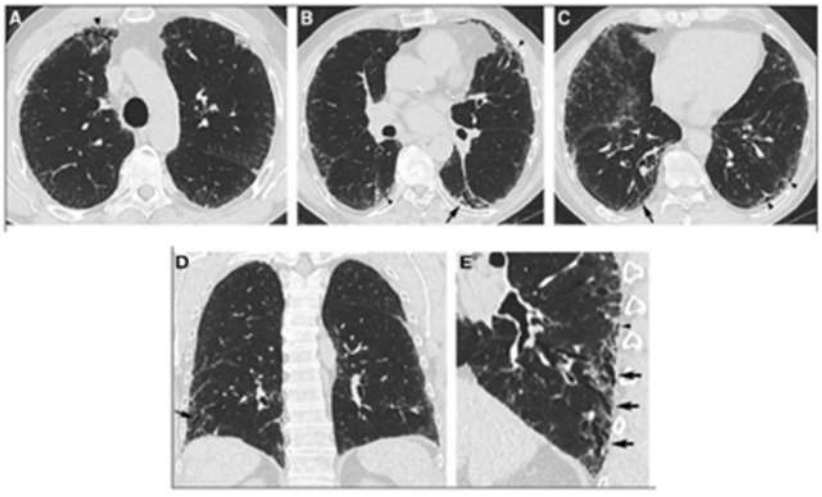

Figure 2. HRCT radiological pattern in probable UIP. (A-C) Transverse and (D) coronal CT radiology of both lungs. (E) Sagittal section shows a reticular pattern with predominant subpleural and basal peripheral bronchiectasis. Peripheral traction bronchiectasis (arrow) is tubular or cystic. No images of honeycomb cysts were found. The diagnosis of UIP is confirmed by histopathological findings.

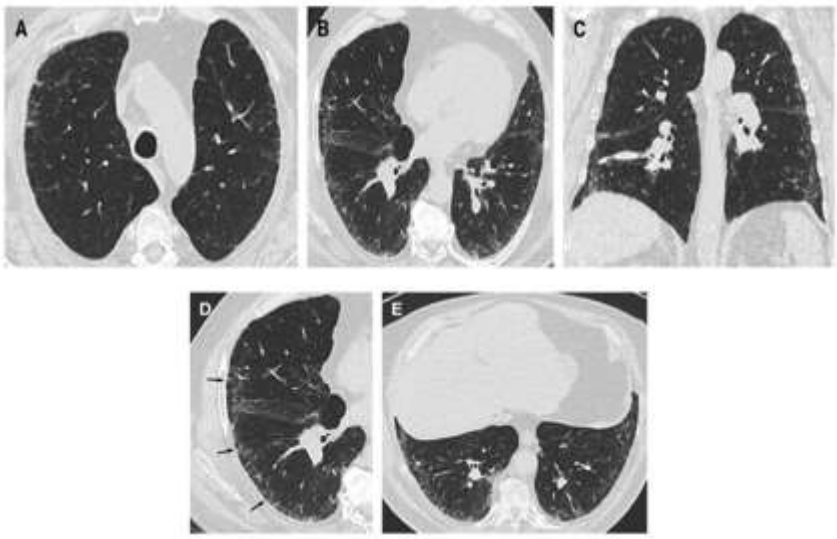

Figure 3. HRCT radiological pattern indeterminate UIP. (A and B) Transverse (C) coronal (D) magnified view of the right lung position supine shows opacity ground glass with subpleural and basal reticulation. (E) Positional transverse section prone indicates infiltration of non-dependent areas. The UIP pattern is proven histologically.

An alternative diagnosis is that there is a clinical suspicion of IPF but the HRCT pattern shows typical other diagnoses such as bronchocentric fibrosis in the upper lobes or excessive mosaic attenuation in interstitial pneumonitis, posterior retraction fibrosis in sarcoidosis or extensive GGO with subpleural sparing in non-specific fibrotic interstitial pneumonia/non-specific interstitial pneumonia (NSIP). The characteristics of volumetric radiological findings with HRCT in alternative diagnoses in the form of chronic hypersensitivity pneumonitis can clearly be seen in Figure 4 below.[5,9,10]

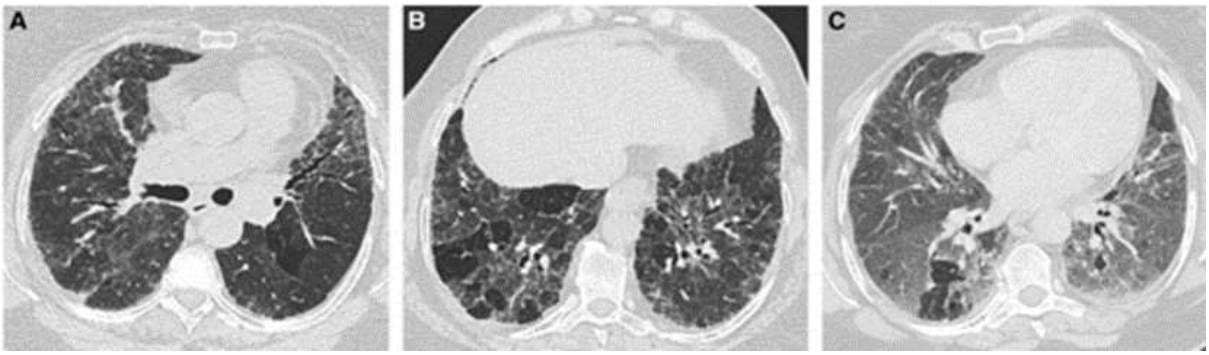

Figure 4. Radiologic patterns of alternative diagnoses. (A-B) Transverse CT slice during deep inspiration shows diffuse lung infiltration. (C) CT transverse section depicts lobular air trapping leading to chronic hypersensitivity pneumonitis.

The main diagnostic criterion for UIP based on histopathology is dense patchy fibrosis accompanied by the formation of honeycomb cysts typically most severe involving the subpleural and paraseptal parenchyma. Mild inflammation is common with infiltration of interstitial lymphocytes and plasma cells associated with hyperplasia of type 2 pneumocytes and bronchial epithelium. The zone of fibrosis consists of dense collagen accompanied by subepithelial foci of fibroblast proliferation and scattered myofibroblasts. A

definitive pathological diagnosis of the UIP pattern is made when all of the above features are present especially when accompanied by the appearance of honeycomb cysts. The categories and description of lung biopsy histopathological findings can be seen in Table 3 and Figure 5.[5,10]

Table 3. Histopathological features and patterns of UIP.

UIP	Probable UIP	Indeterminate UIP	Alternative diagnosis
Dense fibrosis with architectural distortion, destructive fibrosis and/or honeycombing). Predominantly subpleural and/or paraseptal distribution. Partial fibrosis of the lung parenchyma. Fibroblast focus. There are no other diagnostic features.	Histological features of UIP AND There are no other diagnostic features. OR Only honeycombing.	Fibrosis with or without architectural distortion with features other than UIP or other causes. Some histological features of UIP, but with other alternative diagnostic features.	Other histological patterns feature interstitial pneumonia fibrosis on biopsy. Histological findings indicate other diseases (hypersensitivity pneumonitis, Langerhans cell histiosis, sarcoidosis.

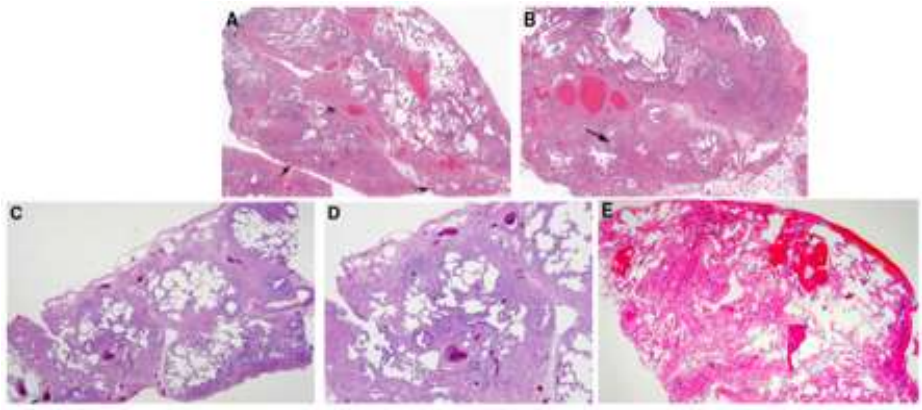

Figure 5. Histopathology of UIP. (A) UIP pattern with characteristic dense subpleural and paraseptal fibrosis accompanied by architecture distortion and honeycomb appearance (B) honeycomb with fibroblast foci. (C) Probable UIP/IPF. (D) Loose fibrosis with no fibroblast foci honeycomb. (AND) Indeterminate UIP/IPF.

The application of UIP histopathological criteria presents its own challenges when using specimens originating from transbronchial lung cryobiopsy (TBLC). This is caused by pathological changes that occur predominantly in the subpleura, so it is not easily accessible by tools, the sample size is small and the possibility of error sampling. The ATS/ERS/JRS/ALAT recommendation states that TBLC is carried out as an alternative measure in establishing a histopathological diagnosis of patients with interstitial lung disease if a surgical lung biopsy cannot be performed and is carried out at a health service center that has a standardized protocol including minimizing risks and maximizing diagnostic procedures followed by multidisciplinary discussion in making a diagnosis.[5]

Management

Until now, definitive pharmacological therapy for IPF has not been found. Immediate treatment is

important to maintain lung function, reduce the risk of acute exacerbations, and improve outcomes.[9,21] Reducing disease progression can increase hope and quality of life. The latest therapeutic developments are starting to be developed for idiopathic pulmonary fibrosis but are still in the clinical trial stage. Many of these clinical trials failed and only two antifibrosis therapies were accepted and recommended by the Food and Drug Administration (FDA) as therapy, namely nintedanib and pirfenidone proven to slow the progression of pulmonary fibrosis and reduce mortality.[8,9] The flow of clinical management of idiopathic pulmonary fibrosis patients developed based on consensus discussions. Management considerations include pharmacological and non-pharmacological therapy. Several IPF pharmacological therapy options that have been tested in phase II-III are described in table 4. Non-pharmacological treatment strategies include symptomatic support therapy, lung transplantation, managing comorbidities, managing acute exacerbations and palliative therapy. The recommendation for lung transplantation in patients with idiopathic pulmonary fibrosis is very strong. Patients at increased risk of death should be referred for lung transplantation at diagnosis. Treatment evaluation is performed every 3-6 months or more frequently in progressive disease. [5,10,18]

Table 4. Pharmacological therapy of idiopathic pulmonary fibrosis,

Drug	Pharmacokinetics
Pirfenidone	Anti fibrosis
Nintedanib	Anti PDGFR, VEGFR, FGFR
Pamrevlumab	Anti-CTGF antibodies
GSK3008348	αvβ6 antagonist
Sildenafil	phosphodiesterase-5 inhibitor
Co-trimoxazole or doxycycline	Antimicrobial drug
Lebrikizumab	Anti-IL13
Carlumab	Anti-CCL2
Simtuzumab	Anti-LOX antibody

International therapeutic guidelines provide conditional recommendations against the use of antacids and gastroesophageal reflux interventions in IPF patients aimed at improving respiratory symptoms. Both medications can be given with conditional recommendations if they aim to improve specific symptoms related to gastroesophageal reflux. Sildenafil has been investigated as a therapy in patients with idiopathic pulmonary fibrosis with severe gas exchange disorders in 2 clinical trials, namely with placebo and a combination of nintendanib. These two clinical trials provided insignificant primary outcomes, but secondary outcomes showed significant benefits and are still under further research. Other therapies in idiopathic pulmonary fibrosis are n-acetylcysteine, steroids, and bronchodilators. This therapy has not been proven to be effective in slowing the progression of IPF.[5,21] Non-pharmacological therapy management of IPF includes pulmonary rehabilitation, education, and support, vaccination, control of comorbidities such as pulmonary hypertension, gastroesophageal reflux, obstructive sleep apnea (OSA) and lung cancer, oxygen supplementation, lung transplantation, and palliative therapy.[5,9,21] Hypoxia during physical activity is a characteristic of IPF patients so oxygen supplementation is necessary in IPF patients with hypoxia. Hypoxia during examination 6 minute walk test (6-MWT) is related to prognosis so oxygen supplementation is also recommended if desaturation occurs <88% during examination.[5,18] Patients at high risk of death should be evaluated for lung transplantation when the diagnosis is made. In 2006, the International Society for Heart and Lung

Transplantation (ISHLT) published guidelines for lung transplant candidates, namely patients with a DLCO of less than 39%, a decrease in CVP of more than or equal to 10% at the 6-month evaluation, a decrease in oxygen saturation below 88% during the 6-MWT and findings of honeycomb cysts on HRCT. Age over 65 years is a relative contraindication. The 5-year survival rate after lung transplantation in IPF is approximately 50%.[5,18] Pulmonary rehabilitation including aerobic and flexibility exercises, education, nutrition, and psychosocial support is especially useful in improving patient productivity and quality of life. Pulmonary rehabilitation is more effective in patients with poor baseline pulmonary functional status. Clinical trials suggest pulmonary rehabilitation in ILD patients can increase exercise capacity, and improve shortness of breath and quality of life with the same benefits also seen in IPF patients. These results support the inclusion of pulmonary rehabilitation as part of the management for patients with ILD and IPF. Further studies are needed to determine the optimal type and intensity of pulmonary rehabilitation therapy in IPF patients.[12,18] Worsening of respiratory symptoms, pulmonary function, progressive fibrosis on HRCT or acute decline in respiratory function are manifestations of disease progression. In patients presenting with acute respiratory deterioration, the possibility of exacerbation should be considered and promptly evaluated for alternative etiologies of acute exacerbation such as pulmonary embolism, pneumothorax, respiratory infection, or aspiration and treated with corticosteroids. All matters related to the management of IPF patients, both pharmacological and non-pharmacological therapy, and monitoring disease progression are briefly described in Figure 11.[5,9,23-26]

Prognosis

Idiopathic pulmonary fibrosis has a poor prognosis with clinical variations between individuals. Retrospective studies suggest a median survival from diagnosis of 3 to 4 years with the primary cause of death being respiratory failure.[3] Older age, male, severe shortness of breath, severe lung function abnormalities, and exacerbations are associated with poor prognosis and disease course which can be seen in Table 5. Every year around 10-20% of idiopathic pulmonary fibrosis patients experience acute exacerbations characterized by worsening of symptoms. accompanied by hypoxaemic respiratory failure with bilateral opacities and/or new consolidation on chest radiology imaging.[3,24]

Table 5. Factors that increase mortality in patients with idiopathic pulmonary fibrosis.[26]

Basic factors
Degree of shortness of breath
DLCO < 40% prediction
Desaturation <88% at 6MWT
Expansion of honeycombing on HRCT
Pulmonary hypertension
Longitudinal factors
Increased shortness of breath
Decrease in FVC value >10% absolute value
Decrease in DLCO value >15% absolute value
Worsening fibrosis on HRCT

The progression and clinical variations mean that IPF cannot be cured and has a poor prognosis with a decline in respiratory function that is difficult to predict. Precise and accurate prognosis predictions can guide management strategies such as pharmacological therapy, lung transplantation, and palliation. Every year around 10%-20% of IPF patients experience life-threatening acute exacerbations.3 In line with Japanese studies, acute exacerbations have been the most frequent cause of death in up to 40% of

cases in IPF patients, but in some cases, the disease can slow unexpectedly after rapid progression.26 Prediction of this difficult clinical course requires simple and accurate prognostic markers.[3,26]

A Japanese cohort study by Kishaba et al in 2021 stated that soft tissue thickness and percentage of functional residual capacity were identified as predictors of mortality in idiopathic pulmonary fibrosis. Soft tissue thickness assessment of the 9th rib provides a new approach to the evaluation of IPF patients. In this case, soft tissue is related to nutrition and disease progression. This is in line with research results which state that malnutrition and reduced BMI are associated with a poor prognosis.14 Another IPF prognosis prediction test, namely a retrospective analysis of monocytes, states that monocyte elevation is one of the parameters for increasing the risk of disease progression, hospitalization, and mortality in IPF. Monocyte count is a prognostic biomarker that is cheap and easy to perform but requires further clinical testing.[27]

2. Conclusion

Idiopathic pulmonary fibrosis is an interstitial lung disease characterized by chronic, progressive fibrosis of lung tissue accompanied by decreased lung function. *irreversible* by unknown causes. Typical clinical findings in patients with idiopathic pulmonary fibrosis are men, aged more than 60 years, who have a history of smoking accompanied by clinical manifestations of cough without phlegm, chronic progressive shortness of breath, crackles in the lung basalts and peripheral lobular fibrosis of the lungs on radiological imaging. Diagnosis by HRCT imaging and/or lung biopsy histopathology leads to common interstitial pneumonia accompanied by the exclusion of other causes of interstitial lung disease. Management includes pharmacological therapy with anti-fibrosis, namely nintendanib and pirfenidone, and non-pharmacological including pulmonary rehabilitation, education and support, vaccination, comorbid control, oxygen supplementation, lung transplantation, and palliative therapy.

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