Review

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Korean Guidelines for Diagnosis and Management of Interstitial Lung Diseases

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Abstract

Interstitial lung disease (ILD) comprises a heterogeneous group of disorders characterized by interstitial compartment proliferation, inflammatory infiltration, and potential fibrosis with abnormal collagen deposition. Diagnosis requires a multidisciplinary consensus integrating clinical, radiological, and pathological findings. Idiopathic interstitial pneumonia (IIP) includes idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia, desquamative interstitial pneumonia, acute interstitial pneumonia, and respiratory bronchiolitis-ILD, each exhibiting distinct prognostic and therapeutic implications. Some non-IPF ILDs progress despite standard treatment, classified as progressive fibrosing-ILD or progressive pulmonary fibrosis (PPF), diagnosed by worsening symptoms, physiological decline, and radiological progression. Nintedanib is conditionally recommended for refractory PPF cases. Combined pulmonary fibrosis and emphysema is characterized by upper-lobe predominant emphysema and lower-lobe fibrosis, frequently complicated by pulmonary hypertension and lung cancer. Interstitial lung abnormality, observed in both smokers and the general population, is associated with increased mortality and disease risk, warranting further research. Despite advancements, refinement in classification, diagnostic criteria, and therapeutic strategies remains crucial for improving patient outcomes.

Keywords: Interstitial Lung Disease; Idiopathic Interstitial Pneumonia; Progressive Pulmonary Fibrosis; Idiopathic Pulmonary Fibrosis; Combined Pulmonary Fibrosis and Emphysema; Pulmonary Fibrosis; Pulmonary Emphysema; Interstitial Lung Abnormalities

Introduction and Idiopathic Interstitial Pneumonia

1. Classification of idiopathic interstitial pneumonia

1) Introduction

Interstitial lung disease (ILD) refers to a group of disorders characterized by proliferation of the lung interstitial compartment, accompanied by the infiltration of various inflammatory cells and, in some cases, fibrosis, leading to abnormal collagen accumulation. There are various opinions regarding the classification and scope of ILD; however, it can generally be divided into two main categories: those with known and those with unknown etiologies. Cases with identifiable causal etiologies can be further subdivided into four major cate-

gories based on the underlying cause (Figure 1)[1].

First, environmental ILD encompasses occupational conditions such as silicosis, asbestosis, and berylliosis, as well as hypersensitivity pneumonitis (HP). Second, iatrogenic ILD refers to lung diseases induced by radiation or medications including chemotherapeutic agents and antiarrhythmic drugs. Third, autoimmune ILD includes conditions associated with connective tissue or autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Additionally, lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH), and pulmonary alveolar proteinosis are classified as ILD. ILD without a determinate causative etiology is defined as idiopathic interstitial pneumonia (IIP). Various types of IIP are classified based on histological findings, each with markedly different prognoses and treatments[1]. Diagnosis requires a comprehensive approach that integrates radiological findings, histopathological evidence, and clinical assessments. These guidelines specifically address IIP among various types of ILD.

2) Classification of IIP

This classification was established based on the 2022 American Thoracic Society/European Respiratory Society (ATS/ERS) classification[2] (Table 1) and is based on a multidisciplinary diagnosis (MDD), a decision-making process that involves clinicians, radiologists, and pa-

Figure 1. Classification of interstitial lung disease. *Myositis: Polymyositis (PM)/dermatomyositis (DM)/anti-synthetase syndrome, which may be considered amyopathic, is a part of myositis. †RB-ILD: While almost all patients are known to have RB-ILD, which is a result of cigarette smoke exposure, RB-ILD and desquamative interstitial pneumonia (DIP) usually coexist. DIP is present in some patients with connective tissue disease, without exposure to cigarette smoke, and for unknown cause, even though it is also associated with cigarette smoke exposure in a majority of patients. ILD: interstitial lung disease; IIP: idiopathic interstitial pneumonia; iNSIP: idiopathic nonspecific interstitial pneumonia; iPPFE: idiopathic pleuroparenchymal fibroelastosis; iDIP: idiopathic desquamative interstitial pneumonia; AFOP: acute fibrinous and organizing pneumonia; IPF: idiopathic pulmonary fibrosis; COP: cryptogenic organizing pneumonia; iLIP: idiopathic lymphoid interstitial pneumonia; AIP: acute interstitial pneumonia; RA: rheumatoid arthritis; SSc: systemic sclerosis; MCTD: mixed connective tissue disease; SLE: systemic lupus erythematosus; HP: hypersensitivity pneumonitis; RB-ILD: respiratory bronchiolitis-associated interstitial lung disease; LCH: Langerhans cell histiocytosis; PAP: pulmonary alveolar proteinosis; LAM: lymphangioleiomyomatosis.

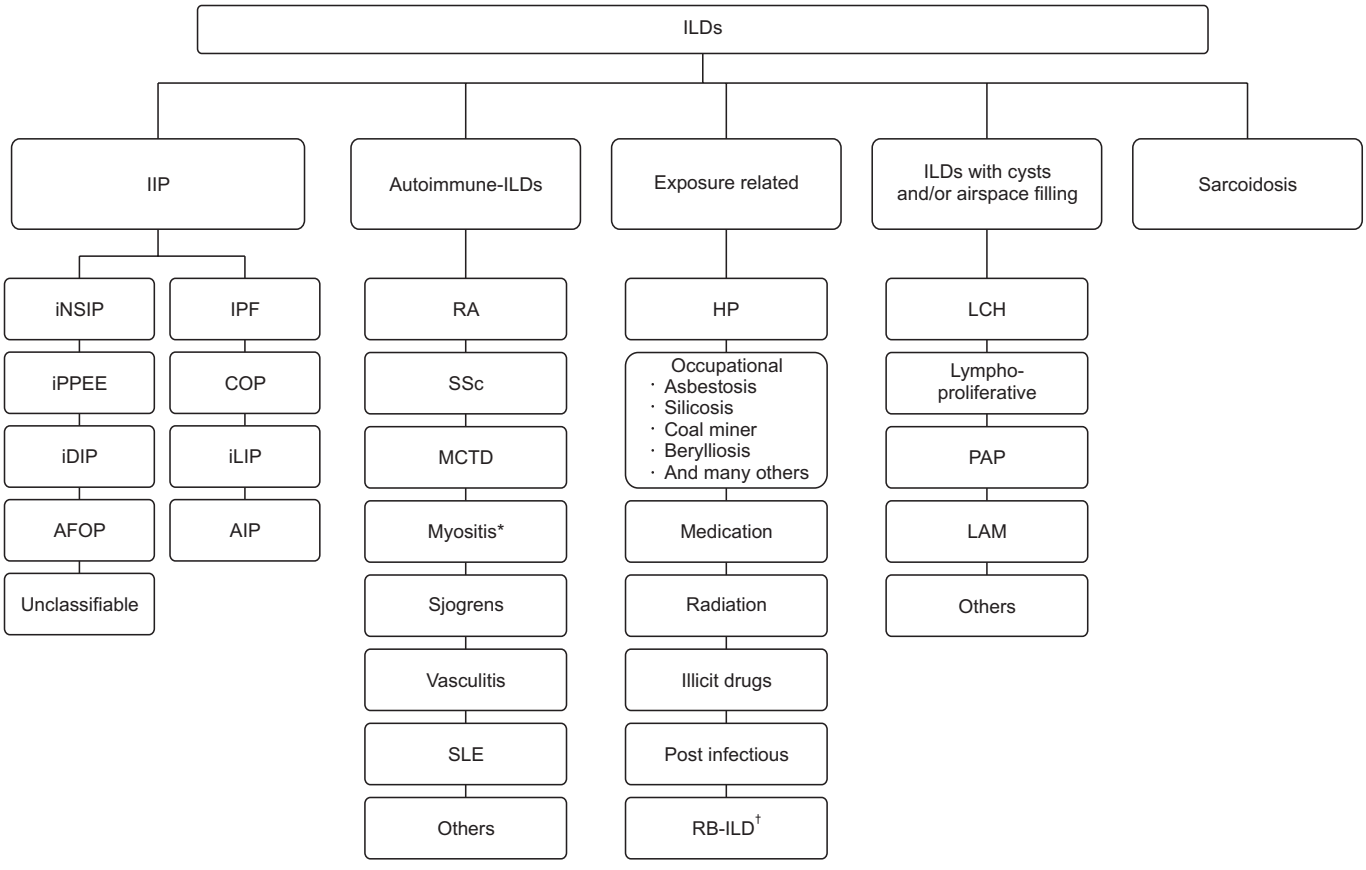


Table 1. American Thoracic Society/European Respiratory Society classification of idiopathic interstitial pneumonias[2]

Idiopathic pulmonary fibrosis, IPF
Idiopathic nonspecific interstitial pneumonia, idiopathic NSIP
Desquamative interstitial pneumonia, DIP
Cryptogenic organizing pneumonia, COP
Acute fibrinous and organizing pneumonia, AFOP
Acute interstitial pneumonia, AIP
Idiopathic lymphoid interstitial pneumonia, idiopathic LIP
Idiopathic pleuroparenchymal fibroelastosis, idiopathic PPFE
Unclassifiable idiopathic interstitial pneumonia, unclassifiable IIP

thologists, as well as clinical data, including smoking history, exposure to hazardous materials (drugs), occupational history, other medical history, and results of pulmonary function tests (PFTs). Patients with a known cause of IIP, such as inhalation of hazardous materials, drugs, or connective tissue diseases (CTD), are excluded from the IIP category[1].

(1) Important differential diagnostic considerations

Hypersensitivity pneumonitis

In some cases of chronic HP, differentiation from idiopathic pulmonary fibrosis (IPF) and idiopathic nonspecific interstitial pneumonia (NSIP) can be challenging, even with high-resolution computed tomography (HRCT) of the chest and lung biopsy. A detailed exposure history of potential causative agents and serum-specific immunoglobulin G antibody testing may aid in diagnosis. However, no causative agent can be identified in approximately 30% of the cases.

Connective tissue disease

CTD is a common cause of interstitial pneumonia, especially NSIP[1]. Clinical and serological evaluations are crucial for differentiating it from IIPs. Various forms of ILDs are commonly observed in RA, SLE, systemic sclerosis, and Sjögren's syndrome[3].

Familial interstitial pneumonia

Family history is reported in 2% to 20% of IIP cases, with heterozygous mutations in surfactant protein C (*SFTPC*), surfactant protein A2 (*SFTPA2*), telomerase reverse transcriptase (*TERT*), and telomerase RNA component (*TERC*) accounting for approximately 20% of all familial interstitial pneumonias[4,5]. More recently, a mucin 1B subunit (*MUCB*) promoter variant was identified as a genetic factor associated with the development of both familial and sporadic IPF[1,6].

Coexisting patterns

Multiple pathologic and/or HRCT patterns may be found in the same patient. In smokers, PLCH, respiratory bronchiolitis-ILD (RB-ILD), desquamative interstitial pneumonia, usual interstitial pneumonia (UIP), and emphysema may coexist. Combined pulmonary fibrosis and emphysema (CPFE) is an example of this coexistence. Such coexisting patterns may be evaluated based on the clinical significance of the individual patterns through MDD[1].

(2) Rare IIPs

Idiopathic lymphoid interstitial pneumonia

Most cases are related to autoimmune diseases or lymphoproliferative disorders (lymphoma, post-bone marrow transplant state, human immunodeficiency virus [HIV], Epstein-Barr virus, etc.) and are rarely idiopathic[1].

Idiopathic pleuroparenchymal fibroelastosis

Pleuroparenchymal fibroelastosis is a rare condition that consists of fibrosis involving the pleura and subpleural lung parenchyma, predominantly in the upper lung lobes. Histologically, it is characterized by alveolar elastosis and fibrosis of the surrounding lung parenchyma. It is clinically associated with a high incidence of pneumothorax and recurrent infections[1,7].

(3) Unclassifiable IIP

IIP may remain unclassified despite MDD, owing to overlapping histological and chest HRCT findings and contradictory clinical, radiological, and pathological findings. This can also occur in CTD and in cases in which a biopsy is performed after pharmacological treatment is initiated. Clear classification criteria and comprehensive data on the clinical presentation of unclassifiable IIP are yet to be established[1].

2. Diagnosis of IIP

1) Medical history

(1) Sex

Among the different types of ILD, LAM usually occurs in women, particularly those of reproductive age. ILD associated with CTD, except for RA, usually occur in women. In contrast, pneumoconiosis, PLCH, and IPF

occur more frequently in men[1].

(2) Pattern of onset

If ILD presents with an acute onset (days to weeks), potential causes such as infection, acute interstitial pneumonia, acute eosinophilic pneumonia, HP, or diffuse alveolar hemorrhage (DAH) should be considered. Subacute onset (weeks to months) suggests differential diagnoses including cryptogenic organizing pneumonia (COP), sarcoidosis, chronic eosinophilic pneumonia (CEP), and drug-induced lung disease. In cases with chronic onset (months to years), IPF, pneumoconiosis, sarcoidosis, and PLCH should be considered[1].

(3) Occupational history

It is essential to consider not only the patient's current occupation, but also the type, duration, and work environment of all previous occupations, as well as the patient's role and work environment[1].

(4) Hobbies and other environmental history

For HP, a detailed history of environmental exposures, including contact with pets, is crucial. Exposure may occur not only from pets kept at home but also in outdoor settings such as parks. A history of symptom improvement several days after the cessation of exposure, followed by recurrence upon re-exposure, can provide valuable diagnostic clues.

(5) Medication history

Both past and current medication histories are important. Gastric juice aspiration owing to gastroesophageal reflux disease slowly leads to ILD development. The use of mineral oil as a laxative or oily nose drops at night may also contribute to the development of ILD. The sequence and duration of drug exposure in relation to symptom onset are important; however, ILD may manifest weeks or years after drug use. In addition, a history of radiation therapy or high-concentration oxygen therapy is important[1].

(6) Smoking history

Smoking history is significant. More than 90% of PLCH patients have a positive smoking history at the time of diagnosis. Patients with RB-ILD or Goodpasture syndrome have been observed to have a prominent history of smoking. Among patients who have been exposed to asbestos, interstitial fibrosis occurs 13 times more frequently in smokers than in nonsmokers. Sarcoidosis and HP usually occur in nonsmokers[1].

(7) Family history

Family history is important for identifying various genetic and metabolic disorders, although they are rare in Korea. Familial incidence can be observed in sarcoidosis or IIP[1].

(8) Travel and other history

Travel history is important because parasitic infections can cause eosinophilia in the lungs. A history of risk factors for HIV infection is also important[1].

2) Symptoms

Symptoms of ILD can occur over months to years and manifest at various levels of progression. Major symptoms include gradually progressing shortness of breath and coughing. Wheezing sounds rarely occur in CEP and HP, whereas substernal chest pain rarely occurs in sarcoidosis. Pleuritic pain can accompany CTD and drug-induced ILD. A spontaneous pneumothorax can cause acute pleuritic chest pain in patients with PLCH, LAM, tuberous sclerosis, or neurofibromatosis. Hemoptysis typically occurs in DAH, LAM, and pulmonary veno-occlusive disease. In ILD, the presence of hemoptysis raises the suspicion of an underlying malignancy[1].

3) Physical examination

Crackles are typically auscultated in the lower lobes of both lungs. Clubbing is commonly associated with progressive fibrotic lung diseases, whereas pulmonary hypertension (PH) or cor pulmonale resulting from chronic hypoxemia may develop in the advanced stages.

4) Radiologic findings

(1) Chest X-ray

Although chest radiography is less sensitive than HRCT for diagnosing ILD, it serves as an initial screening tool. ILD typically manifests as a reticular pattern, nodular pattern, ground-glass opacities, or consolidation predominantly in the bilateral lower lobes on chest X-rays. Chest radiographic findings may be unremarkable during the early stages of ILD[1].

(2) HRCT

Chest HRCT can assess the presence of interstitial pneumonia; the distribution, characteristics, and severity of lung lesions; and the presence of other lung disease combinations[1].

5) Laboratory findings

In patients with suspected ILD, the role of autoimmune antibody testing for CTD remains unclear. Howev-

er, autoimmune antibody testing is recommended if CTD-related symptoms are present. In the 2011 guideline, screening for rheumatoid factor (RF), anti-cyclic citrullinated peptide, and antinuclear antibody (ANA) is advised, even without symptoms suggestive of CTD[1,3].

In a study conducted in the United States, 22% of patients with IPF tested positive for autoimmune antibodies, and these patients showed better prognoses than autoimmune antibody-negative patients. Additionally, a recent study reported that, among patients with a UIP pattern, those who tested positive for one or more autoimmune antibodies or exhibited one or more symptoms or signs of CTD without meeting the criteria for a definitive CTD diagnosis had better prognoses than patients with IPF without these findings.

(1) Specific antibodies

Positivity for antibodies against organic dust or proteins only indicate prior exposure and cannot be used alone for the diagnosis of HP[2]. However, specific antibodies such as anti-glomerular basement membrane antibody or anti-neutrophil cytoplasmic antibody may be useful in certain diagnostic contexts[1].

(2) Nonspecific antibodies

ANA, RF, and anti-topoisomerase I antibody (Scl-70) levels can be helpful in diagnosing interstitial pneumonia accompanied by CTD[1,3].

(3) Angiotensin-converting enzyme

Measurement of blood angiotensin-converting enzyme levels may aid in the diagnosis of sarcoidosis[1,8].

6) PFT and arterial gas analysis

The characteristic PFT findings in ILD include decreased lung compliance and restrictive ventilatory defects characterized by reduced lung volumes, particularly forced vital capacity (FVC) and total lung capacity (TLC), whereas the forced expiratory volume in 1 second (FEV_1)/FVC ratio and airway resistance remain normal. In most patients, the diffusion capacity is reduced, and arterial blood gas analysis in the stable phase may be normal or indicate hypoxemia and respiratory alkalosis, primarily due to ventilation/perfusion mismatch[1].

7) Bronchoalveolar lavage

Bronchoalveolar lavage (BAL) is performed by advancing a flexible bronchoscope into the bronchial branch and instilling 30 to 50 mL of sterile physiological saline solution to retrieve cells and materials from the bronchioles and alveoli. In healthy nonsmokers, the recovered cellular composition consists of approximately 90% macrophages, 10% lymphocytes, and <1% neutrophils. The predominance of specific cell types varies by disease and may aid in the differential diagnosis of ILD. Lymphocyte predominance is observed in conditions such as cellular NSIP, HP, and COP, whereas neutrophilic infiltration is characteristic of IPF. However, given the nonspecific nature and limited diagnostic value of BAL findings, routine BAL is not required for all patients and should be performed at the discretion of the treating clinician[1,8].

8) Lung biopsy

Lung biopsy is the most definitive diagnostic tool and includes transbronchial lung biopsy (TBLB), transbronchial lung cryobiopsy (TBLC), and surgical lung biopsy (SLB) (via open thoracotomy and video-assisted thoracoscopic biopsy)[1].

(1) TBLB

Conditions commonly diagnosed with TBLB include lung sarcoidosis, malignant tumors (bronchoalveolar carcinoma), lymphangitic carcinomatosis, alveolar proteinosis, infections such as *Pneumocystis jirovecii* pneumonia or tuberculosis, and eosinophilic pneumonia[1].

(2) TBLC

Surgical biopsy is the standard histological investigation method; however, its use is limited by high costs and procedural risks. A recent study has demonstrated that TBLC using a cryoprobe can obtain lung tissue samples measuring 40 to 50 mm^2, with a diagnostic yield comparable to that of surgical biopsy in patients with a high suspicion of IIP[8]. TBLC allows for the acquisition of adequate lung tissue, enabling pathologists to establish a definitive histological diagnosis. Notably, the interobserver agreement among pathologists in identifying UIP is also high. Pneumothorax is a common complication, with a reported incidence rate of up to 28%. However, the diagnostic yield of ILD using TBLC remains high (79%). In cases in which definite UIP features are not clearly identified, histopathological evaluation using TBLC can aid in the diagnosis of IPF[2].

(3) Video-assisted thoracoscopic surgery

SLB is the most useful diagnostic tool for ILDs but must be performed selectively with consideration for patient age, systemic status, comorbidities, and complications[2,8]. Indications for SLB include progressive lesions with inconclusive chest HRCT, predictable drug reactions to therapies with high rates of adverse events, such as immunosuppressant use, or cases

requiring differentiation between ILD progression and malignancy or infection[1,2,9]. Relative contraindications include diffuse end-stage lung disease (with honeycomb lesions) due to the high probability of obtaining only fibrotic lung tissue, accompanying severe emphysema, <35% predictive value of lung diffusion capacity, severe hypoxia, and severe heart disease[1,9,10]. The optimal biopsy site is determined using chest HRCT, with tissue samples taken from areas most representative of the disease while avoiding late-stage honeycombing. To improve diagnostic accuracy, at least two adequately sized specimens should be obtained from different lobes. Biopsy of the right middle lobe or the lingular segment of the left upper lobe is generally avoided because of the frequent presence of nonspecific inflammation and passive congestion in these regions. Although histopathological evaluation plays a crucial role in the diagnosis of ILD, SLB alone is insufficient for definitive diagnosis. A multidisciplinary approach incorporating clinical, radiological, and pathological findings is essential[1].

9) Biomarkers

Researchers have shown great interest in identifying biomarkers of IIP, leading to several notable findings regarding the diagnosis, treatment, and prognosis of ILD. Elevated serum levels of proteins associated with epithelial cells or macrophages, such as surfactant protein (SP)-A, SP-D, Krebs von den Lungen-6, chemokine ligand (CCL)-18, and matrix metalloproteinase-7 have been linked to a rapid decline in pulmonary function and reduced survival rate. These proteins can be used as clinically useful biomarkers to identify patients at a high risk of disease progression[11]. Serum SP-A levels are significantly higher in patients with IPF than in those with NSIP or COP, whereas SP-D levels are significantly higher in patients with CTD-associated ILD than in those with IPF. Additionally, BAL fluid reveals distinct immunological patterns, with NSIP exhibiting a helper T-cell type 1–dominant response, whereas IPF is characterized by a helper T-cell type 2–skewed response, along with increased expression of chemokine receptor-7 and CCL7[1].

10) Multidisciplinary discussion

The diagnosis of ILD is often challenging owing to overlapping differential diagnoses, unclear diagnostic criteria for certain conditions, and low interobserver agreement among clinical, radiological, and pathological experts.

A precise diagnosis is essential for determining the prognosis and guiding appropriate treatment. Many international ILD diagnostic guidelines recommend a consensus diagnosis in which pulmonology, thoracic radiology, and pulmonary pathology specialists integrate clinical data, blood tests, chest HRCT findings, and lung biopsy results to reach a comprehensive diagnostic agreement[12]. Additionally, in cases in which CTD-ILD is suspected or requires exclusion, the involvement of a rheumatology specialist is beneficial in MDD[13]. A key study on the utility of MDD demonstrated that implementing MDD improved diagnostic concordance among experts from multiple centers in cases of IPF and CTD-ILD (k value=0.7)[14]. Several studies have also reported significant discrepancies between ILD diagnoses made through MDD and those made solely by individual clinical experts[15-17]. Furthermore, MDD has been found to be particularly beneficial in diagnosing non-IPF ILDs compared with IPF[18]. However, research validating ILD diagnoses established through MDD remains limited, and further studies are needed to assess its impact on final diagnosis and treatment decisions. In summary, MDD has already been recognized as an essential and validated diagnostic tool for ILD, particularly for non-IPF ILD.

Progressive Pulmonary Fibrosis

1. Definition and diagnostic criteria

Among non-IPF ILDs, some exhibit characteristics of progressive fibrosing interstitial lung disease (PF-ILD), demonstrating clinical, radiological, and physiological progression despite standard treatment. However, the definitions and diagnostic criteria for PF-ILD vary across studies.

The 2022 ATS/ERS/Japanese Respiratory Society (JRS)/Asociación Latinoamericana de Tórax (ALAT) clinical guidelines standardized terminology by redefining diseases previously referred to as PF-ILD as progressive pulmonary fibrosis (PPF)[2]. This term now applies to non-IPF ILD in which fibrosis progresses rapidly despite appropriate treatment.

PPF is defined as the occurrence of at least two of the following three criteria within the past year with no alternative explanation: (1) worsening respiratory symptoms; (2) physiological evidence of disease progression, as defined below; and (3) radiological evidence of disease progression, as defined below.

1) Physiological criteria

There is a paucity of published data on physiological measurements in patients with PPF. Therefore, the committee derived the physiological criteria for PPF by extrapolating data from patients with IPF because

the disease behavior and prognosis of IPF and PPF are comparable[2,19]. The committee defined physiological evidence of disease progression as the presence of either of the following findings, if the findings are attributable to worsening fibrosis:

(1) absolute decline in FVC of >5% within 1 year of follow-up;

(2) absolute decline in diffusing capacity of the lungs for carbon monoxide (DL_{CO}, corrected for hemoglobin) of >10% within 1 year of follow-up[2].

2) Radiologic criteria

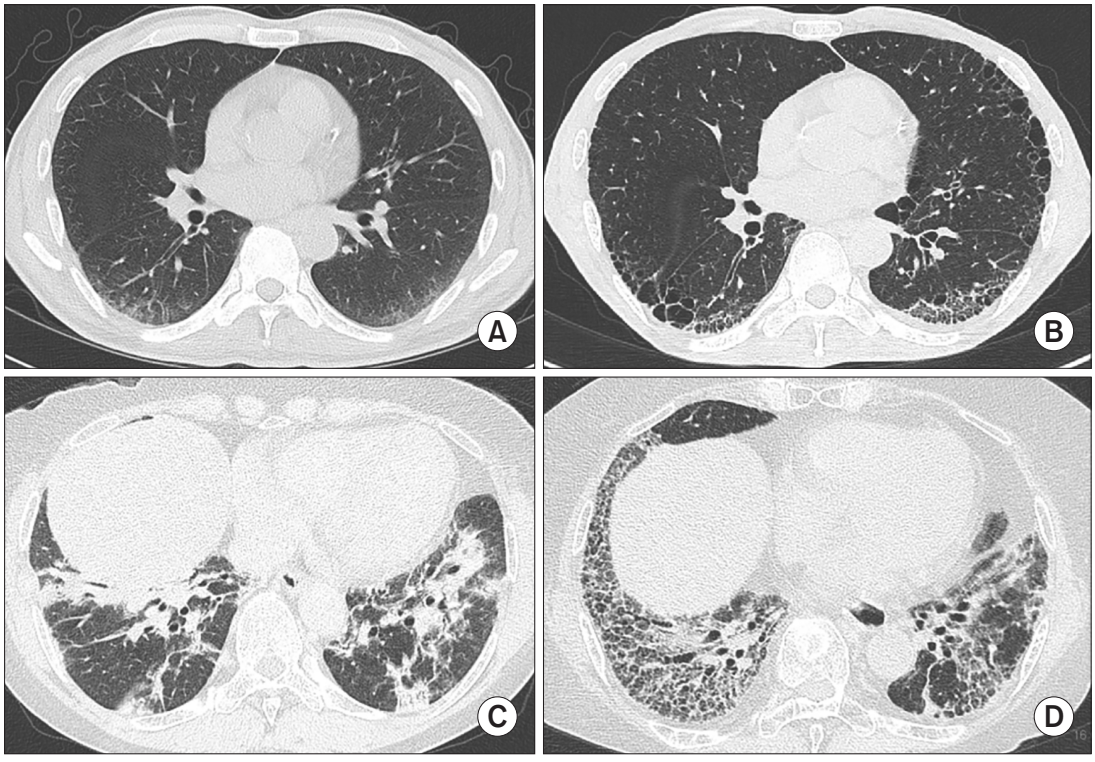
(1) Visual determination of PPF

Progression of fibrosis is typically assessed visually, relying on the percentage of lung volume containing fibrotic features in the upper, mid, and lower lung zones. Transverse, coronal, and sagittal contiguous HRCT sections from the initial and follow-up computed tomography (CT) examinations are compared side-by-side after adjusting for lung volume changes[2] (Figure 2).

Follow-up HRCT is indicated when there is clinical suspicion of worsening fibrosis. However, the optimal interval for follow-up HRCT to determine disease progression remains unknown. Limited data suggest that in patients with systemic sclerosis and stable pulmonary function, repeated chest HRCT within 12 to 24 months from baseline could be useful to promptly detect progression and possibly influence prognosis[20].

It is difficult to predict the proportion of patients with non-IPF ILDs who will develop a progressive fibrotic pattern; however, some HRCT findings in individual patients are considered predictors of disease progression. For example, in addition to the presence of honeycombing and traction bronchiectasis, which are associated with worse prognosis, a greater extent of fibrotic changes is known to be predictive of mortality in IPF, RA-related ILD, systemic sclerosis-related ILD, fibrotic

Figure 2. High-resolution computed tomography (HRCT) of progressive pulmonary fibrosis: a patient with nonspecific interstitial pneumonia (A, B) and a patient with polymyositis-interstitial lung disease (C, D). (A) Initial axial computed tomography (CT) image showing ground-glass opacity with mild reticulation in both lungs, predominantly in the dorsolateral areas of both lower lobes and subpleural areas of both upper lobes. (B) On follow-up HRCT obtained 8 years after the initial study, the progression of pulmonary fibrosis is clearly demonstrated with traction bronchiolectasis, subpleural honeycombing, and architectural distortion with volume loss in the lower lungs and lingula. (C) Initial axial CT image of a patient with polymyositis showing peribronchial and peripheral distribution of air space consolidation with air bronchograms in the lower lungs, suggesting an organizing pneumonia pattern. (D) On follow-up HRCT obtained 4 years after the initial study, significant progression of pulmonary fibrosis is evident, with diffuse and peribronchial distribution of coarse reticulation and traction bronchiectasis.



HP, pulmonary sarcoidosis, and unclassified ILD[2,21].

CT features of early lung fibrosis include fine reticulation, intralobular lines, and architectural distortion (irregular, tortuous pulmonary vessels and airways or distorted lobular anatomy), seen either in isolation or superimposed on ground-glass opacities. This pattern, suggestive of interstitial changes in the early phase, may be observed incidentally on thoracic or abdominal CT scans obtained for other purposes, including screening for lung cancer, and is often associated with histological evidence of fibrosis. Incidentally identified interstitial lung abnormalities (ILAs) are independent risk factors for mortality. At least 40% of subjects with ILAs show progression of CT changes when followed up for 4 to 6 years[2,22,23].

(2) Quantitative assessment of the progression of pulmonary fibrosis

Computer-based quantitative CT (QCT) provides a more objective and reproducible measure of disease progression than visual assessmen[24,25]. Further validation and the adoption of standardized protocols are necessary before QCT can be widely used in the community[2].

2. Evidence-based recommendations for treatment of PPF, other than IPF

Research has been conducted on the possibility that antifibrotic agents that slow the progression of IPF can also delay the progression of PPF[2]. The two antifibrotic agents recommended for the treatment of IPF are pirfenidone, which exhibits anti-inflammatory, antioxidant, and antiproliferative effects, and nintedanib, an intracellular tyrosine kinase inhibitor that suppresses fibrosis.

1) Pirfenidone

A phase 2 randomized clinical trial (uILD, RELIEF study) was conducted to evaluate the effects of pirfenidone[26,27]. Both studies were randomized; however, their interpretations were limited. The studies were small in scale, and the RELIEF study was prematurely terminated owing to insufficient patient enrollment, whereas the uILD study was only conducted on a subset of progressive uILD patients within the PPF cohort. Considering these factors, the 2022 ATS/ERS/ALAT clinical guidelines for PPF recommended additional research to investigate the efficacy, effectiveness, and safety of pirfenidone in PPF patients[2].

2) Nintedanib

A randomized clinical trial (INBUILD) was conducted to evaluate the effects of nintedanib in PPF[28]. The trial showed that the average decline in FVC, a measure of disease progression, was significantly lower in the nintedanib group (107 mL/year), and the progression of ILD was 2.4 times lower in the nintedanib group. However, the effects of nintedanib on the progression of ILD to PPF were not consistent. Based on these findings, the 2022 ATS/ERS/ALAT clinical guidelines for PPF recommend nintedanib as a treatment for PPF in patients with failed standards (conditional recommendation, low evidence level). Further research on the efficacy, effectiveness, and safety of nintedanib in individual ILDs progressing to PPF is recommended[27].

Combined Pulmonary Fibrosis and Emphysema

1. Introduction

Despite its clinical significance and substantial research interest, CPFE remains poorly understood. This disease encompasses a spectrum of fibrotic and emphysematous changes, necessitating differentiation from conditions such as alveolar expansion associated with pulmonary fibrosis and smoking-related interstitial fibrosis (SRIF)[29]. CPFE is not synonymous with IPF because pulmonary fibrosis in CPFE is not always classified as IPF. The lack of consensus on the diagnostic criteria makes it challenging to draw consistent conclusions regarding its clinical features, prognosis, and optimal management[30]. Moreover, whether CPFE should be considered as a distinct disease entity or syndrome remains debatable.

2. Definition

CPFE is defined radiologically as the presence of pulmonary fibrosis in the lower zones and subpleural areas, coexisting with upper-lobe predominant emphysema. While quantification of emphysema is often not feasible, emphysema in CPFE is identified on HRCT as low-attenuation areas with well-defined thin walls or no walls, encompassing at least 5% of the total lung volume. Pulmonary fibrosis is characterized by traction bronchiectasis, honeycombing, volume loss, and ground-glass opacities on HRCT[31].

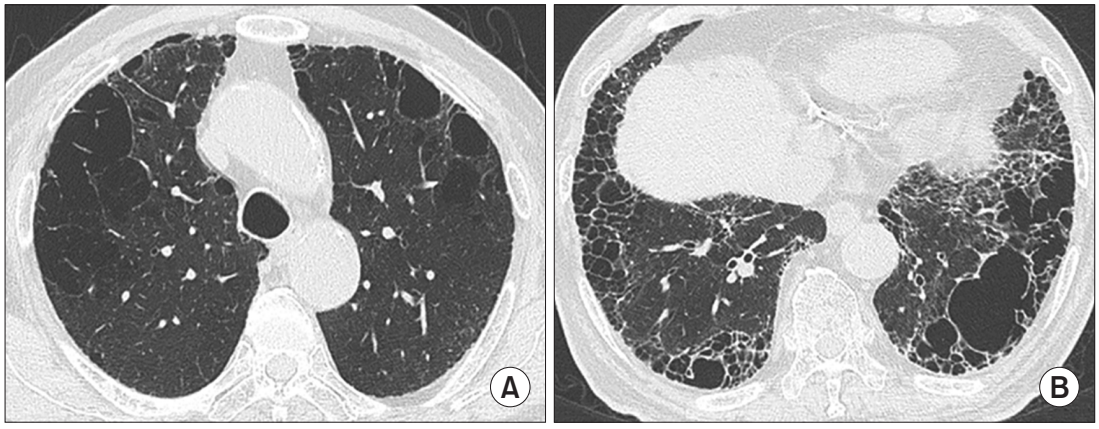
3. Prevalence

The prevalence of CPFE among patients with IPF is estimated to range from 8% to 67%, depending on the population studied and definitions used (Table 2)[32-35]. Higher rates have been reported in Asia and Greece than in the United States. CPFE is observed in 26% to 54% of patients with IIP, with higher rates among hospitalized patients (45% to 71%)[34]. CPFE is also fre-

Table 2. Frequency estimates of combined pulmonary fibrosis and emphysema across different patient populations[32-35]

Population	Reported frequency, %
General population	Unknown
Idiopathic pulmonary fibrosis	8–67
Idiopathic interstitial pneumonia	26–54
Lung cancer, with underlying idiopathic interstitial pneumonia or idiopathic pulmonary fibrosis	55–58
Rheumatoid arthritis–interstitial lung disease	8–58
Systemic sclerosis–interstitial lung disease	5–12
Lung cancer	3–10
Lung cancer screening cohort	0.04
Cohort undergoing chest computed tomography	3–7

Figure 3. Combined pulmonary fibrosis and emphysema in a heavy smoker (A, B). High-resolution computed tomography axial images show upper-lobe predominant emphysema with peripheral bullae (A) and concurrent pulmonary fibrosis with honeycombing predominantly involving the subpleural areas of both basal lungs (B).



quently associated with lung cancer (55% to 58%)[35]. The prevalence of CPFE in the general population is unknown because most data are derived from patients undergoing chest CT for clinical indications.

4. Etiology

1) Exposures and diseases

CPFE is strongly associated with smoking and male sex, with male patients showing a nine-fold higher prevalence than female patients. However, nonsmokers, particularly those with CTDs, may also develop CPFE. Approximately 5% to 10% of patients with systemic sclerosis-associated ILD[36] and 27% of RA-associated ILD cases in nonsmokers demonstrate radiological features of CPFE[37]. Additionally, CPFE has been observed in systemic vasculitis, particularly in microscopic polyangiitis. Environmental and occupational exposure to asbestos and silica has also been implicated.

2) Genetic predisposition and aging

Genetic susceptibility combined with environmental exposure, such as smoking and air pollution, may contribute to the development of both emphysema and fibrosis. Mutations in genes associated with surfactant production and telomerase have been reported in patients with CPFE[38].

5. Clinical features and comorbidities

The mean age of patients with CPFE is approximately 65 to 70 years, with 73% to 100% being male[29]. Primary symptoms include exertional dyspnea and cough. Patients with PH often experience severe dyspnea during physical activity, with the majority classified as New York Heart Association functional class III or IV[39].

The two most notable comorbidities of CPFE are lung cancer and PH. Other comorbid conditions include coronary artery disease, peripheral vascular disease, and diabetes mellitus. However, it is unclear whether these

are more common in CPFE than in IPF without emphysema.

6. Radiologic characteristics

1) Overview

CPFE is defined as the coexistence of emphysema and fibrosis, which can present as overlapping features on HRCT. Differentiating honeycomb cysts from mixed emphysema-fibrosis lesions can be challenging, especially given the high prevalence of a UIP pattern among patients with CPFE (Figure 3). The co-occurrence of emphysema and fibrosis often produces radiologic patterns of thick-walled cystic lesions.

2) Quantification of HRCT abnormalities

HRCT enables semiquantitative evaluation of the extent of the disease, focusing on the relative areas of emphysema and fibrosis. However, standardization of this assessment is lacking.

3) Emphysema quantification

Emphysema in CPFE is primarily evaluated using imaging rather than PFTs. Although visual assessments by experienced radiologists are commonly used, these methods often fail to capture the diversity of emphysema patterns.

4) ILD quantification

Despite its clinical relevance, a minimal threshold extent of pulmonary fibrosis on HRCT has not yet been established for CPFE. Ground-glass opacities, which may reflect inflammation rather than fibrosis, remain a point of contention regarding whether they should be included in fibrosis scoring. Further research is required to clarify this issue.

7. Pulmonary function characteristics

Patients with CPFE exhibit limited exercise capacity and severely reduced DL_{CO}, while airflow and lung volume are relatively preserved[40]. Most patients show an increased FVC/DL_{CO} ratio[36].

Patients with CPFE show higher lung volumes (FVC and TLC), similar FEV_1, increased residual volume (RV), lower DL_{CO}, and lower arterial oxygen partial pressure (PaO_2) than patients with IPF. FEV_1/FVC ratios are generally normal or slightly reduced but may increase with disease progression.

Severe oxygen desaturation during exercise and exertional hypoxemia are common in CPFE, particularly in patients with severe PH[29]. Hypercapnia typically occurs only in the late disease stages.

Currently, no optimal parameters for monitoring CPFE progression have been identified. Changes in FVC, which are often used to track IPF progression, are not reliable indicators of CPFE. Parameters such as DL_{CO}, composite physiologic index, and FEV_1/FVC have been suggested, but require further validation. The ATS Clinical Guideline Committee recommends incorporating clinical, radiologic, and functional findings to monitor

Table 3. Main characteristics of pulmonary function in combined pulmonary fibrosis and emphysema[29,36,40]

Pulmonary function test measurement	Typical abnormality seen in CPFE	Typical abnormality seen in fILD without emphysema
FVC	Decreased or normal (but preserved compared with idiopathic pulmonary fibrosis alone)	Decreased
FEV_1	Decreased or normal	Decreased
FEV_1/FVC	Variable (normal, decreased or increased)	Normal or increased
TLC	Variable (normal, decreased or increased)	Decreased
FRC	Variable (normal, decreased or increased)	Decreased
Residual volume	Variable (normal, decreased or increased)	Decreased
DL_{CO}	Disproportionately decreased	Decreased
Transfer coefficient for carbon monoxide	Severely decreased	Normal or decreased
Saturation during exercise	Severe desaturation	Desaturation
Peak oxygen uptake	Decreased	Decreased

CPFE: combined pulmonary fibrosis and emphysema; fILD: fibrosing interstitial lung disease; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; TLC: total lung capacity; FRC: functional residual capacity; DL_{CO}: diffusing capacity of the lungs for carbon monoxide.

Table 4. Histopathological features of smoking-related interstitial fibrosis and other patterns of fibrotic interstitial lung disease in combined pulmonary fibrosis and emphysema[29]

Pattern of fibrosis	Distribution	Fibroblast foci	Honeycomb change	Interstitial inflammation
SRIF	Patchy, subpleural, peribronchiolar	Rare	Rare	Absent
DIP	Diffuse	Rare	Absent	Present
UIP, probable UIP	Patchy, subpleural, interlobular septa	Present	Present	Patchy, mild (may be more extensive in areas of honeycombing)
F-NSIP	Diffuse	Rare	Absent	Present
Intermediate	Patchy or diffuse	±	±	±

SRIF: smoking-related interstitial fibrosis; DIP: desquamative interstitial pneumonia; UIP: usual interstitial pneumonia; F-NSIP: fibrotic nonspecific interstitial pneumonia.

Table 5. Proposed research definition of combined pulmonary fibrosis and emphysema (for research purposes) and classification criteria of combined pulmonary fibrosis and emphysema clinical syndrome (with clinical relevance)[29]

Research definition of CPFE	Patients with coexistence of pulmonary fibrosis and emphysema must have both criteria on HRCT: Emphysema of any subtype on HRCT defined as well-demarcated areas of low attenuation delimitated by a very thin wall (≤1 mm) or no wall*†,‡ and involving at least 5% of total lung volume§ Lung fibrosis of any subtype‖
Classification criteria of CPFE clinical syndrome: These additional criteria serve research purposes and may be considered depending on the objective of the study	Patients must have CPFE (see above) and one or more of the following: Emphysema extent ≥15% of total lung volume§,¶ Relatively preserved lung volumes and airflow with very or disproportionately decreased DL_{CO}, especially in patients with limited extent of HRCT abnormalities, and in the absence of pulmonary hypertension Precapillary pulmonary hypertension considered not related to the sole presence of emphysema (FEV_1 >60%), fibrosis (FVC >70%), or the etiological context (e.g., absence of connective tissue disease)

*Emphysema generally predominates in the upper lobes but may be present in other areas of the lung or may be admixed with fibrosis. †Emphysema may be replaced by thick-walled large cysts >2.5 cm in diameter (CPFE, thick-walled large cyst variant). ‡Surgical lung biopsy is not required if the HRCT pattern is diagnostic. However, CPFE is suggested if lung biopsies show emphysema and any pattern of pulmonary fibrosis. Emphysema can then be quantified using HRCT. §The extent of emphysema is assessed visually by an experienced radiologist. An emphysema extent of <5% is unlikely to affect physiology or outcome and is more open to interobserver disagreement. ‖Signs of fibrosis on HRCT in patients with interstitial lung disease include architectural distortion, traction bronchiectasis, honeycombing, and volume loss. Therefore, caution must be exercised when identifying honeycombing in patients with associated emphysema. Ground-glass attenuation may be present. Interstitial lung abnormalities are not sufficient to diagnose CPFE. ¶Emphysema extent >15% is associated with relatively stable FVC over time. Several studies have used a 10% threshold; however, an association with FVC outcome has not been demonstrated.
CPFE: combined pulmonary fibrosis and emphysema; HRCT: high-resolution computed tomography; DL_{CO}: diffusing capacity of the lungs for carbon monoxide; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

CPFE progression (Table 3)[29].

8. Pathological features

CPFE is primarily defined based on clinical, functional, and HRCT findings, and lung biopsies are often impractical because of the associated risks (Table 4). Histologically, CPFE combined with emphysema is characterized by distal airway destruction without obvious fibrosis, with features such as patchy fibrotic changes, fibroblast foci, and honeycombing. Smoking-related bronchiolitis and SRIF are frequently observed in CPFE patients[41].

9. Diagnostic criteria

1) Clinical criteria

There are no clear clinical diagnostic criteria for CPFE. However, in patients diagnosed with chronic obstruc-

tive pulmonary disease (COPD), significant reductions in DL_{CO}, despite mild-to-moderate airflow limitations, should prompt HRCT evaluation for CPFE (Table 5).

2) Radiologic criteria

HRCT is the cornerstone for identifying CPFE, allowing the assessment of both emphysema and fibrosis. Differentiating between honeycomb cysts and emphysema can be challenging in some cases[40].

3) Functional criteria

No definitive functional criteria are available for the diagnosis of CPFE. Typical findings include severely reduced DL_{CO} and transfer coefficient (Kco), with relatively preserved airflow and lung volumes. Compared to IPF, CPFE shows higher lung volumes, lower DL_{CO} and Kco values, and increased RV. Relative to COPD, patients with CPFE demonstrate less hyperinflation and lower DL_{CO}[32].

10. Treatment

1) General management

No treatment modalities for CPFE have been established in clinical trials. General management includes smoking cessation, regular exercise, pulmonary rehabilitation, and oxygen therapy[42].

2) Treatment of pulmonary fibrosis

Antifibrotic agents such as nintedanib are effective in slowing the progression of fibrosis, as shown in subanalyses of the INPULSIS and INBUILD trials[43,44]. Therefore, these drugs should be considered in patients with progressive fibrosis.

3) Treatment of emphysema

Bronchodilators and inhaled corticosteroids may be used in accordance with COPD management guidelines, although supporting clinical trial data are limited. Surgical and bronchoscopic interventions for emphysema are generally contraindicated because of severe DL_{CO} reductions.

4) Treatment of PH

PH management includes oxygen supplementation, timely referral for lung transplantation, and supportive therapies. Clinical trials of oral medications for PH, such as endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and soluble guanylate cyclase stimulators, have shown unsatisfactory results[45].

5) Treatment of lung cancer

Approaches to lung cancer management in CPFE are similar to those in other lung cancer patients but have higher complication and mortality rates. Surgery, chemotherapy, and radiation should be tailored to the severity of the underlying ILD and emphysema[46].

11. Prognosis and complications

1) Pulmonary hypertension

PH is reported in 15% to 55% of patients with CPFE[29], with variability attributed to differences in diagnostic methods and patient populations. Estimated systolic pulmonary artery pressures are higher in patients with CPFE than in those with IPF alone[32]. The additional hemodynamic burden imposed by emphysema exacerbates the risk of PH beyond what is attributable to fibrosis severity alone.

2) Lung cancer

The prevalence of lung cancer in patients with CPFE ranges from 2% to 52%[29], depending on the study design. Compared with patients with IPF alone, CPFE patients have an approximately 2.7 times higher lung cancer risk. Squamous cell carcinoma and adenocarcinoma are the most frequently observed histological subtypes, with squamous cell carcinoma more common in CPFE than in the general non-small cell lung cancer population. Most cancers are located in the lower lobes and tend to be diagnosed at advanced stages with invasive features[46]. The presence of CPFE adversely affects the prognosis, with poor outcomes associated with honeycombing, advanced tumor stages, and reduced surgical candidacy. Standard cancer treatments are often limited in CPFE, contributing to increased morbidity and mortality rates.

3) Acute exacerbations

Acute exacerbations similar to those observed in IPF have been reported in patients with CPFE at varying frequencies. Risk factors include higher Gender-Age-Physiology scores, the presence of lung cancer, and post-surgical status[47]. HRCT findings of diffuse ground-glass opacities and/or consolidation can help differentiate exacerbations of fibrosis from emphysema. The prognosis following acute exacerbation of CPFE is better than that following IPF.

4) Mortality and prognostic factors

Patients with CPFE exhibit worse survival rates than those with emphysema alone. Comparisons with IPF have yielded mixed results, with survival reported as

worse, similar, or better, depending on the study[29]. FVC declines more slowly in CPFE than in IPF because of the emphysema-induced preservation of lung volume. However, larger emphysematous lesions are associated with poorer outcomes. Mortality predictors include DL_{CO}, physiological indices, age, and the presence of specific complications such as PH and lung cancer[29].

Interstitial Lung Abnormality

1. Definition

ILA is defined as an incidentally detected radiological abnormality on chest CT. Various definitions have been proposed; however, in 2020, the Fleischner Society issued a position paper defining ILA as non-dependent abnormalities occupying at least 5% of any lung region (six zones: upper, middle, or lower lobes)[48,49].

ILA is not simply a radiologic abnormality but is accompanied by a decline in pulmonary function[50] or clinical symptoms[5]. Therefore, ILA should be distinguished from subclinical ILD detected in high-risk individuals (e.g., those with environmental exposure, CTDs, or a family history of ILD) and preclinical ILD that has yet to manifest symptoms.

2. Prevalence

HRCT is a sensitive modality for detecting ILA. Studies using chest CT for purposes other than ILD screening have reported a prevalence of ILA ranging from 4% to 17%, depending on smoking status[51]. This prevalence is significantly higher than that of lung nodules detected during lung cancer screening[52].

3. Risk factors

Commonly reported risk factors for ILA include advanced age and smoking. Environmental factors such as asbestos exposure[53], occupational exposure[54], and air pollution[55], have also been identified as risk factors. Additionally, genetic factors such as mucin 5B subunit (*MUC5B*) promoter polymorphisms have been linked to familial interstitial pneumonia and IPF.

4. Radiologic findings

Radiologic findings associated with ILA include ground-glass opacities, reticular abnormalities, diffuse centrilobular nodularity, traction bronchiectasis, honeycombing, and non-emphysematous cysts (Table 6 and Figure 4)[49]. Initially, centrilobular nodularity was considered an ILA feature, but the 2020 Fleischner Society position paper excluded it from the definition[49]. Local or unilateral ground-glass opacities, dependent atelectasis that does not persist in the prone position, and pleuropulmonary fibroelastosis are not included in ILA imaging findings (Figure 5).

Table 6. Definitions and subcategories of interstitial lung abnormalities[49]

What are interstitial lung abnormalities (ILAs)?	Incidental identification of non-dependent abnormalities, including ground glass or reticular abnormalities, lung distortion, traction bronchiectasis, honeycombing, and non-emphysematous cysts Involving at least 5% of a lung zone (upper, middle, and lower lung zones are demarcated by the levels of the inferior aortic arch and right inferior pulmonary vein) In individuals in whom interstitial lung disease is not suspected
What are not ILAs?	Imaging findings are restricted to the following: Dependent lung atelectasis Focal paraspinal fibrosis in close contact with thoracic spine osteophytes (Figure 5A) Smoking-related centrilobular nodularity in the absence of other findings (Figure 5B) Mild focal or unilateral abnormality (Figure 5C) Interstitial edema (e.g., in heart failure) Findings of aspiration (patchy ground-glass, tree in bud; Figure 5C)
Preclinical and clinical identification	Preclinical interstitial abnormalities identified during screening of high-risk individuals (e.g., those with rheumatoid arthritis, scleroderma, occupational exposure, familial interstitial lung disease) Findings in patients with known clinical interstitial lung disease
Subcategories of ILAs	Non-subpleural: ILAs without predominant subpleural localization (Figure 4A) Subpleural nonfibrotic: ILAs with a predominant subpleural localization and without evidence of fibrosis* (Figure 4B) Subpleural fibrotic: ILAs with a predominant subpleural localization and with evidence of pulmonary fibrosis* (Figure 4C)

*Fibrosis is characterized by the presence of architectural distortion with traction bronchiectasis, honeycombing, or both.

Figure 4. Interstitial lung abnormality (ILA). (A) Non-subpleural nonfibrotic ILA, screening low-dose chest computed tomography (CT) axial image showing non-subpleural patchy ground-glass opacities in both lower lobes with no reticulation, traction bronchiolectasis, or bronchiectasis. (B) Subpleural nonfibrotic ILA, Screening low-dose chest CT axial image showing subpleural subtle ground-glass opacities in the dorsolateral areas of both lower lobes, with no reticulation, traction bronchiolectasis, or bronchiectasis. (C) On baseline staging workup for colon cancer, a chest CT axial image showed subpleural reticulation in both basal lungs, associated with traction bronchiolectasis and mild lung parenchymal distortion.

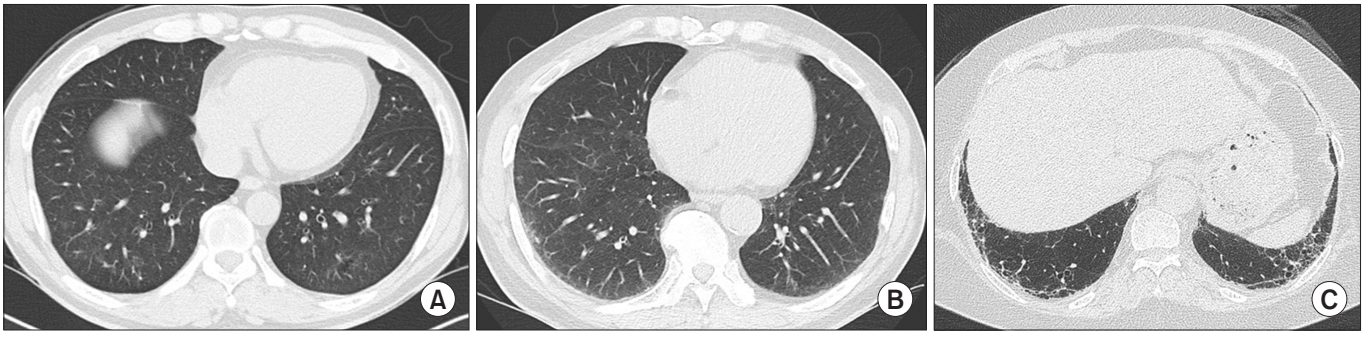
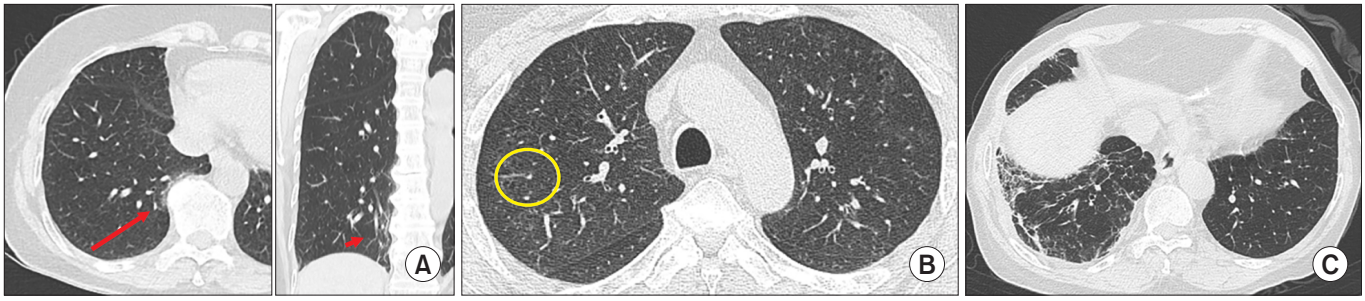


Figure 5. Imaging abnormalities that do not represent interstitial lung abnormalities (ILAs). (A) Focal paraspinal fibrosis (not representative of ILA), chest computed tomography (CT) axial (red arrow) and coronal (short red arrow) images showing a curvilinear fibrotic band in the medial right lower lobe, closely related to osteophytes. (B) Centrilobular nodularity (respiratory bronchiolitis) in a heavy smoker (not representative of ILA). High-resolution CT axial image showing poorly defined ground-glass centrilobular nodules (yellow circle) and mild emphysema in both upper lobes without other findings of interstitial abnormalities. (C) Unilateral focal abnormality (not representative of ILA) in chest CT axial image showing focal reticulation, mild traction bronchiectasis, and architectural distortion in the right lower lobe associated with adjacent pleural thickening, which is thought to be a sequela of pneumonia.



5. Pathologic features

Because ILA is primarily a radiologic concept, there are limited pathological studies. The predominant histopathological findings included nonspecific fibrosis, UIP, SRIF, and NSIP[56,57].

6. Diagnosis

The most widely accepted definition of ILA is based on the 2020 Fleischner Society position paper[49]. ILA is defined as non-dependent abnormalities that involve at least 5% of any part of the lung in an individual who has not previously suspected ILD. Table 6 summarizes the imaging findings included and not included in ILA.

If the examination performed is insufficient (e.g., abdominal CT findings of ILA), a chest CT scan can help evaluate the properties of the ILA. Chest CT should be performed with moderate edge-enhancing thin-section reconstruction (<1.5 mm). Prone-position CT helps to identify dependent opacities (Table 7).

7. Clinical presentation and prognosis

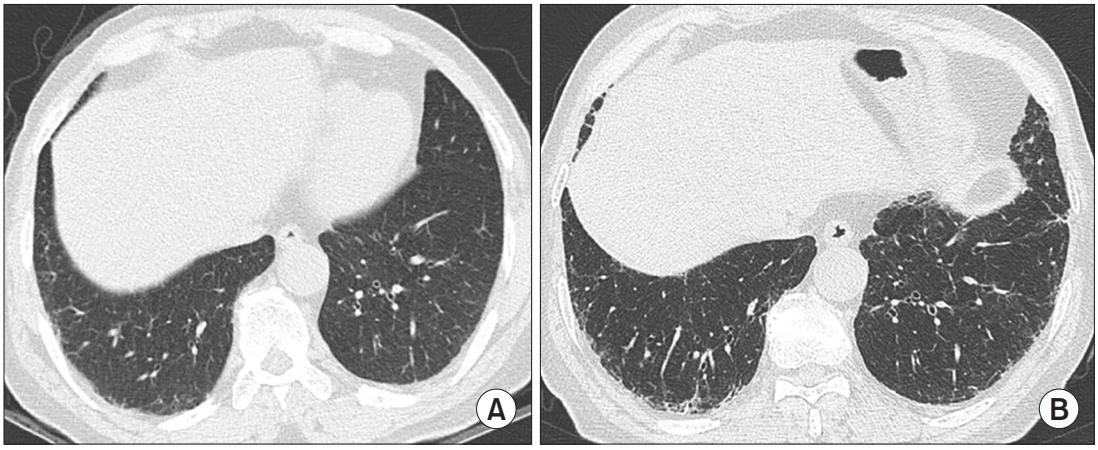
Patients with ILA may present with chronic cough, dyspnea, and reduced exercise capacity in test such as in the 6-minute walking test[6,58,59]. It was also confirmed that progression on imaging was associated with a decrease in FVC. The progression of ILA varies across studies, with some reporting a 20% progression over 2 years[60] and others showing 48% progression over 5 years (Figure 6)[23]. However, not all ILAs progress; therefore, it is necessary to identify the risk factors that

Table 7. Recommendations for the evaluation and reporting of interstitial lung abnormalities[49]

CT protocol	Thin sections (<1.5 mm) are essential Prone and expiratory scans might be necessary to confirm and characterize ILAs
CT description	Axial and craniocaudal distribution CT findings: including ground-glass abnormality, reticular abnormality, traction bronchiectasis, honeycombing, and cysts CT category: non-subpleural ILA, subpleural nonfibrotic ILA, or subpleural fibrotic ILA
Clinical evaluation	Distinguish ILAs from clinically significant interstitial lung disease Identify risk factors for progression Follow-up evaluation
Pathology evaluation	On lung cancer resections, assess background lung from cancer resections and document histological patterns diagnostic of suspicion for interstitial lung disease Review such cases in a multidisciplinary team setting to determine whether ILAs or clinically significant interstitial lung disease is present

CT: computed tomography; ILA: interstitial lung abnormality.

Figure 6. Interstitial lung abnormality (ILA) and long-term progression. (A) Screening low-dose chest computed tomography (CT) axial image showing subtle subpleural reticulation with ground-glass opacities in the dorsolateral areas of both basal lungs, indicating a subpleural ILA. (B) On the follow-up CT obtained 10 years after the initial study, the progression of pulmonary fibrosis iss evident, with increased reticulation, traction bronchiolectasis, and mild architectural distortion in both subpleural basal lungs. Upon clinical review, the patient showed no respiratory symptoms or spirometric abnormalities.



predict their progression.

Radiologic predictors of disease progression include subpleural reticulation, predominant lower-lobe changes, traction bronchiectasis, and honeycombing. Elevated blood monocyte levels[61] and advanced age[60] have also been associated with progression to ILD.

The association between ILA and mortality was consistently confirmed in each related study, including a long-term follow-up study in South Korea[62]. Radiologic features such as traction bronchiectasis[63] and a UIP pattern[60], as well as biomarkers such as growth differentiation factor 15[64], are associated with a higher mortality risk. Moreover, ILA is a poor prognostic factor in lung cancer treatment, increasing the risk of immune checkpoint inhibitor-related pneumonitis[65], radiation pneumonitis[66], and systemic chemotherapy-related pulmonary complications[67]. ILA is also associated with postoperative pulmonary complications in lung cancer surgery[68], especially in case of fibrotic ILA[69]. ILA is linked to higher mortality rates after aortic valve replacement[70] and an increased risk of acute respiratory distress syndrome in sepsis[71]. Therefore, patients with ILA may require close evaluation and monitoring of complications before treatments such as chemotherapy or surgery.

Table 8. Risk factors for progression of interstitial lung abnormalities[49]

Clinical risk factors	Cigarette smoking Other inhalational exposures Medications (e.g., chemotherapy, immune checkpoint inhibitors) Radiation therapy Thoracic surgery Physiological or gas exchange findings at lower limits of normal
Radiological risk factors	Nonfibrotic interstitial lung abnormalities (ILAs) with basal and peripheral predominance Fibrotic ILAs with basal and peripheral predominance but without honeycombing (ILAs with probable usual interstitial pneumonia pattern) Fibrotic ILAs with basal and peripheral predominance and honeycombing (ILAs with usual interstitial pneumonia pattern)

8. Evaluation and monitoring

Owing to limited evidence, the evaluation and monitoring of ILA are primarily based on expert opinions from the Fleischner Society[49]. If initial imaging is insufficient, HRCT should be considered. Identified ILA cases should be evaluated for contributing factors such as smoking, systemic diseases, inhalational exposure, drug toxicity, and aspiration. Patients with respiratory symptoms, pulmonary function abnormalities, or extensive disease on imaging should be referred to a pulmonologist for a multidisciplinary ILD evaluation and standard management. Follow-up monitoring should be tailored to each patient's risk level. High-risk individuals should be closely monitored. If ILD is excluded, follow-up should be considered based on the risk of ILA progression. PFT (3 to 12 months) and imaging follow-up (12 to 24 months) are considered for active monitoring, and early follow-up may be considered depending on the accompanying risk factors (imaging findings, PFT results, and clinical symptoms). In particular, according to the Framingham Heart Study[50] and the AGES-Reikjavik Study[23], follow-up for high-risk groups (Table 8) is clinically important because imaging progression is associated with increased mortality.

Authors' Contributions

Conceptualization: Park SW. Methodology: Park C, Yeo Y, Woo AL, Park SW. Formal analysis: Park C, Yeo Y, Park SW. Data curation: Park C, Yeo Y, Woo AL, Yoo JW, Hong G, Shin JW. Funding acquisition: Park SW. Software: Park C, Yeo Y. Validation: Park C, Yeo Y. Writing - original draft preparation: all authors. Writing - review and editing: Park C, Yeo Y. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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