**Introduction/Dentification**

Idiopathic pulmonary fibrosis (IPF) is a clinical syndrome and considered the most common and the most lethal form of pulmonary fibrosis corresponding to the histologic and imaging pattern of UIP. (百科介绍)

{meltzer2008idiopathic}

Idiopathic pulmonary fibrosis is a chronic disease that manifests over several years and is characterized by scar tissue within the lungs, in the absence of known provocation. Exercise-induced breathlessness and chronic dry cough are the prominent symptoms.

IPF belongs to a family of lung disorders known as the interstitial lung disease (ILD) or, more accurately, the diffuse parenchymal lung diseases (OPLD). Within this broad category of diffuse lung disease, IPF belongs to the subgroup known as idiopathic interstitial pneumonia (IIP). By definition, the etiology of IIP is unknown. There are seven distinct IIPs, differentiated by specific clinical features and pathological patterns (\citep{katzenstein1998idiopathic}). IPF is usually fatal, with an average survival of approximately three years from the time of diagnosis (citep{collard2003changes, flaherty2003prognostic, latsi2003fibrotic}). Older studies suggested that five-year mortality for IPF was only 50%, but this estimate was derived prior to the recognition of non-specific interstitial pneumonia (NSIP), a pathological subtype of IIP that mimics IPF in tis clinical presentation (\citeaiup{carrington1978natural, turner1980cryptogenic, turner1980cryptogenic}). NISIP has a more favorable prognosis and the almost certain inclusion of NSIP cases in older studies of IPF mortality accounts for differences in observed outcome (\citep{bjoraker1998prognostic}). By definition, IPF/UIP must be discriminated from NSIP.

{king2011idiopathic}

Idiopathic pulmonary fibrosis (IPF), the most common form of the idiopathic interstitial pneumonias, is a chronic, progressive, irreversible, and usually lethal lung disease of unknown cause. IPF occurs in middle-aged and elderly adults (median age at diagnosis 66 years, range 55-75 years), is limited to the lungs, and is associated with a histopathological or radiological pattern typical of usual interstitial pneumonia [ATS newest paper].

{xaubet2017idiopathic}

Idiopathic pulmonary fibrosis (IPF) is defined as a chronic fibrosing interstitial lung pneumonia, of unknown etiology, usually affecting adults over 50 years old and associated with the radiological and/or histological pattern of usual interstitial pneumonia. It is the most frequent diffuse interstitial lung disease. The actual incidence and prevalence of IPF is not fully understood.

{martinez2017idiopathic}

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease (ILD) in which progressive lung scarring occurs in the supporting framework (interstitium) of the lungs (\citep{raghu2011official}). IPF is defined on the basis of the resence of a radiographic and/or histopathological pattern of usual interstitial pneumonia (UIP) in the absence of an alternate aetiology for this pattern. UIP usually presents as ‘honeycombing’ (subpleural cystic airspaces with well-defined walls), traction bronchiectasis (dilatation of the bronchi) and peripheral alveolar septal thickening. IPF is thought to begin at the base and periphery (edge) of the lungs, gradually progressing to involve all lung tissue. The disease, which can present as sporadic or familial forms, is associated with increasing cough and dyspnoea (shortness of breath), with a devastating effect on a patient’s quality of life (QOL) (\citep{{kim2015natural}). Improved diagnostic methods are of increasing importance to enable the institution of effective therapies. Recent years have witnessed radical improvements in therapeutic options and their availability, translating into an opportunity to preserve lung function.

{richeldi2017idiopathic}

Idiopathic pulmonary fibrosis is a choronic, progressive, and fibrotic lung disease. Healthy tissue is replaced by altered extracellular matrix and alveolar architecture is destroyed, which leads to decreased lung compliance, disrupted gas exchange, and ultimately respiratory failure and death. In less than a decade, understanding of the pathogenesis and management of this disease has been transformed, and two disease-modifying therapies have been approved, worldwide.

Lutz Beckert

IPF is one of the most affressive and frequent forms of idiopathic interstitial lung disease (ILD). In individuals aged >= 75 years, the prevalence of IPF is eestimated at > 200 cases per 100,000 population, and mean survival is approximately 3 years. Traditionally, IPF was considered an inflammatory disorder, and teatment centred on anti-inflammatory or immunosuppressant medications such as azathioprime, cyclophosphamide and prenisone. However, IPF is now regarded as a fibrotic condition that results from abnormal wound healing after repeate pulmonary damage. A lung injury (the exact cause of which is unknown) affects alveolar epithelial cells (AECs), whose appotosis or ‘reprogramming’ causes a cascade of events: vascular leak; extravascular coagulation; innate immune activaation; fibrolast recruitment, proliferation and activation; and extracellular matrix synthesis and cross-linking. Several causes of alveolar injury have been suggested. These include cigarette smoke, enviromental exposure to toxins (e.g. asbestos, avian toxins), gastro-oesophageal reflux, viral infection, and internal mechanisms such as autoimmunity, genomic instability or telomerase length.

**Disease classifications**

Lutz Beckert

Clinical distriction between IPF, the most common of the idiopathic intertitial pneumonias (IIPs), and other IIPs is particularly important because of the divergent management implications (figure) (\citep{corte2015idiopathic, troy2012management}). Other IIPs are thought to be primarily inflammatory conditions, whereas IPF is primarily a fibrotic disorder. The prognosis for other IIPs is generally much better than that for IPF. In IIPs other than IPF, the key intervention continues to be anti-inflammatory therapy, with the aim being to preserve functional status.

**Diagnosis:**

It is more common in middle age or elderly men and diagnosed by:

1. Histological or imaging pattern of usual interstitial pneumonia (UIP) and
2. Absence of alternative causes such as drug toxicity, environmental exposure (e.g. asbestos) or collagen vascular disease (e.g. scleroderma, rheumatoid arthritis) (百科介绍)

Multidisciplinary approach in tertiary setting is strongly advised. Contributions from pulmonists, chest radiologists, and chest pathologist are crucial reaching the correct diagnosis of IPF.

ATS/ERS (American Thoracic Society and European Respiratory Society) has developed major and minor criteria for the daignosis of IPF in the absence of a surgical lung biopsy:

Major criteria:

1. Exclusion of other known causes of interstitial of interstitial lung idsease (e.g. toxic effects of certain drugs, environmental exposures, connective tissue diseases) abnormal results of pulmonary function studies, including evidence of restriction (reduced vital capacity, often with an increased FEV1/FVC ratio) and impired gas exchange (increased PaO2, decreased PaO2 with rest or exercise, or decreased DLCO).
2. Bibasilar reticular abnormalities with minimal ground-glass opacities at high-resolution CT: definite UIP pattern on HRCT chest
3. Transbronchial lung biopsy or bronchoalveolar lavage shows no features to support an alternative diagnosis

Minor criteria

1. Age>50 years
2. Insidious onset of otherwise unexplained dyspnea on exertion
3. duration of illness being over 3 months
4. bibasilar inspiratory crackles (dry or “Velcro” type) (百科介绍)

{meltzer2008idiopathic}

The actual “gold standard” diagnosis of IPF consists of clinical-radiological-pathological correlation and was defined by consensus conference in the year 2000 and adopted b the American Thoracic and European Respiratory Societies (ATS/ERS) in a statement of guildlines published in the same year []. According to guidelines, the diagnosis of IPF can be considered definitive only in the presence of a surgical (not transbronchial) lung biopsy.

The definite diagnosis of IPF requires alll of the following:

……

{king2011idiopathic}

The diagnosis of IPF often requires a multidisciplinary approach, involving pulmonologists, radiologists, and pathologists experienced in the field of interstitial lung disease \citep{flaherty2004idiopathic}. A pattern indicaive of usual interstitial pneumonia on high-resolution Ctssue obtained by surgical lung biopsy is crucial for the final diagnosis. The major differential diagnostic consideration is fibrotic nonspecific interstitial pneumonia, and other forms of idiopathic interstitial pneumonias and interstitial lung disease associated with occupational or environmental exposure, systemic disease, or drugs need to be excluded.

{richeldi2017idiopathic}

Diopathic pulmonary fibrosis is diagnosed by identification of a pattern of usual interstitial pneumonia on the basis of radiological or histological criteria in patients without evidence of an alternative cause. This approach is endorsed in consensus guidelines worldwide and has helped to standaridise idiopathic pulmonary fibrosis diagnosis. A major challenge to clinicians is exclusion of other idiopathic interstitial pneumonias and of known causes of interstitial lung disease, such as domdetic and occupational exposures, connective tissue disease, and drug toxicity. Such exclusion is of particular importance because the usual interstitial pneumonia pattern is not exclusive to diopathic pulmonary fibrosis and might also be associated with other conditions, including chronic hypersensitivity pneumonitis, asbestosis, connective tissue diseases, and drug toxicity. Many patients have histories of environmentatl exposures, medications, and symptoms that require clinicians to make judgments regarding the relevance of the cause of disease.

{raghu2011official}

Diagnostic criteria and schema for adult patients with ILD and suspected IPF are presented in Figure 3 and Table 6. Careful exclusion of alternative etiologies through multidisciplinary discussion between pulmonologists, radiologists and pathologists expericed in the diagnosis of ILD is of the utmost importance to an accurate diagnosis. In situations in which multidisciplinary discussion is not feasible, it is recommended that patients be referred to experienced clinical experts in ILD for consultation.

The diagnostic criteria for IPF presented in this document have been significantly modified from those stated in the previous ATS/ERS Statement. Given the high-quanlity evidence regarding HRCT specificity for the recognition of histopathologic UIP pattern, surgical lung biopsy is not essential \citep{hunninghake2001utility, raghu1999accuracy, flaherty2003radiological, quadrelli2010radiological}. In the appropriate clinical setting (as described in the clinical presentation section above; this includes a thorough medical, occupational/environmental and family history, physical examination, physiological testing, and laboratory evaluation), the presence of a UIP pattern on HRCT is sufficient for the diagnosis of IPF. Thus, the major and minor criteria for the clinical (i.e., nonpathologic) diagnosis of IPF have been eliminated.

{raghu2011official}

Dianostic criteria

The diagnosis of IPF requires the following:

同上，百度百科中的

Thus, the accuracy of diagnosis of IPF increases with clinical, radiologic, and histopathologic correlation and can be accomplished with a multidisciplinary discussion among experienced clinical experts in the field of ILDs \citep{flaherty2004idiopathic}. This is paricularly relevant in cases in which the radiologic and histopathologic paterns are discordant (e.g., HRCT is inconsistent with UIP and histopathology is UIP). An HRCT or pathologic UIP pattern is not 100% specific to IPF \citep{lynch2006usual, trahan2008role, silva2008chronic}. Discordant histologic patterns on surgical lung biopsy specimens obtained from different segments have been described. Cases with coexisting UIP pattern and fibrotic NSIP pattern (discordant UIP) appear to behave similarly to those with UIP pattern in all lobes (concordant UIP) \citep{monaghan2004prognostic, flaherty2001histopathologic}. This supports the obtainment of surgical lung biopsies from multiple lobes in patients with suspected IPF.

**Epidemiology**

Although rare, IPF is the most common form of IIP.[[6]](https://en.wikipedia.org/wiki/Idiopathic_pulmonary_fibrosis#cite_note-ATS/ERS-6) The prevalence of IPF has been estimated between 14.0 and 42.7 per 100,000 persons based on a USA analysis of healthcare claims data, with variation depending on the case definitions used in this analyses.[[24]](https://en.wikipedia.org/wiki/Idiopathic_pulmonary_fibrosis#cite_note-PulmonaryFibrosis-24)[[8]](https://en.wikipedia.org/wiki/Idiopathic_pulmonary_fibrosis#cite_note-RaghuWeycker-8) IPF is more common in men than in women and is usually diagnosed in people over 50 years of age.[[3]](https://en.wikipedia.org/wiki/Idiopathic_pulmonary_fibrosis#cite_note-Rag2011-3)

The [incidence](https://en.wikipedia.org/wiki/Incidence_(epidemiology)) of IPF is difficult to determine as uniform diagnostic criteria have not been applied consistently.[[3]](https://en.wikipedia.org/wiki/Idiopathic_pulmonary_fibrosis#cite_note-Rag2011-3)[[8]](https://en.wikipedia.org/wiki/Idiopathic_pulmonary_fibrosis#cite_note-RaghuWeycker-8) A recent study from the USA estimated the incidence of IPF to be between 6.8 and 16.3 per 100,000 persons. In the 27 European Union countries, a range of sources estimate an incidence of 4.6–7.4 people per 100,000 of the population,[[61]](https://en.wikipedia.org/wiki/Idiopathic_pulmonary_fibrosis#cite_note-GribbinHubbard-61)[[62]](https://en.wikipedia.org/wiki/Idiopathic_pulmonary_fibrosis#cite_note-NavaratnamFleming-62) suggesting that approximately 30,000–35,000 new patients will be diagnosed with IPF each year.[[24]](https://en.wikipedia.org/wiki/Idiopathic_pulmonary_fibrosis#cite_note-PulmonaryFibrosis-24)[[63]](https://en.wikipedia.org/wiki/Idiopathic_pulmonary_fibrosis#cite_note-EurostatNewsJuly2010-63)

A recent single-centre, retrospective, observational cohort study including incident patients diagnosed with ILD at [Aarhus University Hospital](https://en.wikipedia.org/wiki/Aarhus_University_Hospital) (Denmark) between 2003 and 2009 revealed an incidence of 4.1 per 100,000 inhabitants/year for ILD. IPF was the most common diagnosis (28%) followed by connective tissue disease-related ILD (14%), hypersensitivity pneumonitis (7%) and non-specific interstitial pneumonia (NSIP) (7%). IPF incidence was 1.3 per 100,000 inhabitants/year.[[64]](https://en.wikipedia.org/wiki/Idiopathic_pulmonary_fibrosis#cite_note-HyldgaardHilberg-64)

Due to a heterogeneous distribution of the disease across European countries, epidemiological data needs to be updated through a Europe-wide registry for ILD and IPF. (百科介绍)

{meltzer2008idiopathic}

IPF affects men more than women. In addition, the incidence of IPF increases with age. IPF most commonly appears between the fifth and seventh decades of life, with two-thirds of all cases arising in patients over 60 years of age.

{xaubet2017idiopathic}

The epidemiological studies performed show very variable figures depending on the criteria used to define the disease, study population, methodology and study design. However, it is estimated that the incidence is 4.6-7.4 cases/100,000 and the prevalence is 13 cases/100,000 in women and 20 cases/1000,000 in men. It is unknown whether the incidence and prevalence are influced by ethnic, racial or geographical factors. In recent years, incidence has been reported to be higher, probably due to the improved diagnostic methods and the increased life expectancy.

{richeldi2017idiopathic}

Idiopathic pulmonary fibrosis is the most common type of idiopathic interstitial pneumonia. Although the disease has been considered rare, it occurs with similar frequency to that of stomach, brain, and testicular cancers. Incidence of idiopathic pulmonary firborsis has risen over time, and in Europe and North America is estimated to range between 2.8 and 18 cases per 100,000 people per year. Little data are available for worldwide variation, but incidence might be lower in Asia and South America, where it is estimated to range from 0.5 to 4.2 cases per 100,000 individuals per year.

Idiopahic pulmonary fibrosis is more common in men and is rare in people younger than 50 years (median age at diagnosis is about years) (\citep{raghu2011official, raghu2006incidence}). Although disease course is variable and somewhat unpredictable, the median survival time from diagnosis is 2-4 years (\citep{ley2011clinical}).

**Clinical presentation**

Patients typically present with progressive dyspnea on exertion and chronic dry cough, finger clubbing, chest pain, fatigue, malaise, and weight loss. Pulmonary function test results may be normal in mild disease or shows restriction pattern (i.e. reduced vital capacity and total lung capcacity but near normal residual volume). DLCO is commonly decreased even In with mild cases. (百科介绍)

{king2011idiopathic}

Patients with IPF usually seek medical attention because they suffer chronic and progressive extertional dyspnoea and cough. Bibasilar inspiratory crackles are heard on chest auscultation and frequently finger clubbing is found. The natural history of IPF has been characterised as a steady or slowly progressive lung disorder, and most patients follow this pttern. However, recent findings indicate that IPF is a heterogeneous disease and new clinical pheotypes with distinct patterns of survival are being described. The pathogenic mechanisms are unclear, but a growing body of evidence indicates that the disease is the recent of an abnormal behaviour of the alveolar epithelial cells that provoke the migration, proliferation, and activation of mesenchmal cells, with the formation of fibroblast and myofibroblast foci. Activate myofibroblasts secrete exaggerated amounts of extracelluar matrix molecules with the subsequent destruction of the lung architecture.

{richeldi2017idiopathic}

Patients typically present with non-specific symptoms of exertional dyspnoea with or without dry cough. This presentation might initially be attributed to ageing, deconditioning, or other comorbidities (eg, smoking history, emphysema, cardiovascular disease, or obesity); therefore, clinical suspicion of idiopathic pulmonary fibrosis by primary care physicians is required to prevent diagnostic delays. Occasionally, patients will present acutely, with days to weeks of respiratory worsening, often accompanied by fever and influenza-like symptoms. Theses acute exacerbations require careful diagnostic distinction from other forms of acute interstitial lung disease.

On physical examination, fine, high-pitched bibasilar inspiratory crackles are usually heard (audio) and digital clubbing is present in roughly 30% of patients. Careful attention to signs of connective tissue disease is essential to rule out associated diseses. In established disease, pulmonary function tests identify restrictive disease (reduced total lung capacity) and abnormal gas exchange (reduced capacity for carbon monoxide diffusion). Early disease, or disease coexisting with emphysema that pseudonormalises volumes, might demonstrate normal spiromentry and plethysmography, with only an isolated reduction in diffusion.

Clinical features, imaging, and histopathology all play important roles in the diagnosis of idiopathic pulmonary fibrosis. A patient might receive an idiopathic pulmonary fibrosis diagnosis with varying defrees of diagnostic certainty. A dynamic multidisciplinary discussion between physicains, radiologists, and pathologists experienced in diagnosis of interstitial lung disease increases diagnostic agreement, and thus is considered the diagnostic gold standard, although a few patients remian unclassifiable.

**Pathology**

IPF as the name implies it is idiopathic however there is an association with concurrent or previous history of smoking in 60% of pathients and genetic factors. Up to 5-20% of patients with IPF have a family history of ILD or pulmonary fibrosis. More recently it has been shown that fibroblasts in this process demonstrate neoplastic or neoproliferative characteristics. (百科介绍)

**Genetics**

The rs35705950 single-nucleotide polymorphism (SNP)—a promoter site of an airwya mucin gene (MUC5B)—is strongly associated with IPF and familial pulmonary fibrosis and not seen in other secondary causes of lung fibrosis. Positive rs35705950 SNP in IPF patients is associated with slightly better prognosis and outcome. (百科介绍)

**Histopathology**

Histology shows UIP pattern which is charactacterized by spatial and temporal heterogeneity. One of the hall marks is the absence of inflammation. Spatial heterogeneity denotes biopsy sample showing patchy lung involvement with normal lung interspace between diseased lung. Temporal heterogeneity denotes different stsages of disease seenn on a single specimen, including normal lung, interstitial fibrosis and fibroblastic foci. (百科介绍)

{richeldi2017idiopathic}

When high-resolusion CT features are non-diagnostic, surgical lung biopsy is advised. In-hospital mortality after elective biopsy in patients younger than 65 years and with few comorbidties is less than 2%, but every patient still requires careful consideration as to whether the risks of surgical lung biopsy outweigh the potential benefits of diagnostic information. In older patients, those with comorbidities (updated Charlson score >1), clinically significant physiological impairment, or for non-elective procedures, the risk is greateer and surgical lung biopsy should generally be avoided. When considering undertaking surgical lung biopsy, the pretest probalitiy of a subsequent histopathological diagnosis of usual interstitial pneumonia in patients with possible usual interstitial pneumonia on hight-resolution CT is increased with older age, male sex, and the presence of traction bronchiectasis.

Histopathological findings show that the usual interstitial pneumonia pattern is characterised by interstitial fibrosis with spatial heterogeneity and patchy involvement of lung parenchyma, area of marked fibrosis, architectural distortion, and microscopic honeycombing (cystic airspaces lined by bronchiolar epithelium, typically filled with mucin; figure 3).

{king2011idiopathic}

The main histopathological features of usual interstitial pneumonia, best seen at low magnification, is a heterogeneous appearance with areas of subpleural and paraseptal fibrosis and honeycombing (i.e., cystic fibrotic airspaces lined by bronchiolar epithelium and often filled by mucin and variable numbers of inflammatory cells) alternating wih areas of less affected or normal parenchyma (spatial heterogeneity). Small areas of active fibrosis (fibroblast foci) are present in the background of collagen deposition, and thye reflect the temporal heterogeneity of the process and indicate current ongoing disease. Inflammation is usually mild and consists of a patchy lymphoplasmacytic interstitial infiltrate.

{raghu2011official}

The histopathologic hallmark and chief diagnostic criterion is a heterogeneous appearance at low magnification in which areas of fibrosis with scarring and honeycomb change alternate with areas of less affected or normal parenchyma \citep{ american2000idiopathic, travis2002american} (Figure). These histopathologic changes often affect the subpleural and paraseptal parenchyma most severely. Inflammation is usually mild and consists of a patchy interstitial infiltrate of lymphocytes and plasma cells associated with hyperplasia of type 2 pneumocytes and bronchiolar epithelium. The fibrotic zones are composed mainly of dense collagen, although scattered convex subepithelial foci of proliferating fibroblasts and myofibroblasts (so-called fibroblast foci) are a consistent finding. Areas of honeycomb change are composed of cystic fibrotic airspaces that are frequently lined by bronchiolar epithelium and filled with mucus and inflammatory cells. Smooth muscle metaplasia in the interstitium is commonly seen in areas of fibrosis and honeycomb change.

The differential diagnosis for the UIP pattern on pathology is relatively short, especially when strict criteria for UIP are maintained. The major differential diagnostic considerations include UIP in other clinical settings such as connective tissue disaeses, chronic hypersensitivity pneumonitis (extrinsic allergic alveolitis), and pneumoconioses (especially asbestosis).

Some biopsies may reveal a pattern of fibrosis that does not meet the above criteria for UIP pattern \citep{ american2000idiopathic}. These biopsies may be termed ‘’nonclassifiable fibrosis’’. In the absence of histologic features diagnostic of an alternative condition (e.g., hypersensitivity pneumonitis, sarcoidosis, etc.), such biopsies may be consistent with the diagnosis of IPF in the appropriate clinical and radiologic setting and after careful multididsciplinary discussion.

**Radiographic features**

The CT imaging findings complement the histology. It is more correct to describe characteristic imaging pattern as UIP rather than IPF, a terminology assigned for the idiopathic clinical syndrome of UIP.

A UIP-pattern of fibrosis is characterised by honeycombing cysts and reticular septal thickening with subpleural and posterior basal predominance. Traction bronchiectasis can also be observed, however, this is a general feature of fibrosis notspecific to UIP-pattern. In a subgroup of patients the imaging finding of UIP overlap with NSIP and bioobtpsy may be necessary to obtain the correct diagnosis. (百科介绍).

{king2011idiopathic}

The presence of a usual-interstitial-pneumonia pattern on high-resolution CT is characterised by reticular opacities, often associated with traction bronchiectasis, with little or no ground-glass oapacifications. Honeycombing, manifested as subpleural, clustered cystic airspaces with well-defined walls (typically 3-10 mm in diameter), is common and is critical for making a defite diagnosis [ATS newest paper].

**History and physical**

{meltzer2008idiopathic}

IPF patients experience breathlessness upon exertion. They are often bothered by a dry cough which interferes with daily activities. The onset of symptoms is slow, but sympotoms become progressively worse over time. The initial presentation of breathlessness is commonly attributed to aging, cardiac disease, or emphysema which results in typical delays of diagnosis. Retrospective analysis of IPF patients suggests that symptoms precede dagnosis by a period of 6 conths to 2 years (\citep{kim2006classification}). Symptoms such as weight loss, fever, and arthralgias are unusual in IPF and should prompt an inverstigation for secondary causes of pulmonary fibrosis. Castro-esophageal acid reflux is present in close to 90% of patients with IPF but often occurs without symptoms (\citep{raghu2006high}).

Auscultation of the lungs reveals early inspiratory crackles, predominantly located in the lower posterior lung zones upon physical exam. These rales have a fine acoustic character reminiscent of the sound made by Velcro.

Clubbing is found in approximately 50% of patients with IPF. There are no other physical manifestations, unless corpulmonale has developed in associaion with end-stage disease. In that case, classic signs of right heart failure may be present.

**Physiologic changes**

{meltzer2008idiopathic}

Routine spirometry reveals decreased measures of forced vital capacity (FVC) and forced expiratory volume in one second (FEV1). The ration of FEV1/FVC remains normal (or increased) in IPF, consistent with restrictive physiology. Lung volume measurements confirm restrictive physiology, usually manifest in reduction of total lung capacity (TLC). Restrictive physiology is the consequence of reduced pulmonary compliacne. Changes in compliance can be attributed to the accumulation of parenchymal scar tissue and the subsequent distortion of normal lung architecture.

Gas exchange is impaired in IPF which can be demonstrated by measurement of the diffusion capacity. Declining diffusion capacity can sometimes precede changes in lung volume. Isolated impairment of diffusion capacity can be found during the early stages of IPF.

The resing arterial blood gas is usually normal. Mild hypoxemia and mild respiratory alkalosis can occur in end-tage disease. Although resting arterial oxygen sturation remians normal, oxygen desaturation is commonly found during exercise. The main cause for execise induced hypoxemia is ventilation-perfusion (V/Q) mismatching, as opposed to anatomic shunting or reduced diffusion capacity (citep{agusti1991mechanisms}).

**Natural history and prognosis**

{meltzer2008idiopathic}

The natural history of IPF is incompletely known. IPF usually assumes a course of relentless physiologic deterioration. However, some patients remain stable for extended periods and individual outcomes can be highly variable (\citep{kim2006classification}). Still, long-term survival with biopsy proven IPF is not expected. The median survival time demonstrated in recent studies using the modern definition of IPF is between 2 and 5 years, conting from the time of diagnosis (\citep{collard2003changes, latsi2003fibrotic, bjoraker1998prognostic}).

New insight into the natural history of IPF has been gleaned from secondary analysis of the placebo groups assembled for recent multi-center clinical trials. It appears that three potential clinical course exist: a) slowly progressive disease (the most common); b) disease marked by episodic acute exacerbations; and c) rapidly progressive disease (\citep{kim2006classification}). At present, there are no means for accurately predicting the clinical course. Nevertheless, acute exacerbations deserve special attention.

Lutz Beckert

IPF occurs mainly in middle-aged and elderly individuals and constitutes 20% - 30% of all ILD (\citep{ ryu2014idiopathic}). The clinical course of IPF may take several forms (figure):

Subclinical --- It is widely acknowleged that symptoms typically occur a median of 1-2 years before diagnosis, but ‘subclinical’, radiographic evidence of IPF may occur even before symptoms appear.

Rapidly progressive --- This primarily affects males who are heavy cigarettte smokers. Symptoms are usually evident for < 6 months before the first clinical presentation, and patients with rapidly progressive disease have reduced survival relative to those with a slowly progressive clinical course.

Acute exacerbations --- These are classed as the rapid worsening (within a few days to a few weeks) of symptoms, pulmonary function, and radiographic evidence (e.g. high-resolution computed tomography [HRCT] showing bilateral ‘ground-glass’ opacities and consolidation against a background reticular pattern); this is in the absence of discernible causes such as heart failure, infection, or pulmonary embolism. The prognosis for patients with acute exacerbations is poor.

Slowly progressive --- This is the traditional IPF pheotype and is characterised by slow deterioration of pulmonary function (forced vital capacity [FVC] decreases by a mean of 0.13-0.21L each year), worsening dyspoea, and death within a few years of diagnosis.

{king2011idiopathic}

IPF has a heterogeneous clinical course, and patients have a median survival of 2.5-3.5 years after diagnosis. Clinical phenotypes with distinct patterns of comorbidities and survival are being defined (Figure 2). Worse prognosis is associated with old age (>70 years of age), smoking history, low body-mass index, severe physiological impairment, large radiological extent of desease, and pulmonary hypertension (\citep{ley2011clinical}).

{raghu2011official}

The natural history of IPF has been described as a progressive decline in subjective and objective pulmonary function until eventual death from respiratory failure or complicating comorbidity \citep{carrington1978natural, tukiainen1983prognosis, gross2001idiopathic}. Available longitudinal studies do not allow a clear assessment of median survival in IPF. Several retrospective longitudinal studies suggest a median survival time from 2 to 3 years from the time of diagnosis \citep{bjoraker1998prognostic, flaherty2002clinical, nicholson2000prognostic, rudd2007british, king2001idiopathic}. However, recent data from clinical trials of patient with preserved pulmonary function suggest this may be an underestimate \citep{raghu2004placebo, albera2009effect, king2008build}.

There appear to be several possible natural histories for patients with IPF (Figure 4) \citep{raghu1987idiopathic}. For a given patient, the natural history is unpredictable at the time of the diagnosis. The majority of patients demonstrate a slow, gradual progression over many years. Some patients remain stable while others have an accelerated decline \citep{selman2007accelerated}. Some patients may experience episodes of acute respiratory worsening. It is unknown if these different natural histories represent distinct phenotypes of IPF or if the natural history is influenced by geographic, ethnic, cultural, racial, or other factors. Other comorbid conditions such as emphysema and pulmonary hypertension may impact the disease course \citep{mejia2009idiopathic, wells2003idiopathic, lettieri2006prevalence}.

{king2011idiopathic}

**Stable or slowly progressive course**

Many patients with IPF have a ralatively slow clinical course and usually consult doctors for months to years after the beginning of symptoms (cough and progressive dyspnoea). At presentation, patients have decreased lung volumes and capacities, with hypoxaemia at rest that worsens with exercise. In the placebo groups of large clinical trials, the mean annual rate of decline in forced vital capacity ranges from 0.13L to 0.21L (\citep{ley2011clinical}).

**Accelerated variant**

A subgroup of patients, mainly male cigarette smokers, has a rapidly progressive course with shortened survival, known as accelerated IPF. In these cases, the transcriptional signature indicates the upregulation of several funcional pathways, which mostly operate in alveolar epithelial and mesenchymal domains. Accelerated IPF differs in clinical course and transcriptional profile from the typical slowly progressive form, despite having similar lung function, chest imaging, and histological findings at the time of diagnosis.

Acute exacerbation

Acute exacerbation of IPF is defined by rapid deterioration of the disease in the absence of infection, heart failure, pulmonary embolism, or other identifiable cause (\citep{collard2007acute, tomioka2007acute}). Diagnosis is made by a combination of clinical (worsening of dyspnoea within days to few weeks), physiological (severe decrease of PaO2 in arterial blood), and radiographical findings (bilateral ground-glass opacities and consolidation superimposed on a pattern typical of usual interstitial pneumonia on high-resolution CT) (\citep{silva2007acute}). Acute exacerbation of IPF is estimated to affect 5-20% of cases (\citep{collard2007acute}). Patients with this acute exacerbation have poor outcomes, with mortality exceeding 60% during admission to hospital, and smong those who survive there is a >90% mortality within 6 months after discharge (\citep{wootton2011viral, lettieri2006prevalence}).

**Acute exacerbations of IPF (Complications and comorbidities)**

{meltzer2008idiopathic}

Japanese physicians were the first to describe acute, unexpected deterioration in patients with IPF. This phenomenon has been called the “acute exacerbation” or, more euphemistically, the “terminal complianction” of IPF (\citep{kondoh1993acute, gross1962concept}).

{xaubet2017idiopathic}

The exacerbation of IPF is defined as an acute worsening of respiratory sympotoms, with no clear trigger, leading to severe hypoxemia and worsening prognosis in the short term. Mortality is over 50% and in those cases requiring mechanical ventilation, close to 100%. The annual incidence varies by series but is around 15%. Several studies have established potential risk factors, such as impaired lung function (FVC < 70%), the presence of GER and PH. The etiology of IPF exacerbations is unknown, although several mechanisms have been suggested as initiators of the symptomatology: infectious agents, pollution or pharmacological toxicity. Lung surgery associated with diagnostic tests (bronchoscopic techniques) have also been admitted as predisposing factors.

**Complications and comorbidities**

{martinez2017idiopathic}

Pulmonary and extrapulmonary comorbid conditions are increasingly being recognized as important in patients with IPF \citep{king2017idiopathic} . A systematic review confirmed a high frequency of pulmonary comorbidities, including pulmonary hypertension, COPD and lung cancer; systemic comorbidities including obstructive sleep apnoea, ischaemic heart disease and gastro­ oesophageal reflux were also quite common \citep{raghu2015comorbidities} . One single­centre study demonstrated that 12% of patients with IPF had no comorbid illness, 58% of patients had \citep{raghu2011official, kim2015natural} comorbidities and 30% had \citep{king2011idiopathic, baddini2015many, esposito2015idiopathic, harari2016epidemiology} comorbid conditions \citep{kreuter2016impact} .

**IPF and emphysema (Complications and comorbidities)**

{martinez2017idiopathic}

Another important comorbid condition is combined pulmonary fibrosis and emphysema (CPFE) \citep{cottin2005combined} , the diagnosis of which is generally established with HRCT (FIG. 6) . Although the implications of therapy have not been explicitly studied, the presence of significant emphysema in a patient with IPF decreases the rate of FVC decline \citep{schmidt2010pulmonary, cottin2017effect} . The survival implication of CPFE remains controversial with some suggesting worsened survival compared with IPF and others noting no difference \citep{ryerson2013clinical, jacob2017functional} . Additionally, lung cancer and IPF frequently associate epidemiologically even after adjustment of common and shared risk factors \citep{karampitsakos2017lung} . Lung cancer develop ment is more common in lower lung zones (FIG. 7) and is often of the squamous cell carcinoma subtype \citep{karampitsakos2017lung}. In general, survival is particularly impaired in the setting of IPF and lung cancer.

{meltzer2008idiopathic}

Severeal groups have described a syndrome in shich IPF coexists with pulmonary emphysema (\citep{wells1997lone, wells2003idiopathic, cottin2005combined}). This comes no surprise since both disease are associated with a history of exposure to cigarette smoke. Combined IPF and emphysema is characterized by upper lobe emphysema and lower lobe fibrosis. Physiologic testing of these patients reveals preserved lung volume indices contrasted by markedly impaired diffusion capacity. The incidence of comined iPF and emphysema remains unknown but smaller case seies suggest that this subgroup may comprise up to 35% of patients with IPF (citep{wells2003idiopathic}).

{king2011idiopathic}

Diagnosis of combined pulmonary fibrosis and emphysema is based on high-resolution CT findings that show emphysematous lesions in the upper lobes and usual interstitial pneumonia-like lesions in the lower lobes (\citep{cottin2010pulmonary, mejia2009idiopathic, silva2008idiopathic}). Whether combined pulmonary fibrosis and emphsema is a distinct clinical condition, a different clinical phenotype in smokers developing IPF, or the presence of two different diseases running in parallel is unclear. Patients with combined pulmonary fibrosis and emphysema are commonly men who heavily smoke cigarettes and who have severe dyspnoea on exertion and have relatively conserved lung volumes associated with disproportionate impairment of gas exchange. These patients develop early and severe pulmonary arterial hypertension and they have a worse survival compared with patients with IPF who do no thave emphysema (\citep{cottin2010pulmonary, mejia2009idiopathic}).

Combined pulmonary fibrosis and pulmonary hypertension has a negative effect on prognosis in patients with IPF. This combined disorder is associated with low diffusing capacity for carbon monoxide, shorter walk distances, desaturation during exercise, and an incresed risk of death.

{xaubet2017idiopathic}

Combined pulmonary fibrosis and emphysema (CPFE) is deemed a different entity representing a clinical syndrome. It is more common in males with a significant smoking-habit. Chest X-ray and HRCT show emphysema of the upper lobes and images of pulmonary fibrosis in the lower lobes. Its prevalence is 30-47% in patients with IPF. Spirometry and lung volumes are minimally dimished due to the opposite effect between emphysema-induced hyperinflation and volume loss due to fibrosis. However, DLCO and severe hypoxemia drop dramatically and disproportionately during exercise due to the additive effect of emphysema and fibrosis. Pulmonary hypertension (PH) is more frequent and marked than in patients with IPF and is the main determinant of poor prognosis, which is worse than in IPF without emphysema. There is no specific therapy.

{cottin2005combined}

Emphysema and the idiopathic interstitial pneumonias, including idiopathic pulmonary fibrosis (IPF), are entities defined by distinct clinical, functional, radiological, and pathological characteristics. Combined pulmonary fibrosis and emphysema (CPFE) has been mentioned in passing in series of patients with IPF or has been the subject of case reports or short series (\citep{wiggins1990combined, hiwatari1993pulmonary, doherty1997cryptogenic}), but has not hitherto been specificaaly studied in a large cohort of patients. The current study provides a detailed analysis of the clinical characteristics of a homogenous group of 61 patients with computer tomography (CT) – defined CPFE, thus leading to the individualisation of a characteristic entity, and further shows that the presence of pulmonary arterial hypertension (PAH) at diagnosis is a critial determinant of prognosis in these patients.

{lin2015combined}

Whether the combination of emphysema and pulmonary fibrosis is a distinct clinical entity or not remains unknown. Some consider it as a coincidence of two smoking-related diseases in one person, comparable to the coexistence of lung cancer and COPD. However, previous data had suggested that interstitial lung abnormalities were inversely associated with emphysema in smokers (\citep{washko2011lung}). Actually most former smokders with IPF do not have radiographic evidence of emphysema. Likewise, most patients with emphysema/COPD do not have overt evidence of interstitial fibrosis. Therefore, the combination of pulmonary fibrosis and emphysema may be a distinct consequence of smoking that reflects unique individual susceptibilities.

In 2005, \cite{cottin2005combined} first time put forward a degined syndrome termed “combined pulmonary fibrosis and emphysema (CPFE)”, which is characterized by heavy smoking history, exercise hypoxemia, upper lobe emphysema and lower lobe fibrosis, unexpected subnormal lung volumes and severe reduction of carbon monoxide transfer. The CPFE syndrome comprises a heterogeneous population of patients and a consistent definition of CPFE has not been put forward. High-resolution computed tomography (HRCT) is the manadatory tool to diagnose this syndrome. CPFE is frequently complicated by pulmonary hypertension. Acute lung injury and lung cancer and prognosis of it is poor. Treatments for CPFE patients with severe pulmonary hypertension are less effective other than lung transplantation (\citep{cottin2010pulmonary }).

Identification of patients with CPFE is important because this disorder has its unique natural history. However, unfortunately CPFE has not yet attracted wide attention of clinicians and there is no resesarch systematically constrasting the differences among CPFE, emphysema/COPD and pulmonary fibrosis alone at the same time. The authors here will review the existing knowledge of CPFE and compare it to either entity alone for the first time.

**IPF and pulmonary hypertension (Complications and comorbidities)**

PH in IPF occurs due to several factors, mainly chronic hypoxia-induced vasoconstriction and destruction of the pulmonary capillary bed induced by fibrosis. PH usually appears in advanced stages of IPF and is generally mild, with a 30-45% prevalence. However, there is a subgroup of patients with mild to moderate IPF and severe PH. The development of PH is associated with significant dyspnea, function impairment (particularly DLCO) and decreased exercise capacity. In addition, the prognosis of the disease worsens significantly. Pharmacological treatment is controversial.

{martinez2017idiopathic}

Of the pulmonary comorbid conditions, pulmonary hypertension is the best characterized; its prevalence varies but tends to be noted in 30–50% of patients \citep{king2017idiopathic} . In general, the presence of pulmonary hyper tension has been associated with impaired survival, even when the elevation in pulmonary pressures is mild \citep{hayes2016influence} . Unfortunately, therapeutic trials to date have been unsuccessful and the current recommendation states that vasodilator therapy should be reserved for those enrolled in therapeutic trials or managed at expert centres \citep{king2017idiopathic}.

{raghu2011official}

The majority of data regarding the presence and significance of pulmonary hypertension come from patients with IPF undergoing evaluation for lung transplantation. The presence of pulmonary hypertension (defined as a mean pulmonary artery pressure of . 25 mm Hg at rest) has been associated with increased risk of mortality for patients with IPF (140, 142, 176). In a separate series of 70 patients with IPF, receiver operator characteristic (ROC) analysis suggested a mean pulmonary artery pressure of 17 mm Hg as the best discriminator of mortality (189). These data need to be validated. Echocardiographic estimation of pulmonary artery systolic pressures does not correlate well with right heart catheterization (208–210). Increased pulmonary vascular resistance has also been linked to worse survival (211). It is not clear if IPF with pulmonary hypertension represents a distinct clinical phenotype (IPF–PH).

**Etiology**

{meltzer2008idiopathic}

The term “idiopathic” suggests there are no known causes for IPF. Diagnostic criteria for IPF require exclusion of known causes of interstitial lung disease. However, an evnironmental eriology for IPF is supported by evidence from several sources (\citep{taskar2006idiopathic}). A relationship between environmental exposures and IPF is plausible, has been consistently demonstrated by case-control studies and is analogous to known disease, such as asbestosis, in which environmental material is associated with pulmonary fibrosis.

Meanwhile, cigarette smoking is consistently associated with IPF.

{xaubet2017idiopathic}

The etiology of IPF is unknown, although it is likely that the disease is the consequence of the action of several factors in subjects with genetic predisposition. The relevance of the genetic predispositon is based on the existence of familial forms of the disease. From 2.2 to 3.7% IPFs are familial. It should be noted that members of the same family may be affected by various types of interstitial lung disease, such as non-specific interstitial pneumonia and cryptogenic organizing pneumonia. The most significant genetic abnormalities in the predisposition and evolution of the disease are the gene mutations maintaining the telomere length and located in the telomerase complex, such as TERT, TERC, DKC, or RTEL, surfactant protein C and the Mucin 5B promoter (MUC5B) (\citep{alder2008short, seibold2011common}). Smoking, exposure to silica, brass, steel and wood dust, livestock and agriculture work, and the construction of wooden houses are deemed risk factor (\citep{taskar2006idiopathic}). Gastroesophageal reflux (GER) might play a role in the pathogenesis of IPF and in its natural history since it may lead to aspiration or microaspiration of gastroesophageal content that might be factors triggering the damage of the alveolar epithelial cells that characterizes IPF.

The potential contribution of autoimmunity is based on the fact that the histological and radiological pattern of the usual interstitial pneumonia can be associated with connective tissue disorders, especially rheumatoid arthritis (\citep{fischer2012interstitial, kim2010usual}). In this context, it should be noted that in a recent study usual interstitial pneumonia has been shown to be the main pulmonary condition in the undifferentiated connective tissue disease.

**Pathogenesis**

{meltzer2008idiopathic}

While pathogenetic mechnisams are incompletely understood, the currently accepted paradigm proposes that injury to the alveolar epithelium is followed by a burst of pro-inflammatory and fibroproliferative mediators that invoke reponses associated with normal tissue repair. For unclear reasons, these repair processes never resolve and progressive fibrosis ensures.

The origin of pathological fibroblastfoci within the IPF lesion remains puzzling. Possibilities include differentiation of resident fibroblast precursors and transdifferentiation of epithelial cells into pathological fibroblast phenotypes.

{xaubet2017idiopathic}

Historically it was accepted that IPF was the result of an inflammatory process. Currently it is demonstrated that the disruption of lung tissue and the formation of fibrosis are the result of an abnormal repair of alveolar epithelial lesions resulting in progressive accumulation of extracellular matrix proteins, decreased fibroblast/myofibroblast balance and constant death of epithelial cells, without evidence ofci previous inflammation. Therefore, epithelial cells, fibroblasts and myofibroblasts are considered the main effectors in the progression of the disease.

**Pathophysiology**

{richeldi2017idiopathic}

Historically, idiopathic pulmonary fibrosis was considered a chronic inflammatory disorder, which gradually progressed to established fibrosis. However, at the turn of the century, following the recognition that anti-inflammatory therapy did not improve outcome, this concept was reassessed and, subsequently, an immunosuppressive therapeutic stategy incorporating prednisolone and azathioprine was shown to increase mortality. Idiopathic pulmonary fibrosis is now generally regarded as a consequence of multiple interacting genetic and environmental risk factors, with repetitive local micro-injuries to ageing alveolar epithelium playing a central role. These micro-injuries initiate aberrant epithelial-fibroblast communication, the induction of matrix-producing myofibroblasts, and considerable extracellular matrix accumulation and remodelling of lung interstitium.

**Environmental exposures**

Particulate inhalation is implicated in the pathogenesis and progression of idiopathic pulmonary fibrosis. A history of cigarette smoking is associated with idiopathic pulmonary firbrosis development in most patients (\citep{baumgartner1997cigarette}). However, multiple other environmental exposures have also been associated, including metal and wood dusts, agriculture and farming, viruses, and stone and silica (\citep{raghu2011official, taskar2006idiopathic}).

**Genetic factors**

Increasing evidence indicates that genetic susceptibility plays a part in the development of idiopathic pulmonary fibrosis. Studies (\citep{raghu2011official}) of familial interstitial pneumonia – ie, cases affecting two or more members of the same biological family – have identified rare genetic variants, including genes associated with surfactant dysfunction (SFTPC, SFTPA2) and telomere biology (TERT, TERC, PARN, RTEL). Genome-wide association studies have identified common genetic variants, which account for about a third of the risk of disease development. Although these studies do not indicate a direct causal link, the potential importance of alterations in host defence (MUC5B, ATP11A, TOLLIP), telomere maintenance (TERT, TERC, OBFC1), and epithelial barrier function (DSP, DPP9) was identified.

A common gain-of-function variant in the gene MUC5B promoter region is the risk variant with the largest genetic effect on development of both familial and sporadic idiopathic pulmonary fibrosis (odds ratio 4-8 per allele). The MUC5B variant has low penetrance and in isolation does not seem to be causative of idiopathic pulmonary fibrosis. MUC5B encodes a mucin-5B precursor protein that contributes to airway mucous production and might have an important role in lung host defense. The site of altered MUC5B production has been localised to bronchiolar epithelium, where it is proposed to increase protein concentrations that might either enhance injury as a result of reduced mucocillary clearance or impede normal lung repair.

**Radiological patterns**

{richeldi2017idiopathic}

Hight-resolution CT of the chest enables detailed assessment of lung parenchyma and has revolutionised the investigation of suspected idiopathic pulmonary fibrosis. Reticular opacities, associated with traction bronchiectasis and clusters of subpleural, cystic airspaces of similar diameters (typically 3-10 mm) with honeycombing, in a predominantly bilateral, peripheral, and basal distribution are typical of the usual interstitial pneumonia pattern (figure 3), whereas features such as mosaic attention, gound-glass abnormality, and modules suggest an alternative diagnosis.

Patients with reticular abnormality in a subpleural, basal predominance, but without honeycombing, are considered to have a possible usual interstitial pneumonia pattern.

{raghu2011official}

HRCT is an essential component of the diagnostic pathway in IPF. The optimal HRCT technique for evaluation of ILD is provided in the online supplement. UIP is characterized on HRCT by the presence of reticular opacities, often associated with traction bronchiectasis \citep{nishimura1992usual, johkoh1999idiopathic}. Honeycombing is common, and is critical for making a definite diagnosis. Honeycombing is manifested on HRCT as clustered cystic airspaces, typically of comparable diameters on the order of 3-10 mm but occasionally as large as 2.5 cm. It is usually subpleural and is characterized by well-defined walls \citep{hansell2008fleischner}. Ground glass opacities are common, but usually less extensive thatn the reticulation. The distribution of UIP on HRCT is characteristically basal and peripheral, though often patchy. The presence of coexistent pleural abnormalities (e.g., pleural plaques, calcifications, significant pleural effusion) suggests an alternative etiology for UIP pattern. Micronodules, airtrapping, nonhoneycomb cysts, extensive ground glass opacities, consolidation, or a peribronchovascular-predominant distribution should lead to consideration of an alternative diagnosis. Mild mediastinal lymph node enlargement (usually<1.5cm in short axis) can be seen \citep{hwang2009computed, souza2006idiopathic}. The chest radiograph is less useful than HRCT in evaluating patients with suspected IPF \citep{mathieson1989chronic}.

课题的意义

{richeldi2017idiopathic}

To predict individual patient prognosis, risk models that incorporate demographic, clinical, and physiological variables have been developed, including the du Bois model and the gender, age, physiology index. This index incorporates gender, age, and lung physiology variables to identify three disease stages with a 1 year mortality risk of 6%, 16%, and 39% respectively. The calculation of such an index at diagnosis might aid the clinician to refine prognosis, help to guide management decisions, such as lung transplantation timing, and allow appropriate life planning.