Idiopathic pulmonary fibrosis: state of the art for 2023

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This concise clinical review provides an update on IPF diagnosis, epidemiology, natural history and treatment in the context of new knowledge and the latest clinical practice guidelines https://bit.ly/3vDrRLR

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic lung disease characterised by worsening respiratory symptoms and physiological impairment. Increasing awareness of the clinical manifestations of IPF, more widespread use of computed tomography scans and other potential factors have contributed to a rising prevalence of IPF over the last two decades, especially among people over the age of 65 years. Significant advances in the understanding of the pathobiology of IPF have emerged, and multiple genetic and nongenetic contributors have been identified. The individual patient course and the rate of disease progression in IPF are often unpredictable and heterogeneous. The rate of lung function decline is further modified by treatment with antifibrotic therapies, which have been shown to slow down disease progression. The presence of comorbid conditions may increase symptom burden and impact survival. Clinical monitoring at regular intervals to assess for disease progression by worsening symptoms, physiological parameters and/or radiological features is essential to assess the natural disease course and to guide further management, including prompt detection of complications and comorbid conditions that warrant additional treatment considerations, and timely consideration of referral to palliative care and lung transplantation for the appropriate patient. More studies are needed to determine whether early detection of IPF might improve patient outcomes. The purpose of this concise clinical review is to provide an update on IPF diagnosis, epidemiology, natural history and treatment in the context of new knowledge and latest clinical practice guidelines.

Introduction

The last two decades have been marked by significant progress in our understanding of the causes and mechanisms underlying idiopathic pulmonary fibrosis (IPF). This progress has in part been the result of multidisciplinary efforts to standardise the classification and definitions of the idiopathic interstitial pneumonias and other interstitial lung diseases (ILDs) [1, 2]. Within this framework, IPF has been defined as a specific form of ILD with the radiological and/or histological pattern of usual interstitial pneumonia (UIP) in the absence of environmental factors ascribed to ILD, associated connective tissue disease and other known causes of ILD [3, 4]. This narrow definition enabled the recruitment of homogenous patient populations for clinical trials, and provided important insights into the understanding of disease behaviour, natural course and treatment interventions [5–7]. These insights led to the discovery of two antifibrotic drugs that modify disease behaviour in IPF (pirfenidone and nintedanib) [6, 7].

IPF is a progressive fibrotic lung disease characterised by escalating respiratory symptoms and physiological impairment. This progressive fibrotic behaviour is not unique to IPF and can be seen in a

large and heterogenous group of fibrotic ILDs. Recent studies suggest that the mechanisms underlying IPF are also relevant to other types of ILDs [8]. Studies of the genetic underpinnings of fibrotic ILDs demonstrate that genes associated with increased risk of IPF are also associated with risk of other fibrotic ILDs [8]. In this context, IPF is increasingly being recognised as a prototype of a larger group of lung diseases that exhibit progressive fibrotic behaviour despite distinct aetiologies. Notwithstanding this recent focus on similarities between all fibrotic ILDs, differentiating IPF from other forms of progressive pulmonary fibrosis remains critically important [9, 10]. The diagnosis of IPF has specific treatment implications and is associated with high morbidity, morality and a marked increase in healthcare utilisation [11]. The purpose of this review is to provide an update regarding IPF diagnosis, epidemiology, natural history and treatment in the context of new knowledge and latest clinical practice guidelines addressing IPF diagnosis and management [10, 12, 13].

Diagnosis of IPF

The typical patient clinically suspected of having IPF is over 60 years of age with an unexplained symptomatic or asymptomatic pattern of bilateral pulmonary fibrosis on chest radiography or chest computed tomography (CT) and bibasilar inspiratory crackles on examination. Symptoms often develop insidiously and commonly include dyspnoea on exertion and/or cough. Patients often have a history of smoking and may have other remote environmental or occupational exposures [14]. Middle-aged adults (40–60 years old), especially those at risk for familial pulmonary fibrosis, can rarely present with a similar clinical scenario. The clinical context in which the patient presents determines the clinical likelihood of IPF and should be incorporated into clinical decision making and diagnostic workup. Factors that increase the pre-test probability of IPF include older age, male sex and smoking history, while exposure to antigens known to cause hypersensitivity pneumonitis and the presence of autoimmune features decrease the likelihood [15]. A formal framework that integrates clinical features into the diagnostic approach has recently been proposed [15].

The diagnostic algorithm for IPF was updated in the most recent American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Asociación Latinoamericana de Tórax (ATS/ERS/JRS/ALAT) guideline published in 2022 [10]. The diagnosis of IPF requires exclusion of systemic conditions or exposures that are known to cause ILD, such as connective tissue disease, medications, and environmental factors at work and at home [4, 13]. The initial evaluation of patients suspected of having IPF is performed to identify these known causes of ILD, which may result in a diagnosis of connective tissue disease-associated ILD, fibrotic hypersensitivity pneumonitis, pneumoconiosis, drug-induced ILD or another ILD. Evidence-based international clinical practice guidelines developed by the ATS/ERS/JRS/ALAT and published in 2011 and 2018 emphasise the importance of taking a detailed, prompted medical history, including family medical history, prior medication use, and exposures at home, work and other places that the patient frequently visits [4, 13]. A thorough physical exam with close attention to signs of connective tissue disease should also be performed [16]. The guidelines recommend serological testing to aid in the exclusion of connective tissue disease. The extent of serological testing performed varies based on the clinical context. Basic workup may include a general screen for autoimmunity and inflammatory markers (antinuclear antibodies by immunofluorescence, C-reactive protein and erythrocyte sedimentation rate), rheumatoid arthritis-associated autoantibodies (cyclic citrullinated peptide and rheumatoid factor) and muscle enzymes to screen for myositis (creatine kinase, aldolase and myoglobin). More extensive testing should be performed if there is a reasonable pre-test probability of a non-IPF diagnosis (*i.e.* younger age, atypical risk factors, exam and imaging features), and may include autoantibodies associated with myositis, scleroderma, Sjögren's syndrome and vasculitis, as specified in the 2018 guideline [13]. A referral to a rheumatologist may be considered if the clinical picture and/or serologies raise concern for an autoimmune disease [13].

All patients suspected of IPF should undergo chest high-resolution CT (HRCT) using the established technical parameters for image acquisition and reconstruction [13, 17]. IPF may be confidently diagnosed when a HRCT shows a definite or probable UIP pattern, and further invasive testing to confirm a histological UIP pattern is not needed in the appropriate clinical setting [13, 18]. A definite UIP pattern is defined by the presence of a subpleural and basal predominant pattern of fibrosis, in a heterogeneous distribution (areas of normal lung interspersed with fibrosis), with honeycombing, with or without traction bronchiectasis/bronchiolectasis (figure 1a); in some cases, the upper lobe may be involved and the craniocaudal distribution may be more uniform [13]. While prior guidelines make a distinction between definite and probable UIP (figure 1b) based on the presence of honeycombing, the recent guideline emphasises that honeycombing and traction bronchiectasis/bronchiolectasis occur on a continuum, and honeycombing on HRCT strongly correlates with bronchiolectasis histologically [10]. Both HRCT patterns are associated with a high likelihood of UIP histology, supporting a similar diagnostic approach to both

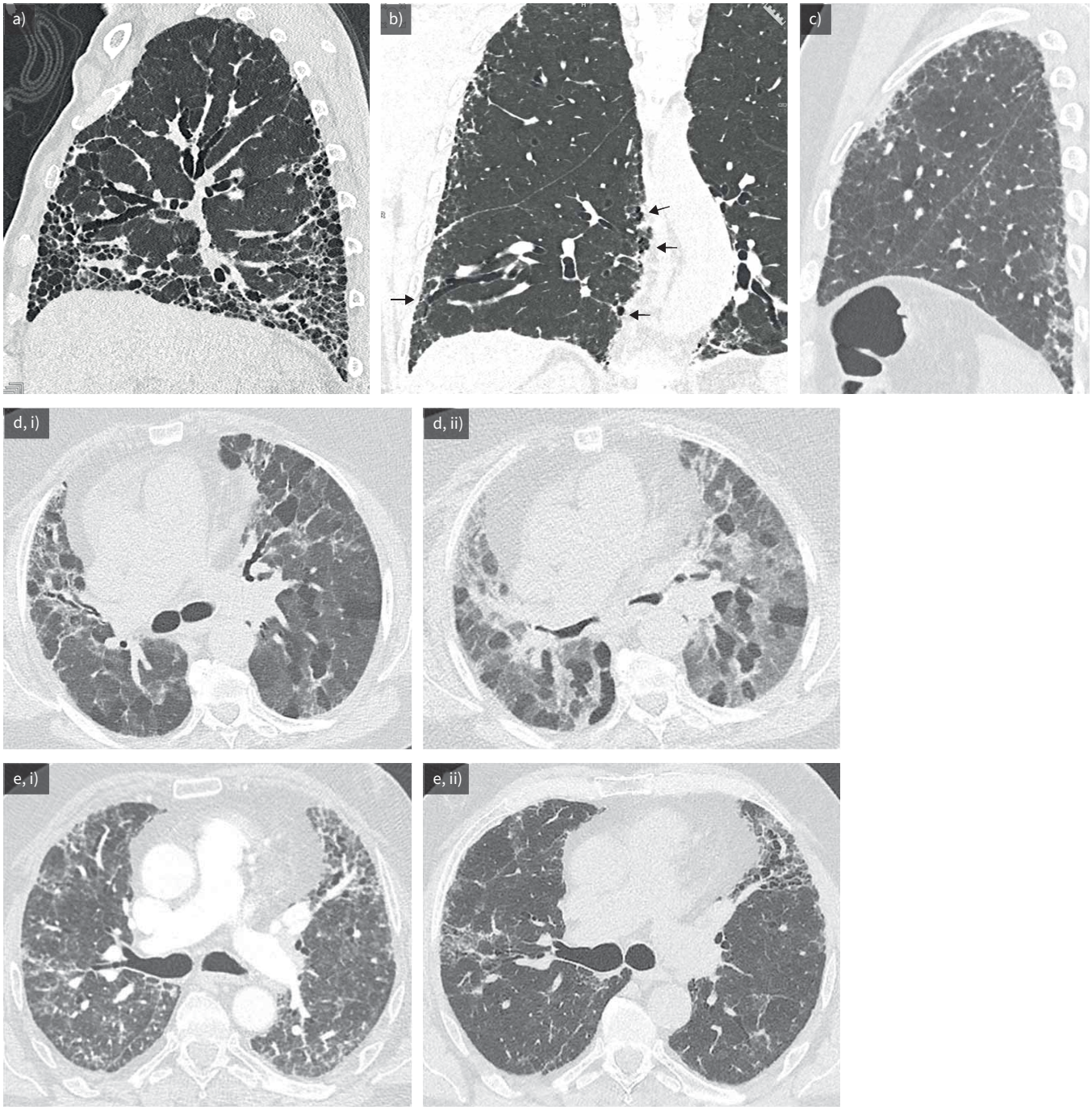

FIGURE 1 Representative images. a) Sagittal high-resolution computed tomography (HRCT) image of the right lung showing a typical usual interstitial pneumonia (UIP) pattern combining subpleural predominant, lower-lung predominant reticular abnormality with honeycombing and traction bronchiolectasis. b) Coronal HRCT image (magnified view of the right lung) showing a probable UIP pattern with peripheral lung infiltration and numerous traction bronchiolectases (arrows) also depicted in the subpleural lung parenchyma of the right lower lobe. c) Sagittal HRCT image of the left lung showing heterogeneous subpleural lung infiltration, mostly composed of ground-glass opacities of various attenuation, illustrating an indeterminate for UIP pattern. d) Transverse HRCT images obtained at i) inspiration and ii) expiration illustrating a case of fibrotic hypersensitivity pneumonitis (*i.e.* alternative diagnosis). d, i) CT features of fine fibrosis in the anterior segments of the right and left upper lobes associated with mild ground-glass opacities, areas of normal attenuating lung parenchyma and hyperlucent lobules in the remaining parenchyma of both lungs (*i.e.* the three-density pattern). d, ii) Widespread lobular air trapping indicative of constrictive bronchiolitis. e) Transverse HRCT sections obtained at the level of the carina, 1 year apart, illustrating CT changes in acute exacerbation. e, i) Chest CT angiography obtained at the time of acute exacerbation, excluding acute pulmonary embolism. e, ii) Same anatomical level of a noncontrast HRCT examination obtained in a stable clinical situation. Note the increase in lung attenuation in e, i) with unchanged features of fibrotic lung infiltration.

patterns [10]. Mediastinal lymph node enlargement is common in patients with IPF and is associated with worse outcomes [19].

The guidelines emphasise the importance of multidisciplinary discussion for the ascertainment of a diagnosis of IPF. Multidisciplinary discussion that integrates clinical, radiological and, when available, histopathological findings has been shown to improve diagnostic confidence and alter therapy in a substantial number of patients [13]. Multidisciplinary input should be sought prior to any invasive testing and cases should be reviewed again after invasive testing is performed.

When HRCT is indeterminate for UIP (figure 1c) or suggestive of an alternative diagnosis (figure 1d), further diagnostic workup may include cellular analysis of bronchoalveolar lavage (BAL) fluid, surgical lung biopsy or transbronchial lung cryobiopsy. These procedures should be performed in patients with an acceptable level of risk for complications and where the findings are expected to affect management. BAL cellular analysis can be helpful to narrow the differential diagnosis of fibrotic hypersensitivity pneumonitis [13, 20, 21]. The newly updated guideline suggests transbronchial lung cryobiopsy as an acceptable alternative to surgical lung biopsy for making a histopathological diagnosis of UIP, based on a growing body of evidence supporting this approach in medical centres with experience performing and interpreting transbronchial lung cryobiopsy [10]. There is also growing experience with the use of a machine learning-enabled genomic classifier for the purpose of identifying UIP on a transbronchial forceps biopsy, which may improve diagnostic confidence and treatment recommendations in certain clinical scenarios [22–24]. However, this technique is not yet widely available and the newly updated guideline makes no recommendation for or against its use [10].

Given that there is overlap in clinical, radiological and even histological features between IPF and other fibrotic ILDs, especially fibrotic hypersensitivity pneumonitis, and that definitive histological confirmation cannot always be accomplished, a standardised approach that incorporates levels of diagnostic certainty in the diagnosis of IPF has been proposed [25]. A provisional diagnosis of IPF can be applied to patients in whom IPF is more likely than not (>50% likelihood of IPF), and is further subdivided into a high confidence (70–89%) and a low confidence (51–69%) diagnosis [25]. This stratification can aid in management and treatment decisions [26]. Each patient's diagnosis should be refined and re-evaluated over time as additional data, including longitudinal disease behaviour, become available [15]. This approach can be applied to the diagnosis of IPF as well as other fibrotic ILDs. An approach that integrates clinical scenarios with guidelines for the diagnosis of IPF and fibrotic hypersensitivity pneumonitis would be useful to pulmonologists worldwide [20, 27].

Incidence and prevalence

The incidence and prevalence of IPF vary based on country/geographic region, case definition and population demographics (table 1) [14, 28–43]. Both metrics increase dramatically with age. The estimated global incidence of IPF ranges from 1 to 13 per 100 000 persons, and prevalence from 3 to 45 per 100 000, with the highest numbers reported in South Korea, Canada and the USA [40]. However, there is substantial heterogeneity in reporting, case definition and study methodologies, and very limited data from Africa or South America. Multiple studies report increasing incidence and/or prevalence of IPF over time, with one

TABLE 1 Population-based incidence and prevalence rates for idiopathic pulmonary fibrosis, by region

	Cases per 100 000
Incidence	
Europe	1–9
North America	7–19
Asia	3–13
Australia	10–11
Prevalence	
Europe	10–40
North America	14–59
Asia	5–40
Australia	32–35

Few published studies report incidence and prevalence in South America, and none in Africa. Information from [14, 28–43].

study reporting a doubling in prevalence between 2000 and 2012 [14, 28, 31, 33, 41, 43, 44]. These trends were not fully explained by increased age or other demographic factors, and may reflect changes in the definition of IPF, more widespread use of CT scans and/or higher rates of diagnosis [33]. With increasing age of the population worldwide, more awareness of the clinical manifestations of IPF and rising prevalence of some of the risk factors (such as air pollution), the global burden is expected to continue to grow.

Risk factors for IPF

Even though IPF is considered a disease of unknown cause, multiple genetic and environmental factors contribute to its pathogenesis (table 2). A family history of pulmonary fibrosis is a strong risk factor for the development of disease and for poor outcomes [45–47]. Affected family members in familial cohorts may not present with the same radiological, clinical and histopathological features, and do not always fulfil criteria for IPF. The term "familial pulmonary fibrosis" is used to describe the spectrum of fibrotic lung disease resulting from inherited determinants [48].

TABLE 2 Risk factors for idiopathic pulmonary fibrosis (IPF)

Risk factor	Description	References
Demographic		
Age	Incidence and prevalence of IPF increase with age, and most patients diagnosed with IPF are over 60 years of age.	[4, 15, 30]
Male sex	Men represent ~70% of all patients with IPF in registries and clinical trials. Occupational exposures may account for some of these differences. However, significant gender bias in the diagnosis of IPF has been reported.	[14, 15, 176–178]
Genetic		
Host defence	*MUC5B* promoter polymorphism rs35705950: presence of the minor allele increases disease risk 3-fold in heterozygotes and 7-fold in homozygotes; the gain-of-function variant leads to greater expression of mucin 5B protein and leads to impaired mucociliary clearance, but the link to disease pathogenesis is incompletely understood. *TOLLIP*: three variants in Toll-interacting protein (TOLLIP) have been shown to be associated with IPF susceptibility among individuals of European ancestry; individuals with these variants have decreased expression of TOLLIP.	[51, 54–56]
Telomere maintenance	Variants in telomere maintenance genes (*TERT*, *TERC*, *PARN*, *RTEL1*, *DKC* and *TINF21*) are associated with both familial and sporadic pulmonary fibrosis. These variants lead to telomere shortening and accelerated cellular senescence, which is thought to play a role in abnormal epithelial repair.	[51, 179–181]
Surfactant processing	Rare variants in genes associated with surfactant processing (*SFTPC*, *SFTPA2* and *ABCA3*) can be found in families with pulmonary fibrosis.	[182–184]
Epithelial integrity	A large genome-wide association study of non-Hispanic White subjects identified associations with variants in genes involved in cell adhesion: *DSP* and *DPP9*. These variants are associated with expression of desmoplakin and dipeptidyl peptidase 9, respectively, and may lead to loss of epithelial integrity.	
Fibrotic signalling	*AKAP13:* polymorphism rs62025270 near A-kinase anchoring protein 13 (AKAP13) has been linked with IPF susceptibility. AKAP13 is a Rho guanine nucleotide exchange factor involved in profibrotic signalling pathways.	[57]
Environmental		
Cigarette smoking	Multiple studies have implicated cigarette smoking as a risk factor for IPF.	[62]
Occupational exposures	Work-related exposures to inhaled dust, asbestos, metal and/or wood dust have been linked with IPF risk.	[61, 185]
Air pollution	Exposure to increased levels of air pollution has been linked with increased incidence of IPF and mortality.	[186, 187]
Comorbid conditions		
Gastro-oesophageal reflux disease	Multiple observational studies have reported on the association of abnormal acid gastro-oesophageal reflux and IPF, but a causative role has not been clearly established.	[94]
Obstructive sleep apnoea	Obstructive sleep apnoea is highly prevalent among patients with IPF and several studies have suggested a mechanistic link in the development of lung fibrosis.	[188]
Lung dysbiosis	Patients with IPF have altered lung microbiome, but a causative role has not been established.	[65, 66, 189]
Viral infections	Viral infection, especially with herpesvirus, has been linked with IPF and exacerbations.	[52]
Other		
Family history	First-degree relatives of patients with IPF have an increased risk of developing pulmonary fibrosis. The risk is similar between sporadic and familial cohorts.	[47]
Short telomeres	Telomere shortening, even in the absence of known telomerase complex mutation, is associated with IPF.	[70]

Both rare and common genetic variants contribute to IPF susceptibility. Rare variants were originally identified in familial disease cohorts, but have also been implicated in sporadic IPF [49–52]. These variants are thought to be highly penetrant, with strong effects on individual IPF risk [53]. Common variants account for a large proportion of the IPF risk in the population, but have smaller effects on individual susceptibility [53]. The best characterised is a gain-of-function variant in the promoter region of *MUC5B* (rs35705950), which leads to greater expression of mucin 5B protein and impaired mucociliary clearance [54, 55]. Other common variants implicated in IPF susceptibility include polymorphisms near A-kinase anchoring protein 13 (*AKAP13*; rs62025270) and several variants in Toll-interacting protein (*TOLLIP*) [56, 57]. The TT genotype of rs3750920 within *TOLLIP*, found in ∼25% of patients with IPF, has been associated with improved outcomes in patients treated with *N*-acetylcysteine [58].

Nongenetic risk factors associated with IPF include older age, male sex, cigarette smoking, and environmental and occupational exposures [14, 59–62]. Several studies have implicated comorbid conditions, as listed in table 2, in the risk for IPF and/or disease progression, although a causative role for these factors has not been established [63–67]. Short telomeres in peripheral blood leukocytes are associated with increased risk of IPF, more rapid disease progression and reduced survival even in the absence of known telomere-related gene mutations [68–70]. Short telomeres may reflect genetic susceptibility due to yet undetermined genes or be markers of cellular senescence that results from accelerated ageing and concomitant environmental exposures and insults [71].

Early detection and screening

Recent studies demonstrate that there is often a long asymptomatic phase before physiological impairments develop in patients with IPF and other fibrotic ILDs. Histopathological abnormalities can be detected in high-risk individuals years before symptoms or radiological abnormalities and abnormal imaging may be present several years prior to diagnosis of clinically defined ILD [52, 72]. The increased use of CT screening for the early detection of lung cancer, and other clinical indications, has led to more frequent recognition of interstitial lung abnormalities (ILAs), which are incidentally detected CT findings that are potentially compatible with ILD [73]. ILAs are found in 2–9% of individuals undergoing CT imaging for lung cancer screening or other indications [73]. Some ILAs likely represent early UIP and/or undiagnosed ILD, but it is unclear which patient will progress to clinically significant ILD [74]. Radiological progression is common, but the progression rate is highly variable, ranging from 20% over 2 years to nearly 50% over 4–6 years, and does not necessarily translate to symptomatic disease and/or physiological impairment [73]. The presence of fibrotic features on CT as well as older age, smoking and some of the genetic risk factors associated with IPF susceptibility increase the risk of progression [73]. Individuals with ILAs and high-risk features should be evaluated for clinically significant ILD and be monitored closely for progression [73]. More research and guidelines are needed to determine the optimal monitoring of patients with ILA and who would benefit from early treatment with antifibrotics.

First-degree relatives of patients with familial pulmonary fibrosis are at high risk for development of IPF and related forms of pulmonary fibrosis, and screening of this population is increasingly being done in research and clinical settings [75]. The most appropriate approach to screening has not been established. Pulmonary function testing and HRCT should be completed for individuals with any respiratory symptoms or abnormal physical examination, and considered for any individuals with risk factors. At least one study showed that family members of individuals with sporadic IPF have a similarly increased risk to those with familial pulmonary fibrosis [47]. Screening programmes to detect ILAs and early pulmonary fibrosis in familial and nonfamilial settings, as well as the role of genetic screening for routine clinical use is unclear, and hence should be formally studied and patient outcomes evaluated.

Natural history of IPF

IPF is a chronic, progressive disease characterised by a gradual decline in lung function, worsening respiratory symptoms and eventual death due to respiratory failure or associated comorbidities [16]. Despite the invariably progressive behaviour of the disease over time, the patient course and the rate of disease progression are unpredictable and heterogeneous (figure 2). Data from placebo arms of clinical trials indicate that the average annual decline in forced vital capacity (FVC) among patients with mild or moderate impairment in lung function is ∼150–200 mL per year (figure 3) [76]. The rate of decline is further slowed in patients treated with pirfenidone or nintedanib [6, 7]. However, rapid/accelerated progression of disease can occur despite antifibrotic treatment and in patients who have been stable for several years without pharmacological treatment [77].

Significant delays in the time between the development of symptoms and a diagnosis of IPF are well documented, with a median time of 1–2 years (figure 2) [78–80]. A large proportion of patients experience

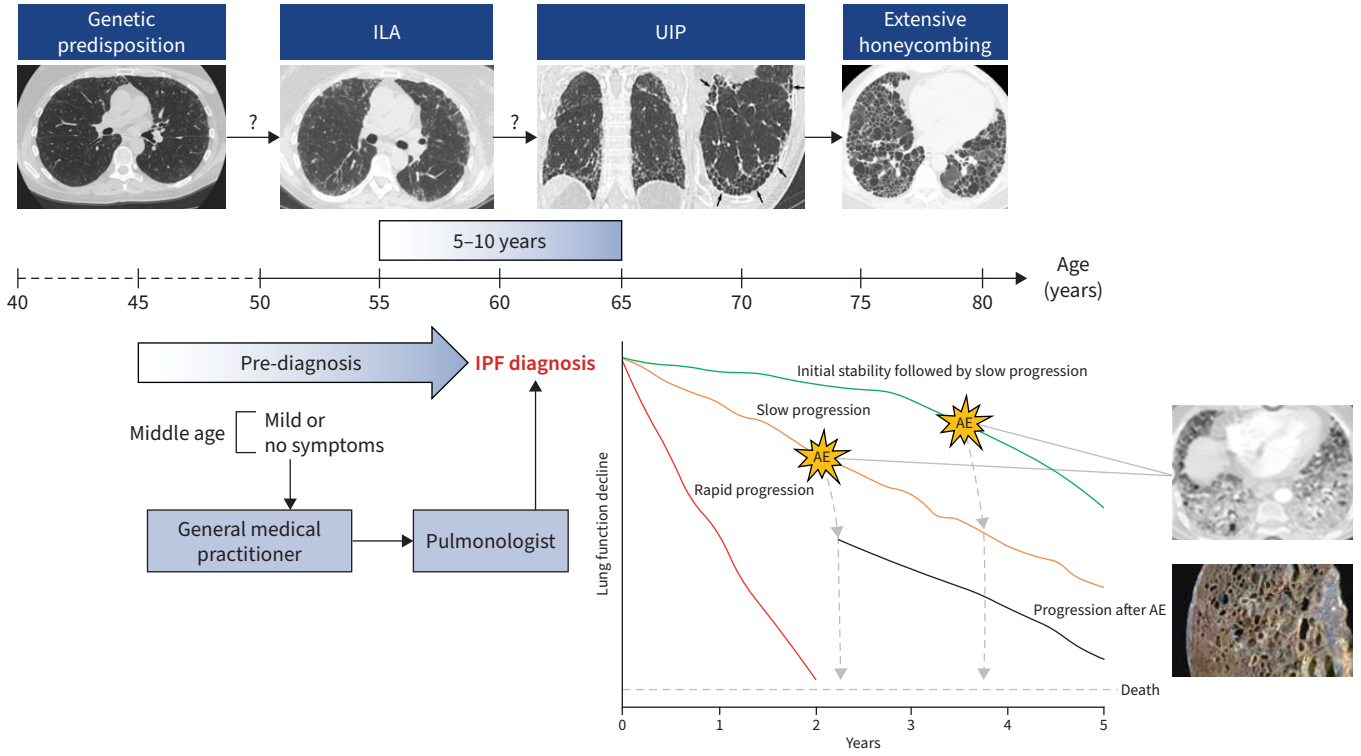

FIGURE 2 Natural clinical course of idiopathic pulmonary fibrosis (IPF). Patients may have evidence of interstitial lung abnormalities (ILAs) on high-resolution computed tomography (HRCT) several years before the diagnosis of IPF can be ascertained per the 2018 IPF guideline [13], although not all ILAs will progress to IPF. During the years prior to the time of diagnosis of IPF, which usually occurs at age 60 years or later, patients may be asymptomatic or have mild symptoms and are often seen and managed by a general medical practitioner. Given that many symptoms are nonspecific, a substantial delay between the onset of symptoms and diagnosis often occurs. Patients with ascertained diagnosis of IPF generally follow one of three courses: 1) most patients follow the pathway of slow decline over 3–5 years since the diagnosis ("slow progression"); 2) some patients experience a more rapid decline in lung function over several months ("rapid progression"); and 3) others remain stable over several years before progressing. Acute exacerbations (AE) can occur at any time and may lead to accelerated loss of lung function or death. Progression of disease is manifested by decline in forced vital capacity and distortion of the lung by extension of honeycomb cysts from subpleural areas in lower lobes to more proximal areas in all portions of lung as seen macroscopically in HRCT scans of the chest over several years and at autopsy. UIP: usual interstitial pneumonia.

respiratory symptoms several years prior to diagnosis [81, 82]. In early disease, exertional dyspnoea or a reduced exercise tolerance may be the only symptoms and are often misattributed to age or deconditioning [81]. Given that these symptoms are nonspecific, patients may be misdiagnosed with other cardiac and pulmonary diseases such as asthma, COPD or heart failure [80, 81]. Studies suggest that diagnostic delays can be improved by timely referrals for CT imaging, improvements in reporting of fibrotic features on diagnostic testing and expedient subspecialty evaluation [83].

Acute exacerbation of IPF

Acute exacerbation of IPF has been defined as an acute, clinically significant respiratory deterioration characterised by evidence of new widespread alveolar abnormality as proposed in 2016 [4, 84, 85]. Chest CT features suggestive of an acute exacerbation include new ground-glass abnormalities and/or consolidations with a background of a definite or probable UIP pattern (figure 1e) [86]. These findings correlate with the histological patterns of acute or organising diffuse alveolar damage or, less commonly, organising pneumonia in zones of relatively preserved lung tissue away from the most fibrotic regions [85].

Historically, definitions differentiated acute respiratory deterioration due to an unidentifiable cause (*i.e.* idiopathic acute exacerbations) from events due to viral or bacterial respiratory infection, aspiration and other identifiable causes; the latter were not included in older definitions of acute exacerbations [4, 85]. However, outcomes after adjudicated idiopathic acute exacerbations are similar to those after other forms of acute respiratory worsening and occult respiratory infection has been reported in some patients with acute

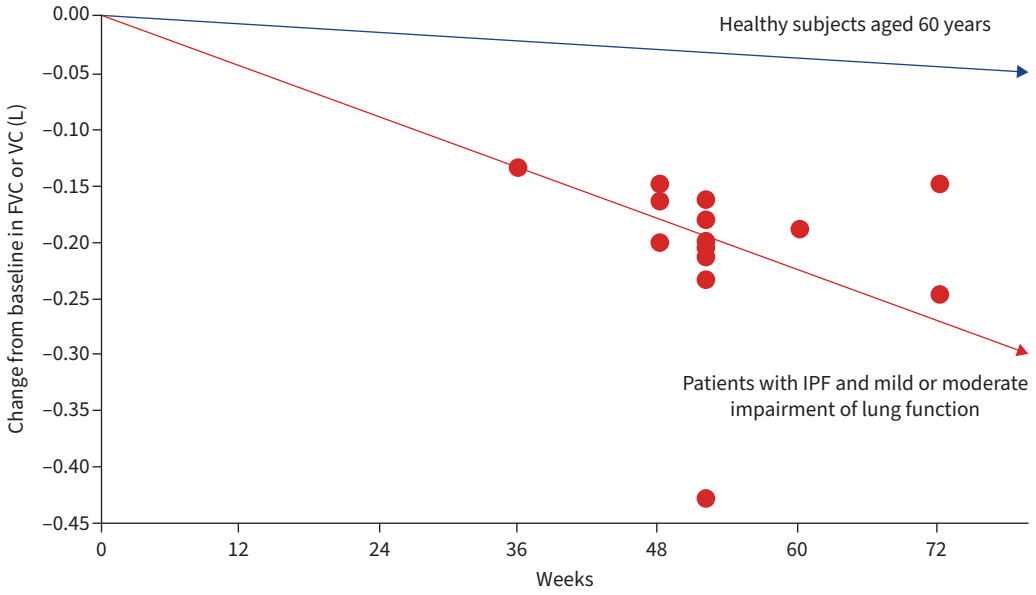

FIGURE 3 Natural course of forced vital capacity (FVC) or vital capacity (VC) decline in patients with idiopathic pulmonary fibrosis (IPF) based on data from placebo arms of randomised clinical trials from the time of enrolment to 72 weeks: the decline in FVC is ∼150–200 mL at the end of 1 year compared with baseline. Each dot represents data from a separate individual clinical trial. Adapted with permission from [76]. The original figure, reproduced with permission, can be found in the supplementary material, along with the citations for the trials referenced in the original figure.

exacerbations [87–89]. The coronavirus disease 2019 (COVID-19) pandemic has further highlighted the impact of viral triggers of acute exacerbations in IPF, with evolving knowledge of acute respiratory decline and poor outcomes among patients with IPF infected with severe acute respiratory syndrome coronavirus 2 [90, 91]. Thus, the distinction between idiopathic and triggered exacerbations might be difficult in many cases.

Data from placebo arms of clinical trials suggest that acute exacerbations are relatively uncommon, occurring in 5–10% of patients per year [6]. However, when suspected acute exacerbations are included, the incidence may be as high as 20% per year [92]. Acute exacerbations occur more commonly in the winter and spring months, supporting infectious triggers in some cases [92, 93]. Other potential triggers include microaspiration, medications and thoracic surgery [94–97]. BAL has previously been cited as a trigger for exacerbations, but a recent large prospective analysis supports the safety of BAL in patients with IPF [98]. Patient factors associated with greater risk of acute exacerbation include low FVC, low diffusing capacity of the lung for carbon monoxide (D_{LCO}), low 6-min walk distance, pulmonary hypertension, poor baseline oxygenation, increased dyspnoea and recent decline in FVC [84, 92]. The median survival after an acute exacerbation of IPF is 3–4 months [92, 99]. The in-hospital mortality in the setting of an acute exacerbation is up to 50% [84, 96, 99].

Comorbidities

Respiratory and nonrespiratory comorbidities are common in IPF, and may increase symptom burden and impact survival [100–104]. In one study, a greater number of comorbidities lowered median survival among patients with IPF from 66 months for those without comorbidities to 35 months for those with four to seven comorbidities [103]. The high prevalence of some comorbidities, such as COPD, lung cancer and cardiovascular disease, is partially attributable to shared risk factors (smoking, older age and genetic). Emphysema and/or COPD have been reported among 6–67% of patients with IPF, depending on the baseline characteristics of the study population, and ∼30% have emphysematous changes on imaging [104]. Combined pulmonary fibrosis and emphysema (CPFE) has been defined as a distinct syndrome, which encompasses different types of pulmonary fibrosis, including IPF, coexisting with emphysema [105, 106]. It is unclear if patients with pre-existing cigarette smoking-associated emphysema manifest a UIP pattern in the same way as patients with IPF without emphysema. Patients with CPFE have paradoxically preserved lung volumes and/or combined obstructive/restrictive ventilatory defects, with marked diffusion

impairment on pulmonary function testing. This condition is frequently associated with pulmonary hypertension [105–107]. The presence of emphysema has an additive effect on outcomes in patients with CPFE, with higher mortality for a given extent of fibrosis [106]. Thus, the total extent of disease on CT (both fibrosis and emphysema) and D_{LCO} should be considered as markers of severity.

Pulmonary hypertension has been documented in 14% of patients with mild to moderate restrictive lung function impairment and no honeycombing, and in 30–50% of those with more advanced IPF [104, 108, 109]. The presence of pulmonary hypertension is associated with poor survival [110]. In one study, median survival for patients with IPF and systolic pulmonary arterial pressure >50 mmHg on transthoracic echocardiogram was only 0.7 years [110]. Several clinical trials failed to show benefit of treatment with endothelin receptor antagonists (ambrisentan, bosentan and macitentan) and riociguat in this patient population [108, 109, 111–113]. In fact, treatment with ambrisentan was associated with worsened respiratory decline in patients with IPF with or without pulmonary hypertension [108]. Potential therapeutic effects have been suggested for sildenafil in secondary end-points of clinical trials, but its efficacy was not determined based on primary end-points [114–118]. Treatment with inhaled treprostinil has been shown to improve exercise capacity in patients with pulmonary hypertension due to interstitial lung disease, including those with IPF [119].

Several studies report an increased incidence of lung cancer among patients with IPF, which may be due to shared risk factors and/or activation of biological pathways that promote the development of lung cancer [104]. Treatment of lung cancer in this population is challenging. Surgical resection and radiation therapy may not be feasible if there is extensive fibrosis [120]. Surgical and medical treatments may trigger acute exacerbations [121]. Antineoplastic agents and novel biological therapies that have revolutionised the treatment of lung cancer have also been associated with increased risk of drug-induced ILD and progression of fibrotic lung disease [122]. The diagnosis of lung cancer in patients with IPF has a significantly negative impact on survival, with an up to 5-fold higher mortality [123].

Other comorbidities include obstructive sleep apnoea, cardiovascular disease, pulmonary embolism and abnormal gastro-oesophageal reflux [104]. Treatment of these comorbidities may positively impact quality of life and survival, but more definitive studies are needed. Depression and anxiety are also commonly reported and may significantly influence quality of life [124]. Attention to these and other comorbidities has to be part of a comprehensive evaluation and management of patients with IPF.

Treatment of IPF

The standard of care for treatment of IPF has evolved significantly over the past decade. Multimodal management approaches are needed to address the needs of patients with IPF (figure 4). There is strong evidence against the use of corticosteroids and other immunosuppressive agents given data from the PANTHER trial, which demonstrated worse outcomes in patients treated with combination immunosuppressive therapy compared with placebo [5]. Currently, two antifibrotic agents, pirfenidone and nintedanib, are approved for the treatment of IPF [6, 7, 12]. Both agents have been shown to slow lung function decline in patients with IPF. In secondary and pooled analyses, both have been shown to improve clinical outcomes, including respiratory hospitalisations and mortality [6, 7, 125, 126]. However, neither agent has been shown to have an impact on patient symptoms, and 20–30% of patients in clinical trials and real-world registries are unable to tolerate them in the long term due to side-effects, primarily gastrointestinal. This highlights a need for more effective, better tolerated agents and trials of new therapeutic options that assess treatment response using clinically meaningful end-points other than 12-month change in FVC, including composite end-points of time to hospitalisation and death [127].

Acknowledging very low quality evidence, the latest guideline suggests not treating patients with IPF with antacid medication and not referring patients for antireflux surgery for the purpose of improving respiratory outcomes [10]. Antacid medications may be used for the treatment of gastro-oesophageal reflux disease and related symptoms, but a systematic review and meta-analysis found that they had no significant effect on disease progression in IPF [128]. To date, there has been one randomised controlled trial of laparoscopic antireflux surgery in patients with IPF and documented abnormal acid gastro-oesophageal reflux [64]. This small trial showed that the surgery is safe in this patient population, but did not demonstrate statistically significant benefit on disease progression, despite numerically fewer acute exacerbations, respiratory-related hospitalisations and deaths in the surgery group. More data are needed on the role of antireflux surgery and other antireflux therapies in IPF.

Other interventions that should be considered for all patients with progressive disease include the use of supplemental oxygen, pulmonary rehabilitation, weight and nutrition management, and lung transplant

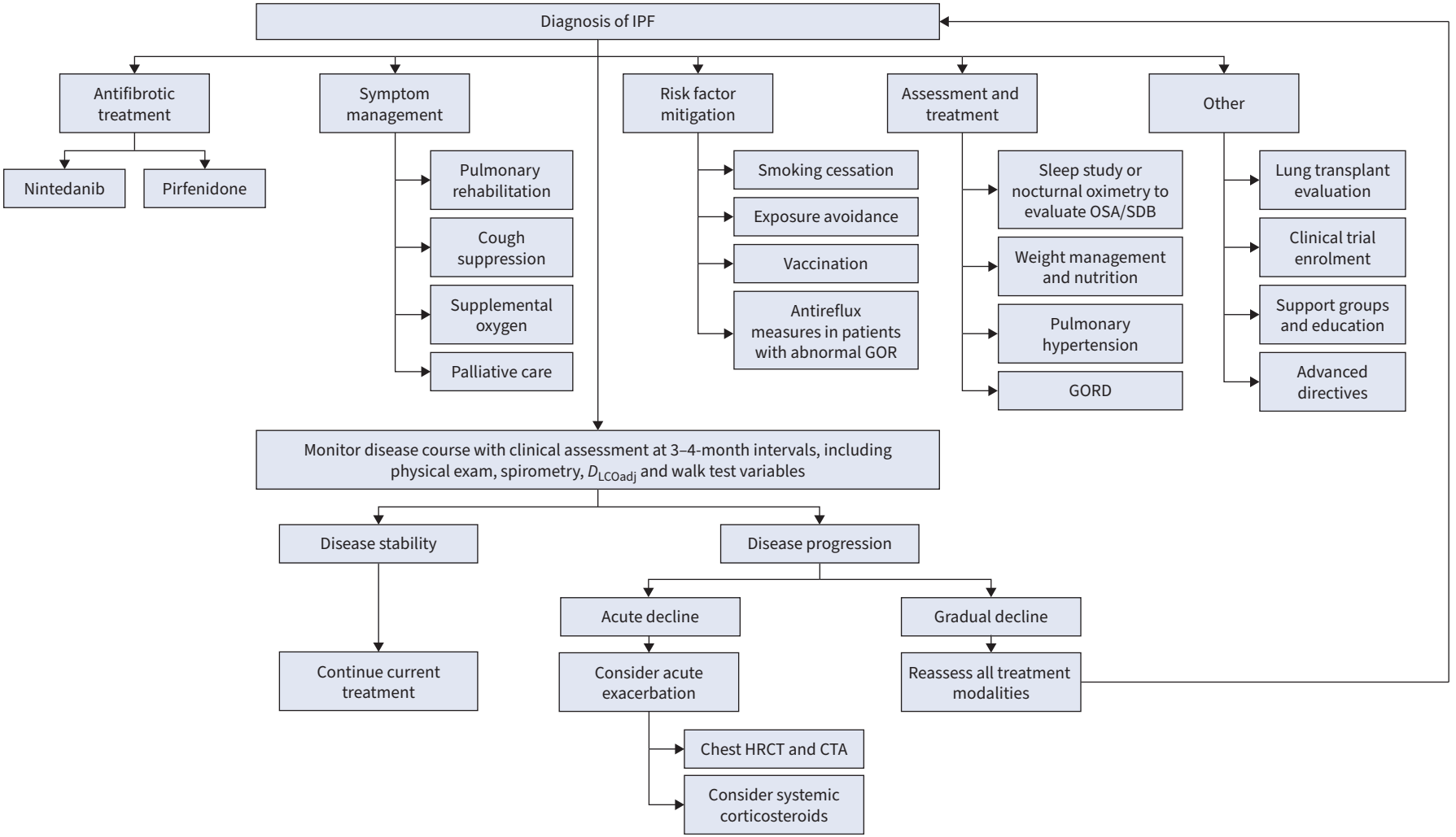

FIGURE 4 Suggested approach to the management of patients with idiopathic pulmonary fibrosis (IPF). Patients with a diagnosis of IPF should be considered for antifibrotic treatment with either nintedanib or pirfenidone. Interventions for dyspnoea and/or cough include pulmonary rehabilitation, supplemental oxygen for resting and/or exertion hypoxaemia, cough suppression and palliative care evaluation. Smoking cessation and avoidance of any ongoing inhalational exposures, along with age-appropriate vaccination should be encouraged. Considerations for assessment of comorbidities include a sleep study or nocturnal oximetry to evaluate obstructive sleep apnoea (OSA)/sleep disordered breathing (SDB), obesity and weight management, pulmonary hypertension, and gastro-oesophageal reflux (GORD). Lung transplant should be considered in the appropriate candidate in a timely manner. Enrolment in clinical trials, education and access to support groups are appropriate considerations. Advanced directives should be discussed in a timely manner. Patients should be monitored to assess disease course at regular intervals, usually every 3–4 months, with a clinical reassessment and measurement of spirometry and diffusing capacity of the lung for carbon monoxide corrected for haemoglobin (D_{LCOadj}). If there is an acute respiratory decline over 4–6 weeks, chest high-resolution computed tomography (HRCT) to evaluate for acute exacerbation and CT angiography (CTA) to rule out a pulmonary embolus should be considered. All treatment modalities should be reassessed when there is disease progression.

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evaluation [129]. Pulmonary rehabilitation has been shown to improve clinical outcomes in patients with IPF, including improved dyspnoea and quality of life [130, 131]. Criteria for lung transplantation vary by centre, but many centres do not have an absolute age cut-off and lung transplantation is increasingly being performed for patients in their late 60s and early 70s [132, 133]. Involvement of palliative care has been shown to be beneficial in alleviating symptom burden for patients and caregivers [134, 135]. Advanced directives and goals of care should be addressed when there is evidence of disease progression. Age-appropriate vaccination should be encouraged. Other considerations include facilitating access to clinical trials and patient/caregiver support groups.

Monitoring and anticipatory guidance regarding acute exacerbations should also occur. The appropriate treatment of acute exacerbations remains uncertain, with a lack of studies that demonstrate improved outcomes with any treatment. Acute exacerbations are commonly treated with corticosteroids, although the recommendations made in the 2011 guideline were weak, and the dosage, administration and duration were not established [4]. In retrospective studies, treatment with corticosteroids was associated with reduced survival among patients with IPF, but the potential for bias and confounding limits any conclusions [136]. Randomised clinical trials regarding the use of corticosteroids and/or other therapeutic interventions for acute exacerbation of IPF are needed. A recent phase 3 clinical trial demonstrated increased 3-month mortality in patients with acute exacerbation of IPF treated with intravenous cyclophosphamide in addition to glucocorticoids, providing evidence that this treatment should be avoided [137]. Another phase 3 clinical trial showed lower survival among patients treated with thrombomodulin alfa for an acute exacerbation of IPF compared with placebo [138]. A thorough search for triggers of the acute exacerbation (*i.e.* infection, aspiration and medications) should be performed and any underlying contributing conditions treated. Given the high morbidity and mortality associated with acute exacerbation, early involvement of palliative care and advanced care planning are essential.

Monitoring for disease progression

Monitoring for disease progression is important regardless of treatment, but the appropriate interval for follow-up and clinical testing varies based on practice setting, local resources available, and patient values and preferences. Progression can be monitored in different ways, which may increase the chance of detecting subtle but clinically relevant deterioration. Monitoring at regular intervals to assess worsening symptoms, physiological parameters (*i.e.* decline in FVC and/or D_{LCO}) and/or radiological features may inform management, including prompt detection of complications and comorbid conditions that warrant additional treatment considerations, advanced care planning conversations, and timely referral for clinical trials and lung transplantation (for the appropriate patient).

Assessments at 3–4-month intervals with spirometry and D_{LCO} have been used in recent clinical trials to detect disease progression, and are commonly practised in expert centres [6, 7]. The frequency of monitoring with CT imaging should be individualised based on clinical and physiological data. It should be considered when significant improvements or deterioration in lung function occur, to re-evaluate the diagnosis or monitor for complications (*i.e.* drug toxicity and acute exacerbation), respectively. Some patients may warrant a noncontrast CT at 12-month intervals, especially if there are additional risk factors for lung cancer, although more studies are needed to establish the incremental value of this approach for the overall population.

Resting and exertional hypoxaemia are associated with increased mortality in patients with IPF, and can be evaluated with a 6-min walk test [139]. Given that disease progression is associated with development of pulmonary hypertension, which may benefit from treatment with inhaled prostanoids and other targeted therapies, screening with transthoracic echocardiography may be considered, especially if there is a decline in D_{LCO} out of proportion to the decline in FVC and/or with any clinical worsening [119, 140]. Disease monitoring should focus on the assessment of patient-centred outcomes, including formal or informal evaluations of health-related quality of life. Several instruments and validated questionnaires to measure this have been developed, and can be used both in the clinical setting and in research to assess treatment response, including a simple visual numerical scale that can be used during clinic visits [141–144].

Biomarkers

Blood biomarkers that can aid in assessing diagnosis, prognosis and treatment response have been described, but none are currently integrated into clinical decision making. Patients with IPF have higher circulating levels of markers of alveolar epithelial injury (SP-A, SP-D and KL-6) and extracellular matrix remodelling (MMP-7, periostin and osteopontin) [145, 146]. IPF patients with progressive disease have higher levels of SP-D, MMP-7, CA19-9, CA-125, ICAM-1, periostin and CYFRA 21-1 [147–151]. Several studies have demonstrated that some of these biomarkers, either individually or as a composite

index, may have value in predicting short-term and overall risk of disease progression and mortality [145, 149]. However, the additive value of biomarkers to other clinical parameters (age, gender, and physiological and imaging abnormalities) has not been established. Blood gene expression signatures can classify patients into groups at high and low risk of death, but they are difficult to incorporate into routine practice [152, 153]. Peripheral blood monocyte count has recently emerged as a promising and easily measurable prognostic biomarker in patients with IPF, with several studies showing that a monocyte count $>0.60\times10^9$ cells·L^{-1} is strongly associated with disease progression and all-cause mortality, with counts $>0.95\times10^9$ cells·L^{-1} indicating a very high risk for poor outcomes [154–156]. No biomarkers have demonstrated utility in the assessment of treatment response to antifibrotic therapy [157]. However, in a retrospective analysis of PANTHER data, age-adjusted blood leukocyte telomere length below the 10th percentile of normal was associated with poor outcomes among those treated with immunosuppression [158]. These findings were replicated in other cohorts and add to the body of data on telomere length as a prognostic biomarker with potential utility in assessing treatment response in fibrotic ILDs [68]. These biomarkers need prospective validation to determine their clinical utility in the context of the current standard of care.

Morbidity and mortality

The median survival for patients diagnosed with IPF has historically been reported at 3–5 years from diagnosis [159]. Among US adults with IPF over the age of 65 years between 2001 and 2011, the median survival time was 3.8 years [43]. In a study from Canada from 2007 to 2011, the 4-year risk of death was 41% [32]. Survival time decreases with increasing age and male sex [32, 43]. Multiple studies report improving survival over the last two decades, which may be explained by earlier diagnosis, reduced use of immunosuppressive medications and improved treatments [43, 44, 160–163]. One recent study reported decreases in age-standardised death rates from ILD in multiple countries across Europe, suggesting that improvements in diagnosis and management of ILD may be contributing [44]. Several nonrandomised clinical studies, as well as pooled data from randomised clinical trials, have demonstrated improved survival with the use of antifibrotic therapy [7, 125, 164]. However, significant disparities in patient outcomes due to race/ethnicity and socioeconomic status remain [165–168].

The number of deaths due to IPF is increasing worldwide, despite data suggesting that survival among those with IPF is improving [31, 43, 160–163, 169–172]. Using the World Health Organization mortality database, the median mortality due to IPF in Europe was 3.75 per 100 000 for men and 1.50 per 100 000 for women in 2011–2013 [169]. Using a more broad definition of pulmonary fibrosis, in the USA the age-adjusted mortality rate in 2017 was 26.7 per 100 000 for men and 16.3 per 100 000 for women, with significant variability based on race/ethnicity [173]. Using death certificate data, the age-adjusted mortality rates per 100 000 population in 2010 ranged from 4.6 in Sweden to 9.9 in Japan; high rates were also seen in the UK (8.5 per 100 000 in England and Wales, and 9.7 per 100 000 in Scotland), and lower rates in Spain and New Zealand (5.3 and 5.6 per 100 000, respectively) [170]. Between 2000 and 2012, there was a 2–3% annual increase in mortality in all countries for which data were available [170]. In the USA, between 1999 and 2017, the age-adjusted morality rose on average by 0.7% per year [174]. Recent studies show that approximately 5500 people in the UK and up to 17 000 people in the USA die from IPF each year [170, 172]. The most common cause of death among patients with IPF is progression of lung disease, often resulting in acute exacerbations, and acute respiratory failure (60–70% of patients) [171, 175]. Other causes include ischaemic heart disease, lung cancer, pneumonia, pulmonary embolism and COPD [174, 175].

Summary and future directions

Over the last two decades, increasing awareness of the clinical manifestations, more widespread use of CT scans and other potential factors have contributed to a rising prevalence of IPF among people over the age of 65 years. Despite substantial advances in the understanding and treatment of IPF over this timeframe, for the vast majority of patients IPF remains a chronic, progressive and fatal lung disease. Recent studies and clinical trials have highlighted mechanistic similarities between IPF and other forms of progressive pulmonary fibrosis. It is increasingly apparent that what differentiates IPF from other types of ILDs is not the presence of fibrosis or its “idiopathic” nature, but rather the fact that IPF is inevitably progressive, which has distinct prognostic and therapeutic implications. It is hoped that ongoing and future studies of molecular probes and machine learning will enable a more accurate diagnosis of IPF and other fibrotic lung diseases with fewer, less invasive procedures and interventions. The currently available antifibrotic agents (pirfenidone and nintedanib) slow disease progression in the majority of patients who are able to tolerate these medications. The challenge facing the field is in identifying novel treatments that can further change the natural history of IPF by either stabilising or reversing the fibrotic process. The answer may lie in the development of therapies that target distinct pathogenetic pathways, combination treatment, management of comorbidities or identification of subgroups of patients with IPF responsive to different

therapeutic approaches. Treatment strategies that improve patient-reported outcomes that are meaningful to patients are urgently needed. Additional gaps include improved methods of prognostication, subphenotyping of patients with genetic markers and precision pharmacogenomic studies, and earlier detection of disease. It is hoped that improved standards of care that go beyond antifibrotic therapy and include better detection and management of comorbid conditions, changes in lifestyle, and new pharmacological treatment options will continue to extend the average life expectancy of patients with IPF well beyond the historically quoted 3–5 years from diagnosis.

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