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REVIEW

Natural history of idiopathic pulmonary fibrosis

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Summary
Idiopathic pulmonary fibrosis (IPF) is a parenchymal lung disease characterized by progressive interstitial fibrosis. IPF has a poor prognosis, with a median survival time of 2–3 years from diagnosis, but varying from a few months to a decade. The natural history of IPF is highly variable and the course of disease in an individual patient is difficult to predict. Some patients with IPF experience rapid decline, others progress much more slowly, and some patients show periods of relative stability interspersed with acute deteriorations in respiratory function.

Many clinical, radiographic, serologic, and histopathologic variables have been shown to predict mortality in IPF. However, the accuracy of these predictors varies due to the retrospective nature of some of the studies and variations in study design. The ability to identify clinical characteristics that predict disease progression and survival would be useful for counseling patients, treatment decision-making, and prompt consideration for lung transplantation. A number of indices for predicting mortality in patients with IPF are available, but they require further validation. As high-resolution computed tomography scans become more widely available and patients with IPF are diagnosed earlier, survival times following diagnosis will improve. Early referral to interstitial lung disease specialty centers is important for accurate diagnosis and may be associated with improved outcomes. The goal of this review is to examine the natural history of IPF, discuss predictors of mortality, and highlight the importance of prompt diagnosis and referral for patients with IPF.

Contents

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia associated with the histopathologic pattern of usual interstitial pneumonia (UIP) [1]. Although IPF is a rare disease, it is one of the most common forms of idiopathic interstitial lung disease (ILD) [2]. The annual incidence of IPF in the USA has been estimated as 6.8—8.8 cases per 100,000 population using narrow case definitions and as 16.3—17.4 cases per 100,000 population using broad case definitions [3]. IPF incidence and prevalence increase with age, are higher among males, and appear to be on the increase in recent years [3].

The processes mediating fibrosis in the lungs of the patients with IPF are not completely understood. However, it is believed that recurrent injury to alveolar epithelial cells activates inflammatory cells, which release fibrogenic growth factors. These perpetuate a cycle of injury, failed repair, and fibrosis via the activation, proliferation, invasion, and apoptotic resistance of fibroblasts and myofibroblasts. This leads to excess deposition of extracellular matrix/collagen in the lung, resulting in pathologic tissue scarring and, ultimately, respiratory failure [4].

The symptoms of IPF include chronic dyspnea and dry cough [1], which significantly impact patients' health-related quality of life (HRQoL) [5,6]. Digital clubbing develops in 25—50% of patients [7]. In contrast to other forms of ILD, weight loss, malaise, fatigue, and fever are not typical symptoms of IPF [7].

According to the latest (2011) international guidelines, the diagnosis of IPF requires the exclusion of other known causes of ILD, the presence of a UIP pattern on high-resolution computed tomography (HRCT) of the chest in patients not subjected to surgical lung biopsy, or specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy [1]. The accuracy of the diagnosis of IPF increases with multidisciplinary discussion among radiologists, pathologists, and pulmonologists who are experienced in the diagnosis of ILD [8,9].

In October 2014, the US Food and Drug Administration (FDA) approved the first drugs for the treatment of IPF in the US: nintedanib (OFEV®) [10] and pirfenidone (ESBRIET®) [11]. Pirfenidone has also been approved for the treatment of IPF in several other countries and regions and in January 2015, nintedanib was approved for the treatment of IPF in the European Union. Both nintedanib and pirfenidone have been shown to reduce disease progression in patients with IPF and mild or moderate impairment of lung function (forced vital capacity [FVC] >50% of predicted value). The efficacy and safety of nintedanib in patients with IPF were assessed in the Phase II TOMORROW trial [12] and in the two replicate Phase III INPULSIS® trials [13]. In these trials, nintedanib 150 mg twice daily given for 52 weeks reduced the annual rate of decline in FVC (the primary endpoint) compared with placebo, with adverse events that were manageable for most patients. Pirfenidone 2403 mg/day has been investigated in three international Phase III trials: the two 72-week CAPACITY trials [14] and more recently, the 52-week ASCEND trial [15]. The CAPACITY trials yielded discordant results for the primary endpoint of change from baseline in FVC % predicted at week 72, with a significant benefit of pirfenidone *vs.* placebo shown in CAPACITY 2 but not in CAPACITY 1. In the ASCEND trial, there was a significant difference in favor of pirfenidone for the same endpoint at week 52. Pirfenidone was associated with a manageable adverse event profile.

Lung transplant remains a treatment option for a minority of patients with IPF and has been shown to improve survival in patients with IPF [1].

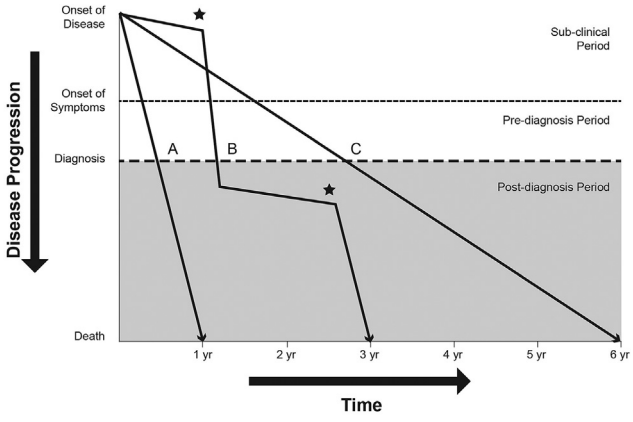
The aim of this review is to examine the natural history of IPF, discuss predictors of mortality, and highlight the

importance of prompt diagnosis and referral for patients with IPF.

Natural history

The prognosis for patients with IPF is poor. Several retrospective studies suggest that the median survival time from diagnosis is 2—3 years [1]. However, the natural history of IPF is highly variable and the course of disease in an individual patient is difficult to predict [16—19]. Some patients with IPF experience rapid decline, others progress much more slowly, and some patients show periods of relative stability interspersed with acute deteriorations in respiratory function (Figure 1) [1,19]. In most patients with IPF, the cause of death is IPF itself (i.e., respiratory failure) [20].

Acute deteriorations in patients with IPF can occur at any time [1,21,22]. They may be due to a known cause such as an infection, or to an unknown cause, in which case the deterioration is defined as an acute exacerbation [1,23]. The etiology of acute exacerbations is not clear. Possible precipitating factors are occult viral infection, air pollution, or acute direct stress such as aspiration, with subsequent acceleration of the fibroproliferative response [23,24]. The incidence of acute exacerbations of IPF is unclear, but they are estimated to occur in 5—10% of patients with IPF annually [1] and they are the leading cause of hospitalization and death in patients with IPF [25,26]. However, in-hospital mortality rates vary considerably (from 27% to 96%) depending on the methodology used [22,27–30]. In a retrospective review of 461 patients with IPF, patients with an acute exacerbation had a significantly shorter median survival time than those without an exacerbation (15.5 *vs.* 60.6 months from diagnosis of IPF) and had lower 5-year survival rates (18.4% *vs.* 50%, respectively) [28].



Ley B, et al. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011;**183**:431–440.
Official Journal of the American Thoracic Society.

Figure 1 Schematic representation of potential clinical courses of IPF. The rate of deterioration to end of life may be rapid (line A), slow (line C), or mixed (line B), with periods of relative stability interspersed with periods of acute decline (stars).

The placebo arms of large Phase II—III clinical trials provide an opportunity to investigate the natural history of lung function decline in patients with IPF. The annual rate of decline in FVC in patients with IPF enrolled in the placebo arms of Phase II—III registration trials was 0.16—0.28 L/year [12,13,15,31—33]. However, these results should be treated with caution, as these trials had a short duration of follow-up (1—2 years) and the patients enrolled in clinical trials are not a random sample of the general population of patients with IPF; many patients with IPF are excluded from clinical trials due to their age, disease severity, or comorbidities.

There is emerging evidence of a group of patients with IPF who are long-term survivors. In a study of 357 patients with IPF, approximately 25% of patients survived for >5 years from diagnosis without transplantation [18]. Survival analyses revealed a progressively increasing median survival dependent on the duration of the disease *i.e.*, the longer that patients with IPF lived, the more likely that they would live even longer. In a recent study at our institution, 106 patients from a clinical database were divided into three categories based on their survival: rapid progressors (≤2 years; $n = 26$), usual survivors (2—5 years; $n = 40$), and long-term survivors (>5 years; $n = 27$) [34]. Compared with the other two groups, rapid progressors were predominantly male, had a greater smoking history, had more comorbidities, and were delayed in pulmonary referral. One possible explanation for the rise in long-term survivors is the wider availability of HRCT scans leading to earlier diagnosis of IPF and, thus, increased survival times following diagnosis.

Predictors of survival/mortality

Many clinical variables have been shown to predict mortality in IPF. However, the accuracy of these predictors varies due to the retrospective nature of some of the studies and variations in study design [1]. The ability to identify clinical characteristics that predict disease progression and survival would be useful for counseling patients, treatment decision-making, and prompt consideration for lung transplantation.

Clinical predictors

Presence of comorbidities

A number of comorbidities are associated with a worse prognosis in patients with IPF. However, it is unknown whether treating comorbidities influences clinical outcomes [1].

Approximately 20—40% of patients with IPF who are evaluated for lung transplantation have pulmonary arterial hypertension (PAH) [35,36]. PAH is associated with lower diffusing capacity of carbon monoxide (DLco), lower exercise capacity (as assessed by the 6-minute walk test [6MWT]), and increased mortality in patients with IPF [35—37].

A cohort study evaluating records of 110 patients with IPF at a respiratory institute in Mexico estimated that approximately 28% of patients with IPF had emphysema

[38]. Further, those with emphysema had a significantly lower mean survival time than those without emphysema (25 *vs.* 34 months) [38]. However, another cohort study of 365 patients with IPF, identified via the University of California San Francisco (UCSF) and Mayo Clinic ILD databases, found that only 8% of patients with IPF had concomitant emphysema, and combined pulmonary fibrosis and emphysema was not associated with worse survival [39]. Patients with IPF, emphysema and secondary pulmonary hypertension have a particularly poor prognosis [40].

The prevalence of gastroesophageal reflux disease (GERD) in patients with IPF may be as high as 87% [41]. It has been hypothesized that chronic microaspiration due to GERD may cause repetitive subclinical injury to the lung, leading to the development or worsening of IPF [42]. The use of gastroesophageal reflux medications has been shown to be a predictor of longer survival time in patients with IPF [43]. A recent study using prospective data from the placebo groups of three randomized clinical trials ($n = 242$) showed that patients who used anti-acid treatments at baseline had reduced FVC decline (estimated difference 0.07 L; 95% CI 0.00—0.14) and fewer exacerbations (0 *vs.* 9 events) at 30 weeks than those who did not [44].

Older age

Older age has been shown to confer a poorer prognosis in some studies [1,19]. However, Nadrous and colleagues reported that younger patients with IPF (<50 years of age) had the same poor prognosis as older patients (median survival time 2.1 years) [45].

Male sex

Data on the effect of gender on mortality in IPF are variable [1,19]. A study of 215 patients that examined gender differences in IPF found that female sex conferred a significant survival advantage over male sex (HR 0.63; CI 0.41—0.97) after adjusting for age, smoking history, DL_{CO}, and maximum desaturation area [46].

Current or former smoker

Smoking has been found to be associated with both increased and decreased mortality in patients with IPF [1,19]. A better outcome in current smokers compared with former smokers may reflect less severe disease at presentation and may represent a "healthy smoker effect". Indeed, this effect may explain earlier reports of better survival in current smokers with IPF compared with former and never smokers.

Lower body mass index (BMI)

In a cohort of 197 patients with IPF, survival was significantly associated with BMI (HR 0.93 for every 1-unit increase in BMI; 95% CI 0.89—0.97) [47]. The reason for a protective effect of increased BMI is unclear, but decreased BMI may be a marker of malnutrition and/or elevated exertional and basal energy expenditure. This association has been confirmed in other cohorts [48].

Dyspnea

Baseline dyspnea and change in dyspnea over time have been shown to predict mortality [49,50], but which dyspnea measurement is most predictive of outcome is unclear [1].

Use of supplemental oxygen

A higher titrated oxygen requirement to maintain oxyhemoglobin saturation (arterial oxygen saturation measured by pulse oximetry [SpO_2]) ≥96% at rest is associated with a greater mortality rate in patients with IPF independent of FVC and 6MWD [51].

Baseline pulmonary function tests (PFTs)

Baseline PFTs have shown varied associations with survival. This may be due, at least in part, to the presence of comorbid conditions that affect PFTs (for example, emphysema, obesity) or to technical differences in testing [1]. The PFTs most commonly associated with prognosis are FVC, total lung capacity (TLC), and DL_{CO} [18,49,52,53]. In a retrospective review of 446 patients with IPF, patients with mild, moderate, and severe disease categorized by FVC % predicted (≥70%, 55—69%, and <55%, respectively) had median survival times of 55.6, 38.7, and 27.4 months, respectively [18]. Patients with mild, moderate, and severe disease categorized by DL_{CO} % predicted (≥50%, 35—49%, and <35%, respectively) had median survival times of 67.3, 47.8, and 31.3 months, respectively [18].

Changes in PFTs

Changes in PFTs may have superior predictive power than baseline PFTs. A decline in FVC over 6 or 12 months reliably predicts mortality [1,49,53—55] (Figure 2). An absolute decline in FVC of ≥10% is predictive of mortality and even marginal declines of 5—10% may also be predictive [49,53,55]. In 1156 patients with IPF enrolled in two clinical trials, 1-year risk of mortality was nearly 5-fold higher in patients with absolute declines in FVC % predicted of ≥10% over 24 weeks (HR 4.78; 95% CI 3.12—7.33), and were >2-fold higher in those with absolute declines of 5—10% (HR 2.14; 95% CI 1.43—3.20), compared with patients who experienced declines of <5% [56]. Richeldi and colleagues have shown that using the relative change in FVC rather than the absolute change maximizes the chances of identifying a ≥10% decline in FVC without sacrificing prognostic accuracy [57]. A decline in DL_{CO} has also been associated with increased mortality, although less consistently [49,53,55]. A reduction in the alveolar-arterial oxygen tension gradient [$P(A—a)O_2$] of >15 mmHg at 12 months has been shown to be predictive of mortality [48]. Six-month change in $P(A—a)O_2$ and TLC may also be predictive [49].

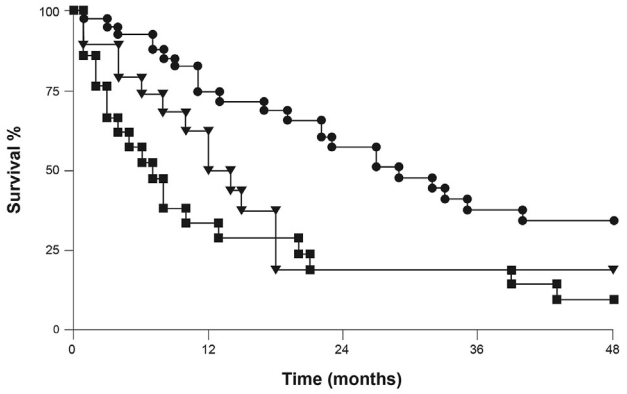


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Figure 2 Four-year survival in relation to the magnitude of serial change in FVC at 6 months in patients with IPF ($n = 84$). Declines of 5—10% (marginal; ▼) and ≥10% (significant; ■) were associated with a worse prognosis than stable disease (●).

6-minute walk test distance (6MWD)

Both baseline 6MWD and change in 6MWD are predictive of mortality; for example, in a study of 822 patients with IPF, a 24-week decline in 6MWD of >50 m was associated with a >4-fold increase in 1-year mortality (HR 4.27; 95% CI 2.57—7.10) [58]. In a recent analysis of data from 748 patients enrolled in a Phase III study, baseline 6MWD of <250 m and 24-week decline in 6MWD of >50 m were independent predictors of mortality (HR 2.12; 95% CI 1.15—3.92 and HR 2.73; 95% CI 1.60—4.66, respectively) [59]. However, the prognostic value of 6MWD in clinical practice may be limited due to lack of standardization [1].

Acute exacerbations

As mentioned previously, acute exacerbations in patients with IPF are associated with high mortality [22,27–29].

Radiographic, histopathologic and serologic predictors

HRCT of the chest is the radiographic standard in the evaluation of IPF, providing vital diagnostic and prognostic information. The extent of fibrosis and honeycombing on HRCT has been shown to predict mortality and to correlate with FVC and DL_{CO}% predicted [60—62]. In a study assessing the correlation between HRCT pattern and survival in patients with IPF, patients with a definite or probable UIP pattern on HRCT had a shorter survival time than patients with an indeterminate HRCT pattern (median survival 2.1 *vs*. 5.8 years) [63]. Interestingly, automated quantification of the volume of parenchymal lung abnormalities on HRCT has also been found to be predictive of mortality [64]. In terms of histopathologic predictors, an increased number of fibroblastic foci has been associated with increased mortality [65—67].

Many circulating blood proteins have been associated with survival in IPF [1,19,68]. A comprehensive review of biomarkers is beyond the scope of this paper, but a recent review summarized the role of biomarkers in predicting progression and mortality in IPF (Table 1) [68]. Although no validated biomarkers are available, these data demonstrate the potential use of biomarkers in predicting prognosis in patients with IPF. Richards and colleagues have published a model that incorporates biomarker and physiologic variables to predict survival [69]. In a derivation cohort of 140 patients with IPF, they analyzed the concentrations of 95 cytokines, chemokines, matrix metalloproteinases (MMPs), and markers of apoptosis and epithelial injury, and determined that five factors (MMP-7, intercellular adhesion molecule-1, IL-8, vascular cell adhesion molecule-1, and S100A12) were predictive of outcomes regardless of age, sex, or baseline PFTs. These were then validated in an independent cohort of 101 patients with IPF. However, the applicability of these biomarkers is hampered by the lack of their routine measurement in clinical practice.

Risk indices

Disease progression and mortality are difficult to predict in IPF due to the highly variable nature of the disease. However, a number of risk indices have been developed.

Using a composite clinical-radiologic-physiologic (CRP) scoring system to evaluate the clinical status of patients with IPF [70], King and colleagues revised and validated the scoring system to predict survival in 238 patients with IPF [65]. However, the CRP score has not been widely adopted in clinical practice as it uses multiple variables that are not routinely measured.

Mura and colleagues developed a risk stratification tool to predict survival and rapid disease progression in a prospective cohort of patients with IPF ($n = 70$) [17]. Multivariate analysis showed that a Medical Research Council dyspnea score (MRCDS) of >3, a 6MWD of <72% predicted and a composite physiologic index (CPI) of >41 at diagnosis were significant and independent predictors of 3-year survival. The Risk stratification ScorE (ROSE) that they developed based on these variables predicted 3-year mortality with 100% specificity (*i.e.*, it did not predict as dying anyone who did survive). Results were confirmed in an independent retrospective cohort of patients ($n = 68$).

du Bois and colleagues developed a scoring system based on independent predictors of mortality in data from two clinical trials ($n = 1099$) [71]. An abbreviated model including age, respiratory hospitalization, FVC% predicted, and 24-week change in FVC% predicted produced estimates of 1-year mortality consistent with the observed data (9.9% *vs*. 9.7%; c-statistic [measure of discrimination] 0.75; 95% CI 0.71—0.79). The addition of 6MWD and 24-week change in 6MWD to the original model improved its ability to predict 1-year mortality (c-statistic 0.8; 95% CI 0.76—0.85) [59].

The simple point-score GAP index and staging system were developed and validated using retrospective data from three geographically distinct cohorts (total $n = 558$) [72]. Four variables are included in the index: gender (G), age (A), and two lung physiology (P) variables (FVC and DL_{CO}). Points

Table 1 Peripheral blood biomarkers in IPF.

Serum biomarker	Differences between IPF and other ILDs	Correlates with			Study lead author and year	Study population	
		Baseline parameter of disease severity	Disease progression/ longitudinal change in parameter	Mortality		Number of subjects	Number of IPF subjects
KL-6	N	—	—	Y	Satoh et al., 2006	219	Not specified: 152 IIP
	N	—	—	—	Ohnishi et al., 2002	115	21
	Y	—	—	—	Ishii et al., 2003	66	19
Surfactant proteins							
SP-A	N	—	—	—	Ohnishi et al., 2002	115	21
	Y	—	—	—	Ishii et al., 2003	66	19
	—	N	—	Y	Kinder et al., 2009	82	82
	—	N	[a]	Y	Greene et al., 2002	543	210
	—	N	N	Y	Takahashi et al., 2000	160	52
SP-D	Y	—	—	—	Ohnishi et al., 2002	115	21
	Y	—	—	—	Ishii et al., 2003	66	19
	—	—	—	—	Kinder et al., 2009	82	82
	—	N	[a]	Y	Greene et al., 2002	543	210
	—	N	Δ%VC/yr, Δ%TLC/yr	Y	Takahashi et al., 2000	160	52
Matrix metalloproteinases							
MMP1	Y	N	—	—	Rosas et al., 2008	322 (D) 33 (V)	74 (D) 9 (V)
MMP7	Y	FVC, DLCO	—	—	Rosas et al., 2008	322 (D) 33 (V)	74 (D) 9 (V)
	—	—	—	[b]	Richards et al., 2011	140 (D) 101 (V)	140 (D) 101 (V)
CCL18	—	TLC, DLCO	ΔTLC	—	Prasse et al., 2007	78 (D) 40 (V)	16 (D) 17 (V)
	—	—	ΔTLC, ΔFVC	Y	Prasse et al., 2009	72	72
VEGF	—	N	ΔVC (subset)	—	Ando et al., 2010	98	41
YKL-40	—	N	—	Y	Korthagen et al., 2011	211	85
	—	DLCO, $AaDO_2$, PaO_2	—	—	Furuhashi et al., 2010	63	41
Osteopontin	N	PaO_2	—	—	Kadota et al., 2005	46	Not specified: 17 ILD
Periostin	Y	Not reported	ΔTLC, ΔFVC	—	Okamoto et al., 2011	105	51
Fibrocytes	—	N	—	Y	Moeller et al., 2009	75	58
T cells							
CD4:CD28%	—	FVC	ΔFVC, ΔFVC rate	Y	Gilani et al., 2010	89	89
Tregs	Y	FVC, DLCO	TLC, FVC	—	Kotsianidis et al., 2009	84	21

Abbreviations: Y, yes; N, no; —, not studied; $AaDO_2$, alveolar-arterial oxygen difference; D, derivation cohort; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; TLC, total lung capacity; Tregs, regulatory T cells; V, validation cohort; IPF, idiopathic pulmonary fibrosis.

[a] Longitudinal data available for a subset of 19 subjects. No significant changes over time, although patients were relatively stable.

[b] MMP7 levels were associated with mortality in derivation cohort, but not validation cohort.

are assigned for each variable to obtain a total score that is used to classify patients as stage I (0—3 points), II (4—5 points), or III (6—8 points). One-year mortality in patients with stages I, II, and III disease was 6%, 16%, and 39%, respectively. Recently, the validity of the GAP index was supported by data from a statewide registry ($n = 474$) [73].

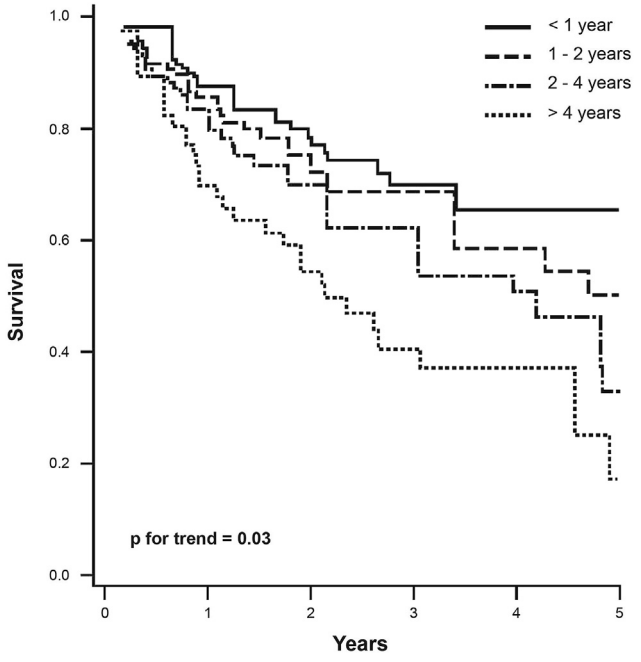
Importance of prompt diagnosis and referral

Many patients with IPF are delayed in receiving the correct diagnosis. In a prospective study in the US of 129 patients with IPF, the median delay between the onset of dyspnea

and referral to a tertiary care center was 2.2 years [74]. In a survey of 1448 patients with IPF and caregivers of patients with IPF, 55% reported a delay of >1 year between the onset of symptoms and diagnosis, and 38% saw >3 physicians before a diagnosis of IPF was established [75]. Moreover, delayed access to a tertiary care centre was associated with a higher risk of death in patients with IPF independent of disease severity [74] (Figure 3).

It is important that patients who may have IPF are referred to a specialist center for diagnosis without delay. In addition to establishing the correct diagnosis, referral to a specialty center enables patients to be given treatment, to be followed regularly to ensure that they receive appropriate care throughout the course of their disease, to participate in patient support groups and to be considered for lung transplantation and clinical trials, Differentiating IPF from the other idiopathic interstitial pneumonias is difficult and is improved by involving a multidisciplinary team, as is often in place in specialized ILD centers [8,9].

In the US, two drugs are approved for the treatment of IPF: nintedanib (OFEV®) [10] and pirfenidone (ESBRIET®) [11]. Pirfenidone has also been approved for the treatment of IPF in several other countries and regions. In addition to treating IPF itself, most comorbidities in patients with IPF should be treated, with the aim of relieving symptoms and improving clinical outcomes [76]. While the role of GERD in the pathophysiology of IPF remains unclear, given the findings of retrospective analyses, GERD should be treated in IPF patients with lifestyle modification and acid suppression therapy, if warranted [77]. Further evaluation of patients with persistent GERD symptoms is needed, and therapeutic options such as weight loss, anti-reflux, or bariatric surgery should be considered [77]. The latest international management guidelines for IPF do not recommend routine treatment of PAH in patients with IPF, though trials of vasodilators may be appropriate in certain cases [1]. There is some evidence that treating PAH with sildenafil benefits patients with evidence of right ventricular systolic dysfunction [78].



Lamas DJ, et al. Delayed access and survival in idiopathic pulmonary fibrosis: a cohort study. *Am J Respir Crit Care Med* 2011;**184**:842–847.
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Figure 3 Survival from the time of evaluation at a tertiary care centre adjusted for age and FVC across quartiles of delayed access to a tertiary care centre.

Supplemental oxygen therapy is strongly recommended for patients with clinically significant resting hypoxemia [1]. However, there are limited data surrounding the use of supplemental oxygen in IPF and further research should be undertaken to define how and when it should be used. Of note, pulmonary rehabilitation may be valuable in patients with IPF [79,80]. The latest international guidelines for the management of IPF state that the majority of patients with IPF should receive pulmonary rehabilitation, although its long-term benefits remain unclear [1].

Ultimately, palliative care should become an integral component of the care of patients with IPF [1,76]. Symptoms such as cough and dyspnea are common, worsen as the disease progresses and are difficult to treat. Limited data suggest that thalidomide and steroids may be beneficial for chronic cough in IPF [81], though these are not used routinely. In addition, high-dose steroids reduced the capsaicin-induced cough index in a small placebo-controlled study [82]. While steroids are not recommended to treat IPF [1], certain patients with severe symptoms may warrant trials of prednisone with close monitoring for toxicity. Chronic opioids should be considered in patients with severe dyspnea and cough, with careful monitoring of side-effects [1].

International guidelines state that patients with IPF should be considered for lung transplantation in a timely manner at the first sign of objective deterioration [1,83]. In the USA, waiting times and mortality on the waiting list have significantly improved for patients with IPF since the introduction of the Lung Allocation Score in 2005, which prioritizes patients for transplant based on their estimated survival time with and without a transplant [84].

Given the unpredictable nature of IPF and its poor prognosis, patients with IPF need the appropriate emotional support to cope with being diagnosed with and living with the disease. It is important that pulmonologists do not adopt a nihilistic attitude to managing patients with IPF, as a positive patient-pulmonologist relationship can help patients to cope with living with IPF [85,86].

Conclusion

IPF is a progressive and ultimately fatal disease, but its course in individual patients is extremely variable. Change in FVC over 6—12 months is a robust prognostic marker in patients with IPF. However, calculating change in lung function can only be performed in retrospect and, therefore, cannot be used to predict the clinical course of IPF at diagnosis. A number of indices for predicting mortality in patients with IPF are available, but they require further validation. Historically, median survival following a diagnosis of IPF has been only 2—3 years, but as HRCT scans

become more widely available and IPF is diagnosed earlier, survival times following diagnosis will improve. Early referral to ILD specialty centers is important for accurate diagnosis and may be associated with improved outcomes.

Conflict of interest statement

The authors have reported to *Respiratory Medicine* the following conflicts of interest:

HJK has served as site principle investigator for IPF clinical trials sponsored by InterMune, Gilead, Sanofi, Celgene, and Centocor. DP and RT served as co-investigators at the University of Minnesota for clinical trials sponsored by InterMune and Gilead. DP and HJK served on a Clinical Advisory Board for InterMune in 2013.

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