A cohort study of Danish patients with interstitial lung diseases

Burden, severity, treatment and survival

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Introduction

The field of interstitial lung diseases (ILD) and especially idiopathic pulmonary fibrosis (IPF) has undergone immense changes during the last ten to fifteen years. The process started with the consensus classification of the idiopathic interstitial pneumonias published in 2002 (1) that created a uniform approach to the diagnosis of these diseases.
The first multicenter randomised controlled trial in idiopathic pulmonary fibrosis (IPF) was started in 1999 and published as recently as 2004 (2). Since then, there has been an exponential increase in the number of subjects enrolling in IPF clinical trials. Recently, the first evidence-based therapy, pirfenidone, developed specifically for the treatment of IPF has become available in most European countries, India and Japan, and new therapeutic options are on their way.
Improved insight into disease mechanisms and analyses of treatment effects in IPF, has led to major changes in therapy with previously used corticosteroids and other immunosuppressive therapies now being abandoned. The new therapeutic options have increased the focus on earlier diagnosis of IPF to allow the initiation of therapy while intervention is still possible.

The primary focus of the studies behind this PhD dissertation was to evaluate the diagnostic approaches in ILD and the distribution of ILD subtypes. Special focus was aimed at IPF diagnostics because the recommended approach was changing at the time the study was initiated.
Several prediction models have been developed for use in IPF and other ILDs, and the availability of reliable tools for prognostic evaluation may help clinical decisions. Therefore, the validation of selected prediction models was included in this study together with a study of comorbidity and its relation to outcome in IPF.
Patients with unclassifiable ILD present a considerable challenge to clinicians, and very few studies of unclassifiable ILD have been published. Therefore, unclassifiable ILD was an obvious focus of this project. The current interest of the study increased, when unclassifiable ILD was made a separate disease entity in the 2013 update of the guidelines from the international respiratory societies.
The overall purpose of the study has been to increase our knowledge and understanding of interstitial lung diseases in the central Denmark region and to use this knowledge to develop and improve the management of patients suffering from these severe diseases.

Background

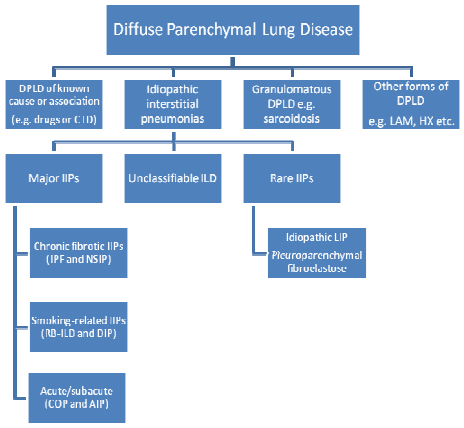
ILD classification and epidemiology

Interstitial lung diseases (ILDs) form a heterogeneous group of rare diseases characterised by varying degrees of pulmonary inflammation and fibrosis. The majority of the cases are idiopathic, but ILDs may be caused by many exogenous factors, such as connective tissue diseases, organic dust and certain drugs. Traditionally, the diseases have been divided into four categories: ILD of known causes, which include connective tissue diseases, drugs and other pathogenic exposure, idiopathic interstitial pneumonias, granulomatous diseases, and a residual group of other ILDs (Figure 1).
Since 2001, the idiopathic interstitial pneumonias (IIPs) have been classified in seven different entities according to the American Thoracic Society/European Respiratory Society (ATS/ERS) International Multidisciplinary Consensus Classification of the IIPs (1) and an update of the guidelines was published in 2013 (3).
What has historically been called cryptogenic fibrosing alveolitis (CFA) according to the classification by Liebow in 1975 (4) and the

pathological classification updated by Katzenstein and Myers in 1998 (5) was undoubtedly a mixture of different entities. The most important disease variants included in the CFA term are known today as usual interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP) and non-specific interstitial pneumonia (NSIP). In the 2001 consensus statement, the term CFA was defined as requiring UIP pathology, and in the 2013 update, the CFA term was removed.

The consensus reached with the 2001 ILD classification has been of major importance in epidemiological studies of ILD, because a simple and operative disease classification is absolutely necessary in obtaining reliable incidence and prevalence estimates. Nevertheless, the true incidence and prevalence of the ILDs are still unknown. The diseases are rare; the correct diagnoses are often difficult and require expertise that is very difficult to obtain outside specialist centres (6). Thus, many patients may remain undiagnosed or misdiagnosed as having other more common pulmonary diseases, and reports from tertiary centres may be subject to referral bias.
Previous European studies have reported ILD incidences between 4.6 and 7.6 per 100,000 inhabitants/year (7-12). A US study reported incidences of 31.5 per 100,000 among men and 26.1 per 100,000 among women (13). In all studies, idiopathic pulmonary fibrosis (IPF) and sarcoidosis were the most frequent diagnoses.

Figure 1
Overview of diffuse parenchymal lung diseases and idiopathic interstitial pneumonias. Modified from the 2013 update on the classification of the IIPs (3)



IPF is the most common of the IIPs, and the one that carries the worst prognosis. Therefore, distinguishing between IPF and non-IPF ILD is a very important part of ILD diagnostics. In 2011, the ATS/ERS/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) guidelines of idiopathic pulmonary fibrosis (14) redefined IPF and introduced a diagnostic algorithm that made surgical lung biopsy unnecessary in patients with a definite UIP pattern on high-resolution computed tomography (HRCT).
In 2013, an update of the IIP guidelines (3) was published that included unclassifiable ILD as a separate disease category, and distinguished major IIPs from rare IIPs and unclassifiable cases. Furthermore, major IIPs are now grouped into chronic fibrosing (IPF and NSIP), smoking-related (DIP and RB-ILD) and acute/subacute IIPs (AIP and COP) (Figure 1). In IPF, the reported incidence in the USA has been estimated at 6.8-17.4 per 100,000 inhabitants/year depending on the criteria used (15, 16). In the UK, an IPF incidence of 4.6 per 100,000 inhabitants/year has been reported (17), and the incidence appears to be rising by 5% per year (18). Incidence data on other IIPs are sparse. To our knowledge, only one previous study (12) reports incidences of non-IPF idiopathic ILDs according to the 2001 guidelines.

IPF
IPF is primarily seen in older adults and is restricted to the lungs. It is a serious and progressive disease with a median survival of 2-3 years. By definition, IPF is a disease of unknown aetiology, but tobacco exposure and possibly environmental exposures are regarded as risk factors (19-21).
The understanding of the mechanisms involved in the pathogenesis of IPF has greatly improved in the last decades. It is believed that the basic mechanism is an imbalance between profibrotic and antifibrotic mediators. The profibrotic mediators promote expansion of extracellular matrix and induce recruitment, proliferation and differentiation of fibroblasts, while the antifibrotic mediators are involved in the tissue remodelling process. Tissue injury leads to activation of these multiple inflammatory, signalling and repair pathways, causing abnormal reepithelialisation and dysregulated remodelling of the extracellular matrix after alveolar injury, which ultimately results in progressive fibrosis. Human and animal studies have supported the theory that oxidative stress plays a role in this dysregulation, and markers of oxidative stress have been identified in the lungs of IPF patients (22, 23).
A familial form of IPF is present when two or more members of the same primary biological family are affected. This is seen in five percent of the cases (24-29). Sporadic and familial IPF are clinically and histologically indistinguishable, although familial forms may develop at an earlier age.

The natural history of IPF is characterised by gradual progression, resulting in respiratory failure and death. Typical symptoms at presentation are dry cough and exertional dyspnoea. IPF is more common in males, with a typical male:female ratio of 3:1. The majority of patients are diagnosed when they are in their sixties or seventies (17, 30, 31). In many cases, the disease is not diagnosed until pulmonary function is severely impaired. Fine crackles at auscultation heard in the basal areas of the lungs, especially on inspiration, are present in the majority of patients with IPF, and this finding must always lead to a thorough diagnostic follow-up. Crackles are not specific for IPF, but may also be a sign of other ILDs, especially NSIP or pulmonary fibrosis associated with connective tissue diseases. Pulmonary specialists are working to increase awareness among physicians of this clinical sign in the hope that it may help in the earlier diagnosis of IPF (32). Earlier diagnosis may allow patients to receive antifibrotic therapy, which has become available for patients with mild to moderate IPF.
The diagnostic criteria of IPF were defined for the first time in 2000 by the ATS and the ERS (33). In the presence of a surgical lung biopsy showing UIP, a definite diagnosis of IPF included exclusion of other causes of ILD, abnormal pulmonary function with evidence of restriction and/or impaired gas exchange, and abnormalities on chest radiographs or HRCT. In the absence of a lung biopsy, the diagnosis was based on the presence of all of the following major criteria and at least three of the four minor criteria. The major criteria were as follows:

1. Exclusion of other known causes of ILD, such as certain drug toxicities, environmental exposures, and connective tissue diseases.
2. Abnormal pulmonary function with evidence of restriction and impaired gas exchange.
3. Bibasilar reticular abnormalities with minimal ground glass opacities on HRCT scans.
4. Transbronchial lung biopsy or bronchoalveolar lavage (BAL) showing no features to support an alternative diagnosis.

The minor criteria were as follows:

1. Age > 50 years
2. Insidious onset of otherwise unexplained dyspnoea on exertion
3. Duration of illness > 3 months
4. Bibasilar inspiratory crackles.

The diagnostic criteria were refined in 2011 (14), when the major and minor criteria were abandoned. The diagnosis of IPF still requires the absence of known causes of interstitial lung disease, including environmental or occupational causes of interstitial lung diseases, exclusion of connective tissue disease and drug-related pulmonary affection, and the presence of a particular radiological and/or histopathological pattern of UIP.
According to the current diagnostic criteria, IPF can be diagnosed without a biopsy in the presence of a typical HRCT pattern known as "definite UIP", which is characterised by predominantly basal and subpleural lung involvement, reticulation and the presence of honeycombing and/or traction bronchiectasis (Table 1). When HRCT findings are not diagnostic of IPF, a thoracoscopic biopsy is required to obtain a certain diagnosis. However, many patients present with severe disease at the time of referral, and the risk of performing a biopsy may be considered too high. In these cases, a definite IPF diagnosis is not obtainable. The "possible UIP" pattern on HRCT may progress to "definite UIP" and then allow a definite IPF diagnosis based on repeated HRCT scan.
In patients who undergo a lung biopsy, the findings of a definite or probable UIP pattern (Table 2) confirm the IPF diagnosis. The combinations of radiology and histopathology findings and the resulting certainty of the IPF diagnosis are shown in Table 3.
The accuracy of the diagnosis increases with multidisciplinary discussion between pulmonologists, radiologists and pathologists specialised in interstitial lung diseases (34), and it is now recommended as an integrated part of the diagnostic work up in IPF and other ILDs.

Unclassifiable ILDs
The diagnosis of ILDs requires a multidisciplinary team of pulmonologists, thoracic radiologists and lung pathologists (3, 34), but nevertheless, a group of patients remains unclassifiable for different reasons. Clinical, radiological and histopathological data may conflict, the surgical risk of a lung biopsy may be too high in patients with severe disease, or the value of diagnostic certainty may not balance the risk of performing a lung biopsy in patients with mild or stable disease. Unclassifiable ILDs have been

Table 1
Radiological criteria for UIP pattern in IPF

Definite UIP	Possible UIP	Not UIP
Subpleural basal predominance	Subpleural basal predominance	Upper- or mid lung predominance
Reticular abnormalities	Reticular abnormalities	Peribronchial predominance
Honeycombing with or without traction bronchiectasis	No inconsistent findings	Severe ground glass opacities (ground glass pattern > reticulation)
No inconsistent findings		Profuse micronodules
		Cysts
		Mosaic-attenuation pattern/airtrapping
		Consolidation

From ATS/ERS/JRS/ALAT IPF guidelines 2011 (14)

Table 2
Histopathological criteria for UIP pattern in IPF

UIP pattern	Probable UIP	Possible UIP	Not UIP (any criteria)
Marked fibrosis/architectural distortion with or without honeycombing, predominantly subpleural/paraseptal distribution	Marked fibrosis/architectural distortion with or without honeycombing,	Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without inflammation	Hyaline membranes
Patchy involvement of lung parenchyma by fibrosis	Absence of either patchy involvement or fibroblast foci, but not both	Absence of other criteria for UIP	Organising pneumonia
Presence of fibroblast foci	Absence of features suggesting alternative diagnosis	Absence of features against a diagnosis	Granulomas
Absence of features suggesting alternative diagnosis	OR Honeycomb changes only		Marked interstitial inflammatory cell infiltrate away from honeycombing
			Predominant airway centred changes
			Other features suggesting alternative diagnosis

From ATS/ERS/JRS/ALAT IPF guidelines 2011 (14)

included as a distinct disease category in the recently published update of the International Multidisciplinary Classification of the

IIPs (3), but still, data on prevalence, disease characteristics and prognosis of unclassifiable ILD patients are sparse. Only one recently published study (35) has focused specifically on patients with unclassifiable lung disease, and found a prevalence of 10% of unclassifiable ILD in a large cohort of ILD patients. Other studies of incidence and prevalence of ILDs (12, 36) have reported that 9.2 to 15.4% of incident ILD cases remained unclassified.

Table 3
Specific combinations of HRCT and histopathology in IPF are required for the diagnosis. A definite UIP pattern gives the diagnosis IPF regardless of the histopathological findings, and biopsy is not required in this situation

		Histopathology				
		UIP	**Probable UIP**	**Possible UIP**	**Unclassifiable fibrosis**	**Not UIP**
	UIP	IPF	IPF	IPF	IPF	Not IPF
HRCT	**Possible UIP**	IPF	IPF	Probable IPF	Probable IPF	Not IPF
	Not UIP	Possible IPF	Not IPF	Not IPF	Not IPF	Not IPF

From ATS/ERS/JRS/ALAT IPF guidelines 2011 (14)

Hunninghake et al. (37) conclude that in interstitial lung disease, a specific diagnosis might be difficult to obtain in approximately 15 to 20% of the cases, even with a surgical biopsy. Further studies addressing the disease patterns and prognostic factors in this large, heterogeneous patient group are needed, and will help to clarify better management strategies and prognostication. In the recent update of the guidelines for IIP (3), the Disease Behaviour Classification was introduced as a pragmatic tool for use in the management of patients with ILD. Based on the observed clinical behaviour, cases can be divided into five different categories, for each of which a treatment goal and a monitoring strategy has been proposed.

The five categories are:

1. Reversible and self-limited
2. Reversible with risk of progression
3. Stable with residual disease
4. Progressive and irreversible with potential for stabilisation
5. Progressive irreversible disease despite therapy.

Some IIPs, such as NSIP, can be associated with all five patterns of disease behaviour. The Disease Behaviour Classification is considered complementary to the IIP classification.

Assessment of prognosis in IPF

The possibility of accurate assessment of prognosis at disease presentation is valuable in most clinical situations and in all subtypes of ILDs. The majority of studies of prognostic factors in ILD have focused on IPF. While the overall prognosis in IPF is poor, the course of disease for the individual patient is variable, and some patients may have stable disease for years. Several different disease courses have been identified (14, 38) (Figure 2). The most frequent is slow but steady worsening of the disease (slow progression). Some patients remain stable, while others have an accelerated decline (rapid progression). A minority of patients

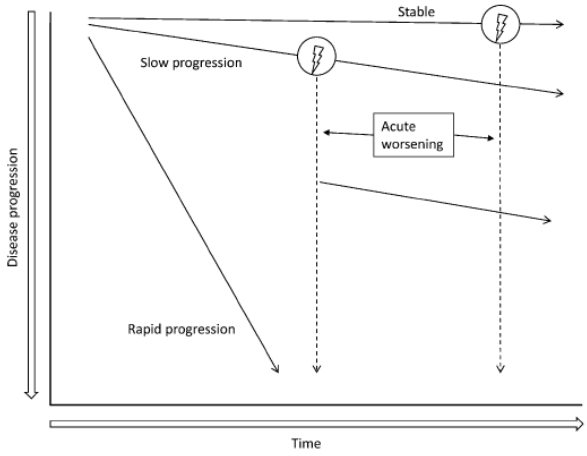


Figure 2
Different disease courses in IPF
From ATS/ERS/JRS/ALAT IPF guidelines 2011 (14)

Table 4
Individual predictors of outcome in IPF

Clinical	Age, gender, smoking status Comorbidity: Pulmonary hypertension, emphysema, gastro-oesophageal reflux
Physiological	Baseline factors: FVC, TLC, DLco Longitudinal factors: Decline in FVC and DLco 6MWT: Desaturation, distance walked, heart rate recovery
Radiological	HRCT: UIP pattern, degree of fibrosis, traction bronchiectasis
Pathological	UIP pattern, fibroblast foci

experience acute exacerbation of their disease, either from a secondary complication such as pulmonary infection, or for unrecognised reasons. These acute exacerbations are often fatal or may cause substantially worsening of the disease (39-43).
Several baseline factors are associated with increased risk of mortality in IPF. Age, gender, baseline level of dyspnoea based on MRC score, baseline level of forced vital capacity or diffusion capacity of carbon monoxide (DLco), desaturation during 6-minute walk test, extent of honeycombing and traction bronchiectasis on HRCT and presence of pulmonary hypertension are all factors known to impact on prognosis (14, 44-49)
Longitudinal factors predictive of increased mortality in IPF have also been demonstrated. A 15% decline in diffusion capacity or a 10%, or even 5 % decline in forced vital capacity (FVC) at 6 months are prognostic determinants of mortality (50-53). Increasing dyspnoea and worsening of fibrosis on HRCT are also prognostic determinants, but no uniform approach to quantification

exists. Certain biomarkers have emerged that may have implications for future diagnostics and management of IPF and other ILDs. These include epithelial or macrophage-related proteins such as surfactant protein A, KL-6, CCL18, MMP-7, ICAM-1 and anti-heat shock protein 70 (54-60). As yet, biomarkers are not part of daily clinical practice. The most commonly used individual predictors are shown in Table 4.
Clinicians tend mostly to rely on lung function parameters (DLco and FVC) to measure disease severity, but this approach is hampered by the wide range of normality (i.e. 80 – 120% of predicted) of all lung function variables.
Several physiological models based on combinations of the above-mentioned factors have been developed (61-65). They may be more accurate prognostically than single factors, but some may also be too complex for a broader application in clinical practice.
The first prognostic model, known as the Clinical-Radiologic-Physiologic scoring system (CRP) (61), was published in 2001 by King et al. and was developed using a cohort of 238 patients who were all diagnosed with IPF based on a lung biopsy. This model included age, smoking history, finger clubbing, the extent of profusion of interstitial opacities and evidence of pulmonary hypertension on the chest radiograph (criteria not stated), the percent predicted TLC, and the PaO2 during maximal exercise. Based on a score constructed from these parameters, survival curves were estimated with a clear separation according to CRP score.

The second prognostic model to be published was the composite physiology index (CPI), which was published in 2003 by Wells et al.(62). The index was derived by fitting pulmonary function tests against disease extent on CT in a regression model. This index was shown to correlate more strongly with disease extent on CT than the individual pulmonary function test. The better fit was ascribed to a correction of the confounding effect of emphysema by correcting for the contribution of emphysema to the lowering of DLco.
Another prognostic model developed for use in IPF was published in 2011 by du Bois et al.(64). The model combined age, respiratory hospitalisation, percent predicted FVC, and 24-week change in FVC. The model was developed in a cohort of patients with mild to moderate IPF who participated in two clinical trials on interferon-gamma, which showed no effect of interferon-gamma treatment on any of the end-points. A total of 1099 patients participated in the trials, and due to the lack of treatment effect, both placebo-treated and actively treated patients were included in the development of this prognostic model. Based on the scoring system, the risk of death within 1 year was calculated.

The study by Mura et al. published in 2012 (65) described the Risk Stratification score (ROSE), based on Medical Research Council dyspnoea score (MRCDS) (66), 6-minute walk test (6 MWD), and the CPI (62). Low risk was defined as MRCDS≤3 (MRCDS 3: On level ground, I have to stop for breath when walking at my own pace), 6MWT>72% and CPI≤41. Intermediate risk was defined as MRCDS>3, 6MWD≤72% or CPI>41. High risk was defined as MRCDS>3, 6MWD≤72% and CPI>41. The resulting ROSE index was able to predict 3-year survival with high specificity (100% in the derivation cohort (n=70) and 91% in the validation cohort (n=68)) of patients newly diagnosed with IPF. The sensitivity was 39% in the derivation cohort and 67% in the validation cohort; however one of the parameters, the MRCDS, was not available in the validation cohort.

In 2012, Ley et al. introduced the GAP index based on gender, age and physiology (FVC and DLco) (63) derived in a cohort of 228 IPF patients and validated in 330 patients. Based on a point-scoring system (GAP index), three stages (stages I, II, and III) could be identified with a 1-year mortality of 6%, 16% and 39%, respectively.
The GAP score has been extended to include other ILD subtypes under the name of the ILD-GAP score (67). It was applied to large patient subgroups with IPF, chronic hypersensitivity pneumonitis, a combined subgroup with idiopathic NSIP or connective tissue disease-associated ILD (CTD-ILD), and unclassifiable disease. The model could be applied across all ILD subtypes and provided disease-specific survival estimates when a disease subtype variable was added that accounted for better adjusted survival in CTD-associated ILD, chronic HP and idiopathic NSIP.
The ILD-GAP model shows comparable mortality distinctions based on disease severity in IPF and the other disease groups. The authors suggest that the differences in survival between IPF and the other disorders reflect later presentation in IPF, and therefore, the results underline the importance of achieving earlier diagnosis in IPF.
Formal CT scoring of disease extent predicts prognosis (68, 69), but is time consuming and requires considerable experience. Goh et al. (70) developed and validated a semi-quantitative CT scoring method in systemic sclerosis-associated ILD that, when combined in a staging system with FVC, was effective in predicting patients with more rapid disease progression and a poorer prognosis.
Recently, prognostic models have been suggested based on HRCT and pulmonary function tests in CTD-ILD, sarcoidosis and chronic hypersensitivity pneumonitis (71-73). The prediction models in IPF and other ILDs are listed in Table 5.

Table 5
Prediction models in ILD

Authors, year of publication	Journal	Name of prediction model	Disease	Number of patients in derivation cohort	Validated
King et al., 2001	AJRCCM	CRP	IPF	238	no
Wells et al., 2003	AJRCCM	CPI	IPF	212	yes
Goh et al., 2007	AJRCCM	-	Scleroderma	215	yes
Du Bois et al., 2011	AJRCCM	-	IPF	1099	no
Mura et al., 2012	ERJ	ROSE	IPF	70	no
Ley et al., 2012	Ann Int Med	GAP model	IPF	228	yes
Ryerson et al., 2013	Chest	ILD-GAP	ILD	1012	In IPF
Wells 2013	ATS/ERS	DBC	ILD	-	no
Walsh 2013	Thorax	-	CTD-associated fibrotic ILD	168	no

Unpublished work from the Interstitial Lung Disease Unit, Royal Brompton Hospital suggests that in idiopathic fibrosing lung dis-

ease (IPF and idiopathic non-specific interstitial pneumonia (NSIP)) patients with a disease extent of >50% or those in whom honeycombing makes up >25% of the interstitial abnormality fall into a poorer prognosis group, and a scoring system is under development that may help the identification of patients who will need palliative support and care (personal communication).

Comorbidities in IPF

Comorbid diseases such as lung cancer and cardiovascular disease may affect the prognosis of patients with IPF. However, the reported prevalence of comorbidity is variable; the impact of comorbidity on survival in IPF is not well characterised, and studies are few.

In a large cohort of American IPF patients identified from medical claims databases, 25% of the patients were diabetics and 25% had coronary artery disease (74). In a small, population-based cohort from Minnesota, USA, that included 47 patients with IPF (16), coronary artery disease was present in 45% of patients, diabetes in 17% and depression in 11%.

A higher prevalence of diabetes in IPF patients compared with the background population has previously been reported (75, 76), but to our knowledge, the survival implication of diabetes in IPF has not been addressed in the literature. Corticosteroids have been widely used in IPF, and may have been a reason for poor glycaemic control in many IPF patients. There is no evidence that corticosteroid therapy modifies the natural history of IPF, and at present, recommendations against its use are strong (14, 77). This change in treatment recommendations for IPF may in itself improve outcome in diabetic IPF patients, but the possible impact of diabetes on prognosis in IPF remains a focus for future research.

A British case-control study showed that ischaemic heart disease was four times more frequent in IPF patients than in age- and gender-matched controls (78), but the study did not assess survival implications in IPF. Cardiovascular disease was also investigated as one of several potential predictors of mortality in a prognostic model developed in a large IPF cohort from two clinical trials (64). Cardiovascular disease was present at baseline in 27% of the patients, and no significant difference in all-cause mortality was found based on the presence of cardiovascular disease. In COPD, cardiovascular disease is known to be an important prognostic factor (79, 80). However, Nathan et al. (81) showed that a subgroup of IPF patients who were transplant candidates had a higher prevalence of coronary artery disease than transplant candidates with COPD, and found that mortality was significantly higher among IPF patients.

IPF therapy

Corticosteroids were used as therapy for IPF until recently, and may have influenced some comorbid diseases such as diabetes and osteoporosis. Other immunosuppressants such as azathioprine and cyclophosphamide have also been abandoned as therapy for IPF. In 2005 the IFIGENIA trial (82) showed that NAC in addition to prednisolone and azathioprine was superior to prednisolone and azathioprine alone, after which triple therapy with prednisolone, azathioprine and N-acetylcystein (NAC) was a preferred treatment option in IPF. The study raised the possibility that NAC was providing the benefit, although it had not been tested against placebo. The recent Panther-IPF study (83) was initiated by the US National Heart, Lung and Blood Institute and was designed to test the widely used regimen prednisolone, azathioprine and NAC triple therapy vs. placebo and NAC alone vs. placebo in newly-diagnosed mild-to-moderate IPF. After a review and analysis of interim data, it appeared that participants treated with triple therapy had more mortality, more serious adverse events, and more drug discontinuations, without evidence of benefit. The NAC only and the placebo arms were continued, and the study is due to report in the near future.

The role of immunosuppressant therapy in IPF is still being discussed. The adverse outcomes in the Panther study cosegregated with the use of high-dose corticosteroid therapy in the first months, and some observers believe that the corticosteroid dosage might have been the critical determinant of the balance between possible benefit and major toxicity (84).

The only therapy for IPF licensed for use in Europe is the antifibrotic agent pirfenidone, which has been investigated in the Capacity trials, PIPF-004 and PIPF-006 (85). One of the identical studies, PIPF-004, showed a decrease in the decline in FVC (4.4% reduction in mean change in percent predicted FVC over 72 weeks), but the other, PIPF-006, did not meet the primary endpoint of change in FVC over 72 weeks. Many of the patients who all had mild to moderate IPF (FVC above 50% and DLco > 35%), remained stable during the study period, meaning that no drug would show any effect. This is illustrated in the PIPF-004 study, where only 30% of the patients lost more than 10% predicted FVC. Results from the pooled analysis of categorical FVC change showed that pirfenidone reduced the proportion of patients experiencing at least a 10% decline by 30% compared with placebo (85, 86). A Cochrane systematic review (87) has provided evidence based on a metaanalysis of available studies and has found a statistically significant treatment effect of pirfenidone on both pulmonary function and progression-free survival. Treatment with pirfenidone was seen to decrease the percentage of patients who experienced a significant decline in FVC by approximately 40%.

The results of two previous Japanese studies (88, 89) are debated for several reasons, but they are in accordance with PIPF-004 and have shown similar effect. Pirfenidone has not been approved in the United States, and the ASCEND trial, which will provide additional information of efficacy and safety of pirfenidone, is now being completed, and the results are expected this spring. A press release has reported results similar to those found in the Capacity trials (90)

In the last decade, the number of randomised controlled trials in IPF has increased immensely, but unfortunately, the majority of the trials have failed to meet their end-points. Interferon-gamma 1b (2, 91, 92), sildenafil (93), bosentan (94), imatinib (95), etanercept (96), warfarin (97), ambrisentan (98) and macitentan (99) are drugs that have been tried in double-blind, randomised, placebo-controlled trials in IPF with negative results. Co-trimoxazole, an antibiotic, failed to meet the primary end-point of effect on FVC when added to standard treatment in IPF, but was associated with improved quality of life and a significant reduction in all-cause mortality (100). Mycophenolate mofetil has been investigated in a very small patient group (n=10) (101); no safety issues occurred, but no beneficial effect was observed.

The tyrosine kinase inhibitor nintedanib that exerts inhibitory effects on at least three pro-fibrotic growth factor receptors, VEGF (vascular endothelial growth factor), PDGF (platelet derived endothelial growth factor) and fibroblast growth factor receptors, has been promising in a phase II-trial (102), and two phase III trials are ongoing.

Reliable, objective parameters to assess disease progression and treatment response are poorly defined. FVC is widely used and regarded as a clinically meaningful measure of IPF disease status. A categorical reduction of ≥10% in FVC has been identified as the

most reliable predictor of mortality and associated with a more than two-fold increase in the risk of death (51, 92, 103). The choice of primary end-points in clinical trials in IPF has been debated. FVC has been used as a surrogate measure for outcome, because it is easily measured and allows clinical trials with a practically feasible number of patients. It is argued by some IPF investigators that the optimal and most relevant end-point is mortality, but it requires large cohorts of patients and long-term studies (104). The stand point of mortality as the best end-point has been taken by one group (105), whereas the other side argue that FVC is a valid and robust measure that fulfils the criteria for an ideal clinical end-point (1, 106-108), since mortality as an end-point requires large cohorts of patients and long observation times, which will make the conduction of clinical studies even more expensive and complicated. Another argument used, is the fact that mortality data are not required for drug registration, whether in other rare respiratory diseases such as pulmonary arterial hypertension and cystic fibrosis or in common respiratory diseases such as lung cancer and chronic obstructive pulmonary disease. In lung cancer, progression-free survival is usually the preferred end-point, and has been suggested as a potential end-point for IPF as well (109, 110). FVC changes have been linked to mortality in several studies (50, 51, 53 92, 103, 111) and have been the preferred end-point in clinical trials. The variable rate of progression makes it difficult to demonstrate efficacy of drugs that slow the progression but do not improve pulmonary function, and there is a lack of molecular biomarkers that indicate disease activity and predict disease course (54, 56, 111)

Major advances in the understanding and management of IPF have been made, starting with the consensus about the classification of the IIPs and continuing with the increasing number of clinical trials. Improved understanding of disease mechanisms has led to major changes in management, e.g. the immunosuppressive regimens being deserted, and the first specific anti-fibrotic therapy becoming available. The focus on earlier diagnosis of IPF has increased, which has probably also increased the attention diverted to other types of ILD. Furthermore, the emergence of a specific therapy may increase awareness of IPF among physicians managing patients with pulmonary diseases. The potential effect of anti-fibrotic therapy in other fibrotic lung diseases is also being investigated, e.g. pirfenidone in systemic sclerosis-related ILD in a phase 2 study currently recruiting participants (112). It is to be hoped that these efforts will lead to novel therapeutic interventions that slow disease progression and improve outcome for patients with interstitial lung diseases.

Hypotheses and aims

The hypotheses of the present PhD thesis were as follows:

1. IPF is the most frequently occurring of the ILDs in the Danish population and has a severe prognosis.

2. Comorbidities such as cardiovascular disease and diabetes are frequent among IPF patients and comorbidity impact negatively on survival.

3. A simple algorithm based on HRCT images and forced vital capacity (FVC) can be used as a predictor of outcome in idiopathic fibrotic interstitial pneumonias (IPF and NSIP)

4. A considerable percentage of ILD patients are unclassifiable even after a thorough diagnostic process. These patients can be characterised based on clinical and radiological findings and in different categories with significant differences in prognosis.

The aims of the project were as follows:

1. To estimate the overall incidence of ILDs in Central Denmark and to characterise the distribution of ILD subtypes based on re-evaluated diagnoses.

2. To characterise the frequency of important comorbid conditions in patients diagnosed with IPF and to evaluate how these comorbidities influence survival.

3. To validate a simple HRCT scoring system as a predictor of outcome in IPF and NSIP.

4. To study ILD patients with unclassifiable diseases and characterise disease patterns, diagnostic processes and factors associated with survival

Methods

The ILD Registry of Central Denmark at Aarhus University Hospital

The ILD registry was established as the foundation of this PhD project, and it was developed in collaboration with radiologists and pathologists from our institution, as well as epidemiologists and a socio-economist from Actelion Pharmaceuticals, who were valuable collaborators in the development. The case report form used for the data entry was developed by the clinical research organisation Factum in Germany.

The registry includes all patients diagnosed with ILD at Aarhus University Hospital and a first visit to the Department of Respiratory Diseases between 1 April 2003 and 31 March 2009. Patients were identified retrospectively from the ICD-10 diagnostic codes in the hospital's computer system (DJ 84 and DJ67, the only codes used at the department at the time). They were cross-checked with lists of patients who had undergone HRCT scans at the Department of Radiology at Aarhus University Hospital to ensure that the patient cohort was as complete as possible.

When a review of the medical records and HRCT scans had confirmed that the diagnosis of ILD was correct, and the date of first visit to the department was within the appropriate time frame, the data were entered into the CRF. The data entry was performed by the PhD student with assistance from a physician colleague who had clinical experience from the department's ILD unit. Data were retrieved from the medical records.

The ILD registry contains information on referral, former or current occupation, social status and comorbidities present at the time of referral or developed during the course of follow-up. Clinical status at referral and at each follow-up visit was registered as well as the results of all examinations performed as part of the diagnostic work up or during the course of follow up: pulmonary function tests, 6 MWT, blood tests, HRCT scans, BAL, TBB, lung biopsy, echocardiography and right heart catheterisation (RHC). Treatment for ILD and for comorbid conditions was also registered.

Patients were retrospectively followed from the time of first visit on suspicion of an ILD to the last visit to the centre, death, transplantation, or discharge from follow-up.
Time of death was registered based on information from the hospital's data system, and cause of death was registered based on the medical records. For patients who were discharged from follow-up, the time and reason for discharge or referral to other hospital were registered. Patients who remained under follow-up were followed up to 15 November 2009, which was chosen as the end of study.
All available HRCT scans were re-evaluated by three thoracic radiologists specialised in ILD, and all final diagnoses were re-evaluated according to the 2002 ATS/ERS Multidisciplinary International Consensus Classification of the IIPs (1) and the 2011 ATS/ERS/JRS/ALAT criteria for IPF (14) by two expert pulmonologists specialised in ILD (Supervisors Ole Hilberg and Elisabeth Bendstrup).

Data collection and assessments
The 2011 ATS/ERS/JRS/ALAT guidelines for diagnosis and management of IPF emphasise a multidisciplinary approach involving pulmonologists, radiologists and pathologists to establish a confident diagnosis. With regards to these 2011 criteria, IPF diagnosis requires exclusion of known causes of ILD, as well as the presence of specific combinations of a radiological and a histopathological pattern of UIP.
In the process of re-evaluation, the terms end-stage fibrosis/extensive fibrotic disease or unclassifiable ILD were used in cases where the diagnostic examinations and re-evaluation failed to meet the 2011 criteria for IPF or any other specified subtype of ILD. End-stage fibrosis/extensive fibrotic disease were used in the presence of severe fibrosis and/or honeycombing on HRCT that did not satisfy the HRCT criteria for a diagnosis of IPF. Furthermore, BAL differential counts, VATS (video-assisted thoracoscopic surgery), which was performed in 19% of these patients, or other findings did not point towards an alternative diagnosis. In other indeterminate cases, the term "unclassifiable ILD" was used. The primary disease evaluation using 2001 ATS/ERS criteria (33) was also recorded in the study database.
Causes of death were registered based on the information from medical records. The follow-up with respect to mortality was based on information from the hospital's currently updated patient administration system and was complete.
The study was approved by The Danish National Board of Health and the Danish Data Protection Agency. In accordance with Danish legislation, informed consent was not required.

Epidemiology study
The incidence estimates are based on the patients (n=344) referred from Aarhus Hospital's main geographic coverage, which is the Central Jutland region with 1.2 million inhabitants (113). Patients referred from other areas (n=87) were not included in the incidence calculations.
Outcome in IPF was assessed using the GAP model (63) that incorporates gender, age, diffusion capacity of carbon monoxide (DLco) and forced vital capacity (FVC), and allows a separation of patients into disease categories with significantly different prognosis.
Comorbidity study
All comorbidities were registered based on information from medical records. A diagnosis of diabetes was registered if the patient received antidiabetic therapy. Osteoporosis was registered in the presence of a DXA scan with T-score below -2.5 or a history of fragility fracture. We defined cardiovascular disease as one or more of the following: ischaemic heart disease, cerebral infarction or peripheral arterial disease. Diagnoses were based on information from patients' medical records, Pulmonary hypertension (PH) was diagnosed in the presence of a tricuspid pressure regurgitation gradient ≥ 40 mmHg, a tricuspid annular plane systolic excursion < 1.8 cm or right ventricular dilatation on echocardiography and/or mean pulmonary artery pressure ≥ 25 mmHg on RHC. Mild PH was defined as tricuspid regurgitation gradient ≤ 60 mmHg or mean pulmonary artery pressure ≤ 35 mmHg, and severe PH was defined as tricuspid regurgitation gradient > 60 mmHg or mean pulmonary artery pressure > 35 mmHg. PH was considered present at the time of diagnosis when the diagnosis was made within 90 days of the first visit to the department. When PH was diagnosed later than 90 days after first visit to the department, it was considered as diagnosed during follow-up. Echocardiography was used as a screening tool for PH prior to referral for RHC. Treatment for comorbid conditions was registered when the patient received the treatment at any time during the study period. Severity of IPF was assessed on the basis of the GAP prognostic model (63).

HRCT scoring system for idiopathic fibrotic interstitial lung disease (IPF and NSIP)
All patients with an available HRCT scan performed as part of the initial evaluation were included in the validation of a scoring system developed at The Interstitial Lung Disease Unit at Royal Brompton Hospital, London, UK. Those patients who had been diagnosed with idiopathic fibrotic interstitial lung disease (IPF and NSIP) at re-evaluation constituted the study group.
HRCT scans (inspiratory phase) with sections of 1 mm in thickness or less were used. Disease extent was assessed by evaluation of HRCT images at five levels: 1. origin of great vessels; 2. main carina; 3. pulmonary venous confluence; 4. halfway between the third and fifth section; 5. immediately above the right diaphragm. Only abnormalities associated with interstitial lung disease were scored:

a. Ground glass attenuation
b. Reticular change
c. Honeycombing

Non-interstitial change (i.e. emphysema, lung nodules etc.) was not regarded as contributing to disease extent. In the majority of cases, the scoring process took no more than 1 minute per scan. All scans were scored independently by two senior pulmonologists with special interest in ILD and by two trainee physicians with less than 6 months' experience in general respiratory medicine and limited experience in ILD.
Before the study was initiated, each physician received instruction confined to the scoring of ten patients' HRCT scans. These ten patients were referred after April 1 2009, and were therefore not included in the study population. In all cases, clinicians were blinded to the clinical diagnosis.

Disease extent was classified as follows:

a. Definitely less than 20%

b. Definitely greater than 20% and less than 50%
c. Indeterminate (i.e. not possible to discriminate between less than or greater than 20% disease extent)
d. Greater than or equal to 50%

Extent of honeycomb changes was classified as:

a. Less than 25%
b. Greater than 25%

In patients with an indeterminate disease extent on HRCT (close to 20% disease involvement), forced vital capacity (FVC) values were used to stage disease as limited or extensive. FVC above 70% was regarded as limited disease and FVC less than 70% was regarded as extensive disease.

Unclassifiable ILD study

In the process of re-evaluation, the terms end-stage fibrosis/extensive fibrotic disease or unclassifiable ILD were used as previously described in cases in which HRCT-scans, BAL differential counts, video-assisted thoracic surgery (VATS) if available, or clinical findings suggested no alternative diagnosis. Registry patients diagnosed with IPF or non-IPF, defined as HP, CTD-ILD or NSIP, were used as controls.

In the assessment of pulmonary function data, we used an increase or decrease of 10% in FVC and/or 15% in DLco as indicators of a significant change in pulmonary function.

BAL cytology was interpreted in accordance with current guidelines (114).

The composite physiology index (CPI) (62) was calculated, and its use as a predictor of mortality in unclassifiable ILD was assessed. We also assessed the prognosis of unclassifiable ILD using the GAP model (63), which has been developed for use in IPF and the ILD-GAP model (67) developed for use in a range of interstitial lung diseases. All patients who had a pulmonary function test performed within 6 months after the first visit were scored according to the GAP and ILD-GAP prognostic models.

Based on assessment of the initial diagnostic examinations and short-term follow-up (<6 months after first visit), we characterised the disease pattern for each patient as self-limited inflammation, major inflammation with risk of progression to fibrosis, stable fibrosis, progressive fibrosis with potential for stabilisation, or inexorably progressive fibrosis, as described by Wells (115) and included in the 2013 update of the International Multidisciplinary classification of the IIPs (3).

Statistical analysis:

Data are presented as mean ± SD if continuous or as frequencies if categorical. Unless otherwise specified, the number of patients with available data (n) was used in the calculation of summary statistics. Comparison was performed using t-test, Wilcoxon rank sum or chi2 test as appropriate.

Survival was analysed with time since first visit as time-scale and estimated by the Kaplan-Meier method. Differences in survival curves were evaluated using the log-rank test.

Differences in hazard ratio (HR) for death were evaluated using Cox proportional hazards analysis. A Cox proportional hazards regression model was used to identify statistically significant variables predicting survival status. The proportional hazards assumption was checked using log-log plots. Unadjusted and adjusted Cox proportional hazards regression analyses were performed, and hazard ratios are presented along with 95% confidence intervals. Adjustment was performed using age and FVC as continuous variables and other variables as categorical. In the comparison of the ILD-GAP model and the DBC model, disease subgroups (1-4 in each model) were used as continuous variable. This was done to assess the contribution of each model since the cohort was of limited size and the number of events (death) did not allow the disease subgroups to enter into the combined model as categorical variables. In the IPF comorbidity study, comorbidities diagnosed during follow-up were assessed as time dependent covariates. A logistic regression model was used for assessment of the use of antidepressants.

For the evaluation of the HRCT scoring system, inter-observer agreement was assessed by Kappa-statistics; Kappa > 0.75 was regarded as excellent agreement, kappa > 0.40 fair to good agreement, and kappa < 0.40 moderate to poor agreement (116). Outcome was examined using Cox proportional hazard analysis. The statistical significance level was set at $p < 0.05$.

All analyses were performed using STATA statistical software (version 12.1; StataCorp, College Station, Texas, USA).

Results

Epidemiology

A total of 431 incident ILD patients were included in the study, and the mean observational period was 25 months (SD=19). The mean duration of symptoms before first visit to the referral centre was 2.4 years (SD=3.1), and the mean time from the first visit until diagnosis was 3.6 months (SD=5.3).

The observed incidence rate of ILD was 4.1 per 100,000 central Jutland inhabitants/year. Incidence increased from 3.8 to 6.6 per 100,000/year during the 6-year observation period (2003-2009). The estimated 2009 incidence of 6.6 per 100,000 inhabitants/year in central Jutland corresponds to 368 new cases/year in Denmark (5,580,000 inhabitants).

A total of 186 patients (43%) were diagnosed with idiopathic ILDs. IPF was the most common diagnosis (n=121/431, 28%).

In patients with IPF, the mean duration of symptoms before first visit to the referral centre was 3.5 years (SD=3.4), and the average time from the first visit until diagnosis was 3.0 months (SD=5.4). IPF incidence was 1.3 per 100,000/year based on the findings in this cohort. Two thirds of the IPF patients (81/121) were referred from pulmonologists at 12 different regional hospitals and one third (40/121) were referred from GPs and non-pulmonary hospital departments in the geographical area served by Aarhus University Hospital. There was no statistically significant difference between the two groups in terms of age, gender, pulmonary function and survival (age p=0.14, gender p=0.42, DLco p=0.76, FVC p=0.26, survival p=0.71).

The estimated incidence of non-specific interstitial pneumonia (NSIP) was 3.0 per million/year, and the incidence of desquamative interstitial pneumonia (DIP) was 2.5 per million/year. Demographics and diagnoses are presented in Table 6.

Table 6
Patient characteristics at time of inclusion

Diagnosis	n (%)	Gender %male (m:f)	Mean age at first visit (SD)	Smoking %, current or previous	Biopsy (%)	BAL (%)	Mean FVC % (SD)	Mean DLco % (SD)
All patients	431 (100)	55 (236:195)	61.0 (14.1)	68	173 (40)	306 (71)	71.3 (22.2)	48.5 (19.0)
Idiopathic pulmonary fibrosis	121 (28)	77 (93:28)	67.4 (8.4)	81	52 (43)	93 (77)	72.0 (20.7)	42.3 (16.4)
Unclassifiable ILD	62 (14)	45 (29:33)	59.3 (14.5)	73	21 (34)	38 (61)	73.7 (22.8)	55.8 (21.4)
Connective tissue disease-related ILD*	54 (13)	41 (22:32)	58.4 (11.9)	59	13 (24)	38 (70)	76.5 (24.5)	51.1 (15.1)
End-stage fibrosis	43 (11)	63 (27:16)	71.5 (8.0)	70	8 (19)	28 (65)	67.8 (20.7)	46.2 (23.5)
Hypersensitivity pneumonitis	32 (7)	63 (20:12)	48.6 (14.6)	34	15 (47)	29 (94)	68.4 (18.7)	51.1 (17.1)
Non-specific interstitial pneumonia	30 (7)	47 (14:16)	53.8 (16.0)	60	26 (87)	26 (87)	60.7 (22.5)	45.6 (14.4)
Desquamative interstitial pneumonia	20 (5)	55 (11:9)	45.6 (13.4)	80	15 (75)	13 (65)	70.1 (19.8)	58.0 (21.9)
Drug-induced ILD**	20 (5)	50 (10:10)	68.0 (11.9)	70	1 (5)	8 (40)	64.2 (25.5)	44.5 (19.5)
Cryptogenic organising pneumonia	10 (3)	50 (5:5)	65.7 (14.1)	60	5 (50)	6 (60)	77.6 (25.6)	57.6 (16.9)
Histiocytosis	8 (2)	38 (3:5)	48.9 (17.4)	100	4 (50)	6 (75)	84.1 (17.5)	44.9 (18.9)
Lymphangio-leio-myomatosis	4 (1)	0 (0:4)	57.4 (14.5)	25	0 (0)	0 (0)	74.5 (10.9)	39.0 (18.9)
Eosinophilic pneumonia	4 (1)	0 (0:4)	55.1 (5.5)	50	1 (25)	3 (75)	68.3 (15.8)	37 (8.5)
Respiratory bronchiolitis ILD	2 (0.5)	100 (2:0)	43.0 (-)	100	0 (0)	1 (50)	97.5 (-)	99.0 (-)
Lymphocytic interstitial pneumonia	2 (0.5)	100 (2:0)	80.0 (-)	100	0 (0)	2 (100)	88.0 (-)	49.0 (-)

Bronchoalveolar lavage (BAL)
Seventy-one percent of the patients (n=306) had a bronchoscopy with BAL as part of their baseline examination. In 169 of these cases, BAL cytological analysis, differential count and flow cytometry results were available. A specific differential cell count was made a standard part of the BAL evaluation in 2007. In specimens analysed before 2007, the cytological analysis was descriptive and contained no specific cell counts. Positive BAL culture was found in 14% (43/306). Streptococcus pneumoniae (n=15) and Haemophilus influenzae (n=14) were the predominant pathogens.
In IPF, a BAL differential count was available in 52 patients. Mean lymphocyte count was 5%, mean neutrophilic count was 11% and mean eosinophilic count was 7%. Mean lymphocyte counts were 15% in NSIP and 52% in HP. Transbronchial biopsy (TBB) was performed in 25% of the patients, and contributed positively to the diagnosis in four cases of hypersensitivity pneumonitis.

Video-Assisted Thoracic Surgery (VATS)
VATS was performed in 40% (173/431) of the patients in the cohort. The highest biopsy rates were seen in NSIP (87%) and DIP (75%). In IPF, 43% (52/121) were biopsied.
The percentage of biopsy-confirmed IPF-diagnoses declined markedly during the years 2003 to 2009, concomitantly with the implementation of the ATS/ERS 2001 recommendations, from more than 90% of patients in 2003 to less than 20% in 2009.
Reasons for refraining from VATS were recorded in all 268 non-biopsied patients. In half of them (n=136), the overall risk of the biopsy procedure was considered too high. The 30-day mortality after VATS was 1% (n=2) and the 60-day mortality was 3% (n=5); Two deaths occurred within the first 30 days: one sudden and unexpected death after 2 days and one death from respiratory insufficiency after 25 days. The three deaths seen in the following 30 days occurred due to acute exacerbation (n=1), persisting pneumothorax with subsequent infection (n=1), and to sepsis with possible fungal infection and cerebral embolism (n=1).

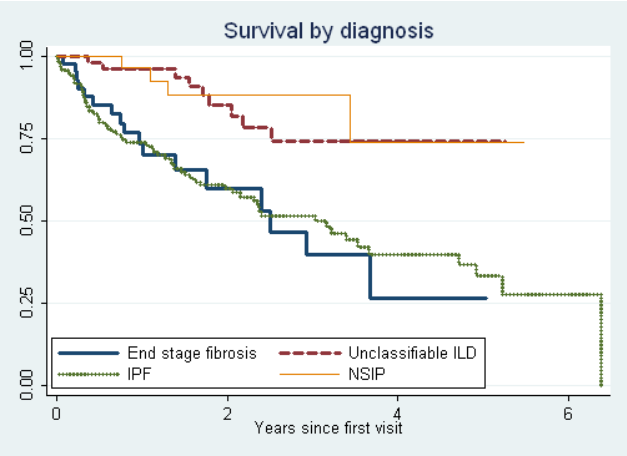


Figure 3
Survival curves for idiopathic pulmonary fibrosis (n=121), end stage fibrosis/extensive fibrotic disease (n=43)
Non-specific interstitial pneumonia (n=30) and unclassifiable ILD (n=62).

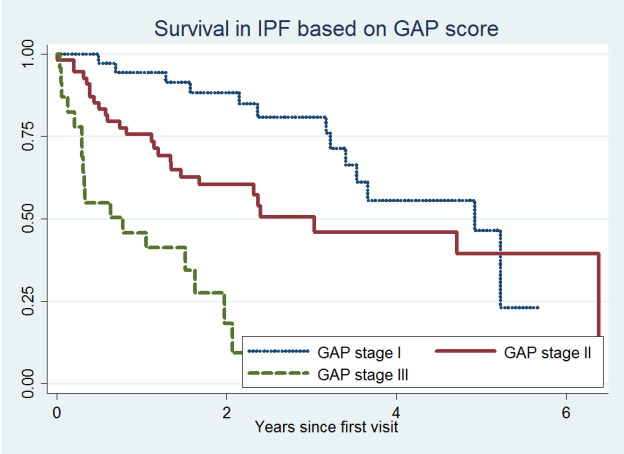


Figure 4
Survival in IPF based on the GAP model.
GAP stage I n=37, GAP stage II n=55, GAP stage III n=23.

Survival in ILD
There were 115 deaths during the observation period. The majority (n=82, 71%) were respiratory deaths, and IPF accounted for 53% (n=61) of all deaths in the cohort.
Mortality was markedly higher for IPF and end-stage fibrosis than for any other diagnosis, and the survival difference between the two groups was not statistically significant (p=0.9). Median survival in IPF was 3 years (range 1 day to 6.4 years) and in end-stage fibrosis 2.5 years (Range 30 days to 3.7 years) (Figure 3). Survival curves in NSIP and unclassifiable ILD appeared statistically similar (p=0.7). Survival at 5 years was 73.6 % in NSIP and 74.3% in unclassifiable ILD.
When IPF patients were stratified into three groups based on gender, age, FVC and DLco according to the GAP model, a highly statistically significant survival difference was found ($p < 0.0001$). One-year survival in GAP stage I was 95% and in GAP stage III 46%. Five-year survival was 46% in GAP stage I and 9% in GAP stage III. The results are shown in Figure 4.

Diagnostic criteria in IPF
Comparison of 2001 ATS/ERS criteria and 2011 ATS/ERS /JRS/ALAT criteria
Following a systematic re-evaluation based on the 2011 criteria, 121 patients were diagnosed with IPF. In 82 of these patients, the re-evaluation confirmed the primary diagnosis based on the medical record. The re-evaluation identified 39 additional patients who met the criteria for IPF. Prior to re-evaluation, the primary diagnoses were unspecific fibrosis (n=35), fibrotic NSIP (n=4) or chronic hypersensitivity pneumonitis (n=1). Other causes of ILD were excluded based on medical history and clinical examination. Serological testing was available in 60% of the patients: primarily antinuclear antibodies (ANA), immunoglobulin M rheumatoid factor (IgM-RF) and antineutrophil cytoplasmic antibodies (ANCA). All patients met the major and minor criteria for IPF when diagnoses were reassessed based on the 2001 ATS/ERS criteria (Table 7). No patients diagnosed as having IPF developed features of connective tissue disease with longitudinal follow-up. Median survival was the same (p=0.44) in patients who were

diagnosed with IPF primarily (n=82) and in patients who were diagnosed at reassessment (n=39).

Table 7
IPF subgroup. Diagnosis based on 2001 criteria

Major criteria	Total n=121	Biopsy n=52	No biopsy n=69
Exposures excluded	121 (100%)	52 (100%)	69 (100%)
Abnormal PFT	121 (100%)	52 (100%)	69 (100%)
HRCT reticulation	121 (100%)	52 (100%)	69 (100%)
Minor criteria			
Age > 50	118 (97%)	49/52 (94%) Age < 50: biopsy: 3/3	69/69 (100%)
Gradual onset of symptoms	121 (100%)	52/52 (100%)	69/69 (100%)
Symptoms > 3 months	121 (100%)	52/52 (100%)	69/69 (100%)
Crackles	97 (80%)	41/52 (79%)	56/69 (81%)
Age > 50	118 (97%)	49/52 (94%) Age < 50: biopsy: 3/3	69/69 (100%)

All 121 patients underwent an HRCT scan. In 60 cases (50%), HRCT showed a definite UIP pattern according to 2011 criteria: presence of subpleural, basal predominance, reticular abnormality, honeycombing with or without traction bronchiectasis, and no inconsistent findings.
Of the 60 patients with a definite UIP pattern on HRCT, 14 were biopsied. All biopsies showed UIP patterns consistent with the IPF diagnosis, (8 definite, 5 probable and 1 possible UIP).
Sixty-one patients had possible UIP patterns on HRCT, i.e. subpleural, basal predominance, reticular abnormality and no inconsistent findings, but absence of honeycombing.
Of the 61 patients with possible UIP on HRCT, 38 had a biopsy: 30 had a definite UIP pattern on histopathology, 7 had probable UIP and 1 patient had a possible UIP pattern. The remaining 23 patients with a possible UIP pattern on HRCT, had no biopsy, but based on the clinical course, IPF was the likely diagnosis (Table 8).

Comorbidity in IPF
A total of 121 IPF patients were included. IPF constituted 28% of the 2003-2009 ILD cohort, and was the most frequent diagnosis. Video-assisted thoracoscopic biopsy was performed in 43% of the IPF patients. Mean follow-up time was 23.6 months (SD=19.2). One-year survival was 73% and 5 year survival was 34%. Smoking was common, with 81% of the cohort being current or previous smokers, and the average number of pack years was 29. Smoking was not associated with poorer survival (HR p=0.19). Demographics and clinical characteristics are shown in Table 9.
In the cohort of 121 patients, 61 deaths occurred during the study period. Forty-one patients were still under follow-up at our institution at the end of the study period, while 15 patients had been

Table 8
2011 diagnostic criteria for IPF.

		Histopathology				
		Definite UIP	Probable UIP	Possible UIP	Non-classifiable fibrosis	No biopsy
HRCT	UIP 60	IPF 8	IPF 5	IPF 1	IPF 0	IPF 46
	Possible UIP 61	IPF 30	IPF 7	Probable IPF 1	Probable IPF 0	Probable IPF 23
	Not UIP	Possible IPF 0	Not IPF 0	Not IPF 0	Not IPF 0	Not IPF 0

Table 9
Demographics and clinical characteristics in the Danish IPF cohort

N	121
Male:female	93:28
% male	77
Age (SD)	67.4 (8.4)
Smoking % (current or previous)	81
Number of pack years	29
Clinical-radiological diagnosis %	57
Histological diagnosis %	43
FVC % predicted (SD)	72.0 (20.7)

discharged for further follow-up at their local hospitals. Four patients underwent a lung transplant.
The most frequent comorbidities among IPF patients in this cohort were arterial hypertension (15%) and ischaemic heart disease (13%). Cardiovascular disease was present in 24 patients (22%) at the time of inclusion and was diagnosed during follow-up in another nine patients (7%). Diabetes was present in nine patients (11%) at the time of inclusion and developed in ten patients (8%) during follow-up; all of these patients had received corticosteroid therapy. Osteoporosis was present in nine patients (7%) at the time of inclusion, and was diagnosed in ten additional patients (8%) during follow-up. Eight of these patients received steroid therapy during follow-up.
Eight patients had a diagnosis of depression and received antidepressant therapy at the time of IPF diagnosis, but a total of 25 patients (21%) received medical treatment for depression during the course of the disease, either selective serotonin re-uptake

inhibitors or tricyclic antidepressants. No difference in the frequency of antidepressant therapy was observed in patients with mild, moderate or severe IPF; the severity assessment was based on the GAP staging system (63).
Lung cancer was diagnosed in seven patients (6%). Follow-up proceeded until November 2009, with a mean observational period of 25 months. The follow-up time was 197 person-years, equivalent to an incidence rate of 3.6% /year. The incidence of lung cancer in the general Danish population was 83/100,000/year for men (0.083%/year) and 64/100,000/year for women (0.064%/year) in 2010 (117). A review of medical records of the patients alive at the end of follow-up, revealed no additional lung cancer cases up to January 2013. Comorbid diseases are summarised in Table 10.

Table 10
Comorbid diseases in the Danish IPF cohort

Comorbid diagnosis	At time of inclusion n (%)	Diagnosed during follow-up n (%)	Total n (%)
Cardiovascular disease*	24 (20%)	9 (7%)	33 (27%)
Arterial hypertension	18 (15%)	4 (3%)	22 (18%)
Ischaemic heart disease	16 (13%)	6 (5%)	22 (18%)
Pulmonary hypertension	12 (10%)	14 (11%)	26 (21%)
Diabetes	11 (9%)	10 (8%)	21 (17%)
Gastro-oesophageal reflux	10 (8%)	-	-
Depression	8 (7%)	17 (14%)	25 (21%)
Osteoporosis	8 (7%)	10 (8%)	18 (15%)
Cerebral infarction	8 (7%)	3 (2%)	11 (9%)
Atrial fibrillation	5 (4%)	6 (5%)	11 (9%)
Lung cancer	0	7 (6%)	7 (6%)
Other cancers**	0	4 (3%)	4 (3%)

***Ischaemic heart disease, cerebral infarction, peripheral arteriosclerosis**
Some patients had more than one diagnosis
**** Bladder, rectum, prostate (2)**

The presence of diabetes at the time of IPF diagnosis meant a statistically significant decrease in survival (Figure 5). The difference persisted after adjustment for age, gender and FVC (HR 2.47, 95%CI 1.04-5.88, p=0.041). Seven out of nine deaths in diabetic IPF patients were fibrosis-related, one was cancer-related and one was of unknown cause. The percentage of fibrosis-related deaths was the same among diabetics and non-diabetics. We found no survival difference based on the presence of cardiovascular disease prior to IPF diagnosis, p= 0.17 (crude) and p=0.27 (adjusted for age, gender and FVC) (Table 11), but cardiovascular disease developed during the follow-up period significantly increased mortality (HR 4.7, 95% CI 2.0; 11.1, p<0.001)(Table 12). Diabetes diagnosed during follow up did not affect survival.

Table 11
Comorbidity at first hospital visit and its association to survival (adjusted for age, gender and FVC)

	n	HR	95% CI	p
Cardiovascular disease	24	1.5	0.73; 3.2	0.27
Diabetes	11	2.5	1.04; 5.9	0.041
Pulmonary hypertension	12	2.2	0.94; 5.2	0.068
Gastro-oesophageal reflux	10	1.6	0.60; 4.4	0.34
GER medication	10	1.0	0.58; 1.8	0.95
Anticoagulant treatment (Non-PH indication)	13	3.3	1.5; 7.2	0.002

Table 12
Comorbidity diagnosed during follow-up and its association to survival (adjusted for age, gender and FVC)

	n	Mean follow-up time to comorbid diagnosis Days (range)	HR	95% CI
Cardiovascular disease	9	516 (118; 986)	4.7	2.0; 11.1
Diabetes	10	597 (78; 1464)	1.1	0.33; 3,8
Pulmonary hypertension	14	620 (192; 1213)	2.2	0.82; 6.0

IPF therapy
The treatment options used for IPF in the years 2003-2009 are listed in Table 13. The treatment patterns changed from prednisolone alone and high-dose methylprednisolone courses to triple therapy after the results of the IFIGENIA trial (82)
Adjusted comparison of treated and untreated groups revealed no significant positive or negative influence on survival (data not shown).
Half of the patients (61/121) received medical therapy for gastro-oesophageal reflux, either because of symptomatic gastro-oesophageal reflux or prophylactically because of concomitant corticosteroid therapy. No difference in survival was seen between the treated and non-treated groups (p=0.74). Symptomatic gastro-oesophageal reflux did not impact on survival (p=0.34). Results are summarised in Table 10.

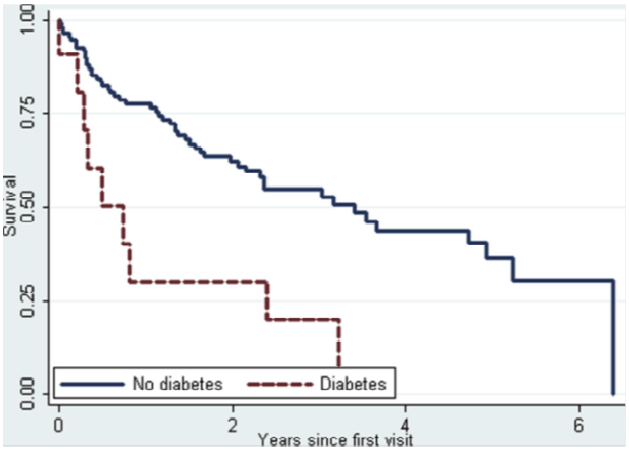


Figure 5
Survival in patients with diabetes at the time of IPF diagnosis compared with patients without diabetes

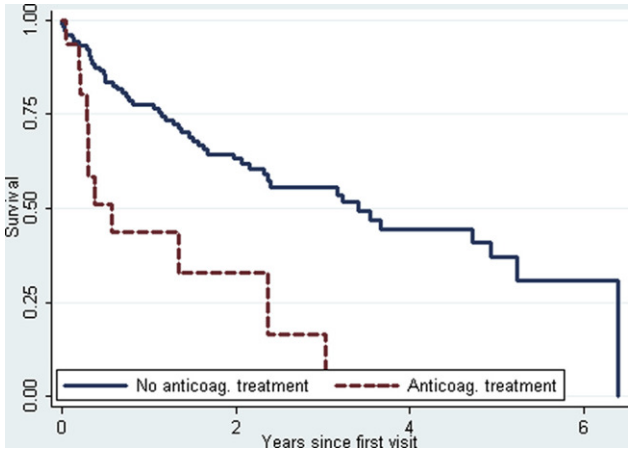


Figure 6
Survival in patients who received anticoagulant treatment on clinical indication compared with patients who did not

Table 13
Therapy given for IPF 2003-2009.

	n	%
Prednisolone	91	75
High-dose methylprednisolone courses	64	53
Both prednisolone and high-dose methylprednisolone courses	52	43
Azathioprine	75	62
N-acetylcysteine *	69	57
Triple therapy**	58	48
Cyclophosphamide	8	7
Oxygen therapy	67	55

*** N-acetylcysteine (NAC) was only used as part of combination therapy, none of the patients received NAC alone.**
****N-acetylcysteine, prednisolone, azathioprine**

Anticoagulant therapy
Sixteen patients received anticoagulant treatment with either warfarin (n=15) or phenprocoumon (n=1). Clinical indications for anticoagulant treatment were deep venous thrombosis (n=3), pulmonary embolism (n=4), artificial heart valve (n=2), atrial fibrillation (n=3), transitory cerebral ischaemia (n=1), and pulmonary hypertension (n=3). A pronounced statistically significant survival difference was seen in favour of the non-treated group (p<0.001) (Figure 6). The difference persisted after adjustment for age, gender and FVC (HR 3.3, 95% CI 1.55- 7.21, p=0.002).
The results were unchanged when we excluded three patients receiving anticoagulants due to pulmonary hypertension (adjusted HR 3.49, 95% CI 1.56-7.81, p=0.002).

Pulmonary hypertension
In 12 patients (10%), the lung disease was complicated by pulmonary hypertension at the time of IPF diagnosis (PH diagnosed within 3 months after first visit to the department). In these patients, unadjusted mortality was significantly higher than in patients without pulmonary hypertension (p=0.048), but the difference did not persist after adjustment for age, gender and FVC (HR 2.2, 95% CI 0.94-5.2, p=0.068). During follow up, 14 additional patients were diagnosed with PH, but the development of PH caused no difference in survival when compared to non-PH patients in the cohort. Twenty-three patients with PH (88%) required long-term oxygen treatment, and six patients (23%) received medical therapy for out-of-proportion pulmonary hypertension.

HRCT scoring system
The demographics of patients with idiopathic fibrotic ILDs are shown in Table 14.
Interobserver agreement was good for the experienced scorers. For the entire cohort, a kappa value of 0.60 was found for overall interstitial abnormalities at a disease threshold of 20%. For a threshold of 50% lung involvement, the kappa value was 0.70, and for a threshold of 25% of the diseased lung being honeycomb changes, the kappa value was 0.73. For trainee physicians, the interobserver agreement was poor (0.22 for overall disease and 0.30 for honeycomb changes). Results for the three subgroups are shown in Table 15.
The following analysis was based exclusively on the results of the experienced scorers, since the interobserver agreement in the trainee group was insufficient for further evaluation.
Idiopathic fibrotic lung disease was seen in 123 patients (IPF=97 and NSIP=26).
For a threshold of 50% disease involvement, a statistically significant survival difference was observed with p<0.0001 and p=0.027. For a threshold of 25% honeycomb changes, the survival difference was equally significant with p values < 0.01 for both scorers. Results are presented in Table 16 and Figure 7. No difference in survival was found between limited and extensive stages for a disease involvement threshold of 20% and use of the 70% FVC threshold in indeterminate cases (the scleroderma staging system

developed by Goh et al. (70)). In a separate analysis of the IPF or the NSIP groups, the separation of survival curves did not reach statistical significance.

Table 14
Demographics, all ILD diagnoses (n=352) and idiopathic fibrotic ILDs (n=123)

Variable	All ILD diagnoses	Fibrotic ILDs (IPF and NSIP)
Age, yr (SD)	61.2 (14.3)	65.1 (12.0)
Male:female (% males)	193:159 (55)	85:38 (69)
Smoking status (%)	never 33 current 17 previous 50	never 24 current 11 previous 65
Baseline FEV1, % predicted	70.3 (22.0)	71.1 (21.2)
Baseline FVC, % predicted	70.9 (22.7)	68.8 (22.4)
Baseline DLco, % predicted	48.3 (19.4)	41.9 (15.7)

Table 15
Interobserver agreement of HRCT score
Kappa >0.75: excellent agreement, kappa >0.40: fair to good agreement, kappa <0.40: moderate to poor agreement

Kappa-values	All ILD diagnoses		CTD-ILD		IPF-NSIP	
	Total involvement	Honeycombing	Total involvement	Honeycombing	Total involvement	Honeycombing
Experienced	0.60	0.73	0.54	0.78	0.50	0.65
Trainee	0.22	0.30	0.13	0.62	-0.01	0.21

Table 16
Survival estimates by HRCT disease involvement (IPF-NSIP subgroup)
Survival expressed as hazard ratios with 95% confidence intervals, in relation to the limited/extensive staging system, categorised using rapid semiquantitative HRCT scoring.

	Fibrotic ILDs	
	>50% disease involvement	>25% honeycomb changes
	HR (95% CI)	HR (95% CI)
Pulmonologist 1	4.8 (2.1-10.8) p<0.0001	2.1 (1.2-3.6) p=0.009
Pulmonologist 2	1.9 (1.08-3.43) p=0.027	2.2 (1.3-3.8) p=0.006

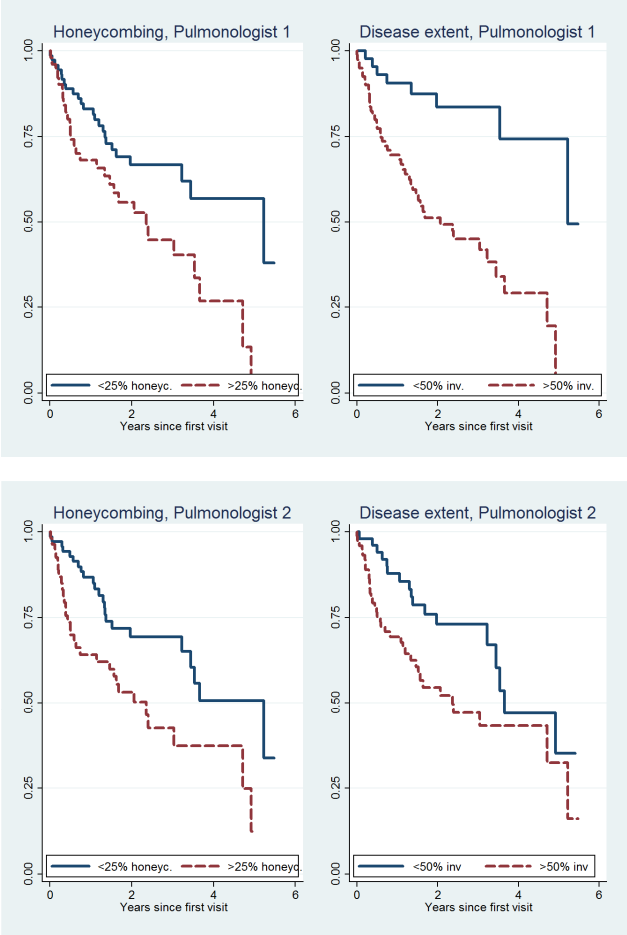


Figure 7
Survival curves based on the observed degrees of honeycombing and disease extent for the scores of pulmonologists 1 and 2.

Unclassifiable ILDs
Of the 431 patients in our ILD Registry, a total of 105 patients were diagnosed with unclassifiable ILD, either end-stage fibrosis (10%) or other unclassifiable ILD (14%), which made these non-specific diagnoses the second most common classification in our cohort; second only to idiopathic pulmonary fibrosis (IPF), which was diagnosed in 28% of the patients. Unclassifiable ILD was more common than CTD-ILD (13%), HP (7%) and NSIP (7%). The patients with unclassifiable ILD were significantly younger than patients with IPF, were less likely to be male, and had better DLco at the time of diagnosis. Compared to non-IPF controls, unclassifiable patients were older and more likely to be smokers, but pulmonary function levels were not significantly different. Demographic and clinical characteristics of unclassifiable ILD, IPF and non-IPF controls are shown in Table 17.

Table 17

Demographic and clinical characteristics at the time of first visit for IPF, non-IPF ILDs and unclassifiable ILD. Patient characteristics are compared between the combined population of unclassifiable ILD and IPF and non-IPF controls.

	All unclassifiable ILDs n=105	IPF n=121	Non-IPF* controls n=116	IPF vs. unclassifiable ILDs p-value	Non-IPF* vs. unclassifiable ILDs p-value
Male gender %	53	77	48	<0.001	0.075
Age (SD)	64.3 (13.6)	67.4 (8.4)	54.5 (14.3)	0.04	<0.0001
Ever smokers %	71	81	53	0.16	0.016
Number of pack years (SD)	29 (18)	30 (17)	26 (20)	0.88	0.28
FVC % predicted (SD)	71.3 (22.1)	72.0 (20.7)	70.0 (23.3)	0.83	0.68
DLco % predicted (SD)	53.0 (22.8)	42.3 (16.4)	50.0 (15.5)	0.0003	0.28
Auscultatory crackles %	51	80	53	<0.001	0.05

***Hypersensitivity pneumonitis, non-specific interstitial pneumonia and connective tissue disease-related interstitial lung disease.**

Patient characteristics

We divided the patients with unclassifiable ILD into two groups according to their HRCT characteristics and found that patients in the end-stage fibrosis group were older (mean age 71.7 vs. 53.9 years) and had lower DLco (mean DLco 46.2% vs. 55.8% predicted) than patients with other unclassifiable ILDs. Gender and FVC were evenly distributed between the two groups (Table 18).

In the end-stage group, the most common reason for a diagnosis remaining unclassifiable was missing histopathological assessment because the high risk of complications prevented biopsy. In the group of other unclassifiable ILDs, stable disease with relatively few symptoms or conflicting radiological and histopathological data were the most common reasons for patients remaining unclassifiable (Table 19). Mortality was significantly higher among the patients in whom the risk of performing a biopsy was considered unacceptably high (HR 3.7, 95% CI 1.37-10.2).

Radiological and histopathological findings

In the end-stage group, the most frequent radiological differential diagnoses included NSIP, possible UIP and chronic HP. In the group of patients with other unclassifiable ILDs, the most frequent radiological differential diagnoses were NSIP, subacute HP and desquamative interstitial pneumonia (DIP) (Table 20).

A bronchoscopy with bronchoalveolar lavage (BAL) was performed in 26 patients with end-stage fibrosis (61%) and in 40 patients with other unclassifiable ILDs (65%). A full differential count was available in a total of 40 cases (other unclassifiable ILDs 19, end-stage 21) (Table 21). Seven patients in the unclassifiable group had a pattern of pronounced BAL lymphocytosis (range 22-84% lymphocytes) and had moderate to severe ground glass opacities on HRCT. Four of these patients underwent a biopsy, but remained unclassifiable. None of the patients with unclassifiable diagnosis had positive precipitating antibodies or exposure that would have suggested a diagnosis of HP.

A lung biopsy was performed in eight (19%) of the patients diagnosed with end-stage fibrosis and in 21 patients (34%) of the patients diagnosed with other unclassifiable ILD. Biopsies from eight patients in the end-stage group showed unspecific fibrosis in six cases, possible UIP in one case, and chronic HP in one case. Nine of the 21 patients in the group of other unclassifiable ILDs who underwent a biopsy had a histopathological diagnosis that conflicted with the radiological findings; seven patients had non-specific or non-representative findings in the biopsy, and five patients had unspecific fibrosis that did not allow a specific diagnosis.

Table 18

Demographic and clinical characteristics at the time of first visit for subgroups of unclassifiable ILD. The two unclassifiable subgroups are compared.

	End-stage fibrosis (n=43)	Other unclassifiable ILD (n=62)	End-stage fibrosis compared with other unclassifiable ILD p value
Male gender %	63	47	0.11
Age (SD)	71.7 (8.0)	59.3 (14.5)	<0.0001
FVC % predicted (SD)	67.8 (20.7)	73.7 (22.8)	0.19
DLco % predicted (SD)	46.2 (23.5)	55.8 (21.4)	0.037
Auscultatory crackles %	77	34	<0.001
LTOT % at first visit	33 (n=14)	16 (n=10)	0.05
LTOT % total	65	26	<0.001

Treatment

A total of 70% of the patients received treatment for their ILD. Prednisolone was most frequently used (65%), followed by azathioprine (20%) and high-dose methylprednisolone courses (18%).

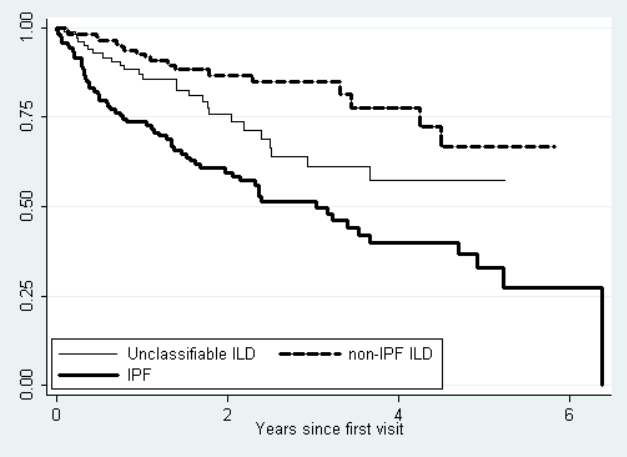


Figure 8
Survival of patients in the combined unclassifiable population (n=105),
IPF (n=121) and non-IPF (n=106).

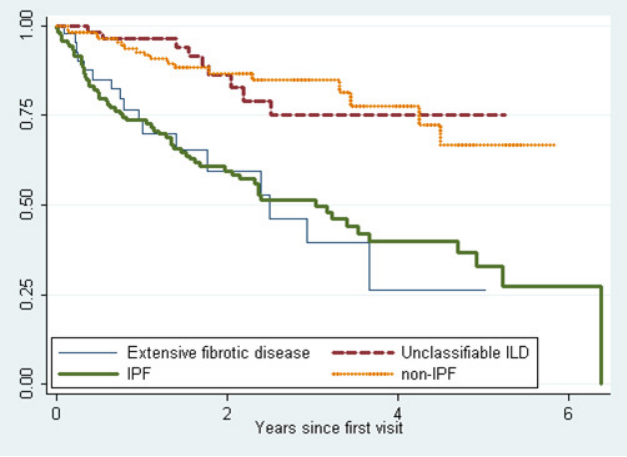


Figure 9
Survival of patients in unclassifiable ILD subgroups (extensive fibrotic disease (n=43) and other unclassifiable ILD (n=62)), non-IPF and IPF.

Disease severity and mortality

The mean follow-up time was 1.8 years (SD 0 .14) and 26 deaths occurred. Seventeen of the deaths (65%) occurred in the end-stage group. Twenty deaths were of respiratory cause; six of these deaths were ascribed to acute exacerbations and eleven deaths to gradual progression of fibrosis. Nineteen patients had neither baseline nor follow-up assessment of DLco; eleven of these patients were unable to perform the test because of severe disease. FVC of the 19 patients without DLco test was significantly lower than FVC of patients with available DLco (52% of predicted vs. 75% of predicted, p=0.0002);

Factors predictive of mortality were the presence of end-stage fibrosis on HRCT, age>70 years, FVC<50%, the CPI, and presence of auscultatory crackles. DLco <35% or inability to perform a measurement of DLco was not statistically significant after adjustment for age and gender (Table 21).

Unadjusted analysis showed a statistically significant difference in survival when the combined population of unclassifiable ILD was compared to IPF and non-IPF patients. Survival curves of combined unclassifiable ILDs and of the two subgroups of unclassifiable ILD compared with IPF and non-IPF ILD are shown in Figure 8 and Figure 9.

One-year and 5-year survival from the first visit to the ILD department was 87% and 57% in unclassifiable ILD, compared with 93% and 67% in non-IPF ILD and 74% and 33% in IPF. The combined population of unclassifiable ILD had a significantly better survival than IPF (HR 10.53 95% CI 0.33-0.84) and significantly worse survival than non-IPF (HR 1.93, 95% CI 1.06-3.54).

After adjustment for age and FVC, the survival difference between all unclassifiable ILD and IPF remained statistically significant (HR 0.55, 95% CI (0.34-0.90), but the difference was not significant between unclassifiable ILD and non-IPF (HR 1.93, 95% CI (0.97-3.36).

We found that the ILD-GAP prognostic model was able to separate patients with unclassifiable ILD into four groups with a significant difference in mortality, (p=0.0003 using log-rank test for equality of survivor functions). The ILD-GAP model identifies patients with a favourable outcome who were not separated when using the original GAP model developed for IPF in this cohort of unclassifiable ILDs (Figure 10).

Table 19
Reasons for ILD considered unclassifiable.

	End-stage fibrosis n=43	Other unclassifiable ILD n=62	End-stage fibrosis compared with other unclassifiable ILD p-value
Risk of biopsy considered too high (n)	26	17	0.001
Stable disease with few symptoms (n)	7	20	0.065
Conflicting clinical, radiological and histological data (n)	8	19	0.165
No biopsy (patient's request) (n)	1	2	-
Reason unclear (n)	1	4	-

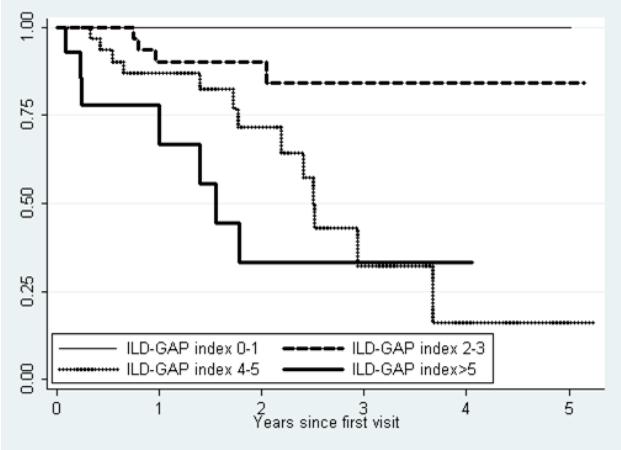


Figure 10
Survival in unclassifiable ILD based on the ILD-GAP index (n=99). ILD-GAP index 0-1, n=11, ILD-GAP index 2-3, n=38, ILD-GAP index 4-5, n=36, ILD-GAP index >5, n=14

Table 20
BAL inflammatory patterns and radiological differential diagnoses

		All unclassifiable ILDs	End-stage fibrosis	Other unclassifiable ILDs
BAL differential count (n=40) **End stage fibrosis (n=21)** **Other unclassifiable ILDs (n=19)**	Normal	11	7	4
	Lymphocytic inflammation (>15%)	9	2	7
	Neutrophilic inflammation (>5%)	8	4	4
	Eosinophilic inflammation (>3%)	6	4	2
	Mixed inflammation	6	4	2
Radiological differential diagnosis **(0-2 assigned to each patient)**	NSIP	43	20	23
	Possible UIP	10	10	0
	Chronic HP	5	5	0
	Subacute HP	18	0	18
	Sarcoidosis	4	0	4
	DIP/RB-ILD	20	0	20

Twenty-four-week follow-up
Twenty-four-week follow-up was available in 86% of the patients (93/105). Disease progression was seen in 26 patients (28%), seven of these patients died within the first 24 weeks. Fifty-six patients had stable or improved lung function; 11 patients had no lung function test at the relevant time. Age, FVC and DLco at the time of diagnosis were not significantly different between patients who had follow-up tests at 24 weeks and those who did not. Mortality was significantly increased in patients who experienced a decline in FVC of 10% and/or a decline in DLco of 15% during the first 24 weeks after diagnosis. This was seen in the combined population (HR 2.88, 95% CI (1.04- 8.02) p=0.043) (Figure 11) and in the group of other unclassifiable ILDs alone (HR 8.03, 95% CI (1.91-33.8), p=0.004) (data not shown). The difference was not statistically significant after adjustment for age and FVC.

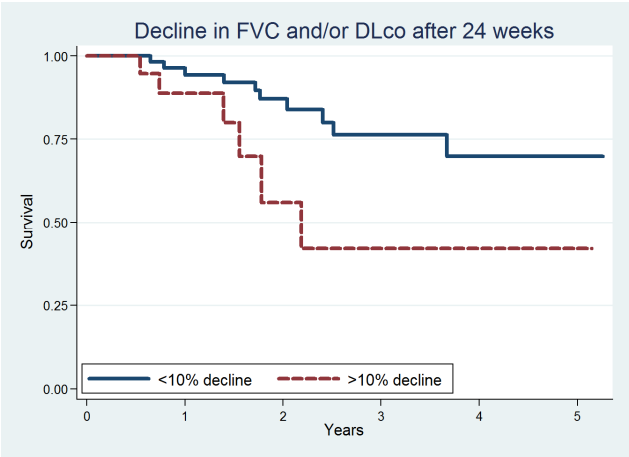


Figure 11
Survival curves based on significant decline in pulmonary function after 24 weeks. (FVC decline >10%, DLco decline >15%, or both)
Decline n=19, no decline n=56

One-year follow-up
One-year follow-up was available in 78% of the patients (82/105). Disease progression was seen in 32 patients (39%) during the first year, 11 of these patients died. Fifty patients (61%) had stable (n=38) or improved (n=12) lung function after 1 year of follow-up. In the combined population, we found a significantly higher mortality in those patients who experienced a decline in lung function during the first year, (HR 3.0, 95% CI (1.0-9.0), p=0.049). The difference remained statistically significant after adjustment for age and FVC as continuous variables.
On assessment of the "other unclassifiable ILD" group alone, the results were similar (HR 8.0, 95%CI (1.9-33.8), p=0.004).

Composite approaches: the ILD-GAP model and the Disease Behaviour Classification (DBC)

The ILD-GAP index was able to separate patients with unclassifiable ILD into four groups with a highly statistically significant difference in mortality (log rank p<0.0003) (Figure 10). On univariate Cox regression analysis we found HR for death 2.8; 95% CI (1.7-4.6).

The DBC separated the patients into four groups with highly statistically significant differences in survival (log rank p<0.0001) (Figure 12). In the categories "Reversible, self-limited" and "Reversible with risk of progression" no deaths occurred, and these two categories were combined in the analysis.

Using the DBC, the majority of patients with extensive fibrotic disease (76%) had progressive disease. This was the case in only 37% of patients with other unclassifiable ILDs (Table 22). The patient distribution in the ILD-GAP and DBC categories is shown in Table 23.

On univariate Cox regression analysis, we found HR for death 3.9; 95% CI (2.2-7.1). In a multivariate regression analysis, both DBC and the ILD-GAP index retained a highly significant individual prognostic value (DBC: HR 3.2; 95% CI (1.7-6.1), ILD-GAP index: HR 2.2; 95% CI (1.3-3.8))

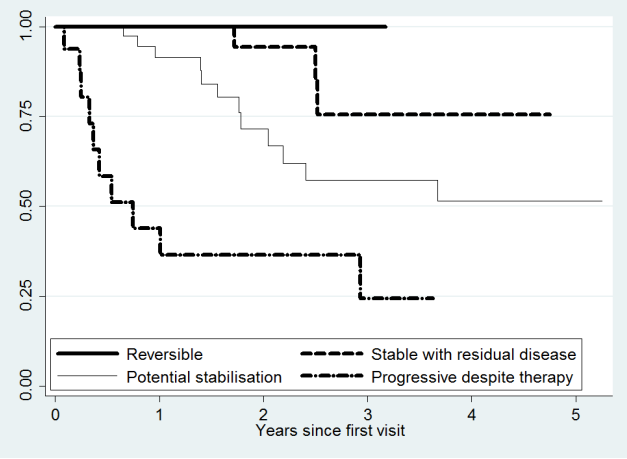


Figure 12
Kaplan-Meier survival curves in patients with unclassifiable ILD based on the Disease Behaviour Classification in the first 6 months after first visit.

Reversible, self-limited (n=3) / reversible with risk of progression (n=10), n=13
Stable with residual disease, n=33
Progressive, irreversible disease with potential for stabilisation, n=40
Progressive, irreversible disease despite therapy, n=16

Discussion

ILD epidemiology

The Danish Board of Health recommends referral to specialised centres of all patients requiring diagnostic investigation and treatment of suspected ILD. The centralisation of these rare diseases at a few public hospitals provides excellent conditions for observational studies.

The first study provides an overview of the incidence of ILDs in central Denmark as well as the distribution of ILD subtypes. The incidence of ILDs of 4.1 per 100,000 inhabitants was comparable to the findings in previous European studies (7-12). IPF was the most common diagnosis, with an incidence of 1.4 per 100,000 inhabitants being rather low compared with other reports. However, we believe that the diagnostic certainty ensured by expert re-evaluation of all diagnoses makes the results reliable. The incidence of ILD might be underestimated in our study due to referral bias. However, we found no difference in age, gender, pulmonary function and survival between patients referred directly from GPs or non-respiratory departments in the geographical area served by the Aarhus University Hospital compared with patients referred from pulmonologists at regional hospitals. These findings argue against an under-representation of older and severely ill patients.

Table 21
Factors associated with mortality among unclassifiable ILD patients in crude and adjusted Cox proportional hazards regression models

	n	HR for death (95% CI) crude	HR for death (95 % CI) adjusted for age and gender
Other unclassifiable ILD	62	Referent group	Referent group
End stage fibrosis	43	4.07 (1.80-9.21)	2.55 (1.04-6.25)
Age < 50 years	19	Referent group	Referent group a
50-70 years	42	3.56 (0.78-16.3)	3.47 (0.76-15.9)
>70 years	44	5.89 (1.32-26.2)	5.97 (1.33-26.9)
Gender			
Female	49	Referent group	Referent group b
Male	56	1.81 (0.80-4.06)	1.81 (0.80-4.08)
FVC >70%	55	Referent group	Referent group
50-70%	26	1.07 (0.37-3.07)	1.29 (0.44-3.77)
<50%	18	2.62 (1.05-6.52)	2.86 (1.13-7.20)
DLco >50%	46	Referent group	Referent group
35-50%	22	1.79 (0.60-5.34)	1.26 (0.41-3.89)
<35% c	32	2.66 (1.03-6.88)	2.30 (0.86-6.17)
Smoking			
No	29	Referent group	Referent group
Yes	75	1.19 (0.48-2.96)	0.99 (0.37-2.65)
Crackles			
No	45	Referent group	Referent group
Yes	54	3.66 (1.45-9.27)	2.73 (1.04-7.18)
Composite Physiologic Index	99	1.03 (1.0-1.05)	1.02 (0.996-1.044)

a adjusted for gender
b adjusted for age
c DLco < 35% or inability to perform the test for pulmonary reason

Table 22
Characterisation of disease patterns according to the Disease Behaviour Classification.

	End-stage fibrosis (n=43)	Unclassifiable ILD (n=62)	Total population (n=105)
Reversible, self-limited disease	0	3	3
Reversible disease with risk of progression	0	10	10
Stable with residual disease	7	26	33
Progressive, irreversible disease with potential for stabilisation	20	20	40
Progressive, irreversible disease despite therapy	13	3	16
Other severe disease*	3	0	3

***Metastatic cancer diagnosed within 2 months after the first visit to the department (n=2) and severe neurological deficit after trauma (n=1).**

Table 23
Cross-tabulation of the ILD-GAP-index and the Disease Behaviour Classification (n=96)

	ILD GAP-Index				
DBC	**0-1**	**2-3**	**4-5**	**>5**	**Total**
Reversible	3	6	3	0	12
Stable with residual disease	4	16	11	2	33
Progressive with potential for stabilisation	4	15	13	6	38
Progressive, irreversible	0	1	8	4	13
Total	11	38	35	12	96

Six patients had no baseline DLco without being unable to perform the test, and three patients were excluded from DBC assessment because of other severe disease.

The number of referrals to our centre rose during the study period. A rising incidence of IPF has been reported (18), but other factors may have played a role, such as improved access to CT scans during the past decade owing to increased focus on early detection of lung cancer. Furthermore, the period saw a stronger GP focus on the diagnosis of chronic obstructive pulmonary disease (COPD) and correct interpretation of spirometry. These factors are likely to have contributed to referral and diagnosis of ILD patients who would otherwise have remained undiagnosed or misdiagnosed with COPD.

The observed IPF proportion of 28% is low, considering that sarcoidosis was not included in the study. In previous studies, IPF accounted for 40-49% of ILD patients after exclusion of sarcoidosis (7-13), but these studies were published before the introduction of the more specific 2011 criteria.

It has also been argued that IPF may be over-diagnosed outside the specialised centres. One study observed that community physicians were more likely to assign a final diagnosis of IPF than academic physicians (6); and a population-based study (16) found that only 10% of cases identified by the use of IPF diagnostic codes proved to be IPF upon re-evaluation. In our cohort, 10% of the patients are diagnosed with end-stage fibrosis. The majority of these patients did not undergo a lung biopsy due to frailty and impaired lung function. Our study shows that survival in this group is indistinguishable from survival in IPF, and it is likely that many of these patients would have been diagnosed with IPF if a full diagnostic work-up had been possible.

IPF diagnostic criteria

The systematic diagnostic re-evaluation increased the number of IPF diagnoses and lowered the number of patients with unclassified ILD. However, 23 patients presented a "possible UIP" pattern on HRCT scan without the possibility of confirming the diagnosis because no biopsy had been performed. These patients fulfilled the previously used 2001 IPF criteria, but were in a diagnostic grey zone when evaluated by the 2011 criteria. Based on careful exclusion of differential diagnoses and evaluation of the disease course, we chose to include these patients in the IPF group. The mean age in this group was significantly higher than in the group of patients who underwent a thoracoscopic biopsy (70.3 years vs. 63.3 years). In patients older than 70 years with a possible UIP pattern on HRCT scan, Fell et al.(118) reported a positive predictive value of 95% of a UIP biopsy pattern. These findings strongly support the IPF diagnosis in this group of patients, and the study by Fell et al. may be helpful in the management of patients in the diagnostic "grey zone" that presents a considerable challenge in clinical practice.

The fibrotic ILDs, including end-stage fibrosis and the fibrosing idiopathic pneumonias (definite, probable and possible IPF and fibrotic NSIP), may be seen as part of the same disease entity. Future revisions of the diagnostic criteria may be able to reflect this as our understanding of the disease process and the prognostic determinants increases.

Video-assisted thoracoscopic biopsies and bronchoalveolar lavage

We found that the use of biopsies in IPF diagnostics declined from 2003-2009 following the introduction of the 2001 ATS/ERS recommendations. The biopsy complication rate was low, with a 30-day mortality of 1% and non-fatal complications in 13% of the cases, all of which is comparable to current standards (119, 120). Our findings also corroborate the recommendation against the use of TBB in IPF diagnostics, since TBB contributed positively to diagnosis in HP only, and not in IPF.

The role of BAL in IPF diagnostics remains an issue for debate, but it may contribute to the exclusion of differential diagnoses, e.g. a cut-off level of 30% lymphocytes in BAL has demonstrated a

favourable power for the diagnosis of IPF (121). We found that characteristic patterns of BAL inflammation contributed to the multidisciplinary assessment in many ILD cases, and BAL cultivation revealed bacterial infection in 14% of the cases. The BAL cell counts were comparable to findings in previous studies (122, 123), although it is a weakness of the study that full BAL differential counts were not available during the first years of the study. Cell counts were available in 55% of the patients who underwent BAL. We investigated the correlation between BAL cell counts and survival in IPF and found no difference in survival based on median cell counts of eosinophils, lymphocytes or neutrophils. The results corroborate a previous study (124) that showed no predictive role of eosinophil and lymphocyte counts with respect to survival. The authors reported a correlation between neutrophil levels and mortality, which could not be confirmed in our study because of the low number of patients where a full BAL cell count was available.

Severity and survival

The differences in outcome among the ILDs are illustrated in this study, and the poor prognosis in IPF is underlined. A recently published study of patients from the placebo groups of two large clinical trials show that mortality rates in mild to moderate IPF are rather low (104), but since the majority of patients are diagnosed at later stages when symptoms have been present for years and pulmonary function is severely impaired, the over-all prognosis in IPF is still dismal. IPF demographics and survival in our cohort are similar to those reported in other IPF populations, and we found respiratory disease by far the most common cause of death. Survival in end-stage fibrosis has not been reported previously, and is indistinguishable from survival in IPF, suggesting that some of these patients would have been diagnosed with IPF had a biopsy been possible or had a follow-up HRCT scan been performed.

This study also validated the combination of gender, age and physiological parameters in the GAP index (63), which separated the patients with IPF into three groups with significantly different mortality and which served as a useful predictor of survival in IPF. The modified GAP score, the ILD-GAP which was introduced recently (67), showed severity-based mortality comparable in IPF and other disease groups. The results also suggest that the differences in survival seen between IPF and other ILDs reflect later presentation and diagnosis in IPF (19, 125). Furthermore, it has been shown that delay in referral to a specialised centre has negative impact on survival after adjustment for pulmonary function at the time of referral (126). In lung cancer, which has in fact many similarities to IPF (110), it has been shown that early palliative intervention improves survival (127). To our knowledge, this has not yet been studied in IPF, but at present, palliative care is the only treatment option for many of these patients and should be established in time. Integration of palliative care into IPF treatment is essential, and strategies for best palliative care in IPF have also become the subject of clinical studies (128-130)

Comorbidities in IPF

The impact of comorbidity on survival in IPF is not well characterised, and studies are few. This study describes the frequency of comorbidities in a Danish IPF cohort with typical demographic and clinical characteristics. The most frequently observed comorbidities were cardiovascular disease (20%), arterial hypertension (15%) and diabetes mellitus (11%). Cardiovascular disease diagnosed during follow-up significantly increased mortality (HR 4.7, 95% CI 2.0-11.1). No difference was found based on cardiovascular disease already present at the time of IPF diagnosis. Diabetes (HR 2.5, 95% CI 1.04-5.9) and anticoagulant treatment (HR 3.3, 95% CI 1.5-7.2) were also factors associated with a significantly higher mortality in this population-based cohort.

Diabetes was a highly significant predictor of mortality in the present study. An increased prevalence of diabetes in IPF has been reported (75-76), but to our knowledge, the survival implication of diabetes in IPF has not previously been addressed. The reasons for the observed difference in survival are not clear, and we have no data to assess the level of diabetes control or compliance to antidiabetic therapy in this cohort, but poor diabetes control due to steroid treatment might have played a role. The change in treatment recommendations for IPF may in itself improve outcome in diabetic IPF patients, but the possible impact of diabetes on prognosis in IPF remains an important focus for further investigations in larger IPF cohorts.

Cardiovascular disease diagnosed during the course of IPF resulted in a highly significant decrease in survival, while cardiovascular disease already present at the time of IPF diagnosis did not impact on survival. Several other studies have shown that cardiovascular disease is frequent among patients with IPF (64,78) No survival difference based on cardiovascular disease was found in a large group of participants in a clinical trial (64) corroborating our findings in a unselected patients in a population-based cohort.

The occurrence of lung cancer was low in the Danish IPF cohort compared with previous studies. Ozawa et al. (131) reported a lung cancer incidence of 20% in a Japanese cohort. Earlier IPF diagnosis and longer observation time in the Japanese cohort owing to long survival seem to account for the difference. In another Japanese study, 17% (9/52) of IPF deaths were ascribed to lung cancer (132), and in the Minnesota cohort (16), 17% (8/47) of the patients developed lung cancer. A large, population-based study from the U.K. (133) compared IPF patients with age- and gender-matched controls, and found a lung cancer rate of 122 per 10,000 person-years among IPF patients and 22.9 per 10,000 person-years among controls. The rate of 3.6% per year found in our study was three times higher than in the British study. In another British study, Harris et al. (134) showed that lung cancer caused 9% of deaths in patients with CFA/IPF. The comparison of studies is hampered by the different methods and study populations used, but all studies show a considerably increased risk of lung cancer in IPF compared with the background population.

The frequency of depression was 21% in our study cohort, based on registered antidepressant use. A previous study reported a diagnosis of depression in 11% of IPF patients (16), while the screening for depression in a mixed ILD cohort (135, 136) revealed clinically relevant depression in 24% of the IPF patients. Depression score was found to be related to dyspnoea and functional status. Another study focused on the quality of life of IPF patients (137) and showed that subjective breathlessness is related to depressive symptoms and to quality of life, and a score indicative of significant depression was found in 23.5% of the patients. It has also been shown that Saint George Respiratory Questionnaire (SGRQ) and the Hospital Anxiety and Depression Questionnaire scores are correlated with the severity of IPF based on pulmonary function parameters (138). The high frequency of antidepressant therapy among patients in our cohort suggests that the recognition of depressive symptoms is coming more into focus. However, the optimal way to address depressive symptoms

in IPF and the role of physical impairment, medical therapy and pulmonary rehabilitation needs further investigation.
Pulmonary hypertension is a serious complication in ILD and was seen in 21% of our patients; almost half of them had PH at the time of IPF diagnosis. A cross-sectional study of a mixed ILD population performed at our centre after 2009 (47) showed a prevalence of PH of 14% in all ILDs and 24% in IPF, a prevalence level that corroborates our findings. We found no survival effect of the presence of PH at the time of IPF diagnosis when adjusted for age, gender and FVC. The number of patients with PH in this cohort was not large enough to allow stratification based on severity of PH. The presence of mild PH did not seem to influence survival, and the number of patients with severe PH in this study was too low to show a survival difference. Parallel to our findings, the study by Hamada et al.(132) estimated pulmonary arterial pressure as part of the initial diagnostic work up, and showed that the presence of PH provided no independent prognostic information in a multivariate regression analysis. In later stages of IPF, PH has been shown to be an important prognostic determinant (139).
Only one patient was diagnosed with sleep apnoea. The condition may have been underdiagnosed, but is receiving increased focus as overweight is becoming more common in the Danish population. None of our patients had concomitant COPD based on FEV1/FVC on spirometry, and only a few patients had emphysema based on RV and TLC levels. Some patients had significant emphysema on HRCT scan, but radiological emphysema quantification was not performed systematically.
Patients receiving anticoagulant treatment for clinical indications had a significantly higher mortality. The impact of warfarin treatment on IPF outcome when warfarin is given on clinical indication has been only briefly addressed in previous studies. The issue of warfarin in IPF has attracted focus in the light of the recently published results of the ACE-IPF trial (97) that showed no clinical benefit of warfarin treatment. The trial was stopped early because treatment with warfarin was associated with an increased risk of mortality in an IPF population that lacked other indications for anticoagulation. The small group of patient on anticoagulant therapy in our study did not allow stratification based on indication for warfarin therapy, and it is difficult to exclude that the concomitant disease itself may affect survival. Warfarin treatment was investigated as a possible predictor of survival in the study of the association of gastro-oesophageal reflux (GER) therapy with survival in IPF (140). Four percent of the patients received anticoagulant treatment, and the association with survival was not significant. However, a recent study by Tomassetti et al. (141) also showed increased mortality in warfarin-treated patients. Further studies in larger patient cohorts are needed to address the question of a connection between concomitant vitamin K antagonists and disease outcome in IPF. Whether new oral anticoagulants such as Factor Xa inhibitors should be preferred over warfarin for anticoagulant therapy in patients with IPF is another issue that needs further investigation.
The role of GER in IPF is still debated. In the Danish cohort, PPI treatment was used by half of the patients as prophylaxis during corticosteroid treatment or for symptomatic GER, and symptomatic GER may have been underreported. Previous studies have demonstrated differences in outcome based on GER medication use. One study has shown improved survival in patients treated with PPI (140), but this finding was not retrieved in our smaller cohort, perhaps because proton pump inhibitor therapy was given prophylactically in many cases. The study by Lee et al., which was based on patients in the placebo arms of three clinical trials in IPF (142), showed a small, but statistically significant difference in FVC decline at 30 weeks in favour of PPI treatment.
Prognostic models in IPF, such as the GAP score (63) or the Composite Physiology Index (CPI) (62), focus on factors directly related to IPF and are strong prognostic determinants. However, none of these models have incorporated the impact of comorbidities, and the role of comorbidity in IPF prognosis is still not clear. In COPD, a newly introduced comorbidity index, the COTE index (143), identifies 12 comorbidities that confer an independent risk of death in COPD patients and complements the BODE index (144) in prediction of survival. For each BODE score quartile, the characterisation of patients by the level of COTE score provides additional prognostic information when added to the BODE score. This model may inspire the incorporation of concomitant diseases into prognostic models in IPF.
Our study is limited by its small size and limited number of patients with each comorbidity. However, it provides valuable information of the occurrence and impact of common comorbid conditions in a population-based cohort of IPF patients, and directs focus towards possible interventions.

HRCT scoring system

Interobserver agreement

We attempted to apply the HRCT scoring system in a cohort of patients with idiopathic fibrotic interstitial pneumonias (IPF and NSIP). The validation of the model in our scleroderma ILD population was not possible because the ILD cohort included only 13 scleroderma patients. One of the advantages of the Scleroderma HRCT staging model is the ability of inexperienced scorers to evaluate HRCTs with high interobserver agreement and reliable prognostic validity. However, we found that the interobserver agreement in our study depended largely on the scorers' experience. The interobserver agreement between the less experienced scorers was markedly lower than for the experienced scorers, suggesting that the evaluation of HRCT scans in ILD is complex, even in a simple model.

IPF and NSIP

We tested the thresholds based on unpublished results of HRCT scorings in idiopathic fibrotic interstitial lung diseases from the Interstitial Lung Disease Unit, Royal Brompton Hospital.
In accordance with their findings, we found that for both experienced scorers, a 50% threshold of disease involvement separated the cohort into distinct survival groups. In the IPF subgroup, 50% of the patients had disease involvement of more than 50% based on the HRCT staging system.
Most patients are diagnosed with IPF at late disease stages (16, 145), which make a 50% threshold clinically relevant for initial prognostic evaluation.
A threshold of 25% honeycomb changes in IPF-NSIP was also discriminative of two groups with a distinct survival difference.
The results of this simple assessment model corroborate previous radiological studies (68, 69, 146) showing that overall fibrosis score and the presence of honeycombing are the most important radiological prognostic factors.
The findings in this study support that a simple HRCT scoring algorithm can be used as part of the early prognostic evaluation in patients with idiopathic fibrosing lung disease when the scoring system is used by pulmonologists with experience in ILD. We are currently in the process of validating a model that includes total disease involvement, extent of honey combing and the CPI (62) as a tool for identifying patients with an unfavourable prognosis and need of palliative care.

Unclassifiable ILD

The problem of unclassifiable ILDs has attracted attention with the recent update of the International Multidisciplinary Classification of the IIPs (3). The present study reports the second population of unclassifiable disease after the initial description by Ryerson et al. (35). We report a prevalence of 24%, which will seem plausible to most clinicians. The proposed disease behaviour classification (115) is complementary to the IIP classification and is particularly useful in patients with unclassifiable ILD. The present study reports the first application of this classification, and shows that it serves as a powerful instrument in prediction of outcome in unclassifiable ILD. The disease pattern identified during short-term follow-up places the majority of patients with extensive fibrotic disease in the categories of progressive disease and the majority of patients with other unclassifiable ILDs in categories of stable or reversible disease. The retrospective evaluation must necessarily cause some loss of accuracy in the disease behaviour classification because clinical nuances at the time cannot be entirely captured in retrospect. The classification stands up well even with this limitation – but it does highlight the need for prospective work.

The weakness of the ILD-GAP index may be the wide range in normal pulmonary function tests. Values from 80% to 120% of predicted may be "normal". However, our study confirms that the ILD-GAP index is a strong predictor of outcome in unclassifiable ILD. When we examined the prognostic value of the disease behaviour classification in a multivariate analysis with adjustment for ILD-GAP index, we found that both composite approaches retain their prognostic value.

In the present study, we also report the characteristics of two subgroups of unclassifiable ILD based on the presence or absence of extensive fibrotic disease. In the 105 patients diagnosed with unclassifiable lung disease, the major reason for remaining unclassifiable was that a biopsy had not been done because of high risk of complications. However, stable or mild disease was another frequent reason for avoiding lung biopsy if it was considered unlikely that the result of the biopsy would change the patient's management or treatment. The findings of this study corroborate the previous estimate that 20% of patients have unclassifiable ILD patterns (37). In our study, the number of patients without histopathological assessment because of stable disease was higher than previously reported (35).

Survival in unclassifiable ILD was significantly better than in IPF controls. Survival was worse in unclassifiable ILD than in the non-IPF group, but no difference was seen on adjusted analysis. This pattern is the same as shown by Ryerson et al. (35), and mortality rates are comparable at 1 and 2 years, but higher at 5 years (43% vs. 31%) in our study.

We assigned our patients with unclassifiable ILD to one of two groups based on radiological and/or histopathological features: one with mixed patterns and predominantly inflammatory features, and one with features of extensive fibrotic disease that probably represent idiopathic fibrosing ILD.

The two subgroups of unclassifiable ILDs had different profiles regarding age, differential diagnoses and diffusion capacity. The observed survival in the extensive fibrotic group was similar to survival in IPF, and it is possible that some of these patients would have been diagnosed with IPF if a lung biopsy or a follow-up HRCT scan had been performed. The remaining unclassifiable patients had disease characteristics and survival similar to those in the non-IPF controls. The majority of these patients showed improvement or stabilisation of their condition at follow-up, and few deaths occurred in this group. Based on HRCT and BAL findings, some of these patients might have been diagnosed with RB-ILD, but due to the lack of histopathological verification, the diagnosis was not assigned.

We assessed the impact of a decline in pulmonary function by using a decline of the same magnitude as known to be of prognostic significance in IPF (50-51) and found that a decline in pulmonary function at 24 weeks was a much weaker prognostic factor than the DBC or the ILD-GAP model (both models based on evaluation within the first six months). The isolated PFT changes may be influenced by the level of therapy during this period, explaining why the prognostic value is weaker than what is seen for the disease behaviour classification in which treatment level would be taken into account.

In a recent study of HP, the combination of auscultatory crackles and radiological reticulation identified HP patients with a higher mortality (147). In the present study, auscultatory crackles were present in 51% of the combined population and 77% of patients in the extensive fibrotic group and are a strong predictor of mortality. These findings may be useful in identifying patients at risk of further deterioration and in need of closer follow-up and intensified treatment, when possible.

Strengths and limitation

The strength of our study is the fact that it is population based. The present PhD project has helped us to obtain an overview of the ILD population in the geographical area served by Aarhus University Hospital. The results of our studies of the IPF population corroborate findings from other centres regarding demographical characteristics and disease severity at the time of diagnosis. This supports our assumption that patients in the other diagnostic categories also have been diagnosed as accurately as possible according to the current diagnostic standards.

It has the weaknesses of a real world setting with missing DLco, some HRCT scans being of suboptimal quality, BAL cell count unavailable in some patients, etc.

None of our patients had concomitant COPD based on FEV1/FVC on spirometry, and only a few patients had emphysema based on RV and TLC levels. Some patients had significant emphysema on HRCT scan, but radiological emphysema quantification was not performed systematically

Conclusion

1. The study of this well-characterised, population-based cohort of Danish ILD patients presents a standardised re-evaluation of diagnoses for all ILD subtypes and a reliable picture of the relative distribution of ILD diagnoses. IPF was the most frequent diagnosis, and the demographic characteristics of the IPF cohort were typical. The GAP index was a valuable prognostic tool that could be used in a clinical setting different from its derivation and primary validation. The re-evaluation of ILD diagnoses led to fewer unclassified cases, but the comparison of the current and previous IPF criteria revealed a group of patients diagnosed with IPF by the 2001 criteria who were in a grey zone when evaluated by the 2011 criteria.

2. The second study suggests an increased mortality in patients with IPF and diabetes and in patients experiencing cardiovascular events in the course of their fibrotic disease. These findings emphasise the need of careful diagnosis and treatment of comorbid-

ities and their risk factors in patients with IPF. In the absence of efficient treatment options for the majority of patients diagnosed with IPF, this may play a role in the effort to optimise the survival of IPF patients. The findings in this study also suggest that anticoagulant treatment with vitamin K antagonists may be associated with a more serious outcome, but further studies of the role of comorbidities and concomitant medication in IPF are needed.

3. A simple HRCT algorithm may, in the hands of pulmonologists experienced in ILD, be useful in the prediction of outcome in idiopathic fibrotic interstitial pneumonias.

4. The fourth study shows that unclassifiable ILD represents almost one fourth of ILD cases, and that clinical and radiological characteristics can be used to identify two subgroups, one with outcome that is similar to IPF and one with outcome similar to NSIP, HP and CTD-ILD. The Disease Behaviour Classification is easily applicable and separates the cohort into groups with highly significant differences in survival. The ILD-GAP model was also a useful predictor of outcome in unclassifiable ILD. When assessed in the same regression model the disease behaviour classification and the ILD-GAP provided individual contribution to the prognostic evaluation.

Perspectives

The present PhD project has improved our knowledge of the distribution and severity of ILD in the geographical area served by Aarhus University Hospital. The knowledge gained from the registry and the studies included in this PhD-thesis have led to the development of other research projects:

In collaboration with the Technical University of Denmark, we have developed a new registry based on our experience with the retrospective ILD registry. The data entry is ongoing, and the aim is to collaborate with other Danish ILD centres in achieving high-quality, population-based data for further studies of interstitial lung diseases in Denmark. In the near future, we hope to be able to study IPF severity at the time of diagnosis and compare the results with our 2003-2009 data.

Our study of comorbidity in IPF was limited by the small size of the cohort. Future studies of the impact of diabetes and other comorbid conditions on prognosis in IPF remain an important focus. It is unclear whether the addition of a comorbidity score would improve the prediction of outcome in IPF and other ILDs. We hope to increase our understanding of comorbidity patterns and their relation to outcome in IPF in a larger cohort based on the prospective ILD registry.

The occurrence of depression and the optimal way to address depressive symptoms in IPF is another important focus of future studies. The role of physical impairment, medical antidepressant therapy and pulmonary rehabilitation need further investigation. In the prospective ILD registry, we have included King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire (148). It measures health status in three domains: breathlessness and activities, chest symptoms and psychological status, and has been validated for use in ILD. We hope that the use of the K-BILD questionnaire will provide important information about patients' self-reported health status, which has not been available in our previous studies.

Our center participates in a recently formed Nordic IPF and ILD network, with the purpose of promoting research collaboration in ILD between the Nordic countries. An agreement has been reached between the participants on a common set of variables to be included in national ILD registries. Based on our experience from the registry, we have had the opportunity to influence the process. The Nordic collaboration will initially focus on NSIP given the low incidence of this disease and the need of a multicenter collaboration to enable studies of epidemiology and outcome.

Furthermore, we have an ongoing collaboration with The Interstitial Lung Disease Unit at the Royal Brompton Hospital, London, UK, on the validation of an HRCT-based scoring system with the purpose of predicting outcome in fibrotic interstitial lung disease. The aim is to identify patients with high risk of mortality and thus, facilitate the initiation of the necessary palliative care at the appropriate time. The scoring system is based on a specific combination of the thresholds of overall disease involvement and honeycomb pattern. The individual impact of each factor was described in the study included in the present PhD dissertation.

We also plan to study a cohort of patients diagnosed with desquamative interstitial pneumonia based on data from patients diagnosed between 2000 and 2014, including data from the present study.
The present PhD study has improved our insight on some aspects of ILD, but furthermore, it has generated new ideas and led to the initiation of new research projects and collaborations.

List of abbreviations

6MWT: six-minute walk test
ACE-IPF: AntiCoagulant Effectiveness in idiopathic pulmonary fibrosis
AIP: acute interstitial pneumonia
ANA: antinuclear antibodies
ANCA: antineutrophil cytoplasmic antibodies
ALAT: Latin American Thoracic Association
ATS: American Thoracic Society
BAL: bronchoalveolar lavage
BODE: Body mass index, airflow Obstruction, Dyspnoea, Exercise capacity
CCL-18: chemokine ligand 18
CFA: cryptogenic fibrosing alveolitis
CI: confidence interval
COP: cryptogenic organising pneumonia
COPD: chronic obstructive pulmonary disease
COTE: COPD specific comorbidity test
CPI: composite physiology index
CRP: Clinical-Radiologic-Physiologic
CT: computed tomography
CTD-ILD: connective tissue disease related interstitial lung disease
DBC: Disease Behaviour Classification
DIP: desquamative interstitial pneumonia
DLco: diffusion capacity of carbon monoxide
DTU: Technical University of Denmark
ERS: European Respiratory Society
FEV1: forced expiratory volume in 1 second
FVC: forced vital capacity
GAP: Gender Age Physiology

GER: gastro-oesophageal reflux
GP: general practitioner
HP: hypersensitivity pneumonitis
HR: hazard ratio
HRCT: high resolution computed tomography
ICAM-1: intercellular adhesion molecule 1
ICD-10: international classification of diseases 10
IgM-RF immunoglobulin M rheumatoid factor
IIP: idiopathic interstitial pneumonia
ILD: interstitial lung disease
ILD-GAP: interstitial lung disease Gender Age Physiology
IPF: idiopathic pulmonary fibrosis
JRS: Japanese Respiratory Society
KL-6: Krebs von der Lungen-6
MMP-7: matrix metalloproteinase-7
MRC: Medical Research Council
MRCDS: Medical Research Council dyspnoea score
NAC: N-acetyl cysteine
NSIP: non-specific interstitial pneumonia
PaO2: partial pressure of oxygen in arterial blood
PDGF: platelet derived growth factor
PH: pulmonary hypertension
PPI: proton pump inhibitor
RB-ILD: respiratory bronchiolitis interstitial lung disease
RHC: right heart catheterisation
ROSE: Risk Stratification Score
SD: standard deviation
TBB: transbronchial biopsy
TLC: total lung capacity
UIP: usual interstitial pneumonia
VATS: video-assisted thoracoscopic surgery
VEGF: vascular endothelial growth factor

Summary

Interstitial lung diseases (ILDs) form a heterogeneous group of rare diseases characterised by varying degrees of pulmonary inflammation and fibrosis. We hypothesised that IPF and unclassifiable ILD were common in a Danish ILD cohort and that prognostic factors based on disease characteristics and comorbidities could be identified

The aims of the PhD study were to describe the demographics of ILD in Central Denmark, to characterise the distribution of ILD diagnoses, and to assess prognostic factors in IPF and unclassifiable ILD.

The study is based on a cohort of 431 ILD patients referred to our department during a 6-year period. All ILD diagnoses were re-evaluated according to current diagnostic criteria. Patients were followed from the time of first visit on suspicion of an ILD to the last visit to the centre, death, transplantation, or discharge from follow-up.

The incidence of ILD was 4.1 per 100,000 inhabitants, and the incidence of IPF was 1.3 per 100,000 inhabitants in Central Denmark. The most frequently occurring ILDs were IPF (28%), unclassifiable ILDs (extensive fibrotic disease and other unclassifiable ILDs) (24%), connective tissue disease-related ILD (14%), hypersensitivity pneumonitis (7%) and NSIP (7%). Cardiovascular disease was present in 21% of the patients. The presence of cardiovascular disease at the time of IPF diagnosis did not lead to increased mortality, whereas cardiovascular disease diagnosed during the course of IPF was a statistically significant predictor of mortality. Our study also showed that diabetes and concomitant anticoagulant therapy were associated with worse outcome in IPF, and that a simple HRCT scoring system could be used in the prediction of outcome in fibrotic ILDs.

The study of unclassifiable ILD revealed two disease categories: one group characterised by extensive fibrotic disease and one characterised by more inflammatory features. The latter group was characterised by younger age and significantly better prognosis. We evaluated the pragmatic disease classification based on the clinical disease pattern included in the 2013 revision of the guidelines of diagnosis and treatment of interstitial lung diseases. We found that it was able to separate patients with unclassifiable ILD into categories with highly significant differences in survival. We also evaluated the ILD-GAP model, which is based on gender, age and pulmonary function (physiology), and found that it was a valuable predictor of survival in unclassifiable ILD. In a multivariate model, the two prediction scores showed significant individual contribution to the prognostic assessment.

The present study has provided the first estimate of ILD and IPF incidence in the Danish population and has shown that demographics and survival of IPF in this cohort were comparable to what has been reported in other studies. Comorbidities were common among patients with IPF, and the results of the study have led us to believe that careful diagnosis and treatment of comorbidities are important in order to optimise outcome in patients with IPF, although our findings need to be confirmed in larger studies.

Unclassifiable ILD is frequent in daily clinical practice but has not been characterised in detail. Our study showed that it was possible to identify predictors of outcome and to validate the ILD-GAP model in this cohort. The study also showed that the Disease Behaviour Classification can be used in the management of patients with unclassifiable ILD.

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