The epidemiology of idiopathic pulmonary fibrosis and interstitial lung diseases at risk of a progressive-fibrosing phenotype

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ILDs with a progressive-fibrosing phenotype appear to be more common in older adults and are associated with a complex network of environmental and genetic factors. Further epidemiological studies are warranted to help identify these patients. http://ow.ly/SY6m30mWytM

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ABSTRACT The availability of epidemiological data relating to interstitial lung diseases (ILDs) has increased over recent years, but information on the prevalence and incidence of ILDs of different aetiologies remains limited. Despite global distribution, the proportion of patients who develop a progressive phenotype across different ILDs is not well known. Disease behaviour is well documented in idiopathic pulmonary fibrosis but idiosyncratic in other ILDs that may present a progressive fibrosing phenotype. Possible reasons may include the heterogeneous nature of the aetiology, the complexity of diagnosis (and subsequent documentation of cases) and the methods employed to retrospectively analyse patient databases. This review presents a broad overview of the epidemiological data available for ILDs that may present a progressive-fibrosing phenotype, collectively and stratified according to clinical classification. We also note where further data are needed in comparison to the well-studied IPF indication.

Introduction

Interstitial lung diseases (ILDs) are rare diseases that share a number of common clinical and pathophysiological features, but also demonstrate a diverse aetiology and prognosis [1]. Varying proportions of patients with ILDs develop a chronic progressive-fibrosing phenotype. Idiopathic pulmonary fibrosis (IPF) can be viewed as the prototype progressive-fibrosing ILD; it is relatively well understood both in terms of epidemiology and disease behaviour [2, 3]. While IPF is by definition a chronic progressive-fibrosing interstitial pneumonia [4], only a proportion of patients with other ILDs develop this phenotype. In those other ILDs, progressive fibrosis can develop at any time during the disease course, but very little is known about why and how frequently this occurs [2]. A terminology recently used to describe fibrosing ILDs with a progressive phenotype is progressive-fibrosing ILD (PF-ILD) [2]. For details on the

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diagnosis and clinical course of ILDs with a progressive-fibrosing phenotype, please refer to Cottin *et al.* [5] in this issue of the *European Respiratory Review*. Data on the prevalence and incidence of ILDs other than IPF with a progressive-fibrosing phenotype are limited, in part due to the complexity and rarity of diagnosis. Consequently, meaningful comparisons of the epidemiology of different PF-ILDs are difficult. This review presents a broad overview of the epidemiological data that are available in relation to ILDs that may present a progressive-fibrosing phenotype, collectively and stratified according to clinical classification, while noting the gaps where further data are needed. Epidemiological data relating specifically to the proportion of patients who develop progressive fibrosis within each of the differing ILDs is not very well documented; therefore, unless specified, the data considered here relate more generally to ILDs, of which a proportion of patients may present with a progressive-fibrosing phenotype.

The epidemiology of IPF

Incidence, prevalence and patient demographics

IPF can be used as a model when considering other ILDs with a progressive-fibrosing phenotype [2]. It primarily occurs in older adults and is characterised by progressive worsening of dyspnoea and lung function [4, 6]. Risk factors reported to be associated with IPF include cigarette smoking, environmental exposures, microbial pathogens and genetic risk factors [4].

Epidemiological data for IPF can vary widely due to variations in the data collection methods and classification terms used (table 1) [11, 12]. Throughout Europe and North America, the estimated incidence of IPF has been reported to range between 2.8 and 19 cases per 100 000 people per year [23–25]. An analysis of national admissions data in Canada reported a higher rate of IPF than other national estimates, with an incidence rate of 18.7 per 100 000 cases and a broad prevalence of 41.8 per 100 000 cases, but noted that direct comparisons were not possible [26]. To further illustrate this point, a recent retrospective analysis of data from at-risk adults in Northern California carried out between 2000 and 2014, applied a commonly used case-finding algorithm to estimate an incidence rate of 6.8 per 100 000 person-years, whereas incidence was lower when using a modified algorithm with an enhanced predictive value (5.6 per 100 000 person-years) [11]. In a second analysis of data from a nationwide database in the USA, the age-standardised, positive value-corrected incidence of IPF was higher, estimated to be 14.6 per 100 000 person-years with a period prevalence of 58.7 per 100 000 persons [12].

The highest rates of IPF in Europe are reported in the UK, with incidence rates between 4.6 and 8.65 per 100 000 people per year, and 6000 people diagnosed annually [6, 23]. The incidence of IPF appears to be lower in Scandinavia, with incidence reported between 1.3 and 4.3 per 100 000 people per year [23]. In Russia, the incidence rate has been estimated to be 4–6 per 100 000 people per year [27]. The lowest rate of IPF globally is in Asia (South Korea, Taiwan and Japan), with incidence rates ranging from 1.2 to 4.16 per 100 000 people per year [23].

The prevalence of IPF increases with age, with the majority of patients aged >50 years at diagnosis and a higher proportion of males than females [6, 25, 26, 28, 29]. A regional observational study of ILD diagnoses performed by Duchemann *et al.* between January and December 2012 in Seine-Saint-Denis, a multi-ethnic county of Greater Paris in France, reported a prevalence rate for IPF of 8.2 per 100 000 [24]. In Canada, the prevalence of IPF was reported to increase from 25.9 per 100 000 population in patients aged 50–59 years, to 507.0 per 100 000 population at ⩾90 years of age [26]. In the UK, 85% of patients diagnosed with IPF are >70 years [6]. However, it is worth noting that a small subset of patients with IPF (0.5–3.7%) may present with familial IPF, in whom the onset of the disease can be earlier [28, 30, 31].

The epidemiology of fibrosing ILDs that may present a progressive phenotype, other than IPF

Idiopathic interstitial pneumonias

Idiopathic interstitial pneumonia (IIP) is a term used to describe a wide range of ILDs characterised by unique clinical, radiological and pathological features [32–34]. Diagnosis of patients with IIP can be challenging due to the mixed patterns of lung injury that may be observed [32, 33].

Idiopathic nonspecific interstitial pneumonia

Idiopathic nonspecific interstitial pneumonia (iNSIP) is a form of IIP that was first introduced as a distinct entity in 2008 [32]. Only a limited number of iNSIP epidemiological studies have been performed.

Incidence, prevalence and patient demographics

The general incidence of iNSIP (regardless of progressive-fibrosing phenotype) is lower than in IPF, with retrospective data of mixed cohorts of IPF and iNSIP patients estimating the prevalence of iNSIP to be 1–9 per 100 000 compared with 2–20 per 100 000 for IPF [35]. The demographic profile of patients with iNSIP

TABLE 1 Incidence of idiopathic pulmonary fibrosis (IPF) in studies using large databases

First author [ref.]	Year	Location	Years studied	Data source type	Condition studied	Case definition	Population demographics	Incidence per 100 000 per year[#]	Rate type
Large database studies									
Europe									
Maher [7][¶]	2013	UK	2000–2012	Nationwide primary care database (CPRD)	IPF	NA	NA	8.65	Crude
Navaratnam [8]	2011	UK	2000–2008	Nationwide primary care database (THIN)	IPF	ICD-9 codes for IFA (515) and PF (516.3)	Overall population of the UK	7.44	Crude
Kornum [9]	2008	Denmark	1995–2000	Nationwide health database	IPF (and ILD)	ICD-10 J84.1	Overall population of Denmark	7.27 4.17	Crude Age-adjusted
			2001–2005	Nationwide health database	IPF (and ILD)	ICD-10 J84.1		5.28 2.91	Crude Age-adjusted
Gribbin [10]	2006	UK	1991–2003	Nationwide primary care database (THIN)	IPF	Read codes for CFA, IFA	Overall THIN population	4.6	Crude
North America									
Ley [11]	2017	NC, USA	2000–2014	Health insurance plan database	IPF	ICD-9 code 516.3, or ICD-9-CM code 516.31	Overall health insurance plan population	6.8 (overall) 3.1 (per 100 000 person-years)	PPV-corrected
Esposito [12]	2015	USA	2006–2012	Nationwide HealthCore Integrated Research Database	IPF	ICD-9-CM code 516.3	Health plan members; age-adjusted value applicable to overall US population	31.9 (broad case definition) 14.6 (per 100 000 person-years)	Age-adjusted, PPV-corrected
Raghu [13]	2014	USA	2001–2011	Medicare database; 5% random sample	IPF	ICD-9-CM 516.3 and 515 ICD-9-CM 516.3	Medicare population aged ⩾65 years	93.7 (overall) 31.1–43.0 (broad) 15.9–31.1 (narrow)	Crude, patients aged >65 years Algorithm-defined exclusions, patients aged >65 years
Fernández Pérez [14]	2010	Olmsted County, MN, USA	1997–2005	Rochester Epidemiology Project (medical record linkage system for healthcare providers)	IPF	ICD-9 code 516.3 Hospital International Classification of Diseases-Adapted codes 517 and 519	Olmsted County population aged ⩾50 years; data adjusted for applicability to overall US white population	8.8 (narrow) 17.4 (broad)	Age-adjusted, sex-adjusted
Ehrlich [15]	2010	CA, USA	1996–2005	Health insurance plan database	IPF PF	ICD-9 516.3/515	Health plan population; data adjusted for applicability to overall US population aged ⩾18 years	9 (non-diabetics) 14 (diabetics)	Crude Age-adjusted, by diabetic status

Continued

TABLE 1 Continued

First author [ref.]	Year	Location	Years studied	Data source type	Condition studied	Case definition	Population demographics	Incidence per 100 000 per year[#]	Rate type
Raghu [16]	2006	USA	1996–2000	Health claims database	IPF	ICD-9 516.3	Health claims database population; data adjusted for applicability to overall US population	16.3 (broad) 6.8 (narrow)	Age-adjusted
South America									
Rufino [17][¶]	2013	Brazil	1996–2010	Ministry of Health data	IPF	ICD-10 J84.1		0.48	Crude
Asia									
Han [18][¶]	2013	South Korea	1992–2010	Healthcare claims from insurance medical cohort	IPF	NA	NA	4.16 (broad) 1.84 (narrow)	Crude, patients >30 years
Lai [19]	2012	Taiwan	1997–2007	Health insurance database/ government records	IPF	ICD-9 516.3	Population of the Taiwan National Health Insurance database	1.4 (broad) 1.2 (narrow)	Crude
Natsuizaka [20]	2014	Hokkaido prefecture, Japan	2003–2007	Ministry of Health, Labor and Welfare data	IPF	ATS/ERS consensus classification	Overall population of Hokkaido	2.23	Crude

International Classification of Diseases (ICD) codes are presented as ICD-nth revision, clinical modification (CM). ICD-10 code J84.1 is currently the most specific code for IPF but may include other idiopathic interstitial pneumonia (IIP). ICD-9 code 516.3 is roughly equivalent; code 515 is "post-inflammatory fibrosis". Broad criteria were: one or more claims with a diagnostic code for IPF, but no claims for another diagnostic code for interstitial lung disease (ILD). Narrow criteria were: as for broad criteria, with a relevant diagnostic test on or before their first diagnosis date. Broad and narrow criteria were based on the 2002 American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines [21]. Probable cases were based on criteria from [22]: received a diagnosis of ILD from a rheumatologist or pulmonary physician; or ILD was the primary discharge diagnosis. Definite cases had a confirmatory diagnosis within 90 days. CPRD: Clinical Practice Research Datalink; NA: not available; THIN: The Health Improvement Network; IFA: idiopathic fibrosing alveolitis; PF: pulmonary fibrosis; CFA: cryptogenic fibrosing alveolitis; PPV: positive-predictive value; IIP: idiopathic interstitial pneumonia; IPF: idiopathic pulmonary fibrosis. [#]: average incidence for the time period available; latest incidence stated where no average was given, incidence extrapolated from ILD data where percentage of IPF cases was given; [¶]: abstract only. Reproduced and modified from [23] with permission.

also appears to differ to that of IPF, with patients tending to be ⩾50 years old, female, nonsmokers, with no prior history of smoking [32, 35, 36]. In comparison to IPF, the prognosis for patients with iNSIP is more favourable [32, 35].

Unclassifiable IIP

Of all patients diagnosed with IIP, a small subgroup (15–25%) remain unclassifiable according to current classification [21, 33, 37], which may be attributable to the mixed pattern of lung injury, inconclusive test results, lack of a lung biopsy due to ineligibility or lack of patient consent [33, 38].

Incidence, prevalence and patient demographics

In the French study performed by Duchemann *et al.* [24], the crude estimated prevalence of unclassifiable ILD was reported to be 0.5 per 100 000, despite surgical lung biopsies having been performed. Patients with unclassifiable ILD due to an inconclusive diagnosis were also identified from an ongoing longitudinal cohort at a specialised centre in California, USA, from 2000 to 2011. The mean age of patients with unclassifiable ILD was 68 years, similar to that observed in the IPF control group (70 years), but the proportion of male cases was lower in the unclassifiable ILD group (53% *versus* 72.8%; p<0.0005) [38]. The observed demographic profile is comparable to that reported across Europe and the USA (table 2) [39]. Among patients with unclassifiable ILD, the percentage of former smokers was lower than in the IPF control group (64% *versus* 76%, respectively) [38].

Connective tissue disease-associated ILD

There is a spectrum of connective tissue diseases (CTDs) characterised by an underlying mechanism of systemic autoimmunity and immune-mediated organ damage, which may develop pulmonary complications throughout the disease course [40–42]. These include rheumatoid arthritis (RA), scleroderma (systemic sclerosis (SSc)), idiopathic inflammatory myopathy (polymyositis and dermatomyositis), Sjögren's syndrome, systemic lupus erythematosus and mixed CTDs [40–43]. RA and SSc are most commonly associated with PF-ILD [43] and are discussed in further detail later.

RA-associated ILD

RA is a systemic and chronic inflammatory disease characterised by joint swelling, tenderness and destruction of synovial joints [44]. Within the RA population, clinically significant ILD occurs in 10–20% of cases and is considered to be an important contributor to morbidity and mortality [41, 45–47]. Risk factors associated with the development of ILD in RA patients include older age, the presence of rheumatoid factor and cigarette smoking (particularly in male patients), which may promote citrullination of lung proteins leading to the development of anti-cyclic citrullinated peptide antibodies, particularly in patients who have developed the shared epitope human leukocyte antigen [48, 49].

Incidence, prevalence and demographic profile

RA is the most common autoimmune disease worldwide, with an estimated prevalence of 0.4–1% [40, 41, 45, 50]. Pulmonary complications are common in RA and different compartments (airway, vasculature, parenchyma and pleura) can all be involved [51]. There is considerable variation in the reported prevalence and incidence of RA-ILD, reflecting the diagnostic methods used and the populations studied [40]. However, RA-ILD is more common in men (unlike RA as a whole) and increases with older age and disease severity [40, 47]. In a retrospective study of data recorded by centres across the UK, 230 patients

TABLE 2 Characteristics of unclassifiable interstitial lung disease patients

Country	Years	Unclassifiable n/total N (%)	With surgical biopsy %	Male %	Age years	FVC %	*D*LCO %
Spain	1995–2004	73/500 (14.6)	26.2	47	66.7±13.6		
China	1999–2009	38/251 (15.1)	100				
Spain	2000–2001	26/511 (5.1)	22.7				
USA	2000–2011	132/1370 (9.6)	31	53	67.8±12.9	69.0±22.1	47.6±19.7
Denmark	2003–2009	62/431 (14)	34	45	59.3±14.5	73.7±22.8	55.8±21.4
Australia	2011–2013	23/232 (9.9)					

Data are presented as mean±SD, unless otherwise stated. Blank cells represent data that were not reported. FVC: forced vital capacity; *D*LCO: diffusing capacity of the lung for carbon monoxide. Reproduced and modified from [39] with permission.

were diagnosed with both RA and ILD over a 25-year period (1987–2012). The median age at diagnosis was 64 years, and the male:female ratio was 1:1.09 [48]. A review of cases treated at two centres in Korea from 1991 to 2008 indicated that 84 patients with a median age of 63 years were diagnosed with RA and usual interstitial pneumonia, with an almost equal distribution of male and female patients (52% and 48%, respectively) [52]. A retrospective analysis of mortality data from the National Center for Health Statistics in the USA from 1988 to 2004 reported 162 032 mortalities associated with RA, of which 10 725 (6.6%) were attributable to RA-ILD [46]. The most common pattern on high-resolution computed tomography in patients with RA-ILD is usual interstitial pneumonia, observed in approximately two-thirds of cases [48, 53, 54].

SSc-associated ILD

SSc is a chronic autoimmune CTD of unknown aetiology, associated with considerable morbidity and increased mortality [55]. Reported percentages of patients with SSc who develop ILD range 35–90%; SSc-ILD often manifests as NSIP and is a major cause of morbidity and mortality [56–59]. Although SSc can occur at any age, patients are usually 30–60 years of age, and women are more likely to develop SSc than men [55, 60, 61]. The cause of SSc is unknown, but its onset is associated with the interaction of environmental factors (including occupational, dietary, medical and lifestyle exposures and possibly infectious agents) in genetically predisposed individuals (*e.g.* African-American race) [55, 58].

Incidence, prevalence and demographic profile

SSc has a worldwide distribution, with a low incidence of 9–19 cases per million per year, but the reported prevalence and incidence rates vary globally, reflecting differences between the diagnostic criteria and statistical methods used when retrospectively analysing data [55, 60]. A retrospective study published in 2008 compared epidemiological data worldwide; the prevalence of SSc was reported to range from seven cases per million in Japan (1974–1976) to 489 per million in Italy (1992) [62]. When excluding studies reporting spatiotemporal clustering or specific population surveys, the adjusted prevalence was reported to be 50–300 per million, with a higher occurrence in the USA and Australia than in Japan and Europe [62]. In Taiwan, the incidence is reported to be 10.9 cases per million, with a prevalence rate of 56 cases per million; whereas in North India, the prevalence is higher at 120 cases per million [63, 64]. In the USA, the incidence rate of SSc is reported to range 0.6–18.7 cases per million per year, with prevalence ranging 4–242 cases per million [61].

Hypersensitivity pneumonitis

Hypersensitivity pneumonitis (HP) is an immunologically initiated lung disease triggered by the repeated inhalation of a large variety of environmental organic antigens and/or chemicals, to which the genetically susceptible subject has been previously sensitised [65]. Little is known about its epidemiology worldwide, and many patients are misdiagnosed as having IPF [66, 67].

Incidence, prevalence and demographic profile

The epidemiology of HP is affected by geographical distribution [68–70]. Between 2011 and 2015, the incidence of occupational HP in the UK was reported to be ∼1.2 cases per million workers per year, with a mean age of 52 years, and a higher rate of diagnosis in men than women (∼80% of cases were male) [66]. In a cohort study of ILDs in central Denmark, 32 (7%) out of 431 patients had HP at the time of inclusion; the mean age was 48.6 years and over half (63%) were male [36]. In a retrospective, US-based database analysis of 150 million enrolees carried out from 2004 to 2013, the prevalence was observed to increase with age from 0.95 per 100 000 in children aged 0–9 years to 11.2 per 100 000 in older adults aged >65 years, with <50% of cases diagnosed in men [71]. Up to 25% met the criteria set for fibrotic HP (prevalence ranged 0.41–0.80 per 100 000 people), which was associated with a higher mortality rate [71]. In the epidemiological study performed by Duchemann *et al.* [24] in France, the prevalence of HP was 2.3 per 100 000 and the incidence was 0.9 per 100 000 per year.

Sarcoidosis

Sarcoidosis is a systemic disease characterised by the formation of immune granulomas in organs, especially in the lungs and lymphatic system [72]. It is estimated that up to 20% of patients diagnosed with sarcoidosis develop fibrotic lung disease, with pulmonary fibrosis presenting as dyspnoea, cough and hypoxaemia [73].

Incidence, prevalence and demographic profile

The global prevalence of sarcoidosis is estimated to be 4.7–64 in 100 000 with an incidence of 1.0–35.5 in 100 000 per year [24, 72, 74]. The incidence and prevalence variations correlate with age, sex, ethnic origin and geography, with the highest rates reported in northern Europe, in African-American individuals and

predominantly in women [72, 75]. The lowest incidence of sarcoidosis was observed in Japan, with one study of 1027 patients reporting an average incidence rate of 1.01 per 100 000 population (0.73 for males and 1.28 for females) [72, 76].

ILDs related to other occupational exposures

A subset of patients diagnosed with ILDs related to other occupational exposures may develop a progressive-fibrosing phenotype over the course of their disease, particularly those with asbestosis or silicosis [77]. Both asbestosis and silicosis are caused by the inhalation of dust, which causes lung injury and fibrosis.

Asbestosis

The prevalence of asbestosis is decreasing worldwide as occupational exposure is decreasing; however, the use of asbestos in commerce and industry remains high in Africa, Asia and South America [77]. In Australia, there were 2041 hospitalisations for asbestosis between 1998 and 2015 [78]. In the UK, the majority of cases of asbestosis are the result of historical exposure [79]. In a retrospective analysis of long-latency respiratory disease (LLRD) between 1996 and 2014, the average annual incidence rate of pneumoconiosis associated with asbestos was 1.9 per 100 000 males (95% CI 1.7–2.2) [79]. The incidence of LLRD including pneumoconiosis, the vast majority of which were attributable to occupational asbestosis exposure, peaked in men and women aged 75–79 years [79].

Silicosis

The prevalence of silicosis is also linked with occupational exposure to free crystalline silicon dioxide or silica, and generally occurs in patients after the exposure has ended [80, 81]. Establishing the prevalence of silicosis is difficult due to the number of industries at risk, the nature of industrial employment, which is often transient, the delayed onset of symptoms post-exposure and the nature of data sources available [77, 82, 83].

The prevalence of silicosis is reported to be higher in low- and middle-income countries (*e.g.* China, Brazil, South Africa) but is also an important health concern in Europe and the USA [81]. Manual workers in low- or middle-income countries often forego the use of control measures such as personal protective equipment, and this could be a contributor to the differences observed between countries [84–86]. Silicosis was first reported in South African gold miners in the early 1900s, and South Africa now has one of the highest rates of silicosis worldwide [87]. There are an estimated 500 000 mineworkers across Southern Africa (Lesotho, Mozambique and Swaziland) and 1.5–2 million ex-mineworkers [88]. In South Africa alone, the proportion of miners diagnosed with silicosis increased from 3% to 33% in black miners and 18% to 22% in white miners between 1975 and 2007 [87]. In 2013, 8095 cases of silicosis were reported in China, with its prevalence continuing to increase over the past decade [89]. In comparison, in the USA, silicosis was the underlying or contributing cause of 1437 mortalities between 2001 and 2010, with a decline in mortality rate from 0.74 per 1-million population in 2001 to 0.39 per million in 2010 [83]. The majority of patients diagnosed with silicosis were male (95.3%), white (86%) and over 45 years of age (98.1%) [83]. In the UK, there are an estimated 20–50 cases of silicosis diagnosed per year, with 10–20 mortalities annually [82]. The majority of cases are reported in men (based on data between 2005 and 2016) [82].

Conclusion

Despite the global distribution of ILDs with a progressive-fibrosing phenotype, their incidence and prevalence are not well defined. This may be related to a number of reasons, potentially to the heterogeneous nature of the aetiology, the complexity of diagnosis (and subsequent recording of cases), the low numbers of patients diagnosed and the methods employed to retrospectively analyse patient databases. ILDs that may present a progressive-fibrosing phenotype appear to be more common in older adults and are associated with a complex network of environmental and genetic factors. Few of the available epidemiological data are from low- or middle-income countries; this may be attributable to factors such as the availability of high-resolution computed tomography and access to healthcare professionals with the expertise needed to differentiate between ILDs. Given the negative associated prognosis, further epidemiological studies are warranted to help identify ILD patients who may develop a progressive-fibrosing phenotype and enable effective clinical management.

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