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Review

Interstitial Lung Disease Epidemiology in the Second Millennium: A Narrative Review

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Abstract: Current epidemiological data about interstitial lung disease (ILD) are still poor. The principal cause of the discordant data is associated with a heterogeneous group of respiratory diseases that includes a large number, about 200 families, with low frequency, distinct and sometimes unknown etiology, and different progression. Furthermore, epidemiological data are limited. Scope of the narrative review is to report ILD incidence and prevalence in Registries from different Countries in the second millennium. We identified 16 ILD Registries (14 prospective and 2 retrospective) from major Countries in Europe (n = 10), Asia (n = 7), North America (n =2) and Oceania (n = 1). Significant discrepancies in ILD and ILD subtypes prevalence and incidence among countries are reported in Registries. These discrepancies could be determined by different ethnicities and socio-economic conditions as well as by updates in disease diagnosis and classification. ILD epidemiological Registries are progressively ameliorating through a better adherence to updated Guidelines and Classification codes. An accurate and definite compilation of ILD epidemiological Registries will be useful for a more precise monitoring of disease progression and treatment.

Keywords: epidemiology; interstitial lung disease; incidence; prevalence; registries

1. Introduction

Current epidemiological data about interstitial lung disease (ILD) are still poor. Principal cause of discordant data is certainly associated with a heterogeneous group of respiratory diseases that includes about 200 ILD types [1–3] with low frequency, distinct and sometimes unknown etiology, and different progression [4]. Furthermore, available epidemiological data are limited [5].

ILD can be divided in two principal categories: 1) ILD of unknown etiology such as the most common subset Idiopathic Pulmonary Fibrosis (IPF), and 2) ILD depending on micro-environmental or professional exposure or associated with toxicity to treatment. Sarcoidosis, IPF, hypersensitivity pneumonitis, ILD associated with connective tissue diseases (CTD) and not defined (or post-inflammatory) fibrosis are the most common ILD [3].

Although ILD etiology is often unknown, it has been demonstrated that the deposition of an excessive quantity of fibrotic tissue in pulmonary interstitium can be caused from micro-environmental exposure, i.e. fungal spore inhalation as in *Aspergillus fumigatus* pneumonitis; drug use as amiodarone treatment for atrial fibrillation or other cardiac rhythm disorders; occupational causes associated with chronic inflammatory diseases; connective tissue diseases; previous pneumonias; and sarcoidosis. Therefore, etiology is an important starting point in ILD clinical diagnosis and classification.

Aim of the narrative review is to report ILD incidence and prevalence in ILD Registries from different Countries in the second millennium.

2. Methods

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We identified 16 ILD Registries performed in different Countries in the second millennium reporting ILD classified by different etiology. Among these Registries 14 were prospective and 2 were retrospective. For completeness we reported also 4 old registries dating back to before the second millennium.

ILD incidence, estimated as the rate of new cases over one year, has been reported in all Registries except the French one. ILD prevalence was not reported in all Registries and was calculated by two different methods: 1) prevalence x 100 000 persons in general population and 2) prevalence estimated as proportion of ILD patients in cohorts from multicenter or single centers studies [6]. Data are reported in Tables as total number of cases and as percentage in parentheses.

Registries in which ILD were classified according to 515 and 516.3 codes of the International Classification of Diseases Ninth Revision Clinical Modification (ICD-9 CM) were taken into special consideration. On October 1th 2015, ICD-9 CM codes were replaced by ICD-10 CM codes-designed to promote international comparability on the collection, processing, classification, presentation and mortality statistics. The ICD-10 CM codes, maintained by the World Health Organization, include greater details, changes in terminology, and expanded concepts for injury, and other related factors, improving accuracy [7]. Prevalence and incidence in ILD subgroups reported by Registries from Europe, Asia, North America, and Oceania were analyzed. Italian Registry was included twice because many ILD data of the first Registry were unavailable. Lastly, Aosta Registry, a single region experience, is reported for the long observational period.

3. Results

Geographically, all major Countries predominantly from Europe (n = 10) and Asia (n = 7) with respect to North America (n =2) and Oceania (n = 1) were represented in ILD Registries (Figure 1).

Figure 1. Map showing the most important ILD Country Registries.

For completeness of the data we have broadened the panorama shortly reporting 4 registries dating back to before the second millennium. The first population Registry of ILD patients was established in Bernalillo County (NM, USA) in 1988 and included the1988-1993 period enrolling 460 ILD patients with 56% prevalent cases and 44% incident cases. [1] (Table 1).

In 2001 Thomeer et al. [8] reported three Registries that included ILD cases in Flandres (Belgium), Germany and Italy in 1992-1999 period. The incidence of CTD-ILD and undefined fibrosis was higher in Flanders than in Germany. In Flanders there was a slight predominance of male patients (especially in ILD due to occupational exposure and/or hypersensitivity pneumonitis), whereas there was a female predominance in Germany. Drug-induced ILD were found in oldest patients in Flanders, particularly those due to amiodarone and nitrofurantoin. A low prevalence of hypersensitivity lung diseases was observed in Italy and a lower percentage of IPF was present in Belgium than in Germany and Italy (Table 1).

Table 1. Incidence and prevalence of Interstitial Lung Disease (1988 – 1999 Registries).

	New Mexico (USA)^		Flanders[$]		Germany[§]	Italy#
Disease	**Incidence**	Prevalence	Incidence	Prevalence	Incidence	Prevalence
Sarcoidosis	16 (7.9)	30 (11.5)	112 (31)	69 (26)	83 (35)	344 (30)
IPF/UIP	63 (31.2)	58 (22.5)	62 (17)	50 (19)	76 (32)	417 (37)
BOOP	N/A	N/A	10 (2.3)	9 (3.4)	16 (6.8)	57 (5%)
(C)EP	N/A	N/A	9 (2.5)	7 (2.7)	0	27 (2.3)
CTD-ILD	18 (6.9)	33 (12.8)	27 (7.5)	19 (7.2)	5 (2.1)	N/A
Goodpasture syndrome, GPA, EGPA	N/A	N/A	5 (1.4)	4 (1.5)	2 (0.8)	25 (2.2)

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Hypersensitivity pneumonitis	5 (1.5)	N/A	47 (13)	32 (12)	25 (11)	50 (4.3)
Drug/Radiation**	7 (3.5)	5 (11.9)	12 (3.3)	12 (5)	6 (2.6)	21 (1.8)
Eosinopihlic granuloma/Histiocytosis X	N/A	N/A	13 (3.6)	7 (2.7)	0	73 (7.2)
Pneumoconiosis***	21 (10.4)	36 (14.0)	19 (5.0)	18 (6.8)	6 (2.6)	N/A
Post-inflammatory pulmonary fibrosis	20 (9.9)	29 (11.2)	33 (9.1)	27 (10)	12 (5.1)	N/A
Others	54 (26.7)	67 (26.0)	13 (3.6)	10 (3.8)	0	124 (11%)

IPF/UIP: Idiopathic pulmonary fibrosis/Usual interstitial pneumonia, BOOP: Bronchiolitis obliterans organizing pneumonia, (C)EP: (chronic) eosinophilic pneumonia, CTD-ILD: Connective tissue disease-interstitial lung disease, GPA: Granulomatosis with polyangiitis (Wegener's), EGPA: Eosinophilic granulomatosis with polyangiitis (Churg-Strauss).**Radiation was not included in New Mexico, Flanders and Germany Registries; ***Coal pneumoconiosis was excluded in Flanders and RIPID Registries. Registry years: ^1988-1990, $1992–1996, §1995, #1997–1999. Data from the Registries published after the year 2000 are then reported.

Data from European Registries are summarized in Table 2.

Total ILD incidence in Spain and Greece ranged between 3 and 7 x 100.000 inhabitants. Moreover, IPF incidence was lower in Greece whereas sarcoidosis incidence was lower in Spain [9–11]. The Turkey Registry showed that sarcoidosis incident cases were the most common within ILD patients (771 cases). Data from the Danish population Registry report that the total ILD incidence was 23 x 100.000 inhabitants, with a higher incidence among males (around 29%) [10,11]. Data from the French Registry indicated a higher prevalence of sarcoidosis (361 cases) and CTD-ILD (145 cases) with respect to other ILD [13].

IPF rate reported in the United Kingdom was approximately 5 x100.000 [14]. This finding is close to the rate calculated in the USA considering a more restricted classification criterion of the disease, while a significantly higher incidence occurs considering broader criteria. The incidence of IPF increased over the years in the United Kingdom (from 3% in 1991-95 to 7% in 2000-2003). Of note, whereas the United Kingdom study indicated that the incidence of IPF was more than doubled during the observation period [14], the population-based data from the USA (Olmsted County) and Denmark [6,12] showed a declining incidence, particularly during the latter years of the study.

The Registry for diffuse infiltrative lung disease named RIPID (Registro Italiano Pneumopatie Infiltrative Diffuse) was created in Italy in 1998 with the scope to obtain a complete national ILD data base. During 1998-2005 period a total of 3152 ILD patients was registered [15]. However, the incidence could not be estimated because the size of the population covered by the participating centers was not exactly estimable except for Bolzano province in first instance and subsequently Aosta region in the period from 2005-2018.

Table 2. Incidence and prevalence of Interstitial Lung Disease in Europe.

	Greece*		Spain$	Turkey§ France#		Italy&	Denmark^
Disease	Incidence	Prevalence	Incidence	Incidence	Prevalence	Incidence	Incidence
Sarcoidosis	60 (23.2)	330 (34.1)	76 (14.9)	771 (34.3)	361 (42.6)	1063 (33.7)	N/A
IPF/UIP	52 (20.1)	189 (19.5)	197 (38.6)	408 (18.2)	98 (11.5)	864 (27.4)	121 (28.1)
CTD-ILD	30 (11.6)	120 (12.4)	51 (10.0)	201 (9.0)	145 (17.1)	N/A	54 (12.5)
HP	7 (2.7)	25 (2.6)	34 (6.6)	82 (3.7)	28 (3.3)	93 (2.9)	32 (7.4)

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Drug	4 (1.5)	17 (1.8)	17 (3.3)	35 (1.6)	31 (3.7)	39 (1.2)	20 (4.6)
Pneumoconiosis	8 (3.1)	20 (2.0)	N/A	241 (10.7)	42 (5.0)	N/A	N/A
Fibrosis unclassifiable	40 (15.4)	82 (8.5)	26 (5.1)	99 (4.4)	66 (7.8)	N/A	62 (14.4)
Others	58 (22.4)	184 (19.0)	110 (21.5)	408 (18.2)	77 (9.1)	N/A	142 (32.9)

IPF/UIP: Idiopathic pulmonary fibrosis/Usual interstitial pneumonia, CTD-ILD: Connective tissue disease-interstitial lung disease HP: Hypersensitivity pneumonitis. Registries years: *2004; $2000-2001, §2007-2009, #Paris area 2012, &1998-2005, ^2001– 2005.

Data from Asia, Canada and Australia are reported in Table 3. Recently, the largest retrospective epidemiology study in Asia was performed by Ye et al. [5] in Hong Kong including 924 ILD patients observed over a 16-year period from January 2005 to December 2020. Global ILD prevalence increased from 23.1 x100.000 in 2005 to 32.6 x 100.000 in 2020 while the incidence decreased from 5.97 x 100.000 to 3.83 x 100.000 inhabitants in the same period. This finding could be related to a better quality of diagnostic procedures in association with adherence to updated Classification Guidelines. The study showed a higher accuracy with respect to other Asia Registries because ILD case identification was validated according to updated guidelines by chest imaging, physical medical notes, clinical examinations, and was made by specialists in respiratory medicine. ILD was divided in two categories: 1) post-inflammatory pulmonary fibrosis and 2) idiopathic interstitial pneumonia coded 515 and 516.3, respectively, in accordance with ICD-9-CM and ICD -10 CM diagnostic codes [5,7].

Table 3. Incidence and prevalence of Interstitial Lung Disease in Asia, Canada and Australia.

	India$		India$$		Pakistan§	China*	China**	Hong Kong&	Saudi Arabia^	Canada+	Australia#
Disease	Incidence	Prevalence	Incidence	Prevalence	Incidence	Incidence	Incidence	Incidence	Incidence	Incidence	Incidence
Sarcoidosis	217 (38.3)	339 (42.2)	85 (7.8)	38 (9.5)	11 (4.3)	123 (6.3)	147 (5.6)	188 (4)	67 (20)	41 (3.2)	44 (6.2)
IPF/UIP	130 (23.0)	170 (21.2)	148 (13.7)	37 (9.3)	95 (37.5)	395 (20.3)	692 (26.5)	3746 (79.8)	77 (23.3)	317 (24.7)	240 (34.0)
CTD-ILD	77 (13.6)	102 (12.7)	151 (13.9)	80 (20.1)	23 (9.1)	356 (18.3)	631 (24.1)	93 (2.0)	115 (34.8)	428 (33.3)	125 (17.7)
HP	69 (12.2)	86 (10.7)	513 (47.3)	190 (47.6)	31 (12.3)	59 (3.0)	62 (2.4)	81 (1.7)	21 (6.3)	97 (7.5)	66 (9.4)
Drug	5 (0.9)	6 (0.7)	N/A	N/A	N/A	13 (0.7)	28 (1.1)	31 (3.7)	4 (1.2)	N/A	7 (1.0)
Pneumoconiosis	6 (1.1)	7 (0.9)	N/A	N/A	3 (1.2)	13 (0.7)	58 (2.2)	N/A	N/A	N/A	11 (1.6)

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Fibrosis unclassifiable	N/A	7 (0.9)	N/A	N/A	4 (1.6)	285 (14.7)	N/A	6 (1.8)	286 (22.3)	51 (7.2)
Others	62 (11.0)	86 (10.7)	187 (17.3)	54 (13.5)	86 (34.0)	344 (13.2) 701 (36.0)	242 (4.9)	40 (12.1)	116 (9.0)	161 (22.8)
						653 (25.0)				

IPF/UIP: Idiopathic pulmonary fibrosis/Usual interstitial pneumonia, CTD-ILD: Connective tissue disease-interstitial lung disease, HP: Hypersensitivity pneumonitis.Registries years: $2015-2017 (single center), $$2015-2020 (multicenter) §2016-2018, *(Guangzhou) 2012-2017, **(Beijing) 2000-2012, &2005-2020, ^2008-2011, +2016-2017, #2016-2019.

Interestingly, the study compared data from Asia with those from other countries and reported that ILD prevalence ranged from 6.27 x100.000 subjects in Belgium to 97.9 x 100.000 subjects in Paris and that ILD incidence ranged from 1 to 32 x 100.000 person-years in Europe, United States (New Mexico Registry), Middle East, and Asia. The prevalence of ILD in Hong Kong was like in Greece but lower than in Paris and in the United States and approximately four-fold higher than in Belgium. The overall ILD incidence in Hong Kong was 5.21 x 100.000 subjects, which was comparable to Greece, Spain, and Central Denmark, but was lower than in India, United States, Turkey, and Paris.

A Registry reporting ILD incidence and prevalence in India (Tricity region) was published in 2022 [16]. Incident cases were 159, 887, 70 and 58 for sarcoidosis, IPF, CTD-ILD and HP, respectively. In the same study the national population incident ILD cases were calculated indicating a strong incidence of HP (513 cases) [16]. The elevated rate of HP in India could be attributable to two opposite realties namely the presence of high technology areas in contrast with rural agricultural regions.

Data from China Registries indicated that IPF was the most frequent subtype followed by CTD-ILD [13]. Analogous findings were present in the Australian Registry [13,17]. By contrast, CTD-ILD was the highest ILD subtype in the Canadian Registry [13,18].

Olson et al. [19] published in 2021 a study on the prevalence and incidence of chronic fibrosing interstitial lung diseases the United States. Although the study could not be considered a Registry, it is the first one aimed to estimate ILD prevalence and incidence in United States, evaluating a total of 37,565,644 patients aged at least 18 years identified from 1 October 2012 to 30 September 2015 with at least 365 days' continuous enrollment. The estimated age- and sex-adjusted prevalence per 100.000 persons of fibrosing ILD (IPF) was 117.8 (95% CI, 116-119). Notably, the study estimated that incidence per 100.000 patient-years of fibrosing ILD and chronic fibrosing ILD with a progressive phenotype was 51.5 and 32.5, respectively. ILD identification without specific diagnosis codes were defined idiopathic non-specific interstitial pneumonia (INSIP) or unclassifiable idiopathic interstitial pneumonia (unclassifiable IIP) based on ICD-9 CM. After an accurate screening the Authors concluded that ILD/ IPF incident cases were 57% for a total of 15,518 cases. The remaining cases were INSIP, unclassifiable IIP and CTD- ILD, occupational ILD, and hypersensitivity pneumonitis.

A single Region experience: Aosta Registry

In 1995-2004 period 128 ILD patients were enrolled in Aosta region, Italy (126,000 inhabitants) (Table 4). According to the American Thoracic Society Criteria recommendation [20] the diagnosis was made on clinical, radiological, and histological data: 59 patients were diagnosed with IPF/UIP, 19 with NSIP and the remaining 50 patients with sarcoidosis (n. 24), GPA (n. 16) and extrinsic allergic alveolitis (n.10). All ILD diagnoses were confirmed by lung biopsy [21]. Interestingly, the Registry was updated in 2018 including data from 2005 to 2018 and showed an increase in ILD incidence including also ILD associated with GPA (Wegener's) and hypersensitivity alveolitis (data not published). These data are at variance with other Registries in which the most frequent diseases were IPF and sarcoidosis. ILD incidence was 7 x 100.000 inhabitants. The accuracy of ILD diagnosis and registration was facilitated because patients were part of a region with a numerically reduced population of residents, they were referred to a single Hospital center, and update courses on pulmonary fibrosis for General Practitioners were done in close collaboration with Hospital

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Specialists. IPF High Resolution Computed Tomography (HRCT) scan and histopathological features are reported here (Figure 2 and Figure 3 A-B).

Figure 2. Series of chest HRCT images showing IPF associated with pulmonary emphysema.

Figure 3. Pathological findings of pulmonary lesions in Usual Interstitial Pneumonia.

Table 4. Interstitial Lung Disease Registry in Aosta Region, Italy (2005 – 2018).

	Number*	Gender		Age median (range)
		Male (%)	Female (%)	
Disease				
NSIP	33 (20.6)	19 (57.6)	14 (42.4)	51 (28-75)
IPF/UIP	73 (45.6)	54 (61.6)	28 (38.4)	64 (27-79)
Sarcoidosis	38 (23.7)	24 (63.2)	14 (36.8)	42 (30-58)
EGPA	16 (10.0)	10 (62.5)	6 (37.5)	64 (48-78)

*Incidence: 7 x 100.000 inhabitants; NSIP: Non-specific interstitial pneumonia, IPF/UIP: Idiopathic pulmonary fibrosis/Usual interstitial pneumonia. EGPA: Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)DISCUSSION.

The Registries published in the second millennium show significant discrepancies in prevalence and incidence of ILD and subtypes among different countries. These discrepancies could be determined by different ethnicities and socio-economic conditions among populations. Moreover, the various updates in ILD diagnosis and classification made over the last twenty years can be cause of instrumental limitation for the diagnosis obtaining misdiagnosis and/or lack of inclusion of possible ILD cases in their respective National Registry. ILD epidemiological Registries are progressively ameliorating through a better adherence to updated Guidelines and Classification codes in disease diagnosis. Notably, most data derive from Hospital files in which only partial data are reported, while ILD population Registries are present only in few cases. Furthermore, selection bias may influence ILD prevalence and incidence in different Countries as data are mainly registered in Internal Medicine or Pneumology Units and do not refer to the entire population. Moreover, either prevalence or incidence data or mixture of both are reported leading to poor statistical significance. Finally, in most Countries, especially in Asia, diagnosis was made only on clinical and radiological findings without histopathological confirmation.

Lastly, Carbone et al. [21] demonstrated in 2007 that two pathological findings are detectable in non-specific interstitial pneumonia (NSIP): i.e. cellular NSIP and fibrotic NSIP with different prognosis at favor of the first subgroup. The important new ‘‘outcome subgroup’’ to emerge was the entity of fibrotic NSIP. These patients made up 20-35% of patients previously diagnosed as IPF or cryptogenic fibrosing alveolitis (CFA)/idiopathic pulmonary fibrosis (IPF) [22,23]. The detection of a further subset of NSIP lead to a more precise classification of ILD patients but at the same time made more complex the compilation of Registries.

4. Limitations and Perspectives

Limitations of published studies consist in the lack of national ILD Registries in very large and densely populated countries such as the USA, China and India. Moreover, diagnosis was made in some Registries only on clinical and radiological findings without histopathological confirmation in misdiagnosed cases.

Accurate diagnosis made by multidisciplinary panels and coding practices according to continuously updated Guidelines will lead to a more precise ILD classification.

A definite compilation of ILD epidemiological Registries will be useful for better monitoring disease progression and treatment especially with anti-fibrotic drugs and lung transplantation.

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Finally, future clinical trials aimed at identifying additional ILD risk factors including genetic and molecular studies and implementation of disease progression scores are needed to improve ILD clinical assessment.

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