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Idiopathic Pulmonary Fibrosis (IPF) incidence and prevalence in Italy

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Abstract. *Background:* Studies of Idiopathic Pulmonary Fibrosis (IPF) epidemiology show regional variations of incidence and prevalence; no epidemiological studies have been carried out in Italy. *Objective:* To determine incidence and prevalence rates of IPF in the population of a large Italian region. *Methods:* in this cross-sectional study study data were collected on all patients of 18 years of age and older admitted as primary or secondary idiopathic fibrosing alveolitis (ICD9-CM 516.3) to Lazio hospitals, from 1/1/2005 to 31/12/2009, using regional hospital discharge, population and cause of death databases. Reporting accuracy was assessed on a random sample of hospital charts carrying the ICD9-CM 516.3, 516.8, 516.9 and 515 codes, by reviewing radiology and pathology findings to define cases as IPF "confident", "possible" or "inconsistent". *Results:* Annual prevalence and incidence of IPF were estimated at 25.6 per 100,000 and 7.5 per 100,000 using the ICD9-CM code 516.3 without chart audit while they were estimated at 31.6 per 100,000 and at 9,3 per 100,000 for the IPF "confident" definition after hospital chart audit. *Conclusion:* The data provide a first estimate of IPF incidence in Italy and indicate that incidence and prevalence in southern European regions may be similar to those observed in northern Europe and North America. *(Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 191-197)*

Key words: Idiopathic pulmonary fibrosis; epidemiology; ICD9-CM

Introduction

Idiopathic Pulmonary Fibrosis (IPF) is the most common and progressive interstitial lung diseases (ILD) (1), presenting more frequently in men in the sixth and seventh decades of life (1-9). The diagnosis of IPF requires case discussion by a multidisciplinary team of specialists, including pulmonologists, roentgenologists, thoracic surgeons and pathologists (1,10). The complexity of roentgenological and pathological features may lead to under-diagnosis and late recognition (11-12), hence impacting upon the assessment of the public health dimension of the disease as much as upon patient management (1).

Earlier epidemiological studies on IPF, based upon registry data, posted IPF incidence between 1 per 100,000 and 4.3 per 100,000 in Spain (13),

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Greece (14) and Norway (15). The relative frequency of IPF among patients seen at interstitial lung disease clinics (13,16-21) were estimated at 17% in Flanders (18), 22% in south-western United States (20), 32% in Germany and 38% in Spain (13). IPF relative frequency in Italy was estimated at 19 to 37% (16). More recently, epidemiological studies analyzing regional or national databases of hospital, general practice and health care organization admission records have been carried out in Europe and the United States. With regard to Europe, a Finnish study estimated IPF countrywide prevalence at 16-18 per 100,000 for the years 1997-1998 (22). Incidence rates of 7.4 per 100,000 have been reported in the United Kingdom, with an increase of IPF incidence of about 5% per year in the past 15 years (23). Published data would suggest that idiopathic pulmonary fibrosis prevalence may be lower in the southern areas of Europe, compared to the northern ones (13-14, 22, 23, 25-26), albeit no explanation is available as to whether the observed differences may be due to ethnic, environmental or lifestyle factors (35). In this regard, the Lazio region, located in central–southern Italy, may typify Mediterranean/Southern Europe and be expected to show lower IPF prevalence, as seen in Spain and Greece (13-14).

The objective of this study was to determine incidence and prevalence of IPF in the Lazio Region, 5,728,688 inhabitants, using hospital admissions and mortality databases of the regional public health system.

Material and methods

Setting and Study Design

This retrospective study was a collaborative project of the Department of Epidemiology, Lazio Regional Health Service (DEP), Rome, which carried out epidemiological and statistical work, and the Department of Biomedicine and Prevention of the University of Roma "Tor Vergata" (DBP), Rome, which coordinated the assessment of ICD9-CM coding accuracy by auditing a random sample of hospital charts in collaboration with six large Lazio Hospitals. The DEP has the mandate to carry out epidemiological research on the Lazio region databases, in accord with the principles embodied in the Declaration of Helsinki. The study was approved by the independent Ethics Committees of the coordinating and the collaborating centres.

Data Sources

The present study was based on the data collected by the regional health information systems. Three databases were used as data sources: the regional Hospital Information System (HIS), the regional Mortality Registry (MR) and the Italian National Institute of Statistics (ISTAT) database. The HIS database contains all the records of admissions, both as inpatient and day-hospital, to private and public hospitals of the Lazio region. They are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). In particular, the HIS database contains demographic descriptors (gender, date and place of birth, place of residence) and hospitalization data including hospital unit(s) of stay, date(s) of admission, in-hospital transfer and discharge and the regional code corresponding to the admitting facility. In addition, it contains up to six primary and secondary diagnostic discharge ICD9-CM codes and up to six procedure ICD-9-CM codes. The MR contains all deaths records of the Lazio region, by cause of death (ICD-9 codes). These data can be linked on the basis of a unique identifier code and are routinely used in epidemiological research (24, 27). The ISTAT database provides official demographics of the Italian resident population.

Study Population and Case Definition

Study subjects were retrospectively identified among the residents of 18 years of age and older of the Lazio region hospitalized (both as ordinary admission and as day hospital admission) in any hospital of the Lazio region, for idiopathic fibrosing alveolitis (ICD9-CM 516.3) – registered as main or secondary diagnosis - from January 1, 2005 to December 31, 2009. In the case of multiple hospitalizations, the first hospital admission was selected for inclusion in the study. These patients were categorized as IPF cases. The population of 18 years of age and older of the Lazio region was of 4,679,760 in 2005 and of 4,727,710 in 2009.

Assessment of Reporting Accuracy

To test the accuracy of reported diagnoses in the hospital discharge datasets, a random sample of 404 medical records carrying the ICD9-CM codes 516.3 (Idiopathic fibrosing alveolitis), 516.8 (Other specified alveolar and parieto-alveolar pneumonopathies), 516.9 (Unspecified alveolar and parieto-alveolar pneumonopathy) and 515 (Post-inflammatory pulmonary fibrosis) was selected from all hospital admissions in six hospitals in Rome for the period 2005-09. The six hospitals accounted for 24% of all the 8827 hospital admissions with the above listed diagnoses in the Lazio Region in the study period. There were no significant differences, as assessed by chi square statistics, in the distribution of demographic and clinical characteristics (including comorbidities such as COPD, respiratory failure, pneumoconiosis, tumors, cardiovascular, cerebrovascular, digestive or genitourinary disease), on the basis of ICD-9-CM coded diagnoses between the subsample and the overall population (excluding the subsample) recorded in the Lazio Region database with hospital discharge diagnostic codes 516.3, 516.8, 516.9 or 515.

Hospital charts were reviewed by a group of pulmonologists (M.A.P., G.P., E.P., R.V., G.P., G.F., F.V., S.M., F.T., F.C.) and by two radiologists (G.S. and A.F.) and by a pathologist (A.O.) for diagnostic accuracy of IPF/UIP following defined criteria. They were: (i) reporting of no other known causes of ILD, (ii) reporting of the presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy, (iii) reporting of specific combinations of HRCT and surgical lung biopsy patterns in patients subjected to surgical lung biopsy (2). Where the CT scan report recorded on the hospital chart was not sufficiently detailed to confirm the diagnosis, CT images were directly reviewed following the recommendations of the ATS/ERS/JRS/ALAT respiratory societies guidelines (1). Following the above criteria, the degree of confidence of the diagnosis of IPF/UIP was ranked as "confident" i.e., a HRCT "UIP pattern", with or without a UIP pattern on lung biopsy, or a HRCT "possible UIP pattern", if associated with a UIP pattern on lung biopsy. Otherwise, cases defined as radiologically "possible" or "inconsistent" were not categorized as IPF diagnoses.

Measures and Statistical Analyses

Incidence and prevalence rates of IPF were determined for the year 2009, by gender and age, on the resident population of 18 years of age and older. The number of incident IPF cases was determined by the number of patients who were hospitalized for the first time between January 1st, 2005 and December 31, 2009 with no other admission for IPF in the nine years preceding the date of first admission recorded during this period. The annual incidence rate was obtained by dividing the number of incident cases by the sum of the population numbers of the Lazio region for each year of this period and expressed as number of cases per 100,000 residents per year. Similarly, the number of prevalent IPF cases in the year 2009 was determined by the number of patients diagnosed with IPF from January 1, 2005 to December 31, 2009 and alive on December 31, 2009. The prevalence rate was obtained by dividing the number of prevalent cases for the number of inhabitants of 18 years of age and older of the Lazio region at December 31, 2009 (n = 4,727,710) and expressed as number of cases per 100,000 residents.

The rates of agreement between the diagnosis recorded into the HIS database and that obtained from the audit of hospital charts were determined by the Cohen's kappa coefficient, a statistical measure of inter-annotator agreement for categorical items. Incidence and prevalence rates were re-assessed using incidence and prevalence of confident IPF as estimated form audited hospital charts.

Results

Two thousand sixty six individuals of 18 years of age or older (mean age 70,3 ± 11,9; 53% male) were retrospectively identified among the residents of the Lazio region for having been hospitalized for idiopathic fibrosing alveolitis (ICD9-CM 516.3) from January 1, 2005 to December 31, 2009, of whom 314 had been previously hospitalized in the years 1996-2005.

Prevalent IPF cases identified in the year 2009 were 1212 (Table I). Prevalence was of 25.6 per 100,000 (CI 95% 25.1-26.2). Prevalence rates varied from 1.8 per 100,000 (CI 95% 1,6-1,9) in the 18-34 years of age group, to 73.5 per 100,000 (CI 95%

Table 1. Number of patients with idiopathic pulmonary fibrosis by gender and age, hospitalized in the Lazio region, years 2005-2009.

	Population 31-12-2009	Prevalent Cases year 2009	Incident Cases /5 years
Total	4727710	1212	1752
Men	2241086	590	941
Age			
18-34	571467	7	8
35-44	465043	26	23
45-54	404409	43	54
55-64	328995	129	160
65-74	265191	201	319
75+	205981	184	377
Women	2486624	622	811
Age			
18-34	556924	13	12
35-44	482785	26	26
45-54	428207	48	49
55-64	366813	97	104
65-74	318092	225	271
75+	333803	213	349

60.2-86.9) in the 75 years of age and older group. Disease prevalence rates in the age groups of 55-64 years and older was higher in males than females (Figure 1).

Incident IPF cases, identified in the five years of the study period according to the 516.3 ICD9-CM code were 1752 (in average 350 cases per year from 2005 to 2009) (Table 1), with an incidence rate of 7.5 per 100,000 (CI 95% 7.3-7.7). Incidence rates varied from 0.4 per 100,000 (CI 95% 0.3-0.4) in the 18-34 age group to 28.1 per 100,000 (CI 95% 27.1-29.2) in the 75 of age and older group. Similarly to prevalence, incidence rates in the age group of 55-64 years and older were higher in males than in females (Figure 2).

A total of 348 charts (86% of those selected) were surveyed. In comparison to the whole population of individuals discharged with the diagnosis codes 516.3, 518.8, 518.9 or 515 in the study period, patients in the subsample were not significantly different with regard to age, gender and comorbidities (data not shown) although they were more likely to be Rome resident and to have higher education. After multidisciplinary discussion, a total of 120 cases were classified as "confident IPF", 148 cases as "possible IPF". The diagnosis of "confident IPF" was validated in 63 out of 75 ICD9-CM 516.3 (interstitial fibrosing alveolitis) coded charts (confirmation rate 84%). In addition, the diagnosis of "confident IPF" was assessed in 49 (24,3%) of the 202 charts selected with the ICD9-CM 515 code and in 8 (11.4%) of the 70 charts selected with either the ICD9-CM 516.8 or the 516.9 codes (Cohen's kappa coefficient 0,5184).

The estimate of the prevalence of IPF, obtained upon the revision of hospital charts for the identification of "confident IPF" cases, was of 31,6 per 100,000 (CI 95% 30.9-32.2) with an estimated incidence of 9,3 per 100,000 (CI 95% 9.2-9.4) (Figure3).

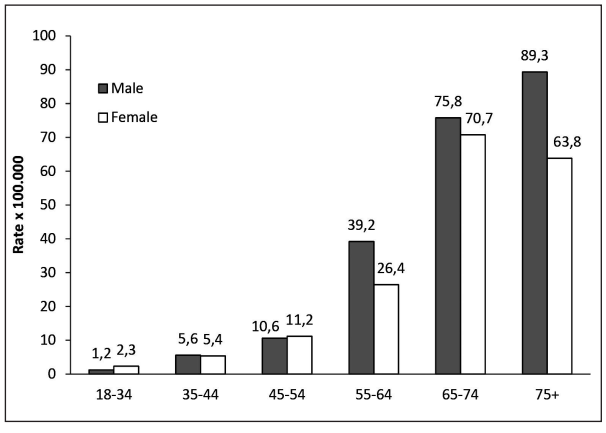

Fig. 1. Prevalence rate (per 100,000) of idiopathic pulmonary fibrosis defined by gender and age. in the Lazio region (Italy), year 2009 .

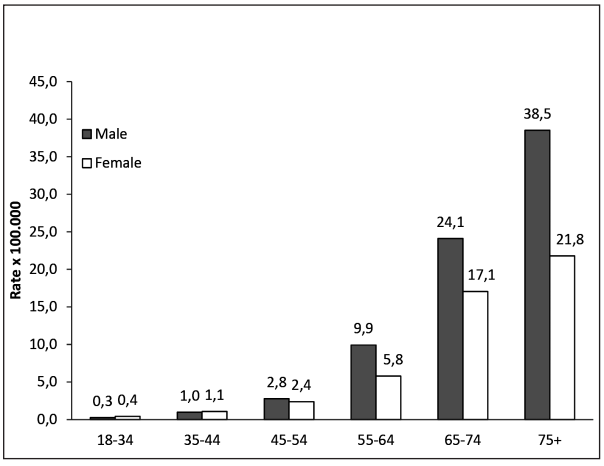

Fig. 2. Annual incidence rate (per 100,000) of idiopathic pulmonary fibrosis defined by gender and age in the Lazio region, years 2005-2009.

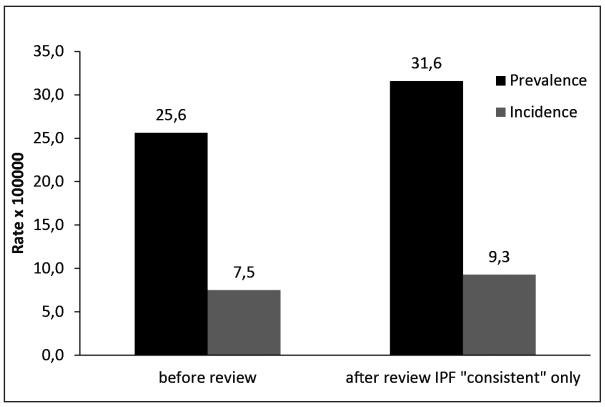

Fig. 3. Prevalence and incidence of idiopathic pulmonary fibrosis in the Lazio region (years 2005-2009), according to the ICD9-CM code 516.3 and the definition of "consistent IPF" following review of a random sample of hospital charts.

Discussion

A significant increase in IPF incidence incidence and mortality rates has been reported in Europe and the United States over the past 20 years (35). In Denmark, estimates of disease incidence have changed from 5.28 per 100,000 in the period 1995-2000 to 7.27 per 100,000 in 2001-2005 (26). In the United Kingdom, two nationwide studies based upon diagnoses of pulmonary fibrosis registered into a computerized general practice database (THIN) reported an increase in incidence rates from 4.6 per 100,000 in 1990-2003 and of 7.4 per 100,000 in 2000-2008 (23). A third United Kingdom study, recently carried out using the Hospital Episode Statistics database, a database recording information on all admissions to National Health Service (NHS) hospitals in England, showed an admission rate for fibrosing alveolitis-clinical syndrome of 14.9 per 100,000 per year, with an increase of 5% per year from 1998 to 2010 (25). Although the incidence data reported by Navaratnam and colleagues refers to admission rates, previous data from the same Authors indicate that admission rates parallel mortality rates in the same population, likely due to low rates of repeated admissions, and may be used to reliably infer disease incidence (23).

In the United States, a geographically based study was conducted in the Olmsted county (Minnesota, USA; population 128,000) in the years 1997-2005 by Fernandez-Perez and colleagues, who estimated IPF incidence to vary from 8.8 to 17.4 per 100,000 per year and prevalence from 27.9 to 63 per 100,000, according to the case definitions of "definite UIP" and "possible UIP", drawn in adherence to the ATS 2002 guidelines (28). Also in the United States, Raghu et al., analyzed a large health care claims database covering more than 3 million people across 20 states. Based upon the presence/absence of specific clinical, pathological and radiological procedures recorded, the Authors defined cases as "broad case" (without specific procedures) or "narrow case" (with specific procedures) to estimate IPF prevalence and incidence at 14.0 and 6.8 per 100,000 for the "narrow case" definition and at 42.7 and 16.3 per 100,000 for the "broad case" definition (6).

We obtained data from the Lazio regional health information systems according to standardized procedures (24). After "clinical" revision of a subsample of medical charts we provided prevalence and incidence estimates strikingly similar to those obtained from northern Europe and northern America studies. IPF crude incidence estimates in European studies vary from 4.3 per 100,000 in the Norwegian study of Von Plessen et al. (15) to 7.4 per 100,000 in the 2011 British study by Navaratnam et al. (23). The USA study of Fernandez Perez et al. posts IPF incidence at 8.8 per 100,000 (28). In addition, disease duration, as based upon the estimate of the ratio of prevalence to incidence, varied form 2.6 years in the Raghu's study (6) to 4.5 in von Plessen's (15), not dissimilarly from our estimate of 3.6 years.

IPF incidence trends by age and gender observed in our study are also strikingly similar to those described in the USA studies (6, 28), pointing to aging and male gender as two important risk factors as did the Taiwanese study reported by Lai and coworkers, although in the presence of a markedly lower prevalence (29).

The study had some methodology limitation. Firstly, our review of hospital admission records was carried out on 348 hospital charts that were extracted from the admissions of six out of the 20 hospitals of the Lazio region filing more than 20 records coded with the 516.3 ICD9-CM codes during the 2005-2009 study period. These six hospitals covered 24% of the total number of 516.3-coded admissions evaluated in the study. Importantly, no significant differences in clinical and demographic features, between this sub-group and the total population evaluated in the study, were apparent.

Secondly, there are limitations inherent in the use of the ICD9-CM 516.3 code for the assessment of IPF epidemiology, as the code includes the non-specific diagnosis "alveolar capillary block syndrome" (30), in addition to "diffuse (idiopathic) pulmonary fibrosis" and the "Hamman Rich syndrome", both synonymous definitions of idiopathic pulmonary fibrosis, chronic or acute (1).

Thirdly, only 0.86% of records examined in the assessment of diagnostic accuracy (0,53% of the total population) carried the 33.28 (Open biopsy of lung) and 34.21 [Trans-pleural thoracoscopy] codes for surgical pulmonary biopsy. It thus appears that surgical biopsies have been carried out in a small minority of patients with possible or inconsistent UIP patterns, possibly due to the reported high morbidity of the procedure in a population of individuals of advancing age. It is also worth considering that, in the absence of treatments of proven efficacy, the indication to invasive procedures for the diagnosis of IPF was not perceived as cogent at the time this patient population was admitted and evaluated (31).

Even with the above methodological limitations, the data suggest that the complexity of the diagnosis of IPF requires multidisciplinary teams with specific experience in interstitial lung disease clinical research (32, 33). In fact, the finding that a sizeable number of revised hospital charts, among those carrying the ICD9-CM 515, 516.8 and 516.9 codes, were eventually re-defined as "IPF confident" cases, strongly suggests that misdiagnosis, or misreporting, of IPF cases may lead to inaccurately low IPF prevalence estimates in hospital admission record-based epidemiological studies. In addition, in the context of the very low number of surgical biopsies carried out on the study population, the large proportion of hospital charts revised as "possible IPF" does indicate another cause for underestimating IPF incidence, while stressing the need to take further the non-invasive diagnostic approach to IPF promoted by the ATS/ERS/JRS/ALAT recent guidelines (1). In this context, it is foreseeable that increased adherence to the ATS/ERS/JRS/ALAT 2011 guidelines and the ATS/ERS updated multidisciplinary classification of idiopathic interstitial pneumonias (34), together with the introduction of the new ICD9-CM-2012 descriptors, will contribute to improve upon the assessment of IPF as a public health problem.

Finally, the study demonstrates, by using a large database encompassing hospital admission of a population of 4.7 million and by validating the database records by means of a multidisciplinary review of a representative sample of hospital chart, that IPF incidence and prevalence in a large central-southern Italian region are strikingly similar to those derived from the hospital and general medicine databases of northern Europe and the United States. As a number of epidemiological studies point to an important role for environmental hazards in IPF incidence and prevalence (36- 39), the findings of this study would suggest that IPF incidence is more likely driven by industrialization, urbanization and western lifestyles than the ethnic variables characterizing different European regions.

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