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Worldwide Idiopathic Pulmonary Fibrosis Prevalence, Morbidity and Mortality

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Abstract

Despite being a rare condition, idiopathic pulmonary fibrosis appears to be spreading, and because of reporting and recognition bias, its incidence and prevalence may be higher than previously thought. It is believed that both host and environmental variables contribute to the chance of developing IPF, and understanding these aspects may help create better preventative and treatment methods. IPF has significant personal and monetary expenses, making therapies to lessen the illness's toll urgently required.

IPF mortality in several countries and showed that, with some regional variations, it is rising over time in the majority of the nations examined. However, rates are more stable and show less volatility than in earlier studies, which may indicate that we are getting close to the genuine level. It's critical to have accurate estimates of the worldwide illness burden now that new treatments for IPF are available. Increases in incidence may actually be the cause of rising mortality rates, but certain trends are probably related to modifications in diagnostic procedures. Future registration systems are expected to be more valuable if death certification is more transparent, accurate, and thorough, and prospective IPF registries that are being established in several nations could offer a linked resource to support the validation of routine mortality data.

Keywords: idiopathic pulmonary fibrosis; prevalence; morbidity; mortality

Introduction

Idiopathic Pulmonary Fibrosis

A specific type of chronic, progressive, fibrotic lung illness with no known cause is called idiopathic pulmonary fibrosis (IPF) [1]. It mostly affects middle-aged to older persons and is distinguished by the typical interstitial pneumonia's underlying histological appearance. It's complicated pathobiology is thought to be influenced by aging-related changes in alveolar epithelial cell integrity, genetic and epigenetic factors, and the reactivation of embryonic signaling pathways [1, 2]. Ventilation is hampered by progressive fibrosis with loss of normal lung tissue, which also impairs gas exchange, causes respiratory discomfort and activity limitations, lowers quality of life, and finally results in mortality. However, there are currently no effective treatments for IPF [3]. Only one medicine has been proven in clinical studies to potentially delay the disease's progression, and only a small percentage of patients can receive surgical therapy with lung transplantation. The field of IPF is currently experiencing a period of considerable opportunity and promise [4].

There is reason to believe that multiple effective treatments are about to be created thanks to key developments in our understanding of disease mechanism, the creation of novel agents by academia and industry, and the establishment of multicenter networks skilled in the management of large clinical trials. An accurate understanding of the epidemiology of IPF will be crucial as management choices for IPF patients advance so that healthcare systems and policy-makers are well-equipped to support care [5]. IPF that affects two or more first-degree relatives who belong to the same biologic family is referred to as familial IPF. Familial IPF is expected to make up about 5% of cases and is typically difficult to tell apart from sporadic occurrences [6].

There are a number of possible risk factors for the emergence of IPF. These comprise smoking, comorbid conditions (particularly gastroesophageal reflux disease [GERD]), occupational and environmental exposures, and genetic polymorphisms. It is crucial to identify IPF risk factors since they may help with early diagnosis, prevention tactics, and cutting-edge treatments [7]. It seems plausible that inhaled exposures caused at least some cases of IPF, according to a number of lines of evidence. First, a variety of putative triggering agents in the pathogenesis of IPF support the idea of recurrent alveolar epithelial cell stress through fundamental science and animal investigations. Second, epidemiologic research has found regional variations in IPF prevalence within nations, particularly in areas with a high level of industrialization [7]. Men are also more prone to get the condition than women, who traditionally have been more likely to smoke and work in dirty jobs. Third, it is undeniable that well-known occupational lung

disorders like asbestosis and silicosis contribute to fibrotic lung disease, raising the prospect that other, less well-known exposures may have a similar effect. Fourth, compared to controls, patients with IPF had increased quantities of inorganic particles in their hilar lymph nodes, according to autopsy investigations [8].

Epidemiology

Idiopathic pulmonary fibrosis (IPF) is a fatal condition with no recognized cause. Epidemiological studies have shown that people with IPF have a risk of developing lung cancer of up to 22%, which is roughly five times higher than that of the general population. Even though the connection between lung cancer and IPF has been thoroughly researched, no distinct common pathogenic mechanism has yet been established [9, 10]. Idiopathic pulmonary fibrosis (IPF), also known as cryptogenic fibrosing alveolitis, is an interstitial lung disease that progresses and has no recognized cause. Although the pathologic characteristics of fibrosis and inflammation are well established, additional diagnostically significant signs are typically not well understood [10]. In fact, there is a misconception in some quarters that IPF's pathologic characteristics are generic and that the diagnosis is only possible by ruling out other histologically distinct entities. IPF has a range of clinical symptoms. There is a wide age range for the disease, with reports of cases in infants and young children as well as middle-aged individuals [11].

Although cases with an abrupt onset and fulminant course have also been reported, the majority of patients appear slowly over many years. In one-third or fewer of patients, corticosteroid or cytotoxic therapy results in a positive response. The discrepancies in age at onset, presentation, clinical history, and responsiveness to medication of some IPF patients have not yet been satisfactorily explained [12]. This research offers proof that there are four different types of interstitial pneumonia that fall within the IPF umbrella. The clinical variability seen among patients with this illness may be explained by a failure to recognize these various entities. This IPF pathologic classification should also help in determining the prognosis, selecting a treatment plan, and improving [13].

Pathologic Classification of Idiopathic Pulmonary Fibrosis

The morphologic spectrum that has historically been referred to as IPF includes four histologically different types of idiopathic interstitial pneumonia. This classification scheme incorporates two additional entities, acute interstitial pneumonia (Hamman-Rich disease) and the recently described nonspecific interstitial pneumonia (NSIP), in addition to maintaining Liebow's original classification of usual interstitial pneumonia (UIP) and desquamative interstitial pneumonia (DIP) [14, 15]. Despite still being significant types of interstitial pneumonia in general, lymphoid interstitial pneumonia and GIP are excluded from the IPF category since they are typically not idiopathic; Giant-cell interstitial pneumonia (GIP), a lymphoproliferative condition frequently linked to immunodeficiencies, is a symptom of hard-metal pneumoconiosis [8]. LIP is a lymphoproliferative disorder. This classification does not include bronchiolitis obliterans with interstitial pneumonia (BIP), also known as bronchiolitis obliterans-organizing pneumonia (BOOP), because pathologically it is more of an intraluminal abnormality than an interstitial one. Additionally, rather than diffuse interstitial shadows, its most typical form is radiographically characterized by patchy air space opacities [14, 16].

Diagnosis

The lack of widespread acceptance of these pathologic subtypes that make up IPF can be attributed to the fact that IPF is frequently diagnosed based solely on clinical evaluation, without the benefit of an open-lung biopsy. Consistent pathologic criteria for diagnosis have not been used, even when biopsy specimens are available [17]. Only the presence of fibrosis and inflammation in variable degrees, a characteristic shared by all idiopathic interstitial pneumonias, was chosen by most investigators as the pathologic criterion for diagnosis [18]. However, significant distinctions between fibrosis and inflammation in terms of distribution, intensity, and type were often overlooked, and these distinctions serve as the foundation for the pathologic classification of both entities.

Mortality of IPF

The percentage of deaths in the general population that are thought to be caused or contributed to by IPF each year is known as IPF-related mortality. Data on IPF-related mortality are mainly derived from death certificates by national registries. These investigations are typically constrained by diagnostic misclassification and disease under-recognition (patients with IPF are not captured) [19]. Mortality increased by 34% over the research period and was greater than previously reported. Men had greater death rates than women, but women's rates rose more quickly, perhaps as a result of shifts in smoking habits [20]. Compared to Blacks and Hispanics, mortality rates were greater in older age groups and among White people. 60% of individuals with IPF had IPF as their primary cause of death. Other prevalent causes of mortality in IPF patients included lung cancer, ischemic heart disease, pneumonia, heart failure, cerebrovascular illness, and pulmonary embolism [21, 22].

Uncertainty exists regarding the causes of the rising IPF mortality, including whether it is a result of recognition or reporting bias or a genuine rise in mortality. In terms of public health, the death rate associated with IPF is comparable to that of numerous cancers, such as non-lymphoma, Hodgkin's renal cancer, and esophageal cancer [20].

IPF Mortality rate in US and UK

Idiopathic pulmonary fibrosis (IPF) is becoming more common, according to earlier studies, in the US and UK [23]. The incidence of IPF in the UK has been tracked using death registrations and primary care data. The term IPF clinical syndrome (IPF-CS) is used to refer to participants in this study because standard clinical data sets were employed [24]. To get a yearly normalized estimated number of deaths, death registration rates by age and stratum between 1968 and 2008 were computed and then applied to the population in 2008 [25]. Poisson regression was used to calculate annual mortality rate ratios. Incidence rates of IPF-CS between 2000 and 2008 were determined using computerized primary care records, stratified by age, sex, and geographic region. Survival rates between calendar years were also examined [26]. From 0.92 per 100 000 people in the 1968–1972 calendar years to 5.10 per 100 000 people in the 2006–2008 calendar years, the annual death certificate recording of IPF-CS increased six-fold over the study period and was more prevalent in men and older age groups [27]. From 2000 to 2008, there was a 35% increase in the incidence of IPF-CS in primary care, with an overall incidence rate of 7.44 per 100 000 person-years. The incidence was higher in Northwest England, among older people, and among men. In the UK, IPF-CS is becoming more common in primary care, and more deaths from this cause are being reported. According to earlier research, the UK experiences more than 5000 new instances of cancer annually [24, 28, 29].

IPF Mortality rate world wide

From 1999 to 2012, information on pulmonary fibrosis mortality was given by ten different nations. According to the most recent data, age-standardized mortality varied between 4 and 10 per 100,000 people, with the lowest rates occurring in Sweden (4.68 per 100,000), Spain (5.38 per 100,000), and New Zealand (5.55 per 100,000), and the highest rates occurring in England and Wales (9.84 per 100,000) and Scotland (10.71 per 100,000), as well as Japan (10.26 per 100,000) [30, 31]. Across all nations, there were consistently seen positive correlations between increasing age and male sex. Idiopathic pulmonary fibrosis was documented as the underlying cause of death in two-thirds of known cases, and somewhere on the death certificate in 80% of instances, according to validation in a local cohort [32, 33]. Despite the fact that death certification will almost probably underestimate genuine mortality, idiopathic pulmonary fibrosis mortality is steadily rising globally. Idiopathic pulmonary fibrosis (IPF) patients were associated with between 28,000 and 65,000 deaths in Europe and between 13,000 and 17,000 deaths in the United States in 2014 [31].

IPF Clinical Syndrome Mortality

The earlier study revealed regional variations in IPF-CS mortality. Crude death rates ranged from 3 per 100,000 to 9 per 100,000, with New Zealand, Sweden, and Spain having the lowest rates and the UK and Japan having the highest [33, 34]. Most of the countries analyzed experienced an increase in age-standardized death rates over time, though some, like the United

Kingdom, saw it more sharply. In the United States, where rates were lower than in the United Kingdom, the rate of rise was the smallest, and utilizing data on multiple cause death, there did not appear to be an increase throughout the time period under investigation [35]. This investigation corroborated the previously described clear connection with male sex and advancing age worldwide. Data on deaths with multiple causes of death showed that these deaths were significantly more common when IPF-CS was not reported as the primary cause of death on the death certificate [35]. IPF-CS was stated as the underlying cause of death in two-thirds of cases in a UK cohort of patients with IPF, and indicated on the death certificate in 80% of instances, indicating that mortality data may understate frequency by 20–30% [36].

The inclusion of worldwide data from numerous nations, including some that have not previously been investigated, as well as our emphasis on data from the first decade of the twenty-first century which has previously only been evaluated in England and Wales are the study's strengths. Our validation cohort is the most recent effort to evaluate the reported causes of death for IPF patients. Previous research from the United Kingdom and the United States in the 1990s has shown that death certification understates disease burden [37, 38]. The combination of national disease incidences using meta-analysis results in a global composite estimate that can be viewed as a synthesis of the best data currently available into global summary statistics, with the high heterogeneity statistics being an inevitable result of correlations among diverse communities and cultures [39].

In light of these findings, numerous investigations have shown a connection between IPF and specific occupational and environmental exposures. Diagnostic misclassification (especially for research conducted before the IPF declarations) presents the possibility of flawed relationships, just like incidence and prevalence estimation studies [39, 40]. A follow-up to the current study in a few years would be helpful to evaluate the impact. International guidance from the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association published in 2011 should help standardize and encourage specific diagnosis.

Conclusion

Data on incidence and death must be coordinated globally as idiopathic pulmonary fibrosis becomes a significant public health issue. The objective of this study is to thoroughly evaluate all existing studies that look at the worldwide disease burden. Idiopathic pulmonary fibrosis is becoming more common, and rates are converging between nations. The main shortcomings of this review study were the trustworthiness and variation of cause-of-death data. A significant portion of patients with IPF will die from another cause, particularly cardiovascular disease or lung cancer, and even if IPF is listed as a contributing factor, multiple cause of death data are not as widely published. Our validation cohort analysis shows that more patients with IPF have the disease listed on their death certificate than in earlier studies. Depending on the depth of the diagnostic work-up performed prior to death, IPF may not be correctly identified or diagnosed when it is the underlying cause of death.

Authors' contributions

All the authors have contributed to the research work and preparation of the final manuscript.

Conflict of interests

The authors declare no conflict of interests.

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Ethical declaration

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