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Epidemiology of Idiopathic Pulmonary Fibrosis

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a type of interstitial lung disease (ILD) classified under idiopathic fibrotic disorders of the lung. It is the most common type of ILD presenting clinically in the seventh decade of life, almost always at the later stage of illness, attributed to its earlier nonspecific presentation. The term IPF is used when no specific cause for pulmonary fibrosis is identified. Initially described in 1944, recent advances in lung biopsy and pathology have described the disease in detail. This led to further classification of ILD. Also, there have been multiple recent studies indicative of an increased incidence. However, accurate epidemiological data for IPF is minimal, with some being contradictory. Inconsistency in the case definition criteria and methodology has resulted in epidemiological inaccuracy when used to detect patients in the study population. To avoid inaccuracy American Thoracic Society collaborated with the European, Japanese, and Latin American Thoracic Society to arrive at a consensus resulting in 2010 IPF evidence-based guidelines. Notable epidemiological differences are observed in the European, American, and Asian countries. Some countries have set up national registries to collect essential patient data for future studies and comparison with other countries. In this topic, we try to glean over the epidemiology of IPF.

Keywords: Epidemiology, Idiopathic, Interstitial, Fibrosis, Lung, Disease

1. Introduction

IPF is a rare pulmonary disease affecting patients often in their sixth or the seventh decade of life. The disease course is progressive, causing permanent damage to the pulmonary tissue resulting in restrictive lung disease and hypoxia. Pharmacological therapeutic options are sparse and limited to new medications such as nintedanib and pirfenidone [1]. Without lung transplantation, IPF is lethal, and the patient dies from acute pulmonary failure in two to four years on average [1]. Lung transplantation has altered the disease course and improved longevity. As it is a rare disease, an accurate, consistent epidemiological methodology needs to be followed for data collection to measure the incidence and prevalence of IPF [1]. The consensus evidence-based guidelines in 2011 guide how to arrive at a diagnosis after ruling out other ILD causes and the need for multidisciplinary specialist's input.

2. Predisposing risk factors

2.1 Age and gender

As the patient's age increases, the IPF incidence increases with a more significant occurrence in men than women as per epidemiological studies [2]. The mean age at which diagnosis was established was 66 years. On average, most patients diagnosed with IPF lie between the age of 40 to 70 years [3]. Occurrence in younger patients (< 40 years) is rare. In most studies, men accounted for most cases except for a Norwegian study which disclosed a higher prevalence in females [4]. A recent study with an IPF score algorithm was generated using logistic regression to measure the exact incidence and prevalence values of 14.6/100,000 person-years and 58.7/100,000 person-years. The IPF score algorithm had a positive predictive value (PPV) of 83.3% [1].

The Gender-Age-Physiology (GAP) index calculated to predict IPF mortality by dividing the IPF into three stages GAP one, two, and three did not anticipate a decline in pulmonary function based on the severity of the GAP index [5]. IPF disproportionately affecting 71% of males was observed in a recent retrospective cohort study [6]. Age-adjusted males were strongly linked to an increased risk (40%) for lung transplantation or death [6]. In males, the cough was associated with dyspnea due to smoking-related airway disease, whereas in females, it was due to acid reflux disease. A lower diffusion capacity than predicted for age, senility, dry or productive cough with phlegm correlated with a decreased survival in males free of transplant compared to females. This may be due to excessive male exposure to risk factors in the environment, such as cigarette or occupational smoke particulate material and sex hormones [6]. Sex hormones modulate the immune system with a humoral immune response augmentation by estrogen and androgens, suppressing the cell-mediated and humoral immune response [7].

Age is a substantial independent predictor of IPF [8]. Aging lung undergoes anatomical and physiological changes predisposing it to IPF. The elderly may have abnormal recruitment of protective mesenchymal cells and fibrocytes in response to acute lung injury [9]. Increased endoplasmic reticulum oxidative stress, unfolded protein response lead to apoptosis of type 2 alveolar epithelial cells increasing susceptibility to IPF in the elderly [10]. Immune changes are seen in adaptive than in innate immunity. Adaptive immunity changes affect the T lymphocytes more than the B lymphocytes. There is a decrease in differentiation, antibody affinity, and interaction with T cells & B cells. There is a decline in naïve T cells (with short telomere and restricted repertoire), transition to Th2 response phenotype, an abnormal increase in memory, and effector cells with large CD28 deficient CD8 endstage clonal population [11, 12]. The T cell response leads to an inadequate vaccination and abnormal viral response [13, 14]. Many IPF patients have a shorter telomere with no detectable mutation in telomerase [15]. The elderly with a short telomere on exposure to susceptible environmental exposure may trigger apoptosis resulting in fibrosis. Old lungs may provide the appropriate local milieu for gammaherpesvirus or any other virus to cause fibrosis [9]. Smoking promotes epigenetic changes in deoxyribonucleic acid methylation, histone modifications, and microribonucleic acid [16].

Increased mortality in IPF is associated with a consecutive increase in oxygen desaturation episodes during a six-minute walk test. Males during their disease course experienced frequent faster desaturation events than females. In contrast to males, the disease progression rate is slower, in females contributing to survival differences. This may contribute to but does not entirely inform more remarkable female survival in IPF. Even in fibrotic diseases, females have lesser fibrosis than males, possibly due to sex hormone exposure [17]. Most females at their diagnosis of IPF are in a

postmenopausal state with diminished estrogen levels. The precise role of hormonal imbalance on the fibrotic process needs clarification with further studies.

2.2 Smoking

Smoking is a practice of burning raw or refined tobacco plant leaves and breathing in the resulting smoke for taste. Smoking is an ancient frequent recreational drug use still in practice. Tobacco smoke contains multiple active chemicals which are either absorbed in the mucosa or delivered to the lungs. Tobacco smoke exposure results in multiple lung diseases such as chronic obstructive pulmonary disease (COPD) and lung cancer. Tobacco smoke contains numerous chemicals exerting various delirious cellular effects on multiple organs affecting their metabolic function. As a primary intermediary, the lung faces the brunt of tobacco smoke exposure in active and passive smokers. Tobacco smoke exposure contains acrolein, benzene, benzopyrene, acetaldehyde, formaldehyde, carbon monoxide, 1,3-butadiene, and tobacco-specific nitrosamines with human toxicity potential. Additionally, the long-term effects of flavors and additives used in cigarettes on tobacco smoke and lung are unknown. Another issue is the lack of regulation regarding performance standards for ingredients used in making cigarettes [18].

Smoking has been included as a potential etiologic agent recently over the last few decades due to its significant prevalence among the IPF patient population [19]. However, the association was proposed as early as 1969, which independently increases the significant risk of IPF disease [20]. Another disease that shares the pathological features of COPD and IPF, known as combined pulmonary fibrosis and emphysema (CPFE), is seen predominantly in male smokers. Smoking may also enhance the systemic immune response to numerous environmental etiological agents, increasing the IPF risk by 60% in smokers [21]. The cytological effect of smoking in IPF can be direct or indirect, impacting the clinical course and survival. The evidence for a direct effect of smoking causing pulmonary fibrosis is minimal [22]. Tobacco use prevalence in IPF patients ranges from 41–83%, the range attributed to the definition criteria used in various studies [3, 23]. Alveoli is the main target of the IPF, resulting in diminished diffusion capacity for carbon monoxide. Alveolar wall fibrosis seen in smokers is due to cigarette smoke exposure, and there is an increase in fibrosis based on the duration and intensity of exposure [24]. Increased oxidative stress in current and ex-smokers may promote IPF disease progression [25]. IPF is also known as senescence disease due to its occurrence in tobacco smoke exposure patients' in an age-dependent style [26].

Smoking results in a small airway inflammatory cell recruitment comprising neutrophils, macrophages, and langerhans cells, resulting in severe immune and other lung cell defects. However, only a few patients end up having clinically significant diffuse lung disease. Probably only a minority of patients progress into a vicious inflammation cycle resulting in IPF due to constant environmental stimuli and lapse of anti-inflammatory mechanisms [23]. A brief outline of the IPF pathogenesis is explained in **Figure 1** [19]. Persistent cigarette smoke exposure (CSE) leads to a predominant M2 macrophage activation in the lung. In contrast to the M1 Phenotype, the M2 macrophages are ineffective in host defense, inadequately clear noxious agents, and increase fibrotic mediators synthesis.

This results in a vicious, inflammatory cascade causing an increased expression of transforming growth factor α 1 (TGF α 1), epidermal growth factor (EGF), and mixed metalloproteinase (MMP) expression on epithelial cells leading to an epithelial to mesenchymal transition of the epithelial cells. This increases the pulmonary myofibroblasts, which are relatively resistant to apoptosis, have a lower activation threshold, augmented profibrotic response, and are activated by apoptosis debris.

Figure 1. Pathogenesis of idiopathic pulmonary fibrosis. RONS, reactive oxygen and nitrogen species; TGF, transforming growth factor; EGF, epidermal growth factor; MMP, matrix metalloproteinase; IL, interleukin.

This leads to an abnormal increase in lung parenchyma myofibroblasts, profibrotic mediators, profibrotic receptor expression, and epithelial cell apoptosis. Finally, the lung parenchyma changes kick in with increased extracellular matrix (ECM) deposition making it difficult for gas exchange. The thick ECM increases lung contractility and decreases lung compliance.

Telomere dysfunction noted in the epithelial precursor cells simulating senescence can be seen sporadically and in patients with genetic abnormalities [27]. In IPF, the primary cell type affected is the alveolar epithelial precursor cell. The Wnt and the Notch signal pathways are essential in sustaining and separating the precursor cells (epithelial and mesenchymal). Defective functioning of these pathways results in pneumocyte loss followed by significant inflammation during defective attempts at repair due to molecular signals' release [27]. Smoking causes a decrease in histone acetylation and methylation, resulting in the antifibrotic cyclooxygenase-2 gene and interferon-gamma inducible protein suppression [19].

In an earlier study comparing survival disparities and smoking status in IPF patients, smokers had lower survival than nonsmokers [27]. Lifetime nonsmokers

had a better outcome than prior smokers and the combination of all smokers, including active and ex-smokers. This survival disparity suggests that smoking results in a decrement of IPF patient's survival. Current smokers had better survival than former smokers due to a healthy smoker effect [27]. The reasoning for this effect is that a smoker with the advanced symptomatic disease will quit smoking for health benefits. In a recent study analyzing differences in severity adjusted survival among active and prior smokers, active smokers' minimal survival benefit diminished on adding age to the model [28]. The healthy smoker effect was absent in this study. The earlier study's survival disparity was not apparent after a composite physiologic index (calculated from the pulmonary function tests) was added to the severity adjustment [27].

Current smokers are younger than ex-smokers and nonsmokers, explaining the more prolonged survival seen in these patients [28]. Smoking-associated comorbidities were frequent in current smokers with more pack-years of smoking than ex-smokers [28]. The frequent comorbidities associated with smoking include cardiovascular disease (CVD), coronary artery disease, hypertension, cerebrovascular disease, diabetes, and heart failure may affect IPF mortality. Females had a higher incidence of asthma and diabetes than males, while active smokers had a higher incidence of COPD and lung cancer than nonsmokers. In the recent study, only a diagnosis of CVD, COPD at any time, and insulin use at the time of diagnosis resulted in a poor survival on severity adjustment analysis [28]. Smoking prevention is an important cause to decrease mortality and morbidity in the western and third world.

2.3 Environmental factors

Occupational disclosure to surrounding elements contributes around 26% population attributable fraction (PAF) of total cases of IPF [29]. This suggests that IPF is a heterogeneous disease. Exposure to environmental agents occurs during the occupation, residence in a specific area, and recreational activities. The exposure may be due to a single agent or multiple agents, which is difficult to quantify. Recently air pollution has been recognized as a critical etiology and an exacerbating factor for IPF [30]. In comparison to the population size exposed to these agents, only a few develop IPF. IPF occurs more so in individuals with genetic susceptibilities exposed to these environmental agents. There are three factors essential in the pathogenesis of IPF; one is the environmental agent exposure, the second is the duration of exposure, while the third is the host response to the persistent exposure controlled by genetic susceptibility. Persistent environmental agent exposure results in a biochemical reaction (in most cases oxidative stress) followed by an insistent immune response to the agent, causing lung fibrosis [31]. As IPF is a rare disease, case-control studies are best suited for it. They come with many challenges regarding data collection as they are subjected to multiple factors that dilute the study's purpose. These factors include disease misclassification (pneumoconiosis classified as IPF), exposure misclassification (recall bias), and variable susceptibility to fibrogenic agents (dose and duration of exposure along with genetic susceptibilities) [31]. Adequate clinical significance is denied to occupational and environmental history when clinical information is obtained from the patients. Pulmonary tissue biopsy analysis in IPF patients with Particle induced X-ray emission revealed a high content of silicon, magnesium, titanium, and high surface silicon to a sulfur ratio [32, 33]. Elementary analysis of hilar and mediastinal lymph nodes using fluorescent x-ray analysis disclosed high nickel content and a minimum silicon elevation [34]. Over the last two to three decades, multiple case-control investigations have identified various environmental agents suspected to be a causative factor for

IPF [35]. These include metal dust (brass, aluminum, arsenic, cadmium, copper, molybdenum, tungsten, cobalt, uranium, vanadium, lead, and steel), raising birds, farming, wood dust, hairdressing, stone cutting/polishing, and organic dust from livestock & vegetation.

A southern European case–control study found two occupations with an increased prospect of having IPF, which increased with the exposure duration. One group included the farmers, veterinarians, gardeners, and the other group included metallurgical and steel industry workers [36]. A self-reported exposure history correlated with the increased risk, and the authors evaluated the history with a job-exposure matrix (JEM). Although an American multicenter study identified multiple jobs related to an increased risk of IPF, the multivariate regression model revealed the strongest link between raising birds and exposure to vegetable or animal dust [37]. Three occupations in the United States of America (USA), namely metal mining, wood building (mobile homes), and structured metal fabricated products, had an increased IPF mortality risk based on the mortality data [38]. A Korean study on dust exposure divulged its impact on IPF patient's prognosis. Patients with exposure had an earlier IPF diagnosis, prolonged symptom duration at diagnosis, and increased mortality than those with no exposure [39].

Organic dust involves farming, gardening, animal husbandry, poultry farming, carpentry, and pesticides. Animal husbandry is an agriculture branch related to animal rearing for food and other products with significant exposure to animal feeds, products, and waste. A multicenter case–control study done in Egypt was the first to reveal an increased IPF risk in females than males [40]. Females were at a higher risk while working in poultry farming, farming with organic dust, and occupational pesticide exposure. Males carried an increased risk in carpentry, chemical, and petrochemical industries occupations. Both sexes had an increased risk with cat or bird exposure. IPF risk was minimal in sales and clerical jobs [40]. A Belgian multidisciplinary team studied 244 IPF patients, divided them based on prior exposure to molds or birds, and simultaneously compared them to chronic hypersensitivity pneumonitis patients. Patients exposed to birds or molds were associated with a decreased fatality than unexposed patients [41].

Mineral and metal dust exposure are well known to increase the IPF risk. A British study done in a major engineering company evaluated IPF mortality in employees exposed to occupational metal exposure. It revealed a strong association between IPF fatality and metal exposure strength and duration [42]. A multicenter Japanese study disclosed that patients with clerical occupations had a lower risk of IPF than patients with prior metal exposure [43]. Hilar lymph nodes histopathological analysis in IPF patients compared to controls revealed excess aluminum and silicon related to an increased risk of IPF [44]. Two smaller South Korean case–control studies revealed an increased IPF risk with exposure to stone, sand, silica, and metal dust [45, 46]. Asbestos occupational exposure results in asbestosis are well established; however, the effects of mild to moderate exposure on IPF are unclear. A study comparing United Kingdom (UK) asbestos imports per year to IPF mortality for any relationship was done. The overall asbestos exposure outcome was not addressed in this study. Linear regression models revealed a significant positive linear association between imports and IPF mortality, suggesting an association between IPF mortality and asbestos exposure [47]. UK is undergoing a national study by the name IPF Job Exposure study (IPF-JES) to evaluate the IPF risk associated with occupational asbestos exposure.

Wood dust exposure during carpentry and woodworks is related to a higher IPF risk and follows a dose–response association in UK based case–control study [48]. A Swedish multicenter case–control study on occupational exposure revealed a higher IPF risk in males with birch dust and hardwood dust exposure and no increased risk

with metal exposure [49]. A similar increased association was observed in an Italian case series and an Egyptian multicenter case–control study [40, 50]. Air pollutants present in the environment may have an important role apart from smoking in IPF incidence. An Italian study evaluated the relationship between IPF occurrence in patients persistently exposed to ambient air pollutants (nitrogen dioxide, particulate matter [aerodynamic diameter less than 10 μm], and ozone) [30]. Final results were not adjusted for smoking which was a limitation of this study. An increment in nitrogen dioxide concentration resulted in a significant IPF incidence rate increase with no association observed with ozone and particulate matter. IPF acute exacerbation risk is higher in patients exposed to nitrogen dioxide and ozone in the prior six weeks [51]. Conflicting results of studies on lung function decline on ambient particulate matter (APM) exposure have been observed. One study revealed an accelerated lung function decrement in patients exposed to APM with an aerodynamic diameter of less than 10 μm , and no relationship was noted with APM with an aerodynamic diameter of less than 2.5 μm [52]. No association with a lung function decrease rate and ambient air pollutant exposure was identified in a 25 patient prospective group study [53]. A large French cohort study evaluated the effect of air pollutants on IPF disease outcomes [54]. Patients exposed to ozone had a higher risk of IPF acute exacerbations, whereas those exposed to APM with an aerodynamic diameter of less than 10 or 2.5 μm had increased mortality. In conclusion, APM exposure regularly can play a role in pathophysiology and may affect IPF disease progression.

A 2019 meta-analysis reviewed the literature and case–control studies. The following exposures (metal dust, silica, wood dust & vapor, gas, dust, or fumes) were significant statistically [29]. The pooled odds ratio for agricultural work was elevated with no significance. A recent South Korean meta-analysis revealed a statistically significant association with pesticide, metal, and wood dust exposure. No significance was observed with stone or sand dust and textile dust exposure. Agricultural workers and woodworkers had a significant increase in IPF risk statistically, whereas no significance was seen in textile workers [55]. In this Japanese study, consumption of fish rich in polyunsaturated fatty acids had a significantly lower odds ratio with regards to IPF, and it may have a suppressive effect on lung fibrosis [56]. A decline in IPF rate is achievable if environmental exposure is modified. It is a demanding process to obtain a detailed exposure history as it is subject to recall bias, difficulty in quantifying heterogeneous exposure intensity and its cumulative variation [57]. Also, it is difficult to identify a specific exposure effect when multiple are in play. For obtaining accurate epidemiological data, a standard operational definition for occupational and environmental history needs to be arrived at based on consensus so that it is easier to compare multiple studies (case–control and cohort) precisely to understand the IPF occurrence. If occupational and environmental exposure results in IPF, implementing measures to alter the exposure or improve the occupational environment may decrease IPF risk, and prevention may become a public health issue.

2.4 GERD (gastroesophageal reflux disease)

Gastroesophageal disease is a suspected risk factor for IPF development and progression currently under intense debate [58, 59]. The prevalence of pulmonary fibrosis was statistically significant in veterans with GERD history compared to healthy controls [60]. GERD incidence in IPF is higher than the average population and ranges from 8–87%. The variation is due to the methods used in diagnosis, diagnosis definition used and the types of data collected [61–63]. The greater incidence could be due to the common risk factors such as smoking and aging [64].

The gastroesophageal abnormalities seen in IPF patients include transient lower esophageal sphincter (LES) relaxations, decreased upper esophageal sphincter tone, and significantly greater proximal esophageal acid exposure cumulatively [65]. The decreased lung compliance in IPF due to fibrosis creates a negative intrapleural pressure which on transmission to the intrathoracic area decreases the LES tone resulting in reflux [66]. In animal models, the burden of proof is most substantial for GERD associated with IPF [67]. Chronic microaspiration insults may lead to pulmonary parenchyma damage attracting persistent inflammation resulting in fibrotic remodeling [68, 69]. Tracheal pepsin is a predictable indicator of aspiration [70]. The presence of bile salts and pepsin in bronchoalveolar lavage (BAL) suggests both acidic and nonacidic refluxate as risk factors for IPF disease [71]. BAL pepsin levels in post-transplant IPF patients were higher than in other chronic lung diseases [72].

PPI (Proton pump inhibitors) used in GERD are a reactive oxygen species scavenger, stimulate antioxidant production, decrease pro-inflammatory cytokines, inhibit profibrotic molecule expression, and decelerate pulmonary epithelial cell apoptosis [73]. Multiple studies and metaanalysis have reviewed the use of PPI in IPF patients for GERD. Initial studies revealed PPI use was associated with fewer acute exacerbations, lower hospitalization rates, lesser radiological fibrosis score, stable or improved lung function, and more extended transplant-free survival [59, 74–76]. GERD symptoms and pathophysiology are well addressed by LARS (Laparoscopic antireflux surgery) as it restores the gastroesophageal junction anatomy and controls both acidic and nonacidic reflux [65]. IPF patients post-LARS had a nonsignificant decline in acute exacerbations, hospitalization related to pulmonary issues, and death than the nonsurgical group in a small group of 72 patients [77]. A pooled analysis on the antacid treatment effect on disease progression in IPF placebo patients included in the pirfenidone trials revealed no improved outcomes [78]. Instead, advanced IPF patients on antacid therapy had a greater risk of pulmonary and nonpulmonary infections. PPI use in IPF patients has given mixed results in studies, possibly due to their inability to correct the GERD anatomy. PPI can only alter the gastric refluxate's pH, making it more alkaline with no acidic and nonacidic microaspiration prevention [65]. A meta-analysis and systematic review evaluated the efficacy and safety of GERD therapy in IPF [79]. It revealed a significant decline in acute exacerbations, mortality related to IPF, and improved transplant-free survival. GERD pharmacological therapy did not result in all-cause mortality reduction. Another meta-analysis via systematic review analyzed the GERD and IPF association, and it revealed a possible association confounded by smoking [80].

In a post-hoc data evaluation of the INPULSIS trials, IPF acute exacerbations frequently occurred on antacid therapy than those not on it [81]. PPI use results in alkaline gastric pH, which loses its bactericidal effect and increases respiratory infections on aspiration [69]. The clinical data available does not agree with a GERD and IPF relationship [82]. In most patients, refluxes are silent with the absence of any symptoms, and the best way to diagnose them is via esophageal MII-pH or high-resolution manometry. Alternatively, bronchoscopy with BAL presence of pepsin and bile salts can be used in IPF [69]. During meta-analysis, a lack of clarity with GERD diagnostic definitions was identified. It was difficult to pinpoint which criteria were used to select the patient and how many met them [78]. The heterogeneous methods used have made it difficult to assess the association. Meta-analysis always encounters various issues with case-control studies and requires accurate interpretation of the association, however small it may be [83]. More extensive randomized trials are needed to study the effect of LARS in IPF patients. Future prospective studies would be better suited to accurately evaluate the evidence and analyze the PPI effect on the IPF clinical course.

2.5 Viral infections

The role of viral infections in IPF pathogenesis is unclear. It could either be an initiator of IPF or could exacerbate a preexisting disease based on the type of viral infection. Immunosenescence predisposes old lungs to viral infections due to T cell inefficiency. Lack of improved outcomes on the treatment of IPF with immunosuppressants indicates the need for an intact immune system to control the disease process [84]. IPF therapy with antiviral medications has improved pulmonary function [85, 86]. Herpesvirus deoxyribonucleic acid (DNA) was recovered in 97% of IPF subjects compared to 36% of controls. This supports the idea of a herpes virus causing chronic antigenic stimulation in lung tissue [85]. Multiple animal models have supported a virus as an etiology for IPF. Experimental horse infection with an equine gammaherpesvirus resulted in pulmonary fibrosis [87]. Murine infection with a *Murine herpesvirus 68* (MHV 68) two to 10 weeks before introducing a fibrotic insult accelerated lung fibrosis even in the presence of a weaker insult [88]. MHV68 pulmonary installation in an old mouse leads to pulmonary fibrosis due to the upregulation of TGF β , which was absent in the younger mice [89]. MHV 68 can cause lung fibrosis after a stem cell transplant in animal models [90]. MHV 68 infection after a fibrotic lung insult can result in fibrosis [91]. MHV 68 in interferon-gamma deficient mice causes pulmonary fibrosis [92].

Serological evidence against herpes virus was detected in IPF patients, including *Epstein-Barr virus* (EBV), *Cytomegalovirus* (CMV), *Herpes simplex virus 1*. CMV antibodies were present in 80% of patients with IPF compared to 30% of control subjects [93]. EBV antibodies were recovered in 60% of IPF patients versus 22% and control in another study [94]. EBV DNA presence in the lung relates with arterial sclerosis and an increase in pulmonary hypertension suggestive of an influence in pulmonary hypertension development [95]. 96% of IPF lungs were positive for EBV DNA versus 71% of controls [96]. 9 out of 29 IPF patients had viral latent membrane protein in the epithelial cells compared to none in control. 61% of IPF patients with a lung biopsy revealed the productive EBV rearrangement of DNA [97]. *Herpes saimiri* DNA was detected in the regenerating epithelium in all IPF patient lung biopsy compared to none in control [98]. *Herpes saimiri* causes infection in 7% of humans, and this infection rate is suggestive of it as an etiological agent for infrequent sporadic IPF [99]. MHV 68 has high homology to *Herpes saimiri*. In sporadic IPF cases, two or more herpesviruses were detected in the lung than a single herpesvirus identified in the familial IPF cases. In the familial IPF cases, the virus was either CMV or *Human herpesvirus 8* (HHV 8) [85]. At-risk family members of IPF patients revealed the presence of epithelial dysfunction and fibrotic remodeling. Biopsy specimens revealed herpesvirus antigen elucidation in alveolar epithelial cells, and a cell-free BAL sample revealed herpesvirus DNA.

Adenovirus gene product E1A upregulates TGF-beta and stimulates epithelial cells to express mesenchymal markers [100]. Administration of adenovirus into the airway resulted in an acute inflammatory lung response followed by fibrosis in a dose-dependent manner [101]. In IPF patients, serology has not revealed significant adenovirus antibodies compared to controls. A Japanese study revealed *hepatitis C* (HCV) antibodies in 28% of IPF patients compared to 3.6% of a controlled cohort [102]. IPF incidence in HCV patients was greater at ten years and 20 years after the infection [103]. In another study involving 62 IPF patients, serology revealed HCV antibodies' presence in only one patient, indicating no increased prevalence [104]. *Torque-Teno Virus* (TTV) single-stranded DNA virus was the most frequent one identified in IPF patients with acute exacerbation [105]. Although it was detected in 36.4% of IPF patients, about 50% died in four years [106]. TTV DNA titer reflects the host's immunosuppressive state due to

treatment [107]. Experimental *Human Boca virus subtype one* infection in human cell culture lines causes respiratory disease and can persist in the lung causing chronic lung disease triggering fibrogenesis [108]. *Human Boca virus* was isolated from BAL in 2 patients in Germany who presented with acute usual interstitial pneumonia due to human bocavirus infection [109].

Two studies evaluated the presence of viral infection in acute IPF exacerbation. In the first study, most cases of acute exacerbation did not have any viral infections. Only TTV was identified in a substantially small number of cases [105]. In the second study, viruses were detected on the nasopharyngeal swabs in 60% of acute IPF exacerbation cases than 43.3% of stable patients. In this study, none of the patients were on any corticosteroids or antimicrobials. In acute cases, the inflammatory cytokines were elevated than in stable IPF and controls [110]. A meta-analysis of retrospective studies disclosed that chronic infection with CMV, EBV, HHV 7 & 8 substantially increased the risk of IPF without acute exacerbation of IPF. HHV 6 was not related to any significant risk of IPF. A nonsignificant greater risk of IPF was seen in younger patients with viral infections [111]. Viral infections predispose aged lungs to fibrosis, either by reactivating the infection or via latency promoting epithelial to mesenchymal transition. Latent infections alter the local milieu by increasing profibrotic mediators but cannot cause fibrosis by themselves and need another local lung insult. Latent viral infection is ineffective in causing acute exacerbations in animal models. The viral ability to increase exacerbations involves lytic replication in animal models not observed in all human patients [99]. CMV and Influenza are unable to use this mechanism to cause exacerbations.

2.6 Bacterial infections

Bacterial infections are suspected to be a cause for acute IPF exacerbations. In mouse lung fibrosis models, *Streptococcus pneumoniae* initiated pulmonary fibrosis via its pore creating cytotoxin pneumolysin, which was preventable by treatment with clarithromycin or amoxicillin at 24 hours or 48 hours [112]. The evaluation of IPF patient lung microbiome reveals staphylococcus and streptococcus species' presence in significant numbers during the disease progression [113]. The bacterial load in IPF patients BAL was larger than controls and the species in abundance were *Haemophilus*, *Streptococcus*, *Neisseria*, and *Veillonella* [114]. In murine models, *Pseudomonas aeruginosa* infection did not lead to augmentation of bleomycin-induced fibrosis [91].

2.7 Geographical and racial factors

To better understand the etiology of IPF, it is ideal for identifying geographical areas with more significant cases and evaluate the involved triggers. A study from Spain analyzed the IPF cases location and consistently highly polluted areas to recognize any risk factors [115]. Locations associated with the higher prevalence of IPF cases correlated maximally with the APM 2.5 μm exposure than other risk factors. Patients in such areas may need screening for IPF to identify these cases early in the disease course. A Japanese study identified substantial ethnic differences regarding the IPF disease course [116]. These studies are essential as they reveal the genetic trait polymorphisms associated with IPF. The incidence of IPF in males is 2.7 times higher than in females in Japan, possibly due to more male smokers than females. Males also have higher mortality than females, with a mortality ratio of 2.68 compared to that of 1.59 in the USA [117]. Clinical data on ethnic disparities with regards to IPF mortality are limited. Acute IPF exacerbation accounts for most deaths in IPF patients, and cardiac disease is a less frequent cause than in

Western countries. The variable used in the prognostification of IPF, such as age and gender, did not perform well in Japanese [118]. The GAP system fared poorly, and no substantial survival differences were noted in different IPF stages. Most Japanese carry single nucleotide polymorphisms (SNPs) rs2736100 in intron 2 of the TERT (Telomerase reverse transcriptase) gene, codes for the telomerase reverse transcriptase.

A retrospective study reviewed the ethnic and racial disparities in USA IPF outcomes using Organ Procurement and Transplantation Network data from 1995 to 2003 [119]. Black and Hispanic patients tended to be female and younger at diagnosis than whites. More significant medical comorbidities (hypertension, diabetes mellitus, and poor performance) were observed in Black and Hispanic patients. Whites had more private insurance, college education and lived in better neighborhood areas. The age-adjusted mortality rate and risk of having double lung transplantation were higher in Blacks and Hispanics. The poor mortality was partly attributed to the poor lung function when they were listed for lung transplantation. Race might be a proxy marker for the genetic makeup producing a specific phenotype [119]. Another retrospective study done in the USA evaluated the ethnic and racial differences based on National Center for Health Statistics data from 1989 to 2007 [120]. Among the IPF total census, 87.2% were Whites, 5.4% Hispanics, 5% Blacks, and others 2.2%. As mentioned in the prior study, Blacks and Hispanics were younger at diagnosis and death. When age and gender were controlled, the race was a significant predictor for IPF death with a similar IPF risk in all races. Hispanics were at an increased death risk from IPF than Whites and Blacks. Blacks had a higher risk of death from pulmonary hypertension and lung cancer than Whites and Hispanic patients. Hispanics were more likely to be coded with IPF than Whites and Blacks. The differences mentioned above are due to blacks dying at an early age and less likely to smoke than Whites. Access to health care has been inadequate due to the lack of medical insurance in Blacks.

2.8 Genetic factors

Familial causes of IPF constitute less than 5% of all cases, with at least two family members being affected [121]. The diagnostic criteria used to identify cases are similar to the one used for sporadic cases. Familial inheritance is via an autosomal dominant pattern with partial penetrance [122]. In 15% of familial cases, the cause is gene mutations encoding the ribonucleic acid (RNA) (TERC) or protein component (TERT) of the telomerase enzyme [123, 124]. Another 25% have sporadic or familial IPF with no telomerase RNA component (TERC) or telomerase reverse transcriptase (TERT) mutation but have circulating leucocyte telomere shortening [125]. A substantial congregation of familial cases was observed in the Finnish population [126]. ELMOD2, a gene on chromosome 4q31, has been identified as a susceptible gene for familial IPF [127]. A significant familial association has been detected with surfactant protein C and A2 gene mutation [121, 128]. Sporadic mutations of surfactant protein C gene are rarely associated with IPF [129]. A Mucin 5B (MUC5B) gene polymorphism of the promoter (rs35705950) is substantially associated with familial and sporadic IPF [130]. MUC5B promoter polymorphism presence can be used for IPF prediction and prognostification; however, it is not seen in 40% of cases [131, 132]. New loci (FAM13A, DSP, OBFC1, ATP11A, DPP9) and prior associations (TERT, MUC5B, TERC) were confirmed by a genome-wide association study in White patients. The newer loci were essential in immune defenses, DNA repair, and cell adhesion [133]. Peripheral blood markers may be used to identify a protein signature made up of MMP 1, MMP 7, MMP 8, Insulin-like growth factor-binding protein 1 (IGFBP1) & tumor necrosis factor

receptor superfamily member 1A (TNFRSA1F), which was able to differentiate IPF patients from healthy controls with a specificity of 98.1% and sensitivity of 98.6% [134]. Higher plasma concentrations of MMP 7, vascular cell adhesion molecule 1 (VCAM-1), IL-8, Intercellular Adhesion Molecule 1 (ICAM-1), and S100 calcium-binding protein A12 (S100A12) predict poor survival in IPF patients [135]. The gene microarray expression process can help in understanding the pathophysiology and therapeutic target candidates [136]. Currently, no genetic factors are associated with sporadic IPF in a consistent pattern.

3. Vital statistics and measures to improve them

Epidemiologic studies carried out before 2013 are highly heterogeneous in their methods and cannot be compared [137]. Even with this heterogeneity, the incidence shows a gradual increase across the world [138]. The IPF incidence has increased in all studies except for two quality studies, one each from Denmark and USA [139, 140]. When all studies are considered, the IPF incidence ranges from 0.22 to 93.7 per 100,000 per year. After removing underreported, South American and Asian studies, the incidence was 2.8 to 9.3 per 100,000 per year for the USA and European studies together [138]. In Europe, the higher rates were observed in the UK, while Scandinavia and Southern Europe revealed lower rates [4, 139, 141–143]. In the USA, using the narrow criteria, the incidence rates were lower at an incidence of 5–8 per 100,000 per year [38, 144, 145]. Incidence rates in South America were at 0.4 to 1.2 per 100,000 per year [146, 147]. East Asia studies based on insurance claims indicate an incidence rate of IPF at 1.2–3.8 per 100,000 per year [148, 149]. In contrast, in Japan, the mortality statistics suggest a greater incidence rate and an adjusted mortality rate of 10.26 per 100,000 [150]. Age-adjusted mortality has accelerated from 3.2 per 100,000 in 1979 to 7.57 per 100,000 from 1999 to 2003 in USA [38, 151]. In the UK, age-adjusted mortality has increased from 2.54 per 100 000 (1968–2008) to 5.5.10 per 100 000 (2005–2008) [141]. In Brazil, mortality had risen from 0.65 per 100 000 in 1996 to 1.21 per 100 000 in 2010 [146].

Overall, increased incidence rates are observed in the UK, European, South American, and East Asian epidemiological studies [141, 146–148, 152, 153]. USA mortality rates have declined as in Denmark after reaching a plateau [2, 139, 154]. Younger patients have a more prolonged median survival due to earlier treatment of recognized comorbidities and avoiding the use of ineffective treatment such as immunosuppressants and corticosteroids [117]. IPF diagnosis and treatment are getting more specific, and widespread acceptance of IPF international guidelines will improve accurate, comparable IPF clinical data [155]. National IPF registries from different countries will yield valuable data on IPF epidemiology. In general, the current IPF epidemiological data does not have substantial consistency.

The ideal sample should be large to validate the clinical diagnosis by medical records review [138]. Uncertainty of diagnosis can be avoided by using internationally accepted guidelines and consolidate its use in all studies. Other things to be considered are liberal use of imaging techniques, avoid broad diagnostic codes to identify IPF, and reinforce clinical guidelines in practicing physicians [138]. IPF score algorithm improved the positive predictive value by incorporating the IPF risk factors to identify fewer false-positive cases accurately [1]. The increasing prevalence can be attributed to the IPF patients living longer than ten years before [117]. Prevalence is affected by disease definition, guidelines used for diagnosis, the difference in methodology, and health care systems. Gender differences are due to smoking habit variations and occupational exposure. Incidence is influenced by diagnostic improvements, population age, availability of drugs,

and improved health care. Mortality is affected by clinical recognition of IPF and diagnostic coding [155]. Insurance databases reveal an underrepresentation of lower socioeconomic strata and non-White patients, impacting the overall incidence and prevalence [1]. Care should be ascertained during medical record review for confirmation as they can be inaccurate. Using medicare beneficiary data excludes younger IPF patients, which a national IPF registry can avoid [117].

4. Conclusion

IPF datasets currently overestimate the prevalence, whereas the questionnaire studies underestimate it. Obtaining the correct epidemiological data is essential in identifying IPF clinical course and prognosis. Initiation and maintenance of a national registry with appropriate epidemiology data collection is an excellent beginning. An attempt should be garnered towards using algorithms or other tools in epidemiological studies to establish their efficacy. Epidemiological studies should attempt to use a similar case definition standardized across multiple countries to compare effectively and decrease the heterogeneity. As the IPF incidence increases, it has become a substantial public health concern. Future studies need to stress clinical epidemiology, pathophysiology & diagnostic biomarkers for an accurate understanding of epigenetic mechanisms and their pathways to provide a clue about future therapeutic targets. Clinical research into the epigenetic processes, disease pathophysiology, and diagnostic procedures needs to be encouraged and supported to improve life quality, prolong survival, and ultimately find a cure.

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Acronyms and abbreviations

IPF	Idiopathic pulmonary fibrosis
ILD	Interstitial lung disease
PPV	Positive predictive value
GAP	Gender-Age-Physiology
COPD	Chronic obstructive pulmonary disease
CPFE	Combined pulmonary fibrosis and emphysema
CSE	Cigarette smoke exposure
TGF	Transforming growth factor
EGF	Epidermal growth factor
MMP	Mixed metalloproteinases

ECM	Extracellular matrix
CVD	Cardiovascular disease
PAF	Population attributable fraction
JEM	Job-exposure matrix
USA	United States of America
IPF-JES	IPF-Job Exposure study.
UK	United Kingdom
APM	Ambient particulate matter
GERD	Gastroesophageal reflux disease
LES	Lower esophageal sphincter
BAL	Bronchoalveolar lavage
PPI	Proton pump inhibitor
LARS	Laparoscopic antireflux surgery
DNA	Deoxyribonucleic acid
MHV	Murine herpesvirus
EBV	Epstein–Barr virus
CMV	Cytomegalovirus
HHV	Human herpesvirus
HCV	Hepatitis C virus
TTV	Torque-Teno virus
SNP	Single nucleotide polymorphism
TERT	Telomerase reverse transcriptase
RNA	Ribonucleic acid
TERC	Telomerase RNA component
MUC5B	Mucin5b
FAM13A	Family with sequence similarity 13, Member A
DSP	Desmoplakin
OBFC1	Oligosaccharide-binding fold-containing Protein 1
ATP11A	ATPase Phospholipid Transporting 11A
DPP9	Dipeptidyl Peptidase 9
IGFBP	Insulin-like growth factor-binding protein
TNFRSA1F	Tumor necrosis factor receptor superfamily member 1A
VCAM	Vascular cell adhesion molecule
IL	Interleukin
ICAM	Intercellular adhesion molecule
S100A12	S100 calcium-binding protein A12

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