Review

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Idiopathic Pulmonary Fibrosis: Where do We Stand and How Far to Go?

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Idiopathic pulmonary fibrosis is a progressive and incurable lung disease characterized by collagen deposition, alveolar inflammation, fibroblast proliferation, and the destruction of lung tissue structures. It is a rare yet severe condition with a high mortality rate, typically leading to death within 3–5 years of diagnosis. The clinical presentation of idiopathic pulmonary fibrosis (IPF) involves a gradual and substantial loss of lung function, ultimately resulting in respiratory failure. Despite more than half a century of intensive research, the origin of IPF remains a mystery. Despite its unknown etiology, several genetic and non-genetic factors have been linked to IPF. Recent significant advancements have been made in the field of IPF diagnosis and treatment. Two oral small-molecule drugs, pirfenidone and nintedanib, have recently gained approval for the treatment of IPF. Pirfenidone exhibits antifibrotic, antioxidant, and anti-inflammatory properties, while nintedanib is a tyrosine kinase inhibitor with selectivity for vascular endothelial growth factor (VEGF) receptors, prostaglandin F (PGF) receptors, and fibroblast growth factor (FGF) receptors. Both of these compounds are capable of slowing down the progression of the disease with an acceptable safety profile. This review provides a brief introduction, historical background, epidemiological insights, and an exploration of various environmental risk factors that may influence the lung microenvironment and contribute to the advancement of IPF. The review also delves into the diagnosis, signaling pathways, and ongoing clinical trials worldwide. A thorough review of the literature was conducted using PubMed and Google Scholar to gather information on various aspects of IPF. Numerous potential drugs are currently under investigation in clinical trials, and the completion of this process is crucial to the ultimate goal of finding a cure for IPF patients. The investigation of the role of genes, surfactant proteins, infectious agents, biomarkers, and epigenetic changes holds the promise of offering earlier and more accurate understanding and diagnosis of IPF. This information could be instrumental in the development of new therapeutic approaches for treating IPF and is expected to be of great interest to researchers.

Keywords: idiopathic pulmonary fibrosis; history; environmental risk factors; management; antifibrotic drugs; biomarkers; clinical trials

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive and incurable lung disease with a bleak prognosis [1], typically resulting in a mean survival of only 3–5 years [2,3]. It is also known by various names, including cryptogenic fibrosing alveolitis, idiopathic fibrosing alveolitis, and common interstitial pneumonia. Common symptoms associated with pulmonary fibrosis, such as fatigue, cough, and dyspnea, have a significant impact on patients' quality of life [4]. Furthermore, it is believed that IPF typically initiates at the lung's base and periphery, gradually extending to involve the entire lung tissue.

Previous studies have indicated that only a minority of patients are eligible for treatment in clinical trials or lung transplantation [5–9]. There is a growing body of evidence suggesting that the pathogenesis of IPF involves intricate interactions among genetic predisposition, epigenetics, environmental factors, and concurrent diseases [10–14]. IPF is characterized by the proliferation of inflammatory cells, damage to the alveolar epithelium, hyperplasia of myofibroblasts and fibroblasts, and the deposition of extracellular matrix [15,16]. Both *in vitro* and *in vivo* studies demonstrate that alveolar epithelial cells can act as a source of fibroblasts through a process known as

"epithelial-mesenchymal transition" [17]. This common fibrotic pathogenesis involves complex activities in various cell types, triggering specific molecular pathways [18]. A dysregulated wound healing response, combined with persistent exposure to allergens, toxic chemicals, and radiation, ultimately leads to lung fibrosis [19]. The anticancer agent bleomycin (BLM) has been identified as an inducer of pulmonary fibrosis and is consequently used to mimic the process of IPF [20]. Studies have reported that Transforming growth factor beta (TGF-β)-mediated epithelial-mesenchymal transition plays a significant role in the pathogenesis of BLM-induced pulmonary fibrosis [21].

Considerable epidemiological evidence supports the notion that IPF is a recognized risk factor for the development of lung cancer, resulting in an increased incidence of lung cancer among patients with IPF [22,23]. The precise etiology of IPF continues to elude the scientific community, but it is believed that a combination of genetic and non-genetic factors, including environmental and occupational exposures, cigarette smoking, infections, toxins, and radiation, may initiate chronic lung tissue damage, ultimately leading to fibrotic remodeling [24–28]. Additionally, there is evidence indicating that several growth factors, such as platelet-derived growth factor, fibroblast growth factor, and vascular endothelial growth factor, play a significant role in the progression of IPF [29,30]. Regrettably, there is no perfect therapy for IPF, although two drugs, Nintedanib and Pirfenidone, have received approval in recent years. These drugs have been shown to only decelerate disease progression and stabilize lung function [31]. Given the limited effectiveness of pharmacological treatments, a single lung transplant remains the sole chance of survival [32]. Nonetheless, clinical trials are being conducted globally in pursuit of a cure.

Earlier research and publications have furnished information on various facets of pulmonary fibrosis up to the present day. In this review, we have endeavored to encapsulate the most pertinent data regarding IPF. Our primary focus lies in elucidating epidemiological aspects, the natural progression of the condition, the evolution of IPF treatment, and the currently established standard treatments.

Historical Background and Challenges in Studying the Epidemiology

According to Papiris *et al* [33], the interstitial lung disease now recognized as IPF was first mentioned in the German-language pathological literature by von Buhl. Some researchers contend that Hamman and Rich were the initial individuals to identify IPF as a new clinical and pathological entity [34,35]. The pivotal contribution of Hamman and Rich lay in their identification and comprehensive description of the clinical and pathological characteristics of a lung disease they termed "acute diffuse interstitial pulmonary fibrosis" [36]. Potter and Gerber [37], who introduced the term "subacute diffuse interstitial pulmonary fibrosis", reported an 8-month extension of life. It was postulated that the severity of the disease and its rate of progression typically varied inversely with age [38]. Though the disease's origin remains enigmatic, possible causes have been suggested, including flu pneumonia, chemical irritants, and hypersensitivity to various substances [39]. Other theories encompass hereditary predisposition, occupational exposure to noxious agents, an autoimmune mechanism, and drug treatment [39]. Scadding [40] proposed the concept of fibrosing alveolitis, emphasizing that the process initiated in the alveoli. In 1993, a case series of three IPF patients who met the acute respiratory distress syndrome (ARDS) criteria marked the inception of modern IPF history [41]. At that time, the standard therapy for stable IPF patients involved the administration of steroids and azathioprine or cyclophosphamide. In response, practitioners opted to increase the steroid dose with steroid pulse administration, reporting improvement [41]. The term "IPF" was introduced by Katzenstein and Myers [42] in 1998 for patients with interstitial pneumonia in whom no identifiable cause of interstitial lung disease was found. IPF, the most prevalent form of interstitial lung disease, presents as common interstitial pneumonia with temporal and spatial heterogeneity [43,44]. The concept of IPF was first elucidated and validated with diagnostic criteria in 2000, establishing it as a distinct clinical entity [45]. Epidemiological studies revealed that IPF patients had a fivefold increased risk of developing lung cancer compared to the general population [46]. Usual interstitial pneumonia (UIP) serves as the pathological hallmark of IPF [47], characterized by a patchwork pattern, interstitial scarring, honeycomb changes, and fibroblastic foci [48]. The extent of fibroblastic foci in IPF patients represents a crucial morphological indicator of an exceptionally poor prognosis [49].

Incidence and Prevalence

Even when statistical adjustments are made to account for differences between studies where possible, the incidence and prevalence of IPF exhibit variations across the globe (Table 1, Ref. [50–75]).

Estimates of the epidemiology of IPF are derived from various data sources. Based on the countries included, adjusted prevalence and incidence rates for IPF are estimated to range from 0.09 to 1.30 and 0.33 to 4.51 per 10,000 population, respectively [50]. These prevalence figures indicate that IPF remains a rare disease. Out of a total of 12 countries, twenty-two studies, with 15 providing incidence and 18 providing prevalence estimates, met the inclusion criteria [51–75]. Adjusted incidence rates per 10,000 persons showed variations, ranging from 0.09 to 0.49 in Europe [59–68], 0.35 to 1.30 in Asia-Pacific countries [51–58], and 0.75 to 0.93 in North America [69–75]. In Asia-Pacific countries, adjusted prevalence estimates spanned from 0.57 to 4.51 [51–58], in Europe from 0.33 to 2.51 [59–68], and in North America from 2.40 to 2.98 [69–75]. Compared to

Table 1. Prevalence and incidence of idiopathic pulmonary fibrosis per country. Modified after Maher *et al.*, 2021 [50].

Country	Mean unadjusted prevalence (per 10,000)	Adjusted prevalence (per 10,000)	95% CI Adjusted prevalence (per 10,000)	Reference	Rare disease threshold (per 10,000)	Reference
Asia-Pacific						
Japan	0.59 1.00	0.89	0.51, 1.55	[51] [52]	<50,000* (no. of cases)	[53]
South Korea	3.52 3.89	4.51	2.99, 6.79	[54] [55]	<20,000* (no. of cases)	[56]
Taiwan (China)	0.49	0.57	0.34, 0.94	[57]	1	[58]
Europe						
Denmark	1.01	1.17	0.56, 2.44	[59]	1–2	[60]
Finland	0.86	0.65	0.36, 1.18	[61]	5	
France	0.2	0.94	0.44, 1.99	[62]	5	
Greece	0.34	0.33	0.21, 0.53	[63]	5	
Italy	2.56 2.12	2.37	1.38, 4.09	[64] [65]	5	[68]
Poland	2.56	2.51	1.55, 4.05	[66]	5	
England	1.16	0.78	0.38, 1.63	[67]	5	
North America						
Canada	2.00 7.27	2.98	1.7, 5.19	[69] [70]	5	[71]
United States	2.81 11.1 0.67	2.4	1.33, 4.34	[72] [73] [74]	<2,00,000* (no. of cases)	[75]

*Indication of the number of cases instead of thresholds.

incidental pulmonary fibrosis, familial pulmonary fibrosis is less common. IPF typically affects individuals between the ages of 65 and 70, with the incidence increasing with age [76]. Globally, the number of IPF patients is on the rise due to several factors, including an aging population, increased awareness of the disease, and improved diagnostic techniques [77,78]. Men have a higher likelihood of developing IPF compared to women [79], and risk factors such as smoking [80], exposure to metal or wood dust [81], and genetic factors [82] are commonly associated with the disease.

The median survival rate for IPF typically ranges from 2 to 3 years, although significant differences exist among subgroups, with younger patients exhibiting a longer median survival [83]. South Korea recorded the highest incidence and prevalence estimates [54,55], reaffirming the rarity of IPF as indicated by these prevalence figures. For future epidemiological studies of IPF, it is imperative to consistently account for factors such as age, sex, smoking status, and the specificity of case definitions [50]. IPF met the criteria for classification as a rare disease in all countries except South Korea when prevalence estimates were compared with country-specific rare disease thresholds. The underlying reasons for these varying outcomes among and within countries remain unclear.

Etiology of Pulmonary Fibrosis

Patients with pulmonary fibrosis often prioritize symptom management. Long-term symptom reduction and the potential for remission of pulmonary fibrosis can be attained through a comprehensive understanding of the disease's etiology. Pulmonary fibrosis encompasses a broad range of etiologies, with diverse triggers that encompass allergies, toxins, radiation, and environmental particles. Here, we discuss some of the known risk factors for pulmonary fibrosis.

Environmental Factors

Environmental factors, categorized as "intrinsic" and "extrinsic" factors, are believed to hold a significant role in the pathogenesis of IPF [84]. The alveolus, composed of alveolar type 1 and 2 epithelial cells, represents a fragile structure susceptible to damage from environmental factors. Numerous epidemiological studies indicate that prolonged exposure to environmental elements like wood, metal, sand, silica, asbestos fibers, coal dust, and stone dust plays a pivotal role in the development of IPF [85]. Additionally, certain occupations, such as those in agriculture and farming involving exposure to organic and inorganic substances, are also implicated in the pathogenesis of IPF [84].

Cigarette Smoking

Exposures of the lung epithelium to environmental factors can elevate the incidence of IPF, affecting both sporadic and familial cases of pulmonary fibrosis. Among the key risk factors, smoking and exposure to metal dust stand out as significant contributors [86]. Cigarette smoke, through epigenetic mechanisms, can disrupt various biological functions, inducing endoplasmic reticulum (ER) stress and an imbalance of microRNA (miRNA), which in turn promotes myofibroblast differentiation and spontaneous lung injury [87]. Studies have previously demonstrated that smoking is a risk factor for the development of IPF, and inhalant exposures like marijuana and cigarette smoking have been associated with a notably increased risk of IPF development [88]. Research suggests that IPF patients with a history of smoking tend to have poorer survival outcomes compared to non-smokers [89]. Chronic exposure to cigarette smoke heightens the risk of IPF by causing DNA damage and mutations in protective genes [90]. Additionally, cigarette smoke extract stimulates the activity of matrix metalloproteinase-2 (MMP-2) by increasing the transcription factor early growth response-1 in human lung fibroblasts [91]. Furthermore, cigarette smoke alters the mechanisms by which alveolar macrophages recognize foreign particles and pathogens, leading to a reduced phagocytic capacity of alveolar macrophages [92].

Infectious Agents

Infections are a common occurrence in IPF patients, with various viruses, bacteria, and fungi capable of damaging alveolar epithelial cells, inducing apoptosis, and modifying the host response to injury [93]. Consequently, microorganisms may play a role in the pathophysiology of IPF [94]. The lung microbiome of IPF patients differs from that of healthy individuals, potentially serving as a persistent stimulus for recurrent alveolar injury [95]. Several pathogenic bacteria, such as streptococci and staphylococci, have been implicated in disease progression [96]. The bacterial load within the lungs can serve as a predictive factor for disease development in IPF patients, once clinical and physiological factors have been considered [97]. Furthermore, viruses like Parainfluenza 1 [98], human immunodeficiency virus 1 [99], measles virus [100], and Parainfluenza 3 virus [98] have also been linked to the pathogenesis of IPF. While the precise mechanisms through which viral infections lead to IPF are not yet fully understood, studies suggest that they may be associated with epigenetic reprogramming, activation of the epithelial-mesenchymal transition, and an increase in TGF expression [101]. Additionally, IPF patients with *mucin 5B (MUC5B*) risk alleles tend to exhibit a significantly reduced bacterial load when compared to individuals who do not carry these risk genes [102].

Genetic

Numerous gene mutations have been suggested as potential orchestrators in the pathogenesis of IPF [103], but whether they represent a direct causal factor or merely an intermediary link remains uncertain. Mutations in surfactant proteins can lead to reduced proliferation of AT2 cells and the secretion of profibrotic markers [104]. Furthermore, mutations in these proteins have been observed to disrupt the proper folding of proteins in the endoplasmic reticulum (ER), resulting in ER stress and the activation of the unfolded protein response (UPR) [105]. When the UPR cannot rectify protein misfolding, it triggers the terminal UPR, leading to cell death [106]. Several researchers have reported increased markers of UPR activation in alveolar epithelial cells (AEC) type II cells in IPF [107].

Normally, telomere length naturally diminishes with age, but exceptionally short telomeres have been associated with premature aging and impaired tissue repair [108]. Genes associated with telomere maintenance (Telomerase reverse transcriptase (*TERT*), Telomerase RNA component (*TERC*), Poly(A) specific ribonuclease (*PARN*), Regulator of telomere elongation helicase 1 (*RTEL1*), Dyskerinpseudouridine synthase 1 (*DKC-1*), Telomerase repeat factor 1 (*TRF1*) interacting nuclear factor (*TINF*)) are linked to the regulation of telomere length [109]. Familial pulmonary fibrosis is defined by the presence of at least two cases of pulmonary fibrosis within the same family. It has been shown that familial pulmonary fibrosis [110] is associated with mutations in telomerase genes (Table 2, Ref. [107,111–113]).

Several authors have reported that mutations in these genes represent a risk factor for the development of IPF [114]. Lung fibroblasts isolated from the lungs of IPF patients are also documented to have shorter telomere lengths compared to age-matched control subjects [115]. These cells exhibit an accelerated replicative senescence during primary culture activity [116].

Telomerase is composed of three major components: Telomerase RNA (TER), Telomerase reverse transcriptase (TERT), and telomerase synergistic protein 1 (hTP1), which stabilizes the RNA and facilitates the assembly of the active enzyme. Numerous mutations in TER and TERT have been identified in IPF patients, all of which precede telomere shortening [117]. Among these, the V144M, R865C, and R865H mutations are associated with IPF. The minor allele rs35705950 has been linked to increased mucin 5B expression in IPF patients [118]. Inheritance of familial pulmonary fibrosis appears to follow an autosomal dominant pattern (Fig. 1) with variable penetrance [119]. In an autosomal dominant inheritance system, having one mutant copy of a gene in each cell is sufficient to cause the disease. However, not everyone inheriting the mutated gene will necessarily exhibit symptoms of familial pulmonary fibrosis.

Table 2. Telomere-related genes associated with familial pulmonary fibrosis.

Name	Gene	Function	References
Poly(A) specific ribonuclease	*PARN*	Involved in TERC RNA maturation	[107]
Dyskerinpseudouridine synthase 1	*DKC-1*	Active role in telomerase stabilization	[111]
Regulator of telomere elongation helicase 1	*RTEL1*	Encodes a DNA helicase that helps stabilize telomeres during RNA replication	[112]
Telomerase RNA component	*TERC*	Encodes the RNA subunit of telomerase (hTR)	[111]
Telomerase reverse transcriptase	*TERT*	Encodes the protein subunit of telomerase (hTERT)	[111]
TRF1 (Telomerase repeat factor 1) interacting nuclear factor 2	*TINF2*	Provides instructions of making part of the shelter in protein complex	[113]

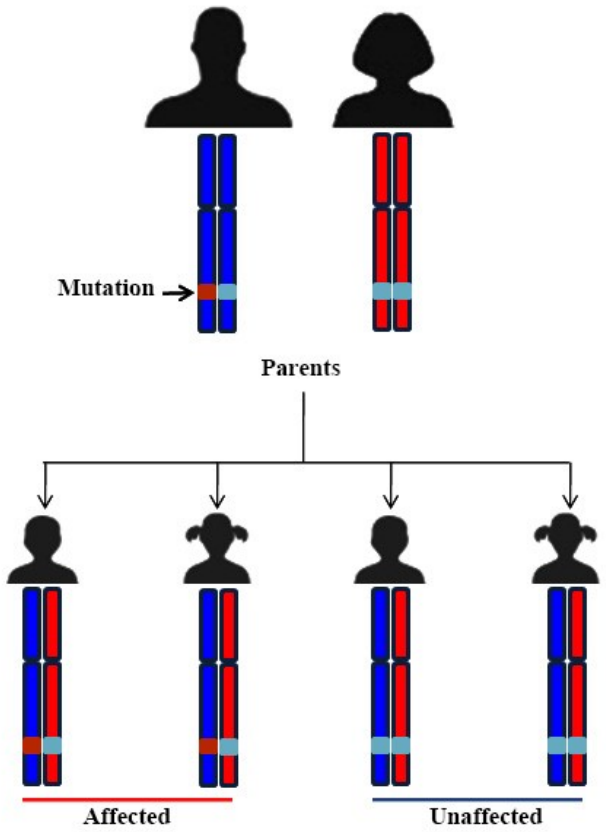

Fig. 1. Inheritance pattern of familial pulmonary fibrosis. The inheritance pattern of familial pulmonary fibrosis follows an autosomal dominant pattern. In this system, having a mutated copy of a gene in parents results in the development of IPF in 50% of their children. The figure was created using Adobe Photoshop 7.0 (Adobe, SAN JOSE, CA, USA) and Microsoft Office 2016 (Microsoft, Redmond, WA, USA). IPF, idiopathic pulmonary fibrosis.

Epigenetic Alterations

Epigenetic modifications are processes that alter gene activity without modifying the underlying genetic code. An expanding body of evidence indicates that epigenetic changes play a significant role in IPF [120]. DNA methylation variations encompass unintentional methylation errors and the hyper- and hypomethylation of cytosine residues in various genes [121]. A genome-wide DNA methylation analysis of lung tissue from 94 IPF patients and 67

Table 3. Consolidated number of clinical trials as per database of privately and publicly funded clinical studies conducted around the world on website, https://clinicaltrials.gov/.

S.N.	Status of clinical trials	Total no. of trials	Study with result	Study without result	Study phase					
1.	Completed	145	59	86	EP = 1 WR = 0	P1 = 37 WR = 5	P2 = 57 WR = 29	P3 = 23 WR = 16	P4 = 5 WR = 5	NA = 22 WR = 4
2.	Withdrawn	9	0	9	EP = 0 WR = 0	P1 = 1 WR = 0	P2 = 6 WR = 0	P3 = 0 WR = 0	P4 = 2 WR = 0	NA = 0 WR = 0
3.	Terminated	35	16	19	EP = 0 WR = 0	P1 = 6 WR = 1	P2 = 14 WR = 8	P3 = 11 WR = 7	P4 = 2 WR = 0	NA = 2 WR = 0
4.	Suspended	0	0	0	EP = 0 WR = 0	P1 = 0 WR = 0	P2 = 0 WR = 0	P3 = 0 WR = 0	P4 = 0 WR = 0	NA = 0 WR = 0
5.	Active & not recruiting	6	0	6	EP = 0 WR = 0	P1 = 1 WR = 0	P2 = 3 WR = 0	P3 = 0 WR = 0	P4 = 0 WR = 0	NA = 2 WR = 0
6.	Enrolling by invitation	2	0	2	EP = 1 WR = 0	P1 = 0 WR = 0	P2 = 0 WR = 0	P3 = 1 WR = 0	P4 = 0 WR = 0	NA = 0 WR = 0
7.	Recruiting	60	0	60	EP = 3 WR = 0	P1 = 17 WR = 0	P2 = 21 WR = 0	P3 = 8 WR = 0	P4 = 1 WR = 0	NA = 10 WR = 0
8.	Not yet recruiting	22	0	22	EP = 0 WR = 0	P1 = 8 WR = 0	P2 = 7 WR = 0	P3 = 3 WR = 0	P4 = 0 WR = 0	NA = 4 WR = 0
9.	Unknown status	24	0	24	EP = 1 WR = 0	P1 = 3 WR = 0	P2 = 5 WR = 0	P3 = 1 WR = 0	P4 = 2 WR = 0	NA = 12 WR = 0

Where: EP, Early Phase; P1, Phase-1; P2, Phase-2; P3, Phase-3; P4, Phase-4; NA, Not Applicable; WR, With Result.

controls revealed 2130 differentially methylated regions, with over one-third of them linked to substantial changes in gene expression, including general genetic abnormalities associated with IPF [122]. Levels of regulatory miRNAs have been shown to exhibit marked differences in IPF patients compared to healthy individuals [123]. The primary causes of epigenetic changes, given their correlation with IPF and their association with DNA methylation, are cigarette smoking and aging [122]. This epigenetic drift, which restricts cell plasticity, may theoretically contribute to the development of age-related diseases like IPF [122,124].

Ageing

Aging is a natural and physiological process that involves cellular senescence, leading to a decline in tissue repair capacity due to a loss of function. Existing literature data indicate that advanced age represents another significant risk factor for the development of IPF [125]. Experimental studies utilizing mice as a model have shown that pulmonary fibrosis is more prevalent in older individuals compared to younger ones [126]. The primary cause of IPF is age-related cellular and clinical changes [127]. The alveolar epithelium is primarily impacted by cellular changes brought about by aging. Cellular senescence of epithelial cells results in lung fibrosis due to an aberrant secretion form of lung epithelium and increased resistance to apoptosis in myofibroblasts [128]. Recent research reveals that lung fibroblasts in aged mice exhibit a fibrogenic phenotype, rendering them resistant to apoptosis and more susceptible to a fibrotic response to injury. These findings are partially linked to elevated levels of plasminogen activator inhibitor-1 (PAI-1), an effector of Transforming growth factor beta (TGF-β)-1 that plays a crucial role in the onset of senescence through the induction of p21 [129].

Esophageal Reflux Disease

When stomach acid flows back into the esophagus, it is diagnosed as gastroesophageal reflux disease (GERD). In GERD patients, there is a risk of inhaling stomach contents, which, over time, can cause damage to the lungs. Recent studies suggested that GERD may play a significant role in the progression of IPF [130]. The prevalence of GERD is observed to be higher in patients with IPF [131]. GERD is believed to result in microaspiration of acids and bases, leading to persistent lung inflammation that contributes to the progression of IPF [132]. Furthermore, it has been reported that in IPF patients, bronchoalveolar lavage fluids (BALF) may contain significant levels of pepsin and bile salts. These substances promote the excessive production of TGF-β, which, in turn, leads to the recruitment and activation of fibroblasts and the deposition of extracellular matrix [133].

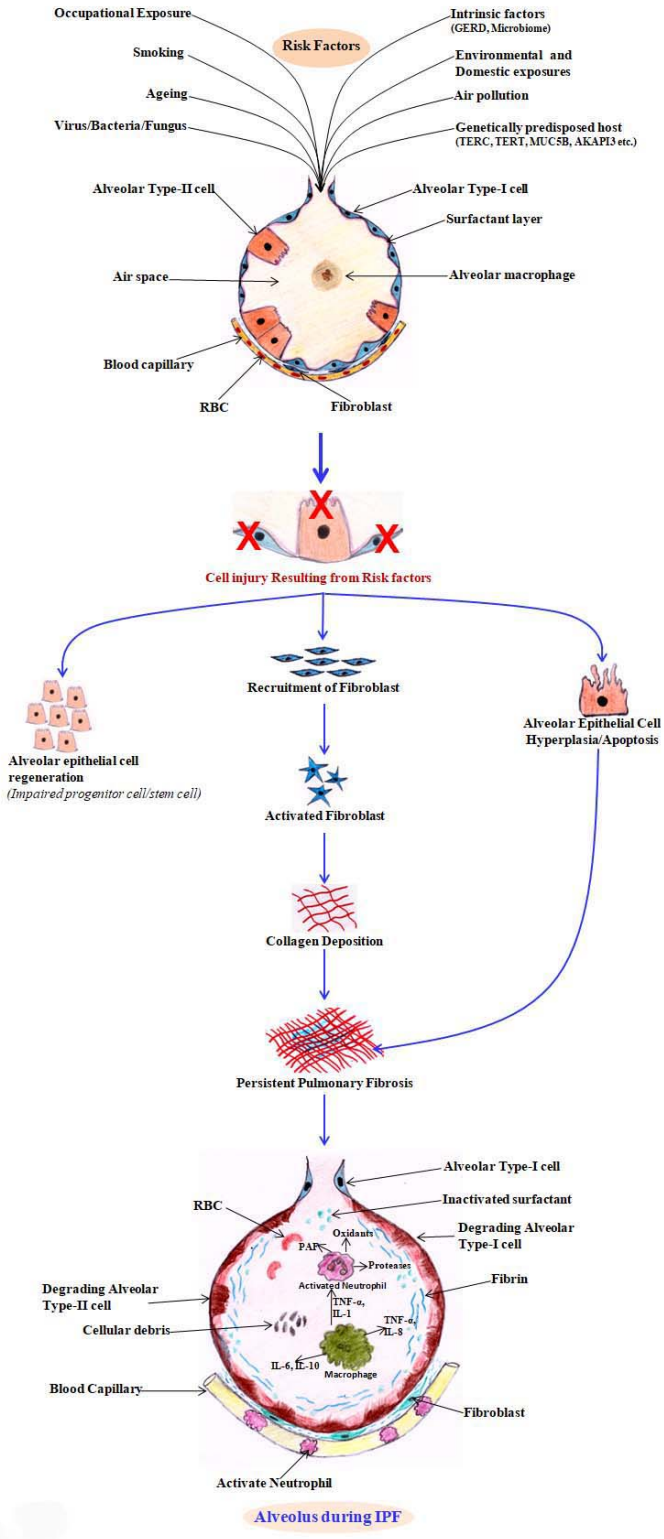

Fig. 2. Diagrammatic presentation showing pathogenesis of idiopathic pulmonary fibrosis. The pathogenesis of IPF involves a complex interplay of environmental risk factors, genetic factors, extrinsic, and intrinsic factors that collectively impact the integrity of epithelial cells. Any single or combination of these factors can lead to the damage of alveolar epithelial cells, triggering the activation of AEC Type-I or Type-II. Subsequently, myofibroblasts begin to secrete substantial amounts of extracellular matrix, which accumulates and ultimately results in severe pulmonary fibrosis. The figure was created using Adobe Photoshop 7.0 (Adobe, SAN JOSE, CA, USA) and Microsoft Office 2016 (Microsoft, Redmond, WA, USA). AEC, alveolar epithelial cells; GERD, gastroesophageal reflux disease; RBC, Red Blood Cell; IPF, idiopathic pulmonary fibrosis; TNF-α, tumor necrosis factor-α; IL, interleukin.

Pathogenesis of Pulmonary Fibrosis

The lung, as the primary respiratory organ, is especially susceptible to infection and injury due to its direct exposure to the external environment. However, it possesses a unique capacity for repair and recovery through a sequence of biological processes [134]. In the case of IPF patients, fibrosis is believed to develop gradually over time [127]. Once diagnosed, the lung's architecture is significantly altered by the disease, and the pathological characteristics include various stages of alveolar epithelial cell damage, the presence of aberrant proliferating mesenchymal cells, and extensive fibrosis (Fig. 2). Prior to diagnosis, the exact mechanisms remain unclear, but current theory suggests that a malfunctioning epithelium is central to understanding the pathogenesis of IPF [135].

Current evidence indicates that in IPF, there is repetitive damage to lung cells known as alveolar epithelial cells, which cover a major portion of the alveolar surface [136]. In the normal repair process, hyperplastic type 2 alveolar epithelial cells (AEC) undergo apoptosis, and the remaining cells differentiate to form type 1 alveolar cells [136]. The cells believed to drive the development of pulmonary fibrosis are considered to be clusters of myofibroblasts [137]. However, the exact origin of myofibroblasts in pulmonary fibrosis remains a subject of controversy [138]. Various processes, including epithelial-mesenchymal transition [139], fibrocyte recruitment [140], trans-differentiation of pericytes [141], or pleural mesothelial cells [142], are proposed to contribute to the pool of myofibroblasts in the fibrotic lung. In IPF patients, apoptosis of the fibrotic cell pool in the lung is insufficient, further impeding the re-epithelialization and the restoration of normal lung architecture [143].

Published studies on human and experimental pulmonary fibrosis indicate that the surrounding non-fibrotic tissue is highly vascularized, while fewer blood vessels are present in fibrotic areas [144]. The increased capillary density in the minimal fibrotic regions could be a compensatory response, but it remains unclear whether neovascularization plays a major role in the dysregulated matrix remodeling in IPF [145]. A range of profibrotic mediators is thought to be involved in the pathogenesis of fibrotic lung diseases, including interleukin (IL)-1, TGF-β, tumor necrosis factor, connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF), IL-13, and fibroblast growth factor (FGF), along with their signaling pathways [146]. TGF-β performs multiple roles, such as promoting chemotaxis and fibroblast proliferation, inducing the differentiation of myofibroblasts through epithelial-mesenchymal transition (EMT), and safeguarding myofibroblasts from apoptosis [147]. TGF-β also inhibits matrix-degrading proteases and increases the production of various tissue inhibitors of metalloproteinases (TIMPs) and profibrotic cytokines [147].

Signal Transduction Pathways in Idiopathic Pulmonary Fibrosis

Numerous genetic and epigenetic alterations result in the abnormal activation of common signaling pathways, such as TGF-β and *Wnt*, which are involved in metaplasia and hyperproliferation of alveolar-type II epithelial cells. The following are the findings regarding the contribution of these signal transduction pathways to the pathogenesis of IPF.

Wnt/β-Catenin Signaling Pathway in Pulmonary Fibrosis

Significant nuclear accumulation of β-catenin is observed at multiple sites, including damaged alveolar structures, bronchiolar lesions, and fibroblast foci, providing strong evidence of the robust activation of this pathway in IPF lung tissue [148]. In the context of cancer pathogenesis, the phosphatidylinositol 3-kinase(PI3K)/AKT pathway is involved, and recent research has identified the expression of PI3K p110 class I isoforms in IPF patients and tissue-derived fibroblast cell lines [149]. Both *ex vivo* fibroblast cell lines and IPF lung homogenates exhibit elevated levels of p110c isoform expression [149]. These findings suggest that PI3K p110c may represent a unique therapeutic target and plays a specific role in the etiology of IPF. In addition, a group of proteins known as "suppressor of cytokine signaling proteins" regulates the JAK-STAT signaling pathway [150]. It has been proposed that the expression of SOCS1 is reduced in IPF patients [151], and this finding is associated with the severe expression of the disease. Another signaling pathway that is activated not only in cancer but also in IPF is the tyrosine kinase signaling pathway [149].

The activation of Wnt/β-catenin signaling stimulates type II alveolar cells to release IL-1β, which possesses pro-inflammatory activity. IL-1β, in turn, enhances TGF-β signaling, leading to the secretion of IL-6 [152]. Both IL-1β and IL-6, acting as both anti-inflammatory and pro-inflammatory cytokines, promote EMT via STAT3 signaling and TGF-β signaling, thereby contributing to pulmonary fibrosis [153]. In bleomycin-treated mice, damaged tissues activate IL-1β through the inflammasome, increasing the presence of neutrophils and lymphocytes, ultimately promoting pulmonary fibrosis [154]. IL-18 stimulates fibroblast senescence by reducing the expression of the anti-senescence protein Klotho. Altered interleukin levels have been shown, both *in vivo* and *in vitro*, to contribute to the development of pulmonary fibrosis through inflammation, EMT, and immune response. IL-37 exhibits an antifibrotic effect by upregulating the marker LC3II and promoting autophagy in fibroblasts, thereby suppressing EMT. However, the expression of IL-37 decreases in IPF patients and in mouse models [155]. Initially considered pro-fibrotic, IL-4 was later assumed to have no effect on pulmonary fibrosis, although it is reported to have different

functions in early and late stages, similar to IL-6 [153,154]. The role of IL-4 in IPF may be subject to debate and requires further investigation.

TGF-β Signaling Pathway in Pulmonary Fibrosis

TGF-β is a extensively studied profibrotic cytokine expressed by every cell in the body. In mammals, there are only three isoforms of TGF-β (TGF-β1, -β2, and -β3), all of which share the same biological properties. It is widely accepted that TGF-β inhibits the proliferation of alveolar type 2 cells [156]. TGF-β is known to induce several processes, including epithelial cell apoptosis, epithelial-to-mesenchymal transition, collagen synthesis, epithelial cell migration, fibroblast proliferation, and transformation into myofibroblasts through the induction of growth factors like connective tissue growth factor and vascular endothelial growth factor [139,157]. TGF-β also promotes fibrotic processes by inhibiting antifibrotic molecules such as hepatocyte prostaglandin E2 and growth factor [158]. Additionally, TGF-β suppresses the growth and repair of alveolar epithelial cells, playing a crucial role in the development of IPF. TGF-β is the most potent factor for initiating myofibroblast differentiation, and it has been reported that the expression of TGF-β is elevated in the lungs of IPF patients [139].

It is widely recognized that TGF-β can also activate MMP2 and MMP9, both of which are implicated in the development of IPF [159]. The activities of MMPs are regulated through various mechanisms, including transcriptional regulation, proenzyme regulation, and a unique family of MMP inhibitors. While MMP-2 has been found to be involved in basement membrane damage in IPF [160], MMP-7 has been associated with the process of re-epithelialization [161]. Oxidants can alter the conformation and activity of extracellular matrix (ECM) proteins by affecting dityrosine-dependent cross-linking reactions [162]. Additionally, TGF-β-activated myofibroblasts may act as a source of oxidant production, thereby disrupting normal lung epithelium [163]. TGF-β has been found to be elevated in tissue samples from both animal models of IPF and IPF patients. Recently, TGF-β was reported to promote epithelial-mesenchymal transition by down-regulating the expression of let-7d [139]. Moreover, TGF-β has been shown to directly increase the transcriptional activation of collagen genes, including collagen 1A1, -A2, and -A3, collagen 5, and collagen 6, through the SMAD (Suppressor of Mothers Against Decapentaplegic) pathway [164,165]. The biological activation of TGF-β is a result of conformational changes in latency-associated peptide (LAP) induced by various agents, including cathepsins, plasmin, calpain, thrombospondin, integrin αvβ6, and MMPs, all of which are commonly found in fibrotic conditions [166,167]. Reports have demonstrated that alveolar macrophages are responsible for nearly all of the active TGF-β production in the bleomycin model of pulmonary fibrosis [168].

Diagnoses of Idiopathic Pulmonary Fibrosis

According to a 2011 joint statement by the American Thoracic Society, the European Respiratory Society, the Latin America Thoracic Association, and the Japanese Respiratory Society, the presence of a UIP pattern on high-resolution computed tomography or certain combinations of radiologic and histopathologic patterns in patients undergoing surgical lung biopsy can provide a definitive diagnosis of IPF [169]. However, before reaching a conclusive diagnosis, it is advisable to engage in multidisciplinary discussions involving experts from various fields, including clinicians, radiologists, pathologists, rheumatologists, and thoracic surgeons [169]. Four radiological parameters for diagnosing a UIP pattern on high-resolution computed tomography (HRCT) include: (1) subpleural basal dominance; (2) reticular abnormality; (3) honeycombing with or without traction bronchiectasis; and (4) the absence of additional features that are inconsistent with the UIP pattern. Even among radiologists who specialize in interstitial lung disease, assessing honeycombing for diagnosing UIP on HRCT exhibits significant interobserver variability [170]. According to a recent post-hoc subgroup analysis of patients from the nintedanib phase 3 INPULSIS program, patients with a potential UIP pattern on HRCT but without confirmation by surgical lung biopsy have a similar disease progression to patients with radiologically confirmed UIP and/or those with surgical lung biopsy confirmation. Moreover, both subgroups respond similarly to treatment with nintedanib [171]. A body of evidence suggests that by combining readily available clinical data, such as older age and different patterns of interstitial involvement on HRCT, a high predictive power for confirming UIP on subsequent histology can be achieved [172]. To provide a more confident diagnosis to patients, significant revisions to the diagnostic HRCT categories were recommended, even in the absence of tissue confirmation.

There has been a recent call to establish consensus on the legitimate goals, organization, and management of multidisciplinary team (MDT) meetings [173]. Furthermore, the majority of MDT assessments primarily focus on diagnosis, while treatment decisions are often left in the hands of pulmonary specialists [171]. Recognizing IPF can be challenging in clinical practice because its symptoms often resemble those of more common conditions such as asthma, chronic obstructive pulmonary disease (COPD), and various cardiac diseases. IPF typically presents with insidious onset and is characterized by symptoms like dyspnea and dry cough. Bronchoalveolar lavage (BAL) is a noninvasive procedure and plays a crucial role in diagnosing certain interstitial lung diseases (ILD), including conditions such as alveolar hemorrhage, alveolar proteinosis, and bronchoalveolar carcinoma. BAL has proven highly valuable in elucidating the key cells of the adaptive immune system responsible for driving inflammation in IPF [174]. In IPF patients, there is an increase in the percentage

and number of polymorphonuclear leukocytes, neutrophil products, eosinophils, eosinophil products, activated alveolar macrophages, alveolar macrophage products, cytokines, chemokines, fibroblast growth factors, and immune complexes [175]. The primary purpose of BAL is to rule out the suspicion of other diseases, such as chronic hypersensitivity pneumonitis, in patients suspected of having IPF.

Biomarkers of Idiopathic Pulmonary Fibrosis

The exploration of biomarkers is a growing field in IPF diagnosis. These biomarkers have the potential to assist in identifying patients at elevated risk of disease progression. Some significant biomarkers identified in IPF include.

Matrix Metalloproteinases

Matrix metalloproteinase-7 (MMP-7), also known as matrilysin, is expressed by lung epithelial cells, mononuclear phagocytes, and fibrocytes [160]. IPF patients exhibit elevated levels of circulating and bronchoalveolar lavage fluids (BALF), MMP-7, establishing circulating MMP-7 as a diagnostic biomarker for the disease [176]. Within the lungs of IPF patients, both lung epithelial cells and macrophages express MMP-7. IPF has been linked to two single nucleotide polymorphisms in the MMP-7 promoter region [177]. These enzymes play a role in regulating ECM components [178]. While over half of patients with MMP-7 present an accurate IPF diagnosis, approximately one-third experience misclassification. MMP-7 holds promise as a reliable indicator of deteriorating lung function and disease progression [179]. However, the lack of consistent, dependable cut-off values across studies hinders its practical application in clinical settings.

Matrix metalloproteinase-1 (MMP-1), also known as collagenase type I, is responsible for breaking down extracellular matrix collagen and typically expressed at low levels in normal lung tissue [178]. When MMP-7 exceeds 2.6 ng/mL and MMP-1 surpasses 8.9 ng/mL, the combination demonstrates a positive predictive value of up to 91% for diagnosing IPF. Although the connection between extracellular matrix deposition, MMP-1 expression, and lung function remains partially understood, the treatment with collagenase has been observed to reduce passive tension and enhance muscle shortening in human bronchial smooth muscle strips [180]. Research indicates that the exogenous administration of MMP-1 intensifies airway contraction, and the pro-contractile effect of Th2 cytokines IL-4 and IL-13 relies on MMP-1 [181]. Transcriptional and immunohistochemical studies consistently reveal significant MMP-1 overexpression in the lungs of IPF patients compared to control subjects [160]. This finding is intriguing because MMP-1 is an enzyme capable of cleaving fibrillar collagens. Studies also suggest that MMP-1 is associated with conditions characterized by excessive degradation of extracellular matrices, as seen in rheumatoid arthritis and emphysema [182]. Collectively, these findings imply that airway remodeling and extracellular matrix deposition may contribute to the exacerbation of airway obstruction and bronchial hyperreactivity by mediating abnormal MMP-1 expression in patients' airways.

Surfactant Proteins

Surfactant proteins (SP) are produced and secreted exclusively by Clara cells, bronchial epithelial cells, and alveolar epithelial cells, and they consist of lipoprotein complexes [183]. These proteins, encoded by the *SFTPA*, *SFTPB*, *SFTPC*, and *SFTPD* genes, include SP-A, SP-B, SP-C, and SP-D [184]. SP-A is a glycoprotein with a molecular weight ranging from 26 to 35 kDa, synthesized by type II alveolar cells in the lung. In contrast, SP-D is a hydrophilic collection with a molecular weight of 43 kDa, belonging to the superfamily of C-type lectins containing collagen and sharing structural similarities with SP-A. SP-D plays a vital role in the innate immune system, binding to specific carbohydrate and lipid structures on the surfaces of protozoa, fungi, bacteria, and viral particles through calcium-dependent interactions [185]. It has also been proposed to have a role in regulating lung inflammation. Surfactant proteins themselves, as well as mutations in the genes responsible for their production, are considered potential indicators of IPF [186]. While the concentrations of SP-A and SP-D in BAL of IPF patients are lower than those in healthy controls, these proteins are significantly elevated in the serum of IPF patients [187]. Their measurement may aid in identifying patients more likely to experience disease progression and worse outcomes [188]. Notably, the higher levels of SP-D in IPF compared to other interstitial lung diseases make it a potential biomarker for differential diagnosis [189]. A meta-analysis supports the use of serum SP-A and SP-D for differentiating IPF and assessing prognosis [187]. These proteins, in addition to Krebs von den Lungen-6 (KL-6) and MMP-7, have been identified as predictive markers in some studies, although in others, only SP-A and SP-D have been shown to be independent predictors of mortality [190].

Krebs von den Lungen-6

Krebs von den Lungen-6 (KL-6) is a high molecular weight glycoprotein expressed on type II pneumocytes and bronchial epithelium [191]. While it is a potential tumor marker, in ILD, it is utilized as a diagnostic and prognostic biomarker [192]. The serum levels of this compound are influenced by polymorphisms in the MUC1 gene, which encodes KL-6 production [193]. It has been proposed that changes in KL-6 during the follow-up of IPF patients can be useful in predicting disease progression [194]. Serial assessments of blood KL-6 in IPF patients may provide more predictive data than physiological markers [195]. Patients with an initial serum KL-6 value of 1000 U/mL and no subsequent elevations in KL-6 tend to have a better prognosis compared to patients with serial elevations in KL-6 or an

initial serum KL-6 value of 1000 U/mL [196]. Higher KL-6 levels in BALF have been associated with more prolonged and severe disease [197]. Patients who develop acute exacerbation (AE) have significantly higher basal levels of KL-6 compared to individuals with stable IPF [198]. In a meta-analysis involving 10 studies on IPF, KL-6 was found to have a stronger correlation with diagnosis than the other three markers studied (SP-A, SP-D, and MMP7) regarding prognostic aspects in IPF [199]. Recent studies have evaluated the reliability of data supporting the use of blood KL-6 levels to predict the prognosis of IPF patients [200].

Mucin 5B

Mucins (MUC2, MUC5AC, MUC5B, MUC6-8, and MUC19) are secreted and released into the extracellular environment [201]. Mucin 5B, one of the major components of respiratory secretions, plays a role in the respiratory system's defense against infections [201]. However, the accumulation of this gel-forming glycoprotein exacerbates the condition of IPF patients, whose gas exchange is already compromised, and complicates their clinical presentation [201]. Overexpression of MUC5B has a detrimental effect on mucociliary clearance, allowing harmful substances to remain in the airways for longer durations, causing damage, and ultimately leading to tissue healing with fibrotic changes [202]. A common single nucleotide polymorphism in the promoter region of the *MUC5B* gene has been linked to an increased risk of IPF [202]. A meta-analysis has confirmed a strong association between the minor T allele and an increased risk of IPF. This analysis also showed a significant correlation between the MUC5B promoter polymorphism *rs35705950* and the risk of developing IPF [203]. In particular, a mutation in the promoter region of the *MUC5B* gene has been associated with a reduced risk of death [204].

Oncomarkers

It has been established that IPF and lung cancer share certain common features. There are similarities in the pathogenetic mechanisms, including genetic and epigenetic alterations, molecular and cellular dysfunction, and activation of specific signaling pathways [205]. These commonalities suggest that specific tumor markers in IPF can be used to assess disease severity and predict prognosis [206]. CA 15-3 is a popular tumor marker used to indicate disease severity in IPF. Another useful marker for IPF is the glycoprotein known as carcinoembryonic antigen (CEA), which serves as a serum tumor marker for colon, rectal, gastric, pancreatic, and breast cancers [207]. Among the 123 serum proteins examined in the PROFILE study of IPF patients, CA19-9, CA125, and SP-D stand out as markers with the highest potential [188]. Analysis of CA19-9 levels in end-stage IPF patients has yielded results consistent with previous studies [208]. Numerous studies in different populations have confirmed that CA19-9 is an accurate marker of disease progression [188,208].

Secretory Protein of Clara Cells

Clara cells produce the 16-kDa homodimeric secretory protein known as Clara Cell 16 (CC16). This protein has been studied as a potential therapeutic agent for various lung diseases and is recognized for its anti-inflammatory and antioxidant properties [209]. Low serum CC16 levels have been associated with declining lung function in both adults and children, as well as an increased risk of death, especially from lung cancer [209]. In contrast, patients with IPF were found to have significantly elevated CC16 levels in both their serum and bronchoalveolar lavage [186]. It's worth noting that while CC16 levels are much higher in IPF, they are also elevated in other interstitial lung diseases like sarcoidosis [209]. The increase in serum CC16 concentrations is believed to be a result of Clara cell activation following injury to the alveolar epithelium. However, more research is required since CC16 levels do not appear to correlate with disease severity, even though CC16 is considered a potential biomarker in various lung diseases.

Telomeres

Research has shown that approximately one-third of individuals with familial idiopathic pulmonary fibrosis (IPF) exhibit telomere shortening and telomerase gene alterations [210]. In a study where peripheral blood leukocytes from IPF patients were examined for telomere length, it was observed that 40% of patients with familial IPF and 25% of those with sporadic IPF had shortened telomeres [211]. In a cohort study involving more than 300 IPF patients, peripheral blood leukocyte telomere length was identified as an independent predictor of mortality [212]. This suggests that assessing telomere length in peripheral blood may serve as a surrogate marker for telomere mutations in the families of individuals carrying these genetic alterations, obviating the need for genetic analysis [213].

Osteopontin

Osteopontin, an acidic phosphorylated glycoprotein, is released by various cell types, including osteoclasts, activated T lymphocytes, and activated macrophages [214]. Experimental mouse models have been utilized to explore the role of osteopontin in the development of pulmonary fibrosis. These models have demonstrated that osteopontin promotes fibroblast migration, adhesion, and proliferation in bleomycin-induced pulmonary fibrosis [215]. Furthermore, a study analyzing lung biopsy specimens from patients with IPF found that osteopontin exhibits the highest expression among all cytokines [186]. In cases of AE of IPF, serum osteopontin levels are significantly higher than those in stable IPF, and this increase is associated with a worse prognosis [216]. However, despite the fact that patients with IPF exhibit the highest levels of osteopontin, there were no significant differences in these levels compared to patients with other ILD subtypes, highlighting the limited utility of this biomarker in differential diagnosis [217].

Periostin

Periostin is a protein that has been found to be highly expressed in the lungs of individuals with IPF [218,219]. The zones of active fibrosis in the lung exhibit the highest periostin expression by fibroblasts [218]. Substances like TGF-β, IL-4, IL-13, and others can stimulate the production of periostin in fibroblasts [219]. Inhibiting the periostin gene or administering neutralizing antibodies has shown to significantly reduce the risk of pulmonary fibrosis induced by bleomycin [220]. Furthermore, periostin functions by activating NF-κB and releasing inflammatory cytokines and chemokines, as well as promoting the growth of pulmonary fibrosis along with inflammatory cytokines like tumor necrosis factor-α (TNF-α) [218]. There is a pressing need to develop a diagnostic test with improved specificity, as elevated serum levels of periostin are also observed in other inflammatory diseases [219]. Additionally, total periostin and monomeric periostin have been demonstrated to be more accurate predictors of short-term deterioration in IPF than conventional markers such as KL-6, SP-D, and LDH [219].

Lysyl Oxidase-2-Like Protein

A group of enzymes, known as lysyl oxidase (LOX) and lysyl oxidase-like protein (LOXL), play a role in stabilizing the ECM by promoting the deposition and accumulation of collagen. There are four LOX isoenzymes (LOX1, LOX2, LOX3, LOX4) encoded by genes located on different chromosomes [221]. Experimental mouse models of bleomycin-induced pulmonary fibrosis have shown increased expression of LOX [216]. Additionally, higher levels of LOXL2 in the blood of IPF patients have been associated with a greater risk of disease progression, although not correlated with disease severity [221,222]. The potential use of LOXL2 as a therapeutic target has been explored in the context of its role in the pathophysiology of pulmonary fibrosis. However, during the second phase of clinical trials, the investigation into the use of an anti-LOXL2 monoclonal antibody for treating IPF patients was terminated due to its ineffectiveness [221]. One of the likely reasons for this failure is the inadequate penetration of the lung tissue, though there was insufficient data for a comprehensive analysis [221].

Fibulin 1

Fibulin (Fbln) 1 is a secretory glycoprotein with a crucial role in alveolar septum development and embryonic morphogenesis [223]. Fbln1 is involved in tissue repair and has been associated with various respiratory diseases [224]. Particular emphasis has been placed on the role of the Fbln1c form in the development of many respiratory diseases, as it promotes fibroblast proliferation and alters the extracellular matrix [224,225]. Experimental mouse models have demonstrated that inhibiting Fbln1c expression reduces collagen deposition around the small airways and inhibits smooth muscle cell proliferation [224]. Mouse models have also highlighted the essential role of Fbln1c in chronic inflammation [224]. As a result, Fbln1 has been suggested as a potential biomarker and therapeutic target in diseases characterized by remodeling and inflammation [225]. There is evidence to suggest that Fbln1 may be involved in the etiology of IPF, as IPF patients exhibit higher serum and lung Fbln1 levels compared to healthy individuals [223]. Elevated blood Fbln1 levels are associated with low lung function and acute exacerbations of the disease [223,226].

Neoepitope

The primary component of the extracellular matrix is collagen, which undergoes normal synthesis and degradation in healthy lungs but is impaired in IPF [227]. During production, procollagen is cleaved, and during degradation, various parts of the collagen molecule are cleaved by MMPs, resulting in different neoepitopes being exposed in each of these processes [227,228]. Neoepitopes and peptides formed during synthesis are released into the bloodstream. Individuals with IPF exhibit higher serum levels of collagen synthesis neoepitopes, specifically type 3 and type 6, compared to healthy individuals of the same age. The increased concentration of these neoepitopes has been linked to the development of IPF [227,228]. Changes in the blood levels of these neoepitopes over time, reflecting fibrosis progression, may serve as predictors of mortality in IPF patients [227,228]. Utilizing biomarkers of collagen synthesis and degradation could enhance clinical trials, prognosis assessment, and treatment selection for IPF [227,228].

Heat Shock Protein 47

Heat Shock Protein 47 (HSP47) is a protein essential for the production and secretion of collagen molecules [229]. Elevated expression of HSP47 is directly associated with the excessive production and buildup of collagen [229]. Studies have demonstrated a significant increase in HSP47 concentration during acute exacerbation of the disease compared to the stable form of IPF [230]. Furthermore, this biomarker has been found to outperform widely studied pulmonary fibrosis indicators such as KL-6, SP-A, and SP-D [230]. Although the precise role of HSP47 in the etiology of IPF remains unclear, it is likely responsible for an additional mechanism of action of pirfenidone in inhibiting fibrotic processes. Pirfenidone may exert its antifibrotic effect, in part by reducing TGF-1-dependent production of HSP47, in addition to directly inhibiting the expression of type I collagen [231].

CC Chemokines

Monocytes, macrophages, and dendritic cells of the myeloid lineage release proteins known as CC (CC stands for the first 2 adjacent cysteine residues in the protein sequence of the chemokine subfamily of cytokines) chemokines. In patients with IPF, alveolar macrophages

produce particularly high levels of CC chemokine ligand (CCL)18 [232]. These alveolar macrophages are alternatively activated by Th2 cytokines, and these activated macrophages play a role in tissue repair and fibrosis [168]. Active macrophages release CCL18, which increases collagen production by lung fibroblasts. Collagen, in turn, triggers the release of CCL18, thus maintaining the fibrotic process [233]. Elevated serum levels of CCL18 in IPF are correlated with disease progression and show a negative relationship with pulmonary function tests [233]. Moreover, pirfenidone, a treatment for IPF, has been found to significantly decrease CCL18 expression in macrophages [233,234].

One of the chemokines involved in attracting mononuclear phagocytes, which in turn promotes inflammation and the formation of tissue fibrosis, is CCL2 [235]. Furthermore, it is most likely the interactions between chemokine ligands and their receptors that trigger fibrocyte recruitment to the lungs [236]. Patients with IPF were found to have significantly higher serum concentrations of this chemoattractant [236]. In contrast to a control group, patients suffering from both acute exacerbations of IPF and the stable form of the disease had significantly higher levels of CCL2 [235]. The same study concluded that CCL2 levels, among other chemokines, did not correlate with patient survival or lung function [235].

CXC Chemokine 13

Dendritic cells release a protein called CXC chemokine 13 (CXC, where CXC stands for cysteines separated by another amino acid in the protein sequence of the chemokine subfamily of cytokines), which is primarily responsible for attracting B lymphocytes to areas of inflammation. In patients with IPF, these cells, as well as altered and differentiated B lymphocytes, are present as antigen-activated B lymphocytes gradually mature [237]. The lungs of IPF patients were found to contain more CXCL13 mRNA than the lungs of control subjects, and their serum CXCL13 levels were higher than those of control subjects. Patients with IPF who had elevated CXCL13 protein levels had a higher mortality rate. Among patients with IPF, those who had recently experienced acute exacerbations or had pulmonary hypertension had the highest CXCL13 levels [238].

Toll-Like Receptor 3

Recent research has linked Toll-like receptors to abnormal fibrogenesis in IPF [239]. Toll-like receptors (TLRs) are primarily involved in recognizing various patterns associated with bacterial, viral, protozoan, and fungal pathogens [240]. Studies on fibroblasts in IPF have shown that primary fibroblasts proliferate uncontrollably, and the presence of TLR3 receptors reduces IFN production [241]. Activation of TLR3 receptors in primary fibroblasts results in decreased TGF synthesis, increased collagen production, and higher metalloproteinase activity, which can also have an antifibrotic effect [242]. A deficiency in TLR3 signaling may lead to an inadequate lung response to viral pathogens, exposing it to chronic cycles of damage and repair believed to underlie IPF pathology [243].

Toll-Interactin Protein

Alveolar type II cells, macrophages, and basal cells in the lung have been found to express Toll-interacting protein (TOLLIP). Gene variations, including *rs111521887* and *rs5743894*, detected in the TOLLIP introns have been associated with IPF susceptibility and have led to a 40–50% reduction in *TOLLIP* gene expression in the lung [186]. Interestingly, the *rs5743890G* allele, while associated with lower IPF susceptibility, is linked to higher mortality in IPF, indicating a potential genetic basis for different clinical outcomes [244]. This TLR inhibitory protein could be useful in identifying various IPF therapy responses in different genotypes [245]. Reduced TOLLIP expression after TLR stimulation leads to increased production of proinflammatory cytokines such as IL-6 and TNF by macrophages [246]. These results suggest that the reduction in the proinflammatory and profibrotic cascade due to TOLLIP expression may have protective effects [243].

Defensins

Small antimicrobial peptides known as defensins are primarily released by neutrophils and epithelial cells and possess antibacterial effects against certain Gram-positive and Gram-negative bacteria, as well as viruses [247]. The gene expression of alpha-defensins 3 and 4 was found to be higher in IPF patients who experienced acute disease exacerbations compared to those who did not [248]. MMP7, whose gene expression is also increased in the lungs of IPF patients, activates alpha-defensins [186]. It has been observed that serum levels of alpha-defensins are elevated in IPF patients compared to healthy individuals and are associated with disease progression [249].

S100 Calcium-Binding Protein

S100A4 belongs to the S100 family, which contains calcium-binding motifs. It promotes pulmonary fibrosis by stimulating the proliferation and activation of fibroblasts and facilitating their transition to myofibroblasts [250]. The clinical significance of S100A4 in the serum of IPF patients is well-established [251]. Higher levels of S100A4 are independently associated with a greater risk of disease progression and mortality, suggesting its potential as a valuable prognostic and therapeutic marker for IPF. Elevated serum S100A4 levels in IPF patients are linked to significantly shorter progression-free survival [252]. The pathogenic role of S100A8/A9 proteins in pulmonary fibrosis stems from their ability to promote fibroblast proliferation and increase collagen production [253]. Both S100A8 and S100A9 are significantly elevated in individuals with acute disease exacerbations and those diagnosed with IPF compared to healthy subjects [254]. Elevated levels of

these two biomarkers have proven to be significant prognostic indicators, as patients with higher concentrations of S100A8 and S100A9 experience significantly lower three-month survival rates [254]. S100A12, another member of the S100 family, plays a crucial role in immune responses and inflammatory processes. In a study involving a large number of IPF patients, elevated serum levels of S100A12 were observed and associated with an unfavorable prognosis for the disease [255].

Anti-Heat Shock Protein 72 Antibodies

Heat shock proteins (HSPs) and autoantibodies targeting these proteins have garnered attention as potential biomarkers in IPF due to their ability to activate monocytes in cell cultures and enhance IL-8 production [256]. Higher concentrations of HSPs in both serum and bronchoalveolar lavage of IPF patients have been associated with more severe pulmonary fibrosis, and IL-8 is considered one of the key mediators in the development of IPF [145]. While the concentration of the same immunoglobulins targeting HSP-72 in IPF patients and those with other interstitial lung diseases did not differ significantly from the levels in healthy individuals, some findings suggest a link between increased levels of HSP-72 autoantibodies in IPF patients and poorer prognosis [257]. Undoubtedly, HSPs and the autoantibodies against them play a role in the etiology of IPF, and further research is necessary to determine how these biomarkers can be effectively utilized for the diagnosis of pulmonary fibrosis.

YKL-40

Patients with IPF exhibit elevated levels of YKL-40, a chitinase-like protein, in their serum and lungs, with its primary expression in alveolar epithelial cells and macrophages [258]. High YKL-40 levels have also been detected in other diseases characterized by severe fibrosis, such as liver cirrhosis, Crohn's disease, and systemic sclerosis [259]. While there is a weak association between these concentration levels, IPF patients with increased YKL-40 levels in both their blood and bronchoalveolar lavage are at a higher risk of mortality [260]. In IPF, sarcoidosis, and asthma, YKL-40 levels show an inverse correlation with lung function [261]. However, it's important to note that YKL-40 is not a specific marker for IPF, and its prognosis value is associated with a cut-off value of 79 ng/mL [186].

Vimentin/Anti-Vimentin Antibodies

Vimentin has been implicated in the invasion of fibroblasts into fibrous foci within the lungs of IPF patients, as it is believed to enhance cell invasiveness [262]. Fibroblasts derived from IPF patients were found to express more vimentin than those from the control group under fasting conditions, triggering the autophagy process [262]. IPF has previously been linked to autophagy process deficiencies that hinder the degradation of extracellular matrix components by storing them in autophagosomes and failing to break down these products after fusion with lysosomes [263,264]. By inhibiting vimentin, the expression of vimentin and the content of type I collagen decreased, reducing the invasiveness of fibroblasts [262]. Several cells involved in the progression of pulmonary fibrosis release vimentin under the influence of TGF-β1 [265], and IPF patients displayed a significantly higher prevalence of this released cytoskeletal protein compared to healthy individuals [265].

Vascular Endothelial Growth Factor-A

In comparison to healthy controls, vascular endothelial growth factor (VEGF) levels are elevated in individuals with IPF [266]. Particularly, the VEGF-A165b protein levels are significantly increased in the lung tissue of IPF patients [266]. Interestingly, the BALF of IPF patients contains lower amounts of VEGF-A compared to control subjects [267]. The concentration of VEGF-A in peripheral blood is associated with the severity and progression of IPF [267]. In non-fibrotic regions of IPF lung tissue, higher alveolar-capillary density is linked to increased VEGF-A expression [267]. Nintedanib, which targets VEGF receptor signaling, slows down disease progression, although its effectiveness as a measure of treatment efficacy has not been definitively established [268].

Endothelin-1

A significant contributor to pulmonary fibrosis is the vasoactive peptide known as endothelin-1 (ET-1). The processes that lead to excessive collagen deposition involve the activation, proliferation, and differentiation of fibroblasts into myofibroblasts [269]. The concentration of ET-1 in the serum of IPF patients was notably higher compared to that in the serum of healthy subjects, while it was significantly lower in the serum of BALF [270].

Interleukin-8

Phagocytes release IL-8 when exposed to inflammatory stimuli, which in turn promotes angiogenesis [271]. In IPF patients experiencing worsening symptoms, significantly higher IL-8 levels were observed, and a 1 pg/mL increase in IL-8 was associated with a 6.7% increase in the probability of death among IPF patients [272]. BAL samples from IPF-AE patients had markedly higher IL-8 levels compared to IPF patients with stable disease [273]. HRCT images revealed that areas of the IPF lung with severe fibrosis contained a much higher percentage of IL-8-positive bronchoalveolar lavage macrophages than BALF from healthy participants [274].

Management of Idiopathic Pulmonary Fibrosis

It is still unclear which medical therapy is the most appropriate for the treatment of IPF. The updated 2015 American Thoracic Society (ATS)/European Respiratory Society (ERS)/JRS/ALAT guidelines recommend the use of both

pharmacologic and non-pharmacologic treatments for patients with IPF [275]. Treating IPF remains a challenge for clinicians and researchers.

Treatment approaches include the following:

1. Encouraging smoking cessation and considering pharmacotherapy when appropriate.

2. Prescribing oxygen therapy for patients with hypoxemia. The goal is to achieve an oxygen saturation of at least 90% at rest, during exertion, or while sleeping.

3. Administering vaccinations to protect patients against pneumococcus and influenza.

4. Referring every patient diagnosed with or likely to have IPF for lung transplantation. Lung transplantation offers a survival benefit for certain IPF patients who currently have no other treatment options. However, one- and three-year survival rates after lung transplantation appear to be lower in patients with acute exacerbations of IPF (AE-IPF) who undergo the procedure while on mechanical ventilation or in the intensive care unit [276].

5. Pharmacotherapy: After extensive efforts, two drugs, nintedanib and pirfenidone, were developed and approved by the US Food and Drug Administration in 2014. However, these two drugs have been shown to slow disease progression and stabilize lung function but not provide a cure [31]. The following components are the primary tools of pharmacotherapy:

Nintedanib

Nintedanib was previously known by its developmental code BIBF1120. It is a small molecule that functions as an intracellular inhibitor of several tyrosine kinases, including the endothelial growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), and platelet-derived growth factor receptor (PDGFR). All of these kinases play a crucial role in the development of IPF [277]. Nintedanib is currently undergoing clinical development for cancer indications, such as non-small cell lung cancer, colorectal cancer, and ovarian cancer. The exploration of nintedanib as a potential treatment for IPF stemmed from its ability to inhibit platelet-derived growth factor receptors, which are implicated in IPF. Nintedanib competitively binds to the ATP-binding clefts of these receptors, blocking intracellular signaling. *In vitro* studies have shown that nintedanib can hinder several processes involved in the progression of pulmonary fibrosis, including fibroblast proliferation, fibrocyte and fibroblast migration and differentiation, and the deposition of ECM in the lungs [278]. Additional research on nintedanib has demonstrated its antifibrotic and anti-inflammatory properties, as it inhibits fibroblast proliferation, myofibroblast differentiation, and the excessive secretion and accumulation of ECM components like fibronectin, proteoglycans, and collagen [268]. However, the direct impact of nintedanib on the host immune response in IPF has not been fully elucidated.

Pirfenidone

Pirfenidone, with its chemical name 5-methyl-1-phenyl-2-(1H)-pyridone, is a synthetic non-peptide molecule that is thought to possess anti-inflammatory, antioxidant, and antifibrotic properties. It has been shown to inhibit fibroblast proliferation and the synthesis of the ECM [279]. However, the precise mechanism of action of pirfenidone in the lung remains not fully understood [279]. Early phase II and III clinical trials in Japan identified pirfenidone as a potential therapeutic option for IPF, leading to its approval for the treatment of IPF in Japan and Europe [280–282]. There is also evidence to suggest that pirfenidone can decrease the production of pro-inflammatory and pro-fibrotic cytokines, such as TGF-β, IL-4, IL-13, and TNF-α, while increasing the production of the anti-inflammatory cytokine IL-10 [281]. Pirfenidone's therapeutic effects have been demonstrated in various preclinical models of fibrosis in multiple organs, including the lung, kidney, liver, heart, and eye [281–286]. The direct immunomodulatory properties of pirfenidone were first investigated in a mouse model of cardiac allograft transplantation [285]. These studies, both *in vivo* and *in vitro*, indicate that pirfenidone acts by suppressing the activation of fibrogenic mediators and growth factors through a variety of mechanisms. In the context of pulmonary fibrosis, pirfenidone has been shown to prevent fibrosis by inhibiting the expression of TGF-β1 and the phosphorylation of SMAD3 in animal models, such as a mouse lung model induced by radiation and a bleomycin-induced lung injury model in rats [281,283]. Additionally, pirfenidone has been found to inhibit TGF-β-mediated fibroblast proliferation and their differentiation into myofibroblasts by reducing signaling induced by TGF-β1/SMAD3 [282,284]. Studies have confirmed that TGF-β1, an important mediator in the fibrotic process, activates the expression of ECM proteins such as fibronectin and collagen types I, II, and III [287]. Pirfenidone can inhibit the protein expression of these mediators when stimulated by TGF-β1, both in lung fibroblasts from patients with IPF and in bleomycin-treated rats [283,288]. Moreover, pirfenidone has been shown to directly suppress the mRNA expression of HSP47, a protein associated with collagen production, in TGF-β1-induced human lung fibroblasts and in a mouse model of pulmonary fibrosis [281]. These findings suggest that pirfenidone acts on multiple targets and pathways involved in fibrosis to exert its antifibrotic effects.

Treatment of Acute Exacerbations of IPF (AE-IPF)

The clinical course varies significantly among individuals with some experiencing a steady or moderate progression, while others encounter rapid deterioration. Moreover, a subgroup faces occasional severe episodes of pulmonary function impairment known as "acute exacerbations" [289]. Although there have been case series reports on alternative treatments for AE-IPF, the limitations in study methodology and small sample sizes make it challenging to ar-

rive at definitive conclusions regarding the effectiveness and safety of these interventions [289,290]. The following section provides a description of the initial trials involving these agents.

Oxygenation

Patients experiencing AE-IPF often exhibit a high inspiratory rate, which can pose challenges for oxygenation when using a conventional low-flow nasal cannula [291]. These patients typically require a substantial amount of oxygen to maintain pulse oxygen saturation levels above 88 percent. In cases of acute hypoxemic respiratory failure without hypercapnia, when low-flow oxygen fails to achieve adequate SpO2, utilizing high-flow oxygen therapy through a nasal cannula may serve as a reasonable alternative [292].

Relief of Dyspnea

In some individuals, alleviating dyspnea can be achieved by addressing hypoxemia with increased oxygen supplementation [293]. Below are some techniques for managing dyspnea in palliative care:

Venous Thromboembolism Prevention. Hospitalized AE-IPF patients are at a higher risk of venous thromboembolism (VTE). It is crucial to implement standard precautions for VTE prevention in these patients.

Acid Inhibitory Therapy. Analysis of data from the placebo groups in three randomized trials has suggested that acid aspiration might contribute to AE-IPF [290]. However, a randomized trial of Nissen laparoscopic fundoplication in 58 stable IPF patients with atypical acid gastroesophageal reflux did not reduce the incidence of acute exacerbations [294]. Stress ulcer prevention guidelines are typically followed when treating patients who were not using antacid medications upon admission [295].

Mechanical Ventilation. The use of noninvasive positive pressure ventilation and low tidal volume mechanical ventilation in AE-IPF has not been formally studied. Its effectiveness is limited in IPF patients who experience sudden deterioration without a clearly identifiable therapeutic trigger [296]. AE-IPF patients hospitalized and/or placed on mechanical ventilation in the ICU face a poor short-term prognosis based on data from multiple cohorts [296,297].

Glucocorticoids

According to international evidence-based guidelines for AE-IPF, systemic glucocorticoids should be administered to most AE-IPF patients [9]. The choice of glucocorticoid treatment depends on the disease's severity and the patient's response to treatment, with dosages typically ranging from prednisone at 1 mg/kg per day administered orally to methylprednisolone at 1 g/day given intravenously for three days to address AE-IPF [6]. Generally, glucocorticoids are gradually tapered over several weeks to months in patients showing a positive clinical response, with close monitoring to prevent any relapse [298,299]. In many cases, glucocorticoids are used as monotherapy. However, some studies have reported similar outcomes in AE-IPF without the use of immunosuppressants [300]. A few cases suggest the presence of concurrent organizing pneumonia, which may respond to glucocorticoid treatment, although autopsy and biopsy data from this cohort often show normal interstitial pneumonia with diffuse alveolar damage [301].

Antibiotics

Upon admitting a patient with radiographic findings suggestive of pneumonia, broad-spectrum antibiotics are often initiated [302]. For IPF patients with viral respiratory infections, such as severe COVID-19, antiviral therapies like nirmatrelvir/ritonavir and remdesivir may be prescribed [303]. In the case of influenza infection, patients should be treated with neuraminidase inhibitors [304]. Occasionally, procalcitonin (PCT) and C-reactive protein (CRP) and other biological markers are employed to differentiate between bacterial and non-bacterial causes of pneumonia [305]. A randomized trial in AE-IPF patients compared PCT-guided antibiotic treatment with treatment determined by the attending physician, revealing no changes in the duration of mechanical ventilation and all-cause mortality [306]. However, the study noted shorter antibiotic use with PCT monitoring [307].

Palliative Care

In light of the grim prognosis for AE-IPF patients, it is essential to seek palliative care consultation to alleviate symptoms and provide support to both the patient and their family [308]. Palliative care can offer important psychosocial support, particularly in terms of alleviating respiratory distress, which is a crucial aspect of end-of-life care [309]. To provide relief from respiratory distress, various palliative measures may be employed, including relaxation techniques, cooling with a ventilator, opiates, benzodiazepines, and occasionally noninvasive ventilation [310]. Some studies suggest that noninvasive ventilation may be effective in reducing dyspnea; however, it is crucial to have a clear discussion about treatment goals, especially with patients who do not wish to pursue life-prolonging interventions [311].

Post-COVID Pulmonary Fibrosis

SARS-CoV-2-related COVID-19 infection continues to resurface with new strains and variants, and many individuals who contracted the virus in the past two years are still grappling with the consequences, particularly lung and other system damage [312–314]. The terminology "post-COVID pulmonary fibrosis" (PC-PF), "post-COVID interstitial lung disease" (PC-ILD), or "post-COVID diffuse lung disease" (PC-DLD) is used to describe conditions characterized by features like traction bronchiectasis and

honeycomb patterns. Functional disability and impaired pulmonary function often accompany these conditions. The natural progression and optimal treatment approaches for post-COVID pulmonary fibrosis remain uncertain.

Clinical Trials and Future Perspectives

The landscape of pharmacologic treatment for IPF has undergone significant changes since the first trial was conducted nearly 30 years ago [315]. These changes reflect advances in our understanding of pathogenic mechanisms, the establishment of standardized diagnostic criteria, and the development of larger randomized clinical trials. Table 3 offers a summary of recently completed and ongoing clinical trials in this field.

The inclusion criteria for IPF patients have become more stringent over the past decade. However, there is still ongoing debate about what constitutes a clinically significant endpoint, making research design challenging. All-cause mortality and non-elective hospitalization have been suggested as the most reliable options [316]. Nonetheless, assessing these endpoints can be prohibitively expensive as it involves enrolling a large number of patients and long-term monitoring. Few studies have demonstrated that the commonly used primary lung function endpoint is truly clinically significant. Nevertheless, patients should be strongly encouraged to participate in randomized, multicenter, placebo-controlled trials since there are currently no approved drugs for the treatment of IPF [9,317]. Referring physicians can access a registry of publicly and privately funded clinical trials on https://clinicaltrials.gov, which lists ongoing or recently completed trials in IPF.

Conclusions

IPF is a rare and debilitating lung disease with an unknown etiology. It is believed to result from a complex interplay of various factors that damage the lung epithelium and disrupt the natural healing process, ultimately leading to fibrosis. Numerous genetic and biological markers have been developed to aid in diagnosis and prognosis. Promising results have been achieved in the search for more effective treatments, with pirfenidone and nintedanib showing potential. Given the involvement of multiple molecular pathways in fibrogenesis, it is suggested that future therapies should adopt a multitarget approach and employ multiple biomarkers. Additionally, research should explore environmental risk factors that may contribute to the development of IPF. By increasing awareness of both intrinsic and extrinsic environmental factors as potential causes of the disease and conducting well-designed investigations, we can pave the way for more effective treatments and a better understanding of the pathogenesis of idiopathic pulmonary fibrosis.

Availability of Data and Materials

The clinical trials are available on the website: https://clinicaltrials.gov/.

Author Contributions

VS, IU and RKK—conceptualization, writing-original draft, supervision and analysis of clinical trials. SG, AS and VKR—concept and design of review article, collection of published articles, analysis and interpretation of data of clinical trials, writing-draft, help and advice on recent references and editorial changes. All the authors have been involved in revising the manuscript critically for important intellectual content. All authors give final approval of the version to be published. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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