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A syndromic framework for progressive pulmonary fibrosis

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Abstract

Pulmonary fibrosis comprises a heterogeneous group of interstitial lung diseases (ILDs) with diverse aetiologies but often convergent clinical behaviour. Idiopathic pulmonary fibrosis (IPF) represents the prototypical fibrotic ILD; however, a substantial proportion of patients with non-IPF fibrotic ILDs develop a progressive pulmonary fibrosis (PPF) phenotype characterised by irreversible functional decline, worsening symptoms, increased healthcare utilisation, and excess mortality. Although traditionally classified according to underlying cause, accumulating epidemiological, clinical, and biological evidence indicates that once progression emerges, fibrotic ILDs share common trajectories that transcend etiologic boundaries. Across IPF and non-IPF PPF, longitudinal decline in forced vital capacity represents the dominant marker of disease activity and prognosis, with similar rates of deterioration and comparable mortality risk. Shared genetic susceptibility factors—particularly variants affecting telomere maintenance and epithelial integrity—together with convergent fibrotic pathways suggest a common biological vulnerability that may influence disease behaviour beyond the original diagnosis. Clinically, patients with PPF exhibit symptom burden, quality-of-life impairment, risk of acute exacerbations, and need for advanced supportive care that largely overlap with those observed in IPF. Randomised clinical trials further reinforce this convergence, demonstrating that antifibrotic therapies attenuate lung function decline across IPF and PPF populations. Overall, current evidence supports the view that PPF might represent a clinical syndrome characterised by shared disease trajectories, common clinical needs, and comparable responses to antifibrotic therapy.

Key messages

• Progressive pulmonary fibrosis may represent a clinical syndrome that transcends the underlying aetiology of interstitial lung disease, reflecting shared biological pathways that drive disease progression.

• Shared genetic susceptibility factors, although present only in a subset of patients, together with convergent biological pathways—including epithelial injury, aberrant repair responses, fibroblast activation and extracellular matrix deposition—support the concept that diverse fibrotic ILDs may ultimately converge toward common mechanisms driving progressive fibrosis

• Functional decline, prognosis, and healthcare needs in progressive pulmonary fibrosis closely resemble those observed in idiopathic pulmonary fibrosis, leading to overlapping clinical management and supportive care requirements.

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• Randomized clinical trials increasingly support a phenotype-driven therapeutic strategy, with antifibrotic agents demonstrating efficacy across different progressive fibrotic lung diseases.

• A syndromic approach to patients with progressive pulmonary fibrosis emphasizes early identification of a progressive phenotype, enabling timely treatment decisions, holistic management, and a shift from aetiology-centred to behaviour-centred care.

Keywords Progressive pulmonary fibrosis (PPF), Interstitial lung diseases (ILDs), Antifibrotic therapy, Phenotype-driven management, Syndromic approach

Introduction

Pulmonary fibrosis encompasses a heterogeneous group of interstitial lung diseases (ILDs) arising from diverse aetiologies, including idiopathic, autoimmune, environmental, and treatment-related causes. Among these, idiopathic pulmonary fibrosis (IPF) has historically represented the prototypical fibrotic ILD and remains the most extensively studied entity [1]. Nevertheless, IPF is a rare disease, with population-based studies estimating an incidence of approximately 3–9 cases per 100,000 person-years and a prevalence ranging from about 10 to 60 cases per 100,000 persons, depending on geographic region, study design, and diagnostic definitions [2]. A similar epidemiological profile characterises many non-IPF fibrotic ILDs when considered individually; systemic sclerosis–associated ILD (SSc-ILD), rheumatoid arthritis–associated ILD (RA-ILD), fibrotic hypersensitivity pneumonitis (f-HP), and idiopathic inflammatory myopathy–associated ILD (IIM-ILD) all represent relatively uncommon conditions at the population level. Epidemiological studies estimate that RA-ILD has a prevalence of approximately 3.2–6 cases per 100,000 persons [3], and longitudinal cohort analyses suggest that 34.6% of patients experience disease progression over a 3-year period [4]. Likewise, clinically significant SSc-ILD remains rare at the population level despite the high proportion of interstitial lung involvement among patients with systemic sclerosis [5]. Data on IIM-associated ILD are more limited, but available cohort studies consistently report pulmonary involvement in a substantial fraction of patients with polymyositis and dermatomyositis [6] and higher in anti-synthetase antibody positive patients [7], reinforcing the concept that fibrotic lung disease occurs across multiple rare systemic disorders. When these conditions are approached strictly as separate diagnostic entities, each qualifies as a rare disease, resulting in fragmented patient populations, limited feasibility of clinical trials, and heterogeneous evidence bases. However, this traditional aetiologic compartmentalisation contrasts with common clinical experience, where a subset of patients across distinct fibrotic ILDs follows a similar progressive course characterised by worsening respiratory symptoms, irreversible decline in lung function, progressive radiological fibrosis, and increased mortality [8]. This observation has led to the emergence of the concept of progressive pulmonary fibrosis (PPF), formally codified in the 2022 ATS/ERS/JRS/ALAT clinical practice guideline [2]. Epidemiological syntheses and registry-based studies suggest that approximately 13–40% of patients with fibrotic ILD other than IPF altogether meet criteria for progression during follow-up, depending on disease subtype, definition of progression, and duration of observation [8–10]. In clinical medicine, a syndrome is traditionally defined as a recognizable constellation of signs, symptoms, functional abnormalities, and outcomes that tend to occur together and characterize a distinct clinical condition, even in the absence of a single unifying aetiology [11]. Syndromic frameworks are commonly adopted when heterogeneous causes converge toward shared clinical behaviour, prognostic trajectories, and management needs. Beyond epidemiology, accumulating evidence suggests that disease behaviour in PPF may be influenced by shared biological and clinical determinants that transcend the initiating aetiology. Genetic susceptibility factors, including variants in telomere-related genes and mucin-encoding genes initially described in IPF, have also been identified in subsets of patients with non-IPF fibrotic ILDs, suggesting partial convergence of pathogenic pathways [12]. Concurrently, large registries and randomised clinical trials have demonstrated that the magnitude and prognostic significance of lung function decline in patients with PPF closely resemble those observed in IPF [8, 9]. These observations challenge a purely aetiology-centred framework for fibrotic ILD once progression has emerged. In this perspective review, we propose that progressive pulmonary fibrosis can be conceptualised as a clinical syndrome in which diverse fibrotic interstitial lung diseases converge toward shared trajectories of progression, clinical manifestations, and management needs (Fig. 1).

Convergent biological susceptibility and genetic risk in progressive pulmonary fibrosis

Although PPF is defined on clinical and functional grounds, accumulating evidence indicates that shared biological susceptibility factors contribute to the development and behaviour of a progressive fibrosing phenotype across distinct interstitial lung diseases. These determinants are not universal, but are enriched in specific patient subsets and appear to modulate disease

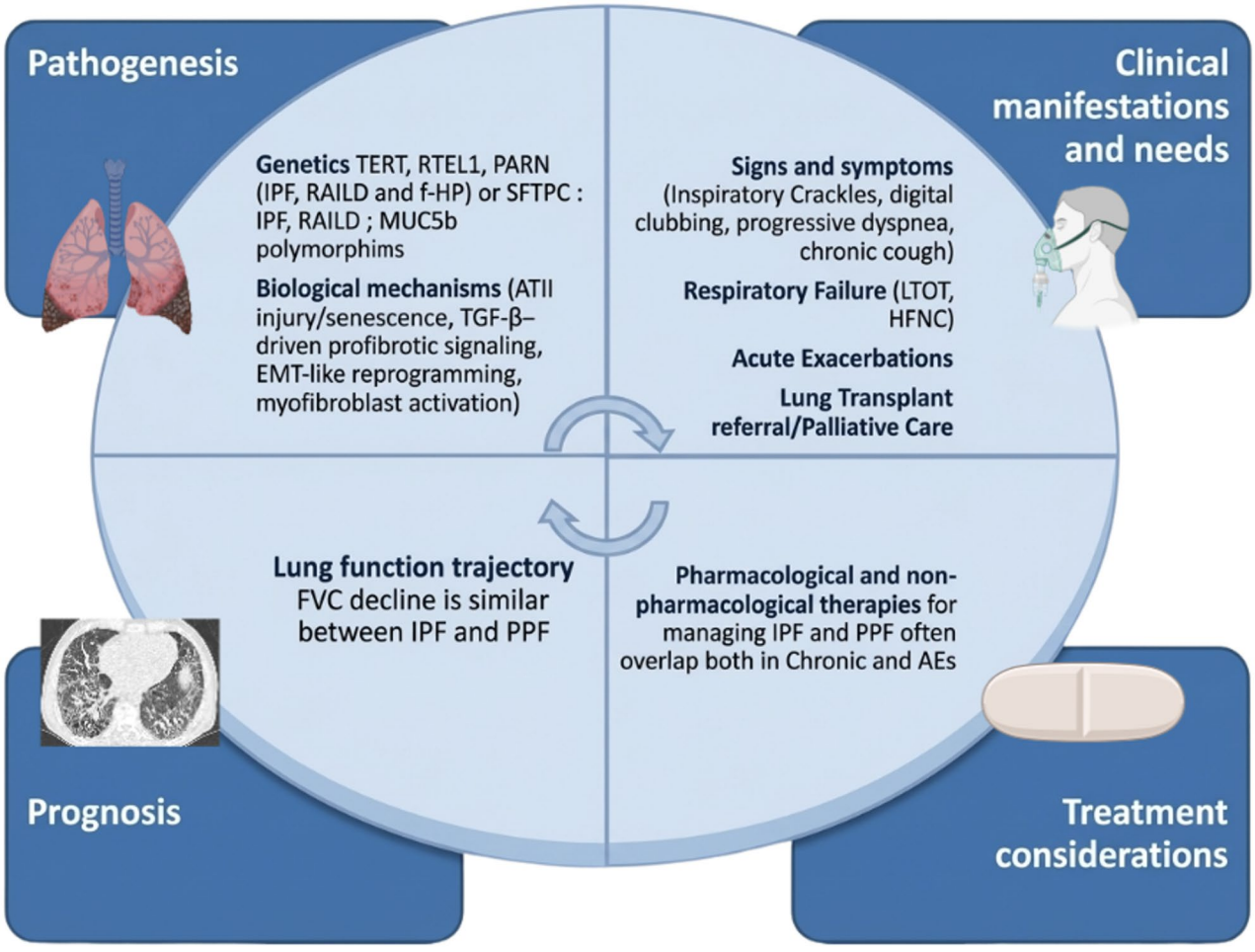

Fig. 1 Progressive pulmonary fibrosis (PPF) as a clinical syndrome. PPF arises from heterogeneous initiating conditions but converges toward shared biological susceptibility, clinical manifestations, disease trajectory, and therapeutic responsiveness. Genetic and epithelial vulnerability factors lower the threshold for fibrosis progression, while decline in forced vital capacity represents the central determinant of prognosis across idiopathic and non-idiopathic fibrotic ILDs. Clinical needs, including symptom burden, acute exacerbations, oxygen supplementation, and referral for lung transplantation, largely overlap once progression is established. The efficacy of antifibrotic therapies across disease entities supports a phenotype-driven, syndromic approach to management. AEs: Acute exacerbations; ATII: Alveolar Type II epithelial cells; EMT: Epithelial–mesenchymal transition; f-HP: fibrotic hypersensitivity pneumonitis; FVC: Forced vital capacity; HFNC: High-flow nasal cannula; IPF: Idiopathic pulmonary fibrosis; LTOT: Long-term oxygen therapy; MUC5B: Mucin 5B; PARN: Poly(A)-specific ribonuclease; PPF: Progressive pulmonary fibrosis; RAILD: Rheumatoid arthritis–associated interstitial lung disease; RTEL1: Regulator of telomere elongation helicase 1; SFTPC: Surfactant protein C; TERT: Telomerase reverse transcriptase; TGF-β – Transforming growth factor beta

trajectory and severity, rather than defining a specific aetiologic diagnosis. Rare pathogenic variants in genes involved in telomere maintenance and alveolar epithelial homeostasis represent the most consistently replicated genetic risk factors across fibrotic ILDs. Variants in telomerase-related genes, including TERT, TERC, RTEL1, and PARN, account for approximately 15–25% of familial pulmonary fibrosis cases and are also detected, at lower frequency, in sporadic IPF and non-IPF fibrotic ILDs [13–15]. Importantly, similar telomere-related variants and short telomere phenotypes have been described in RA-ILD and chronic HP, supporting the existence of a shared biological substrate across clinically distinct fibrotic lung diseases [13, 14]. Crucially, genetic susceptibility appears to influence not only disease onset but also clinical trajectory. Telomere-related variants have been associated with earlier disease progression, steeper decline in forced vital capacity, and worse survival in both IPF and selected non-IPF fibrotic ILDs, including RA-ILD and f-HP, suggesting that genetic background may modulate the risk of progression independently of underlying aetiology [14–16]. These observations align with clinical data showing that telomere-related pulmonary fibrosis is heterogeneous at presentation but uniformly progressive over time, regardless of diagnostic label [14]. Mechanistically, telomere dysfunction is associated with impaired regenerative capacity of alveolar type II epithelial cells, increased cellular senescence, and heightened vulnerability to repetitive lung injury. While these mechanisms do not define a single disease entity,

they plausibly lower the threshold for irreversible fibrosis and accelerate functional decline once fibrotic remodelling is established [15, 17]. In parallel, rare variants affecting surfactant-related genes (SFTPC, SFTPA1, SFTPA2) have been linked to familial and sporadic fibrotic ILDs characterised by heterogeneous radiological patterns, including UIP-like phenotypes [18–20]. While these mutations account for a small proportion of cases, they further reinforce the concept that epithelial vulnerability represents a common upstream determinant of fibrotic progression across diagnostic categories. Beyond rare variants, common genetic risk alleles identified through genome-wide association studies—most notably the MUC5B promoter polymorphism—are shared across IPF, familial pulmonary fibrosis, and subsets of non-IPF fibrotic ILDs [21, 22]. While these variants are neither necessary nor sufficient to cause disease, their presence across multiple fibrotic ILDs supports the notion that convergent molecular pathways influence fibrotic behaviour rather than disease aetiology per se. At present, available evidence does not support routine genetic testing in unselected PPF populations. Nevertheless, from a conceptual standpoint, the overlap of genetic susceptibility factors across IPF and non-IPF fibrotic ILDs provides strong biological plausibility to a syndromic framework. Genetic risk appears to shape disease trajectory, rate of functional decline, and vulnerability to progression, aligning more closely with the PPF phenotype than with traditional aetiologic classifications [13, 14].

Shared clinical needs and convergent disease trajectories in progressive pulmonary fibrosis

Across fibrotic ILDs, the emergence of a progressive phenotype is associated with convergent patterns of physiological decline, symptom burden, healthcare utilisation and acute clinical events, generating a set of shared clinical needs across diseases.

Patterns of physiological decline in progressive pulmonary fibrosis

In IPF progressive loss of lung function represents the defining feature of disease evolution and the strongest predictor of outcome. Across longitudinal cohorts and clinical trials, the mean annual decline in forced vital capacity (FVC) in untreated IPF is consistently in the range of approximately 150–200 mL per year, with substantial inter-individual variability [23, 24]. Importantly, functional decline carries clear prognostic implications: a relative FVC decline ≥ 10% over 12 months is associated with a two- to threefold increase in mortality risk, independent of baseline lung function and demographic factors, and is widely accepted as a clinically meaningful threshold in IPF [25, 26]. Accumulating evidence indicates that once a progressive phenotype emerges, non-IPF fibrotic ILDs follow functional trajectories that closely mirror those observed in IPF. In the INBUILD trial, patients with PPF of non-IPF aetiologies assigned to placebo experienced an annual rate of FVC decline closely comparable to that historically reported in untreated IPF cohorts [27]. This observation is reinforced by large registries and real-world studies, which consistently show that the behavioural phenotype of progression, rather than the underlying diagnosis, determines the pace of physiological deterioration [6–8]. Data from patients with fibrotic hypersensitivity pneumonitis who develop a PPF phenotype suggest rates of FVC decline comparable to those observed in IPF, particularly in the presence of a UIP-like fibrotic pattern [9, 10]. Conversely, in systemic autoimmune rheumatic disorder-ILDs (SARD-ILDs), functional decline often follows a different temporal pattern. Early disease phases may be characterised by slower rates of FVC loss compared with IPF; however, once objective progression criteria are met, subsequent trajectories converge toward those of IPF, with comparable risks of mortality and transplant-free survival [8, 28, 29]. This delayed but convergent behaviour highlights that the onset of progression marks a biological and clinical inflection point, beyond which aetiology exerts a diminishing influence on outcome. Analogously, Change in FVC has therefore become the dominant endpoint in clinical trials across IPF and PPF, as attenuation of FVC decline consistently correlates with improved clinical outcomes [27, 30, 31]. Trajectory-based analyses further refine this concept by demonstrating that patterns of sustained or accelerated FVC decline, rather than single time-point measurements, identify patients at highest risk across fibrotic ILDs [29]. Therefore, the emergence of progression represents a biological transition after which disease behaviour becomes largely independent of the initiating diagnosis and even smaller relative declines in FVC, when persistent over time, are associated with adverse outcomes [25]. However, trajectory-based analyses indicate that progression is not uniformly linear. In a secondary analysis of the PROFILE cohort, four distinct FVC trajectories in IPF, including linear decline, initial improvement followed by decline, early decline followed by relative stabilization, and apparently stable lung function have been described with clearly different survival profiles across clusters [32]. Therefore, in pulmonary fibrosis, disease trajectory—interpreted alongside symptoms and imaging—provides more meaningful prognostic information than isolated functional events. Another important caveat in functional trajectory analysis arises in specific phenotypes such as combined pulmonary fibrosis and emphysema (CPFE), in which the counterbalancing effects of restriction and hyperinflation may blunt changes in lung volumes and make serial FVC less sensitive to disease progression and weaker prognostic

information when compared to IPF [33], whereas DLCO decline may retain greater prognostic value [34].

Imaging beyond physiology: the emerging role of quantitative CT

While longitudinal FVC trajectories provide a robust framework for monitoring disease progression, physiological measurements alone may not fully capture the structural evolution of fibrotic lung disease. However, conventional visual evaluation of HRCT is subject to inter-observer variability, may not correlate to pathologic changes and may fail to detect subtle changes in fibrotic burden over time [35, 36]. Quantitative CT (QCT) approaches have emerged as potential tools to improve the objectivity and reproducibility of imaging assessment. By converting CT data into measurable indices of lung density and parenchymal texture, QCT allows the longitudinal quantification of fibrotic involvement across the entire lung, offering a more continuous representation of structural disease burden than categorical visual scoring. These approaches may be particularly informative in patients with discordant clinical trajectories, where symptoms or functional decline evolve despite apparently stable visual imaging findings [37]. In addition, quantitative imaging analyses have enabled the identification of emerging radiological biomarkers of disease behavior, including measures derived from pulmonary vessel-related structures and other automated features associated with disease severity and progression [38]. Nevertheless, the clinical integration of QCT in PPF remains evolving. Current evidence suggests that quantitative imaging should be viewed as a complementary tool within a multidimensional monitoring framework rather than a standalone marker of disease progression [39]. From a syndromic perspective, the increasing availability of objective imaging biomarkers further supports the concept that progression in fibrotic ILDs should be assessed through integrated physiological, radiological and patient-centered domains, rather than through disease-specific markers alone.

Clinical symptoms and QoL in patients with PPF

PPF is characterised not only by physiological and radiological progression, but also by a high symptom burden that directly shapes functional status, quality of life (QoL), and care needs. Real-world evaluations of patients with PPF consistently identify dyspnoea, cough, and fatigue as dominant symptoms, often present concurrently and persisting or worsening over time [40, 41]. Dyspnoea represents a particularly informative dimension of patient experience in PPF. In the INBUILD population, worse baseline dyspnoea and worsening dyspnoea over 24 weeks—captured using the Living with Pulmonary Fibrosis (L-PF) questionnaire—were associated with an increased risk of short-term disease progression, supporting dyspnoea assessment as a clinically actionable signal beyond spirometry alone [42]. These findings reinforce the clinical value of integrating symptom trajectories into longitudinal monitoring frameworks for PPF [40, 41]. Cough is highly prevalent across progressive fibrotic ILDs and constitutes a major contributor to daily disability and health-related QoL impairment. A systematic synthesis of evidence confirms that cough is persistent in IPF and other ILDs, with multidimensional consequences for physical, psychological, and social functioning [43]. Specifically in PPF, dedicated studies demonstrate that cough is common and is associated with significant decrements in health-related QoL, underscoring cough as a priority symptom domain for supportive interventions and clinical trial endpoints [44]. Recent evidence also highlights the feasibility and potential clinical utility of objective/digital cough monitoring. A 6-month feasibility study in PPF explored long-term wearable cough monitoring and reported that cough intensity metrics could correlate with established patient-reported outcome measures (LCQ and K-BILD), suggesting that objective cough features might complement questionnaires in tracking symptom evolution [45]. Beyond individual symptoms, PPF imposes a broad burden across activities of daily living, emotional well-being, sleep, and social participation. In a real-world study describing the patient journey in IPF and PPF, symptom burden and its functional consequences were prominent, supporting the concept that progressive fibrosis—regardless of initial diagnosis—generates overlapping patient-centred challenges [41]. Longitudinal analyses further show that health-related QoL can deteriorate over time in non-IPF fibrotic ILD and that trajectories differ between patients who do and do not develop a progressive phenotype, supporting QoL measures as sensitive indicators of clinically meaningful progression [44]. Symptoms may progress independently of extrapulmonary disease control in systemic ILDs. The symptom and QoL burden of PPF is particularly relevant in systemic diseases where pulmonary progression may occur despite control of extrapulmonary manifestations. In IIM–associated ILD, recent data on post-myopathic progressive pulmonary fibrosis (PmPPF) suggest that fibrotic lung progression may continue despite stable extrapulmonary disease, supporting the need for sustained pulmonary surveillance and symptom-oriented management even when systemic manifestations appear controlled [6]. Similarly, in hypersensitivity pneumonitis with autoimmune features (HPAF), outcomes related to progression and response to therapy underscore heterogeneity of drivers – HPAF had lower risk of PPF and better response to immunosuppressor when compared to HP- but nonetheless emphasise that symptom and functional monitoring remain central to detecting PPF

evolution [46]. Therefore, integrating symptom assessment and patient-reported outcomes into routine follow-up alongside pulmonary function trends may better reflect the real-world burden of PPF and help identify patients in need of earlier supportive interventions [41, 47].

Healthcare utilization, oxygen supplementation and supportive care

PPF is associated with substantial healthcare utilization, reflecting the cumulative impact of chronic disease management, symptom progression, and treatment escalation. Real-world analyses and administrative claims studies indicate that patients with fibrotic ILD who develop a progressive phenotype require significantly more healthcare resources than those with stable disease [48, 49]. Increased utilization includes more frequent outpatient visits, higher rates of hospitalisation, and greater use of supportive services, patterns that have been consistently observed in IPF and non-IPF progressive fibrotic ILDs [50–53]. In IPF, population-based studies demonstrate higher healthcare use compared with matched controls, supporting the concept that progressive fibrosis is intrinsically resource-intensive [50]. Oxygen supplementation represents a common and clinically relevant component of care in progressive fibrotic ILD. It is frequently prescribed for exertional or resting hypoxaemia and often coincides with disease progression and worsening functional capacity [54, 55]. Systematic reviews and clinical studies indicate that supplemental oxygen improves oxygenation and exercise-related outcomes in fibrotic ILD, although evidence for long-term effects on quality of life and survival remains limited [56]. In routine clinical practice, initiation of oxygen therapy is associated with increased healthcare interactions, including equipment provision, reassessment, and coordination of home-based services [49]. As disease progresses, patients with PPF increasingly require evaluation within specialised ILD centres and consideration for advanced-care pathways, including referral for lung transplantation in selected cases. Reviews addressing advanced ILD management emphasise the complexity of pre-transplant assessment and the need for structured multidisciplinary care models [57]. Importantly, these escalation pathways apply not only to IPF but also to patients with non-IPF progressive fibrotic ILDs, including connective tissue disease–associated ILD, in whom transplant referral criteria and decision-making are broadly comparable [10]. Overall, available evidence indicates that healthcare utilization in fibrotic ILD is primarily driven by disease behaviour, rather than by etiologic classification alone. Once a progressive phenotype is established, patients across different ILD subtypes demonstrate convergent patterns of healthcare use, supporting the adoption of harmonised care pathways within a syndromic approach to PPF [48, 49].

Acute exacerbations of pulmonary fibrosis

Acute exacerbations (AEs) are clinically significant events in PPF that are associated with high rates of hospitalisation, increased healthcare resource utilisation, and elevated short-term mortality compared with stable disease to morbidity and mortality across fibrotic ILDs [58]. Originally characterised in IPF, AEs have been increasingly recognised in non-IPF fibrotic ILDs that display a progressive phenotype, with similar clinical presentation and outcomes [54, 59]. Epidemiological studies indicate that the incidence of AE in IPF ranges widely depending on cohort and definition, but is consistently associated with poor short-term survival and a high risk of subsequent clinical deterioration [60]. In non-IPF fibrotic ILDs, including SARD-ILDs and f-HP, population-based and registry data confirm that AEs occur and carry similarly adverse prognostic implications, supporting the view that AEs are a shared clinical phenomenon rather than an IPF-specific event [58]. Clinical characterisation of AEs demonstrates overlapping features irrespective of ILD subtype, including rapid worsening of dyspnoea, new radiological opacities, deterioration in gas exchange, and exclusion of other causes such as infection or cardiac decompensation [61]. Pathophysiologically, AEs may reflect acute insults on a background of chronic fibrotic vulnerability, with proposed mechanisms including alveolar epithelial injury, aberrant immune responses, and microvascular dysfunction. While the precise triggers remain heterogeneous and incompletely understood, the clinical phenotype of AE—rapid physiological deterioration superimposed on chronic fibrosis—is observed across ILD subgroups with progressive behaviour [50, 54]. From a management perspective, early recognition of AEs in PPF is critical, as these events frequently necessitate escalated interventions, including high-dependency care, empirical treatment for potential triggers, and reassessment of overall prognosis and therapeutic strategy. The occurrence of AE influences subsequent care planning and is an important consideration in risk stratification models for progressive fibrotic ILD [60, 61].

Prognosis indexes and mortality in progressive pulmonary fibrosis

Although the underlying aetiologies vary, prognosis in PPF is more closely linked to disease behaviour and functional trajectory than to diagnostic label. Several cohort studies and registry analyses demonstrate that patients with PPF have survival outcomes that approximate those observed in IPF when similar degrees of functional decline are present [62, 63]. Population-based studies in IPF have consistently reported poor long-term survival,

with median survival in the absence of antifibrotic therapy historically estimated at approximately 3–5 years from diagnosis. In non-IPF fibrotic ILDs, outcomes are more variable, but those patients' meeting criteria for progression exhibit mortality rates and survival curves that increasingly overlap with IPF cohorts. In large observational cohorts, progressive chronic HP and SARD-ILD with a progressive fibrosing phenotype have shown 3- to 5-year survival probabilities comparable to those reported in IPF, particularly when adjusted for age and baseline physiological impairment [64, 65]. Several risk prediction tools have been developed to integrate clinical, physiological, and demographic variables for survival estimation. Among these, the GAP (Gender–Age–Physiology) score—originally derived in IPF—has been applied to diverse fibrotic ILD populations, including progressive non-IPF ILDs, demonstrating reasonable discrimination for mortality risk [66, 67]. Other composite indices that include functional measures, imaging indices, and biomarkers are under evaluation, but available evidence supports the utility of multifactorial models over isolated parameters [68].

Therapeutic implications and landmark trials

The evolution of antifibrotic therapy in fibrotic interstitial lung diseases has been closely linked to the recognition that progressive loss of lung function, quantified by decline in FVC, represents a reproducible and clinically meaningful manifestation of disease activity across aetiologies. Landmark randomized controlled trials have consistently adopted FVC decline as a primary endpoint, enabling direct comparison of treatment effects across IPF, PPF, and selected connective tissue disease–associated ILDs.

Nintedanib

Nintedanib is an oral small-molecule tyrosine kinase inhibitor targeting multiple receptors involved in fibrogenesis, including platelet-derived growth factor receptors (PDGFR α/β), fibroblast growth factor receptors (FGFR 1–3), and vascular endothelial growth factor receptors (VEGFR 1–3). By inhibiting fibroblast proliferation, migration, and extracellular matrix deposition, nintedanib interferes with core profibrotic pathways activated across fibrotic ILDs once progression is established. In IPF, nintedanib demonstrated a consistent reduction in the annual rate of FVC decline across phase III trials, establishing FVC slope as a validated antifibrotic-responsive endpoint [30]. The INBUILD trial extended this paradigm to non-IPF fibrotic ILDs by enrolling patients with objective evidence of progression despite standard management. Nintedanib significantly reduced the annual rate of FVC decline compared with placebo in the overall population, with similar treatment effects across ILD subtypes and in patients with a UIP-like fibrotic pattern on HRCT. Notably, the magnitude of FVC decline in the placebo arm was comparable to that reported in untreated IPF cohorts, reinforcing the concept that PPF exhibits a functional trajectory similar to IPF once progression emerges. In SENSCIS, nintedanib significantly reduced the annual rate of FVC decline in patients with SSc-ILD, including those receiving background mycophenolate therapy, despite patients were enrolled regardless of progressive phenotype [69]. These findings demonstrate that antifibrotic efficacy is preserved even in ILDs with prominent immune-mediated components. Subgroup analyses from INBUILD and real-world cohorts indicate that patients with f-HP and unclassifiable ILD who meet PPF criteria experience rates of FVC decline and antifibrotic treatment effects comparable to other PPF subgroups, although statistical power for individual entities remains limited [70]. These data suggest that nintedanib efficacy aligns with disease behaviour rather than diagnostic category.

Pirfenidone

Pirfenidone exerts antifibrotic and anti-inflammatory effects through modulation of profibrotic cytokines, including transforming growth factor-β–related pathways, reduction of fibroblast activation, and attenuation of collagen synthesis. In IPF, pirfenidone consistently reduced FVC decline and disease progression in phase III trials, supporting regulatory approval [71, 72]. Randomized trials of pirfenidone in non-IPF populations—including progressive fibrosing unclassifiable ILD [73], SSc-ILD [74], and RA-ILD [75]—have generally failed to meet their primary endpoints. Nevertheless, several studies reported numerical or exploratory reductions in FVC decline favouring pirfenidone, particularly in patients with documented progression [8, 76]. For example, in the TRAIL study, which did not meet its primary endpoint (likely due to being underpowered during the COVID-19 pandemic), pirfenidone reduced the 52-week FVC decline—particularly in subjects with a UIP pattern—with a magnitude comparable to nintedanib [75]. A systematic review and meta-analysis suggested a potential antifibrotic signal across PPF populations but highlighted substantial heterogeneity and limited certainty of evidence [76]. Both ERS/EULAR [77] and ACR/CHEST guidelines [78] suggest pirfenidone as treatment option in RA-ILD patients with a UIP pattern.

Nerandomilast

Nerandomilast (BI 1015550) is a preferential phosphodiesterase-4B (PDE4B) inhibitor that increases intracellular cyclic AMP levels, thereby modulating inflammatory signalling and fibroblast activity. Its mechanism targets pathways distinct from those inhibited by tyrosine kinase

inhibitors or pirfenidone. In the phase III FIBRONEER-IPF trial, nerandomilast significantly reduced FVC decline at 52 weeks compared with placebo [79]. Importantly, approximately three-quarters of patients were receiving background antifibrotic therapy, demonstrating that clinically meaningful FVC decline persists despite standard treatment and remains pharmacologically modifiable. The FIBRONEER-ILD program extended these findings to patients with PPF of various aetiologies, showing a comparable reduction in FVC decline both as monotherapy and in combination with nintedanib [80]. Treatment effects were consistent across prespecified subgroups, reinforcing the concept that progressive fibrotic behaviour defines a shared, treatable disease state [80, 81].

Conclusions

Progressive pulmonary fibrosis can be conceptualized as a clinical syndrome, characterized by shared trajectories of functional decline, symptom burden, healthcare utilization, and mortality that transcend traditional etiologic classifications. Genetic susceptibility and convergent biological vulnerability provide mechanistic plausibility for this behavioural convergence. Recognising PPF as a syndromic entity supports a phenotype-driven approach to monitoring, prognostication, and therapy, aligned with emerging clinical trial evidence. Future research should focus on identifying biomarkers capable of predicting the emergence of a progressive phenotype, refining multidimensional monitoring strategies, and designing clinical trials that enrol patients on the basis of disease behaviour rather than diagnostic category. Such an approach may further accelerate the development of effective therapies across the spectrum of fibrotic interstitial lung diseases.

Authors' contributions

F.P.: Conceptualization, Methodology, Writing – original draft, Supervision. F.L.: Writing – review & editing, Validation. M.S.: Writing – review & editing, Validation. A.B.: Conceptualization, Supervision, Writing – review & editing.

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Data availability

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare no competing interests.

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