

UNIVERSITA' DEGLI STUDI DI VERONA

DIPARTIMENTO DI MEDICINA

DOTTORATO DI RICERCA IN

SCIENZE BIOMEDICHE CLINICHE E SPERIMENTALI

CICLO /ANNO XXXVIII/2022

LONG-TERM FUNCTIONAL TRAJECTORIES AND TREATMENT RETENTION WITH NINTEDANIB IN IPF AND PROGRESSIVE SARD-ILD

S.S.D. Medicina e Chirurgia

Coordinatore: Prof. Davide Gatti

Supervisore: Prof. Davide Gatti

Co-Supervisore: Dott. Angelo Fassio

Dottorando: Dott.ssa Loredana Carobene

Abstract

Background

Nintedanib is an antifibrotic treatment for idiopathic pulmonary fibrosis (IPF) and has also demonstrated efficacy in progressive fibrosing interstitial lung diseases (ILDs). However, real-world data on longitudinal functional trajectories and long-term treatment persistence in systemic autoimmune rheumatic disease-associated ILD (SARD-ILD) with a progressive pulmonary fibrosis phenotype remain limited. This study aimed to evaluate longitudinal pulmonary function and long-term nintedanib treatment persistence in patients with IPF and progressive SARD-ILD/PPF in routine clinical practice.

Methods

This multicenter retrospective study included 274 adults treated with nintedanib: 136 patients with IPF and 138 with progressive SARD-ILD/PPF. Longitudinal changes in percentage-predicted forced vital capacity (ppFVC), total lung capacity (ppTLC), and diffusing capacity for carbon monoxide (ppDLCO) were assessed using linear mixed-effects models adjusted for age and sex, with time considered as a continuous variable and patient-specific random intercepts. Differences in longitudinal trajectories between diagnostic groups were assessed using time-by-condition interaction terms. Treatment persistence was evaluated using Kaplan–Meier analysis and Cox proportional hazards regression. Death was subsequently considered as a competing event for treatment discontinuation, with cumulative incidence compared using Gray’s test and predictors of discontinuation assessed using multivariable Fine–Gray regression.

Results

Functional follow-up was available for 129 patients with IPF and 126 with SARD-ILD/PPF. In IPF, ppFVC and ppTLC remained stable over time, whereas ppDLCO showed a significant decline (-0.289 percentage points/month, 95% CI -0.376 to -0.203 ; $p<0.001$). In SARD-ILD/PPF, no significant longitudinal changes were observed in ppFVC (-0.075 /month; $p=0.21$), ppTLC (-0.004 /month; $p=0.96$), or ppDLCO (-0.049 /month; $p=0.36$). The ppDLCO trajectory differed significantly between groups, with a more favorable slope in SARD-ILD/PPF than in IPF (time-by-condition interaction $+0.235$ percentage points/month, 95% CI 0.100 – 0.371 ; $p<0.001$). Treatment persistence was high during the first year, with estimated retention of 95.8% in IPF and 91.9% in SARD-ILD/PPF. At five years, estimated retention was 69.5% and 77.6%, respectively, although estimates were subject to increasing uncertainty because of the limited number of patients remaining under observation. The unadjusted competing-risk comparison of treatment

discontinuation did not reach statistical significance (Gray's test, $p=0.058$). However, in multivariable Fine–Gray analysis, SARD-ILD/PPF was associated with a higher subdistribution hazard of nintedanib discontinuation compared with IPF (sHR 1.66, 95% CI 1.08–2.55; $p=0.021$).

Conclusions

In this multicenter real-world cohort, lung volumes remained broadly stable over time in both IPF and progressive SARD-ILD/PPF patients treated with nintedanib, while ppDLCO declined significantly in IPF but remained stable in SARD-ILD/PPF.

This finding may reflect differences in the underlying pathophysiology and disease trajectories of IPF and SARD-ILD/PPF, which may contribute to the distinct patterns of functional evolution observed in the two groups. However, given the observational design of the study, these findings should not be interpreted as evidence of a differential treatment effect of nintedanib.

Treatment persistence was high during the first year and remained substantial during long-term follow-up, although adjusted competing-risk analysis suggested a higher subdistribution hazard of discontinuation in SARD-ILD/PPF. These findings provide complementary real-world evidence on longitudinal functional trajectories and treatment persistence in patients with fibrotic ILDs treated with nintedanib. Further prospective studies with longer follow-up and systematic assessment of treatment tolerability and dose modifications are warranted to better characterize long-term treatment persistence and functional outcomes.

Index

INTRODUCTION.....	5
INTERSTITIAL LUNG DISEASE.....	5
IDIOPATHIC PULMONARY FIBROSIS.....	8
Diagnosis	8
Radiological Features of UIP.....	9
HRCT Patterns	10
Histopathology Patterns.....	11
Histopathology Features of the UIP Pattern	12
Diagnostic Criteria for IPF.....	12
Diagnostic Approach	13
Clinical course and prognosis	14
Drug therapy.....	16
CONNECTIVE TISSUE DISEASE-ASSOCIATED INTERSTITIAL LUNG DISEASE	17
Systemic Sclerosis associated ILD (SSc-ILD)	18
Rheumatoid arthritis associated ILD (RA-ILD)	20
Idiopathic Inflammatory Myopathies (IIM)	21
DIAGNOSIS AND TREATMENT OF PPF IN FIBROTIC ILD, OTHER THAN IPF.....	24
Definition of Progressive pulmonary fibrosis (PPF).....	24
STUDY RATIONALE AND OBJECTIVES.....	26
MATERIALS AND METHODS	28
Computed tomographic evaluation	29
Pulmonary function tests	29
STATISTICAL ANALYSIS	29
5-year retention rate and competing-risk analysis	30
RESULTS	31
Study population and follow-up.....	31

Longitudinal pulmonary function in IPF.....	32
Longitudinal pulmonary function in SARD-ILD/PPF	32
Comparison of longitudinal trajectories between IPF and SARD-ILD/PPF	33
Additional analyses according to concomitant immunosuppressive treatment in SARD-ILD.....	34
Additional analyses according to HRCT pattern in SARD-ILD.....	35
Additional analyses according to concomitant glucocorticoid treatment in SARD-ILD	36
Five-year treatment retention	36
Competing-risk analysis of nintedanib discontinuation	37
DISCUSSION.....	45
Differences between real-world evidence and clinical trial data.....	49
Limitations	51
CONCLUSIONS.....	52
BIBLIOGRAPHY	54

INTRODUCTION

INTERSTITIAL LUNG DISEASE

Interstitial pneumonia encompasses ~200 rare diseases affecting the lung interstitium, small airways, and alveoli. Classifications have evolved over the years, with the 2025 ERS/ATS update integrating idiopathic and secondary causes and introducing the concept of progressive pulmonary fibrosis (PPF) relevant to therapy (1).

The term ‘interstitial pneumonia’ is retained for continuity, while ‘interstitial lung disease’ (ILD) serves as the overarching term. Some less common interstitial disorders, such as pneumoconiosis or rare histiocytic diseases, are not fully addressed in the latest classification.

Accurate classification is essential for diagnosis, prognosis, and therapeutic decision-making, given the heterogeneous clinical, radiological, and pathological features of these disorders.

The 2025 update also categorizes disorders by predominant injury pattern—interstitial versus alveolar—and further distinguishes fibrotic from non-fibrotic presentations, reflecting both histological and radiological findings (figures 1 and 2) (1).

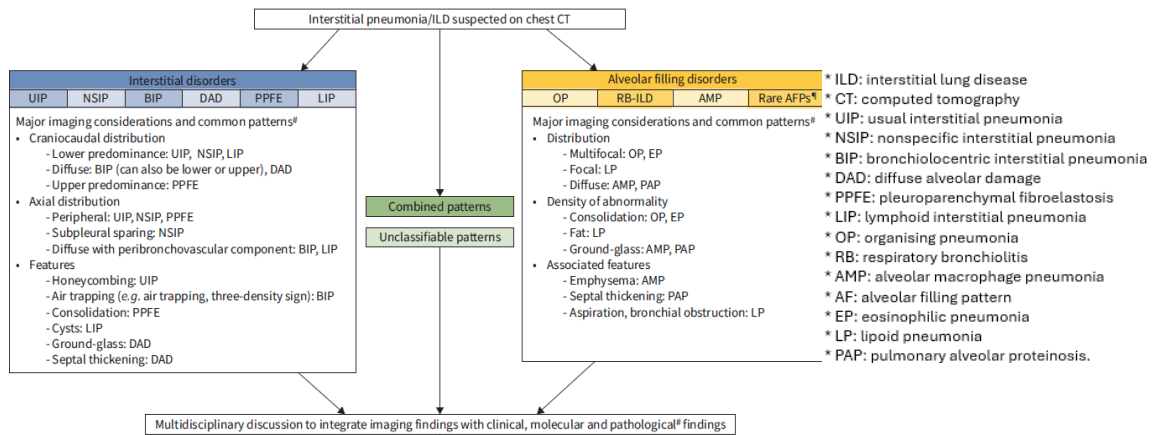


Figure 1. Interstitial, Alveolar and Combined pattern of ILD with description of radiological features. Adapted from Ryerson et al. Update of the international multidisciplinary classification of the interstitial pneumonias: an ERS/ATS statement. Eur Respir J 2025; 66: 2500158 (1).

Classification of Interstitial Lung Diseases (2025)

Interstitial disorders

Secondary interstitial pneumonia	Primary interstitial pneumonia / IIP
Secondary UIP	IPF
Secondary NSIP	iNSIP
Secondary BIP	iBIP
Secondary DAD	iDAD
Secondary PPFE	iPPFE
Secondary LIP	iLIP

IIP	idiopathic interstitial pneumonia
NSIP	nonspecific interstitial pneumonia
AIP	acute interstitial pneumonia
LIP	lymphoid interstitial pneumonia
COP	cryptogenic organising pneumonia
RB	respiratory bronchiolitis
ILD	interstitial lung disease
DIP	desquamative interstitial pneumonia
PPFE	pleuroparenchymal fibroelastosis
UIP	usual interstitial pneumonia
BIP	bronchiolocentric interstitial pneumonia
DAD	diffuse alveolar damage
OP	organising pneumonia
AMP	alveolar macrophage pneumonia
AEP	acute eosinophilic pneumonia
CEP	chronic eosinophilic pneumonia
PAP	pulmonary alveolar proteinosis
prefix "i"	idiopathic

Alveolar filling disorders

Secondary interstitial pneumonia	Primary interstitial pneumonia / IIP
Secondary OP	COP
Secondary RB-ILD	iRB-ILD
Secondary AMP	iAMP
Rare alveolar filling disorders: AEP and CEP, idiopathic/unclassifiable and secondary PAP, exogenous and endogenous lipid pneumonia	

Other

Secondary and primary interstitial pneumonia with combined patterns
Unclassifiable ILD

Disease behaviour

Interstitial versus alveolar filling patterns
Secondary and primary (idiopathic) aetiologies
Combined patterns

Figure 2. New classification of ILD: 2025 revision. Adapted from Ryerson et al. Update of the international multidisciplinary classification of the interstitial pneumonias: an ERS/ATS statement. Eur Respir J 2025; 66: 2500158 (1).

IDIOPATHIC PULMONARY FIBROSIS

Idiopathic Pulmonary Fibrosis (IPF) is a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause. It occurs primarily in older male adults, is limited to the lungs, and is defined by the histopathologic and/or radiologic pattern of UIP. It should be considered in all adult patients with unexplained chronic exertional dyspnea, cough, bibasilar inspiratory crackles, and/or digital clubbing that occur without constitutional or other symptoms that suggest a multisystem disease.

IPF incidence rises with age, typically presenting as insidious dyspnea in the sixth or seventh decade of life. In patients who are younger than 50 years old, the disease may reflect an underlying subclinical CTD or familial IPF.

Risk factors associated with IPF include past cigarette smoking, gastroesophageal reflux, chronic viral infections such as Epstein-Barr virus, hepatitis C, and a family history of ILD.

Many patients with IPF also have other comorbid conditions that include emphysema (combined pulmonary fibrosis and emphysema), lung cancer, pulmonary hypertension, sleep apnea, and coronary artery disease. In some genetic forms, there is also extrapulmonary disease that manifests as bone marrow failure and liver disease.

At least 30% of patients who have sporadic or familial pulmonary fibrosis have genetic predisposing factors that are known to increase the risk of pulmonary fibrosis; however, the identified genetic factors in the telomerase and telomere pathways are also associated with other ILDs (2).

Diagnosis

The onset of IPF is characterised by progressively worsening exertional dyspnea associated with a dry cough. Given the indolent onset and non-specificity of symptoms, patients typically seek medical attention at least six months after the onset of respiratory symptoms. Often, the diagnosis is made only when lung

involvement is sufficient to cause symptoms. Patients rarely report systemic symptoms such as myalgia, fatigue, weight loss, and low-grade fever.

Chest examination in almost all patients with IPF, is characterised by bilateral, basal or mid-basal inspiratory "Velcro-like" crackles that tend to progress toward the upper ranges as the disease progresses. This auscultation, sensitive but nonspecific, can nevertheless be useful in raising clinical suspicion. The progression of fibrotic involvement inevitably leads to the development of respiratory failure, initially latent and then chronic. The most common functional alteration in IPF is restrictive ventilatory deficit, or a reduction in total lung capacity (TLC) with a concomitant and harmonious reduction in all lung volumes, both static and dynamic. Diffusing capacity (DLCO) is the first functional parameter to be altered in the early stages of the disease.

Diagnosis requires exclusion of other ILDs, with HRCT and, if needed, biopsy (2).

The last ATS/ERS Consensus Conference in 2022 confirmed the need to integrate clinical, radiological, and, in some cases, pathology elements, through a multidisciplinary approach involving various specialists (pulmonologist, radiologist, pathologist, rheumatologist) for the diagnosis and management of IPF.

It is therefore essential to refer patients to a centre with consolidated experience in the diagnosis and treatment of this disease (3).

Radiological Features of UIP

High-resolution chest CT plays a key role in the diagnosis of IPF. It is recommended that the exam be performed during inspiration and expiration to assess the presence of air trapping, which is indicative of bronchiolar involvement.

HRCT features frequently seen in UIP include honeycombing, traction bronchiectasis and bronchiolectasis, which may be seen with the concurrent presence of ground-glass opacification and fine reticulation (3).

HRCT Patterns

We may encounter different HRCT patterns: “UIP pattern” (Figure 3), “probable UIP pattern”, “indeterminate for UIP pattern”, and “alternative diagnosis” (Table 1) describes its characteristics (3).

	UIP	Probable UIP Pattern	Indeterminate for UIP	CT Findings Suggestive of an Alternative Diagnosis
Distribution	-Subpleural and basal predominant - Often heterogeneous (areas of normal lung interspersed with fibrosis) -Occasionally diffuse -May be asymmetric	- Subpleural and basal predominant - Often heterogeneous (areas of normal lung interspersed with reticulation and traction bronchiectasis/ bronchiolectasis)	Diffuse distribution without subpleural predominance	- Peribronchovascular predominant with subpleural sparing (consider NSIP) _ Perilymphatic distribution (consider sarcoidosis) _ Upper or mid lung (consider fibrotic HP, CTD-ILD, and sarcoidosis) _ Subpleural sparing (consider NSIP or smokingrelated IP)
CT features	-Honeycombing with or without traction bronchiectasis/ bronchiolectasis -Presence of irregular thickening of interlobular septa -Usually superimposed with a reticular pattern, mild GGO -May have pulmonary ossification	- Reticular pattern with traction bronchiectasis/ bronchiolectasis _ May have mild GGO _ Absence of subpleural sparing	CT features of lung fibrosis that do not suggest any specific etiology	- Lung findings _ Cysts _ Mosaic attenuation or three-density sign _ Predominant GGO _ Profuse centrilobular micronodules _ Nodules (consider sarcoidosis) _ Consolidation _ Mediastinal findings _ Pleural plaques - Dilated esophagus

Table 1. High-Resolution Computed Tomography (HRCT) Patterns in Idiopathic Pulmonary Fibrosis. Adapted from Raghu et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med Vol 205, Iss 9, pp e18–e47, May 1, 2022(3).

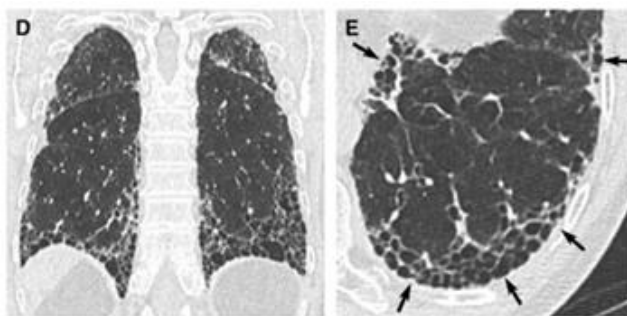


Figure 3. High-resolution computed tomography (CT) images that shows a usual interstitial pneumonia pattern. Adapted from Raghu et al. Diagnosis of Idiopathic Pulmonary Fibrosis: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. AmJRespirCritCareMedVol198, Iss5,ppe44–e68,Sep1,2018(2).

Histopathology Patterns

Pattern UIP is characterized by:

- Dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing);
- Predominant subpleural and/or paraseptal distribution of fibrosis;
- Patchy involvement of lung parenchyma by fibrosis;
- Fibroblast foci;
- Absence of features to suggest an alternate diagnosis.

Pattern PROBABLE UIP is typified by:

- Some histologic features UIP but to an extent that precludes a definite diagnosis of UIP and
- Absence of features to suggest an alternative diagnosis, or honeycombing only.

Pattern INDETERMINATED for UIP is characterized by:

- Fibrosis with or without architectural distortion, with features favoring either a pattern other than UIP or features favoring UIP secondary to another cause and
- some histologic features of UIP, but with other features suggesting an alternative diagnosis.

ALTERNATIVE DIAGNOSIS is marked out by:

Features of other histologic patterns of IIPs (e.g., absence of fibroblast foci or loose fibrosis) in all biopsies and histologic findings indicative of other diseases.

Histopathology Features of the UIP Pattern

The histopathologic hallmark and chief diagnostic criterion of UIP is a low magnification appearance of patchy dense fibrosis that 1) is causing remodeling of lung architecture, 2) often results in honeycomb change, and 3) alternates with areas of less-affected parenchyma (Figure 5). These histopathologic changes typically affect the subpleural and paraseptal parenchyma most severely. Inflammation is usually mild and consists of a patchy interstitial infiltrate of lymphocytes and plasma cells associated with hyperplasia of type 2 pneumocytes and bronchiolar epithelium (3).

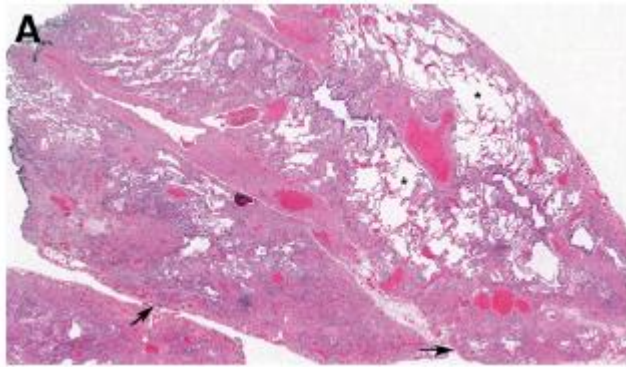


Figure 4. Histopathology pattern of usual interstitial pneumonia (UIP). Adapted from Raghu et al. Diagnosis of Idiopathic Pulmonary Fibrosis: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. AmJRespirCritCareMedVol198, Iss5,ppe44–e68,Sep1,2018(2).

Diagnostic Criteria for IPF

Diagnosis of IPF requires the following:

1. Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, CTD, drug toxicity), and either 2 or 3 points:
2. The presence of **definite UIP pattern on HRCT** (Table 1).

3. The presence of a **probable UIP pattern on HRCT**, in an appropriate clinical context and after multidisciplinary discussion, **without the need for lung biopsy**, or specific combinations (Figure 5) of HRCT patterns (Table 1) and histopathology patterns in patients who undergo lung tissue sampling (3).

HRCT ↓ / Histopathology →	UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
UIP	IPF	IPF	IPF	Non-IPF
Probable UIP	IPF	IPF	Likely IPF	Non-IPF
Indeterminate	IPF	Likely IPF	Indeterminate	Non-IPF
Alternative Diagnosis	Likely IPF	Indeterminate	Non-IPF	Non-IPF

Figure 5. Diagnosis of IPF based on HRCT and lung biopsy. Adapted from Raghu et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med Vol 205, Iss 9, pp e18–e47, May 1, 2022(3).

Diagnostic Approach

Patients with suspected IPF, unexplained dyspnea on exertion, and/or cough with evidence of interstitial lung disease (ILD) should be carefully evaluated for potential and/or identifiable causes of ILD, such as domestic and occupational environmental exposures, connective tissue disease (CTD), or drug toxicity. If a potential cause for ILD is identified, the patient should undergo a thorough evaluation to confirm or exclude other known causes, such as hypersensitivity pneumonitis, CTD, pneumoconiosis, and iatrogenic causes (e.g., drug toxicity, irradiation). If a specific diagnosis is not made or no potential cause for ILD is identified, further evaluation is influenced by the patterns of high-resolution CT (HRCT) images of the chest and supportive clinical findings identified during multidisciplinary discussion to verify or exclude the diagnosis of IPF (figure 6).

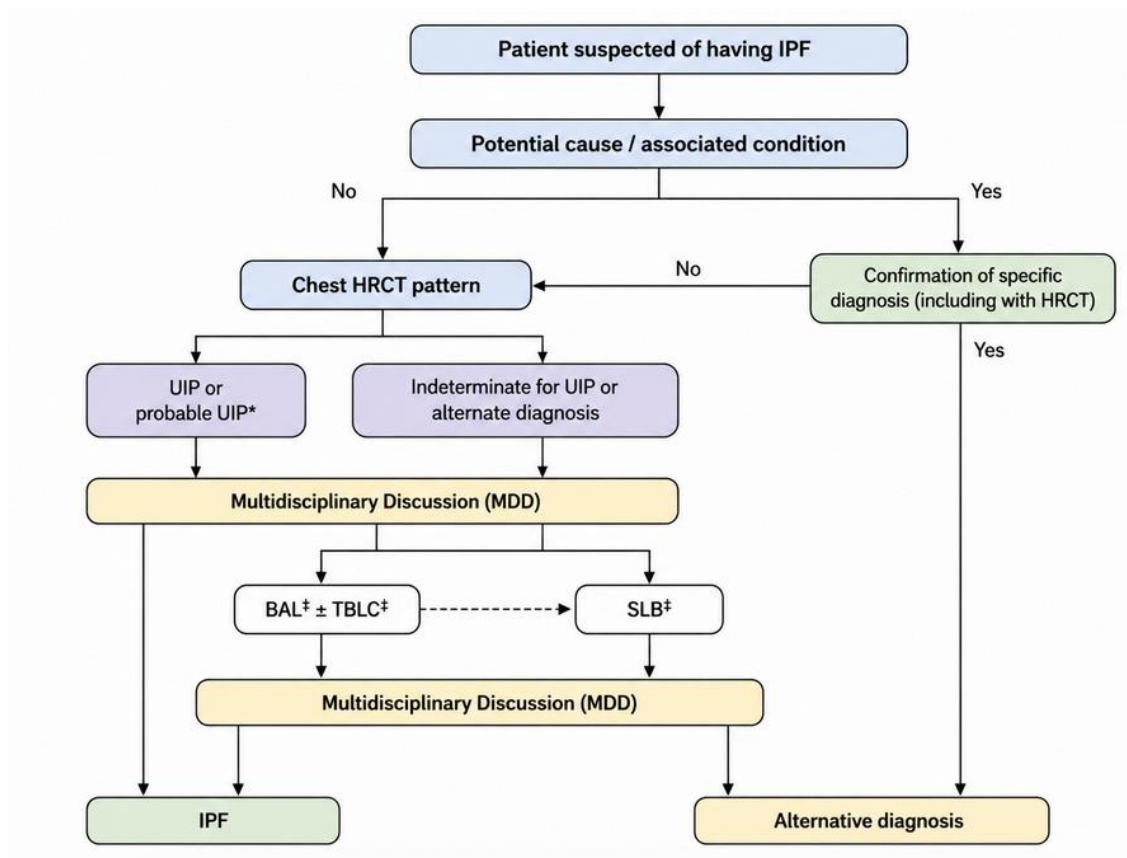


Figure 6. Algorithm for diagnosis of IPF.Adapted from Raghu et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med Vol 205, Iss 9, pp e18–e47, May 1, 2022(3).

Clinical course and prognosis

The prognosis of the disease is poor, with a median survival rate ranging from 2 to 5 years in various case series. Five-year survival is estimated at approximately 20%(4).

The mortality rate of IPF is higher than that observed for many cancers. The natural history of the disease is also influenced by comorbidities, whether clinically manifest or subclinical; among these, pulmonary hypertension and lung cancer can have a negative prognostic impact (5,6).

The clinical course of IPF is therefore highly heterogeneous, so much so that several clinical phenotypes with highly variable prognoses can be distinguished, as expressed by the ATS/ERS:

1. Stable or slowly progressive course, in which the disease progresses gradually and slowly over the course of years.
2. Accelerated course: the disease progresses rapidly.
3. Acute exacerbation: rapid worsening of the disease in the absence of infection, pulmonary embolism, or other identifiable causes.

Acute exacerbations of idiopathic pulmonary fibrosis, or episodes of sudden disease progression (less than 4 weeks) in the absence of infectious processes or other triggers, are characterized by an acute worsening of the clinical, functional, and blood gas levels with rapid progression to respiratory failure. The diagnosis is clinical, pathophysiological, and radiographic. Dyspnea worsens within a few days or weeks, along with a marked reduction in PaO₂ and the appearance of ground-glass opacities and parenchymal consolidations on a UIP pattern. Several risk factors for acute exacerbations have been identified. Collard et al. have defined five diagnostic criteria for acute exacerbation:

1. Diagnosis of IPF.
2. Worsening of dyspnea or gas exchange with a reduction in PaO₂ >10% in the previous 30 days.
3. Presence of ground glass and/or new-onset parenchymal consolidation on chest HRCT.
4. Exclusion of viral, bacterial, or opportunistic infection.
5. Exclusion of pulmonary embolism, cardiogenic decompensation, or other known cause (16).

The clinical history of patients with IPF is characterized by progressive functional decline and a relentless worsening of respiratory exchange. Most patients experience slow disease progression, with relatively long periods of clinical and

functional stability. A poor prognosis is associated with patients with advanced age at diagnosis, tobacco exposure, low body mass index, disease extension on HRCT, and the presence of pulmonary hypertension. A small percentage of patients experience a rapidly worsening course (2).

Drug therapy

Since 2011, the results of randomized clinical trials have significantly changed the treatment of idiopathic pulmonary fibrosis (IPF). Currently, two antifibrotic drugs, pirfenidone and nintedanib, are approved for the treatment of IPF. Both have demonstrated efficacy in slowing disease progression by reducing the decline in forced vital capacity (FVC).

Pirfenidone has shown significant benefits in major clinical trials, including the CAPACITY and ASCEND studies, with reductions in FVC decline, disease progression, and mortality (7–9).

Similarly, nintedanib, a tyrosine kinase inhibitor targeting VEGFR, FGFR, and PDGFR, has demonstrated efficacy in the TOMORROW and INPULSIS trials, showing a significant reduction in the rate of FVC decline and disease progression(7,8).

More recently, advances in the understanding of IPF pathogenesis have led to the development of new targeted therapies. Among these, nerandomilast, a selective PDE4B inhibitor, has shown promising antifibrotic and immunomodulatory effects, with clinical trials demonstrating a reduction in lung function decline and a favorable safety profile(9).

CONNECTIVE TISSUE DISEASE-ASSOCIATED INTERSTITIAL LUNG DISEASE

Interstitial lung disease (ILD) is one of the most frequent manifestations in connective tissue diseases (CTDs) and is associated with high morbidity and mortality. It occurs more frequently in conditions such as systemic sclerosis (SSc), rheumatoid arthritis (RA), idiopathic inflammatory myopathies (IIM), and, less commonly, Sjögren's syndrome (SS), mixed CTD, and systemic lupus erythematosus (SLE). The pathogenesis is thought to involve an immune-mediated process that precedes fibrosis.

In some cases, patients present with features suggestive of autoimmunity without fulfilling criteria for a defined CTD; this condition is referred to as interstitial pneumonia with autoimmune features (IPAF).

The diagnosis and management of CTD-ILD require a multidisciplinary approach. Recent international guidelines from pulmonology and rheumatology societies provide evidence-based recommendations for screening, diagnosis, and monitoring.

HRCT is useful for screening ILD and can also assist in determining the extent and severity of the disease since the presence of bronchiectasis and honeycombing is linked to a higher risk of progression. The most common radiological patterns include usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP), although other patterns may be observed.

According to recent ERS/EULAR guidelines, HRCT screening is recommended at diagnosis in patients with SSc and in selected high-risk patients with RA, IIM, Sjögren's syndrome, and mixed CTD (10).

The diagnostic approach involves exclusion of other causes of ILD and assessment of disease severity and risk of progression. Pulmonary function tests are essential for monitoring but do not replace HRCT for screening, while lung biopsy is generally not required.

Monitoring includes clinical evaluation, periodic pulmonary function tests, and imaging, with closer follow-up in high-risk patients (figure 7).

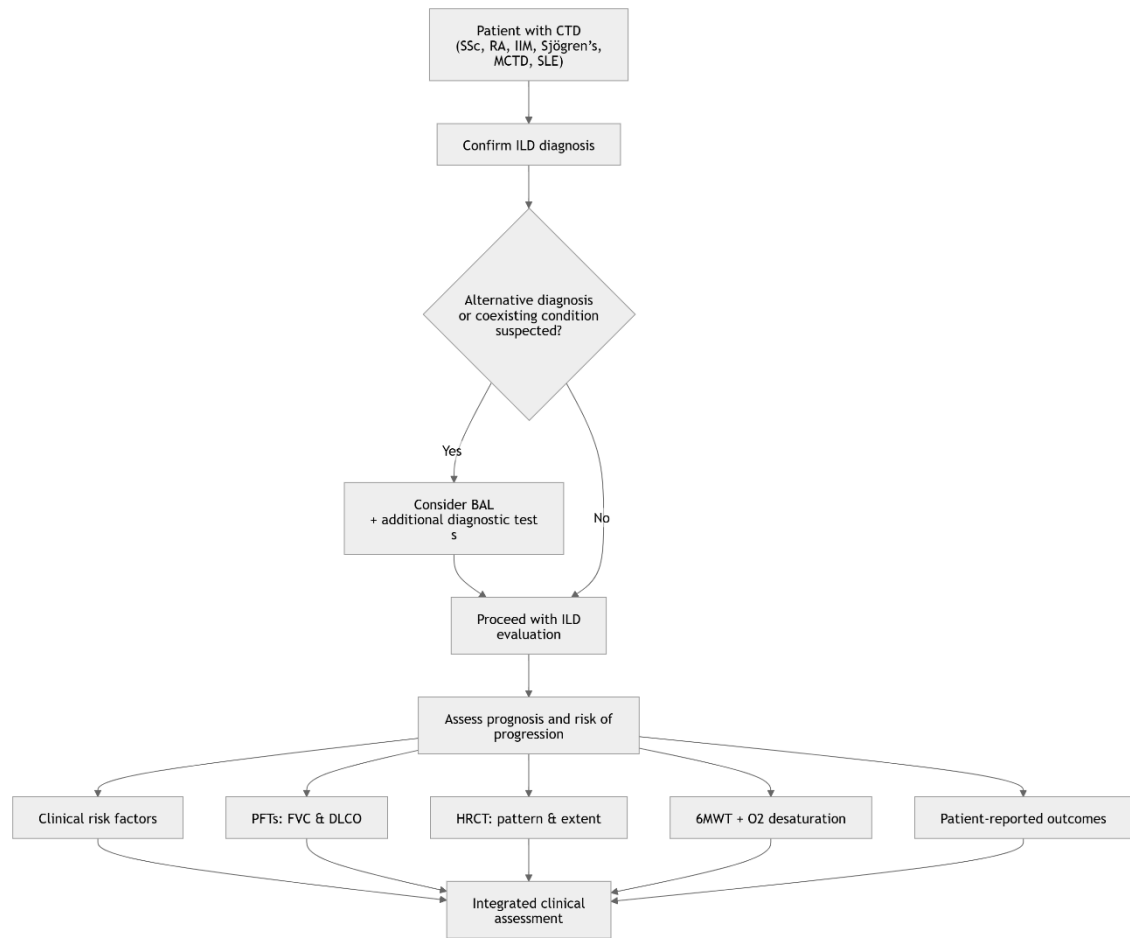


Figure 7. Diagnostic algorithm for interstitial lung disease (ILD) in connective tissue disease (CTD) and rheumatoid arthritis (RA). Adapted from Katerina M. Antoniou ERS/EULAR clinical practice guidelines for connective tissue disease-associated interstitial lung disease, Eur Respir J 2026; 67: 2402533(11).

Systemic Sclerosis associated ILD (SSc-ILD)

Systemic sclerosis (SSc) is a multisystem disease characterized by autoimmunity, vasculopathy, and fibrosis, and is associated with high mortality. Interstitial lung disease (ILD), together with pulmonary hypertension, represents the leading cause of death in these patients. Therefore, screening and monitoring for ILD are essential from the time of diagnosis.

All patients should undergo baseline evaluation with high-resolution computed tomography (HRCT) and pulmonary function tests, including forced vital capacity (FVC) and diffusing capacity (DLCO). The most common radiological patterns are nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP).

ILD may be detected in up to 80% of patients on imaging, although clinically significant disease occurs in a smaller proportion.

Regular follow-up with pulmonary function tests and periodic HRCT is recommended, with closer monitoring in patients at higher risk of progression, such as those with reduced lung function, extensive disease on imaging, or specific autoantibodies (10).



Figure 8. High-resolution chest CT images in ILD-SSc. (Adapted from Balestro, Interstiziopatie Polmonari (IP) associate alle connettiviti: un puzzle articolato; Rassegna di Patologia dell'Apparato Respiratorio V. 38: Fascicolo 3 - Settembre 2023)(12).

Treatment initiation depends on disease severity and risk of progression. Immunosuppressive therapy represents the mainstay of treatment (figure 9). Cyclophosphamide has shown modest efficacy in improving lung function in the Scleroderma Lung Study (SLS I), although its use is limited by toxicity. Mycophenolate mofetil demonstrated similar efficacy with a better safety profile in SLS II and is currently considered first-line therapy (13,14). Biologic agents such as tocilizumab and rituximab have shown potential benefits in selected patients, particularly in early or progressive disease (10).

Antifibrotic therapy has also emerged as an important option. Nintedanib, a tyrosine kinase inhibitor, was shown in the SENSICIS trial to significantly reduce the rate of

decline in FVC in patients with SSc-ILD. It may be considered, particularly in patients with progressive fibrotic disease(15).

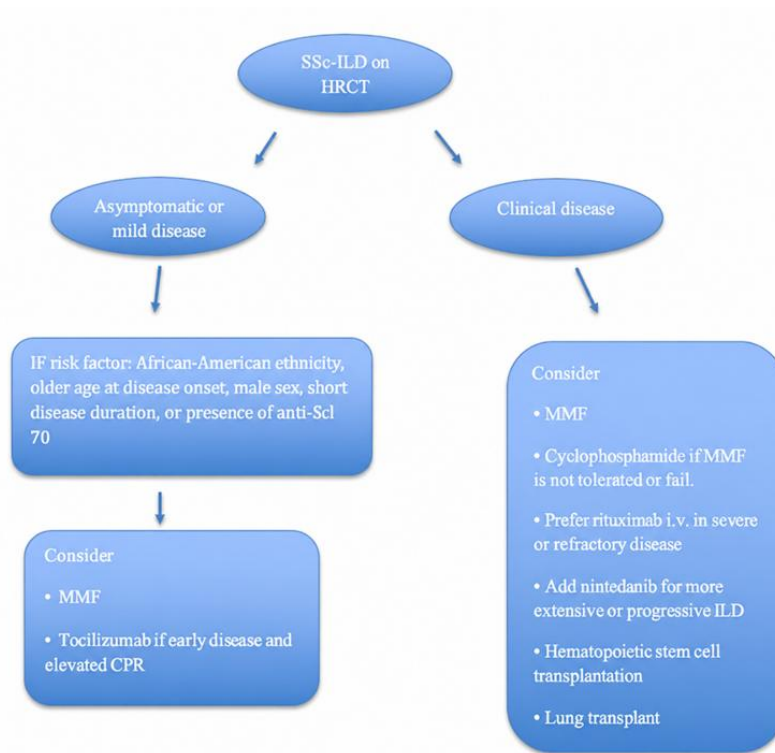


Figure 9. Treatment for systemic sclerosis-associated interstitial lung disease (SSc-ILD). PFT: pulmonary function test; MMF: mycophenolate; and CPR: C-reactive protein. Adapted from Storrer et al.(10).

Rheumatoid arthritis associated ILD (RA-ILD)

Rheumatoid arthritis (RA) is a chronic inflammatory disease, and interstitial lung disease (ILD) is one of its most severe complications, with a prevalence of approximately 10–30%. Usual interstitial pneumonia (UIP) is the most common radiological pattern (Figure 9).

Patients with respiratory symptoms or Velcro crackles should undergo HRCT and pulmonary function tests. In asymptomatic patients, screening is guided by risk factors such as male sex, older age, smoking history, and high autoantibody levels (10,11).



Figure 9. High-resolution chest CT image of a patient with RA. (Adapted from Balestro, Interstiziopatie Polmonari (IP) associate alle connettiviti: un puzzle articolato; Rassegna di Patologia dell'Apparato Respiratorio V. 38: Fascicolo 3 - Settembre 2023)(12).

Disease course is heterogeneous, ranging from stable to progressively fibrosing forms. Risk factors for progression include UIP pattern, decline in pulmonary function, and extent of fibrosis on HRCT.

Treatment is challenging due to limited evidence and potential drug-related pulmonary toxicity. Corticosteroids and immunosuppressive agents such as mycophenolate or cyclophosphamide are commonly used.

Methotrexate does not appear to increase ILD risk and may be continued after individual assessment. Biologic therapies require caution: anti-TNF agents have been associated with ILD worsening, while rituximab and abatacept are generally considered safer options. Tocilizumab may be considered in selected cases.

Antifibrotic therapy with nintedanib has shown efficacy in slowing disease progression in patients with a progressive fibrosing phenotype, while pirfenidone has shown potential benefit in limited studies (16,17).

Idiopathic Inflammatory Myopathies (IIM)

Idiopathic inflammatory myopathies (IIM) are a group of autoimmune diseases that include dermatomyositis, polymyositis, and antisynthetase syndrome. These

conditions may involve multiple organs, and interstitial lung disease (ILD) is the most common extramuscular manifestation and a major cause of mortality.

Autoantibodies are frequently detected and may help define clinical phenotypes. In particular, antisynthetase antibodies and anti-MDA5 are strongly associated with ILD and specific clinical patterns (18).

ILD occurs in approximately 17–36% of patients. HRCT patterns are variable, with nonspecific interstitial pneumonia (NSIP) and organizing pneumonia (OP) being the most common, often overlapping; usual interstitial pneumonia (UIP) is less frequent. Fibrotic forms are associated with worse prognosis (10).

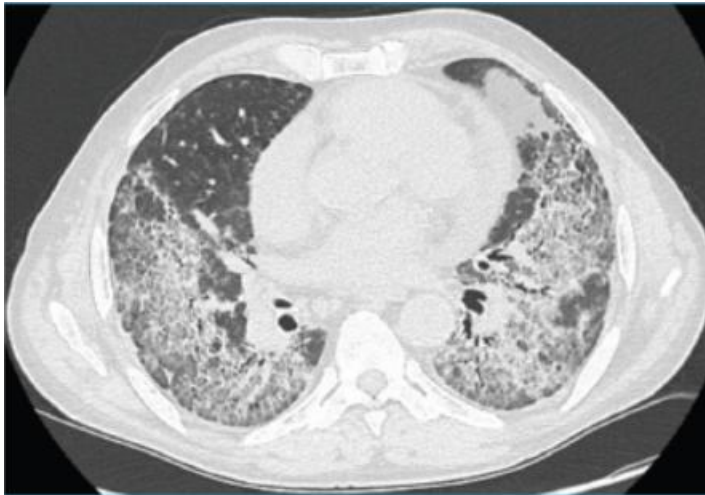


Figura 10. High-resolution chest CT image in a patient with anti-synthetase antibody syndrome. (Adapted from Balestro, *Interstiziopatie Polmonari (IP) associate alle connettiviti: un puzzle articolato*; *Rassegna di Patologia dell'Apparato Respiratorio* V. 38: Fascicolo 3 - Settembre 2023) (12)

Management of IIM-ILD depends on disease severity and progression. Chronic forms are typically treated with corticosteroids with or without additional immunosuppressive agents, whereas rapidly progressive ILD requires early and aggressive combination therapy (Figure 15).

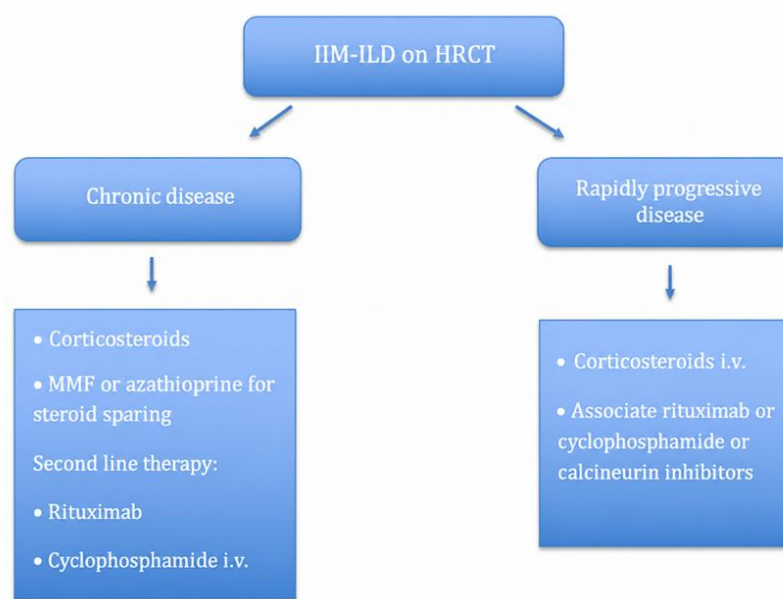


Figure 11. Treatment algorithm for idiopathic inflammatory myositis-associated interstitial lung disease (IIM-ILD). MMF: mycophenolate. Adapted from Storrer et al. (10).

Corticosteroids remain the mainstay of treatment. Immunosuppressive agents such as mycophenolate, azathioprine, calcineurin inhibitors, and cyclophosphamide are commonly used, particularly in progressive or refractory disease.

Biologic therapies, especially rituximab, are effective in selected patients and are often used in refractory cases. Other options, including intravenous immunoglobulins or targeted therapies, may be considered in specific clinical scenarios (Figure 11) (10).

DIAGNOSIS AND TREATMENT OF PPF IN FIBROTIC ILD, OTHER THAN IPF

Definition of Progressive pulmonary fibrosis (PPF)

The 2022 guidelines ATS/ERS/JRS/ALAT defined the concept of PPF and determined radiological and physiological criteria for diagnosis.

In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation:

- worsening respiratory symptoms
- physiological evidence of disease progression
- and radiological evidence of disease progression (figure 16) (3):

Physiological evidence of disease progression (either of the following):

- a. Absolute decline in FVC $\geq 5\%$ predicted within 1 yr of follow-up
- b. Absolute decline in DL_{CO} (corrected for Hb) $\geq 10\%$ predicted within 1 yr of follow-up

Radiological evidence of disease progression (one or more of the following):

- a. Increased extent or severity of traction bronchiectasis and bronchiolectasis
- b. New ground-glass opacity with traction bronchiectasis
- c. New fine reticulation
- d. Increased extent or increased coarseness of reticular abnormality
- e. New or increased honeycombing
- f. Increased lobar volume loss

Figure 12. Definition of physiological and radiological progression. Adapted from Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline; Raghu, Am J Respir Crit Care Med Vol 205, Iss 9, pp e18–e47, May 1, 2022 (3).

Although it is critical to exclude alternative explanations of worsening features for all patients with suspected progression, this is particularly important in patients with worsening respiratory symptoms and/or decline in DL_{CO} .

PPF is not a specific diagnosis but a clinical behavior that can occur across different interstitial lung diseases.

Management depends on the underlying disease, typically including immunosuppressive therapy where appropriate. In patients with progressive fibrosing disease despite standard treatment, antifibrotic therapy is recommended.

Nintedanib is currently the main antifibrotic agent approved for PPF. The INBUILD trial demonstrated that nintedanib significantly slows the decline in lung function compared with placebo across a range of fibrotic ILDs (16).

Treatment does not appear to significantly impact mortality but reduces disease progression. The most common adverse effects are gastrointestinal, which may lead to dose reduction or discontinuation in some patients.

Pirfenidone has been investigated in PPF, but current evidence is limited, and it is not routinely recommended (3).

STUDY RATIONALE AND OBJECTIVES

Idiopathic pulmonary fibrosis (IPF) and fibrosing interstitial lung diseases associated with systemic autoimmune rheumatic diseases (SARD-ILD) are characterized by progressive lung fibrosis, functional decline, and significant morbidity.

In recent years, increasing attention has been given to progressive fibrosing interstitial lung diseases, which may develop a progressive phenotype despite conventional treatment. The concept of progressive pulmonary fibrosis (PPF) was defined in the 2022 ATS/ERS/JRS/ALAT guidelines, which established standardized clinical, functional, and radiological criteria.

These guidelines also introduced the use of antifibrotic therapy in non-IPF fibrotic ILDs, with nintedanib showing efficacy in slowing lung function decline both in IPF (INPULSIS trials) and in PPF across different underlying diseases (INBUILD trial) (7,8,16).

However, data from randomized clinical trials may not fully reflect real-world clinical practice, where patients are more heterogeneous and often receive multiple concomitant therapies. Real-world evidence on the effectiveness, safety, and long-term tolerability of nintedanib in these populations remains limited.

The aim of this study is to characterize the long-term real-world functional trajectories and treatment persistence of patients with idiopathic pulmonary fibrosis (IPF) and systemic autoimmune rheumatic disease-associated interstitial lung disease (SARD-ILD) with a progressive pulmonary fibrosis (PPF) phenotype treated with nintedanib.

Specifically, the study aimed to:

1. evaluate longitudinal changes in pulmonary function, including per cent-predicted forced vital capacity (ppFVC), per cent-predicted diffusing capacity for carbon monoxide (ppDLCO), and per cent-predicted total lung capacity (ppTLC), during nintedanib treatment;

2. compare the longitudinal functional trajectories of patients with IPF and SARD-ILD/PPF, assessing whether the rate of change in pulmonary function differed between the two conditions;
3. account for potential demographic confounding by evaluating longitudinal functional trajectories after adjustment for age and sex;
4. explore, within the SARD-ILD population, whether concomitant immunosuppressive treatment, ongoing glucocorticoid therapy, and HRCT pattern were associated with differences in longitudinal pulmonary function trajectories;
5. assess long-term persistence with nintedanib and characterise treatment discontinuation over a follow-up period of up to five years;
6. compare treatment discontinuation between IPF and SARD-ILD/PPF, taking into account the competing risk of death;
7. identify clinical factors associated with the risk of nintedanib discontinuation using multivariable competing-risk analysis.

Overall, the study was designed to provide a comprehensive real-world assessment of both the longitudinal functional course of fibrosing interstitial lung disease and the long-term persistence of antifibrotic treatment in IPF and progressive SARD-ILD/PPF.

MATERIALS AND METHODS

A multicenter retrospective study was conducted involving adults (≥ 18 years) with idiopathic pulmonary fibrosis (IPF) or systemic autoimmune disease-associated interstitial lung disease (SARD-ILD) characterized by fibrotic progression (PPF), treated with nintedanib. To be included, patients were required to have at least one follow-up pulmonary function assessment, including global spirometry and measurement of diffusing capacity for carbon monoxide (DLCO), or sufficient follow-up information to assess nintedanib treatment persistence. When a second follow-up pulmonary function assessment was available, these additional measurements were also included in the longitudinal mixed-effects analyses.

Data collection was conducted at the integrated pulmonary-rheumatology outpatient clinics of the centres in Verona, Piacenza, Treviso, and Rome, and at the IRCCS "San Gerardo dei Tintori" in Monza and Reggio Emilia. IPF and various SARD-ILDs were included, including systemic sclerosis (SSc), idiopathic inflammatory myopathies (IIM), rheumatoid arthritis (RA), and others (including Sjögren's syndrome, mixed connective tissue disease, and phenotypes consistent with IPAF).

Patients with a current or past history of malignancy, other significant respiratory conditions such as asthma, COPD, or bronchiectasis unrelated to the interstitial lung disease, suspected or confirmed severe pulmonary hypertension, or previous lobectomies or pneumonectomies were excluded. Subjects unable to adequately perform pulmonary function tests or HRCT were also excluded, as were those whose computed tomography (CT) showed patterns other than UIP or NSIP, or the presence of significant emphysema ($\geq 10\%$), acute or chronic infections, pleural effusion, pulmonary oedema, or unclassifiable interstitial lung abnormalities.

All clinical information was retrieved from the respective electronic medical records.

All patients signed informed consent.

Computed tomographic evaluation

All patients underwent thoracic HRCT according to the most recent guidelines. Acquisitions were performed in the supine position, during maximal inspiration, with slice thicknesses ranging from 1 to 1.25 mm and high-resolution reconstruction algorithms. Two experienced radiologists, working blinded to the clinical data, assessed the images, classifying the interstitial pattern as NSIP, UIP/UIP-like, or unclassifiable according to current definitions. Scans affected by respiratory artefacts or technical problems, as well as those compromised by extensive emphysema, non-fibrotic abnormalities, or neoplastic lesions, were excluded from analysis.

Pulmonary function tests

Pulmonary function tests were performed according to ATS/ERS standards (19) and included measurements of per cent predicted of forced vital capacity (ppFVC), per cent predicted of total lung capacity (ppTLC), per cent predicted Diffusion Lung CO (ppDLCO), and absolute FVC values. All measurements were carried out using instruments calibrated in accordance with the recommendations of the respective scientific societies.

STATISTICAL ANALYSIS

Differences between the two diagnostic groups (IPF versus SARD-ILD/PPF) were assessed using the Wilcoxon rank-sum test for continuous variables and the Pearson χ^2 test or Fisher's exact test, as appropriate, for categorical variables. Comparisons among the different SARD-ILD subgroups were performed using the Kruskal-Wallis test for continuous variables, with Wilcoxon rank-sum tests used for pairwise comparisons when appropriate.

The longitudinal analysis of changes in functional parameters over time was conducted using linear mixed-effects models. This methodological choice was deemed most appropriate for several reasons. First, spirometric measurements were

not collected at predefined, homogeneous time intervals, as would be expected in a controlled trial, but rather according to the timing typical of clinical practice. The use of mixed-effects models enables time to be handled as a continuous variable, allowing flexible modelling of the effect of elapsed months and appropriately accounting for the irregular timing of measurements. Second, the repeated measures obtained from each patient inevitably exhibit a within-subject correlation, which is captured by the random term associated with the patient identifier; this avoids underestimation of standard errors and provides more reliable and realistic estimates of trends over time. Third, mixed-effects models offer greater robustness to uninformative missing data, a feature of particular importance in retrospective longitudinal studies, in which not all patients complete the same number of functional assessments.

All primary models included fixed effects for time (months), diagnostic group (IPF vs SARD-ILD), sex, and age, along with a time-by-condition interaction term to evaluate divergent trajectories between groups. Alternative random-effects structures, including random slopes, were evaluated using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC); the parsimonious random-intercept model was retained as random slopes did not improve model fit.

To further investigate potential confounding within the SARD-ILD subgroup, exploratory mixed-effects models were fitted with interaction terms between time and concomitant immunosuppressive categories, ongoing glucocorticoid treatment, or HRCT radiological patterns (UIP/UIP-like vs. non-UIP- NSIP, other). These analyses were performed to assess the potential contribution of concomitant treatments and HRCT pattern to the observed longitudinal functional trajectories.

5-year retention rate and competing-risk analysis

Persistence on nintedanib treatment up to the fifth year of observation was initially assessed using Kaplan–Meier curves and compared using Cox proportional hazards regression, with results reported as hazard ratios (HRs) with 95% confidence intervals (CIs).

Because death before discontinuation represents a competing event, drug retention was further analysed within a competing-risk framework.

Cumulative incidence functions for nintedanib discontinuation were estimated separately for patients with IPF and SARD-ILD/PPF and compared using Gray's test.

Multivariable predictors of discontinuation were identified using Fine–Gray competing-risk regression, adjusting for age, smoking status, long-term oxygen therapy, and disease duration, and reported as subdistribution hazard ratios (sHR) with 95% confidence intervals.

The primary reason for therapy discontinuation was documented for all patients, distinguishing between adverse effects, poor tolerability, patient decision, or other documented causes.

All analyses were performed using RStudio (version 2024.09.1). A p-value less than 0.05 was considered statistically significant.

RESULTS

Study population and follow-up

A total of 274 patients were enrolled in the study, including 136 with IPF and 138 with SARD-ILD/PPF. Baseline characteristics of the overall cohort are reported in Table 2. Compared with patients with SARD-ILD/PPF, patients with IPF were older and more frequently male. Patients with SARD-ILD/PPF had a longer median disease duration and lower baseline ppFVC, ppTLC, and ppDLCO values. No significant differences were observed in BMI, smoking status, or oxygen therapy.

Follow-up pulmonary function data were available for 129 patients with IPF and 126 patients with SARD-ILD/PPF. The median time to the first follow-up pulmonary function assessment was 7 months (IQR 6–12) in patients with IPF and 9 months (IQR 6–12) in patients with SARD-ILD/PPF. A second follow-up assessment was available for 109 patients with IPF (84%) and 80 patients with

SARD-ILD/PPF (63%), with a median follow-up time of 13 months (IQR 12–21) and 17 months (IQR 12–24), respectively. During follow-up, 4/136 patients with IPF and 6/138 patients with SARD-ILD/PPF died ($p = 0.54$).

Longitudinal pulmonary function in IPF

In patients with IPF, linear mixed-effects models showed no significant change in ppFVC over time (estimate: -0.0037 percentage points/month; 95% CI: -0.0949 to 0.0875 ; $p = 0.94$). Male sex was associated with lower ppFVC values (estimate -7.00 , $p = 0.049$), whereas age was not significantly associated with ppFVC (estimate $+0.315$ per year, $p = 0.078$).

Similarly, ppTLC did not change significantly over time (estimate: -0.0705 percentage points/month; 95% CI: -0.1773 to 0.0363 ; $p = 0.20$). Male sex was associated with lower ppTLC values (estimate -7.35 , $p = 0.009$), while age was not significantly associated with ppTLC ($p = 0.70$).

In contrast, ppDLCO decreased significantly over time (estimate: -0.2893 percentage points/month; 95% CI: -0.3762 to -0.2025 ; $p < 0.001$). Neither sex ($p = 0.74$) nor age ($p = 0.43$) was significantly associated with ppDLCO (Table 4).

Longitudinal pulmonary function in SARD-ILD/PPF

Among patients with SARD-ILD/PPF, no significant longitudinal changes were observed in ppFVC, ppTLC, or ppDLCO.

The ppFVC model showed no significant effect of time (estimate -0.0745 percentage points/month, 95% CI -0.1898 to 0.0409 ; $p = 0.21$). Neither sex ($p = 0.76$) nor age ($p = 0.25$) was significantly associated with ppFVC.

Similarly, ppTLC remained stable over time (estimate -0.0035 percentage points/month, 95% CI -0.1273 to 0.1203 ; $p = 0.96$), with no significant associations with sex or age.

The ppDLCO model also showed no significant longitudinal change (estimate – 0.0494 percentage points/month, 95% CI –0.1538 to 0.0550; $p = 0.36$). Neither sex ($p = 0.81$) nor age ($p = 0.16$) was significantly associated with ppDLCO (Table 4).

Comparison of longitudinal trajectories between IPF and SARD-ILD/PPF

In the mixed-effects models including the interaction between time and clinical condition, ppFVC showed no significant time effect in the IPF reference group (estimate –0.003 percentage points/month, $p = 0.96$). Baseline ppFVC was significantly lower in SARD-ILD/PPF than in IPF (estimate –12.58 percentage points, $p < 0.0001$). The time-by-condition interaction was not statistically significant (estimate –0.0718 percentage points/month, 95% CI –0.2180 to 0.0743; $p = 0.34$), indicating no significant difference in longitudinal ppFVC trajectories between the two groups.

For ppDLCO, the time effect in the IPF reference group was significant (estimate – 0.286 percentage points/month, $p < 0.0001$). Baseline ppDLCO was significantly lower in SARD-ILD/PPF (estimate –10.18 percentage points, $p < 0.0001$). The time-by-condition interaction was statistically significant (estimate +0.2354 percentage points/month, 95% CI 0.1000 to 0.3709; $p < 0.001$), indicating different longitudinal ppDLCO trajectories between the two groups.

For ppTLC, the time effect in the IPF reference group was not statistically significant (estimate –0.076 percentage points/month, $p = 0.15$). Baseline ppTLC was significantly lower in SARD-ILD/PPF (estimate –7.63 percentage points, $p = 0.0002$), whereas the time-by-condition interaction was not significant (estimate +0.0706 percentage points/month, 95% CI –0.0936 to 0.2348; $p = 0.40$) (Table 4 and Figure 18).

Additional analyses according to concomitant immunosuppressive treatment in SARD-ILD

Additional mixed-effects models were performed within the SARD-ILD subgroup to assess the potential association between concomitant immunosuppressive treatment and longitudinal pulmonary function. All models were adjusted for sex and age and included an interaction between time and immunosuppressive treatment category (Table 5).

For ppFVC, no significant differences in longitudinal trajectories were observed according to immunosuppressive treatment. The time-by-treatment interaction was not significant for mycophenolate mofetil (MMF; estimate -0.769 , $p = 0.53$), methotrexate (MTX; estimate -0.461 , $p = 0.72$), other immunosuppressive treatments (estimate -0.833 , $p = 0.50$), or rituximab/cyclophosphamide (RTX/Cyc; estimate -0.599 , $p = 0.63$), compared with the reference treatment category. None of the treatment categories was associated with significantly different ppFVC levels. Sex was not significantly associated with ppFVC ($p = 0.56$), whereas age was associated with slightly higher ppFVC values (estimate $+0.293$ percentage points per year, $p = 0.020$).

For ppDLCO, no significant time-by-treatment interactions were observed for MMF (estimate $+0.091$, $p = 0.92$), MTX (estimate $+0.359$, $p = 0.72$), other immunosuppressive treatments (estimate $+0.308$, $p = 0.75$), or RTX/Cyc (estimate $+0.106$, $p = 0.91$). Neither sex nor age was significantly associated with ppDLCO, although age showed a non-significant trend towards lower ppDLCO values (estimate -0.190 per year, $p = 0.076$).

For ppTLC, the time-by-treatment interaction was statistically significant for MTX compared with the reference category (estimate -2.695 percentage points/month, $p = 0.046$). The corresponding interactions were not statistically significant for MMF (estimate -2.417 , $p = 0.067$), other immunosuppressive treatments (estimate -2.495 , $p = 0.062$), or RTX/Cyc (estimate -2.237 , $p = 0.091$). The main effect of time in the reference treatment category was not statistically significant (estimate $+2.300$

percentage points/month, $p = 0.080$). Neither sex nor age was significantly associated with ppTLC.

Additional analyses according to HRCT pattern in SARD-ILD

Additional mixed-effects models were performed to evaluate whether HRCT pattern was associated with longitudinal pulmonary function within the SARD-ILD subgroup. Models were adjusted for sex and age and included an interaction between time and HRCT pattern (Table 5).

For ppFVC, neither the main effect of HRCT pattern nor its interaction with time was statistically significant. Compared with the reference category, the UIP/UIP-like pattern was not associated with significantly different ppFVC values (estimate +4.66, $p = 0.13$), and the time-by-UIP/UIP-like interaction was not significant (estimate -0.081 , $p = 0.50$). The “Other” HRCT category was also not significantly associated with ppFVC (estimate -6.42 , $p = 0.34$), while its interaction with time showed a non-significant trend (estimate +0.625, $p = 0.097$). Neither sex nor age was significantly associated with ppFVC.

For ppDLCO, the UIP/UIP-like pattern was not associated with significantly different ppDLCO values compared with the reference category (estimate +1.52, $p = 0.54$), and the interaction with time was not significant (estimate -0.066 , $p = 0.54$). Similarly, neither the “Other” HRCT category nor its interaction with time was statistically significant ($p = 0.99$ and $p = 0.23$, respectively). Sex and age were not significantly associated with ppDLCO.

For ppTLC, neither UIP/UIP-like disease (estimate +2.04, $p = 0.49$) nor the “Other” HRCT category (estimate +0.16, $p = 0.98$) was associated with significantly different ppTLC values compared with the reference category. No significant time-by-HRCT interactions were observed for UIP/UIP-like disease (estimate -0.014 , $p = 0.92$) or the “Other” category (estimate +0.546, $p = 0.17$). Sex and age were not significantly associated with ppTLC.

Additional analyses according to concomitant glucocorticoid treatment in SARD-ILD

In the ppFVC model, ongoing glucocorticoid treatment was not associated with significantly different baseline ppFVC values (estimate -0.55 , $p = 0.85$). In patients not receiving glucocorticoids, ppFVC decreased significantly over time (estimate -0.222 percentage points/month, $p = 0.0048$). The time-by-glucocorticoid interaction was statistically significant (estimate $+0.328$ percentage points/month, $p = 0.0064$).

For ppDLCO, ongoing glucocorticoid treatment was not associated with significantly different values (estimate $+0.45$, $p = 0.85$), and the time-by-treatment interaction was not significant (estimate $+0.039$ percentage points/month, $p = 0.72$). The main effect of time was also not significant (estimate -0.062 percentage points/month, $p = 0.38$).

Similarly, ongoing glucocorticoid treatment was not significantly associated with ppTLC (estimate -2.31 , $p = 0.40$), and no significant difference in longitudinal trajectory was observed between patients receiving and not receiving glucocorticoids (time-by-treatment interaction estimate $+0.151$ percentage points/month, $p = 0.30$). The main effect of time was not significant (estimate -0.133 percentage points/month, $p = 0.20$) (Table 5).

Five-year treatment retention

Five-year retention data were available for 131 patients with IPF and 107 patients with SARD-ILD/PPF. In the original Kaplan–Meier analysis, treatment retention at 12 months was 95.8% (95% CI 92.2–99.5) in IPF and 91.9% (95% CI 86.6–97.5) in SARD-ILD/PPF. At 36 months, retention was 84.3% (95% CI 77.2–92.1) in IPF and 77.6% (95% CI 67.8–88.9) in SARD-ILD/PPF. At 60 months, estimated retention was 69.5% (95% CI 58.6–82.6) in IPF and 77.6% (95% CI 67.8–88.9) in SARD-ILD/PPF. The number of patients at risk at 60 months was limited, particularly in the SARD-ILD/PPF group.

In the Cox proportional hazards analysis, using IPF as the reference category, SARD-ILD/PPF was associated with a hazard ratio for treatment discontinuation of 1.74 (95% CI 0.89–3.40; $p = 0.106$) (Figure 19).

Competing-risk analysis of nintedanib discontinuation

To account for the competing risk of death, nintedanib discontinuation was additionally analysed using a competing-risk framework. Death was considered a competing event, while patients who remained on treatment at the last available follow-up were censored.

When death was considered as a competing event, the cumulative incidence of nintedanib discontinuation was numerically higher in SARD-ILD/PPF than in IPF, although the difference did not reach statistical significance (Gray's test, $p = 0.058$). The cumulative incidence of discontinuation at 36, 48, and 60 months was 66.3%, 76.4%, and 84.2% in IPF and 80.6%, 90.9%, and 92.3% in SARD-ILD/PPF, respectively. The cumulative incidence of death did not differ significantly between groups (Gray's test, $p = 0.578$).

In multivariable Fine–Gray competing-risk regression, SARD-ILD/PPF was associated with a higher subdistribution hazard of nintedanib discontinuation compared with IPF (sHR 1.66, 95% CI 1.08–2.55; $p = 0.021$), after adjustment for smoking status, oxygen therapy, and disease duration. Smoking status, oxygen therapy, and disease duration were not significantly associated with treatment discontinuation (Table 6).

The corresponding estimates were as follows: former smoker versus active smoker, sHR 1.13 (95% CI 0.39–3.25; $p = 0.830$); never smoker versus active smoker, sHR 1.12 (95% CI 0.38–3.33; $p = 0.840$); oxygen therapy, yes versus no, sHR 0.76 (95% CI 0.49–1.18; $p = 0.230$); and disease duration, per year, sHR 0.99 (95% CI 0.96–1.02; $p = 0.570$).

Variable	IPF (N=136)	SARD-ILD (N=138)	p-value
Age, median (IQR)	75.0 (69.0–79.0)	67.5 (56.0–76.0)	p<0.01
Male sex, n/N	101/136	68/138	p<0.01
BMI, median (IQR)	26.6 (24.2–29.0)	26.5 (23.9–29.0)	p=0.92
Disease duration, years, median (IQR)	4.0 (2.0–5.0)	5.5 (3.0–10.6)	p<0.01
Smoking status	Active 8; Former 88; Never 40	Active 8; Former 72; Never 58	p=0.09
Oxygen therapy, n/N	33/135	48/137	p=0.06
ppFVC baseline, median (IQR)	88.5 (73.9–102.0)	76.0 (61.0–85.3)	p<0.01
ppTLC baseline, median (IQR)	74.0 (65.7–84.0)	69.0 (58.7–80.3)	p<0.01
ppDLCO baseline, median (IQR)	53.8 (46.0–66.6)	44.0 (36.0–54.6)	p<0.01

Table 2. Baseline characteristics of the overall cohort. Interquartile range (IQR), percent predicted forced vital capacity (ppFVC), percent predicted total lung capacity (ppTLC), percent predicted DLCO (ppDLCO).

Cross table for dependent CTD_type							
	N	IIM (n=18)	Other (n=39)	RA (n=40)	SSc (n=36)	SjD (n=5)	Test Statistic
Age	138	51.7 64.5 76.2	58.2 72 77	58.4 68.5 76.0	52.7 65 70.6	64 70.0 77.7	$F_{4,133}=1.33$, $P=0.26$ ¹
Sex: Male	138	0.6 11/18	0.4 17/39	0.6 24/40	0.4 14/36	0.4 2/5	$X^2_4=5.08$, $P=0.28$ ²
BMI	96	21.8 24.4 27.9	24.3 25.3 26.2	25.1 27.9 31.9	24.0 26.9 28.5	24.3 30.0 35.7	$F_{4,91}=2.34$, $P=0.06$ ¹
Disease Duration	136	2.9 4.5 6.1	2.0 4.0 7.8	3.9 8.0 14.1	3.0 6.5 14.2	2.3 8.0 8.0	$F_{4,133}=2.18$, $P=0.07$ ¹
Smoke	138						$X^2_8=26.70$, $P<0.01$ ²
Active		0.1 1/18	0.2 6/39	0.0 1/40	0.0 0/36	0.0 0/5	
Former		0.5 9/18	0.3 13/39	0.8 31/40	0.4 15/36	0.8 4/5	
Never		0.4 8/18	0.5 20/39	0.2 8/40	0.6 21/36	0.2 1/5	
Oxygen_2: O2 yes	137	0.3 5/18	0.4 14/39	0.3 13/39	0.4 14/36	0.4 2/5	$X^2_4=0.77$, $p=0.94$ ²
ppFVC baseline	133	52.2 64.0 80.8	64.2 77.0 84.8	65.8 81.0 93.2	60.2 65.6 81.5	64.1 86.0 89.3	$F_{4,128}=2.75$, $P=0.03$ ¹
ppTLC_baseline	113	53.0 63.0 75.8	61.8 69.0 79.2	64.3 72.0 82.8	57.7 63.0 78.8	57.5 72.0 91.2	$F_{4,108}=1.00$, $P=0.41$ ¹
ppDLCO_baseline	128	34.4 40.4 58.6	34.8 45.5 52.2	36.0 44.0 55.6	38.2 43.0 53.8	32.0 42.0 55.7	$F_{4,123}=0.06$, $P=0.99$ ¹

Table 3. Characteristics of patients with SARD-ILD.

Models	Estimates	95% CI	p-value
IPF ppFVC	-0.0037	[-0.0949, 0.0875]	0.9366
IPF ppTLC	-0.0705	[-0.1773, 0.0363]	0.1974
IPF ppDLCO	-0.2893	[-0.3762, -0.2025]	<0.001
SARD ppFVC	-0.0745	[-0.1898, 0.0409]	0.207
SARD ppTLC	-0.0035	[-0.1273, 0.1203]	0.956
SARD ppDLCO	-0.0494	[-0.1538, 0.0550]	0.355
Interaction ppFVC	-0.0718	[-0.2180, 0.0743]	0.336
Interaction ppDLCO	0.2354	[0.1000, 0.3709]	<0.001
Interaction ppTLC	0.0706	[-0.0936, 0.2348]	0.3999

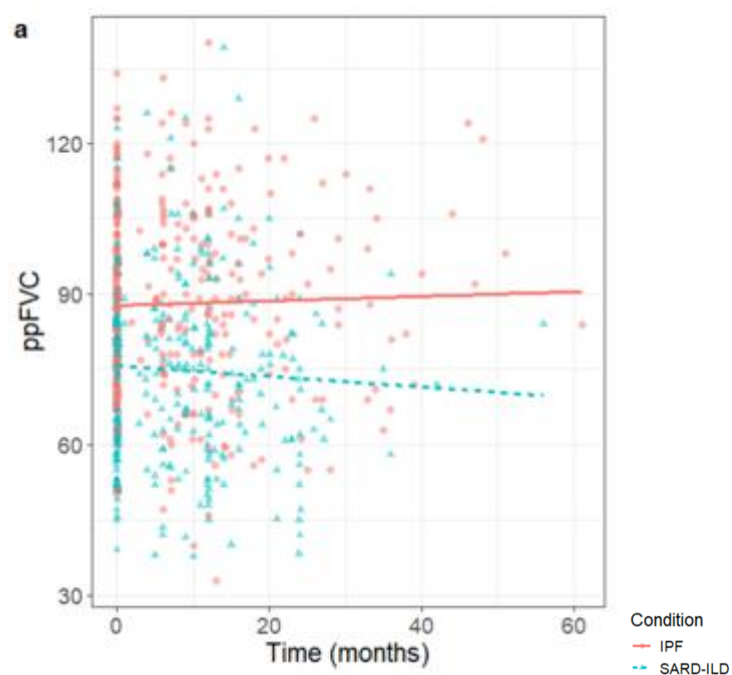
Table 4. Results of linear mixed-effects models applied to respiratory function parameters in subjects with IPF and SARD-ILD/PPF. For each parameter (ppFVC, ppTLC, ppDLCO), the estimates of the fixed effects associated with time (Months) are reported in the models stratified by diagnostic group and in the models with interaction (Months $\times$ Condition), together with the 95% confidence interval and the p-value. In the interaction models, the IPF group is the reference category. Negative values of the estimates indicate a decline in the parameter over time; positive values indicate an increase or a more favorable slope.

Variable	N	IIM (n=18)	Other (n=39)	RA (n=40)	SSc (n=36)	SjD (n=5)	Test Statistic
Immunosuppressants	138						
Abatacept		0.0% (0/18)	0.0% (0/39)	5.0% (2/40)	0.0% (0/36)	0.0% (0/5)	$\chi^2(4) = 81.90, p < 0.001$
MMF		83.3% (15/18)	41.0% (16/39)	0.0% (0/40)	75.0% (27/36)	80.0% (4/5)	
Methotrexate		0.0% (0/18)	0.0% (0/39)	27.5% (11/40)	0.0% (0/36)	0.0% (0/5)	
RTX / CYC		27.8% (5/18)	12.8% (5/39)	20.0% (8/40)	25.0% (9/36)	0.0% (0/5)	
Other IS		11.1% (2/18)	12.8% (5/39)	50.0% (20/40)	2.7% (1/36)	0.0% (0/5)	
HRCT pattern	138						
UIP / UIP-like		16.7% (3/18)	17.9% (7/39)	72.5% (29/40)	19.4% (7/36)	0.0% (0/5)	$\chi^2(8) = 44.63, p < 0.001$
NSIP		83.3% (15/18)	43.6% (17/39)	25.0% (10/40)	80.5% (29/36)	20.0% (1/5)	
Other pattern		22.2% (4/18)	5.1% (2/39)	2.5% (1/40)	0.0% (0/36)	0.0% (0/5)	
Ongoing glucocorticoids	138						
Glucocorticoid use		72.2% (13/18)	23.1% (9/39)	35.0% (14/40)	47.2% (17/36)	60.0% (3/5)	$\chi^2(4) = 8.26, p = 0.082$

Table 5. Immunosuppressants, glucocorticoids and HRCT pattern data in SARD-ILD PPF group.

Predictor	sHR	95% CI	p-value
SARD-ILD vs IPF	1.66	1.08–2.55	0.021
Former smoker vs active smoker	1.13	0.39–3.25	0.830
Never smoker vs active smoker	1.12	0.38–3.33	0.840
Oxygen therapy: yes vs no	0.76	0.49–1.18	0.230
Disease duration, per year	0.99	0.96–1.02	0.570

Table 6. Multivariable Fine–Gray competing-risk regression analysis of predictors of nintedanib discontinuation. Death was treated as a competing event, while patients who remained on treatment at the last available follow-up were censored. Results are reported as subdistribution hazard ratios (sHRs) with 95% confidence intervals (CIs). IPF, idiopathic pulmonary fibrosis; SARD-ILD, systemic autoimmune rheumatic disease-associated interstitial lung disease.



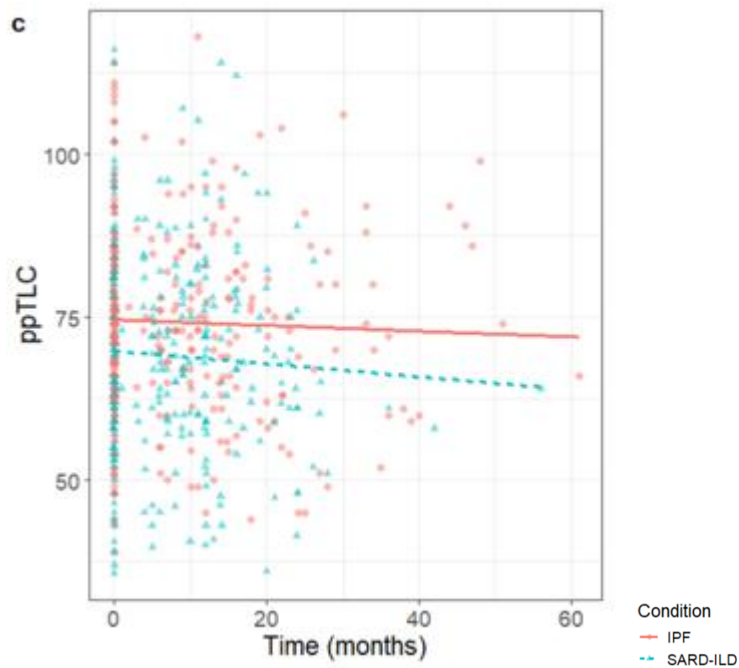
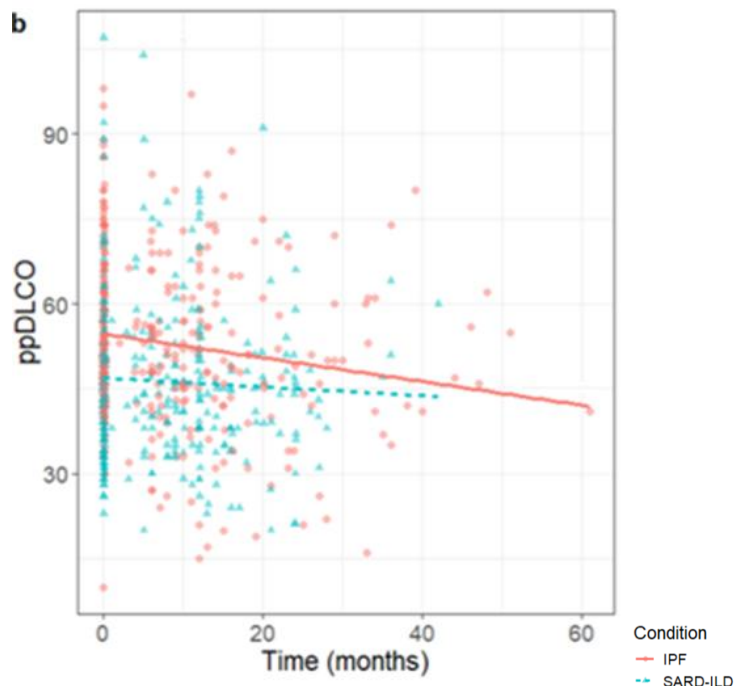


Figure 18. Time trends of ppFVC, ppDLCO, and ppTLC values in the IPF and SARD-ILD/PPF groups. ###: $p < 0.001$ vs. baseline *: p for interaction (IPF * SARD-ILD/PPF) < 0.001 .**

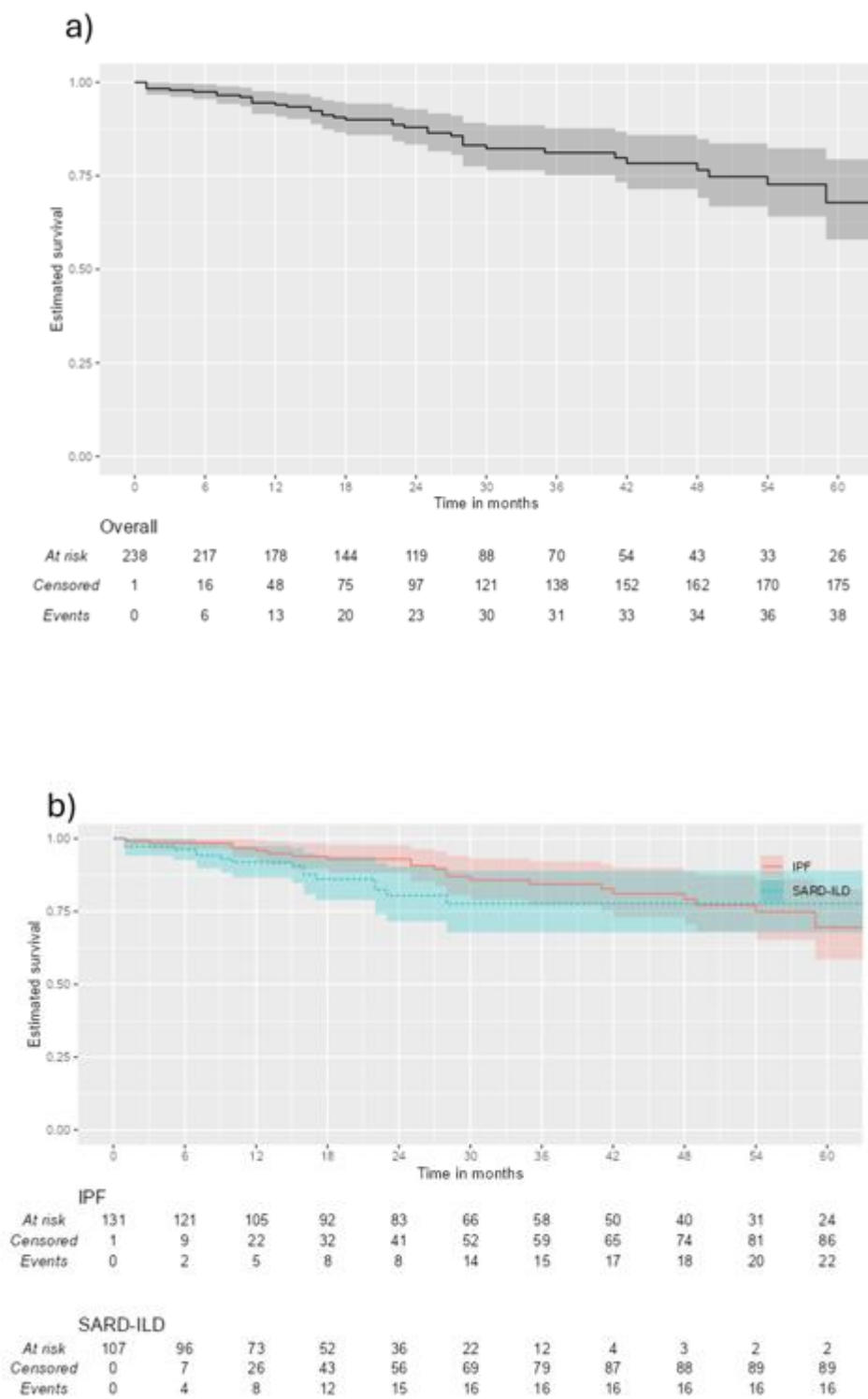


Figure 19. Kaplan–Meier curves for the 5-year retention rate of nintedanib in the overall sample (panel a) and comparison between IPF and SARD-ILD/PPF (panel b).

DISCUSSION

This multicenter retrospective study provides real-world evidence on long-term functional trajectories and treatment persistence in patients with idiopathic pulmonary fibrosis (IPF) and progressive systemic autoimmune rheumatic disease-associated interstitial lung disease (SARD-ILD/PPF) treated with nintedanib.

In our cohort, the IPF population showed a clear predominance of male patients, consistent with previous epidemiological reports. From a functional perspective, lung volumes (ppFVC and ppTLC) remained substantially stable over time after initiating nintedanib, supporting the established role of antifibrotic therapy in slowing disease progression, as previously demonstrated in the landmark INPULSIS trials (7,8).

In contrast, diffusing capacity (ppDLCO) declined significantly despite treatment. This finding is particularly relevant, as DLCO is recognised as a marker of disease impairment in IPF (20). While most clinical studies and trials primarily focus on FVC as the main endpoint in IPF, DLCO is frequently considered a secondary or supportive parameter. However, emerging evidence highlights its independent prognostic value.

In this regard, a previous study demonstrated that a one-year decline in FVC $\geq 5\%$ predicted and in DLCO $\geq 10\%$ predicted were both independently associated with increased mortality risk in IPF patients (21). These findings suggest that monitoring DLCO may provide additional prognostic information beyond FVC alone, reinforcing the clinical significance of the progressive decline in DLCO observed in our IPF cohort.

Moreover, DLCO reflects the integrity of the alveolar–capillary membrane and the efficiency of gas transfer from the alveoli to the bloodstream and is primarily influenced by structural changes in the gas-exchange surface rather than by ventilatory mechanics. For this reason, it represents an early and sensitive marker of interstitial lung disease, often declining before measurable changes in lung volumes become evident (20). Taken together, these considerations support the need to systematically monitor DLCO alongside FVC in both clinical practice and

research settings, as it may provide additional insights into disease progression and treatment response, complementing the evaluation of FVC.

In patients with progressive SARD-ILD/PPF treated with nintedanib, all key functional parameters (ppFVC, ppTLC, and ppDLCO) remained broadly stable over time, with no evidence of significant decline during the follow-up period. These findings indicate that substantial functional deterioration was not observed during treatment and are consistent with the antifibrotic effect of nintedanib previously reported in progressive fibrosing ILDs (16)). However, given the retrospective observational design and the absence of an untreated comparator group, the observed stability cannot be interpreted as a direct measure of treatment efficacy. Rather, it should be considered as a description of the functional trajectory observed in patients receiving nintedanib in routine clinical practice.

It should be noted that the SARD-ILD population is highly heterogeneous, encompassing systemic sclerosis, idiopathic inflammatory myopathies, rheumatoid arthritis, and other connective tissue diseases. Each condition may have distinct lung involvement and progression rates.

Moreover, concomitant immunosuppressive and glucocorticoid treatments may have contributed to the observed functional stability. To address this potential source of confounding, additional analyses were performed within the SARD-ILD subgroup according to concomitant immunosuppressive treatment, ongoing glucocorticoid therapy, and HRCT pattern.

These analyses did not demonstrate consistent differences in longitudinal trajectories of ppFVC or ppDLCO across immunosuppressive treatments, although some heterogeneity was observed in ppTLC.

Similarly, HRCT pattern did not significantly modify the longitudinal trajectories of ppFVC, ppDLCO, or ppTLC. Although these findings reduce the likelihood that the observed functional stability was entirely explained by these factors, residual confounding cannot be excluded because of the retrospective design, the heterogeneity of the SARD-ILD population, and the limited size of some subgroups.

The divergent behaviour of DLCO between the two groups is therefore of particular interest. In IPF, ppDLCO showed a significant decline despite relatively stable lung volumes, whereas no significant longitudinal decline in ppDLCO was observed in SARD-ILD/PPF. This difference may reflect, at least in part, the different biological and clinical characteristics of the underlying diseases. In IPF, progressive involvement of the alveolar-capillary membrane and pulmonary vascular compartment may lead to deterioration in gas transfer despite relative preservation of lung volumes.

Conversely, autoimmune-associated ILDs are characterised by a more heterogeneous interplay between inflammatory, immune-mediated, and fibrotic mechanisms, which may be more amenable to therapeutic modulation. This interpretation is consistent with findings reported by Raman, Muscato, and Boutel (22–24), which underscore the importance of differences in disease phenotype and underlying pathobiology in interpreting functional trajectories in fibrosing ILDs.

Although this difference may reflect distinct underlying pathophysiological mechanisms and disease trajectories, it should not be interpreted as evidence of a differential treatment effect of nintedanib, given the study's observational design and the absence of an untreated comparator group. The potential contribution of concomitant immunosuppressive and glucocorticoid treatments was explored in additional analyses within the SARD-ILD subgroup, which did not reveal consistent differences in ppDLCO trajectories by treatment category.

At baseline, SARD-ILD patients showed significantly lower functional values (ppFVC, ppTLC, and ppDLCO) than IPF patients, despite being younger and having a longer disease duration. This may reflect differences in disease phenotype, diagnostic delay, and referral patterns. Nevertheless, the absence of a significant longitudinal decline in this group may be consistent with a more heterogeneous and potentially modifiable disease course, although this interpretation remains speculative.

From a clinical perspective, these findings have relevant implications. First, they support the use of nintedanib not only in IPF but also in progressive fibrosing ILDs associated with systemic autoimmune diseases, reinforcing current treatment

strategies. Second, they highlight the importance of integrating DLCO assessment into routine follow-up, as changes in gas exchange may provide complementary, potentially earlier information on disease progression than lung volumes alone. Finally, the overall functional stability observed in SARD-ILD/PPF supports the feasibility of integrating antifibrotic therapy into the broader multidisciplinary management of these patients, which frequently includes immunomodulatory treatment based on the underlying systemic disease.

Regarding treatment retention, both IPF and SARD-ILD/PPF groups demonstrated high persistence during the first year of therapy, with rates approaching 94–96%, indicating good tolerability and acceptability of nintedanib in real-world clinical practice. Over time, retention gradually declined, with estimates around 80% at 36 months and approximately 70–78% at 5 years. These findings are consistent with data from pivotal clinical trials such as INPULSIS and INBUILD, suggesting that real-world adherence is broadly comparable to that observed in controlled settings (7,8,16).

However, long-term retention estimates should be interpreted cautiously because the number of patients remaining at risk progressively decreased, particularly in the SARD-ILD cohort. Moreover, treatment discontinuation in routine practice may be influenced by factors that are less prominent or more strictly controlled in randomised clinical trials, including comorbidities, concomitant therapies, patient preferences, and variations in monitoring and management strategies.

When death was considered as a competing event, the difference in cumulative incidence of treatment discontinuation between IPF and SARD-ILD remained non-significant, although a numerical trend toward higher discontinuation in SARD-ILD was observed. In the multivariable Fine–Gray analysis, however, SARD-ILD was independently associated with a higher subdistribution hazard of treatment discontinuation after adjustment for smoking status, oxygen therapy, and disease duration.

This apparent difference between the unadjusted comparison and the multivariable analysis suggests that the relationship between underlying disease and treatment persistence may be influenced by differences in baseline clinical characteristics.

These findings should nevertheless be interpreted cautiously and require confirmation in larger prospective cohorts.

The interpretation of long-term retention should also take into account the different duration of clinical experience with nintedanib between the two populations. Nintedanib has been used in IPF for a substantially longer period than in SARD-ILD, whereas its use in progressive SARD-ILD/PPF became established more recently following the evidence generated by the INBUILD trial (16). Consequently, the shorter follow-up available for functional analyses in the SARD-ILD population compared with IPF is, at least in part, an expected consequence of the more recent introduction of nintedanib into routine clinical practice for this indication. This difference in treatment history should be considered when interpreting long-term comparisons between the two groups.

Our findings partially differ from those reported by Raman and Muscato, likely due to differences in the composition of the progressive fibrosing ILD population. In particular, our study included a broader and more heterogeneous SARD-ILD cohort, while excluding patients with unclear rheumatologic diagnoses or interstitial pneumonia with autoimmune features (IPAF). Moreover, previous studies often focused on specific subgroups, such as rheumatoid arthritis-associated ILD, which represented a large proportion of their cohorts.

Differences between real-world evidence and clinical trial data

An important strength of the present study is that it provides real-world evidence on the long-term use of nintedanib in both IPF and SARD-ILD/PPF, complementing the evidence generated by randomised controlled trials. Although pivotal trials such as INPULSIS and INBUILD demonstrated that nintedanib slows the decline in FVC in patients with IPF and progressive fibrosing ILD, respectively, their study populations were selected according to strict eligibility criteria and were followed under standardised treatment and monitoring conditions (7,8,16).

In contrast, our cohort reflects routine clinical practice, where patients may present with greater clinical heterogeneity, comorbidities, concomitant treatments, variable disease duration, and non-standardised timing of pulmonary function assessments.

These differences are particularly relevant when interpreting the functional trajectories observed in our study. Unlike randomised trials, in which pulmonary function assessments are generally scheduled at predefined intervals and treatment exposure is closely monitored, our retrospective cohort included measurements obtained according to routine clinical practice. The mixed-effects approach allowed us to account for the irregular timing of assessments and the repeated measurements within individual patients, thereby providing an estimate of longitudinal functional trends under real-world conditions. Importantly, the relative stability of ppFVC and ppTLC observed in our IPF population, together with the significant decline in ppDLCO, should therefore not be interpreted as a direct replication of the efficacy endpoints reported in randomized trials, but rather as a description of functional behaviour during treatment in an unselected clinical population.

Another relevant difference concerns the SARD-ILD/PPF population. Whereas INBUILD (16) enrolled patients with progressive fibrosing ILD according to predefined progression criteria, our SARD-ILD cohort comprised a clinically heterogeneous population, including different systemic autoimmune rheumatic diseases and different radiological patterns. In addition, many patients received concomitant immunosuppressive and/or glucocorticoid treatment, reflecting standard management of their underlying systemic disease. Our additional subgroup analyses did not demonstrate consistent differences in ppFVC or ppDLCO trajectories according to immunosuppressive treatment, although some heterogeneity was observed in ppTLC. Similarly, HRCT pattern did not significantly modify longitudinal functional trajectories. These findings should nevertheless be interpreted with caution, given the retrospective design and the limited sample sizes of individual treatment and radiological subgroups.

Finally, the long-term treatment retention observed in our cohort provides information that is complementary to randomised trial data. Whereas clinical trials are generally conducted over predefined periods and under close monitoring, our

analysis allowed treatment persistence to be evaluated for up to five years in routine practice. Despite the progressive decline in retention over time, a substantial proportion of patients remained on nintedanib during long-term follow-up, supporting the feasibility of prolonged antifibrotic treatment in clinical practice. Overall, these differences highlight the complementary nature of randomised controlled trials and real-world studies: while clinical trials provide the most robust evidence of treatment efficacy under controlled conditions, real-world cohorts help assess how these effects translate in heterogeneous patient populations treated and monitored in everyday clinical practice.

Limitations

This study has several limitations that should be considered when interpreting the results. First, its retrospective design limits the standardisation of follow-up intervals and pulmonary function assessments, potentially introducing variability in the timing and number of measurements. Although linear mixed-effects models were used to account for irregularly timed repeated measurements, residual bias inherent to the retrospective design cannot be excluded.

Second, the SARD-ILD population was highly heterogeneous, including systemic sclerosis, idiopathic inflammatory myopathies, rheumatoid arthritis, and other connective tissue diseases, each with potentially different patterns of lung involvement and progression. Although the main longitudinal models were adjusted for age and sex, and additional exploratory analyses within the SARD-ILD subgroup assessed the potential influence of concomitant immunosuppressive treatment, ongoing glucocorticoid therapy, and HRCT pattern, residual confounding related to disease-specific characteristics cannot be completely excluded. Moreover, the relatively small size of some treatment and radiological subgroups limits the precision of these analyses.

Third, treatment-emergent adverse events were not systematically collected in this retrospective cohort. Therefore, a detailed analysis of gastrointestinal toxicity, dose reductions, temporary treatment interruptions, and specific reasons for permanent

discontinuation could not be reliably performed. This limits a comprehensive assessment of long-term nintedanib tolerability in routine clinical practice.

Fourth, although HRCT pattern was included in additional subgroup analyses, quantitative radiological assessment or standardized longitudinal fibrosis scoring was not available. Consequently, radiological progression could not be integrated with changes in pulmonary function. Future prospective studies combining serial quantitative HRCT assessment with functional trajectories may provide a more comprehensive characterisation of disease progression.

Fifth, the duration of follow-up available for longitudinal pulmonary function analyses was relatively limited compared with the five-year treatment retention analysis. This may restrict the ability to fully characterise long-term functional trajectories in slowly progressive fibrotic disorders. The shorter functional follow-up, particularly in SARD-ILD/PPF, should also be interpreted in the context of the more recent introduction of nintedanib into routine clinical practice for progressive fibrosing ILDs compared with its longer-standing use in IPF. In addition, the number of patients remaining under observation at five years was small, particularly in the SARD-ILD/PPF subgroup, resulting in greater uncertainty in long-term retention estimates.

Despite these limitations, this multicenter study provides complementary real-world information on longitudinal pulmonary function and long-term treatment persistence in patients with IPF and progressive SARD-ILD/PPF treated with nintedanib.

CONCLUSIONS

In conclusion, in our multicenter real-world cohort, lung volumes remained broadly stable over time in both idiopathic pulmonary fibrosis (IPF) and progressive SARD-ILD/PPF patients receiving nintedanib. While ppDLCO declined significantly over time in IPF despite relative preservation of lung volumes, it remained stable in the SARD-ILD/PPF population, indicating a more favorable longitudinal trajectory of gas exchange in this group. However, given the observational design and the

absence of an untreated comparator group, these findings should not be interpreted as evidence of a differential treatment effect of nintedanib between the two conditions.

Treatment persistence was high during the first year and remained substantial over long-term follow-up in both groups. When death was considered as a competing event, the difference in the cumulative incidence of treatment discontinuation between IPF and SARD-ILD/PPF did not reach statistical significance in the unadjusted comparison. However, multivariable Fine–Gray analysis identified SARD-ILD/PPF as independently associated with a higher subdistribution hazard of nintedanib discontinuation, highlighting the potential influence of differences in baseline clinical characteristics on long-term treatment persistence.

Importantly, these findings derive from a real-world clinical setting characterised by greater clinical heterogeneity, comorbidity burden, concomitant treatments, and less standardised follow-up compared with randomised controlled trials. This provides complementary evidence on the use of nintedanib in patients encountered in routine clinical practice, while the retrospective design and residual confounding require cautious interpretation of treatment-related effects.

Overall, our findings are consistent with the role of nintedanib in the management of IPF and progressive fibrosing ILDs associated with systemic autoimmune diseases and provide real-world information on longitudinal functional trajectories and long-term treatment persistence. The heterogeneity of the SARD-ILD/PPF population and the potential contribution of concomitant immunomodulatory treatments and disease-specific characteristics emphasise the importance of individualised and multidisciplinary management.

Further prospective studies with longer standardised functional follow-up, systematic assessment of treatment-emergent adverse events and dose modifications, and longitudinal quantitative imaging are warranted to better characterise long-term outcomes and identify predictors of functional progression and treatment persistence. Larger studies may also help clarify the interplay between antifibrotic and immunomodulatory therapies across different SARD-ILD phenotypes.

BIBLIOGRAPHY

1. Ryerson CJ, Adegunsoye A, Piciucchi S, Hariri LP, Khor YH, Wijsenbeek MS, et al. Update of the international multidisciplinary classification of the interstitial pneumonias: an ERS/ATS statement. *Eur Respir J*. 4 dicembre 2025;66(6). doi:10.1183/13993003.00158-2025 PubMed PMID: 40774805.
2. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med*. settembre 2018;198(5):e44–68. doi:10.1164/rccm.201807-1255ST
3. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med*. maggio 2022;205(9):e18–47. doi:10.1164/rccm.202202-0399ST
4. Fernández Pérez ER, Daniels CE, Schroeder DR, St Sauver J, Hartman TE, Bartholmai BJ, et al. Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis: a population-based study. *Chest*. gennaio 2010;137(1):129–37. doi:10.1378/chest.09-1002 PubMed PMID: 19749005; PubMed Central PMCID: PMC2803118.
5. Tomassetti S, Gurioli C, Ryu JH, Decker PA, Ravaglia C, Tantalocco P, et al. The impact of lung cancer on survival of idiopathic pulmonary fibrosis. *Chest*. gennaio 2015;147(1):157–64. doi:10.1378/chest.14-0359 PubMed PMID: 25166895.
6. Carobene L, Spina D, Disanto MG, Micheletto C, Mazzei MA, Paladini P, et al. Lung cancer and interstitial lung diseases: the lack of prognostic impact of lung cancer in IPF. *Intern Emerg Med*. marzo 2022;17(2):457–64. doi:10.1007/s11739-021-02833-6 PubMed PMID: 34524623; PubMed Central PMCID: PMC8964539.
7. Richeldi L, Bois RM du, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis. *N Engl J Med*. 29 maggio 2014;370(22):2071–82. doi:10.1056/NEJMoa1402584

8. Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, et al. Efficacy of a Tyrosine Kinase Inhibitor in Idiopathic Pulmonary Fibrosis. *N Engl J Med*. 22 settembre 2011;365(12):1079–87. doi:10.1056/NEJMoa1103690
9. Raghu G, Rochwerg B, Zhang Y, Garcia CAC, Azuma A, Behr J, et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. *Am J Respir Crit Care Med*. 15 luglio 2015;192(2):e3–19. doi:10.1164/rccm.201506-1063ST
10. Storrer KM, Müller C de S, Pessoa MC de A, Pereira CA de C. Connective tissue disease-associated interstitial lung disease. *J Bras Pneumol Publicacao Of Soc Bras Pneumol E Tisiologia*. 2024;50(1):e20230132. doi:10.36416/1806-3756/e20230132 PubMed PMID: 38536980; PubMed Central PMCID: PMC11095924.
11. Antoniou KM, Distler O, Gheorghiu AM, Moor CC, Vikse J, Bizymi N, et al. ERS/EULAR clinical practice guidelines for connective tissue disease-associated interstitial lung disease. *Eur Respir J*. 22 gennaio 2026;67(1):2402533. doi:10.1183/13993003.02533-2024 PubMed PMID: 40907995; PubMed Central PMCID: PMC12824641.
12. Balestro, Elisabetta | Rassegna di Patologia dell'Apparato Respiratorio [Internet]. [citato 18 marzo 2026]. Disponibile su: <https://www.aiporassegna.it/search/authors/view?givenName=Elisabetta&familyName=Balestro&affiliation=Unit%C3%A0%20Operativa%20di%20Pneumologia%2C%20Azienda%20Ospedale%20Universit%C3%A0%20di%20Padova%2C%20Padova&country=IT&authorName=Balestro%2C%20Elisabetta>
13. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al. Cyclophosphamide versus Placebo in Scleroderma Lung Disease. *N Engl J Med*. 22 giugno 2006;354(25):2655–66. doi:10.1056/NEJMoa055120
14. Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, et al. Mycophenolate Mofetil versus Oral Cyclophosphamide in Scleroderma-related Interstitial Lung Disease: Scleroderma Lung Study II (SLS-II), a double-blind,

- parallel group, randomised controlled trial. *Lancet Respir Med.* settembre 2016;4(9):708–19. doi:10.1016/S2213-2600(16)30152-7 PubMed PMID: 27469583; PubMed Central PMCID: PMC5014629.
15. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al. Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease. *N Engl J Med.* 27 giugno 2019;380(26):2518–28. doi:10.1056/NEJMoa1903076
 16. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. *N Engl J Med.* 31 ottobre 2019;381(18):1718–27. doi:10.1056/NEJMoa1908681
 17. Solomon JJ, Danoff SK, Woodhead FA, Hurwitz S, Maurer R, Glaspole I, et al. Safety, tolerability, and efficacy of pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease: a randomised, double-blind, placebo-controlled, phase 2 study. *Lancet Respir Med.* gennaio 2023;11(1):87–96. doi:10.1016/S2213-2600(22)00260-0 PubMed PMID: 36075242.
 18. Lundberg IE, Tjärnlund A, Bottai M, Werth VP, Pilkington C, de Visser M, et al. EULAR/ACR Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies and their Major Subgroups. *Ann Rheum Dis.* dicembre 2017;76(12):1955–64. doi:10.1136/annrheumdis-2017-211468 PubMed PMID: 29079590; PubMed Central PMCID: PMC5736307.
 19. Stanojevic S, Kaminsky DA, Miller MR, Thompson B, Aliverti A, Barjaktarevic I, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. *Eur Respir J.* 13 luglio 2022;60(1). doi:10.1183/13993003.01499-2021 PubMed PMID: 34949706.
 20. Goldin J, Cascella M. Diffusing Capacity of the Lungs for Carbon Monoxide. In: *StatPearls [Internet].* Treasure Island (FL): StatPearls Publishing; 2026 [citato 27 marzo 2026]. Disponibile su: <http://www.ncbi.nlm.nih.gov/books/NBK556149/> PubMed PMID: 32310609.
 21. Lee H, Kim SY, Park YS, Choi SM, Lee JH, Park J. Prognostic implication of 1-year decline in diffusing capacity in newly diagnosed idiopathic pulmonary fibrosis.

Sci Rep. 17 aprile 2024;14:8857. doi:10.1038/s41598-024-59649-5 PubMed
PMID: 38632477; PubMed Central PMCID: PMC11024342.

22. Raman L, Stewart I, Barratt SL, Chua F, Chaudhuri N, Crawshaw A, et al. Nintedanib for non-IPF progressive pulmonary fibrosis: 12-month outcome data from a real-world multicentre observational study. *ERJ Open Res.* marzo 2023;9(2):00423–2022. doi:10.1183/23120541.00423-2022 PubMed PMID: 36949962; PubMed Central PMCID: PMC10026008.
23. Muscato G, Libra A, Reina C, Gili E, Fruciano M, Martella S, et al. Nintedanib for progressive pulmonary fibrosis in real-world setting: an observational study comparing outcomes with an IPF cohort. *BMC Pulm Med.* 20 gennaio 2026;26(1):73. doi:10.1186/s12890-026-04120-6 PubMed PMID: 41559703; PubMed Central PMCID: PMC12905857.
24. Boutel M, Boutou A, Pitsiou G, Garyfallos A, Dimitroulas T. Efficacy and Safety of Nintedanib in Patients with Connective Tissue Disease-Interstitial Lung Disease (CTD-ILD): A Real-World Single Center Experience. *Diagnostics.* 23 marzo 2023;13(7):1221. doi:10.3390/diagnostics13071221 PubMed PMID: 37046439; PubMed Central PMCID: PMC10093288.