



Occurrence of progressive pulmonary fibrosis and its association with survival in connective tissue disease-associated interstitial lung disease: an international retrospective cohort study

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Abstract

To describe real-world management of connective tissue disease-associated interstitial lung disease (CTD-ILD) and explore associations between progressive pulmonary fibrosis (PPF) onset and clinical outcomes. This international, retrospective cohort included adults with rheumatoid arthritis (RA), systemic sclerosis (SSc), mixed connective tissue disease, and other CTD with associated ILD. PPF was identified using INBUILD and/or ATS/ERS/JRS/ALAT criteria applied in routine care. Analyses were descriptive and exploratory; time-to-event methods assessed selected outcomes and factors associated with PPF onset. Among 357 patients (mean age 61.6 years; 58% female), SSc-ILD (31%) and RA-ILD (29%) were most common. At ILD diagnosis, 21.6% had no respiratory symptoms. During a mean follow-up of 60.5 months, 147 patients (41.2%) met the PPF criteria, at a median of 30.6 months after CTD-ILD diagnosis. Following PPF onset, the most frequently prescribed therapies were corticosteroids (72.8%), mycophenolate mofetil (52.4%), and antifibrotics (51.0%). Lung function data were available for 37.8% at diagnosis and 53.7% at year 5. PPF was associated with greater observed lung function decline compared to non-PPF patients. ILD-related hospitalizations was numerically more frequent within PPF patients (37.4% vs. 28.6%), but the difference was not statistically significant ($P=0.078$). Among patients with PPF, earlier versus later onset, defined by a subtype-specific median split, was associated with poorer observed survival ($P<0.001$). In this retrospective cohort, PPF was observed frequently in CTD-ILD patients, particularly those with SSc-ILD, and was associated with greater lung function decline and higher healthcare utilisation. Earlier PPF onset was associated with higher mortality risk, but missing lung function data, surveillance differences, time-related bias, and residual confounding limit causal interpretation. Prospective studies using harmonised PPF adjudication and time-dependent analyses are needed.

Keywords Connective tissue diseases · Interstitial lung diseases · Pulmonary fibrosis · Rheumatoid arthritis · Systemic sclerosis · Retrospective studies

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Introduction

Interstitial lung disease (ILD) encompasses more than 200 disorders characterised by diffuse inflammation and/or fibrosis of the lung parenchyma [1, 2]. Patients typically present with dyspnoea, cough, hypoxia, and declining lung function, leading to impaired exercise capacity and reduced quality of life [1, 2]. In approximately one-fourth of ILD cases, pulmonary involvement reflects an underlying connective tissue disease (CTD) [1], where ILD is a leading cause of morbidity and mortality [3, 4], contributing significantly to healthcare resource utilisation (HCRU) [5]. Timely diagnosis and treatment are therefore essential to mitigate its clinical and economic burden [6].

Diagnosis of CTD-ILD relies on recognition of disease-specific clinical, serological, and imaging features [7], yet misdiagnosis and diagnostic delays remain frequent [8]. Treatment options are limited and include immunosuppressants, antifibrotic (AF) agents, or combination therapy [6], depending on the underlying inflammatory or fibrotic ILD phenotype, and are often associated with toxicity [6]. Despite recently published clinical guidelines [9–12] and multidisciplinary approaches [13], real-world evidence shows wide variability in CTD-ILD management [14, 15]. Early detection is hindered by subclinical disease, as up to 60% of patients may exhibit ILD on high-resolution computed tomography (HRCT) despite lacking respiratory symptoms [16, 17]. In asymptomatic or mild CTD-ILD cases, treatment initiation criteria remains poorly standardised [18], delaying early intervention and worsening disease outcomes.

Between 20% and 45% of CTD-ILD patients develop progressive pulmonary fibrosis (PPF), a phenotype characterised by irreversible lung scarring and poor prognosis [7], even despite appropriate treatment [19]. PPF can develop at any stage in CTD-ILD, but detection is often delayed by 9–12 months after onset [20], largely due to its non-specific and insidious presentation, along with limited knowledge among non-ILD experts [21]. Such delays are associated with accelerated lung function deterioration and higher mortality [20, 22], highlighting the importance of early and systematic ILD monitoring to facilitate timely identification and treatment initiation.

This study aimed to characterise real-world management practices in patients with CTD-ILD, including systemic sclerosis (SSc), mixed connective tissue disease (MCTD), and other CTD-associated ILDs. Rheumatoid arthritis (RA) was included under the umbrella term CTD, in line with European Respiratory Society (ERS) and European Alliance of Associations for Rheumatology (EULAR) guidelines [10]. The study also assesses treatment patterns, monitoring strategies, and clinical outcomes and explored associations

between PPF onset and survival and ILD-related hospitalizations in a retrospective setting.

Methods

Study design

This retrospective cohort study included CTD-ILD patients from six clinical centres (4 academic) with expertise in rheumatic and respiratory diseases in Belgium, Denmark, Greece, and Portugal, using routinely collected clinical data. All participating sites had access to outpatient, inpatient, and emergency care records.

The study protocol complied with the Declaration of Helsinki. Local review details were as follows: UZ/KU Leuven (The Ethics Committee Research Leuven; Approval date, 15 April 2024; Protocol number, 1305-0043); Hippokration Hospital of Thessaloniki (Administration Office of the 4th district of Macedonia and Thrace; Approval date, 13 June 2024; Protocol number, 1305-0043); Hospital Garcia de Orta (Ethics Committee for Health; Approval date, 25 March 2024; Protocol number, 1305-0043); Unidade Local de Saúde da Região de Aveiro (The Health Ethics Committee of ULSRA; Approval date, 6 June 2024; Protocol number, 1305-0043); Centre Hospitalier Universitaire de Liège (Faculty Ethics Committee; Approval date, 24 October 2023; Protocol number: 1305-0043). Under Sect. 14 [1] of the Danish Act on the Ethical Treatment of Health Science Research Projects, the Research Ethics Committees for the Region of Southern Denmark did not require review (Confirmation date, 27 October 2023; File ref. 23/48744). Because this was a retrospective study of routinely collected data, the applicable committees waived the requirement for written informed consent. This report was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. A completed STROBE checklist is provided in Supplementary Data S3.

Study participants and data sources

Eligible patients were adults (≥ 18 years) at diagnosis with RA-ILD, SSc-ILD, MCTD-ILD, or other CTD-ILD (e.g., Sjögren disease, systemic lupus erythematosus, inflammatory myopathy/antisynthetase syndrome, and undifferentiated connective tissue disease), identified through International Classification of Diseases 9th, 10th, and 11th revision codes or predefined keywords (Supplementary Data S1). The patient identification period spanned from January 2012 to June 2022 (extended to March 2023 in Denmark).

Inclusion required sufficient data on CTD-ILD diagnosis, procedures, and treatments.

Patients were followed from CTD-ILD diagnosis until study end (December 2023; March 2024 for Denmark) or death, whichever occurred first. At diagnosis, ILD was classified as symptomatic or asymptomatic/subclinical. For this retrospective chart review, asymptomatic/subclinical ILD was defined as no documented respiratory symptoms and fibrosing changes involving no more than 10% of lung volume on HRCT, adapted from a previously published definition [23]. This simplified definition was used because the clinical and imaging variables required for more granular classifications were not consistently available. PPF was identified retrospectively using INBUILD trial [24] and/or American Thoracic Society (ATS)/ERS/Japanese Respiratory Society (JRS)/Asociación Latinoamericana de Tórax (ALAT) criteria, as documented and adjudicated during routine care at participating centres [25]. Because the two frameworks differ and key physiological and/or radiological data were incompletely captured in this retrospective cohort, some variability in PPF ascertainment across centres is possible. For exploratory stratified analyses, the subtype-specific median split of time from CTD-ILD diagnosis to PPF onset classified patients as having earlier (at or below median) or later (above the median) PPF onset. This data-driven cutoff has not been clinically validated, does not establish a distinct biological phenotype, and may be influenced by diagnostic delay, surveillance practices, and survivorship.

Outcomes

Outcomes were assessed from the CTD-ILD diagnosis to last available follow-up, including data abstraction on clinical characteristics (e.g., age, gender, body mass index), lung function (FVC%, DLco%, TLC%), treatment, progression, mortality, and ILD-related hospitalizations.

Statistical analyses

This study was primarily descriptive. A minimum sample size of 300 patients was selected to ensure sufficient precision of key estimates (Supplementary Data S2). Continuous and categorical variables were summarised descriptively. Inferential analyses (e.g., Cox regression, log-rank tests, logistic regression) were exploratory and estimated associations rather testing prespecified causal hypotheses. Analyses used complete cases; no imputation of missing data was performed. Kaplan-Meier estimates and log-rank tests were used for selected time-to-event outcomes, and Cox models assessed factors associated with time to PPF onset and selected outcomes. Mixed models for repeated

measures (MMRM) assessed longitudinal lung function and logistic regression examined mortality by timing of PPF onset among patients who developed PPF. Because logistic regression does not account for follow-up duration or censoring, the mortality estimates are exploratory and vulnerable to residual confounding. A PPF versus non-PPF survival comparison was not undertaken because classification of PPF after cohort entry would introduce immortal time bias without time-dependent modelling. Treatment comparisons were descriptive because confounding by indication and time-varying exposure were not addressed. HCRU was assessed using ILD-related hospitalisations and annualised costs derived from country-specific unit costs.

Results

Participant disposition and baseline characteristics

Among 366 identified patients, 357 patients had at least one post-diagnosis healthcare encounter and were included in the study (mean follow-up 60.5 [standard deviation (SD) 35.2] months). Mean (SD) age at CTD-ILD diagnosis was 61.6 (13.2) years, and 58% ($n=207$) were female (Table 1). The most common ILD subtypes were SSc-ILD (31.1%) and RA-ILD (29.4%), while MCTD-ILD accounted for 5.9% of cases and other CTD-ILD for 33.6%. Comorbidities were frequent (77%; Table 1), mainly arterial hypertension (51.6%), gastroesophageal reflux disease (35.3%) and pulmonary hypertension (25.1%) (data not shown). Overall, 45% of patients had a smoking history that varied according to CTD subtype ($P=0.026$). Before their CTD diagnosis, 41.2% of patients already exhibited ILD symptoms. At CTD-ILD diagnosis, 78.4% of patients presented with respiratory symptoms, most often with cough (63.3%), dyspnoea (55.2%), and fatigue (52.9%), while 21.6% were asymptomatic.

Patients who developed PPF (41.2%) had a significantly higher frequency of comorbidities compared to non-PPF patients (86.4% vs. 70.5%, respectively; $P<0.001$: Supplementary Table S1). Patients with earlier versus later onset of PPF following CTD-ILD diagnosis exhibited worse lung function at baseline ($P<0.05$: Supplementary Table S2).

Time from CTD diagnosis to ILD symptom onset, diagnosis, and treatment initiation

The onset of ILD symptoms occurred at a median of 27.1 (interquartile range [IQR]: 4.7–99.0) months following the initial CTD diagnosis. This interval was longest in RA-ILD (76.4 [27.1–149.6] months), compared to SSc-ILD (7.0 [1.0–28.2]), MCTD-ILD (24.5 [9.2–107.4]) and other

Table 1 Baseline characteristics at interstitial lung disease (ILD) diagnosis, overall and by connective tissue disease (CTD) subtype

	Overall (<i>n</i> =357)	SSc-ILD (<i>n</i> =111)	RA-ILD (<i>n</i> =105)	MCTD-ILD (<i>n</i> =21)	Other CTD-ILD (<i>n</i> =120) ^a	<i>P</i> -value
Age [years]	61.6 (13.2)	57.3 (13.5)	67.5 (9.1)	56.0 (15.8)	61.4 (13.5)	<0.001 ^d
Female sex, <i>n</i> (%)	207 (58.0%)	74 (66.7%)	58 (55.2%)	14 (66.7%)	61 (50.8%)	0.074 ^e
BMI [kg/m ²]	26.0 (4.9)	24.9 (4.1)	27.0 (5.2)	26.5 (5.3)	26.1 (5.0)	0.014 ^d
Smoking history ^b [yes], <i>n</i> (%)	162 (45%)	47 (42%)	56 (53%)	8 (38%)	51 (43%)	0.211 ^e
Comorbidities [yes], <i>n</i> (%)	275 (77%)	89 (80%)	87 (83%)	11 (52%)	88 (73%)	0.013 ^e
Time to ILD diagnosis ^c [months], median (IQR)	12.2 (0.3–70.1)	5.6 (0.7–36.1)	56.4 (12.6–122.1)	1.1 (0.5–14.7)	0.3 (0.0–20.0)	<0.001 ^f
FVC% predicted	81.1 (18.7)	82.7 (16.0)	87.8 (19.5)	73.3 (13.6)	77.2 (20.0)	0.058 ^g
DLco% predicted	54.1 (15.2)	53.1 (15.9)	56.4 (15.3)	44.3 (12.3)	55.2 (14.7)	0.325 ^d
TLC% predicted	81.3 (17.0)	81.6 (15.5)	88.3 (15.9)	69.3 (15.1)	79.4 (18.0)	0.044 ^g

Presented as mean (SD) unless otherwise indicated

BMI body mass index, *CTD* connective tissue disease, *DLco* diffusing capacity of the lungs for carbon monoxide, *FVC* forced vital capacity, *ILD* Interstitial Lung Disease, *IQR* interquartile range, *MCTD-ILD* mixed connective tissue disease associated ILD, *RA-ILD* Rheumatoid arthritis associated ILD, *SD* standard deviation, *SSc-ILD* Systemic Sclerosis associated ILD, *TLC* total lung capacity

^aIncludes Sjögren's syndrome, interstitial pneumonia with autoimmune features (IPAF), systemic lupus erythematosus (SLE), anti-synthetase syndrome-ILD, and idiopathic inflammatory myopathies (IIM). ^bPatients who, at baseline, were current or former smokers. ^cTime from underlying CTD diagnosis to ILD diagnosis. ^dKruskal-Wallis test. ^eChi-square test. ^fLog-rank test. ^gANOVA test

CTD-ILD (15.0 [0.7–91.3]) months ($P<0.001$). First ILD symptom was commonly dyspnoea, occurring in 56.7% of patients.

The median time from CTD to CTD-ILD diagnosis was 12.2 months (IQR: 0.3–70.1) (Table 1). This interval was longest in RA-ILD (56.4; 12.6–122.1 months), compared to SSc-ILD (5.6; 0.7–36.1 months), MCTD-ILD (1.1; 0.5–14.7 months), and other CTD-ILD (0.3; 0.0–20.0 months) ($P<0.001$). The interval was longer in PPF than in non-PPF patients (16.0 vs. 5.6 months), and in those with earlier versus later PPF onset (21.0 vs. 10.0 months). However, these differences were not statistically significant ($P>0.05$; Supplementary Tables S1 and S2).

Among treated patients, the median (IQR) time from CTD-ILD diagnosis to treatment initiation was 0.0 (0.0–1.4) months.

Treatment patterns

Corticosteroids were the most prescribed treatment across the study period (74.5%), followed by mycophenolate mofetil (MMF) (45.1%), methotrexate (33.3%), nintedanib (22.1%), hydroxychloroquine (18.5%), azathioprine (17.1%), and biological disease-modifying anti-rheumatic drugs (bDMARDs) such as rituximab (16.2%). Common pharmacological combinations were corticosteroids with bDMARDs (46.2%), AF regimens with nintedanib (22.1%), and biologic bDMARD monotherapy (12.6%).

At PPF onset, 22.7% of all patients were untreated for ILD. The remainder commonly received corticosteroids plus bDMARDs (31.7%), bDMARD monotherapy (21.3%), or AF (4.8%). Following PPF onset, the most frequently prescribed therapies were corticosteroids (72.8%), MMF

(52.4%), and AF (51.0%, Fig. 1). Nintedanib (95% of AF users) was prescribed for a mean (SD) treatment duration of 20.8 (19.1) months, and pirfenidone, although its use was rare (5%), was prescribed for a similar mean duration (20.6 [21.2] months). The most common treatment combinations after PPF onset included corticosteroids with AF and non-biologic DMARDs (24.5%), and corticosteroids with non-biologic DMARDs alone (20.4%). Notably, AF monotherapy was rare, used only in two patients (1.6%).

Disease monitoring

CTD-ILD was monitored primarily through pulmonary function tests (PFT, 88.5%), followed by HRCT (80.7%), laboratory exams (80.4%), and auscultation (78.4%), with mean (SD) time intervals between assessments of 31.2 (30.0), 31.4 (34.0), 31.6 (31.7), and 34.1 (32.3) months, respectively. Post-hoc analysis of the first 3 years after ILD diagnosis revealed more intensive surveillance early in the disease course: PFTs 13.7 (10.6) months, HRCT 10.9 (11.3) months, laboratory exams 12.7 (10.6) months, and auscultation 13.5 (10.6) months.

Clinical outcomes

PPF onset

During follow-up, 147 patients (41.2%) developed PPF, including 11 cases (3.1%) who already met PPF criteria at ILD diagnosis. PPF occurred most often in SSc-ILD (52.3%), followed by RA-ILD (44.8%), MCTD-ILD (38.1%), and other CTD-ILD (28.3%). Median (IQR) time from CTD-ILD diagnosis to PPF onset was 30.6 (11.8–60.5)

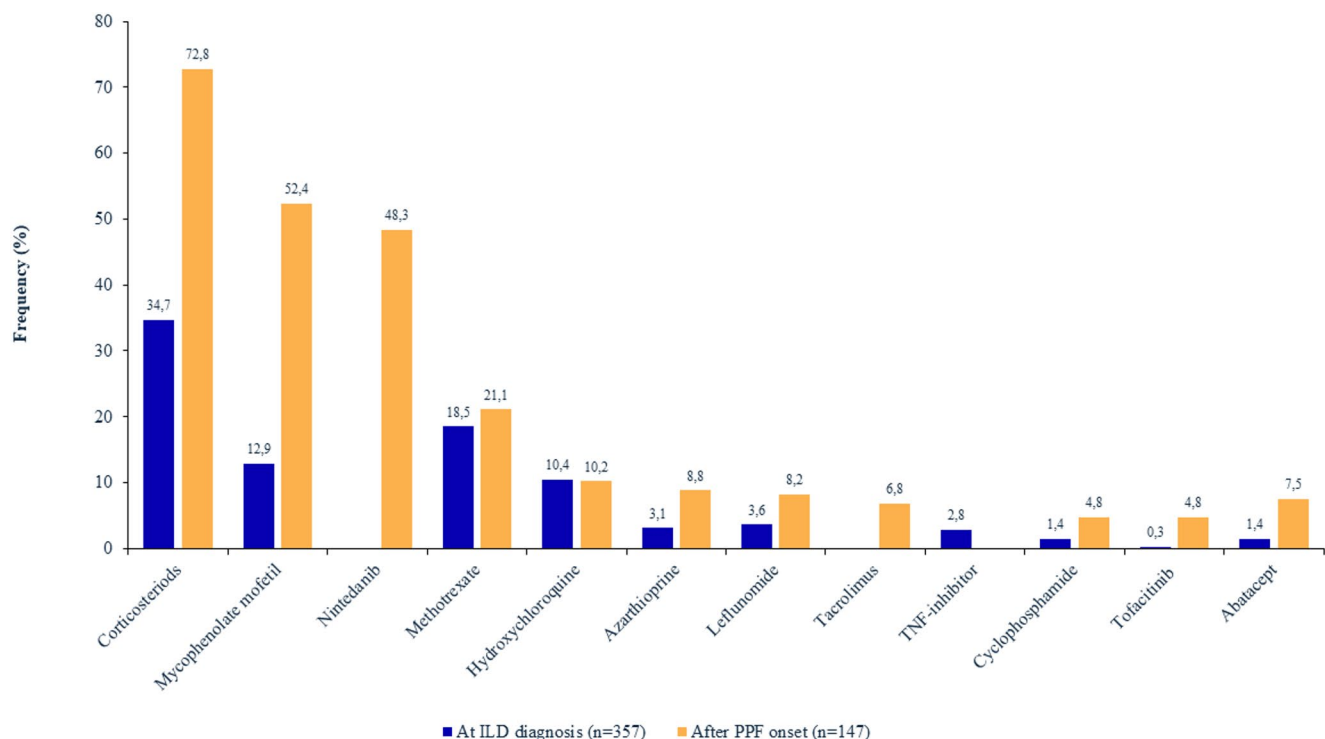


Fig. 1 Most frequently prescribed pharmacological treatments at connective tissue disease-associated interstitial lung disease (CTD-ILD) diagnosis and following onset of progressive pulmonary fibrosis (PPF). Bar chart comparing the frequency (%) of therapies used by patients with CTD-ILD at diagnosis (blue bars; $N=357$) and after onset of PPF (orange bars; $N=147$). Corticosteroids are most common at both time points, increasing from 34.7% at diagnosis to 72.8% after

PPF onset. Use of mycophenolate mofetil (12.9 to 52.4%) and nintedanib (0 to 48.3%) increased markedly after PPF onset. Methotrexate shows a modest increase (18.5 to 21.1%), while hydroxychloroquine remains similar (10.4 to 10.2%). Azathioprine (3.1 to 8.8%), leflunomide (3.6 to 8.2%), tacrolimus (0 to 6.8%), cyclophosphamide (1.4 to 4.8%), tofacitinib (0.3 to 4.8%), and abatacept (1.4 to 7.5%) are used less frequently but generally increase after PPF onset

months and differed significantly across all ILD subtypes ($P=0.010$). Time to PPF onset was longer in RA-ILD (34.4 months; 15.2–56.0) compared to SSc-ILD (22 months; 10.3–62.1), although the difference was not statistically significant ($P=0.41$). Median (IQR) times were 48.3 months (19.5–68.8) for MCTD-ILD and 32 months (12.9–65.7) for other CTD-ILD. Smoking status, baseline comorbidities, and markers of disease severity predicted faster PPF onset (Supplementary Table S3).

Lung function

Lung function data were available from 37.8% of patients at ILD diagnosis and for 53.7% at year 5. Among SSc- and RA-ILD patients, forced vital capacity predicted (FVC%) declined over time, while predicted diffusing capacity for carbon monoxide predicted (DLCO%) and total lung capacity predicted (TLC%) remained relatively stable; although differences among subtypes were not statistically significant ($P>0.05$; Supplementary Figure S1). During the study period, patients with PPF showed progressive declines across all lung function parameters, while those without PPF largely demonstrated preserved lung function (Fig. 2).

At baseline, mean FVC% predicted was slightly higher in patients who developed PPF, but declined progressively to 72.5% at year 5, in contrast to stable values in the mid-80s among non-PPF patients ($P<0.001$). DLCO% predicted was similar at baseline (around 54%) in both groups but declined to 50% by year 2 in PPF, whereas non-PPF patients remained stable around 60–63% ($P<0.001$). TLC% predicted followed the same pattern, decreasing from 80.2 to 70% in PPF versus stable values around 82–87% in non-PPF ($P<0.001$).

Disease progression

Disease progression, defined by a pulmonologist consensus as an absolute FVC decline $\geq 10\%$ over the entire follow-up period [26], occurred in approximately 26% and 13% of patients classified as PPF and non-PPF, respectively. In the overall cohort, the median time to progression was 14.3 (5.7–36.4) months. Kaplan–Meier analysis showed a shorter time to progression in PPF group compared to non-PPF ($P=0.008$; Fig. 3). Since physiological decline is also a component of the used PPF definition, this comparison is not fully independent and should be interpreted descriptively. No

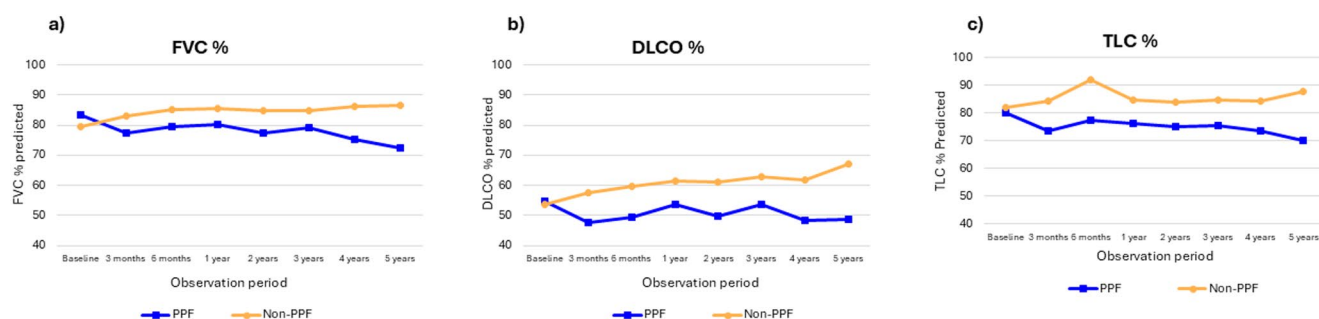


Fig. 2 Mean percent predicted lung function measures in patients with and without progressive pulmonary fibrosis (PPF). *DLCO* Diffusing Capacity of Lung for Carbon Monoxide, *FVC* Forced Vital Capacity, *ILD* Interstitial Lung Disease, *Non-PPF* patients without progressive pulmonary fibrosis, *PPF* Progressive pulmonary fibrosis, *CTD-ILD* Connective tissue disease-associated interstitial lung disease. *LC* Total Lung Capacity. This figure presents the longitudinal changes in lung function in patients with CTD-ILD, comparing patients with PPF (blue) versus non-PPF (orange). Panel (a) displays mean percent-

predicted forced vital capacity (FVC%), (b) mean percent-predicted diffusing capacity for carbon monoxide DLCO%, and (c) mean percent-predicted total lung capacity (TLC%), measured at baseline, 3 months, 6 months, 1 year, and annually up to 5 years. Across all panels, patients with PPF showed similar lung function values than non-PPF patients at baseline and a general decline over time, whereas non-PPF patients maintained more stable and even slightly improved FVC%, DLCO% and TLC% predicted measurements overtime

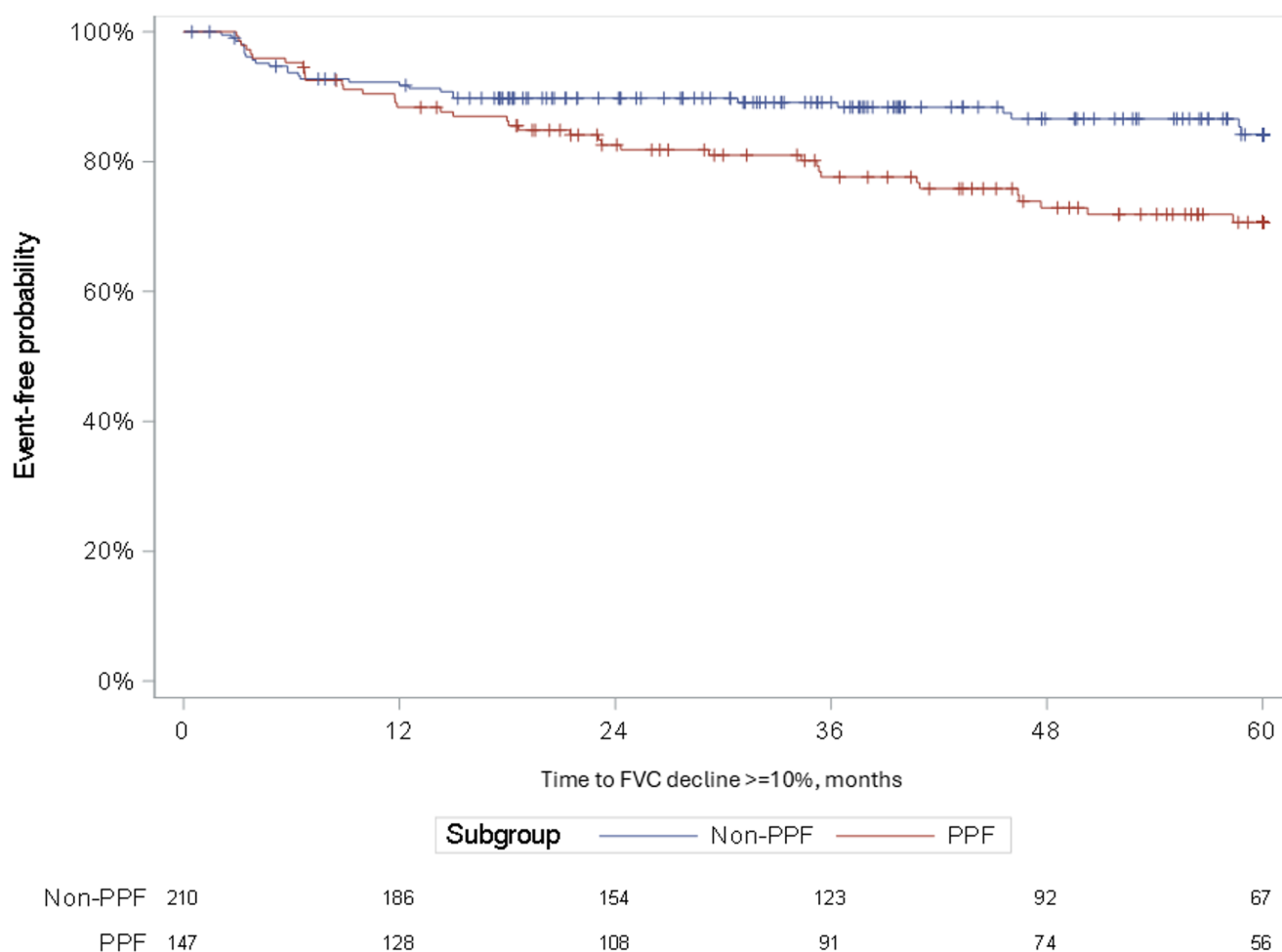


Fig. 3 Time to disease progression ($\geq 10\%$ FVC decline) in CTD-ILD patients with and without progressive pulmonary fibrosis (PPF). *FVC* Forced vital capacity, *non-PPF* patients without progressive pulmonary fibrosis, *PPF* Progressive pulmonary fibrosis, *CTD-ILD* Connective tissue disease-associated interstitial lung disease. In this Kaplan–Meier analysis of time to forced vital capacity (FVC) decline

of $\geq 10\%$ over 60 months (5 years) patients without PPF (solid blue line) exhibited a higher event-free probability (no FVC decline of $\geq 10\%$) throughout follow-up, remaining above approximately 85% at 60 months. patients with PPF (dashed red line) showed a steady decline in event-free probability over time, decreasing to around 70% by 60 months. Censoring is indicated by the vertical tic mark

significant difference was observed between RA-ILD (15.0 months) and SSc-ILD (11.8 months) patients ($P = 0.81$).

Overall survival, and survival by timing of PPF onset

A total of 85 patients (23.8%) died during follow-up, with a median (IQR) time to death of 37.7 (20.9–60.8) months after CTD-ILD diagnosis; 32 deaths (37.6%) were attributed to ILD. Overall survival did not differ significantly by CTD subtype ($P = 0.969$). A Kaplan-Meier comparison of PPF and non-PPF patients was not performed because patients had to survive long enough after cohort entry to meet PPF criteria, creating immortal time bias if PPF were treated as baseline exposure. Among the 147 patients who developed PPF, 38 deaths (25.8%) occurred: 26 in the earlier and 12 in the later PPF group (Table 2). Earlier PPF onset was associated with poorer overall survival, compared with later onset ($P < 0.001$; Fig. 4). In an exploratory logistic model adjusted only for antifibrotic use, later PPF onset was associated with lower odds of death (odds ratio 0.34 [95% CI: 0.15–0.75]; Table 2). This model did not account for follow-up time or censoring and did not adjust for all major prognostic factors and should therefore not be interpreted as causal.

ILD-related hospitalizations

Approximately one-third of patients (32.2%) experienced ≥ 1 ILD-related hospitalization. The proportion of hospitalized patients was higher in the PPF group (37.4%) compared to non-PPF group (28.6%), although the difference did not reach statistical significance ($P = 0.078$). The mean number of hospitalizations per patient was also higher in PPF (mean 2.2; SD 1.75) compared to non-PPF (mean 1.7; SD 1.47).

Table 2 Logistic regression of earlier versus later PPF detection on overall survival, controlling for antifibrotic treatment

Death frequency observed during the study; n (%)	Earlier PPF $N = 73$	Later PPF $N = 74$	Overall $N = 147$
Patients that survived	47 (64.4%)	62 (83.8%)	109 (74.1%)
Patients that died (event)	26 (35.6%)	12 (16.2%)	38 (25.9%)
Logistic regression model	OR	(95% CI)	P -value
PPF onset (Later versus Earlier)	0.34	(0.156–0.758)	0.008
Antifibrotic treatment (Yes versus No)	1.13	(0.525–2.423)	0.758

The median time from CTD-ILD diagnosis to PPF onset by subtype (RA-ILD: 34 months; SSc-ILD: 22 months, MCTD-ILD 48.3 months, and Other CTD-ILD: 32 months) was used as the cut-off point to categorise patients into earlier ($\leq$ median time) versus later ($>$ median time) PPF onset groups

CI Confidence Interval, CTD-ILD Connective tissue disease–associated Interstitial Lung Disease, OR Odds Ratio, PPF Progressive Pulmonary Fibrosis

The median length of stay was 13.0 days (IQR: 4.0–20.0) in PPF, and 10 days (4.0–22.5) in non-PPF ($P = 0.53$). No statistically significant difference was observed in annual costs per patient per year (mean: €2300.0; SD 7533.1 vs. €1631.7; SD 5724.1, respectively: $P = 0.074$).

Discussion

This international European retrospective cohort study described real-world practices in CTD-ILD diagnosis, monitoring, treatment, and outcomes with an exploratory focus on the timing of PPF onset on survival and health-care burden. Compared with previous literature, this study integrated routine clinical care data on diagnostic pathways, monitoring practices, treatment patterns, PPF onset, and longitudinal outcomes across a broad CTD-ILD population from six centres across different countries. It also explores the timing of PPF onset and its association with clinical outcomes. However, the non-standardised PPF ascertainment and incomplete longitudinal data require cautious interpretation.

At the time of ILD diagnosis, most patients presented with non-specific symptoms such as cough or dyspnoea, whereas 21.6% were asymptomatic, factors potentially leading to delayed diagnosis, as reported in previous research [14]. The presence of non-specific or absent symptoms aligns with the recent American Thoracic Society statement [27], which recommends systematic ILD screening in all patients with CTDs at increased ILD risk to identify asymptomatic or early CTD-ILD and improve disease management. The ERS/EULAR guidelines [10] advise more selective screening based on additional risk factors for specific CTD-ILDs. Remarkably, in the current study, 41.2% of patients exhibited ILD symptoms before receiving a CTD diagnosis further complicating CTD-ILD diagnosis and treatment initiation. Notably, the interval from CTD diagnosis to ILD symptom onset and diagnosis was longest in RA-ILD, likely reflecting its insidious and subtle clinical presentation [28] compared to other CTD subtypes. This may contribute to diagnostic delays in routine practice, particularly in the absence of standardized screening guidelines for RA-ILD detection. Furthermore, while the differences were not statistically significant, a longer interval was observed in PPF compared to non-PPF patients, and among those with earlier rather than later PPF onset. Taken together with the previously noted subclinical ILD presentation, this suggests that patients with a longer interval between CTD and ILD diagnosis may have experienced greater disease progression and deterioration by the time PPF was identified, leading to an earlier detection of PPF once ILD was diagnosed.

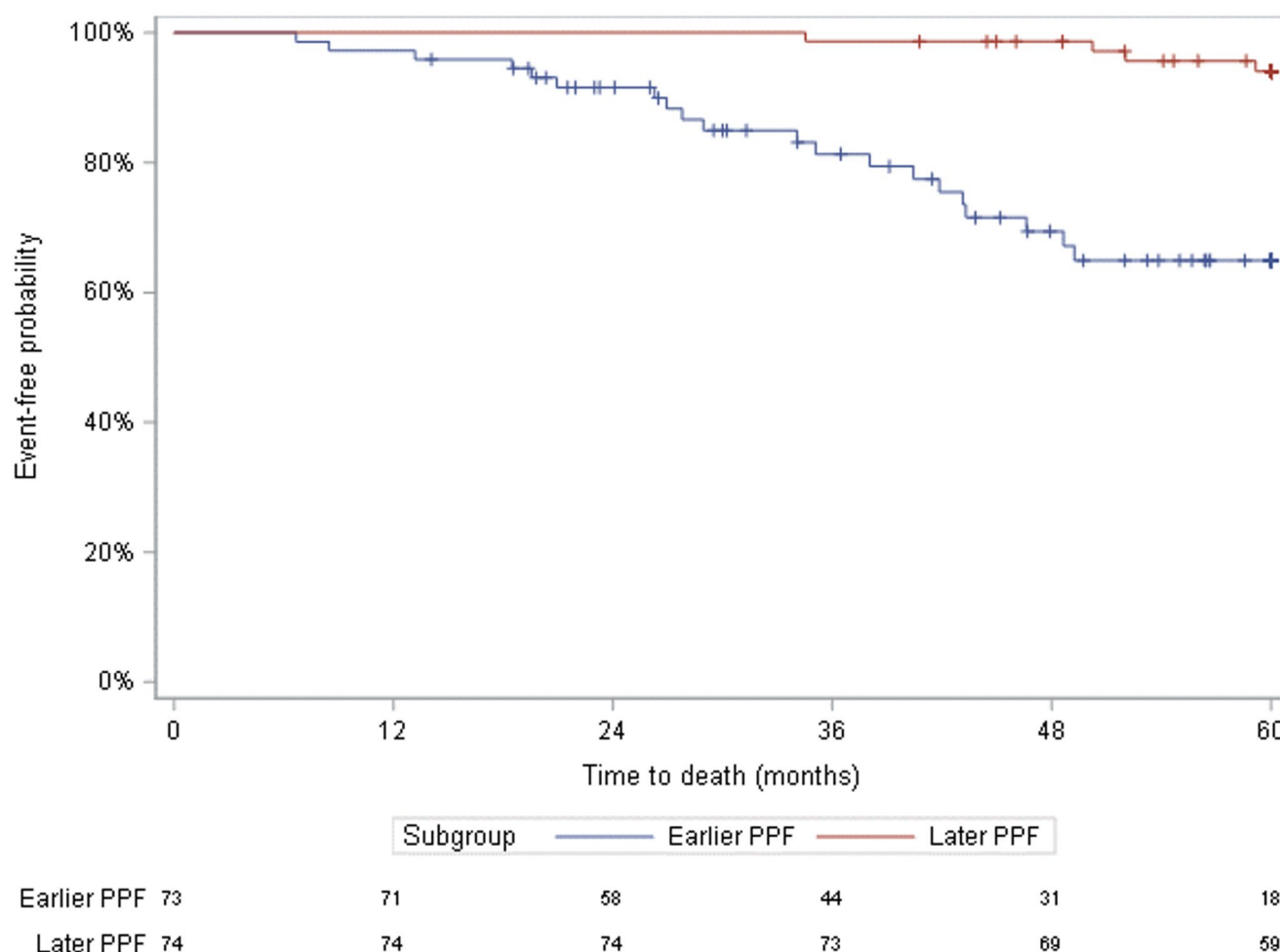


Fig. 4 Time to death (in months) in CTD-ILD patients with earlier versus later onset progressive pulmonary fibrosis (PPF). *PPF* Progressive pulmonary fibrosis, *CTD-ILD* Connective tissue disease–associated interstitial lung disease. In this Kaplan–Meier analysis over 60 months (5 years), patients with earlier PPF onset (solid blue line) exhibited a steady decline in survival over time to approximately 65% by 60 months. In contrast, patients with later PPF onset (dashed red

line) maintained a high event-free probability throughout follow-up, remaining close to 95% at 60 months. Censoring is indicated by the vertical tic mark. The median time from CTD-ILD diagnosis to PPF onset by subtype (RA-ILD: 34 months; SSc-ILD: 22 months, MCTD-ILD 48.3 months, and Other CTD-ILD: 32 months) was used as the cut-off point to categorise patients into earlier ($\leq$ median time) versus later ($>$ median time) PPF onset groups

Monitoring strategies primarily relied on PFTs and HRCT, with similar median PFT intervals across all CTD-ILD subtypes (data not shown), in contrast with current recommendations that advise more frequent PFTs over an extended period in SSc-ILD due to its higher risk of early and aggressive disease [9, 12]. For all CTD-ILDs, more intensive surveillance was identified during the first years post-diagnosis, as recommended for patients with unstable disease [29]. Lung function decline was more pronounced in SSc-ILD, confirming its typically more aggressive course [30, 31], with earlier and more extensive fibrotic involvement. PPF occurred in 41% of patients, with a predominance among those with SSc-ILD and is consistent with previous observations [32, 33]. Although not statistically significant, PPF was detected earlier in SSc-ILD than in RA-ILD, suggesting a more aggressive fibrotic trajectory

following ILD diagnosis and/or higher awareness among pulmonologist and rheumatologists managing SSc patients. However, other reports have shown higher progression rates in RA-ILD compared to SSc-ILD highlighting the disease heterogeneity [34]. Concurrent with previous observations, PPF patients exhibited steady and significant declines in predicted FVC, DLCO, and TLC, whereas lung function remained largely preserved in non-PPF patients [35].

In exploratory analyses, shorter time from CTD-ILD diagnosis to PPF onset was associated with poorer survival, even after adjusting for antifibrotic treatment. This association should not be interpreted as causal; PPF onset timing in a retrospective cohort can be influenced by diagnostic delay (e.g., time from symptom onset to ILD recognition), surveillance intensity, and survivorship/immortal time biases. Nevertheless, our findings are consistent with prior real-world

cohorts suggesting heterogeneity in progression trajectories across fibrosing ILDs [36, 37]. Rather than defining distinct biological “early” versus “late” phenotypes, our results suggest that patients who meet PPF criteria soon after documented CTD-ILD diagnosis may represent a clinically high-risk group, potentially reflecting a more progressive disease phenotype and warranting careful monitoring and timely treatment optimisation, pending confirmation in prospective studies with harmonised PPF adjudication and time-dependent modelling. While “slow” and “rapid” progressors had been defined in idiopathic pulmonary fibrosis (IPF) [38], such phenotypic differentiation has not yet been established in non-IPF PPFs.

Finally, number of hospitalisations, length of stay, and annualised costs were numerically higher among patients with PPF. However, between-group differences in the proportion hospitalised and annual costs were not statistically significant. These findings should therefore be interpreted cautiously, particularly in light of the limited sample size, variability in follow-up duration, and potential confounding inherent to the retrospective study design. Nevertheless, the observed trends are consistent with a greater clinical burden among patients with PPF and highlight the importance of timely identification and management of patients at risk of disease progression.

This retrospective, multicentre study has important limitations. PPF ascertainment was not standardised; centres used INBUILD and/or ATS/ERS/JRS/ALAT criteria within routine care, and the component data needed to reconstruct a single harmonised definition was not consistently available. This created potential misclassification and limits comparability across centres. Pulmonary function data were available for 37.8% of patients at ILD diagnosis and 53.7% at year 5; HRCT and pulmonary function assessment were not available at all sites or time points, and surveillance intervals varied. Complete-case analyses may therefore be affected by selection bias if patients with measurements differed systematically from those without them. Furthermore, the earlier versus later PPF groups were based on subtype-specific median cutoff that has not been clinically validated. Analyses of PPF timing are vulnerable to survivorship and immortal time biases, and logistic regression for mortality did not account for follow-up time or censoring and adjusted only for antifibrotic use. Comparisons of lung function decline between PPF and non-PPF groups are partly circular because physiological decline contributes to PPF classification. Stratification of lung function outcomes within the PPF group by CTD-ILD subtype was not feasible due to data limitations, restricting further subgroup analyses. The pooled “other CTD-ILD” is clinically heterogeneous and should be interpreted with caution. It is also important to note during the identification period (2012–2022), nintedanib was

approved by the European Medicines Agency (EMA) in March 2020 for the treatment of PPF, creating potential calendar-time bias. Nonetheless, this large, international study provides valuable real-world insights into CTD-ILD management. Despite advances, lung function continued to decline, and over 40% of patients developed PPF, leading to early death in almost one fourth within a median of approximately 3 years from ILD diagnosis.

In summary, PPF was observed in 41.2% of this CTD-ILD cohort, predominantly among those with SSc-ILD, and was associated with greater lung function decline and, increased hospitalizations. Among patients who developed PPF, earlier documented onset identified a group with poorer observed survival. Because ascertainment was heterogeneous, lung function data was partially incomplete, and the analyses were susceptible to time-related bias and residual confounding, these findings should be considered as hypotheses-generating. Delayed recognition of ILD remains as a major challenge. Implementing standardized monitoring protocols and earlier identification of patients at risk for PPF are crucial to alleviate morbidity and mortality in CTD-ILD. Further longitudinal studies are warranted to validate early PPF phenotypes and inform personalized management strategies aimed at reducing the clinical and economic burden of CTD-ILD.

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Author contributions JG: conceptualization, data curation, formal analysis, methodology, writing—original draft, writing—review and editing. XMT: conceptualization, data curation, formal analysis, methodology, writing—original draft, writing—review and editing. TD: conceptualization, data curation, formal analysis, methodology, writing—original draft, writing—review and editing. JRD: conceptualization, data curation, formal analysis, methodology, writing—original draft, writing—review and editing. SP: data curation, formal analysis, writing—original draft, writing—review and editing. LS: conceptualization, formal analysis, methodology, project administration, writing—original draft, writing—review and editing. KN: conceptualization, data curation, formal analysis, methodology, writing—original draft, writing—review and editing. MHH: conceptualization, data curation, formal analysis, methodology, writing—original draft, writing—review and editing. ACD: conceptualization, data curation, formal analysis, methodology, writing—original draft, writing—review and editing. ARLAP: conceptualization, data curation, formal analysis, methodology, writing—original draft, writing—review and editing. WAW: conceptualization, data curation, formal analysis, methodology, writing—original draft, writing—review and editing.

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Data availability The data underlying this article cannot be shared publicly or the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

Declarations

Conflict of interest JG reports personal fees for advisory board, work, and lectures from Boehringer Ingelheim, Janssen, SMB, GSK, Pfizer, Daichii-Sankyo, Roche, AstraZeneca, Aquilon, Voliyon, Oncoradiomics, and Chiesi, non-financial support for meeting attendance from AstraZeneca, Chiesi, MSD, Roche, Boehringer Ingelheim, and Janssen. XMT, KN, and MHH are employees of Boehringer Ingelheim B.V. TD has received fees for lectures and participating in advisory board meetings outside this study from Abbvie, Amgen, Boehringer Ingelheim, Elpen, Genesis Pharma, GlaxoSmithKline, Johnson-Johnson, MSD, Lilly, Pfizer, Sobi and UCB. JRD has received outside this study fees for teaching lectures, advisory board consultancy honoraria, and travel grants from Boehringer Ingelheim and advisory board consultancy honoraria from AstraZeneca. SP has received outside this study speaker fees from Boehringer Ingelheim. LS is an employee of TFS HealthScience, ACD has received fees for lectures and participating in advisory board meetings outside this study from Boehringer Ingelheim. ARLAP has declared no conflict of interest. WAW reports grants and fees from Boehringer Ingelheim, Hoffman la Roche, Galapagos and Sanofi, outside the submitted work, paid to his institution.

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