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Progressive Fibrosing Interstitial Lung Diseases: Prevalence and Characterization in Two Italian Referral Centers

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Keywords
Progressive fibrosing · Interstitial lung diseases · Treatment · Mortality · Anti-fibrotic agents

Abstract
Background: The prevalence and natural history of progressive fibrosing interstitial lung diseases (PF-ILDs), and their response to commonly used treatments in real life are largely unknown. ***Objectives:*** The aim of the study was to describe the prevalence, clinical characteristics, management, and outcomes of PF-ILD patients attending 2 Italian referral centers (San Gerardo Hospital, Monza, and San Giuseppe Hospital, Milan) from January 1, 2011, to July 31, 2019. ***Methods:*** From a cohort of non-idiopathic pulmonary fibrosis fibrosing ILD patients with at least 2-year follow-up, we selected only those with progressive disease, defined as per the INBUILD trial, collecting their demographical, clinical, and functional data. ***Results:*** Out of the 245 fibrosing ILD patients, 75 (31%) were classified as PF-ILDs (median age 66 years, 60% males), most frequently idiopathic non-specific interstitial pneumonia (28%), followed by connective tissue disease-associated ILD (20%), chronic hypersensitivity pneumonitis, and sarcoidosis (17% each). Most patients (81%) were categorized as PF-ILDs because of forced vital capacity (FVC) decline ≥10%, while 19% experienced a marginal FVC decline (between 5 and 10%) associated with worsening respiratory symptoms or increasing extent of fibrotic changes on high-resolution computed tomography. Disease progression occurred after a median of 18 months from ILD diagnosis. The vast majority (93%) of PF-ILD patients received prednisolone, alone (40%) or associated with steroid-sparing agents (52%), and 35% of treated patients developed treatment-related adverse events. After ILD progression, the median survival was 3 (interquartile range (IQR) 2–5) years, with a 2- and 3-year mortality rate of 4 and 20%, respectively. ***Conclusions:*** In a real-life setting, approximately one-third of the fibrosing ILD patients showed a progressive course despite treatment. Studies aimed to better phenotype this subgroup of patients are needed.

Introduction

Interstitial lung diseases (ILDs) comprise a heterogeneous group of more than 200 parenchymal lung disorders, which may be idiopathic, related to systemic dis-

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eases or environmental exposures. Besides idiopathic pulmonary fibrosis (IPF), it is well known that other fibrosing ILDs may develop a progressive phenotype, characterized by worsening respiratory symptoms and quality of life, declining lung function, and, ultimately, early mortality despite corticosteroid and immunosuppressive treatment [1, 2]. The progressive fibrosing phenotype may be particularly common in some types of ILDs, such as rheumatoid arthritis (RA)-associated ILD where it can be observed in up to 52% of cases [3]. However, the current prevalence and natural history of progressive fibrosing ILDs (PF-ILDs) are still largely unknown, as well as the therapeutic response to currently utilized immunosuppressive treatments [4, 5].

On the basis of the clinical and pathophysiological similarities between IPF and other PF-ILDs, it has been postulated that such disorders with a progressive phenotype could respond to anti-fibrotic agents, nintedanib and pirfenidone, already approved for IPF treatment [6, 7]. Recently, a phase III, randomized-controlled trial (RCT) proved the efficacy of nintedanib in lowering the annual rate of decline of forced vital capacity (FVC) over 52 weeks in various PF-ILDs [8]. Furthermore, a phase II RCT suggested the efficacy of pirfenidone in reducing the mean change in FVC at 24 weeks from baseline in unclassifiable PF-ILD patients [9].

Nevertheless, there is no consensus about how to clearly define disease progression in patients with non-IPF ILDs, and these criteria used to define PF-ILDs still have to be validated in real-life cohorts [4]. The aim of the present study was to describe the prevalence, clinical characteristics, management, and outcomes of patients with non-IPF PF-ILDs attending the ILD clinic of 2 Italian referral centers, in a real-life setting.

Methods

Study Design and Patients

The study cohort included all patients with a diagnosis of non-IPF fibrosing ILD attending the ILD clinic of 2 Italian ILD tertiary referral centers (San Gerardo Hospital, Monza, and San Giuseppe Hospital, Milan) from January 1, 2011, to July 31, 2019, with at least a 2-year follow-up. Fibrosing ILDs were defined by the presence of reticular abnormalities with traction bronchiectasis with or without honeycombing detected by high-resolution computed tomography (HRCT) performed within 12 months from the first visit. Patients diagnosed with IPF and radiation-induced lung fibrosis were excluded, and those with amyloidosis, bronchiolitis obliterans organizing pneumonia, hemosiderosis, alveolar proteinosis, and lymphangioleiomyomatosis were excluded because they were not commonly characterized by a fibrosing course.

From this cohort of non-IPF fibrosing ILDs, we selected patients with a progressive disease, defined, as per the INBUILD trial[8], by the fulfillment of at least one of the following: criteria for ILD progression over a period of 2 years: (a) FVC decline ≥10%; (b) FVC decline >5 and <10% associated with worsening respiratory symptoms or associated with increasing extent of fibrotic changes on HRCT; (c) worsening of respiratory symptoms and an increased extent of fibrosis on HRCT; (d) after the exclusion of other causes that misinterpreted clinical or radiological worsening, that is, pulmonary embolism, infection, and decompensated heart failure [8].

Final ILD diagnoses were made by an expert multidisciplinary team, including an expert pulmonologist, a radiologist, and a pathologist (the latter when appropriated) on the basis of clinical presentation, radiological findings, and available histopathological features. Lung biopsies (transbronchial or video-assisted thoracic surgery) were performed in 10% of the patients with potentially PF-ILDs during the diagnostic process. Idiopathic nonspecific interstitial pneumonia (iNSIP), chronic hypersensitivity pneumonitis (CHP), acute interstitial pneumonia, sarcoidosis, and fibrosing Langerhans cell histiocytosis were diagnosed by existing criteria [10–13]. Interstitial pneumonia with autoimmune features was diagnosed by the recent consensus statement [14]. Final connective tissue disease-associated ILD (CTD-ILD) diagnoses were made or confirmed by formal rheumatology consultation based on standardized criteria. Combined pulmonary fibrosis and emphysema was defined as the coexistence in the same patient of radiological upper lobe emphysema and lower lobe lung fibrosis [15]. Unclassifiable ILD was defined as nonspecific or conflicting clinical, radiological, or histopathological findings or as unclassified or unclassifiable clinical/radiological conditions in cases where the patient was unable or unwilling to undergo diagnostic procedures [10]. The study was approved by the local institutional review board and did not require patients' informed consent due to the retrospective design.

Data Collection

A clinical research associate identified patients who met the eligibility criteria for fibrosing ILD and disease progression in medical files at the 2 ILD referral centers and extracted the data from the patients' medical files into an anonymized database. Baseline data included age at the time of ILD diagnosis, gender, smoking history, exposures, familiar history of ILD, comorbidities, autoimmune serologies, and serum precipitating antibodies against various microbial and avian antigens. Autoimmune serologies, including antinuclear antibodies, extractable nuclear antigens, antineutrophil cytoplasmic antibodies (ANCA), rheumatoid factor, and anti-cyclic citrullinated peptide (anti-CCP), were routinely performed to rule out CTDs. Serum precipitating antibodies tested in the clinical and/or radiological suspicion of hypersensitivity pneumonitis-included Penicillum Notatum, Aspergillus Fumigatus, Alternaria Alternata, Aspergillus Niger, Micropolyspora Faeni, and pigeons' excrements. Baseline HRCTs were revised and classified into usual interstitial pneumonia (UIP) or non-UIP pattern [16, 17]. UIP-pattern included both typical and probable UIP.

Pulmonary function tests (PFTs) performed during patients' follow-up, including FVC and diffusing lung capacity for carbon monoxide (DLCO), as absolute and percentage of predicted value, were collated at 6-month intervals from ILD diagnosis, if available.

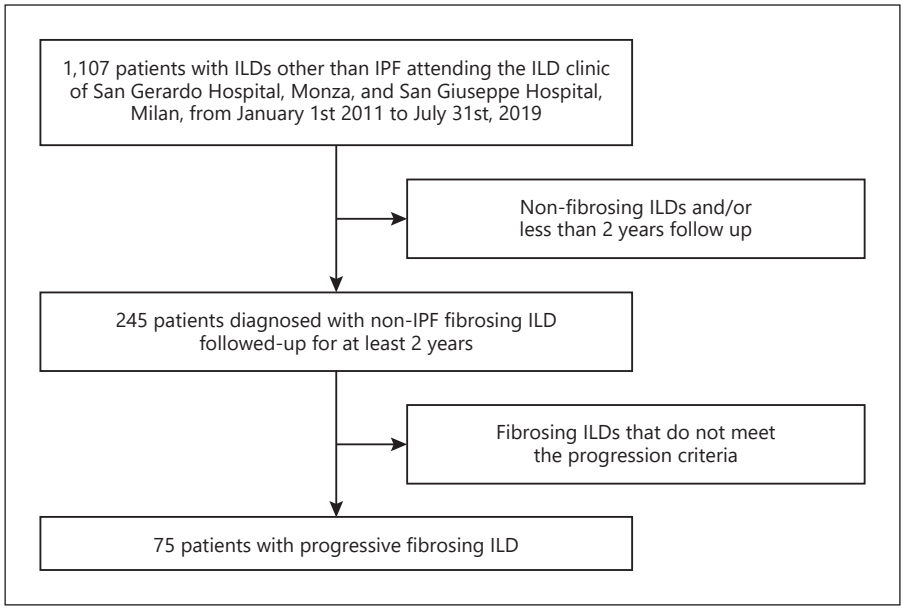

Fig. 1. Patients' selection flowchart. ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

Data about treatment (steroids and/or other immunosuppressant agents), related side effects, hospitalizations, and acute exacerbations were also collected. Systemic steroid starting dose was 0.5–0.75 mg/kg, except in patients in whom high doses were contraindicated (e.g., decompensated diabetes), which was subsequently slowly tapered according to the clinical and functional response. Survival time was defined in years from the date of ILD diagnosis to the date of death or of lung transplant or health-care administrative database search date, July 31, 2019 (assumed as censoring date), if assumed still alive.

Statistical Analysis

Data are presented as median and interquartile range (IQR) if continuous, or as frequencies and percentages if categorical. Time to death or lung transplantation was estimated by Kaplan-Meier curve. Statistical analysis was performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA). Two-sided p values <0.05 were considered statistically significant.

Results

Prevalence of Non-IPF PF-ILD Patients

Of the 245 patients diagnosed with non-IPF fibrosing ILD followed up for at least 2 years, 75 patients (54 attending the ILD clinic of the San Gerardo Hospital, Monza, and 21 from the ILD clinic of the San Giuseppe Hospital, Milan) were classified as having progressive disease (Fig. 1). The most frequently diagnosed ILDs were iNSIP, followed by CTD-ILD (in 4 cases undifferentiated connective tissue diseases, four RA, 3 systemic sclerosis, 2 Sjogren's syndromes, and 2 anti-synthetase syndromes), CHP, and sarcoidosis (Table 1).

Regarding the criteria for defining ILD progression over the 2-year follow-up period, 61 patients (81%) were classified as having a PF-ILD because of FVC decline ≥10%; 14 (19%) experienced an FVC decline >5 and <10% associated with worsening respiratory symptoms or increasing extent of fibrotic changes on HRCT; nobody experienced only worsening respiratory symptoms and increased extent of fibrosis on HRCT without functional decline. Disease progression occurred after a median of 18 (IQR 7–47) months after ILD diagnosis.

Clinical Characteristics

Patients with PF-ILD had a median age of 66 (IQR 58–71) years, were more commonly male (45, 60%), and were active or former smokers (41, 55%). Seven patients (9%) reported a familial history for ILD. Positive exposure history to risk factors known to be responsible for ILD occurrence was reported by 32% of subjects. These risk factors included molds, bird feathers, powders (minerals, glass, and wood), welding fumes, paints, dyes, and glues. Only 40% of patients were assessed with serum precipitating antibodies for hypersensitivity pneumonitis, which were positive in 40% of cases. Autoimmune screening was performed in 63% of cases with positive antinuclear antibodies in 21 patients (45%), positive rheumatoid factor in 8 patients (17%), positive extractable nuclear antigen antibodies in 4 patients (9%), and positive antineutrophil cytoplasmic antibodies in 3 patients (6%).

At the time of ILD diagnosis, the HRCT showed a UIP pattern in 16 cases (21%). Only in 23% of cases, the ILD di-

Table 1. Prevalence of PF-ILD among the cohort of fibrosing ILD

Fibrosing ILD	Whole cohort of fibrosing ILD patients (N = 245), n (%)	PF-ILD (N = 75), n (% of the whole cohort)	% of progressive disease among patients diagnosed with a specific ILD
iNSIP	90 (37)	21 (28)	23
CTD-ILD	47 (19)	15 (20)	32
Stage IV sarcoidosis	32 (13)	13 (17)	41
CHP	31 (13)	13 (17)	40
Unclassifiable ILD	22 (9)	3 (4)	14
IPAF	9 (4)	2 (3)	22
CPFE	5 (2)	4 (6)	80
Pneumoconiosis	4 (2)	0	0
Langerhans cell histiocytosis	3 (1)	2 (3)	67
AIP	1 (0.4)	1 (1)	100
NSIP/OP	1 (0.4)	1 (1)	100

AIP, acute interstitial pneumonia; CHP, chronic hypersensitivity pneumonitis; CPFE, combined pulmonary fibrosis and emphysema; CTD-ILD, connective tissue disease-asssociated ILD; iNSIP, idiopathic nonspecific interstitial pneumonia; IPAF, interstitial pneumonia with autoimmune features; NSIP/OP, overlap nonspecific interstitial pneumonia and organizing pneumonia; PF, progressive fibrosing.

Table 2. PFTs at the time of ILD diagnosis and in the first 2-year follow-up in the cohort of PF-ILDs (N = 75)

Time, months	FVC (L), median (IQR)	FVC % pred, median (IQR)	DLCO % pred, median (IQR)
At ILD diagnosis	2.52 (1.72–3.10)	84 (68–95)	54 (39–69)
6	2.37 (1.66–2.96)	81 (69–90)	51 (46–71)
12	2.37 (1.67–2.85)	79 (68–96)	48 (36–64)
18	2.37 (1.61–2.87)	80 (65–90)	46 (32–57)
24	2.30 (1.60–2.81)	76 (63–90)	42 (26–55)

DLCO, diffusing lung capacity for carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; IQR, interquartile range; PFTs, pulmonary function tests.

Table 3. PFTs during the 2-year period of functional worsening that defined the "progressive fibrosing" phenotype

Time	FVC (L), median (IQR)	FVC % pred, median (IQR)	DLCO % pred, median (IQR)
Time 0	2.53 (1.64–2.92)	83 (69–97)	49 (37–61)
6 months	2.29 (1.58–2.76)	80 (64–90)	49 (38–57)
12 months	2.25 (1.49–2.73)	78 (63–91)	44 (30–58)
18 months	2.12 (1.41–2.78)	75 (58–85)	39 (25–55)
24 months	1.90 (1.33–2.53)	68 (53–82)	37 (20–53)

DLCO, diffusing lung capacity for carbon monoxide; FVC, forced vital capacity; PFTs, pulmonary function tests; IQR, interquartile range.

agnosis was achieved through formal multidisciplinary discussion; the remaining cases were diagnosed through consensus between the respiratory physician and the radiologist.

The majority of patients (51%) had cardiovascular comorbidities, while nobody was diagnosed with lung cancer before ILD diagnosis or during the follow-up period. PFTs in the first 2 years after ILD diagnosis are shown in Table 2. Since disease progression occurred at a different time during patients' follow-up, the PFTs collected during the 2-year period of functional worsening, which is a fundamental part of the definition of PF-ILDs, are reported in Table 3.

Treatment

Pharmacological treatment was given to the vast majority of PF-ILD patients directly after diagnosis (70, 93%), whereas only 5 patients (7%) did not receive any therapy. The most common treatment was prednisone, alone (30 patients, 40%) or in an association with other immunosuppressant steroid-sparing agents (39, 52%); 1 patient (3%) was treated with steroid-sparing immunosuppressants alone.

The median duration of prednisone treatment was 36 [IQR 24–77] months. The most commonly used steroid-sparing agent was azathioprine (20 patients, 51%), fol-

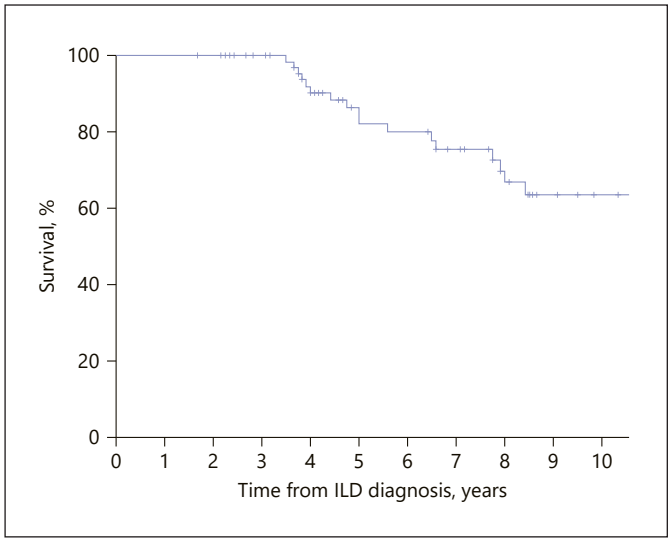

Fig. 2. Survival of non-IPF PF-ILDs from time of ILD diagnosis (Kaplan-Meier curve). ILD, interstitial lung disease; PF, progressive fibrosing; non-IPF, non-idiopathic pulmonary fibrosis.

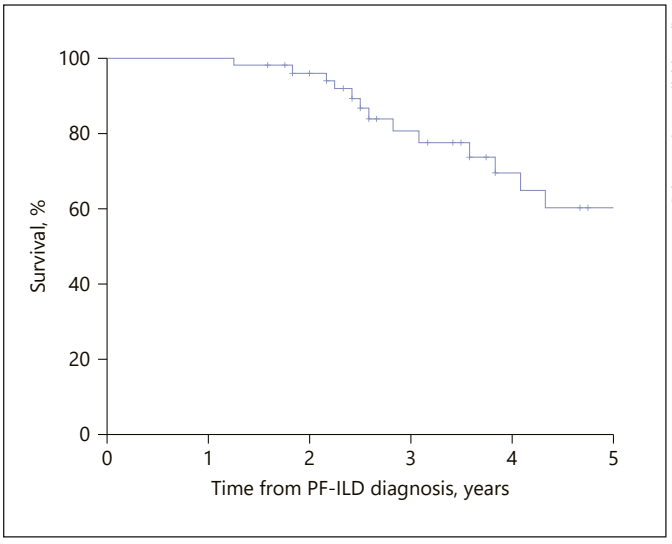

Fig. 3. Survival from PF-ILD diagnosis (Kaplan-Meier curve). PF-ILD, progressive fibrosing interstitial lung disease.

lowed by cyclophosphamide (10 patients, 26%), mycophenolate mofetil (7 patients, 18%), hydroxychloroquine (7 patients, 18%), methotrexate (7 patients, 18%), rituximab (2 patients, 5%), cyclosporine (1 patient, 3%), and tacrolimus (1 patient, 3%).

Of note, 2 patients were enrolled in the RCTs on the efficacy of anti-fibrosing agents in PF-ILDs and received nintedanib and pirfenidone in 1 case each. Of the 69 subjects treated with prednisone, 18 patients (24%) experienced steroid-related side effects. The most frequently reported adverse events were osteoporosis (10 patients, 14%), steroid-induced diabetes mellitus or difficult glycemic control in patients with an already diagnosed diabetes (4 patients, 6%), and cataract, weight gain, and psychosis in 1 case each.

Out of the 40 patients who received immunosuppressant agents, 11 patients (28%) developed treatment-related adverse events, such as hepatotoxicity (4 patients, 10%), gastrointestinal side effects (2 patients, 5%), recurrent infections (2 patients, 5%), and bone marrow cytotoxicity (2 patients, 5%). Thirty patients (40%) were on supplemental oxygen therapy, and in all of them, oxygen therapy was started after disease progression to "progressive fibrosing" phenotype. Six patients (8%) in the whole cohort were evaluated for lung transplantation, also in these cases after disease progression.

Outcomes

During the follow-up period of at least 2 years, there were 19 deaths (25%) and no lung transplantation. Among the 19 deaths, the underlying diagnoses were 5 CHP, 5 CTD-ILDs, 4 iNSIP, 2 CPFE, 1 unclassifiable ILD, 1 acute interstitial pneumonia, and 1 sarcoidosis. Ten patients (13%) experienced an acute exacerbation, which was fatal in only 1 case. Twenty-five patients (33%) had at least one hospitalization due to pneumonia (6 cases), septic shock or pulmonary thromboembolism (2 cases each), and pneumothorax with pneumomediastinum (1 case).

The median survival after ILD diagnosis was 6 (IQR 4–8) years. Noting that patients had at least a 2-year follow-up per inclusion criteria, the 5-year mortality rate after the ILD diagnosis was 15% (Fig. 2). After the diagnosis of ILD progression, the median survival was 3 (IQR 2–5) years. The 2- and 3-year mortality rates after the diagnosis of disease progression were 4 and 20%, respectively (Fig. 3).

Discussion

In a real-life setting, approximately one-third of the fibrosing ILD patients, followed-up for at least 2 years in 2 Italian ILD referral centers, showed a progressive disease course despite steroid or immunosuppressive treatment. Our observed 31% prevalence of PF-ILD patients is similar to that (18–32%) estimated by Wijsenbeek et al.

[18] in a recent survey among 22 ILD experts from United Kingdom, Japan, Germany, and USA. In our cohort, disease progression occurred after a median of 18 months following ILD diagnosis, similarly to the 11–15 months estimated by Wijsenbeek et al. [18].

Interestingly, in our study, the vast majority of patients (93%) were treated at the time of PF-ILD diagnosis (40% with prednisolone as monotherapy and 52% with prednisolone associated with steroid-sparing agents). This evidence suggests that immunosuppressive therapy failed in slowing disease progression in about one-third of the non-IPF fibrosing ILD cases. Nevertheless, 35% of these patients experienced treatment-related side effects. Unapproved treatment with steroid anti-inflammatory drugs and immunosuppressants is used empirically, indeed, despite the absence of RCTs demonstrating the efficacy and safety of these drugs in PF-ILDs [5]. Of concern are the results of the PANTHER-IPF trial showing that the combination therapy with prednisone, azathioprine, and N-acetylcysteine was associated with an increased risk of hospitalization and death [19].

In our cohort, FVC decline >10% over the 2-year follow-up period was the main criterion for identifying fibrosing ILD patients with a progressive phenotype, while only a minority of patients were identified as having a "progressive fibrosing" trend through the other INBUILD criteria, including worsening of respiratory symptoms and radiological involvement. The importance of PFTs is recognized in multiple retrospective studies on NSIP, CHP, RA- and systemic sclerosis-associated ILD, and unclassifiable ILD, in which disease progression, defined by short-term PFT trends, was an independent determinant of mortality [20–24].

As above-mentioned, only a minority of patients in our cohort (19%) were diagnosed with PF-ILD because of the increasing extent of fibrotic changes on HRCT or worsening respiratory symptoms associated with a marginal FVC decline (between 5 and 10%). To date, unfortunately, there is no consensus on how to define disease progression in patients with ILDs. Most clinical trials and observational studies defined ILD progression in terms of FVC decline, but also HRCT can be used to evaluate prognosis in ILDs. In fact, similarly to IPF, the extent of traction bronchiectasis and honeycombing has been reported as predictors of mortality in CHP and CTD-ILD [25–27]. In the near future, quantitative HRCT analysis paired with visual analysis might be used to evaluate disease progression in serial HRCTs in terms of changes in the extent of honeycombing, reticulation, and traction bronchiectasis [28].

The median survival after ILD diagnosis was 6 years; however, we observed a median survival after diagnosis of ILD progression for 3 years. Although direct comparisons cannot be made since we also included patients with <2 years of follow-up after disease progression, the "progressive fibrosing" phenotype course seems to present similarities to that of IPF prior to the advent of anti-fibrotics [29]. Furthermore, while considering the above-mentioned limitations, the proportion of PF-ILD patients who experienced an acute exacerbation (13%) is similar to the annual incidence of acute exacerbations in IPF patients (roughly 5–19%).

Even though the PF-ILD group encompasses various individual ILDs with heterogeneous clinical course and prognosis, the evidence of disease progression despite immunosuppressant treatment and of an overall poor prognosis provides a rationale to consider these PF-ILDs together with IPF [2]. Furthermore, the evidence from preclinical studies that both pirfenidone and nintedanib inhibit fundamental processes in the pathogenesis of fibrosis, irrespective of the trigger, gives the basis to consider the treatment with anti-fibrotic agents also in this heterogeneous ILD class. The recently published SENSCIS [30] and INBUILD [8] trials seem to confirm these data.

Our study is the first to describe, in a real-life setting, the prevalence, clinical features, and outcome of non-IPF fibrosing ILD patients with a progressive phenotype. However, some limitations should be acknowledged apart from the retrospective design. First, our PF-ILD cohort may be potentially not representative of the Italian population of PF-ILD patients because of the different genetic backgrounds across our nation. However, this study population is relatively large, considering the rarity of the ILDs and the fact that these 2 Italian ILD referral centers certify the 62.8% of all the new ILD diagnosis in Lombardia, the most populated region in Italy with 10,060,000 inhabitants in 2019. Second, to identify PF-ILD patients according to the INBUILD trial's inclusion criteria, we selected only patients with non-IPF fibrosing ILD and at least 2-year follow-up. This choice may have led to the exclusion of patients with more severe disease deceased within 2 years from ILD diagnosis or of patients lost during follow-up, possibly underestimating PF-ILD prevalence.

In conclusion, in a real-life setting, approximately one-third of fibrosing ILD patients, followed up for at least 2 years in 2 Italian ILD referral centers, showed a progressive disease course, despite immunosuppressive therapy, associated with a poor prognosis; the clinical behavior of

this heterogeneous group of PF-ILDs appears to be very similar to that of IPF patients. Future well-designed studies aimed to better phenotype this subgroup of ILD patients are most warranted.

Acknowledgements

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Statement of Ethics

Our research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no funding to declare.

Author Contributions

Paola Faverio: conceptualization, data curation, formal analysis, investigation, methodology, and writing – original draft, review, and editing; Martina Piluso: data curation, formal analysis, investigation, and writing – original draft; Federica De Giacomi: data curation, formal analysis, investigation, and writing – original draft; Matteo Della Zoppa: data curation and formal analysis; Roberto Cassandro: data curation; Sergio Harari: conceptualization, data curation, and writing – review and editing; Fabrizio Luppi: conceptualization and writing – review and editing; and Alberto Pesci: conceptualization, data curation, and writing – review and editing.

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