Real-life characteristics and management of patients with fibrosing interstitial lung disease: INSIGHTS-ILD registry

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Shareable abstract (@ERSpublications)
Individuals on antifibrotic therapy often display a more severe disease profile. Interestingly, there is a considerable diversity of treatments and antifibrotic therapy is only partially applied following formal progression criteria. https://bit.ly/4fwMG0M

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Abstract

Background This study aims to report real-life data on the characteristics and treatment patterns of patients with fibrosing interstitial lung disease (ILD; except idiopathic pulmonary fibrosis) across multiple specialised centres in Germany. Eligibility criteria included ILD affecting >10% of lung parenchyma on high-resolution computed tomography, a single breath diffusion capacity for carbon monoxide (D_{LCO}) ⩽80% predicted and active treatment of lung disease.

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Methods As of the interim analysis cut-off, 655 patients (mean±SD age 65.9±11.7 years, 54.5% male) were included. The most common ILD subtypes were fibrosing hypersensitivity pneumonitis (31.2%), fibrosing ILD (22.0%), rheumatoid arthritis and connective tissue disease ILDs (13.0%) and unclassifiable fibrosing ILD (13.0%).

Results Lung function metrics included total lung capacity at 68.3±17.6% predicted, forced vital capacity at 69.8±19.8% predicted, forced expiratory volume in 1 s at 73.7±19.5% predicted and D_{LCO} at 33.8±15.6% predicted. Current treatments included oral steroids (62.6%), antifibrotic therapy (50.7%), azathioprine (14.4%), methotrexate (10.2%) and mycophenolate mofetil (11.1%). Patients on antifibrotic therapy were typically older at diagnosis and registry inclusion, more often male, had more comorbidities, a lower 6-min walk distance and reduced lung function metrics compared with those not on antifibrotic therapy. Notably, 27.3% of the patients on antifibrotic therapy did not meet progression criteria (INBUILD), whereas 40.1% of patients not receiving antifibrotic therapy did meet those criteria.

Conclusion The patient characteristics observed align with those observed in randomised controlled trials and other noninterventional studies. Patients on antifibrotic therapy generally had more severe disease profiles.

Background

Interstitial lung disease (ILD) encompasses a broad and diverse set of over 200 conditions affecting the interstitium, bronchioles and/or alveoli with distinct clinical, radiological and histological features [1]. ILDs vary in their causes, manifestations, progression and treatments [2]. Idiopathic pulmonary fibrosis (IPF) is the most frequent fibrosing form and thoroughly researched type of fibrosing ILD [3].

Diagnosing ILD early and accurately is often a complex task and predicting the course of the disease and how a patient will respond to treatment is equally challenging [4–6]. The term progressive pulmonary fibrosis (PPF) has been introduced in the latest international guideline to describe a subgroup of patients within various ILD entities who develop a progressive fibrotic course potentially responsive to antifibrotic therapy [7]. PPF encompasses a wide range of patients with fibrotic lung conditions except IPF that advance clinically despite standard care, posing a constant challenge for both patients and healthcare providers [8, 9].

The worsening of fibrosis involves an increase in respiratory symptoms, a decline in lung function, a reduction in quality of life and often premature mortality. Various criteria for “progressive fibrosis” have been suggested and used in clinical studies such as INBUILD (Nintedanib in Progressive Fibrosing Interstitial Lung Diseases) [10] for nintedanib and the trial in unclassifiable progressive fibrosing ILD [11] and RELIEF [12] for pirfenidone, indicating disease progression if patients meet any of the following within a 6–24-month timeframe: decline of ⩾10% in forced vital capacity (FVC), a decline of ⩾15% in the diffusing capacity of the lung for carbon monoxide (D_{LCO}) or exacerbating symptoms or radiological worsening with a ⩾5 to <10% relative decrease in FVC [4, 9, 13]. According to the most recent American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Society (ALAT) practice guideline, two out of three conditions must be met within a year for a PPF designation: worsening respiratory symptoms, declining lung function or increased fibrosis on high-resolution computed tomography (HRCT) imaging, provided other causes for deterioration have been ruled out [7]. Notably, none of these criteria has been tested against absence of such criteria in fibrosing ILD (fILD). Importantly, fILDs, apart from IPF, can remain clinically stable and may have overlapping inflammatory features. Therefore, the treatment decisions at first diagnosis of fILD are challenging, ranging from a wait-and-watch strategy to various anti-inflammatory therapy or antifibrotic therapy or a combination of both [6]. Reliable criteria to base this decision on are lacking.

Enhancing clinical outcomes, including survival rates among this group of diseases may depend on a deeper comprehension of its epidemiology, diagnostic range and the impact of new treatments [14]. Therefore, gathering detailed information on the natural progression of fILDs and their PPF phenotype, understanding patient profiles, risk factors of progression and the response to different treatment approaches is crucial.

In Germany, the focus on collecting real-world data has primarily been on IPF through initiatives such as eurIPFnet [15] and INSIGHTS-IPF [16–19], with less emphasis on other ILDs (GOLDnet [20] and EXCITING [21]).

Registry data can provide important information; for instance, they can enhance information from randomised controlled trials, offer essential insights into how drugs are used (especially crucial when new treatments are being introduced) and assess the degree to which clinical guidelines are adhered to in real-world settings [22, 23].

The present INSIGHTS-ILD (Investigating Significant Health Trends in Interstitial Lung Disease) registry was established to gather information systematically and proactively on the traits, diagnostic approaches, treatment trends, quality of life and long-term patient outcomes with fILD. Specifically, we want to assess prospectively the success rates of different treatment decisions in a variable clinical context. Here, we describe the baseline characteristics and initial treatment modalities of a diverse group of 655 patients, distinct from clinical trials, as these individuals were not selectively chosen.

Methods

The conceptual basis and structure of the INSIGHTS-ILD study have been previously outlined in detail [24]. Briefly, INSIGHTS-ILD is an investigator-initiated, observational, multicentre study aimed at documenting the management of ILD patients in a routine-care setting. Launched in February 2022, the study is ongoing and continues to recruit participants.

Approval for the study materials was granted by the Ethics Committee of the Physician Chamber Saxony in Dresden on 5 December 2021, along with subsequent approvals from local ethics committees as required. The study is overseen by a multidisciplinary steering board. The study has been registered in the noninterventional study (NIS) register of the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) under NIS7562, and in the Deutsches Register Klinischer Studien register under DRKS00027389.

The study was initiated by investigators (see authors), the legal sponsor is the GWT-TUD (Gesellschaft für Wissens- und Technologietransfer) in Dresden.

To maintain a high standard of data quality and ensure a sufficient number of patients per centre, the study concentrates on specialised respiratory centres or clinics. Presently, data are being contributed by 32 pulmonary specialty centres spread across Germany.

Patients are eligible for documentation, if they meet all of the following criteria: fILD, which includes all ILD groups (except IPF) including those with idiopathic interstitial pneumonias (IIPs), connective tissue disease-associated interstitial lung disease (CTD-ILD), hypersensitivity pneumonitis (HP), asbestosis, sarcoidosis, *etc*.; age ⩾18 years; ILD on HRCT >10% of lung parenchyma; D_{LCO}⩽80% predicted; on active anti-inflammatory, immunomodulatory and/or antifibrotic therapy; and written informed consent available. Both newly diagnosed (“incident”) and previously diagnosed (“prevalent”) patients were eligible for inclusion in the registry. Incident patients were enrolled after the multidisciplinary team had agreed on an fILD diagnosis, while prevalent cases were enrolled during their routine follow-up visits. Importantly, criteria of progression are documented retrospectively at the time of inclusion but are explicitly not mandatory.

Patients are not eligible for documentation if they meet one or both of the following criteria: diagnosis of IPF (since this has been documented in great detail in the sister study INSIGHTS-IPF [25]) and participation in a controlled trial investigating ILD, if blinded or with investigational drug. To preserve the integrity of “real-life” observations, no other specific exclusion criteria were set, and patients were enrolled consecutively at each site to minimise selection bias.

Initial data collection encompasses demographic information, risk factors and comorbidities. The study specifically captures a detailed account of the patient’s ILD history, diagnostic processes and past and present treatments, both pharmacological (exact dates and doses) and nonpharmacological. Follow-up assessments were conducted biannually (with a 3-month grace period) and hospitalisations, exacerbations of the disease or deaths, along with ongoing treatment strategies were documented.

The extent of lung involvement was assessed using HRCT, with evaluations conducted by experienced radiologists at each participating site. Judgements regarding the usual interstitial pneumonia (UIP) pattern were also made by radiologists at the respective institutions.

Established formulae were used for total lung capacity (TLC) and D_{LCO} from Crapo *et al*. [26], inspiratory vital capacity (IVC) from Quanjer *et al*. [27], FVC, forced expiratory volume in 1 s (FEV_1), and the FEV_1/FVC ratio from Quanjer *et al*. [27], with reference values showing consistency over time and across datasets with more than 1000 subjects. Blood gas analysis was routinely performed from arterialised capillary blood for the ear lobe, including oxygen partial pressure (P_{AO_2}).

TABLE 1 Demographic and clinical characteristics, total and by treatment strategy at baseline

Category	Antifibrotic therapy (n=331)	No antifibrotic therapy (n=324)	All patients (n=655)	p-value
Age, years	67.7±10.5	64.1±12.7	65.9±11.7	<0.001
Sex, female	131 (39.6)	167 (51.5)	298 (45.5)	0.003
Sex, male	200 (60.4)	157 (48.5)	357 (54.5)	
BMI <18.5 kg·m^{-2}	9 (2.7)	6 (1.9)	15 (2.3)	0.009
BMI 18.5–24.9 kg·m^{-2}	124 (37.5)	104 (32.1)	228 (34.8)	
BMI 25.0–29.9 kg·m^{-2}	118 (35.6)	111 (34.3)	229 (35.0)	
BMI ⩾30.0 kg·m^{-2}	80 (24.2)	103 (31.8)	183 (27.9)	
Smoking, never	135 (42.7)	143 (47.5)	278 (45.1)	0.020
Smoking, former	177 (56.0)	145 (48.2)	322 (52.2)	
Smoking, current	4 (1.3)	13 (4.3)	17 (2.8)	
Comorbidities	1.8±1.6	1.6 ±1.4	1.7±1.5	1.000
Duration of symptoms, years	6.8±6.2	6.3±7.8	6.5±7.1	0.455
Age at diagnosis, years	62.6±11.8	59.4±14.7	61.0±13.4	0.002
6-min walk distance, m	338.2±114.9	401.6±118.8	365.1±120.6	<0.001
Borg dyspnoea index at rest	1.2±1.9	1.3±2.1	1.2±2.0	0.368
Borg dyspnoea index after exercise	4.9±2.5	4.8±2.4	4.9±2.4	0.805
Environmental influences	173 (63.8)	129 (53.5)	302 (59.0)	0.023
Gastro-oesophageal reflux disease	51 (16.5)	51 (17.3)	102 (16.9)	0.868
Familial clustering	28 (12.8)	22 (10.0)	50 (11.4)	0.432
Medication exposure	36 (14.3)	19 (8.3)	55 (11.5)	0.057

Data are presented as mean±SD or n (%). BMI: body mass index.

Data collection and statistical analysis

Data are collected through an electronic case report form featuring automatic checks for data plausibility. A minimum of 20% of centres underwent on-site monitoring to verify source data. The sample size was determined based on practicality, without a formal calculation.

Categorical data are presented as frequencies and continuous data are reported as mean±SD or median (interquartile range), based on their distribution. Analyses are primarily descriptive. To compare patients with and without antifibrotic therapy, a Pearson's chi-squared test was applied for categorical data and a Welch t-test for continuous data. R was used for statistical analysis [28]. Missing data were not replaced or imputed in this study, with the exception of missing days (replaced by 15) or months (replaced by July) for medications. Only patients with complete data at the respective time points were analysed.

Results

In this interim analysis of the INSIGHTS-ILD study, a total of 655 patients were evaluated for their characteristics at inclusion into the registry. These baseline characteristics, *i.e.* those recorded at the time of registry enrolment, are presented in tables 1–4 for the entire cohort and separately for patients with and without antifibrotic therapy.

TABLE 2 Lung function (% predicted)

Parameter	Antifibrotic therapy (n=331)	No antifibrotic therapy (n=324)	All patients (n=655)	p-value
Total lung capacity	64.5±17.1	72.2±17.3	68.3±17.6	<0.001
Inspiratory vital capacity	66.0±19.6	73.5±20.9	69.6±20.5	<0.001
FVC	66.6±19.6	73.1±19.4	69.8±19.8	<0.001
FEV_1	71.1±19.0	76.4±19.7	73.7±19.5	<0.001
FEV_1/FVC ratio	112.8±10.6	110.7±10.5	111.8±10.6	0.012
Diffusing capacity for carbon monoxide	32.2±14.9	35.5±16.2	33.8±15.6	0.008

Data are presented as mean±SD. FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s.

TABLE 3 Treatment at baseline

Medication	Antifibrotic therapy (n=331)	No antifibrotic therapy (n=324)	All patients (n=655)
Nintedanib	318 (96.1)	0 (0.0)	318 (48.5)
Pirfenidone	13 (3.9)	0 (0.0)	13 (2.0)
Prednisone/prednisolone	175 (52.9)	235 (72.5)	410 (62.6)
Other steroid	0 (0.0)	3 (0.9)	3 (0.5)
Azathioprine	27 (8.2)	67 (20.7)	94 (14.4)
Cyclophosphamide IV	4 (1.2)	9 (2.8)	13 (2.0)
Cyclophosphamide oral	0 (0.0)	0 (0.0)	0 (0.0)
Mycophenolate mofetil	31 (9.4)	42 (13.0)	73 (11.1)
Rituximab	15 (4.5)	33 (10.2)	48 (7.3)
Methotrexate	24 (7.3)	43 (13.3)	67 (10.2)
Other	14 (4.2)	36 (11.1)	50 (7.6)

Data are presented as n (%). Multiple medications were possible.

In the 24 months prior to enrolment, 298 of 532 patients (56.0%) met at least one of the INBUILD criteria for PPF, 189 of 260 patients (72.7%) with antifibrotic therapy and 109 of 272 patients (40.1%) without antifibrotic therapy.

Total cohort

In the total cohort there were slightly more men (357 of 655, 54.5%) than women. The mean age of the participants was 65.9±11.7 years. The mean body mass index (BMI) was 27.3±5.4 $kg \cdot m^{-2}$. Regarding smoking status, 278 of 617 patients (45.1%) had never smoked, 322 of 617 patients (52.2%) were former smokers and 17 of 617 patients (2.8%) were current smokers. An overview of symptoms is shown in figure 1.

The median time from first symptoms to diagnosis was 0.5 years, and to enrolment 4.5 years. Patients diagnosed 90 days prior to enrolment, *i.e.* incident patients, accounted for 54 of 655 patients (8.2%). Diagnosis was based on multidisciplinary discussion in 360 of 459 cases (78.4%). HRCT was used in combination with histology in 238 of 594 patients (47.6%) and alone in 311 of 594 patients (52.4%). Bronchoalveolar lavage (BAL) was performed in 447 of 587 patients (76.1%).

In terms of risk factors associated with ILD, a significant number of patients reported environmental exposure (302 of 512 patients, 59.0%), gastro-oesophageal reflux disease (102 of 655 patients, 16.9%), drug exposure (55 of 480 patients, 11.5%) and familial clustering (50 of 438 patients, 11.4%). Among the 55 cases where drugs were identified by physicians as being linked to ILD, methotrexate was implicated in 21 cases, simvastatin in 6 cases, venlafaxine in 5 cases, metformin, amiodarone, hydrochlorothiazide and atorvastatin in 4 cases each, rosuvastatin was noted in 3 cases and other drugs were implicated in 3 cases.

TABLE 4 INBUILD criteria in the 24 months before inclusion in the INSIGHTS-ILD study

	Antifibrotic therapy (n=331)	No antifibrotic therapy (n=324)	All patients (n=655)	p-value
Information available	260 (78.5)	272 (84.0)	532 (81.2)	0.095
Relative decline of FVC⩾10% of the predicted value	107 (41.2)	48 (17.6)	155 (29.1)	<0.001
Relative decline of FVC 5% to <10% of the predicted value and increase in fibrosis on HRCT	40 (15.4)	18 (6.6)	58 (10.9)	<0.001
Relative decline of FVC 5% to <10% of the predicted value and increase of respiratory symptoms	48 (18.5)	27 (9.9)	75 (14.1)	<0.001
Increase in respiratory symptoms and increase in fibrosis on HRCT	102 (39.2)	62 (22.8)	164 (30.8)	<0.001
At least one of the criteria is met	189 (72.7)	109 (40.1)	298 (56.0)	<0.001
None of the criteria is met	71 (27.3)	163 (59.9)	234 (44.0)	<0.001

Data are presented as n (%). More than one criterion might apply. INBUILD: Nintedanib in Progressive Fibrosing Interstitial Lung Diseases; INSIGHTS-ILD: Investigating Significant Health Trends in Interstitial Lung Disease; FVC: forced vital capacity; HRCT: high-resolution computed tomography.

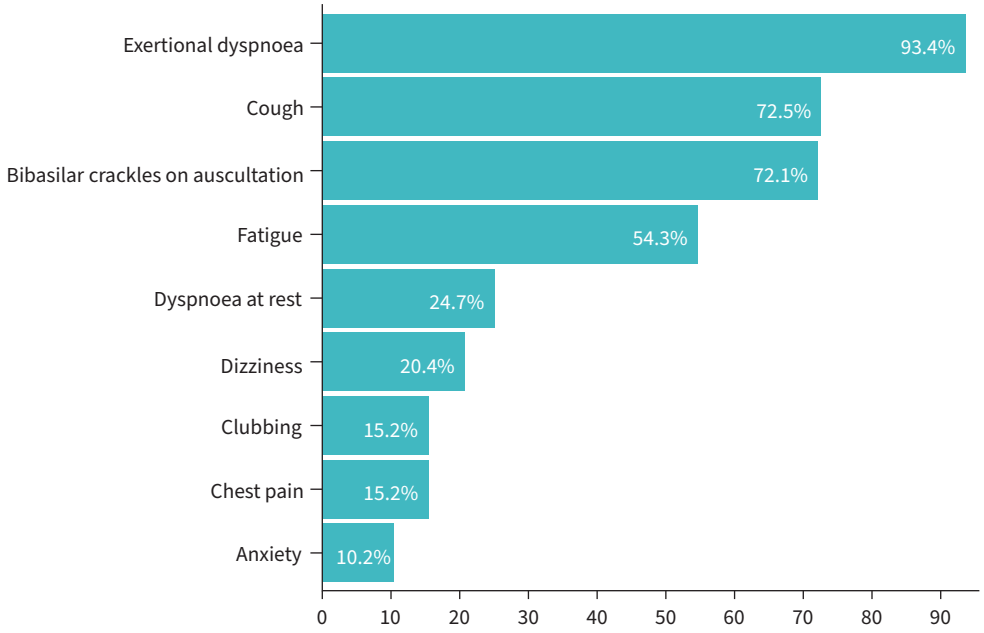

FIGURE 1 Signs and symptoms.

Lung function is presented in table 2 and supplementary figure S1. TLC was 68.3±17.6% pred, IVC was 69.6±20.5% pred, FVC was 69.8±19.8% pred, FEV_1 was 73.7±19.5% pred and D_{LCO} was 33.8±15.6% pred. P_{AO_2} was 71.1±18.5 mmHg.

The extent of lung involvement assessed by the investigators varied, with 114 of 311 patients (36.7%) having 11–20% of lung parenchyma affected, 46 of 311patients (14.8%) having 21–30% affected, 47 of 311 patients (15.1%) having 31–40% affected and 104 of 311 patients (33.4%) having more than 40% affected (figure 2).

According to the ATS/ERS criteria for UIP patterns on HRCT, 114 of 568 patients (20.1%) had a UIP pattern, 65 of 568 patients (11.4%) had a probable UIP pattern and 47 of 568 patients (8.3%) were classified as indeterminate for UIP. Of the remaining 342 of 568 patients (60.2%) patients with an alternative pattern, 91 of 568 patients (26.6%) had HP and 179 of 342 patients (52.3%) had nonspecific interstitial pneumonia (NSIP).

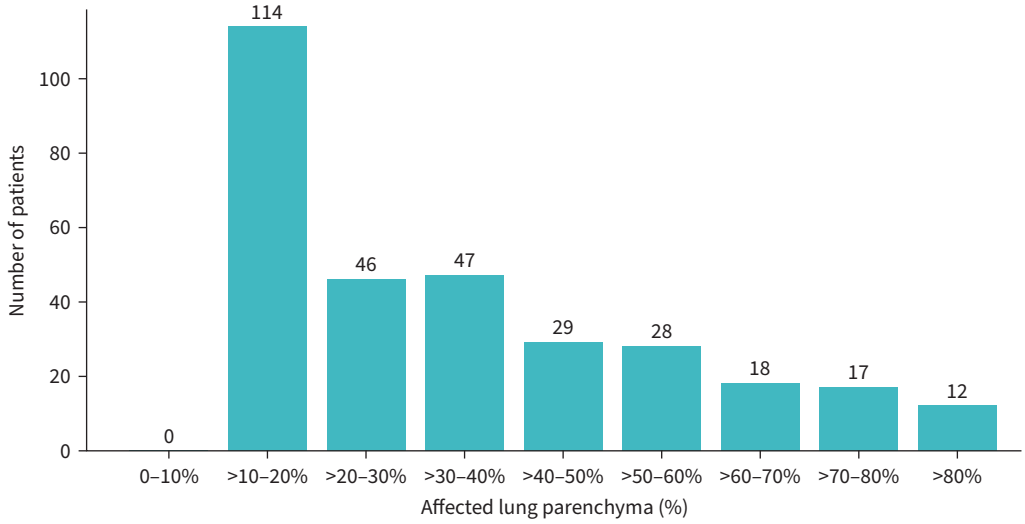

FIGURE 2 Affected lung parenchyma by percentage range in high-resolution computed tomography.

Emphysema was observed in 79 of 655 patients (12.1%), enlarged lymph nodes in 47 of 655 patients (7.2%), dilated distal oesophagus in 20 of 655 patients (3.1%), pleural effusion in 11 of 655 patients (1.7%) and pleural plaques in 8 of 655 patients (1.2%).

To further assess lung pathology, 298 of 582 patients (51.2%) of participants underwent a biopsy procedure. Of these, the majority (192 of 288 patients, 66.7%) underwent transbronchial lung cryobiopsy, 56 of 288 patients (19.4%) underwent surgical lung biopsy and 40 of 288 patients (13.9%) underwent other types of biopsies.

Histopathological analysis according to ATS/ERS criteria showed a UIP pattern in 43 of 298 patients (14.4%), probable UIP in 16 of 298 patients (5.4%) and an indeterminate pattern in 14 of 298 patients (4.7%) of the patients. Additionally, 148 of 298 patients (49.7%) had an alternative pattern. Of these, 58 of 148 patients (39.2%) had an HP pattern and 47 of 148 patients (31.8%) had NSIP. In cases where a definitive diagnosis could not be made, 12 of 298 patients (4.0%) had insufficient material and 43 of 298 patients (14.4%) had nonspecific findings.

World Health Organization functional class was distributed as follows: class I in 27 of 297 patients (9.1%), class II in 135 of 297 patients (45.4%), class III in 114 of 297 patients (38.4%) and class IV in 21 of 297 patients (7.1%). The Borg dyspnoea score was 1.2±2.0 at rest and 4.9±2.4 after exercise. The mean 6-min walk distance was 365±121 m. The median NT-proBNP was 140 $pg \cdot mL^{-1}$. Comorbidities were common, with arterial hypertension being the most frequent (298 of 623 patients, 47.8% of patients with available data), followed by pulmonary hypertension (107 of 601 patients, 17.8%), diabetes mellitus (102 of 623 patients, 16.4%), obstructive sleep apnoea (97 of 602 patients, 16.1%), gastrointestinal reflux disorder (102 of 605 patients, 16.9%) and coronary artery disease (92 of 614 patients, 15.0%).

Half the patients (331 of 655 patients, 50.7%) were receiving antifibrotic therapy, primarily nintedanib (318 of 655 patients, 48.5%) and to a lesser extent, pirfenidone (13 of 655 patients, 2.0%). Patients were receiving oral steroids (any dose) in 410 of 655 patients (62.6%), azathioprine in 94 of 655 patients (14.4%), methotrexate in 67 of 655 patients (10.2%) and mycophenolate mofetil in 73 of 655 patients (11.1%).

Six patients were listed for lung transplantation. According to the investigator's clinical judgement, ILD was stable in 269 of 655 patients (41.1%), slowly progressing in 266 of 655 patients (40.6%), rapidly progressing in 47 of 655 patients (7.2%) and indeterminate in 73 of 655 patients (11.1%) at the inclusion visit. The mean quality of life, using a visual analogue scale of 0–100, was 58±19 points.

Patients with and without antifibrotic therapy

Patients on antifibrotic therapy were older at diagnosis (mean 62.6 years, n=331), compared with 59.4 years, n=324) and at enrolment (mean 67.7 years, n=331), compared with 64.1 years, n=324). They were more often male (200 of 331 patients, 60.4% *versus* 157 of 324 patients, 48.5%) and had a higher prevalence of comorbidities (median 2.0, n=270 *versus* 1.0, n=265). Patients on antifibrotic therapy had a lower 6-min walk distance (mean 338 m, n=212 *versus* 402 m, n=156). Lung function metrics were also lower in patients receiving antifibrotic therapy, including TLC % pred (mean 64.5%, n=324, *versus* 72.2% pred, n=311), FVC (mean 66.6%, n=330, *versus* 73.1% pred, n=321) and D_{LCO} (mean 32.2%, n=303 *versus* 35.5% pred, n=303). Additionally, 71 of 260 patients (27.3%) on antifibrotic therapy did not meet progression criteria (INBUILD), while 109 of 272 patients (40.1%) not on antifibrotic therapy met the criteria.

Characteristics of the most common entities

The most commonly documented ILD entities were HP in 190 of 609 patients (31.2%), fibrosing IIP in 133 of 604 patients (22.0%), rheumatoid arthritis and CTD associated ILDs in 80 of 614 patients (13.0%) and unclassifiable ILD in 80 of 615 patients (13.0%). Patient characteristics in the fibrotic idiopathic interstitial pneumonia, HP, rheumatoid arthritis and systemic sclerosis subgroups are shown in supplementary tables S1–S4.

Discussion

An official ATS/ERS/JRS/ALAT Clinical Practice Guideline defined PPF as at least two of three criteria (worsening symptoms, radiological progression and physiological progression) occurring within the past year without alternative explanation in a patient with an ILD other than IPF [7]. The guideline committee emphasised four points: 1) that PPF is defined separately from IPF (which has been addressed in previous guidelines); 2) that it is not a diagnosis *per se*; 3) that the definition of PPF does not depend on the underlying condition; and 4) that the criteria for PPF should not be based solely on a single clinical trial [7].

Another term, “progressive fibrosing ILD”, was used to define the eligible patient population in the INBUILD trial, which reported a beneficial effect of antifibrotic medication in ILDs other than IPF [9, 10]. The ATS/ERS guideline panel discussed the two alternative terms and ultimately chose PPF. Although the INSIGHTS-ILD study was initiated a few months before the introduction of the new term PPF, the population covered reflects this condition. As the relevance of the currently used progression criteria has never been tested in fILD, the progression criteria were not mandatory for inclusion in our study, but were systematically recorded when available. We included patients who were on active therapy for their ILD, with the expectation that those receiving treatment were more likely to represent individuals with more-advanced disease or greater risk of progression, thereby enriching the cohort for patients who might have higher risk of progression or require a change of therapy during follow-up. Nonetheless, more than half of the patients overall met at least one INBUILD progression criterion and nearly three-quarters of patients on antifibrotic therapy. Interestingly, 27.3% of the patients were on antifibrotic therapy although they did not meet INBUILD progression criteria, indicating “off label” use of (mostly) nintedanib in this subgroup. It will be interesting to observe the further course of this subgroup. On the other hand, 40.1% of patients with fILD who fulfilled at least one of the INBUILD progression criteria were not started on antifibrotic therapy. It will be important to analyse whether this delay will translate into a disadvantage for the patients during follow-up.

It is noteworthy that in this study, ILD was documented mostly by expert sites. The diagnosis was based on HRCT in all patients, and additionally, in 45.5% supported by histology. Compared with current studies in IPF, this study indicates a relatively frequent use of surgical lung biopsies reflecting the difficulties in confirmation of a final diagnosis in this population. BAL was conducted as a supplementary examination in 76.1% of patients, in line with current recommendations from German guidelines and similar to other European national guidelines, which supports the use of BAL as a diagnostic aid [5, 29, 30]. As the fibrotic phenotype often develops during the course of ILD, most patients had a median observation period 3.0 years at the time of inclusion and the proportion of incident cases (diagnosis within 90 days before inclusion) was low (8.2%).

Compared with the IPF cohort in INSIGHTS-IPF (mean age 69 years, 81% males, 6-min walk distance of 279 m, FVC % pred of 69% and D_{LCO} % pred of 38%) [25], patients in INSIGHTS-ILD were younger, with a lower proportion of males, a substantially shorter 6-min walk distance, lower D_{LCO} % pred and the same FVC % pred. Disease severity in the Canadian ILD registry (6-min walk distance of 400 m, FVC % pred of 79% and D_{LCO} % pred of 61%) [31] was lower than in INSIGHTS-ILD. Further, patient characteristics and ILD severity were similar in INBUILD (age 63 years, 54% males, FVC % pred of 69% and D_{LCO} % pred of 46%) [10].

A significant prevalence of comorbidities was recorded, highlighting the challenges in treating this fragile patient group. This emphasises the necessity for enhanced research into primary comorbid conditions, especially cardiovascular diseases, diabetes, pulmonary hypertension, emphysema and reflux. Tailored treatment strategies might be required to meet the specific needs of patients.

Over the past decade, treatment approaches for ILD have significantly evolved both in the USA and also in Europe. Within the INSIGHTS-ILD study, all patients received at least one medication intended to treat the underlying ILD, as per the inclusion criteria. At the time of inclusion, nintedanib was most prevalent antifibrotic drug, whereas pirfenidone was used in only a small minority, due to the fact that pirfenidone is not approved for the use in the PPF indication in Germany. Indeed, current German guidelines recommend nintedanib as the approved first-line treatment for PPF, while pirfenidone may be used “off label” in patients who have failed on or do not tolerate nintedanib [32]. In the absence of a definite trial (but an approval for treatment of IPF), these guidelines recommend further research into the efficacy, effectiveness and safety of pirfenidone in both: 1) non-IPF ILD manifesting PPF in general; and 2) specific types of non-IPF ILD manifesting PPF [7]. The fact that about half the patients were on antifibrotics and half were not, is an optimal starting point for the observation of different courses of patient trajectories during follow-up, taking into account potential differences between these groups.

The rate of steroid monotherapy use was high despite the fact that international guidelines discourage long-term steroid use. Reasons are speculative, but may include treatment of dry cough, previous exacerbations or difficulty in tapering off therapy. A similar pattern in the use of steroids has been described INSIGHTS-IPF [17] and in a survey of UK pulmonologists on real-world experience of nintedanib for progressive fILD [33].

We observed that patients undergoing antifibrotic therapy were older and generally had more severe ILD. This contrasts with the findings from the IPF cohort in the INSIGHTS-IPF study, where patients on

antifibrotic therapy were of similar ages, had a slightly higher proportion of males, performed better on the 6-min walk test and had better FVC and D_{LCO} values [25].

Methodological considerations

INSIGHTS-ILD is a NIS designed to be prospectively, enrolling patients consecutively to minimise selection bias. It employs several quality assurance methods, notably systematic plausibility checks and on-site monitoring to ensure data accuracy through direct comparison with patient records. However, it has inherent limitations. As an observational, nonrandomised study involving only expert centres, it is subject to various risks of bias that could mask actual causal relationships. Treatment decisions by physicians, influenced by factors such as disease severity, duration, comorbidities, *etc*., could lead to allocation or channelling bias, affecting the observed link between treatments and outcomes. The study does not re-evaluate patients, potentially including those with similar diagnoses (IPF) or other causes of UIP patterns on HRCT and/or surgical lung biopsy. Nonetheless, the involvement of specialist centres should ensure high diagnostic accuracy and quality, primarily based on HRCT and biopsy findings [34]. However, focusing solely on ILD expert centres may not fully represent the broader ILD management landscape in Germany.

In summary, this study provides valuable insights into the real-world characteristics and treatment patterns of patients with fILD across multiple fILD specialist centres and large referral hospitals in Germany. The data highlight significant differences between patients receiving antifibrotic therapy and those not on such treatments, with the former group generally displaying more-advanced disease profiles. Importantly, our findings underscore the variability in treatment approaches and the need for further research to optimise therapeutic strategies for fILDs. Future longitudinal analyses from this registry will offer deeper understanding of disease progression and treatment outcomes, helping to inform clinical practice and improve patient care.

Data availability: Data sharing is not applicable to this article as datasets are being generated but have not finally been analysed during the current study.

Provenance: Submitted article, peer reviewed.

INSIGHTS-ILD Registry Group: At the time of writing, the following investigators and their staff contribute to the study (collaborators), in alphabetical order: Ioana Andreica (Rheumazentrum Ruhrgebiet, Herne); Jürgen Behr (LMU Klinikum der Universität München, München Großhadern); Heike Biller (LungenClinic Grosshansdorf GmbH, Großhansdorf); Martin Claussen (LungenClinic Grosshansdorf GmbH, Großhansdorf); Stephan Budweiser (RoMed Klinikum Rosenheim, Rosenheim); Stephan Eisenmann (Universitätsklinikum Halle (Saale), AöR, Halle (Saale)); Ralf Ewert (Universitätsmedizin Greifswald KöR, Greifswald); Wolfgang Gesierich (Asklepios Klinik Gauting GmbH, Gauting); Sven Gläser (Vivantes Klinikum Neukölln, Berlin); Christian Grohé (Evangelische Lungenklinik Berlin Krankenhausbetriebs gGmbH, Berlin); Daniel Grund (Charité – Universitätsmedizin Berlin, Berlin); Achim Grünewaldt (Universitätsklinikum Frankfurt, Frankfurt am Main); Andreas Günther (Universitätsklinikum Gießen und Marburg GmbH, Giessen); Lars Hagmeyer (Wissenschafltiches Institut Bethanien für Pneumologie e.V., Solingen); Matthias Held (Missionsärztliche Klinik Würzburg gGmbH, Würzburg); Joachim Kirschner (CIMS-Studienzentrum Bamberg , Bamberg); Dirk Koschel (Fachkrankenhaus Coswig GmbH, Coswig); Michael Kreuter (Lungenzentrum Mainz, Mainz); Philipp Markart (Klinikum Fulda, Fulda); F. Joachim Meyer (Lungenzentrum München (Bogenhausen-Harlaching), München); Ulrich Neff (Klinikum Nürnberg , Nürnberg); Claus Neurohr (RBK Lungenzentrum Stuttgart, Stuttgart); Claus Neurohr (Am Robert-Bosch-Krankenhaus); Markus Polke (Thoraxklinik Heidelberg gGmbH, Heidelberg); Antje Prasse (Medizinische Hochschule Hannover, Hannover); Frank Reichenberger (Augustinum Klinik München, München); Peter Schramm (München Klinik Bogenhausen, München Bogenhausen); Martin Schwaiblmair (Universitätsklinikum Augsburg, Augsburg); Bernd Seese (Thoraxzentrum Bezirk Unterfranken, Münnerstadt); Dirk Skowasch (Herzzentrum des Universitätsklinikums Bonn, Bonn); Stephan Walterspacher (Klinikum Konstanz, Konstanz); Julia Wälscher (Universitätsmedizin Essen, Essen; Ruhrlandklinik); Michael Weber (Zentralklinik, Bad Berka); Michael Westhoff (Lungenklinik Hemer, Hemer; Deutscher Gemeinschafts-Diakonieverband GmbH); Heinrike Wilkens (Universitätsklinikum des Saarlandes, Homburg); and Hubert Wirtz (Universitätsklinikum Leipzig).

Ethics statement: The study materials (protocol, patient information and informed consent form and other required documents) were approved by the primary ethics committee (Ethics Committee of the Physician Chamber Saxony EK-BR-125/21–1 dated 1 December 2021). Any site that joins the study must provide additional ethics approval, if required by their local institutions. Protocol amendments, if any, will be subject to the same requirements as the original protocol. Written informed consent is a prerequisite for patients to be eligible for documentation in the study.

Author contributions: All authors made substantial contributions to the design and coordination of the study, and were involved in the analysis and interpretation of data. J. Behr, D. Pittrow, M. Kreuter, C. Pausch and D. Koschel wrote the protocol. J. Behr and D. Pittrow wrote the present article, and all authors substantially revised it. All authors approved the final version to be published. Authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved and the resolution documented in the literature.

Conflict of interest: J. Behr received honoraria for consulting and lectures from Actelion, AstraZeneca, BMS, Boehringer Ingelheim, Ferrer, Galapagos, Novartis, Roche and Sanofi-Genzyme. The INSIGHTS-ILD study is funded by Boehringer Ingelheim, Germany. M. Kreuter received honoraria for consulting and lectures from AstraZeneca, BMS, Boehringer Ingelheim, Ferrer, Galapagos and Roche. F. Bonella reports grants to his institution by Boehringer Ingelheim and Roche, and fees for consulting by Savara, Roche, Sanofi and Boehringer Ingelheim. D. Pittrow received consultancy fees from Alfasigma, Amgen, Aspen, Biogen, Daiichi Sankyo, Sanofi-Genzyme, Sandoz/Novartis and MSD. B. Seeliger received honoraria for lectures from Boehringer Ingelheim, AstraZeneca, Berlin-Chemie. S. Budweiser received honoraria for lectures and consulting from AstraZeneca, Boehringer Ingelheim, Berlin-Chemie, BMS, CSL Behring, Daiichi Sankyo, GSK, MSD, Novartis, Roche and Sanofi-Aventis. U. Neff reports lecture fees from Boehringer Ingelheim and Janssen-Cilag. F.J. Meyer received honoraria for lectures from Janssen-Cilag, Pfizer. A. Grünewaldt reports personal fees from Boehringer Ingelheim for lectures and GSK for advisory boards. P. Markart reports honoraria for consulting and lectures from Roche and Boehringer Ingelheim. R. Ewert has received speaker fees and fees for participation in advisory boards from United Therapeutics, OMT, Pfizer, GlaxoSmithKline (GSK), Actelion, Novartis, Bayer HealthCare and Encysive/Pfizer; grants from Actelion and Boehringer Ingelheim; and publication support and industry-sponsored grants from OMT, outside the submitted work. M. Polke received honoraria for consulting and lectures from AstraZeneca, Boehringer Ingelheim and Novartis. D. Koschel reports fees for consulting from Roche and Boehringer Ingelheim. The other authors declare no conflict of interest.

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