INTERSTITIAL LUNG DISEASE AROUND THE WORLD

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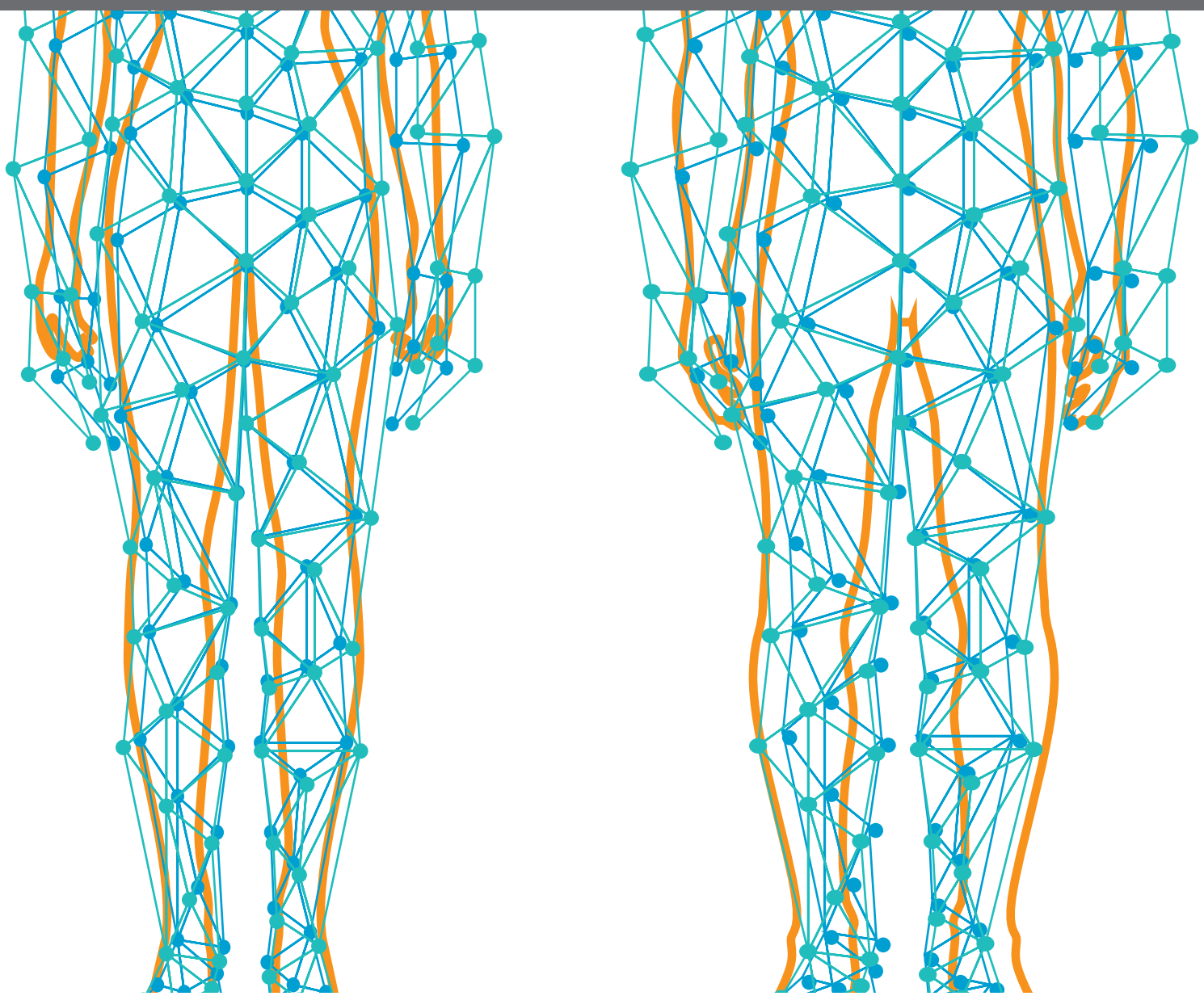

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INTERSTITIAL LUNG DISEASE AROUND THE WORLD

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Editorial: Interstitial Lung Disease Around the World

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Keywords: Interstitial Lung Disease (ILD), idiopathic pulmonary fibrosis, pulmonary fibrosis, inequality in access to healthcare, hypersensitivity pneumonitis (HP), familial pulmonary fibrosis (FPF), air pollution, occupational and environmental exposure

Editorial on the Research Topic

Interstitial Lung Disease Around the World

Interstitial Lung Disease (ILD) comprise a broad spectrum of diseases, with different underlying pathophysiology, disease behavior, and outcomes. For the most prevalent forms of ILD such as idiopathic pulmonary fibrosis (IPF), sarcoidosis and hypersensitivity pneumonitis, international guidelines have been developed and are updated regularly to promote uniformity of diagnosis and treatment, and to enable collaborative research efforts (1–4). However, even for these well-defined diseases, heterogeneity exists in prevalence, disease behavior and outcomes around the world [Kaul et al.; (5–8)]. There are still many unknowns about the impact of geography on these diseases. As many ILDs are thought to originate from an external—often perpetuating—stimulus in a susceptible host, it is likely that environmental and genetic factors explain some of these differences (9). Furthermore, access to diagnosis, care and treatment options also impact disease recognition, outcome, and health related quality of life, which contributes to some notable differences throughout the world (10–14).

Although great advances have been made in recent years on understanding the pathogenesis and advancing the treatment of fibrotic ILDs and ultra-rare ILDs, only a limited part of the world has yet benefitted from these advances. Furthermore, many clinical trials as well as translational studies suffer from a lack of diversity in their study population, with a predominance of Caucasian males from the northern hemisphere included in most studies (13). Fortunately, there have been increasing efforts to expand this narrow scope. First, pharmaceutical companies are now including a broader scope of countries in their clinical trials. For example, when looking at IPF, the CAPACITY trials ran in 13 countries in Europe, Australia and North America, the INPULSIS trials in 24 countries in the Americas, Europe, Asia and Australia, and the ISABELA studies in 26 countries and covering all continents (15–17). Second, academic societies are promoting international collaborations (18). Finally, digital collaborations and communication, accelerated in part by the pandemic, have stimulated surveying and meeting people around the world about their practices and perspectives in different fields of ILD [Polke et al.; (19)]. We hope that these developments will result in more insights about potential pathogenetic differences and disease behavior in ILDs around the world, in addition to promoting access to diagnosis and treatment, especially for middle- and low-income countries.

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Whilst prevention of ILD and reducing exposure to potential causative agents is crucial, this is a complex field. On one hand, country and even location specific interventions are necessary, whilst on the other hand, cross border agreements are crucial to reduce the important factor of air pollution (10, 20, 21). The pulmonary field should keep raising its united voice on the impact of air pollution on lung health. Meanwhile, international collaborative efforts with simple interventions could potentially have great impact, such as initiatives aimed at reducing household air pollution by supplying improved cookstoves (22).

Even though we all acknowledge the need for a more inclusive research field and more equality in access to care and treatment around the world, this is easier said than done. Barriers for conducting clinical trials include lack of financial and human capacity, ethical and regulatory obstacles, operational barriers and competing demands (23). In this issue, we aimed to achieve greater insights into the difference and similarities in ILD around the world by encouraging people from all over the world to submit their research in ILD. Furthermore, we wished to promote cross border collaborations between scientists and clinicians. This has resulted in 11 manuscripts on varying topics in ILD, written by 103 authors from 33 countries.

The manuscript of Kaul et al. describes the heterogeneity of ILD around the world by comparing 17 different epidemiological studies from all over the world. They demonstrate that hypersensitivity pneumonitis is more prevalent in Asia, and particularly in India, whilst in North America and Europe, IPF and sarcoidosis are more prevalent. They discuss the potential reasons and unknowns underlying such differences and call for organization of the ILD research community to develop a shared ontology for disease and collaborative epidemiological studies. That such projects are needed, but will be challenging, is further illustrated by four different studies presented in this ILD around the world issue.

These four studies illustrate that access to diagnosis and treatment, as well as disease phenotype may well-depend on the place you live. The work of van de Sar in collaboration with the European Pulmonary Fibrosis and related disorders federation, showed large differences in diagnostic access that exist between European countries (van der Sar et al.). Data from the well-known EMPIRE registry, comprising 10 central and eastern European countries, show clear differences in access to therapy as well as patient characteristics in a group of nearly 2,500 patients with IPF (Kolonics-Farkas et al.). Polke et al. surveyed 509 pulmonologists from 66 countries on prevention, diagnosis and treatment strategies of acute exacerbations of IPF, which yielded insights into similarities and differences across the world. Their effort also highlights the potential for large international surveys to guide future study design. Last, Gonzalez-Garcia et al. in four Latin American countries demonstrated the potential effect of living at high altitude on co-morbidities for patients with IPF, which supports the need for tailored diagnostic protocols depending on geography.

Health related quality of life (HRQOL) is an important outcome in the care of patients with ILD and is particularly influenced by an individual's cultural and spiritual background and values. Aronson and Suzuki provide an important and comprehensive overview of the global influences on HRQOL assessment and the different tools that exist to assess HRQOL around the world (Aronson and Suzuki). They also identify gaps and provide recommendations for improving HRQOL assessment across the world in ILD.

The research in this issue provides some, even if small, steps forward in our knowledge of ILD around the world. Moreover, we hope that this issue has accelerated new contacts and collaborations throughout the world. We are convinced that expanding our cross-continental networks will lead to more inclusive and conclusive research, which in the end will lead to better care for patients with ILD around the world.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Comorbidities of Patients With Idiopathic Pulmonary Fibrosis in Four Latin American Countries. Are There Differences by Country and Altitude?

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Background: Comorbidities in idiopathic pulmonary fibrosis (IPF) affect quality of life, symptoms, disease progression and survival. It is unknown what are the comorbidities in patients with IPF in Latin America (LA) and if there are differences between countries. Our objective was to compare IPF comorbidities in four countries and analyze possible differences by altitude.

Methods: Patients with IPF according 2012 ATS/ERS/JRS/ALAT guidelines, from two cities with an altitude of ≥2,250 m: Mexico City (Mexico) and Bogotá (Colombia) and from three at sea level: Buenos Aires (Argentina) and Lima and Trujillo (Peru). Comorbidities and pulmonary function tests were taken from clinical records. Possible pulmonary hypertension (PH) was defined by findings in the transthoracic echocardiogram of systolic pulmonary arterial pressure (sPAP) >36 mmHg or indirect signs of PH in the absence of other causes of PH. Emphysema as the concomitant finding of IPF criteria on chest tomography plus emphysema in the upper lobes. ANOVA or Kruskal Wallis and χ^2-tests were used for comparison.

Results: Two hundred and seventy-six patients were included, 50 from Argentina, 86 from Colombia, 91 from Mexico and 49 from Peru. There prevalence of PH was higher in Colombia and Mexico ($p < 0.001$), systemic arterial hypertension in Argentina ($p < 0.015$), gastro-esophageal reflux and dyslipidemia in Colombia and Argentina ($p < 0.001$) and diabetes mellitus in Mexico ($p < 0.007$). Other comorbidities were obesity (28.4%), coronary artery disease (15.2%) and emphysema (14.9%), with no differences between countries. There was more PH in the altitude cities than those at sea level (51.7 vs. 15.3%, $p < 0.001$). In patients from Bogotá and Mexico City, arterial oxygen pressure, saturation ($p < 0.001$) and carbon monoxide diffusing capacity ($p = 0.004$) were significantly lower than in cities at sea level.

Conclusions: In this study with a significant number of patients, we were able to describe and compare the comorbidities of IPF in four LA countries, which contributes to the epidemiological data of this disease in the region. The main results were the differences in comorbidities between the countries and more PH in the subjects residing in the cities of higher altitude, a finding that should be validated in future studies.

Keywords: idiopathic pulmonary fibrosis, comorbidities, Latin America, altitude, pulmonary hypertension

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic fibrosante interstitial disease, progressive, unknown-cause, which occurs mainly in older adults and is limited to the lung (1). Among idiopathic interstitial pneumonias is the most common, with an incidence of 3–9 cases per 100,000 and a prevalence of 18–20 cases per 100,000 (2–4). The natural history of IPF is of progressive decline in lung function, with an average survival of 3–5 years from diagnosis (2, 3, 5, 6).

Respiratory and non-respiratory comorbidities have been identified in IFP, some also associated with aging, being the most common are sleep apnea, pulmonary hypertension (PH) and gastroesophageal reflux (GER). These comorbidities affect patients' quality of life, can increase symptoms, contribute to disease progression and increase mortality (7, 8).

In Latin America there are no studies on the comorbidities associated with IPF. Taking into account the differences between the countries in terms of the prevalence of risk factors and comorbidities in the general population, we consider that there could be differences in the comorbidities of IPF. Additionally, in cities located at high altitude such as Mexico City (2,240 m) and Bogotá (2,640 m), due to the decrease in barometric pressure (PB) and inspired oxygen pressure, the alveolar (PAO_2) and arterial oxygen pressure (PaO_2) are lower compared to sea level. This PaO_2 decreases even more with age (9, 10) and in subjects with lung disease (6, 11–13). Although the decreased PAO_2 causes hypoxic pulmonary vasoconstriction, which can increase pulmonary artery pressure at less advanced stages of respiratory disease (14, 15), there are no studies reporting more PH in patients with IPF living at high altitude.

The respiratory and non-respiratory comorbidities of patients with IPF in Latin America are less known and whether they differ between countries in the region. Taking this into account and the fact that there are no comparative studies that have shown more pulmonary hypertension in patients with IPF living at high altitudes, our objective was to describe and compare IPF comorbidities in four Latin American countries and analyze possible differences by altitude.

Abbreviations: IPF, idiopathic pulmonary fibrosis; PH, pulmonary hypertension; TE, transthoracic echocardiogram; sPAP, systolic pulmonary arterial pressure; GER, gastroesophageal reflux; SAH, systemic arterial hypertension; CAD, coronary artery disease; DM, diabetes mellitus; CVD, cerebrovascular disease; CKD, chronic kidney disease; COAD, chronic occlusive arterial disease; A-aPO_2, alveolar-arterial oxygen tension gradient.

METHODS

Participants

Retrospective study in four Latin American countries. Expert groups on interstitial disease from five cities were asked for demographic data, respiratory function tests, echocardiography, and comorbidities of patients with IPF that meet the diagnostic criteria of the 2011 ATS/ERS/JRS/ALAT guidelines (1). The study included patients diagnosed between 2014 and 2018. The cities included and their altitude were: Bogotá, Colombia (2,640 m); Buenos Aires, Argentina (25 m); Mexico City, Mexico (2,240 m); Lima, Peru (150 m), and Trujillo, Peru (34 m). The study was approved by the Research Ethics Committee of the FNC (Approval Number 201902-24111) and the participants were asked for their authorization to be included in the study by signing an informed consent, maintaining the confidentiality of their data.

Clinical Data and Comorbidities

Clinical records were reviewed to establish the presence of comorbidities at the time of IPF diagnosis. The body mass index (BMI) was used to define obesity ($\geq$30) and underweight ($<$18.5). Emphysema was defined as the concomitant finding of IPF signs on chest tomography (CT) plus emphysema in the upper lobes. Possible PH was defined by findings in the transthoracic echocardiogram (TE) of systolic pulmonary arterial pressure (sPAP) $>$36 mm Hg or indirect signs of PH in the absence of other causes of PH: left ventricular systolic dysfunction with ejection fraction $<$40%, diastolic dysfunction greater than grade I or valvular disease greater to moderate (16). At the time of collecting the information on comorbidities in the clinical records of the patients, it was recorded whether the patients had died. Age, physiology, and comorbidities were used to calculate the TORVAN index, a validated predictive mortality index in IPF (17).

Pulmonary Function Test

Data of forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), FEV_1/FVC ratio, diffusion of carbon monoxide (DLCO), arterial blood gases, meters walked and oxygen saturation (SpO_2) during SMWT, were registered. To compare lung function between countries, the reference values for spirometry and DLCO were calculated in all participants using Crapo's equations (18, 19). The alveolar-arterial oxygen tension gradient (A-aPO_2) was calculated with the simplified alveolar gas equation using the BP of each city.

Data Analysis

In continuous variables, the assumption of normality was evaluated by the Kolmogorov Smirnov-test and they are presented as means and standard deviation or medians and interquartile ranges. In the qualitative variables, proportions were calculated. The ANOVA-test or the non-parametric Kruskall Wallis-test was used to compare demographic data, pulmonary function tests and TORVAN index among the four countries, and the χ^2-test was used to compare the proportions.

To evaluate possible differences in pulmonary hypertension due to altitude, participants with TE from the highest cities (Bogotá and Mexico) were compared with those from sea-level cities (Buenos Aires, Lima, and Trujillo). The Student's *t*-test or the Mann-Whitney-test was used for continuous variables, depending on the distribution of the data, and the χ^2-test for categorical variables. All *p*-values were two-tailed and values <0.05 were considered statistically significant. SPSS version 17 statistical software was used.

RESULTS

Participants

Two hundred and seventy-six patients were included, 50 from Argentina, 86 from Colombia, 91 from Mexico and 49 from Peru, with a mean age of 68.7 ± 8.8 years. Hundred percentage had the requested data, except for the TE result, which could not be obtained in 53 patients (19%). In 83.7% of cases, the pattern on chest CT was definitive UIP and in the remaining 16.3%, a surgical biopsy was performed to confirm the diagnosis. Eighty-one percentage of the total sample were men, with a lower percentage in Peru (59.2%) than other countries ($p < 0.001$). Patients from Argentina had a higher BMI than those from other countries ($p = 0.002$). The smoking index was higher in Argentina ($p < 0.001$) and the years of exposure to wood smoke was higher in Peru ($p < 0.001$). The FVC in the total group was 68.1 ± 19.3 with the highest values in the patients from Colombia ($p < 0.001$). The lowest DLCO values were in patients from Colombia and Mexico ($p < 0.001$). The other demographic data and respiratory function tests are in **Table 1**.

Comorbidities

The most frequent comorbidities in the four countries were PH, systemic arterial hypertension (SAH), GER and obesity (**Table 2**). There were significant differences between countries, with a higher prevalence of PH in Colombia and Mexico ($p < 0.001$), of SAH in Argentina ($p < 0.015$), of GER and dyslipidemia in Colombia and Argentina ($p < 0.001$) and of diabetes mellitus (DM) in Mexico ($p > 0.007$). 28.4% of the patients were obese, with no differences between countries ($p = 0.166$) and only 8 subjects (3.0%) of the total sample were underweight (BMI < 18.5). Other comorbidities such as coronary artery disease and the presence of emphysema on chest CT were also frequent, with no differences between countries (**Figure 1**). The presence of cerebrovascular disease, chronic kidney disease, atrial fibrillation, chronic occlusive arterial disease, and lung cancer was documented in <5% of the participants.

The median number of comorbidities per patient in Colombia and Argentina was two and in Mexico and Peru one ($P < 0.001$; **Table 2**). In the population studied, there were 60 patients (21.7%) without comorbidities, 62 (22.5%) with one comorbidity, 121 (43.8%) with two to three and 33 (12.0%) with four or more. The country with the highest percentage of patients without comorbidities was Peru (46.9%) and the countries with the highest percentage of patients with two or three comorbidities were Colombia and Argentina (56%) ($p < 0.001$; **Figure 2**).

At the time of collecting the information, 23.4% of the patients had died. This percentage of deceased patients was significantly higher in Mexico (47.3%) than in Colombia (23.4%), Argentina (10.9%) and Peru (6.1%) ($p < 0.001$). In the total group, the median TORVAN index was 16.0 (12.0–19.0) and it was significantly higher in Mexico than in Colombia, Argentina and Peru ($p < 0.001$; **Table 2**). Most of the patients in Mexico were classified in TORVAN stages III and V and in Argentina, Colombia and Peru in stages I and II ($p < 0.001$; **Figure 3**).

Differences by Altitude

Of the total of participants, 223 had TE (81%), 73% in cities at sea level and 85% in those of higher altitude. There were no differences in age ($p = 0.680$), sex ($p = 0.755$), or in FVC ($p = 0.392$) between patients with and without TE. The percentage of PH was significantly higher in cities with higher altitude than in those located at sea level, (51.7 vs. 15.3%, $p < 0.001$) (**Figure 4**). In patients with IPF from Bogotá and Mexico City, PaO_2, arterial carbon dioxide pressure ($PaCO_2$), SpO_2 at rest and during exercise, and DLCO were significantly lower than in cities at sea level (**Table 3**). In the cities of higher altitude there was more smoking (67.2 vs. 44.4%, $p < 0.001$), DM (23.7 vs. 13.3%, $p = 0.038$) and coronary heart disease (19.2 vs. 8.1%, $p = 0.014$) and there were no differences in the percentage of patients with emphysema on CT ($p = 0.103$).

DISCUSSION

In this study with a significant number of patients, we were able to describe and compare the comorbidities of IPF in four Latin American countries, which contributes to the epidemiological data of this disease in the region. The main results were the differences in comorbidities between the countries and the higher percentage of PH in the subjects residing in the cities of higher altitude.

As expected in IPF, most of the patients were men (81.5%) and with a high percentage of smoking (59.1%), higher than in the general population of these same countries (20–23). The number of comorbidities per patient was lower and the percentage of patients without comorbidities greater than that described in a previous study in Europa (24), although in the total group, 55.8% of the patients had 2 or more comorbidities. As relevant data, there were differences between countries in the number of comorbidities, being significantly higher in Argentina and Colombia.

TABLE 1 | Participants characteristics and lung function tests.

	Total *N* = 276	Colombia *N* = 86	Mexico *N* = 91	Argentina *N* = 50	Peru *N* = 49	*p*
Age, years	68.7 ± 8.8	69.7 ± 10.6	67.1 ± 7.7	68.5 ± 8.4	69.8 ± 7.8	0.180
Male sex	225 (81.5)	68 (79.1)	84 (92.3)	44 (88.0)	29 (59.2)	<0.001
BMI, kg/m^2	26.9 ± 4.5	26.6 ± 3.9	26.6 ± 3.9	29.1 ± 5.0	25.6 ± 5.5	0.002
Lung biopsy	45 (16.3)	13 (15.1)	22 (24.2)	9 (18.0)	1 (2.0)	0.009
Smoking history	163 (59.1)	63 (73.3)	56 (61.5)	39 (78.0)	5 (10.2)	<0.001
Smoking, pack-years	11.0 (2.5–30.0)	7.0 (1.0–30.0)	8.0 (2.3–20.0)	20.0 (12.0–40.0)	6.0 (3.0–30.0)	<0.001
Wood smoke exposure, years	10.0 (9.0–25.0)	7.0 (6.0–30.0)	10.0 (9.0–15.5)	-	20.0 (10.0–30.0)	0.362
FVC, % predicted	68.1 ± 19.3	75.8 ± 16.4	63.0 ± 19.1	66.5 ± 16.4	65.7 ± 22.7	<0.001
FEV_1, % predicted	72.6 ± 19.9	79.2 ± 18.1	67.1 ± 19.7	71.5 ± 16.3	72.5 ± 22.9	0.001
FEV_1/FVC, %	84.2 ± 7.8	82.0 ± 8.1	84.3 ± 7.7	84.4 ± 7.3	87.7 ± 6.6	0.001
DLCO, % predicted	47.0 ± 17.8	50.0 ± 13.6	40.4 ± 18.5	52.5 ± 18.7	58.9 ± 23.9	<0.001
$PaCO_2$, mmHg	35.4 ± 4.9	34.9 ± 3.3	32.3 ± 4.4	38.9 ± 3.9	42.0 ± 6.2	<0.001
PaO_2, mmHg	60.2 ± 14.2	52.5 ± 7.7	55.7 ± 9.0	83.2 ± 9.6	72.6 ± 5.5	<0.001
SaO_2, %	88.3 ± 5.9	86.4 ± 4.9	86.6 ± 6.1	94.9 ± 1.8	92.9 ± 3.2	<0.001
A-aPO_2, mmHg	15.0 ± 8.9	11.5 ± 7.1	16.6 ± 9.0	17.9 ± 10.5	23.3 ± 6.6	<0.001
SMWT						
Distance, m	425.1 ± 119.4	471.8 ± 111.1	419.8 ± 131.3	403.9 ± 97.2	356.1 ± 113.6	0.001
SpO_2 at the end of the test, %	92.1 ± 3.6	88.9 ± 3.0	92.4 ± 2.6	94.8 ± 2.4	94.7 ± 2.2	<0.001
SpO_2 end of the test, %	82.8 ± 7.7	77.7 ± 6.1	81.9 ± 6.7	87.4 ± 6.7	89.2 ± 6.0	<0.001

P = differences between countries. Values as mean ± SD, median (P25–P75) or N (%).
BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second; DLCO, carbon monoxide diffusing capacity; PaO_2, arterial oxygen pressure; $PaCO_2$, carbon dioxide arterial pressure; HCO_3, bicarbonate; SaO_2, oxygen arterial saturation; A-aPO_2, alveolar-arterial oxygen tension gradient; SMWT, six-minute walking test; SpO_2, oxygen saturation by pulse oximetry.

TABLE 2 | Comorbidities by country.

	Total *N* = 276	Colombia *N* = 86	Mexico *N* = 91	Argentina *N* = 50	Peru *N* = 49	*p*
Number of comorbidities	2.0 (1.0–3.0)	2.0 (1.0–3.0)	1.0 (0.0–2.0)	2.0 (1.0–3.0)	1.0 (0.0–2.0)	<0.001
Pulmonary hypertension	89 (39.9)	38 (47.5)	40 (56.3)	5 (10.4)	6 (25.0)	<0.001
SAH	105 (38.0)	36 (41.9)	25 (27.5)	27 (54.0)	17 (34.7)	0.015
GER	93 (33.9)	37 (43.0)	14 (15.4)	34 (70.8)	8 (16.3)	<0.001
Obesity	77 (28.4)	22 (25.6)	23 (25.3)	19 (42.2)	13 (26.5)	0.166
Diabetes	55 (20.0)	13 (15.1)	29 (31.9)	7 (14.3)	6 (12.2)	0.007
Dyslipidemia	52 (19.3)	27 (31.4)	7 (7.7)	16 (36.4)	2 (4.2)	<0.001
Coronary artery disease	42 (15.2)	17 (19.8)	17 (18.7)	5 (10.0)	3 (6.1)	0.093
Emphysema	41 (14.9)	17 (19.8)	14 (15.4)	8 (16.3)	2 (4.1)	0.101
Hypothyroidism	30 (10.9)	22 (25.6)	1 (1.1)	6 (12.0)	1 (2.0)	<0.001
Cerebrovascular disease	11 (4.0)	2 (2.3)	4 (4.4)	4 (8.2)	1 (2.0)	0.379
Chronic kidney disease	7 (2.5)	4 (4.7)	1 (1.1)	0 (0.0)	2 (4.1)	0.056
Atrial fibrillation	5 (1.8)	2 (2.3)	0 (0.0)	1 (2.0)	2 (4.1)	0.212
COAD	4 (1.5)	0 (0.0)	1 (1.1)	1 (2.0)	2 (4.1)	0.231
Lung cancer	1 (0.4)	1 (1.2)	0.0 (0.0)	0 (0.0)	0 (0.0)	0.505
TORVAN index, points	16.0 (12.0–19.0)	16.0 (13.0–18.0)	19.0 (16.0–22.0)	13.5 (9.0–18.0)	14.0 (9.0–16.0)	<0.001

Values as N (%) or median (P25–P75). P: differences between countries.
SAH, systemic arterial hypertension; GER, gastroesophageal reflux; COAD, chronic occlusive arterial disease.

The most frequent respiratory comorbidities in the four countries were PH and emphysema. The percentage of patients with PH was 39.9%, similar to previous studies. In the systematic review by Raghu (7), the informed prevalence of PH was between 3 and 86%, although most of the data were between 30 and 50%. In 22 (51.2%) of the 43 studies analyzed in this review,

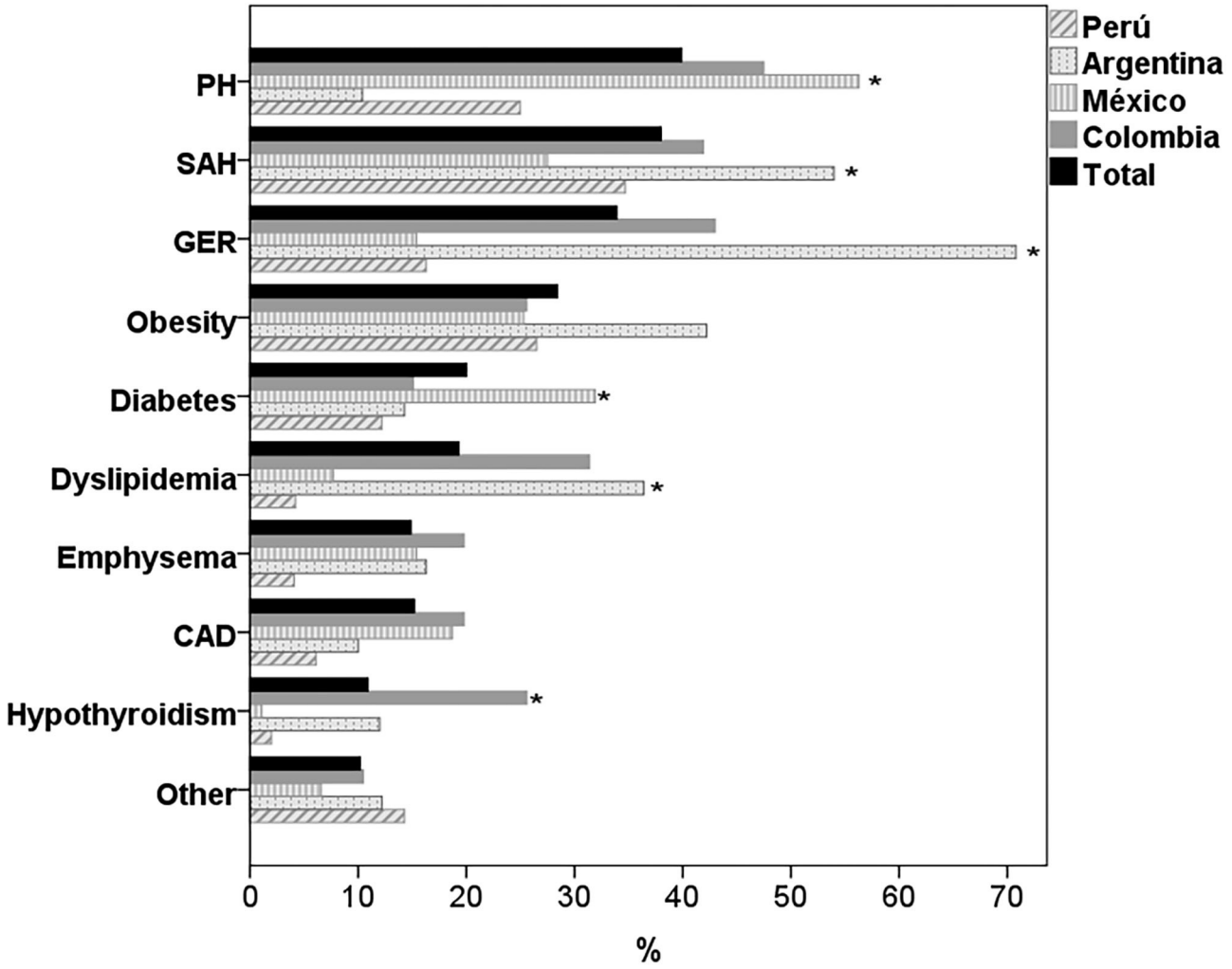

FIGURE 1 | Comorbidities in patients with IPF by country. PH, pulmonary hypertension; SAH, systemic arterial hypertension; GER, gastroesophageal reflux; CAD, coronary artery disease. *$p < 0.05$ for differences between countries.

the prevalence was estimated by sPAP values in the TE with cut-off points between 35 and 40 mmHg, similar to that used in this study. In the studies in which right catheterization was used, which is considered the gold standard for the diagnosis of pulmonary hypertension, the reported prevalence was between 29 and 46% (25).

We highlight the higher percentage of subjects with PH in the TE in the cities of higher altitude (51.7 vs. 15.3%, $p < 0.001$). The mechanism of hypoxic vasoconstriction with a secondary increase in pulmonary vascular resistance triggered by lower PAO_2 values at altitude, the pulmonary artery remodeling described in long-term exposure to hypoxia and the erythrocytosis described in altitude in healthy subjects and in patients with respiratory disease (10, 26), could explain the development of PH in these patients (14, 15). Along the same lines of our data, in previous studies in Mexico City and Bogotá, high prevalence of PH have been described in patients with chronic respiratory disease (27, 28).

As expected, there were differences in arterial blood gases between cities of different altitude. In patients from Bogotá and Mexico City, $PaCO_2$ was lower, explained by the adaptive mechanism of hyperventilation at altitude (10, 29). Due to the decrease in PAO_2, PaO_2 and saturation at rest and during exercise were significantly lower in patients from higher altitude cities. Although the DLCO decrease is a characteristic functional finding of IPF, it was even lower in patients from higher altitude cities, despite having less involvement of the FVC and not having greater emphysema on chest CT, which could be explained due to possible PH in these patients.

Similar to the studies in PH, different definitions have been used to establish the prevalence of emphysema in IPF, such as disease diagnosis codes, questionnaires, pathology findings or CT scan (7). In the studies that have used CT with the definition of the presence or absence of emphysema, without its quantification, the reported prevalence is from 19 to 67% and in those that used the quantification of the extent of

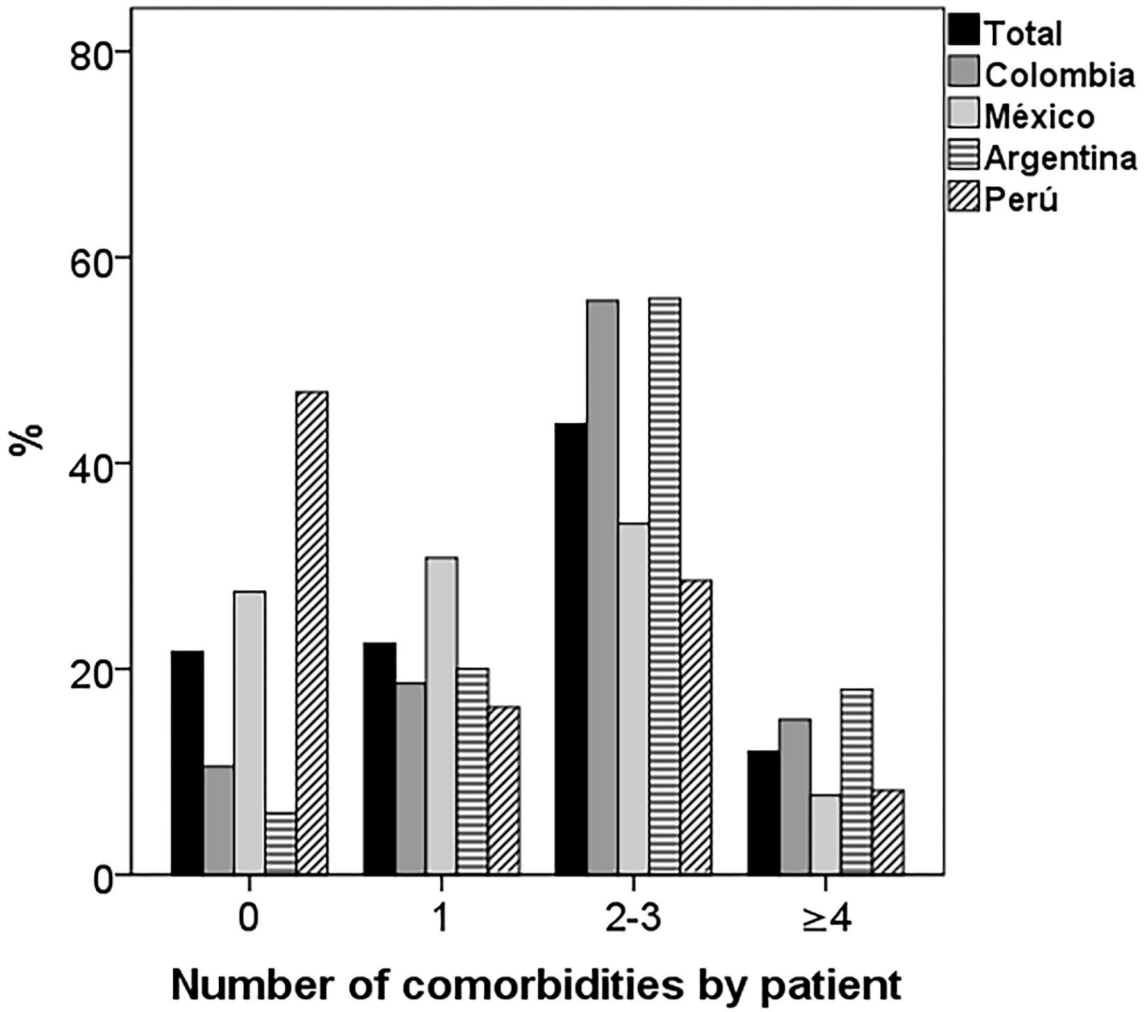

FIGURE 2 | Number of comorbidities per patient by country. There were significant differences in the distribution of comorbidities by country. Most of the patients from Peru and Mexico had one or no comorbidity and those from Colombia and Argentina two or three ($p < 0.001$).

emphysema from 8 to 28%. In this study, the prevalence of emphysema was lower (14.9%) and there were no differences between countries, although there were differences in exposure to tobacco and wood smoke. The smoking rate was higher in Argentina and the years of exposure to wood smoke was higher in Peru.

The most frequent non-respiratory comorbidities in the four countries were SAH, GER, obesity, and DM. The prevalence of SAH in these patients was high (38.0%), although it was similar to some series of patients with IPF (7, 24). The highest percentage of SAH was in Argentina, a country with a higher prevalence of this disease in the general population compared to what was described in Colombia, Mexico and Peru (20–23). 28.4% of the patients were obese, similar to that described in other IPF studies (7, 30). Compared with the general population of these countries, this percentage of obesity was higher than that reported in Peru and Colombia, but lower than that described in Argentina and Mexico (20–23).

Using the cut-off point of BMI $\geq$ 30 to define obesity, there were no significant differences between countries ($P = 0.166$), but there were differences in BMI, which was significantly higher in patients from Argentina ($P = 0.002$). A low percentage of the study patients (3.0%) were underweight, a factor that has been related to a poor prognosis of the disease, as well as weight loss during follow-up (30, 31). The prevalence of DM (20%) was similar to that reported in other studies (10–40%) (7, 32). We highlight that the prevalence of 31.9% of DM in IPF patients from Mexico was significantly higher than the other countries ($p < 0.001$), despite the fact that the prevalence in the general population in the four countries, including Mexico, is <15% (20–23).

The prevalence of GER reported in IPF is highly variable, with values up to 90%, which could be related to the definition used. In the four countries it was 33.9%, but with significant differences between countries, with the highest prevalence in Argentina (70.8%) and the lowest in Mexico and Peru. Hypothyroidism

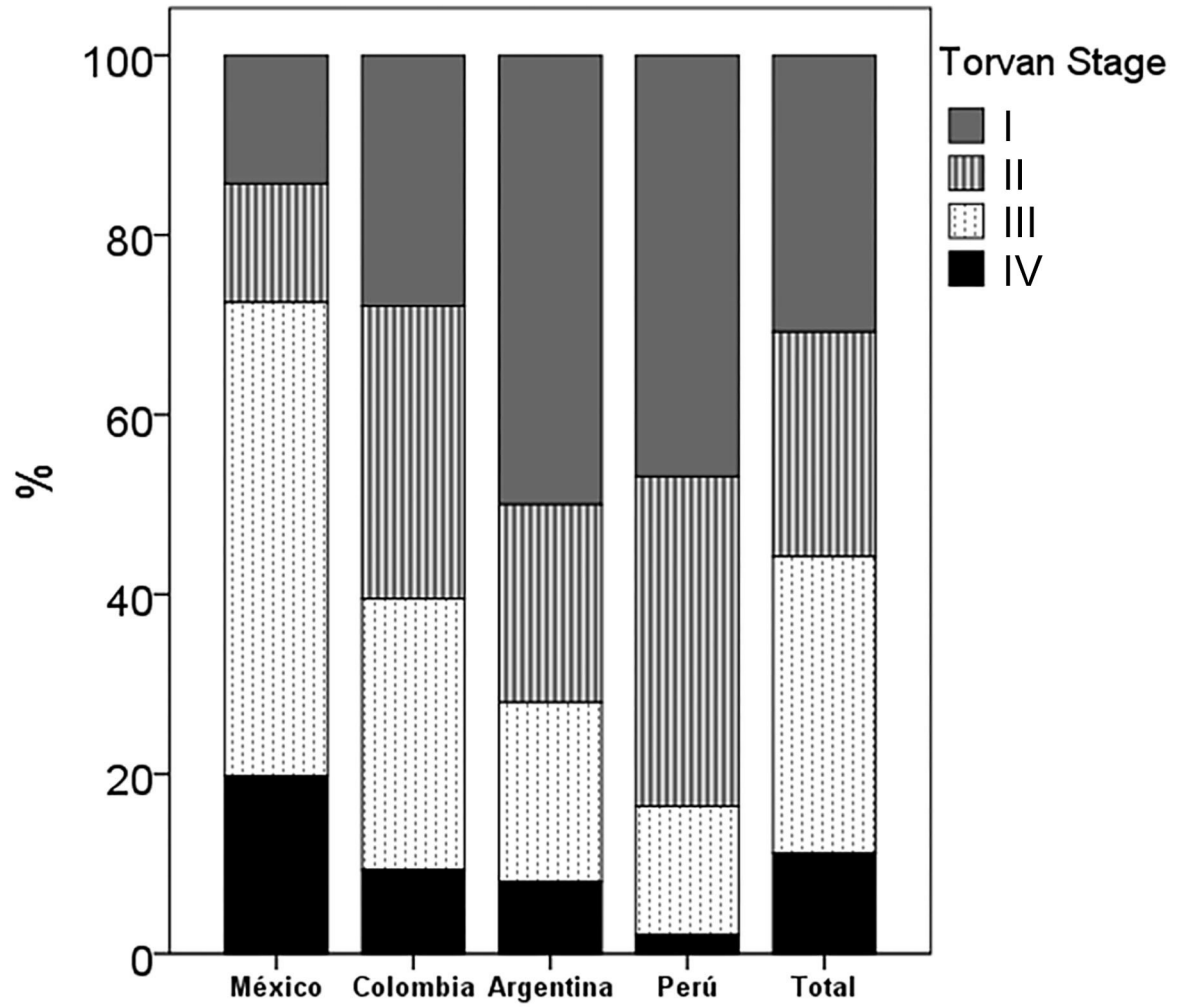

FIGURE 3 | Proportion of patients in the TORVAN states in the total group and in each country. In Mexico, there were more patients in stages III-IV and in Argentina, Colombia and Peru in stages I-II ($p < 0.001$).

is another comorbidity of IPF associated with higher mortality (33). The prevalence of 10.9% in these patients was similar to that reported in other IPF studies and higher than that of the general population reported in studies from other countries (7, 32, 33).

The other comorbidities included in the study had a low frequency, such as cerebrovascular disease, chronic kidney disease, atrial fibrillation, chronic occlusive arterial disease, valvular heart disease and lung cancer, which were present in <5% of the participants. It is noteworthy that in the subjects of these four countries, the percentage of lung cancer was very low (0.4%) and lower than that reported in the literature (4 to 23%) (7, 34), which is probably explained by the significantly lower incidence of lung cancer in the general population of Latin American countries compared to the United States, Europe and Asia (35, 36). Among the patients from the four countries, there were no differences in age, a factor related to greater morbidity, mortality, and use of health resources in patients with IPF (37). Additionally, aging and smoking are part of the pathophysiology of IPF and other coexisting diseases such as emphysema and lung cancer (8, 38, 39).

Although we were unable to perform a mortality analysis that included comorbidities, we observed differences between countries with a significantly higher percentage of dead patients in Mexico. Similarly, the TORVAN mortality prediction index had the same trend between countries. Patients from Mexico had a significantly higher TORVAN score than in the other countries and most of these patients were classified into TORVAN stages III and IV, unlike patients from Colombia, Argentina, and Peru, who were mostly classified as stage I and II. Taking into account that the patients were of similar age, the differences in TORVAN between countries could be explained by a greater functional compromise (lower DLCO and FVC) and a higher percentage of PH and DM in patients from Mexico than in other countries.

The differences in the frequency of comorbidities, between the study countries and with that described in the literature, could be explained by the differences in the lifestyle and diet

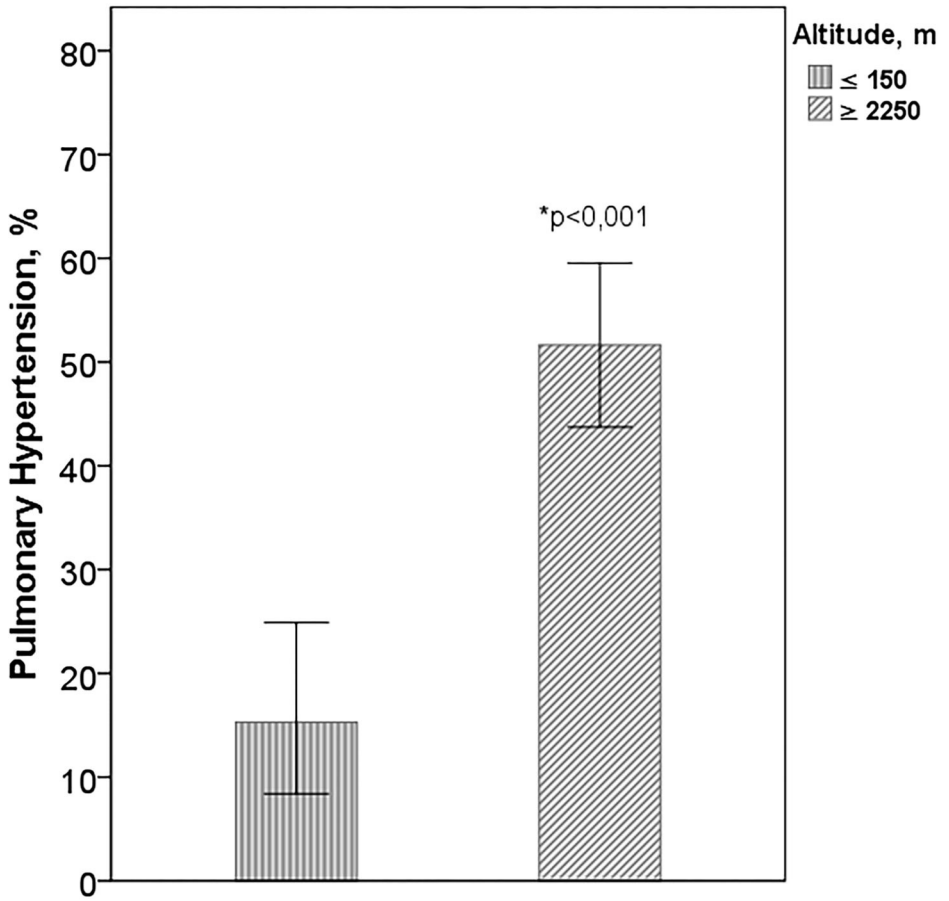

FIGURE 4 | Pulmonary hypertension according to altitude. Altitude: ≥2,250 m Mexico City and Bogotá; ≤150 m: Buenos Aires, Lima, and Trujillo. *Difference between the cities of higher altitude with those of sea level.

of the populations, the history of exposure to tobacco and the prevalence of these comorbidities in general population. Although the study countries belong to the same geographic region, there are important differences between them in the comorbidities reported in national studies of risk factors in the general population (20–23). On the other hand, the differences in comorbidities reported in studies from Europe and the United States can be related to the aforementioned differences in lifestyles, diet and comorbidities in the general population, and probably in the used methodology; as differences in diagnostic methods, the lack of standardized definitions of some comorbidities such as the percentage of extension of emphysema on CT or differences in the diagnostic method used for others such as GER, and the prospective design of several of these studies (7, 25, 40).

As strengths of this work, we highlight that it is the first study in Latin America with a significant number of patients that describes the comorbidities in IPF and the differences between countries, as well as the presence of more pulmonary hypertension in patients with IPF living at altitude. Although this finding could be expected due to the explained pathophysiological mechanisms related to low PAO_2, hypoxic vasoconstriction, increased pulmonary vascular resistance, pulmonary artery remodeling and erythrocytosis, there are no previous studies that have demonstrated a higher prevalence of PH in patients with IPF who live at high altitudes compared to those who live at sea level. We believe that this study contributes to the knowledge of the clinical behavior of IPF and the epidemiology of this disease in the region. Although the TE is not a confirmatory examination of PH, it is accepted that it is a useful tool to establish a diagnosis of possible PH and, as already commented, most of the studies that have established the prevalence of PH in IPF were based on a methodology similar to that used in this study, which allowed us to compare our results (7). It should be noted that due to the age and functional characteristics of patients with IPF, it is generally difficult to perform right catheterization in these patients.

This study has several weaknesses related to the retrospective design based on the clinical reports of the patients. Unlike prospective studies, the possibility of underreporting comorbidities is greater. In addition, we did not have information on the treatment of comorbidities, which may have an impact on the outcomes of the disease, and on the improvement of the quality of life and symptoms of the patients. It is important to

TABLE 3 | Characteristics of participants with echocardiogram by altitude.

	Total	Altitude ≤150 m	Altitude ≥ 2,250 m	*p*
	N = 223	*N* = 72	*N* = 151	
Age, years	68.6 ± 9.1	69.3 ± 8.3	68.3 ± 9.5	0.461
BMI, kg/m^2	27.2 ± 4.4	27.5 ± 5.5	27.0 ± 3.8	0.504
Pulmonary hypertension	89 (39.9)	11 (15.3)	78 (51.7)	<0.001
sPAP, mmHg	43.5 ± 19.7	31.9 ± 15.7	47.5 ± 19.5	<0.001
FVC, % predicted	68.7 ± 18.3	64.1 ± 17.0	70.7 ± 18.5	0.014
FEV_1, % predicted	73.1 ± 19.0	70.2 ± 17.6	74.3 ± 19.5	0.140
FEV_1/FVC, %	84.0 ± 7.9	86.1 ± 7.2	83.0 ± 8.1	0.006
DLCO, % predicted	48.3 ± 17.7	55.0 ± 18.9	46.3 ± 16.9	0.004
$PaCO_2$, mmHg	35.9 ± 4.9	40.3 ± 5.1	34.4 ± 3.9	<0.001
HCO_3, meq/L	23.4 ± 2.9	25.5 ± 3.0	22.6 ± 2.5	<0.001
PaO_2, mmHg	59.4 ± 15.0	81.3 ± 9.4	52.6 ± 8.1	<0.001
SaO_2, %	87.9 ± 6.2	94.2 ± 2.7	85.9 ± 5.6	<0.001
A-aPO_2, mmHg	15.1 ± 9.8	18.0 ± 8.8	13.7 ± 8.7	0.060
SMWT				
Distance, m	428.7 ± 121.3	396.7 ± 103.4	448.0 ± 127.8	0.021
SpO_2 at the end of the test, %	92.1 ± 3.8	95.0 ± 2.4	90.5 ± 3.5	<0.001
SpO_2 end of the test, %	82.9 ± 7.8	88.3 ± 6.4	79.8 ± 6.7	<0.001

Values as mean ± SD, or N (%).
P: differences by altitude.
BMI, body mass index; sPAP, systolic pulmonary arterial pressure; FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second; DLCO, carbon monoxide diffusing capacity; PaO_2, arterial oxygen pressure; $PaCO_2$, carbon dioxide arterial pressure; HCO_3, bicarbonate; SaO_2, oxygen arterial saturation, A-aPO_2, alveolar-arterial oxygen tension gradient; SMWT, six-minute walking test; SpO_2, oxygen saturation by pulse oximetry.
Altitude: ≥2,250 m Mexico City and Bogotá; ≤150 m: Buenos Aires, Lima, and Trujillo.

highlight that in some comorbidities, such as GER, the effect of antacid therapy on disease progression and mortality has been studied. Although benefit in these outcomes has been suggested with proton pump inhibitors (41), most studies have not shown an impact on the progression or survival of IPF (42–44).

An important limitation of the study is that we were unable to perform a multivariate analysis of mortality that included comorbidities. Even so, we found significant differences between countries in the percentage of mortality, which correlated well with the result of the TORVAN index. Also, the evaluation of various IPF comorbidities was not possible. First of all, we do not have data on sleep apnea, a comorbidity described in up to 90% of IPF patients (7, 32), which has been associated with greater cardiovascular comorbidity and risk of death due to intermittent nocturnal hypoxemia (45, 46). Another comorbidity not evaluated was pulmonary embolism, an entity related to higher mortality, but with a low prevalence in IPF (7, 8, 32).

The importance of comorbidities in the clinical course of patients with IPF is clearly recognized, so their identification, treatment and management are part of the comprehensive evaluation of these patients (8, 17, 24, 25). In Latin America, prospective studies are required that include all IPF comorbidities, with standardized definitions, which allow evaluating the impact of these comorbidities on clinical outcomes such as disease progression and mortality.

CONCLUSION

In this study with a significant number of patients, we were able to describe and compare the comorbidities of the IPF in four LA countries, which contributes to the epidemiological data of this disease in the region. The main results were the differences in comorbidities between the countries and the higher percentage of PH in the patients residing in the cities of higher altitude, a finding that should be validated in future prospective studies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Fundación Neumologica Colombiana Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MG-G, ER-Á, and IB-R contributed to the conceptualization and design of the study. MG-G drafted the initial manuscript and guarantor of this work. All authors contributed to data abstraction and analysis, contributed to manuscript writing, and approved the submission of the final manuscript.

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Desaturation-Distance Ratio During Submaximal and Maximal Exercise Tests and Its Association With Lung Function Parameters in Patients With Lymphangioleiomyomatosis

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Background: The desaturation–distance ratio (DDR), the ratio of the desaturation area to the distance walked, is a promising, reliable, and simple physiologic tool for functional evaluation in subjects with interstitial lung diseases. Lymphangioleiomyomatosis (LAM) is a rare neoplastic condition frequently associated with exercise impairment. However, DDR has rarely been evaluated in patients with LAM.

Objectives: To assess DDR during maximal and submaximal exercises and evaluate whether DDR can be predicted using lung function parameters.

Methods: A cross-sectional study was conducted in a cohort of women with LAM. The 6-min walking test (6MWT) and the incremental shuttle walking test (ISWT) were performed, and DDR was obtained from both tests. The functional parameters were assessed at rest using spirometry and body plethysmography. The pulmonary function variables predictive of DDR were also assessed.

Results: Forty patients were included in this study. The mean age was 46 ± 10 years. Airway obstruction, reduced DL_{CO}, and air trapping were found in 60, 57, and 15% of patients, respectively. The distance walked and the DDR for the 6MWT and ISWT were, respectively, 517 ± 65 and 443 ± 127 m; and 6.6 (3.8–10.9) and 8.3 (6.2–12.7). FEV_1 (airway obstruction) and reduced DL_{CO} and RV/TLC (air trapping) were independent variables predictive of DDR during exercises field tests [$DDR_{6MWT} = 18.66–(0.06 \times FEV_{1\%pred})–(0.10 \times DL_{CO\%pred}) + (1.54 \times$ air trapping), $R^2_{adjust} = 0.43$] and maximal [$DDR_{ISWT} = 18.84–(0.09 \times FEV_{1\%pred})–(0.05 \times DL_{CO\%pred}) + (3.10 \times$ air trapping), $R^2_{adjust} = 0.33$].

Conclusion: Our results demonstrated that DDR is a useful tool for functional evaluation during maximal and submaximal exercises in patients with LAM, and it can be predicted using airway obstruction, reduced DL_{CO}, and air trapping.

Keywords: lymphangioleiomyomatosis, exercise tests, respiratory function tests, lung volume measurements, lung diseases

INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a rare neoplastic cystic lung disease that affects, mainly women, ∼5 persons per million (1). It is characterized by the proliferation of abnormal smooth muscle-like LAM cells, resulting in vascular and airway obstruction and cyst formation (2). LAM's main clinical features are progressive dyspnea, pneumothorax, and chylothorax (3). An obstructive pattern, with air trapping, and a reduction in the diffusion capacity of the lungs for carbon monoxide (DL_{CO}) are the most common abnormalities found during pulmonary function tests (PFTs) (4, 5). Functional impairment in subjects with LAM is frequently associated with exercise limitation (6, 7) that seems multifactorial, including ventilatory and gas exchange abnormalities, cardiovascular dysfunction, and muscle fatigue (7–9).

The 6-min walk test (6MWT) is a submaximal exercise test that is widely used to objectively assess the functional exercise capacity in patients with moderate-to-severe pulmonary disease (10), including LAM (7, 11). Although the distance walked is the primary outcome obtained during the 6MWT, other indexes that incorporate desaturation during the test, such as the desaturation–distance ratio (DDR), have been developed. The DDR is the ratio of the desaturation area to the distance walked. DDR has been considered predictive of morbidity and mortality in patients with other respiratory conditions, such as chronic pulmonary obstructive disease (COPD), pulmonary arterial hypertension, idiopathic pulmonary fibrosis, LAM, and those on the waiting list for lung transplantation (12–14). In addition, DDR is associated with pulmonary function and peripheral oxygen saturation (SpO_2) in patients with interstitial lung diseases (ILDs) (15).

The incremental shuttle walk test (ISWT) is a field test that has been commonly used to quantify maximal exercise capacity. It is already known that 6-min walking distance (6MWD) has a good linear relationship with maximal exercise capacity (VO_2peak); however, most patients reach a ceiling effect during 6MWT (16). Likewise, previous studies demonstrated that 6MWT might not properly evaluate physical capacity in patients with LAM (7, 11, 17). Therefore, other field tests should be tested in this population. The ISWT is a more standardized test that has been used to quantify exercise capacity in patients with chronic respiratory diseases leading to similar physiological responses than the cardiopulmonary exercise test (CPET) (10). However, the performance of patients with LAM and DDR values during the ISWT remains unknown. Therefore, our objectives were to assess DDR during ISWT and 6MWT and evaluate whether DDR is associated with lung function parameters.

METHODS

Trial Design and Participants

This cross-sectional single-center study was conducted from September 2018 to January 2020 in a cohort of women with LAM from the ILD outpatient clinic of the Pulmonary Division from a tertiary university hospital in São Paulo, Brazil. The diagnosis of LAM was based on the current guidelines (3, 18) that include pulmonary function, computed tomography, and serum analysis. The protocol was approved by the Hospital Research Ethics Committee (90196617.1.0000.0068), and all patients signed an informed consent form. The patients were clinically stable (no exacerbation/hospitalization for the last 6 weeks) (18), and they maintained peripheral resting oxygen saturation (SpO_2) of $\geq$ 88% in room air. The exclusion criteria were: supplementary oxygen use, other chronic respiratory diseases, musculoskeletal disorders or uncontrolled heart disease, pregnancy, lung transplantation, or any other disabling condition that could interfere with the tests.

Experimental Design

The patients were evaluated during two nonconsecutive visits (maximum 7 days apart). During visit 1, the clinical and anthropometric data were obtained, and the subjects performed PFTs. After recovery, subjects were randomly assigned (http://www.randomization.com) for 6MWT or ISWT by an investigator not involved in the assessments. The allocations were sealed in opaque envelopes. If the subject performed the 6MWT during visit 1, the ISWT was performed during visit 2, and vice versa. DDR was evaluated during both tests.

Measurements

Clinical and Anthropometric Evaluations

The following data were obtained: age, weight, height, identification and contact information, pathological antecedents, presence of comorbidities, and medication use.

Pulmonary Function Tests

Spirometry and body plethysmography (Bodystik Geratherm Respiratory GmbH, Bad Kissingen, Germany) were performed to obtain lung volumes (forced expiratory volume in 1 s, FEV_1, and residual volume, RV), capacities (inspiratory capacity, IC; forced vital capacity, FVC; functional residual capacity, FRC and total lung capacity, TLC), and DL_{CO}. The predicted values were based on the Brazilian population (19–21). The obstructive pattern, air trapping, and reduced DL_{CO} were defined according to the American Thoracic Society/European Respiratory Society criteria (22).

Peripheral Muscle Strength

Quadriceps strength was measured with a load cell integrated into a circuit in a chair fixed on a wooden plank. The load cell was previously calibrated and attached to the base of the chair with an inextensible strap. One side of the strap was fixed in the right ankle and the other in the load cell, keeping the knee flexed at 90°. During the test, the patient was asked to cross the arms on the chest and extend the knee. Three consecutive 5-s efforts were made at 30-s intervals, with visual feedback and verbal encouragement from the investigator. The maximum value was used in the analysis (23).

Dyspnea and Leg Fatigue Perception

The modified Borg scale was used to evaluate the intensity of dyspnea and leg fatigue, by quantifying the effort during the exercise—within a range from 0 to 10 points, where 0 indicated

the absence of symptoms and 10 indicated the worst perception of dyspnea and leg fatigue (24).

Field Exercise Tests

Six-Minute Walking Test

The patient was asked to walk as far as possible along a 30-m corridor for 6-min. The 6-min walk distance (6MWD) was obtained at the end of the test (25). The predicted values for the distance walked were based on the Brazilian population (26). The tests were discontinued if SpO_2 decreased below 80% (10). Before and after the test, heart rate (HR), blood pressure (BP), minimum SpO_2 maintained for at least 10 s, dyspnea, and fatigue symptoms (Borg scale) were assessed. It was considered desaturation if SpO_2 decreased by 4% from the basal level (27).

Incremental Shuttle Walking Test

The ISWT was conducted in an unobstructed and quiet 10-m corridor. The walking speed was determined using a standardized audio signal (beep) that started at 0.5 m/s and was progressively increased by 0.17 m/s every minute for a maximum of 20-min. The ISWT was terminated when the patient indicated that she could not continue or if the operator observed that the patient could not sustain the speed and cover the distance to the cone before the beep (28). $SpO_2 < 80\%$ was considered as the criterion for test discontinuation (10). Before and after the test, the HR, BP, minimum SpO_2 maintained for at least 10 s, dyspnea, and fatigue symptoms (Borg scale) were assessed. Desaturation was characterized by a decrease in SpO_2 of 4% from the basal level (27).

Desaturation–Distance Ratio

The DDR was the ratio of the desaturation area to the distance walked during the exercise tests. DDR was previously described by Pimenta et al. (15), who considered desaturation and distance walked as equally important variables for pulmonary functional assessment. During the 6MWT and ISWT, the patient used at pulse Holter oximeter (Nonin WristOxH 3100, Plymouth, MN, USA) to record SpO_2 and HR every 2 s. All SpO_2 values were obtained and recorded using software (nVISIONH, Plymouth, MN, USA). The desaturation area graph was plotted (DAO_2, desaturation vs. time). DDR was calculated as the ratio of oxygen desaturation area (area under the curve) to the distance walked by the patient (DAO_2/distance walked; **Figures 1A,B**). The patients who performed worst during the tests had higher DDR values.

Statistical Analysis

Data are reported as the mean ± SD for variables with a parametric distribution or as the median (25–75% interquartile range) for the variables with a non-parametric distribution. The Pearson correlation coefficient was used to evaluate the association between the DDRs during the 6MWT (6MWT-DDR) and ISWT (ISWT-DDR) (dependent variables) and selected functional parameters (FEV_1/FVC, FEV_1/FVC%pred, FVCliters, FVC%pred, FEV_1liters, FEV_1%pred, FEV_1/FVC%, TLCliters, TLC%pred, Ratio RV/TLC and RV/TLC%pred, DL_{CO} absolute, DL_{CO}%pred). The linear correlation (r) was considered weak (from −0.3 to 0.3), moderate (from −0.5 to −0.31 or 0.31 to 0.5), strong (from −0.9 to −0.51 or 0.51 to 0.9), or very strong (from −1.0 to −0.91 or 0.91 to 1.0), according to Cohen's classification (29). A forward multiple linear regression analysis was performed, involving variables with linear correlation ($p < 0.2$). The best predictive models were constructed using the best independent coefficient. Receiver operating characteristic (ROC) curves were used to evaluate the sensitivity and specificity of the DDR for every field test. The optimal cut-point was calculated to predict airway obstruction ($\%FEV_1 < 80\%$) (19), reduced DL_{CO} ($DL_{CO} < 75\%$) (22), and air trapping (RV/TLC > 120%) (22). The optimum cutoff points were defined according to the Youden index (30). The level of significance was set at 5% ($p < 0.05$). The data were analyzed using Sigma Stat version 3.5 (Systat Software, Inc., San Jose, CA).

RESULTS

Sixty women were invited. Twenty declined to participate because they lived far from the hospital and would not honor the second appointment. Therefore, 40 women were included, and their clinical, anthropometric, and functional data are presented in **Table 1**. On average, patients showed peripheral muscle strength weakness (58.7% of the predicted). Obstructive pattern, air trapping, and reduced DL_{CO} were found in 60, 57, and 15% of patients, respectively. Twenty-seven patients (67%) were considered as "desaturators" (decrease of >4% from basal SpO_2) during the 6MWT, and 36 patients (90%) presented with desaturation during the ISWT. Nineteen (47.5%) patients were not able to reach the speed imposed by the audio signal during the ISWT, and 21 (52.5%) patients were limited by their symptoms (16 due to dyspnea and 5 due to fatigue). The DDRs obtained during the 6MWT and ISWT were 6.6 (3.8–10.9) and 8.3 (6.2–12.7), respectively.

There were significant linear correlation between the DDR during the 6MWT and ISWT and the independent variables FEV_1 ($r = -0.54$, $p < 0.001$, and $r = -0.58$, $p < 0.001$, respectively), DL_{CO} ($r = -0.62$, $p < 0.001$, and $r = -0.50$, $p < 0.001$, respectively), and RV/TLC ($r = 0.34$, $p = 0.03$, and $r = 0.49$, $p < 0.001$, respectively; **Figures 2A–F**).

The results of the ROC analysis show a high accuracy (area under the ROC curve [AUC] > 0.7) of 6MWT-DDR and ISWT-DDR for predicting airway obstruction ($\%FEV_1 < 80\%$), reduced lung diffusion ($D_{LCO} < 75\%$), and air trapping (RV/TLC > 120%; **Table 2**).

The best multivariate association models were constructed using the variables with the best independent coefficients of determination (R^2). DDRs during 6MWT (DDR_{6MWT}) and ISWT (DDR_{ISWT}) for both models included only FEV_1 (%pred) and DL_{CO} (%pred) and air trapping as a dichotomic variable (where RV/TLC>120% = 1; RV/TLC<120% = 0) were independent variables. In a stepwise multiple linear regression model, the derived prediction equations were as follows:

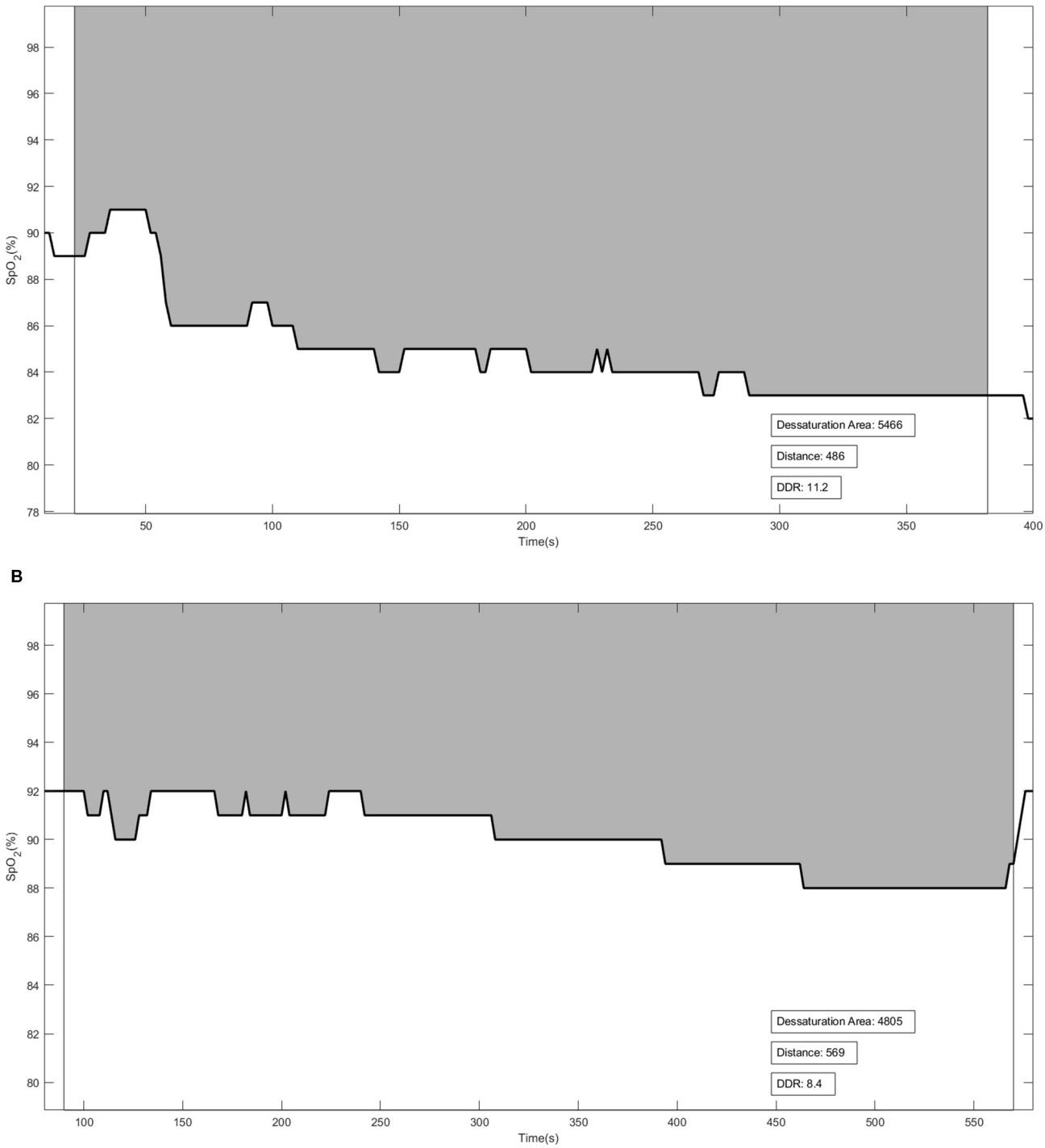

FIGURE 1 | Illustrative figures of the Desaturation-Distance Ratio (DDR) during the 6-min walking test (6MWT) **(A)** and incremental shuttle walking test (ISWT) **(B)**. The solid line represents the oxygen desaturation during the test. DDR was calculated using the ratio between DAO_2 [the gray area—obtained by subtraction between each recorded SpO_2 at every 2 s from 100% (maximal SpO_2)] and the distance walked. Distance in meters.

TABLE 1 | Baseline anthropometrical, clinical, and functional characteristics of the patients with LAM.

Variables	*N* = 40	
Anthropometric data		
Age (years)	46.60 (1.07)	
Weight (kg)	67.40 (14.4)	
Height (m)	1.60 (0.06)	
BMI (kg/m^2)	26.60 (5.30)	
Peripheral muscle strength		
Quadriceps strength (kgf)	24.58 (8.21)	
Quadriceps strength (%)	58.7 (18.80)	
Pulmonary function tests		
FEV_1 (l)	2.14 (0.54)	
FEV_1 (% pred) and FVC (% pred)	75.45 (19.33)	
FVC (l)	2.95 (0.58)	
FEV1 (% pred) and FVC (% pred)	88.2 (19.27)	
FEV_1/FVC (%)	72.63 (12.34)	
DL_{CO} (ml/min/mmHg)	17.31 (4.93)	
DL_{CO} (%pred)	72.12 (20.65)	
RV (l)	1.85 (1.00)	
RV (%pred)	112.5 (44.57)	
RV/TLC (%)	36.61 (10.83)	
RV/TLC (%pred)	121.82 (37.16)	
Field exercise tests	**6MWT**	**ISWT**
Distance (m)	516.70 (63.90)	452.70 (139.30)
Distance (%pred)	95.10 (17.80)	84.70 (22.0)
SpO_2 basel (%)	95.60 (1.90)	95.90 (1.90)
SpO_2 minimal (%)	89.40 (1.90)	86.20 (5.0)
DDR	6.6 (3.8–10.9)	8.3 (6.2–12.7)
Borg D (score)	2 (0.2–4)	4 (3–7)
Borg F (score)	2 (0.7–3)	3 (2–5)
HR (bpm)	107.10 (21.0)	142.20 (23.0)
Desaturation during test (%/total)	67/40	90/40

Data presented as mean (standard deviation), except DDR and Borg, presented in median (25–75%, interquartile range). BMI, body mass index; FEV_1, Forced expiratory volume in the first second; FVC, forced vital capacity; DL_{CO}, carbon monoxide lung diffusion; RV, residual volume; TLC, total lung capacity; l, liters; min, minutes; kg, kilograms; m, meters; ml, milliliters; mmHg, millimeters of mercury; pred, predicted; 6MWT, 6-min walk test; ISWT, incremental shuttle walk test; SpO_2, peripheral oxygen saturation; DDR, desaturation–distance ratio; Borg D, Borg dyspnea; Borg F, Borg fatigue; HR, heart rate; bpm, beats per minute.

$$\mathrm{DDR_{6MWT}} = 18.66 - (0.06 \times \mathrm{FEV_1\%}) - (0.10 \times \mathrm{DL_{CO}\%}) + (1.54 \times \text{air trapping}),$$

$$R^2_{\text{adjust}} = 0.43$$

$$\mathrm{DDR_{ISWT}} = 18.84 - (0.09 \times \mathrm{FEV_1\%}) - (0.05 \times \mathrm{DL_{CO}\%}) + (3.10 \times \text{air trapping}),$$

$$R^2_{\text{adjust}} = 0.33$$

DISCUSSION

To the best of our knowledge, this is the first study to investigate the roles of DDR in a general population of patients with LAM during 6MWT and ISWT and correlate it with functional parameters. The performance of patients with LAM during ISWT was also evaluated for the first time. Our results demonstrated that DDR obtained during the submaximal (6MWT) and maximal (ISWT) exercise tests were associated with the severity of pulmonary impairment, air trapping, and reduced DL_{CO} in patients with LAM. Additionally, our patients had satisfactory exercise capacities during both tests.

We included 40 women, which can be considered a relevant sample considering that LAM is a rare disease that affects ∼5 persons per million adult women (1). Our patients were classified as having good exercise capacities during the 6MWT and ISWT (∼95 and 85% of predicted, respectively). The 6MWT performance in our patients was similar to that observed in previous studies, ranging from 89 to 97% of the predicted distance during the 6MWT in patients with LAM with similar disease severity (7, 11). However, no previous study has assessed the performance of patients during the ISWT.

The DDR is based on the two main variables obtained during the 6MWT, the distance walked, and the decrease in SpO_2 evaluated at regular intervals during the test (15). DDR is a more informative indicator for assessing exercise performance than oxygen desaturation, or the distance walked in isolation. Other advantages of DDR include its assessment through simple and low-cost tests (6MWT and ISWT), and easy application. DDR has been previously evaluated in patients with ILDs and COPD, and it has demonstrated associations with pulmonary function parameters (13, 15, 31). Fujimoto et al. (13) showed that DDR was highly predictive of the degree of emphysema and the enlargement of the pulmonary artery on computed tomography scans in COPD patients.

Oxygen desaturation during 6MWT is associated with a worse prognosis and greater mortality, and it has a good correlation with functional variables at rest, such as FVC, DL_{CO}, and TLC in patients with ILDs (32–34). However, no previous study has evaluated the role of DDR in predicting disease progression and survival in ILDs, including LAM. Pimenta et al. (15) found that DDR was correlated with functional parameters, including DL_{CO} (%pred), FVC (%pred), and FEV_1 (%pred). The authors included 15 patients with LAM and DDR in this subgroup, which was similar to that found in our study (6 vs. 6.6, respectively) (15). A previous study demonstrated that DDR was correlated with the severity of pulmonary cysts on high-resolution computed tomography ($r = 0.77$) in patients with LAM, reinforcing its potential role in evaluating disease severity (12). However, no study has assessed the association between DDR and pulmonary function parameters exclusively in LAM.

Our results demonstrated that DDR is associated with airway obstruction (FEV_1), air trapping (RV/TLC), and DL_{CO} during the 6MWT and ISWT in patients with LAM. Previous investigations have shown that reduced exercise performance in cardiopulmonary exercise testing (CPET) is associated with such functional abnormalities in LAM (7, 8). The main mechanisms

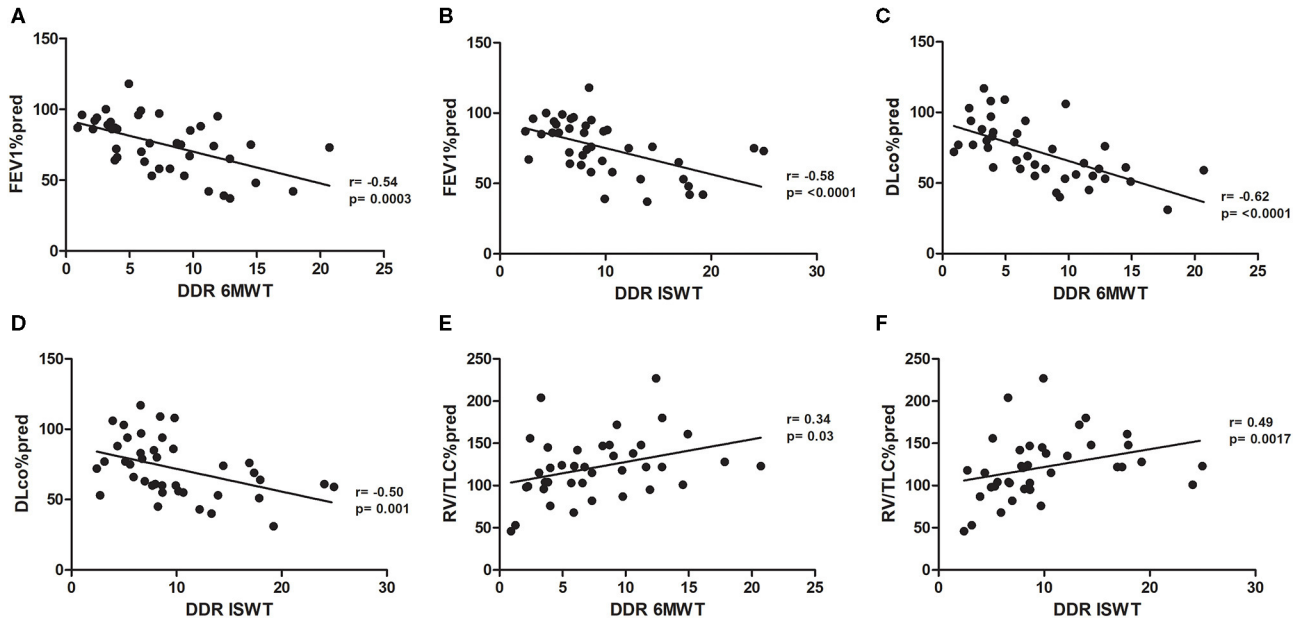

FIGURE 2 | (A) Pearson's correlation between FEV1%pred and DDR 6MWT. **(B)** Pearson's correlation between FEV1%pred and DDR ISWT. **(C)** Pearson's correlation between DL_{CO}%pred and DDR 6MWT. **(D)** Pearson's correlation between DL_{CO}%pred and DDR ISWT. **(E)** Pearson's correlation between RV/LTC%pred and DDR 6MWT. **(F)** Pearson's correlation between RV/LTC%pred and DDR ISWT. FEV1%pred, forced expiratory volume in 1 s as a percentage of predicted; DDR, desaturation distance ratio; 6MWT, 6-min walking test; ISWT, incremental shuttle walking test; DL_{CO}, diffusing capacity of the lung for carbon monoxide as a percentage of predicted; RV, residual volume; TLC, total lung capacity.

TABLE 2 | The optimum cutoff points and ROC curve parameters for prediction of lung function and DDR in patients with LAM.

	Cutoff point	Sensitivity	Specificity	AUC	95%CI
FEV_1 < 80%					
6MWT-DDR	5.9	0.86	0.78	0.85	0.73–0.97
ISWT-DDR	8.5	0.73	0.83	0.85	0.74–0.97
DL_{CO} < 75%					
6MWT-DDR	6.7	0.82	0.89	0.87	0.74–0.99
ISWT-DDR	9.9	0.59	0.94	0.78	0.64–0.93
RV/TLC > 120%					
6MWT-DDR	7.8	0.62	0.78	0.73	0.57–0.89
ISWT-DDR	7.3	0.91	0.67	0.82	0.68–0.96

ROC, Receiver Operating Characteristic; DDR, Desaturation Distance Ratio; LAM, Lymphangioleiomyomatosis; AUC, Area under the curve; CI, Confidence Interval; FEV_1, Forced Expiratory Volume in the first second of the Expiration (airway obstruction); 6MWT, 6-min walking test; ISWT, Incremental Shuttle Walking Test; DL_{CO}, Diffusion Capacity of the Lungs for Carbon Monoxid (reduced lung diffusion); RV/LTC, Residual Volume/Lung Total Capacity (air trapping).

determining exercise cessation include ventilatory limitation, gas exchange impairment, peripheral muscle fatigue, and pulmonary hypertension (7, 8). However, no study has compared DDR with data obtained during CPET.

Obstructive pattern and reduced DL_{CO} were commonly observed in our patients, and they were predictors of DDR evaluated during the 6MWT and the ISWT, besides air trapping. Two DDR prediction equations were obtained, DDR-6MWT ($R^2_{adjust} = 0.43$) and DDR-ISWT ($R^2_{adjust} = 0.33$), based on functional abnormalities that were not previously described. The lung function findings observed in our study were similar to those observed by Li et al. (17) in Chinese patients who presented a mean FVC and FEV_1 of 91%pred and 72%pred, respectively.

In patients with moderate and severe COPD, the distance covered during the ISWT is significantly associated with pulmonary function parameters, such as vital capacity and airway obstruction (FEV_1), as well as health-related quality of life (35). According to Yildiz et al. (36), the ISWT distance is significantly associated with FEV_1 ($r = 0.65$) and FVC ($r = 0.54$) in adults with bronchiectasis. The 6MWT is considered a submaximal field test aimed to assess functional capacity by measuring distance walked within a controlled duration. On the other hand, the ISWT is considered a maximal field test in which patients perform exercises until exhaustion. We are not aware of studies on ISWT in patients with LAM. However, the 6MWT and ISWT presented similar results relative to the predicted values (∼90%, **Table 1**). In addition, the association between the 6MWT and ISWT with lung tests were similar.

Our study has some limitations. Our study was performed in only one center; however, our center is a referral center for LAM in Brazil, and it follows patients from different regions with different severities. We included 40 patients that can be considered significant due to the rarity of the disease. Another limitation is the insufficiency of the sample size for stratifying DDR predictions by age, impairment, or physical activity level. Also, no statement can be made regarding patients on oxygen. Finally, it is important to compare the performances during

the ISWT and cardiopulmonary exercise testing in patients with LAM.

CONCLUSION

In summary, DDR is useful for functional evaluation during submaximal and maximal exercise tests (6MWT and ISWT) in patients with LAM, and it is associated with functional impairment, reduced DL_{CO}, and air trapping. Future studies are necessary to establish the effectiveness of DDR for evaluating exercises, in comparison with CPET, and predicting disease progression, survival, and response to therapeutic interventions in LAM patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comissão em Ética e Pesquisa do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (CAPPesq). Protocol 90196617.1.0000.0068. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DQ promoted the development of the study design, the scheduling of patient appointments, collecting, analyzing, and interpreting the data, as well as writing the article. CS assisted the research helping develop the study design, scheduling patient appointments, collecting, analyzing, and interpreting the data, as well as improving and developing the article. AA and MO promoted the development of the study design and the scheduling of patient appointments. HM assisted us during the process and interpretation of the DDR data. CRRC greatly contributed to develop the study design, analyse, and interpret the data, as well as to help the elaboration of the article. BB supported us by developing the study design, scheduling patient appointments, analyzing, and interpreting the data, as well as helping the later elaboration of the article. CRFC conducted our research and also provided insight and expertise in all stages of the study, from the concept to the design, data collection and analysis, data interpretation, improvements, and the development of the article. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Patient Reported Experiences and Delays During the Diagnostic Pathway for Pulmonary Fibrosis: A Multinational European Survey

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Introduction: Pulmonary fibrosis includes a spectrum of diseases and is incurable. There is a variation in disease course, but it is often progressive leading to increased breathlessness, impaired quality of life, and decreased life expectancy. Detection of pulmonary fibrosis is challenging, which contributes to considerable delays in diagnosis and treatment. More knowledge about the diagnostic journey from patients' perspective is needed to improve the diagnostic pathway. The aims of this study were to evaluate the time to diagnosis of pulmonary fibrosis, identify potential reasons for delays, and document patients emotions.

Methods: Members of European patient organisations, with a self-reported diagnosis of pulmonary fibrosis, were invited to participate in an online survey. The survey assessed the diagnostic pathway retrospectively, focusing on four stages: (1) time from initial symptoms to first appointment in primary care; (2) time to hospital referral; (3) time to first hospital appointment; (4) time to final diagnosis. It comprised open-ended and closed questions focusing on time to diagnosis, factors contributing to delays, diagnostic tests, patient emotions, and information provision.

Results: Two hundred and seventy three participants (214 idiopathic pulmonary fibrosis, 28 sarcoidosis, 31 other) from 13 countries responded. Forty percent of individuals took ≥1 year to receive a final diagnosis. Greatest delays were reported in stage 1, with only 50.2% making an appointment within 3 months. For stage 2, 73.3% reported a hospital referral within three primary care visits. However, 9.9% reported six or more visits. After referral, 76.9% of patients were assessed by a specialist within 3 months (stage 3) and 62.6% received a final diagnosis within 3 months of their first hospital visit (stage 4). Emotions during the journey were overall negative. A major need for more information and support during and after the diagnostic process was identified.

Conclusion: The time to diagnose pulmonary fibrosis varies widely across Europe. Delays occur at each stage of the diagnostic pathway. Raising awareness about pulmonary fibrosis amongst the general population and healthcare workers is essential to shorten the time to diagnosis. Furthermore, there remains a need to provide patients with sufficient information and support at all stages of their diagnostic journey.

Keywords: pulmonary fibrosis, delayed diagnosis, diagnostic journey, survey, patient reported outcomes

INTRODUCTION

Interstitial lung disease (ILD) describes a relatively uncommon group of diseases characterised by inflammation and fibrosis of the lung interstitium. Pulmonary fibrosis is a chronic, and often progressive condition. There is, however, considerable variation amongst patients in terms of aetiology, treatment strategies, and disease course (1). Amongst all types of pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF) is the most prevalent and accounts for about two-thirds of cases. It has the worst prognosis due to rapid disease progression with a mean survival of 4 years from diagnosis without anti-fibrotic therapy (2). Other types of progressive pulmonary fibrosis include chronic hypersensitivity pneumonitis, auto-immune disease related ILD, and occupational diseases such as asbestosis (1). Epidemiological data for all types of pulmonary fibrosis are limited as most registries and studies have focused on IPF or progressive phenotypes only (3). The reported prevalence (per 100,000 persons) of the ILDs that most often result in pulmonary fibrosis is 30.2 for sarcoidosis, 12.1 for ILD related to a connective tissue disease and 8.2 for IPF. Overall, the proportion of ILD patients who develop pulmonary fibrosis varies from 13 to 100% per individual disease (1).

The diagnostic journey usually starts with patients presenting to their primary care physicians with initial symptoms of cough or mild dyspnoea. These non-specific symptoms, combined with the heterogeneity, and rarity of pulmonary fibrosis, as well as requirement for multiple diagnostic investigations, results in a prolonged time to diagnosis with potential delays related to patient factors and healthcare systems (4). Reported time to diagnosis from the onset of initial symptoms varies in different studies but may be up to a median of 2.1 years (IQR 0.9–5.0) (5). Longer time to diagnosis is associated with worse outcomes in IPF (6, 7), causes delayed treatment, leads to more extensive fibrosis (8) and affects patients' well-being. Therefore, it is important to get better insights into patients' experiences during the diagnostic journey to identify reasons for potential delays. Understanding patients' experiences will also help healthcare workers guide and support patients during their diagnosis journey. However, to date, only a few studies have explored the reasons for diagnostic delays using data reported by pulmonary fibrosis patients (9–13). Most analyses are based on retrospective data obtained from healthcare records (5, 7, 8, 14–18).

In this paper, we present data obtained from a multinational patient survey regarding time to diagnosis and potential causes for diagnostic delays, together with patient experiences on the pathway to diagnosis. Based upon these findings, we provide general recommendations to improve the diagnostic process.

METHODS

Survey Design and Distribution

A survey was designed to collect quantitative and qualitative data from patients diagnosed with pulmonary fibrosis across Europe. This survey was developed based upon a market research survey on the IPF patient journey (unpublished data) carried out using a mixture of in-depth telephone interviews with 28 patients and 30 pulmonologists, and online interviews with 315 pulmonologists spanning USA, France, Germany, Italy, Spain, United Kingdom, Australia, Brazil, Canada, and Japan. The patient survey was developed jointly between Galapagos and two patient organisations: Action for Pulmonary Fibrosis (APF, based in the United Kingdom) and the European Idiopathic Pulmonary Fibrosis and Related Disorders Federation (EU-IPFF). Insights from this patient journey research resulted in a questionnaire incorporating both closed and open-ended questions, which focused on the following four stages of the patient journey to identify key points in the delay to diagnosis. The first stage was the time from first onset of symptoms at home, before seeking medical attention in a primary care setting; the second the amount of visits in primary care before being referred to a hospital specialist; the third the time taken to be seen in a hospital by a specialist; and the last the time taken to receive a diagnosis (**Figure 1A**). The survey also gathered data on the overall time from first onset of symptoms to diagnosis and information provided by healthcare workers. Patients were also asked about their feelings throughout the diagnostic journey and to provide advice for patients navigating this journey in the future. No personalised data were collected and all data were anonymised. The questionnaire was designed in English and translated into seven languages (Bulgarian, Dutch, French, German, Hungarian, Italian, and Spanish) by a certified translation agency. It was created using the Typeform® platform. Patients were invited to complete the questionnaire by an e-mail containing a link to the platform. The complete survey in English can be found in the **Supplementary Material 1**.

The survey was disseminated by the EU-IPFF through its member patient organisations in Europe; these organisations distributed the survey to members and other patients through email and social media. Patients with a self-reported diagnosis of pulmonary fibrosis, and who had an email address and

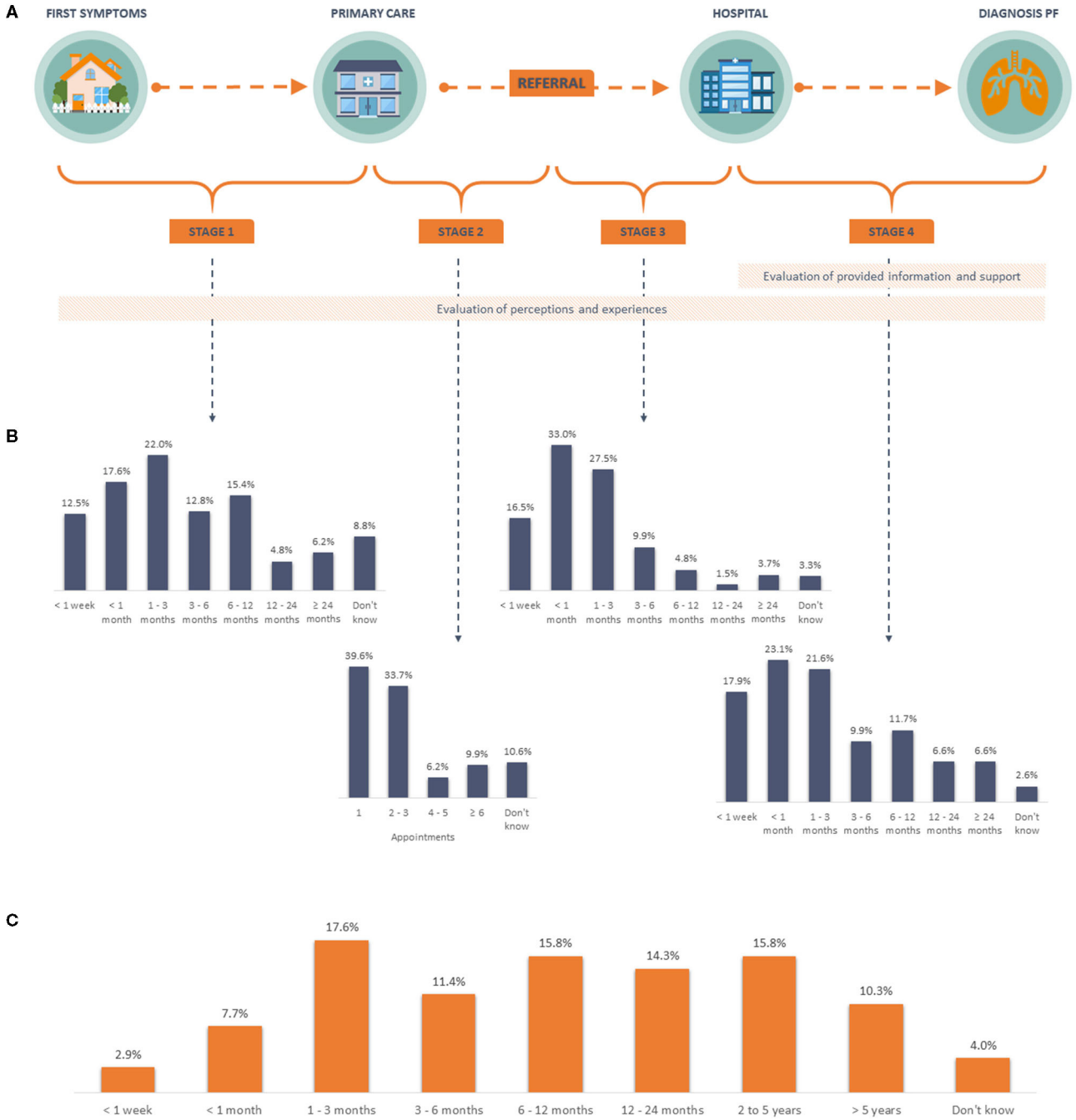

FIGURE 1 | Diagnostic pathway and time to diagnosis. **(A)** Schematic overview of the diagnostic pathway for pulmonary fibrosis, including stages and topics assessed in the survey. **(B)** Patient reported time per stage. **(C)** Patient reported overall time to diagnosis. PF, pulmonary fibrosis.

internet access were eligible to participate. The survey was sent out on 7th June 2020 with a reminder after 2 weeks. It closed on 1st July 2020. Ethical review was not required for this online questionnaire. Patients agreed with the use of their responses for further analysis without collection of personal data and were informed that all data was anonymised.

Data Analysis

Responses in languages other than English were translated into English by a certified translation agency. Open-ended questions were assessed qualitatively and coded or categorised for interpretation. Data were uploaded and calculations were performed in Excel (Microsoft, Redmond, WA, USA). R version 4.0.3 for Mac OS X GUI (PBC,

Boston, MA, USA) was used for creating a word cloud. All responses were included in the analysis, except for blank responses.

Literature Search

In addition to the survey, a literature search on diagnostic delays in ILD, with a focus on pulmonary fibrosis, was conducted in order to provide a complete overview of the available evidence from patient surveys, physician surveys, and medical file analysis.

The systematic literature search was performed in Embase, Medline, Web of science, Cochrane, and Google scholar databases. The following search terms were used: diagnostic delay, time to diagnosis, interstitial lung disease (including sarcoidosis, vasculitis, interstitial pneumonia). Full search and outcome can be found in the **Supplementary Material 2**. Animal studies, paediatric subjects and articles in languages other than English were excluded. The reference list was screened for relevance by title and abstract. Letters to the editor, abstracts, posters, and articles without available full text were excluded.

RESULTS

Respondent Characteristics

Two hundred and seventy three patients from thirteen different countries responded. The largest group of respondents were IPF patients (n = 214, 78.4%), followed by sarcoidosis (n = 28, 10.3%). Other types of pulmonary fibrosis diagnoses accounted for 31 respondents (11.4%) and included patients with autoimmune related disorders, chronic hypersensitivity pneumonitis, and other conditions. The majority of respondents received a diagnosis of pulmonary fibrosis in Spain (21.6%), Belgium (20.1%), United Kingdom (18.3%), Italy (17.2%), or Germany (10.6%). A smaller number of respondents were diagnosed in the Netherlands (3.3%), Bulgaria (2.6%), France (1.8%), Poland (1.8%), Austria (1.5%), Ireland (0.4%), Norway 0.4%), and Romania (0.4%). Shortness of breath, dry cough, and tiredness were the most common initial symptoms in all diagnosis groups (**Figure 2A**).

The total time from initial symptom onset to a final diagnosis of pulmonary fibrosis, varied greatly amongst patients (**Figure 1C**). Overall, nearly 30% received a diagnosis within 3 months, with 31.3% patients with IPF receiving a diagnosis within 3 months, compared to 14.3% for sarcoidosis and 19.4% for other types of pulmonary fibrosis. Moreover, 40.2% of all patients had to wait a year or more to be diagnosed, with the largest difference between the proportion of patient with IPF (36.4%) and other types of pulmonary fibrosis (58.1%).

Stages of the Diagnostic Process

Stage 1: From Initial Symptom Onset to First Primary Care Assessment

More than half of respondents made a first appointment with a primary care physician within 3 months of symptom onset (52.0%), but nearly 30% waited more than 6 months (**Figure 1B**, stage 1). A number of patients responded that they did not delay visiting their doctor (26.7%).

Of all patients with a delay in stage 1 of 6 months or less (n = 177), 65.0% reported a total time to diagnosis of 1 year or less. Where patients with a delay of more than 6 months (n = 72) in this stage, only 34.7% reported being diagnosed within a year.

There were a variety of reasons for delays (**Figure 2B**). In a large number of cases, patients delayed seeking medical advice because they were not concerned about their symptoms. Patients believed symptoms were related to other causes (e.g., cold, smoking, stress; 35.2%), related to age (25.6%), or due to another established disease (5.1%). The main reasons that triggered patients to make an appointment with their primary care physician were worries about their symptoms, including shortness of breath (45.1%), cough (31.9%), and fatigue (20.9%) (**Figure 2C**). For 18.7% of patients, it was the impact of symptoms on their daily activities, especially on physical activity (e.g., sports, climbing stairs, walking, household, gardening) and work-related activities that led them to consult their primary care physician. In addition, some patients were prompted to make an appointment following the suggestion from family members or friends (22.7%), or another physician (7%).

Stage 2: From Start of Primary Care Assessment to Referral to Pulmonologist

At the first primary care appointment, a variety of actions were taken by the treating physicians. Almost half of all patients were referred to a pulmonologist (**Figure 3**). Other reported physician's actions included additional tests (19.0%), treatment for another disease (16.5%), and referral to other specialists rather than a pulmonologist (10.3%). Overall, the majority (73.3%) of patients were referred to a pulmonologist within three primary care visits, but for 9.9% of patients it took six or more appointments (**Figure 1B**, stage 2).

Comparing the different diagnosis groups, 43.2% of IPF patients were referred to a pulmonologist after one primary care visit. This was lower for those with sarcoidosis (28.6%) and other types of pulmonary fibrosis (25.8%). Furthermore, 39.3% of sarcoidosis patients were referred after six or more primary care visits, compared to 6.6% of IPF and 6.7% of other fibrosis types in this cohort.

Stage 3: From Referral to First Hospital Appointment

Once patients were referred to a pulmonary specialist, 76.9% of all patients had their first visit within 3 months (**Figure 1B**, stage 3). This was lower for the subgroup of sarcoidosis patients (50.0%) compared to IPF (79.9%), and other types of pulmonary fibrosis (80.6%). Few IPF patients (2.3%) had a delay of more than a year from referral to first hospital appointment, in contrast to almost a third of the sarcoidosis patients (32.1%). All patients with other types of pulmonary fibrosis were assessed within a year of the referral.

Stage 4: From First Hospital Appointment to Diagnosis Pulmonary Fibrosis

The 273 respondents underwent a total of 1,232 diagnostic tests in the hospital (**Table 1**). The majority of patients reported having performed spirometry (n = 246), blood tests (n = 222) and

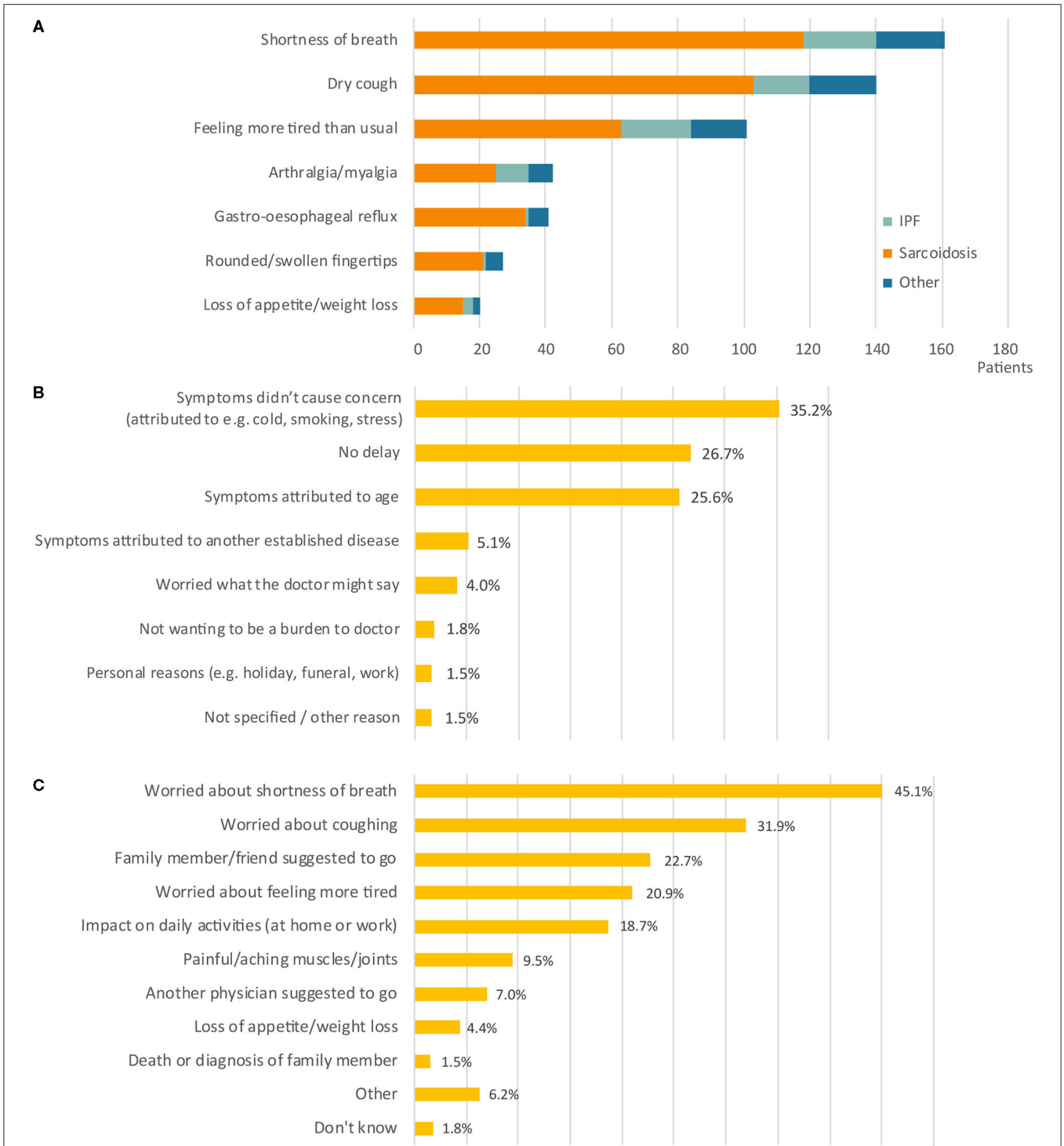

FIGURE 2 | Patient symptoms and motives in stage 1. **(A)** Number of patients (n =) reporting a specific symptom at onset. Bars are divided into diagnosis groups (total responses $n = 532$). **(B)** Reason to delay the initial primary care appointment ($n = 277$). **(C)** Reason to schedule the initial primary care appointment ($n = 463$). Percentages do not add up to 100% as more than one response was allowed. IPF, idiopathic pulmonary fibrosis.

chest imaging (X-ray $n = 209$; CT scan $n = 201$) without large differences in proportions between the diagnosis subgroups. Other tests reported included assessment of 6-min walk test ($n = 149$), lung biopsy ($n = 125$), and bronchoaveolar lavage ($n = 74$). Lung biopsy was more frequently reported by sarcoidosis patients compared to the other subgroups.

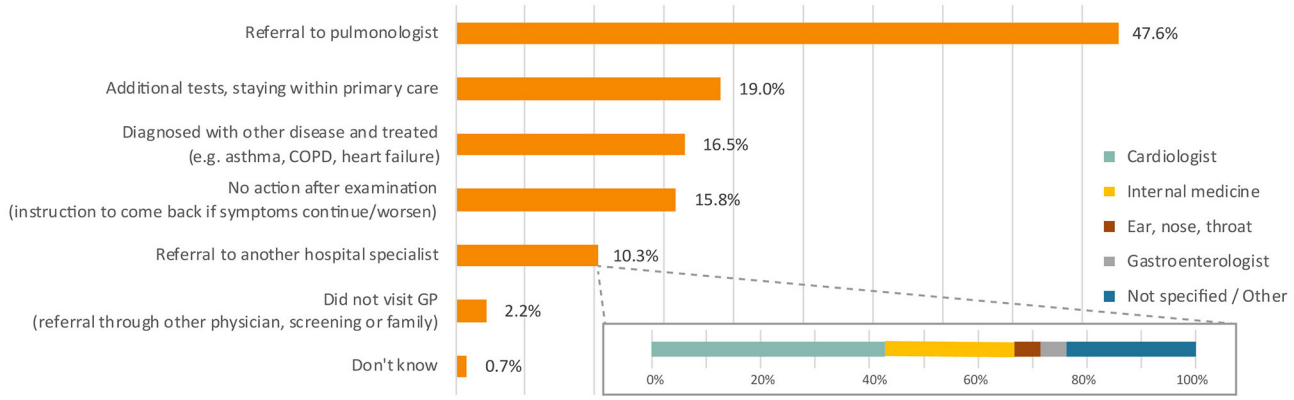

FIGURE 3 | Action of physician at first visit primary care. Percentages do not add up to 100% as more than one response was allowed. Total responses $n = 306$. COPD, chronic obstructive pulmonary disease; GP, general practitioner.

TABLE 1 | Performed tests in hospital before diagnosis.

	IPF ($n = 214$)		Sarcoidosis ($n = 28$)		Other type ($n = 31$)	
Tests	***n* =**	**% of patients in subgroup**	***n* =**	**% of patients in subgroup**	***n* =**	**% of patients in subgroup**
Spirometry	194	90.7%	24	85.7%	28	90.3%
Blood tests	168	78.5%	26	92.9%	28	90.3%
Chest X-ray	161	75.2%	22	78.6%	26	83.9%
CT scan	156	72.9%	19	67.9%	26	83.9%
6-min walk test	120	56.1%	10	35.7%	19	61.3%
Lung biopsy	93	43.5%	19	67.9%	13	41.9%
Bronchoaveolar lavage	49	22.9%	11	39.3%	14	45.2%
Other/Don't know	5	2.3%	1	3.6%	-	-
Tests per patient (mean)	*4.4*		*4.7*		*5.0*	

Number of patients (n =) reporting a specific diagnostic test. Percentages do not add up to 100% as more than one response was allowed. CT, Computed tomography; IPF, idiopathic pulmonary fibrosis.

Although the final diagnosis was made within 3 months of the first hospital appointment for 62.6% of the 273 patients (**Figure 1B**, stage 4), 21.6% took between 3 months and 1 year, and 13.2% took over 1 year; 2.6% did not know how long this took. Small differences were found between the proportion of patients in each diagnosis group who were diagnosed within 3 months (IPF 64.5%, sarcoidosis 50.0%, and other pulmonary fibrosis types 61.3%) and more than 1 year after the first hospital appointment (IPF 11.2%, sarcoidosis 21.4%, and other pulmonary fibrosis types 19.4%).

Experiences and Recommendations

Information Provision

We assessed the patient perceptions on the information provided at the different stages in the diagnostic pathway. During assessment at the hospital (stage 4), 13.6% of patients reported not knowing why certain diagnostic tests were being performed. Almost a quarter (23.6%) of all patients felt they received insufficient information. At diagnosis, most patients (75.6%) received an explanation about their diagnosis from a physician and/or specialist nurse during a consultation. However, only 6.0% percent of patients received educational materials and 6.0% received information related to support groups. A small number (3.0%) reported not having received any information at the time of diagnosis. In response to an open-ended question, patients reported that the discussion with their doctor or nurse was particularly valuable, as well as ongoing follow up appointments at the hospital and contact details to enable them to ask questions or reach out if they were feeling unwell.

The patients stated that they would have benefitted from more information during the diagnostic process, not only after the diagnosis was established. They would have welcomed more information before, at and after diagnosis on the following topics: differential diagnosis, diagnostic tests, available pharmacological, and non-pharmacological therapies, disease course, and prognosis. Respondents would have also liked more information on living with pulmonary fibrosis day-to-day, future perspectives, access to a psychologist, and information on peer support groups for patients and carers.

Emotional Experiences

Patients' perceptions and experiences were retrospectively assessed at different time points during their diagnostic journey. When describing their feelings after the onset of symptoms

FIGURE 4 | Reported feelings during stage 3. Words grouped after coding, ones with minimum frequency of 2 are included in figure ($n = 28$). Full list ($n = 62$) can be found in **Supplementary Material 3**.

before their first doctor's visit ($n = 179$ responses), 65.4% of the respondents experienced negative emotions, 5.6% positive emotions, and the remainder (29.1%) were neutral. When asked to describe feelings after referral to the hospital ($n = 240$ responses), 74.6% of the responding patients experienced negative emotions at that time (16.7% neutral, 8.8% positive) (**Figure 4**).

Recommendations to Patients

Overall, the advice and tips offered by patients to those undiagnosed or living with pulmonary fibrosis were: seeking help early when you experience symptoms, pushing for a speedier diagnosis, seeking as much information as possible from healthcare professionals at all stages, taking regular exercise, joining pulmonary rehabilitation classes to assist with breathlessness, joining patient support groups, remaining positive, pacing themselves, and making the most of their time. General tips for fellow patients regarding mental well-being contained phrases such as: stay calm, stay positive, no stress, don't despair, don't give up, focus on the present, and don't get agitated, frustrated or anxious.

Recommendations to Healthcare

Advices to healthcare workers included performing tests earlier, providing more information and lifestyle advice, gaining more knowledge about pulmonary fibrosis, improving communication between healthcare workers, structuring the diagnostic process better, and earlier start of pharmacological and palliative treatment. More recommendations are listed as quotes in **Supplementary Material 4**.

DISCUSSION

The purpose of this survey was to document the time taken to diagnosis and to identify potential causes of delays at different stages of the diagnostic pathway for pulmonary fibrosis patients in Europe. The second aim was to describe patients' experiences during this journey.

We found that the time to diagnosis varies widely. Only 30% of patients were diagnosed with pulmonary fibrosis within 3 months of symptom onset, while for over 40% of patients it took more than 1 year to be diagnosed. Other studies observed a median time from onset of first symptoms to diagnosis of 7 months (range 0–252) based on a patient survey (9) and 2.1 years (IQR 0.9–5.0) from a retrospective cohort study (5). In 2020, a group of ILD specialists reported a mean time from symptom onset to pulmonary fibrosis diagnosis of 2.3 years (Q1–Q3: 2–3) (19). The proportion of patients in our cohort who took more than a year to be diagnosed is smaller than that reported by other studies of pulmonary fibrosis patients (9, 11). Moreover, in a study of IPF patients, the median time to diagnosis was 13.6 months (range 5.9–39.5; max. 274.3) but 49% of the cohort received a diagnosis after more than 1 year (17). In another study, the median time for establishing a diagnosis was 1.5 years (range <1 week to 12 years) but this was calculated from the time of the first doctors' appointment rather than onset of symptoms (12). Compared to these historical studies, our results suggest fewer patients had such long delays from symptom onset to diagnosis.

Delays in diagnosis can occur at each stage of the patient journey and may be due to both patient- and healthcare-related causes. The longest delay we observed occurred in stage 1 (**Figure 1B**). More delay in this stage translated into a prolonged time to the final diagnosis. Our results show that only a quarter (26.7%) of all patients did not delay their initial appointment with their primary care physician. These findings are similar to results from a patient survey conducted in 2015 (9). A more recent survey amongst IPF patients reported a median delay of 0.1 years for this stage (5). From our survey, those who delayed their appointment reported they had not been concerned about their symptoms. This highlights the need to raise awareness of pulmonary fibrosis amongst the general public, so that individuals seek medical assistance earlier.

The time taken by people being treated in primary care (stage 2) varies. In our survey, almost 40% of patients were referred to a hospital specialist after their first primary care appointment, which is greater than that observed in a study conducted in the USA in 2015 (27.8%) (9). However, Hoyer et al. found that 80% of patients in Denmark (between 2016 and 2019) were referred after 1 or 2 visits to their general practitioner (5). These observations may reflect differences in healthcare systems or in awareness of pulmonary fibrosis between countries.

Of all respondents, 15.3% were referred after 4 or more appointments. Several factors may contribute to delays in primary care. Firstly, initial symptoms in the early stage of the disease can be non-specific and not yet known to be life threatening. In support of this, 42% of IPF patients had a normal lung function when initially assessed in primary care (18). Secondly, primary care physicians may suspect the symptoms to be due to more common respiratory diseases (such as asthma, pneumonia, bronchitis, allergies, and COPD [9]) and decide on a period of observation (20). Such misdiagnosis occurs in up to 41% of patients (5) and can prolong time to establish

an ILD diagnosis (9, 10). Thirdly, primary care physicians may lack knowledge about pulmonary fibrosis. A study in Finland found almost half of referral letters lack key information related to possible ILD diagnosis (18). An e-learning for General Practitioners has recently been launched by the Royal College of General Practitioners in the United Kingdom and patient organisation APF to increase knowledge about symptoms and treatment of pulmonary fibrosis (21). In other countries, similar initiatives are evolving.

Stage 3 is the time between being referred and the patient's actual hospital appointment. Based on our data, 76.9% were assessed by a pulmonologist within 3 months, compared to 91% reported from a Finnish cohort (18). In this Finnish study only referral letters to tertiary care centres were evaluated, which may explain the higher percentage. However, in the United Kingdom and Ireland the time to secondary care respiratory clinic visit [47 days (25–84)] was significantly less than the time to an ILD specialist clinic visit [290 days (133–773)] (16). Given differences in the structure and complexities of healthcare systems, it is difficult to compare data from different countries. To our knowledge, there are no published data as to why delays in stage 3 occur. It may reflect waiting times or patients postponing a hospital clinic appointment.

Delays occurring from the first hospital appointment to final diagnosis (stage 4) can be partly explained by the number of diagnostic tests, access to them (22) and challenges in confirming a specific diagnosis accurately. Patients in our survey underwent on average 4.5 tests per person. The most common were spirometry, blood tests, and radiological chest imaging, similar to those reported by others (9, 14). The proportion of reported lung biopsies was surprisingly high in our cohort (41.9–67.9%), which may reflect variation in healthcare practises, as biopsy rates differ between countries [16.1–1.2% (2013–2019) in England (23), 34.1% in Germany (2012–2014) (24), 20.1% in Italy (2015–2017) (25)].

Several parameters may predict potential delays, as they are associated with an increased time to diagnosis. In our cohort patients with a final diagnosis of IPF experience shorter delays and undergo less invasive diagnostic testing than patients with other diagnoses. These differences may be due to IPF patients presenting with more severe symptoms initially, availability of the IPF international diagnostic guidelines, or availability of tests (22, 26). We can only speculate on this as we did not collect data on disease severity nor have powered for separate subgroup analyses. Another parameter that may influence time to diagnosis are the specific presenting symptoms. When patients present with dyspnoea, the median time to confirm an ILD diagnosis was 307 days, which increased for symptoms as cough and fatigue, to 563 and 639 days, respectively (15). Similarly, Pritchard et al. found an association between dyspnoea and a shorter time to hospital referral, which was not observed for lung crackles or chronic cough (8). Other factors that may contribute to a delayed diagnosis include presence of specific comorbidities, male sex, increased body mass index, older age, previous inhalation therapy use, preserved diffusing capacity and better St. George's Respiratory Questionnaire scores (5, 7, 16, 17). Lastly, abnormal chest imaging is one of the main reasons to initiate a hospital referral from primary care (8, 18) and naming ILD on the thoracic CT radiologic report doubled the likelihood of a referral to a pulmonologist within 6 months (8). Interestingly, performing lung function tests in primary care, which indicated the possibility of ILD did not significantly influence time to CT scan or hospital referral (8).

Patients' Experiences

The pulmonary fibrosis journey to diagnosis generally involves extensive, repetitive, and sometimes invasive testing. Most patients in the survey reported that this causes a considerable burden, which can impact on emotional health, finances, and personal and professional life (9). Shortening the diagnostic journey and assessment at an ILD expert centre results in higher patient satisfaction (12). In addition, our survey highlighted the need to better inform patients during their diagnostic journey, to provide information on how to live with pulmonary fibrosis and advice on lifestyle changes at diagnosis. After diagnosis, providing information on perspectives, and options and discussions concerning symptom management should also be a priority as identified by our respondents. These observations are similar to those reported from surveys and in-depth patient interviews (27, 28). In one paper, authors highlighted that patients need time to come to terms with their diagnosis and that repeated provision of information was essential to fully understand the consequences and implications of their disease (11). However, a survey of ILD professionals in Europe showed that although two-thirds of specialist centres offered patient education only a few patients attended these existing programmes (10). Furthermore, only 6% of patients from our survey were informed about support groups, despite the value of peer support to patients and carers reported not only by our respondents but also from a previous patient survey (12). However, scientific evidence for the benefits of peer support is scarce (29). Regarding caregivers' needs, several patients in our survey highlighted the need to provide them with more information on the patient's experience and practical help on how best to support them (30). Finally, providing details of websites which offer reliable and accurate information is important as many websites contain incorrect or out-dated information (31).

Limitations

In this study, we used a variety of survey methods, which resulted in a good understanding of patients' perceptions and experiences. Nevertheless, using patient reported data is also a weakness of this study. A general limitation of open-ended questions is the variety of responses, which could not be included in the quantitative analysis. Limitations also include patient recall, non-response, and misinformation bias. These factors could have influenced the lung biopsies reported in our cohort, as patients may not differentiate between procedures such as endobronchial biopsies, surgical biopsies, or only bronchoscopy. As the responses were anonymous, we could not confirm information from medical records.

TABLE 2 | Strategies for improving the diagnostic pathway of pulmonary fibrosis patients.

	Stage 1	Stage 2	Stage 3	Stage 4	After diagnosis
Education and information	Increase awareness of PF amongst the general public.	Increase awareness of PF symptoms amongst primary care physicians and nurses.	Inform patients and policy makers on the need for urgency in hospital referral.	Inform patients about the reasons for diagnostic investigation and the differential diagnosis.	Inform patients about drug treatment, non-pharmaceutical treatment (rehabilitation, oxygen therapy, palliative care, lung transplant), prognosis and lifestyle
Improving standard care		Develop criteria for referral for chest CT scan or to a specialist when abnormalities on examination suggest PF.	Regular (virtual) MDDs between general hospital specialist and ILD experts.	Day case assessment with diagnostic investigations and clinical assessment.	Introduce psychological support, helplines and peer groups for patients as part of standard care.
		Better communication between primary care physician and ILD specialist.	Increase the number of ILD specialists in general hospitals.	Availability of DLCO measurement in all hospitals.	Discuss duration and frequency of follow-up visit.
Research areas	Identify the optimum way to provide information about PF to the general population.	Cost-effectiveness of performing chest CT scan in primary care or at community facilities.	Comparing waiting times and diagnostic pathway of PF to other uncommon diseases or disorders with poor prognosis [e.g., cancer (39)]		Assess caregivers' needs on counselling and support.

Content is based on survey outcomes, available literature, and authors' opinions. CT, computed tomography; DLCO, diffusing capacity for carbon monoxide; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; MDD, multidisciplinary discussion; PF, pulmonary fibrosis.

Several factors prevent generalisation of these results to the overall population of patients with pulmonary fibrosis. We used a non-random sample of self-selecting pulmonary fibrosis patients invited via patient associations without a pre-defined number of invited patients, target, or countries. Most organisations have, until recently, focused on supporting and representing IPF patients, which likely accounts for the high number of IPF participants in this survey. Furthermore, patient characteristics, such as gender, age, comorbidities, and stage and/or severity of disease were not collected.

Although there are European guidelines for the diagnostic pathway of IPF and other ILDs, differences exist between countries (10). This may be related to the organisation of healthcare and options for primary care physicians to refer for CT scans or to ILD expertise centres. In our survey, we did not take these differences into account nor collect information on whether a CT chest scan was performed in primary care.

Recommendations Clinical Practice

There is an urgent need to improve the diagnostic journey and recommendations on how to achieve this have been raised in several papers (10, 12, 13). Our findings on patient satisfaction and diagnostic delay endorse this and encourage further improvement. Rapid diagnosis is becoming increasingly important because several treatments are currently available to slow disease progression, improve quality of life, and may extend life expectancy (32–34). Although there are guidelines and other guidance documents on features, diagnosis, and management of ILD (26, 35–37) many patients have a diagnosis that is not confirmed by a multidisciplinary discussion and do not receive treatment (38). Additionally, geographical differences that may influence time to diagnosis and access to treatment still exists between countries (10).

In **Table 2**, we provide concrete strategies for each stage of the diagnostic journey to improve the standard clinical practise and patient satisfaction in order to promote a more rapid pathway for patients with pulmonary fibrosis throughout Europe. These strategies are based upon our survey outcomes, available literature, and expert authors' opinions. Awareness and education in general public, patients, and healthcare workers is a major topic in this field, as well as for other rare lung diseases (40).

CONCLUSION

From the onset of symptoms to diagnosis of pulmonary fibrosis, the patient journey involves delays at each stage of the diagnostic pathway. Most of these delays are avoidable. Based upon our findings, there is a particular need to raise awareness of pulmonary fibrosis in the general population. Additionally, patients' experiences highlight the need for understandable information concerning the diagnostic tests performed, differential diagnosis, final diagnosis, and treatments as well as peer support groups. Improving several aspects of the diagnostic pathway for pulmonary fibrosis is therefore warranted to minimise delays and improve patient satisfaction throughout Europe.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

IvS organised the database and performed the statistical analysis. IvS and SJ wrote the first draught of the manuscript. IvS, SJ, DC, and HP wrote sections of the manuscript. All authors contributed to conception and design of the study and contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.711194/full#supplementary-material

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Epidemiology, Mortality and Healthcare Resource Utilization Associated With Systemic Sclerosis-Associated Interstitial Lung Disease in France

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Objectives: To investigate the clinical characteristics, epidemiology, survival estimates and healthcare resource utilization and associated costs in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) in France.

Methods: The French national administrative healthcare database, the Système National des Données de Santé (SNDS), includes data on 98.8% of the French population, including data relating to ambulatory care, hospitalizations and death. In our study, claims data from the SNDS were used to identify adult patients with SSc-ILD between 2010 and 2017. We collected data on clinical features, incidence, prevalence, survival estimates, healthcare resource use and costs.

Results: In total, 3,333 patients with SSc-ILD were identified, 76% of whom were female. Patients had a mean age [standard deviation (SD)] of 60.6 (14.4) years and a mean (SD) individual study duration of 3.9 (2.7) years. In 2016, the estimated overall incidence and prevalence were 0.69/100,000 individuals and 5.70/100,000 individuals, respectively. The overall survival estimates of patients using Kaplan–Meier estimation were 93, 82, and 55% at 1, 3, and 8 years, respectively. During the study, 98.7% of patients had ≥1 hospitalization and 22.3% of patients were hospitalized in an intensive care unit. The total annual mean healthcare cost per patient with SSc-ILD was €25,753, of which €21,539 was related to hospitalizations.

Conclusions: This large, real-world longitudinal study provides important insights into the epidemiology of SSc-ILD in France and shows that the disease is associated with high mortality, healthcare resource utilization and costs. SSc-ILD represents a high burden on both patients and healthcare services.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier: NCT03858842.

Keywords: epidemiology, cost, pulmonary fibrosis, scleroderma, systemic sclerosis

INTRODUCTION

Systemic sclerosis (SSc) is a rare, heterogeneous, chronic, autoimmune disease characterized by fibrosis of the skin and internal organs (1). Interstitial lung disease (ILD) is a common complication of SSc and normally develops early in the disease (1, 2). ILD is estimated to affect between 19 and 90% of patients with SSc (depending on the study), and around 40% have clinically significant ILD (3–7). It is the leading cause of death in patients with SSc (2), with a 4.6-fold increased risk of mortality compared with the general population (8). Risk factors associated with mortality in SSc-associated ILD (SSc-ILD) are male sex, older age, extent of disease on chest high-resolution computed tomography (HRCT), lower forced vital capacity (FVC), diffusing capacity of the lungs for carbon monoxide (DLco) and pulmonary hypertension (PH) (9, 10). PH is a common complication in patients with SSc and SSc-ILD, and causes up to 33% of SSc-related deaths (11–13).

In North America, the prevalence of SSc is estimated to be 13.5–44.3 per 100,000 individuals (5, 14), and the incidence is estimated at 1.4–5.6 per 100,000 individuals (5). Estimates of SSc-ILD prevalence are less common but one US cohort study estimated it to be 9.8 per 100,000 persons (14). In a Canadian study, the prevalence of SSc and SSc-ILD was 19.1 and 2.3 per 100,000 persons, respectively (15). In Europe, the estimates for prevalence and annual incidence of SSc are lower, at 7.2–33.9 and 0.6–2.3 per 100,000 individuals, respectively. For patients who develop SSc-ILD, the prevalence and annual incidence in Europe are 1.7–4.2 and 0.1–0.4 per 100,000 individuals, respectively (5).

SSc has a substantial negative impact on patient quality of life and places a considerable burden on healthcare resources (1, 16). Patients with SSc have greater healthcare costs than unaffected individuals and patients with ILD have increased healthcare costs compared with patients without ILD (17).

Until recently, there were no drugs approved for the treatment of SSc-ILD. Based on the results of randomized controlled trials (18, 19), the anti-inflammatory drugs cyclophosphamide and mycophenolate mofetil (MMF) have often been used where treatment is considered. More recently, the tyrosine kinase inhibitor nintedanib was shown to reduce the rate of pulmonary function decline in patients with SSc-ILD (20) and has been approved for the treatment of SSc-ILD in the US, Europe, Canada, Japan and Brazil (21–23).

There is a lack of large-scale data on epidemiology, mortality and healthcare resource utilization of patients with SSc-ILD in France. The objectives of this retrospective study were to evaluate the prevalence and incidence of SSc-ILD and the clinical characteristics, survival estimates, and the healthcare resource use and associated direct costs of patients with SSc-ILD in France.

METHODS

Database Used

This was a non-interventional, longitudinal, retrospective, cohort study using administrative claim data extracted from the French national administrative healthcare database, Système National des Données de Santé (SNDS), which is managed by the National Health Insurance Fund [Caisse nationale d'assurance maladie (CNAM)]. The SNDS is a real-world, digital data set of French healthcare utilization and is one of the largest data repositories in the world, including 98.8% of the French population of more than 66 million people (24). It contains anonymous, comprehensive information on sociodemographic characteristics, date of death, all out-of-hospital reimbursed healthcare expenditures (from both public and private healthcare), and all hospital discharge summaries with International Classification of Diseases (ICD)-10 codes. In addition, the SNDS contains direct information on medical diagnoses for patients who have full coverage for all medical expenses by the national health security system, as is the case for the majority of patients diagnosed with SSc in France. The SNDS includes, in particular, the country-wide health insurance data related to ambulatory care [Système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) database], hospitalizations [Programme de médicalisation des systèmes d'information (PMSI)] and death (CépiDc).

Patients with SSc and ILD were identified in the SNDS database between 1 January 2010 and 31 December 2017 (the study period) using ICD-10 codes that appeared on medical claims (**Figure 1**; **Supplementary Table 1**).

Patient Selection

To be included in the analysis, patients had to be aged ≥20 years, meet the criteria for a diagnosis of SSc-ILD, have ≥2-year history in the general reimbursement scheme of the SNDS prior to inclusion date (in order to distinguish between incident and prevalent cases) and be affiliated to the general reimbursement scheme in the SNDS. Patients were included if they had a diagnosis of both SSc and ILD where the ILD diagnosis was either any time after, or within 6 months prior to, SSc diagnosis.

In France, the diagnosis of SSc-ILD is made during a short stay of elective hospitalization (≥1 day) in the majority of patients.

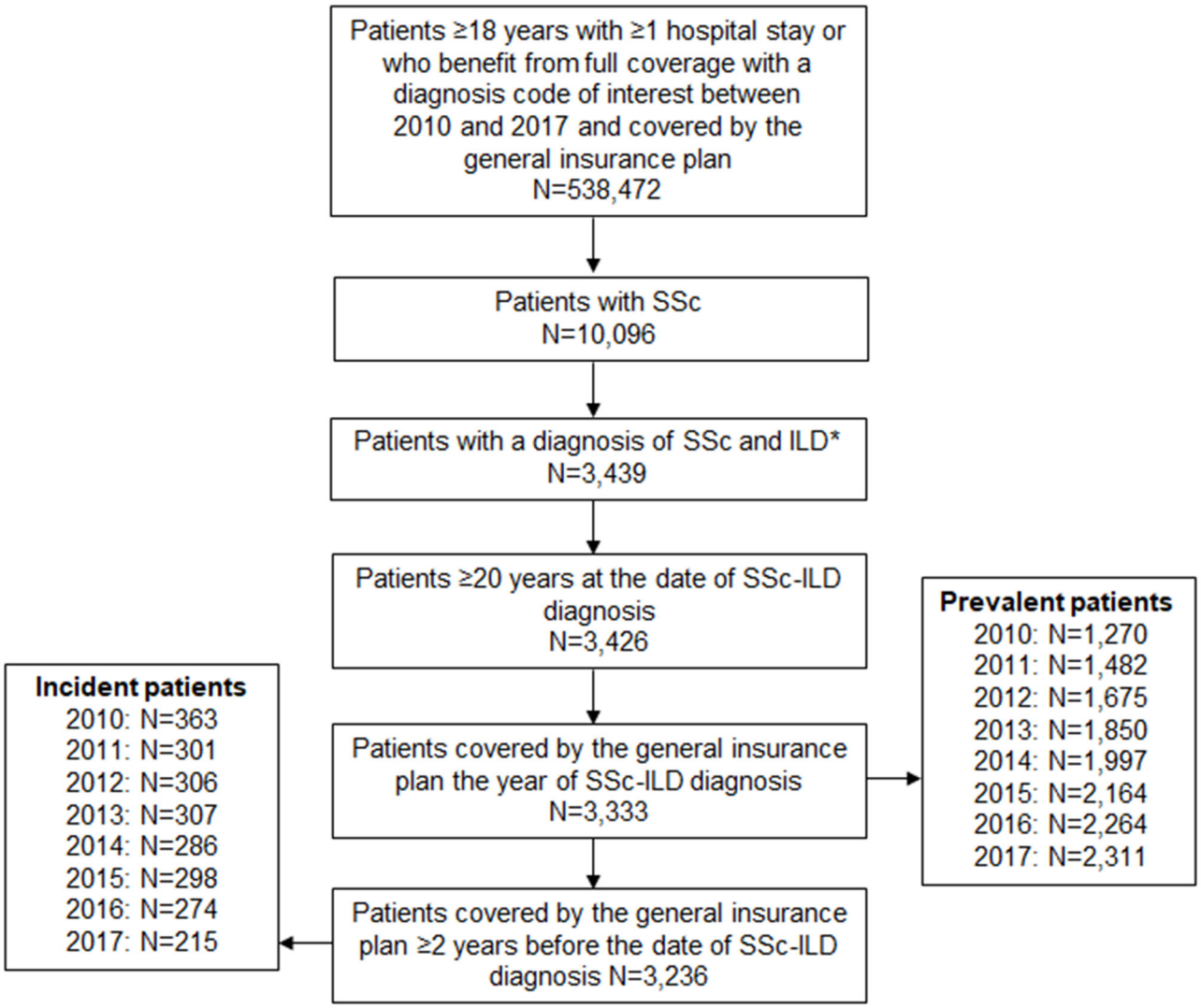

FIGURE 1 | Patient selection. *An eligible adult SSc-ILD patient was defined as a patient with either ≥1 hospital stay with a diagnosis code (principal, related or associated) of lung fibrosis, or ≥1 hospital stay with a diagnosis code (principal, related or associated) of SSc and/or a patient who benefited from full coverage for SSc (patients fully reimbursed for their claims related to SSc). ILD diagnosis could be made after, or within 6 months prior to, SSc diagnosis. ILD, interstitial lung disease; SNDS, Système National des Données de Santé; SSc, systemic sclerosis.

Patients with an SSc-ILD diagnosis before 2010 were included as prevalent patients in 2010. The study period was until the earliest of patient death, end of study (31 December 2017) or last available record (hospitalization or any healthcare reimbursement) in the data source. For patients with a data gap persisting beyond 12 months, the follow-up period was ended at their last record.

The study was approved by the Expert Committee for Health Research, Studies and Assessments [Comité d'expertise pour les recherches, les études et les évaluations dans le domaine de la santé (CEREES)] on 18 August 2018 (TPS 72584) and by the National Commission for Information Technology and Freedoms [Commission Nationale de l'Informatique et des Libertés (CNIL)] on 9 November 2018 (N:918305). The SNDS data are anonymized; therefore, written informed consent is waived for studies analyzing these data sets.

Outcomes

Patients' healthcare resource use was captured under the following categories: medical visits, hospitalizations, tests (laboratory and imaging), pulmonary function tests, pathology, ambulance use, sick leave daily allowances, and drug and non-pharmacologic treatments.

Total and annual costs per patient were estimated in euros during the study period according to the national health insurance perspective. For outpatient healthcare resources [general practitioner (GP) visits, pulmonary specialist visits, nursing and physiologist appointments, laboratory tests, medical procedures and treatments], ambulance use and sick leave daily allowances, the amount reimbursed by the healthcare insurance was directly extracted from the SNDS database. For

hospitalizations, costs were valued taking into consideration reimbursement by the national health insurance. The cost of each stay was valued by the diagnosis-related group [Groupe Homogène de Malades (GHM)] using the official tariffs from the French Diagnosis Related Group prospective payment system (source: Agence technique de l'information sur l'hospitalisation, Médecine chirurgie obstétrique et odontologie 2010–2017 tariffs for private and public institutions) (24, 25).

Statistical Analysis

Descriptive data analyses were performed depending on the criteria. Annual incidence rate was calculated as the proportion of subjects who were first identified as having SSc-ILD during the calendar year of interest (i.e., without any diagnosis of SSc-ILD during the 2 previous years) to all enrollees at risk (i.e., excluding prevalent cases) aged ≥20 years. Annual prevalence rate was calculated for each year as the proportion of all subjects identified as prevalent during the year of interest to all enrollees who were ≥20 years old. Patients contributed to annual incidence only once, but could contribute to prevalence during multiple years.

Crude incidence, prevalence and mortality rates were calculated for the total cohort and by the following subgroups: year of diagnosis (2010–2017), age, sex, and presence of lung cancer and PH in the 12 months prior to inclusion (both mortality only). PH was defined as patients with a full coverage or hospitalization for PH (ICD-10 code I270) in the main, related or associated diagnosis. Lung cancer was identified as patients with full coverage or hospitalization for lung cancer (C34 or D02.2 ICD-10 codes) in the main, related or associated diagnosis. Overall survival (OS) was defined as time from date of inclusion (date of presence of SSc and ILD claims) to date of death due to any cause or end of the study period. Patients were considered lost to follow-up if they had no recorded healthcare use during the follow-up and no death was registered. OS analyses were performed using the Kaplan–Meier method (**Supplementary Methods**).

RESULTS

Demographic Characteristics

Of the 9,817 patients with SSc who met the inclusion criteria, 3,333 (34%) had SSc-ILD (**Figure 1**). The majority of patients with SSc-ILD were female (75.6%). The mean [standard deviation (± SD)] age was 60.6 (± 14.4) years. The mean (± SD) individual duration of follow-up was 3.9 (± 2.7) years. The mean (± SD) time from SSc diagnosis to ILD diagnosis was 0.40 (± 1.16) years (**Table 1**). Most patients had comorbidities, the most common of which were hypertension (66.8%) and gastroesophageal reflux disease (65.8%) (**Supplementary Figure 1**).

Incidence and Prevalence of SSc-ILD

Between 2010 and 2017, the estimated incidence was 0.98–0.53 per 100,000 individuals per year, with incident cases varying between 215 and 363 per year. Between 2010 and 2017, the estimated prevalence was 3.42–5.73 per 100,000 individuals per year, with 1,270–2,311 prevalent cases per year (**Supplementary Table 2**; **Figure 1**).

TABLE 1 | Characteristics of patients with SSc-ILD.

	Patients (*N* = 3,333)
Sex, *n* (%)	
Female	2,521 (75.6)
Age, years	
Mean age (SD)	60.6 (14.4)
Median (IQR)	61.0 (50.0–71.0)
Min–max	20.0–97.0
Time between SSc diagnosis and ILD diagnosis, years	
Mean (SD)	0.40 (1.16)
Median (IQR)	0 (0–0.05)
Age category, *n* (%)	
20–<30 years	73 (2.2)
30–<45 years	378 (11.3)
45–<60 years	1,067 (32.0)
60–<75 years	1,200 (36.0)
≥75 years	615 (18.5)
Individual study period duration, years	
Mean (SD)	3.90 (2.70)
Median (IQR)	3.54 (1.59–6.51)

IQR, interquartile range; SD, standard deviation; SSc-ILD, systemic sclerosis-associated interstitial lung disease.

Survival Estimates of Patients With SSc-ILD

In total, 934 (28.0%) patients died, 2,093 (62.8%) were alive at the end of the study period and 306 (9.2%) patients were lost to follow-up. The OS estimates for all patients at 1, 3, 5 and 8 years were 93.4, 82.2, 70.8, and 55.3%, respectively (**Figure 2A**; **Supplementary Table 3**). At 8 years, the OS estimates were 41.4% for men and 59.7% for women (**Figure 2B**; **Supplementary Table 3**). The median OS for all patients was not reached (**Supplementary Table 3**). Mean (± SD) age at the time of death was 69.1 (± 12.9) years.

Factors associated with mortality were male sex, PH, lung cancer, and older age (age categories 50–<60 years, 60–<75 years and ≥75 years) (**Supplementary Table 4**). For the overall population and for women, more than 50% of patients were alive at the end of follow-up; however, the median OS [95% confidence interval (CI)] for men was 6.9 (6.3–7.6) years (**Supplementary Table 3**). OS estimates at 8 years were higher for younger patients (20–<50 years: 76.9%) compared with patients aged 50–<60 years (63.7%), 60–<75 years (49.6%) and ≥75 years (25.4%) (**Figure 2C**; **Supplementary Table 5**).

OS was also lower for patients with lung cancer or PH [medians (95% CI) of 3.1 (2.5–4.8) and 5.7 (4.7–6.4) years, respectively]. The OS estimates at 1, 3, 5 and 8 years were 78.1, 54.9, 27.7, and 11.1% for patients with lung cancer and 93.6, 82.4, 71.2, and 55.7% for patients without lung cancer. They were 89.2, 68.4, 55.6, and 36.8% in patients with PH and 93.9, 83.5, 72.3, and 57.2% for patients without PH.

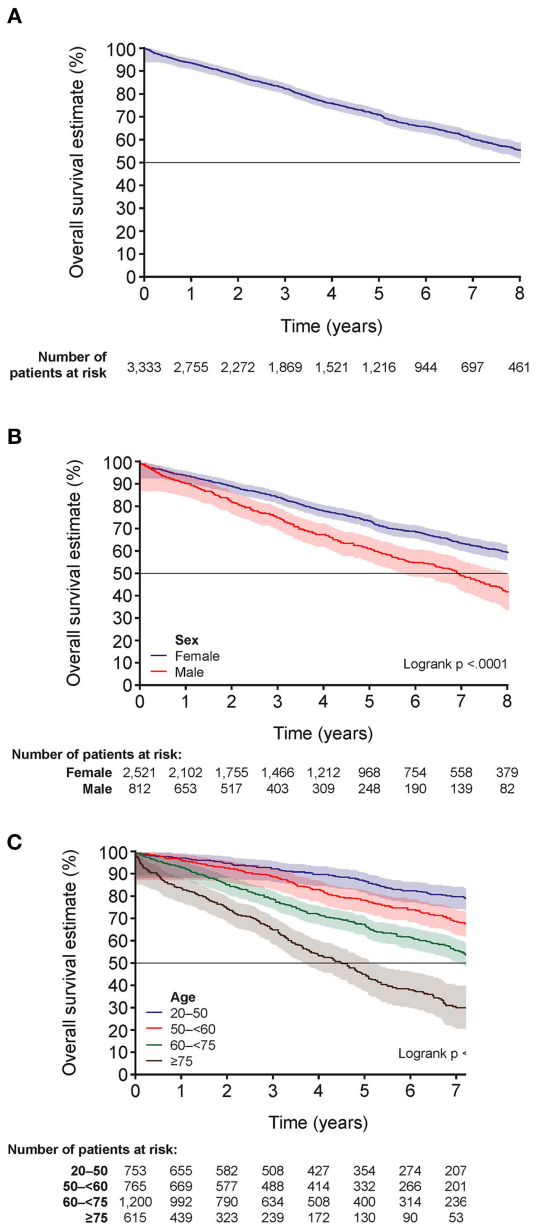

FIGURE 2 | Overall survival estimates for patients with SSc-ILD. **(A)** Overall survival estimates for all patients, **(B)** by sex and **(C)** by age in years. The shading indicates 95% Hall-Wellner band. SSc-ILD, systemic sclerosis-associated interstitial lung disease.

Healthcare Resource Utilization and Cost Evaluation

The healthcare consumption and costs for SSc-ILD patients are shown in **Supplementary Tables 6**, **7** and **Table 2**. The most commonly used drug treatments were glucocorticoids (74.1%), MMF (21.2%) and azathioprine (10.2%) (**Supplementary Table 6**). The annual mean costs (± SD) per patient for drug treatments during the follow-up were €883 (± 8,224) (**Table 2**).

TABLE 2 | Annual costs during the study.

	Cost per patient (€)	
	Mean (SD)	**Median (IQR)**
Total annual cost	25,752.8 (68,911.3)	9,316.4 (3,334.0–23,296.8)
Total drug treatment costs	882.9 (8,224.0)	28.1 (0.6–201.2)
Total non-pharmacologic treatment costs	1,501.1 (11,510.7)	0.0 (0.0–0.0)
Total medical and paramedical costs*	1,682.9 (3,530.6)	641.0 (279.3–1,604.6)
All hospitalization costs	21,538.8 (64,778.0)	6,289.9 (2,025.1–18,116.3)
Total laboratory test costs	56.8 (94.0)	33.8 (0.0–80.7)
Total imaging test** costs	63.4 (347.9)	16.6 (0.0–60.8)
Total pathology costs**	2.2 (26.7)	0.0 (0.0–0.0)
Total pulmonary function test costs**	24.7 (87.7)	0.0 (0.0–24.0)

**Excludes sick leaves, daily allowance and transport costs. **Outpatient only. IQR, interquartile range; SD, standard deviation.*

Nearly all patients (95.7%) had at least one GP visit but only around half (49.4%) were seen by a pulmonary specialist during the study period. 20.7% of patients had sick leave daily allowances (**Supplementary Table 7**). In total, 3,289 (98.7%) patients had ≥1 hospitalization, with a mean (± SD) of 12.6 (± 26.0) hospitalizations during the study. Of all patients, 60.4 and 27.3% were hospitalized due to acute events and PH, respectively, and 22.3% of patients were admitted to an intensive care unit.

The total annual cost of all healthcare use per patient was €25,753, with the highest contributor being hospitalizations costs (€21,539), followed by medical and paramedical costs (€1,683), and non-pharmacologic treatment costs (supplemental oxygen use, palliative care) (€1,501) (**Table 2**).

DISCUSSION

By using a large, real-world database covering most of the population of France, this study provides valuable insights into the epidemiology, mortality, healthcare resource utilization and costs associated with SSc-ILD.

In our study, the majority of patients were female, consistent with other studies (5, 26), and had underlying comorbidities, most commonly hypertension. Most patients were diagnosed with SSc and ILD at the same time, possibly because the majority of patients are diagnosed with SSc-ILD during hospitalization in France and their data are entered into the SNDS when they are hospitalized. Of 9,817 patients with SSc, 3,333 (34%) also had ILD, comparable with the estimate of 35% in Europe in a recent systematic review (5). In a registry of SSc patients in The Netherlands, the percentage of patients with SSc-ILD was 18.8–47.0% depending on the definition used (3). In a Norwegian SSc cohort of 324 patients, 50% of patients had ILD by HRCT (6). The differences may be explained by the different methodologies. In France, it is recommended that patients with SSc are screened for ILD using lung auscultation and chest HRCT (27). Patients with SSc are usually referred to a specialist ILD center where they

are initially screened for ILD by chest examination, pulmonary function tests and HRCT. Patients who are not diagnosed with ILD would then be followed up annually at a specialist ILD center, with an annual physical examination, pulmonary function testing and HRCT on a case-by-case basis. In our study, we identified patients with clinically relevant ILD using ILD diagnosis codes for reimbursement. Conversely, the Norwegian study defined ILD using HRCT review only, which may have led to the inclusion of patients with evidence of ILD on HRCT that was not clinically significant at baseline.

The prevalence of SSc in France has been estimated to be 13.2–15.8 per 100,000 persons (5). The overall incidence of SSc-ILD in our study was higher than a prior estimate of 0.1–0.4 in Europe (5). Furthermore, between 2012 and 2017, the reported prevalence of SSc-ILD was also higher than those estimated in a European systematic review and a study in The Netherlands (3, 5). There was an apparent decrease in incidence and increase in prevalence of SSc-ILD during our study. In 2017, the incidence is likely to be under-represented because of non-identification of cases where a patient with one diagnosis of SSc or ILD in 2017 can only be identified as having SSc-ILD after the study end date. Our study was not designed to track changes in prevalence and incidence over time, and thus trends should be interpreted with caution as we cannot exclude any artifact in the methodology and/or algorithm.

Male sex, older age, extent of disease on HRCT, lower FVC and DLco, and PH are known risk factors linked to mortality in SSc-ILD (9). The development of PH in patients with SSc-ILD significantly reduces patient survival (28). In line with previous studies (9), our study showed that male sex, older age, PH, as well as lung cancer, were factors associated with increased mortality in SSc-ILD.

Our study, based on national, real-world healthcare data in France, shows that SSc-ILD is associated with poor prognosis and high mortality. The OS estimate in our study was 55.3% at 8 years. In comparison, 76.9% of patients with SSc-ILD were alive at 9 years in the European Scleroderma Trials and Research (EUSTAR) France SSc-ILD cohort (29). A meta-analysis of SSc studies found a survival estimate from diagnosis of 74.9% at 5 years, although this included all SSc patients rather than those with SSc-ILD (30). In a French multicenter cohort study of SSc patients, the OS at 10 years was 71.7% (31). In addition, in a Spanish SSc cohort, the survival estimate at 10 years was 93%, although the inclusion criteria likely led to recruitment of patients with milder disease compared with the other cohort studies (32). In these cohort studies involving expert centers, there is greater confidence in the diagnoses, although there may be selection bias present. In our nationwide study, selection bias is less likely but patient inclusion is only based on reimbursement. There may also be some differences in study populations that contribute to the different findings; for example, patients in our study were somewhat older, with a mean age of 60.6 years compared with 56.6 years in the EUSTAR France cohort (29). Patients in our study were identified through hospital claims for SSc and ILD, meaning patients had potentially more severe disease than in EUSTAR. Overall, the different findings between our cohort and other cohorts, in particular the lower OS estimate, may be caused by the differences in methodology leading to selection of different populations of patients.

Nevertheless, our results support other studies showing that SSc-ILD places a considerable burden on patients and healthcare systems (1, 16, 17, 26, 33). Nearly all (98.7%) of the patients in our study were hospitalized at least once and nearly a quarter of patients were hospitalized in an intensive care unit. During the study period, the mean total annual costs of healthcare per patient were substantial at €25,753, with hospitalization costs being the main contributor. In comparison, in a UK retrospective study, the age-weighted median annual healthcare cost per patient with SSc-ILD was £6,375 (26), which is similar to the median total annual healthcare cost of €9,316 in our study. In two US claims database studies, the mean adjusted total direct healthcare cost over 1 year for patients with SSc-ILD was $33,195 (33), and the mean all-cause healthcare cost over 5 years was $191,107 (17).

Our study showed that the most common drug treatment in patients with SSc-ILD was glucocorticoids, even though there is limited evidence for their efficacy, they are associated with scleroderma renal crisis, and they are not recommended as first-line treatments (27, 34–36). In contrast, only 21% of patients received MMF (**Supplementary Table 6**), which is now recommended in SSc-ILD (37). Our study was conducted prior to the approval of nintedanib, a tyrosine kinase inhibitor first indicated for the treatment of idiopathic pulmonary fibrosis (22), by the U.S. Food & Drug Administration and European Medicines Agency for treating adult patients with SSc-ILD (22, 23). However, due to the nature of the data, we do not know what indication or organ involvement in SSc each drug was prescribed for, only that a prescription claim was made.

After diagnosis of SSc-ILD, although the majority of patients with SSc-ILD were seen by a GP during follow-up, only around half were seen by a pulmonary specialist, indicating that many patients were not referred to pulmonologists. This could reflect the lack of treatment options available at the time. In addition, the proportions of patients with diagnostic investigations were lower than expected for some tests; for example, a quarter did not have pulmonary function tests.

A strength of this study is that, in order to identify patients, only those who needed at least one hospitalization with a diagnosis code for SSc or who had full coverage for SSc were included, as per the algorithm for identification of patients in **Supplementary Table 1**. Since the diagnosis of SSc is routinely made in 1-day elective hospitalization, the majority of cases would have been captured. However, patients who had not been hospitalized and who did not have full coverage for SSc during the study period would not have been included. In France, to obtain full coverage for SSc, which means obtaining full reimbursement from the national health security system for claims related to their SSc, patients must submit a claim that has been verified by a physician. Using diagnosis codes and full coverage criteria for SSc allowed us to more accurately identify patients with SSc in our study.

In this large, real-world study, where all-cause mortality data for patients with SSc-ILD in France were collected, there were virtually no missing data despite the large size of the cohort. Although we do not have the causes of death for patients

within this study, all-cause mortality data are robust because the national registry of death certificates in France includes exhaustive and accurate all-cause mortality data. Unlike all-cause mortality, disease-related deaths are subject to potential error because they are dependent on the information available to the physician who establishes a patient's cause of death, and their medical interpretation.

There are several limitations of our study. The date of SSc-ILD diagnosis was the first date where both diagnoses were present (i.e., where a patient had diagnostic codes for both SSc and ILD). Thus, we may have underestimated the timing of SSc-ILD diagnosis in patients whose ILD diagnosis preceded the onset of SSc. Our study used administrative claims data to identify patients with SSc-ILD without supporting clinical data such as pulmonary function tests and imaging results. Patient inclusion was dependent on physicians accurately assigning diagnostic codes for both SSc and ILD, meaning there is the possibility of miscoding or undercoding. Patients with subclinical ILD can have mild lung abnormalities detected by HRCT or pulmonary function tests, but may be asymptomatic and undiagnosed (38). Patients with subclinical ILD who did not have full coverage for SSc may not have been included in this study. Physicians did not code each disease manifestation individually, and this may lead to the burden of illness or comorbidities being underestimated (39). Coding systems and practices may also change over time as they are modified to suit scientific evidence and reimbursement purposes rather than medical care. Direct counts from nationwide healthcare databases may not give reliable incidence data (39). As incidence *per se* cannot be measured retrospectively, our results represent estimates of the incidence. The study was designed to estimate the epidemiology and mortality rate of SSc-ILD but not changes over time or causes of death. We also did not have data on occupational or environmental exposures, which could have affected the OS estimates. Patients with other diseases were not excluded, which may have led to lower OS estimates. Therefore, results regarding OS should be interpreted with caution.

In conclusion, this study shows that SSc-ILD is associated with a high burden of disease, as reflected by high mortality, healthcare resource utilization and associated costs. Improving the diagnosis and management of this complex disease is vital to improve the outcomes of patients with SSc-ILD.

DATA AVAILABILITY STATEMENT

The data sets presented in this article are publicly available on request from the SNDS. Aggregated data can be shared upon request to HCL (contact: anne.metzinger@chu-lyon.fr).

ETHICS STATEMENT

The study was reviewed and approved by the Expert Committee for Health Research, Studies and Assessments [Comité d'expertise pour les recherches, les études et les évaluations dans le domaine de la santé (CEREES)] on 18 August 2018 (TPS 72584) and by the National Commission for Information Technology and Freedoms [Commission Nationale de l'Informatique et des Libertés (CNIL)] on 9 November 2018 (N:918305). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MN and VC: study design. SL, MN, and VC: data analysis and interpretation. All authors wrote, read, and approved the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.699532/full#supplementary-material

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REVIEW
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Hypersensitivity Pneumonitis: Diagnostic and Therapeutic Challenges

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Hypersensitivity pneumonitis (HP) is one of the most common interstitial lung diseases (ILD), that presents unique challenges for a confident diagnosis and limited therapeutic options. The disease is triggered by exposure to a wide variety of inciting antigens in susceptible individuals which results in T-cell hyperactivation and bronchioloalveolar inflammation. However, the genetic risk and the pathogenic mechanisms remain incompletely elucidated. Revised diagnostic criteria have recently been proposed, recommending to classify the disease in fibrotic and non-fibrotic HP which has strong therapeutic and outcome consequences. Confident diagnosis depends on the presence of clinical features of ILD, identification of the antigen(s), typical images on high-resolution computed tomography (HRCT), characteristic histopathological features, and lymphocytosis in the bronchoalveolar lavage. However, identifying the source of antigen is usually challenging, and HRCT and histopathology are often heterogeneous and not typical, supporting the notion that diagnosis should include a multidisciplinary assessment. Antigen removal and treating the inflammatory process is crucial in the progression of the disease since chronic persistent inflammation seems to be one of the mechanisms leading to lung fibrotic remodeling. Fibrotic HP has a few therapeutic options but evidence of efficacy is still scanty. Deciphering the molecular pathobiology of HP will contribute to open new therapeutic avenues and will provide vital insights in the search for novel diagnostic and prognostic biomarkers.

Keywords: lung fibrosis, risk factors, hypersensitivity pneumonitis, prognostic factors, diagnosis

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INTRODUCTION

Hypersensitivity Pneumonitis (HP) is an immune-mediated disease that manifests as interstitial lung disease (ILD) in susceptible individuals after exposure to identified or unidentified inciting agent(s) (1). The disease has a heterogeneous clinical presentation, as well as varied radiological and morphological patterns likely associated with the individual genetic susceptibility, type of antigen, the extent of exposure, and the interaction with other injuring factors (2, 3).

The genetic susceptibility that increases the risk to develop the disease is unclear, and most studies have focuses on polymorphisms in the Major Histocompatibility Complex class II (HLA-DR and HLA-DQ) molecules which are involved in the presentation of antigens by antigen-presenting cells (APCs) and recognized by the respective T-cell receptor on the CD4+ T-cell surface (2–5). More recently, it was found that several interactions involving polymorphisms of either the *SFTPA1*

and/or *SFTPA2*, increase HP risk whereas their interactions with the hydrophobic surfactant proteins (*SFTPB* and *SFTPC*) were associated with a decreased risk to develop the disease (6).

On the other hand, exposure to damaging agents, such as cigarette smoke, air pollution, viral infections, and pesticides also influences the development of the disease as well as the heterogeneous behavior (2, 3, 7–9).

EPIDEMIOLOGY

The definite incidence and prevalence of HP are uncertain because it varies according to the countries and customs, and importantly due to the lack of consensus over a definition of the disease, and the inability to detect the source of antigen exposure leading to a misdiagnosis attributing the patient's findings to another ILD. The incidence of HP has been reported in some countries such as the UK population, where is recorded as ∼1 per 100,000 (10). In the US, a yearly incidence in the range of 1.7–2.7 per 100,000 population, has been recently reported (11), while Japan and France estimate an incidence between 0.3 and 0.9 per 100,000 individuals (12, 13). However, the incidence could be much higher according to one study that reported bird breeder's disease in 4.9 per 100,000 individuals over 10 years or 54.6 per 100,000 bird breeders (1, 14). The proportion of HP among all ILD cases could be higher and may represents around half of the newly diagnosed patients in high prevalent regions. The high variability in incidence and prevalence likely depends of many factors including differences in geographical conditions, local customs and occupational factors of each region and also because only until recently, there is a consensus over a definition of the disease.

ANTIGENS AND SOURCES OF EXPOSURE

Numerous antigens able to induce the disease have been identified and the list is constantly being expanded. The most studied antigens are avian antigens, fungi and thermophilic bacteria in the home or the working environment (15, 16); but there are also numerous reports revealing the association with other type of bacteria, protozoal, other animal proteins, and low-molecular-weight chemical compounds. For this reason, it is very important to investigate the presence of visible mold indoors; occupational environments such as where greenhouses, mushroom farming, compost, other food production methods, and metalworking fluids that could be contaminated by bacterial, mycobacterial, and fungal organisms (17). Even hobby activities may be a source of HP antigens, for example, non-tuberculous mycobacteria have been identified in patients exposed to indoor hot tubs and outdoor pools (18). Finally, specific chemicals used in industry, such as isocyanates and anhydrides, should also be considered as causal antigens. A list with most of the antigens and sources of exposure identified so far can be found in ATS/JRS/ALAT Guidelines (1).

PATHOGENIC MECHANISMS

The Inflammatory Response

The first step is the sensitization to the inhaled antigens which is associated with repeated exposure in individuals with genetic susceptibility to HP. The immunopathological response to the antigens involves T- and B-cells. Progression from sensitization to HP requires the accumulation of CD4+ TH1 cells in the lung, creating a pro-inflammatory microenvironment. Importantly, the suppressive activity of regulatory T cells is impaired, resulting in the amplification of the inflammatory response. IFNγ and TNF promote the accumulation, activation, and aggregation of macrophages, resulting in the development of granulomatous inflammation (4, 19). Also, immune complex-mediated lung injury with specific IgG antibodies may contribute to the inflammatory response.

The Fibrotic Response

Several factors may hamper the resolution of the inflammation, including further exposure to the antigen, which occurs mainly when it has not been identified (20), cigarette smoking, a genetic predisposition that may enhance the development of autoantibodies (21), and other unknown factors.

Several changes in T cell subsets are found in fibrotic HP, which may contribute to the non-resolution of inflammation triggering a fibrotic response, including a decrease of the immunoregulatory and antifibrotic γδ T cells, an increase of CD4+ cells, and a switch from a predominant TH1-like phenotype to a TH2-like phenotype (4, 19). TH2 cells secrete, among others, IL-4 and mainly IL-13 that contribute to a fibrotic response stimulating the TGFβ1 signaling pathway and activating the expansion of fibroblasts population (19, 22, 23). Fibroblasts arrive at the injured areas and differentiate into myofibroblasts, which are responsible for the accumulation of extracellular matrix. At the initial stages of fibrosis, the disease may stabilize or even improve in the pulmonary functional status, however, a subset of patients develops an aggressive phenotype called progressive pulmonary fibrosis that results in the destruction of the lung architecture (24). The mechanisms triggering this devastating phenotype are unclear but may include the type of fibrosis (UIP vs. non-UIP pattern), the aberrant composition and stiffness of the extracellular matrix, and the emergence of some unique profibrotic cell subsets (25).

CLINICAL FEATURES

It has been recently proposed that HP can be classified in fibrotic and non-fibrotic phenotypes (1). This proposal was considered to be more consistently associated with the clinical course, outcomes, and treatment efficiency.

Dyspnea is the main symptom of both non-fibrotic and fibrotic HP. Occasionally, patients with the non-fibrotic disease may present an acute influenza-like syndrome occurring a few hours after a (usually) substantial exposure. In these cases, symptoms gradually decrease over hours/days but may recur with re-exposure. More often, patients with non-fibrotic HP present progressive dyspnea during weeks or a few months together with

constitutional symptoms, including fever, chills, chest tightness, wheezing, and weight loss (3). Patients with fibrotic HP show progressive (usually insidious) exertional dyspnea and chronic cough that develops over months to years. Clubbing may be present and on auscultation may yield inspiratory "velcro" crackles. Some patients display a high-pitched wheeze at the end of inspiration ("chirping" rales) while others describe the presence of inspiratory squeaks, caused by airways involvement (26). Pulmonary function test (PFT) reveal in both fibrotic and non-fibrotic HP a predominantly restrictive defect with DL_{CO} impairment, although some small airway obstruction may be detected in non-fibrotic patients. Finally, in the advanced stage of the disease patients may develop pulmonary arterial hypertension which is more prevalent in hypoxemic patients with greater impairment in lung function and lower exercise capacity (27).

DIAGNOSTIC APPROACH

HP represents a diagnostic challenge and requires a high index of suspicion by the clinician evaluating by the first time a patient with ILD (28, 29). Targeted diagnostic steps should include a thorough evaluation of the ILD patient's history of occupational and environmental antigenic exposures, chest high resolution computed tomography (HRCT), serum specific IgGs for confirmation of exposure or as a screening tool, bronchioalveolar lavage (BAL), and histopathological study in some cases (1, 30, 31).

Evidence of Exposure

Identification of the source of exposure and putative antigen(s) can be difficult. Validated and regionally relevant questionnaires that include occupational, residential, and avocational environments are mandatory (30, 32). Questions should also consider indirect exposures through contact with individuals who may carry antigens on their clothing or other materials. If an exposure is identified, details of duration, extent, and frequency should be obtained and importantly putative cause-effect relationship with symptoms. Evidence-based guidance has been published by WHO suggesting questions that may help clinicians to find out indoor dampness and molds (33). The on-site visual inspection is also useful for identifying obvious exposure sources (30).

Diagnostic Detection of Cellular and Humoral Immune Responses to HP Antigens

Identification of serum-specific Immunoglobulins (ssIGg) may help to recognize the inciting antigen (1, 30). According to the ATS Workshop Report, serum IgG testing against potential antigens associated with HP distinguish this disease from other ILDs with a sensitivity and specificity of 83 and 68%, respectively (30). However, it is important to emphasize that the presence of positive circulating antibodies, is only evidence of exposure to a potential HP antigen but does not prove causality and it may be worthy of further consideration to explore the source (30, 34).

On the other hand, since antigen T-cell mediated immune response plays a pivotal role in the pathogenesis of HP it has been proposed that lymphocyte proliferation testing may be a diagnostic tool (30, 35, 36).

However, studies using this method are scant, usually performed in small cohorts, and primarily in patients suspected to have bird-related HP. In addition, there is no standardized methodology to recommend in clinical practice. Nevertheless, this technique may be a promissory diagnostic tool in the future, mainly in patients with fibrotic HP that do not have detectable antibodies to causative antigens (37).

Chest HRCT Scanning

HRCT plays a pivotal role in the diagnosis of HP. In both fibrotic and non-fibrotic HP, images should be acquired at deep inspiration and after prolonged expiration.

The presence of centrilobular nodules, ground-glass opacities, mosaic attenuation, air trapping, mosaic perfusion are recognized as the principal findings in both fibrotic a non-fibrotic HP (**Figure 1**). The "three-density pattern" which describes a form of mosaic attenuation that combines areas of ground-glass opacification, lobular areas of low attenuation, and normal lung has a specificity of 93% for a diagnosis of fibrotic HP (38). For the fibrotic HP pattern, coexisting lung fibrosis and inflammation with signs of bronchiolar obstruction are highly suggestive. Honeycombing and traction bronchiectasis can be present and may be extensive in severe forms of fibrotic HP. Lung fibrosis can be more severe in the mid or mid and lower lung zones or equally distributed in the three lung zones with relative basal sparing (**Figure 2**) (39).

In general terms, the ATS/JRS/ALAT Guidelines and CHEST Guideline and Expert Panel Report 2021, show similar recommendations to classify HRCT images in the context of fibrotic or non-fibrotic HP (1, 31).

Cell Profile in the Bronchoalveolar Lavage Fluid (BAL)

BAL is a safe and well-tolerated diagnostic tool to evaluate alveolar inflammation. Increased cellularity with lymphocytosis is an important piece to improve the diagnostic likelihood of HP, where a higher percentage of lymphocytes could reflect the degree of alveolitis (**Figure 3**). However, the threshold proportion of BAL fluid lymphocytes that distinguishes HP from non-HP ILD is unclear and is strongly associated with the presence and extent of fibrotic changes (1, 31). Important for interpretation, BAL lymphocytosis may also be influenced by several variables, including, timing relative to antigen exposure, smoking status, and others (40). In general, and according to the ATS/JRS/ALA and CHEST guidelines, and to our own experience, we consider that a 30% threshold is reasonable for use in the differential diagnosis of HP vs. non-HP ILD.

Lung Biopsy

When the diagnosis is uncertain even after multidisciplinary discussion, lung biopsy is indicated. The histological specimen can be obtained by transbronchial cryobiopsy (if the Institution

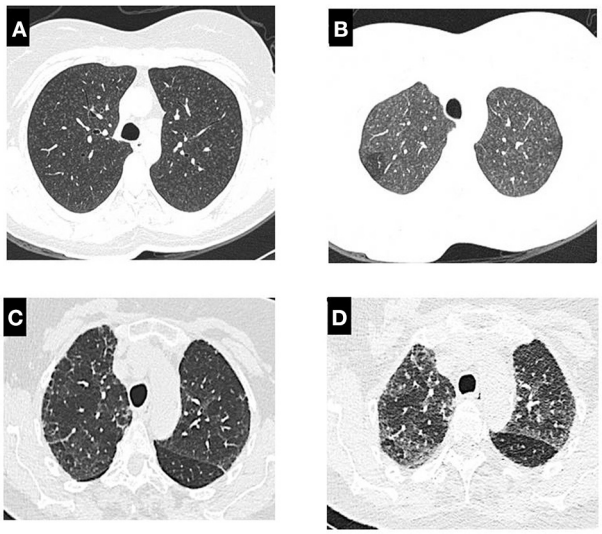

FIGURE 1 | High-resolution computed tomography scan in patients with non-fibrotic HP: **(A)** show inspiratory phase with diffuse centrilobular nodules, **(B)** expiratory phase in the same patient with centrilobular nodules and air trapping in right side; **(C)** in inspiratory phase present subpleural reticular pattern, with mosaic attenuation which is highlighted in the expiratory phase **(D)**.

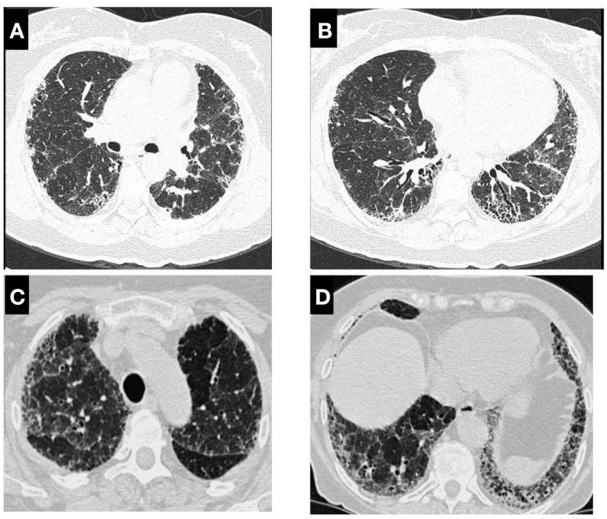

FIGURE 2 | High-resolution computed tomography scan in patients with fibrotic HP. In **(A)**, it is observed bilateral subpleural reticulation and in **(B)** traction bronchiectasis, honey combing and discrete ground-glass opacification and volume loss in left lung; **(C)** show lung fibrosis and areas of low attenuation and the same patient in **(D)** bronchiectasis and persistence of mosaic attenuation.

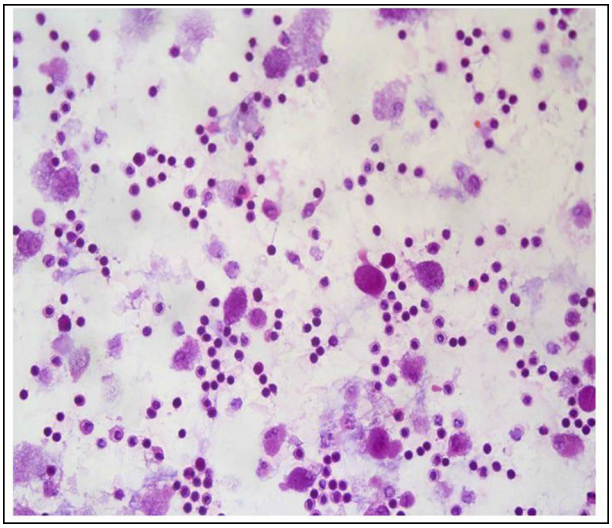

FIGURE 3 | Differential cell count in bronchoalveolar lavage fluid from a patient with hypersensitivity pneumonitis showing strong lymphocytosis. Hematoxylin and eosin staining, magnification: 40×.

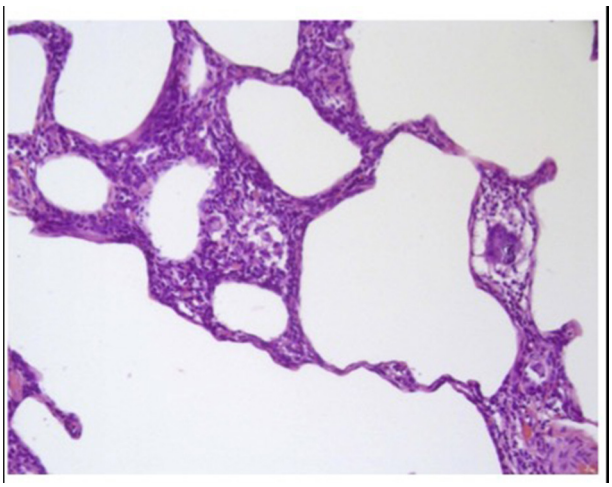

FIGURE 4 | Lung biopsy sample from a patient with non-fibrotic hypersensitivity pneumonitis showing cellular chronic interstitial pneumonia and a poorly formed non-necrotizing granuloma. Hematoxylin and eosin staining, magnification: 40×.

has experience with this technique), or surgical lung biopsy where samples of two different lobes are indicated (41–43).

The histopathological features vary according to the phenotypes. In the case of the non-fibrotic HP, characteristic findings include bronchiolocentric cellular interstitial pneumonia and cellular bronchiolitis of lymphocyte-predominant inflammatory infiltrate, as well as loosely formed granulomas and randomly scattered multinucleated giant cells within the interstitial inflammation (**Figure 4**) (1, 31).

Fibrotic HP differs from non-fibrotic HP in that the underlying chronic interstitial pneumonia and/or bronchiolitis is complicated by fibrosis, which occasionally may overlap with a UIP pattern hindering the differential diagnosis with IPF. In other cases, interstitial pneumonia shows a more uniform and diffuse distribution mimicking fibrotic non-specific interstitial pneumonia or may display features compatible with interstitial

airway-centered fibrosis (1, 31, 44). Findings of non-fibrotic HP may help to distinguish fibrotic HP from other fibrotic lung disorders. Moreover, UIP-like pattern is related with worst survival (1, 45, 46).

Multidisciplinary Discussion

As recommended in all newly diagnosed ILD, multidisciplinary evaluation of patients with suspected HP is advised. Diagnosis is guided by the integration of clinical history and questionnaire, environmental assessment and sampling, HRCT, and BAL, and in select cases, immunologic testing, and histopathological evaluation, which likely will provide the most precise approach to diagnosis. Two recently published guidelines, from ATS/JRS/ALAT (1), and from CHEST (31) recommended diagnostic algorithms based in three domains: exposure identification, HRCT findings, and BAL lymphocytosis, which in the case of the ATS/JRS/ALAT diagnostic criteria is strengthened by histopathologic findings. A recent study showed that the agreement between them in a real-life setting was low for definitive/high-confidence diagnosis (47). Accordingly, we proposed an algorithm for the diagnostic evaluation of HP, based in the same domains used by both guidelines (**Figure 5**).

PROGNOSTIC FACTORS

HRCT and Morphological Phenotypes

The type of fibrotic structural remodeling may indicate an increased risk of early mortality. Particularly, the usual interstitial pneumonia (UIP) pattern either by HRCT or biopsy carry-out the worst prognosis. For example, a study that involved a large cohort of patients, showed that CT honeycombing is highly prevalent in diverse forms of ILD, including HP, and that is associated with marked increased in long-term mortality rate compared with those without honeycombing (48). Likewise, in another study where three radiologically defined phenotypes were identified, it was found that patients with typical UIP-like pattern (that included honeycombing) displayed a median survival similar to IPF (the most aggressive ILD), and significantly lower than in patients with non-honeycomb fibrosis (2.8 vs. 7.95 years) (49). Therefore, CT honeycombing is prevalent in fibrotic HP and identifies a progressive fibrotic phenotype that is associated with increased mortality rates.

UIP findings in the lung biopsy also predict prognosis (1, 45). Interestingly, a biomarker that distinguishes UIP from a non-UIP pattern has been proposed for the diagnosis of IPF. The Envisia Genomic Classifier, through the detection of a 190-gene machine-learning classifier in lung samples obtained from transbronchial biopsies, could assist in the confident diagnosis of UIP (50). However, if this molecular biomarker will be useful (and accessible) in UIP of other fibrotic lung disorders, such as HP, is largely unknown.

Interestingly, some HP patients may present features of pleuroparenchymal fibroelastosis (PPFE) an unusual biopathological process characterized by upper-lobe-dominant progressive pulmonary fibrosis consisting of visceral pleural thickening with collagenous matrix and subpleural elastosis (51), and this association is linked to worsened HP survival (52).

Importantly, using automated computer-based quantitative imaging it was shown that patients with a pulmonary vessel volume above 6 · 5% of the total lung volume, had a rate of disease progression, nearly identical to that of IPF (53).

Genomic and Molecular Risk Factors

There are significant inter-individual differences in the severity and progression of the pulmonary disease in patients with HP that otherwise seem to share similar antigen exposure and other demographic characteristics indicating that some genetic or molecular modifiers may contribute.

For example, it was found that an exaggerated shortening of telomeres was associated with fibrosis and was a strong predictor of poor survival in HP patients. Moreover, short telomere length was also linked to radiographic and histopathologic changes similar to IPF (54).

More recently, it was demonstrated that around 10% of patients with HP carry rare protein-altering variants in telomere-related genes, such as *TERT*, *RTEL1*, and *PARN* (55). Importantly, this finding was associated with shorter peripheral blood telomere length and significantly reduced transplant-free survival.

Likewise, The MUC5B promoter polymorphism rs35705950 minor allele was associated with HRCT evidence of fibrosis and traction bronchiectasis, and in contrast to IPF, showed a statistical tendency toward poorer survival among patients with HP (54).

There is some evidence that some biomarkers may be an independent predictor of disease progression and mortality in HP. The relative change in the serum levels of KL-6/MUC1, a human mucin protein expressed by type 2 alveolar epithelial cells, is associated with rapid progression in patients with fibrotic HP (56). Interestingly, raised KL-6 is associated with early-stage HP suggesting a mechanistic link with the behavior of the lung epithelium (57).

YKL-40 is a chitinase-like protein mainly secreted by inflammatory and epithelial cells, which is involved in the inflammatory response to tissue damage. HP patients who experienced disease progression had higher baseline serum YKL-40 levels than those who remained stable during follow-up. Likewise, HP patients who died had higher baseline serum YKL-40 levels than those who survived (58).

A serum chemokine profile showed that a lower CXCL9, in combination with higher CCL17, was an important predictor of worsening lung function (59). However, is important to emphasize that studies of prognostic biomarkers in HP are scanty, performed in small cohorts, and usually without verification cohorts.

Two recent studies have demonstrated that a subset of patients with HP presents circulating present autoantibodies, without features of autoimmune disease (21, 60). In both studies, the presence of autoantibodies was an independent predictor of increased mortality. Patients carrying the

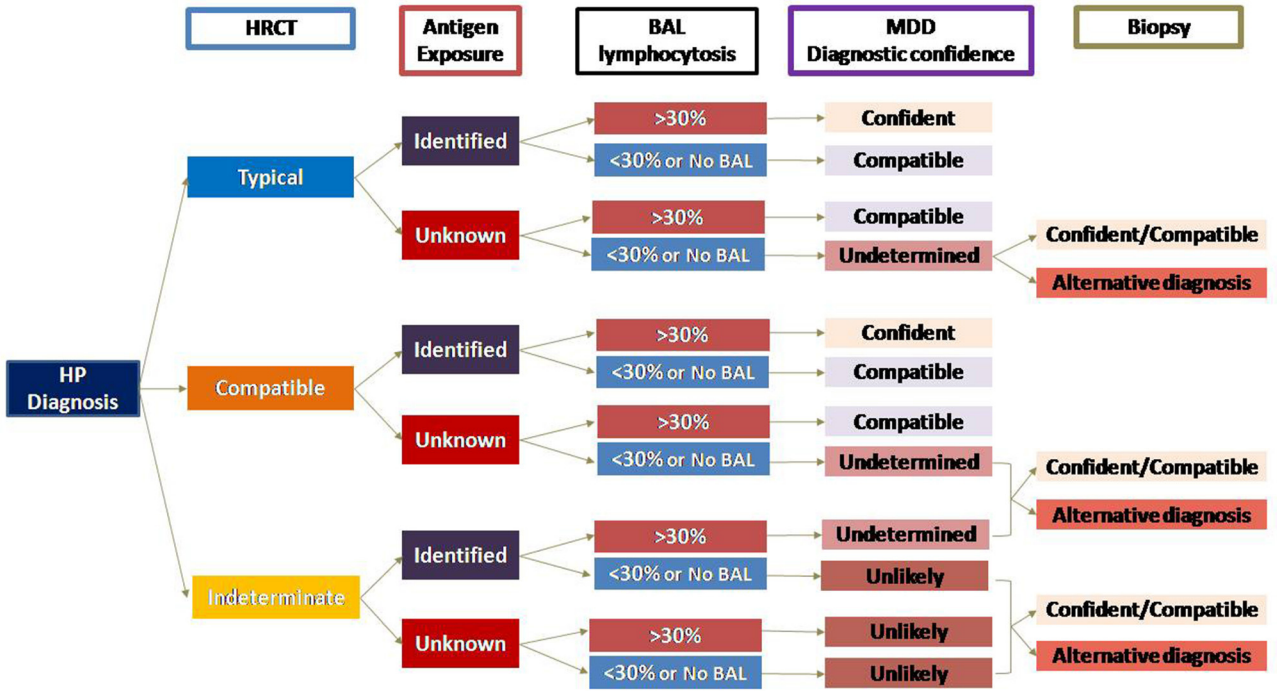

FIGURE 5 | Hypersensitivity pneumonitis diagnostic algorithm. The diagnosis of HP diagnosis relies primarily on three domains: HRCT pattern (according to ATS guideline classification), antigen exposure, and BAL lymphocytosis. This approach is followed by multidisciplinary team discussion where the diagnostic confidence is made. Undetermined or Unlikely HP may require the lung biopsy to orientate to an alternative diagnosis, or occasionally, reveal a hidden HP. Diagnostic confidence: Confident (>90%), Compatible (70%-89%), Undetermined (50%-69%), Unlikely (<50%). NO BAL (Not performed, e.g., patients with comorbidities and/or very low pulmonary function tests, patient's refusal to do the procedure; BAL not available, or other reasons). HP, hypersensitivity pneumonitis; HRCT, high resolution computed tomography; BAL, bronchoalveolar lavage; MDD, multidisciplinary discussion.

haplotype DRB1*03:01-DQB1*02:01, which is part of the 8.1 ancestral haplotype, and a major genetic determinant of autoimmune diseases showed a significant higher risk to develop autoantibodies (21).

Several studies have reported acute exacerbation (AE) in patients with fibrotic HP, following the same definition used in IPF, which results in poor prognosis (61). Recently it was reported as risk factors lower DLco, the presence of UIP-like pattern on HRCT at diagnosis, and cumulative incidence rates of AE showed high in-hospital mortality rate (62).

Finally, some demographic characteristics, such as aging and smoking may contribute to disease progression (3, 19).

THERAPEUTIC APPROACHES

There is no consensus or guidelines for HP management, and most of the evidence arises from retrospective cohort studies or case reports. The therapeutic approach consists mainly of antigen avoidance and pharmacological treatment with corticosteroids/immunosuppressive drugs and, more recently, antifibrotic therapy depending on HP phenotype. In advanced disease with severe clinical and functional deficiency, a lung transplant is indicated.

Antigen Avoidance

Identification and complete antigen avoidance are the mainstays of treatment and patients should be strongly advised to avoid further exposure (1, 19, 30). However, in 40–50% of HP patients the antigen(s) is not identified.

In non-fibrotic HP antigen-avoindance is associated with improved lung function but in fibrotic forms, the effectiveness remains controversial (63). In a cohort of patients with fibrotic HP, FVC remained stable and median survival was greater in patients who reported antigen avoidance while in another study no difference was found suggesting a self-perpetuating mechanism of the disease in fibrotic forms (63, 64). Despite these observations, it is important to make continuous efforts to identify the antigens' source and strongly recommend avoid exposure.

PHARMACOLOGICAL TREATMENT

Non-fibrotic HP

Corticosteroids are often used but the evidence supporting this approach is very limited and comes from studies in farmers lung disease, where pulmonary function improved during early follow-up protecting against progression but without beneficial effect on long term prognosis (65, 66). Recently De Sadeleer et

al., showed that corticosteroid initiation in progressive patients resulted in a reversal with an improvement of lung function (63). An empiric treatment scheme may consist of prednisone (or equivalents) of 0.5 mg/kg/d for 1–2 weeks followed by a gradual tapering until maintenance of 10 mg/d (67). To ameliorate adverse events related to the prolonged corticosteroid use, sparing agents, mycophenolate (MMF) and azathioprine (AZA), might be a treatment option for patients showing progression and/or frequent relapses or in whom antigen avoidance is not possible.

Fibrotic HP

For many reasons, pharmacological treatment in fibrotic HP is challenging. Despite the lack of evidence, corticosteroids alone or associated with AZA or MMF are the most common immunosuppressants used for treating fibrotic HP, with fewer adverse events with combination therapy. In a retrospective study, a modest but significant improvement in DL_{CO} without changes in FVC was observed after 1-year treatment of MMF or AZA (68). The presence of BAL lymphocytosis seems to be associated with a favorable response to corticosteroids alone or in combination, especially with AZA, but only during the first 6 to 12 months of treatment, with FVC decline after this period (63, 69). HRCT honeycombing, low BAL lymphocytosis, and the presence of short telomeres could be factors associated with no response to immunosuppressive therapy (63, 70). Moreover, treatment with corticosteroids alone or in combination with AZA/MMF was associated with increased mortality risk after adjustment in two cohorts of patients with fibrotic HP. This finding is similar to those reported in IPF, probably reflecting a final common pathway in the pathophysiologic processes of advanced fibrosis that underlies these two diseases (25, 71, 72).

There is emerging evidence that Rituximab, an anti CD20 monoclonal antibody, seems to be well-tolerated and may lead to stabilization or improvement of lung function in some patients with fibrotic HP, particularly those without UIP or NSIP pattern (73, 74). Finally, leflunomide, a prototype member of dihydroorotate dehydrogenase (DHODH) enzyme inhibitors, could be an effective sparing immunomodulatory drug with a significant pulmonary function improvement in fibrotic HP, with a most pronounced effect in patients without >20% extent of fibrosis on HRCT (75).

Antifibrotics, pirfenidone and nintedanib, recently became a plausible option for patients who experience disease progression despite antigen avoidance and immunosuppressive treatment. The efficacy and safety of pirfenidone were evaluated in the RELIEF study that was prematurely terminated due to slow recruitment (76). Despite this, 45% of the patients included in the study had fibrotic HP and the addition of pirfenidone to ongoing medication showed slower disease progression as measured by loss of FVC. This data is similar to another real-life study where pirfenidone reduced the decline of vital capacity in a cohort of patients with fibrotic HP (77). By contrast, in a small cohort of patients with fibrotic, advanced HP, we found that adding pirfenidone to the immunosuppressive drugs, showed no effect on FVC compared with the patients using only immunosuppressive therapy, but displayed a tendency to DLCO improvement and a significant improvement in the quality of life evaluated through the total score on the Saint George's Respiratory Questionnaire (78).

The INBUILD trial demonstrated that in patients with progressive fibrosing interstitial disease the annual rate decline in the FVC was significantly lower among patients who received nintedanib than those who received placebo (79). In the fibrotic HP subgroup (26% of the overall population) there was no statistical difference in the rate of FVC decline between nintedanib and placebo, likely because the study was not designed to provide evidence in specific subgroups (80). Finally, in patients with progressive and severe fibrotic HP, it should be considered for a lung transplant (81).

In summary, the management of HP patients should include, antigen avoidance in both HP phenotypes. For patients with non-fibrotic HP who don't have a full recovery after antigen removal, it is suggested corticosteroid treatment with a gradual tapering to achieve a low dose with or without AZA or MMF for patients with frequent relapses or when antigen avoidance it's not possible. In light of the evidence, in fibrotic HP and preferable after careful evaluation with multidisciplinary team discussion using HRCT, BAL, and histopathology findings to identify those with mixed inflammatory plus fibrotic or purely fibrotic disease, immunosuppressive therapy, and antifibrotic treatment should be considered and in advance disease, patients should be included for a lung transplant.

PALLIATIVE CARE

As in many interstitial lung disease that present progressive pulmonary fibrosis phenotype and end-stage disease, the decrease in quality of life of patients with HP represents an additional problem. Quality of life is not only affected by the disease but also by the presence of adverse events associated with the treatment, inability to continue with work or recreational activities and the economic impact for the family. Palliative care should be discussed and initiated early in the disease course, and should be focused not only according patient's needs and preferences but also include caregivers which should be supported throughout the disease trajectory (82).

CONCLUSIONS

The diagnosis and treatment of HP remain complex and challenging because the absence of a single diagnostic gold standard and lack of prospective clinical trials.

For a long time, HP was characterized by duration of symptoms at the time of diagnosis, as acute, subacute, or chronic which was not reliably associated with the prognosis. Consequently, a recently published guideline has proposed that patients should be classified as having fibrotic or non-fibrotic HP, according to the radiological or histopathological findings. These two phenotypes are clearly identifiable and likely show a better association with outcome. The pathogenic mechanisms have not been fully elucidated, and diagnostic and

prognostic biomarkers are lacking. The prognosis of fibrotic HP is poor as in other fibrotic lung disorders, and questions remain unanswered about the optimal therapeutic strategy mainly for fibrotic HP for which large-scale clinical trials are necessary.

AUTHOR CONTRIBUTIONS

MS: conceptualization and writing the first draft. IB-R, MA, and ER-A: review and writing. All authors contributed to the article and approved the submitted version.

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Management of Acute Exacerbation of Idiopathic Pulmonary Fibrosis in Specialised and Non-specialised ILD Centres Around the World

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Background: Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) is a severe complication associated with a high mortality. However, evidence and guidance on management is sparse. The aim of this international survey was to assess differences in prevention, diagnostic and treatment strategies for AE-IPF in specialised and non-specialised ILD centres worldwide.

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Material and Methods: Pulmonologists working in specialised and non-specialised ILD centres were invited to participate in a survey designed by an international expert panel. Responses were evaluated in respect to the physicians' institutions.

Results: Three hundred and two (65%) of the respondents worked in a specialised ILD centre, 134 (29%) in a non-specialised pulmonology centre. Similarities were frequent with regards to diagnostic methods including radiology and screening for infection, treatment with corticosteroids, use of high-flow oxygen and non-invasive ventilation in critical ill patients and palliative strategies. However, differences were significant in terms of the use of KL-6 and pathogen testing in urine, treatments with cyclosporine and recombinant thrombomodulin, extracorporeal membrane oxygenation in critical ill patients as well as antacid medication and anaesthesia measures as preventive methods.

Conclusion: Despite the absence of recommendations, approaches to the prevention, diagnosis and treatment of AE-IPF are comparable in specialised and non-specialised ILD centres, yet certain differences in the managements of AE-IPF exist. Clinical trials and guidelines are needed to improve patient care and prognosis in AE-IPF.

Keywords: idiopathic pulmonary fibrosis, acute exacerbation, questionnaire, pulmonologists, specialised ILD centres, non-specialised ILD centres

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive fibrosing interstitial lung disease associated with a poor prognosis with a five-year survival rate of 20–40% and a median survival time of 2–5 years (1, 2). An acute exacerbation of IPF contributes to the dismal prognosis and disease progression and is defined as an acute, clinically significant respiratory deterioration characterised by evidence of new widespread alveolar abnormality in patients with IPF and after the exclusion of cardiac failure or fluid overload (3). The annual incidence is up to 20%, depending on the population analysed (4, 5). AE-IPF is associated with a median survival of ∼3–4 months (6, 7) and may account for more than 40% of all death in patients with IPF (8). The aetiology is still obscure, but AE-IPF might be triggered e.g. by infection or procedures/operation, or may occur idiopathic (6). Evidence on prevention, diagnosis and therapy of AE-IPF is sparse and no international guidelines exist (3, 9). Accordingly, there is a huge variability with regards to preventive, diagnostic and therapeutic approaches worldwide (10). It is unknown whether these different strategies are partially explainable by differences between specialised and non-specialised ILD centres. Therefore, this study aimed to compare preventive, diagnostic and therapeutic strategies for AE-IPF between specialised and non-specialised ILD centres.

MATERIALS AND METHODS

Questionnaire and Participating Physicians

As described previously (10), as a first step we conducted a literature research on diagnostics, therapy, prevention and management of AE-IPF to identify items to be included in this survey. Then, an expert panel was created, comprising pulmonologists with expertise in the diagnosis and management of ILD working in specialist ILD centres and a track record of publication in this field, to participate in an email-based interview to structure the survey. The final questionnaire consisted of 20 questions regarding diagnosis, treatment and prevention of AE-IPF and suggested future perspectives in AE-IPF research (10). To identify working place (specialised and non-specialised ILD centres), country of origin, number of patients with IPF under care, and estimated number of AE-IPF seen, additional questions were included into this survey. From July 1 2017 to November 30 2017 pulmonologists worldwide with interest in ILD were identified, including the European Respiratory Society assembly on Diffuse Parenchymal Lung Disease, the American Thoracic Society assembly on Clinical Problems, the Japanese Respiratory Society assembly on Diffuse Parenchymal Lung Disease and participants of the IPF Project Consortium (www.theipfproject.com) (11). Nationality, academic status (working at a university hospital or not) or subspecialist interests within respiratory medicine did not influence inclusion eligibility. The questionnaire was provided by the online survey tool SurveyMonkey® from December 2017 to April 2018.

Statistical Analysis

For questions with categorical answers, absolute and relative frequencies were calculated and chi-squared tests were used to assess differences between specialised and non-specialised ILD centres. For questions with answers on a continuous scale, median, first and third quartile, minimum and maximum were determined and differences between continents were assessed using Kruskal–Wallis tests. Due to the exploratory

nature of this survey, all resulting *p*-values are solely to be interpreted descriptively and no adjustment for multiple testing was conducted. *p*-values smaller than 0.05 were regarded as statistically significant. All analyses were conducted using R v.3.4.2 (http://r-project.org).

RESULTS

Participants

Overall, 509 pulmonologists from 66 countries responded. Three hundred and thirty four (65.9%) of the participants worked in a specialised ILD centre, 142 (28.0%) in non-specialised ILD centres i.e. in a general pulmonology department, 4 (0.8%) on an intensive care unit and 27 (5.3%) did not indicate their institution. Physicians working on an intensive care unit or who did not indicate their institution were excluded from the analysis. A total of 436 pulmonologists working in a specialised or non-specialised ILD centre were included in this analysis. On average 331 cases of AE-IPF were seen in specialised ILD centres and 139 in non-specialised ILD centres. **Figure 1** shows the place of work (continent) of the respondents in specialised and non-specialised ILD centres.

Diagnostic Procedures for AE-IPF

Most diagnostic tools, including multi-slice thin-section computer tomography without contrast media (HRCT), CT with contrast media in the absence of clinical suspicion of pulmonary embolism, bronchoalveolar lavage (BAL), echocardiography, assessment for pathogens, NT-proBNP/BNP, D-Dimer and troponins were used similarly between specialised and non-specialised ILD centres. The main difference was the sampling of sputum for microbiology (induced sputum) which was more frequent in non-specialised ILD centres (22 vs. 12%, $p = 0.0106$). Conversely, pathogen testing in urine was performed significantly more often in specialised ILD centres than in non-specialised ILD centres (42 vs. 28%, $p = 0.0068$). 50% of specialised ILD centres screened for RSV (respiratory syncytial virus), compared to only 33% in non-specialised ILD centres ($p = 0.0024$). The use of biomarker KL-6 was higher in non-specialised ILD centres than in specialised ILD centres (24 vs. 15%, $p = 0.0313$). The most relevant diagnostic procedures applied for AE-IPF are shown in **Figure 2**. Other diagnostic procedures such as laboratory parameters or specific pathogens are shown in **Supplementary 1**.

Treatment Approaches for AE-IPF

The majority of participating pulmonologists treated AE-IPF with methylprednisolone or equivalent with a dosage of 500–1,000 mg per day for 3 days followed by a slow tapering similarly in both types of institutions (63 vs. 66%).

Other immunosuppressive therapies such as cyclosporine, cyclophosphamide (i.v. bolus), tacrolimus and rituximab were rarely used in both specialised and non-specialised ILD centres, but cyclosporine was significantly more frequently used in non-specialised ILD centres (13 vs. 6%, $p = 0.0288$).

Other therapies such as polymyxin B hemoperfusion (7 vs. 10%), and plasmapheresis/plasma exchange (4 vs. 5%) were also less commonly used in specialised and non-specialised ILD centres. However, significantly more pulmonologists treated their patients with recombinant thrombomodulin in non-specialised ILD centres than in specialised ILD centres (15 vs. 8%, $p = 0.0342$).

Differences between institutions in the use of treatment strategies are shown in **Figure 3.** *See also* **Supplementary 1**.

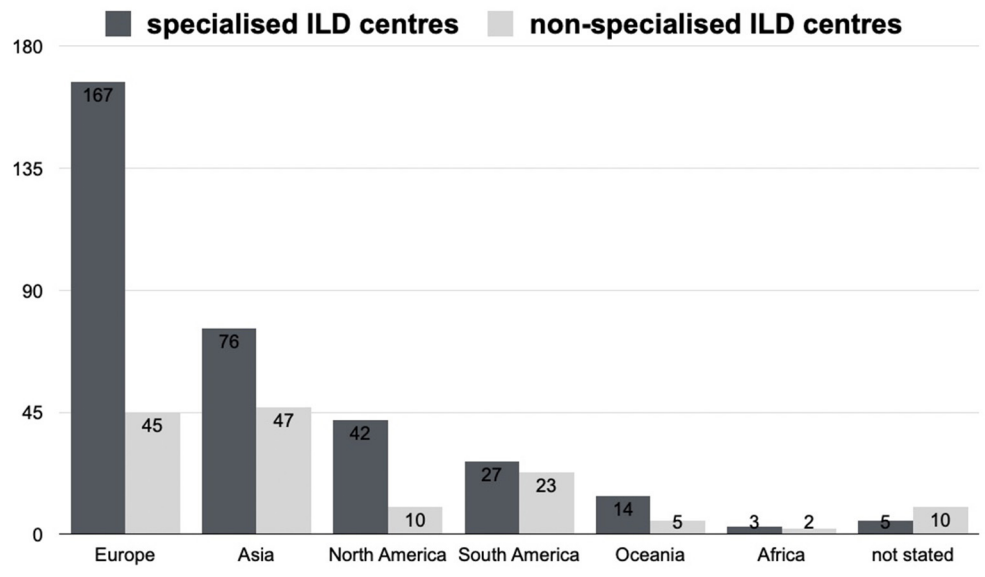

FIGURE 1 | Number of participants in specialised and non-specialised ILD centres from different continents.

Antifibrotic Therapy Management During AE-IPF

In patients without antifibrotic therapy, the majority of the survey participants see a reason to initiate an antifibrotic therapy in the event of an AE-IPF in specialised and non-specialised ILD centres (66 vs. 69%).

The choice of the antifibrotic drug did also not differ significantly between specialised and non-specialised centres (nintedanib 20 vs. 20%, pirfenidone 11 vs. 19%, no preference for specific anti-fibrotic drug 35 vs. 28%).

For patients already on antifibrotic therapy at the time of AE-IPF, there was no significant difference in the approach: 80% of respondents in specialised ILD centres would continue and 5% would discontinue antifibrotic therapy, compared to 70% continuing ($p = 0.0513$) and 7% discontinuing therapy ($p = 0.5491$) in non-specialised ILD centres. The dose was reduced by 1 % in specialised ILD centres compared to 5% in non-specialised ILD centres ($p = 0.0301$), 9% would switch to the alternative antifibrotic therapy in specialist ILD centres and similarly 10% would switch in non-specialised ILD centres ($p = 0.999$).

Different strategies in this situation are also shown in **Figure 4**. For further strategies *see* **Supplementary 1**.

Management of Pulmonary Hypertension (PH) During AE-IPF

In the case of suspected PH on clinical investigations (e.g. echocardiography, BNP, clinical signs) during an AE-IPF, significantly more physicians in specialised ILD centres would start diuretic therapy than in non-specialised ILD centre (54 vs. 41%, $p = 0.0210$). Only a minority in both institutions would perform right heart catheterization in AE-IPF in suspected PH (6 vs. 7%). Seven percentage would start a PH specific treatment after an established PH diagnosis in a specialised ILD centre, significantly more (14%) would do so in a non-specialised ILD centre ($p = 0.0494$). Only 3% of physicians in a specialised ILD centre and 1% in a non-specialised centre would start a PH specific treatment without a confident diagnosis. After stabilisation of AE-IPF, more than 50% of physicians would evaluate a PH specific treatment by subsequently performing right heart catheterization (56 vs. 55%). A quarter of all participating pulmonologists in specialised and non-specialised ILD centres saw no indication for a PH treatment during or after AE-IPF (**Supplementary 1**).

Intensive Care Unit (ICU) and Palliative Care in AE-IPF

With regards to the care for critically ill patients with AE, there were no differences in specialised and non-specialised ILD centres for the use of high-flow oxygen (84 vs. 78%) and non-invasive ventilation (NIV) (72 vs. 77%). 9% of specialised and 11% of non-specialised ILD centres use invasive ventilation for all critical ill patients, whereas 48 vs. 39% respectively would only use invasive ventilation in patients suitable for lung transplantation (LTX) as a bridge to LTX or in very selected cases.

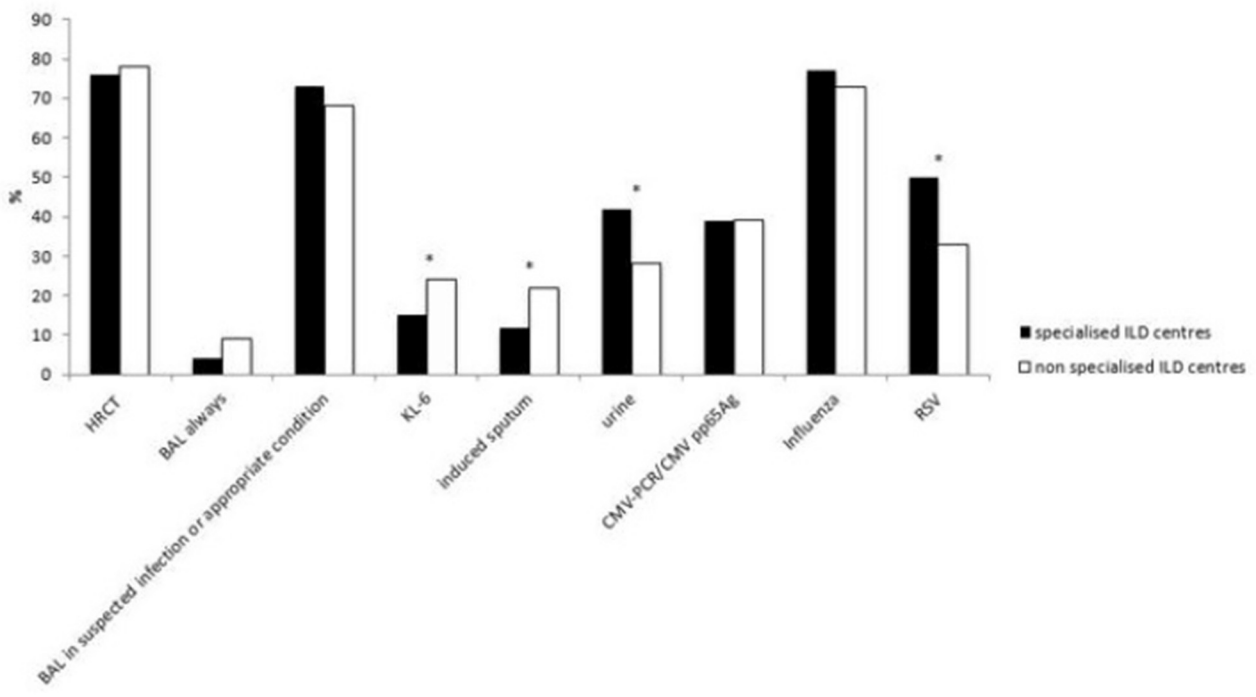

FIGURE 2 | The main diagnostic procedures applied for AE-IPF in specialised and non-specialised ILD centres. Statistically significant differences are labelled with a * (p-value = <0.05).

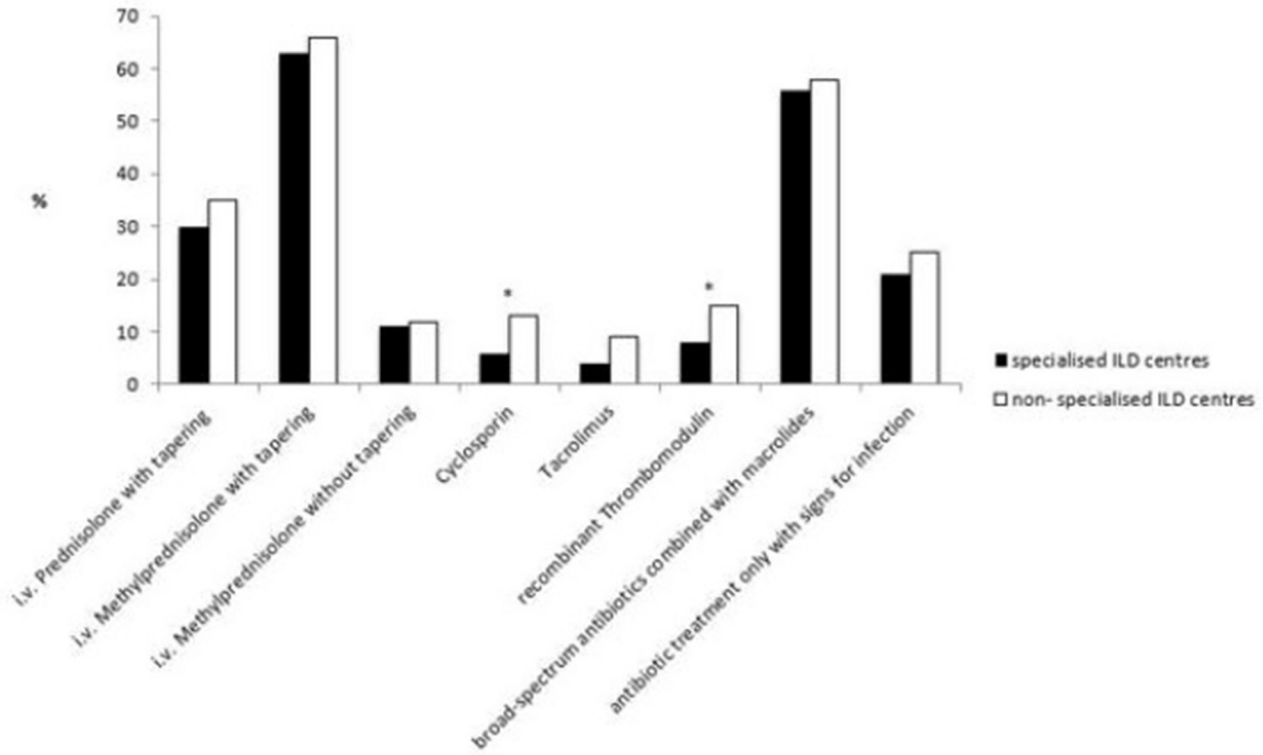

FIGURE 3 | Different treatment strategies towards AE-IPF in specialised and non-specialised ILD centres. Statistically significant differences are labelled with a * (p-value = <0.05).

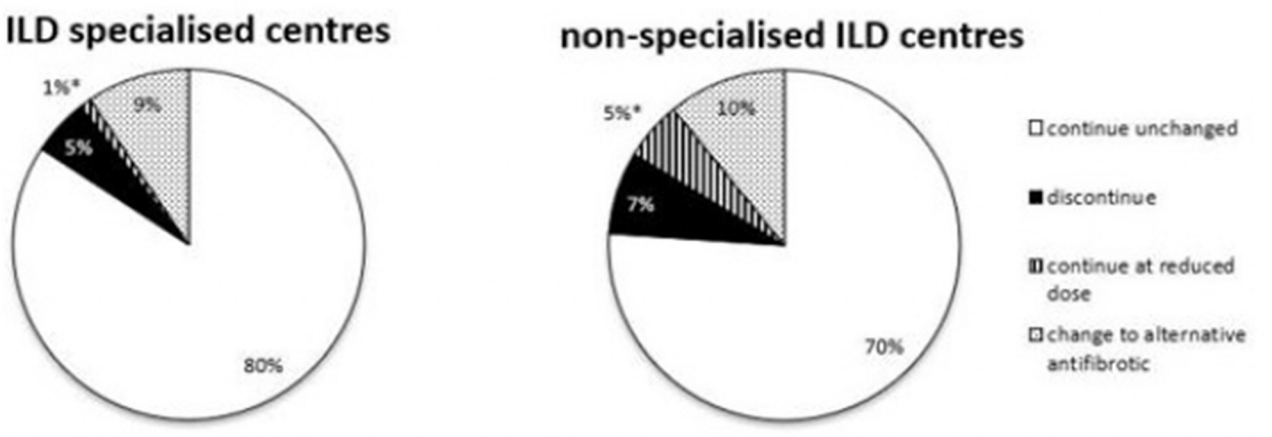

FIGURE 4 | Different strategies in AE-IPF concerning an antifibrotic treatment in specialised and non-specialised ILD centres. Statistically significant differences are labelled with a * (p-value = <0.05).

Significantly more physicians in specialised ILD centres offered extracorporeal membrane oxygenation (ECMO) to patients suitable for LTX as a bridge to LTX than in non-specialised ILD centres (49 vs. 36%, $p = 0.0287$).

Palliative care was considered similarly in both types of institutions (65 vs. 62%).

Institutional differences in these approaches are shown in **Figure 5** (**Supplementary 1**).

Preventive Strategies for AE-IPF

Measures aimed at preventing the occurrence of AE-IPF was equal amongst specialised and non-specialised ILD centres

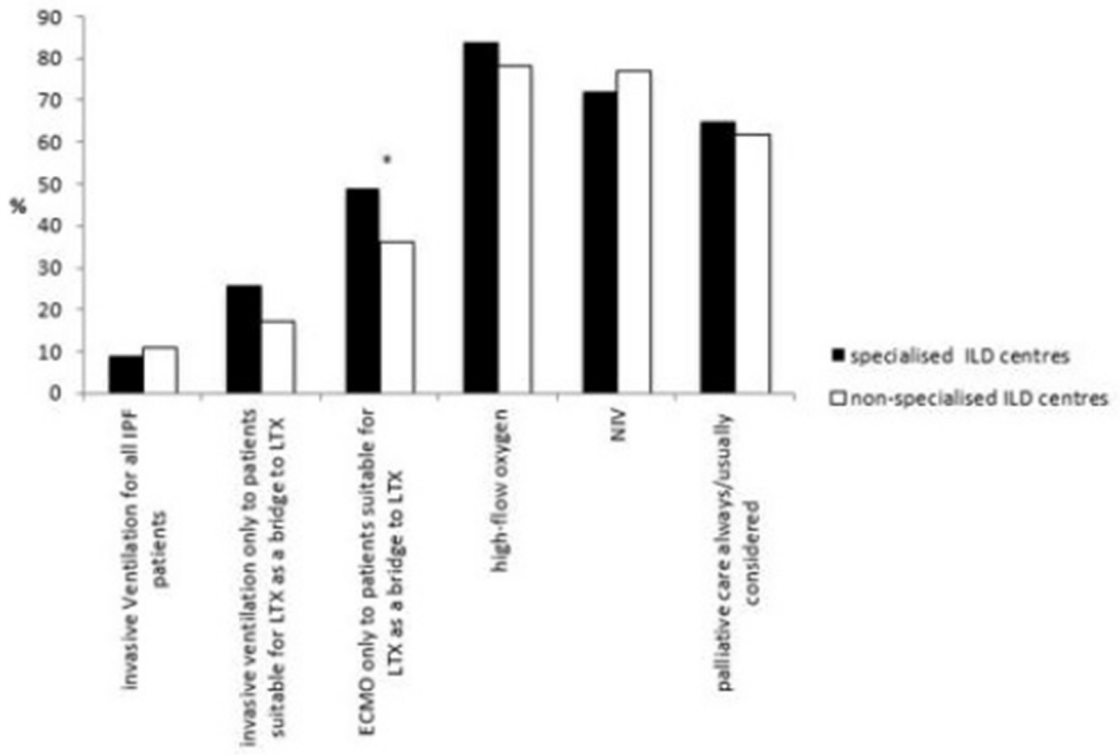

FIGURE 5 | Different management strategies in critically ill patients with AE-IPF in specialised and non-specialised ILD centres. Statistically significant differences are labelled with a * (p-value = <0.05).

and included vaccinations, antifibrotic therapy and pulmonary rehabilitation or other forms of structured exercise therapy. Antacid drugs were prescribed significantly more in non-specialised ILD centres than in specialised ILD centres (61 vs. 50%, $p = 0.0438$) in all IPF patients. Long-term azithromycin, low dose steroids ($\leq$10 mg) and anticoagulation (to prevent AE-IPF) were only used by a minority in both types of institutions.

In terms of planned surgical procedures, significantly more physicians in specialised ILD centres favoured preventive anaesthetic measures such as low tidal volume and avoidance of hyperoxygenation compared to physicians in non-specialised ILD centres (72 vs. 61%, p=0.0368).

Institutional differences in preventive strategies are shown in **Figure 6**. *See also* **Supplementary 1**.

Unmet Needs in AE-IPF

Pulmonologists in both specialised and non-specialised ILD centres advocate more intensive collaboration between different ILD specialists; improved education and training of physicians; education of patients and caregivers as well as enhanced research to improve the understanding of the pathophysiology, diagnosis and management of AE-IPF. Physicians working in specialised ILD centres saw a stronger need for intensified research and projects on the treatment of AE-IPF (90 vs. 80%, $p = 0.0101$). There were more pulmonologists in non-specialised ILD centres who saw a need of improvement in multidisciplinary strategies for diagnosing and discussions than in specialised ILD centres (67 vs. 53%, $p = 0.0088$).

DISCUSSION

Despite the fact that AE-IPF is one of the most common causes of death in IPF (3), evidence on prevention, additional diagnostic approaches besides HRCT and treatment of this complication is sparse and differs significantly worldwide (10). No particular evidence-based guidance exists. Here we report analyses on similarities and differences in the management of AE-IPF in specialised vs. non-specialised ILD centres. The strength of our report was the significant number of physicians who replied to our survey representing both specialised and non-specialised ILD centres.

Diagnostic procedures were almost identical in both specialised and non-specialised ILD centres, including radiology and screening for infections. Molyneaux et al. have showed that there is an increased bacterial load in the BAL of IPF patients with AE-IPF compared to stable IPF patients (12) suggesting a potential causative role in AE-IPF. There is evidence for the contribution of lung microbiota in disease progression and in acute exacerbation (13, 14). Microbiological confirmation may therefore play an important role in the diagnostic process and may be useful for future therapeutic and preventive strategies.

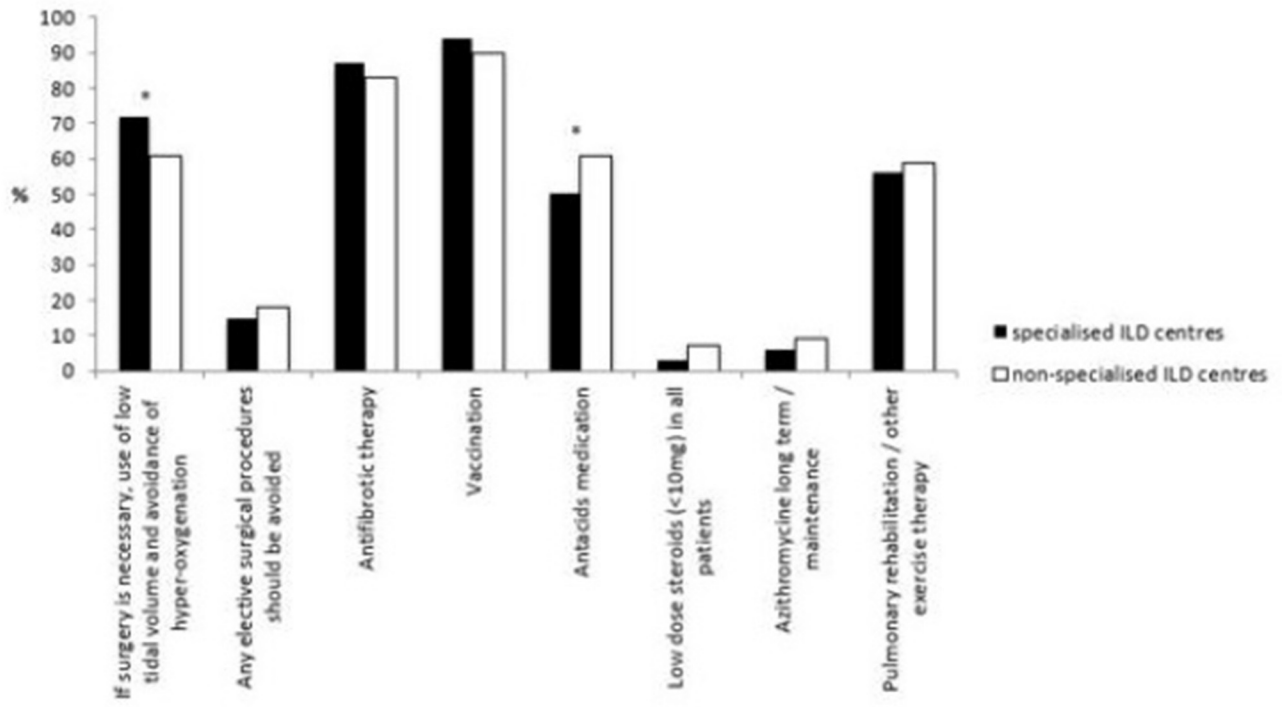

FIGURE 6 | Different preventive strategies in AE-IPF in specialised and non-specialised ILD centres. Statistically significant differences are labelled with a * (p-value = <0.05).

The majority of physicians in specialised and non-specialised ILD centres screen for pathogens in sputum, deemed a safer method to screen for pathogens compared to bronchoscopy. A recent study supports this approach as a positive bronchoscopy only affected management in 13% of patients and resulted in a change of treatment in <5% (15). Furthermore, in the same study, a significant number of patients required intubation and transfer to the ICU with poor extubation success post bronchoscopy (15). Conversely, a study has demonstrated the feasibility and safety of performing BAL aided by NIV as a useful tool for differentiating or confirming triggered AE (16).

Furthermore, there is a similarity in therapeutic approaches. The majority of pulmonologists in specialised and non-specialised ILD centres use antibiotic therapy, namely broad-spectrum antibiotic combined with macrolide. High dose steroids are widely administered in non-specialised and specialised ILD centres in AE-IPF. High dose long-term steroid use was associated with an increased mortality in the PANTHER trial (17) and a history of previous immunosuppression before AE-IPF has a negative impact on mortality (18). Recently, a retrospective study with 82 AE-IPF patients showed that subjects receiving corticosteroids were more likely to require ICU level care and mechanical ventilation and therefore did not benefit from treatment with corticosteroids (19). However, future studies with larger cohorts are necessary to prove the deleterious effects of steroid therapy.

Other immunosuppressants and strategies are used less frequently. Very few pulmonologists never use immunosuppression for AE-IPF. Although there is only low evidence base for the use of more potent anti-inflammatory treatment approaches such as cyclosporine A, intravenous cyclophosphamide or tacrolimus (20–24), they are used by some pulmonologists in non-specialised and specialised ILD centres. A randomised, double-blinded clinical trial of cyclophosphamide in AE-IPF with 120 patients was completed and results are eagerly awaited (https://clinicaltrials.gov/ct2/show/NCT02460588).

The international guidelines recommend avoiding ICU in patients with AE-IPF (weak recommendation) (25) because the mortality of patients with AE-IPF admitted to ICU, particularly in ventilated patients, is high (26). Some patients who do not respond to conventional oxygen therapy benefit from high flow oxygen (27). NIV may be a reasonable option for some critically ill patients (28). Trudzinski et al. showed that ECMO is only an option for patients who are suitable for LTX, as it conferred limited impact on the poor prognosis for those who were not LTX candidates (29). This might be a reason for pulmonologists in no matter what kind of institution to prefer NIV and high-flow oxygen in patients with AE-IPF. Data on this is however limited.

In non-specialised and specialised ILD centres prevention strategies towards AE-IPF were performed to the same extent. Vaccinations were most frequently used; although their use is recommended by the international guideline, there is a lack of evidence to support this recommendation (30).

The approach by physicians to utilise antifibrotic drugs as a form of preventive strategy is supported by recent data of controlled trials that suggest nintedanib may prolong the time to the first AE-IPF (31) and reduces mortality after AE-IPF (32). Pirfenidone reduces the risk for respiratory related hospitalisation in *post-hoc* analyses (33). Data proving a reduced frequency of AE-IPF with pirfenidone is sparse: In a Phase 2 trial of 107 patients Azuma et al. found a significant reduction of AE-IPF in patients using pirfenidone (34). A larger trial could not prove this (35).

While a Japanese study suggested a role for anticoagulants to prevent AE-IPF (Kubo et al.), a more recent study did not support this (36). This is in line with the results shown here: only a minority use anticoagulants to prevent AE-IPF. This is further supported by data suggesting a negative impact of anticoagulants on survival in IPF in general (37, 38).

Besides many similarities in the approach towards AE-IPF, there are also some differences in ILD specialised and non-specialised ILD centres.

PH is common in patients with IPF (39). Its prevalence at baseline means a higher risk for a subsequent AE-IPF, it is associated with a poorer overall survival but until now no specific PH treatment could show a benefit for IPF patients (40, 41). Significantly more pulmonologists in specialised ILD centres start diuretics compared to non-specialised ILD centres, and in line with the lack of benefits for specific PH treatment, most physicians do not use a specific PH treatment.

Many physicians use antacid drugs as a preventive strategy for AE-IPF, significantly more in non-specialised ILD centres. Lee et al. reported a higher pepsin level in the BAL of patients with AE-IPF compared to patients with stable disease (42) and a retrospective analysis showed a positive impact of antacid drugs on the course of IPF (43, 44). Other studies could not repeat this effect and suggested potentially higher rates of respiratory infections (45) and AE-IPF (46). The reason for the difference in the use of anti-acid drugs remains unclear, maybe because specialised ILD centres treat patients who are more ill or receive palliative treatment. Also different prescription rules in different countries or the fact that an old statement published by international societies from 2011 recommended their use (9) may be responsible.

Only a few pulmonologists use low dose steroids as a preventive strategy for AE-IPF, most of them in non-specialised ILD centres. This approach is in line with the international guideline where it is not recommended to use steroids beyond AE-IPF (17, 25). Furthermore, the use of corticosteroids has a negative effect on the outcome of IPF patients who received nintedanib (47).

Both pulmonologists in specialised and non-specialised ILD centres saw a high requirement for improved research strategies for AE-IPF. Significantly more non-specialised ILD centres saw the need for improvement in multidisciplinary strategies for diagnosing and discussion compared to pulmonologists in specialised ILD centres. Multidisciplinary team (MTD) meetings are widely used in the process of diagnostic and patient management (48) and they improve confidence in ILD diagnostics (49). MTD meetings are officially recommended (50). Arguably, MTD are more available in specialised ILD centres.

Many of the differences observed underscore the high and still unmet need for intensive research in AE-IPF. However, others might be associated with strategies applied outside current evidence. This demonstrates how important education in rare diseases and their complications is.

Our survey has some limitations: The survey was not designed for a data driven assessment of management practises but mainly to evaluate attitudes towards different aspects of AE-IPF. Participation was voluntarily and biased by involvement i.e. non-participating centres may have answered differently. Additionally, there was an imbalance between the number of specialised and non-specialised ILD institutions. Moreover, the number of ILD centres and patient numbers and thus experiences of diagnosis and management of AE-IPF may vary from country to country. Arguably, the number of IPF patients and cases of AE-IPF are higher in Japan as an example, than in other countries (51). Therefore, non-specialised ILD centres in Japan may have a higher number of patients to treat and thus greater experience than other non-specialised ILD centres elsewhere. More experienced physicians in the field of AE-IPF might have influenced the results of this questionnaire. Furthermore, the availability of treatments differs clearly between countries/continents, e.g., recombinant thrombomodelin is used almost exclusively in Asia and here by a quarter of all physicians (10). This might explain the fact that thrombomodulin is used more often in non-specialised ILD centres. The same applies for the use of KL-6 in the diagnostic process of AE-IPF. Finally, not all aspects of approaches to AE-IPF could be addressed in the questionnaire. The current COVID-19 pandemic was not part of the questionnaire because it was sent out before. This situation might have a huge impact on how AE-IPF is managed and this was not assed in the survey.

In conclusion, specialised and non-specialised ILD centres throughout the world do only differ in some aspects in the management of AE-IPF. Due to scant evidence and missing focused guidelines basic research and clinical trials have to be performed to establish optimal approaches to this deadly complication.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent

from the participants was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MP and MK contributed mainly to the conception and design of the study. MP wrote the first draft of the manuscript. JK performed the statistical analysis. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.699644/full#supplementary-material

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REVIEW
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Health Related Quality of Life in Interstitial Lung Disease: Can We Use the Same Concepts Around the World?

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Health-Related Quality of Life (HRQOL) is increasingly viewed as an important patient-centered outcome by leading health organizations, clinicians, and patients alike. This is especially true in the interstitial lung disease community where patients often struggle with progressive and debilitating disease with few therapeutic options. In order to test the effectiveness of new pharmacologic therapies and non-pharmacologic interventions globally in ILD, this will require expansion of clinical research studies to a multinational level and HRQOL will be an important endpoint to many. In order to successfully expand trials across multiple nations and compare the results of studies between different communities we must recognize that there are differences in the concepts of HRQOL across the world and have strategies to address these differences. In this review, we will describe the different global influences on HRQOL both generally and in the context of ILD, discuss the processes of linguistic translation and cross-cultural adaptation of HRQOL Patient Reported Outcome Measures (PROMs), and highlight the gaps and opportunities for improving HRQOL measurement in ILD across the world.

Keywords: HRQOL—health-related quality of life, interstitial lung disease, global, cross cultural adaptation, linguistic validation

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INTRODUCTION

Health-related quality of life (HRQOL), or one's quality of life as it relates to health status or disease, is increasingly recognized as an important patient centered-outcome by leading health organizations (1, 2)[1]. HRQOL is a subjective, dynamic, and multidimensional concept that includes domains representative of an individual patients' goals, values, and beliefs (3, 4). Over the past several decades, various conceptual models of HRQOL have contributed to our study of HRQOL in human disease (2, 5–7). These models provide an essential structure for conceptualization of HRQOL, including both the positive and negative aspects, and are often used as a guide for research and practices that promote improved HRQOL in different populations of interest (8). HRQOL frameworks most commonly focus on the physical and psychosocial impacts of health or disease on an individual's ability to live what they consider to be a fulfilling life (9). HRQOL amongst those who share the same or different chronic diseases is often very personal and subjective. This subjectivity will vary even more depending on a person's cultural background and environment. The various domains of HRQOL (e.g., psychosocial, physical etc.) that we intend to measure therefore should ideally be considered in the context of an individual's culture and value system

[1] Population Assessment of Health-Related Quality of Life.

(10, 11). This adds a level of complexity to measurement of HRQOL as we are compelled to recognized that these constructs will differ across different cultural, religious, and socioecological contexts (12). The processes of linguistic and cross-cultural adaptation have allowed for improved measurement of HRQOL across different cultures and languages.

During the past decade, HRQOL has gained much traction as a priority endpoint in the Interstitial Lung Disease (ILD) community. ILD is a group of heterogeneous parenchymal lung diseases with various clinical courses, many of which may be progressive, fibrotic, life altering, and eventually fatal (13, 14). Patients and ILD experts alike have vocalized the importance prioritizing HRQOL as a top area of focus in research studies and clinical practice (15, 16). Though a few therapies are documented to slow progression of disease [as measured by forced vital capacity (FVC)] in idiopathic pulmonary fibrosis (IPF) and the progressive fibrotic form of other ILDs, there is now much interest in how our interventions effectively slow deterioration in HRQOL (17, 18).

Patient Reported Outcome Measures (PROMs) that measure HRQOL gather information directly from the patient (without interpretation by a clinician or anyone else) about their perspective of the quality of their life in the context of their disease and it's treatments (19, 20). There are several PROMs that have undergone validation testing to measure HRQOL in ILD. The most commonly used instruments in the past few decades were originally intended for use in other respiratory diseases, while a handful of newer instruments have been developed for use specifically in ILD and pulmonary fibrosis (21). These "condition" or "disease-specific" PROMs are intended to capture more nuanced information about the impact of living with ILD that is most pertinent to patients with this particular chronic respiratory disease (e.g., breathlessness, cough, fatigue, aspects of psychological well-being) (22). Despite the ILD-targeted items in these instruments, one must be cognizant of the interpretation of the wording of these items for those from other cultures or countries in which the instrument was not developed. For example, dyspnea, or breathlessness is a common ILD symptom that impacts HRQOL. There are various qualitative aspects of this symptom are interpreted differently across different languages and cultures (23–25).

Here we introduce the concept of measuring HRQOL around the world, and as it pertains to specifically to ILD with a focus on linguistics, regional and environmental factors, health literacy and health-care systems, and race, ethnicity, religion and spirituality. We will describe the process of cross-cultural adaptation, the work that has been performed to cross-culturally validate PROMs in ILD, and the potential challenges and opportunities for the future study of HRQOL in ILD on a global scale.

GLOBAL INFLUENCES ON HRQOL

HRQOL generally reflects each individual's perspective on their own health and is widely accepted as one of the most important patient-centered outcomes. HRQOL measures the impact a chronic disease and its treatment have on several domains of one's life and is largely influenced by cultural and spiritual backgrounds. Therefore, it is expected that the concept of HRQOL will differ across communities within a nation, as well as between countries. Given the growing number of international clinical trials and large population health studies it is increasingly important to recognize the global factors that influence accurate measurement of HRQOL, and how to potentially address them. This section focuses on general considerations for assessing HRQOL in chronic illness, which is pertinent when we consider measurement in ILDs.

Language Diversity

Linguistic differences are an important consideration when measuring HRQOL. Historically, most HRQOL instruments have been developed in the English Language. Over the past few decades, various HRQOL scales have been internationally translated and standardized across different languages. Translation approaches are traditionally performed by qualified academicians or language experts. With advancements in technology, online translation has also been made available. Despite the availability, convenience, and cost effectiveness of online translation (e.g., google translate), there is controversy related to the validity of this approach when used as the sole method of translation. It has been suggested that if one were to consider using an online program, a more valid approach is a hybrid method with traditional translation by experts with high-level degrees in linguistics in combination with an online program (26). Whatever approach is chosen, researchers must ultimately decide on the translation and adaptation procedures that are most appropriate for their scope of work with consideration of time constraints and available resources.

In order to use a HRQOL instrument appropriately in a new country or culture, the instrument must not only possess linguistic equivalence, but must also capture the cultural differences in disease expression and perception of HRQOL (27, 28). We will expand upon this process of "cross cultural adaptation" later in this review.

Regional and Environmental Differences

An individual's region of origin and environmental context are important considerations during HRQOL assessment. The built environment, defined as the space in which people spend their time in daily life (e.g., home, neighborhood, transportation, or workplace), is closely associated with their health status (29). Seasonal and weather conditions affect physical activity and psychological states (e.g., winter season, unfavorable weather, or decreased sunlight exposure vs. the more positive alternative) (30). Air pollution represented by particulate matter ($PM_{2.5}$) is associated with increased respiratory symptoms and worsened HRQOL (31, 32). There is also evidence to suggest that habitat may influence HRQOL. For example, there are reported differences in HRQOL scores between those in rural vs. urban environments (33–36). These environmental contextual factors may play a role in our interpretation of HRQOL scores amongst different populations and more work is needed to formulate an approach to addressing this

issue. Few clinical studies have corrected for the various potential regional and environmental effects on HRQOL, and this is an important area of potential investigation in the future.

Health Literacy and Diversity of Healthcare Systems

Health literacy is defined as the ability to access, understand, and effectively use health information (37, 38). Patients with low health literacy have less of an understanding about their medical conditions and treatments. This is associated with the potential to worsen health status and disease outcomes (39, 40). A recent study revealed that older age, higher body mass index, residence far from medical institutions, lower monthly income, and lower education levels are associated with a lower health literacy (41). The access to primary care systems and the presence of reliable, understandable, and comprehensive native language medical information websites also contribute to global differences in health literacy (42). The same intervention for a particular chronic disease may be interpreted differently by two patients depending on their comprehension, which may drastically impact patient decision making. Healthcare professionals have made a large effort to improve the impact of low health literacy, including establishment of universal education systems, but many inequalities still exist (42). While mobile health applications may help to enhance interactive patient-provider communication, there is more investigation needed to creatively adapt this technology for use in more remote and resource-limited parts of the world (17, 43–45).

Race, Ethnicity, Religion, and Spirituality

There is a growing body of literature that reveals the association between race, ethnicity, religion, spirituality and HRQOL. A recent study showed that racial and ethnic differences were associated with differences in HRQOL even within the same community (46). If the prevalence of a certain chronic disease is low in a particular race or ethnic group, the negative impact on HRQOL may become greater (47). A lack of familiarity with a chronic disease in a patient's community may lead to social discrimination, with a negative downstream impact on HRQOL (48). A systematic review focused on the relationship between religiosity/spirituality and quality of life (QOL) in patients with cardiovascular disease found a positive association between mental and emotional well-being, spiritual well-being, intrinsic religiousness, and frequency of church attendance (49). While it is important to recognize that these factors play an important role in HRQOL, there is controversy over the extent to which patients should be subdivided by spiritual and religious beliefs for clinical and epidemiological research (50). In order to address these differences, one potential approach is to focus on the longitudinal relative changes in each individual's HRQOL score, rather than comparing cross-sectional absolute values between different patients, but more work is needed to better define and operationalize this approach.

CROSS CULTURAL ADAPTATION

In the past several decades, the measurement of HRQOL has garnered significant attention as an important endpoint in clinical trials and public health research (51). With the increasing number of multi-country, multi-center trials that are conducted in clinical research there is a growing need for HRQOL measures that can be administered in countries with various languages of origin and amongst different cultural groups where disease expression and health-care system usage may vary (52). In order to administer an HRQOL instrument appropriately in a new country or culture, the instrument must not only possess linguistic equivalence, but must also capture the cultural differences in disease expression and perception of HRQOL (27, 28). This allows investigators to collect accurate information about HRQOL of the whole population in one study (when several countries are represented) and to compare results across different studies both nationally and internationally (53). Development of a new PROM is a rigorous and time intensive process (20). It may take years to gather enough data to prove the instrument possesses adequate validity to use in a clinical trial, often with stringent regulatory approval criteria that must be met (54). Rather than develop a brand-new instrument for each distinct language and culture, current practice is to perform "cross cultural adaptation." This process facilitates the translation of existing and well-validated instruments in a manner that allows the instrument to retain its psychometric properties in a culturally distinct population (55).

There is overwhelming agreement that an instrument should not be simply translated word for word into another linguistic context, as this can compromise the cultural integrity and equivalence of the findings (56). However, there is not a standardized protocol for linguistic validation or cross cultural adaptation, therefore risking poor translation and compromised research data (57, 58).

Several approaches to cross cultural adaptation have been suggested with the goal of maximizing validity and reliability of the instrument that is to be translated into the "target" (or new) language. The Translation and Cultural Adaptation Group (TCA) of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force put forth recommendations for translation and cultural adaptation of PROs in the research community based upon review of the literature and multidisciplinary expert consensus (59). Their recommended approach includes stages of translation and validations testing that require both forward and backwards translation, harmonization that allows for concept equivalence between the source and target language versions of the instrument, review by an expert committee, and cognitive debriefing to assess comprehensibility and cognitive equivalence of the translation by interviewing patients from the target population (60, 61). While the ISPOR task force guidelines provide a rigorous approach to translation, they provide less guidance on further psychometric testing to perform beyond translation and assessment of content validity.

In 1991, the international quality of life assessment (IQOLA) project was established to translate and validate the short-form 36-item health survey (SF-36) (28, 62, 63). The IQOLA project group guidelines encompass a three-stage process that incorporates further psychometric testing; (1) rigorous translation and evaluation process, (2) formal psychometric testing of the assumptions underlying item scoring and construction of multi-item scales, and (3) studies evaluating the equivalence of interpretations across countries (64, 65). Their project with the SF-36 transferred an existing generic HRQOL questionnaire to another culture, a process termed "sequential development". On the other hand, in 1990s, the World Health Organization (WHO) developed the WHO Quality of Life assessment instrument (WHOQOL) simultaneously in fifteen different centers worldwide (2). This type of approach helps to ensure equivalence of concepts at each stage as the questionnaire is developed in multiple languages at the same time, a process termed "simultaneous development". In the 1980-1990s, the European Organization for Research and Treatment of Cancer (EORTC) and the EuroQol Group developed the quality of life questionnaire (QLQ-C30), and the EuroQol-5 dimensions (EQ-5D), respectively (66–68). These questionnaires were generated in one language and then forward and backward translated into multiple languages by multinational discussions, a "parallel development" approach. With these historical developments, various HRQOL questionnaire translations are available for clinical trials, daily clinical practice, population studies, and health economic evaluations around the world.

CROSS CULTURAL ADAPTATION IN ILD

Several patient-reported outcome measures (PROMs) have been adapted for use in ILDs. The PROMs utilized in ILD research and practice are mainly categorized into three groups: (1) disease-specific HRQOL, (2) generic HRQOL, and (3) domain-specific instruments (69). These instruments are ideally chosen as endpoints in research according to the objective of the study and characteristics of the study population. Each of the most common PROMs administered in ILD are at different stages of validation, translation, cross-cultural adaptation, and level of use in clinical trials (**Table 1**). Here we provide an overview of the current state of cross-cultural adaptation of PROMs in ILD.

Disease-Specific HRQOL PROMs

Disease-specific HRQOL PROMs in ILD often provide information about the impact of the patient's lung disease on their quality of life. The St George's Respiratory Questionnaire (SGRQ), which was originally developed for patients with chronic obstructive pulmonary diseases (COPD), is one of the most extensively used PROMs for patients with ILDs (70–92). The SGRQ is relatively well-validated in ILD, however there are concerns regarding the applicability of several of the items to patients with ILD. While the SGRQ length and complicated scoring algorithm may pose some challenges for use in daily clinical practice, it has been translated into a wide range of languages making it a potentially attractive option when conducting multinational studies. The cross-sectional reliability of an IPF-specific version of SGRQ (SGRQ-I), has been reported for patients with IPF, however longitudinal data, language translations, and experiences in clinical trials are limited (93, 94). The COPD Assessment Test (CAT) is a short and simple questionnaire developed for COPD and is reported to correlate well with the SGRQ in IPF and connective tissue disease-associated ILD (CTD-ILD), but experiences in clinical trials is limited (96–98). The King's Brief ILD (K-BILD), is a disease-specific instrument developed in the UK for use in ILD and has been tested in patients with a large number of ILDs (99–102). There is translation and cultural adaptation data for the K-BILD available for several European and South American countries (149, 150), and it is available in multiple languages for use across the globe. Additionally, A tool to Assess the quality of life in Idiopathic Pulmonary Fibrosis (ATAQ-IPF) which was developed initially in the United States to measure HRQOL in Pulmonary Fibrosis has published data on reliability and validity in Chinese patients (cATAQ-IPF) (105, 151).

The Living with IPF questionnaire (L-IPF) (107), developed in the English language, has published initial validation data in a cohort of patients with IPF and has recently expanded applicability as the Living with Pulmonary Fibrosis questionnaire (L-PF) (108). The Patient Experiences and Satisfaction with Medications questionnaire (PESaM) is a unique instrument evaluating patients' expectations, experiences, and satisfaction with disease-modifying drugs (109, 110). This instrument was developed in the Netherlands and provides systematic evaluation of patient experiences and expectations that may allow for improved shared-decision making. For these more newly developed instruments, more data is needed on the applicability across different languages and cultures.

Generic HRQOL PROMs

Generic HRQOL measures are designed to assess the overall health status across the general population, regardless of a specific type of chronic disease that one may have. Many of these instruments have been well-translated into a wide range of languages and well-validated in various ways as mentioned above. These instruments allow us to compare the health status between patients with different chronic diseases and healthy people. They are valued as key secondary endpoints in many clinical trials.

The SF-36 is the most widely used generic HRQOL measure. The validity of the SF-36 in ILDs has been established since the 1990s, with various studies reporting the cross-sectional and longitudinal validity in IPF, and has been used in many clinical trials of patients with ILD (73, 80, 81, 86, 90, 119, 137–141). As the minimal clinically importance difference (MCID) for the SF-36 in IPF varies depending on the cohort, further global validation studies are required. The EuroQol-5 dimensions 5-level (EQ-5D-5L) is also a well-known and widely-translated generic HRQOL measure. EQ-5D-5L was developed by the EuroQol Group to improve the instrument's sensitivity as compared with the previous version (142, 143). The scores obtained from EQ-5D-5L can be used to calculate quality-adjusted life years (QALY), a generic measure of disease burden. QALY measurements enable investigators to assess both the quality and the quantity of life lived and to examine the value of medical interventions (144).

TABLE 1 | Cross-cultural adaptation and linguistic validation of PROMs in ILD.

Patient-reported outcome measure	Validated IDL	Originally development and translations	Multi-center/country clinical trial use in IDL	MCID	References
DISEASE-SPECIFIC					
SGRQ	IPF CTD-ILD	Developed in 1991 English for the UK 170 translations	Yes	IPF: 4–8 CTD-ILD: 4–13	(70–92)
SGRQ-I	IPF	Developed in 2010 English for the UK 1 translation	No	IPF: 4–5	(93–95)
CAT	IPF CTD-ILD	Published in 2009 English for the UK 62 translations	No	IPF: N/A CTD-ILD: 1–4	(96–98)
K-BILD	IPF ILD	Published in 2012 English for the UK 6 translations	Yes	IPF/ILD: 4–8	(83, 99–104)
ATAQ-IPF	IPF	Published in 2010 English for the USA 2 translations	Yes	N/A	(105, 106)
L-IPF (L-PF)	IPF PF-ILD	Published in 2020 English for the USA In translations process	Not yet	Validation process	(107, 108)
PESaM	IPF	Published in 2017 Dutch for Belgium and the Netherlands 1 translation	Not yet	Validation process	(109–111)
CHP-HRQOL	HP	Development and Content Validity Published in 2021 English for the USA Undergoing further validation	Not Yet	Validation process	(112)
DOMAIN-SPECIFIC					
Dyspnea					
UCSD-SOBQ	IPF CTD-ILD	Developed in 1987 English for the USA 53 translations	Yes	IPF: 8 CTD-ILD: N/A	(80, 81, 83, 84, 87, 91, 92, 113–116)
mMRC	IPF ILD	Modified in 1976, 1986 English for the UK 12 translations	No	N/A	(71, 117, 118)
BDI-TDI	IPF SSc-ILD	Published in 1984 English for the USA 96 translations	Yes	IPF: N/A SSc-ILD: 1.5	(90, 119–121)
Cough					
LCQ	IPF	Published in 2003 English for the UK 23 translations	Yes	Chronic cough: 1.3	(91, 122–124)
CQLQ	IPF	Developed in 2002 English for the USA 4 translations	No	IPF: 5	(125)
Fatigue					
FAS	IPF Sarcoidosis	Developed in 2003 Dutch for the Netherlands 2 translations	No	IPF: N/A Sarcoidosis: 4	(126–129)
Anxiety/depression					
HADS	IPF	Developed in 1983 English for the UK 118 translations	Yes	N/A	(130–133)

(Continued)

TABLE 1 | Continued

Patient-reported outcome measure	Validated IDL	Originally development and translations	Multi-center/country clinical trial use in IDL	MCID	References
Sleep disorders					
ESS	IPF	Developed in 1983, and revised in 1997 English for Australia 95 translations	No	N/A	(134–136)
Generic HRQOL questionnaires					
SF-36	IPF SSc-ILD	Developed in 1998 (current version) English for the USA 191 translations	Yes	IPF: 2–4 SSc-ILD: N/A	(73, 80, 81, 86, 90, 119, 137–141)
EQ-5D-5L	ILD	Developed in 2011 Dutch for the Netherlands, English for the UK, Finnish for Finland, Norwegian for Norway, Swedish for Sweden 181 translations	Yes (including EQ-5D)	ILD: 0.005–0.095	(142–145)
PROMIS-29	IPF SSc-ILD	Published in 2005 English for the USA 47 translations	Not yet	N/A	(146–148)

ATAQ-IPF, A Tool to Assess Quality of life in IPF; BDI-TDI, Baseline Dyspnea Index-Transition Dyspnea Index; CAT, Chronic obstructive pulmonary disease Assessment Test; CHP-HRQOL, Chronic Hypersensitivity Pneumonitis Health Related Quality of Life; CQLQ, Cough Quality of Life Questionnaire; CTD-ILD, connective tissue disease associated interstitial lung disease; EQ-5D-5L, EuroQol-5 Dimension-5 Level; ESS, Epworth sleepiness scale; FAS, Fatigue Assessment Scale; GAD-7, Generalized Anxiety Disorder-7; HADS, Hospital Anxiety and Depression Scale; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; K-BILD, King's Brief Interstitial Lung Disease health status questionnaire; LCQ, Leicester Cough Questionnaire; L-IPF, Living with IPF; L-PF, Living with Pulmonary Fibrosis; MCID, minimal clinically important difference; MFI, multidimensional fatigue inventory; mMRC, modified Medical Research Council dyspnea scale; PESaM, Patient Experiences and Satisfaction with Medication; PF-ILD, progressive fibrosing ILD; PROMIS, Patient Reported Outcome Measurement Information System; SF-36, Short Form-36; SGRQ, St George's Respiratory Questionnaire, SGRQ-I, IPF-specific version of the St George's Respiratory Questionnaire; SSc-ILD, systemic sclerosis related interstitial lung disease; UCSD-SOBQ, University of California San Diego-Shortness of Breath Questionnaire.
The number of translations was referred from ePROVIDE™ from MAPI RESEARCH TRUST (https://eprovide.mapi-trust.org) and EQ-5D from EuroQol group (https://euroqol.org).

A recent large cohort study demonstrated the construct validity and MCID of EQ-5D-5L in patients with a variety of fibrotic ILD subtypes (145). The Patient-Reported Outcomes Measurement Information System (PROMIS) is a research initiative launched by the National Institutes of Health to develop the PROMs for clinical research and practice across a wide variety of chronic diseases (146). Some studies have shown that PROMIS-29 accurately reflects the deficit in HRQOL of patients with IPF and systemic sclerosis-associated ILD (SSc-ILD), but it is still not widely used in the field of ILD (147, 148).

Domain-Specific PROMs

Domain-specific PROMs focus heavily on specific symptoms that patients may experience, which in ILD often include dyspnea, cough, fatigue, anxiety/depression, and sleep disturbance. While these PROMs do not measure HRQOL per say, they are important to mention as we know that many of these physical and psychologic symptoms are larger drivers of HRQOL in ILD. Among these, dyspnea and cough are most often assessed in ILD studies.

The University of California San Diego-Shortness of Breath Questionnaire (UCSD-SOBQ), the modified Medical Research Council dyspnea scale (mMRC), the Baseline Dyspnea Index-Transition Dyspnea Index (BDI-TDI), and the dyspnea-12 (D-12) are common questionnaires administered to assess dyspnea in ILD. The UCSD-SOBQ has been administered in different ILD clinical trials and is well-translated in other languages aside from English. The MCID for IPF has been assessed (80, 81, 83, 84, 87, 91, 92, 113–116). The mMRC is a simple and easy tool for use in daily clinical practice and is reported as a useful predictor of mortality. Experience administering the mMRC in clinical trials and the number of linguistic translations is limited (71, 117, 118). The BDI-TDI assesses both baseline and change measures over time. It is well-translated into multiple languages, however there is little reported experience in clinical trials (90, 119–121). The D-12 is a brief and reliable instrument with positive validation data in ILDs but experience in clinical trials and the number of linguistic translations are limited (113, 152, 153).

The Leicester Cough Questionnaire (LCQ) and the Cough Quality of Life Questionnaire (CQLQ) have been used to assess severity, frequency, and impact of cough in patients with ILD. LCQ is a reliable and relatively easy to complete measure, and there is some experience using it in clinical trials. The responsiveness and MCID are not yet reported in ILD (91, 122–124). CQLQ is a comprehensive and responsive measure, and has good cross-sectional validity in IPF, however our experience using this questionnaire in ILD is still limited (125). More studies are needed to assess the validity of cross-culturally adapted versions of these instruments.

REMAINING GAPS AND OPPORTUNITIES

Despite the great strides that have been made to highlight the importance of HRQOL in ILD in the past two decades, there are still many opportunities to internationally and cross culturally improve its measurement. The ILD-specific HRQOL questionnaires (e.g., K-BILD, ATAQ-IPF, or L-IPF/L-PF) are designed to measure the nuanced impacts of ILD on HRQOL more precisely than generic instruments. A limited number of translations and cross-cultural adaptations have been performed on these instruments making them less generalizable for use in a larger international study compared to others that may be less ILD specific, but have been around longer and are more widely established (99–102, 105, 107, 108, 149). For example, questionnaires developed for COPD (e.g., SGRQ) are not specific to ILD, but have a large number of translations and are relatively-well-validated in ILD (70–92). More studies are needed to continue to linguistically validate and cross culturally adapt the new ILD disease-specific instruments. To standardize this process internationally, it will require global consensus and a collaborative approach (95).

There is little information on the international equivalence of the methods we use to validate PROMs, e.g., how we calculate internal consistency, construct validity including correlation with other parameters, and responsiveness. The various global concepts that impact HRQOL have the potential to affect the interpretation of PROMs. These diversities may contribute to different interpretation of the items in a single questionnaire amongst various communities and countries. Although no formal method has been established to address this possibility, subgroup analyses of multinational clinical trials may support the validity of each questionnaire across these communities and nations if similar results are obtained (154–156). We must also recognize that a PROM is ideally chosen to measure a certain outcome based upon the context and objective of the research study. This means that one questionnaire that is deemed appropriate for one trial design may not be the same questionnaire that is ideal for another, even if they are both measuring HRQOL. This adds another layer of complexity for multi-national studies as one must not only choose an instrument that will capture information about HRQOL in multiple languages and cultures, but they must also be comfortable that the instrument is measuring the constructs that are important to answer their particular question.

To date, trials testing medications developed for use in fibrotic ILDs have overwhelmingly targeted the halt of disease progression as reflected by pulmonary function, exercise tolerance, or progression-free survival (82, 103, 115, 157). As disease-specific HRQOL PROMs generally reflect changes in these parameters, these have characteristically been chosen for use in those clinical trials (77, 98, 100). As patient-centered research in ILD expands, future interventions may target the more disease-specific symptoms (e.g., cough, dyspnea, fatigue) (158–160). For these clinical trials, domain-specific PROMs focusing on each symptom may likely be chosen as the primary endpoint and therefore these instruments will need to be adapted for use cross-culturally.

The guidelines for development of PROMs are not internationally unified. Regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have released PROM development guidance as we increasingly recognize the importance of including these measures in clinical trials (161, 162). Recent PROMs including the K-BILD and L-IPF/L-PF adhered strictly to their guidelines during the process of developments (99, 107). Although there is no question that these guidelines are well-established and rigorous, it is necessary to verify whether the same methodology can be adapted in non-English speaking countries where there are different cultural components as well as potentially different resources available.

Finally, we need to consider the international inequalities of HRQOL itself. As discussed in this review, many individual factors are closely associated with a patient's health status. In fact, the global burdens of ILD measured by disability-adjusted life years (DALYs), which is calculated as the number of years lost due to disability or early death, are known to greatly vary across the countries (163). The level of HRQOL impairment may differ in each country, even if the disease severity assessed by pulmonary function is the same. Therefore, an understanding of the baseline health status in any individual country is important. If there is a large difference in the baseline health status between groups, then the evaluation of relative change in each individual or group should be considered. Multinational consortia of researchers with expertise in PROMs and who study HRQOL are needed in order to begin to address some of these gaps on an international level.

CONCLUSION

HRQOL is an increasingly important end point in ILD amongst patients, clinicians, and researchers alike. As our understanding of the disease and its possible therapies expands, we are rapidly accelerating opportunities for clinical trial conduct across the globe. While we have made great strides in the measurement of HRQOL in ILD, we have many opportunities to improve our measurement across cultures and countries. We have identified several ways in which HRQOL may be interpreted differently across the globe and highlighted potential mechanisms for translation and cross-cultural adaptation of HRQOL PROMs, both in general and in ILD. By recognizing these important differences and working together with our colleagues and patients across the globe we have the opportunity to improve the way we study and report HRQOL which will have a substantial impact on the conduct of multinational studies and interventions in the future.

AUTHOR CONTRIBUTIONS

KA and AS contributed equally to the conception and writing of this manuscript. Both authors contributed to the article and approved the submitted version.

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Interstitial Lung Disease Associated With Autoimmune Rheumatic Diseases: Checklists for Clinical Practice

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Background: Interstitial lung diseases (ILDs) are often associated with rheumatic diseases. Their early diagnosis and management are not only difficult, but also crucial, because they are associated with major morbidity and mortality and can be the first cause of death in autoimmune rheumatic diseases (ARDs).

Objectives: By using methodologies, such as Nominal Group Technique (NGT) and Delphi Survey, the aims of this study were (1) to measure consensus between pulmonologists, radiologists, and rheumatologists experienced in the management of ARD-ILD; (2) to highlight the importance of a multidisciplinary approach; and (3) to provide clinicians with a practical tool aimed at improving the prompt recognition and follow-up of ILD associated with ARDs and of any possible rheumatic conditions underlying ILD.

Results: During the NGT round, the Steering Committee defined 57 statements to be used in the Delphi survey. A total of 78 experts participated in the Delphi survey, namely 28 pulmonologists, 33 rheumatologists, and 17 radiologists. During this round, consensus on agreement was reached in 47 statements, while disagreement was not reached in any statements. A secondary questionnaire was drafted by the Steering Committee to obtain clearer indications on ILD-ARD "red-flags" and follow-up. Delphi Panelists took part also in the second-questionnaire survey. Answers from both surveys were used to draft two checklists of "red flags" sign or symptom suggestive of ILD and ARD, respectively, and two checklists on identification and monitoring of rheumatoid arthritis (RA) and systemic sclerosis (SSc) ILD.

Limitations: This study is a consensus work, which cannot produce empiric data, and is limited to the Italian scenario.

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Conclusions: This work showed a high level of agreement, but also shows some divergent opinions between different experts. This underlines the importance of a multidisciplinary approach. Eventually, we believe the drafted checklists can help clinicians in the diagnosis and follow-up of ILD-ARD.

Keywords: interstitial lung disease, autoimmune rheumatic diseases, multidisciplinary team, nominal group technique, Delphi panel survey, red flags and referral indications, consensus, ARD-ILD

INTRODUCTION

Interstitial lung diseases (ILDs) encompass a heterogeneous group of clinical conditions characterized by fibrosis of and/or inflammation the lungs (1). A common cause of ILD is represented by rheumatic diseases; in these conditions, lung involvement is not only common, but can be the main organ involvement (2, 3). Systemic sclerosis (SSc), rheumatoid arthritis (RA), antisynthetase syndrome, Sjogren's syndrome, mixed connective tissue disease (CTD), idiopathic inflammatory myopathies, and systemic lupus erythematosus are often associated with ILD (4). Moreover, a recent international consensus statement proposed "interstitial pneumonia with autoimmune features" as a new definition for ILD underlined by systemic autoimmune condition and not classifiable as any definite CTD, emphasizing the relationship between ILD and autoimmune response (5, 6). In patients with rheumatic diseases, ILD is difficult to diagnose at an early stage, and can be associated with major morbidity and mortality, or even be the leading cause of death (7–13).

Interstitial lung diseases should be managed, from its diagnosis, by a multidisciplinary team (MDT) composed of at least one pulmonologist, one radiologist, and one pathologist (2–4, 14). However, since phenotypic features of both ILDs and systemic autoimmune disorders often overlap, the patient's assessment should not be limited to clinical, radiological, and pathological evaluation, but should also include a clinical–immunological evaluation. The inclusion of an expert rheumatologist to the MDT can significantly reduce invasive procedures and increase diagnostic accuracy (1, 3, 4, 15). Nonetheless, in daily practice, it could be of use having specific and easy-to-use recommendations to improve the diagnosis and follow-up even for clinicians without specific experience in ARD-ILD or when an MDT is not available. This would help reduce diagnostic timing, which is of outmost importance, since a prompt recognition of the pathology would result in better outcomes.

Aims of this work were (1) to measure consensus between pulmonologists, radiologists, and rheumatologists experienced in the management of ARD-ILD; (2) to highlight the importance and raise sensibility on the necessity of a multidisciplinary approach; and (3) to provide clinicians with a practical tool aimed at improving the prompt recognition and follow-up of ILD associated with autoimmune rheumatic diseases (ARDs) and of any possible rheumatic conditions underlying ILD.

METHODS

The project structure is shown in the flowchart (**Figure 1**).

Briefly, a Steering Committee reviewed the available literature and identified six key questions, which were used to generate some statements through the Nominal Group Technique (NGT) (16). The statements were used for a round of an adapted Delphi survey for an expert panel. Answers were used to draft a first checklist and as inputs to design a second, more specific questionnaire. Eventually, results from the second questionnaire were integrated with the result of the Delphi survey by the Steering Committee to define the check lists of red flags and the timing of ILD screening and monitoring.

Steering Committee and Delphi Expert Panel

The members of both the Steering Committee and Delphi Panel are experts on ARD-associated ILDs.

The Steering Committee included different healthcare professionals, namely three pneumologists (SH, AP, FV), three rheumatologists (SB, NDP, MS), one immunologist (LB), and two radiologists (SP, GR). The Steering Committee sought the assistance of a non-clinical chair from an independent scientific consultancy agency (Polistudium srl, Milan, Italy) in order to provide meeting facilitation, material preparation and scientific accuracy. The Steering Committee designed and developed the project, identified the expert panel, generated the statements, reviewed and discussed survey results, and drafted the checklists.

The expert panel comprised members of different therapeutic areas in order to achieve a multidisciplinary overview. Inclusion criteria were clinical experience in ARD associated-ILDs and proven activity in MDTs. Candidate experts were proposed, shared, and approved within the Steering Committee.

Literature Review and Key Questions

The Steering Committee with the help of the non-clinical chair reviewed the most recent literature on the topic and drafted six key questions to be used to generate statements through a NGT round. Domains of the questions comprised (1) risk factors; (2) pulmonary signs and symptoms; (3) rheumatological signs and symptoms; (4) monitoring timing and frequency of pulmonary symptoms in ARD and ARD-ILD patients; (5) rheumatologists' and pulmonologists' sensitivity and attention to the suspicion of ILD; and (6) how to implement multidisciplinary management.

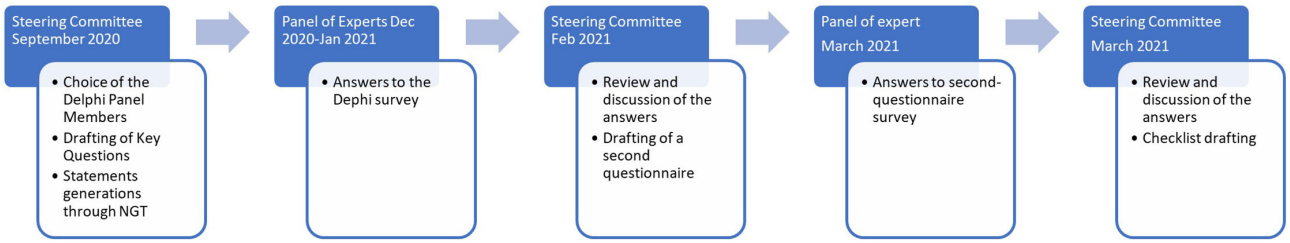

FIGURE 1 | Project flowchart.

Statement Definition

The NGT is a direct and structured technique, based on experts' opinion, aimed at managing meetings organized to make decisions on a specific topic on which there is no strong evidence (16). The NGT was used to generate the statements for the Delphi Panel. At first, the six key questions were asked to the members of the steering committee, who then had the opportunity to independently develop their own thoughts and opinions during the "silent generation" process. Their opinions were presented during an online meeting in September 2020, chaired by a Professional Facilitator. All the opinions (items) were collected and shared with the participants; with the help of the facilitator, items were re-elaborated and similar ones were merged according to a statistical clustering and participants' opinion to draft preliminary statements. Before reaching a final formulation, participants had the opportunity to review and/or comment all items. The so-drafted 57 statements were ranked through an online survey (due to COVID-19 pandemic) in terms of priority and relevance using a 1–5 scale during a second, remotely performed meeting. All 57 statements were considered relevant and kept, eventually drafting the complete list of items.

Adapted Delphi Process

The Delphi Method is a standard method of consensus, used to evaluate in an interactive and anonymous way, through online surveys, the level of agreement (consensus quantification) using a Likert scale (1–5; 1 = total disagreement; 5 = total agreement) and to resolve differences of opinion (consensus development). It takes place through several phases or rounds of expression and evaluation of opinions of a group of appropriately selected experts (17). Consensus on agreement is reached when at least 75% of voters express a vote equal to 4 or 5, according to the indications of the Ministry of Health (18).

Between December 2020 and January 2021, panelists participated to the Delphi online survey and indicated their level of agreement with the statements generated through the NGT.

Second Questionnaire

A qualitative second online survey aimed at outlining, more precisely, what the red flags are and the timing of ILD screening and monitoring was drafted by the Steering Committee after the first Delphi round. The members of the Delphi Panel participated in the online survey.

Statistical Analysis

All data were analyzed with descriptive statistics.

RESULTS

NGT and Delphi Survey

During the NGT round, the Steering Committee answered six key questions and defined 57 statements to be used in the Delphi survey. The key questions statements are reported in **Tables 1, 2**.

In total, 85 experts from different therapeutic areas were invited to join the Delphi Panel (**Supplementary Appendix A**); all the members were based in Italy.

A total of 78 total experts participated in the Delphi survey, composed of 28 pulmonologists, 33 rheumatologists, and 17 radiologists. During this round, consensus on agreement was reached in 47 statements, as shown in **Table 1**. Consensus on disagreement was not reached in any statements. Statements in which consensus was not reached ($n = 10$) are shown in **Table 2**. Due to the practical aim of this paper (i.e., the creation of a checklist regarding useful red flags to suspect ILD in ARD patients and vice versa and regarding screening and monitoring of ILD in ARD patients) this process was adapted by doing a single round; the first-round responses were analyzed by the Steering Committee, who reviewed statements in which consensus had not been reached, discussed the reasons, and provided inputs for the creation of the second, more-in-depth questionnaire.

Second Questionnaire

This first round led to some reflections and conclusions from the committee: (1) there were clear difficulties for reaching consensus in some cases (cf. statement 1.5); differences in views holds despite all members being expert on the topic and part of MDTs—but this is where, in our opinion, value of multidisciplinary resides; (2) some answers from the Delphi survey were conflicting and weren't suitable with our need to give clear indications on patient management; (3) some statements were less relevant for the aim of the paper and were decided not to be investigated with a second round, while others were vague and interpretable. A further reason resides on the practical aim of this paper, which lead us in asking more specific questions to give clearer indications based on opinions of the large number of experts of the Delphi Panel. A detailed questionnaire, with a different structure than the

TABLE 1 | Statements that reached overall consensus.

Statements that reached consensus	Level of agreement (%)			
	Total	Pn	Rh	Ra
Q1: What are the main risk factors for the development of ILD in ARDs?				
1.1—ARDs, in particular, systemic sclerosis, rheumatoid arthritis, and anti-synthetase syndrome, have to be considered important risk factors for the development of ILD.	98	100	94	100
1.2—In the presence of ARDs, the presence of some autoantibodies (anti-JO1, anti-PL 7, anti-PL12, anti-SSA Ro, anti-MDA 5, anti-Scl70, anti-PM/Scl, anti-Th/To) increase the risk of developing ILD.	94	90	97	94
1.3—Some gene variants are associated with a greater risk of developing ILD, particularly for some forms, such as usual interstitial pneumonia.	78	87	**67**	84
1.4—In the case of a patient suffering from systemic sclerosis, there are specific risk factors for the development of ILD, such as male gender, a diffuse form of the disease, and the presence of anti-Scl70 antibodies.	87	81	97	78
1.6—In patients with rheumatoid arthritis, the risk of developing ILD increases in males, smoking patients, with an older age of onset, in proportion to the duration of disease, and the titer of anti-citrulline antibodies.	83	84	88	**72**
Q2: What are the pulmonary signs, symptoms, and investigations that rheumatologists need to evaluate in generating a suspicion of ILD in patients with ARD?				
2.1—A careful anamnesis about the presence of respiratory symptoms is essential in the ARD work-up to evaluate any symptoms of ILD.	91	97	85	94
2.2—A careful thoracic physical examination is essential in the work up of systemic autoimmune diseases to assess the presence of ILD.	87	97	76	94
2.3—The presence of dry cough and exertional dyspnea, not justified by an infectious respiratory or cardiological pathology in progress, can generate the suspicion of ILD in a patient with ARD.	97	100	94	100
2.4—The presence of a feeling of fatigue or chest tightness or digital hippocratism or chest pain can raise the suspicion of ILD in a patient with ARD.	84	86	82	83
2.5—Presence of basal velcro crackles on chest auscultation may raise the suspicion of ILD in a patient with ARD.	92	100	88	89
2.6—Chest x-ray is a poorly specific and insensitive tool to check for the presence of ILD in a patient with ARD.	86	76	97	83
2.7—Spirometry coupled with the CO diffusion test is an investigation to be performed to monitor the course of ILD in a patient with ARD.	97	97	97	100
2.8—The high-resolution CT scan of the chest is the most sensitive and specific radiological method to validate the presence of ILD in a patient with ARD.	100	100	100	100
2.9—If ILD is suspected, a volumetric rather than axial CT scan should be performed, with multiplanar reconstructions and eventual scans in prone decubitus.	89	90	82	100
2.10—Blood–gas analysis allows to evaluate the degree of impairment of gas exchange at rest during ILD in a patient with ARD.	80	79	79	83
2.11—6MWT (Six-Minute Walking Test) allows to evaluate the functional consequences of cardio-pulmonary damage during ILD in a patient with ARD.	80	90	**67**	89
2.12—In case of systemic sclerosis and anti-synthetase syndrome, high-resolution CT of the chest is already recommended at diagnosis.	85	83	88	83
2.13—Within the framing work-up of a diffuse type of systemic sclerosis in early phase or in the presence of predisposing antibodies, high-resolution chest CT scan must always be considered.	92	93	100	78
Q3: What are the rheumatological signs and symptoms that pulmonologists need to evaluate in generating a suspicion of ARD in patients with ILD?				
3.1—Presence of Raynaud's phenomenon, digital edema, skin sclerosis, digital ulcers, telangiectasias, alone or in combination, can generate the suspicion of ARD in a patient with ILD.	91	90	94	88
3.2—Presence of skin manifestations (lower limbs purpura, Gottron's papules, vasculitis, photosensitivity, palmar erythema) can lead to suspicion of ARD in a patient with ILD.	87	83	91	88
3.3—Presence of skin cracks on fingers ("mechanic's hands") can lead to suspicion of ARD in a patient with ILD.	91	86	94	94
3.4—Presence of Sicca syndrome can raise suspicion of ARD in an ILD patient.	76	86	**73**	94
3.5—The presence of arthralgia and morning stiffness can generate suspicion of ARD in a patient with ILD.	77	80	76	77
3.7—Positivity to antinuclear antibodies of a significant titer or $\geq$1/320 may raise suspicion of ARD in a patient with ILD.	85	79	85	94
3.12—In patients with ILD, capillaroscopy should be required at least for patients with Raynaud's phenomenon and for those with specific autoantibodies for systemic sclerosis, mixed connective tissue disease and myositis (anticentromere, anti-Scl70, anti-RNP, specific anti-myositis, anti-synthetase)	100	100	100	100
Q4: What should be the monitoring timing and frequency of pulmonary symptoms in the patient with ARD?				
4.1—Pulmonary symptoms in the ARD patient should be assessed at each visit.	92	93	93	100
4.3—Timing and frequency of pulmonary symptoms monitoring in the ARD patient depend on the specific rheumatic disease.	78	76	82	77

(Continued)

TABLE 1 | Continued

Statements that reached consensus	Level of agreement (%)			
	Total	Pn	Rh	Ra
4.4—In the event of worsening respiratory symptoms in a patient with ARD, a high-resolution chest CT scan should be performed.	87	100	76	88
4.5—Respiratory function tests and carbon monoxide alveolar–capillary diffusion test (DLCO) should be performed every 12 months in patients with ARD, in case of systemic sclerosis every 6–12 months.	86	90	82	88
4.6—Pulmonary symptoms of patients with systemic sclerosis should be monitored every 6 months in case of progressive rheumatic disease.	81	90	**72**	88
4.7—Respiratory function tests and carbon monoxide alveolar–capillary diffusion test (DlCO) should be performed every 12 months in the presence of clinical (systemic sclerosis) or laboratory (predisposing autoantibodies) risk factors in the absence of proven ILD.	90	93	88	88
Q4.1: What should be the monitoring timing and frequency of pulmonary symptoms in the patient with ARD–ILD?				
4.1.1—In case of patients with ARD and ILD, it is necessary, depending on the severity, to evaluate pulmonary symptoms every 3–6 months, carry out spirometry tests every 3–6 months, carry out carbon monoxide alveolar–capillary diffusion tests (DLCO), perform Six-Minute Walking Test (6MWT), and perform echocardiogram every 6–12 months.	85	90	90	**71**
4.1.2—Possible appearance or progression of ILD must be evaluated, in relation to the disease, by high-resolution CT scan of the chest as symptoms vary, in the presence of velcro crackles or worsening of functional tests.	98	97	97	100
Q5: What could be the approaches to increase rheumatologists' and pulmonologists' sensitivity and attention to the suspicion of ILD, in the Italian setting?				
5.1—The creation of a network between different centers of reference, which also favors the organization of national collaborative studies between pulmonologists, radiologists, and rheumatologists, can help to increase rheumatologists' and pulmonologists' sensitivity and attention to suspicion of ILD, in the Italian setting.	96	93	97	100
5.2—Webinar organization, seminars with MDT, and monothematic courses at regional and national level can be useful in increasing rheumatologists' and pulmonologists' sensitivity and attention to the suspicion of ILD, in the Italian setting.	87	90	79	100
5.3—Opportunity increase for meeting and updating with experts, through regional periodic scientific tables with simulation of MDT on paradigmatic cases or participation in multidisciplinary clinics, can be useful to increase rheumatologists' and pulmonologists' sensitivity and attention to the suspicion of ILD, in the Italian setting.	96	93	97	100
5.4—Sharing literature (e.g., creation of a six-monthly scientific bulletin to be distributed to level 1 centers) can be useful in increasing rheumatologists' and pulmonologists' sensitivity and attention to the suspicion of ILD, in the Italian setting.	77	79	**70**	88
5.5—The creation of an informatic platform, where level 1 centers can ask more specialized centers' opinion, can serve to increase rheumatologists' and pulmonologists' sensitivity and attention to the suspicion of ILD, in the Italian setting.	82	90	**73**	88
Q6: What can be ways to implement multidisciplinary management of ARD patients with suspicion of ILD?				
6.1—Creation of shared clinics between rheumatologists and pulmonologists can facilitate multidisciplinary management of rheumatology patients with suspicion of ILD.	95	93	100	82
6.2—Organization of joint training courses between rheumatologists, pulmonologists, radiologists can be useful for implementing multidisciplinary management of rheumatological patients with suspicion of ILD.	97	96	97	100
6.3—Creation of a preferential path of access to rheumatologists and pulmonologists for patients with suspected ILD, secondary to ARD, can favor multidisciplinary management of rheumatological patients with suspicion of ILD.	94	89	94	100
6.4—Sharing of diagnostic classification criteria of both ARD and ILD among the rheumatological and pneumological community, e.g., with the formulation of statements by scientific societies or the organization of regular meetings for the discussion of cases, would favor a multidisciplinary management of rheumatologic patients with suspicion of ILD.	95	100	88	100
6.5—In the case of patients with lung disease not classified with certainty by the pulmonologist, a rheumatological evaluation should also be performed.	82	75	82	94

Pn, pneumologists; Rh, rheumatologists; Ra, radiologists. Values in bold highlight an unmet consensus within a specialty.

Delphi, was thus drafted. This included four sections. In section A, which was addressed only to rheumatologists, the signs and symptoms they would report as red flags to pulmonologists to help suspect ILD in patients with ARD were ranked. Section B had the same structure but was only addressed to pulmonologists and which red flags they would report to the rheumatologist. Section C included questions regarding the tests—and their timing—to be performed on ARD patients without a diagnosis of ILD both in the presence and absence of risk factors for developing ILD. Section D questions were the same as section C but focused on ARD patients with a diagnosis of ILD and on risk factors for ILD progression rather than ILD developing. Questions in section C and D also asked to make the considered risk factors explicit, and to express any adjunctive comments; moreover, they did not only refer to a generic ARD patient, but specifically addressed the following rheumatic diseases: SSc, antisynthetase syndrome, Sjögren's syndrome, RA, and undifferentiated CTD.

TABLE 2 | Statements without overall consensus.

Statements that reached consensus	Level of agreement (%)			
	Total	Pn	Rh	Ra
Q1: What are the main risk factors for the development of ILD in ARDs?				
1.5—The severity of skin involvement in case of systemic sclerosis correlates with an increased risk of ILD.	51	26	**79**	44
1.7—The risk of developing ILD tends to increase with the age of onset of ARD, such as in the case of rheumatoid arthritis.	73	65	**79**	**78**
Q3: What are the rheumatological signs and symptoms that pulmonologists need to evaluate in generating a suspicion of ARD in patients with ILD?				
3.6—Presence of joint deformations can raise the suspicion of ARD in a patient with ILD.	71	**76**	61	**82**
3.8—Presence of alteration in phlogosis indexes can generate suspicion of ARD in a patient with ILD.	35	31	30	53
3.9—Morning functional impotence can raise suspicion of ARD in a patient with ILD.	53	55	49	59
3.10—Presence of subcutaneous nodules may raise suspicion of ARD in a patient with ILD.	66	62	58	**88**
3.11—Presence of a feeling of hyposthenia can generate suspicion of ARD in an ILD patient.	44	41	46	47
Q4: What should be the monitoring timing and frequency of pulmonary symptoms in the patient with ARD?				
4.2—Pulmonary symptoms in ARD patients should be monitored every 12 months for stable rheumatic disease or low-risk patients.	70	66	67	**82**
4.8—In the case of high-risk patients (i.e., diffuse systemic sclerosis with the presence of anti-scl70 antibodies) pulmonary symptoms should be evaluated every 3 months while high-resolution chest CT should be performed every 12 months.	72	**76**	67	**77**
Q6: What can be ways to implement multidisciplinary management of ARD patients with suspicion of ILD?				
6.6—Creation of "smart" digital platforms for each MDT group can facilitate multidisciplinary management of rheumatology patients with suspicion of ILD.	72	68	64	**94**

Pn, pneumologists; Rh, rheumatologists; Ra, radiologists; Values in bold highlight a reached consensus within a specialty.

TABLE 3 | Check list of red flags sign or symptom suggestive of ILD.

Presence of basal velcro crackles on chest auscultation.
Dry cough and exertional dyspnea, not justified by an infectious respiratory or cardiological pathology in progress.

TABLE 4 | Check list of red flags sign or symptom suggestive of ARD.

Skin manifestations (cutaneous sclerosis, purpura of the lower limbs, Gottron's papules, cutaneous vasculitis, photosensitivity, palmar erythema, "mechanic's hands").
Raynaud's phenomenon.
Digital ulcers and telangiectasias, alone or in combination.
Positivity to anti-nuclear antibodies with significant titer (≥1/160).
Presence of muscle weakness associated with an increase in CPK.
Arthralgia, joint swelling or swelling of the hands, morning stiffness.
Dry eyes and dry mouth.

A total of 76 clinicians (31 pulmonologists, 30 rheumatologists, and 15 radiologists) took part in the second survey. All the questions are available as **Supplementary Material** (**Supplementary Tables**).

Red Flags of ILD in Patients With ARD

Rheumatologists should pose particular attention to signs and symptoms shown in **Table 3** since they are useful red flags to suspect an underlying ILD in patients with ARD. If any of these is present, a high-resolution computed tomography (HRCT) should be prescribed.

Red Flags of ARD in Patients With ILD

Pulmonologists should pose particular attention to signs and symptoms shown in **Table 4** since they are useful red flags to suspect an underlying ARD in patients with ILD. If any of these is present, patients should be referred to a rheumatologist.

Screening and Monitoring of ILD in Patients With ARD

Following indications given from the expert panel through the Delphi survey and the second questionnaire, pulmonary symptoms in the ARD patient should be assessed at each visit (item 4.1, **Table 1**). Considering that the ARD-intrinsic risk of onset and developing of ILDs changes according to specific ARDs (items 1, **Table 1**) (19), the timing and type of screening and monitoring must be evaluated according to the specific pathology, and the overall clinical condition of the patient.

ILD in Patients With RA

Clinically evident ILD is usually reported in 7–10% of patients with RA (20, 21), and lifetime risk of RA-ILD of 7.7% has been reported in a population-based cohort study conducted in the USA (22). However, prevalence largely varied according to the different studies and it is significantly higher when consecutive patients are evaluated by HRCT, recording abnormalities compatible with ILD in up to one-third of cases (23–25).

Although the few available data, generally based on retrospective studies, male sex, older age at RA onset, and ever-smokers are associated with RA-ILD in majority of studies (26, 27), mainly for patients with a usual interstitial pneumonia pattern.

TABLE 5 | Identification and monitoring of RA-ILD.

	Respiratory signs and symptoms*	Spirometry and DLCO	HRCT
Baseline/diagnosis time	Check	In presence of respiratory signs or symptoms*	In presence of respiratory signs or symptoms*
Follow-up in patients without a known ILD	Check at every examination*	In presence of respiratory signs or symptoms* or when a pulmonary arterial hypertension is suspected[a,b]	In presence of respiratory signs or symptoms* and/or in presence of significant deficit of functional tests[§]
Follow-up in patients with a known ILD	Check at every examination NB: Worsening of symptoms are suggestive of ILD progression or complications°	Every 3–6 months according to clinical status	Every 12 months according to clinical status[c]

[a] *Do not delay spirometry if DLCO is not available in a short time.*
[b] *Discrepancy between FVC and DLCO deficiency may suggest the presence of pulmonary hypertension.*
[c] *HRCT should be performed (1) in case of a worsening of clinical symptoms or lung function tests or (2) in stable patients to exclude lung cancer and to monitor lung disease.*
[*] *Presence of basal Velcro crackles, dry cough, and exertional dyspnea, not justified by a respiratory infection or cardiological pathology in progress.*
§ *FVC and/or TLC and/or DLCO deficit ≥20%.*
° *Infection, cancer, heart failure, drug toxicity.*

TABLE 6 | Identification and monitoring of SSc-ILD.

	Signs and symptoms*	Spirometry and DLCO	HRCT
Baseline/diagnosis time	Check	Yes	Yes
Follow-up in patients without a known ILD	Check at every examination	Every 6–12 months or in case of onset of respiratory signs or symptoms^	Every 24 months Every 12 months in presence of risk factors[a]
Follow-up in patients with a known ILD	Check at every examination NB: Worsening of symptoms are suggestive of ILD progression or complications°	Every 6–12 months, or every 3–6 months, if risk factors[a] are present	To be performed every 12 months according to clinical status In case of rapid deterioration, re-evaluate the timing

[a] *Risk factors should be assessed at every examination. Risk factors include male gender, diffuse skin disease, and presence of anti-Scl70 antibodies.*
[*] *Presence of basal velcro crackles, dry cough and exertional dyspnea, not justified by a respiratory infection or cardiological pathology in progress.*
° *Infection, cancer, heart failure, drug toxicity.*
^ *Do not delay spirometry if DLCO is not available in a short time.*

Despite contrasting results, anti-citrullinated peptide antibodies (ACPA) have been also associated to ILD. In particular, Correia reported a correlation between ACPA titer and the risk to develop ILD (28). Finally, Doyle reported that a combination of older age, male sex, ever-smoking, RF, and ACPA was strongly associated with RA-ILD (29).

The Steering committee analyzed the answers from both the Delphi and the second survey, discussed such answers, compared them with available literature, integrated them with its opinion, and drafted a practical checklist for screening and monitoring of ILD in patients with RA, as shown in **Table 5**.

ILD in Patients With SSc

Interstitial lung disease is a common manifestation of SSc, with approximately one-third of patients developing progressive ILD (30). Fibrotic non-specific interstitial pneumonia is the most common feature of parenchymal lung disease in patients with SSc-associated ILD, followed by usual interstitial pneumonia. Both the forms appear to have a similar survival in patients with SSc (31, 32). Despite significant improvement in the overall 10-year survival in SSc patients in the last few years, ILD represents a significant cause of morbidity and mortality. Risk factors for the development or progression of ILD among patients with SSc include diffuse cutaneous SSc, male sex, African–American race, older age at disease onset, shorter disease duration, and the presence of anti-Scl-70/anti-topoisomerase I antibody (33–36). However, none of these risk factors is absolute. Clinicians should remember that ILD may develop even in patients with limited cutaneous SSc. In addition, SSc-ILD has a variable and not predictable clinical course. Most patients experience a slow decline in lung function, but others have a rapid progression just after disease onset (37). Different studies showed that the most important predictors of mortality in patients with SSc-ILD are the short-term changes in pulmonary functional parameters (38, 39) and extent of lung fibrosis on HRTC. Despite physicians knowing the established relationship between SSc-ILD and mortality and morbidity well, the lack of a consensus on ILD screening, and monitoring of disease progression raise important implications for a better therapeutic management of SSc-ILD patients, mainly for new available treatment options.

The Steering committee analyzed the answers from both the Delphi and the second survey, discussed such answers, compared them with available literature, integrated them with its opinion, and drafted a practical checklist for screening and monitoring of ILD in patients with RA, as shown in **Table 6**.

ILD in Patients With Other ARD

The other ARD considered in our questions are systemic lupus erythematosus, Sjögren's syndrome, mixed CTD, polymyositis/dermatomyositis, undifferentiated CTD. The risk to develop an ILD varies between different diseases, but in some the mortality related to interstitial lung involvement is very high (i.e., in the antisynthetase syndrome, 28% developed progressive respiratory failure and died) (40). The high heterogeneity spectrum of these diseases either in the risk to develop an ILD either in clinical manifestations and in progression of lung involvement reduced the consensus of the statement that varies from 5 to 75% in the timing of performing CT scan and from 4.5 to 70% in timing to a perform function test.

Regarding identification and monitoring of ILD associated with these ARDs, the respiratory signs and symptoms to be valued are the same as the ones presented for RA and SSc. Diffusing capacity of the lungs for carbon monoxide (DLCO) should be performed annually, or every 3–6 months in case of an already diagnosed ILD. In patients without an ILD diagnosis, HRCT should be performed when clinically indicated from symptoms, or, in patients at high risk for the clinical characteristics of the disease, every 12–24 months. If ILD has been already diagnosed, HRCT should be carried out at least annually.

The Multidisciplinary Approach

All statements addressing how to increase sensitivity and attention to the suspicion of ILD in the Italian setting (Q5 and Q6, **Table 1**) reached consensus. Their approaches include the creation of a network between different centers of reference, webinar/seminar with MDT, monothematic courses, regional periodic scientific tables with simulation of MDT on paradigmatic cases or participation in multidisciplinary clinics, sharing literature, and the creation of an informatic platform, where level 1 centers can ask more specialized centers' opinion.

Statements referring to key question number 6 addressed how to implement multidisciplinary management of ARD patients with suspicion of ILD. Statements that reached consensus suggest the creation of shared clinics between rheumatologists and pulmonologists, the organization of joint training courses between rheumatologists, pulmonologists, and radiologists, the creation of a preferential path of access to rheumatologists and pulmonologists for patients with suspected ILD secondary to ARD, and sharing of diagnostic classification criteria of both ARD and ILD among the rheumatological and pneumological community. The only statement (6.6, **Table 2**) that did not reach consensus suggested the creation of "smart" digital platforms for each MDT group. However, consensus for this statement was reached among the radiologists, likely because of them being more prone in working in a digital setting given their every-day work always involves computers.

DISCUSSION

Interstitial lung disease is often associated with rheumatic diseases. Its early diagnosis and management are not only difficult, but also crucial, because it is associated with major morbidity and mortality and can be the first cause of death in ARDs (7–13). We, therefore, aimed to measure consensus between specialists who can be involved in its management: this is one of the very first studies to address consensus between pulmonologists, rheumatologists, and radiologists. Consensus was high, with 42 out of 50 statements that reached the 75% threshold agreement. No statements reached the disagreement threshold. With this work we also aimed at highlighting the importance of a multidisciplinary approach that includes rheumatologists, and at providing the drafted checklists (see **Tables 3–6**) as a practical tool useful in the prompt recognition and in follow-up of ARD-ILD.

The main strength of this study is the combinations of techniques, such as NGT and Delphi Survey, which allow clinicians firstly to share their own opinion rising from their personal experience, and secondly to work toward an integration of such opinions. This methodology highlights the multidisciplinary approach of this work. The importance of multidisciplinary approaches has been consolidated in the clinical practice, and it is of utmost important to keep such an approach for diagnosis, therapy and follow-up. The evaluation of ILD by an MDT has been proposed as the gold standard for its management (41) but, while up to 20% of ILD cases can be referred to rheumatic conditions, only ∼37% of MDT cases worldwide include a rheumatologist (42); this may create a vicious circle, where rheumatologist referral is up to pulmonologist, who may underestimate clinical manifestation of an ARD. Therefore, if we also consider that ILD can be the leading cause of death for some ARD, and the exclusion of any systemic ARD in any freshly diagnosed ILD is mandatory according to current guidelines, we believe that rheumatologists' non-inclusion in MDTs is not justifiable; their view could potentially complete the evaluation of a pulmonologist, who may overlook important details (15). With regards to this study, when comparing factors taken into account by pneumologists and rheumatologists to decide on the monitoring of the exams, it shows such factors are more lung-related for pneumologists, and more disease-specific for rheumatologists. Clinicians should be aware of this "bias" since it could lead them in taking a wider perspective on the pathology in exam.

Despite the high reached consensus, when we take a more in-depth look to data from the surveys, and consider discussions of the meetings of the steering committee, some discrepancies arose in terms of attitude and management methods of the disease among Delphi panelists, the steering committee, and among clinicians of different expertise. For example, statement 1.5 "The severity of skin involvement in the case of SSc correlates with an increased risk of ILD" reached a level of agreement of 77.8% within rheumatologists, 44.4% between radiologists and 25.8% within pneumologists. While it may be that disagreement occurred because of actual lack of general knowledge or evidence, it could also be argued that agreement occurred for the same reasons. However, we believe this is not the case, since members of the expert panel were chosen for their clinical experience in ARD associated-ILDs and proven activity in MDTs. We think result heterogenicity from the Delphi survey can be explained in several different ways: the presence of specialists with different backgrounds and sensitivities, and with specific experience on different rheumatic diseases; the heterogeneity of rheumatic diseases themselves, which require approaches that cannot be generalized tout-court; a lack of international guidelines (except, partially, on idiopathic pulmonary fibrosis), which may have led panelists in sharing what they can do to the best of the means at their disposal in the everyday clinical setting; the need to reconcile the evaluation of pulmonary involvement with that of the other systemic manifestations of the disease; the difficulties of working in an MDT. Despite discrepancies arising from the variability of different points of view, we managed to integrate such diverse opinions through several meetings

in which statements were discussed, compared to available literature, and our clinical view, and we went so far as to give our opinion based on our experience in MDTs. Notwithstanding differences between specialists, some statements reach a really strong consensus, with one of those being number 2.8 stating that "the high-resolution CT scan of the chest is the most sensitive and specific radiological method to validate the presence of ILD in a patient with ARD," and reaching a level of agreement of 100%. This is coherent with HRCT driving therapeutic choices, given the fact that is useful to identify subclinical outlines, and differentiate ILA from subclinical forms of ARD-ILD (19).

Training clinicians and improving their sensitivity and attention to the suspicion of ARD-ILD can be a valuable solution when working with an MDT is not possible; this happens quite often in the Italian scenario, where the triplet pulmonologist, rheumatologist, and radiologist is not always available, or present within the same structure. Q5 of the Delphi survey addressed how to implement such training; results therefore show which ways clinicians would feel effective if they had to be instructed. The two most-agreed ways are the creation of a network between different centers of reference, which also favors the organization of national collaborative studies between pulmonologists, radiologists, and rheumatologists, and an opportunity increase for meeting and updating with experts, through regional periodic scientific tables with simulation of MDT on paradigmatic cases or participation in multidisciplinary clinics. Other solutions include webinars/seminars with MDT and monothematic courses at regional and national level, the creation of an informatic platform, where level 1 centers can ask more specialized centers' opinion, and sharing literature through scientific bulletin to be distributed to level 1 centers. Improving untrained physicians' sensitivity is the first step toward implementation of ARD-ILD multidisciplinary management. Q6 of the Delphi survey addressed ways for such implementations; statement consensus was reached for four out of five statements. According to the Delphi panelists, the most effective way to implement multidisciplinary management is the organization of joint training courses between rheumatologists, pulmonologists, and radiologists, followed by the creation of shared clinics between rheumatologists and pulmonologists, the sharing of diagnostic classification criteria of both ARD and ILD among the rheumatological and pneumological community (e.g., the formulation of statements by scientific societies or the organization of regular meetings for the discussion of cases), and eventually the creation of a preferential path of access to rheumatologists and pulmonologists for patients with suspected ILD secondary to ARD. On top of this, it must be remembered that being part of an MDT is an ongoing process. Even once multidisciplinary management has been implemented, clinicians need time to adapt to it: levels of agreement between different specialists rise over time, improving diagnostic, and managing performance (15, 43).

The solutions proposed in the statements from Q5 and Q6 could be effective, but they require a lot of time to be carried on and applied. Moreover, not all clinical settings are suitable for having an MDT. Because of this, and to provide all specialties with tools that are shared and recommended by other specialists. We propose some checklists to help recognition and follow up of ARD-ILD; these checklists arise from the integration of results from the Delphi survey, the second questionnaire, and our experience of MDT. Given the irreversibility and high morbidity and mortality rates of ILD (1, 44) a prompt diagnosis is extremely important; the red-flag checklist of respiratory signs and symptoms suggestive of ILD in ARD patients (**Table 3**) can be a useful tool for rheumatologists for the recognition of ILD. On the other hand, the red-flag checklist of systemic signs and symptoms suggestive of ARD in ILD patients (**Table 4**) is addressed to pulmonologist to help them recognize a rheumatic condition underlying ILD. A fast recognition of the presence of an ARD underlying ILD, and vice versa, can help guide therapy and give better outcomes. **Tables 5**, **6** go more in-depth tackling identification and monitoring of ILD in RA and SSc, respectively. They explicit symptoms to be addressed and examinations to be performed and give indication on the timing depending on whether the rheumatic disease has just been diagnosed, or patients are in the follow-up phase with a diagnosed or undiagnosed ILD already. We believe these short, easy-to-consult checklists can help untrained physicians better address these pathologies in the wait of more robust, international guidelines.

This study has four main limitations. Firstly, drafting items and statement can often lead to them being redundant or already addressed in literature Secondly, Delphi panelists could not comment on the relevance or importance of the drafted statements, as well as they could not give a position of "non-opinion." Thirdly, it is limited to the Italian scenario; this may have yielded results that are not in line with other countries' reality, especially when considering every-day clinical practice, which can differ because of different regulations and resources. Finally, albeit based on the experience of a high number of clinicians, it is a consensus work and could not produce empiric data.

CONCLUSIONS

This consensus work showed a high level of agreement, but also shows some divergent opinions between different experts. This underlines the importance of a multidisciplinary approach and of a constant update in overcoming these differences and in enhancing the diagnosis timing and management of patients with ILD-ARD. Given the high morbidity and mortality rates of ILD-ARD, its early recognition is crucial. The expert-shared red-flag checklist of respiratory signs and symptoms suggestive of ILD in ARD patients (**Table 3**) can be a useful tool for rheumatologists for the recognition of ILD, while the expert-shared red-flag checklist of systemic signs and symptoms suggestive of ARD in ILD patients can help the pulmonologist to recognize a rheumatic condition underlying ILD (**Table 4**). Since RA and SSc are two of the most common ARDs that can be associated with ILD, we drafted related checklists on identification and monitoring (**Tables 5**, **6**), which can help tackle these conditions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the planning, implementation, and drafting of the study.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.732761/full#supplementary-material

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Lung Tissue Microbiome Is Associated With Clinical Outcomes of Idiopathic Pulmonary Fibrosis

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Background: Several studies using bronchoalveolar lavage fluid (BALF) reported that lung microbial communities were associated with the development and clinical outcome of idiopathic pulmonary fibrosis (IPF). However, the microbial communities in IPF lung tissues are not well known. This study is aimed to investigate bacterial microbial communities in lung tissues and determine their impact on the clinical outcomes of patients with IPF.

Methods: Genomic DNA extracted from lung tissues of patients with IPF ($n = 20$; 10 non-survivors) and age- and sex-matched controls ($n = 20$) was amplified using fusion primers targeting the V3 and V4 regions of the 16S RNA genes with indexing barcodes.

Results: Mean age of IPF subjects was 63.3 yr, and 65% were male. Alpha diversity indices did not significantly differ between IPF patients and controls, or between IPF non-survivors and survivors. The relative abundance of *Lactobacillus*, *Paracoccus,* and *Akkermansia* was increased, whereas that of *Caulobacter*, *Azonexus*, and *Undibacterium* decreased in patients with IPF compared with that in the controls. A decreased relative abundance of *Pelomonas* (odds ratio [OR], 0.352, $p = 0.027$) and *Azonexus* (OR, 0.013, $p = 0.046$) was associated with a diagnosis of IPF in the multivariable logistic analysis adjusted by age and gender. Multivariable Cox analysis adjusted for age and forced vital capacity (FVC) revealed that higher relative abundance of *Streptococcus* (hazard ratio [HR], 1.993, $p = 0.044$), *Sphingomonas* (HR, 57.590, $p = 0.024$), and *Clostridium* (HR, 37.189, $p = 0.038$) was independently associated with IPF mortality. The relative abundance of *Curvibacter* ($r = 0.590$) and *Thioprofundum* ($r = 0.373$) was correlated positively, whereas that of *Anoxybacillus* ($r = -0.509$) and *Enterococcus* ($r = -0.593$) was correlated inversely with FVC. In addition, the relative abundance of the *Aquabacterium* ($r = 0.616$) and *Peptoniphilus* ($r = 0.606$) genera was positively correlated, whereas that of the *Fusobacterium* ($r = -0.464$) and *Phycicoccus* ($r = -0.495$) genera was inversely correlated with distance during the 6-min walking test.

Conclusions: The composition of the microbiome in lung tissues differed between patients with IPF and controls and was associated with the diagnosis, mortality, and disease severity of IPF.

Keywords: idiopathic pulmonary fibrosis, prognosis, respiratory function tests, microbiota, diagnosis

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrosing interstitial lung disease of unknown etiology (1). It is characterized by worsening dyspnea, impaired lung function, decreased quality of life, and a poor prognosis (1). The pathogenesis of IPF involves both genetic (2, 3) and environmental factors (4, 5). Repeated epithelial injuries caused by multiple environmental factors, such as smoking, micro-aspiration, organic and inorganic dust, and viral infection (4, 5), can lead to the abnormal wound healing process, such as epithelial-mesenchymal transition (6) in genetically susceptible individuals who have a mutation in airway defense (*MUC5B*), telomerase function (*TERT*), or immune responses (*TOLLIP*, *TLR3*, and *IL1RN*) (2, 3, 7). Much evidence supports an association between the etiology of several viruses (8–11), and the development or acute exacerbation (AE) of IPF (12, 13). The fact that combined therapy with steroid, azathioprine, and N-acetylcysteine increases the mortality and hospitalization rates of patients with IPF (14) also suggests that infectious organisms are involved in IPF progression.

Along with the development of culture-independent molecular-sequencing techniques, such as 16s ribosomal RNA (16s rRNA) gene sequencing (15), several studies of bronchoalveolar lavage fluid (BALF) have suggested that lung microbial communities are associated with the clinical course of IPF (16–21). The findings of the Correlating Outcomes With Biochemical Markers to Estimate Time-progression in IPF (COMET) study revealed that an increased bacterial burden in BALF from patients with IPF ($n = 65$), compared with controls ($n = 44$), is associated with a 10% decline in forced vital capacity (FVC) at 6 months and mortality (16). On the contrary, a study of explanted lung tissues from patients with IPF ($n = 40$) showed very low bacterial abundance in IPF lung tissues that was similar to that of negative controls (22). These contradictory findings could be attributed to different types of samples or sample collection times. Therefore, the composition and impact of the lung tissue microbiome at diagnosis on clinical outcomes in patients with IPF are not well defined. Our study aimed to identify the diversity and composition of the bacterial microbial communities in lung tissues at the time of diagnosis and determine their association with clinical outcomes, such as survival, disease severity, and progression in patients with IPF.

MATERIALS AND METHODS

Study Population

All participating patients with IPF were diagnosed between January 2011 and December 2013 at Asan Medical Center, Seoul, Republic of Korea and met the diagnostic criteria of the American Thoracic Society (ATS)/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association statement (1). Samples of lung tissues from patients with IPF ($n = 20$; 10 non-survivors [cause of death: AE = 1, disease progression = 2, unknown = 7]) were aseptically obtained at the time of surgical biopsy for diagnosis, and those from age- and gender-matched controls (lung cancer patients; $n = 20$) with no histological evidence of disease collected aseptically at the time of surgery were obtained from the Bio-Resource Center of Asan Medical Center. None of the patients with IPF or the controls had been treated with antibiotics, steroids, anti-fibrotic agents, or probiotics within 1 month before undergoing surgery. Lung tissues were procured under protocol #2016-1366. This study was conducted in accordance with the Declaration of Helsinki (2013) and was approved by the Institutional Review Board of Asan Medical Center (2018–1096). Written informed consent was obtained from all study participants.

Clinical and survival data of all patients were retrospectively collected from medical records, telephone interviews, and/or the National Health Insurance of Korea. Spirometry, total lung capacity (TLC) determined by plethysmography and diffusing capacity for carbon monoxide (DLco) measured according to published recommendations are expressed as ratios (%) of normal predicted values (23–25). The patients with IPF underwent 6-min walk tests (6MWT) according to the ATS guidelines (26). Baseline clinical data at the time of IPF diagnosis were collected within one month of sample acquisition.

Bacterial 16S rRNA Gene Sequencing

Tissue samples were frozen in liquid nitrogen immediately after collection and stored at −80°C. Genomic DNA was extracted from lung tissues using Mo Bio PowerSoil® DNA Isolation Kits (Mo Bio Laboratories, Carlsbad, CA, USA) according to the instructions of the manufacturer. The variable V3 and V4 regions of the 16S rRNA genes were amplified using the following specific forward and reverse primers with overhang adapters: 5′-TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGCCTACG GGNGGCWGCAG-3′ and 5′-GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGGACTACHVGGGTATCTAATCC-3′, respectively (27). The PCR proceeded using a 5 ng/μl DNA template, 2 × KAPA HiFi HotStart Ready Mix (KAPA Biosystems, Wilmington, MA, USA), and two amplicon PCR forward and reverse primers. The PCR protocol comprised initial incubation at 95°C for 3 min, followed by 25 cycles of 95°C for 30 s, 55°C for 30 s, and 72°C for 30 s, then 72°C for 5 min, and retention at 4°C. After PCR clean-up and index PCR, 300 bp paired-end sequences were pooled on the Illumina MiSeq platform (Illumina Inc., San Diego, CA, USA) as described by the manufacturer for all sample sequencing (28, 29). Distilled water provided in the PCR kit was used as a negative control, and no amplification was identified during the processes.

Reconstruction and Compositional Analysis

Fast Length Adjustment of Short (FLASH) reads, http://ccb.jhu.edu/software/FLASH/), were used for 16S rRNA gene by merging pairs of reads when the original DNA fragments were shortened than two times the length of the reads (30). Pre-processing and clustering were performed using the CD-HIT-operational taxonomic units (OTU; http://weizhongli-lab.org/cd-hit-otu/). Short reads (56,825) were filtered out and extra-long tails were trimmed. After filtering, the remaining reads were clustered

TABLE 1 | Comparison of baseline characteristics between IPF and control groups.

Variables	IPF			Control
	Total	Survivors	Non-survivors	
Number	20	10	10	20
Age, years	63.3 ± 6.2	62.4 ± 6.4	64.2 ± 6.1	67.3 ± 7.4
Male	13 (65.0)	6 (60.0)	7 (70.0)	17 (85.0)
Ever-Smoker	13 (65.0)	7 (70.0)	6 (60.0)	15 (75.0)
PFT, % predicted				
FVC	64.2 ± 14.7	69.2 ± 15.1	60.2 ± 14.0	91.3 ± 16.0*
DLco	54.8 ± 14.8	58.3 ± 17.5	51.3 ± 11.3	97.4 ± 20.6*
TLC	65.9 ± 11.3	68.7 ± 10.2	63.0 ± 12.2	108.4 ± 17.7*
6MWT				
Distance, m	433.6 ± 63.5	452.8 ± 48.9	434.3 ± 77.1	NA
Resting SpO_2, %	96.3 ± 1.6	96.4 ± 1.6	96.2 ± 1.7	NA
Lowest SpO_2, %	90.6 ± 5.8	91.5 ± 5.1	89.6 ± 6.5	NA

*Data are presented as means ± SD or number (%), unless otherwise indicated. 6MWT, 6-min walk test; DLco, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; NA, not available; PFT, pulmonary function test; SpO_2, peripheral oxygen saturation; TLC, total lung capacity; 6MWD, 6-min walk test distance. *P < 0.05 (IPF vs. control).*

at 100% identity. Chimeric reads (254,891) were filtered, and secondary clusters were recruited into primary clusters. After excluding reads with all other noise (5,292,165), the remaining reads (3,484,551) were clustered algorithm into OTUs at a cutoff of 97% (31, 32). Feature tables, such as abundance and representational sequence files, were created using UCLAST in Quantitative Insights Into Microbial Ecology (QIIME1; https://qiime.org) software (33). Taxonomy was assigned based on information about organisms with the closest similarity to the representative sequence of each OTU in the Basic Local Alignment Search Tool (BLAST), version 2.4.0, the NCBI 16S microbial reference database. Taxonomy was not assigned when the query coverage of the best match in the database was <85%, and the identity of the matched area was <85%.

Statistical Analysis

Continuous data were analyzed using Mann–Whitney U tests, and categorical data were analyzed using Fisher exact tests. The decline rate of lung function and exercise capacity for one year was estimated by linear regression analysis. Correlations between the relative abundance of the microbiome and clinical parameters were assessed using Spearman's correlation coefficients (r). The risk of microbial relative abundance for a diagnosis of IPF was expressed as odds ratio (OR) with 95% CI using binary logistic regression. In addition, the risk of microbial relative abundance for IPF mortality was presented as hazard ratio (HR) with 95% CI using Cox proportional hazards regression analyses. Alpha diversity indices that estimate the number of unique OTU in each sample are represented using four indices; Observed estimated the actual number of different taxa evident in a sample, Chao 1 non-parametrically estimated the richness of the species (34), Shannon estimated richness and evenness of species present in a sample considering the distribution of strains belonging to each species (35), and Inverse Simpson measured the probability that two randomly selected objects in a sample belong to the same species (36). Principal coordinates analysis (PCoA), based on weighted UniFrac methods to obtain phylogenetic and quantitative indices for assessing abundance differences among groups (IPF vs. controls, survivors vs. non-survivors), was conducted for all samples using QIIME1 (37). The exploratory and differential microbial compositions were analyzed using QIIME1. All data were statistically analyzed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA), and values with $p < 0.05$ (two-tailed) were considered statistically significant.

RESULTS

Microbial Diversity and Composition

Among 20 patients with IPF, the mean age was 63.3 yr, and 65.0% were male (**Table 1**). Lung function (FVC, DLco, and TLC) was worse in the patients with IPF than in the controls, whereas demographics, lung function, and exercise capacity during the 6MWT did not significantly differ between IPF non-survivors and survivors.

Alpha diversity indexes, such as Observed, Chao 1, Shannon, and Inverse Simpson, did not differ between the IPF and control groups (**Supplementary Figure A1**). However, the PCoA plot revealed dissimilarity in the weighted UniFrac distance between the IPF and controls (**Figures 1A–C**), especially between five of the patients with IPF (non-survivors, $n = 3$; **Figures 1A,C** red circles) and controls, indicating more heterogeneity in the microbial distribution.

Among the 10 most frequent taxa, the genus *Ralstonia* was the most prevalent in the IPF and control groups, followed by *Nocardia* and *Pelomonas* (**Supplementary Figure A2**). On the contrary, *Lactobacillus, Enterobacter, Tetragenococcus,* and *Neisseria* were frequently identified in IPF, whereas *Haemophilus, Caulobacter, Bradyrhizobium*, and *Thermomonas* were prevalent in the controls. The relative abundance of *Lactobacillus* (0.91 [IPF] vs. 0.06% [control], $p = 0.009$), *Paracoccus,* (0.13 vs.

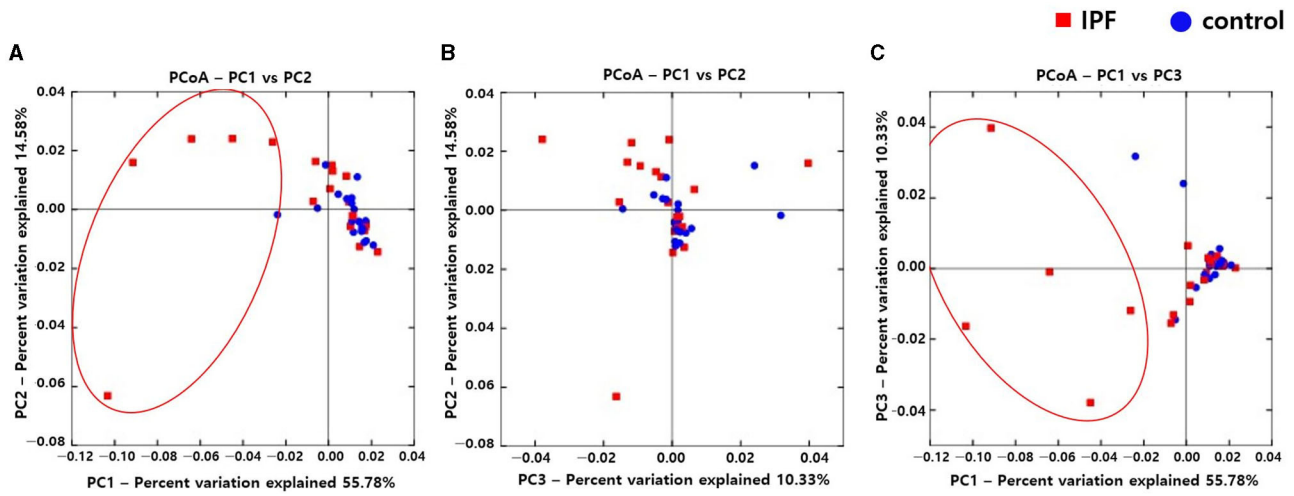

FIGURE 1 | Comparison of principal coordinates analysis using weighted UniFrac method between patients with IPF and controls. Two-dimensional PCoA plots display inter-sample distances by three principal coordinates as PC1 and PC2 **(A)**, PC2 and PC3 **(B)**, and PC1 and PC3 **(C)**. Each dot represents one sample, plotted by a principal component on the *X*-axis and another principal component on the *Y*-axis, and colored by the group. The ratio (%) on each axis presents the contribution of values to discrepancies among samples. IPF, idiopathic pulmonary fibrosis; PCoA, principal coordinates analysis.

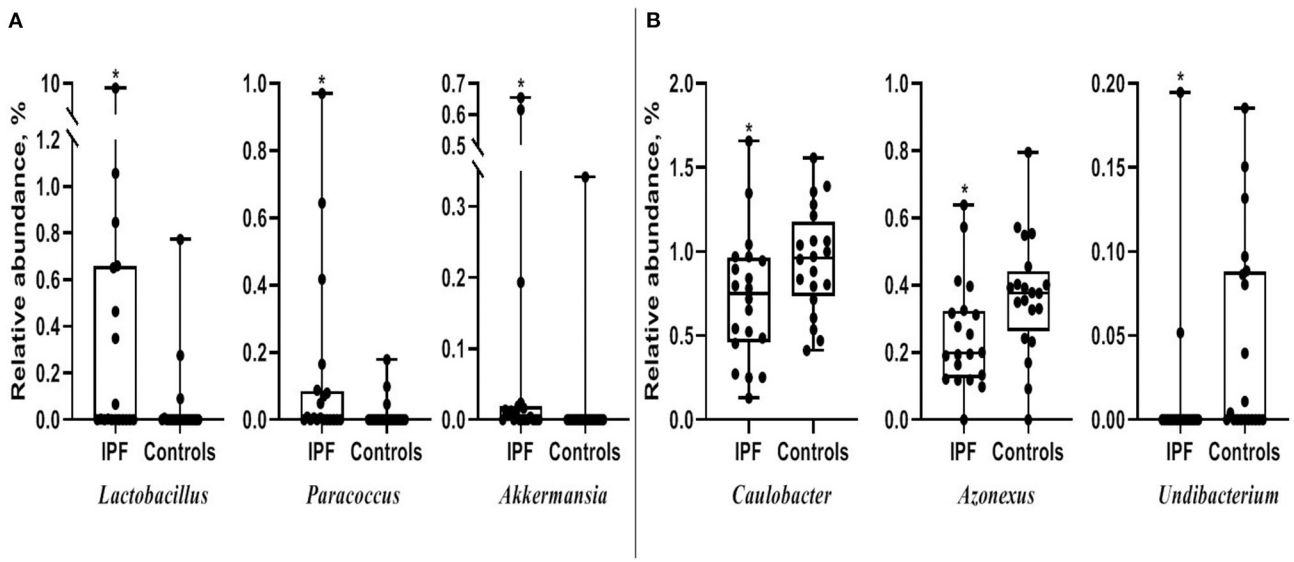

FIGURE 2 | Comparison of relative abundance between patients with IPF and controls. **(A)** Increased and **(B)** decreased in patients with IPF. The box plot shows the minimum, first quartile, median, third quartile, and maximum of relative abundance. *$p < 0.05$. IPF, idiopathic pulmonary fibrosis.

0.02%, $p = 0.013$), and *Akkermansia* (0.08 vs. 0.02%, $p = 0.001$) was higher, whereas that of *Caulobacter* (0.73 vs. 0.95%, $p = 0.040$), *Azonexus* (0.25 vs. 0.37%, $p = 0.021$), and *Undibacterium* (0.01 vs. 0.04%, $p = 0.011$) was lower in patients with IPF than in the controls (**Figure 2**). Logistic analysis adjusted by age and gender independently associated a diagnosis of IPF with lower relative abundance of the genera, *Pelomonas* (OR, 0.352; 95% CI, 0.139–0.891; $p = 0.027$), and *Azonexus* (OR, 0.013; 95% CI, 0.000–0.926; $p = 0.046$; **Table 2**).

Microbial Communities: IPF Non-survivors vs. Survivors

Alpha diversity did not significantly differ between non-survivors and survivors of IPF (**Supplementary Figure A3**). However, the PCoA plot showed that the distribution of microbes differed between non-survivors and survivors (**Figure 3**). Among the 10 most frequent taxa, *Ralstonia* and *Nocardia* were the most common in both groups (**Supplementary Figure A4**). The genus *Streptococcus* was more abundant in non-survivors compared with survivors. In addition, the genera *Neisseria,*

Haemophilus, Rothia, and *Rubrobacter* were frequently detected in non-survivors, while the genera *Tetragenococcus, Enterobacter, Lactobacillus,* and *Caulobacter* were prevalent in survivors. The relative abundance of genera *Bifidobacterium* (2.77 [non-survivors] vs. 0.68% [survivors], $p = 0.003$) and *Olsenella* (0.51 vs. 0.41%, $p = 0.013$) was significantly higher in non-survivors than in survivors (**Figures 4A,B**).

Impact on Survival

The median follow-up period for patients with IPF was 3.0 yr (interquartile range: 1.5–5.4 yr), and the median survival period was 3.1 yr. Unadjusted Cox analysis significantly associated the relative abundance of the *Streptococcus, Sphingomonas, Veillonella*, and *Clostridium* genera with IPF mortality. *Neisseria* and *Granulicatella* were also marginally associated with IPF mortality (**Table 3**). A multivariable model adjusted for age, and FVC selected a higher relative abundance of the *Streptococcus* (HR, 1.993; 95% CI, 1.019–3.901; $p = 0.044$), *Sphingomonas* (HR, 57.590; 95% CI, 1.714–1934.881; $p = 0.024$), and *Clostridium* (HR, 37.189; 95% CI, 1.228–1126.474; $p = 0.038$) genera as independent predictors of IPF mortality.

TABLE 2 | Predictive factors for IPF diagnosis assessed by multivariable logistic regression.

Genus	OR (95% CI)*	*P*-value
Pelomonas	0.352 (0.139–0.891)	0.027
Dyella	0.277 (0.067–1.139)	0.075
Caulobacter	0.154 (0.021–1.105)	0.063
Lactobacillus	12.881 (0.666–249.192)	0.091
Bradyrhizobium	0.051 (0.002–1.102)	0.058
Azonexus	0.013 (0.000–0.926)	0.046

*OR, odds ratio per 1% increase in relative abundance; IPF, idiopathic pulmonary fibrosis. *Adjusted by age and gender.*

Association With Disease Severity

The relative abundance of *Curvibacter* and *Thioprofundum* was positively associated with FVC in patients with IPF, whereas *Anoxybacillus, Enterococcus, Akkermansia,* and *Clostridium* negatively correlated with FVC (**Figure 5A** and **Supplementary Table A1**). The relative abundance of *Thermomonas* and *Peptoniphilus* positively correlated with DLco, whereas that of *Granulicatella* and *Rhodoferax* was positively correlated with TLC.

The relative abundance of the *Aquabacterium*, *Nakamurella*, and *Peptoniphilus* genera was positively correlated, whereas that of the *Fusobacterium*, *Anaerococcus*, and *Phycicoccus* genera was negatively correlated with distance during the 6MWT (**Figure 5B** and **Supplementary Table A2**). The relative abundance of genus *Rhodoferax* and *Lactococcus* was positively correlated with resting and lowest oxygen saturation (SpO_2) during the 6MWT.

Association With Disease Progression

We estimated the decline rate in lung function and exercise capacity for one yr and compared them between survivors and non-survivors (**Table 4**). Non-survivors had a faster decline rate in DLco, and distance and the lowest SpO_2 during 6MWT compared with survivors. The relative abundance of *Granulicatella* and *Paracoccus* genera was positively correlated, while that of the *Novosphingobium* genus was negatively correlated with the decline rate in FVC (**Figure 6A** and **Supplementary Table A3**). The relative abundance of *Bifidobacterium* was positively associated, whereas *Streptococcus was* negatively associated with the decline rate in DLco.

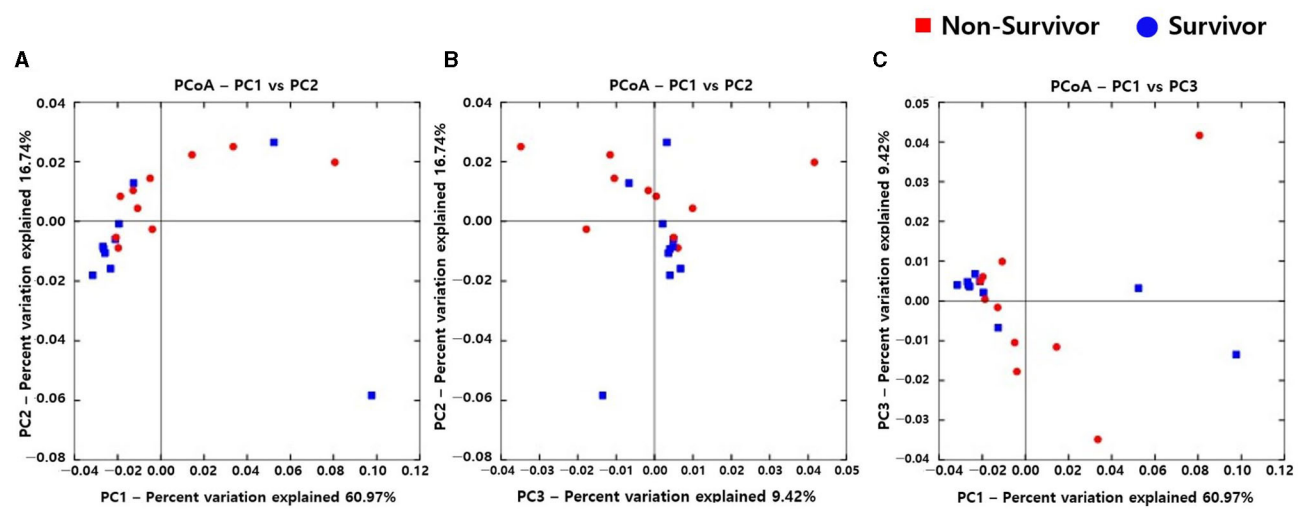

FIGURE 3 | Comparison of principal coordinates analysis outcomes using weighted UniFrac between non-survivors and survivors of IPF. Two-dimensional PCoA plots display inter-sample distances by three principal coordinates as PC1 and PC2 **(A)**, PC2 and PC3 **(B)**, and PC1 and PC3 **(C)**. Each dot represents one sample, plotted by a principal component on the *X*-axis and another principal component on the *Y*-axis, and colored by the group. The ratio (%) on each axis presents the contribution of values to discrepancies among samples. IPF, idiopathic pulmonary fibrosis; PCoA, principal coordinates analysis.

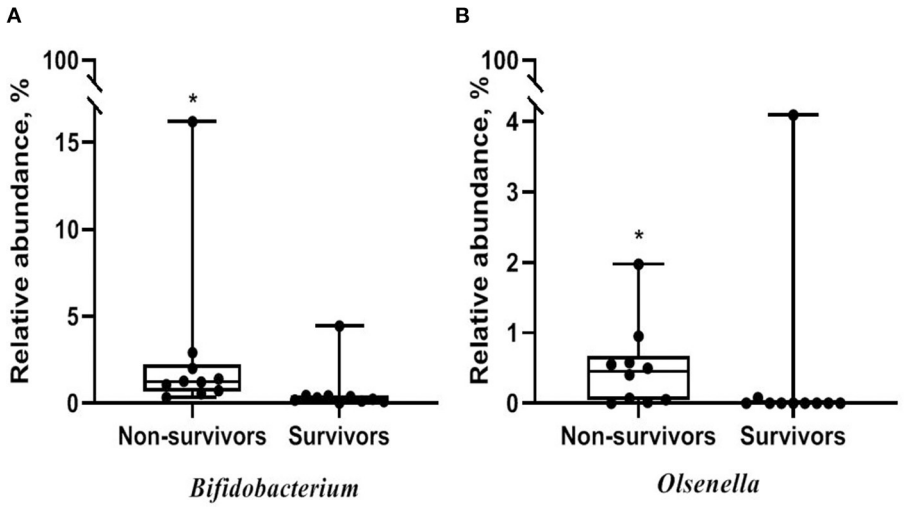

FIGURE 4 | Comparison of relative abundance of microbes between non-survivors and survivors of IPF. **(A)** Genus *Bifidobacterium* **(B)** genus *Olsenella*. The box plot represents minimum, first quartile, median, third quartile, and maximum relative abundance. IPF, idiopathic pulmonary fibrosis. *$p < 0.05$.

TABLE 3 | Risk factors for mortality in patients with IPF assessed using multivariable Cox proportional hazards models.

Genus	Unadjusted		Multivariable*	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Streptococcus	1.389 (1.047–1.842)	0.023	1.993 (1.019–3.901)	0.044
Neisseria	1.500 (0.937–2.400)	0.091	1.500 (0.937–2.400)	0.091
Sphingomonas	57.590 (1.714–1934.881)	0.024	57.590 (1.714–1934.881)	0.024
Veillonella	3.164 (1.026–9.752)	0.045	5.855 (0.821–41.769)	0.078
Granulicatella	14.029 (0.668–294.603)	0.089	14.029 (0.668–294.603)	0.089
Clostridium	37.189 (1.228–1126.474)	0.038	37.189 (1.228–1126.474)	0.038

*CI, confidence interval; HR, hazard ratio. * Adjusted by age and FVC. FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis.*

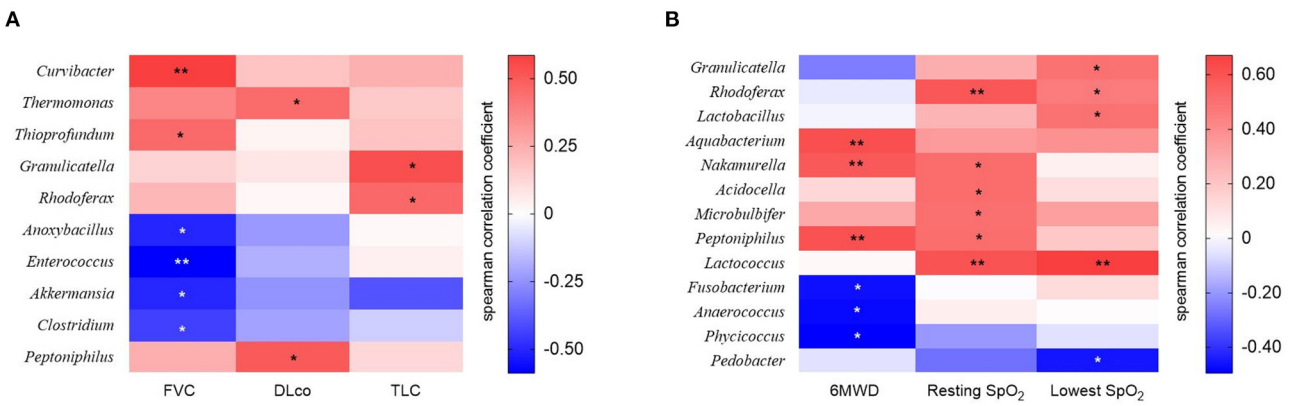

FIGURE 5 | The heatmap showing correlations between relative abundance of bacterial taxa and **(A)** lung function or **(B)** exercise capacity in patients with IPF. Spearman's correlations between the relative abundances of the bacterial genera and lung function and exercise capacity at diagnosis were calculated. Blue: negative correlations; red: positive correlations. *$p < 0.05$, ** $p < 0.01$. DLco, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; TLC, total lung capacity. 6MWD, 6-minute walk test distance; SpO_2, oxygen saturation.

The relative abundance of *Lactobacillus*, *Staphylococcus*, *Granulicatella*, and *Selenomonas* genera was positively correlated with the decline rate of TLC.

The relative abundance of *Staphylococcus* and *Variovorax* was positively associated, while that of *Legionella*, *Anoxybacillus*, *Acidocella*, and *Hyphomicrobium* genera was negatively associated with the decline rate in distance during 6MWT (**Figure 6B** and **Supplementary Table A4**). The relative abundance of *Beijerinckia*, *Mycobacterium*, and *Microbulbifer* genera was positively correlated, whereas that of *Enterobacter genus was* negatively correlated with the decline rate in resting SpO_2. The relative abundance of genus *Staphylococcus* was positively correlated with the lowest SpO_2 during 6MWT.

DISCUSSION

The microbial communities in the lung tissues differed between patients with IPF and controls, and between IPF non-survivors and survivors. When adjusted for age and gender, a decreased relative abundance of genus *Pelomonas* and *Azonexus* was associated with a diagnosis of IPF. A higher relative abundance of the *Streptococcus, Sphingomonas,* and *Clostridium* genera was an independent prognostic factor in patients with IPF and several genera correlated with disease severity and progression.

We found no differences in the alpha diversity of lung tissue microbiomes between patients with IPF and controls, whereas other results of studies of BALF from patients with IPF yielded different results (16, 19). Molineux et al. found a significantly decreased alpha diversity index for the microbiome in BALF samples from 65 patients with IPF at the time of diagnosis (Shannon diversity index, 3.81 ± 0.08 vs. 4.11 ± 0.10; $p = 0.005$) compared with controls ($n = 44$) (16). The Shannon diversity index was also decreased in BALF from mice treated with bleomycin ($n = 6$), compared with control mice ($n = 6$, $p < 0.05$) (19). These contradictory findings could be attributed to differences in baseline demographics and treatment of the subjects in a previous study (16); there were differences in age (68 [IPF] vs. 58.2 years [controls], $p < 0.0001$) and inhaled steroid therapy (6.2 vs. 0.0%, $p =$ not significant) between IPF and controls, and these might affect differences in alpha diversity in microbiome. Our findings were in line with those of Kitsios et al. who identified separate clusters on PCoA plots of Bray-Curtis dissimilarity distances among explanted lung tissues from patients with IPF (n = 40), cystic fibrosis ($n = 5$), and donors ($n = 7$) (22).

The relative abundance of *Lactobacillus* was increased in lung tissues from patients with IPF compared with controls. *Lactobacillus* generally resides in the gastrointestinal and reproductive tract, where it maintains a healthy microecology with lactic acid production (38, 39). However, given the well-known association between IPF and gastroesophageal reflux disease (GERD) (40), the high prevalence of GERD in IPF might contribute to the increase in the relative abundance of *Lactobacillus* in IPF. Moreover, Harata et al.

TABLE 4 | Comparison of changes in lung function and exercise capacity between the survivors and non-survivors among patients with IPF.

	Total	Survivors	Non-survivors
FVC %predicted/year	−0.01 ± 0.04	0.00 ± 0.38	−0.02 ± 0.47
DLco %predicted/year	−0.03 ± 0.05	0.00 ± 0.03	−0.05 ± 0.05*
TLC %predicted/year	0.00 ± 0.04	0.00 ± 0.02	0.00 ± 0.06
6MWD, meter/year	−0.27 ± 0.47	−0.03 ± 0.23	−0.51 ± 0.53*
Resting SpO_2, %/year	0.00 ± 0.02	0.00 ± 0.01	0.00 ± 0.02
Lowest SpO_2, %/year	−0.01 ± 0.02	0.00 ± 0.02	−0.02 ± 0.02*

*Data are presented as means ± standard, unless otherwise indicated. 6MWT, 6-min walk test; DLco, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; PFT, pulmonary function test; SpO_2, peripheral oxygen saturation; TLC, total lung capacity; 6MWD, 6-min walk test distance. *p < 0.05 (survivors vs. non-survivors).*

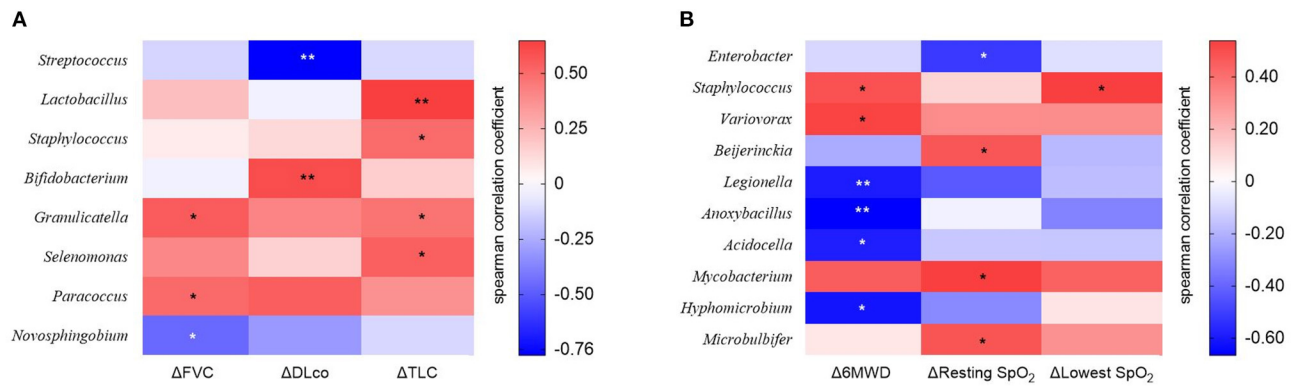

FIGURE 6 | The heatmap showing correlations between relative abundance of bacterial taxa and **(A)** changes in lung function or **(B)** exercise capacity in patients with IPF. Spearman's correlations between the relative abundances of the bacterial genera and decline rate in lung function and exercise capacity for 1 year after diagnosis were calculated. Blue: negative correlations; red: positive correlations. *$p < 0.05$, ** $p < 0.01$. DLco, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; TLC, total lung capacity. 6MWD, 6-minute walk test distance; SpO_2, oxygen saturation; Δ, decline rate for 1 year.

found the increased expression of the mRNA for interleukin-1, tumor necrosis factor, and monocyte chemotactic protein-1 in the respiratory tracts of mice infected with influenza and treated with intranasal *Lactobacillus rhamnosus* than in infected and untreated mice (41). Since proinflammatory cytokines and chemokines are associated with the pathogenesis of IPF (42), the immunoregulatory effect of *Lactobacillus* might contribute to the pathophysiology of IPF. We found a higher relative abundance of *Bifidobacterium* in IPF non-survivors than survivors. *Bifidobacterium* can also produce lactic acid (43, 44), along with *Lactobacillus*. Levels of lactic acid and lactate dehydrogenase-5, which induce the differentiation of fibroblasts into myofibroblasts by activating transforming growth factor (TGF)-ß1, were elevated in lung tissues from patients with IPF ($n = 6$), compared with healthy persons ($n = 6$) (45). Therefore, bacteria that produce lactic acid might also contribute to the progression of IPF.

We independently associated a higher relative abundance of the *Streptococcus* genus with IPF mortality, which is in line with the previous reports (21, 46–48). The COMET-IPF study of 55 patients with IPF found that a higher relative abundance of *Streptococcus* OTU was an independent prognostic factor for disease progression (HR, 1.11; 95% CI, 1.04–1.18; $p = 0.0009$) according to a multivariable Cox proportional hazard analysis adjusted for age, gender, smoking status, and desaturation during the 6MWT (21). Infection with *Streptococcus pneumoniae* significantly increased hydroxyproline levels in lung tissues from mouse models of TGFß1-induced lung fibrosis compared with mock infection (46). In addition, fibrosis and collagen deposition were increased in lung tissues from mice treated with both bleomycin and *Streptococcus pneumoniae* serotype 3 compared with mice that were either treated with bleomycin or infected with *Streptococcus pneumoniae* (48). These results suggested that *Streptococcus* infection could induce IPF disease progression. Furthermore, lung vascular permeability and neutrophil and monocytes counts were increased in BALF from mice treated with pneumolysin (47), which is a pore-forming cytotoxin released by *Streptococcus pneumoniae* that causes alveolar epithelial injury (47).

In this study, the relative abundance of the *Anoxybacillus* genus in IPF lung tissues was correlated with IPF disease severity. The relative abundance of the *Firmicutes* phylum was inversely correlated with FVC in BALF samples from 34 patients with IPF ($r = -0.5514$, $p = 0.0007$) (19). Our results are consistent with these findings because *Anoxybacillus* belongs to the *Firmicutes* phylum and is negatively correlated with FVC. Another study also found an increased relative abundance of *Firmicutes* in BALF from mice treated with bleomycin (19), suggesting that an increased prevalence of the *Anoxybacillus* genus is associated with the pathogenesis of IPF.

This study had some limitations. Although we matched the baseline characteristics, such as age and sex between the IPF and control groups, other confounding factors might have affected the microbial communities. However, we tried not to include patients who had been treated with agents that might affect the microbiota. The number of samples analyzed was not large. Nevertheless, we identified significant differences in the distribution and clinical impact of the microbiomes of patients with IPF compared with controls. Because non-malignant and non-fibrotic lung tissues from lung cancer patients were used as controls, the microbial community in the control group might be affected by lung cancer. However, in studies of lung tissue microbiome of other diseases, it is common to use normal tissue of lung cancer tissue as normal control (49, 50). Even in lung tissue microbiome studies in lung cancer patients, non-cancer tissue from the lung cancer patient was used as a control (50). The cross-sectional design of this study prevented the identification of causal relationships between changes in microbial communities and IPF development. Additional long-term clinical studies should address this issue. Despite these limitations, the strength of our study is that we first revealed the microbial communities in lung tissues from patients when they were initially diagnosed with IPF and the impact of these communities on their survival.

In conclusion, our finding suggests that specific microbial communities in lung tissues from patients with IPF and associations between the relative abundance of some genera and clinical parameters, such as diagnosis, mortality, disease severity, and progression in such patients, imply microbial communities in the lungs play roles in the pathogenesis of IPF.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: NCBI SRA BioProject, accession no: PRJNA761508.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Asan Medical Center (2018-1096). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JS was the guarantor of the manuscript for designing and supervising the entire study. H-YY and JS took responsibility for the data analysis. S-JM contributed to sample collection and preparation. H-YY and JS drafted the initial manuscript. All the authors discussed the results and reviewed the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.744523/full#supplementary-material

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Variability in Global Prevalence of Interstitial Lung Disease

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There are limited epidemiologic studies describing the global burden and geographic heterogeneity of interstitial lung disease (ILD) subtypes. We found that among seventeen methodologically heterogenous studies that examined the incidence, prevalence and relative frequencies of ILDs, the incidence of ILD ranged from 1 to 31.5 per 100,000 person-years and prevalence ranged from 6.3 to 71 per 100,000 people. In North America and Europe, idiopathic pulmonary fibrosis and sarcoidosis were the most prevalent ILDs while the relative frequency of hypersensitivity pneumonitis was higher in Asia, particularly in India (10.7–47.3%) and Pakistan (12.6%). The relative frequency of connective tissue disease ILD demonstrated the greatest geographic variability, ranging from 7.5% of cases in Belgium to 33.3% of cases in Canada and 34.8% of cases in Saudi Arabia. These differences may represent true differences based on underlying characteristics of the source populations or methodological differences in disease classification and patient recruitment (registry vs. population-based cohorts). There are three areas where we feel addition work is needed to better understand the global burden of ILD. First, a standard ontology with diagnostic confidence thresholds for comparative epidemiology studies of ILD is needed. Second, more globally representative data should be published in English language journals as current literature has largely focused on Europe and North America with little data from South America, Africa and Asia. Third, the inclusion of community-based cohorts that leverage the strength of large databases can help better estimate population burden of disease. These large, community-based longitudinal cohorts would also allow for tracking of global trends and be a valuable resource for collective study. We believe the ILD research community should organize to define a shared ontology for disease classification and commit to conducting global claims and electronic health record based epidemiologic studies in a standardized fashion. Aggregating and sharing this type of data would provide a unique opportunity for international collaboration as our understanding of ILD continues to grow and evolve. Better understanding the geographic and temporal patterns of disease prevalence and identifying clusters of ILD subtypes will facilitate improved understanding of emerging risk factors and help identify targets for future intervention.

Keywords: interstitial lung disease, epidemiology—descriptive, global epidemiology, idiopathic pulmonary fibrosis, mortality

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INTRODUCTION

Interstitial lung disease (ILD) describes a heterogenous group of disorders that are subclassified based on similar radiographic or pathologic manifestations. Although several classification schemes exist, generally, ILDs can be subcategorized into: (1) those that occur secondary to a known cause such as a culprit drug or connective tissues disease, (2) idiopathic interstitial pneumonias of which idiopathic pulmonary fibrosis (IPF) is the most common, (3) granulomatous parenchymal lung disease such as sarcoidosis or hypersensitivity pneumonitis, (4) occupational pneumoconiosis, and (5) other rarer forms of diffuse parenchymal lung disease (1, 2).

Prior literature describing the epidemiology of ILDs has utilized national registries, health insurance claims, and social security databases to quantify incidence and prevalence, identify risk factors, and describe disease behavior (clinical presentation, natural history, and outcomes) (3, 4), with a growing body of literature focused on the epidemiology of IPF. Very few studies have examined the global burden of ILD or described the between country variability in disease prevalence and subtype. Better quantifying the geographic burden of ILD and understanding the regional variability can lend insight into new risk factors and identify targets for prevention and intervention. It can also help healthcare systems make informed decisions on how best to allocate resources to meet local needs, which is of particular importance in an era of emerging ILD therapies. The objective of this narrative review is to describe what is known from the English language literature about the geographic variability in ILD prevalence and subtype, discuss potential reasons for the observed heterogeneity, and define current knowledge gaps for future investigation.

We queried the PubMed database to identify relevant studies describing ILD epidemiology. Combination of search terms "epidemiology," "interstitial lung disease," "pulmonary fibrosis," and "prevalence" were used to identify English language studies in humans that had the key search terms in their title or abstract. All abstracts were reviewed for relevance. We excluded studies that focused on a single ILD (ex. IPF only) or were intentionally enriched for certain types of ILD as the goal of this review was to describe the comparative frequency of ILD subtypes. References of key articles were reviewed to supplement the electronic search. A total of 17 studies that described incidence, prevalence and relative frequency of ILD subtypes were identified.

COMPARATIVE EPIDEMIOLOGY OF INTERSTITIAL LUNG DISEASE

North America

One of the first epidemiological studies to evaluate the comparative frequencies of ILDs examined the population burden of disease in Bernalillo County, New Mexico between 1988 and 1990 (5). Patients with ILD were identified through a combination of physician referrals, hospital discharge diagnosis, histopathology reports, and death certificates. Electronic health records were reviewed for diagnostic ascertainment. The median age was 69 years and 52.5% of the cohort was male. The incidence of ILD was 26.1 per 100,000 person-years among women and 31.5 per 100,000 person-years among men (**Table 1**). The prevalence of ILD was 67.2 cases per 100,000 among women and 80.9 cases per 100,000 among men. IPF was the most common ILD, representing 22.5% of prevalent cases, followed by occupational lung disease (14%), connective tissue disease (CTD) ILD (12.8%), and sarcoidosis (11.6%) (**Table 2**, **Figure 1**). The overall prevalence of ILD was 20% higher in males than females, which was driven in part by a higher prevalence of occupational lung disease among men (20.8 per 100,000) compared to women (0.6 per 100,000). Mining is a major industry in New Mexico, which the authors hypothesized likely contributed to the higher prevalence of pneumoconiosis in the male population.

More recently, a Canadian epidemiologic study evaluated the distribution of ILD subtypes among the indigenous population living in Northern Quebec between 2006 and 2013 (6). Patients were identified using a combination of hospitalization databases, home oxygen use registries and physician surveys. Individual cases were adjudicated *via* multidisciplinary discussion (MDD) and a total of 52 cases were identified as definite ILD. There was a high prevalence of IPF (52%) in the cohort followed by CTD-ILD (11.5%). There was a much lower prevalence of occupational lung disease (1.9%) and sarcoidosis (1.9%) than had been observed in Bernalillo County, likely due to different characteristics and risk factors of the underlying source population.

In contrast to the Bernalillo County and Northern Quebec, which were population-based studies, the Canadian Registry for Pulmonary Fibrosis (CARE-PF), a multi-center, prospective registry that recruited patients from six specialized Canadian ILD clinics between 2016 and 2017, noted a much higher frequency of CTD-ILD (33.3%) followed by IPF (24.7%) and unclassifiable ILD (22.3%) (7). All cases were adjudicated *via* MDD. The mean age of the ILD cohort was 64.8 years with a slightly higher preponderance of females (50.7%). The authors hypothesized that the higher proportion of unclassifiable ILD in their cohort was due to a combination of factors including the complexity of cases seen at tertiary care referral centers and the utilization of strict diagnostic criteria for IPF, chronic hypersensitivity pneumonitis (HP), and idiopathic non-specific interstitial pneumonia (NSIP), the latter of which required biopsy confirmation. Thus, it is possible that the prevalence of IPF, HP and NSIP were under estimated in this cohort because of the diagnostic criteria applied.

Europe

Perhaps the most robust epidemiological data examining comparative frequencies of ILDs comes from national registry studies conducted across Europe, the majority of which have demonstrated a high prevalence of IPF and sarcoidosis.

One of the first prospective registry studies evaluated the epidemiology of ILD in Flanders, the northern region of Belgium, between 1992 and 1996 (8). A total of 362 patients were recruited from 20 centers across 5 provinces *via* enrollment surveys completed by physicians. The mean age of the ILD cohort was 52 years old. There was a high prevalence of sarcoidosis (31% when stage I was included, 22% when stage I was excluded), followed by IPF (20%), HP (13%), and CTD-ILD (7.5%). Approximately

TABLE 1 | Incidence and prevalence of interstitial lung disease subtypes.

		Time Period	ILD (All Subtypes)	IPF	CTD	Sarcoid	HP	Drug	Occupational	Unclassifiable
North America										
New Mexico, USA	Incidence	1988–1990	Male 31.5 Female 26.1	Male 10.7 Female 7.4	Male 2.1 Female 3.0	Male 0.9 Female 3.6	–	Male 1.8 Female 1.1	Male 6.2 Female 0.8	–
New Mexico, USA	Prevalence	1988–1990	Male 80.9 Female 67.2	Male 20.2 Female 13.2	Male 7.1 Female 11.6	Male 8.3 Female 8.8	–	Male 1.2 Female 2.2	Male 20.8 Female 0.6	–
Europe										
Flanders (Belgium)	Incidence	1992–1996	1.0	0.22	0.07	0.26	0.12	0.05	0.07	0.10
Flanders (Belgium)	Prevalence	1992–1996	6.27	1.25	0.47	1.94	0.81	0.21	0.35	0.57
Greece	Incidence	2004	4.63	0.93	0.54	1.07	0.13	0.07	0.14	0.71
Greece	Prevalence	2004	17.3	3.38	2.14	5.89	0.45	0.30	0.36	1.46
Denmark	Incidence	2003–2009	4.1	1.3	–	–	–	–	–	–
Paris, France	Incidence	2012	18.3	2.8	3.3	4.9	0.9	1.2	0.8	1.8
Paris, France	Prevalence	2012	71.0	8.2	12.1	30.2	2.3	2.6	3.5	5.0
Turkey	Incidence	2007–2009	25.8	–	–	4.0	–	–	–	–

Incidence and prevalence defined as cases per 100,000.
ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; CTD, connective tissue disease; HP, hypersensitivity pneumonitis.

9.1% of cases were unclassifiable. Notably, the male to female ratio was variable across disease processes with pneumoconiosis and IPF more prevalent among men (M/F ratio of 2.3 and 1.4, respectively) while CTD-ILD was more common in women (M/F ratio of 0.8). Of the HP cases, the majority (75%) were associated with pigeon breeding, impacting more men than women (M/F ratio of 1.5).

A similar distribution of ILD subtypes was observed in Greece (9). In a multi-center ILD registry study, 967 patients were recruited from pulmonary divisions across the country. There was a slightly higher proportion of females in the cohort (53.6%). The mean age of the male population was 58 years old, and the mean age of the female population was 59.3 years old. Sarcoidosis was the most commonly observed ILD subtype (34.1%), followed by IPF (19.5%) and CTD-ILD (12.4%). The prevalence of HP was relatively low (2.6%) and unclassifiable ILDs comprised 8.5% of the cohort. The Greek cohort, similar to other European studies, included stage I sarcoidosis (isolated hilar adenopathy), which may have contributed to the higher proportion of sarcoid cases relative to North American cohorts, which generally only included sarcoidosis stages II–IV (stage II: hilar adenopathy with parenchymal involvement, stage III: parenchymal involvement without lymphadenopathy, and stage IV: predominantly fibrotic disease) in their registries.

A Danish study that sought to describe the incidence of ILDs in central Denmark recruited 431 patients from a single center between 2003 and 2009 (10). Cases were adjudicated *via* MDD. The mean age of the cohort was 61 years and 55% were male. The overall incidence of ILD was 4.1 cases per 100,000 person-years. The study reported a rising annual incidence rate with a peak of 6.6 cases per 100,000 person-years in 2009. The most common ILD was IPF (28%), followed by CTD-ILD (12.5%) and HP (7%). IPF and HP was more common in men (77% and 63%, respectively), while CTD-ILD was more common among women (59%). Notably, sarcoidosis was not included in this cohort.

In Spain, a multicenter registry study that enrolled patients *via* surveys completed by 23 pulmonary medicine clinics between 2000 and 2001 noted an estimated ILD incidence of 7.6 per 100,000 person-years (11). IPF was the most common ILD subtype (38.6%), followed by sarcoidosis (14.9%), CTD-ILD (10%) and HP (6.6%). Approximately 5% of the cases were unclassifiable. Among the CTD-ILD cohort, rheumatoid arthritis was the most common etiology. Similar to observations from the Belgium cohort, pigeon breeding was the most common exposure associated with a diagnosis of HP.

In Italy, the Registro Italiano Pneumopatic Infiltrative Diffuse (RIPID) enrolled 3,152 patients *via* surveys completed by 79 centers across 20 regions (12). The mean age at diagnosis was 54 years with a slightly higher proportion of females (50.9%) in the registry. Sarcoidosis was the most frequently reported ILD (33.7%), followed by IPF (27.4%), which together represented more than 60% of cases. 93 cases (2.9%) of HP were identified.

More recent epidemiologic studies in Europe have focused on using large databases (healthcare claims, mortality, social security) as an alternative to hospital-based registries to define the population burden of ILD. In France, a study that described the population burden of chronic ILDs among people living in Seine-Saint-Denis, a multi-ethnic urbanized area of Greater Paris, noted much higher ILD point prevalence rates than prior registry-based studies (13). Patients were recruited from both physicians' offices and the social security system between January and December 2012. A total of 848 cases were reviewed and validated centrally by an expert MDD. The median age was 55.7 years old with an equal distribution of males and females. The overall incidence of ILD was 18.3 per 100,000 person-years and prevalence was 71 per 100,000 people. In

TABLE 2 | Relative frequency of interstitial lung disease subtypes.

N (%)		Source/ Case Ascertainment	Time Period	IPF	CTD	Sarcoid	HP	Drug	Occupational	Unclassifiable	Other
North America											
New Mexico, USA	202 (incident cases)	County Chart Review	1988–1990	63 (31.2)	18 (8.9)	16 (7.9)	3 (1.5)	7 (3.5)	21 (10.4)	20 (9.9)	54 (26.7)
New Mexico, USA	258 (prevalent cases)	County Chart Review	1988–1990	58 (22.5)	33 (12.8)	30 (11.6)	–	5 (1.9)	36 (14.0)	29 (11.2)	67 (26.0)
Quebec, Canada	52	Indigenous Population MDD	2006–2013	27 (51.9)	6 (11.5)	1 (1.9)	1 (1.9)	–	1 (1.9)	3 (5.8)	13 (25.0)
Canada	1,285	Multi Center MDD	2016–2017	317 (24.7)	428 (33.3)	41 (3.2)	97 (7.5)	–	–	286 (22.3)	116 (9.0)
Europe											
Flanders (Belgium)	264 (incident cases)	Multi Center Survey	1992–1996	59 (22.3)	19 (7.2)	69 (26.1)	32 (12.1)	12 (4.5)	18 (6.8)	27 (10.2)	28 (10.6)
Flanders (Belgium)	362 (prevalent cases)	Multi Center Survey	1992–1996	72 (20.0)	27 (7.5)	112 (30.9)	47 (13.0)	12 (3.3)	20 (5.5)	33 (9.1)	39 (10.8)
Greece	259 (incident cases)	Multi Center Survey	2004	52 (20.1)	30 (11.6)	60 (23.2)	7 (2.7)	4 (1.5)	8 (3.1)	40 (15.4)	58 (22.4)
Greece	967 (prevalent cases)	Multi Center Survey	2004	189 (19.5)	120 (12.4)	330 (34.1)	25 (2.6)	17 (1.8)	20 (2.0)	82 (8.5)	184 (19.0)
Denmark	431 (incident cases)	Single Center MDD	2003–2009	121 (28.1)	54 (12.5)	–	32 (7.4)	20 (4.6)	–	62 (14.4)	142 (32.9)
Spain	511 (incident cases)	Multi Center Survey	2000–2001	197 (38.6)	51 (10.0)	76 (14.9)	34 (6.6)	17 (3.3)	–	26 (5.1)	110 (21.5)
Italy	3,152	Multi Center Survey	1998–2005	864 (27.4)	–	1,063 (33.7)	93 (2.9)	39 (1.2)	–	–	–
Paris, France	848 (prevalent cases)	County MDD	2012	98 (11.5)	145 (17.1)	361 (42.6)	28 (3.3)	31 (3.7)	42 (5.0)	66 (7.8)	77 (9.1)
Asia											
Turkey	2,245 (incident cases)	Multi Center Survey	2007–2009	408 (18.2)	201 (9.0)	771 (34.3)	82 (3.7)	35 (1.6)	241 (10.7)	99 (4.4)	408 (18.2)
India	566 (incident cases)	Single Center MDD	2015–2017	130 (23.0)	77 (13.6)	217 (38.3)	69 (12.2)	5 (0.9)	6 (1.1)	–	62 (11.0)
India	803 (prevalent cases)	Single Center MDD	2015–2017	170 (21.2)	102 (12.7)	339 (42.2)	86 (10.7)	6 (0.7)	7 (0.9)	7 (0.9)	86 (10.7)
India	1,084 (incident cases)	Multi Center MDD	2012–2015	148 (13.7)	151 (13.9)	85 (7.8)	513 (47.3)	3 (0.3)	33 (3.0)	2 (0.2)	149 (13.7)
Pakistan	253	Single Center Chart Review	2016–2018	95 (37.5)	23 (9.1)	11 (4.3)	31 (12.3)	–	3 (1.2)	4 (1.6)	86 (34.0)
China (Guangzhou)	1,945 (incident cases)	Single Center MDD	2012–2017	395 (20.3)	356 (18.3)	123 (6.3)	59 (3.0)	13 (0.7)	13 (0.7)	285 (14.7)	701 (36.0)
China (Beijing)	2,615 (incident cases)	Single Center Chart Review	2000–2012	692 (26.5)	631 (24.1)	147 (5.6)	62 (2.4)	28 (1.1)	58 (2.2)	344 (13.2)	653 (25.0)
Other											
Saudi Arabia	330 (incident cases)	Single Center MDD	2008–2011	77 (23.3)	115 (34.8)	67 (20)	21 (6.3)	4 (1.2)	–	6 (1.8)	40 (12.1)
Australia	705	Multi Center Survey	2016–2019	240 (34.0)	125 (17.7)	44 (6.2)	66 (9.4)	7 (1.0)	11 (1.6)	51 (7.2)	161 (22.8)

MDD, multidisciplinary discussion; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; CTD, connective tissue disease; HP, hypersensitivity pneumonitis.

contrast to other European studies, the prevalence of IPF was much lower in this cohort. The most common diagnosis was sarcoidosis (42.6%), followed by CTD-ILD (17.1%), IPF (11.5%) and occupational lung disease (5%). There was a low prevalence of HP (3.3%). The ancestry-standardized prevalence rates noted a higher frequency of sarcoidosis and CTD-ILDs among patients from North Africa (60 and 26.9 per 100,000, respectively) than in Europeans (10.7 and 5.7 per 100,000, respectively). The ancestry-standardized prevalence of IPF was higher among North Africans than Europeans and Afro-Caribbean (26.9, 5.8, and 4.2 per 100,000, respectively). Adjusted multivariable models demonstrated increased risk of sarcoidosis in Afro-Caribbean (OR 2.9) and North Africans (OR 1.9). The risk of CTD-ILDs was also increased in Afro-Caribbean (OR 4.4) relative to their European counterparts. The authors noted that the area of Seine-Saint-Denis is demographically distinct from that of the general French population with a younger mean age and a higher proportion of people of extra-European ancestry and thus may not be generalizable to the French population at-large. The low prevalence of IPF is likely related to the age distribution, which was skewed toward younger patients.

Asia

Compared to Europe and North America, the English language literature on ILD in Asia has until recently been quite limited. In the last few years, several epidemiologic studies evaluating relative frequency of ILDs have emerged from Turkey, India, Pakistan and China.

In a multicenter cohort study involving recruitment from 31 centers in Turkey, a total of 2,245 cases were identified of which 48.2% were males and 51.8% were females. The mean age was 52 years old. The overall incidence of ILD was 25.8 per 100,000 (14). Sarcoidosis was the most common ILD subtype (34.3%) followed by IPF (18.2%), occupational lung disease (10.7%) and CTD-ILD (9%). There was a low prevalence of HP (3.7%) in the cohort. The study also subcategorized disease burden by sex and age. Among females, sarcoid was the most prevalent (53%), followed by an equal distribution of CTD-ILD (15%) and IPF (15%). For men, the proportion of patients with sarcoid, pneumoconiosis and IPF was nearly equivalent (25% sarcoid, 25% IPF, 24% pneumoconiosis) while prevalence of CTD-ILD (6%) was notably lower. With age, the distributions shifted. For men over the age of 50, IPF was the most common ILD (45%) followed by pneumoconiosis (13%) and then sarcoidosis (8%). For men under 50, sarcoidosis was the most prevalent (42%), followed by pneumoconiosis (36%) with a relatively low prevalence of IPF (6%). High rates of pneumoconiosis in Turkey were postulated to be linked to the denim sandblasting profession resulting in a high burden of silicosis among those with occupational lung diseases.

A few large database studies have evaluated the epidemiology of ILD in India. One single center study recruited 803 patients between 2015 and 2017 and adjudicated cases *via* MDD (15). The mean age of the cohort was 50.6 years old with 50.2% women. Sarcoidosis (42.2%) and IPF (21.2%) were the most common ILD subtypes followed by CTD-ILD (12.7%) and HP (10.7%). Most sarcoid patients (63.4%) had stage II or III disease. RA and systemic sclerosis were the most commonly identified CTD-ILD. Of the patients with HP, the most common exposure was farming (59.3%), followed by exposure to bird feathers (15.1%).

The second epidemiological evaluation of ILD frequencies in India involved a multi-center cohort study, which recruited 1,084 patients from 27 centers between 2012 and 2015 (16). Cases were adjudicated *via* a central MDD. The mean age of registry participants was 55.3 years and 47.2% were male. HP was the final diagnosis in a majority of cases (47.3%), followed by CTD-ILD (13.9%), IPF (13.7%), sarcoidosis (7.8%), and pneumoconiosis (3%). Among patients with HP, 48.1% had been exposed to air coolers, 26.3% to air conditioners, 21.4% to birds and 20.7% to mold in their homes. RA was the most common type of CTD-ILD (38.4%) followed by scleroderma (22.5%). Silicosis was the most common occupational lung disease. The authors noted that compared to other epidemiological studies, a smaller proportion (7.5%) of patients had undergone lung biopsy, which may have led to an underestimation of IPF prevalence, especially as histopathology is often used to differentiate fibrotic HP form IPF. Although the data was presented in aggregate, there was significant within country variability in geographic prevalence of ILD subtypes.

In Pakistan, 253 patients were identified *via* chart review from a single center in Karachi between 2016 and 2018 (17). There was a clear predominance of females (69%) in the registry and the mean age was 49 years old. IPF was the most common disease subtype (37.5%) followed by HP (12.3%), CTD-ILD (9.1%) and sarcoidosis (4.3%). Approximately 37% of patients reported exposure to birds including parakeets, parrots, hens and pigeons.

Two studies examined the epidemiology of ILD in China. The first, retrospectively identified 1,945 patients seen in Guangzhou Institute of Respiratory Health (Southern China) between 2012 and 2017 (18). Case adjudication was done *via* MDD. The mean age at time of diagnosis was 57.9 years and 55.5% of patients were male. The most common ILD subtype was IPF (20.3%), followed by CTD-ILD (18.3%) and interstitial pneumonia with autoimmune features (IPAF) (17.9%). Among the CTD-ILD subgroup, there was a higher proportion of females (60.1%), and RA (32.6%), myositis (25%) and primary Sjogren disease (14%) were the most common CTD subtypes. Although other studies had reported a high percentage of RA-ILD among their CTD-ILD cohorts, the Guangzhou Institute had a much higher prevalence of myositis-ILD than what had been observed in North America, Europe or other parts of Asia. Only 3% of patients were diagnosed with HP. The most common environmental exposure was mold/mildew followed by farming and bird exposure. Relative to other cohorts, especially in Asia, a large number of patients underwent lung biopsy (42.1%).

A second study from China evaluated the distribution of ILD among 2,615 patients of Chinese ancestry admitted to a hospital in Beijing between 2000 and 2012. Patients were identified through chart review. The mean age at diagnosis was 61 years and 59.3% of the cohort was female (19). IPF was the most common ILD subtype (26.5%), followed by CTD-ILD (24.1%) and unclassifiable IIP (13.2%). The most common types of CTD-ILD were

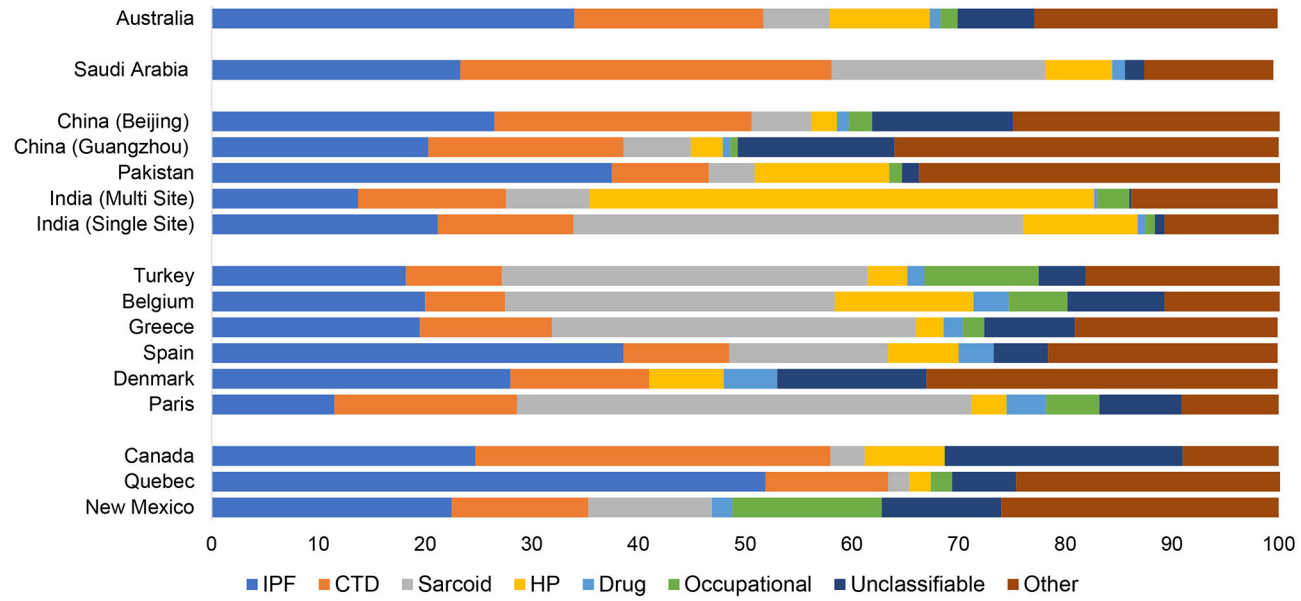

FIGURE 1 | Relative frequency of interstitial lung disease subtype by geography. IPF, idiopathic pulmonary fibrosis; CTD, connective tissue disease; HP, hypersensitivity pneumonitis.

Sjogren disease (11.2%) and RA-ILD (4.6%). Sarcoidosis accounted for 5.6% of cases and pneumoconiosis accounted for 2.2%.

Middle East

There is limited literature on the epidemiology of ILD in the Middle East. One study examined the frequency of ILD subtypes in Saudi Arabia by prospectively recruiting patients with new ILD diagnoses from a single tertiary care center between 2008 and 2011 (20). Cases were adjudicated *via* MDD. A total of 330 patients of native Saudi origin were enrolled with a mean age of 55.4 years and a predominance of females (61.2%) in the cohort. CTD-ILD (34.8%) was the most commonly diagnosed ILD, which included patients diagnosed with IPAF, followed by IPF (23.3%), sarcoidosis (20%), and HP (6.3%). The distribution of sarcoidosis ranged from 12% in stage I, 31% in stage II, 6% in stage III, to 51% in stage IV. The authors postulated that the higher proportion of stage IV sarcoid cases was in part due to referral bias as many patients with stage I and II disease were likely managed in the community. Among patients with HP, an exposure was identified in 66.7% of cases with the most common being birds. Surgical lung biopsies were performed in 22.7% of cases.

Australia

The Australian Interstitial Lung Disease Registry (AILDR) is the largest longitudinal cohort study of ILD in Australia and New Zealand (21). A total of 1,061 patients were recruited from four ILD centers across the continent between 2016 and 2019 *via* surveys distributed to physicians. The mean age of participants was 68.3 years with 54.7% male. The most common diagnosis was IPF (34%) followed by CTD-ILD (17.7%), HP (9.4%) and sarcoidosis (6.2%). The registry also included cases of IPAF (0.4%), which was significantly lower than the frequency of IPAF cases observed in China and the Middle East.

GLOBAL TRENDS IN INTERSTITIAL LUNG DISEASE MORTALITY

The Global Burden of Disease Study noted that ILDs contributed to 0.26% of all-cause mortality in 2017 and that there had been an 86% increase in ILD-related years of life lost over the past two decades (22). The 5-year survival among patients with ILD has been estimated to be 56% (23). However, there is significant heterogeneity in survival by ILD subtypes. The 5-year survival in a national cohort of Danish patients was 34% among those with IPF, 74% in patients with idiopathic NSIP, and 93% among patients with HP (10). Given this variability, current literature has primarily focused on evaluating global trends in ILD mortality by subtype, with most studies focused on IPF.

IPF is a progressive fibrotic lung disease associated with insidious decline in lung function. Historically, the median survival of IPF has been estimated to range from 2 to 5 years (24, 25). However, there is significant variability by subgroup with longer median survival times among younger patients (26). More recent data suggests that in addition to age-related variability in IPF survival, there may be geographic variability as well. In a review of IPF mortality across 10 countries between 1999 and 2012, the age standardized mortality ranged from 4 to 10 per 100,000 with the lowest mortality rates observed in Sweden, Spain, and New Zealand and the highest mortality rates observed in the United Kingdom and Japan (27).

Within the United States, approximately 0.7% of all deaths that occurred between 2004 and 2016 had a diagnosis of pulmonary fibrosis and mortality rates were lower among women, Black, and Asians. There was significant variability in survival by state (28). The reasons for this variability in outcomes both within countries and between countries is unclear. Notably, the majority of these studies were conducted prior to approval and widespread adoption of antifibrotic therapies (pirfenidone and nintedanib), which have been shown to slow disease progression and improve survival. Thus, newer studies may demonstrate changing disease trajectories.

More recently, there has been increasing interest in understanding the prognosis of patients with non-IPF progressive fibrosing interstitial lung disease (PF-ILD) in light of clinical data suggesting that these patients may also benefit from antifibrotic therapies (29). In France, the median overall survival for patients with non-IPF PF-ILD was 3.7 years. Among this subgroup, patients with sarcoidosis had the longest median survival time (7.9 years) and patients with non-HP exposure related ILD had the shortest (2.4 years). These findings are consistent with prior literature that has suggested that the prognosis for patients with sarcoidosis may be better than other forms of ILD.

DISCUSSION

There are limited epidemiologic studies describing the global burden and relatively geographic heterogeneity of interstitial lung disease subtypes, and there are continents (e.g., South America and Africa) without English language literature on the topic. We found that among seventeen methodologically heterogenous studies that examined the incidence, prevalence and relative frequencies of ILD subtypes, the incidence of ILD ranged from 1 to 31.5 per 100,000 person-years and prevalence ranged from 6.3 to 71 per 100,000 people (**Table 1**). In North America and Europe, IPF and sarcoidosis were generally the most prevalent ILDs with the prevalence of IPF ranging from 1.3 per 100,000 in Belgium to 20.2 per 100,000 among males in Bernalillo County, New Mexico. The prevalence of sarcoidosis ranged from 1.94 per 100,000 in Belgium to 30.2 per 100,000 in Paris, France. The relative frequency of occupational interstitial lung disease was highest among patients in Bernalillo County (14%) and Turkey (10.7%) (**Table 2**, **Figure 1**). The relative frequency of HP was higher in Asia, particularly in India (10.7–47.3%) and Pakistan (12.3%), compared to most of the North American and European cohorts. The relative frequency of CTD-ILD demonstrated the greatest geographic variability, ranging from 7.5% of cases in Belgium to 33.3% of cases in Canada and 34.8% of cases in Saudi Arabia.

The reasons for this geographic heterogeneity is likely due to combination of methodological factors and variability in characteristics of the underlying source populations. Most registry-based epidemiologic studies have historically relied on individual patient recruitment from pulmonary clinics, which can lead to selection bias of the referral base, underestimation of true disease burden, and may not be representative of the general ILD population. This type of recruitment is also more likely to exclude certain types of ILDs like sarcoidosis and CTD-ILD, which may be managed by internal medicine physicians or rheumatologists. The Danish cohort excluded sarcoidosis from its registry for this reason (10).

Changing definitions of ILD subtypes due to evolving society guidelines also pose methodological challenges in quantifying temporal trends and comparing changes in relative frequency of ILDs over time. This is particularly true for idiopathic interstitial pneumonias, specifically IPF, for which there have been multiple iterations of clinical practice guidelines over the last decade (30–32). Additionally, new guidelines describing the entity of interstitial pneumonia with autoimmune features (IPAF) have led newer registries to qualify IPAF as a distinct ILD subtype, while other have collated IPAF under the broader umbrella term idiopathic interstitial pneumonia or alternatively under CTD-ILD itself (18, 20, 21, 33). This may partially explain the geographic variability in frequency of CTD-ILD noted in the literature.

Variable methods for case adjudication and differences in diagnostic confidence thresholds likely also contributed to the geographic heterogeneity noted. Of the 17 studies reviewed, approximately half explicitly reported MDD as a requirement for case adjudication. The remainder, primarily multicenter national registries, relied on enrollment surveys completed by referring physicians. Although these surveys included details about patient demographics, pulmonary function tests, high resolution CT scans and pathology when available, the studies did not uniformly report whether MDD was required prior to a final ILD diagnosis. In addition, as there are no universally agreed upon thresholds for diagnostic confidence, some variability may be explained by the stringency of diagnostic criteria applied. For example, registries like the Canadian national registry, which applied more stringent criteria that required biopsy confirmation for a diagnosis of idiopathic NSIP, may have underestimated the prevalence of some ILDs and had a higher proportion of unclassifiable cases (7). On the other hand, very few cases in the Indian registries had pathology available (16). Biopsies are often used to differentiate HP from IPF. Using history and radiology alone in these registries may have led to higher prevalence of HP in those cohorts.

Despite these methodological limitations, some differences observed between registry-based studies, may represent true differences in the demographics and exposures of the source populations. For example, in the Parisian cohort, which specifically evaluated the epidemiology of ILD among Seine-Saint-Denis, a multi-ethnic county of Greater Paris, the calculated ancestry-standardized incidence and prevalence rates of sarcoidosis and CTD-ILDs were higher among patients of North African descent (13). In India, the high prevalence of HP was partially attributed to widespread use of evaporative air coolers, which are prone to mold growth (16). Cohorts with predominantly younger patients or a higher proportion of women noted higher rates of CTD-ILD and lower rates of IPF. In Turkey and Belgium, the sex-standardized frequency of ILD subtypes favored CTD-ILD among women and pneumoconiosis among men (8, 14). A more complete understanding of these risk factors and the role that genetic ancestry may play in ILD

risk can lead to important insight into predisposing factors that contribute to both ILD development and progression. Identification of ILD clusters can shed light on new exposures, their pathogenic mechanisms, and create an opportunity to intervene on modifiable occupation and environmental risk factors.

Mortality data examining the geographic variability in survival by ILD subtype is limited. Current literature suggests that IPF has the worst prognosis. Cohorts with a high proportion of patients with IPF may note higher overall ILD mortality rates associated with high healthcare utilization rates. IPF specific mortality rates may vary by geography. Whether this is due to underlying demographics of source populations or reflective of access to healthcare resources is unclear. Better understanding the reasons for geographic variability in ILD outcomes by subtype can expand our current clinical understanding of disease as well as identify care gaps for potential targeted intervention.

AREAS FOR IMPROVEMENT AND FUTURE DIRECTIONS

There are three areas where we feel additional work is needed to better understand the global burden of interstitial lung diseases. First, a standard ontology with diagnostic confidence thresholds is needed for comparative epidemiology studies of ILD (34). As demonstrated by this review, different authors choose different categorizations schema, employ variable diagnostic thresholds, and utilize different methodologies for establishing diagnosis. A unified set of diagnostic categories and criteria for this work would greatly help aggregate studies into informative reviews.

Second, more globally representative data should be published in English language journals or alternatively be translated into English and made available through open access. Most available epidemiologic studies in English have focused on evaluating disease burden in North America and Europe with only recent data from Asia. There are thus significant knowledge gaps regarding frequency of ILD subtypes in South America and Africa. Japan and South Korea, both major centers for ILD research, are also underrepresented in the English language literature.

Some knowledge gaps may also be due to healthcare infrastructure challenges in developing countries, particularly in South America and Africa, where access to tertiary care referral centers with dedicated chest radiologists and pulmonologists specializing in the diagnosis and management of ILD is limited. In addition, the paucity of data from many developing countries may reflect competing public health priorities, particularly of pulmonary diseases like tuberculosis, which disproportionately impact Asia, South America, and Africa. Multinational collaborative registries between ILD referral centers, like the recently established Latin American Idiopathic Pulmonary Fibrosis Registry (REFIPI), have the potential to consolidate resources and bridge this knowledge gap (35). Building on these types of registries to better understand the burden and relative frequencies of ILD in understudied countries would be informative, especially in light of increasing literature exploring the complex interplay between genetics, environment and ILD.

Third, the inclusion of larger and more community-based cohorts is needed. Extrapolating regional or national epidemiology from single-center, specialty-based cohorts is likely leading to significant mischaracterization of the true distribution of ILDs. The Bernalillo County, New Mexico registry was among the first to use International Classification of Disease (ICD) codes followed by chart review in an attempt to provide more representative and inclusive data, and this may in part explain the higher incidence and prevalence reported (5). The electronic health record (EHR) is a potentially powerful tool for epidemiologists to address the issue of inclusion and generalizability. To date, most EHR based studies in ILD have focused on describing the epidemiology of individual ILD entities, most commonly IPF (26, 36), rather than evaluating comparative frequencies. One study that explored the epidemiology of IPF in U.S. Medicare claims data reported an annual IPF incidence of 93.7 cases per 100,000 person-years and a cumulative prevalence of 494.5 cases per 100,000 people in 2011 (26). These estimates are much higher than incidence and prevalence estimates noted in the majority of registry-based studies. It is possible that the higher incidence and prevalence noted in EHR-based studies reflects overdiagnosis in the absence of multidisciplinary case validation. Alternatively, it is possible that registry-based studies, many of whom recruit from tertiary care referral centers, underestimate population burden of disease. Future work that can leverage claims data as a screening tool to identify possible ILD cases with additional case validation to verify the accuracy of claims-based algorithms may facilitate more accurate estimates of ILD epidemiology. EHR data could also create an opportunity to recruit patients into national registries by leveraging electronic alerts to encourage referral to subspecialty centers for patients who meet EHR screening criteria for ILD.

Improving the functionality of EHR data for research purposes will require a concerted effort by the broader ILD community. Historically, ICD codes have been the primary means of EHR disease identification. However, ICD codes were developed for billing purposes with less attention given to specificity of diagnosis. This has limited their effectiveness for use in research studies. A concerted effort to adopt standardized codes with an emphasis on diagnostic accuracy has the potential to drastically expand the efficiency and speed with which we are able to draw from large, demographically and clinically diverse population-based cohorts. The opportunity to link EHR data with mortality data as is already done the United States Veterans Affairs Healthcare System, can further accelerate our progress.

We believe the ILD research community should organize a global summit to define a shared ontology for disease classification, set diagnostic confidence thresholds, and commit to conducting global claims and EHR-based epidemiologic studies in a standardized fashion. These data could be published in a shared issue of the major specialty journals. Aggregating and sharing data would provide a unique opportunity for international collaboration as our understanding of ILD continues to grow and evolve. These large, community-based

longitudinal cohorts would also allow for tracking of global trends and be a valuable resource for collective study.

CONCLUSIONS

In conclusion, we have summarized the English language literature of the comparative epidemiology of ILD and demonstrated that there is significant geographic heterogeneity in the global disease burden and outcomes. These differences may represent true differences based on demographics and exposures of the source populations or methodological differences in patient recruitment (registry vs. population-based cohorts) and disease classification. Better understanding the geographic and temporal patterns of disease prevalence and identifying clusters of ILD subtypes can facilitate improved understanding of emerging risk factors and help identify targets for intervention. Future work, including a standardized ontology for classification, more globally inclusive studies, and leveraging EHR data with uniform coding practices to develop more generalizable, community-based cohorts, will help advance our understanding of this important group of diseases. We encourage the international ILD community to organize and address this unmet need.

AUTHOR CONTRIBUTIONS

BK, VC, HC, and CV contributed to conception and design of the review. BK wrote the first draft of the manuscript. VC, HC, and CV provided critical feedback. All authors contributed to manuscript revision, read, and approved the submitted version.

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Differences in Baseline Characteristics and Access to Treatment of Newly Diagnosed Patients With IPF in the EMPIRE Countries

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Idiopathic pulmonary fibrosis (IPF) is a rare lung disease with poor prognosis. The diagnosis and treatment possibilities are dependent on the health systems of countries. Hence, comparison among countries is difficult due to data heterogeneity. Our aim was to analyse patients with IPF in Central and Eastern Europe using the uniform data from the European Multipartner IPF registry (EMPIRE), which at the time of analysis involved 10 countries. Newly diagnosed IPF patients ($N = 2,492$, between March 6, 2012 and May 12, 2020) from Czech Republic ($N = 971$, 39.0%), Turkey ($N = 505$, 20.3%), Poland ($N = 285$, 11.4%), Hungary ($N = 216$, 8.7%), Slovakia ($N = 149$, 6.0%), Israel ($N = 120$, 4.8%), Serbia ($N = 95$, 3.8%), Croatia ($N = 87$, 3.5%), Austria ($N = 55$, 2.2%), and Bulgaria ($N = 9$, 0.4%) were included, and Macedonia, while a member of the registry, was excluded from this analysis due to low number of cases ($N = 5$) at this timepoint. Baseline characteristics, smoking habit, comorbidities, lung function values, CO diffusion capacity, high-resolution CT (HRCT) pattern, and treatment data were analysed. Patients were significantly older in Austria than in the Czech Republic, Turkey, Hungary, Slovakia, Israel, and Serbia. Ever smokers were most common in Croatia (84.1%) and least frequent in Serbia (39.2%) and Slovakia (42.6%). The baseline forced vital capacity (FVC) was >80% in 44.6% of the patients, between 50 and 80% in 49.3%, and <50% in 6.1%. Most IPF patients with FVC >80% were registered in Poland (63%), while the least in Israel (25%). A typical usual interstitial pneumonia (UIP) pattern was present in 67.6% of all patients, ranging from 43.5% (Austria) to 77.2% (Poland). The majority of patients received antifibrotic therapy (64.5%); 37.4% used pirfenidone (range 7.4–39.8% between countries); and 34.9% nintedanib (range 12.6–56.0% between countries) treatment.

In 6.8% of the cases, a therapy switch was initiated between the 2 antifibrotic agents. Significant differences in IPF patient characteristics and access to antifibrotic therapies exist in EMPIRE countries, which needs further investigation and strategies to improve and harmonize patient care and therapy availability in this region.

Keywords: IPF, treatment, regional accessibility, registry analysis, Central—Eastern Europe

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a rare, chronic, progressive, fibrotic lung disease associated with poor prognosis and high mortality (1–3). The median survival is between 2 and 5 years (1). Despite the largely undefined etiology, several exogenous environmental, and microbial factors seem to play key roles in the disease (4–7). The natural course of the disease is variable, and the factors that influence disease progression are unknown at an individual level (8).

The incidence of IPF has risen over time, it is between 3 and 9 cases per 1,00,000 per year (9). Regarding the systematic review of J. Hutchinson et al., there is a high variety in incidence and mortality rates depending on the geographic region (9). The overall prevalence of IPF is estimated at 30.2 cases per 1,00,000 (10).

Diagnosis and treatment possibilities of IPF are dependent on the health systems of countries as confirmed by several previous studies (11–13). Healthcare systems deal differently with diagnostic possibilities and availability. Considering treatment, expensive therapies are often introduced later as in wealthier countries and might be limited to a selected population of IPF (14, 15). Many off-label treatments are applied in rare diseases with potentially serious side effects (16).

Uniformity in diagnosis and treatment is crucial to patients dealing with persistent symptoms and uncertainty about the prognosis of their disease with a great impact on their quality of life (17). IPF has a considerable impact on the lives of the patients and the healthcare system (18). Medical professionals play an important role in the care of patients with IPF through patient education, monitoring medication compliance and safety, ensuring optimized medications for comorbidities, and preventive strategies. Patient education and counseling play key role in the shared decision-making model and are necessary for the management of this chronic disease (19).

Patient registries are organized systems that use observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and serve predetermined scientific, clinical, or policy purpose(s). Studies derived from well-designed and well-performed patient registries can provide a real-world view of clinical practice, patient outcomes, safety, and clinical comparative and cost-effectiveness analyses, and can serve as important tools for decision-making purposes (20–22). Comparison among countries is difficult due to data collection heterogeneity.

The aim of our study is to assess the baseline characteristics and treatment possibilities of patients with IPF in the same geographical—Central and Eastern Europe—region, by analysing the data of the European Multipartner IPF Registry (EMPIRE) countries (23).

PATIENT SELECTION AND METHODS

Study Design and Participants

The EMPIRE is a non-interventional, international, multicenter database of patients with IPF in Central and Eastern Europe (23). The objective of the registry is to evaluate the incidence, prevalence, and mortality of IPF in this area in Europe, and to determine the basic characteristics of patients with IPF. Another valuable outcome is the possibility of the comparison of different diagnostic and therapeutic differences among countries and assessment of the baseline characteristics of patients with IPF that participate in the EMPIRE using a uniform database platform.

Patients with IPF included in EMPIRE were diagnosed according to the American Thoracic Society/European Respiratory Society (ATS/ERS) consensus classification (1).

All participants were included in the analysis from the EMPIRE registry between March 6, 2012 and May 12, 2020. Overall, 2,492 newly diagnosed patients were involved from 10 countries: Czech Republic ($N = 971$, 39.0%), Turkey ($N = 505$, 20.3%), Poland ($N = 285$, 11.4%), Hungary ($N = 216$, 8.7%), Slovakia ($N = 149$, 6.0%), Israel ($N = 120$, 4.8%), Serbia ($N = 95$, 3.8%,) Croatia ($N = 87$, 3.5%), Austria ($N = 55$, 2.2%), and Bulgaria ($N = 9$, 0.4%). The detailed patient selection process is shown in **Figure 1**.

Baseline characteristics, high-resolution CT (HRCT) pattern, and treatment data were analysed. Patient baseline demographics, including Gender-Age-Physiology (GAP) score, smoking history, symptoms, detailed lung function values [forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), total lung capacity (TLC), diffusing capacity of the lung for carbon monoxide (DLCO)], diffusing capacity for carbon monoxide (KLCO) and HRCT pattern were analyzed. In addition, information regarding comorbidities was obtained using chart reviews and was included in the analyses. Body mass index (BMI) and the 6-min walk test (6MWT) results were examined. Additionally, the number of patients in the respective groups was provided according to country (**Table 1**).

The study was performed in accordance with the Declaration of Helsinki and ethical approval was obtained in each country according to respective regulations.

Statistical Analysis

The study aimed to evaluate the differences and/or similarities in clinical data and treatment in patients with IPF in Central

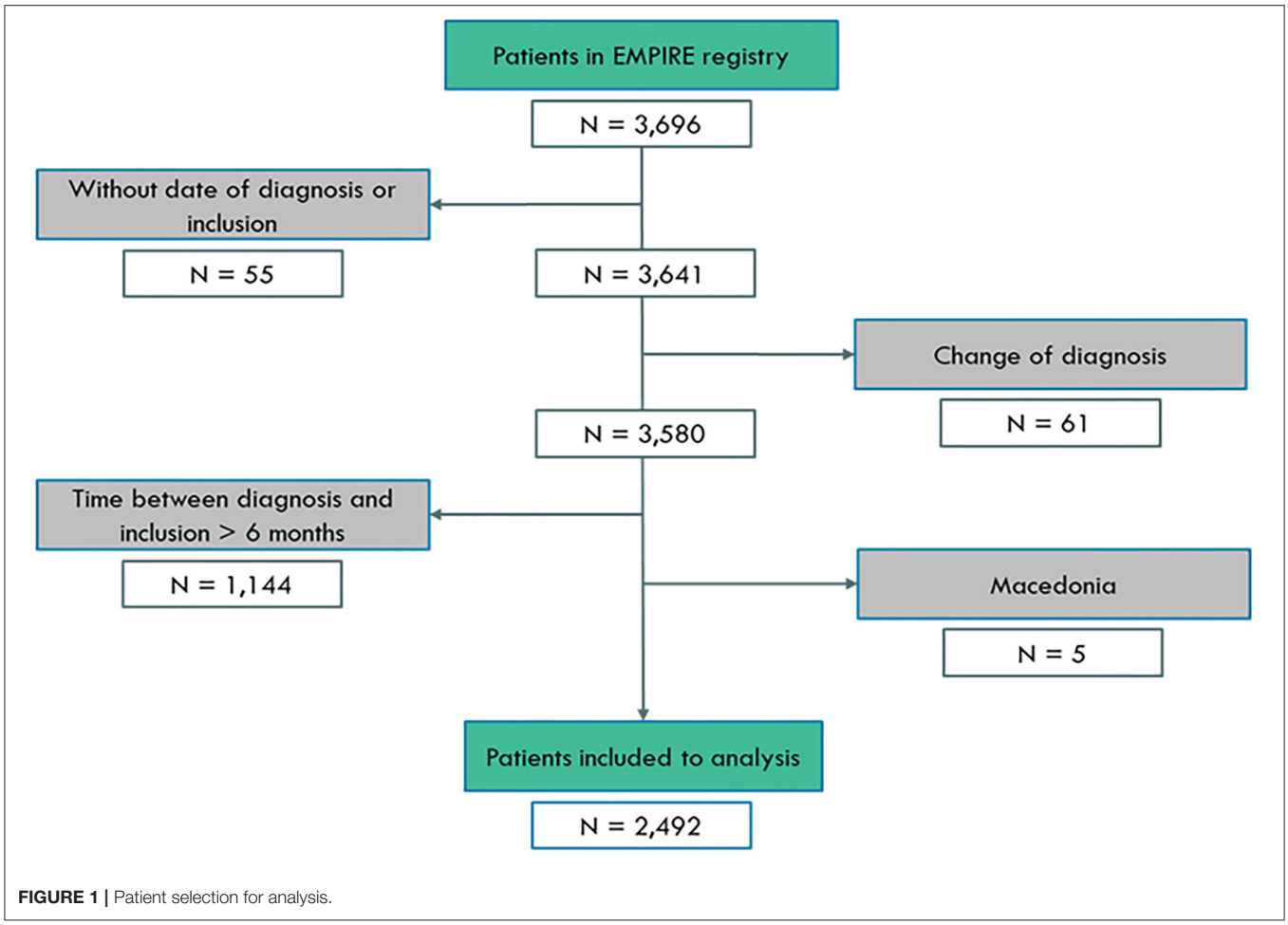

FIGURE 1 | Patient selection for analysis.

and Eastern Europe. A descriptive statistical analysis was performed and included absolute and relative frequencies for categorical variables and medians, with 5th−95th percentile ranges calculated for quantitative variables (in plots that were completed with interquartile range [IQR]). Significant differences among groups were analysed using the χ^2-test for categorical variables and Kruskal–Wallis tests for quantitative variables. If differences were statistically significant, *post-hoc* testing with a Bonferroni correction was used to identify homogeneous groups. The level of statistical significance was set at $p < 0.05$. Analyses were performed using SPSS v25 (IBM Corporation, Armonk, NY, USA) and Stata 14.2. (StataCorp., Lakeway Drive, TX, USA).

RESULTS

Patient Characteristics

Overall, 3,696 patients with IPF participated in the study. Information about the enrollment is shown in **Figure 1**. The final analysis included 2,492 patients. Exclusion of patients where the time of diagnosis and inclusion was over 6 months represented prevalent cases and not incident cases. To analyse the longitudinal outcome, newly diagnosed patients were included in the registry, defined by <6 months between inclusion and diagnosis. Participants with no date of inclusion in the study ($N = 55$) or with an inclusion time that had been more than 6 months compared with the time of diagnosis ($N = 1,144$) or who had a change in diagnosis ($N = 61$) were excluded from the analysis.

Information on EMPIRE member distribution is summarized in **Table 1**. Patients with the highest average age came from Austria; Austrian IPF patients were typically older than patients from most of the other countries. Patients from Serbia were the youngest and appeared to be significantly younger than participants from the Czech Republic, Poland, and Austria. Patients with IPF were more frequently men, and a significantly higher ratio of women was noted in Hungary as in the Czech Republic, Turkey, and Poland. The highest percentile contribution of men was noted in Bulgaria and Austria. In almost every country, more than 50% of patients had a smoking history. Across all countries, patients in Croatia had the highest ratio of patients with a history of smoking, whereas this number was the lowest in Serbia. BMI had the highest average value in Bulgaria, followed by the Czech Republic, and the lowest in Serbia. New York Heart Association (NYHA) class IV dyspnea was very rare among the patients; most frequently, NYHA class II dyspnea occurred, and it was most common among the Slovakian patients. Cough was present in more than two-thirds of the

TABLE 1 | Patient characteristics in individual countries.

	Total *N* = 2,492	**Czech Republic *N* = 971**	**Turkey *N* = 505**	**Poland *N* = 285**	**Hungary *N* = 216**	**Slovakia *N* = 149**	**Israel *N* = 120**	**Serbia *N* = 95**	**Croatia *N* = 87**	**Austria *N* = 55**	**Bulgaria *N* = 9**
Median age, years (range)											
All	2492/69 (54;82)	971/70 (54;82) T, S, R, A	505/68 (52;81) C, A	285/69 (57;84) S, R, A	216/70 (53;82) A	149/67 (48;79) C, P, A	120/67 (55;82) A	95/65 (48;79) C, P, A	87/70 (53;82) A	55/74 (63;87) C, T, P, HU, S, I, R, HR	9/69 (57;83)
Men	1786/69 (54;82)	719/70 (54;82)	383/68 (51;79)	206/69 (57;84)	125/69 (53;82)	97/68 (50;78)	83/69 (57;82)	57/67 (50;79)	64/71 (54;83)	45/74 (64;87)	7/71 (57;83)
Women	706/68 (54;82)	252/71 (54;82)	122/68 (54;83)	79/70 (57;84)	91/70 (54;82)	52/67 (40;81)	37/64 (50;78)	38/63 (44;81)	23/69 (51;76)	10/69 (62;81)	2/69 (68;69)
Sex, *N* (%)											
Men	1786 (71.7%)	719 (74.0%)	383 (75.8%)	206 (72.3%)	125 (57.9%)	97 (65.1%)	83 (69.2%)	57 (60.0%)	64 (73.6%)	45 (81.8%)	7 (77.8%)
Women	706 (28.3%)	252 (26.0%) HU	122 (24.2%) HU	79 (27.7%) HU	91 (42.1%) C, T, P	52 (34.9%)	37 (30.8%)	38 (40.0%)	23 (26.4%)	10 (18.2%)	2 (22.2%)
Smoking, *N* (%)											
Never-smoker	919 (37.1%)	395 (40.7%) T, P, R, HR	155 (30.7%) C, S, R	70 (24.6%) C, HU, S, R	90 (44.3%) P, HR	81 (55.1%) T, P, HR, A	50 (41.7%) HR	53 (56.4%) C, T, P, HR, A	12 (13.8%) C, HU, S, I, R	11 (20.0%) S, R	2 (22.2%)
Ever-smoker	1496 (60.4%)	562 (57.9%)	336 (66.5%)	206 (72.5%)	106 (52.2%)	62 (42.2%)	66 (55.0%)	36 (38.3%)	73 (83.9%)	42 (76.4%)	7 (77.8%)
Current smoker	60 (2.4%)	14 (1.4%)	14 (2.8%)	8 (2.8%)	7 (3.4%)	4 (2.7%)	4 (3.3%)	5 (5.3%)	2 (2.3%)	2 (3.6%)	0 (0.0%)
BMI, kg/m^2 (range)	2443/28.0 (21.7;36.0)	967/28.6 (22.2;36.1) T, R, A	496/27.7 (21.3;34.9) C, R	281/28.0 (22.8;35.9) R	187/27.6 (20.8;37.7)	146/28.1 (22.2;37.1) R	120/27.7 (20.7;36.8)	95/26.1 (21.0;32.0) C, T, P, S	87/27.4 (21.5;34.0)	55/26.4 (21.5;34.2) C	9/29.2 (23.5;35.8)
Dyspnea—NYHA											
I	113 (4.9%)	13 (1.4%) T, P, HU, I, R, HR, A	23 (4.7%) C, P, HU, S, I, R, HR, A	20 (8.3%) C, T, S	31 (16.1%) C, T, S	0 (0.0%) T, P, HU, R, HR, A, M	9 (7.6%) C, T	4 (4.8%) C, T, S	8 (9.9%) C, T, S	5 (11.1%) C, T, S	0 (0.0%)
II	1325 (57.1%)	582 (62.7%)	172 (35.5%)	159 (66.3%)	106 (54.9%)	96 (68.6%)	73 (61.9%)	49 (59.0%)	56 (69.1%)	28 (62.2%)	4 (44.4%)
III	848 (36.5%)	325 (35.0%)	285 (58.8%)	55 (22.9%)	53 (27.5%)	44 (31.4%)	33 (28.0%)	22 (26.5%)	15 (18.5%)	11 (24.4%)	5 (55.6%)
IV	36 (1.6%)	8 (0.9%)	5 (1.0%)	6 (2.5%)	3 (1.6%)	0 (0.0%)	3 (2.5%)	8 (9.6%)	2 (2.5%)	1 (2.2%)	0 (0.0%)
Cough, *N* (%)											
Yes	1,594 (68.0%)	664 (73.0%) S	335 (66.7%) S	180 (64.7%)	118 (65.6%)	69 (51.1%) C, T, R	77 (68.8%)	60 (75.9%) S	53 (60.9%)	31 (57.4%)	7 (87.5%)
Dry	966 (60.6%)	459 (69.1%) T, I, A, B	175 (52.2%) C, A, B	106 (58.9%) A, B	64 (54.2%) A, B	50 (72.5%) A, B	33 (42.9%) C, A, B	42 (70.0%) A, B	25 (47.2%) A, B	8 (25.8%) C, T, P, HU, S, I, R, HR	4 (57.1%) C, T, P, HU, S, I, R, HR
Productive	599 (37.6%)	195 (29.4%)	159 (47.5%)	73 (40.6%)	53 (44.9%)	19 (27.5%)	43 (55.8%)	18 (30.0%)	28 (52.8%)	11 (35.5%)	0 (0.0%)
Unknown	29 (1.8%)	10 (1.5%)	1 (0.3%)	1 (0.6%)	1 (0.8%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	12 (38.7%)	3 (42.9%)
Crackles, *N* (%)	2254 (90.7%)	947 (97.5%) T, P, HU, S, R, A	392 (77.6%) C, P, HU, I, HR	264 (93.0%) C, T	192 (91.0%) C, T	127 (85.2%) C	112 (93.3%) T	83 (87.4%) C	84 (96.6%) T	44 (80.0%) C	9 (100.0%)
Finger clubbing, *N* (%)	874 (35.2%)	423 (43.6%) T, P, S, A	135 (26.7%) C, I, HR	70 (24.6%) C, HU, I, HR	81 (38.6%) P, S, A	26 (17.4%) C, HU, I, HR, B	55 (45.8%) T, P, S, A	27 (28.4%) HR	47 (54.0%) T, P, S, R, A	4 (7.3%) C, HU, I, HR, B, M	6 (66.7%) S, A

(Continued)

TABLE 1 | Continued

	Total *N* = 2,492	Czech Republic *N* = 971	Turkey *N* = 505	Poland *N* = 285	Hungary *N* = 216	Slovakia *N* = 149	Israel *N* = 120	Serbia *N* = 95	Croatia *N* = 87	Austria *N* = 55	Bulgaria *N* = 9
GAP Score, *N* (%)											
I	897(45.0%)	331 (42.1%)	163 (43.8%)	130 (53.5%)	83 (55.3%)	76 (58.5%)	38 (35.8%)	25 (38.5%)	31 (39.7%)	17 (31.5%)	3 (37.5%)
II	904 (45.4%)	380 (48.3%)	164 (44.1%)	97 (39.9%)	57 (38.0%)	46 (35.4%)	56 (52.8%)	33 (50.8%)	42 (53.8%)	27 (50.0%)	2 (25.0%)
III	192 (9.6%)	76 (9.7%)	45 (12.1%)	16 (6.6%)	10 (6.7%)	8 (6.2%)	12 (11.3%)	7 (10.8%)	5 (6.4%)	10 (18.5%)	3 (37.5%)
HRCT pattern, *N* (%)											
UIP	1523 (67.5%)	647 (73.8%) T, HU, S, R, A	284 (62.1%) C, P, A	207 (77.2%) T, HU, S, R, A	119 (58.3%) C, P	76 (56.3%) C, P	75 (76.5%) R, A	42 (49.4%) C, P, I	48 (61.5%)	19 (43.2%) C, T, P, I	6 (66.7%)
Possible UIP	653 (29.0%)	218 (24.9%)	138 (30.2%)	60 (22.4%)	78 (38.2%)	53 (39.3%)	19 (19.4%)	32 (37.6%)	27 (34.6%)	25 (56.8%)	3 (33.3%)
Inconsistent with UIP	79 (3.5%)	12 (1.4%)	35 (7.7%)	1 (0.4%)	7 (3.4%)	6 (4.4%)	4 (4.1%)	11 (12.9%)	3 (3.8%)	0 (0.0%)	0 (0.0%)
Comorbidities											
0	211 (8.5%)	77 (7.9%) P, HU, S, I, R, M	29 (5.7%) P, HU, S, I, R, M	27 (9.5%) C, T, I, R, HR, M	32 (14.8%) C, T, I, HR, M	24 (16.1%) C, T, I, HR, M	0 (0.0%) C, T, P, HU, S, R, A, B, M	16 (16.8%) C, T, P, I, HR, M	2 (2.3%) P, HU, S, R, A, M	3 (5.5%) I, HR, M	1 (11.1%) I
1	449 (18.0%)	144 (14.8%)	73 (14.5%)	65 (22.8%)	55 (25.5%)	45 (30.2%)	5 (4.2%)	35 (36.8%)	8 (9.2%)	15 (27.3%)	4 (44.4%)
2	463 (18.6%)	179 (18.4%)	94 (18.6%)	63 (22.1%)	43 (19.9%)	27 (18.1%)	10 (8.3%)	25 (26.3%)	8 (9.2%)	13 (23.6%)	1 (11.1%)
>2	1369 (54.9%)	571 (58.8%)	309 (61.2%)	130 (45.6%)	86 (39.8%)	53 (35.6%)	105 (87.5%)	19 (20.0%)	69 (79.3%)	24 (43.6%)	3 (33.3%)

Data are N (%) or median (range); GAP, Gender-Age-Physiology.

cases; patients in Serbia and Bulgaria complained about it in most of the cases. Dry cough was more typical than productive cough in every country. Crackles were present in more than 90% of the cases with the highest ratio in the Czech Republic and Bulgaria.

GAP scores I and II had almost the same frequency among all countries and together they accounted for more than 90% of the cases. Slovakian patients had GAP score I most frequently, GAP score II was mostly observable in Croatia, while GAP score III was most common in Bulgaria and Austria.

HRCT lung imaging was described according to the ATS/ERS consensus classification in all patients (1). Usual interstitial pneumonia (UIP) pattern was present in approximately two-thirds of the patients with the highest prevalence in Poland. A possible UIP pattern was the most frequent in Austria, whereas a pattern inconsistent with UIP was most common in Serbia.

Analysis of Lung Function

Baseline lung function values are summarized in **Table 2**. FVC was between 50 and 80% in 49.3% and >80% in 49.3% of the patients. Most IPF-patients with FVC > 80% were registered in Poland, while the lowest number frequency was in Israel. Baseline FEV1% predicted was between 70% and 90% in 40.1% of the cases and >90% in 32.8% of the patients. Most cases with FEV1% > 90% were registered in Slovakia and Poland, while the lowest was in Israel. FEV1/FVC was between 70% and 80% in 22.3%, >80% in 70.6%, and <70% in 7.1% of the patients at the time of enrollment. Most patients with FEV1/FVC > 80% were registered in Slovakia and the highest number of patients with FEV1/FVC < 70% values came from Austria (20%). TLC% predicted had the highest average value in Poland and Slovakia, while the lowest average value in Israel. DLCO% and KLCO% predicted values were the highest in Hungary and the lowest in Serbia. Patients from Slovakia had the biggest average distance of 6MWT, whereas this value was the lowest in the Czech Republic.

In our study, the FVC% predicted values were tested in 91.8% of the total population. The highest ratio appeared in Croatia and Austria as patients in both countries underwent testing for FVC in 100% and the lowest ratio could be seen in Serbia (76.8%). FEV1% predicted was measured in all cases in Croatia (100%), whereas the lowest ratio of patients was in Hungary (76.4%). FEV1/FVC was calculated in most cases in Croatia and the least in Serbia. TLC% predicted evaluation had the highest percentage in Austria (100%), whereas, in Bulgaria, there was no evaluation of TLC% predicted. DLCO% predicted was entered into the registry with the highest patient participation in Austria (98.2%) and the lowest in Hungary (69.0%). KLCO% predicted testing ratios were the following: highest test proportion in Austria and no tested patient for KLCO% predicted in Bulgaria. 6MWT was performed

TABLE 2 | Lung function values and 6-min walk test in individual countries.

Valid *N*/median (5th;95th percentile)	Total *N* = 2,497	Czech Republic *N* = 971	Turkey *N* = 505	Poland *N* = 285	Hungary *N* = 216	Slovakia *N* = 149	Israel *N* = 120	Serbia *N* = 95	Croatia *N* = 87	Austria *N* = 55	Bulgaria *N* = 9
FVC (L)	2293/2.59 (1.36;4.10)	911/2.56 (1.45;3.91) T, P, I	454/2.37 (1.19;3.87) C, P, S, I, HR, A	271/2.92 (1.61;4.54) C, T, HU, I	189/2.35 (1.29;4.05) P, S, HR	131/2.83 (1.55;4.35) T, HU, I	114/1.96 (0.91;3.53) C, T, P, S, R, HR, A	73/2.70 (1.37;4.15) I	87/2.79 (1.53;4.33) T, HU, I	55/2.68 (1.68;4.43) T, I,	8/2.57 (1.43;3.66)
FVC (% predicted)	2267/77 (48;114)	910/76 (50;106) P, S, I, HR	450/74 (45;110) P, S, I, HR	271/87 (59;127) C, T, HU, I	168/76 (43;115) P, S, I	131/85 (52;121) C, T, HU, I	114/63 (34;104) C, T, P, HU, S, R, HR, A	73/81 (47;115) I	87/86 (52;123) C, T, I	55/84 (49;120) I	8/76 (42;115)
FEV1 (L)	2286/2.14 (1.16;3.31)	910/2.20 (1.27;3.27) T, HU, I	451/1.96 (1.03;3.08) C, P, S, I, R	270/2.32 (1.33;3.62) T, HU, I	186/1.97 (1.15;3.32) C, P, S, I	132/2.41 (1.38;3.68) T, HU, I	114/1.71 (0.82;2.90) C, T, P, HU, S, R, HR, A	73/2.34 (1.22;3.54) T, I	87/2.18 (1.28;3.23) I	55/2.26 (1.28;3.35) I	8/2.19 (1.04;2.92)
FEV1 (% predicted)	2258/81 (51;114)	909/81 (55;110) T, P, S, I	448/77 (48;110) C, P, S, I	268/89 (59;122) C, T, HU, I	165/79 (45;115) P, S, I	132/89 (57;124) C, T, HU, I	114/70 (39;103) C, T, P, HU, S, R, HR, A	73/84 (50;115) I	87/81 (55;113) I	54/85 (43;107) I	8/78 (46;110)
FEV1/FVC	2274/84 (68; 97)	900/86 (71; 98) T, P, HR, A	457/83 (70; 96) C, P, HR, AT	270/81 (65; 91) C, T, HU, S, I, R	184/84 (70; 95) P, HR, A	130/85 (68; 96) P, HR, A	114/86 (68; 97) P, HR, A	70/85 (69; 99) P, HR, A	87/78 (56; 94) C, T, HU, S, I, R	54/79 (52; 91) C, T, HU, S, I, R	8/81 (73; 91)
TLC (L)	1984/4.23 (2.21;6.60)	853/4.28 (2.62;6.51) T, S, I, A	280/3.85 (2.08;5.89) C, P, S, A	233/4.67 (0.00;6.98) T, HU, I	181/3.96 (2.11;6.32) P, S, A	124/4.68 (3.06;7.76) C, T, HU, I, R	105/3.77 (2.13;6.16) C, P, S, A	71/4.23 (0.00;6.50) S, A	82/4.19 (2.42;6.92)	55/4.77 (3.20;6.72) C, T, HU, I, R	0/0
TLC (% predicted)	1963/70 (41;100)	854/69 (46;97) T, P, S	279/64 (43;95) C, P, S, A	231/78 (0;109) C, T, HU, I	162/67 (38;100) P, S	124/78 (54;151) C, T, HU, I, R, HR	105/62 (44;92) P, S, A	71/67 (0;100) S	82/69 (45;98) S	55/76 (52;108) T, I	0/0
DLCO%	2126/46.8 (0.0;80.5)	895/46.4 (23.7;73.0) HU, R	384/46.1 (0.0;80.7) HU, R	250/47.9 (0.0;86.6) HU, R	149/59 (24;104) C, T, P, S, I, R, HR, A	130/51 (0;78) HU, R	107/45.4 (20.6;87.0) HU, R	70/30.2 (0.0;59.2) C, T, P, HU, S, I, HR, A	79/42.2 (9.2;72.3) HU, R	54/45.9 (0.0;72.9) HU, R	8/35.6 (19.4;69.7)
KLCO%	2041/75 (0;119)	850/76 (13;115) P, HU, I, R, HR	388/77 (0;123) P, R	220/65 (0;105) C, T, HU, S	153/86 (14;140) C, P, I, R, HR, A	131/76 (0;176) P, R	88/67 (0;104) C, HU	73/53 (0;188) C, T, HU, S	81/65 (15;103) C, HU	54/73 (0;111) HU	0/0
6MWT Distance (m)	1231/390 (168;560)	274/360 (160;530) P, S	373/375 (135;511) P, S	189/420 (235;600) C, T, S	129/400 (170;578) S	72/495 (355;590) C, T, P, HU, I, R, HR	72/403 (90;540) S	39/400 (140;545) S	66/401 (190;540) S	17/460 (196;635)	0/0

in most cases in Croatia, while no 6MWT was done in the case of Bulgarian patients.

Patient Comorbidities

Significant alterations were noted in comorbidities in the different countries. The leading comorbidities were cardiovascular diseases followed by gastrointestinal and pulmonary disorders. Overall, more than half of the patients had more than 2 comorbidities. In general, patients in Serbia had the lowest rate of comorbidities, whereas patients from Israel had a medical history with at least 2 co-occurring disorders. A detailed analysis of comorbidities is shown in **Figure 2**.

Antifibrotic Treatment

More than 50% of the patients received antifibrotic therapy. Pirfenidone and nintedanib use showed significant differences between countries. The use of pirfenidone was the most frequent in Turkey; a significantly higher proportion of Turkish patients received pirfenidone at the time of investigation as compared with the other countries participating in the study. The application of nintedanib was most frequent in Hungary:

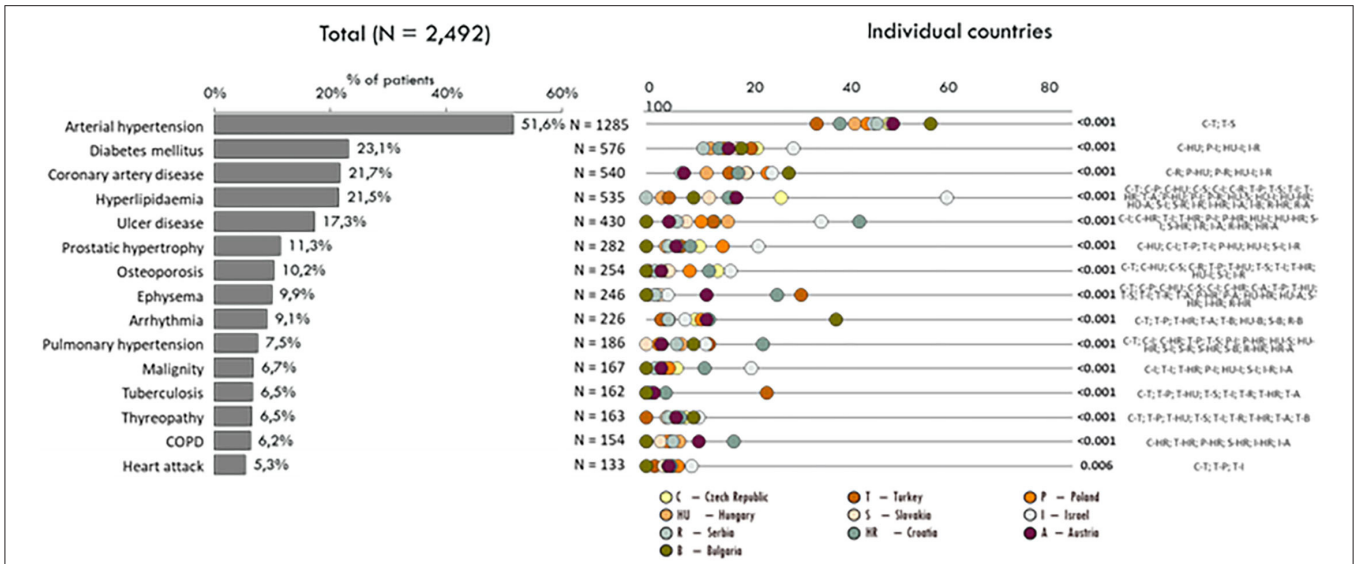

FIGURE 2 | Comorbidities according to the countries.

TABLE 3 | Antifibrotic treatment in individual countries.

	Total *N* = 2492	Czech Republic *N* = 971	Turkey *N* = 505	Poland *N* = 285	Hungary *N* = 216	Slovakia *N* = 149	Israel *N* = 120	Serbia *N* = 95	Croatia *N* = 87	Austria *N* = 55	Bulgaria *N* = 9
Pirfenidone	750 (30.1%)	364 (37.5%) T, P, HU, S, I, R, HR, A	201 (39.8%) C, P, HU, S, I, A	73 (25.6%) C, T, HU, S, I, A	22 (10.2%) C, T, P, S, R, HR	11 (7.4%) C, T, P, HU, I, R, HR	20 (16.7%) C, T, P, S, R, HR	27 (28.4%) C, HU, S, I, A	25 (28.7%) C, HU, S, I, A	6 (10.9%) C, T, P, R, HR	1 (11.1%)
Nintedanib	689 (27.6%)	246 (25.3%)	72 (14.3%)	58 (20.4%)	121 (56.0%)	74 (49.7%)	52 (43.3%)	19 (20.0%)	11 (12.6%)	34 (61.8%)	2 (22.2%)
Switch	169 (6.8%)	94 (9.7%)	22 (4.4%)	8 (2.8%)	15 (6.9%)	0 (0.0%)	18 (15.0%)	3 (3.2%)	6 (6.9%)	3 (5.5%)	0 (0.0%)
None	884 (35.5%)	267 (27.5%)	210 (41.6%)	146 (51.2%)	58 (26.9%)	64 (43.0%)	30 (25.0%)	46 (48.4%)	45 (51.7%)	12 (21.8%)	6 (66.7%)

Data are N (%) or median (range). Data are only expressed as absolute number of patients and corresponding proportion percentage.

more than half of the patients received it as antifibrotic treatment. The summary of antifibrotic treatment can be found in **Table 3**.

As the availability of different antifibrotics might be dependent on the healthcare provider regulation of the individual country, reimbursement, and country-specific regulations are described in **Table 4**.

DISCUSSION

Our data are the first to compare intercountry differences in patients with IPF using the common platform of EMPIRE enabling uniform data input and analysis. While real-world registries have limitations, our results confirm profound differences in baseline characteristics, lung function, HRCT pattern, and comorbidities in the patients with IPF from 10 Central and Eastern European countries.

Maximizing the potential of precision medicine for patients and healthcare services is a major social challenge. Disease registries have great potential to provide insight into real-world data and, consequently, provide information for planning healthcare services (24, 25). With their help, it is easier to collect data about complaints, symptoms, and quality of life of the patients, to investigate the effects and adverse effects of different treatments and to evaluate the disease development. However, registry data may suffer from bias and vary between countries as a result of incomplete registration, precluding measurement of true incidence and prevalence (26). Previously, the European Respiratory Journal emphasized the importance of registry data in IPF: prospective cohorts mean a solution to support patient care and research in complex chronic diseases (26).

Data collected from clinical trials are often misleading due to selection bias. Globally, there are significant differences in the incidence, prevalence, diagnostic approach, therapies, and survival for patients with IPF according to continents and countries. For example, the prevalence of IPF varies widely depending on location, identifying criteria, and year of study, ranging from 3 to 6 per 1,00,000 in the United Kingdom

TABLE 4 | Antifibrotic treatment availability in individual countries.

Country	Year of joining EMPIRE	Number of patients receiving antifibrotic treatment, *N* (% all patients in the given country)	Reimbursement specifics
Czech Republic	2015 (2012–2015 as National Czech Registry of IPF)	• nintedanib: 246 (25.3)	• 2015–2018 covered on individual request Reimbursed since 2018 in patients fulfilling predefined criteria covered by health insurance
		◦ pirfenidone: 364 (37.5)	◦ 2014–2017 covered on individual request Reimbursed since 2017 in patients fulfilling predefined criteria covered by health insurance
Turkey	2016	• nintedanib: 72 (14.3)	• September 23, 2017 Nintedanib received a refund. Free for those with FVC more than 50%, DLCO more than 30%, <10% FVC loss in 6 months
		◦ pirfenidone: 201 (39.8)	◦ October 11, 2016–267 mg capsules and 200 mg tablets received a refund 01 April 2020–600 mg tablets received a refund September 9, 2020–267 mg tablets and 801 mg tablets received a refund. Free for those with FVC more than 50%, DLCO more than 30%, <10% FVC loss in 6 months
Poland	2015	• nintedanib: 58 (20.4)	• 2018 Therapeutic program (fully reimbursed in patients with: FVC ≥ 50% DLCO ≥ 30%). Stopping rule: decrease of 10% in FVC in first year of treatment and then in 6 months assessed every 6 months
		◦ pirfenidone: 73 (25.6)	◦ 2017 Therapeutic program (fully reimbursed in patients with: FVC ≥ 50% DLCO ≥ 30%) Stopping rule: decrease of 10% in FVC in first year of treatment and then in 6 months assessed every 6 months
Hungary	2015	• nintedanib: 121 (56.0)	• 2015–2017: individual request coverage by national insurance Since 2017 according label fully covered by national insurance
		◦ pirfenidone: 22 (10.2)	◦ 2017: According label fully covered by national insurance
Slovakia	2015	• nintedanib: 74 (49.7)	• Available since 2015 based on individual reimbursement
		◦ pirfenidone: 11 (7.4)	◦ Available since 2015 based on individual reimbursement
Israel	2018	• nintedanib: 52 (43.3)	• 2014–2016: Compassionate use program 2016: Fully covered
		◦ pirfenidone: 20 (16.7)	◦ 2016: Fully covered
Serbia	2015	• nintedanib: 19 (20.0)	• 2017: According label, not covered by national insurance, but at the cost of referral institutions (4 University hospitals of Pulmonology) based on decisions of their Consilia for Fibrosis
		◦ pirfenidone: 27 (28.4)	◦ 2016: For all cases of IPF, not covered by national insurance, but at the cost of referral institutions (4 University hospitals of Pulmonology) based on decisions of their Consilia for Fibrosis
Croatia	2016	• nintedanib: 11 (12.6)	• 2017: Fully covered by National Health insurance fund for patients with FVC between 50% and 80% Stopping rule: decrease of FVC >10% at any time during 12 months Reassessment: every 12 months
		◦ pirfenidone: 25 (28.7)	◦ 2017: Fully covered by National Health insurance fund for patients with FVC between 50 and 80% Stopping rule: decrease of FVC >10% at any time during 12 months Reassessment: every 12 months
Austria	2018	• nintedanib: 34 (61.8)	• Available since 2015, the access for patients is based on individual reimbursement. Full reimbursement for IPF no restrictions—systemic sclerosis/progressive fibrosing ILD individual reimbursement
		◦ pirfenidone: 6 (10.9)	◦ Available since 2011, only individual reimbursement for IPF with FVC ≥ 50 and ≤ 80 and stopping rule (10% in 6 months)—new indications still under discussion
Bulgaria	2018	• nintedanib: 2 (22.2)	• Since April 2018 Reimbursed by National Health insurance fund for patients over 50 year old and with FVC between 50 and 80% and DLCO between 79 and 30%. Stopping rule for patients reached DLCO or FVC bellow lower limit Reassessment every 6 month
		◦ pirfenidone: 1 (11.1)	◦ Since April 2018 Reimbursed by National Health insurance fund for patients over 50 year old and with FVC between 50–80% and DLCO between 79 and 30%. Stopping rule for patients reached DLCO or FVC bellow lower limit Reassessment every 6 month

up to 16–18 per 1,00,000 in Finland (27, 28). Individual registries, generally, differ from each other, thus there might be differences regarding inclusion criteria, frequency, and outcome of IPF exacerbations, comorbidities, genetic factors and variance, efficacy and safety of pharmaceutical therapy, predictors of outcome, etc. With international registries, it is possible to create large datasets that enable clinicians and researchers to compare regions, countries, and time periods. According to McCormick et al., who made a comparative analysis of Cystic Fibrosis Registry data from the United Kingdom with other countries, the development of national cystic fibrosis databases has enabled a comparison between countries in key clinical outcomes. However, the authors highlighted the limitation of the study and urged a standardization of data collection between national cystic fibrosis registries to obtain a greater understanding from international and intercontinental comparisons (29).

In this study, we present clinical data from EMPIRE, the registry of patients with IPF from Central and Eastern Europe (23). We evaluated patient baseline characteristics, clinical symptoms, radiological features, spirometric values, and therapeutic solutions to emphasize similarities and differences between 10 countries. Despite living in the same geographical area, there were statistically significant differences regarding all the examined features and parameters. However, through this study, similarities and main differences could be highlighted and the shortcomings in terms of uniformity can be improved in the future. Currently, there are 2 IPF-registries in which Central and Eastern Europe is a partaker, namely EMPIRE and eurIPFreg. There are 12 other IPF-registries in Europe, however, they only include patients from one country (24).

The quality of healthcare system of a country can be estimated, for example, by the proportion of the structured clinical examinations performed (30). While not comparable, clinical data from well-structured IPF national registries might give some hints about diversities in different countries. The national IPF-registry of Spain, the SEPAR National Registry analysed the data from 608 patients between 2012 and 2017 (31). The electronic registry of IPF in the United Kingdom, the UK IPF Registry has counted 2,474 registered patients in the time period of 2013–2019 (32). To the INSIGHTS-IPF registry of Germany, 588 patients were entered between 2012 and 2018 (33). Between 2012 and 2016, 647 patients were registered to the Australian Idiopathic Pulmonary Fibrosis Registry (AIPFR) (8). For example, dyspnea was less frequent in the UK IPF registry, in comparison with the other 4 registries. In AIPFR, better baseline lung function was noted than in the other cohorts. GAP stage I was the rarest in EMPIRE compared with the other 4 registries, while UIP HRCT pattern appeared more often in our analysis. Our data show comparable lung function values for the most published registry data.

The organization of detailed evidence is considered to be a very strict measure as its purpose is also to create clinical practice guidelines (34, 35). Clinical practice guidelines are by their nature general recommendations aimed for broad applicability in the clinical setting. The applicability, however, is limited by numerous factors. The challenge of using guidelines on daily basis is that these guidelines are likely to be disease-oriented and not patient-oriented. Guideline recommendations are mainly based on the disease severity without taking coexistent conditions and other factors (e.g., factors that are used by physicians to individualize diagnosis and treatment), into consideration (36). High-quality meta-analyses and systematic reviews of randomized control trials (RCTs) or RCTs with a very low risk of bias stand in first place on the hierarchy of levels of evidence from published papers (34, 37). RCTs are created to maximize internal validity by studying a strictly defined population in a controlled setting, hence, establishing the efficacy of treatment (36, 38). Their results may have limited applicability to patients in clinical settings (39). These trials generally register a thoroughly selected patient population that meets strict inclusion criteria and exclusion criteria, including regular laboratory and clinical monitoring and measure objective parameters of efficacy. In "real world" clinical practice, however, the patients are unselected, monitoring is likely to be less frequent, and effectiveness is the most relevant outcome (36, 40). Pragmatic trials and observational studies can play an important role in addition to RCTs as they are created to recreate conditions in the daily clinical practice (40). Observational studies examine large groups of patients to evaluate long-term outcomes, examine very important consequences, such as mortality, and examine outcomes that may not be easily assessed by RCTs (e.g., pharmacoeconomic data). Recent analyses of data gained by RCTs and observational studies concluded that the effects of treatment revealed in observational studies were not greater or qualitatively different from those of RCT comparing the same treatments (41, 42). The reliance on RTCs as the highest level of evidence is thus challenged (43). Although observational studies should not replace RCTs, they can be useful in complementing the results of such trials. Well-designed observational studies can identify clinically important differences among therapeutic options and provide information on long-term drug effectiveness and safety (39). As a result of a review that compared the two methods used in good clinical practice concluded that the development of country-specific guidelines or local guidelines for each region would provide more suitable practical solutions. Besides, factors, such as social factors and expenses—that influence choice of the patients—and therapy adherence would be better considered (36).

Randomized control trials play the leading role and are inevitable when developing and testing new pharmaceutical substances. Over the last years—despite being a rare disease—numerous large, multicenter RCTs have been conducted culminating in the approval of 2 drugs for the treatment of IPF (44).

Our data confirmed, that in IPF, significant differences exist in drug availability according to countries, possibly resulting from high costs when introducing new treatments. As we summarized data for nintedanib and pirfenidone, there were no two countries with the same policy for providing these drugs to patients. As a result, regional differences in survival might be observed due to treatment differences arising from national regulations. Comparisons of the effectivity of antifibrotics might be further challenged,

as availability changes over time and over regions. For example, in Australia, antifibrotic treatment was available through clinical trials, special access programs, and private purchase by the time of inclusion in the published AIPFR document (8). Further studies are needed to evaluate the long-term outcome in patients treated with antifibrotics by stratifying cases according to already developed prognostic factors (45).

Healthcare specialists, patient organizations, and EU regulatory bodies should work to cease inequalities in patient care also highlighted in our data.

The limitation of our study is the disproportion in the number of patients from different countries, as it varied from 971 (Czech Republic) to 9 patients (Bulgaria) and 55 (Austria) mainly representing the time of being in the Registry. Differences in center size, the number of centers, time to enrollment and operator practice, and ethnic/cultural heterogeneity might all affect the outcome of the analysis.

CONCLUSIONS

Well-organized and unified registries for patients with IPF are indispensable to achieve better outcomes. In this study, we proved significant differences in the characteristics of patients with IPF and described differences in availability to antifibrotic therapies in EMPIRE countries that needs further investigation and strategies to improve patient care in this region. Equal participation rates and complete data registration in EMPIRE are fundamental to maximize precision. Unified methods and maximal accuracy are key elements to better understanding and more effective treatment of IPF. Inequalities resulting from differences in the availability of antifibrotics should be managed with international cooperation.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because need to file individual inquery to EMPIRE headquarters. Requests to access the datasets should be directed to empire@iba.muni.cz.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the EMPIRE registry protocol was approved in each country by the respective Ethical Committee. Written informed consent was obtained from all individual patients, who were enrolled in accordance with the Helsinki Declaration. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AK-F wrote the first draft of the manuscript. MŠte, NM, KL, VM, MH, MK, DJ, JT-T, MStu, NS, and MV contributed to conception and the design of the study. SL worked out the concept of statistical evaluation and performed statistical analysis. All authors contributed to the data collection, manuscript revision, read, and approved the submitted version.

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