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Epidemiology and risk factors for interstitial lung diseases

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Epidemiology and risk factors for interstitial lung diseases

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Editorial: Epidemiology and risk factors for interstitial lung diseases

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Editorial on the Research Topic
Epidemiology and risk factors for interstitial lung diseases

In this Research Topic, we delve into a series of insightful articles that shed light on various aspects of Interstitial Lung Disease (ILD). This series of manuscripts includes a thorough examination of global ILD prevalence, morbidity, mortality, and future trends. The authors investigate the influence of genetic and various environmental factors on ILD, and examine the utilization of biomarkers, ultrasound, and radiomics for identification and outcome prediction in ILD. The scope of work further extends to the treatment landscape and biases in survival analysis. Collectively, these studies significantly contribute to enhancing our understanding of the complex spectrum of ILDs.

Prior epidemiologic studies have assessed the global burden of ILD in a limited capacity (1). In this series, Zeng and Jiang utilize the 2019 Global Burden of Disease data and demonstrate that 2.28 million men and 2.43 million women had ILD in 2019 worldwide. The age-standardized prevalence, mortality rate, and disability-adjusted life years of ILD and pulmonary sarcoidosis slightly increased from 1990 to 2019, with higher rates in men compared to women. In contrast, rates for pneumoconiosis showed a decreasing trend. Projections for global ILD trends until 2030 indicate stabilization. The study emphasizes the importance of global and country-specific initiatives to address the persistent burden of ILDs and advocates for targeted measures, particularly in regions with high prevalence and mortality rates.

The interplay between genetic predisposition and environmental exposures plays a significant role in the development and progression of ILD (2). In this series, Stanel et al. study familial pulmonary fibrosis (FPF), emphasizing its distinct characteristics, which include earlier onset, rapid progression, and limited response and/or poorer outcomes with treatment with immunosuppression. FPF is associated with heritable variants in telomere-related and surfactant-related genes, telomere shortening, and early cellular senescence. The complexity of FPF is further heightened by the interplay of genetic factors and environmental exposures, particularly air pollution. Lan et al. systematically review the impact of air pollution on ILD. Their meta-analysis demonstrates a significant association between acute exacerbation of idiopathic pulmonary fibrosis (IPF) and particulate matter (PM) 2.5, whereas associations with ozone, nitrogen dioxide, and PM10 remained uncertain. Given the limited number of available studies examining the relationship

between air pollutants and ILD, there is a need for further research to comprehensively understand the intricate relationship between air pollution and ILD development and outcome. The study by Lee et al. observed a higher prevalence of firefighters in an ILD cohort compared to the general population suggesting an association between firefighting and ILD and emphasizing the need for systematic exposure assessments in patients with ILD. Shull et al. conducted a cross-analysis of telomere length and PM2.5 exposure in a cohort of patients with fibrotic ILD. Although no correlation with telomere length was found, this study offers insights for innovative methodologies in understanding the development and prognosis of pulmonary fibrosis.

Identifying high-risk individuals for ILD is crucial for early diagnosis and intervention and involves a combination of clinical assessments, biomarkers, and radiological tools. Li et al.'s cross-sectional study compared clinical features of systemic sclerosis (SSc) in a Chinese patient cohort with and without ILD, identifying significant factors associated with ILD in SSc. The study demonstrates the importance of recognizing specific clinical and laboratory markers for predicting ILD in SSc patients, providing valuable insights for early diagnosis and intervention. Wang et al. explored the role of serum biomarkers and lung ultrasound in connective tissue disease-related ILD (CTD-ILD). The researchers observed significantly elevated levels of B-cell activating factor levels and Krebs von den Lungen-6 levels in CTD patients compared to healthy controls, with even higher levels in those with fibrotic ILD. The study also revealed correlations between these biomarkers and severity of CTD-ILD assessed by lung ultrasound B-lines, and high resolution computed tomography chest. These findings highlight the potential utility of these markers in managing CTD-ILD. A proof-of-concept study by Venerito et al. hints at the transformative potential of radiomic analysis, beyond conventional clinical parameters to predict mortality in patients with rheumatoid arthritis-associated ILD. The study identified five radiomic features associated with mortality in RA-ILD patients, suggesting that radiomics may serve as a valuable digital biomarker for predicting outcomes and therapeutic response in ILD.

Over the past decade, antifibrotic drugs like pirfenidone and nintedanib have been approved to slow disease progression in fibrotic ILD (3). However, concerns about adverse events and skepticism about the efficacy of antifibrotics still exist in the medical community (4). The research study by Tomasetti et al. aims to provide insights into the real-world clinical experience of IPF by reporting data from a 15-year period. Analyzing a cohort of 634 IPF patients diagnosed between 2002 and 2016, the study found an overall median survival of 4.7 years, with a decline in mortality observed after 2012. The findings suggested that the year 2012 marked a turning point, coinciding with the introduction of antifibrotic treatment, the discontinuation of immunosuppressive drugs and advanced diagnostic techniques like transbronchial lung cryobiopsy associated with improved survival. The study also highlighted the positive impact of antifibrotic treatment on reducing the risk of acute exacerbations and hospitalizations. However, retrospective studies such as this are not without bias. Zheng et al. describe the importance of recognizing the impact of immortal time bias in observational studies examining associations between antifibrotic therapy and survival in patients with IPF. The results indicate that using time-fixed and exclusion methods tends to overestimate the effectiveness of antifibrotic therapy in reducing the risk of all-cause mortality, with the time-dependent method identified as the most optimal approach for minimizing this bias. The study emphasizes the importance of appropriate statistical methods in future IPF research to ensure accurate estimations of treatment effects and improve clinical decision-making.

ILDs lead to various symptoms such as shortness of breath, cough and fatigue, which significantly impact the quality of life of affected individuals (5). However, previous studies have not explored the impact of thoracic pain in ILD. The study by Scherer et al., noted that thoracic pain is a prevalent symptom in chronic ILD, especially in pulmonary sarcoidosis, and is associated with further respiratory limitations and worsened hypoxemia in advanced disease stages. The study also discusses the impact of thoracic pain on mental wellbeing, and the potential for early intervention to enhance patients' quality of life.

Many patients turn to internet resources for health information, particularly for rare diseases. Previous studies with IPF found that internet information on IPF is often incomplete and inaccurate (6). Buschulte et al. analyzed the reliability and content of information on sarcoidosis available on the internet, highlighting the need for comprehensive and accurate resources. The study stresses the importance of collaboration between healthcare professionals and patients to enhance the comprehensibility and reliability of information available to individuals' seeking resources on ILD.

As we navigate this multifaceted landscape of ILDs, the studies published in this research collection collectively contribute to a more comprehensive understanding, paving the way for improved diagnosis, management, and, ultimately, better outcomes for patients grappling with this challenging pulmonary condition.

Author contributions

NJ: Writing – original draft, Writing – review & editing. TC: Writing – review & editing. PS: Writing – review & editing.

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BRIEF RESEARCH REPORT
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Interstitial Lung Disease in Firefighters: An Emerging Occupational Hazard

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Introduction: Occupational risk factors for interstitial lung disease (ILD) are a remediable aspect of this progressive pulmonary disorder. The association between firefighting and ILD is unknown. Our objective was to assess the characteristics of firefighters with ILD from a large single-center ILD registry.

Methods: The University of Chicago ILD database was reviewed for patients with a history of firefighting. Clinical information was abstracted from the medical record. The prevalence rate ratio of firefighters in the database compared to the baseline prevalence of firefighting in the Chicago metropolitan area was calculated via the Poisson distribution.

Results: Nineteen firefighters were identified; all were men. A variety of ILD subtypes were seen across the cohort, including four patients with a diagnosis of connective tissue disease. Patients had mild forced vital capacity (FVC) and moderate diffusing capacity for carbon monoxide (DLCO) decrements on presentation; three patients died and two received lung transplantation over an average follow-up time of 76 months. Firefighters were seen at a greater proportion in the ILD registry than in the general population with a prevalence rate ratio of 3.98.

Conclusions: Firefighting was overrepresented in our cohort compared to the general population, suggesting that there may be a causative association between firefighting and the presence of ILD. The wide variety of ILD subtypes observed suggest that all ILD patients should be asked about their occupational history. Further investigation to identify occupational exposures and determine the benefit of remediation is needed.

Keywords: interstitial lung disease, occupational exposure, firefighting, interstitial lung disease risk, case series

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INTRODUCTION

Interstitial lung disease (ILD) is a highly morbid, progressive, and often fatal pulmonary disorder with multiple potential etiologies. These can include autoimmune disease, inhalational exposures, and medications, although some patients ultimately have no cause found (1, 2). As treatments for ILD often slow, but do not stop, disease progression, efforts targeted toward the more proximate cause of ILD could result in improved clinical outcomes (3, 4). Thus, identifying and

mitigating occupational inhalational exposures could represent a method of disease prevention and amelioration.

Firefighters' work exposure to toxic substances has resulted in an increased rate of chronic pulmonary and cardiovascular disease. Recently, first responders in the World Trade Center (WTC) attacks have been demonstrated to have a high rate of obstructive lung disease, autoimmune disease, sarcoidosis, and recent self-reports of pulmonary fibrosis, a devastating form of ILD (5–7). Little is known, however, about non-WTC firefighting and its association with subtypes of ILD formally diagnosed by a multidisciplinary team review and the possibility of concomitant autoimmune disease.

In this study, we reviewed a tertiary care center ILD database for subjects with an occupational history of firefighting. We hypothesized that firefighters would have a disproportionately high prevalence rate in our registry and that firefighters would exhibit a wide range of ILD subtypes, including those related to autoimmune disease. This would represent an important exposure association with ILD, with the potential to be a remediable cause of this often inexorably progressive disease.

METHODS

The University of Chicago ILD Natural History Database, a prospective registry approved by the University's Institutional Review Board (IRB #14163-A), was reviewed for patients with a history of firefighting. The electronic medical record of all patients enrolled in the registry from January 2007 to October 2019 was searched for a history of firefighting. Demographic and historical information, occupational histories, serologies, pulmonary function testing, and imaging reports were reviewed. Antinuclear antibody (ANA) was recorded as clinically significant if the titer was $\geq$1:320. Multidisciplinary ILD diagnosis (MDD) was conducted according to current American Thoracic Society/European Respiratory Society guidelines (8). Survival and lung transplantation status were ascertained and follow-up data was censored on November 1, 2019 or when a participant was lost to follow-up. Discrete variables are displayed as counts and percentages, while continuous variables are displayed as means with standard deviations.

Additionally, ascertainment of the number of employed firefighters in the Chicago-Naperville-Elgin, IL-IN-WI metropolitan area was obtained from the United States Bureau of Labor Statistics. The exact prevalence ratio was calculated comparing the prevalence of firefighting observed in ILD clinic versus the prevalence of firefighting in the general working population, and the probability of observing this prevalence ratio was calculated vs. the Poisson distribution of an observed variable compared to the expectation. Statistical analyses were conducted using Stata (9).

RESULTS

Nineteen firefighters were identified; all were men (**Table 1**). The mean age at time of presentation to clinic was 63 $\pm$ 11 years. Sixteen (84%) self-identified as white, while three (16%) self-identified as Black. Thirteen (68%) had a history of tobacco use with a median of 15 pack-years. Five (26%) reported a history of significant secondhand smoke exposure. None had a family history of ILD, while four (21%) had a family history of connective tissue disease (CTD). Comorbid conditions, including gastroesophageal reflux disease, were common.

Most had a history of longstanding firefighting. The median number of years working as a firefighter was 28, and five (26%) patients reported being hospitalized after exposure to a fire. Three (16%) patients were still firefighting at the time of clinical presentation. Co-exposures (not including tobacco) were common, with eight (42%) patients reporting an additional occupation that has been associated with ILD, six (36%) reporting a hobby that has been associated with ILD, and seven (37%) reporting other domestic mold or bird exposures.

A wide variety of ILD subtypes were observed among this cohort. Ten (53%) firefighters had idiopathic pulmonary fibrosis. Four (21%) patients with previously diagnosed CTD had CTD-ILD; two of those patients had a family history of CTD. Over half (53%) of patients had a positive autoantibody; one third of the cohort had an ANA titer greater than 1:320. Three were given a diagnosis of combined pulmonary fibrosis and emphysema (CPFE); all three of these patients had a history of smoking. One patient each had unclassifiable ILD and sarcoidosis. Five patients had surgical lung biopsy performed; of those, two (40%) had usual interstitial pneumonia (UIP) alone, two (40%) had UIP with organizing pneumonia, and one (20%) had hypersensitivity pneumonitis.

The mean forced vital capacity (FVC) at time of clinical presentation was 72% predicted, while the mean diffusing capacity for carbon monoxide (DLCO) was 51% predicted. Three patients died in follow-up, and two received lung transplantation. Restricted mean survival time for the entire cohort was 76 months.

According to the United States Bureau of Labor Statistics, the prevalence of firefighters employed in the Chicago-Naperville-Elgin metropolitan area in 2018 was 2.82 per 1,000 employed individuals (13,090 firefighters among 4,641,830 individuals). In our ILD cohort, the prevalence of firefighters was 11 per 1,000 (19 firefighters among 1,693 individuals); thus a prevalence rate ratio of 3.98 (95% CI: 2.40–6.22, $p < 0.0001$) was observed in firefighters in the ILD registry compared to firefighters within the working population of the Chicago area.

DISCUSSION

To our knowledge, this study is the first to describe ILD of various subtypes in firefighters not associated with the WTC attacks. Our analysis of a tertiary care center ILD cohort found a high rate of firefighters with a prevalence rate ratio approximately four times that of the general working population. These firefighters had a wide variety of ILD diagnoses, including CTD-ILD, IPF and CPFE. Other inhalational co-exposures were also common, suggesting that multiple exposures could have a synergetic effect

TABLE 1 | Cohort characteristics.

Demographics		Exposure		Disease	
Age, mean ± SD	63 (11)	Ever Smoker, *n* (%)	13 (68%)	Autoantibodies, *n* (%)	10 (53%)
Male, *n* (%)	19 (100%)	Pack years, median (IQR)	15 (0–40)	ANA>1:320	6 (32%)
Race, *n* (%)		Secondhand smoke, *n* (%)	5 (26%)	SSA	2 (11%)
White	16 (84%)	Volunteer firefighter, *n* (%)	3 (16%)	Other	5 (26%)
Black	3 (16%)	Years worked, median (IQR)	28 (20–39)	ILD diagnosis, *n* (%)	
Asian	0 (0%)	Hospitalized after fire, *n* (%)	5 (26%)	IPF	10 (53%)
Family history of ILD, *n* (%)	0 (0%)	Still firefighting, *n* (%)	3 (16%)	CTD-ILD	4 (21%)
Family history of CTD, *n* (%)	4 (21%)	Other work exposures, *n* (%)	8 (42%)	CPFE	3 (17%)
CTD diagnosis, *n* (%)		Construction	4 (21%)	Unclassifiable	1 (5%)
MCTD	1 (5%)	Metal Work	2 (11%)	Sarcoidosis	1 (5%)
Autoimmune myositis	2 (11%)	Other	3 (16%)	Pathology, *n* (%)	
ANCA vasculitis	1 (5%)	Hobby exposures, *n* (%)	6 (32%)	UIP	2 (11%)
Comorbidities, *n* (%)		Bird or mold exposures, *n* (%)	7 (37%)	HP	1 (5%)
CAD	10 (53%)			UIP+OP	2 (11%)
COPD	4 (21%)			FVC %pred	72 (18)
Diabetes Mellitus	2 (11%)			DLCO	51 (16)
GERD	14 (74%)			Death	3 (16%)
				Lung Transplantation	2 (11%)

ILD, interstitial lung disease; CTD, connective tissue disease; MCTD, mixed connective tissue disease; ANCA, Antineutrophil Cytoplasmic Antibodies; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; ANA, antinuclear antibodies; SSA, Sjogren's syndrome related antigen A autoantibodies; IPF, idiopathic pulmonary fibrosis; CPFE, combined pulmonary fibrosis and emphysema; UIP, usual interstitial pneumonia; HP, hypersensitivity pneumonitis; OP, organizing pneumonia; FVC, forced vital capacity; DLCO, diffusing capacity for carbon monoxide.

on the development of ILD and highlighting the interconnected nature of these exposures in the real-world clinical setting.

This study found a disproportionately high rate of firefighters in our ILD patient population compared to the working population of the local metropolitan area. As these patients had all worked as firefighters for years prior to their ILD diagnosis, this finding suggests a potential causal mechanism between firefighting and ILD. Pulmonary fibrosis in WTC first responders has been described, with an increasing incidence related to increasing levels of exposure following the attacks (6). Systematically derived occupational exposure histories are needed in this patient population in order to assess for both a dose-response relationship as well as high-risk activities leading to ILD in firefighters.

We also found a wide variety of ILD subtypes in our firefighting cohort. Li and colleagues' description of pulmonary fibrosis in WTC first responders utilized patient self-report as a case definition, thus no determination of ILD subtype was able to be made (6). Sarcoidosis has been described in both WTC and non-WTC firefighters; however, this subgroup represented a small minority of ILD patients in our firefighting cohort (5, 10). This clinical diversity emphasizes the importance of asking about potentially remediable occupational inhalational exposures, such as firefighting, in all ILD patients regardless of clinical history or multidisciplinary diagnosis.

Inhalational co-exposures were common in firefighters with ILD. Many of these exposures overlapped in the same patients. While frequent co-exposures make assessment of any particular causal exposure especially challenging, they also emphasize the importance of a thorough, systematic exposure assessment on all ILD patients in order to elicit potential opportunities for remediation. Additionally, further work could assess whether multiple exposures increase the risk of severe ILD or other poor clinical outcomes in an additive or multiplicative fashion.

A substantial proportion of patients carried formal diagnoses of CTD in relation to their ILD or had positive serologic testing. In prior investigations of specific CTDs, the relation between tobacco and rheumatoid arthritis (RA) is the most consistent association described (11). The correlation between occupational exposure to mine dust, in particular silica, and autoimmune disorders, particularly systemic sclerosis, is well-described (12). More recently, a high prevalence of systemic autoimmune disease has been described in WTC first responders (7). Our understanding of the role of inhalational exposures in causing autoimmunity and ILD is limited, and precisely which substances are highest risk for causing disease in firefighters remains an area of active investigation.

This study has several limitations. First, the small number of patients and retrospective design make causal inferences difficult to elicit. We were unable to assess for specific job descriptions and exposure intensity for every patient. As this was an analysis of an already existing ILD cohort, we did not have a control population of patients without ILD or healthy firefighters with which to compare clinical features or risk factors. Nevertheless, our comparison with publicly available occupational data suggests the proportion of firefighters in our clinic was higher than that of the working population, and similar methods have been used in the past to suggest a potential causal mechanism between occupational exposures and lung disease (13). Although comparison of firefighting prevalence to the prevalence in the

overall working population is imprecise given not every ILD patient seen in clinic is actively working, including the non-working population in the calculation of non-ILD firefighting prevalence would actually increase the prevalence rate ratio of firefighting seen in our ILD patients.

In summary, we found a higher proportion of firefighters in our ILD registry than was present in the working population, suggesting firefighting may be a novel risk factor for ILD. These patients had a wide variety of clinical presentations, ILD subtypes and autoimmune features. Further work should systematically assess for a dose-response relationship as well as high-risk occupational features in order to strengthen causal associations and identify potentially remediable exposure-related causes of ILD.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions:Protected Health Information. Requests to access these datasets should be directed to cathryn.lee@uchospitals.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Chicago Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by CL, AA, and MS. The first draft of the manuscript was written by CL and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
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Harnessing PM2.5 Exposure Data to Predict Progression of Fibrotic Interstitial Lung Diseases Based on Telomere Length

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Cross-analysis of clinical and pollution factors could help calculate the risk of fibrotic interstitial lung disease (ILD) development and progression. The intent of this study is to build a body of knowledge around early detection and diagnosis of lung disease, harnessing new data sets generated for other purposes. We cross-referenced exposure levels to particulate matter 2.5 (PM2.5) with telomere length of a cohort of 280 patients with fibrotic ILD to weigh impact and associations. There was no linear correlation between PM2.5 and telomere length in our data sets, as the value of the correlation coefficient was 0.08. This exploratory study offers additional insights into methodologies for investigating the development and prognosis of pulmonary fibrosis.

Keywords: pulmonary fibrosis, pollution, telomeres, big data, impact PM2.5

INTRODUCTION

Several characteristics have been associated with an increased risk of fibrotic interstitial lung disease (ILD) development, such as smoking, viral infections, existence of familial aggregation, and telomere dysfunction (1–4). Across all fibrotic ILDs, patients with shortened telomeres have a more accelerated disease progression. Research has also shown that air pollution has a direct effect on lung disease (5). Particulate matter with an aerodynamic diameter of $\leq 2.5\,\mu m$ (PM2.5) is the smallest particulate matter for which we have long-term exposure estimates in Catalonia, and because of its size, it is one of the pollutants that can most easily reach the deepest tissue and alveoli of the lungs. One systematic review of more than 12,000 subjects across 25 studies found associations between air pollution and telomere shortening (6), and PM2.5 has been suggested as a possible cause of COPD in studies as early as 2014 (7). In addition, it has been shown that exposure to PM2.5 resulted in shortened telomeres and altered telomerase activity in human bronchial epithelial cells (8).

Given this background, this study cross-analyzed telomere length and exposure to PM2.5 to determine associations between these known risk factors in our cohort of patients with fibrotic ILD.

METHODS

In this retrospective study, we analyzed a cohort of 280 patients with fibrotic ILD in the northeast region of Spain who were evaluated for telomere length (TL) in our center because of the indication of the potential risk of telomere shortening from 2014 to 2020. The Ethics Committee of Hospital Universitari de Bellvitge (HUB) approved the study, and all the patients provided written informed consent before inclusion. The relative telomere length was assessed at the time of diagnosis by quantitative polymerase chain reaction (qPCR), as previously described (9). Since telomere length changes with age, a Z-score value was obtained to allow for comparisons of telomere length among individuals of different ages and among cohorts (10). The Z-score compares the telomere shortening ratio value in each individual with the age-matched mean and standard deviation (SD) of the values obtained in the controls. A Z-score below the 10th percentile of a normal distribution was considered as severe telomere shortening. In the statistical analysis, a description of the baseline and clinical characteristics of the patients was made according to their distribution. A linear model was estimated using forced vital capacity (FVC) at 3 years as the dependent variable and using baseline forced vital capacity, exposure to PM2.5, industrial exposure, age, and sex as variables of interest.

Disease progression was considered when a patient presented at least two of the following criteria in the absence of any other explanation or cause: (a) worsening of respiratory symptoms,

Abbreviations: AQG, Air Quality Guidelines; COPD, chronic obstructive pulmonary disease; CTD-ILD, connective tissue disease- interstitial lung disease; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; IPAF, interstitial pneumonia with autoimmune features; IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonia; PM 2.5, particulate matter with an aerodynamic diameter of $\leq 2.5\,\mu m$; qPCR, quantitative polymerase chain reaction; uILD, unclassifiable interstitial lung disease; WHO, World Health Organization.

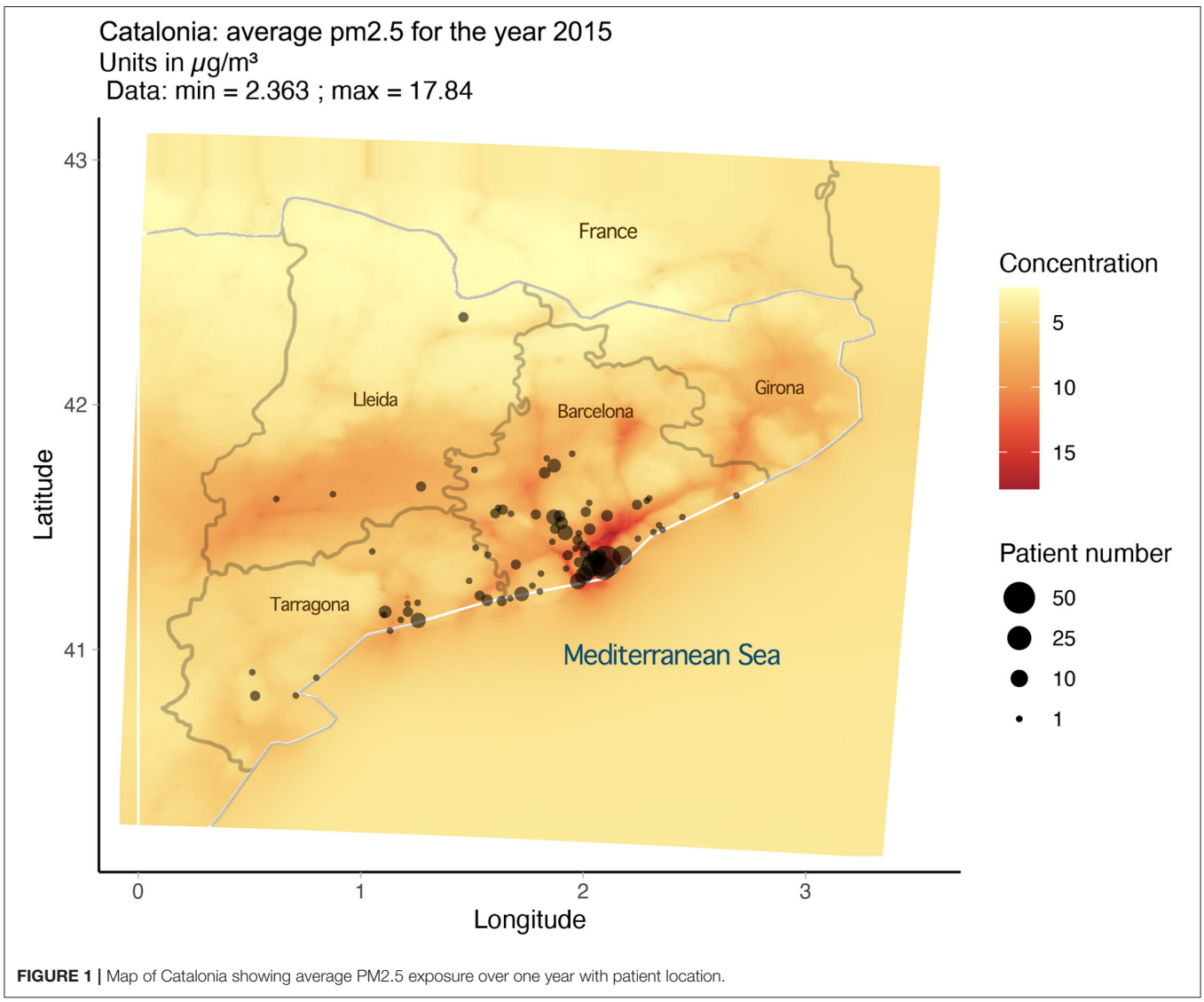

FIGURE 1 | Map of Catalonia showing average PM2.5 exposure over one year with patient location.

(b) physiological progression [absolute decline in the FVC of ≥10% or DLCO (corrected for Hb) of ≥15%], and (c) death. FVC value, over time, was used to analyze potential correlations.

The population analyzed for disease progression was generally older (average age 64.8) and of Spanish nationality. We used their current postal code as the location variable, because the tendency in this population to change residence is very low. Survey data from the province of Barcelona in 2006 show that the age at which people change residence is primarily between 25 and 40 years old; after the age of 60, the likelihood and desire to move is 2–6% (11). According to this survey, 75% of people over 60 in Catalonia believe that where they currently live is the best place to live and that number increases to 81% after the age of 75. Refer **Supplementary Data 2** for further information.

PM2.5 exposure and variables were derived from data from the CALIOPE modeling system (12–15), which has been positively evaluated for epidemiological research (12). As noted in our previous publication (16), the average exposure for PM2.5 for any year in any 1-km area remained consistent from 2001 to 2017. Based on this, the estimates of PM2.5 exposure for 2015 were utilized and extrapolated to serve as an estimate for long-term exposure (2001–2017). Approximate locations for the 280 patients were based on postal code and then plotted using R (version 3.6.0) and the Google Map API and superimposed over the exposure map (**Figure 1**). From this mapping exercise, we can assign an approximate level of long-term exposure to PM2.5 for each subject in the cohort. With the data gathered, we ran a statistical analysis on PM2.5 exposure and Z-score for the cohort.

A complete table of the average PM2.5 exposure and Z-score for each patient can be seen in **Supplementary Data 1**.

RESULTS

The diagnosis for the 280 fibrotic ILD cases was primarily IPF, with 138 cases or 49.2% of the total participants; the next largest number of cases was fibrotic forms of hypersensitivity pneumonitis (HP) with 32 cases or 11.4%. Unclassifiable ILDs (uILD) and the related interstitial pneumonia with autoimmune features (IPAF) formed the third largest group at 26 cases or 9.2% of the participants, followed by diagnoses such as CTD-ILD (24 or 8.5%), non-specific interstitial pneumonia (NSIP) (18 or 6.4 %), smoking-related interstitial fibrosis (SRIF) (11 or 3.9%), fibrosis with organizing pneumonia (6 or 2.1%), and sarcoidosis IV (4 or 1.4%). The remaining cases were other fibrotic ILDs.

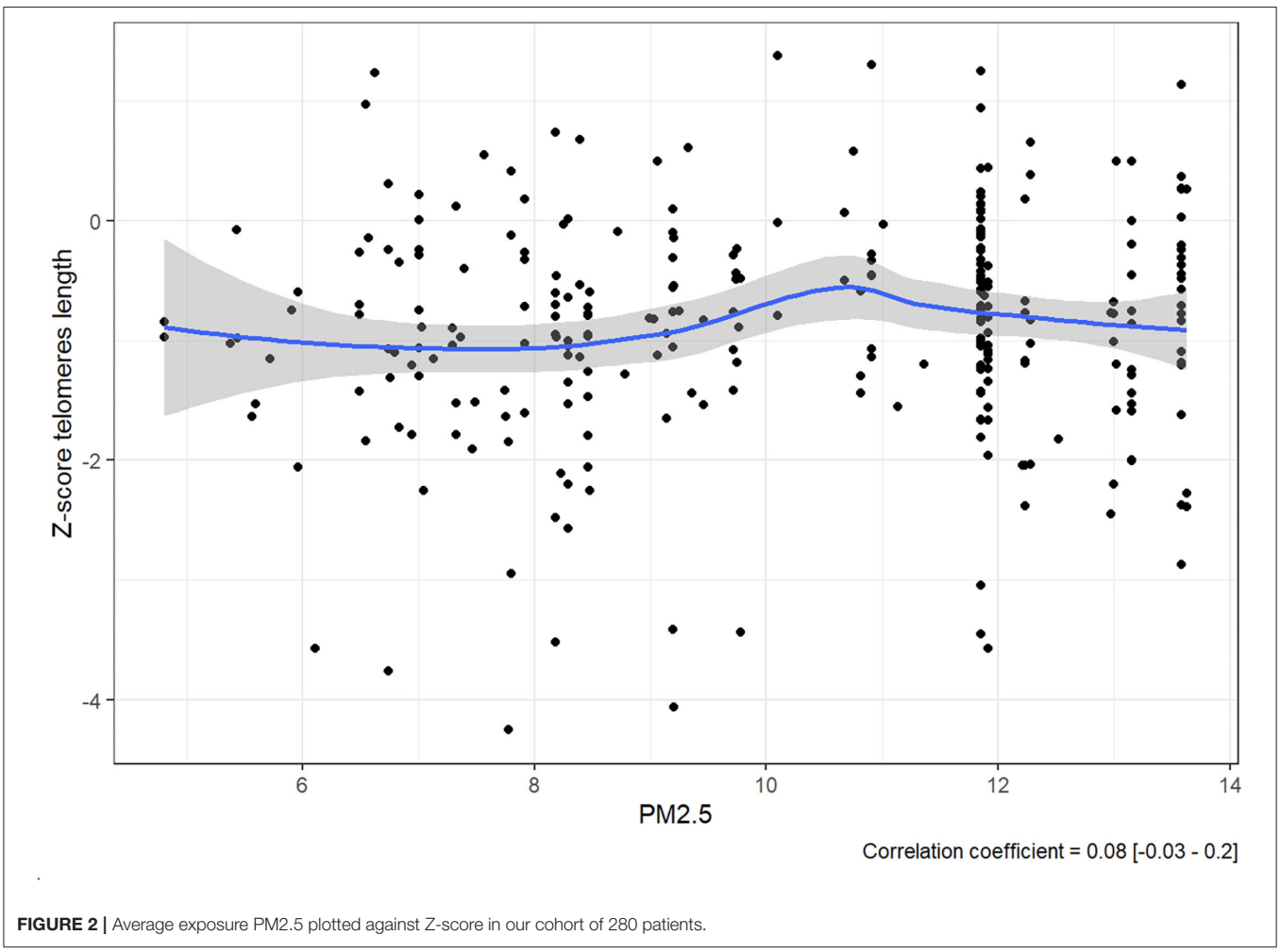

FIGURE 2 | Average exposure PM2.5 plotted against Z-score in our cohort of 280 patients.

TABLE 1 | The covariable "Z-score" is significant in the "Multivariate 1" model.

	Univariate				Multivariate 1			
Predictors	**Estimates**	**std. Error**	**CI**	***p***	**Estimates**	**std. Error**	**CI**	***P***
(Intercept)	87.11	11.13	64.83–109.38	<0.001	8.09	9.26	−10.45–26.63	0.386
Z-score	2.54	5.74	−8.95–14.02	0.660	6.92	3.21	0.49–13.34	0.035
Baseline FVC					1.02	0.09	0.84–1.20	<0.001
Observations	60			60				
R^2/R^2 adjusted	0.003/−0.014			0.698/0.688				
AIC	572.819			503.132				

For every one unit decrease in the Z-score, the forced vital capacity at 3 years (FVC-3y) decreases by about 7 points.

Twenty-nine of the 280 referred family aggregation and 84 presented severe telomere shortening (20 of them had some pathogenic telomere-related gene mutation in RTEL1, TERT, TERC, or DKC1).

The expectation was to see evidence that consistent exposure to higher levels of PM2.5 was correlated to lower Z-score. However, rather than a steady decline in Z-score as PM2.5 increases, there is no linear correlation between them since the value of the correlation coefficient was 0.08 [−0.03, 0.2] (**Figure 2**).

There is, however, an accumulation of cases at the 12 μg/m3 line, and it should be noted that all the 280 members of the cohort were exposed consistently to PM2.5 at levels between 5.565 and 13.631 μg/m3.

DISCUSSION

In 2021, the WHO published updated Air Quality Guidelines (AQG) for PM2.5 as well as other hazardous airborne pollutants. The guidelines, based on data for cause-specific mortality, lead to a recommendation of long-term exposure to PM2.5 at levels of no more than 5 μg/m3 (17). This update means that every subject in the cohort was exposed to levels of PM2.5 above the WHO recommended level.

This observational study is not intended to be conclusive, and further research should be conducted with more specific individual measurements of exposure to PM2.5 and other airborne pollutants; however, we utilized the best data available.

In a more elucidative step, we then analyzed the progression of disease in the 84 patients with severe telomere shortening. Eighty cases had the necessary data available (4 did not complete the 2nd FVC measurement) and were documented with a Z-score in the 10th and 1st percentiles. We then compared their forced vital capacity (FVC) results at baseline and after 3 years. These factors were modeled using a multivariate linear model (**Table 1**). The result of the estimated model of FVC after 3 years using PM2.5 as a predictor was non-significant; however, Z-score was indicative of progression. For every one unit decrease in Z-score, the FVC measure at 3 years after baseline decreased by approximately 7 points. Twenty-eight of the 80 analyzed were smokers, although this did not correlate to telomere shortening. We also compared the diagnosis of the 80 cases, and the numbers were similar to the larger group: of the 80 cases, 40 (50%) were IPF. In this retrospective study, it was not possible to determine at what point in each subject's life environmental pollutants might have begun to affect lung tissue.

A thorough retrospective analysis with multiple risk factors weighted for impact could provide further insight into disease progression in patients with fibrosing ILDs. The long-term objective is to gain further insights into disease development and early diagnosis of ILDs by harnessing big data and analyzing risk factors with additional innovative methodologies.

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/s.

ETHICS STATEMENT

The Ethics Committee of Hospital Universitari de Bellvitge (HUB) approved the study and all patients provided written informed consent before inclusion.

AUTHOR CONTRIBUTIONS

JS was the senior author. MM-M was the authority in review and has last authorship. LP-C and RP contributed equally. CL contributed the essential mapping imagery. All the authors contributed valuable contents to this 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.2022.871898/full#supplementary-material

Supplementary Table 1 | Cohort of 280 subjects with age, gender, telomere length, and individual exposure level to PM2.5 in microns.

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Comparing clinical characteristics of systemic sclerosis with or without interstitial lung disease: A cross-sectional study from a single center of the Chinese Rheumatism Data Center

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Background: We aimed to compare the clinical characteristics of patients with systemic sclerosis (SSc) with or without interstitial lung disease (ILD) to identify relationships with the presence of ILD in SSc at a single center in China.

Methods: A cross-sectional study was conducted using retrospective data from the Chinese Rheumatology Data Center. Patients diagnosed with SSc at the Second Affiliated Hospital of Nanchang University between 2013 and 2022 were included. Demographic and clinical characteristics were compared between patients with SSc with and without ILD. Logistic regression analyses were performed to explore these associations.

Results: A total of 227 patients with SSc were included (male:female ratio = 1:4.82), of which 121 (53.3%) were accompanied with ILD. SSc patients with ILD had a higher percentage of diffuse cutaneous systemic sclerosis (dcSSc), sclerodactyly, loss of finger pad, muscle involvement, left ventricular diastolic dysfunction (LVDD), and pulmonary hypertension (PAH), elevated Krebs von den Lungen-6 (KL-6), and elevated ferritin than those without ILD, and a higher modified Rodnan skin score (mRSS), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) (all $P < 0.05$). Antinuclear antibody (ANA) and anti-scleroderma-70 (anti-Scl-70) positivity was presented frequently in SSc patients with ILD, while SSc patients without ILD were more often anti-centromere antibody (ACA) positive (all $P < 0.05$). On the multivariable analysis, muscle involvement [OR 2.551 (95% CI 1.054–6.175), $P = 0.038$], LVDD [OR 2.360 (95% CI 1.277–4.361), $P = 0.006$], PAH [OR 9.134 (95% CI 2.335–35.730), $P = 0.001$], dcSSc [OR 2.859 (95% CI 1.489–5.487), $P = 0.002$], PLR [OR 1.005 (95% CI 1.001–1.008), $P = 0.020$], elevated

KL-6 [OR 2.033 (95% CI 1.099–3.763), $P = 0.024$], and anti-Scl-70 [OR 3.101 (95% CI 1.647–5.840), $P < 0.001$] were statistically significant associations with SSc patients with ILD.

Conclusion: Systemic sclerosis was found mainly in females. Several important differences in clinical and laboratory characteristics have been demonstrated between SSc patients with or without ILD. Muscle involvement, LVDD, PAH, dcSSc, PLR, elevated KL-6, and Anti-Scl-70 antibody may be associated with SSc in patients with ILD.

KEYWORDS

systemic sclerosis, clinical characteristic, interstitial lung disease (ILD), China, cross-sectional study

Introduction

Systemic sclerosis (SSc), also called scleroderma, is a chronic connective tissue disease characterized by localized or diffuse skin thickening and fibrosis. Apart from the skin, SSc also affects internal organs such as the heart, lungs, and gastrointestinal tract, of which interstitial lung disease (ILD) is a common complication, with an incidence ranging from 25–90% (1), and is the major cause of mortality in patients with SSc (2). The interaction between genetic and environmental factors may lead to immune dysfunction, resulting in various immune cells activated and many inflammatory factors produced, in which T helper cells such as Th2 and Th17 are involved in the pathogenesis of SSc (3, 4). Further research revealed that IL-31 and IL-33, novel profibrogenic cytokines produced by activated Th2, may contribute to the development of SSc (5). Besides, Vitamin D, exerting some of its protective effects in the development of autoimmunity through the regulation of Th2 and Th17 cells, was found deficient in SSc and associated with disease activity (6, 7). However, the pathogenesis of SSc has yet to be completely understood. The course of SSc has a wide spectrum, and not all patients have ILD. Furthermore, in clinical practice, treatment is often initiated after clinical symptoms such as dyspnea or cough to develop, pulmonary function decline, or extensive ILD involvement, contributing to intervention delay in SSc-ILD (8). Consequently, identifying patients at high risk of ILD will help to better manage patients with SSc and provide early diagnosis and treatment for SSc-ILD.

Previous studies have confirmed several risk factors for the presence of ILD in SSc, such as male sex, African–American ethnicity, advanced age at time of diagnosis, diffuse cutaneous skin involvement, presence of anti-Scl-70, lower forced vital capacity (FVC), and diffusing capacity of the lung for carbon monoxide (DLCO) (9). Although SSc is widely distributed across the world, the clinical characteristics vary among ethnic and geographic groups (10–12). Previous studies have mainly focused on white populations or Western countries (13–19), so the possible factors related to the presence of SSc with ILD in Chinese patients are not well known. Therefore, we aimed to summarize the clinical characteristics of SSc patients at a single center in China and compare the demographic, clinical, and laboratory characteristics between SSc patients with or without ILD to identify associations with ILD in SSc.

Materials and methods

Patients

This cross-sectional study used retrospectively collected data from the Chinese Rheumatology Data Center. Patients diagnosed with SSc at the Rheumatology Department of the Second Affiliated Hospital of Nanchang University from 2013 to 2022 were included in the study. All patients met either the 1980 American Rheumatism Association criteria (20) for SSc or the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria (21) for SSc diagnosis. Patients with symptoms similar to those of SSc (rheumatoid arthritis, polymyositis/dermatomyositis, systemic lupus erythematosus, autoimmune liver disease, vasculitis, or any other CTD except Sjögren's syndrome) were excluded. All patients were grouped based on whether or not they had ILD according to high-resolution computed tomography (HRCT) manifestations. This study was approved and supervised by the ethics committee of the Second Affiliated Hospital of Nanchang University. Informed consent was obtained from all study participants.

Data collection

Sex, age at disease onset (since the first non-Raynaud phenomenon symptom), age at first hospital visit, baseline

TABLE 1 Comparison of baselines demographics and clinical features between systemic sclerosis with or without interstitial lung disease.

Variables	Total (n = 227)	SSc with ILD (n = 121)	SSc without ILD (n = 106)	P*
Female	188 (82.8)	100 (82.6)	88 (83.0)	0.941
BMI (kg/m^2), median (IQR)	20.9 (3.9)	20.9 (4.4)	20.7 (3.9)	0.448#
BMI > 24	39 (17.2)	24 (19.8)	15 (14.2)	0.257
Age at disease onset (years), median (IQR)	48.2 (19.4)	46.2 (20.0)	49.4 (19.9)	0.562#
Age at first visit (years), median (IQR)	52.6 (18.3)	51.8 (16.7)	53.4 (18.5)	0.412#
Baseline disease duration (years), median (IQR)	2.1 (4.4)	2.3 (4.6)	1.4 (3.6)	0.181#
Smoking history	27 (11.9)	13 (10.7)	14 (13.2)	0.567
mRSS, median (IQR)	7.0 (12.0)	9.0 (11.5)	5.5 (13.0)	0.019#
PGA (0–3), median (IQR)	1.5 (1.0)	1.5 (1.0)	1.2 (1.0)	0.113#
DcSSc	78 (34.4)	54 (44.6)	24 (22.6)	0.001
Raynaud phenomenon	201 (88.5)	106 (87.6)	95 (89.6)	0.634
Fingertip ulcer	65 (28.6)	41 (33.9)	24 (22.6)	0.062
Loss of finger pad	52 (22.9)	34 (28.1)	18 (17.0)	0.047
Telangiectasia	109 (48.0)	51 (42.1)	58 (54.7)	0.059
Sclerodactyly	130 (57.3)	77 (63.6)	53 (50.0)	0.038
Puffy finger	134 (59.0)	69 (57.0)	65 (61.3)	0.511
Finger contracture	17 (7.5)	9 (7.4)	8 (7.5)	0.975
Proximal skin sclerosis	147 (64.8)	83 (68.6)	64 (60.4)	0.196
Arthritis	27 (11.9)	16 (13.2)	11 (10.4)	0.509
Muscle involvement	34 (15.0)	24 (19.8)	10 (9.4)	0.028
GERD	40 (17.6)	25 (20.7)	15 (14.2)	0.199
Cardiovascular involvement	133 (58.6)	81 (66.9)	52 (49.1)	0.006
Arrhythmia	9 (4.0)	6 (5.0)	3 (2.8)	0.632
LVDD	120 (52.9)	74 (61.2)	46 (43.4)	0.007
Pericardial effusion	42 (18.5)	26 (21.5)	16 (15.1)	0.216
Pulmonary hypertension	20 (8.8)	17 (14.0)	3 (2.8)	0.003
Renal crisis	4 (1.8)	2 (1.7)	2 (1.9)	1.000**

Values are the n (%) unless otherwise indicated. *Chi-square test was used to compare systemic sclerosis with or without interstitial lung disease groups unless otherwise indicated. **Fisher's exact test; #Mann–Whitney U-test. SSc, systemic sclerosis; ILD, interstitial lung disease; BMI, body mass index; mRSS, modified Rodnan skin score; PGA, physician global assessment; GERD, gastroesophageal reflux disease; dcSSc, diffuse cutaneous systemic sclerosis; LVDD, left ventricular diastolic dysfunction.

disease duration (from the onset of the first non-Raynaud phenomenon symptom to be classified as SSc), smoking history, body mass index (BMI), and other demographic characteristics were recorded.

Clinical data included SSc-related symptoms and signs (Raynaud phenomenon, sclerodactyly, loss of finger pad, fingertip ulcer, etc.), organ involvement, physician global assessment (PGA), disease type, modified Rodnan skin score (mRSS), chest HRCT, and echocardiography. Patients were categorized as limited cutaneous systemic sclerosis (lcSSc) or diffuse cutaneous systemic sclerosis (dcSSc) using LeRoy's criteria (22), with systemic sclerosis sine scleroderma considered to be lcSSc. ILD was defined as the presence of alterations on HRCT scans that are consistent with scleroderma-related fibrosis, such as ground-glass opacity, honeycombing, or increased interstitial markings on HRCT scans of the chest. A trained rheumatologist and radiologist independently assessed the images. Another experienced rheumatologist was invited to address the disagreement. The presence of subjective symptoms, including heartburn, reflux, and dysphagia, or reflux esophagitis on gastroscopy or esophageal dilatation on chest CT, was considered as gastroesophageal reflux disease (GERD). Pulmonary hypertension (PAH) was defined as pulmonary artery systolic pressure more than 35 mmHg, according to echocardiography (23). Cardiac involvement is composed of arrhythmia, a decline in left ventricular diastolic dysfunction (LVDD), and pericardial effusion (24). The renal crisis manifests as oliguria, anuria, a progressive increase in serum creatinine, and sudden hypertension (25). Musculoskeletal involvement was also recorded, including muscle damage and arthritis. Arthritis refers to joint tenderness, swelling, or radiographs of the musculoskeletal system showing arthritic changes. Muscle involvement manifested as reduced muscle strength, muscle weakness, and increased creatine kinase levels (CK > 198 U/L), or myogenic damage and myositis according to electromyography and muscle biopsy, respectively (26).

Laboratory tests included white blood cell count (WBC), neutrophil count, lymphocyte count, platelet count, creatine

TABLE 2 Comparison of baselines laboratory features between systemic sclerosis with or without interstitial lung disease.

Variables	Total (n = 227)	SSc with ILD (n = 121)	SSc without ILD (n = 106)	P*
WBC ($\times 10^9$/L), median (IQR)	5.9 (3.2)	6.4 (3.1)	5.4 (2.5)	0.001#
Neutrophils ($\times 10^9$/L), median (IQR)	3.7 (2.6)	4.1 (2.9)	3.4 (2.0)	0.005#
Lymphocytes ($\times 10^9$/L), median (IQR)	1.4 (0.7)	1.4 (0.7)	1.4 (0.6)	0.920#
Platelet ($\times 10^9$/L), median (IQR)	212.0 (98.0)	238.0 (107.5)	194.5 (104.3)	0.001#
NLR, median (IQR)	2.6 (2.1)	2.7 (2.5)	2.5 (1.4)	0.038#
PLR, median (IQR)	150.6 (93.2)	160.0 (97.3)	139.1 (79.4)	0.010#
CK, median (IQR)	83.4 (86.4)	80.2 (111.6)	84.5 (71.0)	0.881#
Elevated ferritin	49 (21.6)	34 (28.1)	15 (14.2)	0.011
Elevated KL-6	135 (59.5)	82 (67.8)	53 (50.0)	0.007
Elevated ESR	170 (74.9)	92 (76.0)	78 (73.6)	0.671
Elevated CRP	60 (26.4)	37 (30.6)	23 (21.7)	0.130
IgG (g/L), median (IQR)	16.1 (8.1)	16.2 (9.1)	15.8 (6.5)	0.578#
IgA (g/L), median (IQR)	2.7 (2.0)	3.0 (1.9)	2.5 (2.1)	0.438#
IgM (g/L), median (IQR)	1.4 (0.9)	1.4 (0.9)	1.3 (0.9)	0.368#
C3 (g/L), median (IQR)	0.8 (0.2)	0.9 (0.2)	0.8 (0.2)	0.175#
C4 (g/L), median (IQR)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.245#
ANA	178 (78.4)	104 (86.0)	74 (69.8)	0.003
Anti-Scl-70	90 (39.6)	58 (47.9)	32 (30.2)	0.006
ACA	58 (25.6)	23 (19.0)	35 (33.0)	0.016
Anti-SSA	71 (31.3)	42 (34.7)	29 (27.4)	0.233
Anti-SSB	14 (6.2)	7 (5.8)	7 (6.6)	0.798
Anti-Ro-52	96 (42.3)	58 (47.9)	38 (35.8)	0.066
Anti-u1-RNP	59 (26.0)	32 (26.4)	27 (25.5)	0.867
RF	73 (32.2)	44 (36.4)	29 (27.4)	0.147

Values are the n (%) unless otherwise indicated. *Chi-square test was used to compare systemic sclerosis with or without interstitial lung disease groups unless otherwise indicated. #Mann–Whitney U-test. SSc, systemic sclerosis; ILD, interstitial lung disease; WBC, white blood cell; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CK, creatine kinase; KL-6, Krebs von den Lungen-6; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; C3, complement 3; C4, complement 4; ANA, anti-nuclear antibody; Anti-Scl-70, anti-scleroderma-70; ACA, anti-centromere antibody; RF, rheumatoid factor; anti-u1-RNP, anti-u1-ribonucleoprotein.

kinase, ferritin (>191 ng/ml was defined as elevated), Krebs von den Lungen-6 (KL-6) (>500 U/mL was defined as elevated), C-reactive protein (CRP) level (>8 mg/L defined as elevated), erythrocyte sedimentation rate (ESR) (>15 and >20 mm/h for males and females was referred to as elevated, respectively), immunoglobulin G (IgG), IgA, IgM, complement 3 (C3), C4, and autoantibody status [antinuclear antibody (ANA), anti-scleroderma-70 (anti-Scl-70) antibody, anticentromere antibody (ACA), anti-u1-ribonucleoprotein (anti-u1-RNP), SSA, SSB, anti-Ro52, rheumatoid factor (RF)]. The neutrophil to lymphocyte ratio (NLR) is the absolute count of neutrophils divided by the absolute count of lymphocytes. Platelet to lymphocyte ratio (PLR) is calculated as the absolute count of platelets divided by the absolute count of lymphocytes.

Statistical analysis

SPSS for Windows, version 26.0 (IMB Corp., Armonk, NY, USA) was used for data analysis. Kolmogorov–Smirnov test of normality was carried out for measurement data. Normally and non-normally distributed variables were presented as means with standard deviation (SD) and medians with interquartile range (IQR), respectively. Continuous values between groups were compared using the Mann–Whitney test. Chi-squared test or Fisher's exact test was adopted to compare categorical variables, including proportions, between groups. Univariable and multivariable analyses were carried out logistic regression. Odds ratios (ORs) with 95% CIs were calculated. P less than 0.05 were considered statistically significant.

Results

The baseline demographic and clinical characteristics of 227 patients with SSc are shown in Table 1. The majority of patients (82.8%) were female. The proportion of overweight (BMI > 24) and smokers was 17.2 and 11.9%, respectively. There were 74 cases (34.4%) with dcSSc, 149 cases (65.6%) with lcSSc, and 121 (53.3%) accompanied by ILD. The median age at disease onset and age at diagnosis was 48.2 (IQR 19.4) and 52.6 (IQR 18.3) years respectively, and the median baseline disease duration was

2.1 (IQR 4.4) years. The median mRSS and PGA were 7.0 (IQR, 12.0) and 1.5 (IQR, 1.0), respectively. SSc patients with ILD had a higher percentage of dcSSc than those without ILD (44.6 vs. 22.6%, $P = 0.001$), as did the mRSS [9.0 (IQR 11.5) vs. 5.5 (IQR 13.0), $P = 0.019$].

Clinical manifestations included Raynaud phenomenon, found in 201 (88.5%) patients, proximal skin sclerosis in 147 (64.8%), puffy finger in 134 (59.0%), sclerodactyly in 130 (57.3%), telangiectasia in 109 (48.0%), fingertip ulcers in 65 (28.6%), loss of finger pad in 52 (22.9%), and finger contracture in 17 (7.5%). Other organ involvement manifestations comprised of cardiovascular disease (58.6), ILD (53.3%), GERD (17.6%), muscle involvement (15.0%), arthritis (11.9%), PAH (8.8%), and renal crisis (1.8%). Cardiovascular involvement included LVDD found in 120 (52.9%) patients, pericardial effusion in 42 (18.5%), and arrhythmia in 9 (4.0%). In SSc patients with ILD, the prevalence of sclerodactyly, loss of finger pad, muscle involvement, LVDD, and PAH was higher than in those without ILD (63.6 vs. 50.0%, $P = 0.038$; 28.1 vs. 17.0%, $P = 0.047$; 19.8 vs. 9.4%, $P = 0.028$; 61.2 vs. 43.4%, $P = 0.007$; 14.0 vs. 2.8%, $P = 0.003$, respectively). **Table 1** presents the baseline demographic and laboratory characteristics of patients at baseline.

Table 2 shows the baseline laboratory features of 227 patients with SSc. The median NLR and PLR were 2.6 (IQR 2.1) and 150.6 (IQR 93.2), respectively. The proportions of SSc patients with increased ferritin, elevated KL-6, elevated CRP levels, and ESR were 21.6, 59.5, 26.4, and 74.9%, respectively. The median CK, IgG, IgA, IgM, C3, and C4 were 83.4 (IQR 86.4), 16.1 (IQR 8.1), 2.7 (IQR 2.0), 1.4 (IQR 0.9), 0.8 (IQR 0.2), and 0.2 (IQR 0.1), respectively. Regarding the autoantibodies, antinuclear antibodies (ANA) were the most common, observed in 78.4% of patients (178/227), followed by anti-Ro-52 (42.3%), anti-Scl-70 (39.6%), RF (32.2%), anti-SSA (31.3%), anti-u1RNP (26.0%), ACA (25.6%), and anti-SSB (6.2%). The median NLR and PLR were higher in SSc patients with ILD than others [2.7 (IQR 2.5) vs. 2.5 (IQR 1.4), $P = 0.038$; 160.0 (IQR 97.3) vs. 139.1 (IQR 79.4), $P = 0.010$, respectively], and SSc patients with ILD had higher proportions of elevated ferritin, elevated KL-6, ANA positivity, and anti-Scl-70 positivity (28.1 vs. 14.2%, $P = 0.011$; 67.8 vs. 50.0%, $P = 0.007$; 86.0 vs. 69.8%, $P = 0.003$; 47.9 vs. 30.2%, $P = 0.006$, respectively), while SSc patients without ILD were more often ACA positive (33.0 vs. 19.0%, $P = 0.016$, respectively).

Univariate and multivariate logistic analyses were performed to determine the clinical and laboratory factors associated with ILD in patients with SSc (**Table 3**). In univariate logistic analysis, loss of finger pad, sclerodactyly, muscle involvement, LVDD, PAH, dcSSc, NLR, PLR, elevated ferritin, elevated KL-6, Anti-Scl-70 antibody, and ACA were statistically significant ($P < 0.05$) (**Table 3**). The identified variables were subjected to a forward stepwise multiple logistic regression. The multivariable analysis demonstrated that associations with ILD in patients with SSc and muscle involvement [OR 2.551 (95% CI 1.054–6.175), $P = 0.038$], LVDD [OR 2.360 (95% CI 1.277–4.361), $P = 0.006$], PAH [OR 9.134 (95% CI 2.335–35.730), $P = 0.001$], dcSSc [OR 2.859 (95% CI 1.489–5.487), $P = 0.002$], PLR [OR 1.005 (95% CI 1.001–1.008), $P = 0.020$], elevated KL-6 [OR 2.033 (95% CI 1.099–3.763), $P = 0.024$], and Anti-Scl-70 antibody [OR 3.101 (95% CI 1.647–5.840), $P < 0.001$] were statistically significant (**Table 3**).

Discussion

Pulmonary involvement is a destructive complication that affects life expectancy in patients with SSc. In the present study, we summarized the demographic and clinical characteristics of SSc at a single center in China, and compared the differences between SSc patients with and without ILD, with aimed to develop our understanding of ILD in patients with SSc, potentially facilitating early diagnosis, accurate stratification, pre-emptive therapy, and thus improve patient performance (27).

It is well known that SSc is a predominantly female disease, and its peak incidence is between 30 and 50 years of age. Similar to previous studies (28), our data showed that SSc commonly occurs in females, and the median age at disease onset was 48 years. Vascular complications dominate the clinical picture of scleroderma, of which Raynaud phenomenon was the most common initial clinical symptom, with an incidence of 88.5% in this study. In addition, other typical manifestations such as proximal skin sclerosis, puffy finger, sclerodactyly, telangiectasia, fingertip ulcer, and loss of finger pad also prevalently occur in patients with SSc, and this frequency was largely similar in previous studies (29–33). In this study, sclerodactyly and loss of the finger pad occurred more frequently in SSc patients with ILD than in others. Furthermore, a previous study found a correlation between finger pad loss/depressed finger end scars and SSc lung involvement, which aligns with findings from our study (34). Therefore, we speculate that pathological changes in the body surface can reflect internal organ lesions. In addition, the proportion of localized scleroderma in SSc patients was high, accounting for 65.6%, indicating that lcSSc was more common than dcSSc, which is consistent with domestic and international reports (31, 32, 35–42). The differences in clinical patterns and prognosis between patients with dcSSc and lcSSc have been well reported in many previous studies (29, 32, 33). Our study revealed markedly more dcSSc than lcSSc in SSc patients with ILD, which is supported by similar findings from the European Scleroderma Trials and Research (EUSTAR) group and other studies, proving the significance of LeRoy's criterion (22) in clinical implications.

Renal crisis, the most serious complication of SSc, occurred in 1.8% of SSc patients in this research, consistent with a previous study reporting the renal crisis in the Chinese

TABLE 3 Logistic regression analysis of clinical characteristics associated with the presence of ILD in SSc*.

Variables	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Loss of finger pad	1.911 (1.004 − 3.636)	**0.049**		
Sclerodactyly	1.750 (1.029 − 2.977)	**0.039**		
Muscle involvement	2.375 (1.078 − 5.233)	**0.032**	2.551 (1.054 − 6.175)	**0.038**
LVDD	2.054 (1.208 − 3.490)	**0.008**	2.360 (1.277 − 4.361)	**0.006**
PAH	5.612 (1.596 − 19.731)	**0.007**	9.134 (2.335 − 35.730)	**0.001**
dcSSc	2.754 (1.543 − 4.914)	**0.001**	2.859 (1.489 − 5.487)	**0.002**
NLR	1.155 (1.017 − 1.312)	**0.027**		
PLR	1.005 (1.001 − 1.008)	**0.008**	1.005 (1.001 − 1.008)	**0.020**
Elevated ferritin	2.371 (1.207 − 4.656)	**0.012**		
Elevated KL-6	2.103 (1.227 − 3.604)	**0.007**	2.033 (1.099 − 3.763)	**0.024**
Anti-Scl-70	2.129 (1.232 − 3.679)	**0.007**	3.101 (1.647 − 5.840)	**<0.001**
ACA	0.476 (0.259 − 0.875)	**0.017**		

*All variables with a *p*-value below 0.05 from the univariable analysis were entered in multivariable analysis (forward logistic regression). SSc, systemic sclerosis; ILD, interstitial lung disease; LVDD, left ventricular diastolic dysfunction; dcSSc, diffuse cutaneous systemic sclerosis; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; KL-6, Krebs von den Lungen-6; anti-Scl-70, anti-scleroderma-70; ACA, anti-centromere antibody. Bold values indicate $P < 0.05$.

population to be approximately 1% (33) but lower than that of patients in the Caucasian population (16). In the past 30 years, with the subsequent widespread adoption of angiotensin converting enzyme inhibitors, mortality from the renal crisis has decreased from 42 to 6% (43). Currently, pulmonary complications like PAH and ILD are the major causes of death (2), with incidences of 8.8 and 53.3%, respectively, in this study. A large meta-analysis that included 27 studies with 5,250 participants indicated that the pooled prevalence of ILD among SSc patients in East Asia was 56% (95% CI, 49–63%) (44), which is in line with our study. However, ultrasonic cardiogram examinations were used to estimate pulmonary pressure instead of right heart catheterization, and the thresholds defined by the studies differed, making direct comparisons among studies difficult. In addition, digestive system involvement, mainly GERD, was common in SSc patients, with an incidence of 17.6% in our study, similar to that reported in other Chinese cohorts (29, 31). Moreover, a previous study reported an association between gastroesophageal reflux and ILD in SSc (14, 15), yet these findings were not confirmed in our study.

Cardiac involvement, mainly LVDD, is also frequently seen in systemic sclerosis, found in 52.9% of our SSc population, higher than 31.4%, as found by Hu et al. They adopted more stringent criteria to define LVDD (32). Diastolic dysfunction has been regarded as the outcome of myocardial fibrosis, originating from a coronary microcirculation anomaly and deemed as the pathological hallmark of SSc myocardial disease (45). Previous studies have found that digital pits are significantly more common in SSc patients with LVDD and PAH (46). In addition to the loss of finger pad, LVDD and PAH were significantly associated with ILD, supporting the hypothesis that vascular injury may be one of the common mechanisms for the development and progression of interstitial lung lesions. Interestingly, Zhou et al. revealed that patients with SSc with myopathy tended to present with PAH, ILD, and cardiac involvement (47), which is similar to our results that myopathy was closely related to the presence of ILD in SSc, as revealed by multivariate analysis. Therefore, complex relationships exist among myopathy, PAH, cardiac involvement, and ILD, which require further investigation.

Similar to other connective tissue diseases, SSc is associated with autoantibodies specific to anti-Scl-70 and ACA. Unlike United States, Japan, Australia, and most European countries (35–40), the proportion of anti-Scl-70 (39.6%) antibodies was higher than ACA (25.6%) in this study, which is similar to the frequency of autoantibodies in other Chinese SSc cohorts (12, 31–33). Additionally, the frequencies of anti-Scl-70 and ACA in Chinese patients with SSc are extremely close to that demonstrated by a nationwide multicenter cohort of SSc data from Korea (42.5% Scl-70 and 25.5% ACA) (42). These studies indicate that geography and ethnicity may greatly impact on the occurrence of SSc-associated antibodies. Nevertheless, similar to findings from other ethnic populations (40, 48, 49), the presence of Scl-70 in Chinese patients with SSc was significantly correlated with ILD, whereas ACA was associated with low pulmonary involvement.

Systemic sclerosis-interstitial lung disease is a chronic inflammatory disease involving lymphocytes, neutrophils, and platelets and participates in the regulation of complex inflammatory and immune responses in the organism (50). The NLR and PLR perform well in the assessment of several autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and so on (51–53). In the present study, PLR, but not NLR, was confirmed to be significantly correlated

with the presence of ILD in SSc in multifactorial analysis. In addition, other indicators of inflammation status, such as ferritin, were shown to be higher in SSc patients with ILD than in others in this study, which also supports the above theory. KL-6 is a salivary liquefied glycoprotein, primarily expressed on the surface of type II alveolar epithelial cells, and has been widely confirmed to be correlated with the development and progression of ILD (54–56), similar to the correlation between KL-6 and lung involvement shown in our study.

The advantages of our study are inclusion of a huge number of patients from a single center, thereby reducing possible effects of population heterogeneity. However, some limitations have to be acknowledged in this study. Firstly, it was a cross-sectional study with causality that could not be determined. Second, pulmonary arterial hypertension was estimated indirectly by echocardiography, which may have biased our results. Lastly, this research was carried out in a single rheumatology center, and thus may fail to represent the entire spectrum of SSc in China.

In summary, SSc is characterized mainly by a female predominance. Several important differences in clinical and laboratory characteristics have been observed between patients with SSc with or without ILD. Muscle involvement, LVDD, PAH, dcSSc, PLR, elevated KL-6, and anti-Scl-70 antibody may be associated with ILD in SSc. Future longitudinal cohort studies, including larger populations and longer-term follow-ups, to evaluate cause-effect relationships, are desirable.

Data availability statement

The datasets used during the current study are available from the corresponding author on reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of The Second Affiliated Hospital of Nanchang University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XD designed the study and revised the manuscript. XD, HL, XZ, LY, JS, JF, XF, RZ, JR, and QG collected the data. HL performed the data analysis and drafted the first version of the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Serum B-cell activating factor and lung ultrasound B-lines in connective tissue disease related interstitial lung disease

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Objective: To investigate the role of serum B-cell activating factor (BAFF) and lung ultrasound (LUS) B-lines in connective tissue disease related interstitial lung disease (CTD-ILD), and their association with different ILD patterns on high resolution computed tomography (HRCT) of chest.

Methods: We measured the levels of BAFF and KL-6 by ELISA in the sera of 63 CTD-ILD patients [26 with fibrotic ILD (F-ILD), 37 with non-fibrotic ILD (NF-ILD)], 30 CTD patients without ILD, and 26 healthy controls. All patients underwent chest HRCT and LUS examination.

Results: Serum BAFF levels were significantly higher in CTD patients compared to healthy subjects (617.6 ± 288.1 pg/ml vs. 269.0 ± 60.4 pg/ml, $p < 0.01$). BAFF concentrations were significantly different between ILD group and non-ILD group (698.3 ± 627.4 pg/ml vs. 448.3 ± 188.6 pg/ml, $p < 0.01$). In patients with ILD, BAFF concentrations were significantly correlated with B-lines number ($r = 0.37$, 95% CI 0.13–0.56, $p < 0.01$), KL-6 level ($r = 0.26$, 95% CI 0.01–0.48, $p < 0.05$), and Warrick score ($r = 0.33$, 95% CI 0.09–0.53, $p < 0.01$), although all correlations were only low to moderate. B-lines number correlated with Warrick score ($r = 0.65$, 95% CI 0.48–0.78, $p < 0.01$), and KL-6 levels ($r = 0.43$, 95% CI 0.21–0.61, $p < 0.01$). Patients with F-ILD had higher serum BAFF concentrations (957.5 ± 811.0 pg/ml vs. 516.1 ± 357.5 pg/ml, $p < 0.05$), KL-6 levels (750.7 ± 759.0 U/ml vs. 432.5 ± 277.5 U/ml, $p < 0.05$),

B-lines numbers (174.1 ± 82 vs. 52.3 ± 57.5, $p < 0.01$), and Warrick score (19.9 ± 4.6 vs. 13.6 ± 3.4, $p < 0.01$) vs. NF-ILD patients. The best cut-off values to separate F-ILD from NF-ILD using ROC curves were 408 pg/ml for BAFF (AUC = 0.73, $p < 0.01$), 367 U/ml for KL-6 (AUC = 0.72, $p < 0.05$), 122 for B-lines number (AUC = 0.89, $p < 0.01$), and 14 for Warrick score (AUC = 0.87, $p < 0.01$) respectively.

Conclusion: Serum BAFF levels and LUS B-lines number could be useful supportive biomarkers for detecting and evaluating the severity and/or subsets of CTD-ILD. If corroborated, combining imaging, serological, and sonographic biomarkers might be beneficial and comprehensive in management of CTD-ILD.

KEYWORDS

B-cell activating factor, lung ultrasound, B-lines, KL-6, high resolution CT, connective tissue disease related interstitial lung disease

Introduction

Interstitial lung disease (ILD) is a major pulmonary complication in connective tissue disease (CTD), associated with poor prognosis and increased mortality (1, 2). The prevalence and the clinical behavior of CTD-ILD is highly variable in different rheumatic diseases, ranging from long-term stability to acute exacerbation and life threatening situations (3, 4). The unpredictable progression and outcomes make precise personalized medicine in this clinical scenario challenging. Therefore, to find sensitive, feasible, and repeatable biomarkers associated with CTD-ILD progression could be important (5–7). Although the pathophysiology of CTD-ILD is incompletely understood, immune dysregulation, and multiple pro-inflammatory cytokine may play an important role in this process (8). Local uncontrolled cytokine release probably drives the immune damage and, ultimately, may cause acute or chronic lung injury. In some circumstances this can lead to catastrophic outcomes (9). Bronchoalveolar and serological cytokine concentrations could reflect the alveolar and interstitial structural inflammation, damage, and healing. Among them, B-cell activating factor (BAFF) might play a crucial role in this pathogenesis (10). BAFF belongs to the tumor necrosis factor superfamily and is a key cytokine involved in B-cell differentiation, maturation, survival, and auto-antibody production. The overexpression of BAFF is associated with autoimmunity diseases onset and activity (11, 12), as well as a biomarker to assess response to therapy. Recent studies, most in idiopathic inflammatory myositis (IIM) patients, showed that plasma BAFF concentrations were significantly higher in ILD patients compared to those without ILD and were associated with the presence of anti-Jo-1 antibody (13, 14). These findings indicated that BAFF might be a promising biomarker for IIM-ILD.

Lung ultrasound (LUS) has been extensively used to detect parenchymal disease in the past two decades, including pneumothorax, pneumonia, pulmonary edema, and lung fibrosis (15, 16). B-lines, a comet-tail artefact, is the sonographic hallmark of ILD. B-lines number, morphology and distribution mirrored the severity and extent of interstitial involvement (17, 18). Previous studies showed B-lines number significantly correlated with high resolution computed tomography (HRCT) score, pulmonary function tests (PFTs) parameters, clinical features, and serum Krebs von den Lungen-6 Antigen (KL-6) levels (19, 20). Furthermore, multiple studies from different centers and races, consistently found LUS has excellent sensitivity and negative predictive value for CTD-ILD (21–23), compared to HRCT as the gold standard. In addition, the innate features of ultrasound, includes more feasible, user-friendly, radiation-free, and less expensive make it can play an important role in screening and follow-up (24).

However, to the best of our knowledge, the relationship between B-lines and serum BAFF levels in CTD-ILD has never been reported. In this pilot study, we investigated the inter-relationships among serum levels of BAFF, KL-6, LUS B-lines number, and HRCT Warrick score in patients with CTD-ILD, and their association with different ILD patterns on HRCT of chest, in order to primarily explore their role in the management of CTD-ILD.

Abbreviations: AUC, area under curve; BAFF, B-cell activating factor; BMI, body mass index; CTD-ILD, connective tissue disease related interstitial lung disease; F-ILD, fibrotic interstitial lung disease; HRCT, high resolution computed tomography; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; IPAF, interstitial pneumonia with autoimmune features; KL-6, Krebs von den Lungen-6; LUS, lung ultrasound; MCTD, mixed connective tissue disease; MDA-5, anti-melanoma differentiation-associated gene 5; NF-ILD, non-fibrotic ILD; pSS, primary Sjogren's syndrome; RA, rheumatoid arthritis; ROC, receiver operating characteristic; SSc, systemic sclerosis; UCTD, undifferentiated connective tissue disease.

Materials and methods

Patients and controls

Ninety-three consecutive CTD patients from the Shantou Central Hospital were enrolled, of which 63 patients were diagnosed with ILD (ILD group) and 30 patients did not have ILD (non-ILD group). Twenty-six age and sex matched healthy individuals without inflammatory, or autoimmunity disease, or pulmonary diseases were used as controls. Complete medical histories, physical examinations and laboratory data were conducted in all patients. Patients with a history of asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, lung cancer, occupational lung disease, radiation lung disease, heart failure, renal failure, children (<18 years old), and pregnancy were excluded from the study. The study was approved by the Shantou Central Hospital Ethics Committee (no. 2022-037). All investigations were conducted in compliance with the Declaration of Helsinki and all patients provided written informed consent.

Chest high resolution computed tomography examination and assessment

High resolution computed tomography of the chest was performed in all patients using 128 multi-slice CT (SIEMENS SOMATOM Definition Flash CT, German). All patients were scanned in the supine position from the lung apex to the diaphragm during end-inspiration. The acquisition parameters were as follows: 1 mm collimation and 0.9–1.2 pitch, 120 kV tube voltage and 110 reference mAS. Edge-enhancing B70 kernel was obtained by using filtered back projection for clinical reading with lung window. No intravenous contrast agent was employed. The duration of the CT acquisition was 1–3 s. Matrix was 512 × 512, and the effective dose was in the range of 1–3 mSv. The presence and pattern of ILD were defined by HRCT findings assessed by a radiologist (25). The ILD group was further divided into fibrotic ILD (F-ILD) or non-fibrotic ILD (NF-ILD) according to the radiologic patterns including honeycombing, traction bronchiectasis, and/or volume loss (26). The Warrick score was used to assess HRCT ILD severity and extent by two experienced radiologists, who evaluated jointly while blinded to the clinical, serological, and sonographic information.

Lung ultrasound examination and assessment

Commercially available ultrasound equipment with a 2.5–3.5 MHz cardiac sector transducer was used (Siemens Medical Solutions, Erlangen, Germany) in this study. Lung ultrasound was performed by two senior ultrasound physicians who were blinded to clinical, serological, and radiographic information about patients. Ultrasound images were obtained by recording the number of B-lines in a total of 50 scanning sites (27). The sum of B-lines yielded a score reflecting ILD extent (28). A B-line was defined as a discrete laser-like vertical hyperechoic reverberation artifact arising from the pleural line, extending to the bottom of the screen without fading, and moving synchronously with respiration (29).

Measurement of serum B-cell activating factor and Krebs von den Lungen-6 concentration

The serum was stored at −80°C. Serum BAFF level was evaluated using Human BAFF/BLyS/TNFSF13B DuoSet ELISA and DuoSet Ancillary Reagent Kit 2 (R&D Systems, cat. nos. DY124-05 and DY008, respectively) according to the manufacturer's instructions. The detection range for BAFF was 39.1–2,500 pg/ml. Serum KL-6 concentration (U/ml) was measured with a chemiluminescent enzyme immunoassay method (LUMIPULSE G2100, Japan) in the study population. The detection range for KL-6 was 50–10,000 U/ml.

Statistical analysis

Differences for continuous parametrically distributed variables between ILD and non-ILD groups were analyzed by ANOVA, while non-parametrically distributed data were analyzed by Chi-square using the SPSS version 16 (SPSS, Chicago, Illinois, USA). Correlations among total B-lines number, serum BAFF and KL-6 level, and Warrick score were assessed with Pearson correlations using GraphPad Prism 5.0 (GraphPad Software Inc., San Diego, CA, USA). The optimal cut-off values were determined from a receiver operating characteristic curves (ROC) using MedCalc statistical software version 12.3.0. The sensitivity, specificity, and area under the ROC curve (AUROC) were used as diagnostic performance indicators. The optimal cutoff point was identified according to Youden tests. A p-value of < 0.05 was regarded as significant.

Results

Characteristics of the patient group

Ninety-three patients (65 women, 28 men) with a diagnosis of CTD (49 rheumatoid arthritis, 15 idiopathic inflammatory myopathies, 11 primary Sjogren's syndrome, 9

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TABLE 1 CTD Patients' demographic and clinical features.

	ILD (n = 63)	Non-ILD (n = 30)	F-ILD (n = 26)	NF-ILD (n = 37)
Age (years)	59.7 ± 11.0	50.7 ± 12.9	59.4 ± 13.6	60.0 ± 8.6
Sex (female/male)	45/18	20/10	17/9	28/9
Duration of disease (years)	3.0 ± 4.0	4.2 ± 5.3	3.6 ± 4.7	2.6 ± 3.3
BMI (kg/m^2)	22.4 ± 3.0	22.8 ± 3.8	22.2 ± 3.5	22.4 ± 2.6
Smoking status				
Former smoker, n (%)	6 (9.5)	2 (6.7)	3 (11.5)	3 (8.1)
Current smoker, n (%)	10 (15.9)	4 (13.3)	6 (23.1)	4 (10.8)
Diagnosis				
RA, n (%)	28 (44.4)	21 (70)	10 (38.5)	18 (48.6)
IIM, n (%)	13 (20.6)	2 (6.7)	5 (19.2)	8 (21.6)
IPAF, n (%)	9 (14.3)	0 (0)	6 (23.1)	3 (8.1)
pSS, n (%)	7 (11.1)	4 (13.3)	3 (11.5)	4 (10.8)
SSc, n (%)	3 (4.7)	0 (0)	2 (7.7)	1 (2.7)
Overlap, n (%)	2 (3.2)	2 (6.7)	0 (0)	2 (5.4)
MCTD, n (%)	1 (1.6)	0 (0)	0 (0)	1 (2.7)
UCTD, n (%)	0 (0)	1 (3.3)	0 (0)	0 (0)
Serum BAFF level (pg/ml)	698.3 ± 627.4	448.3 ± 188.6	957.5 ± 811.0	516.1 ± 357.5
Serum KL-6 level (U/ml)	563.8 ± 573.8	284.0 ± 132.0	750.7 ± 759.0	432.5 ± 277.5
B-lines total number	102.6 ± 91.2	N/A	174.1 ± 82	52.3 ± 57.5
Warrick score	16.2 ± 5.0	N/A	19.9 ± 4.6	13.6 ± 3.4

BAFF, B-cell activating factor; BMI, body mass index; CTD, connective tissue disease; F-ILD, fibrotic interstitial lung disease; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; IPAF, interstitial pneumonia with autoimmune features; KL-6, Krebs von den Lungen-6; MCTD, mixed connective tissue disease; N/A, not applicable; NF-ILD, non-fibrotic interstitial lung disease; pSS, primary Sjogren's syndrome; RA, rheumatoid arthritis; SSc, systemic sclerosis; UCTD, undifferentiated connective tissue disease.

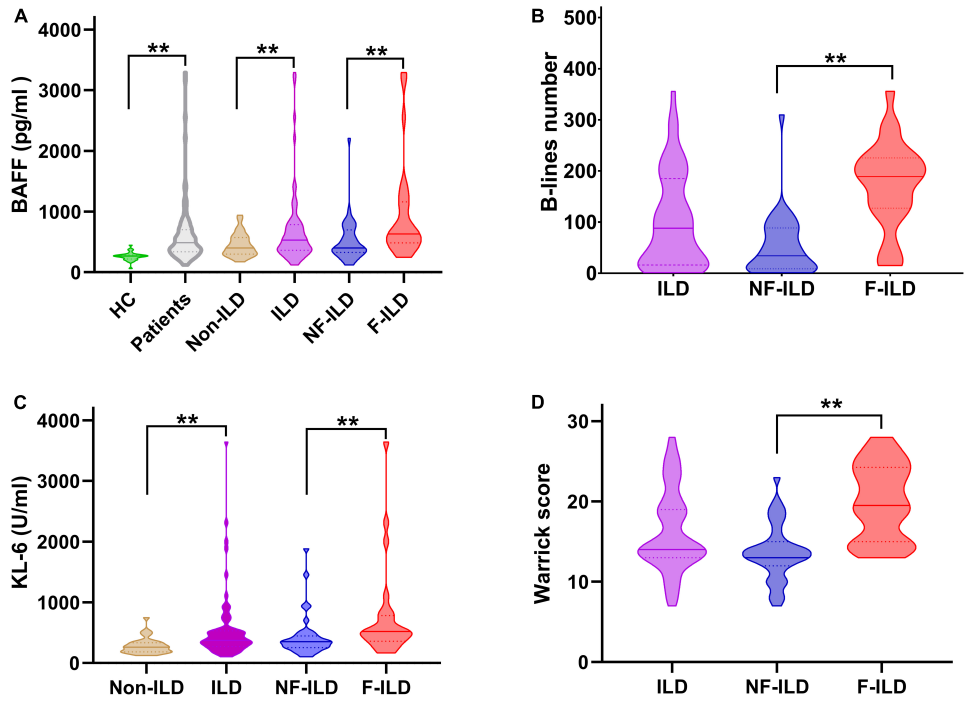

FIGURE 1
Distribution of serum **(A)** BAFF (pg/ml) and **(C)** KL-6 (U/ml) levels, **(B)** B-lines number, and **(D)** HRCT Warrick score in different groups. BAFF, B-cell activating factor; F-ILD, fibrotic interstitial lung disease; HC, healthy control; HRCT, high resolution computed tomography; ILD, interstitial lung disease; KL-6, Krebs von den Lungen-6 Antigen; NF-ILD, non-fibrotic interstitial lung disease. $^{**}P < 0.01$.

interstitial pneumonia with autoimmune features, 4 overlap, 3 systemic sclerosis, 1 mixed connective tissue disease, and 1 undifferentiated connective tissue disease) were included in our study. Demographic, clinical, serological and radiologic data are described in Table 1.

Serum levels of B-cell activating factor in healthy controls, patients, and subgroup patients with fibrotic interstitial lung disease and non-fibrotic interstitial lung disease

Serum levels of BAFF were significantly higher in patients compared to the healthy controls (617.6 ± 288.1 pg/ml vs. 269.0 ± 60.4 pg/ml, $p < 0.01$). BAFF concentrations were significantly different when comparing the ILD to non-ILD groups (698.3 ± 627.4 pg/ml vs. 448.3 ± 188.6 pg/ml, $p < 0.01$). When patients were sub-grouped according to HRCT ILD patterns, the F-ILD had significantly higher BAFF levels compared to NF-ILD (957.5 ± 811.0 pg/ml vs. 516.1 ± 357.5 pg/ml, $p < 0.01$) (Figure 1).

Serum levels of Krebs von den Lungen-6 in patients, and subgroup patients with fibrotic interstitial lung disease and non-fibrotic interstitial lung disease

Serum levels of KL-6 were significantly higher in patients with ILD compared to patients without ILD (563.8 ± 573.8 U/ml vs. 284.0 ± 132.0 U/ml, $p < 0.01$). In subgroup analysis, the value of KL-6 was significantly higher in patients with F-ILD vs. NF-ILD (750.7 ± 759.0 U/ml vs. 432.5 ± 277.5 U/ml, $p < 0.01$) (Figure 1).

B-lines number and Warrick score in interstitial lung disease patients, and subgroup patients with fibrotic interstitial lung disease and non-fibrotic interstitial lung disease

In the CTD-ILD group, mean B-lines number and Warrick score were 102.6 ± 91.2 and 16.2 ± 5.0, respectively. B-lines number was significantly higher in F-ILD group compared to NF-ILD group (174.1 ± 82 vs. 52.3 ± 57.5, $p < 0.01$). F-ILD patients had more higher Warrick score compared to NF-ILD group (19.9 ± 4.6 vs. 13.6 ± 3.4, $p < 0.01$) (Figure 1).

Correlation among serum levels of B-cell activating factor and Krebs von den Lungen-6, B-lines number and Warrick score in interstitial lung disease patients

In CTD patients with ILD, BAFF concentrations were statistically significantly correlated with B-lines number ($r = 0.37$, 95% CI 0.13–0.56, $p < 0.01$), KL-6 level ($r = 0.26$, 95% CI 0.01–0.48, $p < 0.05$), and Warrick score ($r = 0.33$, 95% CI 0.09–0.53, $p < 0.01$), although the correlations were low. A statistically significant positive correlation between B-lines number and the Warrick score ($r = 0.65$, 95% CI 0.48–0.78, $p < 0.01$), and KL-6 levels ($r = 0.43$, 95% CI 0.21–0.61, $p < 0.01$) was confirmed (Figure 2).

Receiver operating characteristic analysis comparing serum B-cell activating factor and Krebs von den Lungen-6 levels, B-lines number, and Warrick score between patients with fibrotic interstitial lung disease and non-fibrotic interstitial lung disease

The ROC curve analysis allowed us to use this cohort as a development cohort to define the cut-off values for BAFF and KL-6 while using these patients as a validation cohort for B-lines and Warrick scores. The B-line numbers and Warrick score separating patients with F-ILD from NF-ILD patients were 122 and 14, with areas under the ROC curve (AUC) of 0.89 for B-lines number (sensitivity 76.9%, specificity 97.3%), and 0.87 for Warrick score (sensitivity 80.8%, specificity 73%). The cut-off points for BAFF and KL-6 were 408 pg/ml and 367 U/ml, respectively while the AUC were 0.73 for serum BAFF (sensitivity 84.6%, specificity 54.1%) and 0.72 for KL-6 (sensitivity 76.9%, specificity 67.6%) (Figure 3). The relevant data are shown in Table 2.

Discussion

B-cell activating factor, also known as B Lymphocyte Stimulator (BLyS), is an important regulator of B-cell survival and differentiation. A growing body of evidence suggests that activation of B-cells participates in the pathogenesis of respiratory diseases, such as chronic obstructive pulmonary disease, asthma, pneumonia, and idiopathic pulmonary fibrosis by secretion of pro-inflammatory cytokine and auto-antibody (30). In bleomycin-induced lung fibrosis, genetic ablation of BAFF or BAFF neutralization by a soluble receptor significantly

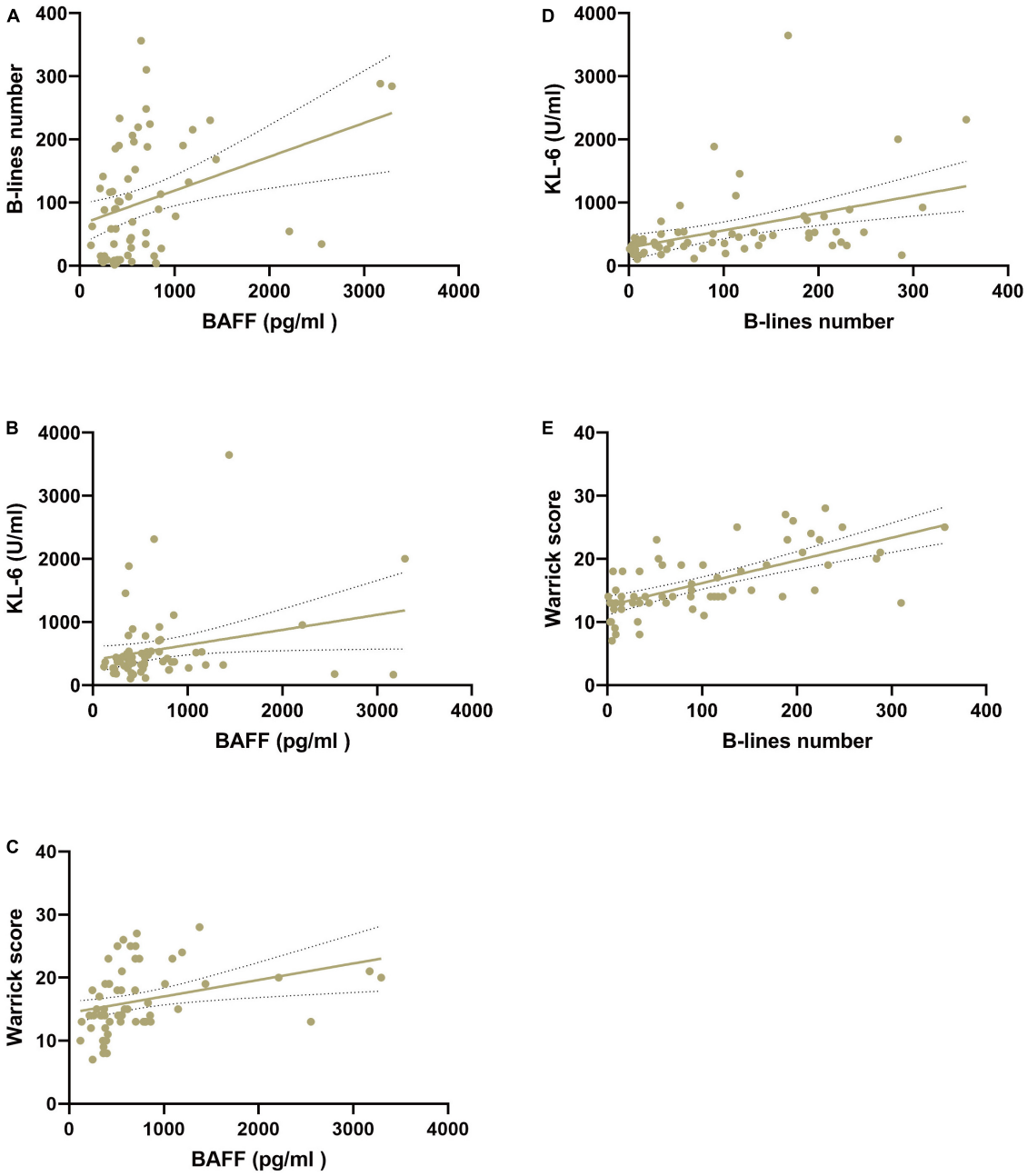

FIGURE 2
Correlation among serum BAFF (pg/ml) and KL-6 (U/ml) levels, B-lines number, and HRCT Warrick score in patients with CTD-ILD. **(A)** Correlation of serum BAFF levels and B-lines number. **(B)** Correlation of serum BAFF levels and KL-6 levels. **(C)** Correlation of serum BAFF levels and Warrick score. **(D)** Correlation of serum KL-6 levels and B-lines number. **(E)** Correlation of B-lines number and Warrick score. BAFF, B-cell activating factor; HRCT, high resolution computed tomography; KL-6, Krebs von den Lungen-6 Antigen.

attenuates pulmonary fibrosis and IL-1β levels (30). In the SSc animal model, BAFF contributed to the skin and lung fibrosis by increasing IL-6-producing effector B-cells and suppressing IL-10-producing regulatory B-cells (31). Previous clinical studies found that BAFF levels significantly increased in patients with IIM-ILD compared with IIM without ILD (13). Immunohistochemistry showed BAFF was strongly expressed in patients with CTD-ILD, mainly in alveolar macrophages in the air space, parenchymal lymphoid follicles, fibroblasts and alveolar walls (32). Taken together, these results indicated that BAFF could play an important role in CTD-ILD pathogenesis.

Our study found that serum levels of BAFF in patients were significantly higher than in the healthy controls. Furthermore, we found significantly increased BAFF levels in patients with

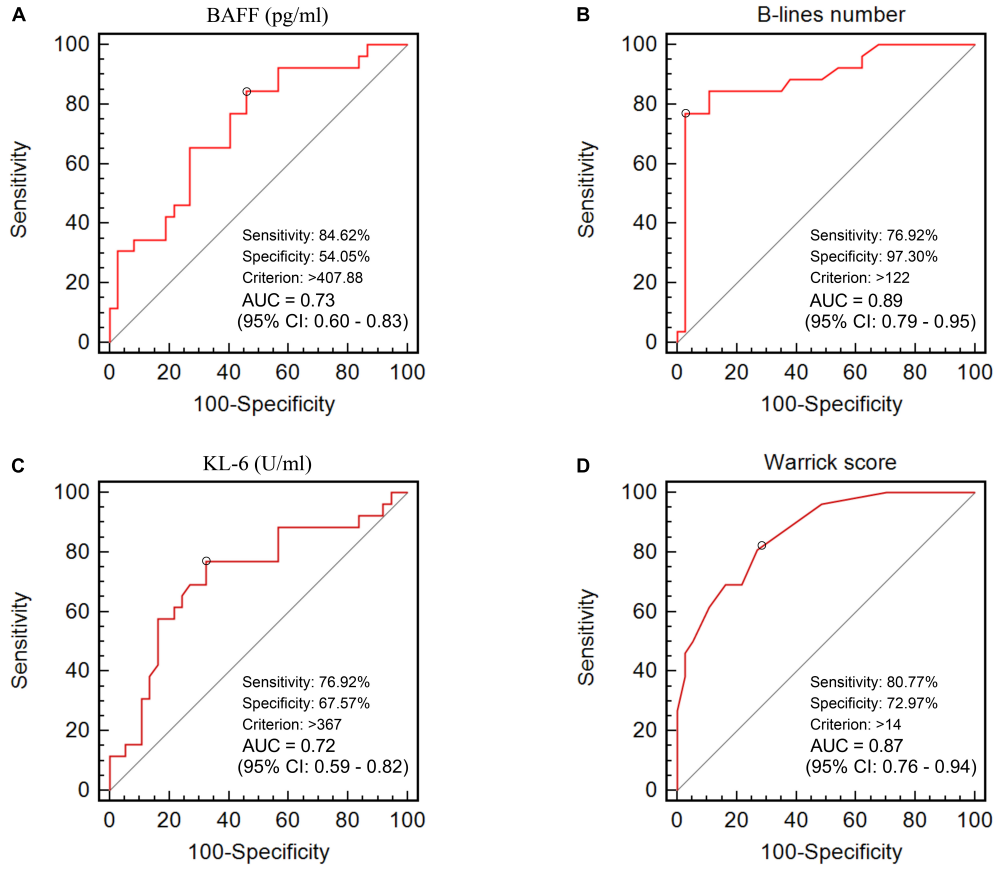

FIGURE 3
The area under the receiver operating characteristic curves of **(A)** BAFF level (pg/ml), **(B)** B-lines number, **(C)** KL-6 level (U/ml), and **(D)** HRCT Warrick score for the discrimination between F-ILD and NF-ILD.

TABLE 2 Receiver operating characteristic analysis of BAFF, KL-6, B-lines, and Warrick score in discriminating F-ILD from NF-ILD.

	Cut-off value	AUC	Sensitivity (%)	Specificity (%)	Accuracy (%)	*P*-value
BAFF (pg/ml)	408	0.73	84.6	54.1	66.7 (53.7–78.1)	<0.001
KL-6 (U/ml)	367	0.72	76.9	67.6	71.4 (58.7–82.1)	<0.01
B-lines number	122	0.89	76.9	97.3	88.8 (78.4–95.4)	<0.001
Warrick score	14	0.87	80.8	73	76.2 (63.8–86)	<0.001

AUC, area under curve; BAFF, B-cell activating factor; F-ILD, fibrotic interstitial lung disease; KL-6, Krebs von den Lungen-6; NF-ILD, non-fibrotic interstitial lung disease.

ILD compared to patients without ILD. Our findings were consistent with previous data, mostly reported from IIM cohorts. In general terms, these results showed that elevated serum BAFF level is strongly associated with ILD in CTD patients. To investigate the relationship between BAFF and different CTD-ILD patterns, the ILD group was further divided into fibrotic ILD (F-ILD) and non-fibrotic ILD (NF-ILD) (26). Subgroup analysis revealed that the serum BAFF concentration was significant higher in F-ILD than NF-ILD. Zhao et al. reported that plasma BAFF levels were significantly higher in usual interstitial pneumonia associated with autoimmune diseases and inversely correlated with PFT values (33). Our ROC analysis identified the best cut-off value of serum BAFF to discriminate F-ILD and NF-ILD was 408 pg/ml, with a sensitivity of 84.6% and a specificity of 54.1% (AUC = 0.73, $p < 0.01$). These findings indicate that BAFF levels may reflect ILD fibrotic severity and be a moderately useful biomarker for distinguishing F-ILD from NF-ILD, also suggesting that BAFF might be a new potential target for therapy in patients with CTD-ILD as well.

Belimumab, an anti-BAFF monoclonal IgG1λ antibody produced by recombinant DNA technology has been approved by the FDA for the treatment of moderate SLE patients. Recently, indications for belimumab were expanded to include

lupus nephritis and juvenile lupus (34–36). Although there is no FDA indication for ILD treatment, intravenous belimumab successfully treated two cases with refractory organizing pneumonia and non-specific interstitial pneumonia related to SLE (37, 38). Relevant data are still scarce, but the rationale for belimumab treatment for CTD-ILD is increasing and it should be assessed in regard to its efficacy and safety in the future.

We found some, although low correlations between serum BAFF and KL-6 level. KL-6 is identified as a sensitive and early biomarker associated with type II alveolar epithelial cell injury, permeability, and regeneration. Elevated serum or bronchoalveolar lavage fluid KL-6 concentration could reflect incipient alveolar and interstitial inflammation (39, 40). Higher KL-6 (>1,000 U/ml) levels indicated greater mortality and worse prognosis (41). One plausible explanation for our results, showing only low correlations of these two cytokines, may be that BAFF and KL-6 reflect different phases of ILD progression. The development of ILD in CTD may be initiated through alveolar epithelial cell microinjuries (KL-6 elevation) that leads to a persistent immuno-inflammatory phase with production of cytokines (BAFF elevation), chemokines and growth factors responsible for the expansion of fibroblast and myofibroblast populations. This in turn may lead to dysregulated tissue repair, parenchyma destruction, and scarring (30, 42, 43).

In the CTD-ILD group, BAFF levels were positively correlated with lung ultrasound B-lines number (r = 0.37, $p < 0.01$) and HRCT Warrick score ($r = 0.33$, $p < 0.01$), although the correlations were low. This may indicate that BAFF is subject to other influences or reflects other pathogenetic mechanisms. If corroborated with further research, it indicates that BAFF concentrations may play a supportive role and would be best used in combination with other measurements.

B-lines number was significantly correlated with serum KL-6 levels ($r = 0.47$, $p < 0.01$) and HRCT Warrick score ($r = 0.67$, $p < 0.01$), replicating our previous results.

Also, B-lines number was significant higher in patients with F-ILD compared to NF-ILD. The cut-off value for B-lines to segregate the F-ILD from NF-ILD was 122. The results demonstrate that increased B-lines are associated with more severe lung fibrosis assessed by the Warrick score. To the best of our knowledge, this is the first study to investigate the relationship between lung ultrasound B-lines and BAFF in patients with CTD-ILD. The application of pulmonary parenchymal ultrasound has been highlighted and extensively performed in different clinical settings in the past two decades (44, 45). Multiple B-lines were a sensitive sign of ILD, even in the subclinical and very early stages (21, 24), more B-lines were an indicator of more severe ILD as well (17). LUS's non-invasive, inexpensive, relatively feasible nature make it a tempting target as a screening tool (24, 46) or as a tool for follow-up of specific patients (47, 48). It could also be used in conjunction with other measurements (e g., with anti-MDA-5 antibody) for prognostic functions in patients with IIM-ILD (20, 49–51) or to support other measurements such as PFT or HRCT. The principal issue in all of these cases is a full understanding of contextual and confounding factors, requiring significant further research with multiple appropriate controls in larger trials, before adoption of LUS as a fully validated tool in CTD-ILD management.

To date, the standardization and validation of LUS examination in CTD-ILD screening and follow-up have not yet been completed. Different scoring methods and probe frequency are used in clinical operation. In addition, the calculation of the number of B-lines depends on the subjective judgment of the operator. Notwithstanding, low frequency convex probe with better penetration (more suitable for B-lines detection) and 50 scanning points (more comprehensive for B-lines assessment) applied in our study, as well as two senior ultrasound physicians cooperation, would partially help overcome the aforementioned defects.

A limitation of our data is that this is a retrospective study. Further it is from a single center with a relatively small sample size and a lack of sufficient samples across CTDs to be confident of the results for any single disease. The heterogeneous disease phenotypes, treatments and activities might affect BAFF or KL-6 levels. In addition, because approximately a third of patients failed to complete pulmonary function tests, the relationship among BAFF level, B-lines number, and PFTs variables were incomplete. Finally, the pathogenetic significance and timing of the tested cytokines are incompletely understood.

Conclusion

In conclusion, in this pilot study, we demonstrated that BAFF levels and B-lines number are associated with CTD-ILD severity and phenotype, although correlations are low to moderate, so that these biomarkers might best be used as supportive measures with other measures of CTD-ILD. Cut-off points were proposed to separate fibrotic from non-fibrotic ILD but larger trials with more controls and diverse CTDs will be necessary before these cut-off points can be fully adapted. These findings indicate that combining serological, imaging and sonographic biomarkers could play an important role in the management of CTD-ILD in the future.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Shantou Central Hospital Ethics

Committee (no. 2022–037). The patients/participants provided their written informed consent to participate in this study.

Author contributions

YW and XX: conceptualization. AM, ZX, and GZ: data curation. JL: formal analysis. YW: funding acquisition, project administration, and writing—original draft. SH: investigation. SZ and GD: methodology. KZ: resources. SC: software. DF: supervision. WZ and JZ: validation. MM-C: visualization. LG, CB, and A-MH-V: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Radiomics to predict the mortality of patients with rheumatoid arthritis-associated interstitial lung disease: A proof-of-concept study

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Objectives: Patients with rheumatoid arthritis (RA) and interstitial lung disease (ILD) have increased mortality compared to the general population and factors capable of predicting RA-ILD long-term clinical outcomes are lacking. In oncology, radiomics allows the quantification of tumour phenotype by analysing the characteristics of medical images. Using specific software, it is possible to segment organs on high-resolution computed tomography (HRCT) images and extract many features that may uncover disease characteristics that are not detected by the naked eye. We aimed to investigate whether features from whole lung radiomic analysis of HRCT may alone predict mortality in RA-ILD patients.

Methods: High-resolution computed tomographies of RA patients from January 2012 to March 2022 were analyzed. The time between the first available HRCT and the last follow-up visit or ILD-related death was recorded. We performed a volumetric analysis in 3D Slicer, automatically segmenting the whole lungs and trachea *via* the Lung CT Analyzer. A LASSO-Cox model was carried out by considering ILD-related death as the outcome variable and extracting radiomic features as exposure variables.

Results: We retrieved the HRCTs of 30 RA-ILD patients. The median survival time (interquartile range) was 48 months (36–120 months). Thirteen out of 30 (43.33%) patients died during the observation period. Whole line segmentation was fast and reliable. The model included either the median grey level intensity within the whole lung segmentation [high-resolution (HR) 9.35, 95% CI 1.56–55.86] as a positive predictor of death and the 10th percentile of the number of included voxels (HR 0.20, 95% CI 0.05–0.84), the voxel-based pre-processing information (HR 0.23, 95% CI 0.06–0.82) and the flatness (HR 0.42, 95% CI

0.18–0.98), negatively correlating to mortality. The correlation of grey level values to their respective voxels (HR 1.52 95% CI 0.82–2.83) was also retained as a confounder.

Conclusion: Radiomic analysis may predict RA-ILD patients' mortality and may promote HRCT as a digital biomarker regardless of the clinical characteristics of the disease.

KEYWORDS

radiomics, rheumatoid arthritis-associated interstitial lung disease, high-resolution computed tomography, biomarker, LASSO

Introduction

Patients with rheumatoid arthritis (RA) have decreased survival compared to the general population (1, 2). RA-associated interstitial lung disease (RA-ILD) is a common extra-articular manifestation of RA. The median survival of RA-ILD patients is about 3–7 years, which is markedly reduced compared to RA patients without ILD and the general population (3–5). Detection of RA-ILD varies widely by different research methods. Consequently, the reported prevalence of RA-ILD reflects such high variance, with studies based on chest computed tomography (CT) scans indicating RA-ILD presence in 10–30% of patients. Despite the recent advance with potential diagnostic biomarkers such as the MUC5B promotor variant (6) or sound analysis of vesicular murmur (7), there is a scarcity of factors capable of predicting RA-ILD long-term clinical outcomes. In oncology, radiomics allows for comprehensive tumour phenotype quantification by examining medical images' characteristics. In brief, using specific software, it is possible to segment organs on CT images to extract a massive number of features that have the potential to uncover disease characteristics that fail to be seen by the naked eye. The hypothesis of radiomics is that the distinctive imaging features between disease forms may help make a prognosis and predict the therapeutic response for various conditions, thus providing valuable information for personalised therapy and patient management (8). We aimed to investigate whether features from whole lung radiomic analysis of high-resolution computed tomography (HRCT) might alone predict mortality in RA-ILD patients.

Materials and methods

We retrieved the consecutive HRCTs of patients affected with RA according to 2010 EULAR/ACR criteria (9), and RA-ILD followed at the Rheumatology departments of two Italian tertiary centres from January 2012 to March 2022. To be included in such retrospective analysis, HRCTs had to have been carried out at one of the Radiology departments of the same centres, and the DICOM files had to have been stored in the respective picture archiving and communication systems (PACS). We recorded the time interval between the first available HRCT and the last follow-up visit or eventual death for physician-reported ILD-related causes on death certificates for each patient. We also recorded clinical and demographic characteristics together with rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA) status. We excluded patients with known overlapping connective tissue disease or secondary Sjogren's syndrome. In particular, we considered only HRCT examinations with 0.625–1.25-mm slice thickness and full-inspiration scans from the lung apices to below the costo-phrenic angles. Both centres used the following parameters: tube voltage set at 120 kV; tube current: fixed mAs depending on the patient body weight; pitch: 0.8 or more, adjusted on the seriousness of patient dyspnoea, collimation: 0.6 mm; images were reconstructed from raw data using a slice thickness of 0.6 mm with an index of 0.4 mm using an edge-enhancing algorithm. All images were viewed at a window setting optimised for assessment of the lung parenchyma (width 1,500 HU; level −700 HU).

The study was approved and reviewed by the local Ethical Committee (Biopure registry, IRB Approval n.5940, Azienda Ospedaliera Universitaria di Bari). All patients gave their written informed consent.

Segmentation and radiomic features extraction

We performed a volumetric analysis and visualisation in 3D Slicer[1], automatically segmenting the whole lungs and trachea

1 http://www.slicer.org

via the Lung CT Analyzer project[2]. As previously described elsewhere (10), such an extension allows fully reproducible automated whole lungs and trachea segmentation using 13 manually marked points. Three points were placed in axial and coronal views inside the right and the left lung, and one point in the trachea (further details in **Supplementary material**). For each HRCT, segmentation was repeated twice by a rheumatologist and a radiologist in order to check for radiomic feature stability (see below). Two expert radiologists then reviewed the latter segmentations to confirm that all lung parenchyma had been appropriately isolated.

The PyRadiomics platform was developed for cancer research with the US National Cancer Institute grant 5U24CA194354 (8). It can extract radiomic data from medical imaging loading, pre-process the image and segmentation maps, calculate features using the different feature classes, and return results as continuous variables in CSV format. In a Python 3.9 environment, the PyRadiomics API (version 3.01) was implemented to extract 120 features for segmented regions (see **Supplementary material** for further technical details). Such features, including skewness and kurtosis, together with more specific texture-related ones, comply with feature definitions as described by the imaging biomarker standardization initiative (IBSI) (8).

Collinearity was checked, and all redundant features were removed (i.e., with a correlation higher than 0.8 as an absolute value, see **Supplementary material**). We carried out feature z-score standardisation before the next step.

Statistics

Intraclass correlation coefficient (ICC) was used to test radiomic feature stability by comparing the abovementioned segmentations. The survival function was plotted with the Kaplan–Meier estimate together with the at-risk table. Cox survival analysis and least absolute shrinkage and selection operator (LASSO) regression univariable analyses were performed to assess the association of each radiomic feature with death. Values of $p < 0.20$ were selected as candidate variables. The method of LASSO was used to determine predictors as such procedures demonstrated superior accuracy than stepwise elimination (11). As a proof-of-concept study, demographics and disease characteristics were not included in the regression model to demonstrate the feasibility and investigate the association of features alone with RA patients' death. Cox-Snell residuals were plotted against the Nelson–Aalen cumulative hazard rate function to test the model's reliability. Stata 17 (StataCorp, TX, USA), together with Python 3.9 herein invoked with Pystata API, numpy 1.22, pandas 1.4.3, and scikit-learn 1.1.2 libraries, were used on a terminal powered by an Apple™ Silicon M1Max with 64 GB RAM.

2 https://github.com/rbumm/SlicerLungCTAnalyzer/

Results

We retrieved HRCTs of 30 RA-ILD patients, 11 males (36.67%) with median age [interquartile range (IQR)] of 72 (65–78) years at the instrumental examination. They had established RA with median disease duration (IQR) of 132 (65–278) months. ACPA positivity was found in 25 out of 30 patients (83.33%), whereas RF-positive individuals were found in 18 out of 29 (62.97%). Usual interstitial pneumonia (UIP) was the most frequent finding (18/30, 60%) at HRCT, followed by unclassifiable patterns (8/30, 26, 67%). Non-specific interstitial pneumonia (NSIP) in two patients (6.67%), whereas organising pneumonia (OP) and lymphocytic interstitial pneumonia (LIP) were found in one patient, respectively (3.33%, for both). Thirteen out of 30 patients (43.33%) were on methotrexate at HRCT examination, whereas 19 out of them (63.33%) were treated with biologic agents and two with baricitinib (6.67%). Complete patient characteristics and ILD patterns are shown in **Table 1**. The mean follow-up time (± standard deviation) was 37.99 ± 29.50 months median survival time (MST—IQR) was 48 months (36–120 months). Thirteen out of 30 (43.33%) patients died during the observation period, and the cause of death was attributed to ILD as judged by the physician. Kaplan–Meier survival function was plotted in **Figure 1A**.

The death cause was acute ILD exacerbations in 38.46% of cases (5/13) and pneumonia in 23.07% (3/13). Finally, another 38.46% (5/13) of death certificates and health records reported generic "RA-ILD" as the cause of death.

The automatic segmentation allowed for the comprehensive and precise isolation of RA-ILD lung parenchyma and upper airways coherent with radiologist judgement in all cases at the first attempt (**Figure 2**). The segmentation procedure took a mean 3.13 ± 2.11 min on average. Such a procedure showed excellent feature stability with ICC = 1, indicating perfect reliability between operators. After checking for collinearity (**Supplementary Figure 4**), only 22 features were retained (see **Supplementary material** for the full list).

After the LASSO-Cox procedure, the model included the features:

- The median grey level intensity within the whole lung segmentation mask [coded as original_firstorder_median, high-resolution (HR) 9.35, 95% CI 1.56–55.86].
- The 10th percentile of the number of voxels included in the whole lung segmentation mask (coded as original_firstorder_10Percentile HR 0.20, 95% CI 0.05–0.84).
- 3D Slicer voxel-based pre-processing information (coded as diagnostics_Imageoriginal_Mean, HR 0.23, 95% CI 0.06–0.82).
- Flatness—the relationship between the largest and smallest principal components in the whole lung mask (coded as original_shape_Flatness, HR 0.42, 95% CI 0.18–0.98).

- Correlation of grey level values to their respective voxels in the Grey level co-occurrence matrix (coded as original_glcm_Correlation, HR 1.52 95% CI 0.82–2.83), retained as a confounder.

We observed that the hazard function followed the 45-degree line very closely except for huge values of time (**Figure 1B**).

Discussion

Patients with RA-ILD have an increased disease burden, reduced quality of life and physical function, severe respiratory symptoms, and worse RA disease. ILD also leads to substantial healthcare costs and interactions; 72% have an all-cause inpatient admission, and 76% have an all-cause emergency department visit. Finally, as mentioned above, they also experience excess mortality compared to the general population and patients with RA without ILD (1, 2, 12). In this scenario, it is conceivable that improving patient management and follow-up is of utmost importance. Many efforts have been made to improve early ILD diagnosis. Investigating the role of potential perturbations to pulmonary mucosa in airways seems to be an approach with concrete potential. In fact, the MUC5B promotor variant in RA patients has been associated with a threefold increased risk for ILD (6).

TABLE 1 Patient characteristics.

	Available observations	
Male, *n* (%)	30	11 (36.67)
Age at HRCT, years, median (IQR)	30	72 (65–78)
RA disease duration, month, median (IQR)	30	132 (65–278)
RF positivity, *n* (%)	29	18 (62.07)
ACPA positivity *n* (%)	30	25 (83.33)
ILD pattern at HRCT, (*n*%)	30	
UIP		18 (60)
NSIP		2 (2.67)
LIP		1 (3.33)
OP		1 (3.33)
Unclassifiable		8 (26.67)
Therapy at HRCT, *n* (%)	30	
MTX		17 (56.67)
Tocilizumab		7 (23.33)
Abatacept		6 (0.20)
Rituximab		5 (16.66)
Anakinra		1 (3.33)
Baricitinib		2 (6.67)

ACPA, anti-cyclic citrullinated peptide antibodies; HRCT, high-resolution computed tomography; LIP, lymphocytic interstitial pneumonia; ILD, interstitial lung disease; IQR, interquartile range; MTX, methotrexate; NSIP, non-specific interstitial pneumonia; OP, organising pneumonia; RA, rheumatoid arthritis; RF, rheumatoid factor; UIP, usual interstitial pneumonia.

Furthermore, an algorithm (Vector) to detect the presence of velcro crackles in pulmonary sounds showed promising results for screening RA patients suspected of ILD and who should be directed to HRCT for the diagnosis (12). But, only a few tools seem to have the potential for driving treatment strategy (13–15), mostly involving the shifts in levels of selected serum proteins, such as CXCL11/I-TAC and matrix metalloproteinase-13, which may not be available in routine clinical practice. Radiomics has been helpful in phenotyping cancers (8, 16, 17). It can quantify a large panel of phenotypic characteristics, such as shape and texture, potentially reflecting biologic properties like intra- and inter-tumour heterogeneities and related distinct treatment responses (8). An advantage of radiomics is the standardised procedure for extraction, relying on open-source libraries but dependent upon the segmentation of the region of interest of medical images, which can be obtained by an expert radiologist or machine learning algorithms.

In this study, we applied radiomics to baseline HRCT of the lungs of RA patients with ILD to search for predictors of mortality. To this end, we used an automated segmentation tool allowing whole lung and trachea segmentation. In literature, such a procedure appeared precise and accounted for high user reliability (10, 18). The same was true when we used this tool on ILD parenchyma in all our patients, despite two different CT machines and slice thickness, enabling us to extract 120 radiomic features for our analysis systematically. We found a model including n.5 radiomic features associated with RA_ILD patients' death, with good fitting except for large values of the time. Adjusting for original_glcm_Correlation, the radiomic feature original_firstorder_median was positively correlated, whereas original_firstorder_10Percentile, diagnostics_Imageoriginal_Mean and original_shape_Flatness radiomic features were negatively correlated to ILD-related mortality.

Our results confirm that lung imaging has prognostic potential. In this regard, they are somewhat consistent with the report from Oh et al. using quantitative HRCT (QCT) scores to predict mortality in RA-ILD (19). They analyzed a retrospective cohort of 144 RA-ILD patients diagnosed at a single centre between 1999 and 2015. All patients had HRCT performed at RA-ILD diagnosis, and baseline clinical data included autoimmunity status, inflammatory markers, pulmonary function tests, and medication use. To assess the baseline, HRCTs were assessed by an automated quantification system (AQS) that divided each lung image into small

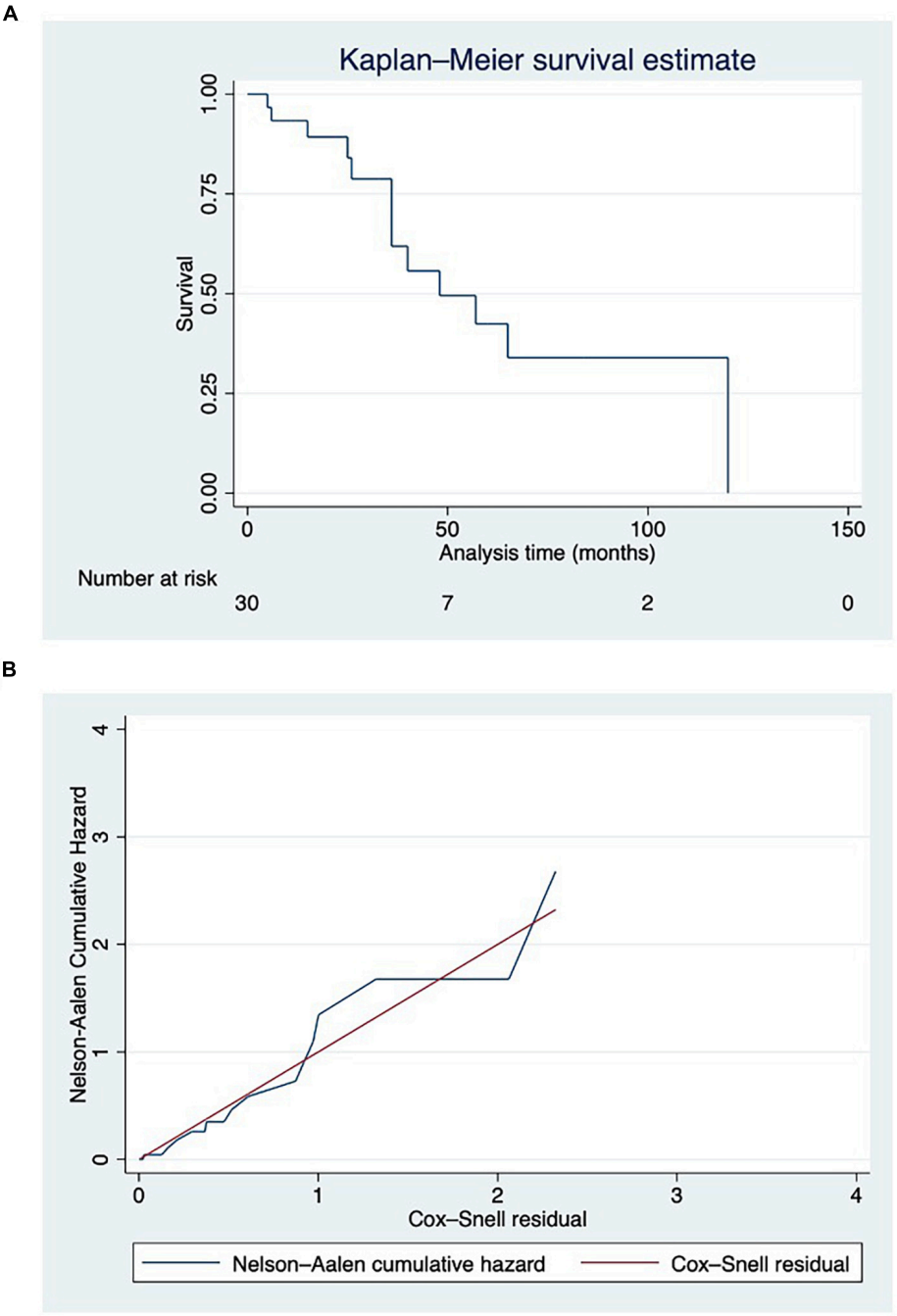

FIGURE 1
(A) Survival function displayed using Kaplan–Meier estimate, with at-risk table. Deaths have been reported in parentheses. **(B)** Cox-Snell residuals plotted against the Nelson–Aalen cumulative hazard rate function to test the reliability of the model. Hazard function followed the 45-degree line very closely except for huge values of time.

regions of interest and scored each region of interest for the presence of reticulation, architectural distortion, ground-glass opacification, and honeycombing. By combining these scores, the AQS generated a quantitative lung fibrosis score (QLF) capable of predicting RA-ILD outcomes but also independently associated with mortality after adjustment for age, baseline erythrocyte sedimentation rate (ESR), and pulmonary function tests (20). Although similar in its fundamentals, the radiomics approach offers several advantages. Radiomic features may be used with genomic data leading to the so-called radiogenomics, which showed potential for both diagnosis and prognosis in oncology research (8). This appears particularly interesting in

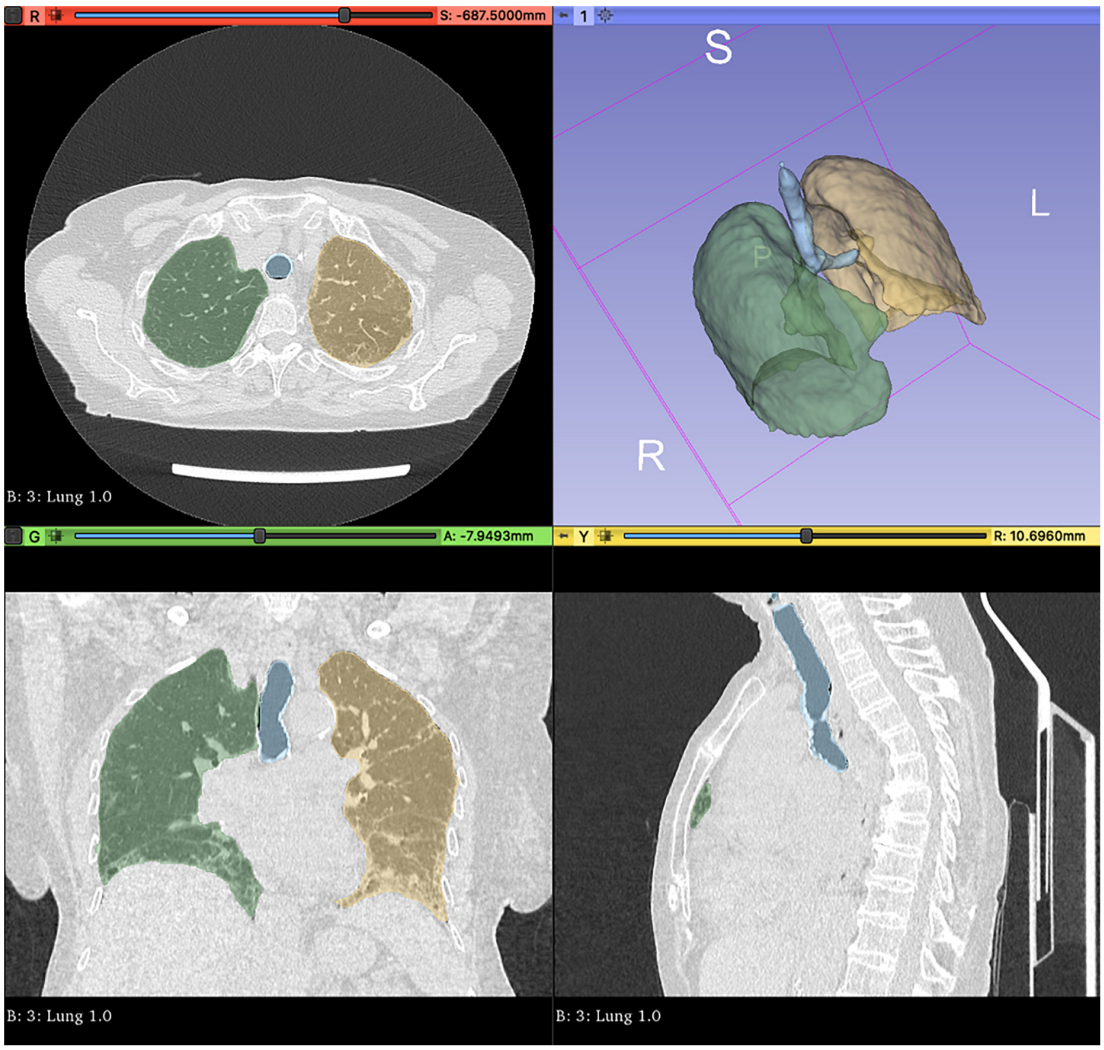

FIGURE 2
Automated whole lungs and trachea segmentation using 3D Slicer (http://www.slicer.org) *via* the Lung CT Analyzer project (https://github.com/rbumm/SlicerLungCTAnalyzer/).

RA-ILD given the recent findings about MUC5B- related ILD risk (6). Furthermore, the whole lung radiomics does not miss information from apparent healthy parenchyma, contributing to the image and tissue characteristics analysis that a naked-eye approach would never consider. Finally, *de novo* radiomic feature extraction may be easily standardised and does not rely on algorithm training.

We must acknowledge some weaknesses of our study. First, as the proof-of-concept method, we analyzed a small-sized retrospective cohort. As already mentioned, we did not apply non-linear machine learning methods, which might provide better modelling of radiomic features than linear methods. This preliminary study demonstrated that several radiomics features are predictors of RA-ILD patients' mortality in the absence of demographics and disease-related characteristics. It is also conceivable that using a large, annotated dataset of radiomics features from HRCT-segmented whole-lung parenchyma, it could be possible to discriminate RA-ILD from interstitial lung involvement of different connective tissue diseases. More extensive studies with internal and external validation on independent cohorts are needed to confirm that a radiomics approach could be adopted in routine clinical practice. Further research is required to enable HRCT to provide digital biomarkers of RA-ILD outcomes.

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 the Comitato Etico Interregionale. The patients/participants provided their written informed consent to participate in this study.

Author contributions

VV, AM, and MS designed the study and wrote the manuscript. VV and AS did the data analysis. ML and GC gathered the patient data. FI supervised each step of the whole study. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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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.2022.1069486/full#supplementary-material

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The influence of immortal time bias in observational studies examining associations of antifibrotic therapy with survival in idiopathic pulmonary fibrosis: A simulation study

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Background: Immortal time bias (ITB) has been overlooked in idiopathic pulmonary fibrosis (IPF). We aimed to identify the presence of ITB in observational studies examining associations between antifibrotic therapy and survival in patients with IPF and illustrate how ITB may affect effect size estimates of those associations.

Methods: Immortal time bias was identified in observational studies using the ITB Study Assessment Checklist. We used a simulation study to illustrate how ITB may affect effect size estimates of antifibrotic therapy on survival in patients with IPF based on four statistical techniques including time-fixed, exclusion, time-dependent and landmark methods.

Results: Of the 16 included IPF studies, ITB was detected in 14 studies, while there were insufficient data for assessment in two others. Our simulation study showed that use of time–fixed [hazard ratio (HR) 0.55, 95% confidence interval (CI) 0.47–0.64] and exclusion methods (HR 0.79, 95% CI 0.67–0.92) overestimated the effectiveness of antifibrotic therapy on survival in simulated subjects with IPF, in comparison of the time–dependent method (HR 0.93, 95% CI 0.79–1.09). The influence of ITB was mitigated using the 1 year landmark method (HR 0.69, 95% CI 0.58–0.81), compared to the time–fixed method.

Conclusion: The effectiveness of antifibrotic therapy on survival in IPF can be overestimated in observational studies, if ITB is mishandled. This study adds to

the evidence for addressing the influence of ITB in IPF and provides several recommendations to minimize ITB. Identifying the presence of ITB should be routinely considered in future IPF studies, with the time–dependent method being an optimal approach to minimize ITB.

KEYWORDS

immortal time bias, idiopathic pulmonary fibrosis, time–dependent, landmark, observational research

Highlights

- **Question:** How immortal time bias (ITB) can affect effect size estimates of antifibrotic therapy on survival in patients with idiopathic pulmonary fibrosis (IPF)?
- **Findings:** The effectiveness of antifibrotic therapy on survival in patients with IPF can be overestimated in observational studies, if ITB is mishandled. Identifying the presence of ITB should be routinely considered in future IPF studies, with the time–dependent method being an optimal approach to minimize ITB.
- **Meaning:** Clinical decisions based on biased estimations may have potentially detrimental impact on clinical practice. This study adds to the evidence for addressing the influence of ITB in IPF studies and provides methods to ensure the true effect of treatments are estimated to ensure appropriate treatment for patients with IPF in future observational studies.

Introduction

Definition of immortal time bias

In the early 1970s, two observational studies (1, 2) examined associations between heart transplant and survival of patients and reported superior survival in treated patients compared to untreated controls. However, Gail (3) noted that there was an artificial survival advantage in the transplanted group, related to all treated patients needing to survive until time of treatment.

Immortal time refers to the waiting period before participants begin to receive interventions (e.g., antifibrotic therapy) since they will never become a treated patient if they die first or are censored (4, 5). However, no such period is allowed for the controls. When it is not adequately dealt with in analysis, a systematic error of immortal time bias (ITB) can occur, which distorts the real associations between interventions and outcomes in observational studies (6, 7).

Susceptibility of idiopathic pulmonary fibrosis studies to ITB

Immortal time bias commonly occurs in cohort studies due to the nature of their observational settings. Idiopathic pulmonary fibrosis (IPF) studies examining associations between interventions and time–to–event outcomes are particularly susceptible to suffer from the influence of ITB due to two key reasons. First, identifying a specific commencement date for medication use may be difficult in available data sources, especially for individuals with a rapid disease trajectory, which may limit abilities to measure the immortal time. In practice, patients with IPF commonly experience a substantial duration of symptoms (such as cough and shortness of breath) before diagnosis. A previous study (8) found that the median time delay from symptom onset to diagnosis was 2.1 years, and 41% (n = 84) of incident patients with IPF reported initial misclassification of respiratory symptoms. Second, IPF is characterized by a high mortality risk, with a median survival time of about 3 years (9, 10). Observation periods in IPF studies are commonly short, and thereafter immortal person–time may account for a large proportion of the total observation period (person years) in the intervention group, which may induce substantial biases.

Persistence of unaddressed ITB in IPF studies

The influence of ITB has been addressed in many disease areas such as diabetes (11), cancers (12), rheumatic diseases (13), orthopedics (14), and chronic obstructive pulmonary disease (COPD) (15), however, there is a paucity of data on the influence of ITB in IPF studies (16–19).

Several cohort studies (20, 21) have reported the protective effect of anti–gastric fluid reflux therapy on survival in IPF, while this survival benefit may have been affected by the influence of ITB (22, 23). In 2021, a meta–analysis (24) including 18 cohort studies reported the protective effect of antifibrotic therapy on survival of IPF; however, none were assessed or corrected for the influence of ITB. A recent commentary (25) has highlighted that the effectiveness of antifibrotic therapy in reducing the risk of death in IPF may be overestimated by the influence of ITB in a German cohort study (17).

Current methods to mishandle immortal time in observational studies

Both time–fixed and exclusion methods are conventional but biased in IPF studies during analysis (26). The time–fixed method is defined as Cox proportional hazards regression models with

a time–fixed definition for the study intervention, which can introduce misclassification bias by counting immortal person–time as part of the intervention group (11, 27). The exclusion method is defined as Cox models with a complete exclusion of immortal person–time from the analysis, which can introduce selection bias (11, 27).

Appropriate methods to handle immortal time in observational studies

Both time–dependent and landmark methods are unbiased approaches and can be used to account for ITB (11, 28). The time–dependent method is defined as Cox models with a time–dependent definition for the study intervention. Any immortal person–time is added to the untreated comparator group for analysis (11). The landmark method is defined as Cox models with a landmark time, which excludes participants who have died or are censored before the landmark time (28). Participants are classified as exposed (intervention) group or unexposed (comparator) group based on their exposure status from cohort entry until the landmark time, and any newly exposed subjects during subsequent follow up after the landmark time are categorized into the comparator group (28). Although those two appropriate methods are gradually used in recent observational studies in the field of interstitial lung diseases (29, 30), there have been no studies in the field of IPF that evaluated effects of antifibrotic therapy with the incorporation of ITB.

The objectives of our methodological study

With the above backdrop in mind, this methodological study aims to identify the presence of ITB in observational studies examining associations between antifibrotic therapy and survival in patients with IPF and illustrate how ITB may affect effect size estimates of those associations by assessment methods.

Materials and methods

Identification of ITB

A newly published ITB Study Assessment Checklist (4) was used to identify the presence of ITB in observational studies; this checklist includes five items: cohort entry, immortal time, intervention eligibility period, observation period, and statistical methods. From the IPF studies reviewed, cohort entry is defined as the time of IPF diagnosis if known or recruitment to a cohort if not. Immortal time is defined as the time between cohort entry and the initiation of antifibrotic therapy. Intervention eligibility period is defined as the duration of antifibrotic therapy for participants. Specific observation period for the intervention and comparator group is also needed to be provided. As mentioned previously, four statistical techniques include time-fixed, exclusion, time-dependent, and landmark methods.

We used the studies included in a recent meta–analysis (24) of survival benefit of antifibrotic therapy as examples to identify the presence of ITB. Two investigators (QZ and IC) independently assessed the presence of ITB and identified the statistical methods used in each observational study. If the intervention was a time–dependent exposure and there was an immortal time during the follow up, potential for ITB was deemed to exist. All discrepancies were discussed and resolved by consensus with a third investigator (AJP).

A simulation study

To illustrate how ITB may affect the effectiveness of antifibrotic therapy on survival in IPF, we used a simulated dataset of subjects with IPF since access to the real world data was not available (22).

A simulation study is commonly used to estimate performance of statistical methods and illustrate how those methods can be utilized into practice (31). Individual survival data were simulated from a Weibull distribution with a proportional hazard function and censored at 5 years by using the "survsim package" in STATA (32). A hypothetic treatment variable (antifibrotic therapy) was generated from a binomial distribution with parameters n = 1,000 and p = 0.5. We incorporated the effect of antifibrotic therapy by defining a median background survival time of 3 years and a hazard ratio (HR) of death of 0.55, as estimated from a meta–analysis (24). For ITB illustration, we simulated that each subject with antifibrotic therapy had 1 year of immortal time.

Kaplan–Meier survival curves and Log-rank tests were used to compare 3 years survival between simulated subjects with and without antifibrotic therapy using the four statistical methods. In addition, Cox proportional hazards regression models were used to calculate crude HR [95% confidence interval (CI)] for mortality when ITB was considered. The time-dependent method was considered as the current gold-standard in this analysis (11, 28). We further quantified the difference in the effect estimates between the time-dependent method and other methods including time-fixed, exclusion, and landmark, as follows (33):

$$\text{Difference} = \frac{(\text{HR from other methods}) - (\text{HR from time dependent mothod})}{(\text{HR from time dependent mothod})} * 100\%$$

Considering there are high heterogeneities on survival times or mortality outcomes in studies reporting IPF-related antifibrotic therapy (24), a sensitivity analysis was conducted to validate our estimates. We repeated the analyses defining a median background survival time of 2 years, and a HR of death of 0.38 in the unadjusted Cox model as estimated from a previous cohort study (19). For ITB illustration, we simulated that each subject with antifibrotic therapy had 1 year of immortal time.

All statistical analyses were conducted using STATA version 17.0 (34).

Results

Identification of ITB

There were 18 cohort studies (16–19, 35–48) in a recent meta–analysis (24), while one study (45) reporting white blood cell counts, and one study (46) reporting cross–sectional area of erector spinae muscle as the main intervention of interest were excluded from this study.

Of the 16 included studies (Table 1), 14 (16–19, 35, 37–39, 41–44, 47, 48) were the subject of ITB due to using time–dependent interventions (i.e., participants starting use of antifibrotic therapy at any time during the follow up period). Two studies (36, 40) were detected with uncertain status for ITB with obscure description of timelines for both intervention and comparator groups.

For statistical methods, the time–fixed method was used in ten studies (18, 19, 35, 37–39, 42–44, 47) and exclusion method was used in other four studies (16, 17, 41, 48). Specific statistical methods were not applicable in the remaining two studies (36, 40).

A simulation study

Simulated subjects

Of the 1,000 simulated subjects with IPF, 483 were assigned to "take" antifibrotic therapy (antifibrotics users), and 517 did not receive antifibrotic therapy (non–users). The median (25th–75th percentiles) observation period from cohort entry to death was 3.5 (2.0, 5.0) years for the total population, 4.5 (2.7, 5.0) years for antifibrotics users, and 2.9 (1.5, 4.9) years for non–users, respectively.

Time-fixed method

Immortal time was 483 person years, which accounted for 26% of 1,855 person years for antifibrotics users in the time–fixed method. Immortal person–time were ignored and incorporated in the treated group (Figure 1A). The 3 years survival rate of antifibrotics users was significantly higher than non–users (71 vs. 48%; $P < 0.001$) (Figure 2A). Antifibrotics users had a significantly decreased risk of all–cause mortality compared to non–users using the time–fixed method (HR 0.55, 95% CI 0.47–0.64; $P < 0.001$) (Table 2).

Exclusion method

All immortal person–time were excluded from the study in the exclusion method (Figure 1B). There was a significant difference in the 3 years survival rates between antifibrotics users and non–users using the exclusion method (56 vs. 48%; $P = 0.003$) (Figure 2B). Antifibrotics users had a significantly decreased risk of all–cause mortality compared to non–users using the exclusion method (HR 0.79, 95% CI 0.67–0.92; $P = 0.003$) (Table 2).

TABLE 1 Assessment of immortal time bias (ITB) in published studies reporting effects of antifibrotic therapy on survival of participants with idiopathic pulmonary fibrosis (IPF).

References	Country	ITB checklist*					Presence of ITB	Statistical methods
		C1	C2	C3	C4	C5		
Hosein et al. (40)	Canada	No	NA	NA	NA	No	NA	NA
Jo et al. (19)	Australia	Yes	Yes	No	Yes	No	Yes	Time-fixed
Margaritopoulos et al. (43)	Greece	Yes	Yes	No	Yes	No	Yes	Time-fixed
Zubairi et al. (48)	Pakistan	Yes	Yes	No	No	No	Yes	Time-fixed
Cerri et al. (36)	Italy	No	NA	NA	Yes	No	NA	NA
Dempsey et al. (16)	USA	Yes	Yes	No	Yes	No	Yes	Exclusion
Fernández-Fabrellas et al. (39)	Spain	Yes	Yes	No	No	No	Yes	Time-fixed
Kaunisto et al. (42)	Finland	Yes	Yes	No	Yes	No	Yes	Time-fixed
Zurkova et al. (48)	Czech Republic	Yes	Yes	No	Yes	No	Yes	Exclusion
Kang et al. (41)	South Korea	Yes	Yes	No	Yes	No	Yes	Exclusion
Adegunsoye et al. (18)	USA	Yes	Yes	No	Yes	No	Yes	Time-fixed
Alhamad et al. (35)	Saudi Arabia	Yes	Yes	No	Yes	No	Yes	Time-fixed
Behr et al. (17)	Germany	Yes	Yes	No	Yes	No	Yes	Exclusion
Dhooria et al. (37)	India	Yes	Yes	No	Yes	No	Yes	Time-fixed
Feng et al. (38)	China	Yes	Yes	No	Yes	No	Yes	Time-fixed
Moon et al. (44)	South Korea	Yes	Yes	No	Yes	No	Yes	Time-fixed

*The ITB Study Assessment Checklist; ITB: immortal time bias; IPF: idiopathic pulmonary fibrosis; NA: not applicable.
C1: Does study report cohort entry time–point for both intervention and comparator groups.
C2: Does immortal time exit in this study.
C3: Does study report intervention eligibility period for the intervention group.
C4: Does study report observation period for all groups.
C5: Does study report appropriate statistical methods (time–dependent or landmark methods) to address immortal time bias.

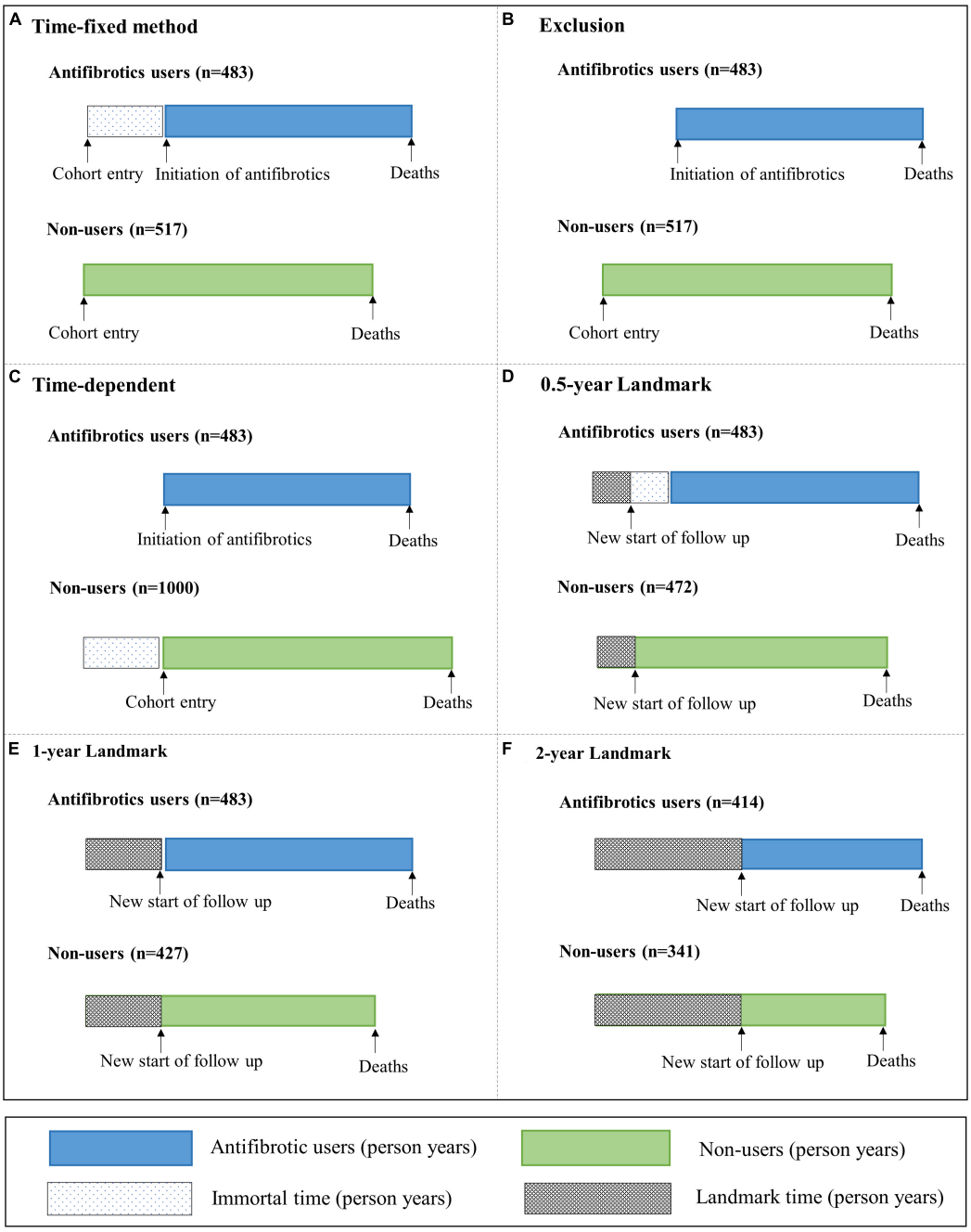

FIGURE 1
Illustration of allocating immortal time in four different methods. **(A)** Time–fixed method, **(B)** exclusion method, **(C)** time–dependent method, and **(D–F)** landmark method. For the time–fixed method, the immortal time was ignored and incorporated in the treated group. For the exclusion method, the immortal time was excluded from the study. For the time–dependent method, the immortal time was switched into the control group, with an additional 483 subjects being added into the control group. For the landmark method, 0.5, 1, and 2 years landmarks excluded 45, 90, and 245 simulated subjects who had died prior to this time point, respectively. Immortal time was defined as the time from cohort entry to the initiation of antifibrotic therapy. Landmark time was defined as a fixed time point, which was the same for all subjects.

Time-dependent method

All immortal person–time were switched into the control group in the time–dependent method, with an additional 483 subjects being added into the control group (Figure 1C). The 3 years survival rates for antifibrotics users and non–users were similar (56 *versus* 53%; $P = 0.391$) (Figure 2C). There was no significant association between antifibrotic therapy and survival in subjects with IPF using the time-dependent method (HR 0.93, 95% CI 0.79–1.09; $P = 0.391$) (Table 2).

Landmark method

For the landmark method, 0.5, 1, and 2 years landmarks excluded 45, 90, and 245 simulated subjects who had died prior to this time point, respectively (Figures 1D–F). For the 0.5 year

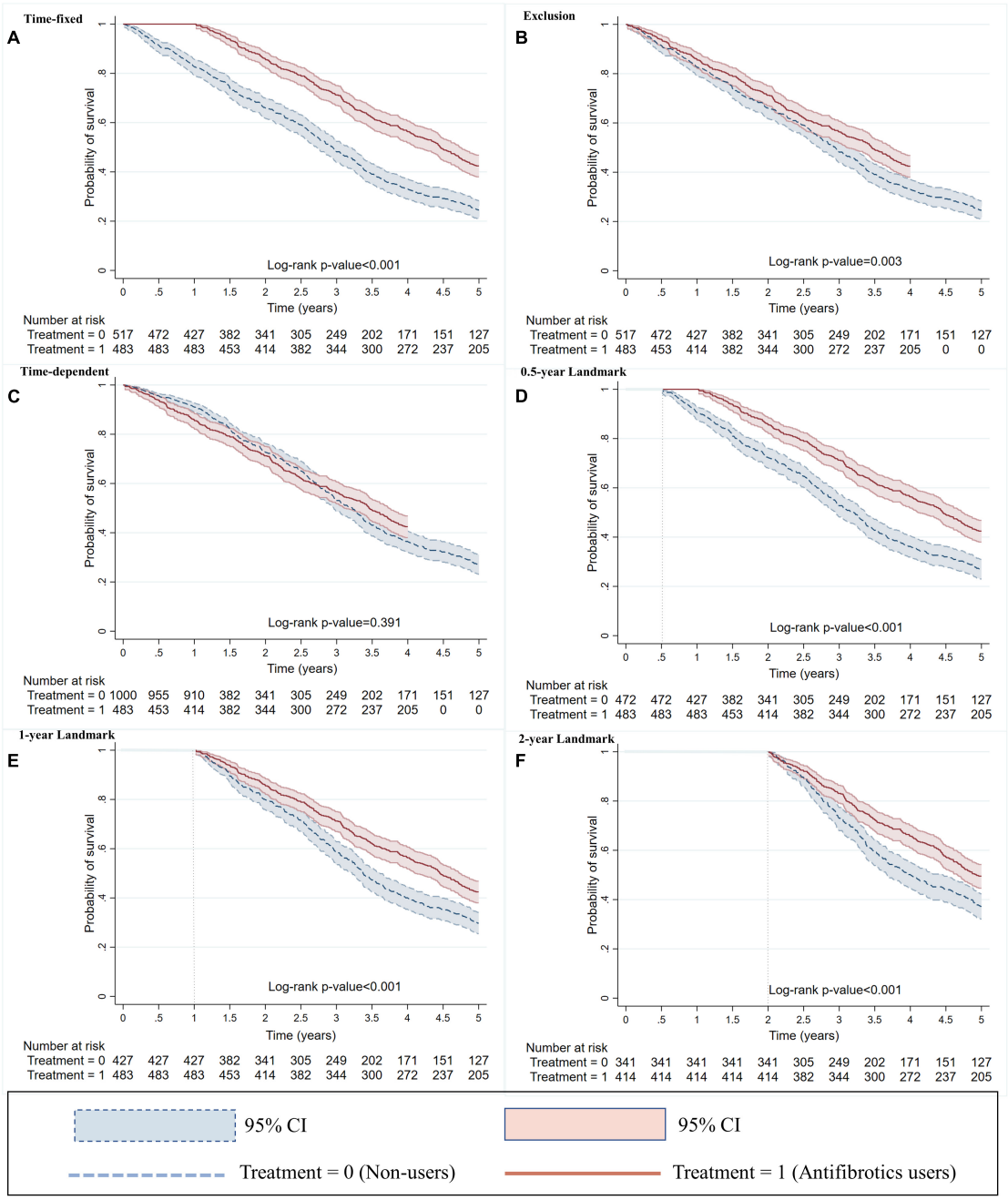

FIGURE 2
Kaplan–Meier survival curves with methods of **(A)** time–fixed, **(B)** exclusion, **(C)** time–dependent, and **(D–F)** landmark. For the time–fixed method, the immortal time was ignored and incorporated in the treated group. For the exclusion method, the immortal time was excluded from the study. For the time–dependent method, the immortal time was switched into the control group, with an additional 483 subjects being added into the control group. For the landmark method, 0.5, 1, and 2 years landmarks excluded 45, 90, and 245 simulated subjects who had died prior to this time point, respectively. Immortal time was defined as the time from cohort entry to the initiation of antifibrotic therapy. Landmark time was defined as a fixed time point, which was the same for all subjects.

landmark method, the 3 years survival rate of antifibrotics users was significantly higher than non-users in subjects who survived more than 6 months (71 *versus* 53%; $P < 0.001$) (Figure 2D). For the 1 year landmark method, there was a significant difference in the 3 years survival rates between antifibrotics users and non–users in subjects who survived more than 1 year (71 *versus* 58%; $P < 0.001$) (Figure 2E). For the 2 years landmark method, the 3 years survival rate of antifibrotics users was significantly higher than non–users in subjects who survived more than 2 years (83 *versus* 73%; $P < 0.001$) (Figure 2F). Antifibrotics users were associated with a significantly decreased risk of all–cause mortality compared to non–users using 0.5 year landmark (HR 0.61, 95% CI 0.52–0.71; $P < 0.001$), 1 year landmark (HR 0.69, 95% CI 0.58–0.81; $P < 0.001$), and 2 years landmark (HR 0.69, 95% CI 0.57–0.84; $P < 0.001$), respectively (Table 2).

TABLE 2 An illustration of the influence of immortal time bias (ITB) on associations between antifibrotic therapy and survival in simulated subjects with idiopathic pulmonary fibrosis (IPF) using four statistical methods.

	Antifibrotics users		Non−users				
	Person years*	Deaths	Person years*	Deaths	Crude HR (95% CI)	*P*-value	Difference (%)#
(a) Time−fixed method							
Immortal person−time	483	0	0	0	–	–	–
At risk person−time	1,372	278	1,517	390	–	–	–
Total	1,855	278	1,517	390	0.55 (0.47, 0.64)	<0.001	−41
(b) Exclusion method							
Immortal person−time	0	0	0	0	–	–	–
At risk person−time	1,372	278	1,517	390	–	–	–
Total	1,372	278	1,517	390	0.79 (0.67, 0.92)	0.003	−15
(c) Time−dependent method							
Immortal person−time	0	0	483	0	–	–	–
At risk person−time	1,372	278	1,517	390	–	–	–
Total	1,372	278	2,000	390	0.93 (0.79,1.09)	0.391	0
(d) 0.5 year landmark method							
Immortal person−time	483	0	0	0	–	–	–
At risk person−time	1,372	278	1,504	345	–	–	–
Total	1,855	278	1,504	345	0.61 (0.52, 0.71)	<0.001	−34
(e) 1 year landmark method							
Immortal person−time	483	0	0	0	–	–	–
At risk person−time	1,358	281	1,469	300	–	–	–
Total	1,841	281	1,469	300	0.69 (0.58, 0.81)	<0.001	−26
(f) 2 years landmark method							
Immortal person−time	414	0	0	0	–	–	–
At risk person−time	1,335	209	1,339	214	–	–	–
Total	1,749	209	1,339	214	0.69 (0.57, 0.84)	<0.001	−26

Illustration models with methods of (a) time−fixed, (b) exclusion, (c) time−dependent, and (d)−(f) landmark. For the time−fixed method, the immortal time was ignored and incorporated in the treated group. For the exclusion method, the immortal time was excluded from the study. For the time−dependent method, the immortal time was switched into the control group, with an additional 483 subjects being added into the control group. For the landmark method, 0.5, 1, and 2 years landmarks excluded 45, 90, and 245 simulated subjects who had died prior to this time point, respectively. Immortal time was defined as the time from cohort entry to the initiation of antifibrotic therapy. Landmark time was defined as a fixed time point, which was the same for all subjects.

*Time from cohort entry until the occurrence of deaths.

#Difference in the effect estimates between the time-dependent methods and other methods.

ITB, immortal time bias; IPF, idiopathic pulmonary fibrosis; HR, hazard ratio; CI, confidence interval.

Difference in the effect estimates between four methods

Table 2 shows the difference in the effect estimates between the time-dependent method and other methods. Compared to the time-dependent method, use of time-fixed and exclusion methods overestimated the effectiveness of antifibrotic therapy in reducing the risk of all−cause mortality by 41 and 15%, respectively. For the 0.5, 1, and 2 years landmark methods, effectiveness of antifibrotic therapy was overestimated in reducing the risk of all−cause mortality by 34, 26 and 26%, respectively, compared to the time-dependent method.

Sensitivity analysis

After simulating data with a different background survival time and HR of death, our results remained consistent (Supplementary 1). Compared to the time-dependent method, use of time-fixed and exclusion methods overestimated the effectiveness of antifibrotic therapy in reducing the risk of all−cause mortality by 39 and 15%, respectively. For the 0.5, 1, and 2 years landmark methods, effectiveness of antifibrotic therapy was overestimated in reducing the risk of all−cause mortality by 32, 24 and 26%, respectively, compared to the time-dependent method.

Discussion

Main findings

To the best of our knowledge, this is one of few studies that highlights the importance of identifying and accounting for the influence of ITB in the field of IPF studies. We used the ITB Study Assessment Checklist to identify the presence

TABLE 3 Description of seven observational studies of the effects of interventions on study outcomes using various statistical methods for handling immortal time bias (ITB).

References	Country	Study size	Study subjects	Interventions*	Outcomes	Statistical methods	HR (95% CI)
Suissa (49)	Canada	3,524	COPD	Inhaled corticosteroids	All–cause mortality	Time–fixed	0.72 (0.58–0.88)#
						Time–dependent	0.94 (0.81–1.09)#
Shintani et al. (50)	USA	224	Mechanically ventilated patients	Delirium in the ICU	ICU length of stay	Time–fixed	1.90 (1.30–2.70)
						Time–dependent	1.10 (0.70–1.60)
Lévesque et al. (11)	Canada	11,661	Diabetes	Statins	Disease progression	Time–fixed	0.74 (0.58–0.95)
						Time–dependent	1.97 (1.53–2.52)
Mi et al. (28)	USA	52,741	COPD	Inhaled corticosteroids	3 years mortality	Time–fixed	0.55 (0.53–0.57)
						Exclusion	0.66 (0.64–0.69)
						Time–dependent	0.97 (0.93–1.00)
						3 months landmark	0.94 (0.90–0.97)
						6 months landmark	0.99 (0.95–1.03)
						9 months landmark	1.02 (0.97–1.06)
						12 months landmark	1.01 (0.97–1.07)
Weberpals et al. (12)	Germany	9,876	Prostate cancer	Beta–blockers	All–cause mortality	Time–fixed	0.68 (0.60–0.77)
						Time–dependent	1.13 (1.00–1.28)
			Colorectal caner			Time–fixed	0.51 (0.47–0.57)
						Time–dependent	1.15 (1.05–1.26)
			Lung caner			Time–fixed	0.42 (0.38–0.46)
						Time–dependent	1.04 (0.96–1.13)
			Pancreatic cancer			Time–fixed	0.34 (0.22–0.51)
						Time–dependent	1.10 (0.84–1.44)
Wallis et al. (33)	Canada	38,340	Men aged ≥ 66 years	Tertile 1; exposure of TRT ≤ 120 days	All–cause mortality	Time–fixed	1.23 (1.14–1.33)
						Time–dependent	1.11 (1.03–1.20)
				Tertile 2; exposure of TRT 121–510 days		Time–fixed	1.02 (0.95–1.11)
						Time–dependent	0.90 (0.83–0.97)
				Tertile 3; exposure of TRT ≥ 511 days		Time–fixed	0.56 (0.52–0.61)
						Time–dependent	0.67 (0.62–0.73)
Choi et al. (51)	Korea	16,769	Ulcerative colitis	5–Aminosalicylic acid	Incidence of colorectal cancer	Time–fixed	0.18 (0.09–0.35)
						6 months landmark	0.58 (0.35–0.97)
						1 year landmark	0.59 (0.32–1.09)
						2 years landmark	0.55 (0.25–1.19)

*"Intervention" might be an intervention, treatment, or exposure.
#Rate ratio; ITB, immortal time bias; COPD, chronic obstructive pulmonary fibrosis; ICU, intensive care unit; TRT, testosterone replacement; HR, hazard ratio; CI, confidence interval.

of ITB in observational studies, and a simulation study (for the first time in the world) to illustrate how ITB can overestimate the survival impacts of IPF-related antifibrotic therapy in observational studies. Our findings have demonstrated the time–dependent method to be an optimal statistical approach to minimize ITB in IPF studies where immortal time is identified.

The importance of addressing ITB in IPF studies

Observational studies examining effectiveness of medications on survival are highly susceptible to ITB in IPF due to substantial diagnostic delay and poor survival time. Further, time-fixed and

exclusion methods are commonly used in IPF studies, which leads to overestimate the effectiveness of medications on survival in observational studies (22).

No examples of the assessment of ITB influence on survival of IPF using time–dependent or landmark methods have been published to date. Seven studies (11, 12, 28, 33, 49–51) were selected from a search for ITB literature based on PubMed, which were regarded as examples to illustrate how ITB can affect effect size estimates in other population. Detailed search strategies were provided in **Supplementary 2**. It has been demonstrated in previous studies that there could be substantial adjustments to the effect size estimates for interventions after correction for ITB (**Table 3**). ITB may also on some occasions lead to a reversal of the true effect estimate of interventions. For example, a previous study (52) reported that participants with type 2 diabetes using statins had a delay in disease progression (HR 0.74, 95% CI 0.58–0.95) compared to those without using stains; however, this association was reversed after correcting for ITB in the same dataset (HR 1.97, 95% CI 1.53–2.52) (11).

Identification of ITB

Of the 16 studies reviewed, we found that 14 studies were detected with presence of ITB based on the ITB checklist, while there were insufficient data for assessment of two others. This is consistent with a recently published Letter to Editor (26) that summarized observational studies reporting the effectiveness of antifibrotic therapy on mortality of IPF and identified 14 studies (16–19, 35, 41, 42, 44, 45, 53–57) presenting ITB. Compared to a previous study (26), we have included more studies and have provided more detailed information by using the ITB checklist and conducting a simulation study to identify and account for ITB in IPF studies. Furthermore, Kaplan-Meier survival curves are plotted for illustrating correction of ITB, which could be used to identify the presence of ITB through observing the initial part of the survival curves when there is substantial variation in the slopes between antifibrotics users and non–users. The immediate marked separation of survival plots where present in previous IPF studies means that ITB was not taken into account (17, 19). In addition, all STATA code for data generation and modeling are given in **Supplementary 3** which provide detailed information to repeat our analyses or validate our results in real datasets for future studies.

Correction of ITB

Our simulation study showed that use of time–fixed and exclusion methods overestimated the effectiveness of antifibrotic therapy in reducing the risk of all–cause mortality by 41 and 15%, respectively, compared to the time–dependent method. This is consistent with the findings of a methodological study which examined the effectiveness of inhaled corticosteroids on survival in a real dataset of patients with COPD (28). By using various methods to handle ITB, the investigators found that both the time–fixed method (HR 0.55, 95% CI 0.53–0.57) and exclusion method (HR 0.66, 95% CI 0.64–0.69) considerably overestimated the effectiveness of inhaled corticosteroids in comparison of the time–dependent method (HR 0.97, 95% CI 0.93–1.00) which the authors identified as a "gold standard."

The time–dependent method is closest to the true effect of interventions on study outcomes that was first reported in 1974 by Mantel and Byar (58). In the early 2000s, Suissa (49, 59, 60) comprehensively addressed the potential influence of ITB on associations between medications (such as inhaled corticosteroids and beta–agonists) and survival in COPD. However, such an optimal approach requires adequate information to calculate the immortal time.

The landmark method is an alternative approach to the time–dependent method that was introduced in 1983 by Anderson et al. (61). We found that this method can mitigate the influence of ITB compared to the time–fixed method, but its performance highly dependent on the timepoint chosen. Thus, multiple landmark time points are commonly set to account for ITB. A previous study (28) set four landmark time points (3, 6, 9, and 12 months) to examine the effectiveness of inhaled corticosteroids on survival in COPD, but only found a significant effect at a 3 months landmark model. It should be noted that subjects who have died are excluded prior to the landmark time, thus the effect of antifibrotic therapy should be interpreted as being among subjects who survive at least to the defined landmark time. In addition, use of landmark method has a key limitation: subjects are excluded from the analysis which reduces statistical power; this is particularly important in critical care research where events are usually more common early in the disease process in subjects with severe diseases such as IPF.

Strengths and limitations

This study adds to the evidence for addressing the influence of ITB in IPF studies and provides several recommendations to minimize ITB in future observational studies. First, the ITB Study Assessment Checklist should be used to avoid ITB at the stage of study design and data analysis. f, the prevalent new-user design provides a comparison of exposed patients with time-matched unexposed controls during follow up, which might avoid ITB. (23) Third, a longer observation period can be used to mitigate the influence of ITB by reducing the proportion of immortal person–time in the total observation period (person years) in the intervention group. While this might be difficult in some patients with rapid disease progression. In addition, studies should collect and utilize adequate data to calculate immortal person–time. Lastly, the use of time–dependent and landmark methods can account for the influence of ITB in observational studies during data analysis.

Lack of validating our results in a real-world dataset is the main limitation for this study. Our simulation study can only confirm the direction of ITB and illustrate how it can overestimate the survival impacts of IPF-related antifibrotic therapy, while this study is limited to estimate the real magnitude of the effect size of this bias. In addition, the simulated data are generated based on a few reasonable assumptions in support of the modeling that illustrate the impact of ITB, while there are high heterogeneities on survival times and mortality outcomes for IPF-related antifibrotic therapy reported from a previous meta-analysis (24). However, results from our sensitivity analysis remained consistent after

simulating datasets based on a different background of survival time and mortality outcome. Future studies should quantify the effect size estimates of the influence of ITB on associations between antifibrotic therapy and survival in patients with IPF based on data linkage with filling of prescriptions, although it could be challenging for getting the data required for such analyses.

Conclusion

The effectiveness of antifibrotic therapy on survival in IPF is likely to be overestimated in observational studies, if ITB is not handled appropriately. Identifying the presence of ITB should therefore be routinely considered and reported in future IPF studies, and we recommend the use of time–dependent method to optimally account for the influence of ITB in observational studies. Clinical decisions based on biased estimations may have potentially detrimental impact on clinical practice. This study provides methods to ensure the true effect of treatments are estimated to ensure appropriate treatment for patients with IPF in future observational studies.

Data availability statement

The original contributions presented in this 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 for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

QZ designed the study and wrote the first draft of the manuscript. PO contributed to the statistical review and manuscript writing. EW, IC, BG, JC, and HA contributed to the study design and manuscript writing. AP contributed to the conceptualization, study design, and manuscript writing. All authors contributed to the revisions and agreed to the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1157706/full#supplementary-material

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Thoracic pain in patients with chronic interstitial lung disease—an underestimated symptom

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Introduction: Prevalence and predisposing factors for the development of thoracic pain (TP) in patients with chronic interstitial lung disease (cILD) are largely unknown. Underestimation and insufficient therapy of pain can lead to worsened ventilatory function. Quantitative sensory testing is an established tool for characterization of chronic pain and its neuropathic components. We investigated frequency and intensity of TP in cILD patients and the potential association with lung function and quality of life.

Materials and methods: We prospectively investigated patients with chronic interstitial lung disease to analyze risk factors for the development of thoracic pain and quantify thoracic pain through quantitative sensory testing. In addition, we studied the relationship between pain sensitivity and lung function impairment.

Results: Seventy-eight patients with chronic interstitial lung disease and 36 healthy controls (HCs) were included. Thoracic pain occurred in 38 of 78 patients (49%), most frequently in 13 of 18 (72%, p =0.02) patients with pulmonary sarcoidosis. The occurrence was mostly spontaneous and not related to thoracic surgical interventions (76%, p =0.48). Patients with thoracic pain showed a significant impairment of mental well-being (p =0.004). A higher sensitivity to pinprick stimulation during QST can be observed in patients with thoracic pain (p <0.001). Steroid treatment was associated with lower sensitivity within thermal (p =0.034 and p =0.032) and pressure pain testing (p =0.046). We observed a significant correlation between total lung capacity and thermal (p =0.019 and p =0.03) or pressure pain sensitivity (p =0.006 and p =0.024).

Conclusion: This study was performed to investigate prevalence, risk factors and thoracic pain in patients with chronic interstitial lung disease. Thoracic pain mostly occurs spontaneous as a frequent symptom, and seems to be an underestimated symptom in patients with chronic interstitial lung disease, especially those with pulmonary sarcoidosis. Timely identification of thoracic pain may allow starting symptomatic treatment at early stage, before impairment in quality of life occurs.

Clinical Trial Registration: https://www.drks.de/drks_web/, Deutsches Register Klinischer Studien (DRKS) DRKS00022978.

KEYWORDS

chronic interstitial lung disease, thoracic pain, prevalence of thoracic pain, risk factors, quantitative sensory testing

1. Introduction

Interstitial lung diseases (ILDs) are chronic diseases characterized by diffuse inflammation and/or fibrosis of the lung parenchyma, leading to restrictive ventilatory impairment, progressive dyspnea and respiratory insufficiency (1–3). The diagnosis is mainly based on clinical and high resolution computed tomography (HRCT) findings (1). Quality of life in IPF/ILD patients is impaired, especially due to cough and shortness of breath (4–7).

Although the exact frequency is unknown, a subgroup of IPF/ILD patients develops thoracic pain (TP), sometimes migrating, sometimes localized, which is difficult to classify especially in absence of a history of thoracotomy or any other thoracic intervention, and is often not associated with cough (8). Inadequate recognition and management of TP could lead to inspiration limitation, contraction of expiratory muscles, and consecutively to enhanced restriction, aggravating hypoxemia in advanced stage of disease (9).

Quantitative sensory testing (QST), developed within the framework of the German Research Network "Pain" and used worldwide since 2002 as a routine tool to assess pain (10), is a validated tool to assess sensory and nociceptive perception, as well as identifying neuropathic components of pain (11, 12). Patient responses to different physiological stimuli are recorded to quantify and qualify somatosensory integrity and pain sensitivity (13).

Aim of this study was to systematically investigate frequency and intensity of thoracic pain in cILD patients and explore possible correlations with lung function impairment as well as deterioration of quality of life.

2. Materials and methods

2.1. Study subjects

The study prospectively investigated patients with cILD and a control group of healthy controls (HCs). Study participants were consecutively recruited among patients with cILD followed at the Ruhrlandklinik between April 2017 and November 2019.

Inclusion criteria were an interstitial lung disease diagnosed according to American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria 2013 (14). Patients with unclassifiable ILD, incomplete data set or acute thoracic pain caused by any recent events (embolism, pneumothorax) or surgical interventions (including open lung biopsy) during the past 6 month, were excluded. Exclusion of acute causes was based on Chest X ray and complete lung function test during routine follow up visits.

As a control group, we investigated HCs with age > 18 years, no pre-existing lung diseases, no chronical pain syndromes, no pre-existing analgesic medication or neurological conditions such as polyneuropathy. Healthy controls were recruited among the employees of our institution after an accurate anamnestic screening for underlying diseases or conditions associated with chronic thoracic pain. The study was approved by the local ethics committee of the Medical Faculty of the University Duisburg-Essen (16-7028-BO), and registered in the German register of clinical studies (DRKS00022978). Written informed consent was obtained from all participants.

2.2. Questionnaires

All questionnaires were collected prior to performing QST. The Short Form 12 (SF-12) questionnaire was employed for assessing health-related QoL regarding physical and mental well-being (15). The painDETECT questionnaire was used to evaluate potential neuropathic pain (16). The painDETECT total score ranges between 0 and 38 and denotes the possibility of a neuropathic pain component being present (<13 very unlikely, 13–18 likely, >19 certainly). The number of pain areas was recorded by the body scheme of the painDETECT questionnaire.

2.3. Thoracic pain definition and quantitative sensory testing

TP was defined as persistent or intermittent pain ≥1 in the numeric rating scale (NRS), the most frequently used pain assessment scale (17).

QST is an established psychophysical test protocol for the quantitative evaluation of somatosensory function (18). The test is based on standardized somatosensory stimuli for which participant responses are recorded. Thirteen parameters can be obtained from seven separate test procedures involving nociceptive and non-nociceptive sensations (10). The same calibrated thermal and mechanical stimuli are always set in the same test sequence. For the present study, the following 10 QST-parameters were obtained in the given order: cold detection threshold (CDT), warm detection threshold (WDT), cold pain threshold (CPT), heat pain threshold (HPT), mechanical detection threshold (MDT), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS), dynamic mechanical allodynia (DMA), wind-up ratio (WUR), and pressure pain threshold (PPT) (Extensive description in Supporting information). The correlation of the scores with impairment of sensitivity and pain perception can vary, for some scores being positive (WDT, HPT, MDT, MPS, DMA, and WUR) and for others negative (CDT, CPT, MPT, and PPT).

QST was performed by two trained examiners. Participants were trained in QST procedures by performing all tests on one hand, once. Subsequently, QST measurements were performed on both sides of the thorax. Patients were instructed not to look at the test area.

2.3.1. Thermal measurement

Thermal measurement was performed with a Medoc TSA 2001-II device (Medoc, Israel) (19, 20). The contact area of the thermode was 30 × 30 mm. Baseline temperature was 32°C for skin adaption. The subject was requested to stop the stimulus with linearly increasing intensity (1°C/s) immediately when perceiving the onset of cooling (CDT), warming (WDT), or the additional sensation of burning, stinging, drilling or pulling (CPT, HPT). The measurement was terminated by the patient through pressing a button, or when reaching the cut-off temperatures of 0°C and 50°C. Each temperature threshold was obtained three times per target area. Thresholds were calculated as the arithmetic mean temperature of the three consecutive measurements (18).

2.3.2. Mechanical detection threshold

MDT was measured with modified von Frey filaments made of optic glass fibers (OptiHair2-Set, Marstock Nervtest, Germany) that

exert forces between 0.25 and 512 mN increasing by a factor of two from filament to filament (21, 22). The contact area of the filaments was a small epoxy beat with a diameter of 0.30–0.45 mm. Participants were asked to close their eyes, so that they could not observe the application of filaments, and were instructed to immediately report any perceived touch sensation within the target area. The force of the filaments was incrementally increased until the participant reported the first touch sensation. The force of the last filament used was noted as the first suprathreshold value. After this, filaments were applied in incrementally decreasing force until the patient did not report a touch perception. The force of the last filament was noted as the first infrathreshold value (23). This procedure was repeated five times per target area. The threshold was determined as the geometric mean of five supra-and infrathreshold values (18).

2.3.3. Mechanical pain threshold

MPT was measured with a PinPrick-Set (MRC Systems GmbH, Germany) that exert forces between 8 and 512 mN increasing by a factor of two from pinprick to pinprick (24). The contact area of the pinpricks is 0.2 mm diameter. The sensation of pinpricks is produced by the weight of the needle resting on the skin of patient. Patients were instructed to report whether the touch of a pinprick evoked the sensation sharpness, or not. In increasing forces, the force of the first pinprick described as sharp had to be noted as the first suprathreshold value, followed by descending stimuli until the first pinprick is only a touch, noted as infrathreshold value. As for the MDT, five ascending and descending series of stimuli were performed per target area. The MPT was calculated as the geometric mean of five infra-and suprathreshold values (18).

2.3.4. Mechanical pain sensitivity/dynamic mechanical allodynia

Using needle stimulators of different intensities, a stimulus–response curve of MPS was generated (23). Seven different stimulus intensities were applied in a randomized sequence including each stimulus intensity five times per area. The patient evaluated the individual pain intensities directly after each individual stimulus according to a numeric rating scale between 0 and 100. DMA was examined according to the same test scheme as described for MPS. A moving touch stimulus (cotton swab, Q-tip, brush), which normally does not lead to painful perception, was applied between the needle stimuli. Each of these three non-noxic stimuli was applied five times per area. A total of 50 stimuli (touch and needle stimulus) were applied on both sides of the thorax and the painfulness was recorded numerically. As a measure for the sensitivity to pain, the geometric mean value of pain ratings for needle (MPS) and touch (DMA) stimuli was calculated (18).

2.3.5. Wind-up ratio

WUR was determined with a pinprick of 128 mN. A single stimulus alternated with a train of 10 pinprick stimuli (1/s) within an area of 1 cm^2. The single stimulus and the stimulus train were rated by the patient on a numeric rating scale between 0 and 100, separately. The procedure was repeated five times. The wind-up ratio was calculated as the arithmetic mean pain rating of the five trains divided by the arithmetic mean pain rating of the five single stimuli (18).

2.3.6. Pressure pain threshold

PPT was measured using a pressure gauge device (FDN 200, Wagner Instruments, United States) with a contact area of 1 cm^2 and pressure limit of 20 kg/cm^2, equivalent to 2,000 kPa. The algometer was applied to the thenar of the respective test side, as testing on the chest is not possible due to the insufficiently large contact area to the muscles in the intercostal space. The application was made manually, with an increasing force of 50 kPa/s, corresponding to 0.5 $kg/cm^2/s$. Participants were asked to indicate the onset of a burning, stinging, drilling or pulling sensation. Application of pressure was stopped on feedback and the force reached was recorded as the threshold (25, 26). The procedure was repeated three times per target area. Pressure pain threshold was calculated as the arithmetic mean of these three measurements (18).

2.4. Pulmonary function tests and blood gas analysis

Measurements including FVC, forced expiratory volume in 1 s (FEV1), TLC and DLCO were carried out with Vyntus® SPIRO or Vyntus® PNEUMO and Masterscreen Body from Carefusion/Vyaire Medical. Blood gas analysis was performed with ABL from Radiometer to measure arterial oxygen tension, arterial carbon dioxide tension, arterial oxygen saturation, and alveolar-arterial oxygen tension difference. Lung function tests were performed at the time of QST.

2.5. Statistics

Variables distribution was calculated by using Kolmogorov–Smirnov test. Descriptive statistics (frequency and mean ± standard deviation) were performed. Non normally distributed variables are presented as median with interquartile range (IQR). Sample size was calculated based on a number of 360 patients with a new diagnosis of ILD per year at our institution and the fact that up to 10% of them are expected to have TP not dependent on surgical procedures (estimated population size 36). The minimum sample size of ILD patients with TP is 33 with a confidence level of 95% (95%CI) and a margin of error of 5%.

Comparison between cILD patients and HCs were tested using the Mann–Whitney *U*-test or Student's *t*-test for continuous variables and chi-square test for categorical variables. Correlations between continuous variables were calculated by using Pearson or Spearman correlation tests. We considered $p \leq 0.05$ to be statistically significant. Statistical analysis was performed with SPSS 27.0 (SPSS Inc., Chicago, United States).

3. Results

3.1. Studied subjects

We enrolled 81 patients with cILD followed at our Institution between April 2017 and November 2019, mostly in the outpatient clinic. As a control group, 36 healthy subjects were included. Three patients were excluded from testing because QST or lung function were not completed. cILD patients and HCs differed significantly in female percentage, age and pack/years (Table 1).

TABLE 1 Demographic data of patients with chronic interstitial lung disease and healthy controls.

Group	Patients with chronic ILD (N =78)	Healthy controls (N =36)	p-value
Women	25 (32%)	20 (56%)	0.017*
Age (year), mean ± SD	65.0 ± 13.0	45.8 ± 14.9	<0.001
Smoking years (pack years)	8 (0.0–30)	0.0 (0.0–7)	0.002
Alcohol units per week	0.0 (0.0–3)	2 (0.0–5)	0.001
Respiratory comorbidities			
COPD	5 (6%)	–[a]	–
Asthma	7 (9%)	–[a]	–
Pre-existing treatments with analgesic or potential analgesic effect	36 (46%)	–[b]	–
Non-opioid analgesics	24 (31%)	–[b]	–
Opioids	12 (15%)	–[b]	–

Otherwise indicated, values are expressed as median and IQR. Mann–Whitney-U-test for comparison was used. *T-test for comparisons was used.
[a]Pre-existing pulmonary disease was an exclusion criterion for healthy controls.
[b]The intake of analgesic medication was an exclusion criterion for healthy controls.

3.2. Frequency of thoracic pain and correlation with demographics and clinical characteristics

TP occurred in 38 (48.7%) of 78 examined patients with cILD (Table 2). Time since initial diagnosis of cILD did not differ between patients with and without thoracic pain (p =0.07; Table 2). TP occurred more frequently in patients with pulmonary sarcoidosis (72%) (p =0.02) than in those with other cILDs (47%), and less frequently in patients with EAA (29%) (p =0.07). TP was spontaneous in 76% of cases, related to previous thorax interventions in 5%, and of unknown origin (not indicated by the patients) in 19% of cases.

There were no differences according to gender, age, pack/years or alcohol units per week between cILD patients with (TP+) and without thoracic pain (TP−). The intake of non-opioid analgesics was higher in TP+ compared to TP− patients (17 vs. 7, p =0.009), the intake of opioids did not differ between the groups. Furthermore, we did not detect any difference in frequency of previous interventions between TP+ and TP− (Table 2).

3.3. Questionnaires

In the physical health summary scale, we did not observe any difference between TP+ and TP− patients, whereas mental health score was significantly more impaired in TP+ compared to TP− patients (median 47, IQR 34–57 vs. 56, IQR 50–59; p =0.004; Table 2). The total score of the pain detect questionnaire was significantly higher in TP+ patients (p <0.001) but did not reach values that are indicative of neuropathic pain. The number of pain areas was significantly higher in TP+ patients (p <0.001) ranging from 0 to 7 pain areas without differences in localization of pain.

3.4. Quantitative sensory testing

TP+ patients had higher MPS compared to TP− on both body sides and a significant difference in MPT (p =0.008) and DMA (p =0.012) on the left body side reflecting a higher sensitivity to pinprick stimulation. Measurements of CDT, WDT, CPT, HPT, MDT, WUR, and PPT did not differ between TP+ and TP− patients (Table 3).

Patients under corticosteroid treatment had lower sensitivity within thermal testing and pressure pain testing compared to patients without steroids. Differences in HPT were significant on the right side (median 49, IQR 44–50°C vs. 46, IQR 41–48°C, p =0.034) and left side (median 49, IQR 43–49°C vs. 44, IQR 40–47°C, p =0.032) of the body, while CPT was only significant on the right side (median 0.5, IQR 0–23°C vs. 16, IQR 5–25°C, p =0.032) and PPT only significant on the left side (median 7, IQR 5–9 kg/cm^2 vs. 7, IQR 5–9 kg/cm^2, p =0.046).

3.5. Correlation with lung function impairment

A significant direct correlation between total lung capacity (TLC) and PPT on the right side of the body in cILD patients was found (p =0.001; r_S =0.371), independent from the presence or absence of TP (Figure 1). In TP+ patients, TLC directly correlated with CDT (p =0.019; r_S =0.388 and p =0.030; r_S =0.362) and PPT (p =0.006; r_S =0.452 and p =0.024; r_S =0.375) on both sides of the body, meaning that the higher are the values of TLC, the better was cold sensitivity and the lower was the pressure pain sensitivity (Figures 2, 3).

3.6. Comparison to healthy controls

Significant differences between cILD patients with thoracic pain (TP+) and HCs could be observed in CDT [p =0.021 (right); p =0.002 (left)], MPS [p =0.001 (right); p =0.002 (left)], DMA [p =0.006 (right); p =0.003 (left)] and PPT [p =0.007 (right); p =0.047 (left)] on both body sides and in HPT (p =0.045) only on the left body side (Table 4). TP+ patients showed lower sensitivity within thermal testing, increased values on numeric rating scale during pinprick stimulation and higher sensitivity to pressure pain. Between cILD patients without thoracic pain (TP−) and HCs we found significant differences in HPT

TABLE 2 Demographic data of patients with chronic interstitial lung disease with and without thoracic pain.

Group	ILD patients With thoracic pain	ILD patients Without thoracic pain	*p*-value
Patients	38 (49%)	40 (51%)	
Women	15 (39%)	10 (25%)	0.17
Age (year)	64.0 ± 12.8	65.9 ± 13.3	0.37*
Smoking years (pack years) (median, IQR)	2 (0.0–31)	13 (0.0–30)	0.47*
Alcohol units per week (median, IQR)	0.0 (0.0–1)	0.0 (0.0–5)	0.47*
ILD disease duration prior to QST (month)	30 ± 70	28 ± 42	0.07
Diagnosis			
IPF	11 (29%)	12 (30%)	0.92
NSIP	4 (11%)	2 (5%)	0.36
EAA	5 (13%)	12 (30%)	0.07
DIP	2 (5%)	1 (3%)	0.53
Sarcoidosis[a]	13 (34%)	5 (13%)	0.02
Other ILD	3 (8%)	8 (20%)	0.13
Respiratory comorbidities			
COPD	3 (8%)	2 (5%)	0.6
Asthma	4 (11%)	3 (8%)	0.64
Lung function testing			
Oxygen dependency (L/min)	2.7 ± 1.0	3.5 ± 1.4	0.34
TLC (L)	5.2 ± 1.3	5.0 ± 1.5	0.49
TLC (%)	82.1 ± 16.7	74.8 ± 16.9	0.06
FEV1 (%)	69.9 ± 19.6	73.1 ± 18.4	0.6
IVC (L)	2.9 ± 1.2	2.9 ± 1.1	1
IVC (%)	75.5 ± 17.9	73.8 ± 20.6	0.62
Tiffeneau index (%)	98.9 ± 14.5	107.6 ± 13.2	0.015
DLCO (%)	49.3 ± 17.5	41.5 ± 17.7	0.11
paO_2	73.1 ± 14.8	70.8 ± 10.9	0.12
Previous interventions			
No intervention	15 (39%)	19 (48%)	0.48
Transbronchial biopsy	15 (39%)	17 (43%)	0.79
Surgical lung biopsy	8 (21%)	4 (10%)	0.18
SF-12			
Physical health summary scale (median, IQR)	31 (24–39)	34 (26–48)	0.11*
Mental health summary scale (median, IQR)	47 (34–57)	56 (50–59)	0.004*
painDETECT (median, IQR)	7 (3–12)	0.0 (0.0–4)	<0.001*
Areas of pain (median, IQR)	2 (1–4)	1 (0.0–3)	<0.001*
Pre-existing treatments with analgesic or potential analgesic effect			
Non-opioid analgesics	17 (45%)	7 (18%)[b]	0.009
Opioids	7 (18%)	5 (13%)[b]	0.47
Steroids	15 (39%)	17 (43%)	0.79
Tricyclics	2 (0.05%)	1 (0.03%)	0.59
Onset of pain symptoms			
Spontaneously	29 (76%)		
After intervention	2 (5%)		
Statement not possible	7 (18%)		

Otherwise indicated, values are expressed as mean ± SD. *T*-test for comparisons was used.
IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia; EAA, exogenous allergic alveolitis; DIP, desquamative interstitial pneumonia; ILD, interstitial lung disease; COPD, chronic obstructive pulmonary disease; TLC, total lung capacity; FEV_1, forced expiratory volume in 1 s; IVC, inspiratory vital capacity; DLCO, diffusing capacity for carbon monoxide; paO_2, oxygen partial pressure. *Mann–Whitney-*U*-test for comparison was used.
[a]Of them, 5 patients had stage I, 12 patients had stage II, and 1 had stage III.
[b]Treatment with analgesic medication in patients without thoracic pain was related to other reasons like back pain or joints (rheumatoid arthritis and arthrosis).

TABLE 3 Comparison of quantitative sensory testing in patients with cILD with and without thoracic pain.

Group	ILD patients with thoracic pain	ILD patients without thoracic pain	*p*-value
N (%)	38 (49%)	40 (51%)	
Right body side			
CDT (cold detection threshold) [°C]	29 (25–30)	29 (27–30)	0.61
WDT (warm detection threshold) [°C]	37 (35–39)	36 (35–38)	0.31
CPT (cold pain threshold) [°C]	11 (3–24)	2 (0.0–25)	0.31
HPT (heat pain threshold) [°C]	47 (42–50)	48 (44–50)	0.54
MDT (mechanical detection threshold) [mN]	7 (4–17)	5 (2–10)	0.13
MPT (mechanical pain threshold) [mN]	30 (10–62)	34 (20–95)	0.09
MPS (mechanical pain sensitivity)	9 (5–19)	2 (0.7–7)	<0.001
DMA (dynamic mechanical allodynia)	0.0 (0.0–0.4)	0.0 (0.0–0.0)	0.21
WUR (wind-up ratio)	0.3 (0.2–0.5)	0.2 (0.1–0.5)	0.06
PPT (pressure pain threshold) [kg/cm^2]	6 (5–8)	7 (6–9)	0.25
Left body side			
CDT (cold detection threshold) [°C]	29 (27–30)	30 (27–30)	0.91
WDT (warm detection threshold) [°C]	37 (35–38)	36 (34–38)	0.22
CPT (cold pain threshold) [°C]	19 (5–26)	5 (0.0–26)	0.10
HPT (heat pain threshold) [°C]	45 (41–49)	47 (43–49)	0.58
MDT (mechanical detection threshold) [mN]	7 (3–18)	6 (3–15)	0.66
MPT (mechanical pain threshold) [mN]	23 (11–42)	50 (22–116)	0.008
MPS (mechanical pain sensitivity)	10 (4–18)	2 (0.4–5)	<0.001
DMA (dynamic mechanical allodynia)	0.0 (0.0–0.7)	0.0 (0.0–0.0)	0.012
WUR (wind-up ratio)	0.4 (0.3–0.6)	0.3 (0.2–0.6)	0.38
PPT (pressure pain threshold) [kg/cm^2]	6 (5–8)	7 (5–8)	0.45

Otherwise indicated, values are expressed as median and IQR. Mann–Whitney-*U*-test for comparisons was used.

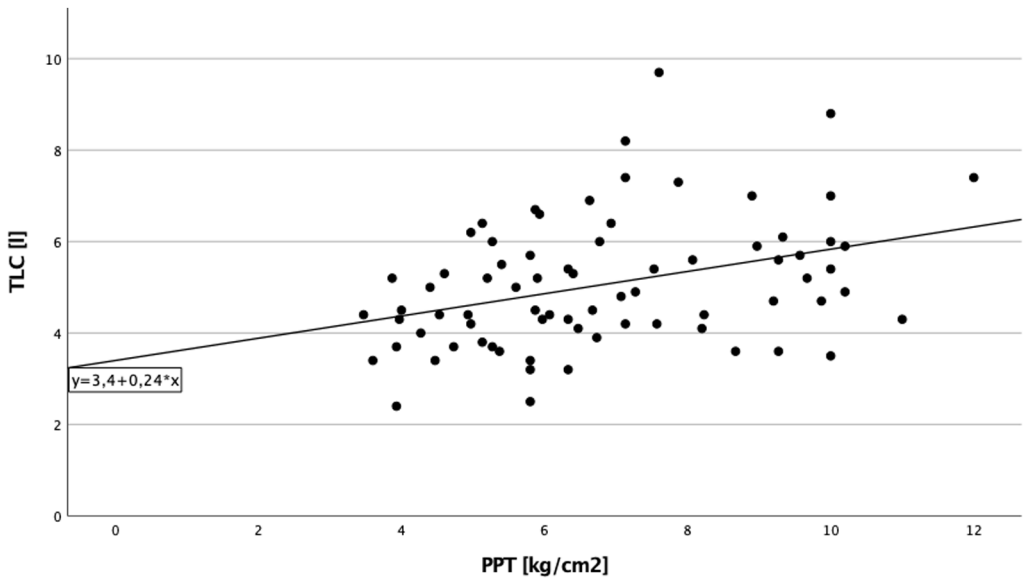

FIGURE 1
Total lung capacity and pressure pain threshold cILD-patients. Correlation between total lung capacity and pressure pain threshold on the right side of the body in all patients with chronic interstitial lung disease. Higher values in total lung capacity are positively correlated with higher results in pressure pain threshold, and Spearman's rank correlation coefficient is r_S=0.371 (p=0.001), which describe a lower sensitivity to pain.

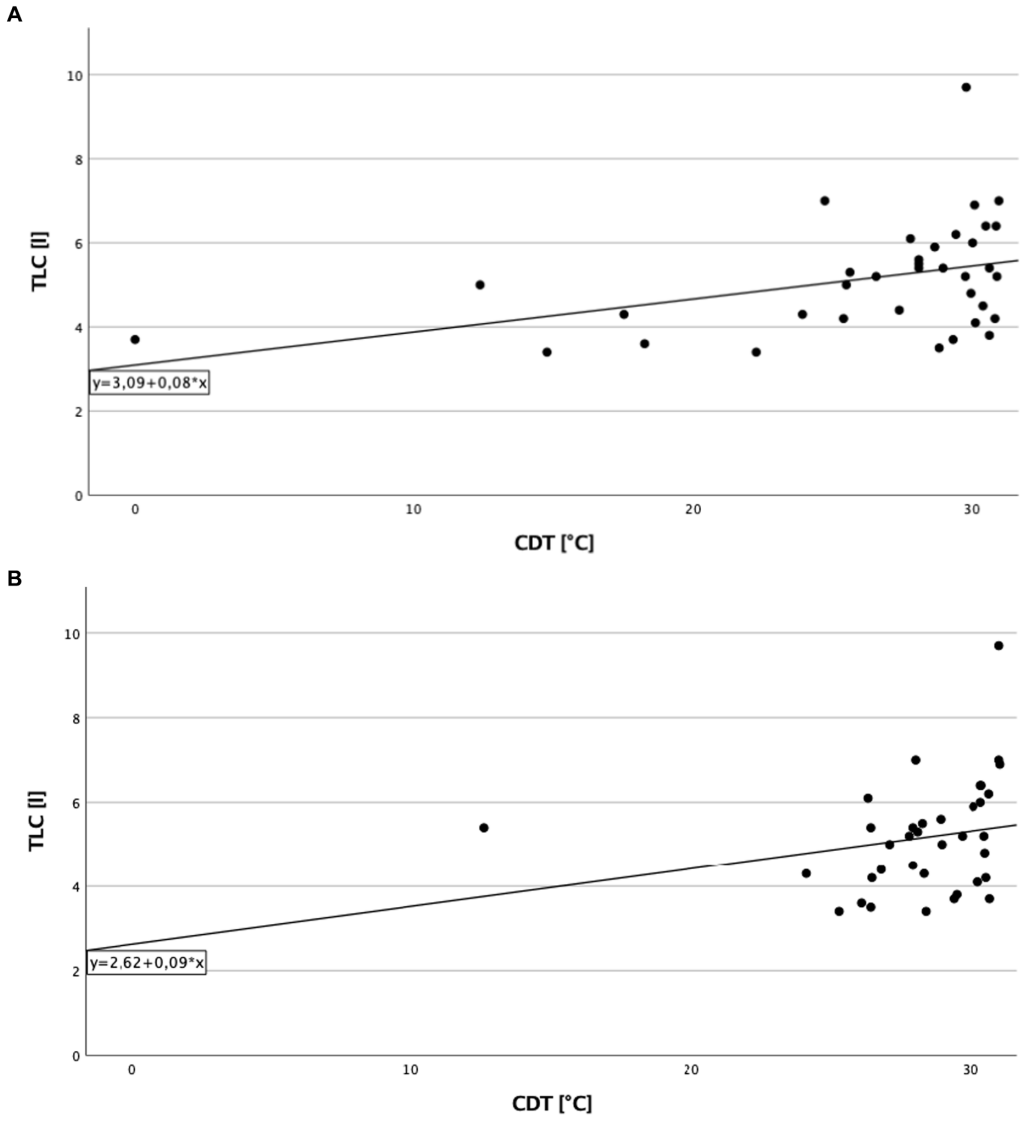

FIGURE 2
Total lung capacity and cold detection threshold in patients with thoracic pain. **(A)** On the right side of the body. Correlation of total lung capacity and cold detection threshold on the right side in patients with thoracic pain. Higher values in total lung capacity are positively correlated with higher results in cold detection threshold, and Spearman's rank correlation coefficient is r_s=0.388 (p=0.019). **(B)** On the left side of the body. Correlation of total lung capacity and cold detection threshold on the left side in patients with thoracic pain. Higher values in total lung capacity are positively correlated with higher results in cold detection threshold, and Spearman's rank correlation coefficient is r_s=0.362 (p=0.030).

[p =0.025 (right); p =0.005 (left)] and MPT [p =0.001 (right); p <0.001 (left)] on both sides and in CDT (p =0.005), CPT (p =0.009) and MPS (p =0.017) on the left side of the body (Table 5). TP– patients showed lower sensitivity within thermal testing, delayed sensation of sharpness and decreased values on numeric rating scale during pinprick stimulation compared to HCs.

4. Discussion

This is the first study specifically investigating thoracic pain in patients with chronic interstitial lung disease. Thoracic pain occurred in 48.7% of patients with chronic interstitial lung disease, most frequently in those with pulmonary sarcoidosis. Moreover, we found an association of thoracic pain with lung function and quality of life. Pain intensity did not differ between patients with pulmonary sarcoidosis and the other patients with chronic interstitial lung disease.

Thoracic pain seems to be an underestimated symptom in patients with chronic interstitial lung disease and, in general, knowledge on thoracic pain in patients with interstitial lung disease is scarce. A recent study reported that the prevalence of pain in ILD patients was 62% compared to 25% in healthy controls, with thoracic pain being the most frequent form (46%), followed by joint and limb pain (27). In that study, the occurrence of chest pain was higher in patients with idiopathic pulmonary fibrosis than those with CTD-ILD. Moreover, an association was found between intensity of pain, dyspnea, and quality of life.

In our study, pain usually occurred spontaneously, and appeared to be related to the disease itself rather than to previous interventions. It is likely that this kind of pain is associated with the fibrotic

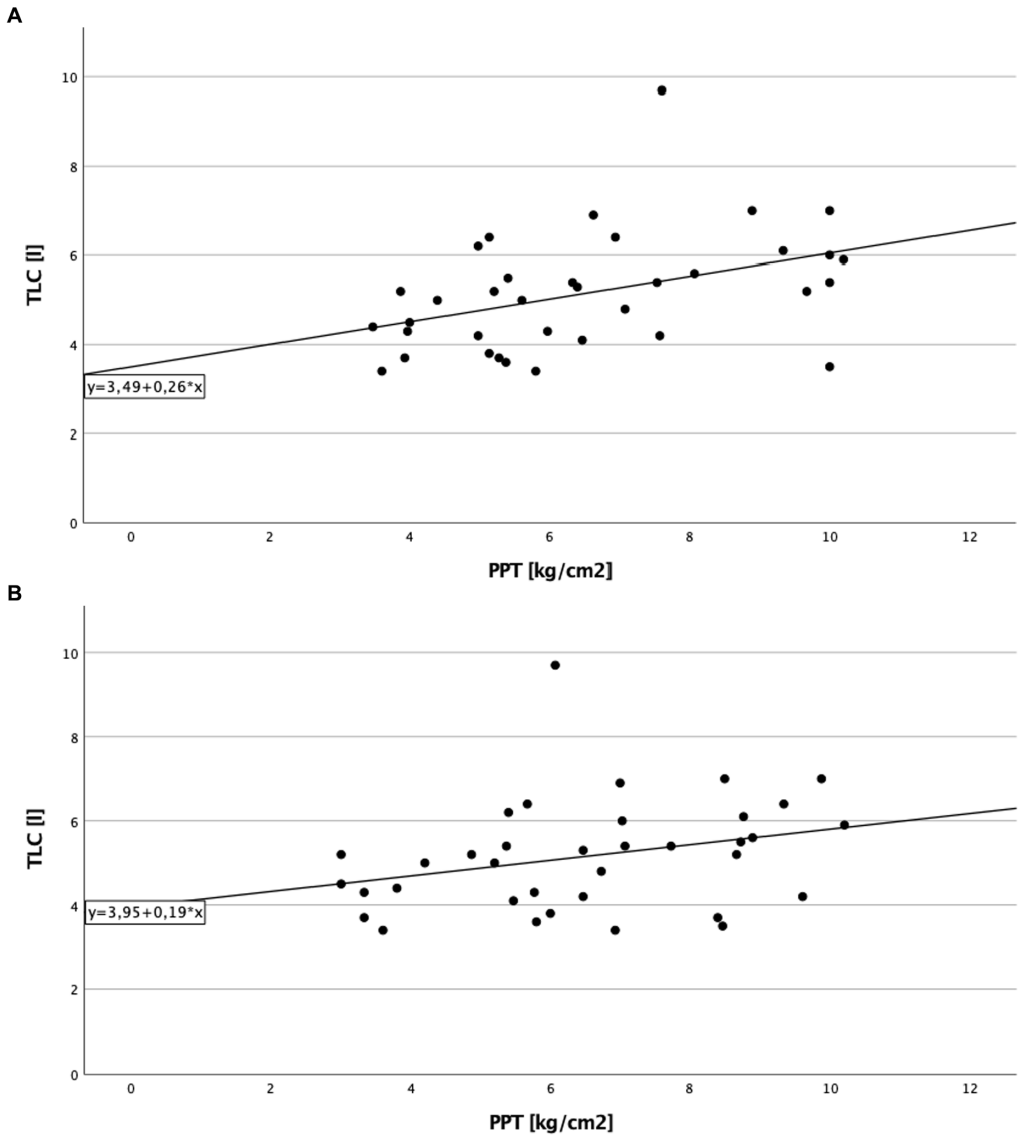

FIGURE 3
Total lung capacity and pressure pain threshold in patients with thoracic pain. **(A)** On the right side of the body. Correlation of total lung capacity and pressure pain threshold on the right side in patients with thoracic pain. Higher values in total lung capacity are positively correlated with higher results in pressure pain threshold, and Spearman's rank correlation coefficient is r_S=0.452 (p=0.006), which describe a lower sensitivity to pain in association to better lung function testing. **(B)** On the left side of the body. Correlation of total lung capacity and pressure pain threshold on the left side in patients with thoracic pain. Higher values in total lung capacity are positively correlated with higher results in pressure pain threshold, and Spearman's rank correlation coefficient is r_S=0.375 (p=0.024).

involvement and consequent thickening of the pleura, especially in idiopathic pulmonary fibrosis, where the fibrotic changes are predominantly localized in the subpleural area. In patients with pulmonary sarcoidosis, on the other side, thoracic pain may be related to an involvement of small nerve fibers. It has been reported that small fiber neuropathy occurs in 30%–50% of sarcoidosis patients, with pain and paresthesia being the most common symptoms (28, 29). Further studies are needed to elucidate the origin of thoracic pain in ILD patients.

With regard to pain characterization, significant signals in specific tests among the whole quantitative sensory testing were observed in cILD patients. Comparing cILD patients with thoracic pain and healthy controls, the observed significant differences in cold detection threshold, heat pain threshold, dynamic mechanical allodynia and pressure pain threshold mean a lower sensitivity to thermal testing and increased sensibility to pressure at the thenar. In addition, the lower values in cold detection threshold and cold pain threshold, and higher values in heat pain threshold in patients without thoracic pain compared to healthy controls underline the lower sensitivity to thermal stimuli of cILD patients. In contrast, patients without thoracic pain point out higher values in mechanical pain threshold as well as lower values in numeric rating scale in mechanical pain sensitivity compared to healthy controls, which discloses a lower sensitivity against pinprick stimulation and contrasts with the higher sensitivity to pinpricks in patients with thoracic pain. In summary, thoracic pain in ILD compared to healthy controls seems to be characterized by decreased

TABLE 4 Comparison of quantitative sensory testing in patients with cILD with thoracic pain and healthy controls.

Group	ILD patients with thoracic pain	Healthy controls	*p*-value
N (%)	38 (66%)	20 (34%)	
Right body side			
CDT (cold detection threshold) [°C]	29 (25–30)	30 (28–31)	0.021
WDT (warm detection threshold) [°C]	37 (35–39)	36 (35–37)	0.056
CPT (cold pain threshold) [°C]	11 (3–24)	21 (9–26)	0.16
HPT (heat pain threshold) [°C]	47 (42–50)	46 (41–48)	0.15
MDT (mechanical detection threshold) [mN]	7 (4–17)	6 (3–13)	0.31
MPT (mechanical pain threshold) [mN]	30 (10–62)	15 (9–40)	0.16
MPS (mechanical pain sensitivity)	9 (5–19)	5 (1–8)	0.001
DMA (dynamic mechanical allodynia)	0.0 (0.0–0.4)	0.0 (0.0–0.0)	0.006
WUR (wind-up ratio)	0.3 (0.2–0.5)	0.4 (0.2–0.6)	0.59
PPT (pressure pain threshold) [kg/cm^2]	6 (5–8)	8 (6–10)	0.007
Left body side			
CDT (cold detection threshold) [°C]	29 (27–30)	30 (29–31)	0.002
WDT (warm detection threshold) [°C]	37 (35–38)	36 (35–38)	0.09
CPT (cold pain threshold) [°C]	19 (5–26)	24 (18–27)	0.12
HPT (heat pain threshold) [°C]	45 (41–49)	43 (40–47)	0.045
MDT (mechanical detection threshold) [mN]	7 (3–18)	6 (3–14)	0.66
MPT (mechanical pain threshold) [mN]	23 (11–42)	15 (9–29)	0.23
MPS (mechanical pain sensitivity)	10 (4–18)	4 (1–7)	0.002
DMA (dynamic mechanical allodynia)	0.0 (0.0–0.7)	0.0 (0.0–0.0)	0.003
WUR (wind-up ratio)	0.4 (0.3–0.6)	0.3 (0.2–0.5)	0.19
PPT (pressure pain threshold) [kg/cm^2]	6 (5–8)	7 (6–9)	0.047

Otherwise indicated, values are expressed as median and IQR. Mann–Whitney-*U*-test for comparisons was used.

perception and pain sensitivity in response to thermal stimuli. Moreover, patients with thoracic pain compared to healthy controls showed an increased sensitivity to pinprick stimuli and pressure pain.

We observed that subjects under long-term corticosteroid treatment had a lower sensitivity to temperature and pressure during quantitative sensory testing. This may be explained by the analgesic effect of corticosteroids as described in previous studies (30).

Similarly to the study by Shen et al. (27), we did not find a correlation between lung function tests and the intensity of thoracic pain. Nevertheless, positive correlations between total lung capacity and sensitivity to stimuli, i.e., cold detection threshold as well as pressure pain threshold in all cILD patients (not only those with thoracic pain) were found. The positive correlation between total lung capacity and cold detection threshold shows that patients with mild or no ventilatory restriction can perceive coldness similarly to healthy subjects, whereas a more pronounced restriction in patients with advanced ILD seems to be associated with a pathologically reduced perception of coldness. This may indicate that the fibrotic changes of the lung tissue affect nerval pathways of the thorax.

The positive correlation between total lung capacity and pressure pain threshold indicates that higher pressure on the thenar is necessary to trigger a painful sensation in patients with better values in total lung capacity. This means that patients with more pronounced restriction have a hypersensitivity to pressure at the thenar. In patients with sarcoidosis, the hypersensitivity at the thenar could possibly be explained by a generalized sensitivity to pain in other parts of the body associated with a chronic pain syndrome or small fiber neuropathy (31).

Thoracic pain seems to cause a limitation of mental well-being in patients with thoracic pain. An association between pain in patients with ILD and impaired quality of life was observed by Shen et al. (27). Our study confirms recent investigations in patients with pulmonary sarcoidosis, in whom the loss of mental well-being and concentration impairment have been reported with high frequency (32). Similar to the observations of Shen et al. (27), by using the painDETECT questionnaire we could detect more pain areas in patients with thoracic pain than in patients without thoracic pain. This was reflected by the significantly higher consumption of non-opioid analgesics in patients with thoracic compared to those without. Since medication burden is an important factor impacting patients quality of life, early pain identification and management could lead to a better preservation of quality of life in ILD patients.

This study has several limitations. First, the sample size of the present study does not allow to perform subgroup analyses or prediction model to investigate risk factors for thoracic pain. Second, we did not include patients with lung diseases other than ILDs as a control group. This may lead to overestimation of thoracic pain as symptom in ILD, as the prevalence of pain in

TABLE 5 Comparison of quantitative sensory testing in patients with cILD without thoracic pain and healthy controls.

Group	ILD patients without thoracic pain	Healthy controls	*p*-value
N (%)	40 (67%)	20 (33%)	
Right body side			
CDT (cold detection threshold) [°C]	29 (27–30)	30 (28–31)	0.07
WDT (warm detection threshold) [°C]	36 (35–38)	36 (35–37)	0.41
CPT (cold pain threshold) [°C]	2 (0.0–25)	21 (9–26)	0.052
HPT (heat pain threshold) [°C]	48 (44–50)	46 (41–48)	0.025
MDT (mechanical detection threshold) [mN]	5 (2–10)	6 (3–13)	0.66
MPT (mechanical pain threshold) [mN]	34 (20–95)	15 (9–40)	0.001
MPS (mechanical pain sensitivity)	2 (0.7–7)	5 (1–8)	0.058
DMA (dynamic mechanical allodynia)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.054
WUR (wind-up ratio)	0.2 (0.1–0.5)	0.4 (0.2–0.6)	0.051
PPT (pressure pain threshold) [kg/cm^2]	7 (6–9)	8 (6–10)	0.10
Left body side			
CDT (cold detection threshold) [°C]	30 (27–30)	30 (29–31)	0.005
WDT (warm detection threshold) [°C]	36 (34–38)	36 (35–38)	0.93
CPT (cold pain threshold) [°C]	5 (0.0–26)	24 (18–27)	0.009
HPT (heat pain threshold) [°C]	47 (43–49)	43 (40–47)	0.005
MDT (mechanical detection threshold) [mN]	6 (3–15)	6 (3–14)	0.79
MPT (mechanical pain threshold) [mN]	50 (22–116)	15 (9–29)	<0.001
MPS (mechanical pain sensitivity)	2 (0.4–5)	4 (1–7)	0.017
DMA (dynamic mechanical allodynia)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.34
WUR (wind-up ratio)	0.3 (0.2–0.6)	0.3 (0.2–0.5)	0.68
PPT (pressure pain threshold) [kg/cm^2]	7 (5–8)	7 (6–9)	0.17

Otherwise indicated, values are expressed as median and IQR. Mann–Whitney-*U*-test for comparisons was used.

patients with chronic obstructive pulmonary disease is reported with 32%–60% (33). Moreover, it is known that the prevalence of fibromyalgia is higher in patients with sarcoidosis. Unfortunately, fibromyalgia was not systematically investigated in our cohort. Furthermore, the lack of a matched control group may lead to biased results since the controls are younger and more likely to be female. Third, the cross-sectional study design does not allow drawing any conclusion about long-term consequences of thoracic pain on lung function, quality of life, or disease course. Moreover, we were not able to analyze the temporal relation with onset of ILD symptoms since data on duration of thoracic pain were not available. Fourth, previous treatment with corticosteroids and analgesics could have led to underestimation of thoracic pain in our patients' population. Finally, in quantitative sensory testing it is difficult to distinguish between faked and true loss or gain of sensation as well as central and peripheral abnormalities can lead to the same deficit in measurement.

This study was performed to investigate prevalence and risk factors of thoracic pain in patients with chronic interstitial lung disease. Thoracic pain mostly occurs spontaneous as a frequent symptom in chronic interstitial lung disease patients, especially in pulmonary sarcoidosis. Timely identification of thoracic pain may allow starting symptomatic treatment at early stage, before impairment in quality of life occurs.

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 Ethics Committee of the Medical Faculty of the University Duisburg-Essen. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MS and FB are responsible for all content of the manuscript, contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. SK contributed substantially to the study design and the writing of the manuscript. JF-B contributed substantially to the data analysis and the writing of the manuscript. GW contributed substantially to the study design, data analysis, and the writing of the manuscript. UC contributed substantially to the data interpretation and the writing of the

manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

FB and UC received speaker and advisor honoraria, travel and research grants from Boehringer Ingelheim Pharma, not related to this study.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

The handling editor PS declared a past co-authorship with the author FB.

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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.2023.1147555/full#supplementary-material

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Glossary

CDT	cold detection threshold
COPD	chronic obstructive pulmonary disease
CPT	cold pain threshold
cILD	chronic interstitial lung disease
DIP	desquamative interstitial pneumonia
DLCO	diffusing capacity for carbon monoxide
DMA	dynamic mechanical allodynia
EAA	exogenous allergic alveolitis
FEV_1	forced expiratory volume in 1 s
HCs	healthy controls
HP	hypersensitivity pneumonitis
HPT	heat pain threshold
HRCT	high resolution computed tomography
IIP	idiopathic interstitial pneumonias
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
IVC	inspiratory vital capacity
MDT	mechanical detection threshold
MPS	mechanical pain sensitivity
MPT	mechanical pain threshold
NRS	numerical rating scale
NSIP	nonspecific interstitial pneumonia
paO_2	oxygen partial pressure
PAP	pulmonary alveolar proteinosis
PPT	pressure pain threshold
QoL	quality of life
QST	quantitative sensory testing
RBILD	respriratory bronchiolitis
TLC	total lung capacity
TP	thoracic pain
TP+	patients with thoracic pain
TP−	patients without thoracic pain
WDT	warm detection threshold
WUR	wind-up ratio

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Historical eye on IPF: a cohort study redefining the mortality scenario

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Rationale: Therapies that slow idiopathic pulmonary fibrosis (IPF) progression are now available and recent studies suggest that the use of antifibrotic therapy may reduce IPF mortality.

Objectives: The aim of the study was to evaluate whether, to what extent, and for which factors the survival of IPF in a real-life setting has changed in the last 15 years.

Methods: Historical eye is an observational study of a large cohort of consecutive IPF patients diagnosed and treated in a referral center for ILDs with prospective intention. We recruited all consecutive IPF patients seen at GB Morgagni Hospital, Forlì, Italy between January 2002 and December 2016 (15 years). We used survival analysis methods to describe and model the time to death or lung transplant and Cox regression to model prevalent and incident patient characteristics (time-dependent Cox models were fitted).

Measurements and main results: The study comprised 634 patients. The year 2012 identifies the time point of mortality shift (HR 0.58, CI 0.46–0.63, $p < 0.001$). In the more recent cohort, more patients had better preserved lung function, underwent cryobiopsy instead of surgery, and were treated with antifibrotics. Highly significant negative prognostic factors were lung cancer (HR 4.46, 95% CI 3.3–6, $p < 0.001$), hospitalizations (HR 8.37, 95% CI 6.5–10.7, $p < 0.001$), and acute exacerbations (HR 8.37, 95% CI 6.52–10.7, $p < 0.001$). The average antifibrotic treatment effect estimated using propensity score matching showed a significant effect in the reduction of all-cause mortality (ATE coeff −0.23, SE 0.04, $p < 0.001$), acute exacerbations (ATE coeff −0.15, SE 0.04, $p < 0.001$), and hospitalizations (ATE coeff −0.15, SE 0.04, $p < 0.001$) but no effect on lung cancer risk (ATE coeff −0.03, SE 0.03, $p = 0.4$).

Conclusion: Antifibrotic drugs significantly impact hospitalizations, acute exacerbations, and IPF survival. After the introduction of cryobiopsy and antifibrotic drugs, the prognosis of IPF patients has significantly improved together with our ability to detect IPF at an earlier stage.

KEYWORDS

idiopathic pulmonary fibrosis, interstitial lung disease, pirfenidone, nintedanib, cryobiopsy

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing interstitial lung disease of unknown etiology associated with the radiological and/or histological pattern of usual interstitial pneumonia, with a median survival time of 3–5 years from diagnosis (1). Lung function declines in all IPF patients, and acute exacerbations or lung cancer can occur at any time in the disease course, increasing healthcare resource utilization, hospitalizations, and ultimately leading to death (2–4).

During the last decade, clinical trials have led to the approval of pirfenidone and nintedanib, the first two antifibrotic drugs with a specific indication for IPF (5, 6). Clinical trials have demonstrated that nintedanib and pirfenidone reduce lung function decline in IPF patients, with significant effect across subjects with both preserved forced vital capacity (FVC) (7, 8) and more advanced disease (9). IPF has a mortality rate that is similar to that of several cancers, and all-cause mortality would be the most clinically meaningful and preferred primary outcome in treatment trials. However, the necessary size, duration, and cost of mortality-powered studies in mild-to-moderate IPF are substantial and prohibitive (10); therefore, efficient clinical trials of feasible size and duration have been designed to show mainly to slow disease progression. Recently, a growing body of evidence has shown that pirfenidone and nintedanib reduce the risk of acute deterioration in lung function and improve life expectancy (11–13). Pooled analysis, meta-analysis, and IPF registries have shown that pirfenidone reduces the risk of death (14–16). However, the strength of those recent studies is hampered by methodological limitations. All-cause mortality in the trial population was low (3.1% in the pirfenidone and 6.5% in the placebo pooled group) and to what extent the results of this highly selected population followed using a rigid research methodology are generalizable to real-world patients remained unclear (17). A recent study evaluated survival trends in the United States showing a decline in IPF-related mortality from 2004 to 2017, but factors related to this mortality change remained unexplained (18). Real-world experiences of IPF registries report a mortality reduction similar to what was observed in pooled analysis and meta-analysis, but fail to capture the temporal trend in overall survival, do not include all possible covariates that might be associated with survival including time-dependent intermediate factors as hospitalizations, acute exacerbations, and lung cancer and do not apply a matching strategy to adjust for the inevitable heterogeneity of a real-life IPF populations (11, 19, 20).

The concern for adverse events and a quote of skepticism on antifibrotic efficacy are still rooted in some pulmonary physicians, leading to the possible risk of delayed treatment (21).

In this study, we report 15 years of real-life clinical experience, which to our knowledge is the largest monocentric prospective IPF cohort ever published. This study was designed to identify the shift in IPF patients' mortality observed in recent years and the factors that have driven this change. The primary objective was to define overall survival and to identify any relevant change in survival trends. The secondary objectives were to identify the clinical and demographic prognostic factors contributing to the observed shift in mortality.

Methods

Study design and patient selection

This is an observational cohort single-center study that follows the STROBE guidelines. We recruited all consecutive patients who received a multidisciplinary diagnosis of IPF at GB Morgagni Hospital, Pulmonary Unit, between January 2002 and December 2016 (15 years). The quality of data was improved by the introduction of the database of standardized data forms and internal checks, and follow-up data were collected with prospective intention. The expert multidisciplinary team used both ATS/ERS guidelines and Fleischner Society white paper criteria (1, 22, 23). All data were extracted from the Pulmonary Unit ILD database in which patients were enrolled using a standardized initial assessment (function, HRCT, BAL, laboratory tests including autoimmunity in all cases, and biopsy in selected cases) and a follow-up structured with prospective intention (visit every 4–6 months with clinical and functional evaluations, HRCT, and echocardiography on a yearly basis). We extracted clinical information from medical records using a standard form, as detailed in the Supplementary material, page 2.

The study was approved by the Comitato Etico di area vasta ROMagna, Italy (CEROM approval protocol number 8571/2017). Patients provided informed consent according to current local and national legislation.

Outcomes

The primary outcome was to define overall survival, identifying any relevant change in survival trends and the time point at which the mortality switch occurred. We compared survival stratified by year of diagnosis, and we characterized two distinct historical cohorts with different survival profiles. Clinical and demographic factors considered clinically relevant and/or potentially associated with survival were analyzed in order to identify the factors contributing to the observed shift in mortality.

Statistical analysis

Continuous data were described with the mean and standard deviation (SD) and categorical data as counts and percent. We used Student's *t*-test and the chi-square test to compare groups of interest. We used survival analysis methods to describe and model the time to death or lung transplant, including rates per 100 person years and 95% confidence intervals (95% CI) and Kaplan–Meier cumulative event-free survival and 95% CI to describe; we used Cox regression to model prevalent and incident patients characteristics; in this case, time-dependent Cox models were fitted. We computed hazard ratios (HR) and 95% CI. We assessed graphically the proportional hazard assumptions by plotting the observed and predicted survival curves. Multivariable models included non-collinear variables that were considered of clinical

FIGURE 1
Geographical distribution of patients with the diagnosis of IPF made at our center. Numbers were approximated to 10 patients per star represented in the graph.

relevance and gave a signal at the univariate analysis ($p < 0.2$). The Harrell's C statistic was computed to assess discrimination. We also computed the average treatment effect after propensity score matching.

No imputation of missing data was performed given the low number of missing data in the variables of interest.

Propensity-score-based matching was used to select control patients similar to patients receiving treatment (matched by age, gender, comorbidities, and pulmonary function—% of pred. FVC and % of pred. DLco).

All statistical analyses were performed using STATA 15 (StataCorp, College Station, TX, USA).

Role of funding source

This investigator-initiated study was funded by F. Hoffmann-La Roche Ltd; Genentech, Inc. The sponsor had no role in the study design, data collection, analysis, final report, and decision to submit for publication. ST and VP had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Population

In total, 634 patients were diagnosed within the prespecified protocol window (between the year 2002 and the year 2016) and met protocol requirements as detailed in the Supplementary material (Supplementary Figure S1, page 2 of the Supplementary material).

Approximately 99.7% ($N = 632$) of patients were Caucasian, and 0.3% ($N = 2$) were Hispanic (from South America). At the time of diagnosis, all patients were Italian residents, coming from all but one Italian region, mainly central and southern Italy (Figure 1). Patients' characteristics are summarized in Table 1.

Overall survival trends over time

Of the 634 IPF patients included in the study, definite outcome data (date of death or last known visit) were available for all cases. At the time of censoring the data, 335 patients had died

TABLE 1 Clinical Characteristics of the patients according to diagnosis period.

		Diagnostic period			
	Missing values	Entire cohort	(2002–2011)	(2012–2016)	*p*-value
		N = 634	*N* = 286	*N* = 348	
Age (yr.)		66.8 ± 8.6	65.6 ± 8.8	67.7 ± 8.3	0.0003
Gender N (%) of male patients		478 (75.4)	219 (76.6)	259 (74.4)	0.53
Family history of ILDs		127(20)	55 (19.2)	72 (20.7)	0.65
Current Former Smokers N (%)	10	444(71.1)	211 (74.8)	233 (68.1)	0.04
Pack years	288	30.6 ± 22.2	31.3 ± 21.5	30.0 ± 22.9	0.29
Comorbidities. N (%)		536(84)	236 (82.5)	300 (86.2)	0.20
Emphysema		115(18.1)	53 (18 5)	62 (17.8)	045
Lung cancer		61(9)	36 <12 (6)	25 (7.2)	0.016
Pulmonary hypertension	204	219(50)	133 (62.7)	86 (39.4)	<0.0001
Body Mass Index	20	27.7 ± 4.1	27.8 ± 4	27.5 ± 4.2	0.45
Functional measures					
FVC (% of predicted)	5	77.3 ± 19.2	74.5 ± 19.8	79.6 ± 18.4	0.0005
FEV1 (% of predicted)	8	84.4 ± 20. 4	80.3 ± 20.6	87 ± 19.7	<0.0000
DLco (% of predicted)	13	50.1 ± 16.6	47.4 ± 16.7	52 4 ± 16.2	0.0001
Use of oxygen under exercise N (%)	26	143(23.5)	76 (28.6)	67 (19.6)	0.006
mMRC	171	1.7 ± 0.8	1.8 ± 0.7	1.6 ± 0.8	0.003
6min walking test distance (m)	270			385.5 ± 123.8	0.08
Diagnostic procedures			SD ±		
HRCT definite UIP N (%)		406 (64)	195(68)	21(60)	0.029
Lung cryobiopsy N (%)		141 (22)	20 (7.0)	121 (34.8)	<0 000
Surgical lung biopsy N (%)		95 (15)	73 (25.5)	22 (6.3)	<0.000
Patients with BAL lymphocytosis >30% N (%)	184	24 (5.3)	13 (6.7)	11 (43)	0.18

Plus-minus values are means ± SE. Abbreviations: FEV1, forced expiratory volume in one second; FVC, forced vital capacity; DLco, carbon monoxide diffusion capacity; ILDs, interstitial lung diseases. P values are calculated with Mann-Whitney test) and compare the two time periods (2002–2011 to 2012–2016). Comorbidities denotes the number of patients with one or more comorbidity excluding emphysema, lung cancer and pulmonary hypertension. 6 min WT was conducted with or without oxygen supplementation as needed. Pulmonary hypertension likelihood was estimated by echocardiography.

(52.8%) and 25 had been transplanted (3.9%). Overall median survival was 4.67 years (25th−75th percentile 2.26–8.07 years). For the 360 patients who died or were transplanted, the median time to event was 2.71 years (25th−75th percentile 1.5–14.48 years). The rates for 1-year, 3-year, 5-year, and 8-year survival were 90% (SE 0.011, CI 0.74–0.81), 67% (SE 0.19, CI 0.643–0.70), 46% (SE 0.02, CI 0.42–0.50), and 26% (SE 0.026, CI 0.21–0.31), respectively. The estimated rate of death was 15.12 (95% CI 13.63–16.75) per 100 persons per year. Supplementary Figure S2 page 3 of the Supplementary material shows the overall survival of the IPF population.

To model survival trends over the period of diagnosis, we split the population both by calendar year of diagnosis and by grouping patients every 3 years (2002–2004; 2005–2007; 2008–2010; 2011–2013; 2014–2016) and 5 years (2002–2206; 2007–2011; 2012–2016). The difference in mortality risk was not statistically significant when stratified by calendar year (survival trends are shown in Supplementary Figure S3 page 4 of the Supplementary material). When stratified every 3 years, the mortality declined in the last triennium (2014–2016), unadjusted HR 0.60, CI 0.37–0.98; $p = 0.04$ but was not significant after adjusting for age, gender, FVC, DLco HR 0.66, CI 0.40–1.10; $p = 0.40$ (Supplementary Figure S4 page 5 of the Supplementary material). For the 3-year time point, the estimated area under the ROC curve was 0.52. The sharpest reduction in mortality was observed stratifying patients every 5 years. The observed reduction in mortality risk in the last quinquennium (2012–2016) was HR 0.58, CI 0.43–0.79 (unadjusted), $p < 0.001$ and HR 0.63, CI 0.46–0.86, $p < 0.001$ after adjusting for covariates (Supplementary Figure S5 page 6 of the Supplementary material). For the 5-year time point, the estimated area under the ROC curve was 0.39. In our patients' cohort, the year 2012 identifies the time point of fracture from the past. Survival difference for the diagnostic period before and after the year 2012 is shown in Figure 2. The observed reduction in mortality risk for the diagnostic period before and after 2012 was HR 0.58, CI 0.46–0.63, $p < 0.001$ (unadjusted) and HR 0.66, CI 0.52–0.83, $p = 0.001$ after adjusting by age, gender, FVC, and DLco.

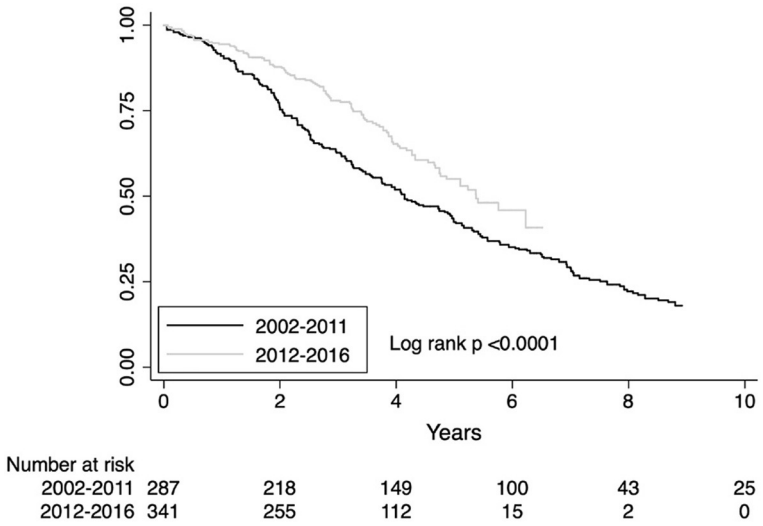

FIGURE 2
Survival estimates for the diagnostic period before or after 2012.

Over-time changes in IPF clinical profile

To identify clinical factors that may have changed over time, we compared clinical characteristics of IPF cases diagnosed in the last 5-year period (2012–2016) to those diagnosed in the first decade (2002–2011), as reported in Table 1. Compared to the first decade, patients who underwent an IPF diagnosis after 2012 were slightly older. Overall, the burden of comorbidities did not change over time, including emphysema, but the prevalence of both lung cancer (from 12.6% to 7.2%, $p = 0.016$) along with the likelihood of pulmonary hypertension (62.7% to 39.4%, $p < 0.0001$) significantly decreased. Patients diagnosed in the last 5 years had a slightly better preserved lung function, as measured by % of predicted FVC (74.5% and 79.6%, respectively), % predicted FEV1 (80 and 87.0, respectively), and % predicted DLco (47.4 and 52.4, respectively) ($p < 0.001$ in all three groups comparison). Accordingly, the dyspnea index (1.8 and 1.6, $p < 0.003$) and the use of oxygen under exercise (28.6% and 19.6%, $p < 0.006$) were significantly less frequent in patients diagnosed in the last quinquennium compared to the previous decade. In the last 5 years at our center, we have observed a significant increase in the total number of IPF diagnoses (from 286 to 348), along with an increased prevalence of cases confirmed by lung biopsy (from 31.8% to 39.4%, $p < 0.049$). This escalation has been mainly driven by the implementation of transbronchial lung cryobiopsy (TBLC, up to 34.8% of cases) which has minimized the role of surgical lung biopsy (SLB, down to 6.3% of cases).

Potential prognostic factors

Univariate analysis of potential clinical prognostic factors

Univariate analysis suggested that the time period of diagnosis (before/after 2012), age, pulmonary hypertension and lung cancer, functional impairment (% pred FVC, % pred FEV1, % pred DLco), grade of dyspnea (mMRC), use of oxygen under exercise, and diagnosis confirmed by cryobiopsy were all significant prognostic factors for overall survival ($p < 0.05$), as shown in Table 2.

Multivariable analysis of potential clinical prognostic factors

Table 2 shows the results of the Cox regression analysis. There was a significantly greater risk of mortality associated with the diagnosis period (before/after 2012), the presence of lung cancer, and functional impairment as measured by % of predicted FVC, % of predicted FEV1, and % of predicted DLco. The presence of family history for ILDs, age, gender, smoking history, comorbidities (excluding lung cancer), use of oxygen under exercise, grade of dyspnea, and diagnosis confirmed by cryobiopsy were non-significant when adjusted for covariates.

Intermediate potential prognostic factors: lung cancer, hospitalizations, acute exacerbations, and disease progressions

Lung cancer, hospitalizations for any cause, and acute exacerbations were all less frequent in the last quinquennium compared to the previous decade (lung cancer $N = 25$, 7% compared to 36, 13%, $p = 0.016$; hospitalizations $N = 115$, 52% compared to $N = 56$, 19%, $p < 0.001$; acute exacerbations $N = 36$, 12.5% compared to $N = 87$, 40%, $p < 0.001$). The prevalence of patients who experienced a disease progression was higher in cases diagnosed after the year 2012 ($N = 225$ 43.5% before 2012 compared to $N = 292$, 56.5% after 2012), but more patients had only one progression in this group (1POD $N = 251$, 85%; 2 POD $N = 22$, 7.5% 3POD $N = 4$, 1.4% diagnosis after 2012), whereas, in the cohort of patients diagnosed before 2012, the number of patients with multiple POD was significantly higher (1POD $N = 140$, 62%; 2 POD $N = 25$, 20%; 3 or more POD $N = 18$, 8%).

TABLE 2 Statistical distributions of potential prognostic factors.

	Univariate analysis			Multivariate analysis	
	Rate per 100p/y	HR (95% CI)	*p* value	HR (95% CI)	*p*-value
Period of diagnosis (2012–2016)	10.6 (8.8–12.7)	0.58 (0 46–0.73)	<0.0000	0.58 (0.40–0.83)	0.003
Age (years)	16.4 (14.4–18.8)	1.02 (0.01–1.03)	0.0008	1.02 (1–1.04)	0.18
Gender Male	15.6 (13.8–17.3)	1.14 (0.89–1.46)	0.28	1.09 (0.7–1.6)	0.65
Family history of ILDs	13.14 (10.6–16.9)	0.83 (0.6–1.1)	0.15	–	–
Current former smokers	15.8 (614–17.8)	1.19 (0.94–1.50)	0.15	–	–
Pack years		1.01 (1–1.02)	0.42	–	–
Comorbidities^	14.8 (13.2–16.5)	1.08 (0.99–1.18)	0.09	–	–
Emphysema	15.7 (12.3–20)	1.07 (0.8–1.4)	0.62	–	–
Lung cancer	24.8 (18.8–32.9)	1.78 (1.32–2.41)	**0.0001**	2.24 (1.38–3.63)	**0.001**
Pulmonary hypertension	17.5 (14.9–20.5)	1.57 (1.21–2.04)	**0.0006**	0.98 (0.69–1.39)	0.9
Body mass index	–	0.99 (0.97–1.02)	0.68	–	–
Functional measures					
FVC (% of predicted)	–	0.97 (0.97–0.98)	**<0.0000**	0.95 (0.92–0.98)	**0.002**
FEV1 (% of predicted)	–	0.98 (0.97–0.98)	**<0.0000**	1.03 (1–1.06)	**0.041**
DLco (% of predicted)	–	0.95 (0.95–0.96)	**<0.0000**	0.96 (0.94–0.97)	**<0.000**
Use of oxygen under exercise	27.6 (23–33–1)	2.57 (82.05–3.2)	**<0.0000**	1.2 (0.9–1.7)	0.85
mMRC & 2	19.1 (16.5–22.1)	1.7 (1.3–2.2)	**<0.0000**	0.89 (0.6–1.25)	0.5
Diagnostic procedures					
Lung cryobiopsy	5.8 (4.05–8.4)	0.34 (0.23–0.5)	**<0.0000**	1.06 (0.6–1.8)	0.8
Surgical lung biopsy	15.2 (12.1–19.3)	0.94 (0.72–1.23)	0.65	–	–
Patients with BAL lymphocytosis >30%	15.6 (9.4–25.8)	1.13 (0.67–1.91)	0.64	–	–

*Rate per 100 persons year if Age > 65. ^Comorbidities number excluding emphysema, lung cancer and pulmonary hypertension; rate per 100-person year was calculated for patients with one or more comorbidity. Bold values are highlighted in bold to distinguish them as statistically significant values from those that are not statistically significant.

Time-dependent Cox regression analysis showed that intermediate factors (i.e., lung cancer, hospitalizations, acute exacerbations, and disease progressions) were all significantly associated with a greater risk of mortality. Lung cancer increased mortality risk HR 4.46 (95% CI 3.3–6), $p < 0.001$. Patients with one or more all-cause hospitalizations showed an increased risk of death HR 7.20 (95% CI 5.64–9.20), $p < 0.001$. Similarly, patients with one or more acute exacerbations had a significantly increased risk of death HR 8.37 (95% CI 6.52–10.7), $p < 0.001$, and patients with one or more disease progression at follow-up had a significantly increased risk of death HR 9.08 (95% CI 5.8–14.2), $p < 0.001$.

Treatment

Idiopathic pulmonary fibrosis treatment at our center significantly changed after 2012. As shown in Table 3, the use of antifibrotic has completely overcome both the previously common immunosuppressive treatment with azathioprine and the less common use of cyclophosphamide. The use of both corticosteroids and Warfarin has been reduced to one-third in this fragile population.

In the subgroup of patients treated with antifibrotics compared to any other treatment, the number of hospitalizations for any cause was significantly reduced (45% vs. 65%, $p < 0.001$) and the reduction was significant with both antifibrotic drugs: pirfenidone 36% vs. 56%, $p < 0.001$ and nintedanib 16% vs. 23%, $p < 0.052$. Similarly, acute exacerbations were less frequent in patients treated with antifibrotic drugs (39% vs. 64%, $p < 0.001$) and in both treatment subgroups (pirfenidone 32% vs. 54%, $p < 0.001$ and nintedanib 11% vs. 24 %, $p < 0.003$). Whereas, both hospitalizations and acute exacerbations were more frequent in patients treated with immunosuppressive drugs compared to any other treatment regimen (hospitalizations 22% vs. 12%, $p < 0.002$ and acute exacerbations 24% vs. 13%, $p < 0.002$).

Kaplan–Meier survival estimates for treatment subgroups are shown in Figure 3. The average antifibrotic treatment effect coefficient estimated by propensity score matching showed a significant reduction in mortality rate, acute exacerbations, and hospitalizations as shown in Table 4. Immunosuppressive treatment showed a significant increase in mortality, acute exacerbations, and hospitalizations. The propensity score matched analysis did not identify any significant correlation between the use of antifibrotics or immunosuppressive treatment and the incidence of lung cancer (data shown in the Supplementary Table S1, page 7).

TABLE 3 Treatment approaches according to diagnosis period.

	Entire cohort	(2002–2011)	(2012–2016)	*p*-value
	N = 634	*N* = 286	*N* = 348	
Pirfenidone, *N* (%)	273 (43)	76 (27)	197 (57)	< 0.001
Nintedanib, *N* (%)	112 (18)	18 (6)	94 (27)	< 0.001
Immunosuppression, *N* (%)	99 (16)	88 (30)	11 (3)	< 0.001
Azathioprine, *N*	90	80	10	
Cyclophosphamide, *N*	9	8	1	
Corticosteroids only, *N* (%)	142 (22)	98 (34)	44 (12)	<0.001
Warfarin, *N* (%)	36 (6)	26 (9)	10 (3)	0.001

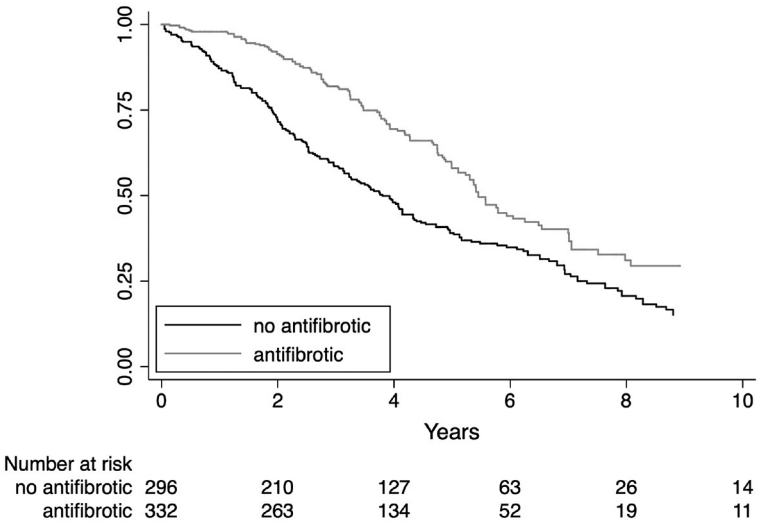

FIGURE 3
Survival estimates by treatment.

Discussion

The year 2012 identifies the time point of fracture from the past, with a significant reduction in mortality risk for IPF (HR 0.58, 95% CI 0.46–0.63). Among all the clinical factors that have been evaluated in this study, a more preserved lung function and antifibrotic treatment are the only determinants of a better prognosis, whereas lung cancer and immunosuppressive treatment are related to a worse survival. The year 2012 at our center coincided with both the introduction of antifibrotic treatment and transbronchial lung cryobiopsy (TBLC) for the diagnosis of ILDs that significantly increased patients' referrals to our unit and the volume of new IPF cases identified.

Some clinical differences noted between the two different IPF time groups are of speculative interest. In the most recent cohort (i.e., after 2012), baseline lung function is more preserved, and this can have contributed to the observed lower prevalence of pulmonary hypertension and lung cancer, comorbidities that tend to occur at more advanced stages. The timely management of patients is a real hope for the future, given the negative prognostic impact that a delayed diagnosis and treatment have (24). Neither familial IPF nor lymphocytosis on BAL had a meaningful impact on mortality risk. Based on our preliminary findings, we can postulate that those variables should not influence physicians' diagnostic perception, nor delay the treatment decision. However, we recognize the limits of this retrospective single-center study, and we believe that this issue should be more appropriately investigated in a prospective analysis.

Antifibrotic treatment has clearly shown in phase III randomized and controlled clinical trials to slow disease progression (5, 6). The pooled analyses of CAPACITY, ASCEND, and INPULSIS trials have shown that nintedanib can reduce the incidence of acute exacerbations (5) and pirfenidone can reduce both respiratory hospitalizations (25) and mortality (14). The population of those clinical trials may significantly diverge from what we observe in real life where patients are older, sicker, and often with numerous comorbidities (14, 17). The first large real-world observational retrospective PS-matched study that compared overall survival in treated and non-treated patients showed reduced all-cause mortality in the treated cohort, but left many open questions about the impact of antifibrotics on clinically relevant intermediate events such as acute exacerbations and lung

TABLE 4 Impact of treatment on mortality, acute exacerbations, and hospitalizations.

Outcome	Treatment	ATE coeff	SE	*p*-value
Death and lung transplant	Any antifibrotic	−0.23	0.04	**<0.001**
	Pirfenidone	−0.24	0.04	**<0.001**
	Nintedanib	−0.2	0.001	**0.001**
	Any immunosoppressive agent	0.36	0.05	**<0.001**
	Corticosteroids only	0.2	0.07	0.06
Acute Exacerbations	Any antifibrotic	−0.15	0.04	**<0.001**
	Pirfenidone	−0.13	0.05	**0.006**
	Nintedanib	−0.06	0.05	0.2
	Any immunosoppressive agent	0.13	0.06	**0.040**
	Corticosteroids only	0.1	0.08	0.2
Hospitalizations	Any antifibrotic	−0.15	0.05	**0.002**
	Pirfenidone	−0.19	0.05	**<0.001**
	Nintedanib	−0.01	0.05	0.800
	Any immunosoppressive agent	0.12	0.06	**0.049**
	Corticosteroids only	0.22	0.08	**0.006**

ATE, average treatment effect; SE, AI robust standard error; CI, confidence interval.
The average treatment effect was estimated using propensity score matching (covariates: age, % of predicted FVC, % of predicted DLco, and lung cancer). Bold values are highlighted in bold to distinguish them as statistically significant values from those that are not statistically significant.

cancer (26). Our study corroborates previous findings showing a significant mortality risk reduction for both antifibrotic treatments, pirfenidone and nintedanib, and explores the possible impact of antifibrotics on acute exacerbations and lung cancer. In the antifibrotic-treated patients, we observed a significant reduction in the risk of acute exacerbations, and hospitalizations for any cause. Combining all evidence, we can hypothesize that the mortality reduction observed in antifibrotic-treated patients is the result not only of the slowed functional decline, but also of the prevention of acute exacerbations leading to hospitalizations, for both drugs. The lack of statistical significance of the average treatment effect for nintedanib in the PS-matched analysis should be interpreted with great caution due to the significantly smaller number of patients in this treatment group compared to pirfenidone. Despite the lower lung cancer prevalence observed in recent years (7.2% vs. 12.6%, $p = 0.016$), the propensity score analysis showed no effect of antifibrotic treatment on lung cancer incidence, and the lower prevalence of lung cancer may merely reflect the milder disease observed in the recent cohort. Our findings do not support the results of previous retrospective studies, conducted on small series of patients (83 treated with pirfenidone, only two cases of lung cancer observed vs. 178 not treated, $N = 39$ lung cancer observed), that showed a dramatically decreased incidence of lung cancer in patients treated with pirfenidone (2.4% vs. 22%) and a decreased risk on multivariate analysis (HR 0.11, 95% CI 0.03–10.46) (27). We can hypothesize that the absence of a matched analysis may have hampered those preliminary results, but larger prospective multicenter studies should better address this important issue in the future.

The propensity score-matched analysis showed a clear increased mortality risk for IPF patients treated with immunosuppressive drugs, mostly azathioprine combined with steroids, whereas no effect on mortality was observed for patients treated with steroids only. When in 2012 the PANTHER trial revealed that patients in the combination therapy (prednisone–azathioprine–NAC), compared with the placebo group, had an increased rate of death (8 vs. 1, $p = 0.01$) and hospitalization (23 vs. 7, $p < 0.001$), the triple therapy approach was abandoned in clinical practice (28). However, some skepticism permeated the scientific community based on uncertainty about whether the reported adverse findings were specific to the use of azathioprine or the combination of azathioprine and steroid therapy, that in the trial was used at higher doses compared to clinical practice (29). Of note, although increased mortality was observed in patients receiving triple therapy, no functional worsening was found in this group, and roughly, one-third of patients receiving the combination therapy discontinued all three medications (30). Our results finally shed light on these areas of uncertainty confirming that the increased mortality risk observed for azathioprine treatment in IPF is linked to an increased risk of acute exacerbations and that the previously reported adverse findings apply at large in IPF. A recent study by Alqalyoobi et al. reported a decrease in in-hospital mortality for IPF patients admitted in academic hospitals (all-cause mortality, respiratory failure-associated mortality, and mechanical ventilation-associated mortality), but not for those admitted in non-academic hospitals. The major limits were the use of an administrative database (NIS) and the lack of data about antifibrotic treatment. The reasons of the observed difference remain unclear. However, the authors suggest a possible stronger adherence to 2015 IPF treatment guidelines at academic centers and our data corroborate the hypothesis that antifibrotic treatment could have influenced the observed decrease in in-hospital mortality for IPF patients admitted in academic hospitals (31).

All intermediate potential prognostic determinants (i.e., lung cancer, acute exacerbations, hospitalizations for any cause, and

disease progression) showed a clear correlation with higher mortality risk at time-dependent analysis. Our results are in line with previous studies that documented an increased mortality risk for coexisting lung cancer (HR 5, 95% CI 2.91–8.57) (4), acute exacerbations (in-hospital mortality 50–90%) (3), respiratory hospitalizations (HR 6.22, 95% CI 4.07–9.49), and disease progression (HR 7.06, 95% CI 4.21–11.84) (32, 33).

Our study has several limitations. Although the cases were followed with prospective intention, real-world database management decisions for each patient were based on individual clinical practice rather than the trial protocol. Second, because this was not a clinical trial, we cannot make accurate comparisons between different treatment groups. Importantly, while most patients reported starting antifibrotic medications at baseline, some patients reported starting when the drug became available. Additionally, start times as well as medication use and comorbidities are self-reported and their accuracy may be limited. The number of treated patients between pirfenidone and nintedanib at that time was imbalanced in favor of pirfenidone because that was the drug that hit the market first in our region.

In conclusion, this large monocentric study investigates for the first time 15 years of real-life IPF history showing that the prognosis of our patients in the last 5 years has significantly improved and that both the introduction of antifibrotic treatment and the discontinuation of immunosuppressive drugs have significantly contributed to this change. The introduction of cryobiopsy and antifibrotic treatment at our site has coincided with a significant increase in patients' referrals and earlier diagnoses. The role of antifibrotic drugs in slowing functional decline, preventing acute exacerbations, and improving survival is confirmed in real-life settings. However, the preventive role of antifibrotic for lung cancer remains to be elucidated. Immunosuppression (azathioprine treatment combined with low doses of steroids) is proven to be harmful and should be discouraged in ascertained UIP/IPF patients. Low doses of steroids used alone do not seem to impact the prognosis of our patients and can be used in selected cases, carefully balancing advantages and possible side effects.

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

The studies involving human participants were reviewed and approved by Comitato Etico di area vasta ROMagna, Italy (CEROM approval protocol number 8571/2017). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conception and design: ST, CR, SP, and VP. Acquisition, analysis or interpretation and drafting the manuscript for important intellectual content: ST, SP, CR, AW, JR, AD, LD, CK, VL, LG, FL, ER, and VP. Full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis: ST and VP. All authors contributed to the article and approved the submitted version.

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Conflict of interest

ST declares speaker's fee from Boehringer-Ingelheim, Roche, Erbe, PulmoniX. VP declares speaker's fees from Boehringer-inghelhem, Erbe, Ambu, and Roche.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1151922/full#supplementary-material

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Is the internet a sufficient source of information on sarcoidosis?

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Introduction: Many patients use the internet as a source of health information. Sarcoidosis is a complex disease, and internet resources have not yet been analyzed for reliability and content on sarcoidosis.

Aims: Our study aimed to investigate the content and the quality of information on sarcoidosis provided by internet resources.

Methods: Google, Yahoo, and Bing were searched for the term "sarcoidosis," and the first 200 hits were saved in each case. Those websites that met the inclusion criteria (English language, no registration fees, and relevant to sarcoidosis) were then analyzed by two independent investigators for readability, quality (HON, JAMA, and DISCERN), and content (25 predefined key facts) of the provided information.

Results: The websites were most commonly scientific or governmental ($n = 57$, 46%), and the median time since the last update was 24 months. Quality was rated with a median JAMA score of 2 (1; 4) and a median overall DISCERN score of 2.4 (1.1; 4.1), both scores represent partially sufficient information. In total, 15% of websites had a HON certificate. Website content measured by the median key fact score was 19 (ranging from 2.5 to 25) with the lowest scores for acute vs. chronic course of the disease, screening for extrapulmonary disease, and diffuse body pain. Poor results were achieved in industry websites and blogs ($p = 0.047$) with significant differences regarding definition ($p = 0.004$) and evaluation ($p = 0.021$).

Discussion: Sarcoidosis-related content of internet resources is partially sufficient; however, several important aspects are frequently not addressed, and the quality of information is moderate. Future directions should focus on providing reliable and comprehensive information on sarcoidosis; physicians from different disciplines and patients including self-support groups should collaborate on achieving this.

KEYWORDS

sarcoidosis, information, internet, quality, content

Introduction

Sarcoidosis is a rare inflammatory granulomatous disease that can affect almost every organ and therefore varies greatly in the course of disease and severity (1). Depending on the organ manifestation, different symptoms can be present, such as dyspnea and cough for pulmonary sarcoidosis, as well as other common symptoms such as fatigue, arthralgia, and body pain (2). It is possible to achieve a cure in many patients. Treatment options are not well established due to a lack of evidence (3), and progression despite treatment occurs in 10–30% of patients with pulmonary sarcoidosis (1). In these severe cases, including the symptom burden and adverse effects of treatment, the patient's quality of life can be substantially impaired (4, 5).

Many patients use internet resources to inform themselves about their health. This is especially true for rare diseases (5) and can lead to a positive impact on quality of life (6). Fisher et al. showed for idiopathic pulmonary fibrosis (IPF), a rare interstitial lung disease, that information on the internet is frequently incomplete and inaccurate (7). Providing adequate information is a particular challenge in sarcoidosis because of the complexity and variability of the disease (8), whilst information on sarcoidosis has been identified as an important need for curing the disease (5).

Our study aimed to evaluate the content and the quality of information on sarcoidosis provided by internet resources.

Methods

Our study was designed as established by Fisher et al. for IPF (7) and was approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg, Germany (S-435/2021).

Search strategy and website selection

On 1 August 2021, the three most common search engines (Google, Yahoo, and Bing), which together represent over 96% of the global search market (9), were searched for the term "sarcoidosis." Before the search was performed, all cookies and histories of web browsers were deleted. This process was repeated individually for the three search engines, and the first 200 hits were saved in each case.

The websites and first generation links within the same domain were then screened systematically for inclusion by one author (KB). Exclusion criteria included duplicates and non-English websites, those requiring registration or enrolment fees, websites not relevant to sarcoidosis, and those that had a clear scientific motive but lacked patient-related focus.

Data extraction and website evaluation

General information about the included websites was collected, including URL, search rank, host country and continent, and most recent update and sponsoring (advertisement). Each website was assigned to one of the following five categories: scientific/governmental, foundation/advocacy, news/media, industry/for profit, and personal commentary/blog. In addition, it was recorded whether a Health on the Net (HON) code certification existed. The HON code certification has been created for websites offering health information and is provided by an independent organization (10). The Flesch Reading Ease Score [FRES, (11)] and Flesch Kincaid Grade Level [FKGL, (12)] were determined for all website text.

Subsequently, each website and the first-generation links were analyzed thoroughly for content. We defined 25 key facts on sarcoidosis based on current guidelines (2, 13, 14) together with experts in this field (MW, NK, and MK) and decided whether they were fully addressed (1 point), partially addressed (0.5 points), or not addressed (0 points). The key facts were sub-grouped into different categories such as definition, symptoms, risk factors, evaluation, management, and outcome. Finally, wrong or misleading facts were also listed.

For quality analysis of information, we used the DISCERN instrument (15) and *Journal of the American Medical Association* (JAMA) dichotomous benchmarks considering the items such as authorship, attribution, disclosure, and currency (Supplementary material S1) (16). The DISCERN instrument is a validated questionnaire that can be applied to any disease to assess the quality of patient information. DISCERN consists of 16 questions, including 8 on reliability, 7 on specific details regarding treatment choices, and 1 on overall quality. Each question is scored from 1 (quality criterion has not been fulfilled) to 5 (completely fulfilled; Supplementary material S2) (15).

The results were compared after each website had been evaluated independently by two experienced investigators (KB and PH). Re-evaluation of the websites was followed by a discussion between the two reviewers in the case of remaining disagreements, defined as initial scores differing by more than 1 point (DISCERN) or more than 0.5 points (key facts).

Statistical analysis

Statistical data evaluation was performed in a descriptive manner and is provided as absolute numbers (percentages), median [minimum; maximums], and mean [standard deviation (SD)]. Between-group differences of websites by category were analyzed by the Kruskal–Wallis test. The Mann–Whitney U-test and unpaired *t*-test were used to test for inter-group comparisons depending on the availability of the HON foundation certificate. Statistical significance was set by a two-sided p-value of < 0.05. No adjustment was made for multiple testing. Data analysis was performed using Excel and RStudio 2022.12.0.

Results

Website characteristics

The first 200 hits from Google, Yahoo, and Bing included 212 duplicates. Subsequently, 206 websites were excluded because they were not directed at a patient audience (scientific websites), 32 due to requiring registration fees, and 26 for not being relevant

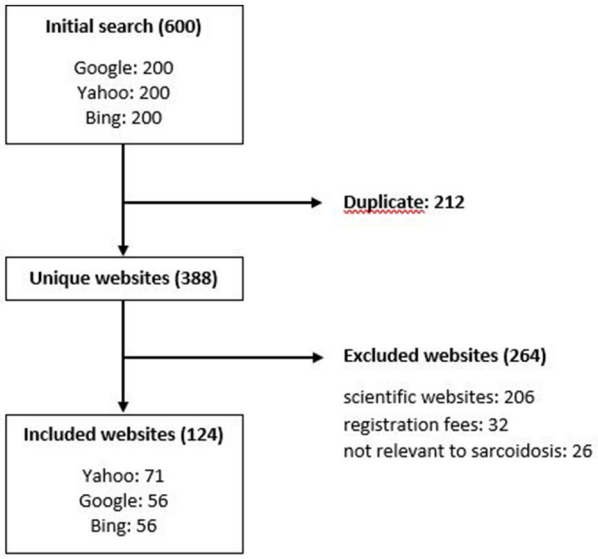

FIGURE 1
Search results and selection for English websites. Each included website was assigned to all search engines where hits were registered.

to sarcoidosis. The final analysis included 124 unique websites (Figure 1), as listed in the (Supplementary material S3).

The characteristics of the included websites are listed in Table 1. Most websites were included from Yahoo (n = 71, 57.3%) and 56 websites each of Google and Bing (45.2% each). Scientific or governmental websites were the most common website type (n = 57; 46%), followed by 30% news/media (n = 37). Advertising was present on 35% of websites. The majority of websites did not have a certification from the HON foundation (n = 106, 85%). The Median JAMA score was 2 (1; 4), representing partially sufficient information. The median overall DISCERN score was 2.4 (1.1; 4.1).

Readability was analyzed by the Flesch Reading Ease Score (42, SD 13) and Flesch Kincaid Grade Level (9, SD 2). The scores corresponded to the best understanding by the college or (FRES) university graduates (FKGL) and thus stand for difficult readability. There were no differences in readability between different website categories (Supplementary material S4).

Median time since the last update was 24 months (0–323) for the 64 websites (52%) that reported this information (Figure 2). Foundation/advocacy websites tended to be more current (median 17 months, ranging from 13 to 82) in comparison to industry websites (median 102 months) and blogs (median 70 months, ranging from 1 to 84; Supplementary material S4).

Website content

The median key fact score was 19 (ranging from 2.5 to 25), indicating that most websites addressed a majority of the content thought to be relevant to patients. The evaluation of website content revealed relevant differences with regard to different key facts and website categories (Figure 3). The definition of sarcoidosis was mostly well explained, e.g., sarcoidosis as a granulomatous systemic disease (89%) and heterogeneous presentation with various organ involvement (94%). However, the differentiation between the acute and chronic course of the disease was not mentioned in 47% of the websites and only partially discussed in 24%. Common symptoms of the disease including dyspnea (85%) and cough (73%) were often fully addressed. Other symptoms including fatigue (64%), diffuse body pain (50%), and skin involvement (48%) were less frequently explained. Most websites discussed key components of the diagnostic evaluation, including radiology (78%) and biopsy (60%). In contrast, 41% of the websites contained no information and 19% had partial information on screening for extrapulmonary disease. Information on lung function (38%) and blood tests and biomarkers (40%) was seldom presented. The role of corticosteroids (79%) and the findings that many patients do not require therapy (69%) were often stated; in contrast, biologicals (32%) and additional therapies (30%) were rarely mentioned. Information on risk factors and outcomes was provided on 59–66% of the websites.

Wrong or misleading facts were presented on 15 websites (12%), which mostly concerned the therapy of sarcoidosis. Corticosteroids were either presented as absolutely necessary or with a long therapy duration of 12 months or more in contrast to the recent ERS clinical practice guidelines (2). One website listed corticosteroids as the only treatment option and another stated that no treatment is necessary for cardiac sarcoidosis.

Comparison between the different website categories showed the highest scores (i.e., best content) for scientific/governmental, foundation/advocacy, and news/media websites. In contrast, poor results were observed for industry websites and blogs (p = 0.047). Significant differences across sites were found with respect to definition (p = 0.004) and evaluation (p = 0.021). Very few industry websites and blogs contained information on evaluation and management.

Finally, the websites were examined for a possible association between search rank and content. Therefore, websites were sorted by a primary criterion "sum key fact score." There was no clear association between search rank and content.

Website quality

Website quality was measured with the DISCERN instrument and yielded values in a medium range (3 points, range 1–5). Based on all rated websites, poor results were achieved for the questions on sources of information (1 point, range 1–5), currency of information (2 points, range 1–5), and additional sources of information (2 points, range 1–5). Regarding the quality of information on treatment choices (Section Methods of DISCERN), almost all categories were barely fulfilled with a median score of 2 points. Risks of treatment were rarely mentioned (1.5 points, range 1–5; Figure 4).

Foundation and advocacy websites reached the highest DISCERN scores in all three sections (Table 2). In contrast, industry websites achieved poor results ($p < 0.001$). This was particularly evident for items 9–15 regarding the quality of information on treatment choices ($p < 0.001$).

TABLE 1 Characterization of unique websites.

Overall unique websites, *n* (%)			124 (100)
General information	Website category, *n* (%)	Scientific/Governmental	57 (46)
		Foundation/Advocacy	16 (13)
		News/media	37 (30)
		Industry/for-profit organization	9 (7)
		Personal commentary/blog	5 (4)
	Host continent, *n* (%)	Europe	19 (15)
		North America	95 (77)
		South America	0 (0)
		Asia	3 (2)
		Australia	7 (6)
		Africa	0 (0)
		Antarctica	0 (0)
	Sponsored websites, *n* (%)	Yes	44 (35)
		No	80 (65)
General quality of medical information	HON foundation certificate	Yes (%)	18 (15)
		No (%)	106 (85)
	JAMA score	Median (range)	2 (1–4)
Patient- focused information	Sum DISCERN score	Median (range)	2.4 (1.1–4.1)
	Readability	Flesch Reading Ease Score, Mean (SD)	42 (13)
		Flesch Kincaid Grade Level, Mean (SD)	9 (2)
	Specific entity-related content	Sum key fact score, Median (range)	19 (2.5–25)

HON, Health on the Net; JAMA, Journal of the American Medical Association; SD, standard deviation.

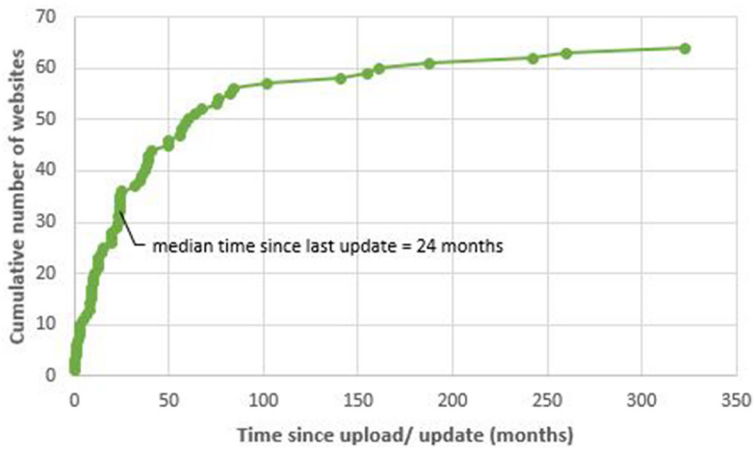

FIGURE 2
Time since website upload. The plot shows the websites ordered by their time since upload/update until the date of assessment in months. Only websites with available publishing/update dates were included ($n = 64$).

The JAMA score differed between website categories with the highest median score for news/media (3, range 1) and poor results for industry websites (1, range 1; $p < 0.001$; Supplementary material S4). Certification from the HON foundation was present in 7% of scientific websites ($n = 4$) and 38% of news/media ($n = 14$). Websites with HON certification had higher JAMA scores ($p < 0.001$) and better results in summed DISCERN score ($p = 0.003$). In addition, they tended to have better evaluations of content measured by summed key fact score ($p = 0.015$). No correlation was found between

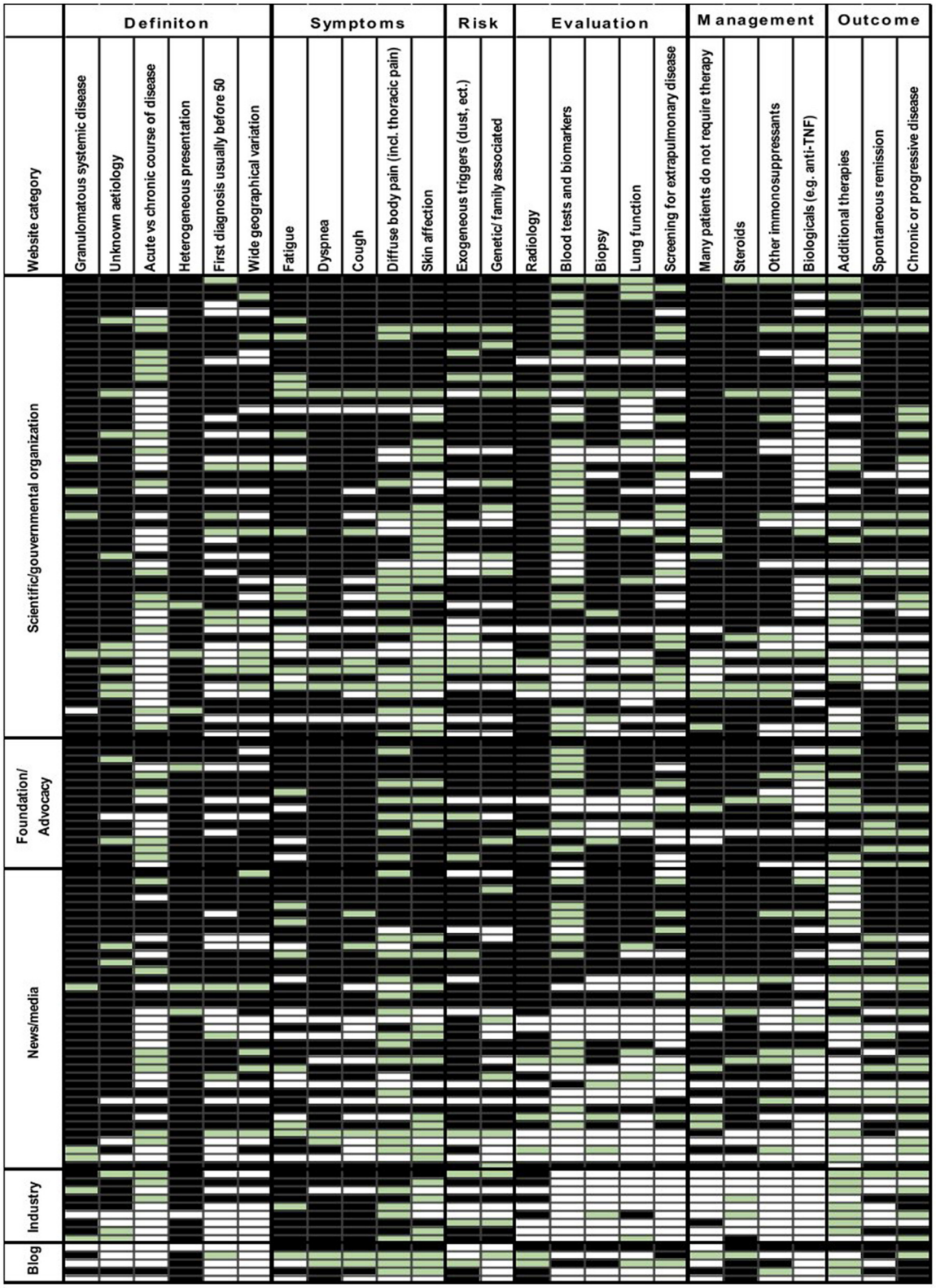

FIGURE 3
Key fact scores for English websites. Key fact items (columns, $n = 25$) are shown for single websites (rows, $n = 124$). The categorial key fact item scoring is 0 (not addressed), 0.5 (partially addressed), and 1 (fully addressed). The websites are grouped by website category. ACE, angiotensin-converting enzyme; IL-2, interleukine 2; anti-TNF, anti-tumor necrosis factor. 0: white, 0.5: green, and 1: black.

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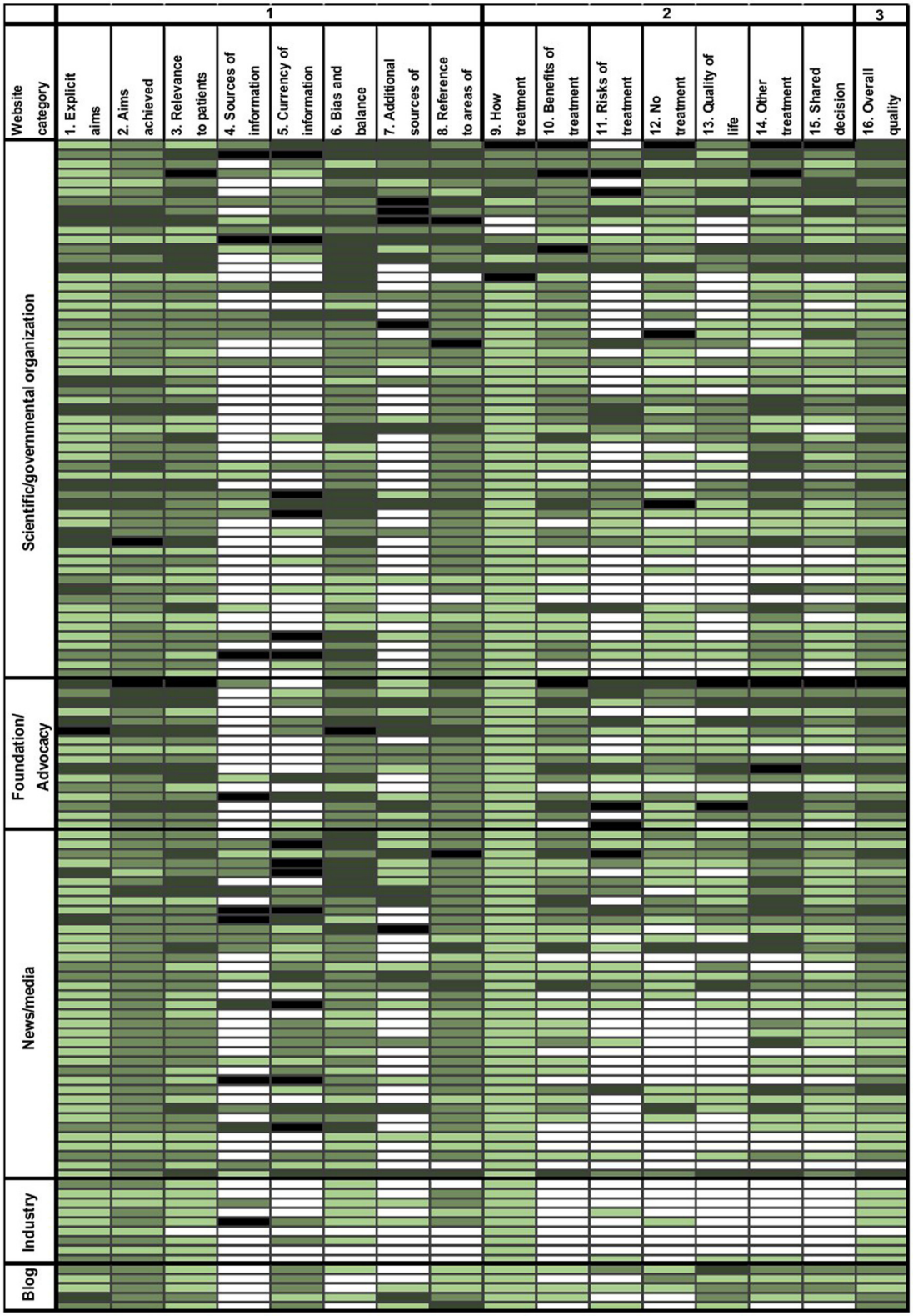

FIGURE 4
DISCERN scores grouped by website category. DISCERN score items (columns, $n = 16$) are shown for single websites (rows, $n = 124$). The categorial DISCERN item scoring ranges between 1 (not addressed) and 5 (fully addressed). 1: white, 2: light green, 3: green, 4: dark green, and 5: black.

TABLE 2 Sum DISCERN scores for different sections by the website category.

	Scientific/ governmental	Foundation/ advocacy	News/media	Industry/ for profit	Personal commentary/blog	*p*-value
Section 1 (items 1–8): Is the publication reliable? median (range)	2.6 (1.8–4)	2.8 (2–3.8)	2.5 (1.6–3.5)	1.8 (1.3–2.8)	2.1 (1.9–2.8)	0.002
Section 2 (items 9–15): How good is the quality of information on treatment choices? median (range)	2.1 (1–4.3)	2.6 (1–4.7)	1.9 (1–3.7)	1 (1–1.4)	1.9 (1.3–2.7)	<0.001
Section 3 (item 16): Overall rating of the publication median (range)	3 (2–4)	3 (2–5)	3 (1–4)	2 (1–2)	3 (2–3)	0.002
Overall median (range)	2.5 (1.4–3.8)	2.9 (1.6–4.1)	2.4 (1.4–3.5)	1.5 (1.1–2)	2.2 (1.8–2.4)	<0.001

HON certification and readability (FRES $p = 0.349$ and FKGL $p = 0.682$).

In addition, the websites were sorted by search rank and a secondary criterion "DISCERN sum overall," and no clear association was found between the search rank and the quality of the websites.

Discussion

Within the framework of this study, we investigated the content and the quality of internet resources on sarcoidosis. Therefore, 124 eligible English websites were systematically evaluated with different validated instruments. Sarcoidosis-related content of internet resources showed to be partially sufficient. However, several important aspects are frequently not addressed, and the quality of information is moderate. This is highly relevant because the internet presents a common source of health information to patients. In a German survey-based study, 94% of patients with sarcoidosis used the internet to obtain information on their disease (17). To the best of our knowledge, this has not been studied to date.

Most of the websites that met the inclusion criteria were scientific/governmental websites. In a comparison analysis of IPF, the largest group was also scientific/governmental (7). Just as with IPF, most eligible websites were found on Yahoo (7). Websites in our analyses were frequently not up to date with a median time since the last update of 24 months indicating that the information provided on these sites may not reflect the current status of guideline recommendations, especially regarding new therapies such as biologics (2). Information on industry websites and blogs was particularly outdated, but in comparison, foundation/advocacy websites were best updated.

In general, there was greater quality content provided on scientific/governmental websites, and less content on news/media websites, which were particularly lacking details on evaluation and management. Consistent with our results, scientific websites on IPF similarly provided the most content (7) as did Youtube videos on lymphangioleiomyomatosis (LAM) (18).

Overall, website content measured by predefined key facts was acceptable with a median of 19 out of 25 points. However, several aspects were not addressed regardless of the website category. These included the acute vs. chronic course of the disease, screening for extrapulmonary disease, and the common symptom of diffuse body pain. These findings are consistent with a German survey, where relevant information gaps included fatigue and diffuse pain as well as the different courses of disease (17). Additionally, information gaps included the management of sarcoidosis and were further accentuated by reporting of wrong or misleading facts that primarily concerned false information regarding the necessity and duration of corticosteroid therapy as well as treatment indications. Only one-third of the websites provided adequate information on biologics and additional therapies such as rehabilitation. Patients with sarcoidosis often want to be involved in treatment decisions in terms of a shared decision-making process (19), which can lead to better outcomes and treatment adherence (8). However, in a Dutch study, 57% of sarcoidosis patients stated that they cannot find sufficient information about their disease (19); one of the reasons for this is likely the heterogeneity and complexity of sarcoidosis (8). Even with other diseases, such as cancer, the information needed for participating in shared decision-making is often not available on the internet (20). Our results have highlighted that information on the management and therapy of sarcoidosis is often missing or misleading. This poses challenges for all parties involved. If the information available on the internet differs from that of the attending physician, this can lead to negative interactions and disruptions in doctor–patient relationships (21).

In addition to often missing relevant content, the quality, reliability, and readability were also found to be moderate to poor in our analyses. Readability corresponded to college or university graduates, which is far beyond what is recommended for health information disseminated to a patient audience, e.g., the National Institutes of Health (NIH) recommend a grade of 6–7 reading level meaning that comprehension should be easy or fairly easy to read (22). The median DISCERN score of 2.4 points and the median JAMA score of 2 points also shows that the quality of websites is not sufficient, particularly with respect to the currency of information and information on treatment choices (especially risks of treatment). In addition, very poor scores regarding sources of information are another important factor, although citing sources is essential in terms of reliability. In comparison to other diseases, the quality of internet resources measured by DISCERN and JAMA was also poor for IPF (7) and breast cancer (20), while in contrast,

information on prostate cancer achieved good results (23). The quality of online health information, in general, has been studied in several meta-analyses (24); until 2002, 70% of the analyzed studies stated that the quality was a problem (25), and from 2002 to 2013, the quality of online health information was found to be problematic in 55% of the analyzed studies (26). This lack of reliability poses a special challenge to patients who may have greater difficulty recognizing risk and bias in online information (7). Thus, 63.4% of sarcoidosis patients reported the internet to be a reliable source of information despite the limitations of this source (17).

This study illustrates several problems in internet resources on sarcoidosis. It should be emphasized that quality was often insufficient, and information was lacking concerning some very relevant aspects, especially with regard to therapy. Therefore, we require better guidance and methods for patients, where they can obtain information about their disease. One possible tool could be HON certification as this resulted in better DISCERN and JAMA scores and tended to be connected to better content.

This study has some limitations. We analyzed websites in English only. Therefore, our results are mainly helpful to patients who use English-language information on the internet. Content and quality of internet resources on sarcoidosis may vary in other languages. In addition, only the largest three platforms, namely Google, Yahoo, and Bing, were searched. We performed our search on a single date; therefore, we did not consider changes in content over time. Furthermore, we have only searched for the term "sarcoidosis," possible abbreviations as well as different terms for the disease, e.g., Löfgren syndrome, have been disregarded. Websites with registration fees were not included in our analysis; we cannot exclude that these websites may not have a higher content quality than the free-to-use sites reported here. The content analysis was based on previously defined key facts by various sarcoidosis experts, which are therefore not validated. Demographic data of the website readers are lacking. Thus, it is not possible to find a correlation between the readers and website categories. Despite these limitations, we have identified important gaps in the quality of online patient-directed sarcoidosis health information.

Conclusion

Our results clarify that the content and quality of internet resources on sarcoidosis are acceptable but with several important aspects that are frequently not addressed. In order to facilitate shared decision-making, efforts should be directed toward obtaining reliable and comprehensible information, especially due to the complexity of the disease and the increase in different treatment options. For this purpose, physicians from different disciplines and patients including self-support groups should collaborate together.

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

The study was approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg, Germany (S-435/2021).

Author contributions

KB, CG, and MK were responsible for the study design and this was adapted to a study in IPF by CR and JF. The key facts were developed by KB, MW, NK, and MK. Website evaluation was performed by KB and PH. KK was responsible for the statistical analyses. KB was a major contributor in writing the manuscript. FW and FH had contributions to the conception of the work and for the preparation of the final manuscript. All authors read and approved the final manuscript.

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Conflict of interest

KB received payment for lectures from Boehringer Ingelheim and a grant from Sarkoidose-Netzwerk e.V. JF has received grant funding from the University of Toronto and the Canadian Pulmonary Fibrosis Foundation and has received honoraria from Boehringer Ingelheim and AstraZeneca. CR reports grants from Boehringer Ingelheim and Hoffman la Roche; consulting fees from Boehringer Ingelheim, Hoffman la Roche, Astra Zeneca, Veracyte, Ensho, and Pliant Therapeutics; payment for lectures from Boehringer Ingelheim, Hoffman la Roche, and Cipla Ltd.; and support for attending meetings from Cipla Ltd., and Boehringer Ingelheim (unrelated to this submission). FH reports payment for lectures from Astra Zeneca, GSK, and Chiesi and is a part of the Data Safety Monitoring Board from Apogenix. MK reports grants, consulting fees, and payment for lectures from Boehringer Ingelheim and Roche. KK was employed by Limbach Gruppe SE.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1217146/full#supplementary-material

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Global trends of interstitial lung diseases from 1990 to 2019: an age–period–cohort study based on the Global Burden of Disease study 2019, and projections until 2030

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Background: Interstitial lung diseases (ILDs) are indispensable components of chronic respiratory diseases and global health challenges. We aimed to explore the global long-term changes in the prevalence, mortality, and disability-adjusted life years (DALYs) of ILDs; investigate the independent effect of age, period, and cohort; and project the disease burden over the next decade.

Methods: Data were retrieved from the Global Burden of Disease (GBD) database 2019. The joinpoint regression model was used to calculate the average annual percent change (AAPC). An age–period–cohort (APC) analysis was employed to measure the independent effect of age, period, and cohort. The Bayesian age–period–cohort (BAPC) model was used to project the global epidemiological trends until 2030.

Results: From 1990 to 2019, the age-standardized prevalence rate (ASPR), age-standardized mortality rate (ASMR), and age-standardized disability-adjusted life years (DALYs) rate (ASDR) of interstitial lung disease and pulmonary sarcoidosis (ILD) slightly increased from 52.66 per 100,000 [95% uncertainty interval (UI) 44.49 to 61.07] to 57.62 per 100,000 (95% UI 49.42 to 65.67), from 1.76 per 100,000 (95% UI 1.41 to 2.22) to 2.17 per 100,000 (95% UI 1.5 to 2.62), and from 41.57 per 100,000 (95% UI 33.93 to 51.92) to 46.45 per 100,000 (95% UI 35.12 to 54.98), whereas the ASPR, ASMR, and ASDR of pneumoconiosis decreased. High social-demographic index (SDI) regions possessed the highest ASPR, whereas low-middle SDI regions had the highest ASMR and ASDR, followed by low-SDI regions in ILD. Middle-SDI regions reported the highest ASPR, ASMR, and ASDR in pneumoconiosis. The age effect showed that the rate ratio (RR) was high in older adults. Period effect indicated that the RR of prevalence increased over time, whereas the RR of mortality and DALYs decreased in men but increased in women. The cohort effect exhibited that the more recent birth cohort had a higher RR than the previous cohort in prevalence. We projected that ASPR, ASMR, and ASDR would stabilize with little variation over the next decade.

Conclusion: The global burden of ILDs remains relatively severe, especially among older adults, in low- and middle-SDI regions. Effective measurements are expected to improve this situation.

KEYWORDS

interstitial lung disease, pneumoconiosis, Global Burden of Disease (GBD), age–period–cohort (APC) analysis, prevalence, mortality, projection

1. Introduction

Interstitial lung diseases (ILDs) cover more than 200 diseases, characterized by inflammation or fibrosis within the pulmonary mesenchyme, alveolar wall, and alveolar space, defined by their causes and distinct histopathological features, from extremely rare to relatively common (1, 2). Sarcoidosis is a granulomatous disease that can affect virtually any organ, in which pulmonary involvement is highly prevalent (3). Fibrosis has frequently been observed in sarcoidosis, and as a confounding histological feature, other conditions such as fibrotic ILDs and pneumoconiosis (particularly when associated with dust) are also associated with this finding (3). The pulmonary manifestations of sarcoidosis vary significantly, ranging from asymptomatic to life-threatening cases, with pulmonary fibrosis accounting for most cases of mortality associated with the disease (4). Identifiable causes of ILDs include occupational exposure, drugs or radiation therapy, and connective tissue disease (CTD-ILD) (5). Patients with unknown causes are defined as those with idiopathic interstitial pneumonia, of which idiopathic pulmonary fibrosis (IPF) is the most common and lethal type, associated with gene polymorphisms related to host defense and cell repair (6, 7).

ILDs can cause irreversible lung damage, resulting in an impaired quality of life, permanent physical disabilities, and respiratory failure, imposing a significant burden on society. One of the first published ILDs registries in New Mexico suggested that the prevalence of ILDs in the general population may be greater than previously estimated and that 90% of the reported occupational diseases in China were pneumoconiosis (8, 9). Additionally, ILDs are considered the primary cause of death in patients with systemic sclerosis, and the mortality rate of IPF has increased by 9.85% from 2000 to 2017 in the United States (10, 11). Moreover, with CTD-ILD, people experience a lower employment rate and workplace productivity loss estimated at $13,593 per person; the mean total 5-year cost for rheumatoid arthritis patients with ILDs was US $173,405 (12, 13).

The Global Alliance against Chronic Respiratory Diseases (GARD) is devoted to initiating a comprehensive approach to fight chronic respiratory diseases, with the vision of a world where all people breathe freely (14). Understanding the informative epidemiological estimates of ILDs in specific regions and populations enables us to formulate better health-related policies, facilitate the reasonable allocation of healthcare resources, and alleviate the burden of ILDs. Nevertheless, comprehensive data on ILDs on a global scale are scarce. Previous studies have mainly analyzed specific types of ILDs and were limited to localized regions (15–17). In this study, the results of the updated Global Burden of Disease (GBD) 2019 on ILDs are presented. We visualized the prevalence, mortality, and disability-adjusted life years (DALYs) data of ILDs from the GBD2019 by age, sex, year, and region; analyzed the age, period, and cohort effects on the changes in prevalence, mortality, and DALYs; and projected the overall trends of ILD until 2030.

Abbreviations: AAPC, average annual percent change; APC, annual percent change; APC, age–period–cohort; ASDR, age-standardized disability-adjusted life years rate; ASMR, age-standardized mortality rate; ASPR, age-standardized prevalence rate; BAPC, Bayesian age–period–cohort; CI, confidence interval; CTD-ILD, connective tissue disease-related interstitial lung disease; DALYs, disability-adjusted life years; EAPC, estimated annual percent change; GARD, the Global Alliance against Chronic Respiratory Diseases; ILD, interstitial lung disease and pulmonary sarcoidosis; ILDs, interstitial lung diseases; IPF, idiopathic pulmonary fibrosis; RR, rate ratio; SDI, social-demographic index; UI, uncertainty interval; YLDs, years lived with disability; YLLs, years of life lost.

2. Methods

2.1. Data source

In the International Classification of Diseases, 10th edition (ICD-10), the codes of "other respiratory diseases principally affecting the interstitium" were J80–J84, among which J84 was the code for "other interstitial pulmonary diseases," the code of "sarcoidosis" was D86 and that of "pulmonary sarcoidosis" was D86.001, and the codes of "lung diseases due to external agents" were J60–J70, among which J60 was the code for "coal worker's pneumoconiosis" and J61 was the code for "pneumoconiosis due to asbestos and other mineral fibers." In the GBD study, interstitial lung diseases (ILDs) and pulmonary sarcoidosis are defined as a collection of chronic respiratory diseases that impair lung function and oxygen uptake through scarring and/or inflammation. Pneumoconiosis is defined as a chronic lung disease typified by lung scarring and other interstitial damage caused by exposure to dust and other containments—usually through occupational exposure. The relevant ICD codes for ILD are J84 and D86, the American Thoracic Society was used as the gold-standard definition for ILD, and exposure types such as coal, asbestos, and silica were used to model pneumoconiosis (18).

Data on global ILDs prevalence, mortality, and DALYs from 1990 to 2019 were retrieved from the GBD2019 study, which covers 204 countries and territories, providing comprehensive and standardized estimations of 369 diseases and injuries and 87 risk factors, engaging a large network of individual collaborators with specialties in various topic areas. The data source for the GBD study includes censuses, household surveys, civil registration and vital statistics, disease registries, health service use, air pollution monitors, satellite imaging, disease notifications, and other sources. The cause of death database is composed of vital registration, verbal autopsy, registry, survey, police, and surveillance data. Data sources using alternative case definitions or measurement methods were adjusted using network meta-regression to the reference definition or measurement method to be comparable. To standardize the cause of death data, which is organized in a hierarchical list containing four levels, protocols were used to address differences in ICD codes due to national variation or revision. There are three main standardized tools in the GBD study, including the Cause of Death Ensemble model, a highly systematized tool to analyze the cause of death data; spatiotemporal Gaussian process regression, a set of regression methods that borrow strength between locations and over time for single metrics; and DisMod-MR, a Bayesian meta-regression tool that allows evaluation of all available data on prevalence, mortality, and remission for a disease. More details on methodological

information and modeling strategies in the GBD study were published elsewhere as Supplementary material (18–20).

The prevalence data for ILDs were primarily derived from hospital inpatient and insurance claims data. Mortality data were derived from vital registration systems, censuses, and surveys. The verbal autopsy was excluded from the model as the sensitivity of verbal autopsy algorithms to detect specific chronic respiratory diseases is poor (18). DALYs are the sum of years lived with disability (YLDs) and years of life lost (YLLs). YLD was calculated by multiplying the prevalence of each sequela, and YLL was calculated by multiplying the number of deaths. Age-standardized rates were based on the GBD global reference population. Social-demographic index (SDI) represents a population's social and economic development status for each location year; a higher index suggests a more developed society. We downloaded the data from the GBD query tools (https://vizhub.healthdata.org/gbd-results/), and GraphPad Prism 9.4.1 and R 4.2.1 were utilized to visualize the data.

2.2. Joinpoint regression analysis

Trends in the age-standardized prevalence (ASPR), mortality (ASMR), and DALYs rate (ASDR; per 100,000) of ILDs were evaluated using Joinpoint Software 4.9.1, and the data from GBD were processed in Excel 2019 and R 4.2.1. The modeling strategy of the Joinpoint software was the grid search method, which was used to establish the possible connection nodes (Joinpoint nodes) and calculate the sum of squares errors and mean squared errors in each situation. Five points was the maximum number allowed in our study. The internal trends of each independent interval were evaluated using the annual percent change (APC) and 95% confidence interval (CI), and a comprehensive evaluation of the overall trend was performed using the average APC (AAPC) and 95% CI. Each p-value was determined using the Monte Carlo method, and a p-value of < 0.05 was considered statistically significant (21).

2.3. Age–period–cohort analysis

The APC Web Tool (https://analysistools.cancer.gov/apc/) and R 4.2.1 were employed for data processing (22). We separated the ASPR, ASMR, and ASDR of ILD into consecutive 5-year age intervals, ranging from 0–4 to 95–99 years, and the period from 1990 to 2019 into successive 5-year segments, as it was stipulated in the APC framework that the age and period intervals must be identical. Timepoint values (1992, 1997, …, 2017) were used to replace the 5-year periods to avoid a temporal overlap of the adjacent birth cohorts from 1990 to 2019. The age group of 40–44 years, period 2000–2004, and birth cohort 1955–1959 were selected as the references for age, period, and cohort effect, respectively. The rate ratio (RR) indicates the value of a particular age, period, or cohort compared with the reference value. RR > 1 suggests that the factor has a higher risk of disease than the reference. Local drifts indicate APCs, whereas net drifts indicate the overall APCs. Wald's chi-square tests were used to estimate the significance of parameters and functions. All statistical tests were two-tailed.

2.4. Projection of model development

The Bayesian age–period–cohort (BAPC) model was used to conduct the projections. This model has been verified to be superior to many other linear power models and achieves more sensible projections. One study suggested that the probabilistic forecasts obtained using the BAPC model were well-calibrated and not too wide (23). Based on the integrated nested Laplace approximations, the BAPC model assumed that the effect of age, period, and cohort adjacent in time was analogous. The classifications of age groups and periods were the same as those in the APC model. We conducted the BAPC analysis using the R package "BAPC."

2.5. Ethics statement

No animal studies, no human studies, and no potentially identifiable human images or data are presented in this study.

3. Results

3.1. Global, regional, and national trends in the prevalence, mortality, and DALYs of ILDs

According to GBD 2019, an estimated 2.28 million [95% uncertainty interval (UI) 1.95 to 2.61] men and 2.43 million (95% UI 2.07 to 2.8) women worldwide had ILD in 2019 (Figure 1A). From 1990 to 2019, ASMR slightly increased from 2.34 per 100,000 (95% UI 1.6 to 3.18) to 2.72 per 100,000 (95% UI 1.66 to 3.55) in men and from 1.34 per 100,000 (95% UI 1.02 to 1.87) to 1.76 per 100,000 (95% UI 1.11 to 2.16) in women (Figure 1B). ASDR increased from 52.38 per 100,000 (95% UI 37.18 to 71.76) to 55.47 per 100,000 (95% UI 36.9 to 70.32) in men and from 32.86 per 100,000 (95% UI 25.81 to 43.75) to 38.99 per 100,000 (95% UI 28.09 to 46.8) in women, with the annual rate of change of 0.06 (95% UI −0.2 to 0.45) and 0.19 (95% UI −0.06 to 0.43), respectively (Figure 1C). Regarding pneumoconiosis, all the cases and age-standardized rates in men were much greater than those in women. The ASPR of pneumoconiosis in men increased from 78.54 per 100,000 (95% UI 65.35 to 96.72) in 1990 to 95.82 per 100,000 (95% UI 81.99 to 111.95) in 1996 and then gradually decreased to 69.7 per 100,000 (95% UI 58.6 to 81.77) in 2017 and increased to 71.36 (95% UI 60.05 to 83.86) in 2019 (Figure 1D). Both the ASMR and ASDR of pneumoconiosis in men decreased in the last three decades, with the annual rate of change of −0.56 (95% UI −0.63 to −0.41) and −0.46 (95% UI −0.55 to −0.33), respectively. However, number of deaths and DALYs due to pneumoconiosis remained almost unchanged between 1990 and 2019 (Figures 1E, F).

The ASPR of ILD was the highest in high-SDI regions, at 101.21 per 100,000 (95% UI 87.66 to 113.79) in 2019, and a slight upward trend was observed in high-SDI regions from 1990 to 2019, with an annual rate of change of 0.17 (95% UI 0.11 to 0.22); little difference

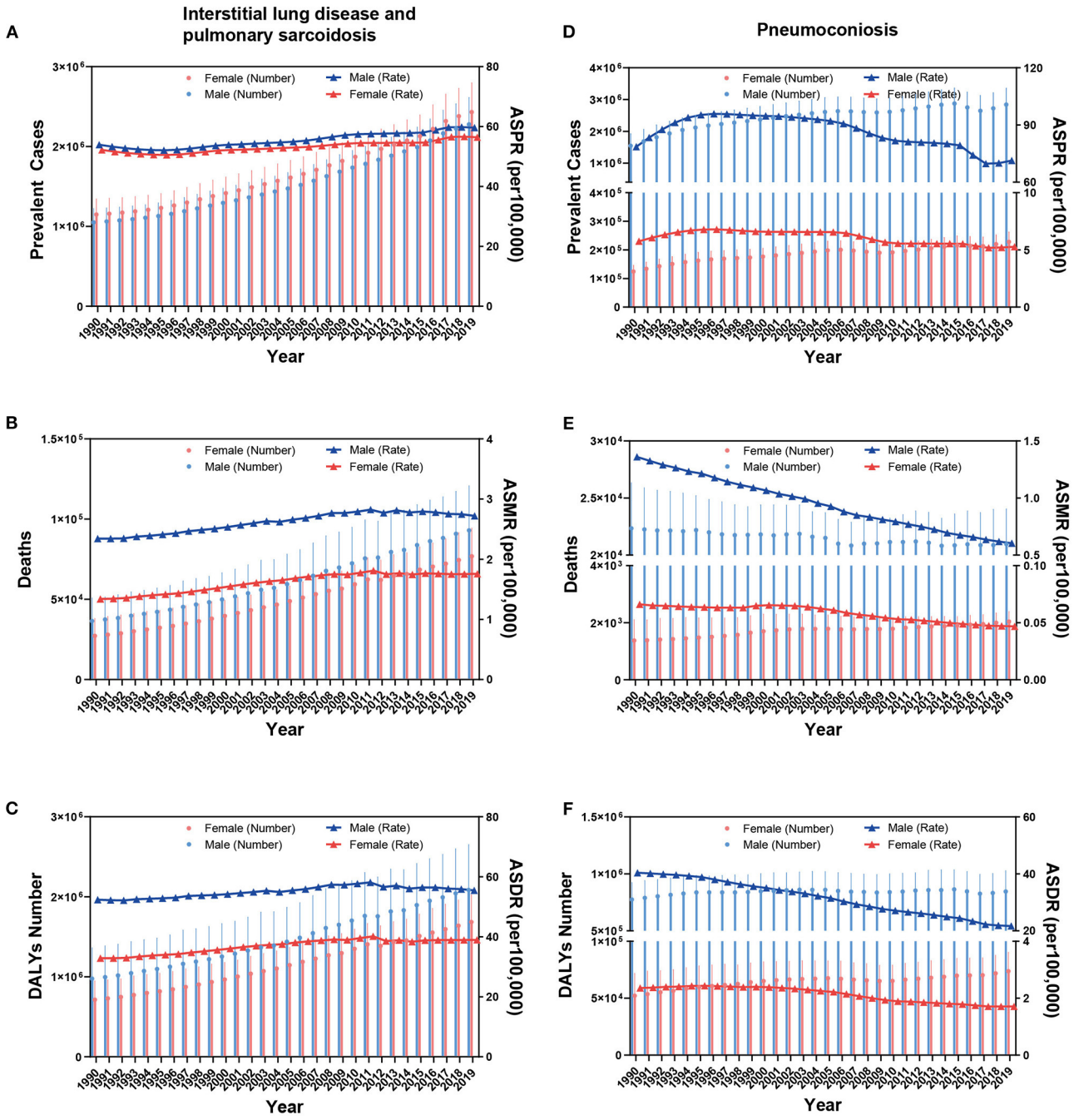

FIGURE 1
Global prevalent cases, ASPR **(A, D)**, deaths, ASMR **(B, E)**, DALYs number, and ASDR **(C, F)** of ILDs by sex from 1990 to 2019.

was presented in other SDI regions (Figure 2A). Analogous trends were observed for ASMR and ASDR. The low-middle SDI regions possessed the highest ASMR and ASDR, whereas the high-middle SDI regions had the lowest, at 3.75 per 100,000 (95% UI 2.51 to 5.15) and 1.14 per 100,000 (95% UI 0.81 to 1.34) in ASMR and 78.56 per 100,000 (95% UI 54.31 to 107.04) and 26 per 100,000 (95% UI 20.53 to 30.04) in ASDR in 2019. In high-SDI regions, mild uptrends were exhibited; however, in other SDI regions, the trends almost leveled off from 1990 to 2019 (Figures 2B, C). As for the ASPR of pneumoconiosis, the middle-SDI regions had the maximal rate, at 58.47 per 100,000 (95% UI 48.81 to 69.34) in 2019, followed by the high-middle SDI regions (Figure 2D). The ASMR and ASDR in all SDI regions decreased from 1990 to 2019, and the middle-SDI regions possessed the highest rate, from 0.74 per 100,000 (95% UI 0.52 to 0.94) in 1990 to 0.33 per 100,000 (95% UI 0.27 to 0.4) in 2019 in ASMR and from 28.21 per 100,000 (95% UI 21 to 34.99) in 1990 to 15.52 per 100,000 (95% UI 12.39 to 19.44) in 2019 in ASDR; the low- and high-SDI regions had relatively low

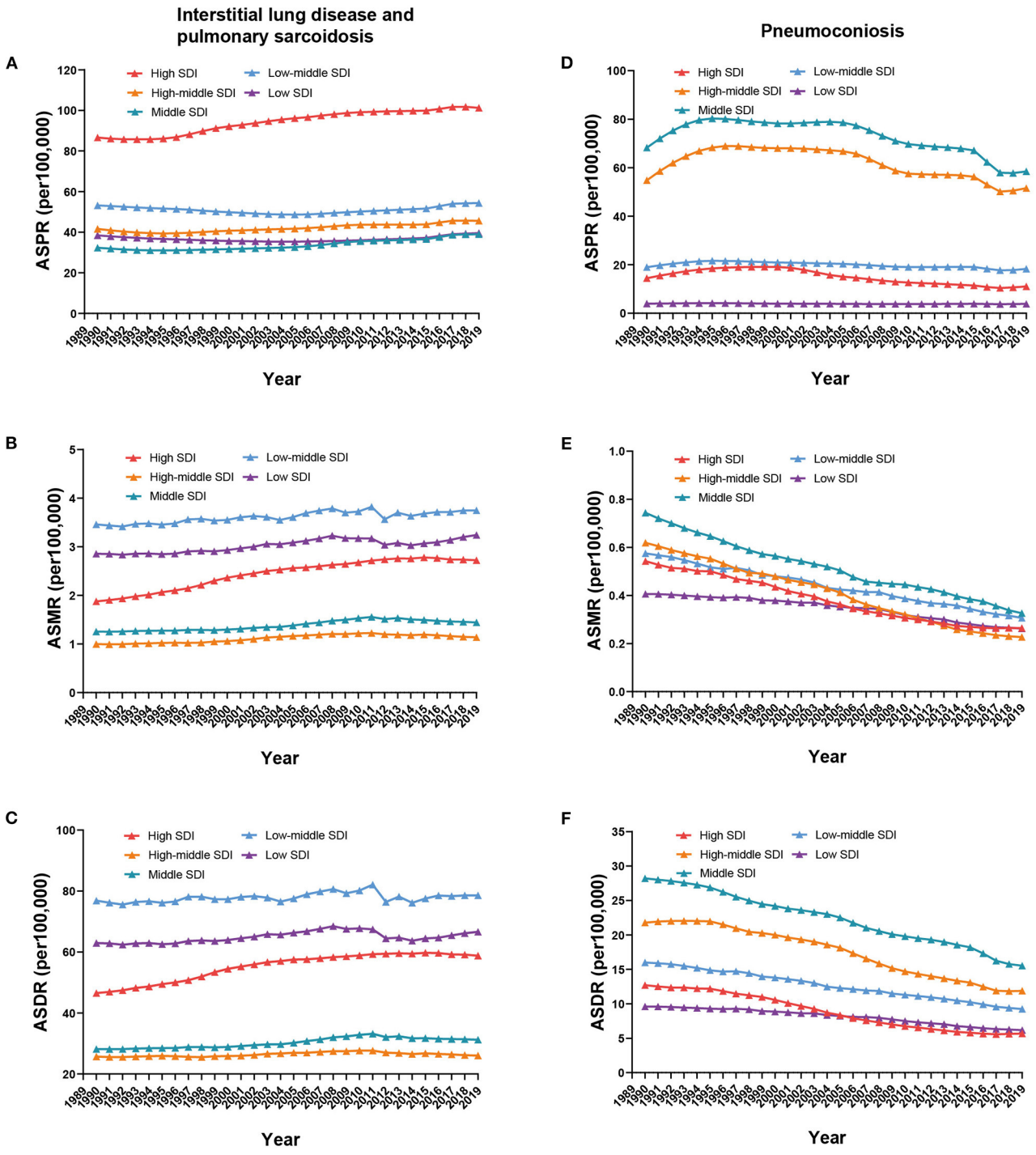

FIGURE 2
Global ASPR **(A, D)**, ASMR **(B, E)**, and ASDR **(C, F)** of ILDs by SDI regions from 1990 to 2019.

rates, with 0.26 per 100,000 (95% UI 0.12 to 0.37) and 0.26 per 100,000 (95% UI 0.23 to 0.3) in ASMR and 6.17 per 100,000 (95% UI 3.09 to 8.6) and 5.67 per 100,000 (95% UI 5 to 6.44) in ASDR in 2019 (Figures 2E, F).

The ASPR, ASMR, and ASDR of ILD and the SDI value in 204 countries and territories in 1990 and 2019 were determined. In 1990, Brunei, Japan, and the United States ranked as the top three countries with the highest ASPR. Maldives had the highest ASMR and ASDR, followed by Peru (Supplementary Table 1). In 2019, the areas with a higher ASPR were Japan, Peru, Chile, Brunei, the United States, Greenland, Palau, and Maldives, all with over 120 per 100,000. Bolivia had the maximal ASMR, at 11.53 per

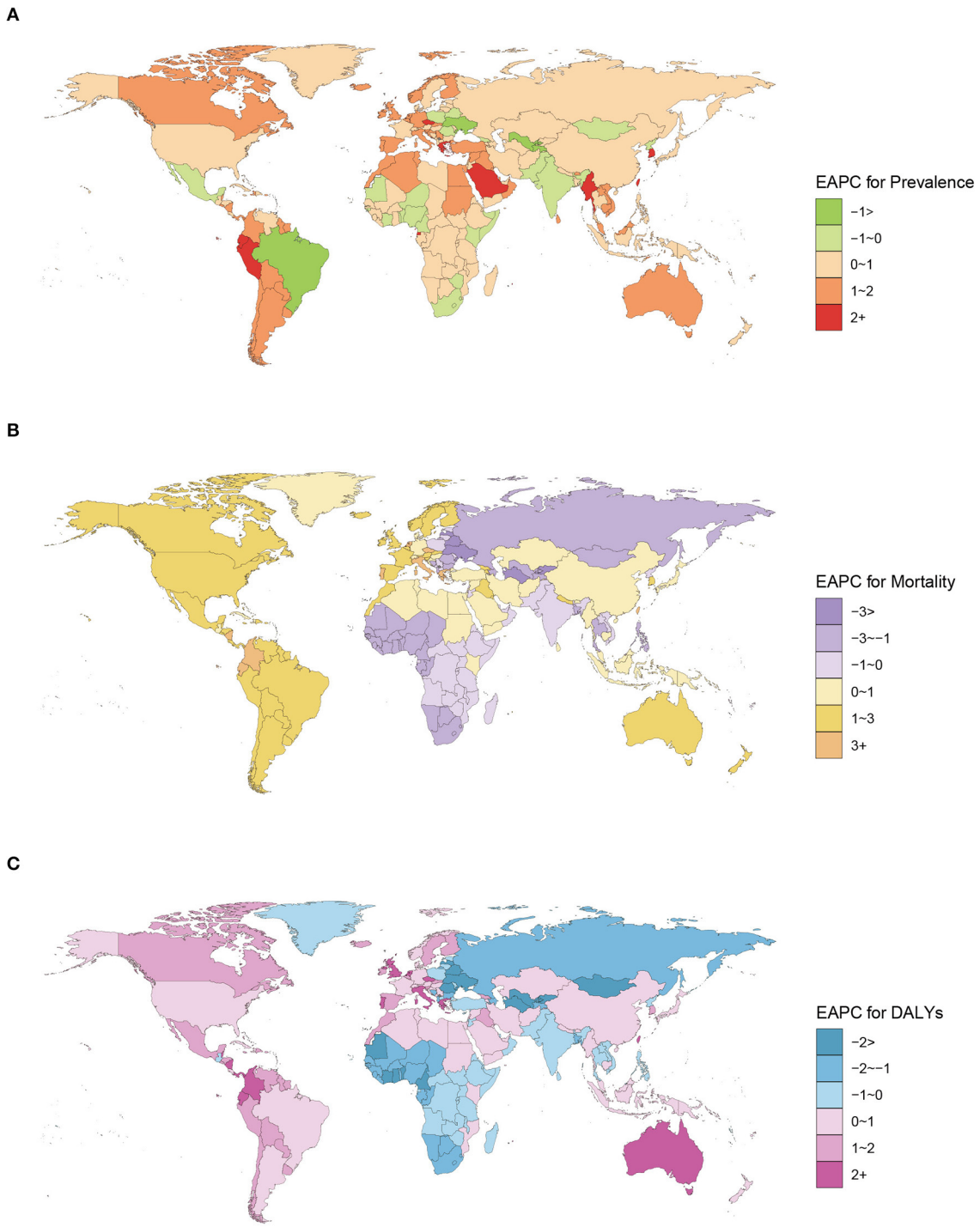

FIGURE 3
EAPC for prevalence **(A)**, mortality **(B)**, and DALYs **(C)** of ILD in 204 countries and territories from 1990 to 2019.

100,000 (95% UI 8.33 to 15.48), followed by Peru. ASDR was the highest in Nepal, Bolivia, and Peru and exceeded 190 per 100,0000 (Supplementary Table 2). From 1990 to 2019, ASPR increased in most countries and territories, with higher estimated APC (EAPC) values scattered worldwide (Figure 3A). Most African and South Asian countries and territories had EAPC values of ASMR and ASDR below 0, whereas in North America, South America, and Oceania, the majority of EAPC values were positive (Figures 3B, C). The EAPCs of ASPR, ASMR, and ASDR of pneumoconiosis are shown in Supplementary Figure 1.

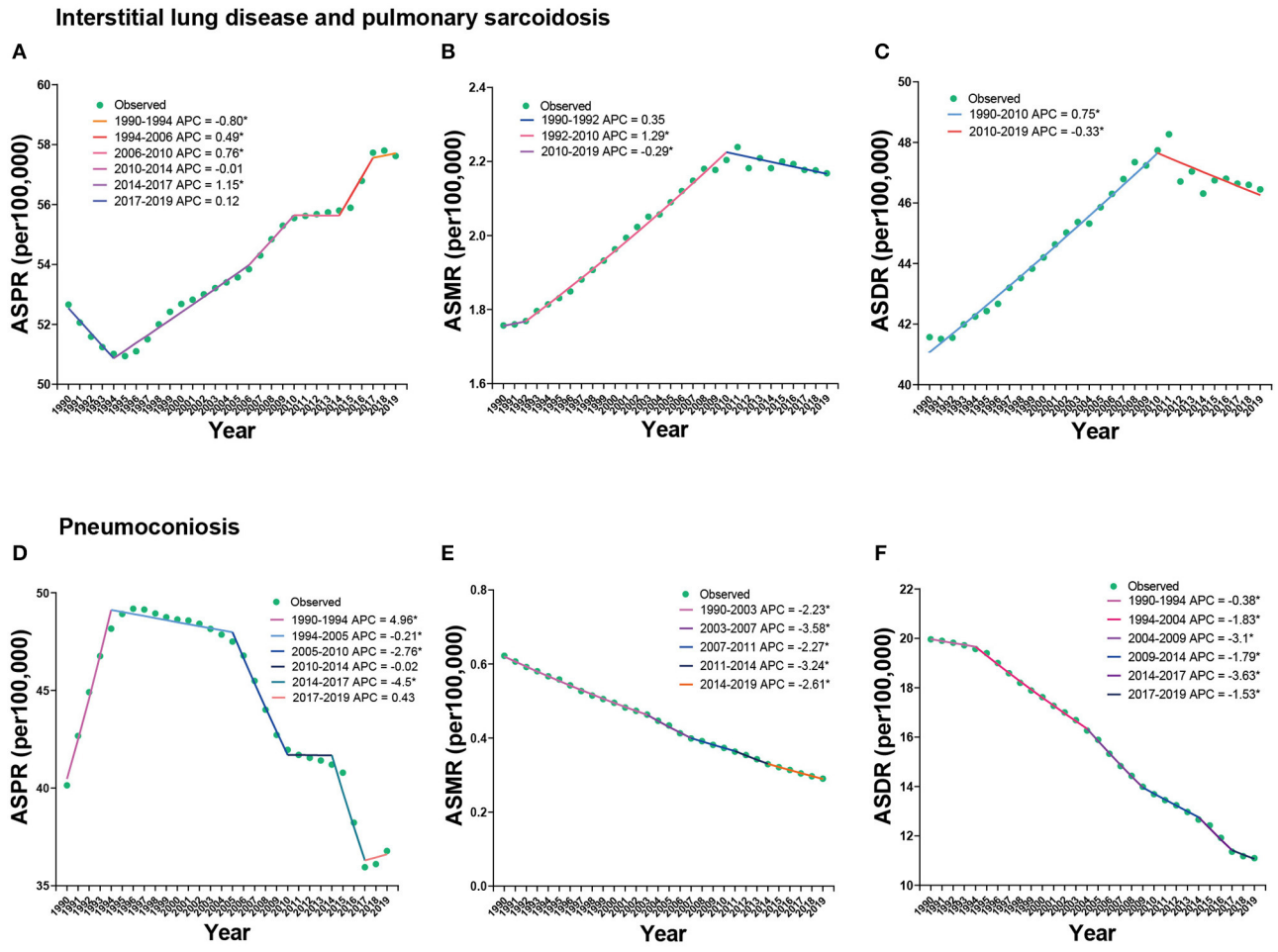

FIGURE 4
Joinpoint regression analysis of ASPR **(A, D)**, ASMR **(B, E)**, and ASDR **(C, F)** of ILDs from 1990 to 2019.

3.2. Joinpoint regression analysis

Figure 4 shows the Joinpoint regression analysis of the overall trends of ILDs. The ASPR of ILD increased from 1990 to 2019, with an AAPC of 0.32 (95% CI 0.19 to 0.46), but a mild descending trend was exhibited from 1990 to 1994, with the APC of −0.8 (95% CI −1.13 to −0.48) (Figure 4A). The ASMR of ILD increased from 1992 to 2010 and then decreased from 2010 to 2019, with APC of 1.29 (95% CI 1.23 to 1.34) and −0.29 (95% CI −0.45 to −0.14), respectively (Figure 4B). Similarly, the ASDR of ILD increased from 1990 to 2010 and then decreased until 2019 (Figure 4C). The ASPR of pneumoconiosis fluctuated, increasing from 1990 to 1994, with APC of 4.96 (95% CI 4.53 to 5.4), and then decreasing until 2017 (Figure 4D), whereas the ASMR and ASDR kept decreasing, with AAPC of −2.59 (95% CI −2.73 to −2.46) in ASMR and −2.01 (95% CI −2.12 to −1.9) in ASDR (Figures 4E, F). We further calculated the APCs and AAPCs of ILD in each sex, as shown in Supplementary Table 3. All AAPC values were between 0 and 1 and showed statistically significant differences. Nevertheless, the APCs of ASMR and ASDR in women from 2008 to 2019, which represented declining trends, were not statistically significant (Supplementary Table 3).

3.3. Descriptive analysis of the prevalence, mortality, and DALYs of ILD by age, period, and cohort

ASPR increased with increasing age in all periods, peaked in the age group of 75–79 years, and then slightly decreased or leveled off. In the age group of >70 years, ASPR increased over time, especially from 1997 to 2012, whereas in the other age groups, only subtle changes were noted. The most recent birth cohort had the lowest ASPR (Figures 5A–C). With increasing age, ASMR increased, and with time changes, it also increased in the older age groups. Similarly, the more recent birth cohort had a lower ASMR (Figures 5D–F). ASDR exhibited a similar trend with ASPR and ASMR, except for a slight increase in the most recent birth cohort (Figures 5G–I).

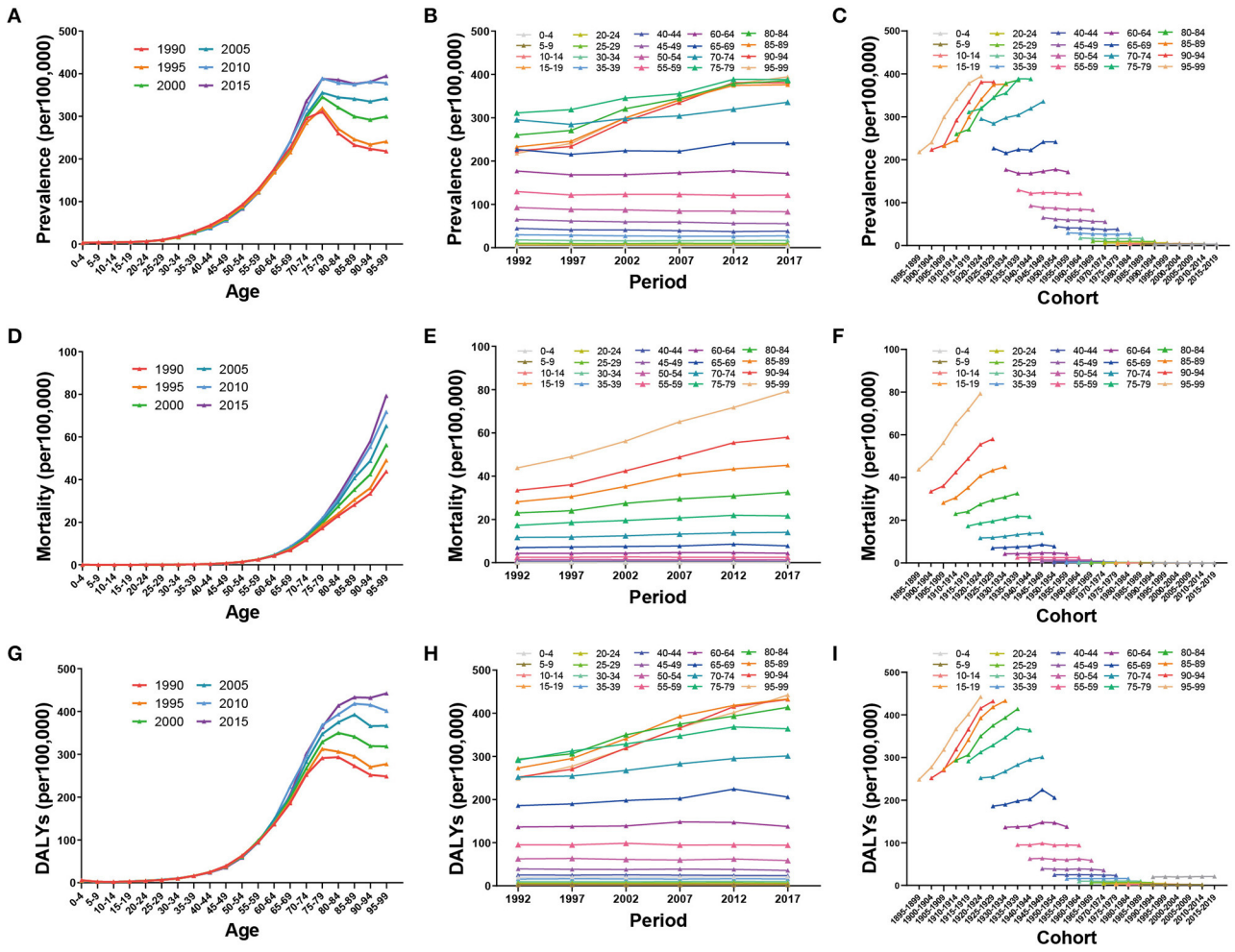

FIGURE 5
Global trends of prevalence, mortality, and DALYs by age **(A, D, G)**, period **(B, E, H)**, and cohort **(C, F, I)** of ILD from 1990 to 2019.

3.4. Age–period–cohort effects on the prevalence, mortality, and DALYs of ILD

After controlling for period and cohort effect, the RR of ASPR, ASMR, and ASDR increased rapidly with increasing age and particularly in the age group >55 years. The RR of ASPR, ASMR, and ASDR for both sexes in the 80–84 age group was 8.2 times (95% CI 8.06 to 8.34), 33.64 times (95% CI 33 to 34.29), and 8.81 times (95% CI 8.71 to 8.91) more than that of the reference group, respectively. Moreover, the RR of the age effect was higher in men than in women in most age groups (Figures 6A, D, G).

After controlling for age and cohort effect, the RR of ASPR increased over time, from 0.99 (95% CI 0.98 to 1) in 1992 to 1.09 (95% CI 1.08 to 1.1) in 2017, being relatively consistent in both sexes. In men, the RR of ASMR and ASDR increased from 1992 to 1997 and then decreased from 1997 to 2017, whereas in women, the RR increased from 1992 to 2007 and then slightly decreased from 2007 to 2017 (Figures 6B, E, H).

After controlling for age and period effect, the RR of ASPR exhibited an upward trend from the birth cohort 1895 to 1899 to the birth cohort 1950 to 1954, then the trend mildly fluctuated, and slightly increased until the most recent birth cohort. Regarding ASMR and ASDR, the RR presented a trend of fluctuating variation as the birth cohort changed. Intriguingly, men and women showed relatively opposite trends, from 1.12 (95% CI 0.94 to 1.34) to 0.81 (95% CI 0.63 to 1.04) in ASMR and from 1.02 (95% CI 0.82 to 1.28) to 0.83 (95% CI 0.77 to 0.9) in ASDR in men and from 0.77 (95% CI 0.67 to 0.89) to 1.19 (95% CI 0.91 to 1.55) in ASMR and from 0.73 (95% CI 0.64 to 0.84) to 1.14 (95% CI 1.06 to 1.21) in ASDR in women (Figures 6C, F, I).

The net and local drifts are provided in Supplementary Table 4. According to Wald's chi-square tests, the APC models generally showed significant differences (Supplementary Table 5).

3.5. Projections of the global trends of ILD until 2030

As presented in Figure 7, we projected that the ASPR, ASMR, and ASDR of ILD would stabilize with little variation over the next decade, with the rate higher in men than in women (Figures 7A–C). ASPR would slightly increase from 57.34 per 100,000 (95% CI 56.14

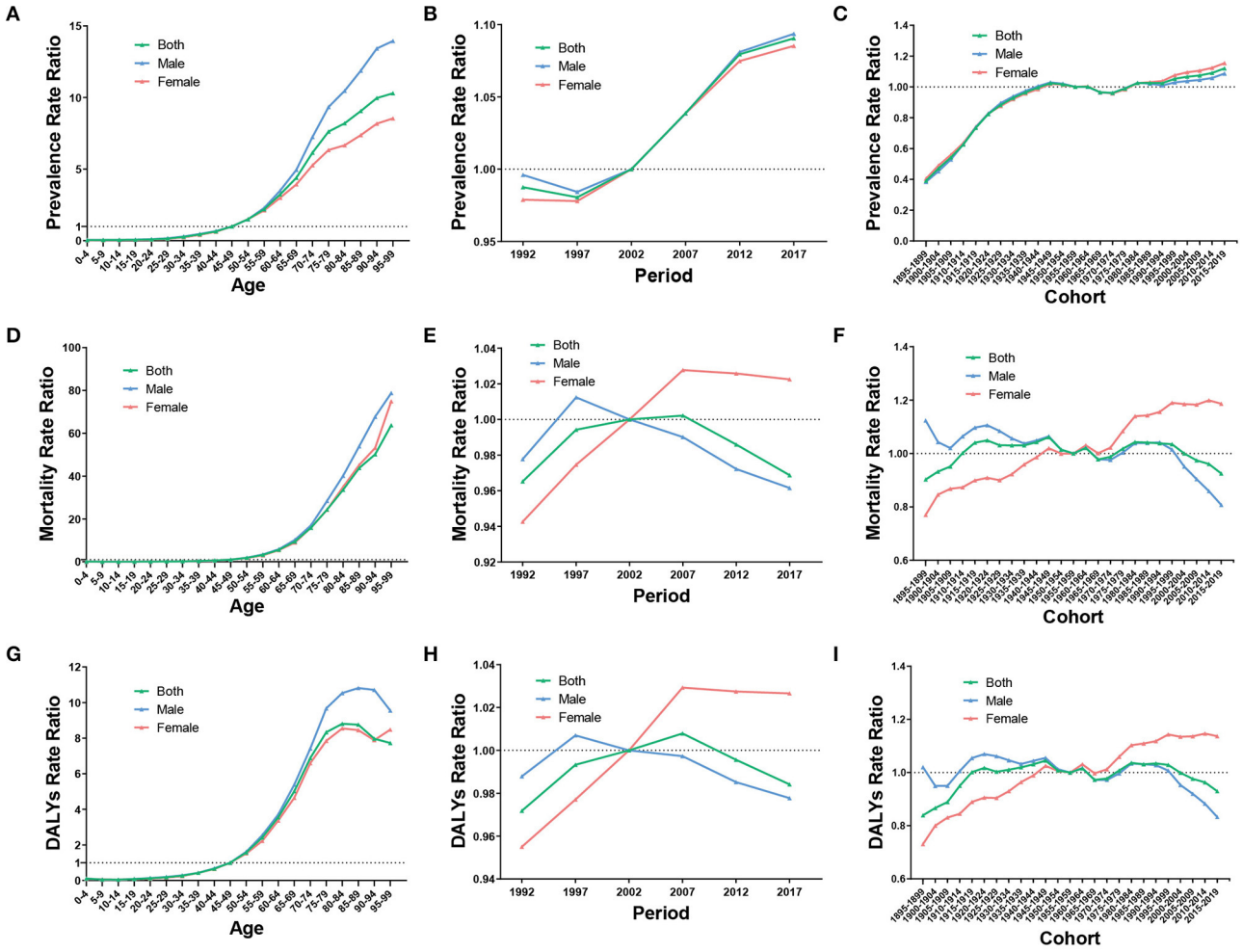

FIGURE 6
RR of prevalence, mortality, and DALYs due to age **(A, D, G)**, period **(B, E, H)**, and cohort **(C, F, I)** effect of ILD from 1990 to 2019.

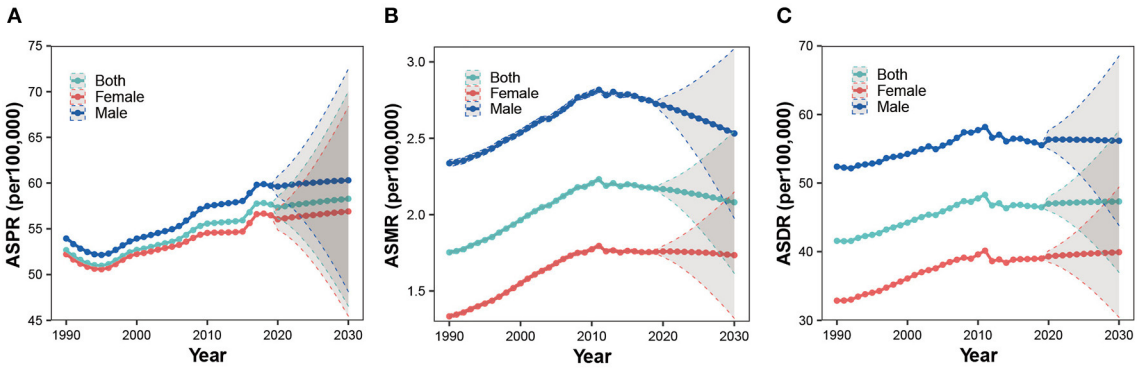

FIGURE 7
Projections of ASPR **(A)**, ASMR **(B)**, and ASDR **(C)** of ILD among both sexes, men and women, until 2030.

to 58.55) in 2020 to 58.28 per 100,000 (95% CI 46.54 to 70.02) in 2030; ASMR would mildly decrease from 2.17 per 100,000 (95% CI 2.13 to 2.21) in 2020 to 2.08 per 100,000 (95% CI 1.61 to 2.55) in 2030; and ASDR would slightly increase from 46.99 per 100,000 (95% CI 45.93 to 48.05) in 2020 to 47.32 per 100,000 (95% CI 36.97 to 57.66) in 2030.

4. Discussion

This study showed that the global ASPR, ASMR, and ASDR of ILD slightly increased or leveled off, whereas that of pneumoconiosis decreased from 1990 to 2019. Nevertheless, the prevalent cases, deaths, and DALYs numbers of ILD increased, whereas those of pneumoconiosis remained with little variation since first estimated in 1990, which is probably due to global population growth and population aging adjusted by age-standardized estimates (18). Despite global efforts made to alleviate the burden of chronic respiratory diseases, the burden of ILDs remains relatively severe and should not be neglected (24). However, the burden of pneumoconiosis has been mitigated over the last three decades, which is probably attributed to industrial injury compensation and many measures that have been implemented to protect workers from dust inhalation (25, 26). Nevertheless, the age-standardized incidence rate of asbestos has increased globally, despite the use of asbestos being completely banned in many countries, which indicates that asbestos regulation policies were not sufficient and effective (27).

For ILD, the high-SDI regions had the highest ASPR, whereas the low-middle and low-SDI regions had the highest ASMR and ASDR. Diagnostic tools such as computed tomography and multidisciplinary discussions are crucial for the diagnosis of ILD (28). Low income was correlated with a higher risk of comorbidities and adverse outcomes in patients with sarcoidosis (29). The availability and accessibility of abundant medical resources in high-SDI regions contributed to the diagnosis of ILD and perhaps led to the highest prevalence rate. Furthermore, a lack of appropriate diagnosis, optimal treatment, and adequate healthcare systems in low-middle and low-SDI regions may result in higher mortality and DALYs rates (30). Moreover, the black race is considered a risk factor for progressive fibrosis and death in systemic sclerosis-related interstitial lung disease and sarcoidosis (31). As the GARD proposed, low- and middle-income countries are especially in need to foster country-specific initiatives to alleviate the ILD burden (14). Notably, ASPR, ASMR, and ASDR increased the most in high-SDI regions despite robust healthcare services, which may indicate that either ILD was associated with many risk factors that have not been fully addressed or the present provisioned resources are still insufficient (18).

Regarding pneumoconiosis, the middle-SDI regions had the highest ASPR, ASMR, and ASDR, followed by the high-middle SDI regions. Occupational exposure to asbestos, silica, and coal dust is closely associated with pneumoconiosis. Many substitutes have replaced asbestos, and measures have been taken to control asbestos imports in many developed countries. Russia, China, and Kazakhstan rank among the top three asbestos producers, possibly due to the low cost and tensile strength of asbestos (32). Moreover, silicosis is a serious problem, particularly in developing countries, and is often underreported due to inadequate surveillance (33). Finding suitable alternatives, implementing preventive policies, and improving the workplace environment are of great significance in these regions.

In 2019, Bolivia had the highest ASMR for ILD, followed by Peru; ASDR in Bolivia and Peru also ranked ahead among the 204 countries and territories. Furthermore, ASPR, ASMR, and ASDR in the two countries showed an upward trend from 1990 to 2019. Both located in South America, Bolivia, and Peru are well-known for their abundant mineral resources, particularly Bolivia. Although natural resources are advantageous in these two developing countries, public health is alarming. Workplace exposure contributes substantially to the burden of multiple chronic respiratory diseases, such as IPF, for instance, has a population-attributable fraction of 26% (34). In addition to the high ILD burden, participants in a study living in proximity to mining sites near Potosi, Bolivia, had higher frequencies of hypertension, hematuria, and ketonuria, and the majority of adobe brick houses in Potosi, Bolivia, contained concentrations of bio-accessible Pb and As, which represent a potential health risk (35, 36). Therefore, effective measures are urgently required to protect residents from contaminated environments.

The global prevalence, mortality, and DALYs of ILDs were higher in men than in women, which was consistent with the findings of previous studies (8, 37). However, CTD-ILD was more prevalent in women, possibly because they are more susceptible to connective tissue disease (38). Tobacco smoking has an independent detrimental effect on IPF, and alveolar wall fibrosis occurs in smokers; historically, men smoke more than women, which may account for the higher burden of ILDs in men (39, 40). Sex hormone regulation also plays a vital role in pro-inflammatory and pro-fibrotic factors, with estrogens enhancing inflammation and remodeling, whereas androgens may have the opposite effect (41). Moreover, most workers exposed to toxic particles in the workplace were men, the sociologically dominant labor force.

Age effects showed a high RR of prevalence, mortality, and DALYs in older adults. Some ILDs occur secondary to drugs, therapies, and connective tissue diseases, and the prevalence of connective tissue diseases remains high in older adults due to longer life expectancies and better tolerated treatments, which may lead to a high RR of prevalence in the older age groups (42). Moreover, age-related telomere shortening, protein folding, and oxidation may damage the alveolar epithelium in IPF, which is strongly correlated with older age (43). Comorbidities play a significant role in the dramatic increase in the RR of mortality and DALYs in older adults. Chronic obstructive pulmonary disease, cardiovascular diseases, and autoimmune disorders are common in older adults with ILD, and chronic respiratory diseases are highly associated with aging (44–46). Furthermore, relatively bad medical adherence and depression in older adults may also affect the prognosis of ILD (47, 48). Age effects have impacted the slightly elevated trends of ILD over the last three decades, associated with global demographic changes in which the proportion of the population over 70 years increased from 3.77% in 1990 to 5.99% in 2019 (49). An increase in the proportion of the population with high RR results in an elevated trend of ILD (50). Chronic disabling illness secondary to ILD in older adults might be preventable through patient-centered care aiming to improve the quality of life and decrease the use of health services (51).

Period effects showed that the RR of prevalence increased over time and was above the average risk after 2002. In terms of mortality and DALYs, the RR increased before 2007 and then decreased for the total population. From the perspective of global social development, economic growth stimulated medical

advances such as imaging and functional tests; thus, the diagnosis of ILD may be more precise and common, as many ILDs are rare and difficult to diagnose, resulting in an increased RR of prevalence. Global achievements in tobacco smoking may explain the decreased RR of mortality and DALYs in men (52). Notably, the GARD was launched in 2007, and more than 20 countries have initiated activities since then, which may have contributed to the decreased RR in the total population (53). Furthermore, reduction in air pollution, prevention of allergen contact, improvement in the workplace environment, and enhancement of public health awareness may also affect the trends of ILD (20).

Cohort effects showed that the RR of prevalence increased with the birth cohort more recently, whereas that of mortality and DALYs fluctuated strikingly, with men showing decreased RR, women, increased RR, and the total population, leveled off RR. Smoking cessation in men and a higher prevalence of connective tissue disease in women may be reasons for this sex disparity. Despite the ILD burden being heavier in men, the RR in women had increased as the birth cohort changed, and women were also supposed to pay adequate attention to ILD. Genetic background and epigenetic modifications have been identified as important factors in fibrotic lung diseases, among which the MUC5B promoter polymorphism is a common gene variant (54). It is difficult to explain the variation in the cohort effect. Perhaps genetics, exposure to a wide range of environmental risk factors, eating and living lifestyles, and mental health all contribute to the cohort effects of ILD.

We projected that the ASPR, ASMR, and ASDR of ILD would stabilize with mild variations over the next decade. Given that population aging is a global phenomenon, an increase in the proportion of older adults would result in an increasing prevalence. Medical advances, such as imaging, may also lead to an upward trend in ILD prevalence. As for mortality, in addition to medical developments, global achievements in tobacco smoking would also account for a downward trend, especially in men. As mentioned above, ILD remains a global health challenge, and the alleviation of the ILD burden is of great significance. Patient education, decision-sharing, smoking cessation, and pneumococcal and influenza vaccines are essential for ILD management (31). Treatments aimed at ameliorating the disease or retarding its progression while improving or maintaining the quality of life are recommended, including pulmonary rehabilitation (55).

Compared with previous studies on ILDs epidemiology that mainly focused on a specific form of ILDs and localized in a certain region, our study used data retrieved from the GBD database, providing a global perspective to make comparisons between different countries and territories. As many ILDs are associated with occupational exposure, our study may offer some guidance for policymakers in implementing control regulations, especially in low- and middle-SDI regions. Moreover, this is the first study to analyze the independent effects of age, period, and cohort on ILD prevalence, mortality, and DALYs and found that the age effect played a crucial role in ILD. For countries confronting population aging, the social burden of chronic diseases such as ILD should be seriously considered.

This study had some limitations. First, because ILDs encompass a variety of diseases, their classification and diagnosis remain difficult, and the epidemiology may vary significantly in each kind of ILDs. Thus, more studies on the epidemiology of a specific kind of ILDs are expected. Second, our prediction model based on previous data may not have been founded on current political realities; for instance, the undercutting of regulations on inhalation exposure may result in an increasing trend of ILDs. Third, the input prevalence data for the GBD study were primarily derived from hospital inpatient records and insurance claims; however, claims data can be unreliable (18). In counties with low- or low-middle SDI, a lack of medical expertise and equipment may result in undiagnosed and unregistered cases. Finally, as some counties are vast, the evaluation of the disease burden at the country and territory levels may have varied considerably between different provinces. Therefore, large cohort studies are needed in each region to measure the local burden of ILDs.

5. Conclusion

The ASPR, ASMR, and ASDR slightly increased for ILDs and decreased for pneumoconiosis from 1990 to 2019. In ILDs, the high-SDI regions possessed the highest ASPR, whereas the low-middle SDI regions had the highest ASMR and ASDR, followed by the low-SDI regions, possibly because of the disequilibrium of medical resources. For pneumoconiosis, the middle-SDI region had the highest ASPR, ASMR, and ASDR. Control regulations for reducing occupational exposures are needed in these regions. Older adults have a high risk of ILD, and the age effect played a significant role in the increase of ASPR, considering the global population aging. The global trends of ILDs would stabilize with minimum variation and remain relatively high over the next decade. Global actions and country-specific initiatives are needed to mitigate the burden of ILDs.

Data availability statement

The original contributions presented in the study are publicly available. This data can be found here: https://vizhub.healthdata.org/gbd-results/.

Author contributions

DJ and QZ conceived the study. QZ analyzed the data and wrote the manuscript. All authors approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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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.2023.1141372/full#supplementary-material

SUPPLEMENTARY FIGURE 1
EAPC for prevalence **(A)**, mortality **(B)**, and DALYs **(C)** of pneumoconiosis in 204 countries and territories from 1990 to 2019.

SUPPLEMENTARY TABLE 1
ASPR, ASMR, and ASDR (per 100,000) of ILD, and SDIs in 204 countries and territories in 1990.

SUPPLEMENTARY TABLE 2
ASPR, ASMR, and ASDR (per 100,000) of ILD, and SDIs in 204 countries and territories in 2019.

SUPPLEMENTARY TABLE 3
Joinpoint regression analysis for global trends of ASPR, ASMR, and ASDR (per 100,000) of ILD among both sexes, males, and females from 1990 to 2019.

SUPPLEMENTARY TABLE 4
Local drifts and net drifts for global trends of ASPR, ASMR, and ASDR (per 100,000) of ILD among both sexes, males, and females from 1990 to 2019.

SUPPLEMENTARY TABLE 5
Wald Chi-Square tests for estimable functions in the APC model.

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Genetic and environmental factors in interstitial lung diseases: current and future perspectives on early diagnosis of high-risk cohorts

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Within the wide scope of interstitial lung diseases (ILDs), familial pulmonary fibrosis (FPF) is being increasingly recognized as a specific entity, with earlier onset, faster progression, and suboptimal responses to immunosuppression. FPF is linked to heritable pathogenic variants in telomere-related genes (TRGs), surfactant-related genes (SRGs), telomere shortening (TS), and early cellular senescence. Telomere abnormalities have also been identified in some sporadic cases of fibrotic ILD. Air pollution and other environmental exposures carry additive risk to genetic predisposition in pulmonary fibrosis. We provide a perspective on how these features impact on screening strategies for relatives of FPF patients, interstitial lung abnormalities, ILD multi-disciplinary team (MDT) discussion, and disparities and barriers to genomic testing. We also describe our experience with establishing a familial interstitial pneumonia (FIP) clinic and provide guidance on how to identify patients with telomere dysfunction who would benefit most from genomic testing.

KEYWORDS

familial pulmonary fibrosis, familial interstitial pneumonia, telomere shortening, interstitial lung disease, environment, genetics, FPF, FIP

1. Introduction

The scope of interstitial lung diseases (ILDs) is extremely wide (over 200 disorders). The most common fibrotic ILD is idiopathic pulmonary fibrosis (IPF) (1). Besides ILDs of a granulomatous origin (e.g., sarcoidosis) and those of a known cause (e.g., asbestosis), the classification for idiopathic interstitial pneumonias (IIPs) has been agreed 10 years ago and likely needs to be reviewed as new data emerges on the interplay between genetic and environmental factors (2).

The terminology to refer to cases of ILD with a familial predisposition can be confusing. While initial reports used the term "familial IPF," this would not account for the heterogeneity of ILD diagnoses in affected family members (not all relatives being diagnosed with IPF) (3). A commonly used term is familial pulmonary fibrosis (FPF) which expands the definition to cases of fibrotic ILDs within the same family. In addition, familial interstitial pneumonia (FIP) applies to families in which two or more cases of IIPs are diagnosed; e.g. index case (also called proband) having IPF, and a sibling diagnosed with fibrotic non-specific interstitial

pneumonia (NSIP) (3). Finally, we may even use "familial ILD" to expand the definition to pedigrees where some relatives have fibrotic IIPs, while others are diagnosed with non-IIP ILDs or non-fibrotic ILDs, as we have encountered such families in our practice.

2. Genomic features of familial pulmonary fibrosis

2.1. Telomere shortening

Telomeres consist of non-coding DNA (*TTAGGG*) and associated proteins thought to maintain genomic integrity during repeated cell divisions. Critical TS can lead to diverse clinical syndromes (4). *Dyskeratosis congenita* is a prototype of a TS condition, which is described as a triad of oral leukoplakia, reticular pigmentation of the neck/upper chest and dysplastic nails (5). It can be associated with other features which may also be found in telomere-related FPF, such as bone marrow failure, myelodysplasia, and leukemia (6). TS syndrome can also be associated with immunodeficiency, neurological or retinal conditions (5, 7).

Telomere length decreases with age even in the absence of fibrotic lung pathology. However, this appears to be more pronounced in ILD patients (8). Those carrying a pathogenic variant (also called mutation) in a telomere-related gene (TRG) generally have shorter telomeres (<25th percentile) compared to age matched controls; while only 50% of ILD patients >60 years old and *TERT*, *TERC* or *RTEL1* mutations had a telomere length > 10th percentile (9). Short telomere length is associated with worse clinical outcomes in fibrotic ILD (10–12) and poor tolerance to immunosuppressive treatments (13, 14).

Telomere abnormalities, including TS, have also been identified in sporadic cases of IPF and other forms of pulmonary fibrosis (PF) (10, 15, 16).

2.2. Pathogenic variants in telomere-related genes

TRGs include *TERT, TERC, RTEL1, PARN, DKC1, TINF2, NOP10, NHP2, ACD, NAF1, ZCCHC8, RPA, POT1* (5). *TERT* (telomerase reverse transcriptase) and *TERC* (telomerase RNA component) are components of the telomere complex which is a group of proteins and RNA that drive the addition of telomeric repeats (*TTAGGG*) to the ends of chromosomes and were the first TRGs identified in FPF (4).

The mean age of ILD diagnosis in patients with TRG mutation is approximately 58 years (16). Clinical features include a usual interstitial pneumonia (UIP) radiological pattern on chest CT which can be seen in up to 54–74% of ILD cases with TRG mutations although other radiological patterns can be present. Radiological and histological patterns can vary even within the same family (16–18). *Hematological abnormalities*, such as anemia (17–27%), macrocytosis (24–41%) or thrombocytopenia (8–54%) may be associated to ILD (16, 17). Patients with *DKC1*, *TINF2* and *TERC* mutations are more likely to have hematological involvement compared to those with *TERT*, *PARN* or *RTEL1* mutations (16). Asymptomatic *liver function abnormalities* (i.e., increased liver transaminases) can also be found in 5–27% TRG mutation patients and *early hair greying* is noted in 15–40% (11, 19).

2.3. Pathogenic variants in surfactant-related genes and MUC5B polymorphism

Surfactant-related genes (SRGs) include *SFTPC* which has an autosomal dominant mode of inheritance with frequent *de novo* mutations, but low frequency in FPF cases (<5%) (5). *ABCA3* is mostly associated with respiratory failure in the newborn but severe adult ILD has been reported. *NKX2.1* encodes the protein TTF1 which regulates surfactant protein as well as *ABCA3* gene transcription. While NKX2.1 mutation mostly causes neonatal disease it can result in an atypical UIP pattern in adults (5, 20–23). In childhood, SRG mutations are the most common, whereas in adults, TRG pathogenic variants are more common (5, 24).

The single-nucleotide polymorphism rs35705950 in the promoter of the gene encoding mucin 5B (MUC5B) was shown to be associated with both FIP and sporadic IPF (25). It showed a significant signal in large genome-wide association studies and has been associated with various fibrotic ILDs (10, 26–29). However, given the high prevalence of the *MUC5B* rs35705950 minor allele promoter variant and low penetrance, genotyping of the variant is not currently part of FPF gene investigations in most countries (5). Fortunately in the UK, *MUC5B* is listed in the FPF panel, as well as SRGs and TRGs, as part of the National Genomic Test Directory for rare and inherited disease (30).

In FPF, there is overall a 50% chance of inheriting a deleterious allele in first-degree relatives (autosomal dominant) (5). Penetrance is generally incomplete, higher for SRGs (24) compared to TRGs, and expressivity is variable. The absence of TRG mutations in a family member of an index case does not exclude risk of disease due to other telomere abnormalities. The average age of ILD onset is lower in SRG compared to TRG mutation carriers. Pulmonary-only disease is more common in patients with SRG versus TRG pathogenic variants (5).

2.4. Senescence – the aging lung

Cellular senescence is characterized by a state of cell cycle arrest (31). PF is considered a disease of senescence (aging) with fibrogenesis requiring an interplay between genetic predisposition and repeated exogenous insults (i.e., environmental). Animal models have confirmed that increasing age and having mutations in TRGs (e.g., *TERT*) favor the development of fibrosis following infectious or noxious challenge. Immune processes can also be affected by cellular senescence (such as T cell dysfunction and shifting to Th17 responses leading to immune dysregulation and propensity to autoimmune responses) and environmental exposures can accelerate this process (31, 32). Genomic instability due to *TERT* or *ABCA3* mutations and fibrogenic exposures can lead to lung epithelial cell phenotypes that correspond to age-induced senescence (33).

There is evidence that acute exacerbations of IPF may correlate to air pollution, possibly mediated by senescence in inflammatory cells (34, 35). Fibroblast senescence can be triggered directly by environmental stress as well as indirectly by neighboring senescent cells altering the cellular microenvironment (36, 37). The window

when environmental challenge occurs, as well as the dose and repeated exposure, play a role in senescence and fibrotic responses (33, 38).

3. Air pollution and environmental impact on genetic predisposition

Air pollution may trigger alterations on the airway mucosal surface by overwhelming ciliary and macrophage clearance mechanisms leading to oxidative stress and transporting toxic metals and particulates into the blood stream (39). It has been associated with increased incidence and worse outcomes in IPF, but large cohorts are required to validate these findings (40). Tobacco smoke, ozone exposures leading to oxidative stress by generating reactive oxygen species, lead and nitrosamines have also been linked to TS (41). Some of these effects may occur prenatally, e.g., in mothers exposed to high $PM_{2.5}$ (particulate matter with an aerodynamic diameter $\leq 2.5\,\mu m$) air pollution (42). The onset of acute exacerbations of IPF was linked to air pollution, notably increased ozone concentrations (35).

Long term cumulative exposure to air pollution can increase the incidence of IPF, which is additive to genetic predisposition (43). Single gene mutations are thought to have relatively small effects, hence polygenic risk scores (PRS) have been proposed (44). Data from a large epidemiological study of 433,738 participants seems to support a role for air pollution in the pathogenesis of IPF in individuals stratified by PRSs. Those with a high PRS (13 single nucleotide polymorphisms) exposed to airborne pollutants had the highest risk of IPF incidence compared to low air pollution and low PRS in terms of adjusted hazard ratios (95% CI): for $NO_2 = 3.94$ (2.77–5.6), $NO_x = 3.08$ (2.21–4.27), $PM_{2.5} = 3.65$ (2.6–5.13), and $PM_{10} = 3.23$ (2.32–4.5) (43).

Exposure of human bronchial epithelial cells to $PM_{2.5}$ can lead to dose-dependent epigenomic modifications, altered telomerase activity and TS (45). IPF patients exhibit epigenomic modifications including widespread DNA methylation alterations in lung tissue which seem to occur near genes linked to PF (such as *TOLLIP*, *NOTCH1*, *FBXO32*) (46, 47). Resistance to fibroblast was linked to histone modifications, and fibroblast proliferation appears to be regulated by noncoding RNAs (40). Increased road traffic-derived PM_{10} exposure as measured by air pollution monitors in Beijing was associated with decreased histone H3 methylation (48). Increased PM_{10} exposure has also been associated with accelerated forced vital capacity (FVC) decline in IPF patients (34). Increased levels of both $PM_{2.5}$ and PM_{10} were associated with higher IPF mortality (35).

4. Clinical considerations in FPF

4.1. Disease progression in familial versus sporadic fibrotic ILDs

Progressive pulmonary fibrosis (PPF) is the dominant phenotype seen in familial cases. There is evidence to suggest that FPF is worse, faster progressing and has higher mortality than sporadic fibrotic ILD, although data is incomplete and at times contradictory (5). In a small study, a 9.9% annual rate of FVC decline was seen in familial IPF patients compared to 4.9% in those with sporadic IPF (not statistically significant, $p = 0.12$) (49). The average annual rate of FVC decline amongst 115 ILD patients with TRG mutations (46% of whom had IPF) was found to be 300 ml (regardless of gene involved) (16). The mean survival from diagnosis in FPF appears to be between 2.4 and 7.3 years (18, 50). In a cohort of 1,262 ILD patients, survival was found to be worse in FPF compared to sporadic PF, both for IPF cases (HR for death or transplant of 1.8 [95% CI, 1.37–2.37]) and non-IPF ILD (HR for death or transplant of 2.08 [CI: 1.46–2.96]) (51). Regardless of the ILD diagnostic label, there was no difference in median survival comparing familial IPF to familial non-IPF (16).

4.2. Dedicated familial interstitial pneumonia clinics

As genomic tests can be expensive or only reimbursed when certain criteria are met, it is recommended to pre-screen patients based on family history and clinical features of TS prior to testing (Tables 1, 2) (5, 52). In our opinion, the easiest way to organize testing is by running dedicated FIP clinics. This allows to pool together patients with rare ILDs, screen relatives, offer personalized medicine and identify associated conditions (e.g., hematological diseases). More time for explanations can be given by a trained healthcare provider leading to a better patient experience. Genetic and psychological counselling, specialist ILD nursing and research can also be integrated within the FIP clinic structure.

Appropriate counselling and a tactful approach are necessary because genomic testing can be seen as opening a "Pandora's box." It often leads to major changes in patients' lives and those of their relatives. In our experience with the Manchester FIP clinic, most patients are extremely interested in genomic tests if the wider context is clearly explained, and a pathway exists to deal with possible results. Importantly, testing provides an answer to the question "Why did I get ILD?" which leads to better acceptance of the ILD diagnosis and treatment requirements. Many patients are also very interested in research projects.

TABLE 1 Clinical features of short telomere syndrome which can be elicited during consultations of patients affected by familial pulmonary fibrosis and their relatives.

Clinical features of telomere shortening: ONE or more of these features
1. Fibrotic ILD diagnosis before age 50
2. One or more relatives with ILD or known mutations in SRGs or TRGs
3. Other relevant personal or family history:
(a) *Hematological abnormalities*: macrocytosis, neutropenia, lymphopenia, thrombocytopenia, myelodysplasia, acute leukemia, bone marrow failure
(b) *Hepatic abnormalities*: unexplained elevated liver enzymes, portal hypertension, hepato-pulmonary syndrome, liver cirrhosis
(c) Autoimmune abnormalities or connective-tissue disease features
(d) Significant and premature hair greying, or developing streaks of grey hair (age < 30 years)
(e) Early unexplained menopause (age < 45 years)
(f) Frequent malignancy in the family
(g) Dyskeratosis congenita or aplastic anemia

Features are adapted from the European Respiratory Society statement on familial pulmonary fibrosis (5) and Molina-Molina et al. (52).

TABLE 2 Eligibility for genomic testing for familial pulmonary fibrosis as per the latest version of UK National Genomic Test Directory for rare and inherited disease (53).

UK NHS National Genomic Test Directory – Testing Criteria for Rare and Inherited Disease, version 5.1, May 2023
R421 Pulmonary Fibrosis Familial testing criteria: ILD and ONE of the following:
1. ILD, no identifiable cause or association, and age < 50 years.
2. Family history of ILD regardless of identifiable cause or association.
3. For suspected telomerase complex mutations, testing to be considered in the absence of 1. and 2. above if one or more of the following are present in addition to ILD: • Unexplained hematological abnormalities including macrocytosis, anemia, thrombocytopenia, leukopenia and/or lymphopenia; premature greying, • Or unexplained liver function abnormalities. • Consideration of lung transplantation.

4.3. Impact on ILD multidisciplinary team (MDT) decisions

In our experience, familial and sporadic cases with telomere dysfunction frequently have atypical ILD presentations, and this can delay referral to an ILD specialist center, accurate diagnosis, and timely treatment.

As FPF cases may progress faster than sporadic ones, more frequent follow-up with lung function monitoring and early lung transplant referral should be considered as part of the MDT discussion, ideally involving transplant specialists and genetic counsellors. Transplant outcomes between FPF and sporadic PF were comparable (54, 55), therefore knowledge of a familial aggregation, TS or identified mutation should not automatically be considered contraindications for lung transplantation (54). Special considerations should be given to personalizing immunosuppressive regimens and the post-transplant follow-up as patients with telomere dysfunction (TS and/or TRG mutation) may be at increased risk of complications (13, 14, 56, 57).

Antifibrotics are just as useful in FPF as in sporadic fibrotic ILDs (IPF and PPF). Immunosuppression can increase the risk of complications and efficacy may be limited in patients who require such treatments (e.g., to treat fibrotic hypersensitivity pneumonitis) (14). It would be reasonable to encourage smoking cessation and avoidance of other inhalational exposures.

4.4. Interstitial lung abnormalities and early diagnosis

Interstitial lung abnormalities (ILAs) on chest CT scanning are a common finding in relatives of FPF patients (5). They are defined as incidental findings of nondependent abnormalities which affect >5% of any lung zone (upper, middle, lower), where ILD was not previously suspected. Respiratory symptoms may be present, and this may indicate early ILD. Three subtypes of ILAs have been described: non-subpleural nonfibrotic, subpleural nonfibrotic, subpleural fibrotic (58, 59).

Previous studies have demonstrated a prevalence of ILAs on lung cancer screening of 4–20% (60–63). Recent data from Manchester found a prevalence of ILAs on low-dose chest CT scanning of 3.9%, and 40.7% of these individuals with ILAs were subsequently diagnosed with ILD within 5 years (64).

Interstitial lung abnormalities are associated with radiological progression and mortality (64). Having traction bronchiectasis or bronchiolectasis is an important radiological risk factor to predict adverse outcomes (65, 66).

4.5. How to screen relatives of FPF patients?

There is no clear pathway or optimal age for screening relatives of FPF patients. As there is a 1–3-year delay between symptom onset and diagnosis for FPF patients, this represents an opportunity for early diagnosis (67).

It is recommended that all first-degree relatives of FPF patients should have a screening chest high-resolution CT (HRCT) scan especially if they have non-resolving respiratory symptoms (chronic cough and dyspnea) (5). The prevalence of interstitial lung changes on CT screening of first-degree relatives of FPF patients has been reported as 14–25% (5). Among first-degree relatives of FPF without overt ILD at screening, 19.4% developed extensive HRCT abnormalities or clinical ILD at 5 years. Also, 63.3% of patients with limited ILAs at enrolment experienced progression compared to only 6.1% of patients with normal HRCT at baseline (68).

Lung function is important for screening and follow-up, but simple spirometry may not identify early cases since FVC < 80% predicted in asymptomatic relatives is rare. However, relatives with ILAs have a lower diffusing capacity of the lung for carbon monoxide (DLCO) than those with normal HRCT (68, 69). Annual lung function testing may identify trends of decline. The role of home spirometry monitoring has not been explored in this population but may hold promise for the future.

Additionally, due to the high prevalence of other TS features, a full blood count (FBC) and liver function testing should also be performed in first-degree relatives (5).

Certain relatives may be more open to screening, while others would prefer to wait and clinicians should abide by their preferences, to not cause undue anxiety. Eligible relatives may also be offered genomic testing, usually via local/regional Clinical Genetics services who follow-up families of the proband.

To date, there is no consensus on the frequency and duration of clinical, functional, and radiological evaluations of first-degree relatives of FPF patients. Management could be customized through a risk assessment, considering resources available in each country/national health system.

Figure 1 outlines a potential screening strategy for relatives of FPF patients.

5. Disparities and barriers to genomic testing

Although patients with PF were found to have disproportionately short leukocyte telomere length (LTL), there was very little genetic variability in cohorts (to account for ethnic and socio-economic differences around the world). LTL decreased with age, more so in PF

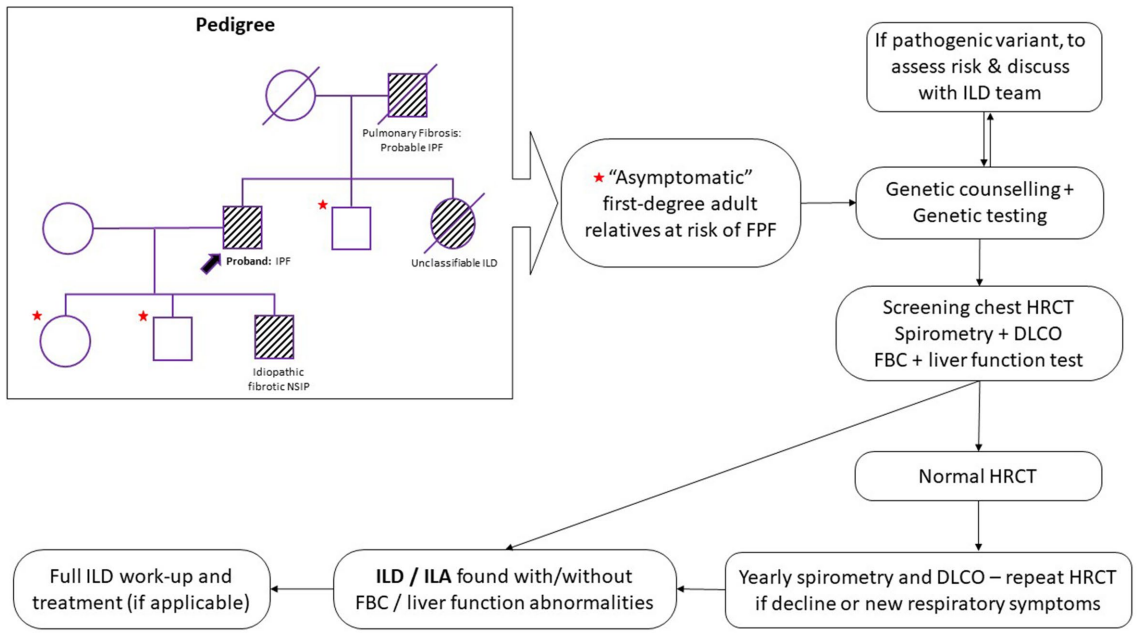

FIGURE 1
Proposed screening and monitoring pathway for first-degree relatives of familial pulmonary fibrosis (FPF) patients. HRCT, high resolution computed tomography; DLCO, diffusing capacity of the lung for carbon monoxide; FBC, full blood count; ILD, interstitial lung disease; ILA, interstitial lung abnormalities; IPF, idiopathic pulmonary fibrosis; NSIP, non-specific interstitial pneumonia.

patients compared to controls ($R = -0.28$, $p < 0.0001$). It appears that sex-adjusted LTL below median is uniformly associated with chronological age and increased risk of mortality in all racial groups although in the Asian population it was not statistically significant (White = HR 2.21, [95%CI: 1.79–2.72], Black = HR 2.22 [1.05–4.66], Hispanic = HR 3.40 [1.88–6.14], Asian = HR 2.11 [0.55–8.23]) (8). Fibrotic lung disease seems to occur several years earlier in African American compared to White patients (70). Patients of Black ethnicity are less likely than those of White ethnicity to have lung transplantation and have worse outcomes even when controlling for confounding factors, socio-economic status (as per the area deprivation index – ADI), donor cause of death, blood type nor HLA mismatch (71, 72). Further research to determine if ethnic differences or socio-economic disparities drive outcomes in FPF are needed (73).

The availability of genomic testing, telomere length measurement and whole genome sequencing varies greatly around the world, making it difficult to standardize global recommendations. At the time of this writing, a 25-gene panel test for FPF is available in the UK, but telomere length measurement is not reimbursed by the health service (30). Local laws and practice regarding genetic counselling can also vary greatly around the world (74).

6. Conclusion

In our opinion, actively eliciting a family history of ILD and other rare conditions, as well as asking about TS features (Tables 1, 2) could be a cost-effective way of identifying relatives at risk of developing ILD. We hypothesize that FPF is more frequent than previously thought, but patients are rarely asked specifically about it during routine ILD consultations. We believe that dedicated FIP clinics can improve care through personalized medicine, early screening and diagnosis in "asymptomatic" relatives, genomic testing, rapid access to antifibrotic medication and early lung transplant referral. We also feel that environmental exposures should be elicited due to the additive risk in FPF (43), and this can be done by using standardized questionnaires (75).

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.

Author contributions

SS and PR-O contributed equally to the conceptualization and literature search. JC contributed to summarizing the key points from the references. SS and PR-O structured the manuscript. SS, JC, and PR-O provided comments and contributed equally to finalizing the draft manuscript for submission. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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The impact of air pollution on interstitial lung disease: a systematic review and meta-analysis

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Introduction: There is a growing body of evidence suggesting a causal relationship between interstitial lung disease (ILD) and air pollution, both for the development of the disease, and driving disease progression. We aim to provide a comprehensive literature review of the association between air pollution, and ILD, including idiopathic pulmonary fibrosis (IPF).

Methods: We systematically searched from six online database. Two independent authors (DL and CF) selected studies and critically appraised the risk of bias using the Newcastle-Ottawa Scale (NOS). Findings are presented through a narrative synthesis and meta-analysis. Meta-analyses were performed exclusively when there was a minimum of three studies examining identical pollutant-health outcome pairs, all evaluating equivalent increments in pollutant concentration, using a random effects model.

Results: 24 observational studies conducted in 13 countries or regions were identified. Pollutants under investigation encompassed ozone (O_3), nitrogen dioxide (NO_2), Particulate matter with diameters of 10 micrometers or less (PM_{10}) and 2.5 micrometers or less ($PM_{2.5}$), sulfur dioxide (SO_2), carbon monoxide (CO), nitric oxide (NO) and nitrogen oxides (NOx). We conducted meta-analyses to assess the estimated Risk Ratios (RRs) for acute exacerbations (AE)-IPF in relation to exposure to every 10 $\mu g/m^3$ increment in air pollutant concentrations, including O_3, NO_2, PM_{10}, and $PM_{2.5}$. The meta-analysis revealed a significant association between the increased risk of AE-IPF in $PM_{2.5}$, yielding RR 1.94 (95% CI 1.30–2.90; $p = 0.001$). Findings across all the included studies suggest that increased exposure to air pollutants may be linked to a range of health issues in individuals with ILDs.

Conclusion: A scarcity of available studies on the air pollutants and ILD relationship underscores the imperative for further comprehensive research in this domain. The available data suggest that reducing levels of $PM_{2.5}$ in the atmosphere could potentially reduce AE frequency and severity in ILD patients.

KEYWORDS

air pollution, interstitial lung disease (ILD), idiopathic pulmonary fibrosis (IPF), ozone (O_3), nitrogen dioxide (NO_2), particulate matter ($PM_{2.5}$, PM_{10}), sulfur dioxide (SO_2)

1 Introduction

Interstitial lung disease (ILD) refers to a group of chronic lung disorders (1) characterized by inflammation and fibrosis of the lung interstitium (2, 3) including idiopathic pulmonary fibrosis (IPF), sarcoidosis, hypersensitivity pneumonitis, and connective tissue disease associated ILD (CTD-ILD) (4). Symptoms vary, but commonly include breathlessness, cough, and fatigue (5–8), and these symptoms can significantly decrease quality of life (QoL) for individuals with ILD. Moreover, prevalent comorbid conditions including gastro-oesophageal reflux disease (GORD), obstructive sleep apnoea (OSA), and depression can further contribute to the negative impact on QoL (5).

Prognosis is highly variable amongst ILD patients, with some patients having very rapid progression, and others a more indolent disease course. IPF, in particular, is associated with a high symptom burden, significant comorbidities, and a shortened life expectancy (9–12), with a 5-year mortality rate of 69% when not receiving antifibrotic treatment (13).

Recognized risk factors for the development of ILD include advanced age, male sex, genetic factors, smoking, medications, systemic autoimmune diseases, and occupational or environmental exposures (14–22). In the past decade, the impact of geographic factors, specifically air pollution, on lung health has received growing attention. Air pollutants have been identified as triggers for exacerbations of COPD and are associated with worsened asthma symptoms (23, 24). These pollutants also play a role in increasing the likelihood of lung cancer in individuals at risk (23, 24). Furthermore, there is evidence indicating an elevated risk of respiratory infections (24, 25), including tuberculosis (25) associated with exposure to air pollutants.

Air pollution is a complex combination of solid particles, liquid droplets, and various gases (26). It originates from a wide array of sources, including household fuel combustion, industrial smokestacks, vehicle emissions, power generation, the open burning of waste, agricultural activities, desert dust, and numerous other origins (26). Common air pollutants measured include particulate matters, where particles with an aerodynamic diameter of equal or less than 2.5 micrometre ($PM_{2.5}$) and particles with an aerodynamic diameter of 10 micrometre (PM_{10}), ozone (O_3), nitrogen dioxide (NO_2), carbon monoxide (CO) and sulfur dioxide (SO_2) (26).

There has been increasing interest in the relationship between air quality and ILD with most studies and review papers focusing on IPF. In this systematic review with meta-analysis, we evaluate the relationship between air pollution and the broader ILD population. By incorporating all ILD subgroups, we aim to provide a comprehensive overview of the association between various pollutants and health outcomes, and to inform the understanding of underlying mechanisms and the potential public health implications.

2 Methods

2.1 Review protocol

The review followed the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline (27). Given the specific focus on potential associations between exposure and clinical outcomes, instead of applying the conventional PICO (Population, Interventions, Comparators, and Outcomes) framework, the PEO (Patient, Exposure of interest, and Outcome) approach was employed (28). In this framework, the population of interest focused on two primary groups: those with a diagnosis of ILD and those who subsequently develop ILD. The exposure of interest is air pollution. The outcome examined is the impact of air pollution on ILD patients, including but not restricted to, acute exacerbation of ILD, disease progression, hospitalisation, and mortality rates associated with ILD and the risk of ILD development in the general population exposed to air pollution (Table 1). Our primary objective is to comprehensively explore the diverse impacts of air pollution on ILD. We anticipate encountering a spectrum of outcomes and surrogate markers beyond those explicitly specified, allowing for a thorough examination of this complex relationship.

2.2 Eligibility criteria

All authors engaged in thorough deliberation and reached a consensus regarding the inclusion and exclusion criteria. Inclusion criteria for this review were: (1) original research studies; (2) human studies; (3) studies examining the pollutants of interest in individuals diagnosed with ILD or in the general population who develop ILD. Exclusion criteria were: (1) studies exploring the impact of air pollution on general lung health and respiratory disease other than ILD; (2) studies focusing on other risk factors such as occupational factors in ILD; (3) studies measuring indoor exposure; and (4) qualitative studies.

2.3 Search strategy and information sources

Articles were searched for using the following six electronic databases: PubMed, Medline, Cochrane Library, CINAHL, Embase, and Scopus with latest search carried out on 20 July 2023. The key terms used were: (Air quality or air pollution or environment*) and (impact or outcome or relationship or effect or association) and (Pulmonary Fibrosis or interstitial lung disease or ILD). Key terms were searched as key words rather than subject headings to explore the topic as widely as possible. The search was then limited to the years 2000 to the present and "English Language".

Apart from the electronic databases search, a snowball search technique (29) was used to find similar papers to the identified key papers. A secondary manual search of the reference lists was also carried out if the title suggested relevance to the searching terms. In

TABLE 1 PEO worksheet (impact of air pollution on interstitial lung disease).

Population	Individuals with ILD or general population
Exposure of interest (independent variable)	Air pollution
Outcome (dependent variable)	Impact of air pollution on individuals with ILD, or risk of developing ILD in general population

addition, articles that are not able to be obtained from on-line library were requested through the Royal Prince Alfred Hospital library.

2.4 Study selection

Two independent authors (DL and CF) selected studies for inclusion. During the selection process, disagreements regarding the inclusion of specific articles meeting the predefined criteria were successfully resolved through discussion and consensus between the selecting authors. Studies lacking individual-level data, such as ecological studies, were considered for inclusion in the review but were ultimately excluded from the meta-analysis.

2.5 Data collection and data items

In this systematic review, data from each of the included studies were extracted, encompassing the first author's name, publication year, study design, study population, sample size, country, mean age, sex, ILD diagnosis criteria, air pollution metrics, and the key findings. We collected risk estimates from the preferred model of choice by each study author (some of which were presented in abstracts). These estimates included hazard ratios (HR), risk ratios (RR), or odds ratios (OR), along with their corresponding 95% confidence intervals (CIs). We then entered the extracted data from the articles into an Excel spreadsheet for analysis. To ensure reliability, the primary author (DL) extracted the complete data, while co-author (CF) independently verified the accuracy and completeness of the extracted information. Any disagreements were adjudicated and resolved by senior investigator (TC).

2.6 Study risk of bias assessment

The risk of bias (30) of included studies was performed using the Newcastle-Ottawa Scale (NOS), a validated tool for assessing the quality of nonrandomized studies (31). It follows a "star system" approach, evaluating three perspectives: selection of study groups, comparability of groups, and ascertainment of exposure or outcome of interest in case–control or cohort studies. Each item is assigned one point, except for comparability, which can score up to two points.

To ensure precision and clarity in evaluating the comparability section of this review, a study receives one star if it controls or adjusts the age and sex for analysis. Additionally, if the study incorporates additional factors, such as smoking status, forced vital capacity (FVC), antifibrotic treatment, average temperature, and humidity, into the analysis to adjust for potential confounding effects, it qualifies for an additional star.

The adequacy of follow-up time of the cohorts was determined based on the assessed outcomes within each study, including long-term and short-term outcomes according to the definition provided in the 2021 World Health Organization's (WHO) Air Quality Guidelines (AQG). Long-term exposure is characterized by an average measurement taken over one or several years, while short-term exposure is defined as a measurement taken over a period ranging from minutes to days (26).

The maximum possible score is nine. Quality is categorised as good, fair, or poor based on stars awarded in each domain. The majority of the included studies in this review were cohort and case–control studies. The evaluation of bias risk in these types of studies using the NOS was conducted independently by two investigators (DL and CF). It is worth noting that for ecologic studies, there is no established and validated tool for evaluation of quality (32). As a result, the assessment of the five ecologic studies was primarily descriptive. The remaining one study is a panel study. Its limitations are also described.

2.7 Data analysis

Due to the scarcity of studies focusing on the same pollutant and health outcome, the findings are presented through a narrative synthesis method. Meta-analyses were performed exclusively when there was a minimum of three studies examining identical pollutant-health outcome pairs, all evaluating equivalent increments in pollutant concentration. Due to variations in study design, methodology, and study populations, a random effects model was implemented.

For meta-analysis, given the variations in methodology across the studies, an inverse-variance approach was applied for the assessment of their relative significance (33). Within each study, we computed the standard error (SE) and the natural logarithm (log) of both Hazard Ratios (HR) and Odds Ratios (OR). These log-transformed HR and OR values were treated as equivalent to log Risk Ratio (logRRs). Alongside the SE, we calculated the pooled Risk Ratio (RR) for the meta-analysis. This approach mirrors the methodology previously employed (34). The 0.05 level (two-sided) was used to indicate significance of *p*-values.

For studies included in the meta-analysis, the RRs were used for the measure of association between air pollutants and health outcomes for comparing equivalent increases in pollutant concentration. In cases where RRs or ORs for gaseous pollutants were in parts per billion (ppb), they were converted to $\mu g/m^3$ at standard conditions (25°C) first. The heterogeneity in effect sizes was assessed using the I^2 statistic (35). The consideration of publication bias was deemed unnecessary due to the limited number of studies addressing the same pollutant and health outcome. All statistical analyses and meta-analyses were conducted with RevMan 5.4 software (Cochrane Collaboration).

3 Results

3.1 Study selection

The study selection process is summarised in Figure 1. Initially, a total of 6,291 records were identified through database searching. All search results from the database were imported into Endnote 20 to remove duplicates. After eliminating 1,200 duplicates, 5,091 records remained and underwent the initial screening based on their titles and abstracts. Subsequently, 5,035 records were excluded based on specific inclusion and exclusion criteria. The remaining 56 studies underwent a comprehensive review. During this review, 34 records were deemed ineligible and were subsequently removed, leaving a total of 22 papers sourced from the electronic database for inclusion in this literature

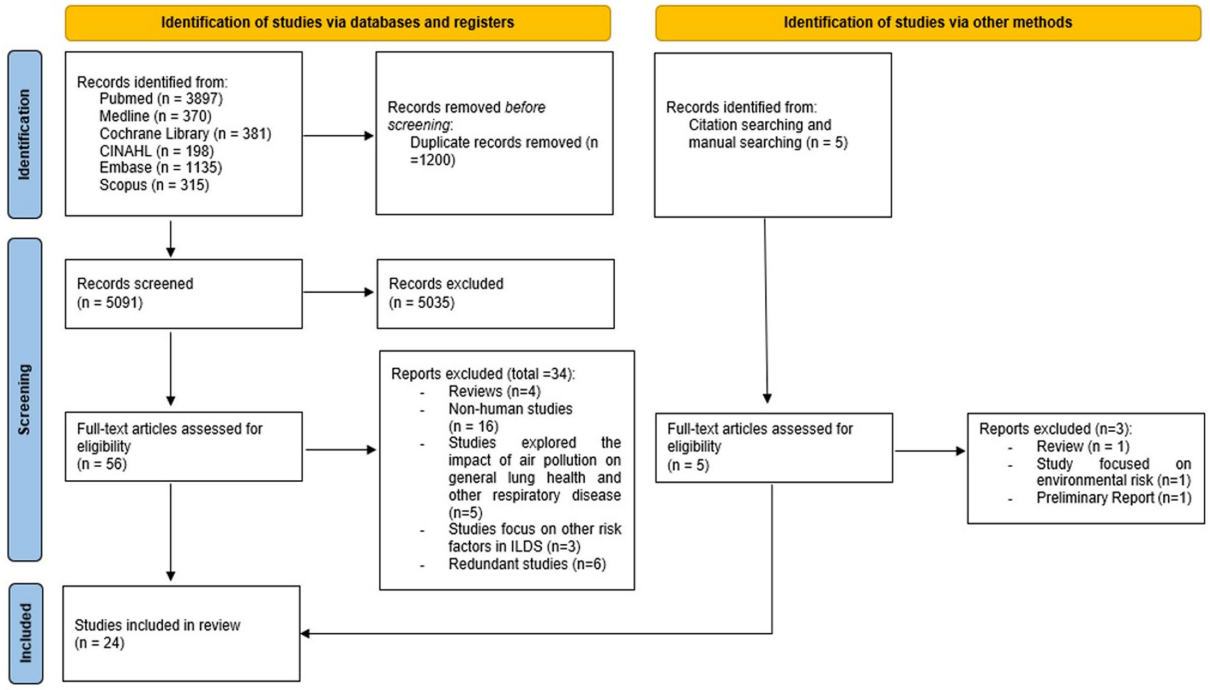

FIGURE 1
PRISMA 2020 flow diagram for study selection.

review. Among the 34 ineligible papers, six contained duplicate content that was already present in other included papers, despite having different titles. Therefore, these six duplicate papers were removed from the selection to avoid redundancy in the literature review (36–41).

Five additional records were identified through citation and manual searching. One study emerged as a preliminary report (42). An attempt to communicate with the authors to gain a deeper comprehension of methods and analysis was unsuccessful, resulting in the exclusion of that report. Of the remaining four studies, two meeting the eligibility criteria were included. In summary, our systematic literature review comprised a total 24 papers (Figure 1).

3.2 Study characteristics

Studies were conducted across various countries, representing diversity of geography, culture, and population ethnicity (Table 2). Six studies were conducted in the United States (44, 46, 48–50, 62), representing a quarter of all the included studies. Three studies were conducted each in Spain (53, 54, 63) and South Korea (43, 57, 64). Two studies each came from France (47, 65) and mainland China (59, 60). The remaining studies were conducted in Italy (45), Chile (51), Taiwan (52), Japan (55), Greece (56), the United Kingdom (61), and Australia (66). A collaborative effort between investigators from the USA and Canada resulted in a study evaluating North American ILD populations and air pollution (58).

All 24 selected studies were observational in nature. Among these, 17 studies were published in the last 5 years (2019–2023), while the remaining seven studies were published between 2014 and 2018 (43–49). Population sizes varied widely, ranging from 16 participants to 10 million inhabitants. The mean population ages ranged from 53 to 73.7 years old. Of the studies that reported sex distribution, 207,108 (46.5%) participants were male, and 238,166 (53.5%) participants were female.

The majority of studies (20 studies) enrolled participants from individuals diagnosed with ILD groups, with the exception of four studies that recruited individuals from the general community (44, 45, 50, 61). Among the patient groups with ILD participants, 14 studies included participants with IPF only in their study populations. Five studies focused on non-IPF ILD patients including fibrotic sarcoidosis (49), a connective tissue disease (CTD) population with and without associated ILD (52), fibrotic ILD (fILD) (58), rheumatoid arthritis associated ILD (RA-ILD) (60), and systemic sclerosis (SSc)-associated ILD (SSc-ILD) (65). The last study is a case–control study that involved individuals who had received diagnoses of idiopathic interstitial pneumonias (IIPs) (55) including those with IPF.

Among the 24 studies incorporated in the analysis, seven studies scrutinized the link between short-term exposure to air pollution and its impact on health outcomes (43, 46, 49, 51, 55, 59, 60). Fourteen studies delved into the connection between long-term exposure to air pollution and health outcomes (44, 45, 48, 50, 52, 54, 56–58, 62, 64–66). The remaining three studies examined the effects of both short-term and long-term exposure (47, 53, 63).

3.3 Risk of bias in studies

Eighteen of the 24 analysed studies were cohort or case control studies, and their assessment was conducted using the NOS tool as described above. NOS scores were assigned to each study by consensus. Among the appraised 18 studies, 12 received a full score of

TABLE 2 Summary of studies examined the impact of air pollution on interstitial lung disease (ILDs).

First author & year (reference)	Study population	Sample size	Country	Age years (mean ± SD)	Males/females	ILD diagnosis criteria	Air pollution metrics	Key findings
Johannson K. A., 2014 (43)	Patients with IPF	436	South Korea	62.8 ± 7.9	345/91	IPF diagnosis re-confirmed as per 2011 ATS/ERS/JRS/LARA Guideline	Mean and maximum Levels of O_3, NO_2, PM_{10}, SO_2 and CO over the 6 weeks preceding the date of AE. Cumulative exposures were calculated over the entire period, from IPF diagnosis to date of censoring.	• Higher exposure to O_3 and NO_2 in the preceding 6 weeks increased the risk of acute exacerbation in IPF. • Air pollution potentially contributes to the development of acute exacerbation in IPF. • No statistically significant correlation was found between cumulative exposure to air pollution and mortality.
Sack C., 2017 (44)	Participants of the Multi-Ethnic Study on Atherosclerosis (MESA)	2,265	United States	59.8 (9.4)	1059/1206	ILD defined based on HRCT scans	Annual average exposure levels of $PM_{2.5}$, NO_X, NO_2, and O_3	• The odds of Interstitial lung abnormalities (ILAs) increased 1.77-fold per 40 ppb increment in NOx (95% CI 1.06 to 2.95, $p = 0.03$). • No association was found between ILAs and ambient $PM_{2.5}$, O_2, or O_3 concentrations.
Conti S., 2018 (45)	Inhabitants of Lombardy, Italy	Almost 10 million inhabitants	Italy			IPF diagnosis based on International Classification of Diseases (ICD-9-CM) code 516.3	Average concentrations over 2005–2010 for NO_2 and O_3, and over 2005–2009 for PM_{10}	• The incidence of IPF was not associated with the concentration of PM_{10} and O_3. • There is a significant association between the incidence of IPF and cold season NO_2 concentration: a 10 μg·m − 3 increase in NO_2 is associated with a 7.93% (95% CI 0.36–16.08%) higher incidence rate of IPF. • Inhalation of traffic-related pollutants, such as NO_2, may be involved in the development of IPF.
Johannson K. A., 2018 (46)	Patients with IPF	25	United States	73.6 ± 7.5	21/4	IPF diagnosis re-confirmed as per 2011 ATS/ERS/JRS/LARA Guideline	Mean levels of O_3, NO_2, $PM_{2.5}$, and PM_{10} over 2 to 5 weeks preceding clinical measurements; mean and maximum level over 40 weeks period	• Higher average exposures to NO_2, $PM_{2.5}$, and PM_{10} were associated with lower FVC in patient with IPF. • Week-to-week changes in FVC were independent of air pollution exposure.

(Continued)

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TABLE 2 (Continued)

First author & year (reference)	Study population	Sample size	Country	Age years (mean ± SD)	Males/females	ILD diagnosis criteria	Air pollution metrics	Key findings
Sesé L., 2018 (47)	Patients with IPF	192	France	67.9 ± 11.2	148/44	IPF diagnosis based on 2000 ATS/ERS diagnosis criteria	Short-term effect: mean level of O_3, NO_2, $PM_{2.5}$, and PM_{10} over the 6 weeks preceding the date of AE. Long-term effect: cumulative exposure levels from IPF diagnosis to the date of the event or censoring	• Onset of acute exacerbation (AE) was significantly associated with an increased mean level of ozone in the six preceding weeks. • Mortality was significantly associated with increased levels of long-term exposure to PM_{10} and $PM_{2.5}$. • No association was observed between AE or Mortality and NO_2. • Disease progression was not associated with increased cumulative concentrations of NO_2, O_3, PM_{10} or $PM_{2.5}$
Winterbottom C. J., 2018 (48)	Patients with IPF	135	United States	68 (46–92)	101/34	IPF diagnosis re-confirmed as per 2011 ATS/ERS/JRS/LARA Guideline	Daily mean levels of PM 2.5 and PM_{10} between 2007 and 2013	• Increased exposure to PM_{10} was significantly associated with accelerated FVC decline, with each 5 mg/m^3 increase corresponding to a 35 cc/y decline in FVC (95% CI, 6–65 cc/y). • Increased exposure to $PM_{2.5}$ was significantly related to an accelerated rate of oxygen use increase during the 6MWT, with each 5 $\mu g/m^3$ increase corresponding to a 1.15 L/y increase (95% CI, 0.03–2.26 L/y). • No association was found between the proximity of subjects' residences to major roads and highways.
Pirozzi C., 2018 (49)	Patients with fibrotic sarcoidosis	16	United States	59 (53.25, 62.5)	4/12	Sarcoidosis diagnosis based on American Thoracic Society (ATS) criteria (1999)	Average Levels of $PM_{2.5}$ and O_3 for 7, 10, and 14 days preceding each study visit	• Short-term $PM_{2.5}$ exposure was linked to increased severity of respiratory and QoL symptoms according to the KSQ. • $PM_{2.5}$ exposure was not associated with FEV1, FVC, episodes of FEV1 decline >10%, or respiratory symptoms measured by SGRQ or LCQ. • Short-term ozone exposure was not associated with any health outcomes measured by the SGRQ, LCQ, or KSQ.

(Continued)

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TABLE 2 (Continued)

First author & year (reference)	Study population	Sample size	Country	Age years (mean ± SD)	Males/females	ILD diagnosis criteria	Air pollution metrics	Key findings
Rice M. B., 2019 (50)	Participants from Framingham study	2,618	United States	59.5 ± 11.9	1299/1319	ILAs diagnosis Based on CT scans	5-year (2004–2008) average levels of $PM_{2.5}$, Elemental carbon (EC) and O_3	• Higher long-term exposure to EC was associated with increased odds and progression of ILAs on chest imaging. • No significant association was found between $PM_{2.5}$ or O_3 and the incidents or progression of ILAs.
Dales R., 2020 (51)	Patients with a primary diagnosis of IPF	3,989	Chile		1665/2324	IPF diagnosis based on International Classification of Diseases, 10th Revision (ICD-10) J84.1	Annual average of 24 h means of CO, NO_2, SO_2, $PM_{2.5}$ and PM $_{10}$, and 8-h daily maximum level of O_3 over 0 to 6 days before admission and over the 30 days before admission	• NO_2 and PM_{10} are the strongest independent pollutants associated with increased hospitalization. • CO and SO_2 had significant positive association with hospitalisation ($p < 0.05$), but lost association when use two pollutant models. • The air pollution levels within 3 days before admission had the most substantial impact on IPF patients. • Acute increases in air pollution are a risk factor for hospitalization of patients with a primary diagnosis of IPF.
Chen H. H., 2020 (52)	Patients with connective tissue diseases (CTDs)-ILD	505 CTD-ILD and 2020 non-ILD CTD	Taiwan, China	CTD-ILD 60.1 ± 14.7/ non-ILD CTD 59.4 ± 14.0	CTD-ILD 125/380 non-ILD CTD 500/1,520	CTD-ILD diagnosis based on ICD-9 code 515 and 516.36	Mean levels of $PM_{2.5}$, PM_{10}, NO_2, CO, SO_2 and O_3 1 year prior to the index date.	• Patients with CTD-ILD had slightly lower average exposure to $PM_{2.5}$, PM_{10}, and SO_2 compared to patients with non-ILD CTD, but not statistically significant. • O_3 exposure (10 ppb) (aOR, 0.51; 95%CI, 0.33 to 0.79) showed an inverse association with the risk of ILD development in patients with CTD in Taiwan.
Mariscal-Aguilar P., 2021 (53)	Patients with IPF	52	Spain	66 ± 10	41/11	IPF diagnosis based on ATS/ERS criteria (unsure which version)	Mean levels of $PM_{2.5}$, PM_{10}, NO_2, CO, SO_2, and O_3 (from the previous 12 weeks prior to death for mortality, mean level between 2013 and 2019 for disease progression.)	• Increased exposure to carbon monoxide (CO) was significantly associated with increased mortality. • No association was found between any of the other investigated air pollutants and IPF mortality or severity.

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TABLE 2 (Continued)

First author & year (reference)	Study population	Sample size	Country	Age years (mean ± SD)	Males/females	ILD diagnosis criteria	Air pollution metrics	Key findings
Shull J. G., 2021 (54)	Patients with IPF	379	Spain			IPF diagnosis based on central expert ILD multidisciplinary discussion (MDD)	Annual mean concentration of $PM_{2.5}$ over 1 year in 2015	• Prevalence of IPF is higher in areas of elevated $PM_{2.5}$ concentration. • Mapping IPF can help identify geographic regions at higher risk for disease development and potential triggers.
Tahara M., 2021 (55)	Patients with idiopathic interstitial pneumonias (IIPs) (152 IPF and 200 other subtypes of IIPs)	352	Japan			IIPs diagnosis based on HRCT, surgical lung biopsy (SLB) samples and MDD	Daily and monthly mean concentrations of SO_2, NO, NO_2, NOx, CO, O_3, $PM_{2.5}$ and PM_{10}	• Short-term exposure to $PM_{2.5}$ is associated with a significant risk of acute exacerbation (AE) of IPF. Each 10 μg/m^3 increase in $PM_{2.5}$ amplified the risk of AE-IPF by approximately 2.5 times. • Significant positive associations were observed between the monthly mean exposure to NO, NO_2, NOx, $PM_{2.5}$, and AE-IIPs. • No significant relationship was observed between AE-IPF incidence and exposure to SO_2 and O_3.
Tomos I., 2021 (56)	Patients with IPF	118	Greece	72 ± 8.3	88/30	IPF diagnosis based on 2011 ATS/ERS/JRS/LARA Guideline	Annual mean levels of O_3, NO_2, PM_{10} and $PM_{2.5}$	• Long-term exposure to NO_2, $PM_{2.5}$, and PM_{10} increased the risk of AE-IPF, independent of age, lung function impairment, anti-fibrotic treatment, and smoking status. • Long-term exposure to O_3 is positively linked to increased serum IL-4 levels (an inflammatory mediator) (p = 0.014), whilst $PM_{2.5}$, PM_{10} and NO_2 were inversely associated with %changes of IL-4 (p = 0.003, p = 0.003, p = 0.032) and osteopontin (p = 0.013, p = 0.013, p = 0.085) in AE-IPF patients.
Yoon H-Y, 2021 (57)	Patients with IPF	1,114	South Korea	65.7 ± 8.2	897/217	IPF diagnosis based on 2011 ATS/ERS/JRS/LARA Guideline and MDD	Annual mean levels of PM_{10} and NO_2	• Exposure to NO_2 is associated with increased mortality risk in patients with IPF, especially in elderly males. Each 10-ppb increase in NO_2 concentration is linked to a 17% higher mortality rate. • PM_{10} was not associated with IPF mortality in all patients and in subgroups stratified by age or sex.

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TABLE 2 (Continued)

First author & year (reference)	Study population	Sample size	Country	Age years (mean ± SD)	Males/females	ILD diagnosis criteria	Air pollution metrics	Key findings
Goobie G. C., 2022 (58)	3 cohort patients with fibrotic interstitial lung disease (fILD)	6,683	United States and Canada	67 (57–73)	3653/3030	fILD diagnosis were made by specialist ILD physicians: IPF diagnosis as per ATS/ERS/JRS/ALAT 2018; Hypersensitivity pneumonitis diagnosis as per ATS/JRS/ALAT 2020	Monthly mean exposures 5 years pre-enrolment or precensoring for total PM $_{2.5}$ and its constituents (SO_4^{2-}, NO_3^-, NH_4^+, black carbon, organic matter, sea salt, and soil)	• $PM_{2.5}$ exposure of 8 μg/m^3 or higher was associated with higher mortality risk across all cohorts. • Increasing exposure to sulfate, nitrate, and ammonium $PM_{2.5}$ constituents was associated with increased mortality, lower baseline lung function, and increase in Lung Function decline, and more rapid disease progression in patients with fILD.
Liang L., 2022 (59)	Patients with IPF	11,974 IPF admissions	China			Primary discharge diagnosis of IPF based on ICD-10: J84.1	Daily mean concentrations of PM_{10}, $PM_{2.5}$, NO_2, O_3, SO_2	• Significant association between higher $PM_{2.5}$ concentrations and increased risk of IPF hospitalization at no time lag(lag0) and short-term exposure periods. • Significant positive associations were observed at lag0 between IPF hospitalization and SO_2, O_3, and NO_2 in men only. • Positive associations were seen for moving averages of 0–30 days between IPF hospitalization and PM_{10}, NO_2, and SO_2, but not with $PM_{2.5}$ or Ozone.
Liu B., 2022 (60)	Patients hospitalized for rheumatoid arthritis associated with interstitial lung disease (RA ILD)	221 RA-ILD admissions	China			Diagnosis of RA-ILD as per 1987 ACR criteria for RA, ILD by HRCT reviewed by rheumatologist and radiologist.	Monthly mean concentrations of $PM_{2.5}$, PM_{10}, SO_2, O_3 and NO_2	• There was a significant correlation between ambient air pollutant concentrations ($PM_{2.5}$, PM_{10}, SO_2, and NO_2) and monthly hospitalizations for RA-ILD. • $PM_{2.5}$, PM_{10}, and SO_2 had the most significant effect on the month (lag 0), and NO_2 was most related to RA-ILD at a lag of two months (lag 2). • For each 10μg/m^3 increase in $PM_{2.5}$, PM_{10}, SO_2 and NO_2, the monthly admissions of RA-ILD increased by 0.875, 0.548, 1.968, and 1.534%, respectively. • Higher O_3 levels to be inversely associated with hospitalizations for RA-ILD.

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TABLE 2 (Continued)

First author & year (reference)	Study population	Sample size	Country	Age years (mean ± SD)	Males/females	ILD diagnosis criteria	Air pollution metrics	Key findings
Cui F., 2023 (61)	Participants from the UK Biobank	433,738	United Kingdom	56.4 ± 8.1	199,363/ 234,375	IPF diagnosis based on ICD-10: J84.1	Annual average concentrations of NO_2, NOx, $PM_{2.5}$ and PM 10	• The mean (median) concentrations of NO_2, NOx, $PM_{2.5}$ and PM_{10} were 26.65 (26.13), 43.99 (42.21), 9.99 (9.93) and 16.23 (16.03) $\mu g \cdot m^{-3}$ • Significantly increased risk of incident IPF was associated with individual exposures to NO_2, NOx and $PM_{2.5}$. • The combination of air pollutants and genetic susceptibility has additive effects on IPF risk. • Participants with high polygenic risk scores (PRS) and high air pollution had the highest risk of incident IPF.
Goobie G. C., 2023 (62)	Two cohort of IPF patients	1,059	United States	69 (61–74)	772/287	IPF diagnosis made by a specialist ILD clinician, as per clinical practice guidelines	Monthly mean of $PM_{2.5}$ (from 2000 to 2018) and its constituents (SO_4^{2-}, NO_3^-, NH_4^+, black carbon, organic matter, sea salt, and soil) (from 2000 to 2017)	• Higher $PM_{2.5}$ and its constituent exposures were associated with higher global DNA methylation (DNAm) in patients with IPF. • Global DNAm may serve as a biomarker of short and long-term exposures to ambient pollution in IPF patients.
Mariscal-Aguilar P., 2023 (63)	Patients with IPF	69	Spain	73.70 ± 7.72	53/16	IPF diagnosis based on patients' medical record at the time of each admission	Mean concentration of CO, NO_2, O_3, and NOx over 1, 3,6, 12 and 36 months before an event	• Higher average values of CO, NO_2, and NOx were significantly associated with an increased likelihood of chronic respiratory failure in different periods in IPF patients. • Significant associations were found between the average levels of NO_2, O_3, and NOx and the probability of hospital admissions due to respiratory causes and mortality in these patients.
Yoon H. Y., 2023 (64)	Patients with IPF	946	South Korea	65.4 ± 8.1	765/181	IPF diagnosis based on 2011 ATS/ERS/ JRS/LARA Guideline and MDD	Annual average concentrations of NO_2 and PM_{10}	• Exposure to NO_2 increases the risk of disease progression in IPF. A 10-ppb increase in NO_2 concentration was associated with a 10.5% increased risk of progression. • No association was found between PM_{10} and disease progression in IPF patients.

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TABLE 2 (Continued)

First author & year (reference)	Study population	Sample size	Country	Age years (mean ± SD)	Males/females	ILD diagnosis criteria	Air pollution metrics	Key findings
Roeser A., 2023 (65)	Patients with Systemic sclerosis (SSc)-associated ILD	181	France	53 (42.5–64)	37/144	SSc diagnosis based on 2013 American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) classification criteria and ILD diagnosis based on 2018 ATS/ ERS/JRS/ALAT Guidelines	Annual mean concentrations of $PM_{2.5}$, PM_{10}, NO_2, and O_3	• The mean (SD) exposure levels during the 5 years preceding ILD diagnosis for the study population were 27.9 (8.4) μg/m^3 for NO_2 (range 9.9–42.2), 44.2 (6.0) μg/m^3 for O_3 (range 36.5–74.6), 23.5 (3.3) μg/m^3 for PM_{10} (range 15.6–30.0) and 15.6 (2.4) μg/ m^3 for $PM_{2.5}$ (range 9.6–20.3). • High levels of O_3 exposure are associated with more severe SSc-associated ILD at diagnosis, and progression at 24 months. • No significant associations were found for PM exposure or NO_2 exposure
Zheng Q., 2023 (66)	Patients with IPF	570	Australia	70.9 (8.2)	401/169	IPF patients from Australian IPF Registry – IPF diagnosis made by referring respiratory physician	5-year annual mean concentrations of $PM_{2.5}$ and NO_2	• Living near a major road and increased $PM_{2.5}$ were both associated with an increased rate of annual decline in DLco, but not associated with a faster decline in FVC. • No association was found between NO_2 and lung function decline. • Median (25th–75th percentiles) annual $PM_{2.5}$ and NO_2 were 6.8 (5.7, 7.9) μg/m^3 and 6.7 (4.9, 8.2) ppb. • No significant association of increased $PM_{2.5}$ (HR 1.16, 95% CI 0.88 to 1.53) or NO_2 (HR 1.06, 95% CI 0.85 to 1.33) with rapid progression of IPF.

O_3, ozone; NO_2, nitrogen dioxide; PM, particulate matter; $PM_{2.5}$, particulate matter with a diameter of 2.5 micrometres or less; PM_{10}, particulate matter with a diameter of 10 micrometres or less; SO_2, sulfur dioxide; CO, carbon monoxide; NO, Nitric Oxide; IPF, idiopathic pulmonary fibrosis; ILAs, interstitial lung abnormalities; FVC, Forced vital capacity; AE, Acute exacerbation; NOx, Nitrogen Oxides; SGRQ, Saint George Respiratory Questionnaire (SGRQ) measures the impact of respiratory symptoms on overall health, daily life, and perceived well-being, and queries symptoms over the past three months and "these days"; LCQ, Leicester cough questionnaire (LCQ) is a 19-item quality of life (QoL) measure of cough over the prior two weeks; KSQ, King's Sarcoidosis Questionnaire (KSQ) is a validated questionnaire for assessing general health status and lung specific health status; Elemental carbon (EC), a traffic related $PM_{2.5}$ constituent; DLco, diffusing capacity of the lungs for carbon monoxide; SO_4^{2-}, sulfate; NH_4^+, ammonium; NO_3^-, nitrate; PFF, Pulmonary Fibrosis Foundation; Simmons, Simmons Center for Interstitial Lung Disease Registry; aOR, adjusted odds ratio; aHR, adjusted hazard ratio.

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9/9 (43, 44, 47, 48, 50, 56–58, 61, 62, 65, 66), indicating high quality research. Four studies received a score of 8/9 (49, 52, 53, 64), one study received a score of 7/9 (55), and one study was scored as 6/9 (46). All 18 studies were considered to be of good to high quality.

The limitations identified in the remaining six studies involved data sources, accuracy of diagnoses, measurement of exposure, and potential confounding factors. Most studies had limitations of potential underestimation or misclassification of cases due to data sources or diagnostic coding (45, 51, 54, 59). Additionally, there was a lack of adjustment for individual-level factors (45, 51, 59, 60), and limited data on certain pollutants (54, 59) or occupational history (45, 59). Some studies had limited statistical power due to small sample size and limiting generalisability to broader populations or regions (60, 63) (Table 3).

3.4 Findings: impact of air pollutants on ILDs

Air pollution have been found to have multiple impacts on ILDs (Supplementary Table S1).

3.4.1 Air pollution and mortality in IPF or fibrotic interstitial lung disease (fILD)

Six studies involving 8,546 participants examined the association between air pollution and mortality in individuals with IPF (43, 47, 53, 57, 63) or fILD (58). Among these studies, five studies investigated NO_2 (43, 47, 53, 57, 63), four studies involved O_3 (43, 47, 53, 63), and three studies each examined PM_{10} (47, 53, 57), and $PM_{2.5}$ (47, 53, 62).

The findings regarding the association between NO_2 and O_3 were inconclusive. Specifically, three studies did not detect any association between the average levels of NO_2 and O_3 in the 12 weeks preceding an individual's death (53), the cumulative long-term NO_2 and O_3 exposure from the time of IPF diagnosis to the event date (43, 47), and IPF mortality. However, Mariscal-Aguilar et al. (63) reported a link between elevated mean levels of NO_2 and O_3 and higher probability of IPF mortality in individuals exposed to these pollutants for 1–3 months for O_3, and 2–36 months for NO_2. Additionally, Yoon et al. (57) found a positive association between NO_2 and IPF mortality (95% CI 1.030–1.344, $p = 0.016$).

Variable impact of PM_{10} exposure has been described. Although two studies (53, 57) failed to detect any connection between short and long-term mean levels of PM_{10} and IPF mortality, a separate study (47) revealed a positive link. This study demonstrated that long-term cumulative exposure to elevated PM_{10} levels was associated with increased IPF mortality (HR 2.01; 95% CI 1.07–3.77; $p = 0.03$).

Regarding $PM_{2.5}$ exposure, Mariscal-Aguilar et al. (53) reported no discernible link between the mean level of $PM_{2.5}$ over the 12 weeks preceding death and IPF mortality, whereas Sesé et al. (47) revealed a significant correlation between long term cumulative exposure and IPF mortality (HR 7.93; 95% CI 2.93–21.33; $p < 0.001$). Another study exploring the effects of $PM_{2.5}$ and its constituents on mortality in patients with fILD (58) showed that $PM_{2.5}$ exposure of 8 $\mu g/m^3$ or higher over a 5-year period was associated with increased mortality across all fILD patient groups (HR, 1.18; 95% CI, 1.02–1.37; $p = 0.03$).

In Mariscal-Aguilar et al. study (53), the mean CO level assessed 12 weeks before death was associated with increased IPF mortality (OR 2.45; 95% CI 1.39–4.56; $p = 0.005$). Conversely, Mariscal-Aguilar et al. (63), did not find any association between CO exposure and IPF mortality. However, this same study did reveal a positive association between increased mean concentrations of nitrogen oxides (NOx) and IPF mortality over a 12-36-month period (63).

3.4.2 Air pollution and disease progression (IPF and systemic sclerosis-associated ILD, SSc-ILD)

Three studies (1708 participants) explored the link between air pollution and the progression of IPF (47, 64, 66). Among the four pollutants, namely PM_{10}, $PM_{2.5}$, O_3, and NO_2, the results showed that PM_{10} (47, 64), $PM_{2.5}$ (47, 66), and O_3 (47) had no relationship with the disease progression in IPF patients. However, the results regarding NO_2 were inconclusive.

In the study conducted by Sesé et al. (47), researchers examined cumulative concentrations of these pollutants from the date of IPF diagnosis to the event, while Zheng et al. (66) assessed 5-year annual mean concentrations. Neither study found a link between NO_2 levels and progression of IPF. However, Yoon et al. study (64) reported that a 10-ppb increase in NO_2 concentration was associated with a 10.5% increase in the risk of IPF disease progression (HR 1.105; 95% CI 1.000–1.219, $p = 0.048$) after adjusting for covariates.

Additionally, a study of 181 participants with SSc-ILD, examined the relationship between air pollution and the severity at diagnosis and with progression of ILD at 24 months (65). Increased O_3 mean (SD) exposure levels during the 5 years preceding ILD diagnosis were associated with worse disease severity at diagnosis (adjusted OR: 1.12, 95% CI 1.05–1.21; $p = 0.002$) and disease progression at 24 months (OR: 1.10, 95% CI 1.02–1.19; $p = 0.02$), while $PM_{2.5}$, PM_{10}, and NO_2 showed no association with the severity or progression of ILD.

Furthermore, one study involving 181 participants diagnosed with SSc-ILD investigated the association between air pollution and the severity of the disease at diagnosis and its progression over a 24-month period (65). Elevated levels of O_3 exposure were significantly linked to more severe SSc-ILD both at the time of diagnosis (aOR: 1.12, 95% CI 1.05–1.21; $p = 0.002$) and progression at 24 months (aOR: 1.10, 95% CI 1.02–1.19; $p = 0.02$). However, no significant associations were identified between exposure to particulate matters (PM_{10} and $PM_{2.5}$) or NO_2 and the disease severity or its progression.

3.4.3 Air pollution and the risk of acute exacerbation of ILD (AE-IPF and AE-IIP)

Four studies (1,098 participants) investigated the potential association between air pollution and acute exacerbation of IPF (AE-IPF) (43, 47, 55, 56) including O_3, NO_2, PM_{10}, $PM_{2.5}$, SO_2, CO, NO and NOx. Among these, SO_2 and CO were examined in two of the studies, with no association found between short-term exposure to higher levels of these pollutants and incidence of AE-IPF (43, 55). A study conducted by Tahara et al. (55) also examined NO and NOx, with significant and near-significant association between increase in NO (OR 1.46; 95% CI 1.11–1.93; $p = 0.008$) and NOx (OR 1.24, 95% CI 0.99–1.53; $p = 0.052$) concentrations and AE-IPF.

We conducted meta-analyses to assess the RRs for AE-IPF in relation to exposure to every 10 $\mu g/m^3$ increment in air pollutant concentrations, including O_3, NO_2, PM_{10}, and $PM_{2.5}$ (as illustrated in Figure 2). The study by Johannson et al. (43) expressed effect sizes per standard deviation increase in pollutant. However, it was excluded because we could not locate, in the main or supplementary text, a description of the SD on a continuous scale (43).

The meta-analysis revealed a significant association between the increased risk of AE-IPF in $PM_{2.5}$, yielding RR 1.94 (95% CI 1.30–2.90;

TABLE 3 Critical appraisal of selected studies.

				Newcastle-Ottawa scale appraisal				
First author & year (reference)	Study design	Sample size	Limitations	Selection	Comparability	Outcome	Score	Quality
Johannson, 2014 (43)	Cohort	436		****	**	***	9	Good
Sack C., 2017 (44)	Cohort	2,265		****	**	***	9	Good
Johannson, 2018 (46)	Cohort	25		***	**	*	6	Good
Sesé, 2018 (47)	Cohort	192		****	**	***	9	Good
Winterbottom, 2018 (48)	Cohort	135		****	**	***	9	Good
Pirozzi, 2018 (49)	Cohort	16		***	**	***	8	Good
Rice, 2019 (50)	Cohort	2,618		****	**	***	9	Good
Mariscal-Aguilar, 2021 (53)	Cohort	52		***	**	***	8	Good
Tomos, 2021 (56)	Cohort	118		****	**	***	9	Good
Yoon, 2021 (57)	Cohort	1,114		****	**	***	9	Good
Goobie, 2022 (58)	Cohort	6,683		****	**	***	9	Good
Cui, 2023 (61)	Cohort	433,738		****	**	***	9	Good
Goobie, 2023 (62)	Cohort	1,059		****	**	***	9	Good
Yoon, 2023 (64)	Cohort	946		****	**	**	8	Good
Roeser, 2023 (65)	Cohort	181		****	**	***	9	Good
Zheng, 2023 (66)	Cohort	570		****	**	***	9	Good
Chen, 2020 (52)	Case–Control	2,525		****	**	**	8	Good
Tahara, 2021 (55)	Case–Control	352		***	**	**	7	Good
Conti, 2018 (45)	Ecologic	Almost 10 million inhabitants	1. Potential underestimation of incident cases of IPF due to reliance on administrative databases. 2. Uncertainty regarding the accuracy of diagnosis codes. 3. Proxy use of incident diagnosis date as disease onset. 4. Limited data on individuals who moved before 2005. 5. Potential residual confounding from unmeasured risk factors such as occupation and smoking.					

(Continued)

TABLE 3 (Continued)

First author & year (reference)	Study design	Sample size	Limitations	Newcastle-Ottawa scale appraisal				
				Selection	Comparability	Outcome	Score	Quality
Shull, 2021 (54)	Ecologic	379	1. Inability to quantify precise air pollution exposure prior to diagnosis. 2. Potential underestimation of prevalence in rural areas and small towns. 3. Other pollutants such as NO_2 and O_3 were not examined.					
Liang, 2022 (59)	Ecologic	11,974	1. Ecological study design limits individual-level predictions. 2. Individual-level factors like smoking and socioeconomic status were not adjusted for. 3. Lack of data on time-varying factorsand specific residential addresses. 4. Outcome measurement limitations due to the primary diagnosis of IPF was coded by clinicians at discharge, which may have led to misclassification. 5. Constraints in analysing multiple pollutants and lack of occupational history.					
Liu, 2022 (60)	Ecologic	221	1. Exclusion of hospital outpatients may underestimate the impact of exposure. 2. Use of average daily data from fixed-site monitoring stations may not reflect individual exposure levels accurately. 3. Low statistical power due to limited incidences of RA-ILD. 4. Study conducted in a single district, limiting generalizability of results					

(Continued)

TABLE 3 (Continued)

				Newcastle-Ottawa scale appraisal				
First author & year (reference)	Study design	Sample size	Limitations	Selection	Comparability	Outcome	Score	Quality
Dales, 2020 (51)	Ecologic	3,989	1. Lack of detailed personal information relevant to interstitial disease like smoking. 2. Lack of a more detailed description of the diagnosis. Inaccuracies in disease definition due to errors in both clinical diagnosis and diagnostic coding.					
Mariscal-Aguilar, 2023 (63)	Panel	69	1. Two-centre and limited sample size. 2. Lack of consideration for workplace air pollution. 3. Missing data on temperature and humidity. 4. Inability to control for all confounding factors. 5. Lack of diversity in exposure levels since the majority of patients reside in the same region.					

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor): good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain. Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain. Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

$p = 0.001$). However, the link between O_3, NO_2 and PM_{10} and the risk of AE-IPF remained uncertain, with RR 0.97 (95% CI: 0.61–1.53; $p = 0.89$) for O_3, RR 1.24 (95% CI 0.90–1.71; $p = 0.19$) for NO_2, and RR 1.18 (95% CI 0.66–2.13; $p = 0.58$) for PM_{10}, respectively.

Tahara et al. (55) (352 participants) also investigated the link between air pollution and the risk of acute exacerbations of idiopathic interstitial pneumonias (AE-IIPs). Their study revealed positive associations between the average monthly exposure to NO, NO_2, NOX, and $PM_{2.5}$, and AE-IIPs. Specifically, for every 10 ppb increase, the aOR was 1.50 (95% CI 1.19–1.88; $p = 0.001$) for NO, 1.99 (95% CI 1.22–3.27; $p = 0.006$) for NO_2, and 1.29 (95% CI 1.08–1.53; $p = 0.004$) for NOX. Additionally, for every 10 ug/m^3 increase, the aOR was 2.88 (95% CI 1.69–4.91; $p \leq 0.001$) for $PM_{2.5}$. However, there was no significant association found between the average monthly levels of SO_2, O_3, CO, PM_{10}, and AE-IIPs.

3.4.4 Air pollution and lung function (baseline and decline in IPF, decline in fibrotic sarcoidosis patients)

Five studies (46, 48, 49, 58, 66) involving a total of 5,907 participants explored the relationship between air pollution and the decline in lung function among individuals with IPF or other fibrotic ILD. The pollutants investigated included $PM_{2.5}$, PM_{10}, O_3, and NO_2. Four studies found no significant association between $PM_{2.5}$ levels and decline in FVC (46, 48, 49, 66). The sole study indicating an association was conducted by Goobie et al. (58) in patients with fILD. They observed that a 1 μg/m^3 increase in the 5-year pre-censoring $PM_{2.5}$ exposure, as assessed through adjusted meta-analysis across three cohorts, was linked to an additional 0.15% decrease in FVC percentage estimated per year (HR0.15, 95% CI -0.42 to 0.12, $p = 0.29$). Investigation of the constituents of $PM_{2.5}$ revealed that higher exposures to sulfate, nitrate, and ammonium were correlated with a more accelerated annual decrease in the FVC percent predicted (SO_4^{2-}: β −2.53, 95% CI -4.45 to −0.62, $p = 0.01$); (NO_3-: β-1.72, 95% CI -2.86 to −0.58, $p = 0.003$); (NH_4^+: β-5.93, 95% CI -10.18to −1.69, $p = 0.006$).

The same study (58) also identified associations between $PM_{2.5}$ and its constituents, particularly SO_4^{2-} and NH_4^+, and diffusing capacity of the lungs for carbon monoxide (DLco) decline. The adjusted meta-analysis showed non-significant association between total $PM_{2.5}$ (HR: −0.05; 95% CI −0.31 to 0.21; $p = 0.70$), but significant association with its constituents SO_4^{2-} (β: −2.12; 95% CI −3.93 to −0.30; $p = 0.02$), and NH_4^+ (β: −4.66; 95% CI −8.77 to −0.54; $p = 0.03$). In the study by Zheng et al. (66), they also found a positive link between increased $PM_{2.5}$ levels and DLco decline in IPF patients. Specifically, for each

interquartile range (IQR) increase of 2.2 μg/m^3 in $PM_{2.5}$, there was an additional 0.9% predicted/year (95% CI −1.6 to −0.3) accelerated decline in DLco.

For PM_{10}, Johannson et al. (46) did not observe any association between higher cumulative mean exposures or maximum exposures to air pollution and a more rapid decline in FVC or FEV1 over a duration of up to 40 weeks. In contrast to this, Winterbottom et al. (48) demonstrated that for every 5 μg/m^3 increase in PM_{10} concentration, there was an additional decline of 46 mL per year in FVC (95% CI, 12–81 mL/y; $p = 0.008$). Neither NO_2 (46, 66) nor O_3 (46, 49), were found to be associated with a more rapid decline in lung function.

Among the five studies, two studies (6,708 participants) examined the association between air pollutants and baseline lung function (46, 58). Both studies identified a correlation between elevated air pollution levels and lower baseline lung functions. Johannson et al. (46) observed that increased mean levels of NO_2($p = 0.03$), $PM_{2.5}$($p = 0.02$), and PM_{10}($p = 0.003$) over the study period were significantly linked to reduced FVC % predicted. Goobie et al. (46) found that an increase in $PM_{2.5}$ and its constituent mixture by one quantile was associated with decreased baseline FVC, specifically, higher MC is associated with a significant 3.38% decrease in the estimated baseline percentage of FVC (β-3.38; 95% CI −4.88 −1.87; $p < 0.001$) and a 3.64% decrease in the estimated baseline percentage of DLCO (β −3.64; 95% CI −4.61 to −2.66; $p < 0.001$).

3.4.5 Air pollution and incidence of ILD

Three studies, which collectively involved nearly 10 million inhabitants from Italy (45), 379 IPF participants from Spain (54), and 433,738 participants from a biobank in the UK (61), investigated the connection between air pollution exposure and the incidence of IPF. They showed that NO_2, $PM_{2.5}$, and NOx were linked to an increased incidence of IPF. In the Italian study (45), the authors demonstrated that an increase of 10 μg/m^3 NO_2, was associated with an increase in the IPF incidence rate from 6.39% (95% CI −3.62–17.45) to 7.55% (95% CI −0.76–16.56%), depending on the season. In the UK study (61), the adjusted hazard ratios for IPF were aHR 1.11 (95% CI 1.03–1.19; $p = 0.006$) for NO_2, aHR 1.07 (95% CI 1.01–1.13; $p = 0.02$) for NOx, and aHR 1.09 (95% CI 1.02–1.17, $p = 0.01$) for $PM_{2.5}$, for each interquartile rise in these pollutants. Shull et al. (54) underscored the positive link between increased incidence of ILD and $PM_{2.5}$, revealing that the highest $PM_{2.5}$ concentrations, ranging from 20 to 24.6 μg/m^3, were in areas of traffic congestion, industrial zones, the airport, and the ports of Barcelona. These areas, rather than the most densely populated ones, exhibited a higher aggregation of IPF cases. No significant association was discovered between the incidence of IPF and the concentrations of PM_{10} (45, 61) or O_3 (45).

Two studies (4,883 participants) investigated the association between ambient air pollution and the likelihood of subclinical ILD or ILA (44, 50). Both studies observed a positive connection between NOx and elemental carbon (EC) exposure and the occurrence of ILD or ILA. Sack et al. (44) showed that for each 40-ppb increase in NOx concentration, the OR for ILD was 1.77 (95% CI 1.06–2.95, $p = 0.03$). In a separate study (50), an IQR difference in 5-year EC exposure of 0.14 μg/m^3 was associated with an OR of 1.27 (95% CI 1.04–1.55, $p = 0.02$) for ILA. The same study also noted an OR of 1.33 (CI 1.00 to 1.76, $p = 0.05$) for the progression of ILA. Neither study showed an association between exposure to $PM_{2.5}$ and ozone (O_3) and the presence of ILA and Sack et al. study (44) showed no association between ILA incidence and NO_2 exposure.

One case–control study (52) involving 2,525 participants examined the link between air pollution exposure and the development of ILD in patients with a variety of CTD diagnoses. The study revealed that individuals with CTD-ILD had somewhat lower average exposure to $PM_{2.5}$, PM_{10}, and SO_2 when compared to patients with non-ILD CTD. However, these differences were not statistically significant. For every 10-ppb increase in O_3 exposure, there was a decrease in the risk of developing ILD (aOR 0.51; 95% CI 0.33–0.79; $p = 0.002$).

3.4.6 Air pollution and hospitalisation (IPF and RA-ILD)

Three studies (51, 59, 63) involving a total of 16,032 participants explored the impact of various air pollutants, namely NO_2, O_3, $PM_{2.5}$, CO, SO_2, NO_X, on hospitalisation incidence in patients with IPF. In all three studies, the investigation focused on the exposure to NO_2 and O_3, and consistently revealed a positive correlation between the mean concentration of NO_2, whether it was from short-term or long-term exposure, and the incidence of hospitalization. Nevertheless, the findings regarding O_3 were inconclusive. Mariscal-Aguilar et al. (63) found an association between elevated mean O_3 levels during the month preceding admission and a heightened rate of hospital admissions. In contrast, Dale et al. (51) did not observe a statistically significant association in their two-pollutant model. Liang et al. (59) showed a positive association with short-term increased level of O_3 exposure in men and hospital admissions (RR: 1.045; 95% CI 1.000–1.092; $p = 0.05$) per IQR increase of 85 μg/m^3, but not with average O_3 exposure over the 30 days period before admission.

Two of these studies also investigated $PM_{2.5}$, Dale et al. (51) found a positive association (RR 1.29, 95% CI 1.09–1.54, $p = 0.003$) between short-term elevated average level of $PM_{2.5}$ (for an IQR Increase) and an increased incidence of hospitalisation. Liang et al. (59) also observed a positive association with short-term $PM_{2.5}$ exposure (RR: 1.049, 95% CI 1.024–1.074, $p = 0.0001$) for lag0 and RR 1.031 (95% CI 1.007–1.056; $p = 0.01$) for a moving average 0-1 days, both per IQR of 72 μg/m^3. However, this association was not evident for average $PM_{2.5}$ exposure over 0–30 days. PM_{10} level was found to be one of the strongest independent pollutants associated with increased hospitalisation (51) (RR 1.31; 95% CI 1.12–1.53; $p < 0.001$), but less statistically significant in Liang et al.'s study (per 86 μg/m^3: RR 1.021, 95% CI 0.994–1.049, $p = 0.13$) (59).

CO exposure was initially found to have a positive association with hospitalisation (51), but this association was lost when using two-pollutant models. In contrast, Mariscal-Aguilar et al. (63) did not find any association between incidence of hospitalisation and CO levels. Regarding SO_2 exposure, Dale et al. (51) initially demonstrated a positive correlation between elevated SO_2 concentration and hospitalization during univariable analysis, with a relative risk (RR) of 1.20 (95% CI 1.07–1.34, $p < 0.05$), but this relationship lost significance when two-pollutant models were applied. Liang et al. (59) identified an association between short-term SO_2 exposure and hospitalization in men. Elevated exposure to NO_X concentrations, as examined by Mariscal-Aguilar et al. (63), was significantly linked to the incidence of hospitalization in IPF patients for respiratory causes, particularly with exposures spanning 6, 12, and 36 months.

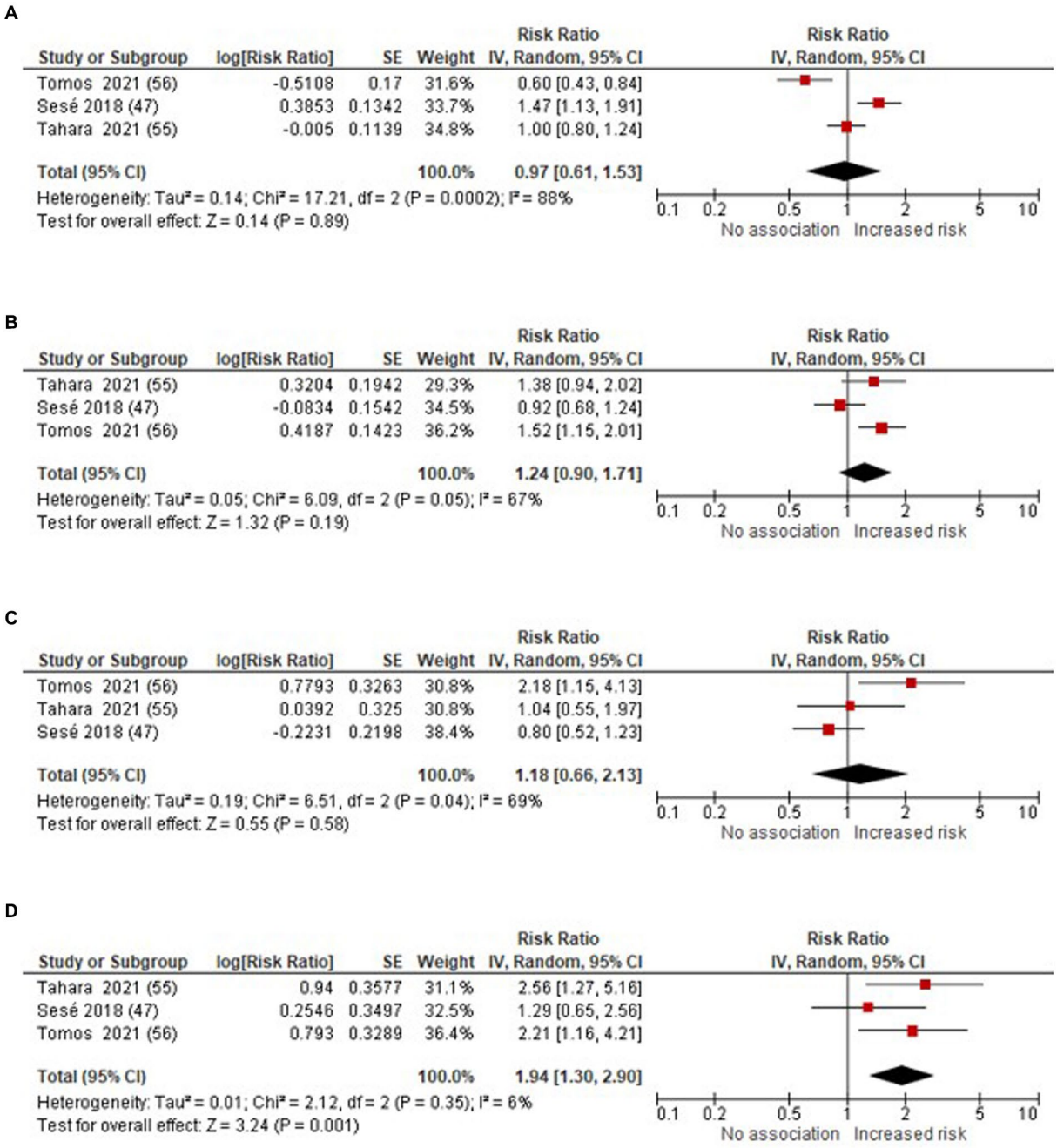

FIGURE 2
Forest plot: air pollutants (per 10 μg/m^3 increase in air pollutants concentrations) and the risk of AE-IPF **(A)** O_3 **(B)** NO_2 **(C)** PM_{10} **(D)** $PM_{2.5}$.

A single study focusing on RA-ILD patients (221 participants) (60), found that per 10 μg/m^3 increase in $PM_{2.5}$, PM_{10}, SO_2, and NO_2 were each significantly associated with increased monthly hospitalisation admissions. The study showed both higher mean and cumulative concentrations of O_3, for every 10 mg/m^3 increase in the 0–2-month lag, displayed an inverse relationship (Excess risk −0.304 to −0.393; and − 3.383 to −0.406) implying that higher levels of O_3 were linked to lower rates of hospitalisations for RA-ILD.

3.4.7 Air pollution and supplemental oxygen requirement

One study (135 patients with IPF) (48) examined the link between air pollution and supplemental oxygen requirement during the 6-min walk test (6MWT) in IPF patients. The findings revealed an association between higher mean level of $PM_{2.5}$ and an increase in oxygen requirement to maintain saturation >=88% during the 6MWT, with each 5 μg/m^3 increase in $PM_{2.5}$ exposure corresponding to a 1.15 (95% CI, 0.03–2.26; $p = 0.044$) increase in O_2 requirement.

3.4.8 Air pollution and development of chronic respiratory failure in IPF

In a study involving 69 individuals with IPF (63), researchers examined the relationship between air pollution and the occurrence of chronic respiratory failure, as defined by baseline arterial blood gases (ABG), measured while they were breathing room air, with a partial pressure of oxygen (PO_2) below 60 mmHg (63). Elevated exposure to CO, NO_2, and NOx were found to be significantly associated with a higher risk of developing chronic respiratory failure. Specifically, for every 0.1 mg/m^3 increase in CO, the OR was 1.62 (1.11–2.36) ($p = 0.01$) over a 3-month period and 1.84 (1.1–3.06) during the 6 months leading up to the event. For each 10 μg/m^3 increase in NO_2 and NO_x: the OR for NO_2 was 1.65 (1.01–2.66) ($p = 0.04$) at 6 month prior to the event. For NOx, the OR was 1.12 (1.01–1.23) ($p = 0.03$) at 3 months and 1.20 (1.03–1.38) ($p = 0.01$) at 6 months of exposure before the event.

3.4.9 Air pollution and questionnaire outcomes in fibrotic sarcoidosis patients

In a study involving 16 participants with fibrotic sarcoidosis (49), correlations between short-term air pollution exposure and health outcomes were evaluated through validated health related QoL questionnaires. With each IQR increase in the 14-day average of $PM_{2.5}$ levels, a decrease in general and lung-specific health status was observed as measured by the King's Sarcoidosis Questionnaire (KSQ) (General: −6.60, 95% CI −12.51 to −0.68,; Lung-specific: −6.91, 95% CI −12.73 to −1.09) The study did not find any association between short-term O_3 exposure and respiratory symptoms or QoL metrics, using the Saint George Respiratory Questionnaire (SGRQ), Leicester cough questionnaire (LCQ), and KSQ.

3.4.10 Air pollution and surrogate markers

DNA methylation (DNAm) can be inherited and influenced by air pollution in adults (67, 68). Aberrant DNAm patterns lead to reduced DNA stability and changes in gene expression and mutations, which can contribute to health problems (67, 68). Goobie et al. examined 1,059 participants from two groups of patients with IPF: 313 from the Simmons cohort and 746 from the PFF cohort (62). They investigated the association between $PM_{2.5}$ (and its constituent components) with global DNAm (%5 mC) in patients with IPF. This study found an association between monthly mean levels of $PM_{2.5}$ and its constituents' exposure and increased level in %5 mC (β = 0.02, 95%CI 0.0003–0.05, $p = 0.047$) over the 3-month period before sampling. The results in the 1-year period before sampling were consistent but did not reach statistical significance in both cohorts (Simmons cohort: β = 0.03, 95%CI −0.004 to 0.06, $p = 0.09$; PFF cohort: $\beta = 0.03$, 95%CI −0.007 to 0.06, $p = 0.12$). Increased levels of sulfate, nitrate, ammonium, and black carbon components were also linked to elevated %5 mC across multiple models.

One study of 118 participants with IPF (56) examined the relationship between prolonged exposure to air pollution and the presence of serum inflammatory markers. The study found that an increase of 10 μg/m^3 in the mean O_3 level from the previous year was positively correlated with the percentage change in IL-4 (an inflammatory mediator) among AE-IPF patients ($p = 0.014$). Conversely, $PM_{2.5}$, PM_{10}, and NO_2 levels showed an inverse association with the percentage changes in IL-4 ($p = 0.003$, $p = 0.003$, $p = 0.032$) and osteopontin ($p = 0.013$, $p = 0.013$, $p = 0.085$) among the same group of patients.

4 Discussion

In this comprehensive systematic review, of the link between air pollution and ILD, including IPF we evaluated 24 studies which met the inclusion criteria. The pollutants under investigation include $PM_{2.5}$, PM_{10}, O_3, NO_2, CO, SO_2, NOx, and NO. All of these pollutants were considered in the assessment of AE-IPF risk. The meta-analyses performed showing a significant association between AE-IPF and $PM_{2.5}$, while the association between O_3, NO_2, PM_{10}, and AE-IPF risk remained uncertain.

4.1 Particulate matter ($PM_{2.5}$ and PM_{10})

Particulate matter, a blend of solid particles and liquid droplets present in the atmosphere, includes $PM_{2.5}$ and PM_{10} (69). $PM_{2.5}$ is characterized as fine inhalable particles, typically measuring 2.5 micrometres or less in diameter, while PM_{10} is described as inhalable particles, generally having diameters of 10 micrometres or less (69). $PM_{2.5}$ arises as a result of sophisticated atmospheric interactions involving combustion and the conversion of gases into particles (70, 71). It originates predominantly from a range of sources, encompassing the combustion of coal, oil, gasoline, diesel, and wood, as well as high-temperature industrial operations including those conducted in smelters and steel mills (71). Additionally, vehicle exhaust emissions and the burning of biomass contribute significantly to the production of $PM_{2.5}$ (71, 72). PM_{10} is produced through the fragmentation of larger solid particles, the presence of biological materials like pollen grains, and the dispersion of wind-blown dust from agricultural areas, soil surfaces, unpaved roads, and dust generated by traffic (70). Additionally, it can originate from non-combustible substances such as fly ash (70).

Particulate matter has the potential to lead to severe health issues. $PM_{2.5}$ has the tendency to settle deep within the respiratory airways, potentially penetrating into the alveoli, in some cases, being absorbed into the bloodstream (69, 70). This makes it particularly challenging to eliminate from the body. PM_{10} comprises particles that are larger in size, yet they are still small enough to penetrate into the lungs (70). Elevated levels of both $PM_{2.5}$ and PM_{10} have been associated with higher rates of all-cause mortality, cardiovascular mortality, respiratory mortality, and mortality due to lung cancer (73).

Most of the included studies in this analysis evaluated $PM_{2.5}$and $PM_{10.}$ It is interesting that both $PM_{2.5}$ and PM_{10} were associated with increased hospital admissions without apparent influence on the progression of IPF. One possible explanation for this finding lies in the temporal dynamics of $PM_{2.5}$ and PM_{10} exposure. $PM_{2.5}$ infiltrates alveoli (69, 70), while PM_{10} deposits in the upper respiratory tract (25), both capable of precipitating acute respiratory exacerbations necessitating hospitalization. However, it appears that these exposures may not have a lasting impact on the lung function decline (FVC%), which serves as an indicator of disease progression in the studies under consideration (47, 64, 66). This is consistent with the findings that there was no significant association between $PM_{2.5}$ (46, 48, 49) or PM_{10} (46, 48, 66) with lung function decline.

4.2 Ozone (O_3)

O_3 can be categorized into two types: beneficial stratospheric ozone and detrimental ground-level O_3 (74). Stratospheric ozone

serves as a shield against the harmful ultraviolet radiation from the sun, protecting living organisms (74). Conversely, ground-level O_3 has been linked to elevated all-cause mortality rates, respiratory mortality, hospital admissions for asthma-related issues, and visits to emergency rooms (73).

Ground-level O_3 is not directly released into the atmosphere; rather, it forms through a complex sequence of reactions involving oxides of nitrogen (NOx) and volatile organic compounds (VOC) when exposed to heat and sunlight (70, 74). VOCs are compounds that characterized by their high vapor pressure, and their primary sources predominantly include emissions from industrial and agricultural activities (25). Additionally, VOCs can stem from sources such as wildfires, vegetation, animals, and vehicles (25). Due to the reaction mechanism with heat and sunlight, O_3 tends to attain elevated, unhealthy levels primarily during hot, sunny days in urban settings (25, 74).

Our findings regarding O_3 are varied. Interestingly, an inverse correlation was found between O_3 concentration and hospitalization incidence in RA-ILD and the development of ILD in patients with CTDs (52). This interesting outcome warrants careful interpretation because the protective influence of O_3 against ILD risk appears to be consistently observed solely in patients with systemic lupus erythematosus (SLE), rather than in those with other CTDs (52). Increased O_3 levels necessitate a reaction mechanism involving heat and sunlight (25, 74). Given that photosensitivity is a well-established exacerbating factor for SLE (75), it implies that individuals with SLE may opt to stay indoors to avoid direct sunlight. This behaviour could potentially explain why heightened levels of O_3 appear to correlate with a reduced risk of ILD among SLE patients, as they may, in fact, experience lower O_3 exposure.

4.3 Nitrogen oxides (NOx), nitric oxide (No) and nitrogen dioxide (NO_2)

NOx encompasses a collection of exceedingly reactive gases, consisting of varying proportions of nitrogen and oxygen, with the most common components being NO_2, NO, and nitrous oxide (N_2O) (76). The primary sources of NOx emissions encompass motor vehicles, electric utilities, and a diverse array of industrial, commercial, and residential activities involving fuel combustion (76).

This review encompassed an exploration of NOx in four distinct studies. Positive correlations were identified for all health outcomes under investigation. Remarkably, the findings indicated significant links between NOx and the occurrence of subclinical ILD (44), heightened mortality rates in individuals with IPF (63), an increased risk of experiencing AE-IPF and AE-IIPs (55), elevated occurrences of IPF (61), higher hospitalization rates among those with IPF (63), and a hastened progression towards chronic respiratory failure in this population (63). Although each health outcome was examined in separate studies, it's noteworthy that NOx consistently showed a positive association with these risks. This recurring pattern strongly suggests that NOx may play a significant role in exacerbating these health issues in ILDs. This finding underscores the importance of further research and attention to the potential health impacts of NOx exposure and calls for comprehensive efforts to mitigate NOx emissions and protect public health.

Within industrial combustion processes, NO predominates, often surpassing NO_2 in both quantity and concentration (76, 77). However, the majority of NO molecules eventually undergo oxidation, transforming into the more toxic NO_2 gas (77). NO is harmful to human health and can result in eye and throat irritation, chest tightness, nausea, headaches, and a gradual decline in physical strength (76). NO was assessed in a single study, which revealed that an increased concentration of NO was significantly linked to an elevated risk of AE-IPF and AE-IIPs (55). Elevated levels of nitric oxide are recognized for their inflammatory characteristics (78), potentially fostering an inflammatory setting that could trigger exacerbation events in interstitial lung diseases. However, it is crucial to note that this finding originates from a solitary study, emphasizing the necessity for further investigations to validate and substantiate these results.

NO_2 is a gas and strong oxidant (70). NO_2, in conjunction with other NOx components, engages in chemical reactions with the previously mentioned VOCs in the air, leading to the formation of O_3 (70, 79). Additionally, NO_2 serves as a crucial precursor to other secondary pollutants, including organic, nitrate, and sulfate particles, which are measured as part of PM_{10} or $PM_{2.5}$ particulate matter (70). NO_2 predominantly enters the atmosphere through the combustion of fuel (79). It arises from the emissions produced by vehicles such as cars, trucks, and buses, as well as from power plants and off-road machinery (79). Elevated levels of NO_2 are associated with increased rates of all-cause mortality, respiratory mortality, hospital admissions related to asthma, and visits to the emergency room (73). It's interesting to note that NO_2, which is a component of NOx, appears to have distinct effects on various health outcomes. Our findings found that NO_2 exhibited a significant positive correlation with an increased incidence of hospitalization in IPF (51, 59, 63) and RA-ILD (60), a heightened risk of AE-IIPs (55), lower lung function (46), and the development of chronic respiratory failure (63). However, no associations were detected between NO_2 and the severity at diagnosis and progression at 24 months of SSc-ILD (65), lung function decline in IPF (46), or the incidence of subclinical ILD/ILAs (44).

4.4 Carbon monoxide (CO)

CO is a toxic gas that is colourless, has no odour or taste (26). It is generated when carbonaceous fuels such as wood, gasoline, coal, natural gas, and kerosene undergo incomplete combustion (26). CO exhibits a greater affinity for binding with haemoglobin, potentially resulting in diminished oxygen transport to vital organs (70). Elevated levels of CO are linked to a rise in hospital admissions and visits to the emergency room attributable to ischemic heart disease (73).

Our review found that CO was positively associated with the development of chronic respiratory failure (63) and had mixed results in terms of its relationship with mortality in IPF (53, 63). The presence of a positive association with the onset of chronic respiratory failure suggests a potential mechanism wherein increased levels of CO in the ambient air may bind to haemoglobin and lead to a decrease in the PO_2 (63).

4.5 Sulfur dioxide (SO_2)

SO_2 is an invisible gas that readily dissolves in water (70). Its primary source arises from the combustion of fossil fuels conducted

by power plants and various industrial activities (70, 80). Smaller contributions to SO_2 emissions come from natural occurrences such as volcanic activity, as well as vehicles, locomotives, ships, and heavy machinery utilizing high-sulfur content fuels (70, 80). Increased SO_2 concentrations have been reported as contributing to heightened rates of all-cause mortality, hospital admissions for asthma-related issues, visits to emergency rooms, and respiratory mortality (73).

This review found a positive link between SO2 and hospitalization in RA-ILD (60). However, for hospitalization incidence in IPF patients, the findings were mixed (51, 59). No significant associations were identified between SO_2 and mortality in IPF (53), the risk of AE-IPF (43, 55), or the risk of AE-IIPs (55). The diversity in these findings may stem from varying geographical locations and levels of exposure. Two studies showing a positive association both reported a higher mean SO_2 concentration than the other four studies, with a mean SO_2 concentration of 28.15 ± 19.08 μg/m3 (60) and 23.6 μg/m3 (51).

4.6 Limitations

In this review we included a substantial number of participants. Nevertheless, it's imperative to acknowledge certain limitations. Firstly, the studies encompassed in this review only spanned 13 countries or regions, which represents a relatively small portion of the global population. Secondly, a limited number of studies examined each specific health outcome, potentially not providing a comprehensive reflection of the true outcomes. It's crucial to be caution when interpreting the meta-analysis results concerning the association between air pollutants and the risk of AE-IPF, primarily due to the significant heterogeneity observed, ranging from 67 to 88% across the studies, except for $PM_{2.5}$(6%). Additionally, we acknowledge that potential confounding factors such as temperature, humidity, seasons, and occupational environments can impact the results. Socioeconomic status can also play a significant role in ILD incidence and outcomes. IPF patients with lower economic status experienced poorer survival outcomes, despite adjusting for occupational exposure and geographical origin (81).

Another significant constraint is that the various studies opted for different outcome measures, making it impossible to conduct a meta-analysis encompassing all the desired outcomes. Moreover, a notable limitation stems from the substantial variation in population sizes observed across studies, spanning from 16 participants to 10 million. Lastly, our study was not pre-registered with PROSPERO.

5 Conclusion

This comprehensive review highlights the need for further research efforts to gain a deeper understanding of the complex relationship between air pollution and ILDs. Future investigations should endeavour to incorporate real-time data collection methodologies, encompassing factors including the duration spent indoors and in traffic, which could provide valuable insights into individual exposure patterns. Additionally, there is a need for the standardization of the parameters being measured across various studies, ensuring consistency and comparability of findings. Moreover, employing multi-pollutant models in future research would be beneficial in resolving the complex interaction of various pollutants in affecting ILD outcomes.

The available data hints at the likely benefit for public health intervention. Specifically, there is compelling evidence to suggest that reducing levels of $PM_{2.5}$ in the atmosphere could potentially lead to a reduction in the frequency and severity of acute exacerbations (AE) in individuals with ILDs. This finding bares significance, as AE in ILD patients has been consistently linked to high mortality rates, frequent hospitalizations, and elevated healthcare costs (82). The potential benefits from the interventions could not only improve individual health outcomes but also alleviate the burden on healthcare systems and resources.

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.

Author contributions

DL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft. CF: Supervision, Validation, Writing – review & editing. LT: Supervision, Writing – review & editing. LK: Conceptualization, Supervision, Writing – review & editing. TC: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

TC reports fees for work on scientific advisory boards for Boehringer Ingelheim, Roche, Bristol Myers Squibb, Vicore, and DevPro, grants from Boehringer Ingelheim, Roche, and Bristol Myers Squibb, Galapagos, Biogen, outside the submitted work. LT reports speaker's fees for Boehringer Ingelheim, outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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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.2023.1321038/full#supplementary-material

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