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Progressive fibrosing interstitial lung disease: From bench to bedside

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Progressive fibrosing interstitial lung disease: From bench to bedside

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Editorial: Progressive fibrosing interstitial lung disease: from bench to bedside

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Editorial on the Research Topic
Progressive fibrosing interstitial lung disease: from bench to bedside

Introduction

Pulmonary fibrosis is a debilitating and potentially progressive lung disease characterized by the excessive accumulation of fibrotic tissue within the lung parenchyma, leading to impaired gas exchange and respiratory failure. Despite significant advances in our understanding of the pathogenesis and management of pulmonary fibrosis, the disease remains a therapeutic challenge. To date, the gold standard for the diagnosis of progressive pulmonary fibrosis (PPF) is a holistic evaluation through multimodal assessment including the analysis of clinical symptoms, pulmonary function test (PFT), histopathological evaluation and high-resolution computed tomography (HRCT) of the chest (1).

This editorial aims to shed light on the current state of research and clinical approaches in the field of PPF, emphasizing the need of early biomarkers helping clinicians to identify PPF at the earliest stage and also new potential therapeutic targets aiming to stop the uncontrolled fibrotic process. This Research Topic currently includes 15 original research articles on the diagnosis/prognosis of PPF, based on the identification of news biomarkers, multi-scale analysis of clinical informations and parameters, which results on the development of prediction models. These research articles are from interdisciplinary collaboration (clinicians, researchers and industry partners) and emerging technologies. All contributions to this Research Topic focus on one or more of the research areas highlighted above.

Clinical management

Despite the recent progress in understanding the molecular mechanisms of pulmonary fibrosis, the clinical management of patients with progressive disease remains a complex challenge. Indeed, as stated in the recent guidelines (2), clinicians have to wait the reduction of PFT and/or a PPF based on imaging analysis. ATS/ERS recommendations state that diagnostic criteria for PPF are a combination of two criteria including: worsening symptoms over time, HRCT-proven fibrotic progression and/or an absolute decline from baseline in FVC ($\geq$5%) or DLCO ($\geq$10%) over 1 year of follow-up.

In a review article, Stanel and Rivera-Ortega have discussed about the perspectives in early diagnosis and monitoring for progressive fibrosing interstitial lung diseases (PF-ILD). In a retrospective study, Chiu et al. have examined the prognostic relevance of PPF definitions, and shown that it did not differ between simplified PPF, INBUILD and ATS/ERS/JRS/ALAT 2022 criteria. A recent study by Takei et al. highlights the need to consider an evaluation of health-related quality of life when assessing PPF in patients with idiopathic pulmonary fibrosis.

Currently available therapies, such as antifibrotic drugs, primarily target the fibrotic process but have limited efficacy in preventing early disease progression. As a result, a comprehensive and personalized approach to patient care is required. Clinical trials evaluating combination therapies, precision medicine approaches, and novel drug delivery systems hold promise for improving patient outcomes and quality of life (Wu et al.).

Emerging technologies and biomarkers

The advent of advanced technologies has revolutionized the field of pulmonary fibrosis research. High-throughput genomics, proteomics, and metabolomics have allowed researchers to identify novel biomarkers associated with disease progression and prognosis. These biomarkers not only aid in early diagnosis but also serve as valuable tools for monitoring treatment response and predicting outcomes. Additionally, innovative imaging techniques, such as HRCT and functional lung imaging, contribute to a more precise assessment of disease severity and progression (3).

With this topic, several studies have developed predictive/prognostic model for PF-ILD based on machine learning algorithms by combining clinical informations (Shao et al.; Lee et al.; Zhang et al.; Niu et al.).

Translational research

Translational research acts as the critical link between bench research and clinical practice, facilitating the transition of promising experimental findings into real-world applications. In the context of PPF, translational studies have demonstrated the efficacy of several novel therapeutic interventions in preclinical models (4). From anti-fibrotic drugs to gene and cell-based therapies, these advancements offer hope for the development of effective treatments that can halt or even reverse disease progression.

Abbreviations: EMT, epithelial-mesenchymal transition; HRCT, high-resolution computed tomography; F-ILD, fibrosing interstitial lung diseases; PF-ILD, progressive fibrosing interstitial lung diseases; PFT, pulmonary function test; PPF, progressive pulmonary fibrosis.

Bridging the gap between bench and bedside

The journey from bench to bedside is essential in translating scientific discoveries into effective clinical interventions. Bench research plays a pivotal role in unraveling the underlying molecular mechanisms driving PPF. Investigating key cellular pathways, such as epithelial-mesenchymal transition (EMT), myofibroblast activation, and dysregulated immune responses, has contributed significantly to our understanding of disease pathogenesis (5–7). Fundamental discoveries led to the identification of potential therapeutic targets, paving the way for novel treatment strategies.

Collaboration and data sharing

To accelerate progress in the field of PPF, collaboration and data sharing among researchers, clinicians, and industry partners are of paramount importance. Sharing research findings, clinical data, and biological samples through established networks and databases can foster synergistic efforts and enable more comprehensive analyses (Tomassetti et al.; Quan et al.). Moreover, collaborative efforts facilitate the validation of preclinical research findings in diverse patient populations, ultimately leading to more robust and reliable clinical recommendations.

Importance of patient advocacy and support

Lastly, it is crucial to acknowledge the invaluable role of patient advocacy groups and support networks in raising awareness about PPF. These organizations provide a platform for patients, caregivers, and researchers to collaborate, share experiences, and advocate for improved access to care, research funding, and better overall understanding of the disease. By amplifying patient voices and perspectives, we can drive meaningful change in the field and ensure that scientific advancements are translated into tangible benefits for those affected by the disease.

Conclusion

The journey from bench to bedside in the realm of PPF research holds immense potential for advancing our understanding and treatment of this debilitating disease of high unmet medical need. Through the integration of bench discoveries, translational research, and innovative clinical approaches, we can bridge the gap between scientific knowledge and patient care. By fostering collaboration, embracing emerging technologies, and prioritizing patient advocacy, we can work toward a future where PPF is no longer an insurmountable challenge, but a conquerable condition.

Author contributions

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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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ORIGINAL RESEARCH
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Risk Factors of Silicosis Progression: A Retrospective Cohort Study in China

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Background: Silicosis poses a threat to workers' health due to the irreversible lung lesions.

Design: A retrospective cohort study.

Methods: A total of 259 patients [80 worked with artificial stone (AS), 179 with non-artificial stone (non-AS)] with confirmed silicosis were included in this study. Forty-one of AS and 91 of non-AS had approximately 2 years' follow-up records [lung function tests and high-resolution computer tomography (HRCT)]. Compared with the first records, increased, densified, or newly emerging lesions in lung HRCT images were judged as progression of the disease. Cox proportional hazards models were used to determine the risk factors. Kaplan–Meier survival curve and log-rank test were used to compare prognostic factors for cumulative risk of progression.

Results: In 132 patients with median follow-up of 24.0 months (IQR, 13.8, 24.9), 66 patients showed progression, in them, 36 (87.8%) were from AS group and 30 (32.9%) from non-AS group. Working experience of AS processing (hazard ratio, 5.671; 95% CI, 3.048–10.550) and complicated silicosis in CT images (hazard ratio, 2.373; 95% CI, 1.379–4.082) were the main risk factors associated with progression. Forced vital capacity decreased after 1-year (241.5 vs. 55.2 mL) and 2-year (328.1 vs. 68.8 mL) follow-up in the two groups (AS vs. non-AS). History of anti-tuberculosis medication, chest oppression and pain, ground-glass opacity, pleural abnormalities, and restrictive pulmonary dysfunction were more frequently found on HRCT images in the AS group than non-AS group. Lung functions (DL_{CO}, %) were lower in the current/former smokers than the non-smokers ($P < 0.05$) in AS patients.

Conclusion: Prevention and protection rules are needed to be enforced in the occupation involving AS processing; smoking may be associated with declined lung function in AS patients.

Keywords: artificial stone, complicated silicosis, HRCT, lung function, progression

INTRODUCTION

Silicosis caused by inhalable respirable crystalline silica, is a worldwide occupational lung disease (1); the progression of pulmonary lesions accompanied with cough, expectoration, chest oppression, and shortness of breath, leading to lethal fibrosis (2). Silicosis is widely prevalent in those who working in mining, quarrying, cutting, and polishing (3); it kills more than 10,000 people every year in the world (4), mainly in developing countries (5). According to a report based on data from Global Burden of Disease Study 2017 (6), the overall age-standardized incidence rate of silicosis decreased by an average of 0.8% per year in 1990–2017 globally.

However, in recent years, silicosis has become an issue of concern, due to the processing of artificial stone (AS). AS materials have a higher silica content (>90%) when compared with natural alternatives (2–30%) (7). It has been found that the time of occupational exposure in AS-associated silicosis cases was less, but progression of the disease was faster than classical silicosis (8, 9).

Up to now, there is no report on risk factors for the cumulative progression in silicosis. Previous studies have shown that high-resolution computer tomography (HRCT) has higher sensitivity in detecting pulmonary nodular changes [including progressive massive fibrosis (PMF), pulmonary bullae, emphysema, and changes in pleura and mediastinal hilum] (10–13). In this study, we collected medical information of patients and focused on the cases with around 2-year follow-up records of HRCT and respiratory function tests. We combined HRCT data with indices of lung function for evaluating progress of the disease (14). This is the first report to compare the cumulative progression rate between patients with artificial stone-associated silicosis and non-artificial stone-associated silicosis.

MATERIALS AND METHODS

Study Population and Procedures

From April 2011 to April 2021, a total of 432 male native Chinese with silicosis who visited the Pneumoconiosis Department of Shanghai Pulmonary Hospital were included in the retrospective cohort study. All the patients left the previous dust environment after being diagnosed as silicosis. We collected all the electronic medical records of the patients and set up a database, which included information such as age at diagnosis of silicosis, age at first dust exposure, years of dust exposure, time from dust exposure to illness, smoking status, respiratory symptoms, indices for respiratory function, and HRCT radiographs of the chest.

Exclusion criteria were: (1) cases with active pulmonary tuberculosis, non-tuberculous mycobacteria (NTM) infection, lung tumor, respiratory infection, pneumothorax, pleural effusion, asthma, and bronchiectasis at the time of first visit; (2) patients without lung function and chest HRCT tests; (3) patients without the information of dust exposure; (4) patients who reject taking part in this study.

After exclusion, 259 patients were left, in which 132 patients were with HRCT records in about 2-year follow-up periods (**Figure 1**).

Respiratory Function and High-Resolution Computer Tomography Tests

Respiratory function tests were performed according to the ATS/ERS recommendations and measured with a clinical spirometer (Jaeger Crop., Höchberg, Germany) by specialists from the department of the pulmonary function in Shanghai Pulmonary Hospital (15–17). The main ventilatory pulmonary function indicators (18, 19) including forced vital capacity (FVC, %), forced expiratory volume in 1 s (FEV_1, %), FEV_1/FVC ratio, and diffusing capacity of the lung for carbon monoxide (DL_{CO}, %) were analyzed. Meanwhile, according to the prediction model of Wells et al. (20), we calculated the compound physiological index (CPI). The calculation formula is as follows: CPI = 91.0 – (0.65 × DL_{CO}, %) – (0.53 × FVC, %) + (0.34 × FEV_1, %).

All patients underwent HRCT and respiratory function tests upon admission. According to the size of the mass in the HRCT image, patients were divided into simple silicosis group and complicated silicosis group. Complicated silicosis is defined by the presence of nodules measuring 1 cm or more (10, 11, 21, 22). The increase and densification of lesions, or newly emerging lesions, are defined as progression (12), and stability is defined as no significant change of HRCT manifestations at least 22 months. The diagnosis of patients was made by two qualified physicians from the pneumoconiosis department and HRCT images were read by two experienced doctors from radiology department. According to the comparison results, patients were then grouped into the stable group (stable in 22.1–32.6 follow-up months) and progressive group (progress in 1.1–35.9 follow-up months).

Statistical Analysis

Cox proportional hazards models were used to determine the risk factors for progressing of disease according to HRCT imaging. The Kaplan–Meier survival curve and log-rank test were used to compare prognostic factors with a cumulative risk of progression over time. The epidemiological and clinical variables between the two groups are expressed as Means ± standard deviation (SD), Median (interquartile range, IQR), and percent of individuals. The Student's *t*-test, Mann–Whitney *U*-test, Chi-square test, or Fisher's exact test were used to evaluate differences between the two groups, as appropriate. All data analyses were conducted using SPSS version 25.0 (IBM SPSS, Chicago, IL, United States) with the prominence level set to 5%.

RESULTS

Comparison of Baseline Characteristics of Silicosis Patients

The total of 259 patients were divided into AS group (80 patients) and non-AS group (179 patients) according to their working history with artificial stone. We first compared the

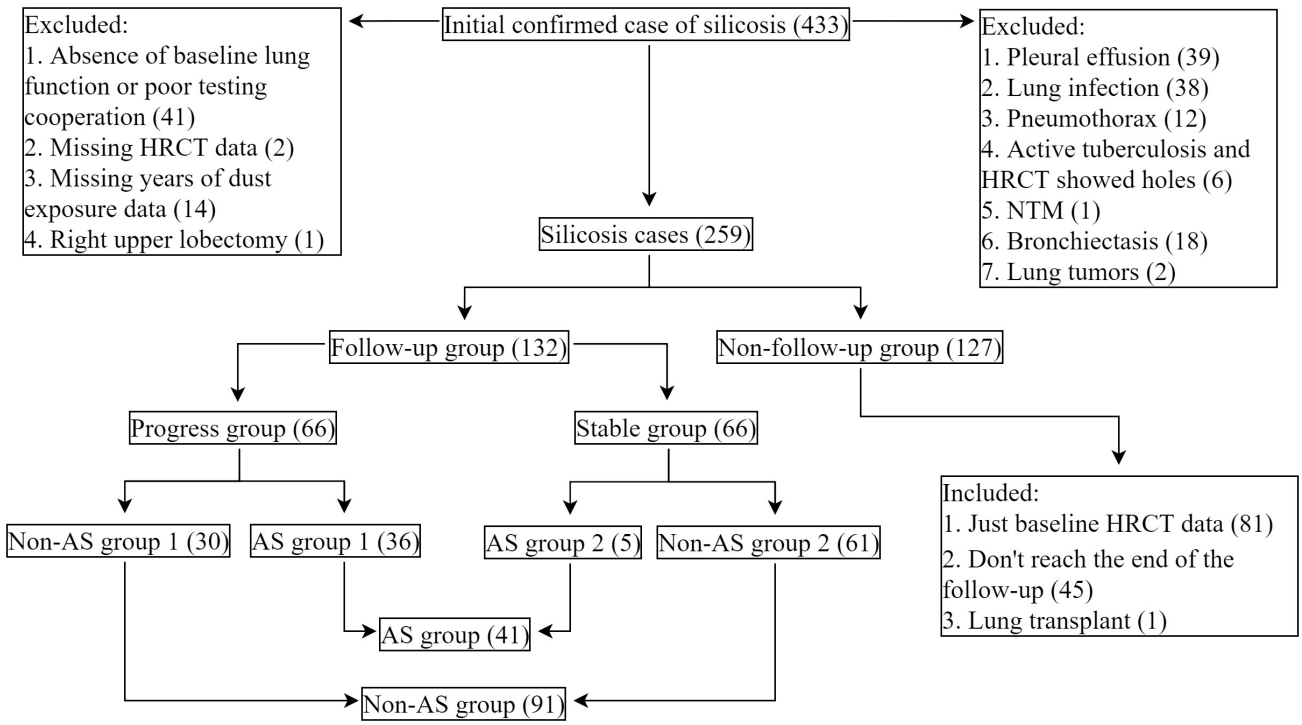

FIGURE 1 | Study flowchart. Cases of silicosis in Shanghai Pulmonary Hospital, Shanghai, China (2011.04–2021.04). AS-associated silicosis group is referred to as AS group; non-AS-associated silicosis group is referred to as non-AS group.

baseline data between the AS and the non-AS, the latter one included 66 patients with working history of quarrying, 15 patients with coal mining, 28 cases with sand blasting, 13 cases with granite fabrication, 21 cases with refractory, 9 cases with tunneling, 15 cases with metal mining, and 12 cases with other types of work.

The median age at diagnosis of silicosis in AS group [35.5 years (IQR, 29.9, 46.4)] is younger than non-AS group [51.4 years (IQR, 45.5, 58.9)] and with less time of dust exposure [7.0 years (IQR, 5.0, 8.0) vs. 18.00 years (IQR, 10.0, 27.0)]. The shortest time of dust exposure among all patients was only 1.5 years (in the AS group) and the longest was 43 years (in the non-AS group) (all $P < 0.05$) (**Table 1**).

The age of first dust exposure in the AS group was older than that in the non-AS group. The ratio of patients with a history of anti-tuberculosis treatment in the AS group (11.2%) was higher than those in the non-AS group (4.4%). The median time from the dust exposure to diagnose as silicosis in the AS group was 7.0 years (IQR, 4.9, 9.5), significantly shorter than 25.3 years (IQR, 17.6, 35.2) in the non-AS group (all $P < 0.05$) (**Table 1**).

As sandblasting is also associated with severe silicosis and accelerated progress of the disease (23, 24), we also compared the characteristics of the 28 sand-blasting workers with 151 other workers in the non-AS group (non-AS group 3), and with those of AS patients. As shown in **Supplementary Tables 1, 2**, patients with history of sand-blasting were at the similar ages at diagnosis of silicosis with the other patients in non-AS groups. The years of dust exposure and time from dust exposure to illness in the sand-blasting patients were between those of AS group ($P < 0.05$) and of non-AS group ($P < 0.05$).

In the 259 patients, 13.8% (27.7% in the AS group and 7.1% in the non-AS group) patients only had mass shadows in lung on HRCT images in previous physical examination without clinical symptoms. There were more patients with cough and expectoration, chest oppression and pain, ground-glass opacity, and pleural abnormalities in the AS group than in the non-AS group (all $P < 0.05$), no significant difference were found between the groups on ratios of mass shadow and mediastinal and hilar lymphadenopathy (**Table 1**).

Lung Function in Patients at Baseline

In the AS group, the baseline average values of FVC (%) and FEV_1 (%) of patients were decreased (the normal values of the two indices are >80.0%), while the average of FVC (%), FEV_1 (%), FEV_1/FVC, and DL_{CO} (%) were all within the normal ranges in the non-AS group (**Figure 2**). Restrictive pulmonary dysfunction (FVC, % <80.0%) were observed in 57.5 and 24.5% of the two groups, respectively ($P < 0.001$), while obstructive pulmonary dysfunction (FEV_1/FVC < 70.0%) occurred in 10.0 and 32.0% of patients ($P < 0.001$), and diffusion dysfunction (DL_{CO}, % <80.0%) occurred in 35.1 and 24.0% of patients ($P = 0.078$). Also, there is a significant difference with FEV_1 in the two groups ($P < 0.05$).

The CPI score calculated by respiratory function tests in the AS group at initial evaluation were higher than those in the non-AS group (**Table 2**).

TABLE 1 | Demographic characteristics and HRCT features of AS group versus non-AS group.

Characteristics	AS group (*n* = 80)	Non-AS group (*n* = 179)	*P*-value
Demographic characteristics[a]			
Age at diagnosis of silicosis, years	35.5 (29.9, 46.4)	51.4 (45.5, 58.9)	**<0.001**
Age at onset of dust exposure, years	28.0 (22.0, 37.5)	23.0 (17.0, 23.0)	**<0.001**
Years of dust exposure, years	7.0 (5.0, 8.0)	18.0 (10.0, 27.0)	**<0.001**
Time from dust exposure to illness, years	7.0 (4.9, 9.5)	25.3 (17.6, 35.2)	**<0.001**
Current/former smoker, n (%)[b]	32 (40.0)	64 (35.8)	0.513
History of anti-tuberculosis treatment, n (%)[b,c]	9 (11.2)	8 (4.4)	**0.042**
Complicated silicosis, n (%)[b]	26 (32.5)	51 (28.5)	0.514
HRCT features[a]			
Appears with clinical symptoms, n (%)	60 (72.3)	155 (92.9)	**<0.001**
Cough and expectoration, n (%)	40 (50.0)	141 (78.8)	**<0.001**
Chest oppression and pain, n (%)	43 (53.7)	69 (38.5)	**0.023**
Mass shadow, n (%)	31 (38.8)	55 (30.8)	0.205
Pleural abnormalities, n (%)	34 (42.5)	43 (24.0)	**0.003**
GGO, n (%)	21 (26.3)	7 (3.9)	**<0.001**
Mediastinal and hilar lymphadenopathy, n (%)	55 (68.8)	126 (70.4)	0.790

[a]P-value from Mann–Whitney U-test, data are presented as median (IQR) unless otherwise indicated. [b]P-value from Chi-square test, data are presented as percent of individuals. [c]Patient received preventive anti-tuberculosis treatment 2 years before the first admission. GGO, ground-glass opacity. Significant p-values (P < 0.05) are provided in bold.

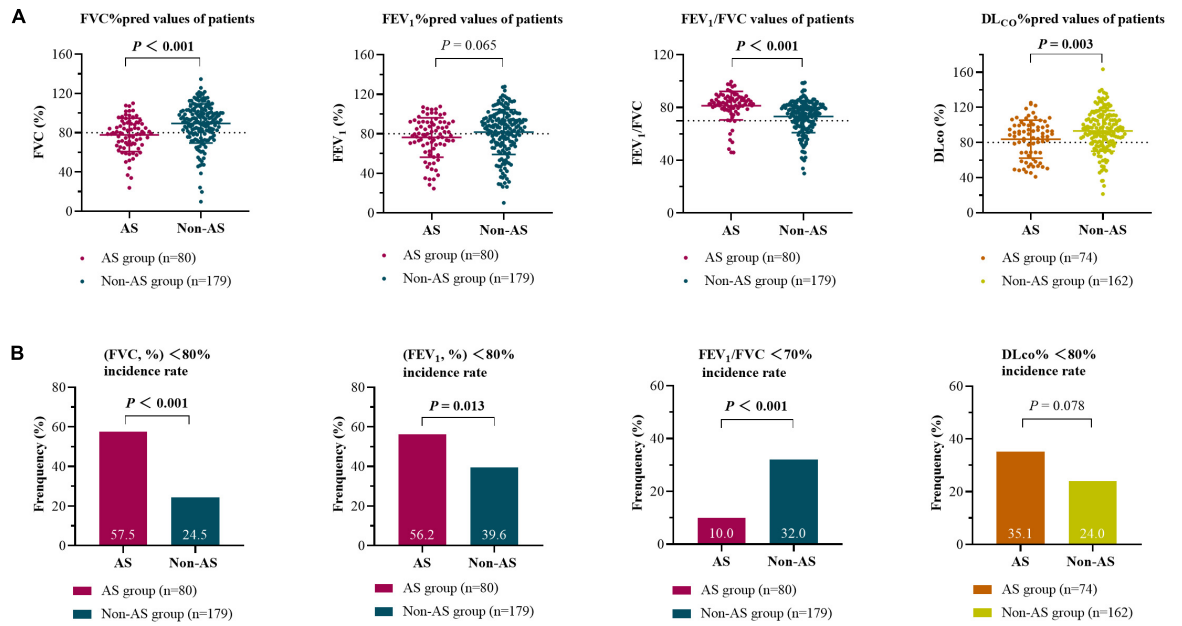

FIGURE 2 | Baseline lung function (measured/predicted) for silicosis with AS group and non-AS group **(A)** and the incidence of pulmonary dysfunction in the two groups **(B)** at the first registration. The area above the dotted line represent the normal ranges of the indices. The differences between groups were analyzed by Student's *t*-tests **(A)** and Chi-square tests **(B)**. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; DL_{CO}, diffusing capacity of the lung for carbon monoxide.

The current or former smokers had statistically lower values of DL_{CO} (%) (P = 0.022) or tendency of lower FEV_1 values (P = 0.053) in AS group but not in non-AS group (**Table 2**).

Lung Function in Patients at 0-to-1-Year and 0-to-2-Year Follow-Up

We collected and compared the data of respiratory function tests from patients of AS group and non-AS group with complete records during 0-to-1-year (AS, n = 13, non-AS, n = 25) and 0-to-2-year (AS, n = 10, non-AS, n = 26) follow-up. The results showed that the average FVC, FEV_1, and DL_{CO} in the AS group were all significantly decreased at either 1 year (**Figures 3A,C,E**) or 2 years (**Figures 3B,D,F**) compared with the baseline records; while only average FEV_1/FVC in the non-AS group showed a significant decrease in both 1- and 2- years follow-up tests (data not shown). The lung function indices shown as percentages of the predicted values had similar changes in the two groups as the changes of the actual values (**Supplementary Figures 1A–F**).

TABLE 2 | Baseline lung function characteristics with AS group versus non-AS group.

Variable	AS group (n = 80)			Non-AS group (n = 179)			P-value[b]
	Total (n = 80)	Current/former smoker (n = 32)	Non-smoker (n = 48)	Total (n = 179)	Current/former smoker (n = 64)	Non-smoker (n = 115)	
FVC, %	77.7 ± 17.0	74.3 ± 17.2	80.0 ± 16.6	89.4 ± 19.8	88.2 ± 21.2	90.0 ± 19.1	**<0.001**
FEV_1, %	76.3 ± 20.0	**70.9 ± 20.4**	**79.7 ± 19.0[c]**	81.7 ± 22.7	80.2 ± 23.2	82.5 ± 22.4	0.065
FEV_1/FVC, %	81.4 ± 10.8	78.9 ± 10.9	82.9 ± 10.5	73.1 ± 12.2	72.2 ± 12.2	73.5 ± 12.2	**<0.001**
DL_{CO}, %[a]	83.7 ± 21.6	**76.8 ± 21.9**	**88.4 ± 20.3[d]**	93.2 ± 23.1	91.3 ± 23.2	94.3 ± 23.2	**0.003**
CPI scores	21.1 ± 16.2			10.3 ± 16.3			**<0.001**

[a]Data from 74 patients in AS group (current/former smoker n = 30, non-smoker n = 44) and 162 patients in non-AS group (current/former smoker, n = 59, non-smoker, n = 103). [b]P-value from Paired Student's t-test between data from total patients of AS groups and non-AS group, data are presented as mean ± SD. [c]P = 0.053, [d]P = 0.022 compared between current/former smoker and non-smoker. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; DL_{CO}, diffusing capacity of the lung for carbon monoxide; CPI, composite physiological index. Significant p-values (P < 0.05) are provided in bold.

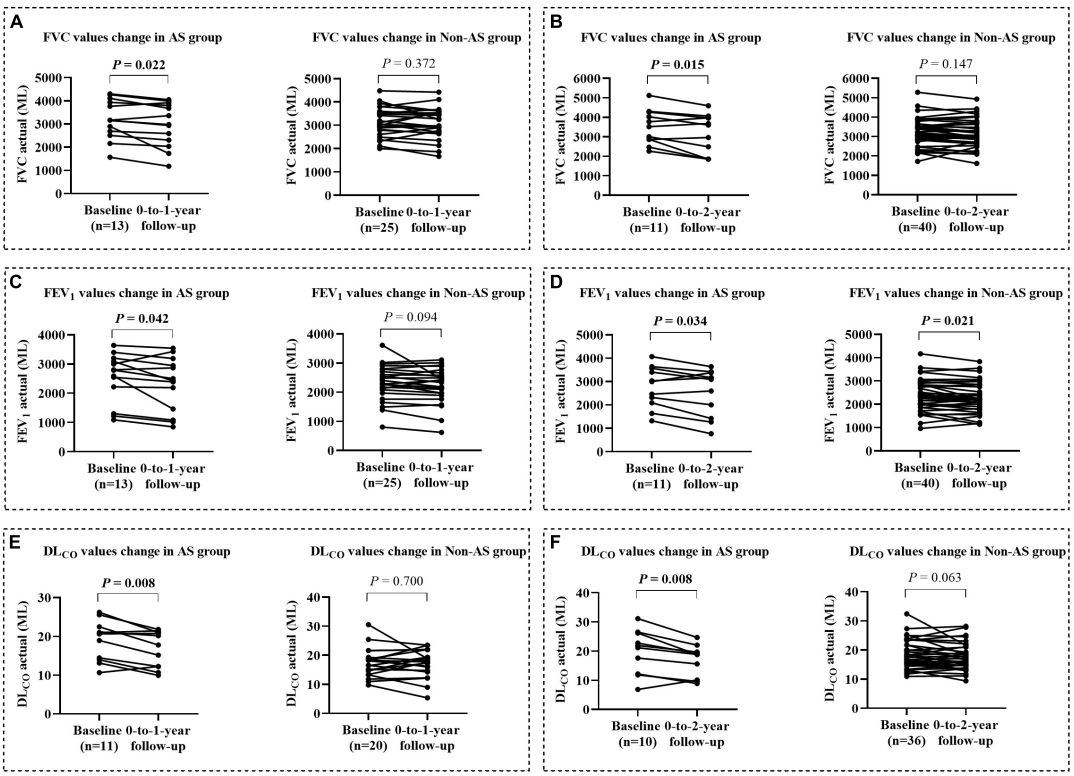

FIGURE 3 | The changes of lung function from baseline to the values at 0-to-1-year and 0-to-2-year followed up in AS and non-AS groups. Changes of FVC, FEV_1, and DL_{CO} (mL) from baseline to the values after 1 **(A,C,E)** and 2 years **(B,D,F)** follow-up. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; DL_{CO}, diffusing capacity of the lung for carbon monoxide.

Risk Factors in the Progression of Silicosis

The progression was used as follow-up endpoint in the analysis of follow-up records from 132 patients with median follow-up time of 24.0 months (IQR, 13.8, 24.9). During the follow-up, progression occurred in 66 patients (50.0%).

The association between the progression with working experience of AS processing, complicated silicosis in CT images, years of dust exposure, baseline FVC (%), age at diagnosis of silicosis, and smoking status were analyzed by Multivariate Cox proportional hazards models. The results adjusted by working experience of AS processing and/or age at diagnosis of silicosis showed that patients with working experience of AS processing (hazard ratio, 5.671; 95% CI, 3.048–10.550) and with complicated silicosis (hazard ratio, 2.373; 95% CI, 1.379–4.082) had significantly higher risks of progression during the follow-up periods (all $P < 0.01$) (**Table 3** and **Figure 4**).

Comparison of Disease Progression Rates in Silicosis Patients

The 132 patients were also sub-grouped into AS group (41 patients) and non-AS group (91 patients) according to their working experience of AS processing. During the follow-up, the

TABLE 3 | Factors associated with silicosis progress in multivariate Cox proportional hazards model[a].

	Unadjusted			Adjusted[c]		
	HR	**95% *CI***	***P*-value**	**HR**	**95% *CI***	***P*-value**
Working experience of AS processing (yes)	4.422	2.688–7.274	**<0.001**	5.671	3.048–10.550	**<0.001**
Complicated silicosis	1.786	1.057–3.017	**0.030**	2.373	1.379–4.082	**0.002**
Age at diagnosis of silicosis	0.977	0.957–0.997	**0.023**	1.016	0.993–1.039	0.184
Baseline FVC (%)	0.998	0.997–0.999	**0.038**	0.996	0.982–1.009	0.519
Smoking status (current/former)[b]	1.243	0.740–2.090	0.411	1.221	0.725–2.059	0.453

[a]The risk factors in the Multivariate Cox proportional hazards models were determined based on clinical experience and the studies of Leon-Jimenez et al. (31). [b]Patients who had quitted smoking 1–10 years before the first registration were in former smokers, and those who had quitted for more than 10 years were in never smokers. [c]Estimations were adjusted by working experience of AS processing and/or age at diagnosis of silicosis. AS, artificial stone; FVC, forced vital capacity; HR, hazard ratio; SE, standard error; CI, confidence interval. Significant p-values (P < 0.05) are provided in bold.

disease progression rates of patients in the AS group and the non-AS group were 87.8% (36/41) and 32.9% (30/91), respectively (**Figure 5**). Among them, 26.6% (8/30) of patients with simple silicosis in the AS group developed PMF, while none developed PMF (0.0%) in the non-AS group.

The Kaplan–Meier survival curve and log-rank test based on the results of Cox proportional hazards models were used to compare the difference of stability probability (1-progress probability) between the AS group and the non-AS group. The median time of stability in the AS group was 14.4 months (IQR, 11.3, 17.5), which was less than 29.3 months (IQR, 24.1, 34.4) in the non-AS group (log-rank, 40.57; $P < 0.001$) (**Figure 5**).

When patients with or without working experience of AS processing were further stratified as subgroups of simple and complicated silicosis, respectively, a significant difference in time of stability between the subgroups (simple silicosis vs. complicated silicosis) was found only in the patients with AS processing history ($P < 0.001$, **Figure 5**).

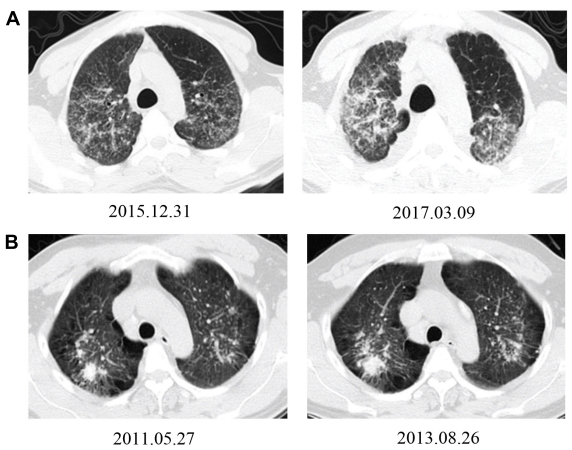

FIGURE 4 | Typical HRCT images show progression from patients working with AS and non-AS. **(A)** A 36-year-old man had been working in AS cutting and home installing for 6 years. The HRCT image from the first registration (upper-left) and rapid progression after 15 months follow-up, with an increase of small nodules in both lung lobes; some of them connected into pieces, with pleural adhesions (upper-right). **(B)** A 40-year-old man had been working in metal mining for 7 years. The HRCT images from the first registration (lower-left) and slow radiological progression after 27 months follow-up period with an slightly enlargement in the upper right lung mass, increment in emphysema and bullae, enlargement and calcification in mediastinal lymph nodes (lower-right).

DISCUSSION

According to the data from the global report (25), the incidence counts of silicosis patients in 2017 was 23,700. However, reported patients are only the tip of the iceberg, particularly in developing countries (21). In recent years, an increasing number of silicosis patients among workers exposed to high amounts of dust (more than 90% of crystalline silica) caused by processing kitchen and bathroom countertops has been found (26–29). The prevalence AS-associated fast-forward silicosis has drawn special attention (30).

It is the first report about the comparison of the cumulative risk of progression between patients with silicosis with two different occupational exposure environments. In this study, we found that the patients in AS group had significantly higher risks of disease progression than patients in the non-AS group after adjusting by common/previous reported progression risk factors (31). We showed that a significant difference in the progression rate between simple and complicated silicosis was found only in the AS group.

During the follow-up times, our results show that working experience of AS processing was the main risk factor for patients in the progression of silicosis, which increased 5.671 folds of risk of progression with a shorter median time of stability in AS patients than in non-AS processing (14.4 months vs. 29.3 months). In a larger cohort study of the miners, patients with PMF increased 9.4% in a 22-year follow-up after dust exposure (32). Recently, Leon-Jimenez et al. (31) from Spain observed 106 newly diagnosed patients with artificial stone-associated silicosis had PMF increased 31.1% after a mean 4-year follow-up. Our study furthered to find that, the ratio of patients with simple silicosis developed PMF increased 26.6% in the AS group, while no patients developed PMF in non-AS group in the follow-up. Consistently, the progress probability in AS group of patients was significantly higher than that in the non-AS group (87.8 vs. 32.9%).

Meanwhile, the AS-associated silicosis is with a sharp decline in lung function. A study from Spain (31) showed a decrease

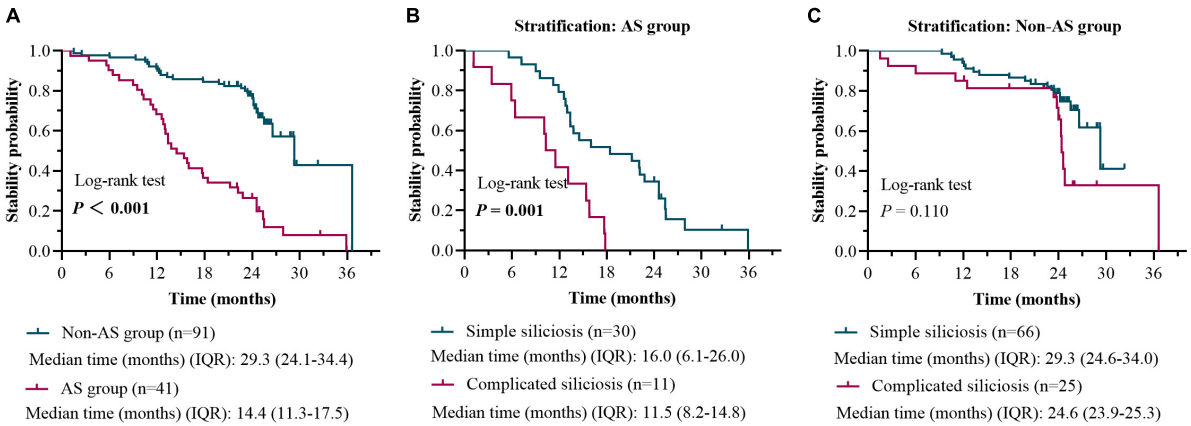

FIGURE 5 | HRCT stability rate in patients with the AS group versus the non-AS group during 0-to-2-year follow-up **(A)**. HRCT stability rate in patients with simple silicosis versus the complicated silicosis in the AS group during 0-to-2-year follow-up **(B)**. HRCT stability rate in patients with simple silicosis versus the complicated silicosis in the non-AS group during 0-to-2-year follow-up **(C)**.

in average FVC of 86.8 mL per year in 106 patients with AS-associated silicosis. Our results showed that after 1-year and 2-year follow-up, average FVC values of patients in the AS group decreased more than those in the non-AS group (241.5 vs. 55.2 mL, 328.1 vs. 68.8 mL). At baseline, lung function in the AS group was also worse than that in the non-AS group (FVC, %: 77.7 ± 17.0 vs. 89.4 ± 19.8; DL_{CO}, %: 83.7 ± 21.6 vs. 93.2 ± 23.1). In addition, 57.5% of patients in the AS group with restrictive pulmonary dysfunction, which was similar to the previous report about the most common type of lung function impairment in patients with AS- associated silicosis (33). CPI is commonly used to evaluate the severity of idiopathic pulmonary fibrosis (IPF) disease (20). A higher CPI score in AS group than in non-AS group also indicated that the patients in the AS group had a more serious impairment in lung function on the whole.

The median age at diagnosis of silicosis in the AS group was 35.5 years (IQR, 29.9–46.4), significantly younger than that in the non-AS group. The workers with working experience of AS processing at a younger age have been reported by Hoy et al. (average age 36 years) in Australia and other studies (26, 27). Several studies have reported on time of dust exposure in silicosis patients. Qiao Ye's team from China (34) reported an average dust exposure time of 6.1 years in 18 patients with AS-associated silicosis. A study conducted in metal mines and pottery factories in China found that the average time of dust exposure in 2,857 silicosis patients was 18.4 years (35). Similar to previous reports, the time of dust exposure of patients in the AS group in our study was 7.0 years (IQR, 5.0–8.0), which was significantly shorter than 18.0 years (IQR, 10.0–27.0) in the non-AS group (36), and the shortest exposure time was only 1.5 years.

In our previous investigation of processing sites for patients with AS-associated silicosis (37), α-quartz content in dust in the air of 5 processing workshops and installation sites were 70–99%, with mass concentrations of (127.6 ± 17.3) mg/m^3, respectively. It is 255 times higher than the permissible concentration-time weighted average (PC-TWA, <0.5 mg/m^3) in China. As the patient with AS-associated silicosis is relatively younger and has a shorter time of dust exposure than patients with classical silicosis, more prevention and protection rules are needed to be enforced in this occupational field.

Patients in the AS group were more likely to have chest oppression and pain (53.7%). In addition, the number of patients with the history of anti-tuberculosis treatment is more in AS group than those in non-AS group silicosis (11.2 vs. 4.4%). It may indicate that the imaging manifestations of AS-associated silicosis are similar to tuberculosis at the early stage, and the differential diagnosis may be more difficult than those in the non-AS group. In terms of imaging, our study found that patients were more likely to appear pleural abnormalities and ground-glass opacity in the AS group than those in the non-AS group, which were similar to a previous report from China (34).

The impact of smoking on silicosis is still controversial. Smoking was considered a risk factor for silicosis in earlier studies (38), but some study reported that there was no significant association between silicosis and smoking status (39). Previous data (34) indicated that there was no significant difference in the effects of smoking on lung function between the artificial stone-associated silicosis and natural stone-associated silicosis. However, our study indicated that, in the AS group, smoking is associated with reduced DL_{CO} (%) value, and may be reduced FEV_1 value too (P = 0.053). Although no impact was found in smoking status on progression of the disease, it may be a risk factor for decreased lung function in the AS group.

In addition, sandblasting workers as fast-forward silicosis but in non-AS group in this study caught our attention. The 28 patients in sand-blasting sector were older than AS sector, but were at the similar ages of the other non-AS patients. The years of dust exposure and the time from dust exposure to illness in sand-blasting sector were longer than those in AS sector but less than other patients in non-AS sector. The progress in sand-blasting cases were slower than AS cases, however, showed a tendency of 2–3 folds faster than that in non-AS cases but without statistical significance. Small size of the sand-blasting

sector might be one reason, as 5 in these 28 cases did sieving work thus may exposure to less concentration of dust.

We also compared some of our results in the AS group with the reported data in sandblasting. In one study (40), CT findings in 50 male patients with denim sandblasters were evaluated. Pleural thickening was positive in 19 cases (38%), similar to our result in AS group (42.5%). In another report (41), the ages at first admission in 83 living man participants (96.4% of them had been diagnosed with silicosis) were 23 ± 6 years, and the exposure duration were 41 ± 27 months. The exposure duration in the report is much shorter than 11.0 (6.0, 18.0) years in the 28 sand-blasting in our study.

In tracking the background of the 28 sand-blasting workers, 21 were found from state-owned enterprises in Shanghai and 7 from other areas in China. Protective equipment and measures normally can be available by state-owned enterprise workers, therefore the concentration of dust in their working environment might be far less than that in the environment of artificial stone cutting, and the disease progress relatively slower than AS cases. However, the comparison between sandblasting and AS-associated silicosis in China need more data before reaching a conclusion.

As this is a retrospective study, some drawbacks may exist. For example, few patients had lung function tests during the follow-up period, therefore we were unable to explore the correlation between smoking, the decline in lung function and the progression of HRCT, especially in AS group. In addition, the data were from a single medical center and a lack of long-term follow up from the patients also caused the limitation to our research.

CONCLUSION

Patients with the AS-associated silicosis had more than 5 folds higher risk of developing progression with a significant decline in lung function than the patients from the non-AS group during a 2-year follow-up. Complicated silicosis progresses faster than simple silicosis only occurred in the AS group. More evidence is needed to determine whether smoking status will increase the progressing incidence of AS-associated silicosis.

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 Institutional Review Board of Tongji University (project approval number: K18-142). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

HQ, YF, and LM applied conception, designed the research, and wrote the article. HQ, WW, JW, JH, LQ, XH, and YW collected the clinical data. CM, WY, and LM interpreted the lung function data. LM, JS, and CM interpreted the radiologic data. HQ, WW, YW, LM, and YF analyzed and interpreted the clinical data. YF and GY provided financial support fund and conducted the entire research. All authors read and approved final 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.2022.832052/full#supplementary-material

Supplementary Figure 1 | The changes of lung function indices (% predicted values) from baseline to the values at 0-to-1-year and 0-to-2-year followed up in AS and non-AS groups. Changes of FVC, FEV_1, and DL_{CO} (% predicted values) from baseline to the values after 1 **(A,C,E)** and 2 years **(B,D,F)** follow-up. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; DL_{CO}, diffusing capacity of the lung for carbon monoxide.

Supplementary Table 1 | Demographic characteristics of AS group versus sandblast group and Non-AS group versus sandblast group.

Supplementary Table 2 | Factors associated with silicosis progress in multivariate Cox proportional hazards model.

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A New Predictive Model for the Prognosis of MDA5$^+$ DM-ILD

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Purpose: The purpose of this study is to analyze clinical information and combine significant parameters to generate a predictive model and achieve a better prognosis prediction of dermatomyositis-associated interstitial lung disease with positive melanoma differentiation-associated gene 5 antibody (MDA5$^+$ DM-ILD) and stratify patients according to prognostic risk factors appropriately.

Methods: We retrospectively reviewed 63 patients MDA5$^+$ DM-ILD who were treated in our hospital from January 2018 to January 2021. Our study incorporated most clinical characteristics in clinical practice to explore the associations and predictive functions of clinical characteristics and prognosis. Student's *t*-test, Mann-Whitney *U*-test, chi-squared test, Pearson correlation analysis, Cox regression analysis, R, receiver operating characteristic curves (ROC curves), and Kaplan-Meier survival curves were performed to identify independent predictors for the prognosis of MDA5$^+$DM-ILD.

Results: In all the 63 patients with MDA5$^+$DM-ILD, 44 improved but 19 did not. Poor prognosis was found more frequently in patients who were older, clinically amyopathic variant of dermatomyositis (CADM), and/or with short duration, short interval of DM and ILD, long length of stay, fever, dyspnea, non-arthralgia, pulmonary infection, pleural effusion (PE), high total computed tomography scores (TCTs), ground-glass opacity (GGO), consolidation score, reticular score and fibrosis score, decreased forced vital capacity (FVC), forced expiratory volume in 1s (FEV1), albumin, A/G, glomerular filtration rate (GFR) and tumor necrosis factor α (TNFα), high titer of anti-MDA5, proteinuria, high levels of monocyte, lactate dehydrogenase (LDH), ferritin (FER), neuron specific enolase (NSE) and glucocorticoid, antibiotic, antiviral, and non-invasive positive pressure ventilation (NPPV). The multivariate Cox regression analysis demonstrated that duration, fever, PE, TCTs and aspartate transaminase (AST) were independent predictors of poor prognosis in patients with MDA5$^+$DM-ILD. The nomogram model quantified the risk of 400-day death as: duration ≤4 months (5 points), fever (88 points), PE (21 points), TCTs ≥10 points (22 points), and AST ≥200 U/L (100 points) with high predictive accuracy and convenience. The ROC curves possessed good discriminative ability for combination of fever, PE, TCTs, and AST, as reflected by the area under curve (AUC) being.954, 95% CI 0.902–1.000, and sensitivity and specificity being 84.2 and 94.6%, respectively.

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Conclusion: We demonstrated that duration, fever, PE, TCTs, and AST could be integrated together to be independent predictors of poor prognosis in MDA5+ DM-ILD with highly predictive accuracy.

Keywords: interstitial lung disease, anti-MDA5, dermatomyositis, prognosis, nomogram

INTRODUCTION

Dermatomyositis (DM), a multisystem autoimmune disease and a common subtype of idiopathic inflammatory myopathy (IIM), attracts attention from the medical field. In addition to typical skin and muscle involvement, respiratory, digestive, and circulatory system damage, and even malignant tumor can complicate DM. CADM accounts for ∼20% of all DM cases. Approximately 87% of MDA5+ DM-ILD cases fulfilled Sontheimer's CADM criteria in a Chinese multi-centered cohort (1). ILD, with an incidence of 5–80% and a high risk in positive ARS antibodies and Black ethnicity, is one of the important respiratory lesions in patients with DM (2). Overall, the prognosis of ILD in IIM is good: 50–66% may be expected to have a stable disease course over a substantial period of time. Frustratingly, the remaining proportion will show signs of worsening lung disease within 12 months.

MDA5, a cytoplasmic RNA helicase belonging to the retinoic acid-inducible gene-I (RIG-I) family, which can recognize ds-RNAof viruses and plays an important role in the innate immune system during RNA viral infections, has been identified as a DM-specific autoantigen (3, 4). Anti-MDA5, a 140-kDa polypeptide and one of the myositis-specific autoantibodies named after its autoantigen, was first found in 2005 by immunoprecipitation in Japanese patients (5). The incidence of MDA5+ DM ranges from 10 to 20% in Japan, 17.6–22.6% in China, and 7–13% in the United States (6–9). The cumulative 100-month survival rate for the entire patients with MDA5+ DM is 66%, and fatal outcomes occur remarkably often within the first 6 months of the diagnosis (10). Patients who responded to therapy and survived had a significantly lower mean titer of anti-MDA5, which was significantly decreased down to below the cutoff level after treatment, while those who did not respond and died had a high level of anti-MDA5 (7, 11), indicating from the side that anti-MDA5 titer is also useful for evaluation of treatment response.

Patients with DM with anti-MDA5 are prone to develop ILD, with a probability of 50–100% (8, 12, 13). Current views regard anti-MDA5 level as a novel parameter for monitoring disease activity and a good predictor of rapidly progressing ILD (RP-ILD) and decreased survival in patients with DM or CADM (11, 14). Early cohort studies reported a high 6-month mortality varying from 33 to 66% in MDA5+DM-ILD (10, 15, 16). A multivariate logistic analysis reported by Chen et al. (9) showed that anti-MDA5 is an independent risk factor for death in DM-ILD. Previous studies on the predictive role of clinical characteristics for MDA5+DM-ILD are relatively limited. For instance, the relationship between serum ferritin level and abnormality of T cell counts and the disease activity of RP-ILD was reported (17). As the increase of both the morbidity and mortality in MDA5+ DM-ILD and the etiology and pathogenesis remaining unknown, early recognition of risk factors for death is particularly important. The aim of this research project is, therefore, to try and establish a meritorious predictive model of prognosis in MDA5+ DM-ILD.

MATERIALS AND METHODS

Patients and Inclusion Criteria

We retrospectively reviewed all patients with MDA5+DM-ILD from the Department of Rheumatology and the Department of Respiratory and Critical Care Medicine between January 2018 and January 2021 who fulfilled the Bohan and Peter (18, 19) myositis criteria for DM or the Sontheimer (20) criteria for CADM and ILD imaging features. A total of 63 patients were identified. Clinical characteristics consisted of basic information, prognosis, clinical symptoms and signs, complications, treatment means, imaging information, pulmonary functions, and laboratory examinations. We followed all the enrolled patients, and the primary outcome of interest was mortality during the 400-day follow-up.

Acquisition and Analysis of Computed Tomography Imaging

All CT scans were obtained in the supine position using one of the following scanners: SOMATOM Perspective, SOMATOM Spirit, or SOMATOM Definition AS+ (Siemens Healthineers, Forchheim, Germany). Scans were conducted from the level of the upper thoracic inlet to the inferior level of the costophrenic angle, and images were reconstructed with a slice thickness of 1 or 1.5 mm.

For each patient, predominant CT patterns such as GGO, consolidation, reticulation, emphysema, thickening of the adjacent pleura, pleural effusion, presence of nodules or masses, honeycombing, bronchiectasis, and interlobar pleural traction were independently reviewed by two experienced observers according to the Fleischner Society glossary (21). CT evidence of fibrotic-like changes was defined as the presence of traction bronchiectasis, parenchymal bands (22), and/or honeycombing (21, 23, 24). To quantify the extent of pulmonary abnormalities (GGO, consolidation, reticulation, and fibrotic-like changes), a semiquantitative CT score (25) was assigned on the basis of the area involved in each of the five lung lobes (right upper, middle, and lower, and left upper and lower lobes): 0, no involvement; 1, <5%; 2, 5–25%; 3, 26–49%; 4, 50–75%, and 5, >75%. Total CT score was calculated by summing the individual lobar scores (possible scores range from 0 to 25).

TABLE 1 | Basic information of MDA5+DM-ILD.

Characteristics	Total (*N* = 63)	Not improved (*n* = 19)	Improved (*n* = 44)	*P*-value
Age, years	49.16 ± 12.16	56.95 ± 7.81	45.80 ± 12.22	0.000
Sex, male/female	26/37	10/9	16/28	0.229
Ever smoker, *n* (%)	10 (15.9)	2 (10.5)	8 (18.2)	0.698
CADM, *n* (%)	22 (34.9)	11 (57.9)	11 (25.0)	0.012
Duration, m	7.83 ± 14.53	2.87 ± 3.50	9.97 ± 16.85	0.010
Interval of DM and ILD, m	5.47 ± 13.63	1.16 ± 3.40	7.33 ± 15.85	0.017
Length of stay, days	15.11 ± 9.89	21.21 ± 15.29	12.48 ± 4.44	0.024
Fever, *n* (%)	34 (54.0)	18 (94.7)	16 (36.4)	0.000
Cough, *n* (%)	39 (61.9)	15 (78.9)	24 (54.5)	0.067
Dyspnea, *n* (%)	40 (63.5)	18 (94.7)	22 (50.0)	0.001
Arthralgia, *n* (%)	46 (73.0)	10 (52.6)	36 (81.8)	0.017
Myalgia or myasthenia, *n* (%)	49 (77.8)	14 (73.7)	35 (79.5)	0.854
Skin ulcer, *n* (%)	23 (36.5)	4 (21.1)	19 (43.2)	0.094
Gottron sign, *n* (%)	23 (36.5)	7 (36.8)	16 (36.4)	0.971
Helicotrop rash, *n* (%)	43 (68.3)	10 (52.6)	33 (75.0)	0.080
Raynaud phenomenon, *n* (%)	9 (14.3)	2 (10.5)	7 (15.9)	0.867
Pulmonary infection, *n* (%)	35 (55.6)	19 (100.0)	16 (36.4)	0.000
Pleural effusion, *n* (%)	23 (36.5)	14 (73.7)	9 (20.5)	0.000
Subcutaneous emphysema, *n* (%)	1 (1.6)	1 (5.3)	0 (0.0)	0.302
Mediastinal emphysema, *n* (%)	20 (3.2)	1 (5.3)	1 (2.3)	0.516
Pleural thickness, *n* (%)	17 (27.4)	4 (21.1)	13 (30.2)	0.486
Internal malignancy, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Glucocorticoid, *n* (%)	63 (100.0)	19 (100.0)	44 (100.0)	
Glucocorticoid, mg	159.02 ± 208.45	326.32 ± 284.65	86.77 ± 105.02	0.002
Immunosuppressor, *n* (%)	40 (63.5)	11 (57.9)	29 (65.9)	0.544
Antibiotic, *n* (%)	48 (76.2)	19 (100.0)	29 (65.9)	0.010
Antiviral, *n* (%)	17 (27.0)	11 (57.9)	6 (13.6)	0.000
Anti-fibrosis, *n* (%)	21 (33.3)	8 (42.1)	13 (29.5)	0.332
NPPV, *n* (%)	12 (19.0)	12 (63.2)	0 (0.0)	0.000
Survival time, days	298.89 ± 152.45	102.00 ± 95.27	400.00 ± 0.00	0.000

The dosage of glucocorticoid was changed to that of methylprednisolone. Immunosuppressors included ciclosporin, cyclophosphamide, tripterygium wilfordii glycosides, mycophenolate mofetil, thalidomide, leflunomide, tacrolimus, and methotrexate. Antifibrotic drugs referred to nintedanib and pirfenidone. CADM, clinically amyopathic variant of dermatomyositis; DM, dermatomyositis; ILD, interstitial lung disease; NPPV, non-invasive positive pressure ventilation.

TABLE 2 | Pulmonary examinations for MDA5+DM-ILD.

Characteristics	Total (*N* = 63)	Not improved (*n* = 19)	Improved (*n* = 44)	*P*-value
TCTs	14.06 ± 12.49	23.21 ± 14.14	10.02 ± 9.28	0.001
GGO score	5.05 ± 4.51	7.32 ± 5.19	4.05 ± 3.83	0.007
Consolidation score	3.05 ± 4.25	6.63 ± 5.27	1.47 ± 2.43	0.001
Reticular score	2.76 ± 3.42	4.26 ± 3.77	2.09 ± 3.06	0.020
Fibrosis score	3.23 ± 4.20	5.05 ± 5.02	2.42 ± 3.56	0.022
FVC (L)	2.60 ± 0.88	2.12 ± 0.52	2.75 ± 0.92	0.022
FEV1 (L)	2.09 ± 0.68	1.75 ± 0.33	2.19 ± 0.72	0.022
FEV1/FVC	81.18 ± 9.40	83.91 ± 12.14	80.37 ± 8.53	0.357
DL_{CO} (mmol/min/kPa)	4.92 ± 2.25	4.06 ± 2.26	5.18 ± 2.23	0.253

TCTs, total CT score; GGO, ground-glass opacity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1s; DL_{CO}, diffusion capacity of the lungs for carbon monoxide.

Pulmonary Function Test

The patients underwent standard pulmonary function testing (PFT) including ventilatory function and diffusion function using Pulmonary Function Testing System (MasterScreen, CareFusion Germany 234 GmbH or Vyaire Medical GmbH) with indoor temperature 24°C, relative humidity 50–70%, and standard atmospheric pressure 760 mmHg. Among all tested indexes, we had principally concentrated on FVC, FEV1, FEV1/FVC, and diffusion capacity of the lung for carbon monoxide (DL_{CO}). The results were normalized with age-, sex-, height-and weight-matched control subjects.

Anti-MDA5 Examination

Serum samples were routinely collected from the patients at initial hospitalization. Anti-MDA5 was detected using commercially available kits (EUROIMMUN, Lübeck, Germany) by Guangzhou Oumeng Medical Laboratory, with a positive control provided in the kit and a negative control provided in the buffer. The criteria for interpretation of results were based on the staining degree of antigen band recognized automatically with EUROBlotOne (EuroImmun, Lübeck, Germany): negative (–) for colorless, doubtful [(+)] for very weakly colored, weakly positive (+) for weakly colored, positive (++) for strongly colored, and strongly positive (+++) for the same intensity with the quality control blot.

Statistical Analysis

Continuous variables were presented as the mean with standard deviation and categorical variables were expressed as frequency with percentage, and differences between clinical characteristics and prognosis were compared by Student's *t*-test or Mann-Whitney *U*-test and chi-squared test. Significant variables were

TABLE 3 | General laboratory tests for MDA5+DM-ILD.

Characteristics	Total ($N = 63$)	Not improved ($n = 19$)	Improved ($n = 44$)	*P*-value
Leukocyte, G/L	5.56 ± 2.83	6.61 ± 4.28	5.10 ± 1.79	0.052
Monocyte, G/L	0.41 ± 0.20	0.53 ± 0.20	0.35 ± 0.17	0.001
Monocyte, %	7.91 ± 3.64	8.95 ± 3.02	7.47 ± 3.82	0.140
Neutrophil, G/L	4.24 ± 2.67	5.20 ± 4.01	3.82 ± 1.72	0.059
Neutrophil, %	73.75 ± 11.24	76.11 ± 8.02	72.73 ± 12.32	0.202
Lymphocyte, G/L	0.83 ± 0.42	0.78 ± 0.32	0.85 ± 0.45	0.581
Lymphocyte, %	16.78 ± 9.11	13.70 ± 7.18	18.11 ± 9.60	0.078
Blood urine				
Negative, *n* (%)	44 (75.9)	9 (56.3)	35 (83.3)	0.070
Positive, *n* (%)	14 (24.1)	7 (43.8)	7 (16.7)	
Proteinuria				
Negative, *n* (%)	36 (62.1)	6 (37.5)	30 (71.4)	0.017
Positive, *n* (%)	22 (37.9)	10 (62.5)	12 (28.6)	
AST, U/L	94.48 ± 121.17	150.63 ± 161.88	70.23 ± 90.58	0.054
ALT, U/L	70.63 ± 103.17	94.63 ± 84.83	60.02 ± 109.54	0.226
LDH, U/L	371.81 ± 145.23	458.05 ± 142.07	333.71 ± 130.89	0.001
Alb, g/L	32.68 ± 4.74	29.31 ± 3.77	34.14 ± 4.39	0.000
Glb, g/L	27.68 ± 5.05	27.27 ± 3.25	27.85 ± 5.68	0.615
A/G	1.22 ± 0.29	1.08 ± 0.21	1.28 ± 0.30	0.006
CK, U/L	201.30 ± 300.15	236.26 ± 374.21	185.48 ± 263.69	0.545
GFR, ml/(min/1.73 m^2)	111.65 ± 21.96	100.95 ± 28.74	115.76 ± 17.49	0.025
Bun, mmol/L	4.47 ± 3.21	5.81 ± 5.32	3.89 ± 1.37	0.137
Cr, μmol /L	62.40 ± 80.92	84.87 ± 146.37	52.69 ± 12.36	0.351
ESR, mm/h	34.67 ± 23.69	38.56 ± 24.57	33.05 ± 23.42	0.412
CRP, mg/L	16.80 ± 27.58	31.72 ± 44.49	10.26 ± 10.85	0.059
FER, μg /L	1,082.04 ± 870.39	1,512.62 ± 1,125.17	866.75 ± 623.90	0.033
CEA, μg /L	7.05 ± 5.39	8.74 ± 7.13	6.26 ± 4.25	0.142
CYFRA, ng/ml	5.70 ± 8.19	9.54 ± 12.23	3.40 ± 2.63	0.075
SCCA, ng/ml	2.51 ± 10.96	5.48 ± 17.86	0.72 ± 0.44	0.320
NSE, μg /L	20.10 ± 8.59	25.11 ± 10.16	17.10 ± 5.89	0.003

AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase; Alb, albumin; Glb, globulin; CK, creatine kinase; GFR, glomerular filtration rate; BUN, blood urea nitrogen; Cr, creatinine; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; FER, ferritin; CEA, carcino-embryonic antigen; CYFRA, cytokeratin 19 fragment; SCCA, squamous cell carcinoma antigen; NSE, neuron-specific enolase.

TABLE 4 | Immunologic tests for MDA5+DM-ILD.

Characteristics	Total ($N = 63$)	Not improved ($n = 19$)	Improved ($n = 44$)	*P*-value
Anti-MDA5				0.024
Weakly positive, *n* (%)	7 (11.1)	0 (0.0)	7 (15.9)	
Positive, *n* (%)	25 (39.7)	11 (57.9)	14 (31.8)	
Strongly positive, *n* (%)	31 (49.2)	8 (42.1)	23 (52.3)	
$CD3^+$ T, %	72.46 ± 12.13	70.15 ± 13.84	73.46 ± 11.37	0.367
$CD4^+$ T, %	46.70 ± 13.19	48.04 ± 15.87	46.12 ± 12.05	0.630
$CD8^+$ T, %	23.14 ± 11.19	19.41 ± 10.15	24.75 ± 11.36	0.112
B lymphocyte, %	17.54 ± 9.71	17.26 ± 8.54	17.67 ± 10.33	0.891
NK lymphocyte, %	7.95 ± 7.72	9.88 ± 11.59	7.04 ± 4.98	0.230
IL-2, pg/ml	2.62 ± 1.26	2.74 ± 1.01	2.57 ± 1.36	0.657
IL-4, pg/ml	2.59 ± 1.11	2.77 ± 0.98	2.52 ± 1.16	0.458
IL-6, pg/ml	39.76 ± 92.17	30.61 ± 54.40	43.71 ± 104.81	0.639
IL-10, pg/ml	5.77 ± 3.01	6.24 ± 3.51	5.57 ± 2.82	0.475
TNFα, pg/ml	10.56 ± 26.26	3.08 ± 1.77	13.67 ± 30.82	0.047
IFNγ, pg/ml	2.61 ± 1.39	2.54 ± 1.48	2.64 ± 1.38	0.809

IL, interleukin; TNF, tumor necrosis factor; IFN, interferon.

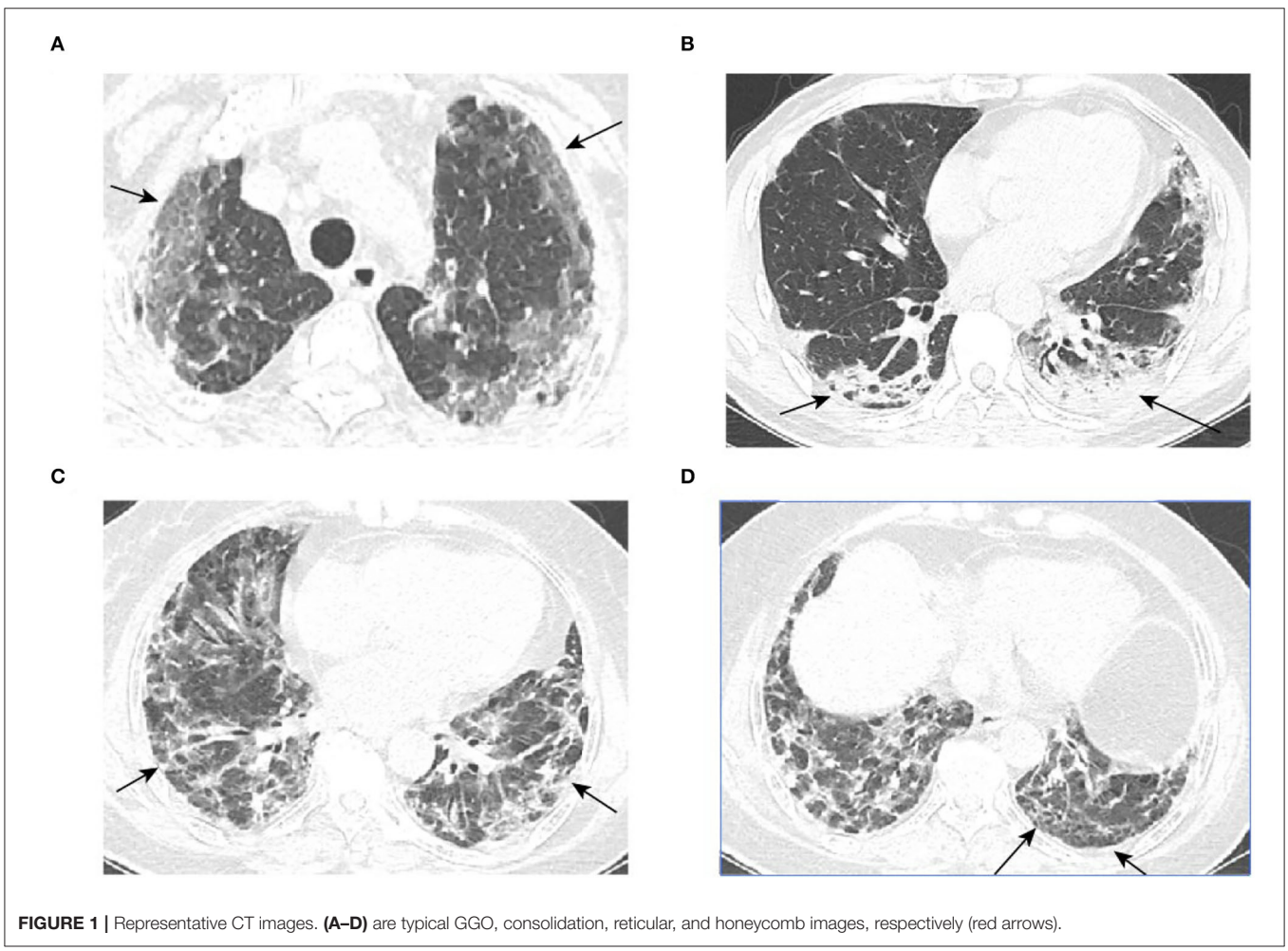

FIGURE 1 | Representative CT images. **(A–D)** are typical GGO, consolidation, reticular, and honeycomb images, respectively (red arrows).

selected for Pearson correlation analysis and univariate Cox regression analysis. Significant ($P < 0.05$) and clinically focused variables in the univariate Cox regression analysis were selected for further multivariate Cox regression analysis. Regression coefficients were regarded as weights for the variables in ROC curves. The nomogram applied to create the scoring system was developed with independent risk factors based on multivariate Cox regression analysis using the "*rms*" package in R. Survival rates were calculated using the Kaplan-Meier method. A two-sided *P*-Value <0.05 was defined as statistically significant. All the analyses were performed using SPSS 25.0 and GraphPad Prism 8.0.2.

RESULTS

Patients and Clinical Characteristics

Among the 63 patients with MDA5$^+$DM-ILD admitted in our hospital between January 2018 and January 2021, 44 survived and improved, but 19 lost their lives during the 400-day follow-up. The 400-day mortality in our data of all the 63 patients with MDA5$^+$DM-ILD was 30.16%. The clinical characteristics are summarized in **Tables 1–4**, **Supplementary Table 1** based on prognosis. Of the 19 patients who died during follow-up, 11 (57.9%) and 8 (42.1%) were confirmed to be anti-MDA5-positive and strongly positive, respectively. The group included nine women (47.4%) and 10 men (52.6%) with a median age of 56.95 years (range 40–68) and mean TCTs of 23.21 (range 6–54), and 2 (10.5%) being smoker, and 11 (57.9%) being CADM. Of the 44 patients who improved, 7 (15.9%), 14 (31.8%), and 23 (52.3%) were confirmed to be anti-MDA5 weakly positive, positive, and strongly positive, respectively. This group included 28 women (63.6%) and 16 men (36.4%) with a median age of 45.8 years (range 19–72) and mean TCTs of 10.02 (range, 0–39), and 8 (18.2%) being smoker and 11 (25%) being CADM.

Association Between Clinical Characteristics and Prognosis

The clinical characteristics of the patients with MDA5$^+$ DM-ILD are summarized in **Tables 1–4**, **Supplementary Table 1** according to basic information, pulmonary examinations, general laboratory tests, and immunologic tests based on their prognosis in the 400-day follow-up. CT scores of each lobe assessed by fibrotic-liking changes including GGO score, consolidation score, reticular score, and fibrosis score are shown in **Supplementary Table 2**.

Previous research determined that prognosis was poor in elderly patients with MDA5$^+$ DM-ILD (12). In our study, poor prognosis was found more frequently in acute-onset patients (2.87 ± 3.5 vs. 9.97 ± 16.85, $P = 0.01$). Abnormal symptoms such as fever (94.7% vs.36.4%, $P < 0.001$) and some complications such as pulmonary infection (100.0% vs. 36.4%, $P < 0.001$) and pleural effusion (73.7% vs. 20.5%, $P < 0.001$) were significantly associated with high mortality. The Gottron sign, skin ulceration, and heliotrope rash are characteristic cutaneous phenotypes in patients with MDA5$^+$ DM and are significantly associated with increased risk of subacute ILD or RP-ILD (6, 26, 27). However, our results did not find that the signs above had an apparent link with prognosis of patients with MDA5$^+$ DM-ILD. All the 63 patients here were not diagnosed with any internal malignancy. Despite many scholars suggesting MDA5$^+$ DM is likely to complicate malignancy, malignancy is uncommon in MDA5$^+$ DM-ILD, with an incidence of <5% (15, 28). As expected, TCTs, GGO score, consolidation score, reticular score, and fibrosis score were higher in patients with poor prognosis. Representative CT images of GGO, consolidation, and reticular and fibrotic changes are shown in **Figure 1**. In contrast, the value of FVC and FEV1 was lower in poor prognosis. It had been noted the severely affected pulmonary function especially the baseline FVC% was validated to be the most significant prognostic factor to predict

TABLE 5 | Correlation analysis of clinical characteristics and prognosis.

Characteristics	Prognosis		Survival time	
	Pearson	*P*-value	*Pearson*	*P*-value
Age	0.424	0.001	−0.365	0.006
CADM	0.317	0.011	−0.293	0.028
Duration	−0.226	0.075	0.294	0.028
Interval of DM and ILD	−0.210	0.099	0.258	0.054
Length of stay	0.408	0.001	−0.414	0.002
Fever	0.537	0.000	−0.509	0.000
Dyspnea	0.426	0.000	−0.379	0.004
Arthralgia	−0.302	0.016	0.272	0.043
Pulmonary infection	0.588	0.000	−0.538	0.000
Pleural effusion	0.507	0.000	−0.526	0.000
TCTs	0.491	0.000	−0.385	0.003
GGO score	0.337	0.007	−0.223	0.099
Consolidation score	0.565	0.000	−0.479	0.000
Reticular score	0.295	0.020	−0.297	0.026
Fibrosis score	0.291	0.022	−0.170	0.211
FVC	−0.305	0.075	0.276	0.126
FEV1	−0.280	0.103	0.262	0.148
Anti-MDA5	0.039	0.762	−0.051	0.709
Leukocyte	0.246	0.052	−0.279	0.038
Monocyte	0.426	0.001	−0.482	0.000
Neutrophil	0.239	0.059	−0.279	0.038
Proteinuria	0.313	0.017	−0.293	0.035
AST	0.307	0.014	−0.407	0.002
LDH	0.398	0.001	−0.378	0.004
Alb	−0.472	0.000	0.482	0.000
A/G	−0.307	0.014	0.273	0.042
GFR	−0.305	0.025	0.227	0.124
CRP	0.361	0.005	−0.353	0.010
FER	0.353	0.009	−0.254	0.072
TNFα	−0.186	0.192	0.181	0.224
CEA	0.217	0.142	−0.221	0.141
CYFRA	0.367	0.020	−0.320	0.047
NSE	0.217	0.142	−0.459	0.003
Glucocorticoid	0.532	0.000	−0.410	0.002
Antibiotic	0.367	0.003	−0.386	0.003
Antiviral	0.458	0.000	−0.366	0.006
NPPV	0.738	0.000	−0.649	0.000

the 6-month all-cause mortality based on a multi-center MDA5$^+$ DM-ILD data with a cutoff value of 50%, which means mortality being 15% while FVC% >50% and mortality being 70% while FVC% <50% (29, 30).

A new AI algorithm-based analysis suggested that "MDA5 score" may serve as an applicable prognostic predictor for MDA5$^+$ DM-ILD (31). Regarding the laboratory examination indicators in our research, we found that poor prognosis patients had more positive and strongly positive anti-MDA5 results ($P = 0.024$) than the survivors. Research studies have mentioned that predictive cytokines and chemokines including IL-6, IL-8, IL-10, IL-15, IL-18, TNFα, IFN-α, IP-10, and CX3CL1 had high levels in MDA5$^+$ DM-ILD (32–35), especially CX3CL1, which was identified as involved in the pathogenesis of MDA5$^+$ DM-ILD with a strong correlation of $r = 0.89$ between anti-MDA5 titer and CX3CL1.

Early and intensive immunomodulatory therapy has some effects on clinical parameters such as cytokines, antibodies, and hyperferritinemia and may lead to better prognosis of concomitant ILD (29). Nakashima et al. (36) reported that combined immunosuppressive therapy markedly improved the prognosis from 28.6 to 75%. An existing report revealed that the application of non-invasive positive pressure ventilation was an independent risk factor for survival (37). Based on this study, we were surprised to find that patients who received a larger dose of glucocorticoid (326.32 ± 284.65 vs. 86.77 ± 105.02, $P = 0.002$), antibiotic therapy (100% vs. 65.9%, $P = 0.01$), antiviral therapy (57.9% vs. 13.6%, $P < 0.001$), and NPPV (63.2% vs. 0%, $P < 0.001$) were more inclined to suffer a bad end. We had to owe poor prognosis after receiving intensive therapies to their complex and severe status liking secondary multiple infections. Although a previous clinical trial suggested that pirfenidone, in addition to conventional immunosuppressive treatment, did not result in improvement in terms of survival (38). We wanted to see if there is anti-fibrosis benefit. However, contrary to our expectations, the results showed that anti-fibrosis therapy did not improve the outcomes, maybe because the population incorporated was small and the follow-up was short.

Besides, we specially analyzed the correlation between the above clinical characteristics showing significant differences with prognosis and the survival time in the 400-day follow-up through Pearson correlation coefficient (**Table 5**). Majority of the results were consistent with those aforementioned.

Prediction of the Prognosis of MDA5$^+$DM-ILD

The above studies have revealed some significant differences and associations between clinical characteristics and prognosis. Based on them, we next performed a univariate Cox regression analysis. Although there were many significant indicators included in our research, we selected only seven of them for the univariate Cox regression analysis following the rules of statistics (one indicator for 10 observations). As seen in **Table 6**, the univariate Cox regression analysis showed that fever, pulmonary infection, pleural effusion, TCTs, AST, and FER were significantly correlated with the prognosis of MDA5$^+$DM-ILD. Then, inclusion of these factors and duration together in the multivariate Cox regression analysis revealed that duration, fever, PE, TCTs, and AST remained independent variables for predicting the prognosis of MDA5$^+$DM-ILD. That is to say, acute onset (HR 0.827, $P = 0.011$), fever (HR 17.486, $P = 0.012$), pleural effusion (HR 0.174, $P = 0.001$), high TCTs (HR 1.048, $P = 0.011$),

TABLE 6 | Cox regression analysis of various predictive factors for the prognosis of MDA5$^+$ DM-ILD.

Characteristics	Univariate HR (95% CI)	*P*-value	Multivariate HR (95% CI)	*P*-value
Duration		0.056	0.827 (0.704–0.972)	0.011
Fever	0.052 (0.007–0.388)	0.004	17.486 (1.861–164.255)	0.012
Pulmonary infection	61.142 (1.494–2,501.471)	0.030		
Pleural effusion	8.061 (2.884–22.532)	0.000	0.174 (0.059–0.511)	0.001
TCTs	1.049 (1.020–1.078)	0.001	1.048 (1.011–1.086)	0.011
AST	1.005 (1.002–1.008)	0.001	1.005 (1.002–1.009)	0.004
FER	1.000 (1.000–1.001)	0.032		

TABLE 7 | ROC analysis of duration, fever, PE, TCTs, and AST.

Characteristics	AUC	Youden index	95% CI	Sensitivity	Specificity	*P*-value
Duration	0.757	0.410	0.623–0.890	56.8%	84.2%	0.002
Fever	0.784	0.569	0.664–0.905	94.7%	62.2%	0.001
PE	0.787	0.575	0.652–0.923	73.7%	83.8%	0.000
TCTs	0.788	0.569	0.671–0.905	94.7%	62.2%	0.000
AST	0.738	0.465	0.604–0.871	78.9%	67.6%	0.004
Combination	0.954	0.788	0.902–1.000	84.2%	94.6%	0.000

Combination: the combination of fever, PE, TCTs, and AST.

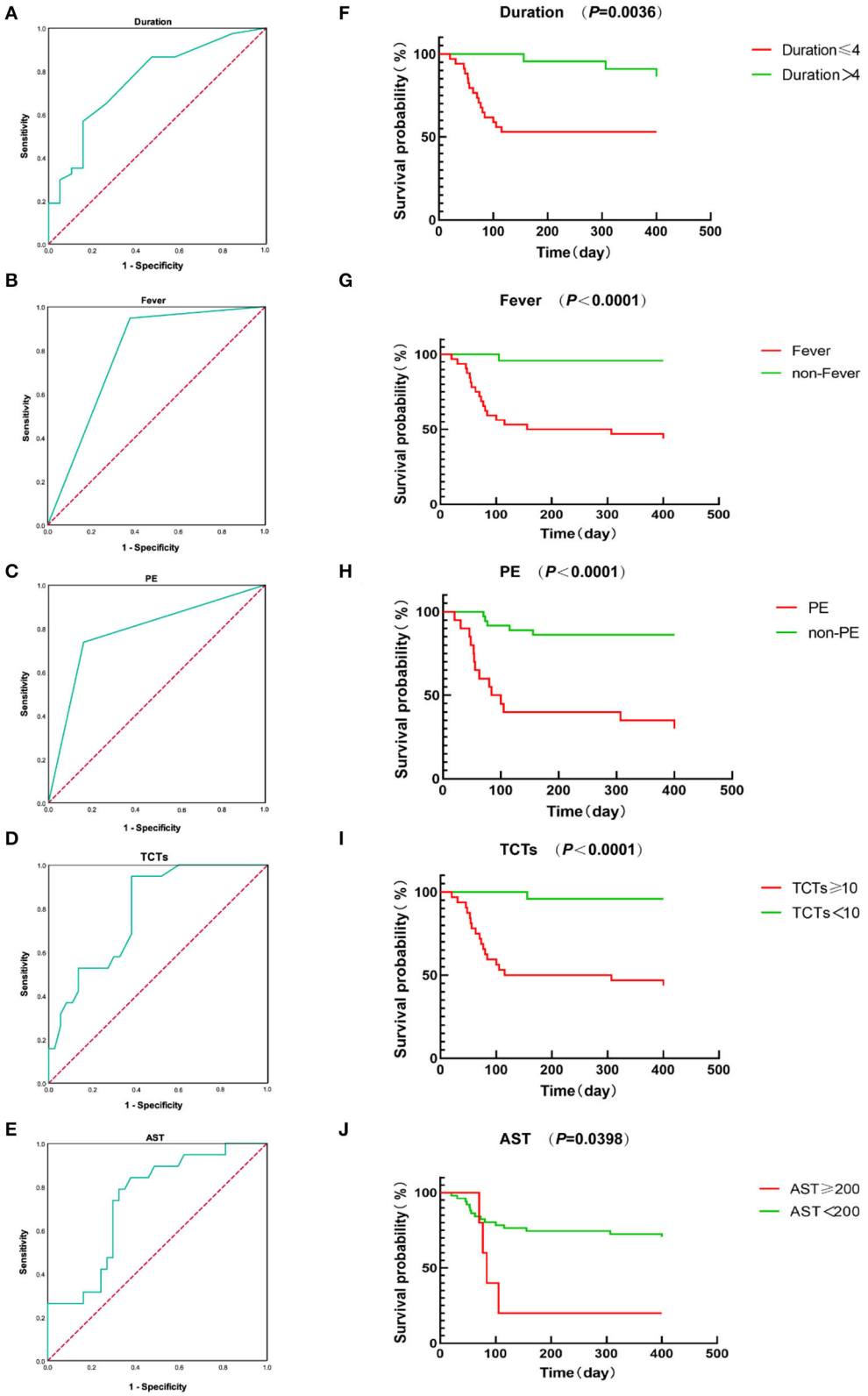

FIGURE 2 | (A–E) ROC curves of duration, fever, PE, TCTs, and AST. **(F–J)** Kaplan-Meier survival curves of duration, fever, PE, TCTs, and AST.

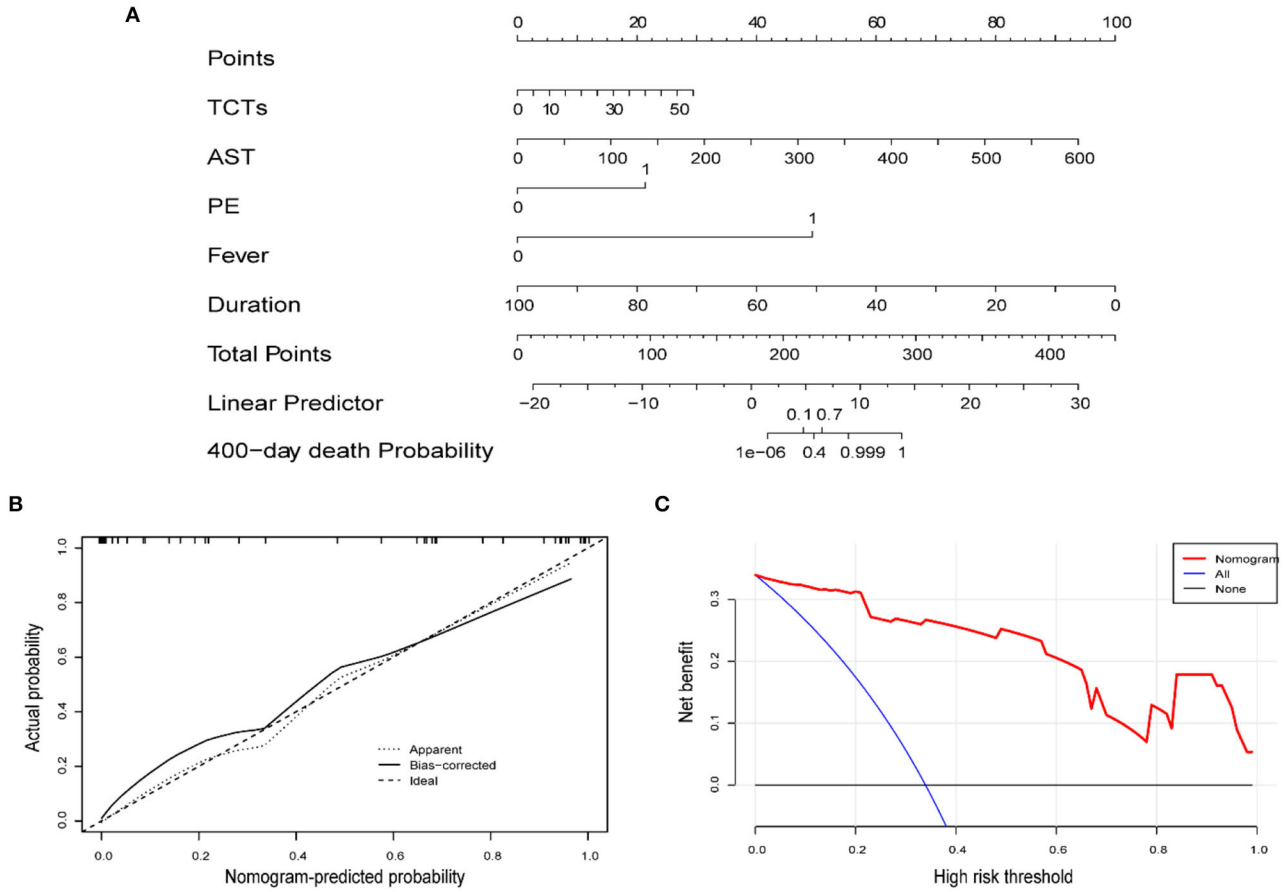

FIGURE 3 | (A) Nomogram predicting the prognosis of MDA5$^+$DM-ILD. **(B)** Calibration curve of the nomogram. **(C)** DCA of the nomogram.

and high AST (HR 1.005, $P = 0.004$) were significant predictors of poor prognosis for MDA5$^+$DM-ILD. Additionally, an ROC curve analysis was conducted to evaluate the predictive value of these factors (**Table 7** and **Figures 2A–E**).

Development of Prognostic Nomogram Models of MDA5$^+$DM-ILD

A nomogram to predict the mortality of MDA5$^+$DM-ILD was preliminarily constructed on the basis of multivariate Cox regression results (**Figure 3A**). Particularly, the nomogram was generated by assigning a weighed score on the point scale to each independent predictor. A higher score calculated from the sum of the assigned number of points for each prognostic parameter in the nomogram corresponds to a higher likelihood of death. The calibration curve showed that this predictive nomogram exhibited good calibration (**Figure 3B**). Moreover, a decision curve analysis (DCA) was conducted to assess the clinical utility of the predictive nomogram in **Figure 3C**.

To make this predictive model more convenient for physicians to use in clinical practice, we modified three predictors (duration, TCTs, and AST) into binary variables. Then three transformed binary variables together with fever and PE were used to conduct another nomogram model, in which all five predictors were evaluated with specific integer points: duration $\leq$4 m (5 points), fever (88 points), PE (21 points), TCTs $\geq$10 points (22 points), and AST $\geq$200 U/L (100 points) (**Figures 4A–C**). Then, we obtained Kaplan-Meier survival curves subdivided by duration $\leq$4 mouths, fever, PE, TCTs $\geq$10 points, and AST $\geq$200 U/L (**Figures 2F–J**). In the end, we created a new indicator by combining fever, PE, TCTs, and AST, which possessed good predictive ability, as reflected by an AUC of.954 (**Table 7** and **Figure 5**).

DISCUSSION

The presence of MDA5$^+$ DM-ILD can seriously impair the quality of life and shorten the survival of patients. The 6-month mortality of patients with MDA5$^+$ DM-ILD ranges from 33 to 66% (10, 15, 16). A multicenter observational study (39) from 37 medical centers including 121 patients showed that MDA5$^+$ RP-ILD had a noteworthy high mortality rate. Early and intensive immunomodulatory therapy has some effects on clinical parameters such as cytokines, antibodies,

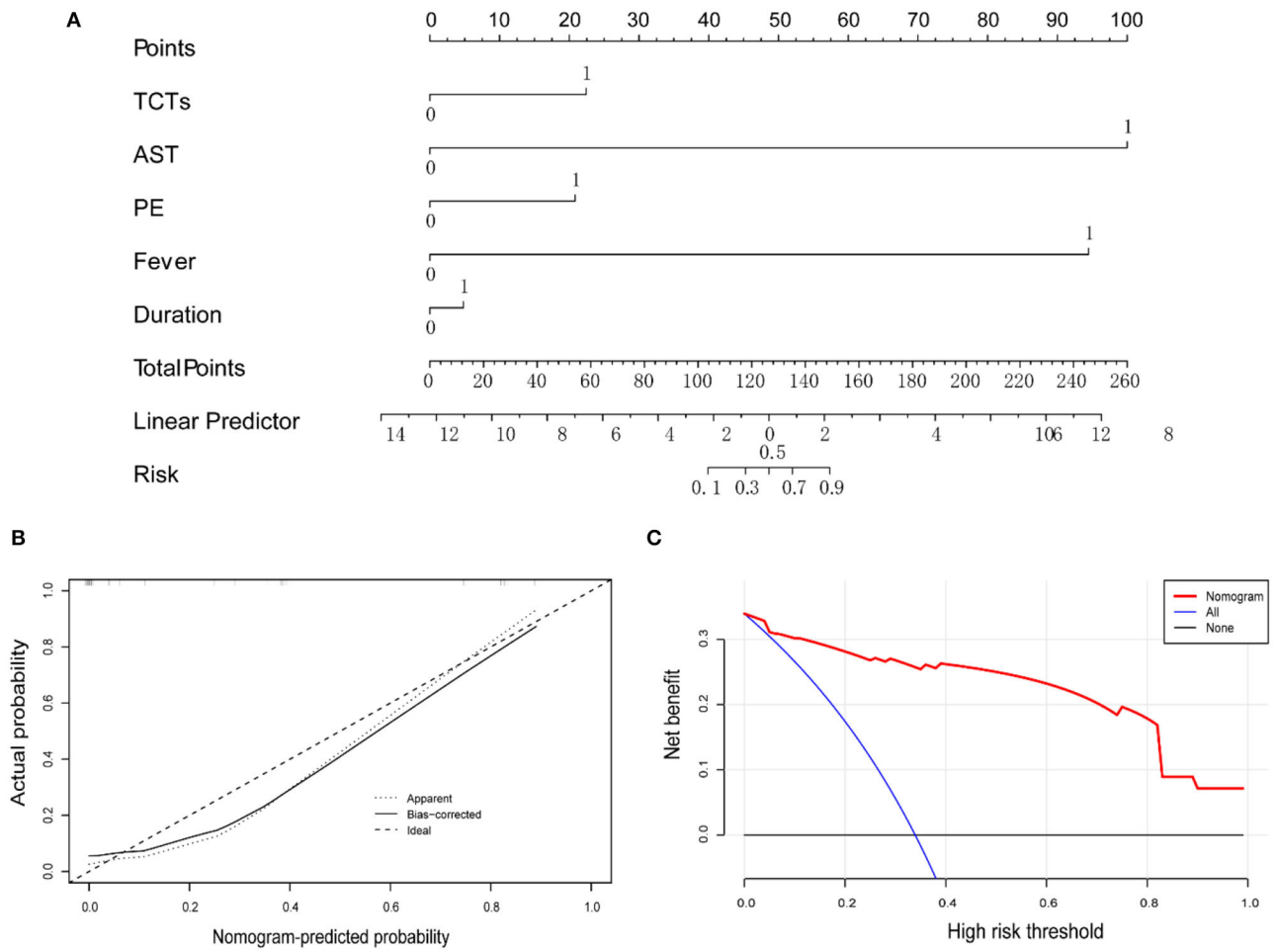

FIGURE 4 | (A) Nomogram predicting the prognosis of MDA5$^+$DM-ILD, while all predictors are binary variables. **(B)** Calibration curve of the nomogram. **(C)** DCA of the nomogram.

and hyperferritinemia, and may lead to better prognosis of concomitant ILD (29). Nakashima et al. (36) reported that combined immunosuppressive therapy markedly improved the prognosis from 28.6 to 75%. An existing report revealed that application of NPPV was an independent risk factor for survival (37). Previous studies on the predictive role of clinical characteristics for patients with MDA5$^+$DM-ILD were relatively limited. Our study aimed to design a novel quantitative tool so clinicians can predict the probability of death. Thus, we integrated a total of 122clinical characteristics, 46 of which are shown in **Supplementary Table 1**. Although numerous clinical features were associated with prognosis, the clinical significance of a single index in the prediction of prognosis was quite limited because of one-sidedness. As a result, we selected the independent variables duration, fever, PE, TCTs, and AST, all being routine clinical practice, based on the multivariate Cox regression analysis to construct a predictive model.

Nakashima et al. (40) determined that the prognosis was poor in MDA5$^+$DM-ILD patients who went through a long interval from appearance of skin lesions to diagnosis of ILD. Our data indicated the average course of disease and interval of DM and ILD in poor prognosis patients was 2.87 and 1.16 months, respectively, meaning acute onset of DM and ILD and serious, fractious conditions. Tanizawa et al. (14) also indicated that high fever was associated with poor prognosis of DM-ILD. Pleural effusion (73.7% vs. 20.5%, $P < 0.001$) was significantly associated with high mortality in this research. We systematically evaluated every patient's CT imaging and made points according to standard as mentioned above, finding the poor prognosis population getting visibly higher points not only on TCTs but also on GGO score, consolidation score, reticular score, and fibrosis score. It was reported that consolidation, GGO, and reticular opacities were distinctive findings in high-resolution computed tomography (HRCT) (14, 41) and that an initial right middle lobe GGO score of $\geq$2 (GGO $\geq$5% of the lobe) was a poor prognostic factor (42) for patients with MDA5$^+$DM-ILD. Besides, a semi-quantitative HRCT scoring method including GGO, consolidation, and fibrosis was applied for the assessment of MDA5$^+$ DM-ILD and confirmed an

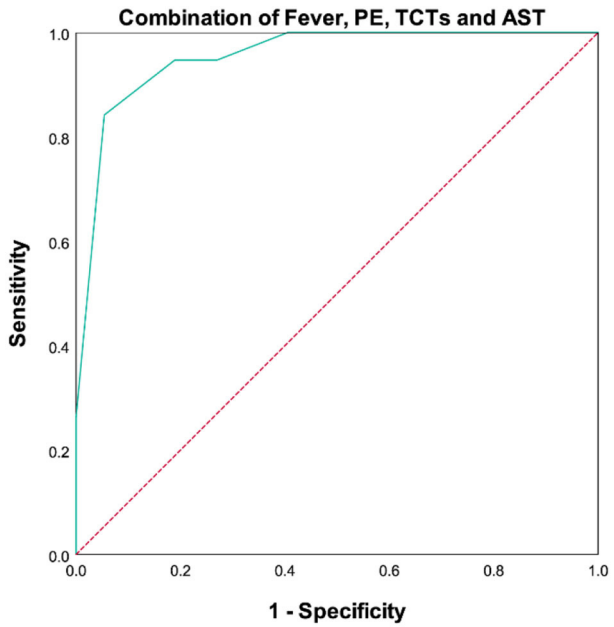

FIGURE 5 | ROC curves of combination of fever, PE, TCTs, and AST.

independent risk factor for 1-year mortality (43). However, the fibrosis components were heavily weighted in this scoring method. Recent research studies including an AI algorithm-based analysis named "AI score" revealed that lower zone GGO and consolidation demonstrated to be correlated with RP-ILD and were applicable prognostic predictors for MDA5$^+$ DM-ILD (31, 44). Besides, the scores of microhemorrhage, capillary disorganization, spontaneous pneumomediastinum, and neoangiogenesis were significantly correlated with known poor prognosis factors of DM-ILD and total fibrosis scores of chest HRCT (37, 45, 46). Some research studies (9, 29, 37, 40, 47) have reported that anti-MDA5-positive and non-survivors presented higher serum AST level.

We can believe that each enrolled index in our model has a definite guiding function and an undoubted effect on clinic work. However, this model was generated in a specific patient population and specific clinical characteristics. Inevitably, this model may not be the standard model that represents all patients with MDA5$^+$ DM-ILD and covers all possible clinical indicators. What we can do is to build a model that is as comprehensive and reliable as possible under existing conditions. Therefore, we suggest that one flaw of our model is that hyperferritinemia was not included. In fact, hyperferritinemia has been indicated as a key risk factor for patients with MDA5$^+$ DM and RP-ILD (1, 10, 48–51). It is just that our model dropped it in the fitting process for some reason. Nevertheless, non-hyperferritinemia in the model does not mean that hyperferritinemia is not important, and it absolutely can be an independent prognostic factor.

Different predictive models have been reported in the past 10 years. "FLAIR score," including ferritin, LDH, semi-quantitative anti-MDA5 grade, HRCT imaging score, and RPILD/non-RPILD based on a large-scale Chinese single-center cohort (n = 207), was proposed to predict mortality in CADM-ILD (1). Other reports also stated that ferritin, LDH, and KL-6 were independent high-risk factors for poor outcomes (1, 52, 53). A multivariate logistic regression analysis (27) previously indicated that positive anti-MDA5, elevated CRP, and decreased counts of lymphocyte can provide a precise prediction for RP-ILD in patients with CADM. The evidence-based risk prediction model using CRP and KL-6 combined with anti-MDA5 might also be useful for predicting prognosis in patients with DM-ILD; it is called the MCK (MDA5, CRP, and KL-6) model, identifying patients at low (<15%), moderate (15–49%), or high risk (≥50%) of mortality based on the number of risk factors. Respiratory physiological parameters such as lower arterial partial pressure of oxygen (PaO2) and higher alveolar-arterial oxygen difference (AaDO2) have been associated with the development of RPILD and poor prognosis in several small-sample MDA5$^+$ DM/CADM studies (10, 42). Unfortunately, the heterogeneity of these cohorts was obvious, and the pulmonary function and structure evaluation were suboptimal.

This is the first time that duration, fever, PE, TCTs, and AST are recommended together as a predictor for the prognosis of MDA5$^+$ DM-ILD. This nomogram has high predictive accuracy and can be applied in most hospitals because of convenience. With the aim of establishing a novel scoring system, we converted the nomogram into a scoring system. If the total score is over 116 points, a high probability (≥30%) of mortality exists. Meanwhile, when we combined fever, PE, TCTs, and AST together, a nice predictive function can be seen: AUC being.954, sensitivity being 84.2%, and specificity being 94.6% on the ROC curve. Hence, this method is not only feasible and simple but could also accurately recognize poor prognosis with high calibration.

This study is not exempt from limitations. First, this study was based on retrospective data, and the validity of the retrospective data was limited. Moreover, the size of the sample included in this study was small. Next, the nomogram model was not validated in the external validation set from other medical centers. Finally, our follow-up time was relative short, lacking assessment of long-term survival conditions. Therefore, multicenter validation of the scoring system with a large study population is urgently needed to obtain high-level evidence for its clinical application in the future.

In conclusion, the predictive model for the prognosis of MDA5$^+$ DM-ILD assists in identifying cases accurately, intensifying treatment early, and saving as many patient lives as possible in clinical practice. This study is based on a unicentric and small sample of participants suggesting a favorable predictive performance and should be further validated in multicenter prospective studies in the near future.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data are being expanded for use in another study. Requests to access the datasets should be directed to 476839887@qq.com.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

QN and L-qZ conceived the study, collected the data, and performed the analysis. QN wrote the manuscript. W-lM, LX, X-rW, X-lH, and FY made suggestions on the revision of manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.908365/full#supplementary-material

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Clinical, imaging, and blood biomarkers to assess 1-year progression risk in fibrotic interstitial lung diseases—Development and validation of the honeycombing, traction bronchiectasis, and monocyte (HTM)-score

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Introduction: Progression of fibrotic interstitial lung disease (ILD) leads to irreversible loss of lung function and increased mortality. Based on an institutional ILD registry, we aimed to evaluate biomarkers derived from baseline patient characteristics, computed tomography (CT), and peripheral blood for prognosis of disease progression in fibrotic ILD patients.

Methods: Of 209 subsequent ILD-board patients enregistered, 142 had complete follow-up information and were classified fibrotic ILD as defined by presence of reticulation or honeycombing using a standardized semi-quantitative CT evaluation, adding up typical ILD findings in 0–6 defined lung fields. Progression at 1 year was defined as relative loss of ≥10% in forced vital capacity, of ≥15% in diffusion capacity for carbon monoxide, death, or lung transplant. Two-thirds of the patients were randomly assigned to a derivation cohort evaluated for the impact of age, sex, baseline lung function, CT finding scores, and blood biomarkers on disease progression. Significant variables were included into a regression model, its results were used to derive a progression-risk score which was then applied to the validation cohort.

Results: In the derivation cohort, age, monocyte count ≥0.65 G/L, honeycombing and traction bronchiectasis extent had significant impact. Multivariate analyses revealed the variables monocyte count ≥0.65 G/L (1 point) and combined honeycombing or traction bronchiectasis score [0 vs. 1–4 (1 point) vs. 5–6 lung fields (2 points)] as significant, so these were used for

score development. In the derivation cohort, resulting scores of 0, 1, 2, and 3 accounted for 1-year progression rates of 20, 25, 46.9, and 88.9%, respectively. Similarly, in the validation cohort, progression at 1 year occurred in 0, 23.8, 53.9, and 62.5%, respectively. A score ≥2 showed 70.6% sensitivity and 67.9% specificity, receiver operating characteristic analysis for the scoring model had an area under the curve of 71.7%.

Conclusion: The extent of honeycombing and traction bronchiectasis, as well as elevated blood monocyte count predicted progression within 1 year in fibrotic ILD patients.

KEYWORDS

traction bronchiectasis, honeycombing, monocyte count, forced vital capacity (FVC), diffusion capacity (DL), idiopathic pulmonary fibrosis, autoimmune disease, lung fibrosis

Introduction

Until recently, interstitial lung diseases (ILD) with an assumed underlying pathophysiological mechanism of inflammation, like hypersensitivity pneumonitis (HP) or ILD associated with autoimmune diseases, were mostly treated using anti-inflammatory therapies, e.g., immunomodulatory, or immunosuppressive agents (1). With few exceptions, (2–5) this was, however based on only little high-quality evidence. After the advent of the anti-fibrotic drugs Pirfenidone and Nintedanib had fundamentally changed the therapeutic landscape in IPF (6, 7), increasing evidence also suggested their use in systemic sclerosis (SSC)-ILD or progressive fibrosing ILD other than IPF (8–12). With regards to these advances, recent studies and guidelines support a treatment strategy based on disease phenotype, irrespective of the underlying ILD diagnosis (13). Patients with "inflammatory" ILD considered likely to respond to anti-inflammatory therapies should receive such treatment, however if progressive fibrosis occurs, anti-fibrotic agents should be used either as monotherapy or as an add-on (8, 13–17). However, in non-IPF ILD with fibrotic features in imaging that have not yet shown progression, existing evidence still does not allow to draw conclusions on which kind of treatment to be initiated primarily (18).

Numerous biomarkers have been reported to be associated with mortality and disease progression in IPF and other fibrotic ILD, such as the presence of honeycombing or traction bronchiectasis (19–21), disease extent (21, 22), previous functional worsening (23), peripheral blood monocyte count (24), or family history of ILD (25). High hopes also rest upon proteomic biomarker panels derived from patient blood, but those are not widely available in clinical practice yet (26). Some of these biomarkers have already been included into clinical scores, such as the gender-age-physiology (GAP) model for IPF and other ILD subtypes (27, 28), or the staging system by Goh et al. for SSC-ILD (22). However, particularly in the heterogeneous group of fibrotic non-IPF ILD, a risk prediction score offering guidance for initial clinical management has not been established yet.

We thus aimed to develop a scoring system for estimating 1-year progression-risk in a cohort of patients with radiologically evident fibrotic ILD based on our institutional ILD registry.

Materials and methods

Patients evaluated in this study were retrospectively extracted from the institutional ILD registry of Johannes Kepler University Hospital Linz, which was conducted in concordance with the Declaration of Helsinki and was approved and reassessed on a yearly basis by the ethics committee of the Medical Faculty of Linz (study number I-26-17). This study was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies (29).

As described in previous publications (30, 31), all patients discussed by the local ILD-board were included into a prospective registry between 2017 and 2021. Patients enregistered had undergone standardized baseline evaluation including high-resolution computed tomography (HRCT), blood analyses including autoimmune antibody screening, and pulmonary functions tests (PFT). To be included in the present analysis, patients were required to have fibrotic ILD as determined by the presence of reticular lung abnormalities or honeycombing on initial HRCT. Also, survival and PFT follow-up for at least 1 year after primary evaluation needed to be available. Anti-inflammatory or anti-fibrotic treatment was considered relevant and ILD-specific, when it had been given for a minimum of 6 weeks and when it was primarily prescribed due to ILD, but not for controlling other diseases or

TABLE 1 Baseline patient, treatment, and pulmonary function test characteristics in all patients, the derivation, and the validation cohort as well as in the derivation cohort according to progression at 1 year.

Variable	All patients (n = 142)				Derivation cohort (n = 95)		
	All patients (n = 142)	Derivation cohort (n = 95)	Validation cohort (n = 47)	P-value	Stable at 1 year (n = 59)	Progression at 1 year (n = 36)	P-value
Baseline characteristics							
Mean age (SE)	67.0 (1.1)	66.8 (1.3)	67.4 (1.8)	0.829	64.3 (1.8)	70.9 (1.5)	0.021
Age ≥ 70 years (%)	47.2	48.4	44.7	0.674	40.7	61.1	0.053
Female sex (%)	36.6	39.0	31.9	0.413	42.4	33.3	0.381
Treatment characteristics (%)							
Anti-inflammatory	52.1	57.9	40.4	0.183	64.4	47.2	0.310
Anti-fibrotic	12.0	9.5	17.0		6.8	13.9	
Anti-inflammatory and anti-fibrotic	7.0	5.3	10.6		3.4	8.3	
No ILD-specific therapy	28.9	27.3	31.9		25.4	30.6	
Pulmonary functions tests; mean (SE)							
FVC (L)	2.9 (0.1)	2.9 (0.2)	3.0 (0.2)	0.945	2.9 (0.1)	2.9 (0.1)	0.890
FVC (% pred.)	81.3 (1.5)	80.4 (2.0)	83.2 (2.3)	0.542	79.9 (2.7)	81.3 (3.1)	0.779
FEV1 (L)	2.3 (0.1)	2.4 (0.1)	2.2 (0.1)	0.306	2.3 (0.1)	2.3 (0.1)	0.869
FEV1 (% pred.)	82.8 (1.6)	82.4 (2.6)	84.0 (2.2)	0.732	80.5 (2.8)	85.4 (3.0)	0.279
FEV1/FVC	80.5 (0.7)	80.8 (0.9)	79.7 (1.0)	0.169	80.4 (1.3)	81.5 (1.2)	0.808
DLCO [mmol/(min × kPa)]	4.5 (0.1)	4.5 (0.2)	4.6 (0.2)	0.895	4.5 (0.2)	4.4 (0.2)	0.982
DLCO (% pred.)	55.2 (1.5)	54.7 (1.8)	56.2 (2.6)	0.593	54.6 (2.3)	54.8 (2.7)	0.730

P-values are for comparison between the respective groups. SE, standard error; ILD, interstitial lung disease; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; DLCO, diffusion capacity for carbon monoxide. Bold values indicate statistically significant variables.

TABLE 2 Baseline peripheral blood biomarkers in all patients, the derivation, and the validation cohort as well as in the derivation cohort according to progression at 1 year.

Peripheral blood biomarkers [mean (SE)]	All patients (n = 142)				Derivation cohort (n = 95)		
	All patients (n = 142)	Derivation cohort (n = 95)	Validation cohort (n = 47)	P-value	Stable at 1 year (n = 59)	Progression at 1 year (n = 36)	P-value
Absolute leukocyte count (G/L)	8.8 (0.3)	8.7 (0.3)	9.0 (0.5)	0.447	8.7 (0.5)	8.6 (0.5)	0.517
Absolute neutrophil count (G/L)	6.3 (0.3)	6.3 (0.4)	6.2 (0.4)	0.544	6.5 (0.5)	6.0 (0.4)	0.833
Absolute lymphocyte count (G/L)	1.7 (0.1)	1.6 (0.1)	1.8 (0.1)	0.187	1.6 (0.1)	1.6 (0.1)	0.945
Absolute monocyte count (G/L)	0.6 (0.1)	0.6 (0.1)	0.7 (0.1)	0.144	0.5 (0.1)	0.7 (0.1)	**0.001**
Absolute eosinophil count (G/L)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.685	0.2 (0.1)	0.2 (0.1)	0.638
C-reactive protein (mg/dL)	1.2 (0.2)	1.2 (0.2)	1.3 (0.5)	0.322	1.0 (0.2)	1.4 (0.4)	0.398
Lactate dehydrogenase (U/L)	248.3 (7.5)	251.7 (8.8)	241.3 (14.0)	0.299	256.3 (13.4)	244.1 (12.1)	0.903
Serological IPAF domain (%)	46.8	50.0	40.0	0.267	50.9	48.6	0.831

P-values are for comparison between the respective groups. SE, standard error; IPAF, interstitial pneumonia with autoimmune features. Bold values indicate statistically significant variables.

underlying conditions like extrapulmonary manifestations of rheumatoid arthritis.

High-resolution computed tomography images were acquired according to protocols suggested by the relevant guidelines(32). If clinically feasible, prone imaging was preferred to differ opacities in dependent lung areas from true interstitial lung abnormalities (33). During the respective ILD-board session, a specialist ILD-radiologist assessed the presence of parenchymal nodules, reticular abnormalities, honeycombing, consolidations, ground glass opacities, emphysema, mosaic attenuation, and traction bronchi(-ol)ectasis in an upper-, middle- and lower-lung area as defined by thirds of the largest cranio-caudal diameter in the sagittal reconstructions, leading to scores from zero to six, as described for our previously

TABLE 3 Baseline computed tomography scores in all patients, the derivation, and the validation cohort as well as in the derivation cohort according to progression at 1 year.

		All patients (n = 142)				Derivation cohort (n = 95)		
Computed tomography finding scores (%)	**Score**	**All patients (n = 142)**	**Derivation cohort (n = 95)**	**Validation cohort (n = 47)**	***P*-value**	**Stable at 1 year (n = 59)**	**Progression at 1 year (n = 36)**	***P*-value**
Parenchymal nodules	0	79.6	75.8	87.2	0.139	69.5	86.1	0.118
	1–4	14.8	19.0	6.4		25.4	8.3	
	5–6	5.6	5.2	6.4		5.1	5.6	
Reticular abnormalities	0	1.4	1.1	2.1	0.494	0.0	2.8	0.071
	1–4	31.7	34.7	25.5		42.4	22.2	
	5–6	66.9	64.2	72.4		57.6	75.0	
Honeycombing	0	83.1	86.3	76.6	0.288	93.2	75.0	**0.035**
	1–4	11.3	8.4	17.0		5.1	13.9	
	5–6	5.6	5.3	6.4		1.7	11.1	
Ground glass opacities	0	56.3	53.7	61.7	**0.021**	49.2	61.1	0.366
	1–4	24.7	21.0	31.9		25.4	13.9	
	5–6	19.0	25.3	6.4		25.4	25.0	
Consolidations	0	78.2	77.9	78.7	0.917	76.3	80.6	0.389
	1–4	18.3	19.0	17.0		18.6	19.4	
	5–6	3.5	3.1	4.3		5.1	0.0	
Mosaic attenuation	0	80.3	76.8	87.2	0.143	74.6	80.6	0.619
	1–4	19.7	23.2	12.8		25.4	19.4	
	5–6	0.0	0.0	0.0		0.0	0.0	
Emphysema	0	80.3	79.0	83.0	0.360	83.1	72.2	0.284
	1–4	16.9	16.8	17.0		11.9	25.0	
	5–6	2.8	4.2	0.0		5.0	2.8	
Traction bronchiectasis	0	16.2	15.8	17.0	0.915	20.3	8.7	**0.043**
	1–4	64.1	65.2	61.7		67.8	61.1	
	5–6	19.7	19.0	21.3		11.9	30.6	
Pulmonary artery/aorta	0	87.3	86.3	89.4	0.608	89.8	80.6	0.202
diameter ≥1	1	12.7	13.7	10.6		10.2	19.4	
Volume reduction (lobes)	0	46.5	49.5	40.4	0.291	56.2	41.7	0.345
	1	48.6	47.4	51.1		44.1	52.8	
	2	4.9	3.2	8.5		1.7	5.5	

P-values are for comparison between the respective groups. Bold values indicate statistically significant variables.

reported evaluations (30, 31). Each finding was then scored as absent, limited or abundant using cut-off values based on statistical modeling of the leading variables as explicated below. Additionally, aortic- and pulmonary artery diameters were measured and the number of lobes with visual signs of volume reduction was assessed.

Blood samples were analyzed using a Sysmex® XN-3000 hematology analyzer (Sysmex Europe GmbH, Norderstedt, Germany) for blood cell counts and a Cobas® 8,000 modular analyzer (Roche Diagnostics International AG, Rotkreuz, Switzerland) for C-reactive protein (CRP), lactate dehydrogenase (LDH), and rheumatoid factor. Autoimmune serology testing was performed *via* a EuroPatternMicroscope®, a Dynex®, and a EuroBlotOne® platform by Euroimmun (EUROIMMUN Medizinische Labordiagnostika AG, Lübeck, Germany) for anti-nuclear (ANA), anti-neutrophil cytoplasmatic (ANCA) and other disease-specific antibodies, using the respective kits acquired from Euroimmun. Patients were considered to have significant autoimmune findings, if these fulfilled the serological domain of the interstitial pneumonia with autoimmune features (IPAF) criteria (34).

Pulmonary function tests included spirometry, body plethysmography, and measurement of diffusion capacity (JAEGER MasterScreen PFT/Body/Diffusion®, CareFusion, San Diego, United States of America), PFT biomarkers parameters specifically analyzed in this study were forced vital capacity (FVC, L/% predicted), forced expiratory volume in 1 s (FEV1, % predicted), FEV1/FVC ratio and diffusion capacity for carbon monoxide (DLCO, single breath method, mmol/(min × kPa)/%predicted). Normal values for spirometry were based on the GLI-2012 equations (35), those for body

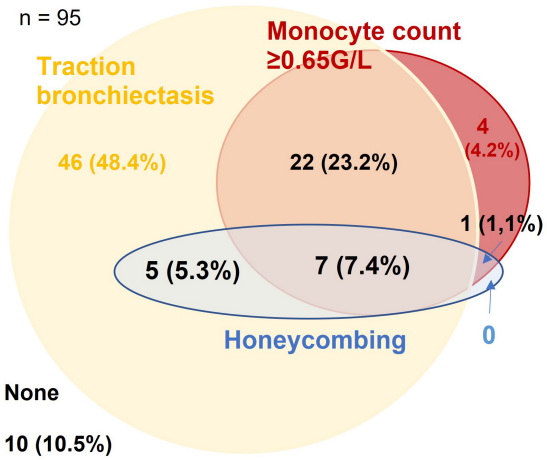

FIGURE 1
Venn-diagram for presence of traction bronchiectasis, honeycombing, and monocyte count ≥0.65 G/L in the derivation cohort. Figures are given as *n* (% of the cohort).

plethysmography and diffusion capacity on the 1993 ERS/ECCS regressions (36).

Progression of ILD at 1 year was defined as a composite endpoint of either ≥10% relative decrease in FVC, ≥15% in DLCO, by death or lung transplant within the first year after primary evaluation and ILD-board discussion, regardless of when the event had occurred within that time span. In patients who did not have follow-up lung function testing at 12 months but at least once after inclusion in the previous and in the subsequent year, the respective 12-months FVC and DLCO value was interpolated assuming a linear change.

Two-thirds of the eligible patients were randomly assigned to a derivation cohort used for score development: Baseline patient characteristics including PFT results, laboratory biomarkers and HRCT scores were evaluated for their properties to differ between progressive and non-progressive patients using a *t*-test, Mann–Whitney U test, Chi-Square-test or Fisher's exact test depending on normal distribution and scales of measure. Biomarkers showing a clinically relevant signal in visual analysis and in statistical testing were further evaluated in a binary logistic regression model. If necessary, cut-off values for key prognostic variables were calculated using the CUTPOINTR-package in R (R: A language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria; Version 3.6.0)[1], using a manually defined level of significance ($p < 0.05$), the minimum number of patients per subgroup (>10% of total *n*) and the minimum number of cut-off points (≤2) to evaluate the optimum cut-off value by regression analysis. Odds ratios for variables found to have a significant interaction with disease progression were then used to create a weighed progression-risk score with an optimum AUC in the receiver operating characteristics (ROC) analyses. The resulting score was finally tested in the remaining third of patients as validation cohort. All statistical analyses were performed using R, for all tests performed, a p-value < 0.05 was regarded statistically significant.

1 https://www.R-project.org

Results

Of a total of 209 patients enrolled between 2017 and 2021, 142 met the criteria to be included into the analysis. Most patients had been diagnosed with autoimmune-associated ILD (24%), followed by idiopathic NSIP (21%), and IPF (16%) as shown in Supplementary Table 1.

Respective baseline characteristics, PFT and HRCT findings for all patients, the derivation and the validation cohort are shown in Tables 1–3. There were no significant differences between the derivation and validation cohort except for the distribution of ground glass opacity extent. In the derivation cohort, a significant association with disease progression could be detected for older age ($p = 0.021$), absolute monocyte count ($p = 0.001$), honeycombing ($p = 0.035$), and traction bronchiectasis ($p = 0.043$).

The optimum cut-off value for monocyte count was determined at ≥0.65 G/L ($p = 0.008$). Honeycombing, traction bronchiectasis and monocyte count ≥0.65 G/L were present in 13.7, 84.2, and 35.8% of patients, respectively, with overlaps as shown in Figure 1. A total of 7.4% of patients had evidence of all three domains, 10.5% had none.

Reflecting the relatively low number of patients presenting with honeycombing, we implemented a combined score of the maximum honeycombing or traction bronchiectasis (HON/TBR) extent. The optimum cut-off values for limited and abundant extent of the leading HRCT variables honeycombing and traction bronchiectasis were determined at 0, 1–4, and 5–6 lung fields, respectively. The combined variable could also be shown to have a statistically significant interaction with progression at 1 year ($p = 0.023$). The relationship of HON/TBR extent as well as of monocyte count with number and fraction of progression events is shown in Figures 2,3.

Both variables, together with other known prognostic biomarkers and variables showing marked differences in initial analyses, were included in a regression model as shown in Table 4.

Based on the multivariate analysis results, a clinical score to assess progression-risk was derived by dividing the respective odds ratios by four and then rounding to even numbers. The score was subsequently referred to as the Honeycombing, Traction bronchiectasis and Monocyte (HTM)-score. As shown in Table 4, 1 point was counted for evidence of limited HON/TBR (scores 1–4) and for monocyte count ≥0.65 G/L, 2 points were counted for abundant HON/TBR (scores 5–6). This led to a maximum score of three for patients with abundant HON/TBR and elevated monocytes. In the derivation cohort,

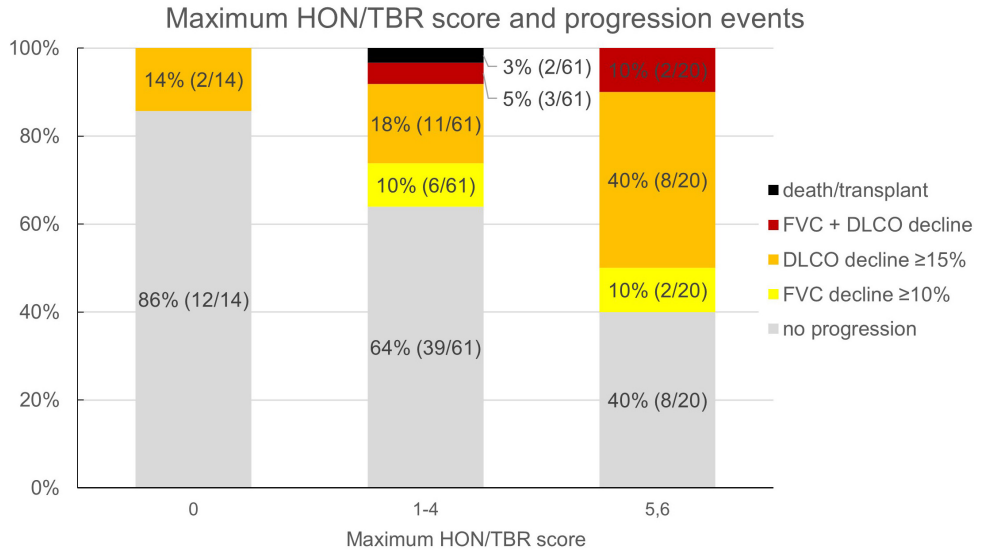

FIGURE 2
Honeycombing/traction bronchiectasis score and fraction (number) of progression events. HON/TBR, honeycombing/traction bronchiectasis; FVC, forced vital capacity; DLCO, diffusion capacity for carbon monoxide.

scoring resulted in progression rates of 20% in patients with 0 points (2/10), 25% for 1 point (11/44), 46.9% for 2 points (15/32), and 88.9% for 3 points (8/9) as shown in **Figure 4**, together with the number and fraction of progression events.

In the validation cohort, similar results could be shown: In the 45 of 47 evaluable patients (two patients had no blood monocyte count available), patients with a score of 0 progressed in 0% ($n = 0/3$), those with 1 in 23.8% ($n = 5/21$), with 2 in 53.9% ($n = 7/13$), and with 3 in 62.5% ($n = 5/8$). The ROC curve had an area under the curve of 71.7% as shown in **Figure 4**. Under the assumption of a score ≥ 2 as cut-off for progression, the score model showed a sensitivity of 70.6% and a specificity of 67.9%.

The same analyses were also attempted using the cut-off values for progressive pulmonary fibrosis (PPF) recently suggested by the novel ATS/ERS/JRS/ALAT guidelines (12), using absolute instead of relative decline and lower cut-offs of a 5% FVC and 10% DLCO decline to denote progression. A slightly higher portion of patients (two more) had progressive disease using this classification in the whole patient cohort. Forty-three (30%) had progression in both models, 13 (9%) had progression only using absolute, 11 (8%) only using relative lung function decline, while 75 (53%) did not progress in both models. Applying these cut-off values to the derivation cohort analogously to the previously described approach, no variable showed statistical significance.

Discussion

Our findings from this retrospective, registry-based score evaluation and validation study involving patients with fibrotic ILD suggest that disease progression within 1 year was associated with the extent of honeycombing and/or traction bronchiectasis and peripheral blood monocyte count. We propose the HTM score as a prognostic tool for assessing progression-risk in fibrotic ILD patients, regardless of their underlying diagnosis or treatment.

Our findings integrate well into the existing knowledge on prognostic biomarker scores already described in various ILD, the most commonly used being the GAP-score originally developed for IPF patients and the staging algorithm by Goh et al. for SSC-ILD (22, 27). These indicate higher risk for male sex, older age, larger disease extent, and more advanced lung function impairment, respectively, however in very distinct cohorts: IPF patients are known to be predominantly male and usually of an advanced age (12, 37, 38), while SSC-ILD patients are more likely female, younger and more frequently show active lung inflammation (39–41). In our presented cohort, a larger variety of fibrotic ILD patients were evaluated together, comprising patients with ILD associated with autoimmune diseases or autoimmune features, idiopathic NSIP, chronic HP, and IPF. Apart from IPF, which expectedly had the highest progression rate (57%), all other major diagnostic subgroups consistently showed progression rates between 30 and 40% (**Supplementary Table 2**), which integrates well into existing evidence (12, 14). Importantly, results of sensitivity and specificity analyses as shown in the ROC curve in **Figure 5** were comparable with those of established prognostic scores such as GAP and the composite physiologic index (CPI) used for assessment of mortality risk (22, 42), or the SPO_2 and ARthritis (SPAR) model used for prognosis of progression in SSC-ILD (43).

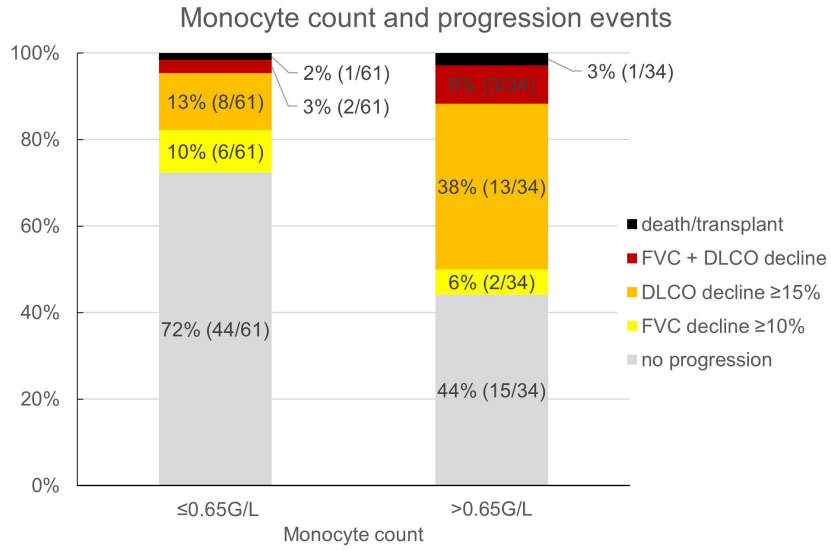

FIGURE 3
Monocyte count and fraction (number) of progression events. FVC, forced vital capacity; DLCO, diffusion capacity for carbon monoxide.

TABLE 4 Uni- and multivariate models for progression at 1 year and scoring of significant variables.

Variable	Univariate		Multivariate		Score points
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	
Age ≥70 vs. <70 years	2.29 (0.98–5.35)	0.055			–
Sex (female vs. male)	0.68 (0.29–1.61)	0.191			–
Traction bronchiectasis/honeycombing 1–4 vs. 0	3.39 (0.69–16.5)	0.132	3.38 (0.67–17.3)	0.142	1
Traction bronchiectasis/honeycombing 5–6 vs. 0	**9.00 (1.57–51.46)**	**0.014**	**8.54 (1.43–51.2)**	**0.019**	**2**
Reticular lung abnormalities 5–6 vs. 0–4	2.48 (0.97–6.37)	0.059			–
Blood monocyte count ≥0.65 vs. <0.65 G/L	**3.28 (1.36–7.89)**	**0.008**	**3.16 (1.27–7.88)**	**0.014**	**1**
Blood lymphocyte count ≥1.6 vs. <1.6 G/L	1.02 (0.44–2.34)	0.971			–
Forced vital capacity (L)	0.98 (0.65–1.49)	0.933			–
Diffusion capacity for carbon monoxide [mmol/(min × kPa)]	0.94 (0.72–1.22)	0.632			–

Reticular lung abnormalities score of 0 was only present in one patient, thus the scores were merged to 0–4. OR, odds ratio; CI, confidence interval. Bold values indicate statistically significant variables.

Still, our proposed HTM-score with an AUC of 71.7% is certainly not a perfect prognostic tool. Alone, it should neither be used for therapeutic decisions, nor does it alleviate the expert physician's responsibility to individually assess and follow every ILD patient thoroughly. However, there is rapidly increasing evidence that fibrotic ILD progression is paralleled by high mortality and that anti-fibrotic therapies should be established as soon as possible in such cases. We know from between-trial comparisons of placebo-groups in various trials on nintedanib that progression rate in non-IPF ILD like SSC-ILD may be lower as compared to IPF, but the net therapeutic effect of anti-fibrotics on disease progression itself seems comparable in different fibrotic ILD entities (8–11, 44, 45). Nevertheless, at the moment most treatment guidelines and expert opinions regarding non-IPF ILD such as ILD associated with autoimmune diseases or HP suggest anti-inflammatory drugs or observation as first-line option (13, 14, 46–48), while anti-fibrotic treatment with nintedanib is only recommended upon evidence of significant fibrotic disease progression (12). Still, fibrotic ILD progression can occur early and is usually irreversible. In contrast, reported response rates to anti-inflammatory therapies in fibrotic ILD are only modest and furthermore, such treatment can also result in increased morbidity and mortality in some patients (49). A considerable fraction of patients would undoubtedly benefit from earlier initiation of anti-fibrotic therapy, either alone or in combination with anti-inflammatory drugs. Our proposed score allows for a reasonably accurate estimation of progression-risk within the

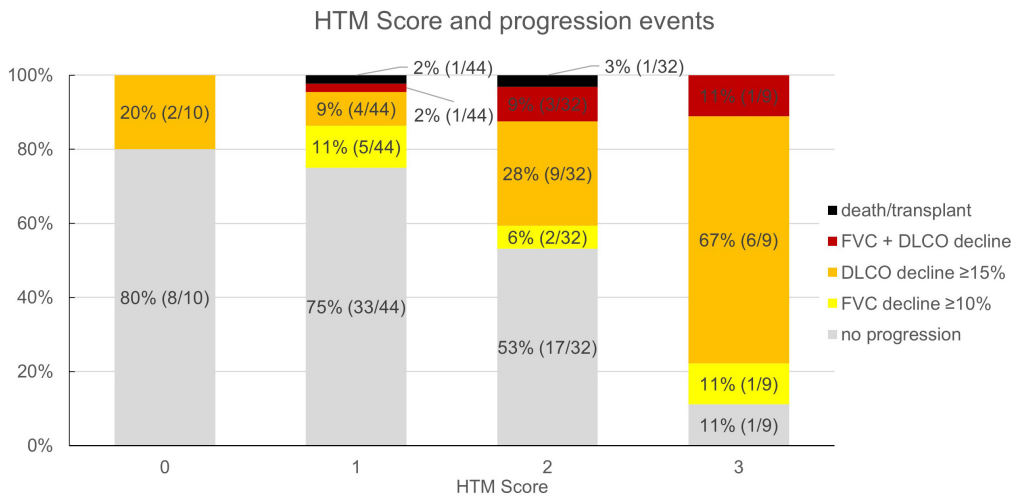

FIGURE 4
Honeycombing, traction bronchiectasis, and monocyte score and fraction (number) of progression events in the derivation cohort (n = 95). HTM, honeycombing, traction bronchiectasis, and monocyte; FVC, forced vital capacity; DLCO, diffusion capacity for carbon monoxide.

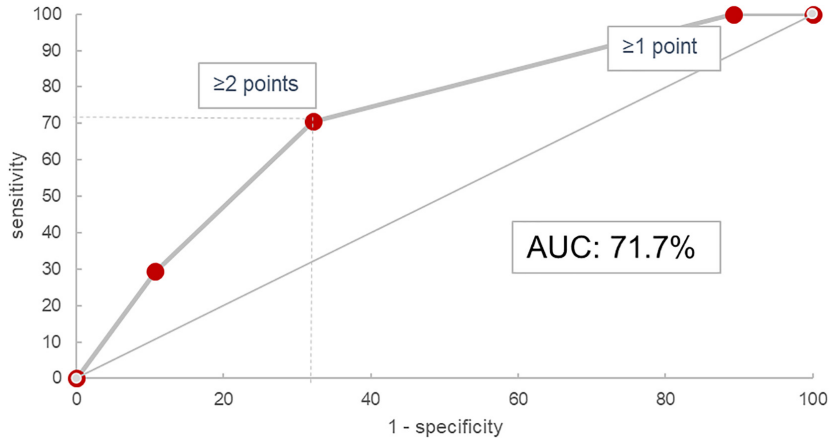

FIGURE 5
Receiver operating characteristic curve for the HTM score in the validation cohort. AUC, area under the curve.

first year, based on widely available and easy to assess routine biomarkers. It could thus facilitate early initiation of anti-fibrotic treatment by prompting either more aggressive therapy earlier in the course of disease or at least closer monitoring for progression in patients identified to be at high risk.

We are aware that only recently, lower FVC and DLCO cut-off values for disease progression in PPF have been suggested by the ATS/ERS/JRS/ALAT guidelines (12), and our model could not be reenacted using these. However, one must keep in mind that these novel lung function progression criteria are intended to be applied together with clinical and radiological measures of disease progression that were not available in follow-up of our patients. Thus, our applied thresholds for progression necessarily needed to be higher to differ between clinically significant deterioration and physiological variation with a reasonable sensitivity and specificity. In line with that, Pugashetti et al. recently showed that a previous decline in FVC of ≥10% was the best biomarker for 5-year transplant-free survival in non-IPF ILD patients (50).

In our cohort, DLCO decline was the most frequent indicator of disease progression. However, DLCO had not been widely adopted as biomarker of disease progression in ILD until recently (12), due to its known methodologically determined variability and a variety of confounding factors like emphysema or pulmonary hypertension (12, 30, 51–53). We have analyzed progression-risk in association with presence and extent of emphysema as well as with pulmonary artery to aorta diameter as a surrogate for pulmonary hypertension and did not find

statistically significant or clinically meaningful interactions as shown in **Table 1**. Also, despite its limitations, assessment of DLCO decline was included in the 2022 PPF criteria, due to its well established association with mortality in various ILD (12, 54, 55). A threshold of 15% relative decline in DLCO has repeatedly been used to denominate progression in various ILD studies (11, 43, 53), however this was now replaced by a threshold of 10% absolute decline in the recent guidelines (12). Concerning our statistical methods, the use of interpolation to assess the course of lung function variables at 1 year may require further discussion. However, an exploratory analysis excluding all patients with missing PFT at 1 year ± 2 months from the validation cohort (n = 17; 36%) showed a nearly equal AUC of 71.6% in the ROC analysis as explicated in **Supplementary Figure 1** and **Supplementary Table 3**.

Another obvious limitation of this study is the absence of exact quantification of radiological changes. In our scores, only presence or absence of various radiological changes was assessed in the defined lung fields, but not the exact quantity of these changes within these fields. Thus, also the determined cut-off values to denote limited and abundant extent bear some uncertainty and may reduce comparability with other studies. Rather than exact quantification, our radiological evaluation approach reflects a fast and "eyeballing" evaluation of either absence, limited presence, or abundance of defined HRCT abnormalities. Therefore, it can be performed rapidly and requires neither costly software, nor a specialist radiologist. It may also be advantageous that the occasionally difficult differentiation between honeycombing and traction bronchiectasis is not necessary here (56). Nevertheless, an exact quantification of radiological abnormalities would be feasible using computer-based quantification algorithms, but these are not yet available to the wider clinical practice. In any case, our results of honeycombing and traction bronchiectasis being the main prognostic imaging biomarkers towards disease progression are well in line with studies using both visual scoring approaches and computer-based quantification systems (19, 21, 57).

Monocyte count has been repeatedly reported as significant prognostic biomarker for disease progression in various ILD (24, 58, 59), however it may be altered by extrapulmonary factors such as infections or medication(60–62). On the other hand however, routine blood cell counts are widely available and cheap to assess. Associations of immunomodulatory drugs with monocyte counts have been evaluated in smaller studies and indicated no or only small influence of such therapies (63, 64). Anti-fibrotic treatment on the other hand may decrease peripheral blood monocyte counts (59). In our cohort however, the majority of patients received ILD-specific treatment only after initial evaluation and inclusion into the ILD registry, so that such treatment effects are unlikely to have influenced the presented outcomes.

Pending further validation, the HTM-score can only be interpreted in the context of the underlying patient collective, which included a broad spectrum of different fibrotic ILD consecutively discussed by an experienced ILD-board in a university tertiary referral hospital. This may have led to the inclusion of rather complex cases, especially with an emphasis on ILD in rheumatological conditions, likely at the cost of more overt cases like IPF or sarcoidosis. Patients were included into this study regardless of their consecutive therapy which may have influenced the individual disease course over the first year. Only a minority of patients received anti-fibrotic therapy, which may be due to the more restrictive prescription regulations at the time of evaluation. On the other hand, a wide variety of anti-inflammatory therapies were applied, most commonly corticosteroids, and non-biological disease modifying drugs, at different doses and durations. Therefore, our classification of "anti-inflammatory therapy" constitutes only a minimum consensus for a very heterogeneous variable, which was necessary to enable any statistical analysis. Using random assignment to a derivation and a validation cohort, we sought to minimize temporal variability within the cohort. In addition, it appears unlikely that one diagnostic or therapeutic subgroup could have biased our results: Diagnosis categories (**Supplementary Table 2**) and treatment characteristics (**Table 1**) showed no significant interaction with disease progression and treatment modalities were well balanced between diagnostic subgroups, with the exception of a higher usage of anti-inflammatory medication in CTD-ILD (**Supplementary Figure 2**).

We conclude that our proposed HTM score was effective for prognosis of progression within the first year in a cohort of fibrotic ILD patients. This could enable earlier detection of progressive fibrosis and aid timely initiation of adequate therapy. Our results reflect the current knowledge of prognostic biomarkers in fibrotic ILD, and they could be reenacted in a randomly assigned validation cohort. Still, these findings warrant further validation in larger cohorts and using enhanced imaging modalities like computer-based HRCT quantification tools.

Data availability statement

As mandated by the ethics committee, publication or dissemination of any possibly identifiable patient data from the present registry is prohibited. The dataset used for the present analyses contains very detailed and thus possibly identifiable patient data. Therefore, publication of the full database is not possible. However, upon reasonable request to the authors and if permitted by the ethics committee in an amendment to the study protocol, anonymized data can under certain circumstances be shared.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Medical Faculty of Linz. The patients/participants provided their written informed consent to participate in this study.

Author contributions

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

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.2022.1043720/full#supplementary-material

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Progressive fibrosing interstitial lung disease in rheumatoid arthritis: A retrospective study

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Background and objective: Rheumatoid arthritis associated-interstitial lung disease (RA-ILD) is the most common pulmonary manifestation of rheumatoid arthritis (RA) and an important cause of mortality. In patients suffering from interstitial lung diseases (ILD) from different etiologies (including RA-ILD), a significant proportion is exhibiting a fibrotic progression despite immunosuppressive therapies, defined as progressive fibrosing interstitial lung disease (PF-ILD). Here, we report the frequency of RA-ILD and PF-ILD in all RA patients' cohort at University Hospital of Liège and compare their characteristics and outcomes.

Methods: Patients were retrospectively recruited from 2010 to 2020. PF-ILD was defined based on functional, clinical and/or iconographic progression criteria within 24 months despite specific anti-RA treatment.

Results: Out of 1,500 RA patients, about one third had high-resolution computed tomography (HRCT) performed, 89 showed RA-ILD and 48 PF-ILD. RA-ILD patients were significantly older than other RA patients (71 old of median age vs. 65, $p < 0.0001$), with a greater proportion of men (46.1 vs. 27.7%, $p < 0.0001$) and of smoking history. Non-specific interstitial pneumonia pattern was more frequent than usual interstitial pneumonia among RA-ILD (60.7 vs. 27.0%) and PF-ILD groups (60.4 vs. 31.2%). The risk of death was 2 times higher in RA-ILD patients [hazard ratio 2.03 (95% confidence interval 1.15–3.57), $p < 0.01$] compared to RA.

Conclusion: We identified a prevalence of PF-ILD of 3% in a general RA population. The PF-ILD cohort did not seem to be different in terms of demographic characteristics and mortality compared to RA-ILD patients who did not exhibit the progressive phenotype yet.

KEYWORDS

interstitial lung disease, lung fibrosis, rheumatoid arthritis, epidemiological characteristics, disease progression, survival

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease affecting 0.5–1% of the general population (1, 2). Through the development of biologic or Janus kinase inhibitor therapies, the joint prognosis of RA patients has improved significantly (3). Nevertheless, some extra-articular manifestations, including pulmonary involvement, are a major contributor to morbidity and mortality (4–6). Interstitial lung disease (ILD), referred to as rheumatoid arthritis-associated interstitial lung disease (RA-ILD), is the most common pulmonary manifestation (6–8). Understanding its pathogenic and clinical characteristics is crucial because no specific strategic therapy has not been established yet and patients remain difficult to treat (3). A low disease activity in the joints could prevent the emergence, progression and exacerbation of RA-ILD (3). It typically develops in the fifth or sixth decade and can be diagnosed up to 10 years after RA but sometimes occurs before joint symptoms (4, 9–12). According to the PERSEIDS study, it's prevalence in Europe ranges from 1 to 18.1 per 10^5 persons and among all subtypes of ILDs that are non-idiopathic pulmonary fibrosis (IPF), RA-ILD had the highest incidence in Belgium in 2018 (13).

More generally, in patients suffering from ILDs (including RA-ILD), a significant proportion is exhibiting a fibrotic progression despite appropriate treatment and regardless of the underlying ILD, defined as progressive fibrosing interstitial lung disease (PF-ILD) (14–16). Clinical, radiological and prognostic similarities are described with IPF which is the archetype of PF-ILD: accelerated respiratory failure, frequent exacerbations and early mortality (14, 16).

In 2019, the INBUILD trial used arbitrary criteria for progression of ILD within 24 months before screening, despite standard treatment with an agent other than nintedanib or pirfenidone (17):

- a relative decline in the forced vital capacity (FVC) of at least 10% of the predicted value;
- or a relative decline in the FVC of 5% to less than 10% of the predicted value and worsening of respiratory symptoms or an increased extent of fibrosis on high-resolution computed tomography (HRCT) of the chest;
- or worsening of respiratory symptoms and an increased extent of fibrosis on HRCT.

Among a global RA patients' cohort, this retrospective study investigates the frequency and compares the characteristics and mortality rates of RA-ILD (vs. other RA) patients and PF-ILD (vs. other RA-ILD) patients.

Abbreviations: ACPA, anti-citrullinated peptide antibodies; ATS, American Thoracic Society; CI, confidence interval; CRP, C-reactive protein; CTD-ILD, connective tissue disease-related interstitial lung disease; DLCO, diffusing lung capacity for carbon monoxide; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NSIP, non-specific interstitial pneumonia; RA, rheumatoid arthritis; RA-ILD, rheumatoid arthritis-associated interstitial lung disease; PF-ILD, progressive fibrosing interstitial lung disease; PFT, pulmonary function test; RF, rheumatoid factor; TLC, total lung capacity; UIP, usual interstitial pneumonia.

Materials and methods

Population study

Patients were retrospectively recruited from our ambulatory care policlinic at University Hospital of Liège in Belgium from 01-01-2010 to 01-01-2020 based on a systematic evaluation of electronic hospital record using specific key word (RA). We selected patients suffering from RA according to ACR/EULAR 2010 Classification Criteria for Rheumatoid Arthritis (18). RA-ILD was defined as patients experiencing lung fibrosis of at least 10% of the lung parenchyma based on a systematic review by pneumologists on available HRCT of the chest.

Among RA-ILD patients, PF-ILD was defined according to INBUILD criteria [see "Introduction" section (17)]. Disease progression was considered at every hospital visit, using overlapping windows of 24 months prior to each hospital visit, until the first event meeting the definition criteria for progression was confirmed (after exclusion of other possible causes of progression: acute decompensated heart failure, bacterial or viral infection and/or ILD acute exacerbation). The end of follow-up was defined as the date of last follow-up visit, death, or lung transplant.

Age was defined at time *T* (i.e., the latest date on which patient underwent, in order of preference: A HRCT of the chest, a pulmonary function test (PFT) or a pneumology or rheumatology consultation). Biological values were the values occurring closest to time *T*. PFT values were the latest available. Treatments were defined at time *T*.

Statistics

Qualitative variables were described using frequency tables, while continuous quantitative variables were described using statistical summaries (median and interquartile range).

Simple logistic regression models were performed. For each model, *p*-values were reported. If the odds ratios of the simple logistic regressions could not be calculated directly, a Haldane correction was performed and the *p*-value of the Fisher exact test was provided.

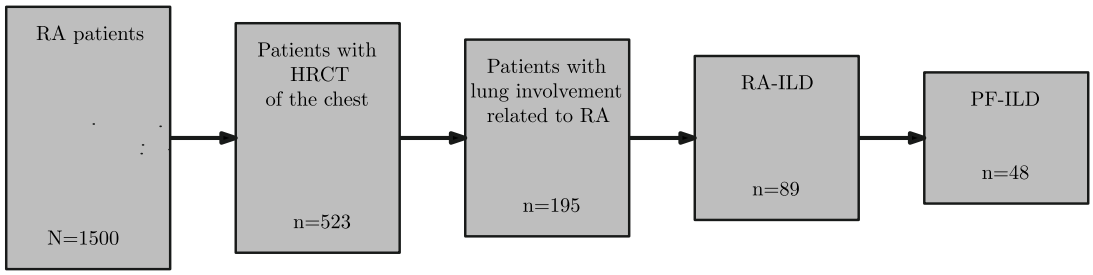

FIGURE 1
Flowchart of RA cohort. RA, rheumatoid arthritis; HRCT, high-resolution computed tomography; RA-ILD, rheumatoid arthritis associated-interstitial lung disease; PF-ILD, progressive fibrosing interstitial lung disease.

In order to allow for certain analyses, a logarithmic normalization of the PFT and biological data was performed. More precisely, a classical log transformation was performed for leukocytes (10^3/mm^3), platelets (10^3/mm^3) and fibrinogen (g/L) and a translational log(– + 0. 1) was applied to measurement of CRP (mg/L).

Overall, survival was represented since the first available PFT by a Kaplan-Meier curve, compared between considered populations by Log-Rank test and supported by the Hazard Ratio (Manted-Haenszel).

Results were considered significant at the 5% uncertainty level ($p < 0.05$). The calculations were performed using SAS version 9.4 and the figures using Matlab 2019b.

No external funding was obtained and the study was conducted by clinicians on their own time.

The protocol was approved by the ethics committee of University Hospital of Liège (Belgian Number: B707201422832; ref: 2022/52).

Results

According to Figure 1, we identified out of a global cohort of 1,500 RA patients, 523 (34.9%) patients with at least one available HRCT of the chest, 195 (13.0% of 1,500) patients exhibiting a significant lung involvement associated with RA and RA-ILD in 89 cases (5.9%). More than half of the latter (48 patients, 53.9%) fulfilled the definition of PF-ILD.

Subjects' demographic, pulmonary functional, biological and treatment characteristics are listed in Tables 1, 2.

Subjects' demographic characteristics

Compared to other RA patients, RA-ILD patients were significantly older (65 years old of median age vs. 71, $p < 0.0001$), with a greater proportion of men (27.7 vs. 46.1%, $p < 0.0001$) and a higher percentage of smoking history. There were no statistically significant demographic differences regarding age, gender and smoking status between RA-ILD and PF-ILD cohorts.

Pulmonary function tests

Spirometric values were lower than predicted values for all cohorts.

Other RA patients' cohort had significantly higher total lung capacity (TLC) (97.0 vs. 82.0% expressed as predicted values, $p < 0.0001$), diffusing lung capacity for carbon monoxide (DLCO) (66.0 vs. 52.5% expressed as predicted values, $p < 0.0001$), DLCO/alveolar ventilation (76.5 vs. 83% expressed as predicted values, $p = 0.013$) and FVC compared to RA-ILD patients (91.0 vs. 83.0% expressed as predicted values, $p = 0.0077$).

Of interest, there was no significant difference with regard to forced expiratory volume in the first second (FEV1) between those two cohorts.

There were no statistically significant functional differences regarding PFT values mentioned above between RA-ILD and PF-ILD cohorts.

Criteria for disease progression and PFT relative changes within 24 months in PF-ILD patients are listed in Supplementary Table 1.

Biological values

Compared to other RA patients, RA-ILD patients were exhibiting an increased leukocyte count (8 870/mm^3 vs. 7 470/mm^3, $p = 0.0008$), with a higher proportion of neutrophils (69.3 vs. 62%, $p = 0.017$), a lower percentage of lymphocytes (18.4 vs. 25.6%, $p = 0.031$) and a higher CRP value (8.9 mg/l vs. 4.1 mg/l, $p = 0.023$). Rheumatoid factor (RF) was more frequently positive in RA-ILD patients (602/1,117 vs. 50/72 patients, $p = 0.011$) while there was no difference concerning anti-citrullinated protein antibodies (ACPA).

TABLE 1 Comparison of patients' characteristics between RA-ILD (n = 89) and other RA patients (n = 1,411).

	RA-ILD n = 89	Other RA patients n = 1,411	P-values
Age, years	71 (66–76)	65 (55–74)	<**0.0001**
Gender (male/female), n	41/48	374/1,037	<**0.0001**
Smoking history, %	70.9	63.1	**0.0014**
TLC [a], %pred	82.0 (64.0–94.0)	97.0 (82.0–106.5)	<**0.0001**
FVC [a], %pred	83.0 (66.0–98.0)	91.0 (78.0–104.0)	**0.0077**
FEV1 [a], %pred	80.0 (61.5–98.0)	86.0 (68.0–98.0)	0.31
DLCO [a], %pred	52.5 (39.5–62.5)	66.0 (50.0–79.0)	<**0.0001**
DLCO/VA [a], %pred	76.5 (62.0–87.5)	83.0 (66.0–94.5)	**0.013**
Hemoglobin, g/dl	12.70 (11.8–14.1)	13.20 (11.8–14.1)	0.47
Platelet count, 0.103/mm^3	274.0 (212.0–334.0)	265.0 (217.0–330.5)	0.61
Leukocyte count, 0.103/mm^3	8.87 (6.8–11.5)	7.47 (5.9–9.9)	**0.0008**
Lymphocytes, %	18.4 (11.0–29.1)	25.6 (16.4–32.8)	**0.031**
Monocytes, %	7.3 (5.7–9.3)	7.70 (5.80–10.0)	0.16
Neutrophiles, %	69.3 (55.5–79.6)	62.0 (53.6–72.8)	**0.017**
CRP, mg/l	8.9 (1.6–33.7)	4.1 (1.3–18.6)	**0.023**
Fibrinogen, g/l	3.9 (3.1–5.6)	3.9 (3.1–5.1)	0.93
ACPA positivity [b], n	50	665	0.72
Rheumatoid Factor positivity [c], n	50	602	**0.011**
Erosive RA [d], n	27	479	0.16
Treated with oral corticosteroids[e], n	26	353	0.28
Treated with methotrexate[f], n	25	578	/
Treated with leflunomide[g], n	1	75	/
Treated with tumor necrosis factor-alpha inhibitors[g], n	15	260	/
Treated with rituximab[g], n	3	33	/
Treated with tocilizumab[g], n	3	24	/
Treated with abatacept[g], n	2	37	/

Continuous variables are expressed as median (interquartile ranges).
[a]At least one PFT was available for 79 RA-ILD patients and 375 other RA patients.
[b]Information about ACPA was available for 67 RA-ILD patients and 1,072 other RA patients.
[c]Information about rheumatoid factor was available for 72 RA-ILD patients and 1,117 other RA patients.
[d]Information about erosive RA was available for 33 RA-ILD and 657 other RA patients.
[e]Information about oral corticosteroids was available for 69 RA-ILD and 1,122 other RA patients.
[f]Information about methotrexate was available for 40 RA-ILD and 816 other RA patients.
[g]Information about leflunomide, tumor necrosis factor-alpha inhibitors, rituximab, tocilizumab and abatacept was available for 37 RA-ILD and 752 other RA patients. RA-ILD, rheumatoid arthritis-associated interstitial lung disease; RA, rheumatoid arthritis; TLC, total lung capacity; %pred, % of predicted value; FVC, forced vital capacity; FEV1, forced expired volume in 1 s; DLCO, diffusion lung capacity for carbon monoxyde; DLCO/VA, DLCO/alveolar ventilation; g/dl, grams per deciliter; mm^3, cubic millimeter; mg/l, milligram per liter; g/l, gram per liter; ACPA, anti-citrullinated peptide antibodies; U/ml, units per milliliter; U/l, units per liter. Bold values mean p-value < 0.05.

Concerning PF-ILD and other RA-ILD patients' comparison, the only biological significant difference was a lower platelet count in PF-ILD patients (253.10^3/mm^3 vs. $310.5.10^3$/mm^3).

Treatment characteristics

Although treatments were not recorded for all patients, use of corticosteroids, methotrexate and biological therapies (tumor necrosis factor alpha inhibitors, rituximab, tocilizumab and/or abatacept) reported equally among RA-ILD patients (26, 25, and 23 patients, respectively). In PF-ILD patients, biological therapies were reported more often than corticosteroids and methotrexate (18 vs. 16 and 12 patients, respectively), whereas in other RA patients, methotrexate was the most frequent treatment (578 patients vs. 353 on corticosteroids and 429 on biological therapies).

High-resolution computed tomography analysis

According to Figure 2, the most frequent lung involvement thought to be associated with RA was bronchiectasis (up to 50% of all patients with lung involvement), followed by non-specific interstitial pneumonia (NSIP) pattern (27.7%), lung nodules (26.2%), usual interstitial pneumonia (UIP) pattern (12.3%), and others (4.6%).

TABLE 2 Comparison of patients' characteristics between PF-ILD (n = 48) and non-PF-ILD patients (n = 41) among RA-ILD (n = 89).

	PF-ILD n = 48	Non-PF-ILD n = 41	P-value
Age, years	72 (66–77)	70 (65–75)	0.43
Gender (male/female), n	23/25	18/23	0.71
Smoking history, %	79.5	60.0	0.26
TLC[a], %pred	83.0 (65.0–96.0)	78.0 (63.0–88.0)	0.76
FVC[a], %pred	81.0 (66.0–97.0)	84.0 (70.0–99.0)	0.75
FEV1[a], %pred	80.0 (65.0–92.0)	80.0 (61.0–98.0)	0.58
DLCO[a], %pred	53.0 (37.0–62.0)	52.0 (41.0–63.0)	0.74
DLCO/VA[a], %pred	78.0 (62.0–87.0)	70.0 (58.0–96.0)	0.98
Hemoglobin, g/dl	13.00 (11.80–14.40)	12.5 (11.2–13.0)	0.08
Platelet count, 0.103/mm^3	253.0 (195.0–301.0)	310.5 (228.0–418.0)	**0.03**
Leukocyte count,0.103/mm^3	8.15 (6.6–12.3)	9.14 (7.43–11.45)	0.44
Lymphocytes, %	22.7 (13.2–30.6)	16.9 (10.3–26.0)	0.59
Monocytes, %	7.30 (5.8–10.2)	7.35 (4.7–8.8)	0.46
Neutrophiles, %	67.1 (53.9–79.3)	72.1 (58.4–79.7)	0.60
CRP, mg/l	8.40 (1.5–28.8)	11.6 (2.4–63.9)	0.33
Fibrinogen, g/l	3.71 (3.1–5.4)	4.1 (3.0–5.9)	0.25
ACPA positivity[b], n	29	21	0.87
Rheumatoid Factor positivity[c], n	29	21	0.95
Erosive RA[d]	17	10	0.88
Treated with oral corticosteroids[e], n	16	10	0.64
Treated with methotrexate[f], n	12	13	/
Treated with leflunomide[g], n	0	1	/
Treated with tumor necrosis factor-alpha inhibitors[g], n	11	5	/
Treated with rituximab[g], n	3	0	/
Treated with tocilizumab[g], n	3	0	/
Treated with abatacept[g], n	1	1	/

Continuous variables are expressed as median (interquartile ranges).
[a]At least one PFT was available for all 48 PF-ILD patients and for 31 non-PF-ILD patients. 10 patients were suffering from stable RA-ILD without symptomatic evolution or CT scan evolution and were included based on the clinical assessment. No PFT was available for this sub-cohort.
[b]Information about ACPA was available for 39 PF-ILD patients and 28 non-PF-ILD patients.
[c]Information about rheumatoid factor was available for 41 PF-ILD patients and 31 non-PF-ILD patients.
[d]Information about erosive RA was available for 21 PF-ILD patients and 12 non-PF-ILD patients.
[e]Information about oral corticosteroids was available for 40 PF-ILD and 29 non-PF-ILD patients.
[f]Information about methotrexate was available for 23 PF-ILD and 17 non-PF-ILD patients.
[g]Information about leflunomide, tumor necrosis factor-alpha inhibitors, rituximab, tocilizumab and abatacept was available for 22 PF-ILD and 15 non-PF-ILD patients. PF-ILD, progressive fibrosing interstitial lung disease; TLC, total lung capacity; %pred, % of predicted value; FVC, forced vital capacity; FEV1, forced expired volume in 1 s; DLCO, diffusion lung capacity for carbon monoxyde; DLCO/VA, DLCO/alveolar ventilation; g/dl, grams per deciliter; mm^3, cubic millimeter; mg/l, milligram per liter; g/l, gram per liter; ACPA, anti-citrullinated peptide antibodies; U/ml, units per milliliter; U/l, units per liter; RA, rheumatoid arthritis. Bold values mean p-value < 0.05.

ILD patterns in RA-ILD and PF-ILD groups are listed in Table 3. Among RA-ILD patients, NSIP pattern was the most frequent (60.7%) followed by UIP (27.0%) and other or mixed patterns (12.6%). In PF-ILD patients, NSIP was also the most frequent pattern (60.4 vs. 31.2% for UIP and 8.3% for mixed or other patterns).

Survival analysis

RA-ILD patients exhibited higher mortality rates than RA patients without ILD ($p < 0.01$) (Figure 3). The risk of death was 2 times higher among the RA-ILD group [hazard ratio 2.03 (95% confidence interval (CI) 1.15–3.57)] compared to RA patients. The relevance of the statistical evaluation comparing mortality between RA-ILD and PF-ILD groups was considered to be non-significant as only 9 patients died in the PF-ILD group.

Discussion

A progressive phenotype was observed in approximately 3% of a global RA cohort and in up to 50% of an RA-ILD cohort in this retrospective study.

RA-ILD patients were older than the general RA population with a male predominance and an increase in tobacco exposure.

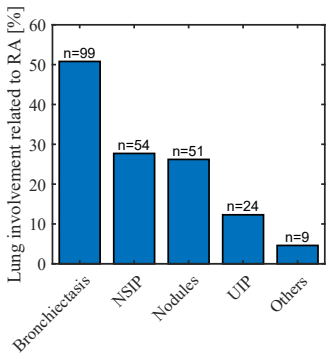

FIGURE 2
Lung involvement related to RA. NSIP, non-specific interstitial pneumonia; UIP, usual interstitial pneumonia.

TABLE 3 Interstitial lung disease patterns in RA-ILD (*n* = 89) and PF-ILD patients (*n* = 48).

	RA-ILD *n* = 89	PF-ILD *n* = 48
NSIP, n (%)	54 (60.7%)	29 (60.4%)
UIP, n (%)	24 (27.0%)	15 (31.2%)
Mixed pattern or other pattern, n (%)	11 (12.6%)	4 (8.3%)

RA-ILD, rheumatoid arthritis-associated interstitial lung disease; PF-ILD, progressive fibrosing interstitial lung disease; NSIP, non-specific interstitial pneumonia; UIP, usual interstitial pneumonia.

Confirmatory, previous studies already identified that RA-ILD typically develops in the fifth or sixth decade and the male-to-female ratio may be as high as 2:1 in some studies (whereas RA-non-ILD more often occurs in women) (4, 9, 10, 19).

Cigarette smoking has been shown to increase expression of the enzyme responsible for citrullination in the lungs, transforming arginine into citrulline and creating new epitopes against which autoantibodies, called anti-citrullinated protein antibodies (ACPA) can react (20, 21). In a large Swedish cohort study, smoking and having a double copy of the shared HLA-DR epitope increased the risk of RA by 21-fold compared to patients without this combination (22). This suggests that, in case of a genetic predisposition, smoking may promote anti-citrulline autoimmunity, a possible pathophysiological mechanism for the development of RA and RA-ILD (5).

Six percent of RA patients involved in this study were suffering from RA-ILD. This prevalence is most likely underestimated because of the retrospective design of the study and the restricted number of patients with available chest HRCT. Although HRCT currently replaces lung biopsy in standard practice for the diagnosis of RA-ILD (23, 24), underdiagnosis probably persists because of the poor symptomatology and the lack of awareness of clinicians regarding RA-ILD (23). Symptoms may also be masked by the lack of exercise performed by RA patients due to their joint symptoms or due to steroids induced myopathy (23). Studies estimate that 45–68% of patients show involvement on HRCT or PFTs while only 10% have clinically active RA-ILD (25, 26). In our study, RA-ILD represented 17% of all RA patients with an available HRCT. A further limitation was that RA-ILD group was compared to the general RA population rather than only patients with an available HRCT because it was assumed that patients without HRCT were asymptomatic and therefore with a low probability of suffering from any lung disease. Besides, the systematic review of the HRCTs was performed by pneumologists (and not expert radiologists).

Among described HRCT patterns, UIP is usually the most described, reaching 40–65% of RA-ILD cases depending on the studies followed by NSIP, affecting approximately 10–40% of patients (10, 27). In disagreement with these findings, NSIP was more frequent in the present study among RA-ILD and PF-ILD patients (including 60.7 and 60.4% of cases, respectively), while UIP was found in 27 and 31.2% of patients. This observation is thought to be due to the restricted number of RA-ILD patients in our study.

Confirmatory to previous studies, RA-ILD patients showed significantly higher mortality rates than RA patients without ILD. According to Hyldgaard et al., RA-ILD patients die 2–10 times more than those without ILD (28). Other studies show that fibrotic lung involvement is responsible for 10–13% of RA-associated mortality, making it the second leading cause of death after cardiac involvement and that mean survival times vary from 2.6 to 10 years (4, 29–31). This high mortality rate, together with the fact that most patients present subclinical findings, raises the question of early screening for ILD signs among RA patients.

Moreover, UIP pattern is generally associated with a more severe prognosis compared to NSIP (32, 33). However, according to Solomon et al., regardless of the UIP or NSIP pattern, patients with a 10% decline in FVC (% predicted value) had an increased risk of mortality, implying an increased risk of death in case of functional decline defined as a 10% decline in FVC (30).

Nearly 50% of RA-ILD patients showed a PF-ILD phenotype in the present study. This percentage is higher than in the PERSEID study, a large European retrospective study, demonstrating a progressive pattern in 38% of RA-ILD patients (13). We believe that screening PF-ILD patients is of potential interest for the therapeutic management of RA-ILD patients. Treatment of RA-ILD is currently mainly based on retrospective studies due to the absence of randomized controlled trials studying the impact of RA specific therapies on the evolution of ILD in comparison to the standard of care (4, 27, 34). Historically, it was recognized that drug-related pulmonary toxicity could be a confounding factor in RA whereas several studies suggested that this was previously over-estimated (27, 35).

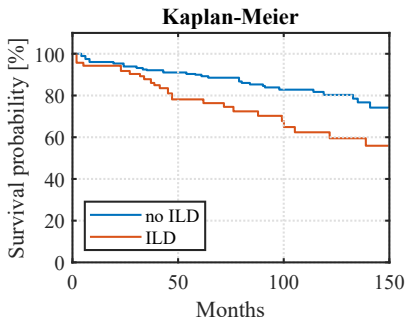

FIGURE 3
Survival curves from first available pulmonary function test comparing RA-ILD to other RA patients. Rheumatoid arthritis-associated interstitial lung disease (ILD) patients exhibited higher mortality rates than rheumatoid arthritis patients without ILD (noILD) ($p < 0.01$). noILD, no interstitial lung disease; ILD, interstitial lung disease.

In the particular context of PF-ILD, regardless of the underlying etiology, parenchymal fibrotic changes seen in patients suffering from progressive ILD are thought to have common mechanisms of self-reinforcing progressive fibrosis (including impaired cellular repair, fibroblast proliferation, and alveolar dysfunction) (14, 15, 18). This calls for a homogeneous therapeutic strategy using, in particular, antifibrotics drugs which demonstrated their efficacy in IPF, the archetype of PF-ILD (14–16, 31). Confirmatory, the INBUILD trial, a double-blind, placebo-controlled, phase 3 trial conducted in 15 countries, showed that patients suffering from PF-ILD were presenting a significant reduction of lung decline over time (17). RA-ILD patients, especially with the UIP pattern, share common epidemiologic, clinical, genetic and radiologic features with IPF patients (4, 27, 34, 36, 37) increasing the rationale of using anti-fibrotic therapies in this particular subgroup. Genetic similarities regarding variant of the MUC5B promoter known to be a major risk factor for IPF have been found in RA-ILD: Juge et al. observed that this variant was more frequent in RA-ILD than in unaffected controls (adjusted odds ratio, 3.8; 95% CI, 2.8–5.2; $p = 9.7 \times 10^{-17}$) (38, 39).

The use of antifibrotic therapies in RA-ILD (and especially PF-ILD) is further supported by a mouse model in 2018 showing a reduction of both fibrosis and joint disease after nintedanib use in RA-ILD mice (40). In addition, pirfenidone reduces levels of interleukine-6 and tumor necrosis factor alpha, two cytokines involved in the pathogenesis of RA (41). Wu et al. showed that pirfenidone inhibited fibroblast to myofibroblast transition in lung fibroblasts from RA-ILD patients (42).

The INBUILD study showed that the FVC decline over 52 weeks was significantly lower in patients with PF-ILD of various origins (except IPF) treated with nintedanib compared with placebo. In the overall population, the adjusted rate of decline in the FVC was −80.8 ml per year with nintedanib and −187.8 ml per year with placebo, for a between-group difference of 107.0 ml per year (95% CI, 65.4–148.5; $p < 0.001$) (17). A *post hoc* subgroup analysis suggested a benefit of treatment in terms of slowing the decline of FVC in all PF-ILD subgroups, including connective tissue disease-related interstitial lung disease (CT-ILD) (and involving 89 patients with RA-ILD) (43).

In the future, randomized controlled trials are necessary in order to study the efficacy of these antifibrotic therapies in RA-ILD and to determine valid screening tools. As for screening some complications in other autoimmune diseases (e.g., bone remodeling markers in systemic scleroderma), various biomarkers could be of interest in order to identify RA-ILD patients at risk of progression but still need to be thoroughly validated before being implemented in clinical use (44, 45).

For the first time, American Thoracic Society (ATS) published guidelines for "progressive pulmonary fibrosis" (PPF) definition in 2022 (46). They define PPF in patients meeting at least two of the three following criteria occurring within the last year in the absence of alternative explanation: worsening of respiratory symptoms, physiological evidence of disease progression (absolute decline in FVC of > 5% or absolute decline in DLCO of > 10%) and radiological evidence of disease progression. The decision was made to maintain the use of INBUILD criteria for "PF-ILD group" in the present study as it was conducted prior to the ATS publication (17). These ATS guidelines suggest the use of nintedanib in patients who have failed standard management for fibrotic ILD, other than IPF, by referring mainly to INBUILD study and its *post hoc* analysis as evidence, implying that the use of its inclusion criteria are in line with the therapeutic possibilities in these patients (17, 46). Meanwhile, the 2022 ATS definition should be considered in future prospective studies.

Conclusion

In conclusion, the current study provides valuable information about RA-ILD and PF-ILD patients in a single-center academic cohort of patients suffering from RA. These results show a 6% prevalence of RA-ILD with half of them presenting a progressive phenotype. While RA-ILD have a higher mortality rate and are mainly older men with lower PFT values and higher smoking status and CRP values compared to other RA patients, there were no differences concerning survival and other characteristics between RA-ILD and PF-ILD patients. There remains an unmet need to identify at the earliest stage patients suffering from the progressive phenotype with a specific screening and therapeutic strategy based on further dedicated large clinical trials.

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 Ethics Committee of University Hospital of Liège (Belgian Number: B707201422832; ref: 2022/52). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

AD was the lead writer of the original draft and contributed equally to others to conceptualization (ideas; formulation or evolution of overarching research goals and aims), data curation, investigation, methodology and visualization (preparation, creation, and presentation of the work). MH contributed equally to others to conceptualization, data curation, formal analysis, investigation, methodology, validation (verification of the overall replication and reproducibility of the results and the other research outputs), and review of writing. ME, NM, and MT contributed equally to data curation, formal analysis, investigation, and methodology. ME contributed to review of writing. CR, OM, A-NF, FG, CD, and PM contributed equally to review of writing. FG contributed equally to others to data curation and investigation. RL and MM contributed equally to supervision and review of writing. JG was leader in conceptualization, methodology, resources and review of writing and contributed equally to investigation, supervision, and validation. All authors contributed to the article and 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.2022.1024298/full#supplementary-material

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New prognostic scoring system for mortality in idiopathic pulmonary fibrosis by modifying the gender, age, and physiology model with desaturation during the six-minute walk test

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Background: Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial lung disease (ILD) with variable and heterogeneous clinical course. The GAP (gender, age, and physiology) model had been used to predict mortality in patients with IPF, but does not contain exercise capacity. Therefore, our aim in this study was to develop new prognostic scoring system in the Korea IPF Cohort (KICO) registry.

Materials and methods: This is a retrospective study of Korean patients with IPF in KICO registry from June 2016 to August 2021. We developed new scoring system (the GAP6) based on the GAP model adding nadir saturation of percutaneous oxygen (SpO_2) during six-minute walk test (6MWT) in the KICO registry and compared the efficacy of the GAP and the GAP6 model.

Results: Among 2,412 patients in KICO registry, 966 patients were enrolled. The GAP6 model showed significant prognostic value for mortality between each stage [HR Stage II vs. Stage I=2.89 (95% CI=2.38–3.51), HR Stage III vs. Stage II=2.68 (95% CI=1.60–4.51)]. In comparison the model performance with area under curve (AUC) using receiver operating characteristic (ROC) curve analysis, the GAP6 model showed a significant improvement for predicting mortality than the GAP model (AUC the GAP vs. the GAP6, 0.646 vs. 0.671, $p<0.0019$). Also, the C-index values slightly improved from 0.674 to 0.691 for mortality.

Conclusion: The GAP6 model adding nadir SpO_2 during 6WMT for an indicator of functional capacity improves prediction ability with C-index and AUC. Additional multinational study is needed to confirm these finding and validate the applicability and accuracy of this risk assessment system.

KEYWORDS

idiopathic pulmonary fibrosis, interstitial lung disease, mortality, prognosis, six-minute walk test

Introduction

Idiopathic pulmonary fibrosis (IPF) is a typical and progressive chronic fibrosing interstitial lung disease (ILD) with a highly variable clinical course and poor outcomes (1). Despite recent advances, including anti-fibrotic agents, and increasing awareness of IPF, its mortality rate is still high, and the median survival time is only 2.5–4 years (2–4). Moreover, the clinical course and prognosis vary widely according to the presence of acute exacerbation, comorbidities, disease severity, and availability and side effects of anti-fibrotic agents (5–7).

Staging systems of disease severity are crucial and useful for determining prognosis and guiding management decisions. Several clinical prediction models have been developed for patients with IPF, and the gender, age, and physiology (GAP) model is most commonly used (8–10). The GAP model is simple and convenient to use and has been demonstrated to be reliable for predicting survival in previous studies (9, 11). However, the GAP model has some limitations. In a validation study of the GAP model, there was a lack of discriminative performance for predicting prognosis according to stage or over a long term (12, 13). Also, the GAP model is based on gender, age, and lung function data as baseline predictors without considering other important predictors, including exercise capacity and hypoxemia. The six-minute walk test (6MWT) is a basic test recommended in international guidelines due to its simplicity, and desaturation during 6 MWT is a strong predictor of mortality in IPF patients (5, 14). Therefore, our aim in this study was to develop a new prognostic scoring system modifying the GAP model with desaturation during the 6MWT using data from the Korea IPF Cohort (KICO) registry.

Materials and methods

Study subjects

Patients with IPF included in the KICO registry from June 2016 to August 2021 were enrolled in this retrospective study. A total of 23 universities and teaching hospitals in Korea was involved in the KICO registry, and IPF diagnosis was based on multidisciplinary discussion (MDD) among health care professionals, including a pulmonologist, radiologist, and pathologist, according to the criteria of the American Thoracic Society (ATS)/European Respiratory Society (ERS) guideline (14, 15). Medical records of patients were reviewed using KICO web-based registry data.[1] This study was approved by the Institutional Review Board of Haeundae-Paik Hospital (approval no. 2021-07-017), and the requirement for written informed consent was waived due to the retrospective nature of this study.

Validation of the GAP model

Total GAP score was calculated by four clinical variables of gender (women: 0 point, man: 1 point), age (0–2 point), FVC (0–2 point), and DLco (0–3 point). The GAP stage was classified into three stages based on the total GAP score. Validation of the GAP model in the KICO registry was performed to evaluate the effectiveness of the new scoring system modifying the GAP model with desaturation during 6MWT. Total GAP

[1] http://IPF.crf.kr

score calculations and disease stage classifications were completed based on the criteria originally suggested by Ley et al. (9). We evaluated the 1-, 2-, and 3-year mortality rates at each stage or score based on the GAP index.

Development of a new scoring system modifying the GAP model

Baseline values at IPF diagnosis were considered as predictors in this study. After Cox proportional hazards regression analysis to predict survival, desaturation during 6MWT was confirmed to be a statistically significant predictor in addition to variables of the GAP model. Thus, we selected and added desaturation during 6MWT to the GAP model and developed the new scoring system, known as GAP6, to predict mortality in IPF patients. We added the points for desaturation in the GAP6 model according to the coefficients of the Cox regression models, and a nomogram consisting of five variables with point contributions was created using the GAP6 model. Finally, we compared the efficacy for predicting prognosis between the GAP model and the GAP6 model using the C-index and area under the receiver operating characteristic (ROC) curve (AUC).

Statistical analysis

Data are presented as frequency with percentage for categorical variables and mean ± standard deviation (SD) for continuous variables.

Overall survival probability was estimated with the Kaplan–Meier method. The difference between the three disease stages was assessed using the log-rank test. The time interval was measured from the day of diagnosis until death or last follow-up. Death from all causes was included. Univariate and multivariate Cox proportional hazards models were fit to examine the relationships between survival time and patient characteristics.

Nomogram development began by identifying patient characteristics predictive for overall survival in the multivariate Cox model. These characteristics were gender, age, forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide (DLco), and nadir saturation of percutaneous oxygen (SpO2).

Univariate and multivariate analyses using binary logistic regression were performed to identify prognostic factors independently related to 3-year mortality. In addition, to compare model performance, ROC curve analysis was performed to assess the sensitivity and specificity of the modified GAP score and staging system to predict 3-year mortality.

All statistical analyses were carried out using SPSS version 26.0 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.), R version 4.1.2 (R Core Team [2021]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL, https://www.R-project.org/), and MedCalc Statistical Software version 19.2.6 (MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org; 2020). $p < 0.05$ was considered statistically significant.

Results

Study population and baseline characteristics

A total of 2,412 patients was registered from June 2016 to August 2021 in the KICO registry (Figure 1). Of them, 463 patients were excluded because they did not meet the international criteria for IPF diagnosis after central and individual institutional MDD reviews. Additionally, among 1,949 patients with IPF, 222 with incomplete data for gender, age, physiologic variables, or survival data were also excluded. Finally, 966 patients were included in the analysis. The baseline characteristics of these patients are summarized in Table 1. The mean age was 71.2 years, and men (81.1%) were more common than women. The mean age at diagnosis of IPF was 68.2 years (men vs. women, 68.1 vs. 68.7 years; $p = 0.301$). Most patients exhibited a mild restrictive ventilator defect (FVC, % predicted between men and women, 73.9% vs. 74.9%, $p = 0.471$) and reduced DLco. During 6MWT, the mean distance was 412.7 m and the nadir SpO2 was 90.1%. More than two-thirds of the patients had been treated with anti-fibrotic agents, and there was no difference in treatment according to gender (men vs. women, 71.8% vs. 71.1%, $p = 0.846$).

Validation of the GAP model

The GAP model revealed 507 patients with GAP stage I (52.5%), 390 patients with GAP stage II (40.4%), and 69 patients with GAP stage III (7.1%) (Table 2). The median duration of follow-up was 60.4 months. Of the 966 included patients, 440 (45.5%) died during the study period. The median time to death was 83.8 months (95% confidence interval [CI], 75.2–92.4 months). A total of 257 patients (26.6%) died within 3 years, and the observed cumulative mortality rate differed significantly according to GAP stage (log-rank test, $p < 0.001$). Survival was significantly different by disease stage (hazard ratio [HR] stage II vs. stage I, 2.52 [95% CI, 2.07–3.08]; HR stage III vs. stage II, 2.64 [95% CI, 1.52–4.61]) (Figure 2). In the analysis of survival probability using Kaplan–Meier plotting, the 3-year mortality rates for the GAP stage I, II, and III groups were 2.4, 6.5, and 50.1%, respectively. A statistically significant difference was found among the GAP stage I, II, and III groups (log-rank $p < 0.001$).

Development of a new scoring system modifying the GAP model

The Cox proportional hazards regression analysis to verify the significance of nadir SpO2 (HR, 0.972; 95% CI, 0.960–0.984; $p < 0.001$) as a predictive variable showed that each prognostic factor except gender contributed to predict the survival in patients with IPF (Table 3). A higher nadir SpO2 significantly increased survival. Therefore, we added nadir SpO2 to the GAP6 model. According to the nomogram, the GAP6 model consisted of 5 variables. Information about the nomogram itself, such as the point–linear predictor unit mapping and total point–survival probability mapping, is shown in Supplementary Figure 1. We added the points for nadir SpO2 to the GAP6 model according to the coefficients of the Cox regression models, and the nomogram created using the GAP6 model consisted of five variables with point contributions (Table 4). The index score of the sum of the point contributions for each of the five characteristics was then calculated; an index score of 0–3 points indicated stage I (low risk), that of 4–6 points indicated stage II (intermediated risk), and that of 7–9 points indicated stage III (high risk) disease. In addition to variables in the GAP6 model, the presence of lung cancer (HR 1.88; 95% CI, 1.43–2.46, $p < 0.001$) and the use of antifibrotic agents (HR 0.76, 95% CI, 0.559–0.862, $p = 0.001$) during the follow-up period were significantly associated with mortality in the

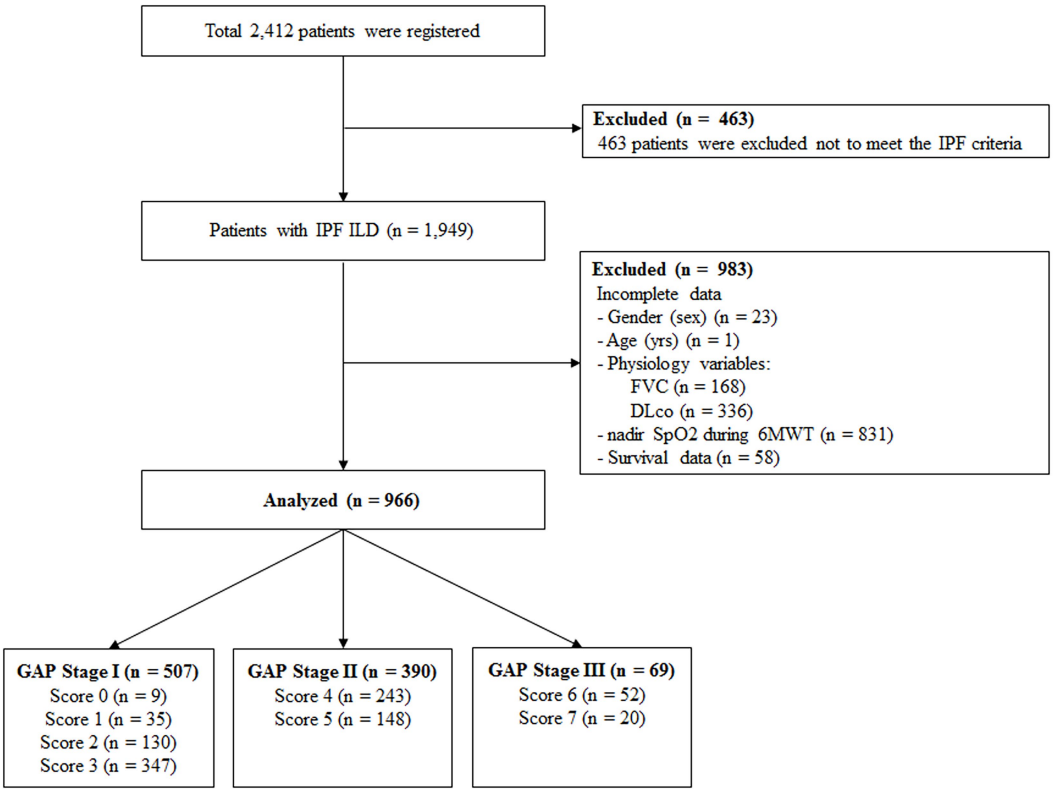

FIGURE 1
Overview of study design IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung disease; FVC, functional vital capacity; DLco, diffusing capacity of the lung for carbon monoxide; SpO2, saturation of percutaneous oxygen; 6MWT, six-minute walk test; GAP, gender, age, and physiology.

multivariable analysis. However, this analysis aims to develop predicting risk for mortality according to baseline characteristics in patients with IPF, the presence of lung cancer and the use of antifibrotic agents after diagnosis did not be included in the GAP6 model.

The GAP6 model revealed 442 patients with stage I (45.8%), 446 patients with stage II (46.2%), and 78 patients with stage III (8.1%) disease (Table 5). Figure 3 shows that survival differed significantly by disease stage (HR stage II vs. stage I, 2.89 [95% CI, 2.38–3.51]; HR stage III vs. stage I, 7.77 [95% CI, 4.66–12.96]; HR stage III vs. stage II, 2.68 [95% CI, 1.60–4.51]). In the analysis of survival probability using Kaplan–Meier plotting, the 3-year mortality rates for the modified GAP6 stages I–III groups were 2.3, 5.5, and 42.9%, respectively. A statistically significant difference was found among the modified GAP stages I–III groups (log-rank $p < 0.001$).

Comparison of the GAP model and the GAP6 model using the KICO registry

The GAP model included 507 patients with stage I, 390 patients with stage II, and 69 patients with stage III disease. However, the difference between proportion of patients in each stage group between the GAP and GAP6 models were significant (McNemar–Bowker test $p < 0.001$). Among 507 patients with GAP stage I, 65 patients were allocated into the GAP6 stage II group, and 17 of 390 patients with GAP stage II were allocated into the GAP6 stage III group. Also, 8 of 69 patients with GAP stage III were allocated into the GAP6 stage II group. The 1-, 2-, and 3-year mortality rates (Kaplan–Meier estimates) at each stage based on the GAP and GAP6 models are shown in Table 6. Based on the GAP6 model, the C-index value was 0.691 (95% CI, 0.650–0.698), showing an improvement compared to the value calculated based on the GAP model (0.674 [95% CI, 0.667–0.715]). Therefore, with the use of the GAP6 model, the C-index value for mortality slightly improved from 0.674 to 0.691.

We compared the risk of death predicted by the GAP and GAP6 models with the observed mortality using calibration plots and goodness-of-fit statistics (Hosmer–Lemeshow test; e-Figure 2). Models for which expected and observed probabilities in GAP stages are similar are considered to be well calibrated. The solid line in Supplementary Figure 2 represents a perfect agreement between predicted and observed risks. We found that the GAP6 model predicted the 3-year mortality rate more accurately than the GAP model, although the predicted and observed risks were not significantly different across the three stages (Hosmer–Lemeshow $p = 0.369$ for GAP and $p = 0.903$ for GAP6).

We compared the model performance with AUCs using ROC curve analysis. There was a significant difference between the GAP and the GAP6 models (AUC GAP vs. GAP6, 0.646 vs. 0.671; $p < 0.0019$; Figure 4).

Discussion

The GAP model has been widely used to predict mortality in patients with IPF. However, the model has some limitations not to incorporate important variables for predicting mortality such as exercise capacity. Therefore, we developed a GAP6 model for the Korean population by adding nadir SpO2 as a predictor variable when

TABLE 1 Baseline clinical characteristics of the patients.

Characteristics	All patients (n=966)
Male	783 (81.1)
Age (years)	71.23 ± 7.69
Ever-smokers	714 (75.4)
Height (cm)	163.14 ± 8.36
Weight (kg)	64.71 ± 10.24
BMI (kg/m^2)	24.40 ± 6.38
Radiologic pattern on HRCT	
UIP	470 (48.7)
Probable UIP	408 (42.2)
Home O2	159 (16.5)
mMRC	
Grade 0	195 (22.3)
Grade 1	333 (38.1)
Grade 2	255 (29.2)
Grade 3	73 (8.4)
Grade 4	17 (1.9)
Blood gas	
PaO_2, mmHg	98.14 ± 38.64
BNP	260.46 ± 1230.83
Pulmonary function test	
FVC, % predicted	74.16 ± 15.47
DLco, % predicted	61.45 ± 18.99
FEV1/FVC, %	86.60 ± 15.78
Six-minute walk test	
Distance (m)	412.73 ± 184.97
Nadir SpO_2, %	90.11 ± 6.78
RVSP, mmHg (n = 176)	31.15 ± 10.77
BAL fluid analysis	
Neutrophil, %	17.37 ± 19.83
Lymphocyte, %	13.60 ± 14.77
WBC	484.86 ± 773.51

Values are presented as mean ± standard deviation or number (%).
BMI, body mass index; HRCT, high resolution computed tomography; UIP, usual interstitial pneumonia; mMRC, modified medical research council; PaO_2, partial pressure of oxygen; BNP, brain natriuretic peptide; %FVC, forced vital capacity % predicted; %DLco, diffusing capacity of the lung for carbon monoxide % predicted; FEV1/FVC, the ratio of forced expiratory volume at 1 s (FEV1) over forced vital capacity 9(FVC); SpO_2, saturation of percutaneous oxygen; RVSP, right ventricular systolic pressure; BAL, bronchoalveolar lavage; WBC, white blood cell.

TABLE 2 Gender, age, and physiology (GAP) index and number (%) of patients.

Variable	GAP points	No. of patients
Gender		
Female	0	183 (18.9)
Male	1	783 (81.1)
Age (years)		
≤60	0	87 (9.0)
61–65	1	133 (13.8)
>65	2	746 (77.2)
Physiology		
FVC, % predicted		
>75	0	455 (47.1)
50–75	1	456 (47.2)
<50	2	55 (5.7)
DLco, % predicted		
>55	0	590 (61.1)
36–55	1	292 (30.2)
≤35	2	84 (8.7)
Median (range)		
GAP stage		
Stage I	0–3	507 (52.5)
Stage II	4–5	390 (40.4)
Stage III	6–7	69 (7.1)

Values in parentheses are percentages.
GAP, gender, age, and physiology; FVC, forced vital capacity; predicted; DLco, diffusing capacity of the lung for carbon monoxide.

calculating the GAP score. The GAP6 model improves the prediction ability with C-index and AUC.

The 6MWT is a practical and objective measure of functional exercise capacity, easy to perform, and reproducible (16, 17). In terms of IPF, exercised capacity, represented by distance and desaturation during 6MWT, is severely reduced due to the nature of IPF, including an abnormal gas-exchange response characterized by a significant decrease in arterial oxygen and increased differences between oxygen concentration in the alveoli and arterial system in the efficiency of alveolar ventilation (18, 19). In previous research, desaturation during 6MWT has been reported to be a significant predictor of mortality in patients with IPF (20, 21). Therefore, we hypothesized that nadir SpO2 representing desaturation is an important predictor of mortality and developed a new scoring system, GAP6, by adding nadir SpO2 to the GAP model.

In general, gender had been considered a significant predictor for mortality in patients with IPF (22, 23). However, in this study, gender did not trigger a statistically significant difference as a predictor for mortality in the Cox proportional hazards regression analysis and nomogram in the GAP model. Recent studies support this result of our investigation. Estrella et al. reported in 608 patients from the IPF national registry of the Spanish Respiratory Society that there was no statistically significant difference in mortality in men vs. women (HR, 1.5; 95% CI, 0.94–2.3, p = 0.092) (24). Lucile et al. in 246 patients from a French national multicenter prospective cohort demonstrated that women appear to be older with less frequent history of smoking and occupational exposures but survival comparable to that of men (HR, 0.85; 95% CI, 0.58–1.25, p = 041) (25). We suggested that no gender differences in age at diagnosis, lung function, or adherence to anti-fibrotic agents might be the reason for the same mortality rates of men and women in this study.

In the KICO registry, the 1- and 2-year mortality rates were significantly lower than those reported by Ley et al. in 2012 (2). A recent study of an IPF cohort with 562 patients showed a result similar to that of our study (26). The reason for such a result of lower mortality rate might be that, as anti-fibrotic agents were developed and widely

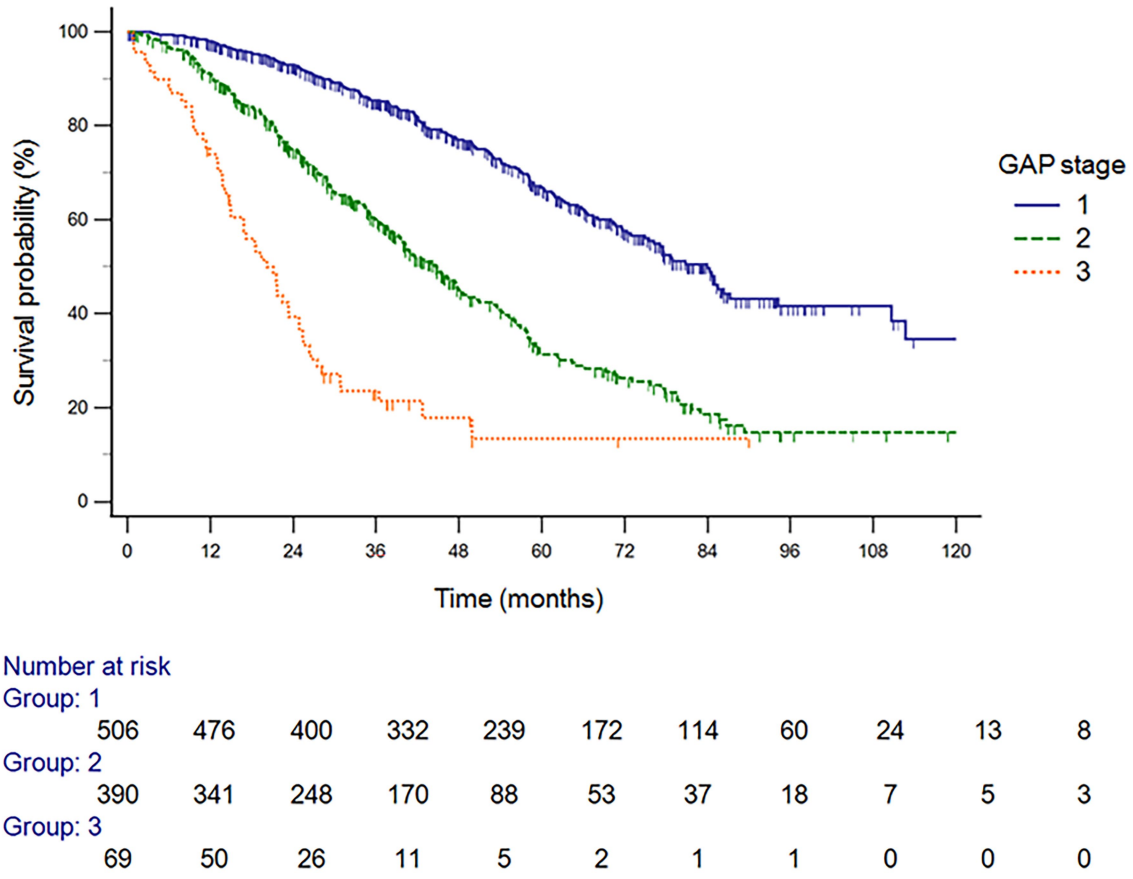

FIGURE 2
Survival probability analysis using Kaplan–Meier plotting, the 3-year mortality rates for the GAP stage I, II, and III groups GAP, gender, age, and physiology.

TABLE 3 Survival analysis with Cox proportional hazard model.

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Sex (M/F)	1.071	0.842–1.362	0.575	1.004	0.787–1.281	0.976
Age (years)	1.037	1.024–1.050	<0.001	1.040	1.027–1.053	<0.001
FVC, % predicted	0.962	0.955–0.968	<0.001	0.979	0.972–0.986	<0.001
DLco, % predicted	0.963	0.957–0.968	<0.001	0.975	0.969–0.982	<0.001
Nadir SpO_2 (%)	0.951	0.943–0.959	<0.001	0.972	0.960–0.984	<0.001

M, male; F, female; FVC, forced vital capacity; DLco, diffusing capacity of the lung for carbon monoxide; SpO_2, saturation of percutaneous oxygen.

employed in real-world practice, more patients were diagnosed actively at an early stage, resulting in the opportunity to receive appropriate treatment. Therefore, a new method for prognosis reflecting the real-world situation is warranted in the new era of anti-fibrotic agents.

In this study, the GAP6 model showed a better ability to predict mortality with C-index and AUC improvement than the GAP model. In the KICO registry, the proportion of anti-fibrotic agent use was higher than previously reported in other registry studies (10, 26, 27). Also, we added nadir SpO2 representing desaturation during the 6MWT to reflect functional capacity, which resulted in a statistically significant reclassification of patients in stages II and III. We assumed that 3-year mortality in the GAP model was overestimated due to a lack of consideration of functional capacity and the use of anti-fibrotics in the KICO registry; therefore, GAP6 is more useful to predict 3-year mortality. In the reality of increased and generalized anti-fibrotics use, we hope the result of our study will be more meaningful.

In addition to predictors of gender, age, physiology, and functional capacity in GAP6, there are several prognostic factors of mortality in patients with IPF (8, 28–31). In the Cox proportional hazards regression analysis in this study, body mass index (BMI), modified dyspnea scale of the Medical Research Council, and distance during 6MWT were independent prognostic factors of mortality. Also, the GAP6 model does not imply sequential change or decline of physiology and variables of 6MWT. Therefore, development of a new prognosis scoring model in IPF composed of other variables or sequential changes of existing variables is needed.

TABLE 4 Prognostic index based on presence of factors.

Characteristic	Point contribution		
	0	1	2
Gender	Female	Male	–
Age (years)	≤60	61–65	>65
FVC, % predicted	>75	50–75	<50
DLco, % predicted	>55	36–55	≤35
Nadir SpO_2 (%)	≥90	≤80–90	<80

The total points were distributed to the three stages as appropriate.
FVC forced vital capacity; DLco, diffusing capacity of the lung for carbon monoxide; SpO_2, saturation of percutaneous oxygen.

TABLE 5 GAP6 index and number (%) of patients.

Variable	GAP points	No. of patients
Gender		
Female	0	183 (18.9)
Male	1	783 (81.1)
Age (years)		
≤60	0	87 (9.0)
61–65	1	133 (13.8)
>65	2	746 (77.2)
Physiology		
FVC, % predicted		455 (47.1)
>75	0	456 (47.2)
50–75	1	55 (5.7)
<50	2	
DLco, % predicted		
>55	0	590 (61.1)
36–55	1	292 (30.2)
≤35	2	84 (8.7)
Nadir SpO_2		
≥90	0	637 (65.9)
≤80–90	1	264 (27.3)
<80	2	65 (6.7)
GAP6 stage		
Stage I	0–3	442 (45.8)
Stage II	4–6	446 (46.2)
Stage III	7–9	78 (8.1)

Values in parentheses are percentages.
GAP6, gender, age, and physiology with desaturation during six-minute walk test; FVC, forced vital capacity; DLco, diffusing capacity of the lung for carbon monoxide; SpO_2, saturation of percutaneous oxygen.

There are some limitations to this study. First, this was a retrospective study involving a single Korean cohort, and this might call into question the generalization of our findings to other cohorts. However, baseline and clinical characteristics, including a high rate of anti-fibrotic agent use, were similar to those of other recent cohort studies (24, 32, 33). The KICO registry includes recent data reflecting current real-world trends of diagnosis and anti-fibrotic agent use. Therefore, this study might be helpful in many ongoing and future cohort studies of patients with IPF. Second, we used nadir SpO2 as an indicator of desaturation during 6MWT. There was no consensus on the predictor of desaturation during 6MWT. Previous studies showed that desaturation defined as a ≥ 4% decrease in pre-exercise SpO2 during 6MWT is a significant predictor of mortality (20, 34). Since there were no data on pre-exercise SpO2 in the KICO registry, this study has the limitation that the relative decline of SpO2 between baseline and nadir could not be used as a predictor for desaturation. Third, we developed the GAP6 model based on the GAP model, adding desaturation to validate and compare the efficacy of the GAP6 model. However, gender was not a significant predictor in the KICO registry, and other predictors might be useful. Further research considering predictors other than the GAP variables is needed in the near future. Forth, about half patients in KICO registry were included in this study due to missing data of 6MWT. The missing data was concentrated in the early period of enrollment, and careful interpretation is required to possible selection bias.

Conclusion

The GAP model is a valuable tool for determining prognosis in patients with IPF. However, the GAP model did not accurately predict the 3-year mortality rate among patients in the KICO registry, and the calibration at 3 years was not satisfactory. Therefore, we designed the GAP6 model by adding nadir SpO2 as a new risk-assessment system. The GAP6 model improves the prediction ability with C-index and AUC; however, additional multinational research is needed to confirm these findings and validate the applicability and accuracy of this risk-assessment system.

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 Institutional Review Board of Haeundae-Paik Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

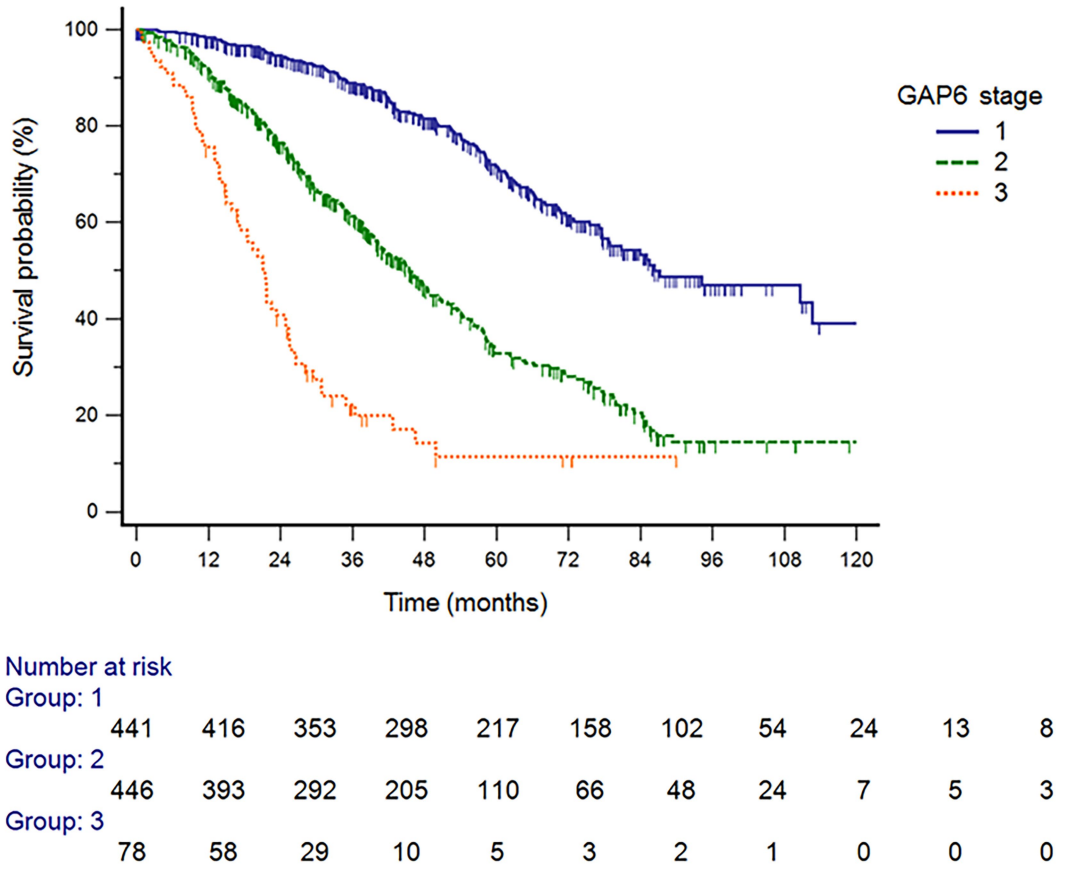

FIGURE 3
Survival probability analysis using Kaplan–Meier plotting, the 3-year mortality rates for the GAP6 stage I, II, and III groups GAP6, gender, age, and physiology with desaturation during six-minute walk test.

TABLE 6 Mortality rates for patients in different stages according to the original and modified GAP model.

Stage	Original GAP	GAP6
1-year mortality		
Stage I	0.8%	0.7%
Stage II	2.1%	1.6%
Stage III	17.4%	15.4%
2-year mortality		
Stage I	1.4%	1.6%
Stage II	4.1%	3.6%
Stage III	33.5%	29.6%
3-year mortality		
Stage I	2.4%	2.3%
Stage II	6.5%	5.5%
Stage III	50.1%	42.9%
C-index	0.674	0.691
(95% CI)	(0.650–0.698)	(0.667–0.715)

GAP, gender, age, and physiology; CI, confidence interval; GAP6, gender, age, and physiology with desaturation during six-minute walk test.

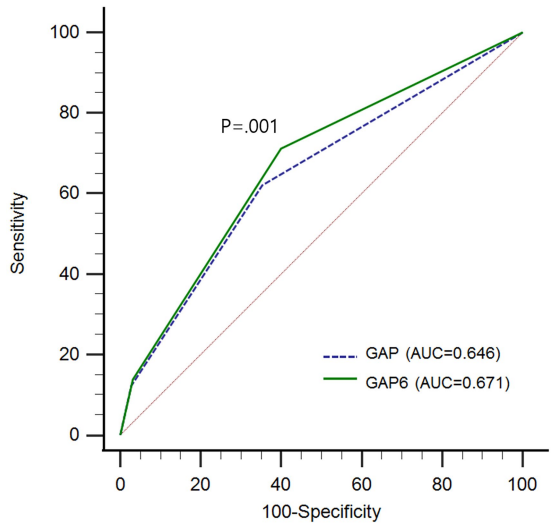

FIGURE 4
Comparison of predictive performance between GAP model and GAP6 with area under curves (AUCs) using receiver operating characteristic (ROC) curve analysis GAP, gender, age, and physiology; GAP6, gender, age, and physiology with desaturation during six-minute walk test; AUC, area under curve; ROC, receiver operating characteristic.

Author contributions

MP had 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. SC, YK, YK, SP, JP, YJ, JoL, S-TU, T-HK, YK, and BS contributed substantially to the study design. H-kL, S-HY, HL, S-HK, E-JL, HC, HK, EH, and W-YL dedicated to data analysis and interpretation. JaL, JJ, H-JJ, SK, MC, HY, SJ, JS, and HL contributed to the writing of the manuscript. All authors participated in the interpretation of the data, shared critical feedback and provided final approval for submission.

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.2023.1052129/full#supplementary-material

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Machine learning-based prediction of candidate gene biomarkers correlated with immune infiltration in patients with idiopathic pulmonary fibrosis

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Objective: This study aimed to identify candidate gene biomarkers associated with immune infiltration in idiopathic pulmonary fibrosis (IPF) based on machine learning algorithms.

Methods: Microarray datasets of IPF were extracted from the Gene Expression Omnibus (GEO) database to screen for differentially expressed genes (DEGs). The DEGs were subjected to enrichment analysis, and two machine learning algorithms were used to identify candidate genes associated with IPF. These genes were verified in a validation cohort from the GEO database. Receiver operating characteristic (ROC) curves were plotted to assess the predictive value of the IPF-associated genes. The cell-type identification by estimating relative subsets of RNA transcripts (CIBERSORT) algorithm was used to evaluate the proportion of immune cells in IPF and normal tissues. Additionally, the correlation between the expression of IPF-associated genes and the infiltration levels of immune cells was examined.

Results: A total of 302 upregulated and 192 downregulated genes were identified. Functional annotation, pathway enrichment, Disease Ontology and gene set enrichment analyses revealed that the DEGs were related to the extracellular matrix and immune responses. COL3A1, CDH3, CEBPD, and GPIHBP1 were identified as candidate biomarkers using machine learning algorithms, and their predictive value was verified in a validation cohort. Additionally, ROC analysis revealed that the four genes had high predictive accuracy. The infiltration levels of plasma cells, M0 macrophages and resting dendritic cells were higher and those of resting natural killer (NK) cells, M1 macrophages and eosinophils were lower in the lung tissues of patients with IPF than in those of healthy individuals. The expression of the abovementioned genes was correlated with the infiltration levels of plasma cells, M0 macrophages and eosinophils.

Conclusion: COL3A1, CDH3, CEBPD, and GPIHBP1 are candidate biomarkers of IPF. Plasma cells, M0 macrophages and eosinophils may be involved in the development of IPF and may serve as immunotherapeutic targets in IPF.

KEYWORDS

gene biomarker, immune infiltration, idiopathic pulmonary fibrosis, machine learning algorithm, CIBERSORT

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is not only a chronic disorder but also a progressive interstitial lung disease. The aetiology of IPF remains unclear, with its pathological presentation being usual interstitial pneumonia (UIP) (1). IPF is an infrequently diagnosed disease with an incidence of approximately 2.8–9.3 per 100,000 population in Europe and North America. Epidemiological data on IPF are scarce in China; however, its incidence has remarkably increased in recent years (2). IPF progresses gradually at the early stage, leading to diffuse fibrosis of the lungs and eventually respiratory failure and death (3). At present, a few drugs are available for treating IPF; among which, pirfenidone and nintedanib have demonstrated evident curative effects. Traditional Chinese medicine (TCM) may play a central role in managing IPF (4). Owing to the limited understanding of the pathogenesis of IPF and the lack of early intervention strategies, IPF has become a serious life-threatening disease (5). The prognosis of individuals with IPF is poor, with an estimated median survival of approximately 3 years (6). Therefore, identifying new biomarkers for the diagnosis of IPF is important for improving its treatment and prognosis.

Early and definite diagnosis of IPF is the initial step to improving the clinical treatments and survival rate of patients with IPF. To date, several biochemical markers have been associated with the occurrence of IPF and used as references for its clinical diagnosis (7, 8). However, they are inefficient for early detection of IPF owing to their limited sensitivity and specificity. Genetic factors may play a key role in the pathogenesis of IPF. IPF is a complicated and multifactorial illness that develops through the synergy of genetic and environmental factors (9, 10).

The principal processes associated with the development of IPF as a chronic lung disorder include inflammation and fibrosis. Inflammatory cytokines produced by immune cells can result in fibroblast activation, angiogenesis and connective tissue cell proliferation (11). Additionally, immune dysregulation can enhance the progression of IPF and involves numerous biomarkers associated with the prognosis of IPF (12). Studies on animals and humans have demonstrated that innate and adaptive immune processes may exacerbate the existing fibrotic responses (13).

In recent studies, microarray technology has been used in combination with machine learning algorithms to discover new genes associated with different conditions, which may serve as diagnostic and prognostic biomarkers. Additionally, scholars have suggested that immune cell infiltration, which is closely related to these disease-associated genes, plays a substantial role (14, 15). However, to date, only a few studies have employed microarray technology and machine learning algorithms to verify the role of immune cell infiltration in IPF and identify probable diagnostic markers for IPF.

In this study, three microarray datasets of IPF were extracted from the Gene Expression Omnibus (GEO) database and combined into a metadata cohort. Differentially expressed genes (DEGs) between tissues of patients with IPF and healthy individuals were identified using data from the metadata cohort. The DEGs were analysed through Gene Ontology (GO) functional annotation analysis, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis, Disease Ontology (DO) enrichment analyses and gene set enrichment analysis (GSEA). Subsequently, machine learning algorithms were used for identifying candidate gene biomarkers of IPF. The identified genes were verified in a validation cohort from the GEO database. Receiver operating characteristic (ROC) curves were plotted to assess the prognostic value of the detected biomarkers in both metadata and validation cohorts. The cell-type identification by estimating relative subsets of RNA transcripts (CIBERSORT) algorithm was used to evaluate the proportion of immune cells in the lung tissues of patients with IPF and healthy individuals based on their gene expression data. Additionally, the correlation between the detected biomarkers and infiltrating immune cells was examined.

2. Materials and methods

2.1. Microarray data

The matrix files of the GSE21369, GSE24206 and GSE110147 datasets were acquired from the NCBI GEO database[1]. Data in the GSE21369 and GSE24206 datasets were acquired based on the GPL570 platform of Affymetrix Human Genome U133 Plus 2.0 Array (16, 17), whereas data in the GSE110147 dataset were acquired based on the GPL6244 platform of Affymetrix Human Gene 1.0 ST Array (18). The GSE21369 dataset included 11 lung tissue samples from patients with IPF and 6 lung tissue samples from healthy individuals. The GSE24206 dataset included 17 lung tissue samples from patients with IPF and 6 lung tissue samples from healthy donors. The GSE110147 dataset included 22 lung tissue samples from the recipient organs of patients with IPF and 11 normal lung tissue samples from tissue flanking lung cancer resections.

Probes in all datasets were transformed to gene symbols using their probe annotation files. The probe average was determined as the final expression value of genes if more than one probe corresponded to the same gene symbol. The three datasets were combined to obtain a metadata cohort for subsequent integrative analysis.

In addition, the GSE53845 dataset based on the GPL6480 platform of the Agilent-014850 Whole Human Genome Microarray 4x44K G4112F was used as the validation cohort. It included lung tissue samples from 40 patients with IPF and 8 healthy individuals (19).

2.2. Processing of data and screening of DEGs

The 'SVA' package in R was used to pre-process data in the metadata cohort and eliminate batch effects (20). The 'limma' package in R was used for data normalisation, background correction and identification of DEGs between 50 patients with IPF and 23 healthy individuals in the metadata cohort (21). Adjusted (adj) p-values of <0.05 and |log2 fold change (FC)| values of >1 were considered the threshold values for identifying significant DEGs. The 'pheatmap' package was used to construct a heatmap for demonstrating the expression levels of the identified DEGs.

2.3. Enrichment analyses of DEGs

The 'clusterProfiler,' 'DOSE' and 'GSEABase' packages were used for GO functional annotation, KEGG pathway enrichment and DO enrichment analyses and GSEA to examine substantial functions of the DEGs (22–25).

1 http://www.ncbi.nlm.nih.gov/geo/

GO analysis incorporates three aspects, namely, molecular functions (MFs), cellular components (CCs) and biological processes (BPs). The 'c2.cp.kegg.v7.0.symbols.gmt' gene set from the Molecular Signatures Database (MSigDB)[2] was used as a reference for GSEA (26, 27). The primary finding of GSEA is the enrichment score (ES), which indicates the extent to which a gene set is overexpressed at either the top or bottom of a list of ranked genes. Positive and negative ESs demonstrate gene set enrichment at the top and bottom of the ranked list, respectively. In this study, genes with |normalised ESs (NESs)| of >1, p-values of <0.05 and adj p-values of <0.25 were considered remarkedly enriched.

2.4. Screening of candidate gene biomarkers

To identify remarkable predictive variables, two machine learning algorithms were used to screen for genes associated with IPF. Least absolute shrinkage and selection operator (LASSO) is an algorithm of regression analysis that uses regularisation to enhance the reliability of predictions (28). LASSO analysis was performed using the 'glmnet' package in R to identify genes associated with the diagnosis of IPF (29). Support vector machine (SVM) is a supervised and extensively used machine-learning approach that functions in not only classification but also regression (30). To alleviate overfitting, the recursive feature elimination (RFE) algorithm was used to select optimal genes from the metadata cohort (31). To identify genes with the highest discriminative power, SVM–RFE was implemented using the 'e1071' and 'kernlab' packages in R (32, 33).

The overlapping genes between the two algorithms were defined as candidate gene biomarkers. Thereafter, the expression of these genes was verified in the GSE53845 dataset.

2.5. Diagnostic value of the identified gene biomarkers in IPF

To investigate the predictive value of the identified gene biomarkers, ROC curves were plotted based on the mRNA expression data of 50 patients with IPF and 23 healthy individuals in the metadata cohort. The area under the ROC curve (AUC) was evaluated to determine the diagnostic value of the genes. The AUC value was subsequently verified in the GSE53845 dataset.

2.6. Determination of immune cell subtypes

The CIBERSORT algorithm[3], a bioinformatic analytical tool, was used to evaluate the relative proportion of infiltrating immune cells based on the gene expression data of patients with IPF and healthy individuals. The CIBERSORTx tool from the Alizadeh Lab and Newman Lab is used to impute gene expression profiles and estimate the abundance of member cell types in a mixed cell population using the gene expression data (34, 35). In this study, the CIBERSORTx tool was used to evaluate the abundance of 22 types of immune cells (reference set that had 1,000 permutations in the LM22 Signature Matrix file downloaded from CIBERSORTx).

Thereafter, the 'corrplot' in R was used to assess the distribution of the abundance of the 22 types of infiltrating immune cells and the correlation among them. The 'vioplot' package in R was used to construct violin plots for demonstrating differences in immune cell infiltration between patients with IPF and healthy individuals.

2.7. Analysis of the correlation between infiltrating immune cells and candidate genes

The correlation between the expression of candidate genes and the infiltration levels of immune cells was investigated through Spearman's rank correlation analysis in the R program. The 'ggplot2' package was used to visualise the resulting relationships (36).

2.8. Statistical analysis

The R software (version: 4.0.3) was used for all statistical analyses. Continuous variables were compared between groups using two tests: The Student's t-test was used to compare normally distributed variables, whereas the Mann–Whitney U test was used to compare abnormally distributed variables. The 'glmnet' package was used for LASSO regression analysis, whereas the 'e1071' and 'kernlab' packages in R were used for SVM–RFE. ROC curves were plotted and AUC values were evaluated to assess the diagnostic efficacy of the candidate gene biomarkers. Spearman's correlation analysis was performed to examine the correlation between the expression of candidate genes and the infiltration levels of immune cells. All statistical tests were two-sided, and p-values of <0.05 were considered significant. For screening DEGs between patients with IPF and healthy individuals, adj p-values of <0.05 and |log2 FC| values of >1 were defined as the threshold values. For GO, KEGG and DO enrichment analyses, adj p-values of <0.05 were considered significant. For GSEA, genes with |NESs| of >1, p-values of <0.05 and adj p-values of <0.25 were considered significantly enriched.

3. Results

3.1. Detection of DEGs

The gene expression data of 50 patients with IPF and 23 healthy individuals in the metadata cohort (GSE21369, GSE24206 and GSE110147) were retrospectively analysed (Supplementary File 1). After eliminating batch effects, DEGs between patients with IPF and healthy individuals were identified using the 'limma' package. Based on the threshold of adj p-values of <0.05 and |log2FC| values of >1, 494 DEGs were identified, including 302 upregulated (log2FC > 1) and 192 downregulated (log2FC < −1) genes (Supplementary File 2). A volcano plot and heatmap demonstrating the expression of these DEGs are shown in Figures 1A,B, respectively.

3.2. Enrichment analyses

GO analysis revealed that the DEGs were remarkably enriched in BPs such as extracellular matrix (ECM) organisation, extracellular structure organisation, detoxification of copper ions, stress response to

2 http://www.gsea-msigdb.org/gsea/msigdb

3 https://cibersortx.stanford.edu/

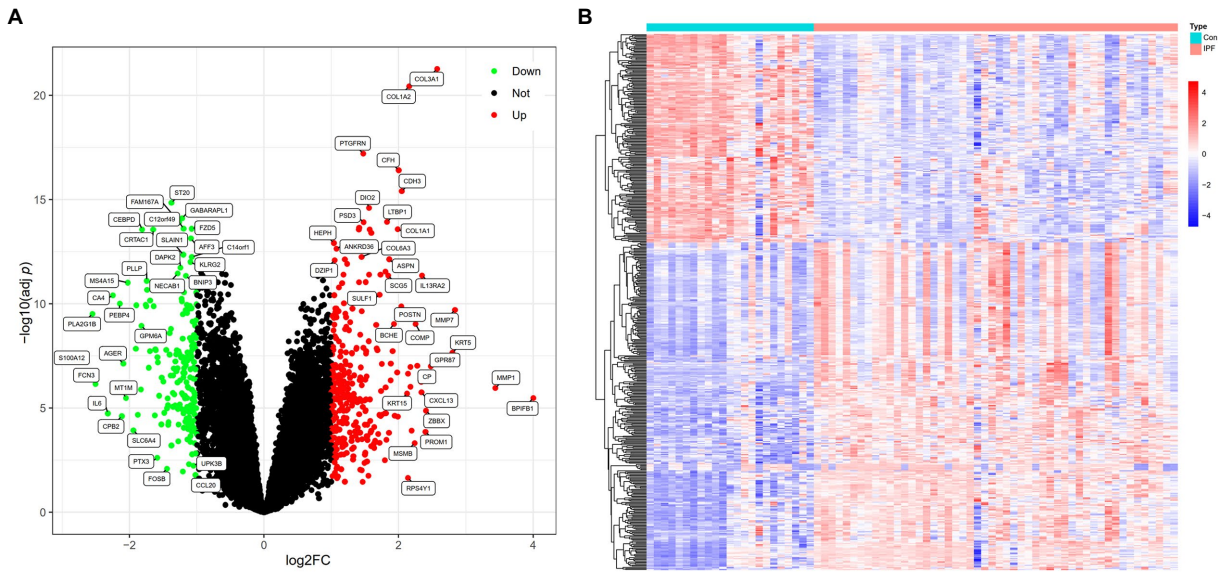

FIGURE 1
DEGs between patients with IPF and healthy individuals. **(A)** Volcano plot of DEGs identified based on the threshold of |log2FC| values of >1 and adj *p*-values of <0.05; the green (Down) and red (Up) dots represent downregulated and upregulated genes in patients with IPF, respectively; the black dots (Not) represent genes that are not differentially expressed between patients with IPF and healthy individuals. **(B)** Heatmap demonstrating the expression levels of the DEGs in 23 healthy individuals (Con) and 50 patients with IPF (IPF); red represents high expression, and blue represents low expression.

copper ions, detoxification of inorganic compounds and other related processes. Additionally, the DEGs were substantially enriched in CCs such as collagen-containing ECM, endoplasmic reticulum lumen, ciliary plasm, axoneme and plasmalemma-bound cell projection cytoplasm and MFs such as ECM structural constituents, integrin binding, ECM structural constituent contributing to tensile strength, dynein light intermediate chain binding and adenosine triphosphate (ATP)-dependent/minus-end-directed microtubule motor activity (Supplementary File 3). The top 10 GO terms ranked based on their adj *p*-values are shown in Figure 2A.

KEGG pathway enrichment analysis revealed that the DEGs were remarkedly enriched in pathways associated with mineral absorption, interleukin 17 (IL-17) signalling, advanced glycation end product (AGE) receptor (RAGE) signalling in diabetic complications, protein digestion and absorption, relaxin signalling, TNF signalling, malaria, ECM–receptor interaction and rheumatoid arthritis (Supplementary File 4). The top nine KEGG pathways ranked based on their adj *p*-values are shown in Figure 2B.

DO enrichment analysis was also performed to determine the functions of the DEGs. The results revealed that the DEGs were primarily associated with various illnesses (Supplementary File 5); among which, sarcoidosis, collagen disease, rheumatic disease, interstitial lung disease and pulmonary fibrosis are associated with IPF. The 20 DO terms ranked based on their adj *p*-values are shown in Figure 2C, and the 10 main diseases associated with IPF are shown in chord plots with the related genes in Figure 2D.

GSEA revealed that the DEGs were enriched in pathways associated with cytokine–cytokine receptor interaction, ECM–receptor interaction, Janus-activated kinase signal transducers, activators of transcription (JAK–STAT) signalling, mitogen-activated protein kinase (MAKP) signalling and focal adhesion (Supplementary File 6). The 5 gene sets enriched at the top of the ranked list (NES > 1) ranked based on their *p*-values are shown in Figure 2E, whereas the 5 gene sets enriched at the bottom of the ranked list (NES < −1) ranked based on their *p*-values are shown in Figure 2F.

3.3. Identification and validation of candidate gene biomarkers

Two algorithms were used to screen for potential diagnostic biomarkers for IPF. The DEGs were screened using the LASSO regression algorithm, resulting in the identification of 18 variables as diagnostic biomarkers (Table 1; Figure 3A). A subset of eight genes among the DEGs was determined using the SVM–RFE algorithm (Table 2; Figure 3B). The four overlapping genes between these two algorithms were eventually identified as candidate diagnostic biomarkers, including collagen type III alpha 1 chain (COL3A1), cadherin 3 (CDH3), CCAAT enhancer-binding protein delta (CEBPD) and glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1) (Figure 3C).

To assess the reliability and accuracy of the four candidate genes, their expression was verified in the GSE53845 dataset (Supplementary File 7). The expression of COL3A1 and CDH3 was higher in the lung tissues of patients with IPF than in those of healthy individuals ($p < 0.05$; Figures 4A,B), whereas the expression of CEBPD and GPIHBP1 was remarkably lower in the lung tissues of patients with IPF than in those of healthy individuals ($p < 0.05$) (Figures 4C,D). These results were consistent with those of differential expression analysis in the metadata cohort. Therefore, the four genes were considered candidate diagnostic biomarkers for further analysis.

3.4. Diagnostic efficiency of the four candidate biomarkers in IPF

ROC curves were plotted to examine the efficiency of the four biomarkers in distinguishing patients with IPF from healthy individuals. The AUC values of COL3A1, CDH3, CEBPD, and GPIHBP1 were 0.996 (95% CI, 0.984–1.000) (Figure 5A), 0.980 (95% CI, 0.948–1.000)

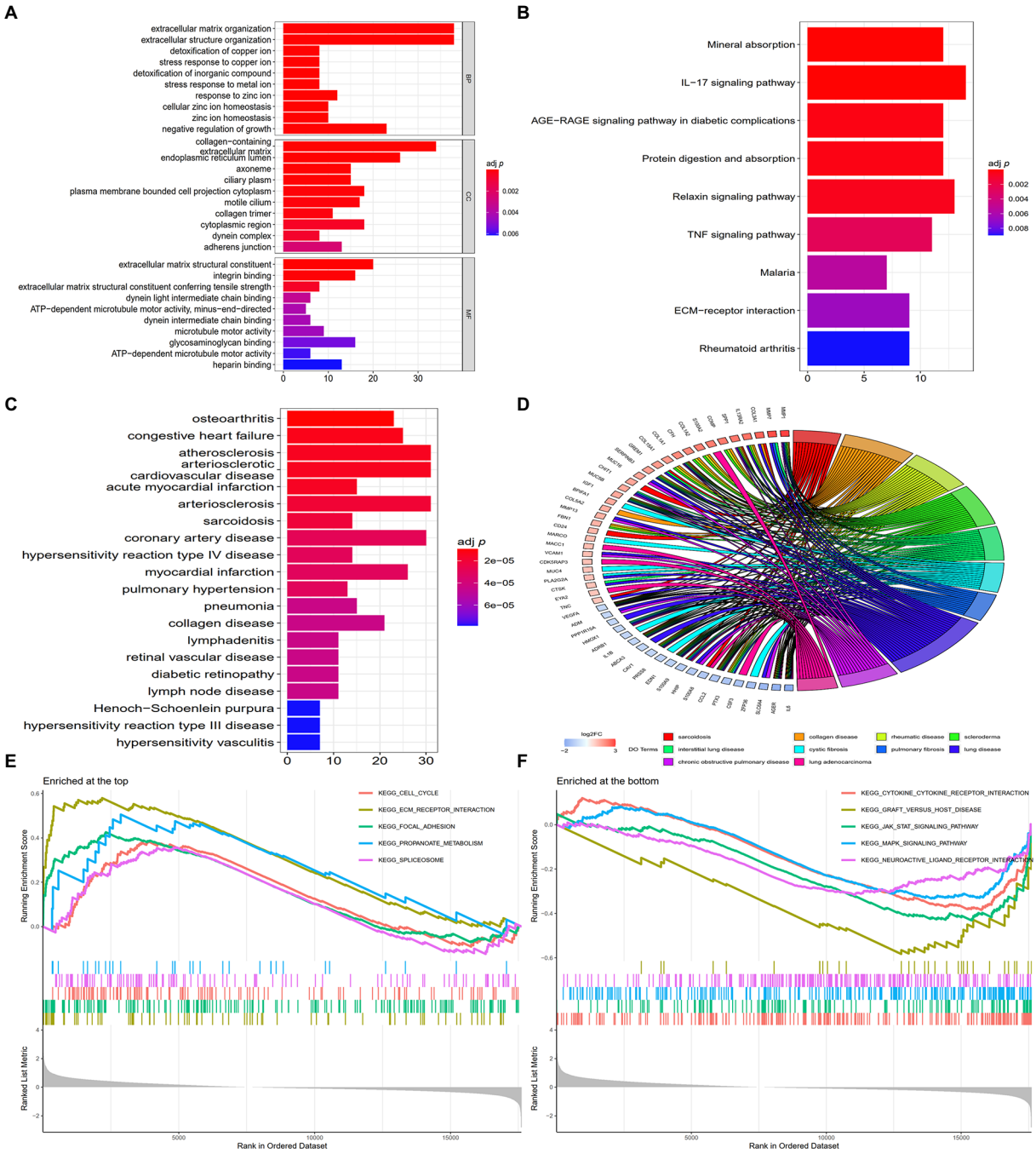

FIGURE 2
Enrichment analyses of DEGs. **(A)** The top 10 GO terms ranked based on their adj *p*-values. BP, biological process; CC, cellular component; MF, molecular function. **(B)** The nine enriched KEGG pathways. **(C)** The top 20 DO terms ranked based on their adj *p*-values. **(D)** Chord plot demonstrating the 10 main enrichments associated with IPF based on DO analysis, and gene names with the connection represent their enriched genes. **(E)** The 5 enriched gene sets at the top of the ranked list (NES>1) indicate higher expression in IPF. **(F)** The 5 enriched gene sets at the bottom of the ranked list (NES<−1) indicate lower expression in IPF.

(Figure 5B), 0.982 (95% CI, 0.952–1.000) (Figure 5C) and 0.946 (95% CI, 0.851–0.998) (Figure 5D), respectively, indicating that the four biomarkers had satisfactory diagnostic value. Additionally, the biomarkers had adequate discriminative capability in the GSE53845 dataset, with an AUC value of 0.825 (95% CI, 0.597–0.981) for COL3A1 (Figure 5E), 0.969 (95% CI, 0.897–1.000) for CDH3 (Figure 5F), 0.766 (95% CI, 0.634–0.887) for CEBPD (Figure 5G) and 0.917 (95% CI, 0.819–0.988) for GPIHBP1 (Figure 5H). These results suggest that the four candidate biomarkers have high diagnostic capability.

3.5. Immune cell infiltration

The CIBERSORT algorithm was used to evaluate the abundance of immune cells based on data extracted from the LM22 signature matrix file (Supplementary File 8). The results are shown in Supplementary File 9.

The distribution of 22 types of infiltrating immune cells in the IPF and control groups is demonstrated in Figure 6A. The correlation among the infiltration levels of 22 types of immune cells is demonstrated in

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TABLE 1 Identification of 18 variables using the LASSO regression algorithm.

Gene symbol	Description
COL3A1	Collagen type III alpha 1 chain
CDH3	Cadherin 3
ST20	Suppressor of tumorigenicity 20
CEBPD	CCAAT enhancer-binding protein delta
CRTAC1	Cartilage acidic protein 1
HEPH	Hephaestin
DZIP1	DAZ-interacting zinc finger protein 1
MS4A15	Membrane spanning 4-domains a15
LOC100131541	Not applicable
GPIHBP1	Glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1
IRS2	Insulin receptor substrate 2
SCARNA17	Small Cajal body-specific RNA 17
LRRN1	Leucine-rich repeat neuronal 1
MYOCD	Myocardin
FNDC1	Fibronectin type III domain containing 1
CHI3L2	Chitinase 3-like 2
LYVE1	Lymphatic vessel endothelial hyaluronan receptor 1
TSPAN11	Tetraspanin 11

Figure 6B (regulatory T cells [Tregs] were not correlated with any other cell and are hence not shown).

The abundance of resting natural killer (NK) cells ($p < 0.001$), M1 macrophages ($p = 0.049$) and eosinophils ($p < 0.001$) was lower in the lung tissues of patients with IPF than in those of healthy individuals. However, the abundance of plasma cells ($p = 0.002$), M0 macrophages ($p < 0.001$) and resting dendritic cells (DCs) ($p = 0.008$) was higher in the lung tissues of patients with IPF than in those of healthy individuals (Figure 6C).

3.6. Correlation between candidate biomarkers and infiltrating immune cells

Spearman's rank correlation analysis was performed to examine and visualise the correlation between the expression of the four candidate genes and the infiltration levels of immune cells (Supplementary File 10).

COL3A1 expression was positively correlated with the infiltration levels of M0 macrophages ($r = 0.38$, $p = 0.001$), plasma cells ($r = 0.33$, $p = 0.005$) and activated NK cells ($r = 0.26$, $p = 0.024$) and negatively correlated with the infiltration levels of resting NK cells ($r = -0.48$, $p < 0.0001$), eosinophils ($r = -0.48$, $p < 0.001$), activated DCs ($r = -0.34$, $p = 0.003$), neutrophils ($r = -0.27$, $p = 0.020$) and monocytes ($r = -0.25$, $p = 0.036$). The detailed results are shown in Figure 7A.

CDH3 expression was positively correlated with the infiltration levels of M0 macrophages ($r = 0.54$, $p < 0.001$), plasma cells ($r = 0.53$, $p < 0.001$), resting DCs ($r = 0.49$, $p < 0.001$) and memory B cells ($r = 0.37$, $p = 0.002$) and negatively correlated with the infiltration levels of eosinophils ($r = -0.44$, $p < 0.001$), resting NK cells ($r = -0.44$, $p < 0.001$), M1 macrophages ($r = -0.28$, $p = 0.016$) and monocytes ($r = -0.24$, $p = 0.044$). The detailed results are shown in Figure 7B.

CEBPD expression was positively correlated with the infiltration levels of resting NK cells ($r = 0.44$, $p < 0.001$), activated DCs ($r = 0.39$, $p < 0.001$), eosinophils ($r = 0.35$, $p = 0.002$), neutrophils ($r = 0.31$, $p = 0.009$) and monocytes ($r = 0.28$, $p = 0.018$) and negatively correlated with the infiltration levels of activated NK cells ($r = -0.41$, $p < 0.001$), M0 macrophages ($r = -0.38$, $p = 0.001$), M2 macrophages ($r = -0.36$, $p = 0.002$), resting DCs ($r = -0.35$, $p = 0.002$), memory B cells ($r = -0.26$, $p = 0.026$) and plasma cells ($r = -0.25$, $p = 0.035$). The detailed results are shown in Figure 7C.

GPIHBP1 expression was positively correlated with the infiltration levels of M1 macrophages ($r = 0.25$, $p = 0.033$) and eosinophils ($r = 0.24$, $p = 0.041$) and negatively correlated with the infiltration levels of M0 macrophages ($r = -0.49$, $p < 0.001$), resting DCs ($r = -0.29$, $p = 0.015$) and plasma cells ($r = -0.27$, $p = 0.021$). The detailed results are shown in Figure 7D.

4. Discussion

IPF is an interstitial condition characterised by UIP. At present, IPF cannot be cured and often has an unsatisfactory prognosis. Although numerous related studies have been reported, the mechanisms underlying the onset and development of IPF remain unclear (37). Epithelial–mesenchymal transition, ECM deposition and lung remodelling may be involved in the onset and progression of IPF (38–40).

Owing to the lack of biomarkers for early diagnosis of IPF, patients often miss the best opportunity for treatment, leading to progressive disease progression. Therefore, it is important to investigate the molecular mechanisms of biomarkers associated with the onset and development of IPF and identify therapeutic targets. Additionally, studies have reported that immune cell infiltration can clear ageing alveolar epithelial cells and play a role in the occurrence and development of IPF (41, 42). Therefore, the relationship between IPF-associated genes and infiltrating immune cells should be examined to improve the prognosis of IPF.

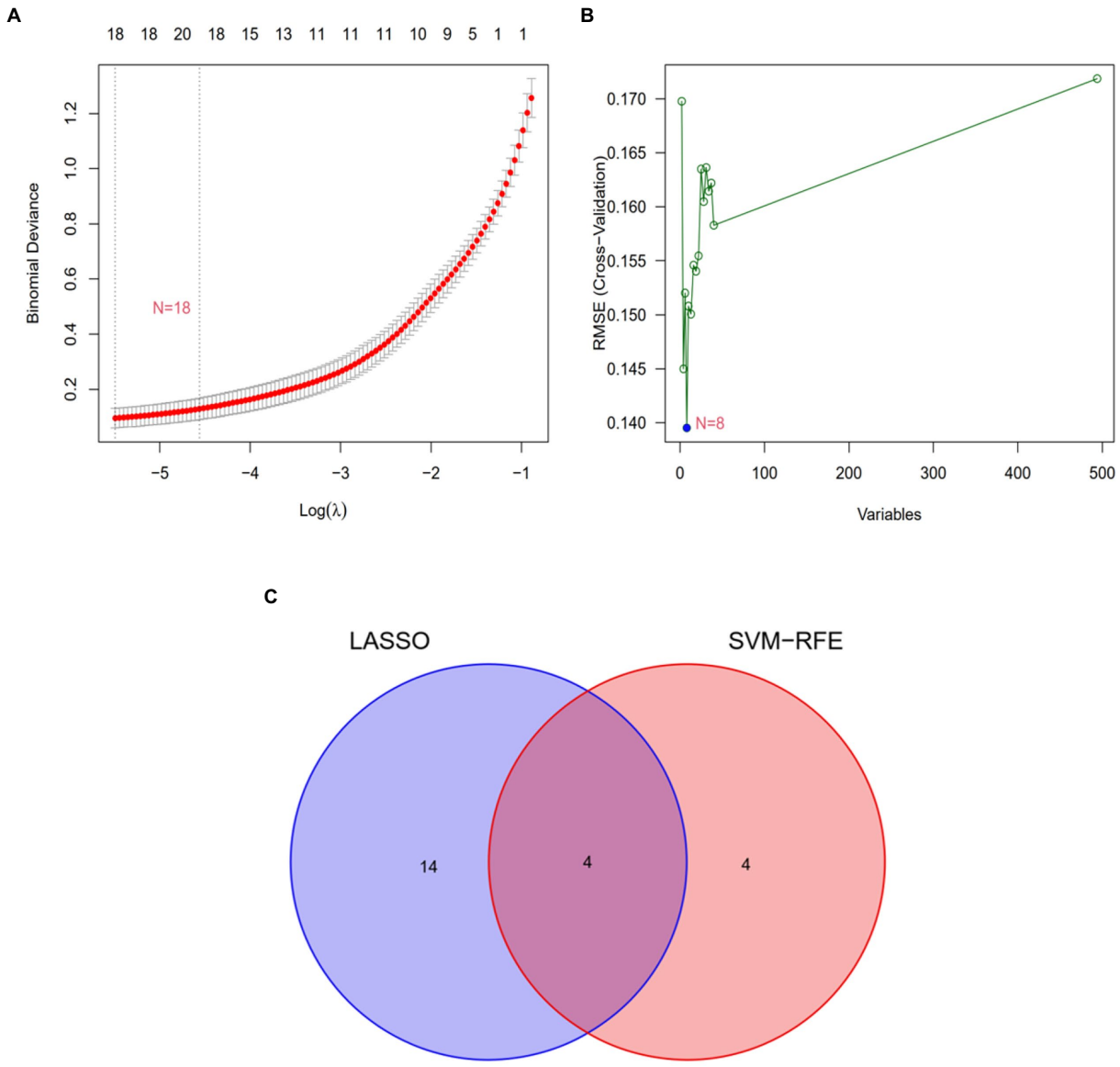

FIGURE 3
Screening of candidate gene biomarkers using two machine learning algorithms. **(A)** Tuning feature selection using the LASSO algorithm. **(B)** A plot of biomarker selection using the SVM-RFE algorithm. **(C)** Venn diagram demonstrating the four diagnostic markers (COL3A1, CDH3, CEBPD, and GPIHBP1) shared by the LASSO and SVM-RFE algorithms.

TABLE 2 Identification of eight variables using the SVM−RFE algorithm.

Gene symbol	Description
COL3A1	Collagen type III alpha 1 chain
TSHZ2	Teashirt zinc finger homeobox 2
COL1A2	Collagen type I alpha 2 chain
CDH3	Cadherin 3
PSD3	Pleckstrin and Sec7 domain-containing 3
CEBPD	CCAAT enhancer-binding protein delta
PTGFRN	Prostaglandin F2 receptor inhibitor
GPIHBP1	Glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1

Recent studies have reported that IPF-related microRNAs (miRNAs) play an important role in the diagnosis and treatment of IPF (43–45). In previous studies, we have constructed a modulatory network of putative IPF-related miRNAs and messenger RNAs (mRNAs), which validates some miRNA–mRNA axes with TCM treatment of a bleomycin-induced IPF mouse model (4, 46). However, a few studies have examined the

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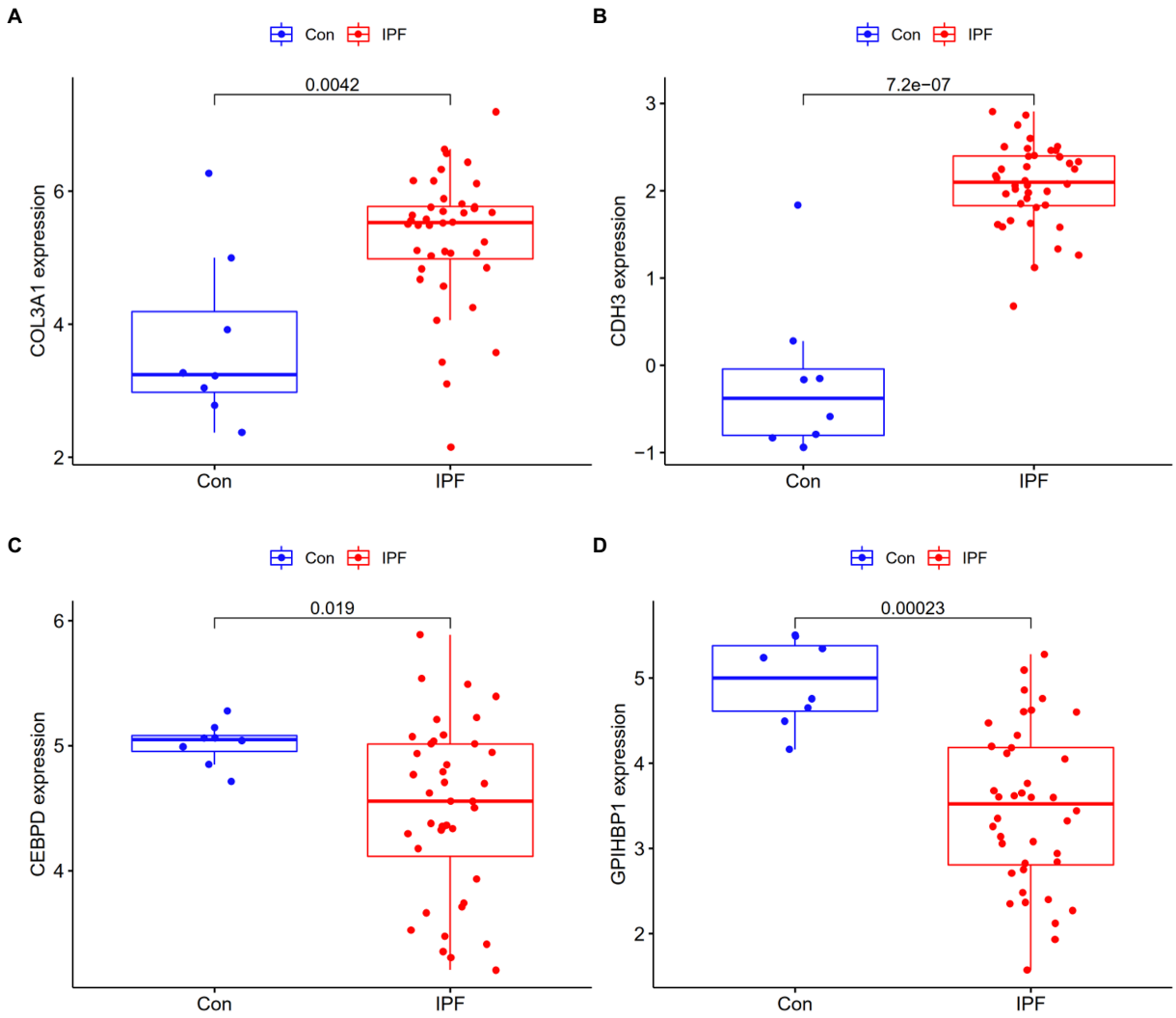

FIGURE 4
Validation of the expression of candidate genes in the GSE53845 dataset. **(A)** The expression of COL3A1 was higher in the lung tissues of patients with IPF (IPF) than in those of healthy individuals (Con). **(B)** The expression of CDH3 was higher in the lung tissues of patients with IPF than in those of healthy individuals. **(C)** The expression of CEBPD was lower in the lung tissues of patients with IPF than in those of healthy individuals. **(D)** The expression of GPIHBP1 was lower in the lung tissues of patients with IPF than in those of healthy individuals.

relationship between abnormally expressed genes and immune infiltration in IPF. In this study, we identified candidate gene biomarkers for the diagnosis of IPF and examined their correlation with immune cell infiltration in IPF.

First, three microarray datasets were extracted from the GEO database and merged into a metadata cohort, which included 50 patients with IPF and 23 healthy individuals. A total of 494 DEGs were identified, including 302 upregulated and 192 downregulated genes. GO analysis revealed the DEGs were significantly enriched in BPs such as ECM organisation, extracellular structure organisation, detoxification and stress response to copper ions and detoxification of inorganic compounds; CCs such as collagen-containing ECM, endoplasmic reticulum lumen, ciliary plasm, axoneme and plasmalemma-bound cell projection cytoplasm and MFs such as ECM structural constituent, integrin binding, ECM structural constituent conferring tensile strength, dynein light intermediate chain binding and ATP-dependent/minus-end-directed microtubule motor activity. The functions of DEGs were primarily related to ECM, indicating that the DEGs are closely related to ECM and participate in the development of IPF (38–40). KEGG analysis revealed that the DEGs were significantly enriched in pathways associated with absorption of minerals, IL-17 signalling, AGE–RAGE signalling in diabetic complications, protein digestion and absorption, relaxin signalling, TNF signalling, malaria, ECM–receptor interaction and rheumatoid arthritis. These pathways are primarily related to ECM and immune responses. DO enrichment analysis revealed that the DEGs were mainly associated with sarcoidosis, collagen disease, rheumatic disease, interstitial lung disease and pulmonary fibrosis. These diseases are associated with IPF and share some pathological characteristics with IPF. GSEA revealed that the DEGs were enriched in pathways associated with cytokine–cytokine receptor interaction, JAK–STAT signalling, ECM–receptor interaction, MAKP signalling and focal adhesion. These pathways are related to ECM, inflammation and immune responses. These findings are consistent with those of previous studies, indicating that inflammatory responses involving cytokines play a role in the pathogenesis of IPF (47–50).

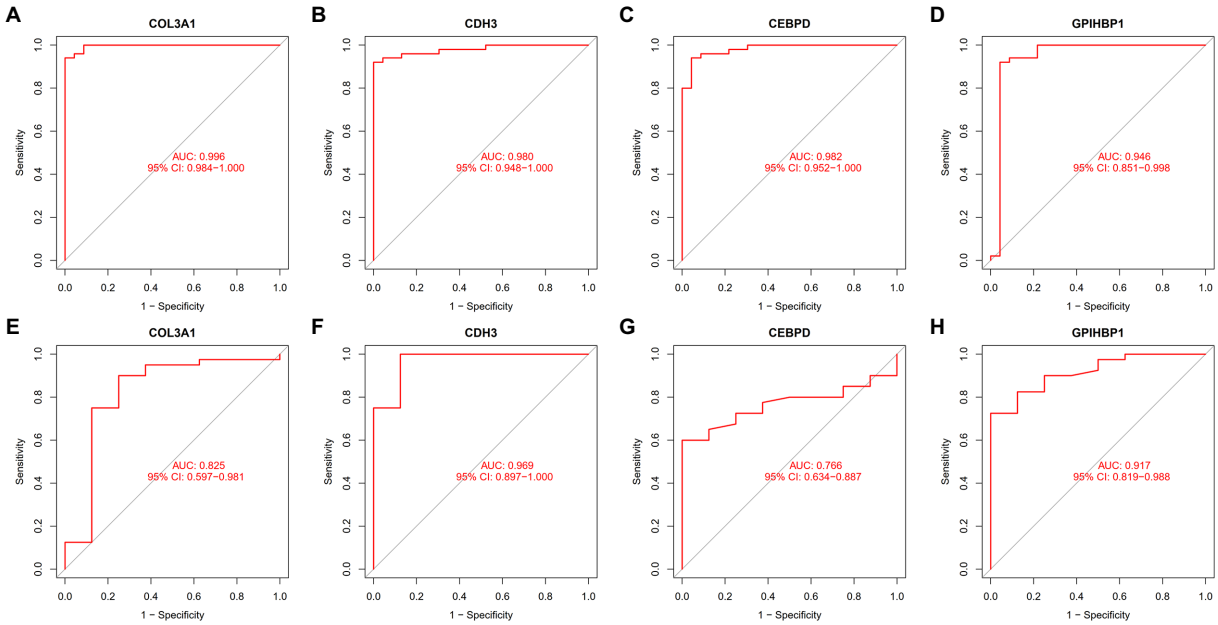

FIGURE 5
ROC curves demonstrating the diagnostic efficiency of the four candidate biomarkers. **(A)** ROC curve of COL3A1 after fitting to one variable in the metadata cohort. **(B)** ROC curve of CDH3 after fitting to one variable in the metadata cohort. **(C)** ROC curve of CEBPD after fitting to one variable in the metadata cohort. **(D)** ROC curve of GPIHBP1 after fitting to one variable in the metadata cohort. **(E)** ROC curve of COL3A1 after fitting to one variable in the GSE53845 dataset. **(F)** ROC curve of CDH3 after fitting to one variable in the GSE53845 dataset. **(G)** ROC curve of CEBPD after fitting to one variable in the GSE53845 dataset. **(H)** ROC curve of GPIHBP1 after fitting to one variable in the GSE53845 dataset.

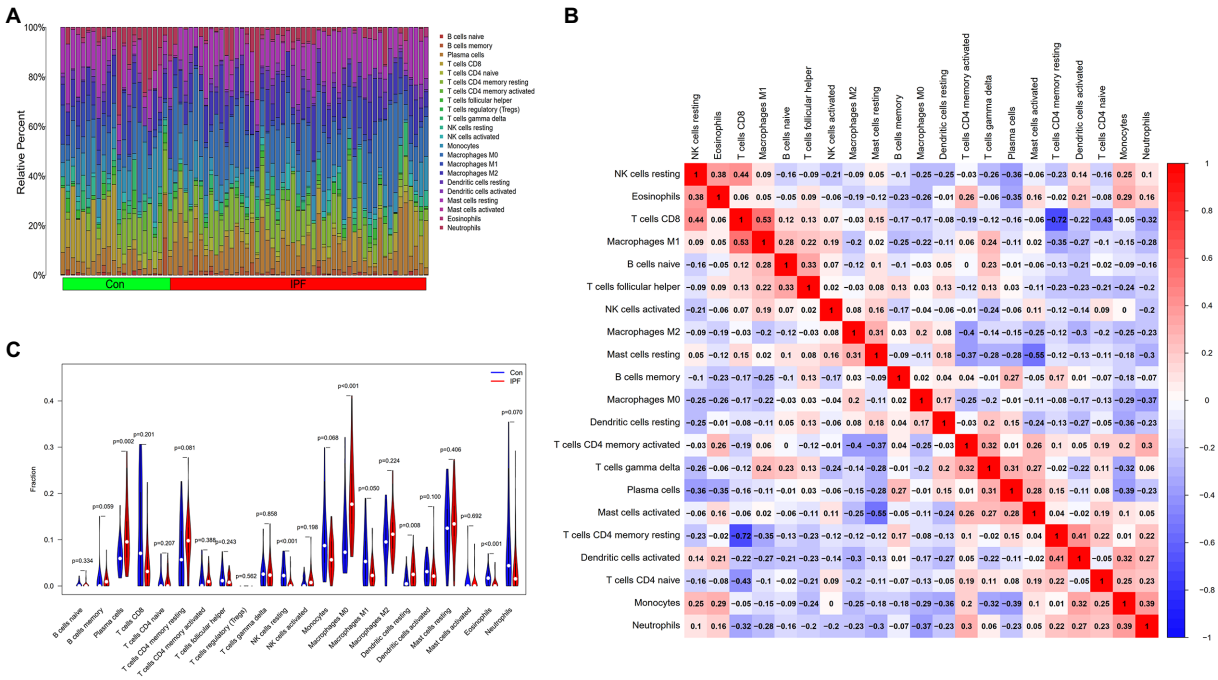

FIGURE 6
Distribution of infiltrating immune cells and the correlation among their infiltration levels. **(A)** Relative abundance of 22 immune cell subtypes in patients with IPF (IPF) and healthy individuals (Con). **(B)** Correlation among the infiltration levels of 21 immune cell subtypes (Tregs are not shown); both horizontal and vertical axes demonstrate immune cell subtypes. Red, blue and white represent higher, lower and the same correlation levels, respectively. **(C)** Comparison of the abundance of 22 immune cell subtypes between patients with IPF and healthy individuals. Blue and red colours represent the infiltration levels of healthy individuals and patients with IPF, respectively.

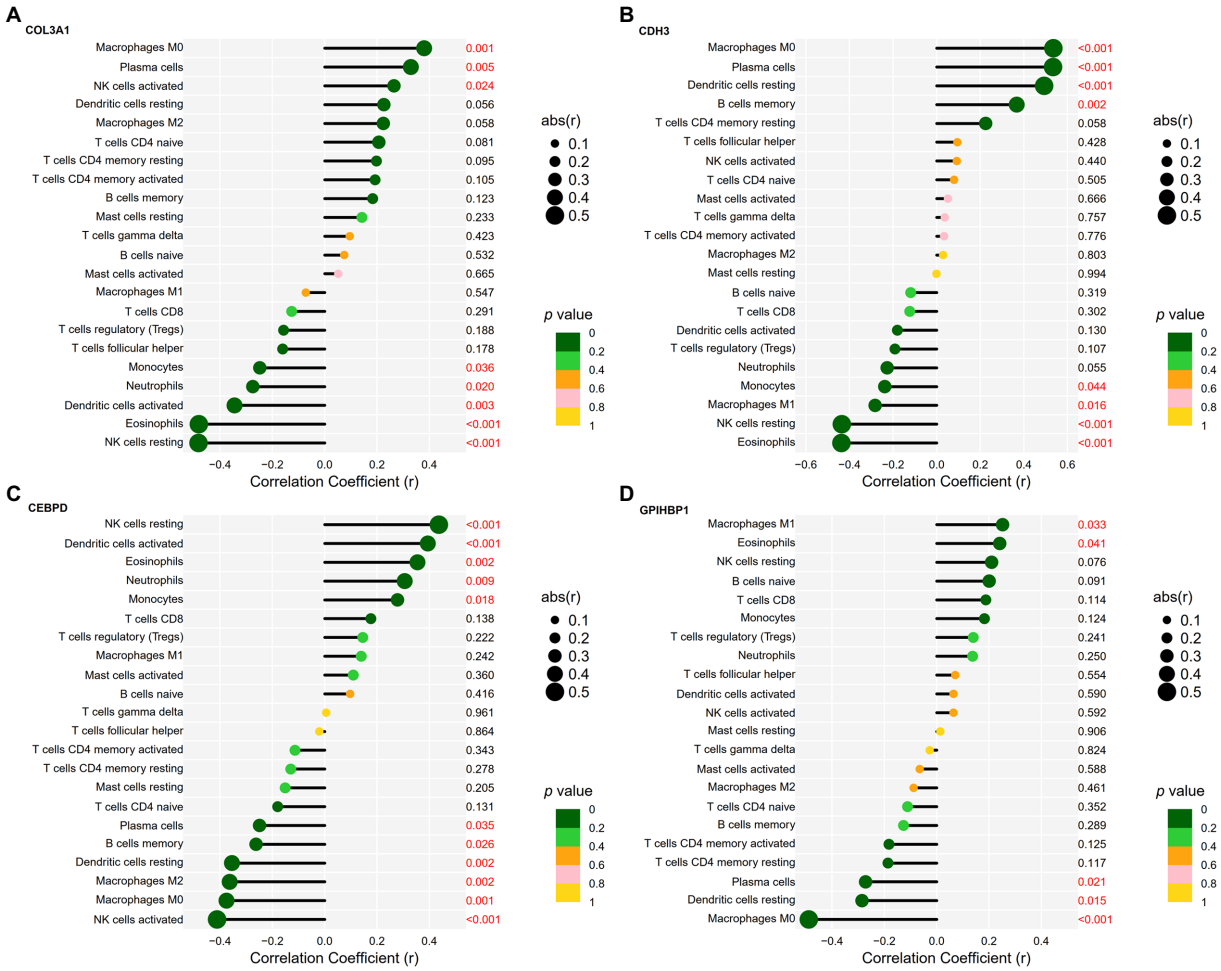

FIGURE 7
Correlation between candidate genes and infiltrating immune cells in IPF. **(A)** Correlation between COL3A1 expression and the infiltration levels of immune cells in IPF. **(B)** Correlation between CDH3 expression and the infiltration levels of immune cells in IPF. **(C)** Correlation between CEBPD expression and the infiltration levels of immune cells in IPF. **(D)** Correlation between GPIHBP1 expression and the infiltration levels of immune cells in IPF.

With the significant advancement of science and technology, machine learning algorithms are widely used for identifying gene biomarkers and predicting disease status (51, 52). The LASSO algorithm uses regularisation to enhance the predictive accuracy (53). SVM has better performance in classification and prediction and is extensively used in disease diagnosis or medical assistance. However, it is only useful for two-group classification tasks. To avoid overfitting, the RFE algorithm can be used. Therefore, the accuracy of the classification of multiclass issues may be addressed using the SVM–RFE technique (54). CIBERSORT, a bioinformatic algorithm, is widely used to measure immune cell infiltration (34, 35). In this study, the LASSO and SVM–RFE algorithms were used to determine candidate biomarkers among the DEGs, and the CIBERSORT algorithm was used to evaluate the abundance of infiltrating immune cells in IPF.

Using the two machine learning algorithms, four candidate genes associated with the diagnosis of IPF were identified, including two upregulated genes, namely, COL3A1 and CDH3, and two downregulated genes, namely, CEBPD and GPIHBP1. The expression of these genes was verified in the validation (GSE53845) cohort. Significant differences were observed in the expression of the four genes between patients with IPF and healthy individuals in the validation cohort. These results were consistent with those of differential expression analysis in the metadata cohort. Additionally, ROC analysis revealed that the genes had a high diagnostic capability. The GSE53845 dataset contains gene expression data derived from the lung tissue samples of 40 patients with IPF and 8 healthy individuals. Because these data are derived from clinical patients, they are valid and reliable. Therefore, the abovementioned four genes were identified as candidate gene biomarkers.

COL3A1 encodes the pro-alpha 1 chains of type III collagen, which is a type of fibrillar collagen distributed in extensible connective tissues, including the skin, uterus, intestine, lung, and the vascular system, usually in association with type I collagen (55). CDH3 is a cadherin superfamily member that encodes cadherin. Multiple transcript variants are produced as a result of alternative splicing, and at least one of them encodes a preproprotein that is processed proteolytically to form a final glycoprotein. Five extracellular cadherin repeats, a greatly conserved cytoplasmic tail and a transmembrane region comprise the calcium-dependent cell–cell adhesion protein encoded by CDH3 (56). CEBPD, an intron-less gene, encodes a transcription factor with a leucine zipper domain that can attach as a homodimer to a particular DNA regulatory segment. It can also form heterodimers with CEBP-alpha, a related protein. The encoded protein plays an essential role in modulating genes involved in immune and inflammatory responses and may

be involved in the modulation of genes associated with macrophage activation and/or differentiation (57). GPIHBP1 is a protein that enhances the lipolytic digestion of triglyceride-rich lipoproteins in capillary endothelial cells. It is a glycosylphosphatidylinositol-anchored lymphocyte antigen-6 family member that plays a critical role in delivering lipoprotein lipase from the subendothelial regions to the capillary lumen (58).

Dysregulated expression of COL3A1 may affect the development of IPF through regulation of IPF-related biological processes, and the expression level of COL3A1 is correlated with the prognosis of IPF (59). COL3A1 is a potential biomarker for assessing the progression of IPF and non-small cell lung cancer (NSCLC). It may help to elucidate molecular mechanisms underlying the progression of IPF and NSCLC and serve as a potential therapeutic target for IPF (60). CEBP homologous protein (CHOP) enhances alveolar epithelial cell (AEC) senescence through the nuclear factor-kappa B (NF-κB) pathway in pulmonary fibrosis (61). Additionally, it enhances the production of sonic hedgehog in type II AECs and stimulates the hedgehog signalling pathway in fibroblasts in pulmonary fibrosis (62). Hypoxia-inducible factor 1 alpha (HIF1A) can trigger endoplasmic reticulum stress and CHOP-mediated apoptosis in AECs, thereby playing a role in the development of IPF (63). Therefore, the four candidate genes as well as the abovementioned non-IPF-related genes warrant further intensive investigation.

CIBERSORT was used to evaluate the infiltration levels of immune cells in patients with IPF and healthy individuals. Several immune cell subtypes were found to be involved in key biological processes associated with IPF. The infiltration levels of plasma cells, M0 macrophages and resting DCs were higher and those of resting NK cells, M1 macrophages and eosinophils were lower in patients with IPF than in healthy individuals. These cells may be associated with the onset and progression of IPF.

Inflammatory and immune cells play an important role in the progression of IPF. Some results of this study are consistent with those of previous studies. The expression of FK506-binding protein (FKBP) prolyl isomerase 11 (FKBP11) is elevated in the lung tissues of patients with IPF, and FKBP11 specifically localises to antibody-producing plasma cells (64). In a study, compared with control mice, bleomycin-treated mice had an increased proportion of pulmonary IgA(+) germinal centres and plasma cells, and autoreactive IgA was identified as a diagnostic biomarker for IPF (65). M1 macrophages play a crucial role in wound healing following alveolar epithelial damage, whereas M2 macrophages are necessary for resolving inflammatory responses that develop in the lung. IPF is a pathological outcome resulting from disrupted wound healing in response to repeated injury to the lung (66). NF-κB facilitates the production of proinflammatory cytokines to exacerbate M1 macrophage polarisation (67). Pirfenidone suppresses transforming growth factor-β, which is associated with M2 macrophage polarisation and fibroblast activation and has anti-fibrotic properties (68). Polarised M1 macrophages can be converted to M0 macrophages after 12 days of incubation in a cytokine-insufficient medium or re-differentiated into a different cell phenotype after being cultured further in a different polarising medium (69). DCs are major contributors to the pathogenesis of IPF (70). In bleomycin models, lung DCs are important proinflammatory cells that maintain pulmonary inflammation and fibrosis (71). Fms-related receptor tyrosine kinase 3 ligand is overexpressed in the serum and lung tissues of patients with IPF and may facilitate the accumulation of lung DCs during pulmonary fibrogenesis (72). The proportion of resting NK cells is lower in the lung tissues of patients with IPF than in those of healthy individuals (73). Eosinophil is a principal source of several crucial pro-fibrogenic cytokines, especially in the initial stages of fibrosis (74).

COL3A1 may serve as a molecular biomarker for assessing prognosis and immune infiltration in pan-cancer (75). Collagen genes play an important role in regulating the immunosuppressive microenvironment and epithelial–mesenchymal transition in glioma and may serve as therapeutic targets for glioma (76). Biomarkers associated with collagen synthesis and degradation have the potential to enhance clinical trials in IPF and may be used for prognostic assessment and therapeutic decision-making in clinical settings (77). CDH3 is associated with immune infiltration in papillary thyroid carcinoma (78). CEBPD has been identified as a diagnostic biomarker for nonalcoholic fatty liver disease using machine learning algorithms and is associated with immune cell infiltration (79). In this study, the expression of COL3A1, CDH3, CEBPD and GPIHBP1 was correlated with the abundance of various immune cells including plasma cells, M0 macrophages and eosinophils. In particular, the expression of CDH3, CEBPD and GPIHBP1 was correlated with the abundance of resting DCs; the expression of COL3A1, CDH3 and CEBPD was correlated with the abundance of resting NK cells and the expression of CDH3 and GPIHBP1 was correlated with the abundance of M1 macrophages. The relationship of the four genes with these immune cells has been reported in some related studies. The infiltration of plasma cells has been associated with the expression of CDH3 and CEBPD (80, 81), whereas that of macrophages has been associated with the expression of COL3A1, CDH3 and CEBPD in multiple diseases (80, 82–84). In-depth experimental studies should be conducted to investigate the relationship between the four genes and immune cells in IPF.

Although this study was rigorous, its limitations should also be acknowledged. Although we collected as many samples as possible by combining the three datasets, the sample size of the metadata cohort is small. Additionally, the sample size of the validation cohort is also small. Because the role of the four biomarkers and infiltration of immune cells in IPF were examined using bioinformatic algorithms, in-depth studies with large sample size should be conducted to validate the findings. We will verify the results in a clinical cohort in future studies, with immunohistochemical detection of lung transplant specimens. Additionally, we will perform single-cell RNA sequencing on lung tissue and blood samples to verify whether the expression of the four genes is altered in immune cell clusters.

5. Conclusion

COL3A1, CDH3, CEBPD, and GPIHBP1 are potential biomarkers for the diagnosis of IPF. Plasma cells, M0 macrophages and eosinophils (associated with these four genes) may be involved in the development of IPF and serve as immunotherapeutic targets for the treatment of IPF.

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 authors.

Author contributions

YZ, HZ, EA-A, HH, and YC conceived and designed the study and wrote the manuscript. YZ, CW, QX, WJ, and HZ were responsible for data collation and analysis. YZ, EA-A, HH, and YC supervised the study. YZ, HZ, and YC revised the manuscript. All authors have read and approved the final 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.

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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.2023.1001813/full#supplementary-material

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Present and future perspectives in early diagnosis and monitoring for progressive fibrosing interstitial lung diseases

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Progressive fibrosing interstitial lung diseases (PF-ILDs) represent a group of conditions of both known and unknown origin which continue to worsen despite standard treatments, leading to respiratory failure and early mortality. Given the potential to slow down progression by initiating antifibrotic therapies where appropriate, there is ample opportunity to implement innovative strategies for early diagnosis and monitoring with the goal of improving clinical outcomes. Early diagnosis can be facilitated by standardizing ILD multidisciplinary team (MDT) discussions, implementing machine learning algorithms for chest computed-tomography quantitative analysis and novel magnetic-resonance imaging techniques, as well as measuring blood biomarker signatures and genetic testing for telomere length and identification of deleterious mutations in telomere-related genes and other single-nucleotide polymorphisms (SNPs) linked to pulmonary fibrosis such as rs35705950 in the MUC5B promoter region. Assessing disease progression in the post COVID-19 era also led to a number of advances in home monitoring using digitally-enabled home spirometers, pulse oximeters and other wearable devices. While validation for many of these innovations is still in progress, significant changes to current clinical practice for PF-ILDs can be expected in the near future.

KEYWORDS

progressive fibrosing interstitial lung disease, progressive pulmonary fibrosis, interstitial lung disease, idiopathic pulmonary fibrosis, PF-ILD, PPF

1. Introduction

Within the complex landscape of interstitial lung diseases (ILDs), a widely studied disease and a major new concept have emerged with the publication of the updated 2022 ATS/ERS/JRS/ALAT clinical practice guideline: progressive pulmonary fibrosis (PPF). (1) While idiopathic pulmonary fibrosis (IPF) is a diagnosis of exclusion, with an unknown etiology and a grim prognosis rivaling most cancers, (2) PPF includes a multitude of ILDs, of both known and unknown origin, that share a progressive disease behavior.

As there is currently approved antifibrotic therapy for progressive fibrosing interstitial lung diseases (PF-ILD)—nintedanib, there is some confusion among clinicians as to what definition to use for establishing progression. The PPF criteria (1), as well as the nintedanib for PF-ILD INBUILD trial inclusion criteria (3) are most often used. Other definitions exist, based on two other studies (pirfenidone in unclassifiable ILD [uILD] and RELIEF) as well as criteria proposed by Cottin et al. (4)—all definitions are detailed in Table 1.

TABLE 1 Summary of several definitions which could be used in clinical practice to define progression of fibrosing interstitial lung diseases.

Definition of progression in fibrosing ILDs	
PPF criteria (1)	Two of the following criteria met within the last year without an alternative explanation: 1. Worsening respiratory symptoms
	2. Lung function decline within 1 year of follow-up—either of absolute decline in forced vital capacity (FVC) ≥ 5% predicted, or absolute decline in DLCO (corrected for hemoglobin) ≥ 10% predicted
	3. Radiological progression—defined in the 2022 ATS/ERS/JRS/ALAT guideline (1) "as one or more of the following: a. Increased extent or severity of traction bronchiectasis and bronchioloectasis b. New ground-glass opacity with traction bronchiectasis c. New fine reticulation d. Increased extent or increased coarseness of reticular abnormality e. New or increased honeycombing f. Increased lobar volume loss"
INBUILD criteria (3)	At least one of the following criteria met within 24 months, despite standard treatment with a therapy other than nintedanib or pirfenidone: 1. Relative decline in the FVC ≥ 10% of the predicted value
	2. Relative decline in the FVC > 5% to <10% of the predicted value **plus** worsening respiratory symptoms **or** increased fibrosis on chest HRCT
	3. Worsening respiratory symptoms **and** increased fibrosis on chest HRCT
Pirfenidone in uILD criteria (5)	Either of the following criteria met within the previous 6 months: 1. Absolute decline in FVC > 5% of percent predicted **or** 2. Worsening respiratory symptoms not explained by cardiac, vascular, pulmonary (except ILD) or other causes
RELIEF criteria (6)	Within 6–24 months prior to inclusion, annualized (absolute) decline in FVC ≥ 5%
Cottin et al. proposed criteria (7)	Either of the following criteria met within a 24 month period: 1. Absolute decline in FVC ≥ 10% 2. Absolute decline in DLCO ≥ 15% 3. Worsening respiratory symptoms 4. Worsening radiological appearance accompanied by a ≥ 5 to < 10% relative decrease in FVC

FVC = forced vital capacity, DLCO = diffusing capacity of the lung for carbon monoxide. HRCT = high-resolution computed tomography, uILD = unclassifiable interstitial lung disease.

Choosing how to document progression has practical implications in obtaining reimbursement for nintedanib, where specific local requirements may need to be met.

Assuming that non-IPF ILDs can behave similarly to IPF and meet criteria for PF-ILD in up to 32% of cases (8), we aimed to summarize and discuss some of the emerging trends in the diagnosis and monitoring of this varied group of conditions, occasionally drawing parallels to IPF as the prototype of progressive fibrotic ILD. The clinical characteristics of the various non-IPF ILDs that could be included under the PF-ILD umbrella have been reviewed previously (9).

2. Current and future directions

2.1. The importance of multidisciplinary team discussion

Multidisciplinary team (MDT) consensus diagnosis for ILD as a gold standard has been suggested; however, the practice of organizing these meetings varies greatly around the world. Before the COVID-19 pandemic, a survey performed across 64 countries by the Respiratory Effectiveness Group (REG) revealed that 76% of centers held formal MDT meetings and the majority (80%) were face-to-face (10). This survey is currently being repeated to better understand how teleworking and the pandemic have influenced MDT practices. It is not clear how MDT discussions are organized in developing countries and what are the opportunities for improvement.

Requirements including a quiet setting with a video projection system, at least one radiologist present, access to high-quality HRCT of the chest, and a standardized template summarizing patient data were deemed essential components of the MDT meeting in a recent Delphi survey of ILD experts (11). Diagnosis of connective-tissue disease-associated ILD (CTD-ILD) would require the presence of a rheumatologist or immunologist for the MDT discussion. However, just over a third of all centers in the REG survey routinely involved these specialists in the discussion (10).

There are benefits to holding MDT meetings, including increased diagnostic confidence and inter-observer agreement, and lower rates of unclassifiable ILD diagnoses. The meetings also provide a forum for discussion and sharing knowledge and experience (12). As we emerge from the COVID-19 pandemic, virtual MDT discussions have brought new opportunities, especially by increasing the number of attendees (including trainees and non-specialist physicians). However, virtual meetings can be less accessible in resource-poor areas, less focused, and prone to "technical" difficulties. Preserving patient confidentiality may also prove difficult in virtual settings (13).

The future of ILD MDT discussion is likely going to include genetic testing data and input from relevant specialists (i.e., clinical genetics, lung transplant physicians) due to recent discoveries of accelerated progression and worse responses to immunosuppression in patients with familial forms of ILD or sporadic cases with a genetic component

(e.g., telomere dysfunction). There is significant support from clinicians, as well as patients and their relatives for genetic testing (14).

In our experience, MDT consensus also builds diagnostic confidence from a patient perspective and provides reassurance that an entire ILD team is involved in care provision. In our center, ILD specialist nurses and pharmacists also regularly attend MDT discussions to provide their own unique input regarding potential tolerability and interactions when considering treatments for PF-ILD.

2.2. Imaging and CT quantitative analysis

Early attempts at defining imaging biomarkers for ILD progression were focused on chest CT patterns present at diagnosis. The finding of a usual interstitial pneumonia (UIP) pattern on chest CT in hypersensitivity pneumonitis (HP) was associated with a similar rate of lung function decline in PF-ILD compared to IPF. Similarly, in rheumatoid arthritis associated ILD (RA-ILD), UIP was identified as a major predictor of decline (15). However, there can be significant inter- and intra-observer variability for visual radiological evaluation, especially in non-UIP pattern fibrosis.

Some progress has been made in improving the diagnostic and monitoring accuracy of ILDs using artificial intelligence. The Computer Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER) program seemed to be able to differentiate between IPF and CTD-ILD, showing differences in analysis of peripheral volume of reticulation (greater in IPF versus CTD) and vascular-related structure (VRS) volume (greater in IPF versus CTD) (16). In IPF patients, CALIPER quantification scores for ILD (ILD%) and pulmonary vascular-related structures (PVRS%) were shown to correlate with forced vital capacity (FVC) at baseline evaluation and during disease progression, with faster increases in scores in patients who were not treated with antifibrotics (17). For non-IPF ILDs, similar findings are starting to emerge, with reticulation and traction bronchiectasis scores (QLF) predicting survival in RA-ILD (18) and convolutional neural network approaches in HP showing correlation with lung function parameters (19).

There are however inherent challenges. Machine learning algorithms require "training" using quality data and there are issues with validating the accuracy of the results. Furthermore, most studies have been retrospective, with not enough longitudinal data to estimate whether automated quantitative CT analysis will indeed positively impact clinical outcomes (20). A recent systematic review confirmed the need to increase diagnostic accuracy and gather prospective data (21). The PREDICT-ILD study will hopefully shed some light on the use of CT quantification for predicting lung function trajectories in fibrotic ILDs and correlate scores with genetic predisposition and markers of endothelial damage (NCT05609201).

Although not validated for routine clinical practice, a promising area of investigation is the use of magnetic-resonance imaging (MRI) based techniques for the evaluation of ILDs of different etiologies. Conventional MRI has inherent difficulties in imaging the lung parenchyma; however, techniques such as ultrashort echo time or dynamic contrast-enhanced MRI can be helpful for imaging the lung vasculature. Inhaled hyperpolarized ^{129}Xenon gas MRI can provide a functional assessment of alveolar-capillary diffusion as well as ventilation and intra-acinar gas diffusion (22). So far, ^{129}Xe ventilation or oxygen enhanced-MRI biomarkers were not able to discriminate between the different types of ILD in one small study (23). However, dynamic contrast-enhanced perfusion MRI seemed to correlate with pulmonary vascular disease progression in IPF (24) which would be a relevant biomarker in the monitoring of PF-ILD. Further assessment of ^{129}Xe MRI is also underway as part of the UKILD consortium (in the evaluation of post COVID-ILD patients) (25)

2.3. Home monitoring for PF-ILD

The COVID-19 pandemic has catalyzed the development of home monitoring strategies for fibrotic lung disease, as many centers struggled to maintain face-to-face patient encounters and availability for hospital-based lung function testing became severely reduced. The severity of lung function impairment has been demonstrated to be one of the most important predictors of worse outcomes in non-IPF PF-ILDs (15).

Home spirometry involves providing patients with a device that normally connects to their smartphone *via* Bluetooth®, allowing real-time uploading of results to a patient portal (which may also be accessible to the physician). Normally, initial training and device setup are done in clinic, the patient then being asked to perform home spirometry according to a set schedule (i.e., once daily, once weekly). Instructional videos are sometimes available, and some platforms allow automated reminders to be set up with the goal of increasing adherence.

A systematic review has shown that patient adherence to home spirometry was satisfactory (>75%) and values measured at home correlated significantly with those measured in-hospital (26) Interestingly, the variability in home-measured FVC values may actually be an independent predictor for fibrotic ILD progression (27) Increasing adherence can be achieved by setting up automated email reminders when a measurement is not performed when expected (28), providing comprehensive initial and refresher training to patients, or using a spirometry schedule which is more acceptable (rather than daily measurements) (29). The optimal timing and frequency of testing to account for diurnal variation has not yet been established (30).

Home spirometry allows for trends in lung function decline to be generated, which is of great importance in monitoring and increasing diagnostic accuracy for PF-ILD. Additionally, as many patients could not be seen often enough during the pandemic, a role emerged for home spirometry to aid with early diagnosis of acute exacerbations of ILD (26).

While useful in a clinical setting, there are accuracy limitations to incorporating home spirometry FVC decline as a primary endpoint in clinical trials for PF-ILD, as demonstrated in a phase 2 study of pirfenidone for unclassifiable PF-ILD (5). In this study, estimating the rate of FVC decline proved difficult due to technical difficulties with the device and implausible measurements. Similar issues were encountered in two other studies aiming to describe ILD disease behavior using home spirometry (STARLINER and STARMAP) (29). Despite the limitations, high patient satisfaction with home spirometry monitoring has been reported (30, 31).

Ambulatory pulse oximetry coupled with activity monitoring has been used to provide continuous data on peripheral oxygen saturation (SpO2) to help optimize long-term oxygen treatment (32). Consumer-level activity trackers (e.g., Fitbit, San Francisco, CA, United States) can record multiple parameters including step counts, heart rate, heart rate variability, SpO2, and skin temperature. Data from a small study in sarcoidosis reported an improvement in exercise performance in patients wearing an activity tracker compared to controls (33).

Perceived positive effects may drive many patients to self-initiate activity monitoring using wearables. Integrating these data into clinical care may prove difficult, due to variability in measurements and inability to deconstruct proprietary algorithms which present recorded data in a consumer-friendly format. It is unknown which parameters will yield the greatest clinical benefit, however this area of research is promising (30).

Cough-frequency monitoring can provide objective symptomatic monitoring for PF-ILD patients to aid in treatment decisions (i.e., prescribing cough suppressants). Existing devices such as the VitaloJAK (Vitalograph, Buckingham, United Kingdom) or the Leicester Cough Monitor (University Hospital Leicester, Leicester, United Kingdom) have been mostly used in clinical trials, and there may be limitations to their use in outpatient settings (34). Methods which involve cough monitoring *via* smartphone applications are currently being developed (35). The main drawback of implementing cough monitoring at scale is the need to protect patient privacy, as sound needs to be recorded and analyzed.

2.4. Blood biomarkers

Much of the work regarding serum and plasma biomarkers in ILD has so far focused on IPF. Since there is overlap between IPF and non-IPF PF-ILDs with respect to molecular pathways, emerging data suggest that there is also overlap in the biomarkers of interest (36). While it is unlikely that a single biomarker would explain the full spectrum of PF-ILD, combining several markers into "signatures" can enhance their clinical utility.

In IPF, a progression index based on 4 biomarkers (osteopontin—OPN, matrix metallopeptidase-7—MMP-7, intercellular adhesion molecule-1—ICAM1, and periostin—POSTN) was found to be superior to the clinical GAP score (gender, age, and lung physiology) in predicting progression at 12 months (37). A combination of MMP-7, pulmonary and activation-regulated chemokine (PARC), and surfactant-protein D (SP-D) increased the predictive value of clinical features, positive rheumatoid factor, and anti-cyclic citrullinated peptide antibodies for RA-ILD (38). Bowman et al. also recently used a proteomic approach to identify 17 biomarkers for PF-ILD which had consistent associations across different ILDs and chest HRCT imaging patterns. This data support a shared pathophysiology across the PF-ILD spectrum and paves the way for using a proteomic signature for defining progressive fibrosis. The ITGB6 marker (which represents the β6 subunit of integrin αvβ6, a critical activator of TGF-β) was found to have the strongest association with progressive fibrosis (39).

Prospective data on the use of biomarkers in influencing clinical outcomes are still lacking. One of the main aims of the INJUSTIS study (currently recruiting) is to obtain longitudinal data on biomarkers which predict progressive fibrosis in non-IPF patients (NCT03670576).

2.5. Genetic biomarkers

An ever-increasing body of evidence suggests that the development of ILD is rooted in genetic factors. The study of familial cases has yielded a number of deleterious mutations in several telomere-related genes (TRGs), which lead to premature telomere attrition. These include telomerase reverse transcriptase (TERT), telomerase RNA component (TERC), dyskerin (DKC1), regulator of telomere elongation helicase (RTEL1), poly(A)-specific ribonuclease (PARN), surfactant protein C (SFTPC) and A2 (SFTPA2), and the shelterin complex (also known as the telosome, and consisting of TRF1, TRF2, RAP1, TIN2, POT1, and TPP1) (40, 41). Telomere dysfunction has been implicated in all forms of ILD, of which many have a progressive fibrosing phenotype (42). There is significant overlap between IPF as a prototype of progressive fibrotic lung disease (IPF) and other PF-ILDs (43)

Using genome-wide association studies (GWASs), several groups found a strong association between the rs35705950 single-nucleotide polymorphism (SNP) in the MUC5B promoter and IPF and interstitial lung abnormalities (ILAs) (44–46). The MUC5B variant was also associated with the risk of developing a UIP pattern on chest CT scanning in HP and RA-ILD which confers the highest risk of fibrosis progression (47, 48). In HP patients, the MUC5B high-risk polymorphism was found in approximately a quarter of patients compared to 10% in the general population (48). Research into novel causes fibrosis also revealed correlations suggesting an overlap between genetic predisposition for fibrotic conditions (i.e., IPF) and severe COVID-19 (49).

From a clinical perspective, although the overall phenotype may not be different in familial versus sporadic ILD cases, disease onset tends to be early. Within the same family, heterogeneity of ILD diagnosis may be possible, which is not fully understood, but may relate to an interplay with environmental and developmental factors (50). Sporadic IPF cases with an early onset (age < 60 years) had a higher likelihood of having telomere shortening, notably if they also featured immunological or hematological abnormalities (51). Telomere attrition was found in up to a quarter of patients with sporadic IPF and up to half of those with familial pulmonary fibrosis (52).

Heterozygous mutations in TRGs were associated with a uniformly progressive fibrotic phenotype (regardless of ILD diagnosis) and patients had a mean annual decline in FVC of 300 ML, which is more rapid than the 130–210 ML/year FVC loss seen in placebo arms of IPF clinical trials (53).

Progressive fibrosing interstitial lung disease treatment often involves immunosuppressant therapy and clinicians need to carefully monitor patients with telomere shortening due to a greater risk of developing treatment-related side effects (as seen in IPF with the PANTHER-IPF trial and fibrotic HP) (54, 55). Complications and worse outcomes after lung transplantation were noted for patients with short telomeres (54). However, in a Spanish cohort of 20 patients with fibrotic ILD who underwent lung transplantation (12 with and 8 without telomere shortening), post-transplant 1-year survival was > 80% regardless of telomere dysfunction, with improvement in the quality of life and manageable complications (56). Loss of clinical efficacy of immunosuppression is also suggested by findings of mycophenolate treatment only leading to improvement in fibrotic HP patients who had normal leukocyte telomere length (57).

Telomere dysfunction may confer a higher likelihood of negative responses to environmental insults (such as exposure to particulate matter) although such research is mired with difficulties in determining correlations without confounding (58).

Taken together, these findings implicate a definite role for genetic predisposition in the development of PF-ILD. In practical terms, this means that clinicians should actively ask about family history and identify clinical features of telomere dysfunction when diagnosing and treating PF-ILD; and to refer at-risk individuals for genetic testing as appropriate.

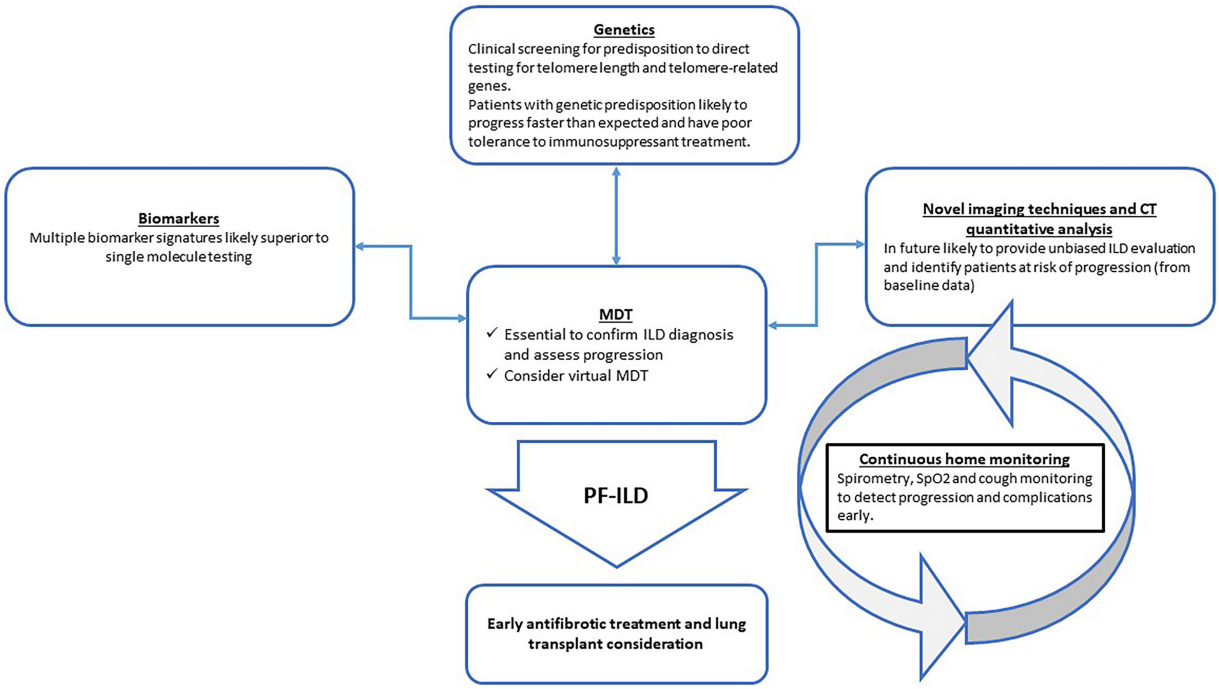

FIGURE 1
Proposed integration of novel tools to improve early diagnosis and monitoring of progressive-fibrosing interstitial lung diseases (PF-ILDs) in the clinical setting. MDT=multi-disciplinary team; CT=computed tomography; SpO2=peripheral oxygen saturation.

3. Discussion

There has been significant progress in improving the accuracy of PF-ILD diagnosis and developing novel monitoring strategies. Early identification of patients at risk of PF-ILD by deconvoluting the complex landscape of genetic predisposition and other biomarkers holds the promise of avoiding inherent delays in diagnosis, which currently requires documented evidence of decline in symptoms, lung function or imaging parameters over 12–24 months (Figure 1).

The INBUILD trial showed that antifibrotic treatment with nintedanib versus placebo in PF-ILD reduced the annual adjusted rate of FVC decline from approximately 180 ML to 80 ML, with an even greater difference seen in those with a UIP pattern on imaging (3), leading to a conditional recommendation for nintedanib in PF-ILD (1). Early initiation of treatment is essential.

Technological approaches are likely to become a routine part of PF-ILD monitoring in the near future and it is important to become familiarized with the various home spirometry, pulse oximetry, and activity monitoring platforms. Although further validation of these devices is required, many patients are already using them to gain personal health insights and clinicians should be ready to integrate this data into routine follow-up.

Machine learning tools are likely to help reduce inter- and intra-observer variability of imaging data, which will allow for more accurate ILD diagnosis and identifying those patients most at risk of progression.

Finally, in our opinion, large improvements in the care of PF-ILD patients could be obtained by simple adjustments to clinical practice, such as encouraging a standardized approach to ILD MDT discussion involving expert opinion from specialist centers (which can be done virtually) and by routinely asking about family history to uncover at-risk relatives of ILD patients early.

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 have both contributed equally to the conceptualization, literature review, drafting of the manuscript and approved the final 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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Fine-tuning characterization of patients with interstitial pneumonia and an underlying autoimmune disease in real-world practice: We get closer with Nailfold videocapillaroscopy

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Objectives: To assess performance of interstitial pneumonia (IP) with autoimmune features (IPAF) criteria in clinical practice and describe the utility of additional workup in identifying patients with underlying connective tissue diseases (CTD).

Methods: We set a retrospective study of our patients with autoimmune IP, who were allocated to CTD-IP, IPAF or undifferentiated autoimmune IP (uAIP) subgroups according to the updated classification criteria. Presence of the process-related variables comprising IPAF defining domains was scrutinized in all patients, and, when available, the results of nailfold videocapillaroscopy (NVC) were recorded.

Results: Thirty nine out of 118 patients, accounting for 71% of former undifferentiated cases, fulfilled IPAF criteria. Arthritis and Raynaud's phenomenon were prevalent in this subgroup. While systemic sclerosis-specific autoantibodies were restricted to CTD-IP patients, anti-tRNA synthetase antibodies were also present in IPAF. In contrast, rheumatoid factor, anti-Ro antibodies and ANA nucleolar patterns could be found in all subgroups. Usual interstitial pneumonia (UIP) / possible UIP were the most frequently observed radiographic patterns Therefore, the presence of thoracic multicompartimental findings as also performance of open lung biopsies were useful in characterizing as IPAF those UIP cases lacking a clinical domain. Interestingly, we could observe NVC abnormalities in 54% of IPAF and 36% of uAIP tested patients, even though many of them did not report Raynaud's phenomenon.

Conclusion: Besides application of IPAF criteria, distribution of IPAF defining variables along with NVC exams help identify more homogeneous phenotypic subgroups of autoimmune IP of potential relevance beyond clinical diagnosis.

KEYWORDS

connective tissue diseases (CTD), interstitial pneumonia (iP), nailfold videocapillaroscopy, interstitial pneumonia with autoimmune features (IPAF), anti synthetase syndrome

Introduction

Interstitial lung diseases (ILD) or interstitial pneumonia (IP) are a group of conditions characterized by chronic damage at the lung parenchyma resulting from an abnormal remodeling and sustained inflammatory response upon an initial injury of the alveolar and/or microvascular structure. While sharing clinical, radiological and functional characteristics, ILD show a wide range of presentations and a variable risk of functional deterioration and fibrosis development. Their heterogeneity relies not only on different etiologic backgrounds but also on host-dependent factors, which account for a variety of perpetuating mechanisms (1). In order to improve the standard of care of these patients it is fundamental to correctly characterize individual phenotypes both as regards to the underlying disease and to the participation of targetable processes.

The investigation of an underlying condition in patients with ILD can be challenging. After an exhaustive workup aimed to rule out distinct etiologic factors, such as drugs and other environmental toxics, infectious agents, allergens, genetic disorders or some neoplasms, most patients can be classified into any of the following diagnostic groups: autoimmune connective tissue disease (CTD) associated IP, granulomatous processes and idiopathic IP (IIP), of which idiopathic pulmonary fibrosis (IPF) is the most characteristic form (2). Although the IIP diagnosis accounts for approximately 15% of ILD cases, the group of CTD-IP is expanding as a result of recent advances in the characterization of autoantibodies as well as in CTD-classification criteria. It is expected that this tendency will continue to grow in the next few years while, in parallel, the number of IIP forms will go down, since most of the patients could have an autoimmune substrate (3, 4). This fact is anticipated, due to the unfavorable prognosis of IPF as compared to CTD-IP (5).

In clinical practice, there is a substantial overlap between CTD-IP and IIP suggesting a continuum in the pathogenesis of chronic fibrotic IP processes (6). In 2015, a joint European Respiratory Society (ERS) - American Thoracic Society (ATS) Task Force on undifferentiated forms of CTD-IP developed preliminary criteria for the classification of patients as Interstitial Pneumonia with Autoimmune Features (IPAF) in order to identify patients with high suspicion of an underlying autoimmune process but not fulfilling criteria for a definite CTD (7).

Nailfold videocapillaroscopy (NVC) is an accesible and non-invasive image technique which allows the direct exam of microvessels morphology. This examination is principally performed in patients with Raynaud's phenomenon -or in those ones with a clinical suspicion of systemic sclerosis (SSc)-to confirm the presence of SSc typical vasculopathy (8). However, microvascular involvement may be associated to additional CTDs, such as dermatomyositis and the anti-aminoacyl tRNA synthetase syndrome (ARS). It should be underlined that these entities do not necessarily present with Raynaud's phenomenon. Subsequently, NVC is being increasingly used by rheumatologists in the assessment of patients with subtle or overlapping CTD features. The latter include patients with IP, since this manifestation may reflect organic involvement of SSc and related CTDs. In this regard, capillary loss at nailfolds has been shown to associate with IP in patients with SSc, but NVC abnormalities have also been found in patients diagnosed with other CTD-IP, IPAF or even in IPF (9). At present, in spite of its routinary use in Multidisciplinary IP Clinics, the precise utility of this examination in the accurate classification of patients with IIP remains to be established (9).

In this study, we have reviewed the cohort of patients attending our Multidisciplinary Clinic for autoimmune ILD in order to find out the prevalence of both IPAF and IPAF-defining items as well as the presence of abnormalities in NVC searching for a better characterization of the patients.

Methods

Study population

The study was conducted in accordance with the declaration of Helsinki and was approved by Jimenez Diaz Foundation University Hospital Ethics Committee. Data were collected by retrospective chart review. The study population comprised patients attending the Jimenez Diaz Foundation University Hospital multidisciplinary autoimmune ILD Clinic between January 2011 and January 2020. Patients were not directly involved in their participation. Presently, all patients with active follow-up at our Clinic are offered participation in a multicenter prospective register of patients with autoimmune IP of Madrid (NEREA register). The authors will disseminate the study results to the NEREA cohort of patients. We will provide a short summary of our principal findings at the NEREA web site and send a hard copy to the participating centers to be available at the multidisciplinary ILD clinics.

Inclusion criteria and subgroup definitions

In order to be included in the analysis, patients needed have a clinical diagnosis of ILD in the context of an autoimmune disease, after ruling out alternative etiologies (10). In all cases, the final diagnosis had been confirmed by a multidisciplinary team with the participation of Radiologists, Pathologists, Rheumatologists and Pulmonologists. Only patients with at least 3-year follow-up from diagnosis or a fatal outcome were included. Based on the updated classification criteria for the different CTD (8, 11–15) and on Fischer's IPAF criteria (7), patients were re-classified by the investigators. Those of them not fulfilling any of these criteria were grouped as undifferentiated autoimmune interstitial pneumonia (uAIP). Besides, patients were diagnosed with anti-aminoacyl tRNA synthetase syndrome (ARS) following Solomon's preliminary criteria (16).

Additional data in patients' characterization

Along with demographics, all relevant data for the classification of the disease, which included the assessment of the IPAF domain-defining variables, were listed. In those patients who had undergone a diagnostic surgical lung biopsy, the histopathological findings were registered.

Nailfold videocapillaroscopy

When available, the result and characteristics of NVC performed as per clinical practice during diagnostic workup were also recorded. All nailfold videocapillaroscopy (NVC) studies had been performed according to an internal protocol which complies with EULAR recently launched recommendations (17). Briefly, patients are instructed to avoid smoking, cafeine or manicure before the examination and a short period

of acclimatizationto room temperatura is set. Studies performed before 2014 were done with a Zuzi® Optical stereomicroscope (optical magnification of 50x) and an adapted Optikam® camera or with an USB Digital Microscope video epiluminiscence Dino-Lite® (200x magnification). A Nikon SMZ-745 T stereomicroscope with 6.7x - 50x zoom range equipped with a led stand, white epi-illuminators and an 12 MP (pixel size 1.85 micrometer) resolution USB camera (DFK 33UX226, The Imaging Source) is used from 2014 onwards. Image capturing and processing is done with The Imaging Source software. For an improved image acquisition, the nailfolds are bathed with a thin layer of immersion oil (Sigma-Aldrich). Acquisition and interpretation are performed by trained rheumatologists.All images are automatically coded and stored. Supplementary File 1 shows definition of NVC abnormalities as applied in this study along with an illustration of the standardized evaluation of lesions (17, 18). For the purpose of this study, all the images were reviewed by the same blinded examiner.

Statistical analysis

Descriptive statistics are shown as frequencies (%) or mean (SEM) and median. Differences in categorical variables were analyzed with Pearson's Chi2 test or Fischer's exact test, while quantitative measures were compared with independent two sample T test or ANOVA followed by Dunnett's t test when applicable. Associations are shown as odds ratio with CI95 or as positive and negative predictive values where applies. A 2-sided p value of 0.05 was considered significant.

Results

Cohort characteristics

One hundred and eighteen patients, whose characteristics are shown in Table 1, were included. Most of the patients in our cohort were Spanish, followed by a 10% of Hispanics. There was a predominance of women (69% of the patients). Median disease duration was 8 years and total follow-up was 984 patient-years (PY). Thirty one disease-related deaths occurred during this period (3.1/100PY). According to current classification criteria, 53% of the patients ($n = 63$) had a definite CTD, while an additional 33% ($n = 39$) fulfilled IPAF criteria and 14% ($n = 16$) remained unclassified. There was a marked difference between diagnostic subgroups as regards to age at onset, being patients diagnosed with a CTD 9.15 ± 3.3 years younger than those with IPAF (p 0.017), and 11.8 ± 4.5 than those of the uAIP group (p 0.026). Comorbidities did not substantially differ between groups. Table 2 summarizes demographics of the CTD-IP subgroup, which mostly comprised patients with rheumatoid arthritis (RA, $n = 22$), inflammatory myopathies (IM, $n = 21$) and systemic sclerosis (SSc, $n = 16$). As it is shown in the Table, some patients met classification criteria of 2 different CTDs. On the other hand, there were 21 patients in the cohort fulfilling criteria for ARS, whose characteristics can be found in Supplementary File 2. Of note, according to current classification criteria, 15 (71%) of the latter patients were included in the CTD-IP diagnostic group, while 6 (29%) of them could not be classified as a definite CTD but fulfilled IPAF criteria instead. Supplementary File 3 provides an overview of the considerable overlapping between conditions evidenced in our study population.

As regards to disease onset, 38% of the patients presented with an isolated pulmonary condition, including 12 patients (19%) of the CTD subgroup. Notwithstanding, most of the latter could be classified by the Rheumatologist during diagnostic workup. There were only 3 patients who changed diagnosis later on due to the appearance of new manifestations. These were 1 patient initially classified as uAIP who developed definite RA within the first year of symptoms, and 2 additional patients presenting with IPAF who met criteria for an IM and for SSc at 12 and 36 months from ILD diagnosis, respectively. In addition, 2 patients from the IPAF group developed ARS criteria over time, but still did not meet criteria for IM or another CTD, hence keeping their initial classification.

Distribution of interstitial pneumonia with autoimmune features defining items in the diagnostic subgroups

Characterization of the process according to the IPAF defining variables is summarized in Supplementary File 4. As regards to clinical features, inflammatory arthralgia / arthritis (49%) and Raynaud's phenomenon (20% of cases) were relatively prevalent in the IPAF group, while in contrast, SSc highly specific traits -such as sclerodactyly or digital scars- were only found in patients diagnosed with CTD-IP.

With respect to immunological markers (Supplementary File 4), RF and ANA could be found in the 3 groups, with titers not differing significantly between them. Considering ANA, the presence of anti-Ro60, low titers of anti-dsDNA antibodies and Hep2 indirect immunofluorescence (IFA) nucleolar patterns was observed within the uAIP subgroup, together accounting for a 50% of cases fulfilling the serological IPAF domain. In contrast, all myositis specific antibodies (MSA) were allocated to either of CTD or IPAF subgroups, while SSc-specific autoantibodies were exclusively described in patients fulfilling SSc classification criteria. Finally, ACPA were only associated to CTD-IP or IPAF cases, albeit the latter had significantly lower titers ($p < 0.001$).

Remarkably, there was a predominance of UIP/possible UIP patterns in our cohort (42% of cases) as compared to 33% of non-specific interstitial pneumonia (NSIP) patterns, which were second in frequency. The distribution of radiographic patterns between diagnostic groups did not reach significant differences. Since UIP does not score as an IPAF morphological trait, additional requirements were needed in order to assign these patients to the IPAF subgroup. The value of thoracic multi-compartment involvement or signs was reflected by their appearance in 27 and 45% of patients from the CTD and the IPAF subgroups, respectively. In particular, there were 13 patients diagnosed with IPAF who did not fulfil the clinical domain (Supplementary File 5). Interestingly, 4 of them with an UIP/possible UIP pattern and 2 other with an unclassifiable IP pattern could meet IPAF criteria due to the presence of thoracic multi-compartment involvement or signs in the CT scans. As shown in Supplementary File 5, there were 2 further cases who did not meet the radiographic domain either, but were classified after performance of a surgical lung biopsy. These consisted of a patient with a possible UIP pattern plus high RF titer and another one with an unclassifiable radiographic pattern and anti-Ro52 antibodies.

Nailfold videocapillaroscopy

An nailfold videocapillaroscopy (NVC) had been performed as part of the workup in 68 of our patients (58%) of whom 26 were

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TABLE 1 Study population. All patients were diagnosed with autoimmune interstitial pneumonia.

	Total cohort (*n* =118)	Clinical subgroups			Multigroup comparisons	Two-group comparisons difference: mean±SEM [CI95]		
		CTD-IP (*n* =63)	IPAF (*n* =39)	uAIP (*n* =16)		CTD-IP vs. IPAF	CTD-IP vs. uAIP	IPAF vs. uAIP
Women, *n* (%)	82 (69)	48 (76)	26 (67)	8 (50)	ns			
Hispanic, *n* (%)	12 (10)	9	2	1	ns			
Age at onset, mean (SEM), *median*	59 (1), *62*	55 (2), *56*	64 (3), *66*	66 (34), *70*	*p* 0.004	dif: 9.1 ± 3.3 [1.3; 16.8] p 0.017	dif: 11.8 ± 4.5 [1.2; 22.4] p 0.026	ns
Age at endpoints, mean (SEM), *median*	70 (1), *72*	68 (2), *68*	73 (2), *75*	75 (2), *77*	*p* 0.07	ns	ns	ns
Disease duration (year), mean (SEM), *median*	8.3 (0.5), *8*	8.4 (0.7), *8*	8.9 (1), *8*	6.9 (1), *6.5*	ns	ns	ns	ns
Follow-up, patient-years	984	527	347	110				
First manifestation								
pulmonary, *n* (%)	45 (38)	12 (19)	22 (56)	11 (69)	*p* < 0.001	*p* < 0.001	*p* 0.001	ns
Extra-pulmonary, *n* (%)	44 (37)	35 (56)	7 (18)	2 (13)				
Synchronic, *n* (%)	29 (25)	16 (25)	10 (26)	3 (19)				
Smoking exposure								
Never	53 (45)	34 (54)	13 (33)	6 (37)	*p* 0.024	ns	*p* 0.021	ns
Past	43 (36)	16 (25)	17 (44)	10 (62)				
Active	20 (17)	12 (19)	8 (20)	0				
SPY, mean (SEM), *median*	31.5 (3.9)	30 (7) *16*	35 (6) *35*	27 (8) *20*	ns			
Comorbidities at onset, *n* (%)	59 (50)	36 (57)	16 (44)	10 (62)	ns			
Past or present history of cancer, *n* (%)	20 (17)	12 (19)	7 (18)	1 (6)	ns			
Organ-specific autoimmune condition, *n* (%)	34 (29)	17 (27)	9 (23)	8 (50)	ns			
Deaths, *n* (%)	31 (26)	14 (22)	10 (26)	7 (43)	ns			

Patients are allocated to three clinical subgroups according to fulfillment of classification criteria for a definite connective tissue disease (CTD-IP), interstitial pneumonia with autoimmune features (IPAF) or none (uAIP) at the end of follow-up.

diagnosed with IPAF and 14 with uAIP. Of note, abnormal NVC findings were found in 14 (54%) and 5 (36%) of the patients from these two groups, respectively (Figure 1A). An SSc-specific pattern was observed in 5 (19%) of the IPAF patients, but in none with uAIP. Abnormal capillary shapes, such as twisting, ramifications and angiogenesis, were observed in patients from the 2 diagnostic subgroups (Figure 1B). Interestingly, 25 out of the 43 patients with NVC abnormalities did not have Raynaud's phenomenon and some of them even fail to display any other digital lesions (Supplementary File 6). Subsequently, we analyzed which of the process-related variables along with Raynaud's phenomenon could better predict the presence of abnormalities at NVC. As detailed in Table 3, both the presence of telangiectasia (p 0.023) and an NSIP radiographic pattern (p 0.041) were associated to abnormal NVC findings. An SSc pattern was found in all patients with digital ulcers (p 0.049), whereas the presence of giant capillaries was strongly associated to telangiectasia (p 0.004), digital ulcers (p 0.035), Raynaud's phenomenon (p 0.027) and puffy fingers (p 0.017). Intriguingly, of all autoantibodies, anti-Ro predicted capillary enlargement (p 0.027), giant capillaries (p 0.024) and angiogenesis (p 0.046), while the presence of ramifications could be predicted by an ARS diagnosis (p 0.024) or an NSIP pattern (p 0.012).

TABLE 2 CTD-IP cases. Patients are allocated according to fulfillment of classification criteria for the different connective tissue diseases (CTD) at the end of follow-up.

	Rheumatoidarthritis	Systemicsclerosis	Inflammatorymyopathy	Sjögren	Lupus	Mixedconnectivetissuedisease
Number	21 + 1 overlapping case	14 + 2 ovarlapping cases	20 + 1 overlapping case	4 + 1 overlapping case	1 ovarlapping case	1
Women, *n* (%)	16 (73)	12 (75)	15 (75)	4 (100)	1 (100)	1 (100)
Eversmoker, *n* (%)	10 (48)	4 (29)	14 (67)			
Smoking status, *n*: never, past, active smoker	12, 5, 5	12, 4, 0	7, 7, 7	4, 0, 0	1, 0, 0	1, 0, 0
Age at onset, mean (SEM) *median*	60.1 (3.4) *62*	46.8 (4.5) *48*	51.8 (2.4) *53.5*			
Age at endpoints, mean (SEM) *median*	76.3 (2.4) *80*	61.4 (3.9) *63*	60.8 (2) *61.5*			
Disease duration, mean (SEM) *median*	9.1 (1.5) *8*	9.1 (1.3) *8.5*	6.8 (1.1) *6.5*			
Follow-up, (patient-years)	200	146	139	53	9	3
Respiratory onset, *n*	4	3	3	2	0	0
Extra-respiratory onset, *n*	18	10	5	2	1	1
Synchronic pulmonary and extra pulmonary disease at onset, *n*	0	3	13	1	0	0

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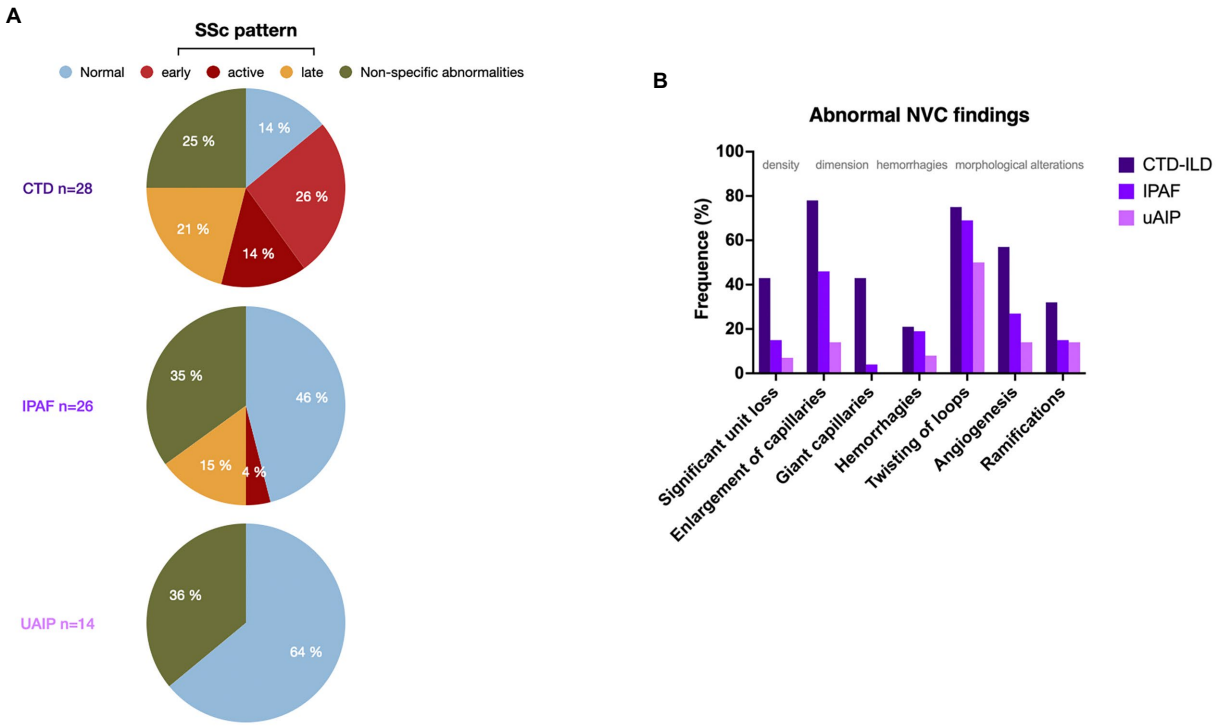

FIGURE 1
(A) Patterns of nailfold videocapillaroscopy (NVC) in the three diagnostic groups shown as percentage of the studies performed. **(B)** Distribution of nailfold videocapillaroscopy (NVC) abnormalities in the patients from the 3 diagnostic groups shown as percentage of the studies performed. SSc: systemic sclerosis. CTD: connective tissue disease, IPAF: interstitial pneumonia with autoimmune features. uAIP: undifferenciated autoimmune interstitial pneumonia. ILD: interstitial lung disease.

Discussion

We present data from a retrospective cohort of similar demographics to other reported IIP populations (19, 20). Also alike many working groups, there was a considerable number of patients diagnosed with undifferentiated or pulmonary-dominant CTD before the concept of IPAF was introduced. In our patients, IPAF criteria showed a good performance in capturing former undifferentiated ILD cases. Up to 71% of the patients without an overt CTD could be classified using IPAF definition, which is remarkable considering that classification criteria of most CTD have been updated in the last few years in order to include patients at early stages of the disease.

However, the IPAF subgroup possible comprises distinct disease subtypes. Seeking to stratify patients according to more homogeneous criteria, we further explored distribution of the individual IPAF-defining items in the whole cohort. The fact that SSc-specific autoantibodies as well as digital lesions, such as sclerodactyly and scars, were limited to the subgroup of CTS-IP patients, not only supports the accuracy of the current SSc classification criteria, but also indicates that these traits might add little value to the identification of IPAF cases. Conversely, an important amount of IPAF patients overlapped with the ARS syndrome, either by sharing a defining antibody or typically-associated clinical features. This fact has been observed already, as well as the tendency of IPAF with ARS-related manifestations or antibodies to evolve to a definite CTD over time (21–23). In this regard, the need to consider segregation of ARS-like cases from other IPAF patients has been recently put forward (24, 25). Indeed, ARS antibodies have shown an invaluable role both in defining CTD overlapping phenotypes and in forecasting prognosis (26, 27). However, the fact that only anti-Jo1 antibodies are included as serological marker in the latest IM classification criteria leaves a diagnostic gap for those patients with non-anti-Jo1 ARS antibodies, which is currently being filled with the IPAF definition as also with preliminary sets of classification criteria for ARS syndrome (28). In order to bypass the gnosologic conundrum it is tempting to consider the presence of these highly specific antibodies as definitory of an underlying CTD in subjects with ILD, even in the absence of other manifestations. This would be of particular interest in those patients with ARS antibodies who present with a pulmonary-dominant disease and an UIP-like radiographic pattern, as has been described (29). This situation can be visualized in 1 patient from our IPAF cohort with anti-Jo1 who underwent a diagnostic surgical lung biopsy. Also to highlight is the presence of anti-Ha and anti-KS antibodies in 2 patients from our IPAF subgroup with pulmonary-dominant forms of ILD. Some years ago, these patients would have been difficult to characterize since commercial detection kits for these antibodies were not available (30). This suggests that patients with an autoimmune IP could remain uncaptured with current IPAF criteria. Along the same line, the group of Karolinska has uncovered the presence of serum immune-reactivity toward practically all aminoacyl tRNA synthetases in patients with IM. Although the relevance of these findings is yet to be clarified, it appears that closing the serological gap of the ARS syndrome could increase sensitivity for IPAF diagnosis (31).

In contrast with MSA and SSc-specific antibodies, the interpretation of positive RF, anti-Ro antibodies or low titers of anti-dsDNA and ACPA in patients with a pulmonary-dominant condition is challenging and performance of a surgical lung biopsy at the beginning of the

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TABLE 3 Predictors of nailfold videocapillaroscopy (NVC) major alterations.

	Telangiectasia	Digital ulcers	Raynaud'sphenomenon	Puffyfingers	Ro	NSIP	ARS
OVERALL PATTERN							
SScpattern		100% PPV; 56% NPV; *p* 0.049					
ABNORMAL NVC FINDINGS	PPV 100%; NPV 42%; *p* 0.023					OR 2.9 [1; 8.3] *p* 0.041	
Capillarydimension							
Enlargement of capillaries	PPV 100%; NPV 53%; *p* 0.006	100% PPV; NPV 50%; p 0.057	OR 3.73 [1.2; 11.3] *p* 0.02		OR 3.21 [1.13; 9.1] *p* 0.027		
Giantcapillaries	OR 10.6 [2.1; 53.3] *p* 0.004	OR 7.8 [1.1; 52.8] p 0.035	OR 4.16 [1.2; 14.7] *p* 0.027	OR 7.56 [1.4; 39.6] *p* 0.017	OR 4.5 [1.2; 16.6] p 0.024		
Hemorrhages	OR 6.37 [1.3; 30.7] *p* 0.021						
CapillaryShapes							
Angiogenesis					OR 2.84 [1.0; 7.9] p 0.046		
Ramifications						OR 5.9 [1.5; 23.5] p 0.012	OR 4.18 [1.2; 14.5] p 0.024

NSIP: non-specific interstitial pneumonia. ARS: anti synthetase syndrome. PPV: positive predictive value. NPV: negative predictive value. OR: odds ratio. Square brackets show 95% confidence intervals.

disease -particularly in patients showing UIP radiographic patterns– might be a good choice both to correctly characterize the disease but also to better understand pathophysiological processes involved.

In this study, we have postulated that the assessment of digital microvascular pathology with NVC would increase sensitivity for the detection of IPAF, since the presence of NVC abnormalities is considered highly indicative of an undelying CTD. Particularly, the presence of giant capillaries or the combination of significant capillary loss and abnormal shapes predicts the development of SSc in patients with Raynaud's phenomenon or with SSc-specific autoantibodies. Moreover, severity of the NVC lesions in patients with SSc might herald the development of SSc-IP, as it has been recently pointed out (32). Indeed, NVC is being increasingly used in the characterization of ILD patients and a clinical suspicion of an underlying CTD. A recently published metaanalysis concluded that the "late SSc" NVC pattern could associate to ILD not only in the context of CTD but also in patients diagnosed with IPAF or IIP (9). Nonetheless, formal studies approaching the relationship between qualitative NVC findings and the different ILD phenotypes are necessary (9, 32). Our study provides relevant information in this respect. We underscore that many patients without Raynaud's phenomenon showed NVC abnormalities, including some who displayed an SSc pattern. Our data are in agreement with previous descriptions in patients with ARS (33) in whom an association with capillary ramifications was observed. As expected, digital macroscopic alterations within the clinical domain of the IPAF definition were found to associate with NVC abnormalities. However, as illustrated in our study, these alterations may be subtle or even absent and still the patients can have NVC abnormalities. As regards to other disease-related features, an NSIP pattern or the presence of anti-Ro antibodies were also associated to NVC alterations, findings which further support the potential role of this exam in the classification of unclear ILD cases. In our cohort, addition of NVC abnormalities to IPAF clinical criteria would have allowed classification of 4 of our uAIP patients, who had an NSIP (or a mixed NSIP-OP) pattern and an additional one with an UIP pattern, no extra-pulmonary clinical findings and anti-Ro antibodies. Nonetheless, in contrast with IPAF cases, none of the uAIP patients displayed an SSc specific NVC pattern, but non-specific abnormalities, which are less defined and potentially subject to the examiner interpretation. This fact highlights the need of expert consensus in this field (34).

In summary, we provide a thorough description of the characteristics of patients with autoimmune IP from a real-world cohort, illustrating that the assessment of the individual IPAF defining items can help identify homogeneous subgroups of the disease beyond the diagnostic classification. This segregation is necessary in order to advance to a precision-based medicine in this complex field (35). In addition, while some clinical features appear to be under-represented in patients without an overt underlying CTD, performance of NVC should be encouraged since it might help improve current IPAF definition and further distinguish 2 types of disease according to the presence or absence of autoimmune vasculopathy.

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 The HU Fundación Jiménez Díaz-IIS Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

FR-B: contributed to the conception of the work, data acquisition and interpretation and manuscript writing. MR-N: contributed to the conception of the work, definition of variables, interpretation of data and revising the manuscript. CM: contributed to data acquisition and revising the manuscript. LE: contributed to data analysis and manuscript writing. MM-B: contributed to data acquisition and revised the manuscript. MS: contributed to data acquisition and revised the manuscript. OD: contributed to data acquisition and interpretation and revised the manuscript. OS-P: contributed to the conception of the work and the data acquisition, analysis and interpretation, and manuscript writing. All authors contributed to the article and 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.2023.1057643/full#supplementary-material

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Clinical implications of interstitial pneumonia with autoimmune features diagnostic criteria in idiopathic pulmonary fibrosis: A case control study

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Background: A subgroup of IPF patients can meet IPAF criteria (features suggesting an underlying autoimmune process without fulfilling established criteria for a CTD). This study was aimed to evaluate whether IPAF/IPF patients compared to IPF patients differ in clinical profile, prognosis and disease course.

Methods: This is a retrospective, single center, case–control study. We evaluated 360 consecutive IPF patients (Forlì Hospital, between 1/1/2002 and 28/12/2016) and compared characteristics and outcome of IPAF/IPF to IPF.

Results: Twenty-two (6%) patients met IPAF criteria. IPAF/IPF patients compared to IPF were **more frequently females** (N =9/22, 40.9% vs. N =68/338, 20.1%, p =0.02), suffered more frequently from gastroesophageal reflux (54.5% vs. 28.4%, p =0.01), and showed a higher prevalence of **arthralgias** (86.4% vs. 4.8%, p <0.0001), **myalgias** (14.3% vs. 0.3%, p =0.001) and **fever** (18.2% vs. 1.9%, p =0.002). The serologic domain was detected in all cases (the most frequent were ANA in 17 and RF in nine cases) and morphologic domain (histology features) was positive in 6 out of 10 lung biopsies (lymphoid aggregates). Only patients with IPAF/IPF evolved to CTD at follow-up (10/22, 45.5%; six rheumatoid arthritis, one Sjögren's and three scleroderma). The presence of IPAF was a positive prognostic determinant (HR 0.22, 95% CI 0.08–0.61, p =0.003), whereas the isolated presence of circulating autoantibody did not impact prognosis (HR 1.00, 95% CI 0.67–1.49, p =0.99).

Conclusion: The presence of IPAF criteria in IPF has a major clinical impact correlating with the risk of evolution to full blown-CTD during follow-up and identifying a subgroup of patients with a better prognosis.

KEYWORDS

idiopathic pulmonary fibrosis, interstitial lung diseases, interstitial pneumonia with autoimmune features, disease behavior, mortality, circulating autoantibodies

Introduction

In 2015, ATS/ERS international task force defined the criteria describing a new research entity named IPAF (interstitial pneumonia with autoimmune features) (1). This entity identifies patients with an idiopathic interstitial pneumonia (IIP) that have clinical, serologic, or morphologic features suggesting an underlying autoimmune process but do not meet established criteria for a connective tissue disease (CTD) (2). IPAF patients are more frequently female presenting with non-specific interstitial pneumonia (NSIP) pattern in the majority of cases (3, 4). Despite the apparently divergent profile of IPAF compared to idiopathic pulmonary fibrosis (IPF), this association has been described in some retrospective cohorts (3, 5–8).

IPF can be reclassified as IPAF when, in addition to the usual interstitial pneumonia (UIP) pattern, have a combination of one feature from at least two of three different domains; clinical, serologic or morphologic [either pathological (i.e., coexisting histopathology pattern of UIP with interstitial lymphoid aggregates with germinal centers, diffuse lymphoplasmacytic infiltration, and less frequently NSIP/OP overlap) or related to a multi-compartment involvement (i.e., unexplained pleural effusion or thickening, unexplained pericardial effusion or thickening, unexplained intrinsic airway disease, unexplained pulmonary vasculopathy)] (1, 5).

The paucity of studies investigating the impact of IPAF features on IPF natural history provides a strong rationale for the present study that was conducted in a large and well-defined IPF cohort using rigorous inclusion criteria for IPAF and was aimed to evaluate whether IPAF/IPF patients compared to IPF patients have a different prognosis and disease course.

Materials and methods

Study design and patient selection

In this single-center, retrospective, investigator initiated comparative study, we evaluated consecutive patients presenting to the pulmonary unit of the GB Morgagni Hospital (Forlì, Italy) with suspected interstitial lung disease who received a multidisciplinary diagnosis of IPF (between January 1, 2002, and December 28, 2016). Patients with incomplete clinical data, less than 3 months of follow-up and those without a complete autoimmune clinical and serological evaluation performed at our center were excluded. Baseline and follow-up data were collected as detailed in the Supplementary material, p. 2. Given the wide time spam of diagnosis, all IPF diagnosis were reviewed based on ERS/ATS 2018 criteria. Criteria for IPAF inclusion followed the ERS/ATS 2015 statement, details are reported in the Supplementary material, p. 3 (2).

This study was approved by the Comitato Etico di area vasta ROMagna, Italy (CEROM approval: protocol number 30/2020 I.5/284).

Outcomes

The primary endpoint was the prognostic significance of the presence of IPAF among IPF patients. This was measured by comparing transplant-free survival for IPF with IPAF to that of IPF without IPAF.

Secondary endpoints included:

(1) The prognostic significance of the presence of positive autoimmune serology alone (i.e., without IPAF) in IPF patients, compared to IPAF/IPF and to IPF only (i.e., no positive serology and no IPAF). This was measured comparing transplant-free survival for IPF with positive autoimmune serology to that of IPF with IPAF and to that of IPF only.

(2) Evaluation of natural history: development of full-blown CTD at follow-up. We described the baseline characteristics and compared the prevalence of CTD at follow-up between three patients subgroups: IPF with IPAF, IPF with positive autoimmune serology alone (i.e., without IPAF) and IPF only (i.e., no positive serology and no IPAF).

Statistical methods

For baseline data, the summary descriptive statistics were be generated with categorical data displayed as absolute numbers and relative frequencies. Continuous data were shown as mean (SD) for normally distributed data or as median (interquartile range) for skewed distribution. Comparisons between groups was performed using a *t*-test or Chi^2 test, as appropriate. We used exact probability values (*p* values) and an alpha level of 0.05.

For regression analysis, sample size calculation met the rule of thumb of at least 10 observation per variable, with 170 observed events we could evaluate 17 variables without overfitting. The small size of missing data allowed an analysis restricted to individuals with complete information on all variables of the main analysis (complete case analysis). The fundamental method of univariable/multivariable analysis was Cox regression. Causal model based on previous literature was used to identify confounders: age, gender, smoking status, comorbidities and disease severity. The models were formulated by systematically removing predictors that were not significant using a backward selection procedure removing variables with *p*-values ≥ 0.2 and excluding covariates with significant collinearity ($r > 0.8$) at univariate analysis. The proportional hazard assumption for each predictor was tested using approximate score statistic of linear correlation between the rank order of failure times in the sample and Schoenfeld partial residuals. We calculated hazard ratios (HRs) for overall mortality analyses. Patients were censored at death, lung transplant, or date of last known follow-up. Data cut-off was December 28, 2016. Results are reported as HRs, 95% CIs and *p* values, and are shown graphically as Kaplan–Meier survival curves. All statistical analyses were performed using STATA 15.

Results

Population

We extracted from the Forlì database 703 consecutive IPF patients, between January 1, 2002 and December 28, 2016. Among those 360 met protocol requirements and were included in the study. A vast minority ($N = 274$) was excluded due to the lack of rheumatologic and/or serologic

Abbreviations: ATS, American Thoracic Society; ERS, European Thoracic Society; IPAF, Interstitial pneumonia with autoimmune features; IIP, Idiopathic interstitial pneumonia; CTD, Connective tissue disease; NSIP, Non-specific interstitial pneumonia; IPF, Idiopathic pulmonary fibrosis; UIP, Usual interstitial pneumonia; NSIP/OP, Non-specific interstitial pneumonia/organizing pneumonia; ANA, Anti-nuclear antibodies; ANCA, Anti-neutrophil cytoplasmic antibody; ENA, Extractable Nuclear Antigen; CCP, Cyclic citrullinated peptide; RF, Rheumatoid factor.

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TABLE 1 Patient characteristics and comparison between IPAF/IPF and non-IPAF/IPF.

	Total cohort	IPAF/IPF	non-IPAF/IPF	Non-IPAF/IPF		*p*-val*
				Positive serology	Negative serology	
Sample size, *N*	360	22	338	43	295	
Female sex, *N* (%)	77 (21.4)	9 (40.9)	68 (20.1)	12 (27.9)	56 (19.0)	**0.020**
Age, median (IQR)	66.4 (8.53)	66.5 (8.55)	64.4 (8.08)	64.9 (7.3)	66.7 (8.7)	0.200
Current or former smokers, *N* (%)	255 (71.1%)	14 (63.6)	241 (71.5)	32 (76.2)	209 (70.8)	0.430
Family history of ILDs, *N* (%)	58 (16.1)	1 (4.5)	57 (16.9%)	7 (16.3)	50 (16.9)	0.130
Patients with comorbidities, *N* (%)	279 (77.5)	19 (86.4)	260 (76.9%)	30 (69.8)	230 (78.0)	0.300
N of comorbidities, median (range)	1.15 (0.90)	1.40 (1.14)	1.14 (0.89)	0.97 (0.83)	1.16 (0.89)	0.100
Lung cancer, *N* (%)	33 (9.2)	1 (4.5)	32 (9.5)	6 (14.0)	26 (8.8)	0.400
Pulmonary hypertension, *N* (%)	117 (39.9)	6 (31.6)	111 (40.5%)	15 (41.7)	96 (40.3)	0.400
GERD, *N* (%)	107 (30.1)	12 (54.5)	95 (28.4%)	17 (39.5)	78 (26.8)	**0.010**
% of pred. FVC, mean (SD)	79.64 (18.98)	86.72 (14.25)	79.18 (19.18)	78.53 (22.13)	79.27 (18.75)	0.070
% of pred. DLco, mean (SD)	52.53 (17.23)	59.41 (16.96)	52.08 (17.18)	58.78 (15.57)	51.83 (17.40)	**0.050**
GAP stage						
GAP stage I, *N* (%)	249 (69.5)	18 (81.8)	231 (68.8%)	26 (60.5)	205 (70.0)	0.200
GAP stage II, *N* (%)	100 (27.9)	4 (18.2)	96 (28.6%)	15 (34.9)	81 (27.6)	0.290
GAP stage III, *N* (%)	9 (2.5)	0	9 (2.7%)	2 (4.7)	7 (2.4)	0.440
Symptoms onset^						
Acute, *N* (%)	16 (5.2)	2 (10)	14 (4.9)	2 (5.0)	12 (4.9)	0.330
Subacute, *N* (%)	41 (13.5)	3 (15)	38 (13.4%)	7 (17.5)	31 (12.7)	0.840
Chronic, *N* (%)	247 (81.2)	15 (75)	232 (81.7%)	31 (77.5)	201 (82.4)	0.460
Symptoms						
Cough, *N* (%)	204 (60.9)	13 (59.1)	191 (61.0%)	26 (60.5)	165 (61.1)	0.860
Dyspnea, *N* (%)	308 (91.9)	19 (86.4)	289 (92.3%)	42 (97.7)	247 (91.5)	0.320
Arthralgias, *N* (%)	34 (10.1)	19 (86.4)	15 (4.8%)	10 (23.3)	5 (1.9)	**<0.0001**
Myalgias, *N* (%)	4 (1.2)	3 (14.3)	1 (0.3)	1 (2.3)	0 (0.0)	**0.001**
Recurrent fever, *N* (%)	10 (2.9)	4 (18.2)	6 (1.9)	1 (2.3)	5 (1.9)	**0.002**
Weight Loss, *N* (%)	2 (0.6)	0 (0.0)	2 (0.6)	0	2 (0.7)	0.710
Signs						
Velcro, *N* (%)	299 (90.6)	20 (95.2)	279 (90.3)	40 (93.0)	239 (89.8)	0.450
Digital clubbing, *N* (%)	32 (9.7)	3 (14.3)	29 (9.4)	10 (23.3)	19 (7.1)	0.460
Progression to full-blown CTD	10 (2.7)	10 (45.5)	0	0	0	**<0.0001**

Values are expressed as mean (SD), median (IQRs), numbers (column %). Statistically significant *p*-values are reported in bold. **p*-Value comparing IPAF/IPF to non-IPAF/IPF.
^Acute onset: < 1 month, Subacute onset < 6 months, chronic onset > 6 months.

evaluation performed at our center. The flow chart of cases inclusion is presented in the Supplementary Figure S1 (p. 4). Clinical characteristics of included and excluded cases were similar, but the prognosis was worse in the included group of patients compared to excluded (HR adjusted for age, gender, smoke, %FVC, %DLco and lung cancer was 1.39, 95%CI 1.11–1.73, $p = 0.003$), as detailed in the Supplementary material, p. 5–7. Twenty-two (6%) patients met IPAF criteria (IPF/IPAF cases). Among the remaining 338 IPF cases that did not meet IPAF criteria, 43 (12% of the total) showed isolated autoimmune serology positivity lacking other positive domains. Characteristics of patients are reported in Table 1.

IPAF cases compared to non-IPAF cases

Comparison between IPAF/IPF patients and non-IPAF/IPF patients is shown in Table 1. IPAF/IPF patients compared to non-IPAF/IPF were **more frequently females** (N = 9/22, 40.9% compared to N = 68/338, 20.1%), p = 0.02. No significant differences were noted in age, smoking history, family history and comorbidities profile with the notable exception of **GERD** that was significantly more prevalent in IPAF/IPF compared to non-IPAF/IPF (54.5% compared to 28.4%, p = 0.01). The pulmonary function profile showed **a slight but significantly higher DLco** in the IPAF/IPF patients (59.41 vs. 52.8, p = 0.05) and a marginally higher FVC not statistically significant (86.72 vs. 79.18, p = 0.07) without significant differences in the GAP stage distribution. Similarly to non-IPAF/IPF patients, IPAF/IPF patients presented in the vast majority with a chronic onset (75%) of dyspnea (86.4%) and/or cough (59.1%). However, in contrast to what observed in non-IPAF/IPF patients, all IPAF/IPF patients presented with at least one systemic symptom, with a strikingly higher prevalence of **arthralgias** (86.4% vs. 4.8%, p < 0.0001), **myalgias** (14.3% vs. 0.3%, p = 0.001) and **fever** (18.2% vs. 1.9%, p = 0.002) compared to non-IPAF/IPF. Further rheumatologic evaluation of arthralgias revealed inflammatory arthritis only in IPAF/IPF cases, as shown in Table 2.

Non-IPAF/IPF: Comparison between cases with and without circulating autoantibodies

Among the 338 IPF patients that did not meet IPAF criteria, 43 (12.7%) showed a positive autoimmune serology.

All cases showed isolated positivity for a single class of autoantibodies. Four patients (4/43, 9%) showed ANCA positivity and one of them developed a full-blown vasculitis after 10 years of follow-up (familial form of IPF with first degree relatives affected by both IPF and CTD-related ILDs). Seventeen (39%) patients had an isolated anti-thyroid positive autoimmunity, all were clinically identified as autoimmune thyroiditis without evidence of systemic autoimmune disease. 11 (11/43, 25%) patients showed isolated ANA positivity, two ENA, two anti-CCP, and 7 RF positivity. None of them developed CTD at follow-up.

Comparison of clinical characteristics of non-IPAF/IPF cases with and without positive autoimmune serology are reported in Table 1. There were no statistically significant differences in the clinical and functional profile of the two subgroups (p values >0.05, not shown) with two notable exceptions: (1) **higher prevalence of arthralgias in the non-IPAF subgroup with positive** autoantibodies (N = 10, 23%) compared to non-IPAF with negative autoantibodies (N = 5, 1.9%), p < 0.0001. Those patients were not classified as IPAF because arthralgias was interpreted by the rheumatologist as non-specific. (2) **higher prevalence of digital clubbing** in the non-IPAF subgroup with positive autoantibodies (N = 10, 23%) compared to non-IPAF with negative autoantibodies (N = 19, 7.1%), p = 0.003.

Survival analysis

Primary outcome: The prognostic significance of the presence of IPAF among IPF patients

The presence of IPAF criteria in patients who received a multidisciplinary diagnosis of IPF was associated with significantly lower overall mortality compared to IPF patients lacking IPAF criteria. Despite the small number of cases (N = 22), the difference was robust both by univariate analysis HR 0.17 (95% CI 0.06–0.46, p < 0.0001) and after adjusting for age, sex, lung cancer, pulmonary function variables (%pred FVC and %pred DLco) and diagnosis before or after 2011, HR 0.22 (95% CI 0.08–0.61, p = 0.003). Univariate and multivariate analyses are reported in Table 3. Beside the presence of IPAF criteria the other variables significantly associated with a different prognosis were age, pulmonary function (i.e., % of predicted FVC and % of predicted DLco) and the presence of lung cancer. Median follow-up time was 4.53 years for IPAF/IPF (IQR 3.17–7.50) and 3.39 years for Non-IPAF/IPF (IQR 2.06–5.12). Overall mortality rate per 100 person-year and survival at 1, 3, and 5 years were all significantly different between the two groups, data are reported in Table 4. Figure 1 shows the Kaplan–Meier plot for transplant-free survival of IPAF/IPF and non-IPAF/IPF cases.

Secondary outcome: The prognostic significance of the sole presence of positive autoimmune serology

Comparison between IPF with positive serology and IPF only

When analysis was confined to IPF patients not meeting IPAF criteria (N = 338) the presence of positive autoimmune serology (N = 43) did not impact patients' prognosis, unadjusted HR 1.01 (95% CI 0.69–1.48), p = 0.96 and HR 1.00 (95% CI 0.67–1.49), p = 0.99 after adjusting for age, sex, lung cancer and pulmonary function variables (%pred FVC and %pred DLco). Overall mortality rate per 100 person-year and survival at 1, 3, and 5 years were all similar between the two groups, data are reported in Table 4. Figure 2 shows the Kaplan–Meier plot for transplant-free survival of IPAF/IPF and non-IPAF/IPF cases with and without positive autoimmune serology.

Secondary outcome: The evolution to full blown connective tissue disease

Only IPF cases with IPAF features developed full-blown CTD at follow-up. Among IPAF/IPF cases 10 patients (10/22, 45.5%) developed CTD: rheumatoid arthritis (6/22, 27%), scleroderma (3/22, 14%) and one Sjogren. Mean latency time from IPAF diagnosis to CTD diagnosis was 21.5 months (range 6–60 months).

The characteristics of the 22 IPAF cases are reported in Table 2. Fourteen patients were treated with low doses of prednisone and two of them with triple therapy (azathioprine, n-acetyl-cysteine and prednisone). All of them antedates the publication of the PANTHER trial. (9) All 10 IPAF/IPF patients diagnosed after the year 2012 (when antifibrotics became available at our center) were treated with antifibrotics and continued antifibrotic therapy after IPAF diagnosis. Among those, five patients developed CTD (four rheumatoid arthritis and one scleroderma): three of them continued antifibrotics only and two switched to immunosuppressive treatment only. Only one patient diagnosed with IPAF/IPF, that has never developed a clear CTD, is currently treated with the combination of immunosuppressant (prednisone and mofetil-mycophenolate) and nintedanib due to disease progression.

Discussion

To the best of our knowledge this is the first study evaluating IPAF features and clinical meaning in a well-defined cohort of IPF patients, showing that IPF patients can present IPAF features in a minority of

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TABLE 2 IPAF/IPF cases characteristics.

ID	Age	Sex	Latency time from IPF to IPAF	IPAF diagnostic domains				Latency time from IPAF to CTD	CTD at FUP	Treatment
				Serologic domain	Clinical domain	Lung biopsy	Morphologic Domain			
1	43	M	Concurrent	ANA >1:160 nucleolar		TBLC and SLB	Interstitial lymphoid aggregates with germinal centers (UIP)			CYC; Esbriet
2	74	F	2 years	RF; ANTI-CCP; ANA>1/320	Raynaud's phenomenon			22 months	Rheumatoid Arthritis	Nintedanib; Leflunomide
3	67	F	9 years	ANA >1:640 nucleolar; (Anti-TG)	Inflammatory arthritis and polyarticular morning joint stiffness ≥60 min	TBLC	UIP			Prednisone
4	73	M	4 years	ENA (anti Ro 52)	Inflammatory arthritis; Distal digital tip ulceration (sicca syndrome)			2 years	Sjogren	Pirfenidone; Nintedanib
5	75	F	4 years	ANA>1:320; ANTI-CEMP-B	Inflammatory arthritis (and recurrent low grade fever)					Azathioprine, NAC, Prednisone
6	75	F	Concurrent	(ANA<1:80); RF; ANTI-CCP > 340	Inflammatory arthritis					Nintedanib
7	61	M	4 years	ANA>1:160 nucleolar	Inflammatory arthritis (sicca syndrome)	TBLC	Interstitial lymphoid aggregates with germinal centers (UIP)			Esbriet
8	57	F	Concurrent	ANA>1/320; ANTI-CEMP-B	Inflammatory arthritis	TBLC	Interstitial lymphoid aggregates with germinal centers (UIP)	1 year	Scleroderma	Prednisone, Ciclosporine, RTX
9	64	F	5 years	ANA >1:320 speckled	Inflammatory arthritis					Untreated
10	78	F	3 years	ANA >1:640	Inflammatory arthritis and polyarticular morning joint stiffness ⩾60 min					Esbriet
11	63	M	3 years	RF; ANTI-CCP; ANA>1/320	Inflammatory arthritis					Prednisone
12	70	M	Concurrent	ANA>1:320; RF; ANTI-CCP	Inflammatory arthritis			2 years	Rheumatoid Arthritis	Esbriet; Nintedanib

(Continued)

TABLE 2 (Continued)

ID	Age	Sex	Latency time from IPF to IPAF	IPAF diagnostic domains				Latency time from IPAF to CTD	CTD at FUP	Treatment
				Serologic domain	Clinical domain	Lung biopsy	Morphologic Domain			
13	69	M	1 year	ANA>1:320; RF	Inflammatory arthritis	SLB	Interstitial lymphoid aggregates with germinal centers (UIP and few giant cells)			Nintedanib
14	76	F	6 years	ANA 1/640 omogeneo	Inflammatory arthritis and polyarticular morning joint stiffness ≥60 min; myalgias	TBLC	UIP	2 years	Rheumatoid Arthritis	Azathioprine, NAC, Prednisone
15	53	M	2 years	RF; ANTI-CCP	Inflammatory arthritis	SLB	Interstitial lymphoid aggregates with germinal centers (UIP)	1 year	Rheumatoid Arthritis	Esbriet; Prednisone
16	68	M	2 years	ANA >1/320	Inflammatory arthritis; Raynaud phenomenon			7 months	Scleroderma	Pirfenidone
17	72	M	Concurrent	ANA >1/320	Inflammatory arthritis					Prednisone
18	72	M	1 year	ANA >1/320; antiCCP, RF	Inflammatory arthritis	SLB	UIP	6 months	Rheumatoid Arthritis	Prednisone; Leflunomide; CYC
19	76	F	3 years	ANA>1:320; RF; (Anti-TPO)		TBLC	Interstitial lymphoid aggregates with germinal centers (UIP)			Esbriet; Nintedanib, MMF, prednisone
20	59	M	Concurrent	ANA>1:320; ANCA-MPO	Raynaud's phenomenon			2 years	Scleroderma	Prednisone
21	39	F	Concurrent	ENA: Anti-Ro (SS-A)	Inflammatory arthritis	SLB	UIP			Prednisone
22	64	M	Concurrent	RF; ANTI-CCP; ANCA-MPO	Inflammatory arthritis and polyarticular morning joint stiffness ≥60 min			5 years	Rheumatoid Arthritis	Pirfenidone; Prednisone, Leflunomide

cases (6%) with a clinical profile and natural history strikingly divergent from that of IPF. IPAF/IPF compared to IPF is characterized by:

(1) a significantly better prognosis;
(2) a high risk of evolution to full blown CTD (45.5%), that among IPF patients seems exclusive of those presenting with IPAF features;
(3) a specific clinical profile with a higher prevalence of females and gastroesophageal reflux. Most notably, systemic signs and symptoms, rare in IPF, are universally present in IPAF/IPF (inflammatory arthropathy, myalgias and fever) and are associated with at least one positive autoimmune finding on serology (most commonly elevated levels of ANA and/or RF).

To define IPAF in this cohort of IPF patients we have meticulously applied the current IPAF ERS/ATS criteria to the clinical and serological features. The morphologic domain was defined by histopathology patterns (by surgical or transbronchial cryobiopsy) of UIP with interstitial lymphoid aggregates with germinal centers and/or diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles), and these features were

TABLE 3 Univariate and multivariate transplant-free survival analysis comparing IPAF/IPF to non-IPAF/IPF total number of cases IPAF/IPF *n* =22, non-IPAF/IPF *N* =338.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	1.03 (1.01–1.05)	**0.002**	1.03 (1.01–1.05)	**0.001**
Sex Female	0.90 (0.65–1.26)	0.55	1.00 (0.71–1.40)	0.98
Smoking history	1.20 (0.88–1.63)	0.25	–	–
Comorbidities (yes/no)	0.91 (0.67–1.24)	0.56	–	–
Number of comorbidities	1.07 (0.92–1.24)	0.40	–	–
Lung cancer (yes/no)	1.94 (1.32–2.85)	**0.001**	2.61 (1.72–3.97)	**<0.0001**
Gastroesophageal reflux	0.94 (0.70–1.26)	0.66	–	–
Pulmonary function				
% pred FVC	0.98 (0.97–0.98)	**<0.0001**	0.99 (0.98–1.00)	**0.002**
% pred DLco	0.97 (0.96–0.97)	**<0.0001**	0.97 (0.96–0.98)	**<0.0001**
Diagnostic period (before or after 2011)	0.56 (0.40–0.79)	**0.001**	0.58 (0.40–0.83)	**0.003**
Diagnosis of IPAF/IPF	0.17 (0.06–0.46)	**<0.0001**	0.22 (0.08–0.61)	**0.003**

Statistically significant *p*-values are reported in bold. IPF, idiopathic pulmonary fibrosis; IPAF, interstitial pneumonia with autoimmune features; FVC, forced vital capacity; DLco, carbon monoxide diffusing capacity.

TABLE 4 Survival analysis for the primary outcome of the study: IPAF/IPF compared to non-IPAF/IPF and for the secondary outcome of the study: non-IPAF/IPF with positive autoimmune serology compared to non-IPAF/IPF without positive autoimmune serology.

	Primary outcome		Secondary outcome: non-IPAF/IPF	
	IPAF/IPF	Non-IPAF/IPF	Positive serology	Negative serology
Sample size	22	338	43	295
Number of deaths	4	197	30	167
Number of lung transplants	0	16	2	14
Median time of follow up in years (IQRs)	4.53 (3.15–7.50)	3.39 (2.06–5.12)	3.88 (2.03–5.85)	3.29 (2.07–4.96)
Mortality rate per 100 py	3.13 (1.17–8.34)	16.26 (14.21–18.59)	17.42 (12.32–24.63)	16.06 (13.89–18.29)
Transplant free survival				
At 1 year	100%	92% (95% CI 0.89–0.94)	93% (95% CI 0.79–0.97)	93% (95% CI 0.88–0.95)
At 3 years	95% (95% CI 0.71–0.99)	65% (95% CI 0.60–0.70)	66% (95% CI 0.50–0.78)	65% (95% CI 0.59–0.70)
At 5 years	89% (95% CI 0.63–0.97)	47% (95% CI 0.41–0.53)	51% (95% CI 0.34–0.65)	46% (95% CI 0.40–0.52)

present in one third of IPF/IPAF cases (6/22). The multi-compartment involvement was defined using more stringent criteria: unexplained pleural or pericardial effusion or thickening, or by the presence of unexplained airway disease as seen by histopathology (follicular bronchiolitis or constrictive bronchiolitis). Interestingly none of our IPF/IPAF patients met the multi-compartment features following these restricted criteria. This punctilious approach led to a prevalence of IPAF among IPF cases lower than previously described, but with a strikingly prognostic divergence that previous studies could not detect (5).

We show that the presence of IPAF criteria is a strong positive prognostic determinant (overall mortality HR 0.22, 95% CI 0.08–0.61, $p = 0.003$). Age, lung cancer, pulmonary function (% of pred FVC and % of pred DLco), diagnostic time period (before/after 2011) and IPAF were all significant prognostic factors at both univariate and multivariate survival analysis. IPAF/IPF patients compared to IPF had a significantly lower overall mortality rate per 100 persons year (3.13 vs. 16.26) and a significantly better prognosis (survival at 3 and 5 years 95% vs. 65 and 89% vs. 47%, respectively). Previous studies have compared the prognosis of IPAF to that of historical IPF patients cohorts, showing that IPAF carries a better prognosis compared to IPF (4, 10). However, in those studies patients with IPAF/IPF were either not included (4) or mixed with a majority of non-IPF (NSIP/OP) cases (10). The present study does not include all types of IPAF, it rather focus on patients initially classified as having IPF. Notably no cases were having suspected CTD-ILD. We believe that this is a strength of this study, because here we highlight for the first time that IPAF reclassification can be clinically relevant when a diagnosis of IPF has been made, having prognostic implications that may potentially alter management.

The Oldham study (5) is the most solid study that compared IPAF/IPF (defined by Oldham as IPAF with UIP) to IPF reporting a prevalence of IPAF among IPF patients significantly divergent to what we report in this study (18% vs. 6%), but without survival differences. A possible reason for this discrepancy is the divergent profile of our IPAF/IPF population compared to that of Oldham et al. In our study all but two patients met clinical and serological domain criteria (90%, compared to 6.1% of the Oldham study). Including pulmonary hypertension and FVC/DLco ratios above 1.6 in the definition of multi-compartment criteria, Oldham et al. may have included a higher number of advanced IPF patients with PH in the IPAF group, those patients having selectively poor outcomes may explain the lack of outcome difference observed in that study. In line with this hypothesis is the observation that the presence of multicompartment features can increase the overall mortality risk (HR 2.1, 95% CI 1.19–3.38, $p = 0.009$) (5).

In the absence of IPAF criteria the sole presence of autoantibodies in IPF did not influence survival. It is difficult to compare our results with the existing literature on this topic because our study was not powered to detect the prognostic significance of specific antibodies. In the literature the effect of ANA and RF on all causes mortality does not seem

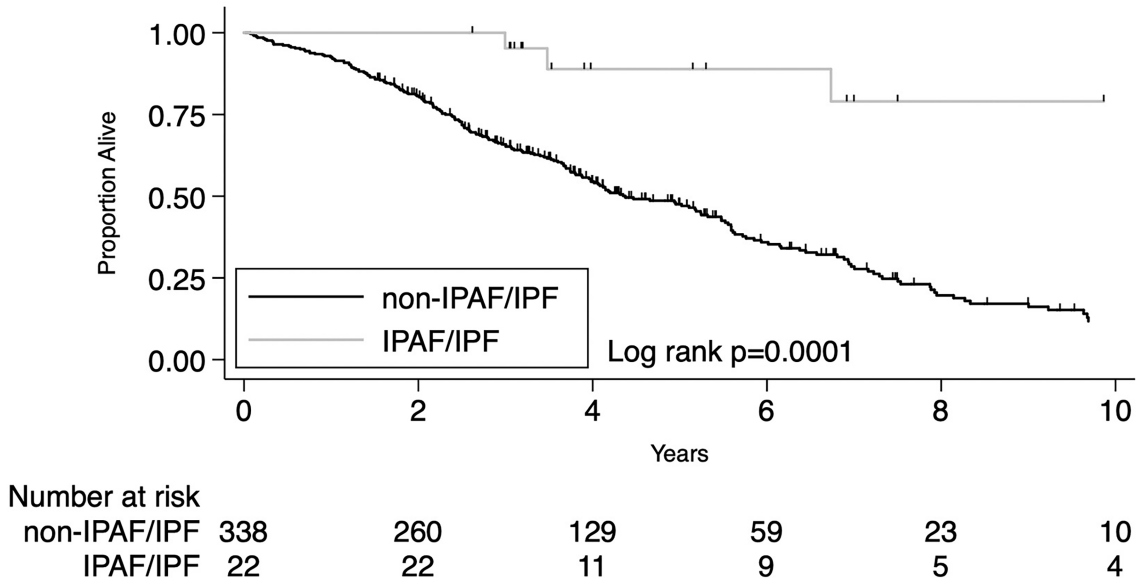

FIGURE 1
Primary outcome: KM plot for IPF diagnosis meeting IPAF criteria compared to IPF not meeting IPAF criteria.

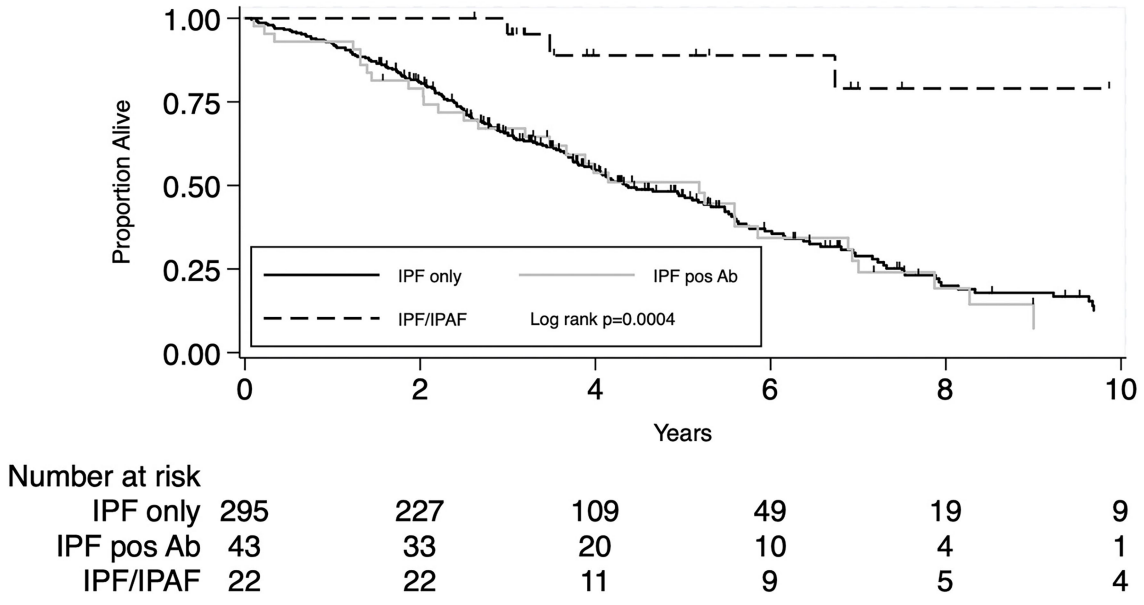

FIGURE 2
Secondary outcome: KM plot for IPF diagnosis meeting IPAF criteria compared to IPF not meeting IPAF criteria with and without positive autoimmune serology.

significant. (11) The subsequent development of CTD has been shown to occur in 2.5% of patients previously diagnosed with idiopathic interstitial pneumonia and is in line with the prevalence here observed (10/360, 2.7%) (5, 11, 12). The nice overlap between our data and older studies may suggest that we are evaluating similar cohorts of patients, but with the novel notion that adding IPAF criteria to the simple detection of circulating autoantibodies can significantly improve our ability to predict CTD development and to identify the patients with better prognosis. The finding that only patients with IPAF/IPF evolve to a definite CTD (10/22) underscores that this patient group is clinically divergent and autoimmunity appears the driver of mechanistic process of the disease.

This study has several limitations: the retrospective and monocentric study design, the high rate of cases exclusion (343cases due to unavailability for review of autoimmune tests that are often performed by patients at their local hospital), the very small sample size of IPAF cases ($N=22$) imbalanced compared to the controls groups [$N=43$ non-IPAF/IPF positive serology, $N=295$ non IPAF (IPF negative serology)]. Biases related to the observational retrospective design of this study spanning over a wide time period (2002–2016) are alleviated by the consecutive enrollment of patients, the reassessment of all IPF diagnosis based on ERS/ATS 2011 guidelines and the introduction in the multivariate survival analysis of the diagnostic time period (before/after the year 2011) as a dummy variable. However, concerns about the high dropout rate, a price we had to pay to achieve a highly accurately selected IPAF population with serology and rheumatology evaluation completed at our center, are only partially mitigated by the observation that the

excluded cases compared to included cases had homogeneous clinical profile, although a slightly divergent prognosis.

Conclusion

To the best of our knowledge, this is the first study showing that the presence of IPAF criteria in IPF has a major clinical impact correlating with the risk of evolution to full blown-CTD during follow-up (45.5% of IPAF/IPF patients develop CTD, none in the non-IPAF/IPF subgroup) and identifying a subgroup of patients with a clearly better prognosis (IPAF/IPF overall mortality adjusted HR 0.22).

Future prospective and larger studies will help to better define IPAF diagnostic criteria and their utility to identify in IPF specific subgroups with different prognosis and treatment response.

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

This study was approved by the Comitato Etico di area vasta ROMagna, Italy (CEROM approval: protocol number 30/2020 I.5/284). Written informed consent [from the patients/participants OR patients/participants legal guardian/next of kin] was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

ST, CR, SPu, SPi, AW, JR, MB, and VP: conception and design. ST, SPu, CR, MB, AW, JR, AD, SPi, FG, FL, ER, VL, MC, and VP: acquisition, analysis or interpretation, and drafting the manuscript for important intellectual content. VP had 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. 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; and 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.2023.1087485/full#supplementary-material

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Clinical efficacy of tetrandrine in artificial stone-associated silicosis: A retrospective cohort study

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Background: Outbreaks of silicosis have occurred among workers in the artificial stone (AS) industry, and there is currently no effective antifibrosis treatment for silicosis.

Design: A retrospective cohort study.

Methods: We retrospectively analyzed the clinical data of 89 artificial stone-associated silicosis patients treated in Shanghai Pulmonary Hospital (China). Patients who agreed to be administered tetrandrine entered the observation group and those who disagreed entered the control group. Changes in chest HRCT, pulmonary function, and clinical symptoms of patients in two groups were compared pre- and post-treatment.

Results: After treatment for 3–12months, 56.5%–65.4% of patients in the observation group showed improvements in HRCT imaging, while there was no improvement in the control group ($p<0.05$). Disease progression occurred in 0%–17.4% of patients in the observation group after 3–12months of treatment compared with 44.4%–92.0% of patients in the control group ($p<0.05$). After 3months of treatment, the forced vital capacity (FVC), forced expiratory volume in 1s (FEV_1), and diffusing capacity of the lung for carbon monoxide (DLco) in the observation group increased by 136.7±189.2mL ($p< 0.05$), 124.2±169.9mL ($p<0.05$), and 1.4±2.3mL/min/mmHg ($p>0.05$), respectively, while those in the control group decreased (145.8±356.5; 107.5±272.1; 1.9±3.8). After 6months of treatment, FVC, FEV_1, and DLco in the observation group increased by 207.8±372.2mL ($p>0.05$), 107.8±295.2mL ($p>0.05$) and 0.7±6.0mL/min/mmHg ($p>0.05$), respectively, while those of the control group decreased (383.3±536.7; 215.6±228.9; 1.4±1.7). The incidences of clinical symptoms such as cough, expectoration, dyspnea, chest tightness, and chest pain in the observation group were decreased-after treatment (all $p<0.05$), while the incidences of these symptoms increased in the control group, although the change was not statistically significant (all $p>0.05$).

Conclusion: Tetrandrine can control and delay the progression of AS-associated silicosis fibrosis, with improved chest HRCT imaging and pulmonary function.

KEYWORDS

anti-fibrotic agents, artificial stone-associated silicosis, accelerated silicosis, tetrandrine, HRCT

Introduction

Artificial stone (AS) has been widely used in the manufacture of kitchen and bathroom countertops since the 1980s (1). The popularity of this product has increased all over the world due to its compact structure, low water absorption, high temperature resistance, and corrosion resistance. The first case report of AS-associated silicosis was published in Spain in 2010 (2). Since then, outbreaks of silicosis among AS workers have been reported around the world (3–5). It has been noted that AS-associated silicosis progresses more rapidly and has a worse prognosis than non-AS-associated silicosis due to exposing dust containing crystalline silica over 90% (6–8). Importantly, there is currently no effective antifibrosis treatment for silicosis.

Tetrandrine (Tet) is a bisbenzylisoquinoline alkaloid isolated from the root of *Stephania tetrandra* (9). Although the treatment effect of this compound on silicosis has been studied since the 1980s, its effect on the progression of silicosis fibrosis, especially in accelerated silicosis, remains to be established. Most previous studies about the effect of Tet on silicosis have focused on pulmonary function and clinical symptoms (10–12), while the manifestations of the condition in computed tomography imaging, a method used routinely for evaluation of lung disease, are still unclear. Therefore, in this study, we retrospectively analyzed the clinical data of AS-associated silicosis patients who had been treated with or without Tet in Shanghai Pulmonary Hospital (China) in recent years and focused on the high-resolution computed tomography (HRCT) findings.

Materials and methods

Study participants

In this retrospective cohort study, we analyzed the clinical data of patients with AS-associated silicosis who were treated in Pneumoconiosis Department of Shanghai Pulmonary Hospital between December 2015 and December 2021. Patients who agreed to be prescribed Tet entered the observation group and those who disagreed entered the control group.

Eligibility

Patients were enrolled to this study according to the following inclusion criteria: (1) aged between 18 and 70 years; (2) exposed to AS dust while cutting, grinding, and drilling AS slabs before visiting hospital; (3) diagnosed as silicosis; (4) removed from continued dust exposure; and (5) had more than one chest HRCT examination performed. A total of 284 patients met the inclusion criteria. Patients with comorbidities such as tuberculous mycobacterial infection, lung tumor, respiratory infection, pneumothorax, pleural effusion, and asthma were excluded. Patients with other interstitial lung diseases or those with heart, brain, liver, kidney, and other organ dysfunction were also excluded. After exclusion, 89 patients were left, in which 47 patients were of observation group and 42 of control group (Figure 1).

Therapeutic method

The patients in the control group were given symptomatic treatments as needed such as inhaled or oral bronchodilators, mucolytics as Mytol Standardized. Besides symptomatic treatment, the patients in the observation group received Tet (Zhejiang Jinhua Conba Biopharma Co., Ltd.; SFDA approval no. H33022075) administered at 60 mg/dose, three times per day for 6 days and then stopped for 1 day; this course of treatment lasted 3 months. After stopping for 1 month, the next course of treatment was administered.

End-point measures

The primary end-point was the change in HRCT after treatment determined by re-reading and recording of images obtained pre-treatment, compared with those obtained at 3 months (after 2–4 months of treatment), 6 months (after 5–7 months of treatment), and 12 months (after 10–14 months of treatment) by a radiologist and a qualified physician from the pneumoconiosis department. The following indicators were recorded: ground-glass opacity (GGO), nodule opacity, progressive massive fibrosis (PMF), patchy opacity, emphysema, bullae, and dot-line opacity (13). Any of the following identified after treatment were classified as HRCT progression: (1) diffuse GGOs appear or increase; (2) PMF appear or extend; (3) diffuse nodules opacities increase; (4) emphysema and bullae appear or worsen. Any of the following identified after treatment were classified as HRCT improvement: (1) diffuse GGOs decrease or resolve; (2) smaller PMF without perifocal emphysema or worsening bullae; (3) diffuse nodules reduction; and (4) patchy opacities reduction. Stable HRCT was defined as no progression or improvement after treatment.

Secondary end-points were pulmonary function and clinical symptoms. Pulmonary function tests were performed as per the ATS/ERS recommendations (14, 15) and measured with a clinical spirometer (Jaeger Crop., Höchberg, Germany) by specialists from the department of pulmonary function in Shanghai Pulmonary Hospital. The pulmonary function indexes pre-treatment and at 3 months (after 2–4 months of treatment), 6 months (after 5–7 months of treatment), and 12 months (after 10–14 months of treatment) were obtained from the patients' medical records. The following pulmonary function indexes were recorded: forced vital capacity (FVC) and its percentage of the predicted value (FVC%); forced expiratory volume in 1 s (FEV_1) and its percentage of the predicted value (FEV_1%); and diffusing capacity of the lung for carbon monoxide (DLco) and its percentage of the predicted value (DLco%).

The occurrence of clinical symptoms (cough, expectoration, dyspnea, chest tightness, and chest pain) in the two groups pre-treatment and at 3 months (after 2–4 months of treatment), 6 months (after 5–7 months of treatment), and 12 months (after 10–14 months of treatment) was recorded from the medical records.

Adverse effects: Adverse effects related to Tet treatment in the observation group were recorded according to outpatient and inpatient medical records.

Statistical analysis

Quantitative data that were consistent with normal distribution were expressed as the mean ± standard deviation (SD), and the differences between groups were evaluated by Student's *t*-test. When the variance was uneven, the corrected *t*-test was used. Quantitative data that were not consistent with normal distribution were expressed as the median and interquartile range, and the differences between groups were

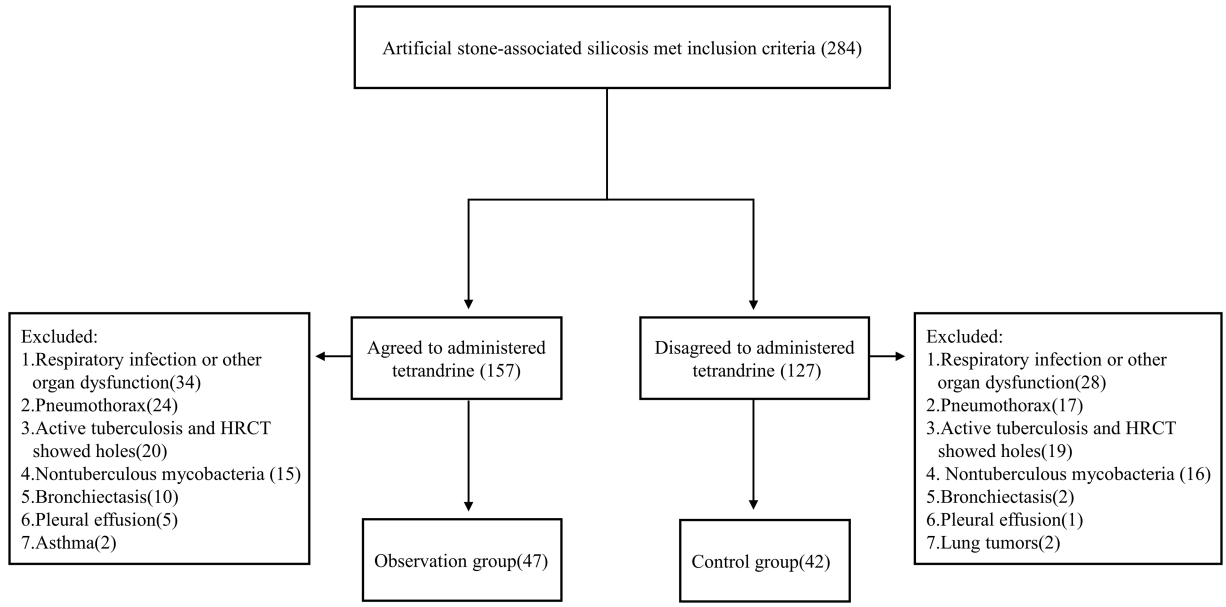

FIGURE 1
Study Flowchart of Patient Enrollment.

TABLE 1 Demographic characteristics of the observation and control groups.

Characteristics	Observation (n=47)	Control (n=42)	χ^2/t	Value of p
Male, n (%)	47 (100.0)	41 (97.6)	0.003	0.955
Age at treatment (years)	37.4 ± 12.1	37.7 ± 8.6	0.095	0.924
Age at onset of dust exposure (years)	29.4 ± 10.6	28.4 ± 7.4	0.540	0.591
BMI (kg/m^2)	24.1 ± 3.3	22.9 ± 3.5	1.524	0.132
Dust-exposure time (years)	6.4 ± 3.6	6.9 ± 3.6	0.582	0.562
Current/former smoker, n (%)[a]	27 (57.5)	22 (52.4)	0.230	0.632
PMF, n (%)	16 (34.0)	8 (19.1)	2.532	0.112

BMI, body mass index; PMF, progressive massive fibrosis.
[a]Patients who had quit smoking 1–10 years before the first registration were classified as former smokers, and those who had quit for more than 10 years were classified as never smokers.

evaluated by the Mann–Whitney U-test. Qualitative data were expressed as relative numbers, and the Chi-square test or Fisher's exact test was used for comparison between groups. The Kaplan–Meier method was used to estimate the rate of progression, and the log-rank test was used to compare the distribution of survival curves between two groups. All data analyses were conducted using SPSS version 25.0, Microsoft Excel 2021 for database construction, and GraphPad Prism 8.3.0 for drawing. $p < 0.05$ was set as the threshold for statistical significance. It should be noted that indications of pulmonary function were not consistent with normal distribution, non-parametric tests were adopted for the statistical significance of the differences. To facilitate intuitive interpretation of the data, normally distributed data were presented.

Results

Demographic characteristics

A total of 89 patients were enrolled in this study consisting of 47 cases in the observation group (average age 37.4 ± 12.1 years) and 42 cases in the control group (average age 37.7 ± 8.6 years). There were no significant differences in age, sex, body mass index (BMI), dust-exposure time, smoking status, or PMF rates between the two groups (all $p > 0.05$; Table 1). The shortest dust-exposure time among all subjects was 2 years and the longest was 20 years.

Case examples

In Case 1, a 26-year-old male in observation group with 5 years of exposure, the manifestation observed in the HRCT images did not show deterioration over 31 months and pulmonary function improved. In Case 2, a 29-year-old male in the control group with 6 years of exposure, aggravated on HRCT and pulmonary function over 32 months. In Case 3, a 44-year-old male in observation group with 8 years of exposure, HRCT progressed and pulmonary function decreased in 27 months after first registration and improved after 20 months' treatment with Tet (Figure 2).

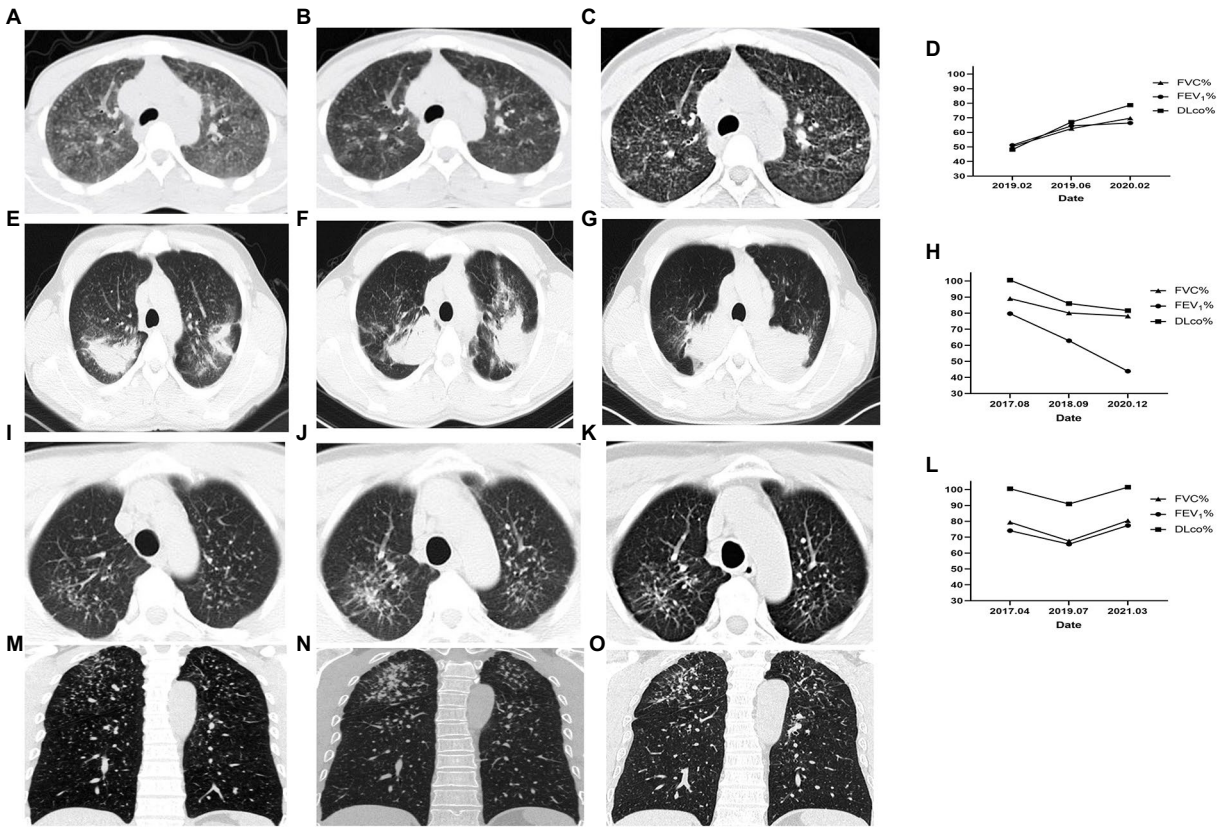

FIGURE 2
Changes of HRCT and pulmonary function of representative cases. Case 1 of the observation group. **(A)** HRCT showed diffuse GGOs, extensive nodular opacities, and para-aortic lymph node enlargement at baseline. **(B)** GGOs was significantly reduced after 4months. **(C)** GGOs dissipated without coalescence or PMF emerging after 31months of treatment. **(D)** The pulmonary function indexes FVC%, FEV_1%, and DLco% showed an increasing trend. Case 2 of the control group. **(E)** HRCT showed PMF on bilateral lungs at baseline. **(F)** The left lung PMF enlarged and the right lung PMF contracted centripetally with emphysema developing 13months later. **(G)** The lesion on HRCT continued to progress and the emphysema worsened. **(H)** Correspondingly, the pulmonary function gradually decreased. Case 3 began Tet treatment after the second HRCT. **(I,M)** Cross-sectional and coronal HRCT images showed diffusely distributed nodules at baseline. **(J,N)** Nodule opacities increased and coalescence emerged in the right upper lung 27months later. **(K,O)** GGO around the coalescence in the right upper lung dissipated and the coalescence had not progressed after 20months of Tet treatment. **(L)** The pulmonary function decreased over 27months without Tet treatment and increased over 20months with Tet treatment. This case was included in the observation group.

Changes in HRCT

The chest HRCT characters of AS-associated silicosis were GGO, nodule opacities, patchy opacity, PMF, emphysema, bullae, and dot-line opacity. There were no significant differences between the observation and control groups in the incidence of changes in GGO, nodule opacities, patchy opacity, PMF, emphysema, bullae, and dot-line opacity at baseline (all $p > 0.05$).

After 3, 6, and 12 months of treatment, the rates of improvement in the HRCT features in the observation group were 65.38, 56.52, and 63.16%, respectively, while no improvements were observed in the control group, with a statistically significant difference between the two groups ($p < 0.001$, Table 2). Improvements in HRCT imaging are mainly manifested by the reduction or dissipation of ground-glass opacities, the reduction of nodal opacities, and the shrinkage of PMF. The rates of progression rates in the control group at 3, 6, 12 months were 52.94, 44.44, and 92.00%, while the rates in the observation were 0, 17.39 and 5.26%, respectively, with a statistically significant difference between the two groups ($p < 0.001$, Table 2).

Pulmonary function

Most of the subjects exhibited restrictive ventilatory dysfunction and impaired diffusion function at baseline. In the 3-month cohort, the FVC%, FEV_1%, and DLco% values of the control group were all significantly higher than those of the observation group at enrollment ($p < 0.05$; Table 3). After 3 months of treatment, both FEV_1% and DLco% values of the observation group increased, while those of the control group decreased, with statistically significant differences between the pre- and post-treatment values of these indexes between the two groups ($p < 0.05$; Table 3). In the 6-month cohort, the FVC% and FEV_1% values of the observation group increased, while those of the control group decreased, with statistically significant differences between the pre- and post-treatment values of these indexes between the two groups ($p < 0.05$; Table 3).

In the 3-and 6-month cohorts, the average increases of FVC in the observation group were 136.7 ± 189.2 mL ($p = 0.029$) and 207.8 ± 372.3 mL ($p = 0.133$), respectively, while the average increases in of FEV_1 were 124.2 ± 169.9 mL ($p = 0.028$), 107.8 ± 295.2 mL ($p = 0.305$), respectively, and the averages increases of DLco were 1.4 ± 2.3 mL/min/

TABLE 2 Changes in HRCT features of the observation and control groups after treatment [*n* (%)].

Group	Changes	Observation	Control	Fisher	Value of *p*
3 M		***n* = 26**	***n* = 17**	28.419	<0.001
	Improved	17 (65.4)	0		
	Stable	9 (34.6)	8 (47.1)		
	Progressive	0	9 (52.9)		
6 M		***n* = 23**	***n* = 9**	9.476	0.007
	Improved	13 (56.5)	0		
	Stable	6 (26.1)	5 (55.6)		
	Progressive	4 (17.4)	4 (44.4)		
12 M		***n* = 19**	***n* = 25**	38.102	<0.001
	Improved	12 (63.2)	0		
	Stable	6 (31.6)	2 (8.0)		
	Progressive	1 (5.3)	23 (92.0)		

TABLE 3 Changes of pulmonary function indexes of the observation and control groups after treatment.

Groups	Indicators	Time	Observation	Control	*t*	Value of *p*
3 M			***n* = 12**	***n* = 12**		
	FVC%	Before	62.7 ± 16.6	78.0 ± 10.1	2.729	0.012
		After	67.0 ± 18.3	76.1 ± 15.3	1.335	0.196
		Difference	4.3 ± 4.7	−1.9 ± 9.1	2.072	0.054
	FEV_1%	Before	57.1 ± 17.2	76.2 ± 11.5	3.203	0.004
		After	61.6 ± 19.8	74.7 ± 16.3	1.767	0.091
		Difference	4.5 ± 5.4	−1.6 ± 7.8	2.214	0.037
	DLco%	Before	66.6 ± 19.8	83.6 ± 15.6	2.266	0.034
		After	74.4 ± 16.4	74.6 ± 19.3	0.022	0.983
		Difference	6.2 ± 10.5	−7.0 ± 15.7	2.33	0.030
6 M			***n* = 9**	***n* = 9**		
	FVC%	Before	64.3 ± 19.3	75.8 ± 18.2	1.306	0.210
		After	69.4 ± 23.7	68.0 ± 22.0	0.132	0.897
		Difference	5.2 ± 8.6	−7.8 ± 10.9	2.715	0.015
	FEV_1%	Before	59.8 ± 19.3	68.3 ± 25.0	0.807	0.432
		After	62.9 ± 24.84	62.9 ± 28.7	0.003	0.998
		Difference	3.1 ± 8.2	−5.3 ± 5.8	2.538	0.022
	DLco%	Before	77.1 ± 16.8	74.0 ± 29.0	0.273	0.789
		After	79.0 ± 16.6	67.5 ± 28.1	1.05	0.309
		Difference	1.9 ± 26.5	−6.5 ± 5.6	0.928	0.367

mmHg ($p = 0.068$), 0.7 ± 6.0 mL/min/mmHg ($p = 0.838$), respectively (Figure 3). Pulmonary function improvement cases were accompanied by a decrease or disappearance of GGO on HRCT images.

In the 3-, 6-, and 12-month cohorts, the average decreases of FVC in the control group were 145.8 ± 356.5 mL, 383.3 ± 536.7 mL, and 250.0 ± 388.8 mL, respectively (all $p > 0.05$), while the average decreases in FEV_1 were 107.5 ± 272.1 mL ($p = 0.198$), 215.6 ± 228.9 mL ($p = 0.022$), and 266.4 ± 419.3 mL ($p = 0.061$), respectively, and the average decreases in DLco were 1.9 ± 3.8 mL/min/mmHg ($p = 0.132$), 1.4 ± 1.7 mL/min/mmHg ($p = 0.037$), and 2.4 ± 2.0 mL/min/mmHg ($p = 0.004$; Figure 3).

Cumulative progression rate

The cumulative progression curves of the two groups based on HRCT progression as the terminal event are shown in Figure 4. There was a statistically significant difference in the cumulative progression rate between the control group (median progression survival time 8.367 months, 95% CI 4.57–12.16) and the observation group (Log-Rank $p < 0.001$). The cumulative progression rate in the observation was significantly lower than that in the control group.

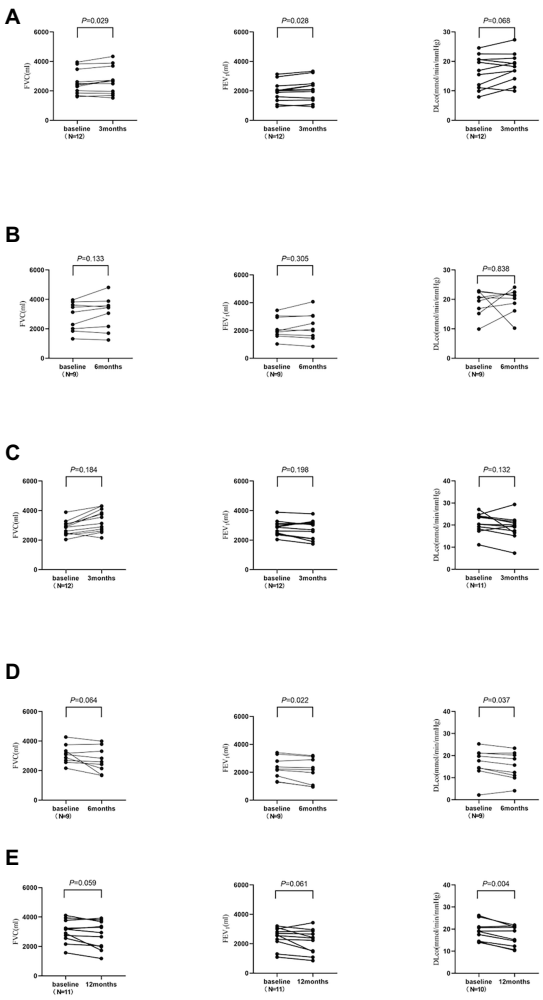

FIGURE 3
The changes of pulmonary function in the observation group and control group. DLco was not measured for one subject in each of the 3-month and 12-month cohorts. **(A)** The 3-month cohort of observation group. **(B)** The 6-month cohort of observation group. **(C)** The 3-month cohort of control group. **(D)** The 6-month cohort of control group. **(E)** The 12-month cohort of control group.

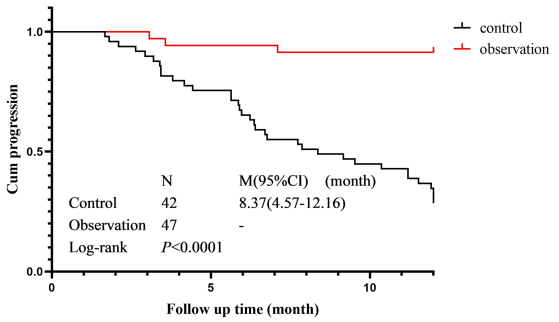

FIGURE 4
Cumulative progression rate in the observation group and control groups.

Clinical symptoms

There were no significant differences in the incidence of clinical symptoms including cough, expectoration, dyspnea, chest tightness, and chest pain between the two groups at baseline (all $p > 0.05$). The incidence of all clinical symptoms in the observation group reduced in the 3-, 6-, and 12-month cohorts, with significant differences compared with those in the control group (all $p < 0.05$; Table 4).

Adverse effects

The adverse effects related to Tet in the observation group included facial pigmentation (9/47, 19.2%), diarrhea (4/47, 8.5%), skin itching (2/47, 4.3%), nausea (1/47, 2.1%), fatigue (1/47, 2.1%), lethargy (1/47, 2.1%), and transient hepatic dysfunction (1/47, 2.1%).

Discussion

Silicosis is a systemic disease characterized by pulmonary fibrosis, mainly caused by long-term inhalation of dust containing free silica. AS-associated silicosis is characterized by a shorter dust-exposure time, faster disease progression, higher lung transplantation rate, and mortality than natural stone silicosis (16). HRCT showed AS-associated silicosis with a 1-year progression rate of 72.2% (16). For a long time, there is no specific treatment for silicosis. Treatment of the comorbidities (such as tuberculosis) is the main treatment for silicosis, which is far from enough for the patients, especially for accelerated silicosis. It is necessary to take measures for controlling the progression of fibrosis so as to delay the decline of lung function and reduce premature deaths. Effective anti-fibrotic drugs are urgently required to treat accelerated silicosis with rapid progression and a higher mortality rate (16, 17). Drug screens for the treatment of silicosis were carried out in China since the 1970s, and tetrandrine was one of chemicals selected with potential effects.

Results from animal experiments indicated that Tet could promote the activity of superoxide dismutase (SOD) in lung tissue, inhibit the release of fibrotic factor from lung macrophages, and attenuate lung inflammation. Tet also inhibited the synthesis and release of glycosaminoglycans and lipids, inhibited the transcription of collagen genes, and degraded the collagen in the silicic nodules formed, thereby reducing and delaying silicosis fibrosis (18–20).

In our study, 56.5–65.4% of the patients in the observation group showed improvement in HRCT after 3–12 months of treatment. Cumulative progression rate analysis also showed that the progression rate of the observation group was significantly lower than that of the control group. The FVC, FEV1, and DLco values of the observation group improved with varying degrees after 3–6 months, while significant decreases in FEV_1 and DLco were observed in the control group. Improvements in lung function were always accompanied by improvements in HRCT imaging. These results are consistent with the early clinical research reported in the 1990s, which showed that treatment with combination of Tet with quinolyl piperazine hydroxyl phosphate (QOHP) or poly-2-vinyl pyridine-nitrogen oxide (PVNO) resulted in obvious inhibition of the process of fibrosis and improvement of clinical symptoms. Accelerated silicosis with the combination

TABLE 4 Change of clinical symptoms [*n* (%)].

Indicator	3M			6M			12M		
	Observation (*n*=42)	Control (*n*=35)	Value of *p*	Observation (*n*=25)	Control (*n*=19)	Value of *p*	Observation (*n*=22)	Control (*n*=27)	Value of *p*
Cough									
Before	37 (88.1)	31 (88.6)	0.948	22 (88.0)	17 (89.5)	0.879	19 (86.4)	24 (88.9)	0.789
After	15 (35.7)	33 (94.3)	<0.001	11 (44.0)	19 (100.0)	<0.001	9 (40.9)	27 (100.0)	<0.001
Expectoration									
Before	25 (59.5)	24 (68.6)	0.411	15 (60.0)	13 (68.4)	0.565	12 (54.6)	19 (70.4)	0.253
After	19 (45.2)	27 (77.1)	0.004	11 (44,0)	15 (79.0)	0.020	9 (40.9)	22 (81.5)	0.003
Dyspnea									
Before	26 (61.9)	25 (71.4)	0.379	16 (64.0)	13 (68.4)	0.759	14 (63.6)	19 (70.4)	0.617
After	16 (38.1)	27 (77.1)	0.001	10 (40.0)	15 (79.0)	0.010	7 (31.8)	23 (85.2)	<0.001
Chest tightness									
Before	36 (85.7)	32 (91.4)	0.437	21 (84.0)	17 (89.5)	0.600	18 (81.8)	23 (85.2)	0.751
After	19 (45.2)	35 (100.0)	<0.001	12 (48.0)	19 (100.0)	<0.001	10 (45.5)	27 (100.0)	<0.001
Chest pain									
Before	24 (57.1)	15 (42.9)	0.212	14 (56.0)	8 (42.1)	0.361	13 (59.1)	16 (59.3)	0.990
After	10 (23.8)	17 (48.6)	0.023	6 (24.0)	11 (57.9)	0.022	6 (27.3)	17 (63.0)	0.013

treatment showed X-ray improvement rates (22.4%) higher than other silicosis patients (5.7%) (21). In another study, treatment with Tet for 6 months resulted in improvements on chest X-rays in 24.8% of 117 silicosis patients (22). The higher rate of improvement in HRCT features in the observation group of the current study may be due to the higher density resolution of this imaging technique compared with chest X-rays.

Some limitations of this study should be noted. As a retrospective study, there may be selective bias exists in the study subjects; and cases with insufficient lung function test information were also a problem. Furthermore, in this study, we collected clinical data during only 12 months of treatment, the long-term efficacy of Tet treatment in accelerated and chronic silicosis patients remains to be established. Even so, the striking results achieved by the study cannot be ignored. As artificial stone-associated silicosis is a type of progressive fibrosing interstitial lung diseases (PF-ILD), this study indicated that the potential effect of Tet in treatment of other PF-ILD is worthy of further investigation.

Conclusion

Tet had a definite therapeutic effect on patients with accelerated silicosis with improvements in HRCT features and pulmonary function combined with delayed progression of fibrosis, few adverse effects were recorded.

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 Medical Ethics Committee of Shanghai Pulmonary Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

W-hW, Y-hF, C-yM, and LM applied conception, designed the research, and wrote the article. W-hW, LM, L-mH, JS, and HQ collected the clinical data. W-lY and LM interpreted the lung function data. S-wZ and Z-dC interpreted the radiologic data. W-hW, L-mM, Y-hF, G-hY, and JL analyzed and interpreted the clinical data. Y-hF and LM provided financial support fund and conducted the entire research. All authors contributed to the article and 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.

Publisher's note

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Prognostication of progressive pulmonary fibrosis in connective tissue disease-associated interstitial lung diseases: A cohort study

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Background: Connective tissue diseases-associated interstitial lung disease (CTD-ILD) is a heterogeneous condition that impairs quality of life and is associated with premature death. Progressive pulmonary fibrosis (PPF) has been identified as an important risk factor for poor prognosis. However, different criteria for PPF are used in clinical studies, which may complicate comparison between trials and translation of study findings into clinical practice.

Methods: This is a retrospective single center study in patients with CTD-ILD. The prognostic relevance of PPF definitions, including INBUILD, ATS/ERS/JRS/ALAT 2022, and simplified progressive fibrosing (simplified PF) criteria, were examined in this cohort and validated in the other reported Dutch CTD-ILD cohort.

Results: A total of 230 patients with CTD-ILD were included and the median follow-up period was six (3—9) years. Mortality risk was independently associated with age (adjusted HR 1.07, $p<0.001$), smoking history (adjusted HR 1.90, $p=0.045$), extent of fibrosis on high-resolution computed tomography (HRCT) at baseline (adjusted HR 1.05, $p=0.018$) and baseline DLCO (adjusted HR 0.97, $p=0.013$). Patients with regular pulmonary function tests in the first 2 years (adjusted HR 0.42, $p=0.002$) had a better survival. The prognostic relevance for survival was similar between the three PPF criteria in the two cohorts.

Conclusion: Higher age, smoking, increased extent of fibrosis and low baseline DLCO were associated with poor prognosis, while regular pulmonary function evaluation was associated with better survival. The INBUILD, ATS/ERS/JRS/ALAT 2022, and simplified PF criteria revealed similar prognostication.

KEYWORDS

interstitial lung diseases, connective tissue diseases, pulmonary fibrosis, outcome predictors, immune-mediated inflammatory diseases

Introduction

Connective tissue diseases (CTD) are characterized by dysregulation of the immune system resulting in inflammation and subsequent tissue damage followed by fibrosis. In CTDs with lung involvement, inflammation and/or fibrosis of pulmonary parenchyma leads to deterioration of lung function, cough and shortness of breath. Interstitial lung disease (ILD) occurs in approximately 15% of CTD patients, depending on the type of CTD, and is associated with high mortality and decreased quality of life (1).

The disease course of CTD-associated ILD (CTD-ILD) is heterogeneous. Therefore, clinical characteristics and risk factors for poor prognosis are crucial in managing patients with CTD-ILD. In previous studies, several biomarkers, fibrotic high-resolution computed tomography (HRCT) at baseline, senior age, smoking, steroid use and progressive pulmonary fibrosis have been identified as predictors of poor prognosis in CTD-ILD (2–4).

Particularly, rapid deterioration of respiratory symptoms, lung function and progressive fibrosis on HRCT are referred to as progressive fibrosing interstitial lung diseases or progressive pulmonary fibrosis (PPF) (3, 5–7). Identification of patients with PPF is crucial for clinical practice, as these patients have a poor prognosis and may benefit from antifibrotic drugs similar to patients with idiopathic pulmonary fibrosis (IPF) in randomized controlled trials (8, 9); however, the definition of PPF criteria differ between studies. Furthermore, the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax (ATS/ERS/JRS/ALAT) defined scientific societies-approved criteria in the 2022 guideline (7). The variety in criteria complicates study comparison and clinical implication. In this study, we aimed to explore the prognostic relevance of the different PPF criteria in patients with CTD-ILD.

Methods

Study population

This is a single center retrospective cohort study performed at the ILD Center of Excellence, St. Antonius Hospital, Nieuwegein, Netherlands. Patients diagnosed with CTD-ILD or interstitial pneumonia with autoimmune features between 2005 and 2021 were included when at least a baseline HRCT was available (10–12). Baseline was defined as the time of ILD diagnosis. All patients were discussed in multidisciplinary team meetings. Clinical characteristics, laboratory results and pulmonary function tests (baseline, 6 months, 1 year, and 2 years) were retrieved from the electronic medical records. This study was approved by the Medical Research Ethics Committees United (MEC-U, number R05-08A) and all patients provided written informed consent.

Pulmonary imaging

High-resolution computed tomography results were collected at baseline, 1 and 2 years. Baseline HRCT patterns were classified according to the classification for idiopathic interstitial pneumonia (13, 14), listing as consistent with usual interstitial pneumonia (UIP), probable UIP, alternative diagnosis or indeterminate for UIP. Probable and consistent with UIP were summarized as UIP. The alternative diagnosis was then classified as non-specific interstitial pneumonia [NSIP, including fibrotic, cellular, or mixed (15)], lymphocytic interstitial pneumonia (LIP), organizing pneumonia (OP), desquamative interstitial pneumonia, nodular lymphocytic hyperplasia, pleuroparenchymal fibro-elastosis and acute interstitial pneumonitis (AIP). The predominant HRCT features were categorized into fibrotic, including features as reticulation and honeycombing, or inflammatory, including ground-glass opacity and consolidation (3, 16–18). The changes in fibrosis and inflammation over time were classified as progression, stable, or regression. Extent of fibrosis on HRCT was evaluated at all time points. HRCTs were evaluated by two experienced thoracic radiologists who were blinded to clinical information and pathology diagnosis.

Criteria for progression

The INBUILD criteria included patients with ≥10% relative decline in percentage of predicted forced vital capacity (FVC), ≥5 and <10% relative decline in FVC with progressive fibrosis on HRCT or worsening of respiratory symptoms, or deterioration of both HRCT fibrosis and respiratory symptoms within 2 years despite standard (anti-inflammatory) treatment (8). The ATS/ERS/JRS/ALAT 2022 criteria were met with at least two of the following criteria; worsening of respiratory symptoms, fibrotic progression on HRCT and lung function deterioration [≥5% absolute decline in FVC and/or ≥10% absolute decline in percentage of predicted hemoglobin adjusted diffusing capacity of the lung for carbon monoxide (DLCO)] occurring within 1 year and without alternative explanation (7). The simplified progressive fibrosing (simplified PF) criteria were met with any of the following: ≥10% relative decline in FVC, ≥15% relative decline in DLCO, or progression of fibrosis on HRCT within 2 years [Supplementary Table S1; (3, 6)].

The prognostic relevance for mortality over time was evaluated for the INBUILD criteria, the ATS/ERS/JRS/ALAT 2022 criteria, and simplified PF criteria. The prognostic relevance of the three PPF criteria was then validated in a previously published Dutch CTD-ILD cohort at University Medical Center Utrecht (UMCU) (3).

Statistical analysis

Categorical variables were presented in frequencies, and the difference between groups was examined in Fisher's exact test. The distribution of the data was assessed in histograms. The continuous variables were presented in medians (interquartile range, IQR), and the difference between groups was determined using the Wilcoxon rank sum test. The hazard ratios (HR) for mortality risks were calculated using Cox regression, and variables with a value of $p < 0.1$ were included in a multivariable analysis with age, gender, smoking, comorbidities, and underlying CTD. The prognostic relevance for mortality and the PPF criteria was examined in the time-dependent receiver operator characteristic (ROC) model and visualized in area under curve (AUC) over time. Risk factors for PPF were examined in logistic regression. Missing data were omitted from each regression analysis. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using R 4.0.3.

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Results

Patient characteristics

A total of 230 patients were included in this cohort, of which 122 (53%) were female. The median age was 63 (IQR 54—69) years. The median follow-up period was 6 (3—9) years. The underlying CTD diagnosis included rheumatoid arthritis (RA) in 77 patients (33%), idiopathic inflammatory myopathies (IIM) in 38 (17%), primary Sjögren's syndrome (pSS) in 33 (14%), undifferentiated connective tissue disease (UCTD) in 32 (14%), systemic sclerosis (SSc) in 24 (10%), mixed connective tissue disease (MCTD) in eight (3%), systemic lupus erythematosus (SLE) in eight (3%), overlap syndrome in six (3%), spondyloarthropathy in three (1%), and antineutrophil cytoplasmic antibody-associated vasculitis in one (0.4%). Patients with RA, including RA overlap syndromes, were older [median 65 (IQR 62—73) years] than non-RA patients [median 60 (50—67) years, $p < 0.001$]. A total of 133 (58%) patients were past smokers, and 13 (6%) patients were current smokers. The median tobacco exposure was 18 (10—30) pack-years at baseline. In 104 (45%) patients, the diagnosis of CTD and ILD occurred within 6 months of one another. ILD was diagnosed in 100 (43%) patients with pre-existing CTD for more than 6 months, and the median CTD duration at ILD diagnosis was 6 (IQR 2—13) years. Twenty-six (11%) patients were diagnosed with CTD more than 6 months after ILD diagnosis. Antinuclear antibodies were positive in 106 (46%) patients. Other autoantibodies were detected, including rheumatoid factor in 71 (31%) patients, anti-SSA in 70 (30%), anti-citrullinated peptide antibodies in 61 (27%), and anti-Jo-1 in 25 (11%). The median body mass index was 27 (IQR 24—30). The median Charlson's comorbidity index was 3 (IQR 2—4), including 32 (14%) coronary artery disease, 23 (10%) diabetes mellitus, 14 (6%) chronic obstructive pulmonary disease, 12 (5%) cerebrovascular accident, 11 (5%) heart failure, eight (3%) pulmonary arterial hypertension, six (3%) peripheral vascular disease (PVD) and three (1%) chronic kidney disease. The most commonly used immunomodulators at baseline were corticosteroids in 165 (72%) patients, methotrexate in 64 (28%), azathioprine in 55 (24%), mycophenolate mofetil in 47 (20%), and hydroxychloroquine in 45 (20%). Four patients were on antifibrotics at baseline [nintedanib ($n = 2$) and pirfenidone ($n = 2$)] (Table 1).

TABLE 1 Patient characteristics.

Baseline characteristics	Patients
Age, median (IQR)	63 (54—69)
Gender (Female), *n* (%)	122 (53)
BMI, median (IQR)	27 (24—30)
Immunomodulators, *n* (%)	
Corticosteroids	165 (72)
Steroid dose (mg/day), median (IQR)	15 (5—30)
Azathioprine	55 (24)
Mycophenolate mofetil	47 (20)
Methotrexate	64 (28)
Leflunomide	12 (5)
Hydroxychloroquine	45 (20)
Cyclophosphamide	34 (15)
Sulfasalazine	12 (5)
Rituximab	22 (10)
Tumor necrosis factor inhibitors	29 (13)
Abatacept	3 (1)
Tocilizumab	3 (1)
Tofacitinib	1 (0.4)
Anti-fibrotics, *n* (%)	
Nintedanib	2 (1)
Pirfenidon	2 (1)
Charlson's comorbidity index, median (IQR)	3 (2—4)
Autoantibodies, *n* (%)	
Antinuclear antibody	106 (46)
Rheumatoid factor	71 (31)
Anti-citrullinated peptide antibodies	61 (27)
Anti-dsDNA	5 (2)
Anti-SSA	70 (30)
Anti-SSB	16 (7)
Anti-U1-RNP	12 (5)
Anti-SM	5 (2)
Anti-SCL-70	12 (5)
Anti-RNA polymerase III	1 (0.4)
Anti-centromere	8 (3)
Anti-PM-SCL	8 (3)
Anti-Jo-1	25 (11)
Anti-PL12	7 (3)
Anti-Th/To	3 (1)
Anti-Ku	3 (1)
Anti-Ej	2 (1)
Anti-Oj	1 (0.4)
Anti-SAE	2 (1)
Anti-MDA5	1 (0.4)
Anti-TIF1γ	1 (0.4)
Anti-Mi2α	1 (0.4)
Anti-Mi2β	2 (1)
Anti-MPO	1 (0.4)
Anti-PR3	1 (0.4)
Anti-Cardiolipin IgG	1 (0.4)
Anti-Cardiolipin IgM	1 (0.4)
Anti-β2-glycoprotein IgG	2 (1)
Negative for autoantibodies, *n* (%)	21 (9)

IQR, interquartile range; BMI, body mass index.

Radiology and pulmonary function progression

Various HRCT patterns were observed at baseline: UIP in 63 (27%, of whom 35 patients had RA) patients, fibrotic NSIP in 21 (9%), cellular NSIP in 25 (11%), mixed NSIP in 79 (34%), OP in 34 (15%), LIP in four (2%), AIP in one (0.4%), two (1%) combined OP and mixed NSIP, and one (0.4%) indeterminate. UIP patterns were observed in 35 (45%) RA patients, including RA overlap syndrome, and 28 (18%) in other CTD, $p < 0.001$. HRCT features were predominantly fibrotic in 117 (51%) patients and predominantly inflammatory in 113 (49%). The predominantly fibrotic HRCT consisted of 63 (100%) UIP, 31 (39%) mixed NSIP, 21 (100%) fibrotic NSIP, one LIP, and one indeterminate pattern. Patients with fibrotic HRCT patterns were older compared to patients with inflammatory patterns [respectively, 65 (IQR 60—74) and 59 (IQR 49—65) years old,

$p < 0.001$]. Low extent of fibrosis [<20% (19)] on baseline HRCT occurred in 214 (93%) patients; in the predominant fibrosis group, 102 (87%) patients had low extent of fibrosis on HRCT at baseline. In patients with predominantly inflammatory patterns, 38 out of 68 patients (56%) had less inflammation at 1 year and 26 out of 47 patients (55%) at 2 years. HRCTs were unavailable in 95 patients at 1 year (50 in the predominantly fibrotic and 45 in the predominantly inflammatory group), and 144 patients at 2 years of follow-up (78 in the predominantly fibrotic and 66 in the predominantly inflammatory group).

In the first 2 years, 112 (49%) patients had regular pulmonary function tests at 6 months, 1 year, and 2 years. The serial change in pulmonary function was shown in Figure 1. A relative decline ≥10% in FVC was seen in 22 (10%) patients at 6 months, 22 (10%) at 1 year, 32 (14%) at 2 years and 39 (17%) at the last follow-up. A relative decline ≥15% in DLCO was observed in 20 (9%) patients at 6 months, 28 (12%) at 1 year, 40 (17%) at 2 years and 40 (17%) at the last follow-up (Supplementary Figure S1).

Progressive pulmonary fibrosis in the first 2 years was observed in 61 (27%) patients meeting INBUILD criteria, 53 (23%) meeting ATS/ERS/JRS/ALAT criteria, 136 (59%) meeting simplified PF criteria and 125 (54%) when using simplified PF criteria with a threshold for HRCT ≥5% increase in the extent of fibrosis. The prevalence of PPF in each CTD was shown in Supplementary Table S2. Diagnosis of SSc, azathioprine use, PVD, regular follow-up pulmonary function, NSIP pattern and ANA positivity were revealed as predictors for more than two PPF criteria in univariable analysis; TNF inhibitor use was associated with reduced PPF risk. After multivariate adjustment, PVD and NSIP pattern remained significant as predictors for more than two PPF criteria (Supplementary Table S3). In RA patients, baseline HRCT with fibrotic NSIP pattern was associated with PPF meeting ATS/ERS/JRS/ALAT criteria (OR 6.04, $p = 0.012$) and INBUILD criteria (OR 7.60, $p = 0.004$). For other CTDs, no risk factors could be identified for more than two PPF criteria.

Survival analysis

During follow-up, 68 (30%) patients died. The cause of death was ILD related in 17 (25%) patients, malignancy in nine (13%), COVID-19 in five (7%), other pulmonary infection in four (6%), heart failure in two (3%) and combined ILD and heart failure in four (6%), thrombosis in one (1%) and unknown in 26 (38%). Survival was independently associated with age (adjusted HR 1.07, $p < 0.001$), smoking history (adjusted HR 1.90, $p = 0.045$), and extent of fibrosis on HRCT at baseline (adjusted HR 1.05, $p = 0.018$). Higher baseline DLCO (adjusted HR 0.97, $p = 0.013$) and regular pulmonary function tests in the first 2 years (adjusted HR 0.42, $p = 0.002$) were associated with better survival (Table 2). In subgroup analysis, the association between UIP patterns and mortality was insignificant in RA patients (HR 1.3, $p = 0.448$) but significant in patients with other CTDs (adjusted HR 2.27, $p = 0.030$).

None of the PPF criteria (in the first 2 years) achieved significant relation with mortality in Cox regression. The prognostic relevance did not differ between simplified PF criteria, INBUILD and ATS/ERS/JRS/ALAT criteria; the prognostic value improved in simplified PF criteria with defining HRCT progression with a ≥5% increase in fibrosis. The prognostic relevance of the PPF criteria with mortality

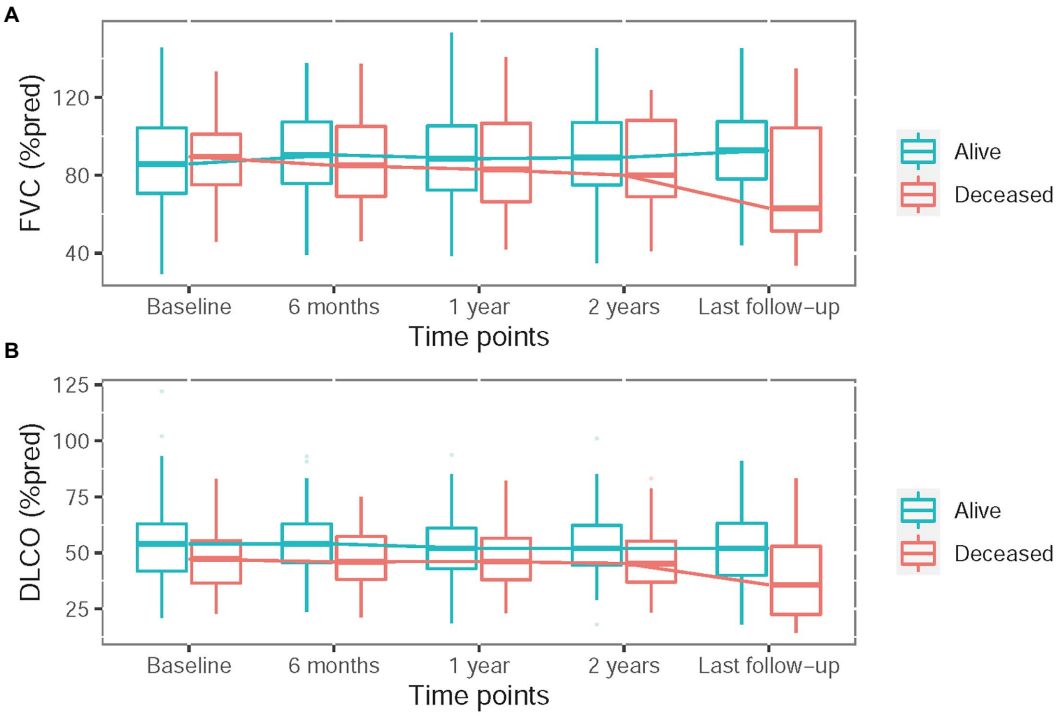

FIGURE 1
Serial change in pulmonary function test including percentage of predicted forced vital capacity (FVC) **(A)** and hemoglobin adjusted diffusing capacity of the lung for carbon monoxide (DLCO) **(B)**.

TABLE 2 Prognostic factors for survival.

Risk	HR	*p*-value	Adjusted HR	*P*-value
Male	2.19	0.002*	1.63	0.093
Age	1.08	<0.001*	1.07	<0.001*
Charlson's score	1.47	<0.001*		
PAH	3.16	0.028*	2.29	0.118
Smoking history	2.46	0.002*	1.90	0.045*
RA	2.32	<0.001*	1.18	0.555
CTD duration	1.04	0.005*	1.02	0.232
TNFi	1.89	0.040*	1.71	0.142
Hospitalized infection	1.82	0.017*	1.25	0.405
Extent of fibrosis	1.03	0.019*	1.05	0.018*
DLCO	0.98	0.030*	0.97	0.013*
Regular PFT	0.399	<0.001*	0.42	0.002*
UIP	2.71	<0.001*	1.61	0.077
mNSIP	0.52	0.021*	0.60	0.078
OP	0.44	0.038*	0.53	0.129
NSIP	0.581	0.027*	0.78	0.327
Fibrotic patterns	2.56	<0.001*	1.64	0.094

PAH, pulmonary arterial hypertension; RA, rheumatoid arthritis; CTD, connective tissue disease; TNFi, tumor necrosis factor inhibitors; DLCO, percentage of predicted hemoglobin adjusted diffusing capacity of the lung for carbon monoxide; PFT, pulmonary function test; UIP, usual interstitial pneumonia; mNSIP, mixed non-specific interstitial pneumonia; OP, organizing pneumonia. *$p < 0.05$.

risk over time in both cohorts is shown in Figure 2; The prognostic value of PPF criteria increased during the first 3 years and achieved a plateau thereafter in both cohorts.

Discussion

This study explored the characteristics of patients with early CTD-ILD and their prognostic correlation with PPF. Increased age, smoking, and increased extent of fibrosis were associated with higher mortality risk, while higher baseline DLCO and regular pulmonary function tests were associated with reduced mortality risk. The prognostic relevance with mortality did not differ between simplified PF criteria, INBUILD and ATS/ERS/JRS/ALAT 2022 criteria.

The risk factors associated with mortality in this cohort are in line with identified risk factors in previous studies. Age and smoking are overarching risk factors across diseases (20). Patients with early diagnosis and subsequently low extent of fibrosis on HRCT and better DLCO, have a larger window of opportunity to initiate treatment in order to decrease the risk of progression. In addition, a large proportion of patients in this study had low extent of fibrosis at baseline, in contrast to previous studies, including the INBUILD trial and the validation cohort, in which more patients had high extent of fibrosis (3, 8). The correlation between mortality and PPF was also more prominent in patients with extensive lung fibrosis than in those with limited lung fibrosis in another SSc-ILD cohort (6).

In several studies, UIP pattern was observed more often in RA patients and was associated with mortality and DLCO decline (21, 22). In our study, RA patients were older and had UIP patterns more frequently than patients with other CTDs. However, this was not significantly associated with mortality. We did find an association with UIP pattern and mortality in the non-RA group. Similarly, in a recent RA-ILD study, UIP pattern was not associated with mortality or FVC decline at 2 years (23). A possible explanation is that treatment strategies in RA have improved tremendously in the last decades, whereas disease control in other underlying CTD diseases has proven more challenging. Moreover, not only UIP pattern was associated with predominant fibrosis; also, fibrotic NSIP and some other patterns could be linked to predominant fibrosis and were associated with increased risk for PPF. This finding is in line with the results of the validation cohort; predominantly fibrotic HRCT patterns revealed an increased risk for PPF (3, 18). Patients with predominantly inflammatory HRCT may respond better to anti-inflammatory treatment than those with predominantly fibrotic HRCT and therefore reduce the risk of PPF.

There may be a different risk profile of PPF in each CTD, while baseline severity, including lung function and HRCT, seems to be an overarching risk. In the European Scleroderma Trials and Research (EUSTAR) database, a large registry of SSc patients in Europe, male gender, higher modified Rodnan skin score and reflux/dysphagia symptoms were associated with FVC decline over 5 years in patients with SSc-ILD (24). In patients with RA-ILD, low baseline FVC/DLCO, UIP pattern, and steroid-use (>10 mg/day) were associated with progressive lung function decline (25). A positive serum anti-MDA5 is associated with rapid progression in IIM patients, but distinct clinical course was observed in subgroups (26, 27).

In recent years, PPF has received attention in trials increasingly, especially after the randomized trials with antifibrotic treatment. The natural history of PPF in ILD, including CTD-ILD, appears to be comparable with idiopathic pulmonary fibrosis (IPF) (28). Nevertheless, definitions of PPF vary across studies. The ATS/ERS/JRS/ALAT 2022 criteria were the first consensus of scientific societies

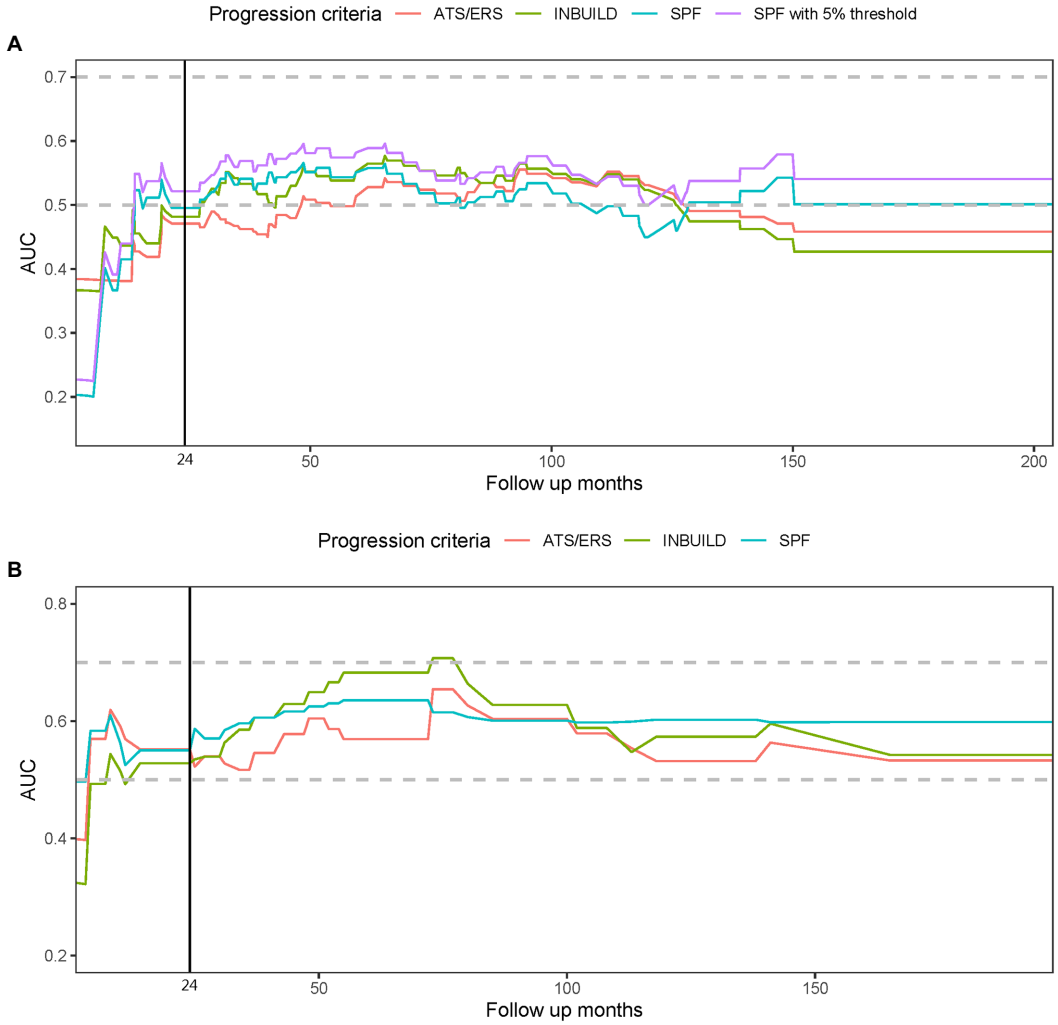

FIGURE 2
The prognostic relevance to mortality and progressive pulmonary fibrosis (PPF) is shown in this time dependent receiver operator characteristic (ROC) model. The figure demonstrates the area under the ROC curve (AUC) over the follow-up period in this cohort **(A)** and the validation cohort **(B)**. The vertical line indicates the timepoint of 24months when PPF was identified. A higher AUC reflects a better correlation of the criteria with prognosis. The PPF criteria, including ATS/ERS/JRS/ALAT criteria (ATS/ERS), INBUILD criteria (INBUILD), and the simplified progressive fibrosing criteria (SPF), did not substantially outcompete each other. The prognostic value in AUC improved in SPF with defining HRCT progression with a≥5% increase in fibrosis (SPF with 5% threshold) in the present cohort **(A)**.

but were based on data from IPF (7). As emphasized in the ATS/ERS/JRS/ALAT 2022 guideline, PPF should be utilized in prognostication instead of diagnosis. We examined the prognostic correlation of these PPF criteria in the time-dependent ROC model. The prognostic correlation with mortality was similar between the three PPF criteria and achieved a plateau after 3 years in this cohort (predominant CTD in RA) and the validation cohort (predominant CTD in SSc); the AUC in time-dependent ROC model was higher in the validation cohort than this cohort.

The strength of this study is that we validated the prognostication with two real world CTD-ILD data. The prognostic relevance was visualized in time dependent ROC model. Most patients were diagnosed early with low extent of fibrosis at baseline. However, the proportion of missing data was relatively high and can be regarded as limitation of this study (Supplementary Figure S1). As the St. Antonius Hospital is an ILD referral center, patients are often evaluated once for expert opinion after which follow-up will take place at local hospitals, which could largely explain the missing data at follow-up. In addition, patient reported respiratory symptoms were not systematically scored in the medical records, therefore we did not include this parameter in our analysis. In the validation cohort, 23 (15%) patients reported symptom progression from dyspnea on exertion to dyspnea at rest or oxygen requirement in the first 2 years. Because of the missing data at follow-up, the proportion of patients with PPF may be underestimated. Nonetheless, regular pulmonary function test in the first 2 years was associated with a significant preferable prognosis. A second limitation is that the reading of HRCT, which relies on experienced radiologists, may be variation in interobserver agreement, and radiological progression of most of the criteria is descriptive (3, 7–9, 29, 30). An artificial intelligence-aided quantitative HRCT evaluation could improve accurate detection of changes, although these techniques are not universally available yet (31, 32). Since

CTD-ILD is a heterogenous manifestation, further research in biomarkers and artificial intelligence-aided HRCT analysis could support tailored clinical decision making.

In conclusion, we identified risk factors for mortality and examined prognostication of PPF in CTD-ILD patients. CTD-ILD is a rather heterogenous disease and the current PPF criteria may not be applicable universally. Disease control of the underlying CTD, multidisciplinary evaluation and systematic assessment of respiratory symptoms, pulmonary function, and HRCT are instrumental to identify high-risk patients and tailor treatment strategies (33). Further research is needed to explore optimal use of PPF criteria in managing patients with CTD-ILD.

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 Medical Research Ethics Committees United. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Y-HC, JL, JG, and JS conceptualized this study. MK and AW retrieved the clinical data. HE and LL analyzed the pulmonary images. Y-HC, MV, PW, AJ, JL, JG, and JS interpreted the clinical data. Y-HC, MK, and PW performed the formal analysis. Y-HC wrote the original draft. AW performed the data management. All authors have critically reviewed and agreed on all versions of the article, the article submission, and taking responsibility for all aspects of the work.

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Conflict of interest

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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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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1106560/full#supplementary-material

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Interstitial lung disease associated with inflammatory myositis: Autoantibodies, clinical phenotypes, and progressive fibrosis

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Progressive pulmonary fibrosis is generally diagnosed when interstitial lung disease progression occurs in the absence of any other cause, and a subset of patients with myositis and associated interstitial lung disease may develop progressive pulmonary fibrosis. Numerous autoantibodies (e.g., against tRNA-synthetase, MDA5, Ro52) increase the risk of this clinical feature in myositis and we speculate that serum biomarkers, sought using the most sensitive laboratory techniques available (i.e., immunoprecipitation) may predict pulmonary involvement and allow the early identification of progressive pulmonary fibrosis. We herein provide a narrative review of the literature and also present original data on pulmonary fibrosis in a cohort of patients with myositis and serum anti-Ro52 with interstitial lung disease. Our results fit into the previous evidence and support the association between anti-Ro52 and signs of pulmonary fibrosis in patients with inflammatory myositis. We believe that the combination of available and real-life data has significant clinical relevance as a paradigm of serum autoantibodies that prove useful in determining precision medicine in rare connective tissue diseases.

KEYWORDS

antisynthetase, autoantibodies, progressive pulmonary fibrosis, antinuclear antibodies, idiopathic inflammatory myopathy, connective tissue disease

1. Introduction

Idiopathic inflammatory myopathies include clinical subtypes represented by dermatomyositis (DM), polymyositis (PM), immune necrotizing myositis, antisynthetase syndrome (ASSD), and inclusion-body myopathy. This is a spectrum of chronic inflammatory and autoimmune conditions characterized by variable clinical and immunological features (1), such as the prominent skin involvement or the vasculitis in DM (2), the coexistence of Raynaud phenomenon, arthritis, muscle damage, and interstitial lung disease (ILD) in ASSD (3), features that are generally absent in the immune necrotizing or inclusion-body myopathies (4, 5). Whether patients diagnosed with PM should be regarded as a separate group or rather included in the others remains a topic for debate (6).

There have been reports of a growing number of myositis-specific (MSA) and myositis-associated (MAA) autoantibodies in different conditions to predict organ involvement and

comorbidities. While MSA are found almost uniquely in patients with idiopathic inflammatory myopathies, MAA are also observed in other connective tissue diseases such as systemic sclerosis, systemic lupus erythematosus, or Sjögren's syndrome (7). Based on their specific nature and the observation that their coexistence is virtually exceptional, MSA have been proposed to become major determinants for the taxonomy of idiopathic inflammatory myopathies (8) and different specificities can help stratifying patients into groups with homogenous phenotypes (6, 9). As an example, DM with positive anti-Mi-2 antibodies is associated with severe muscle involvement (10), whereas anti-MDA5 antibodies positivity is associated with clinically amyopathic DM, peculiar skin features, and rapidly-progressive ILD (11).

While idiopathic inflammatory myopathies represent less than 5% cases of ILD observed by pulmonologists (12), the prevalence of ILD has been estimated as 40% in idiopathic inflammatory myopathies, reaching highest prevalence rates in ASSD and in clinically amyopathic DM (13, 14) where it is associated with significant morbidity and mortality (15, 16). As we are going to describe in the present review, the risk of developing ILD, its phenotype and progression vary significantly in different idiopathic inflammatory myopathies (17) and an adequate identification of MSA and MAA is expected to predict ILD onset and outcome.

2. Progressive pulmonary fibrosis in rheumatology

The concept of progressive pulmonary fibrosis (PPF) has been introduced to indicate every fibrosing ILD other than idiopathic pulmonary fibrosis which demonstrates clinical and/or radiological and/or functional signs of progression with no primitive explanation (18). It has been estimated that up to 40% of ILD cases other than idiopathic pulmonary fibrosis evolve into a PPF phenotype (19). While the incidence of progressive fibrosis in patients with idiopathic inflammatory myopathy-ILD remains unclear (20), there are reports suggesting that a considerable proportion of subjects may evolve to PPF during the disease course in the presence of established risk factors (15, 21) such as older age, extensive fibrosis at high-resolution computed tomography (HRCT) (i.e., traction bronchiectasis, usual interstitial pneumonia – UIP pattern), progression or non-stabilization with initial therapy, and short telomere syndromes (22). Fibrotic HRCT pattern at baseline, diabetes mellitus and steroid-use have been identified as risk factors for PPF in patients with connective tissue disease-ILD (23). Short disease course, African American ethnicity, and gastro-esophageal reflux are considered specific risk factors for PPF in patients with systemic sclerosis-ILD, whereas the smoking status is associated with PPF in rheumatoid arthritis-associated ILD, and the extension of lung involvement at HRCT is a risk factor in both systemic sclerosis-ILD and rheumatoid arthritis-ILD (22). The results of the SENSCIS and INBUILD trials have shown that nintedanib is an antifibrotic treatment that leads to significant reduction in forced vital capacity 1-year decline in patients with systemic sclerosis-ILD and progressive fibrosing ILD (24, 25).

Older age, reduced forced vital capacity, ground-glass opacities, acute and subacute onset, and extent of abnormalities at HRCT represent unfavorable prognostic factors for idiopathic inflammatory myopathy-associated ILD in a meta-analysis by Kamiya and Colleagues; in the same report, anti-Jo-1 antibody was associated with favorable outcomes (26) but the authors admitted the low quality of supporting data. When considering only ASSD, features such as signs of fibrosis at HRCT, smoking status, and lung damage biomarkers (such as surfactant protein D) have been associated with worse outcomes (21, 27). However, these studies evaluated the prognosis of idiopathic inflammatory myopathy-ILD without distinguishing specific clinical, functional, and radiological trajectories. Taken altogether, the lines of evidence demonstrate no established risk factors for PPF in patients with idiopathic inflammatory myopathy-ILD, and the proportion of these patients undergoing PPF remains largely unknown.

3. Autoantibodies in idiopathic inflammatory myopathy-ILD at risk for progressive pulmonary fibrosis

Myositis autoantibodies are ideal candidates for precision medicine, being associated with clinical features and prognosis with one of the highest degrees of specificity among serum autoantibodies, as also demonstrated in ILD patients (28). Table 1 summarizes the major elements of the association between myositis autoantibodies and ILD (11, 28–50). Chronic, insidious, non-specific interstitial pneumonia (NSIP) with extensive ground glass opacity is the most common manifestation of ILD in patients with ASSD (29), especially when combined with organizing

TABLE 1 Association between myositis-specific and associated antibodies, the risk and clinical features of idiopathic inflammatory myopathy-ILD.

Autoantibody	Association with ILD	ILD pattern	Associated ILD features
Antisynthetase (28–31)	Strong	NSIP*, OP, UIP	Chronic, high mortality
MDA5 (11, 32, 33, 50)	Strong	OP*, NSIP	Rapidly-progressive, acute-subacute, refractory to therapy
PM/Scl (28, 39–42)	Strong	NSIP	Late onset, chronic, indolent
Ro52 (47–49)	Strong	Various	High predictor of ILD, poor outcomes if associated with anti-MDA5 and antisynthetase
NXP2 (28, 35)	Doubtful	NSIP, OP	Typically indolent
SRP (38)	Doubtful	NSIP	Good response to therapy
Ku (43–46)	Doubtful	Unknown	Refractory to therapy, impacts on prognosis
TIF1-gamma (34)	Weak	N.R.	N.R.
Mi-2 (36)	Weak	N.R.	N.R.
HMGCR (37)	Weak	N.R.	N.R.

*Most frequently observed pattern.
ILD, interstitial lung disease; N.R., not reported; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; UIP, usual interstitial pneumonia.

pneumonia; however, a UIP pattern can be observed in up to 10% cases and is associated with PPF (3, 30). The risk of ILD in patients with ASSD is highest with anti-PL-7, anti-PL-12, and anti-EJ antibodies (31). However, ILD is the leading cause of mortality in ASSD, independent of the serologic status (28), as for the anti-MDA5 syndrome characterized by aggressive, rapidly evolving ILD as recently confirmed (11, 50). Organizing pneumonia pattern with extensive, bilateral and consolidations at HRCT are typical of this subset, whereas signs of fibrosis are poorly represented (32), and pulmonary histology can show features of diffuse alveolar damage (33). Additional MSA are less frequently associated with the ILD onset, as in the case of anti-TIF1-gamma antibodies, which may be detected when malignancy coexists (34). A reduced risk of ILD has been reported with anti-NXP2 antibodies (28), but recent evidence has shown some inconsistency with this hypothesis (35). Indeed, a significant prevalence of NSIP and organizing pneumonia was reported in a cohort of anti-NXP2 positive patients, even if ILD tended to be clinically indolent (35). Anti-Mi-2 positivity is associated with a lower incidence of ILD, with good response to immunosuppressants, and favorable outcomes when compared to other forms of idiopathic inflammatory myopathies (36). The spectrum of immune-mediated necrotizing myopathies has been traditionally considered at low risk for extra-muscular manifestations, especially in anti-HMGCR positive cases associated with statin exposure (37). Nonetheless, recent data have suggested a significant prevalence of NSIP in patients with anti-SRP myositis, showing good treatment response and clinical stability throughout disease course (38). Antibodies directed at the nucleolar antigens PM/Scl-75 and PM/Scl-100 are frequently associated with late-onset, chronic NSIP in patients with PM/systemic sclerosis overlap (28, 39), and cases of isolated ILD have been reported in patients testing positive for such specificities (39). Anti-PM/Scl antibodies are found more often in patients with favorable outcomes (40), and no difference in survival was observed in a cohort of patients with anti-PM/Scl syndrome, irrespective of ILD (41). The PM/Scl-75 component is more frequently detected than the PM/Scl-100 (42) autoantigen, reported more frequently in association with a more active, inflammatory phenotype of myositis and ILD (39). Further evidence is required to demonstrate whether antibodies directed toward the two subunits are associated with different disease manifestations and might benefit from different therapies. Anti-Ku autoantibodies are rarely detected in patients with connective tissue diseases, and they can be associated with various clinical manifestations (43), including ILD especially when associated with myopathy (44) and in the absence of other detectable autoantibodies (45). While rare, the anti-Ku antibody is of outstanding importance when managing idiopathic inflammatory myopathy-ILD, since cases of resistance to corticosteroids and immunosuppressants have been reported (46).

Anti-Ro52 antibodies still represent one of the most common autoantibodies in patients with connective tissue diseases (51, 52), with high prevalence of ILD with unfavorable outcomes (47–49). In particular cases, the coexistence of anti-Ro52 and anti-MDA5 antibodies has been associated with aggressive and rapidly progressive ILD in anti-MDA5 syndrome (53, 54) but there are conflicting data on the prognostic role of anti-Ro52 antibodies when associated with other MSA (55, 56). Of note, signs of lung fibrosis at HRCT were described in patients with ILD in mixed connective tissue disease and anti-Ro52 positivity (57), while lower prevalence of fibrosing ILD was found in a cohort of anti-Ro52 positive subjects with Sjogren's syndrome compared to Ro52-negative patients (58). Remarkably, no autoantibody is currently able to predict PPF development in patients with idiopathic inflammatory myopathy-ILD. Given their prevalence and current clinical significance, elucidating the role of anti-Ro52 antibodies in this sense represents a major clinical unmet need.

3.1. Myositis autoantibodies associated with progressive pulmonary fibrosis in research and routine laboratories

There is currently no consensus on the autoantibody testing methodology beyond indirect immunofluorescence for antinuclear antibodies (ANA), generally the first-line for suspected connective tissue disease (59). In fact, autoantibodies in idiopathic inflammatory myopathies are associated with different staining patterns at indirect immunofluorescence (60) and ANA negativity has been reported in up to 50% of these patients in large cohorts (61, 62). Indeed, several myositis antigens (e.g., aminoacyl-tRNA-synthetases, MDA5, SRP) reside in the cytoplasm, and this can lead to false-negative ANA staining. However, indirect immunofluorescence is able to detect ANA suggestive of overlap syndromes, such as systemic sclerosis (63), and additional techniques such as immunoprecipitation still remain the gold standard to detect MSA and MAA. This method allows the testing of almost all known myositis antigens, analyzing antigens in their native conformation thus with highest sensitivity and specificity, and it is directed toward both protein and RNA components. Ultimately, immunoprecipitation provides conclusive evidence in most cases also for rare and uncommon autoantibodies (64) but the method is laborious, and expertise is required to perform it adequately. As a consequence, most diagnostics laboratories usually employ automated techniques, as immunoblot assays and enzyme-linked immunosorbent assays (ELISA), with variable sensitivity and specificity in the detection of several MSA and MAA (63), to screen for multiple antigens at once. The performance of myositis immunoblot might be inferior when compared to gold standard techniques (63) and multiple MSA positivities in single patients have been reported with the use of immunoblot (65) but results should be interpreted with caution. Combining ANA indirect immunofluorescence and immunoblot has been proposed to implement the diagnostic performance in patients with idiopathic inflammatory myopathies (66). Discrepancies between the antigen individuated with immunoblot and ANA staining pattern should orient toward a false-positive immunoblot result (67); when applied to an appropriate clinical context (as is the case of suspected idiopathic inflammatory myopathy-ILD), immunoblot can prove helpful (68). Other autoantibodies, such as anti-Ro52, are not detectable by immunoprecipitation and require specific changes in the immunoprecipitation assays protocol (69, 70). The serological discrimination of anti-Ro52 from anti-Ro60 antibodies is essential because they are associated with different clinical entities (71) thus overcoming the historical 'anti-Ro/SSA' denomination (without distinction between the two antigens) that should be abandoned (71).

4. Results of our monocentric study on anti-Ro52 in idiopathic inflammatory myopathy-ILD

We retrospectively analyzed a cohort of patients with idiopathic inflammatory myopathies, and described the main demographic, clinical, and serological features, focusing on the anti-Ro52 status. We also analyzed on patients with idiopathic inflammatory myopathy-ILD, comparing clinical, functional, radiological (HRCT), and serological characteristics. Serum immunoprecipiation for MSA/MAA was performed according to established methods (72) while anti-Ro52 antibodies were tested by ELISA.

Supplementary Table 1 illustrates the characteristics of the cohort of 55 patients with a diagnosis of idiopathic inflammatory myopathy included in the study. ANA at titer ≥1:160 were detected in 42/55 (76%) patients, and anti-Ro52 ELISA tested positive in 14/55 (25%) sera. Median ages at diagnosis were 52.5 years (range 38.5–60.5 years) in the anti-Ro52 negative group, and 48.5 years (range 45–62 years) in the anti-Ro52 positive group. No significant differences in the gender ratio, prevalence of malignancy and coexisting autoimmune disorders were observed between the two groups. ILD was significantly more prevalent in the anti-Ro52 positive group (79%) than in the anti-Ro52-negative group (37%; $p = 0.007$), while no difference was observed for other clinical manifestations such as myositis, skin rash, Raynaud phenomenon, arthritis, dysphagia, and cardiomyopathy. As for autoimmune serological results, antisynthetase antibodies occurred much more frequently in the Ro52-positive group, but no significant differences were reported for anti-MDA5, anti-PM/Scl, and other MSA/MAA status between the two groups.

Table 2 summarizes the main features of patients with idiopathic inflammatory myopathy-ILD based on their anti-Ro52 status. The Ro52-positive group was younger (median age 49 versus 55 years in Ro52-negative subjects), but no significant differences were retrieved in terms of demographic and clinical features (including baseline creatine kinase values), except for a predominance of Raynaud phenomenon in the Ro52-negative group. The two groups did not differ in terms of pulmonary function tests, as baseline values of forced vital capacity and diffusing capacity for carbon monoxide were similar and the proportion of patients with worsening pulmonary function was comparable. Imaging findings from baseline HRCT were analyzed for the detection of ground glass opacities, consolidations, and signs of fibrosis (defined as the presence of subpleural reticulation, traction bronchiectasis, and/or honeycombing) (18), and no differences were observed in terms of consolidations between the two groups. Remarkably, ground glass opacity was significantly more frequent in patients testing negative for anti-Ro52 antibodies and signs of fibrosis were more prevalent in patients with anti-Ro52 positivity (82%) than in negative subjects (30%, $p = 0.0189$). As for serological results, a higher prevalence of antisynthetase antibodies was confirmed in the Ro52-positive group, also when considering the ILD subgroup, while no differences were found for ANA, anti-MDA5, anti-PM/Scl, and other MSA/MAA.

TABLE 2 Demographic, clinical, autoimmune features of the studied cohort of patients with inflammatory myositis and ILD, based on their anti-Ro52 status.

	Ro52 positive (n=11)	Ro52 negative (n=15)	p
Age, years (range)	49 (45–71)	55 (49–63)	–
Female sex	10 (91)	11 (73)	0.2607
Malignancy	3 (27)	1 (7)	0.1718
Overlap AID	3 (27)	4 (27)	1.0000
Myositis	8 (73)	12 (80)	0.6810
Skin rash (DM)	9 (82)	12 (80)	0.9001
Raynaud's phenomenon	3 (27)	10 (67)	0.0481
Capillaroscopy alterations	7 (64)	9 (60)	0.8389
Arthritis	5 (45)	5 (33)	0.5416
Cardiomyopathy	2 (18)	4 (27)	0.5984
Dysphagia	2 (18)	6 (40)	0.2387
Basal FVC	93 (82–102)	95 (84–105)	0.8259
FVC decline >5% over 1 year	4/6 (67)	3/7 (43)	0.4056
Basal DLCO	67.5 (59–79)	67 (54–76)	0.6527
DLCO decline >10% over 1 year	1/6 (17)	1/7 (14)	0.8858
Ground glass opacity	4 (36)	8/10 (80)	0.0472
Consolidations	1 (9)	2/10 (20)	0.4820
Signs of fibrosis	9 (82)	3/10 (30)	0.0189
Elevated baseline CPK	5 (45)	12 (80)	0.0695
ANA ≥1:160	10 (91)	12 (80)	0.4509
Antisynthetase antibodies	7 (64)	2 (13)	0.0081
Anti-MDA5	0 (0)	1 (7)	0.3797
Anti-PM/Scl	1 (9)	3 (20)	0.4509
Other MSA/MAA	1 (9) (TIF1-gamma)	3 (20) (TIF1-gamma, SAE, RNP)	0.4509

AID, autoimmune disease (i.e., thyroiditis, psoriasis, coeliac disease, lichen planus, systemic lupus erythematosus, autoimmune hepatitis, rheumatoid arthritis, autoimmune gastritis); ANA, antinuclear antibodies at a titer ≥ 1:160; CPK, creatine phosphokinase; DLCO, diffusing capacity for carbon monoxide; DM, dermatomyositis; FVC, forced vital capacity; GGO, ground glass opacities; HRCT, high-resolution CT scan; ILD, interstitial lung disease; MAA, myositis-associated antibodies; MSA: myositis-specific antibodies; PFT: pulmonary function tests.

4.1. Data interpretation

As shown in our monocentric analysis on anti-Ro52 patients with idiopathic inflammatory myopathy-ILD, anti-Ro52 antibodies are strong predictors of ILD development, significantly associated with antisynthetase antibodies, as confirmed by previous findings (52, 56). We extensively describe the association between anti-Ro52 positivity and signs of lung fibrosis at HRCT in a cohort of patients with idiopathic inflammatory myopathy-ILD, similar results were achieved for mixed connective tissue disease-ILD (57). It should be kept in mind that fibrosing signs at HRCT represent the risk for PPF in patients with connective tissue disease-ILD (23), and antifibrotic therapy is now advised when PPF develops (18). In our cohort, anti-Ro52 antibodies were not associated with a functional decline of lung capacity over 1

year of observation, but we are aware that this might be due to the small sample size and to the short period of observation. Finally, the presence of ground glass opacity was negatively correlated with anti-Ro52 status, suggesting that anti-Ro52 might play a role in more chronic, insidious, fibrosing processes than in acute/subacute subtypes.

Ro52/TRIM21 is a E3-ubiquitin ligase owing to the TRIM superfamily and several members of this superfamily are involved in fibrosing processes, including lung fibrosis (73). TRIM21 interacts with TGF-beta expression and function (73), and regulates the inflammatory response, e.g., balancing the pro-inflammatory effects of NF-kB (74). Pirfenidone is an antifibrotic drug currently approved for the treatment of idiopathic pulmonary fibrosis (75) and the drug acts by down regulating pro-fibrotic signaling pathways, molecules, and cells, although precise molecular mechanisms are still to be explored (76). TRIM21 expression in idiopathic pulmonary fibrosis lung fibroblasts is regulated by pirfenidone (77), and Ro52/TRIM21 activity might be correlated with lung fibrosis in patients with idiopathic pulmonary fibrosis. These aspects may be applicable to other forms of PPF, considering the crucial role of TRIM proteins in the pathogenesis of fibrosis. Anti-Ro52 antibodies correlate with lung fibrosis at HRCT and, thus, they could represent a risk factor for PPF, especially in case of idiopathic inflammatory myopathy-ILD. Further studies are required to support the hypothesis of increased risk of lung fibrosis and PPF in anti-Ro52 positive patients with idiopathic inflammatory myopathies myositis-ILD, and to elucidate the possible role of Ro52/TRIM21 in the pathogenesis of lung fibrosis. A potential role of pirfenidone therapy in patients with progressive fibrosing idiopathic inflammatory myopathy-ILD might be hypothesized, especially in case of anti-Ro52 positivity. Antifibrotic therapy has changed the course and prognosis of idiopathic pulmonary fibrosis, and similar results are expected in patients with PPF, including cases of idiopathic inflammatory myopathy-ILD. A precision medicine approach, based on the correct autoantibody determination, is required to offer targeted immunosuppressive and antifibrotic therapies to patients with idiopathic inflammatory myopathy-ILD.

5. Conclusion

It is crucial to screen for idiopathic inflammatory myopathies in patients with ILD and a cluster of myositis autoantibodies is significantly associated with ILD onset in these patients. Currently, there is no established risk factor for PPF in patients with idiopathic inflammatory myopathy, and serum autoantibodies are ideal candidates in this sense. We report and discuss the implications of the association between anti-Ro52 antibodies and lung fibrosis in a cohort of patients with idiopathic inflammatory myopathies, and we speculate that anti-Ro52 may represent a risk factor for PPF in these patients. Data from larger cohorts and longer follow-up periods are required to corroborate this hypothesis. Other myositis autoantibodies should be also tested.

Data availability statement

The data that support the findings of this study are available from the corresponding author, CS, upon reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by Humanitas Research Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

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

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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.

The reviewer GDL declared a past co-authorship with the author(s) MDS to the handling editor.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1068402/full#supplementary-material

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Unmet needs and perspectives in rheumatoid arthritis-associated interstitial lung disease: A critical review

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Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by synovitis as the most common clinical manifestation, and interstitial lung disease (RA-ILD) represents one of the most common and potentially severe extra-articular features. Our current understanding of the mechanisms and predictors of RA-ILD is limited despite the demonstration that an early identification of progressive fibrosing forms is crucial to provide timely treatment with antifibrotic therapies. While high resolution computed tomography is the gold standard technique for the diagnosis and follow-up of RA-ILD, it has been hypothesized that serum biomarkers (including novel and rare autoantibodies), new imaging techniques such as ultrasound of the lung, or the application of innovative radiologic algorithms may help towards predicting and detecting early forms of diseases. Further, while new treatments are becoming available for idiopathic and connective tissue disease-associated forms of lung fibrosis, the treatment of RA-ILD remains anecdotal and largely unexplored. We are convinced that a better understanding of the mechanisms connecting RA with ILD in a subgroup of patients as well as the creation of adequate diagnostic pathways will be mandatory steps for a more effective management of this clinically challenging entity.

KEYWORDS

progressive pulmonary fibrosis, biomarkers, immunology, precision medicine, rheumatoid arthritis, interstitial lung disease, clinical trials, lung ultrasonography

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease in which an autoimmune mechanism causes chronic inflammation which predominantly involves the synovia at the peripheral joints (1). Although the disease etiology remains largely unknown, genetic predisposition, environmental triggers, and aberrant immune system activation are well established factors determining RA pathogenesis (2). A large proportion of patients report extra-articular manifestations, including cardiovascular, respiratory, and cutaneous involvement (3). The presence of extra-articular manifestations may in some cases predate the clinical onset of

arthritis, may require specific management measures, and ultimately impact therapy (3, 4). Focusing on the respiratory manifestations of RA, it has been estimated that lung disease accounts for 10%–20% of mortality in subjects with RA, being inferior only to cardiovascular events (5). While the lung parenchyma, airways, pleura, and vasculature may all be affected, RA-associated interstitial lung disease (RA-ILD) is the most common and potentially severe manifestation, as it can present with a progressive fibrosing phenotype (6). Acute exacerbations of RA-ILD are defined as a rapidly progressing, potentially life-threatening respiratory decline characterized by new extensive alveolar abnormalities superimposed on underlying pulmonary fibrosis (7). Acute exacerbations are a rare but severe complication carrying a 12% to 64% mortality (8–11). To provide a better overview of RA-ILD, we will herein review the prevalence, risk factors, clinical characteristics, and therapeutic perspective of RA-ILD.

Prevalence, incidence, and mortality of RA-ILD

It has been estimated that RA-ILD explains about 8% of all cases of ILD (12). The prevalence of IL among patients with RA ranges between 1.8% and 67% and according to a recently published meta-analysis, the prevalence of clinically detected RA-ILD is also lower than radiologically detected cases (13). Chest high-resolution computed tomography (HRCT) is the most sensitive technique to screen for the presence of ILD in patients with RA and allows its characterization and quantification (14). The presence of symptoms and signs (i.e.: exercise dyspnea, cyanosis, inspiratory velcro-like crackles, digital clubbing) makes "clinically-driven" detection of RA-ILD ineffective and leads to delayed diagnosis at later stages (15). Thus, the use of different case finding methods explains, at least in part, the heterogeneity of RA-ILD prevalence that is reported in the literature.

Second, with the adoption of HRCT in clinical practice, an increase in RA-ILD prevalence has been observed over time (16). ILD has been detected in up to 7.5% subjects with early RA (17), while interstitial lung abnormalities (ILA, *vide infra*) may be more common (18). It has been estimated that 10% patients with established RA have clinically significant ILD (i.e., signs and symptoms, latent respiratory insufficiency, severe lung function impairment) (19). Moreover, ILD can precede RA clinical onset in a significant proportion of cases (20). Third and last, genetic susceptibility can be hypothesized to explain geographical differences (21).

While RA-associated general mortality has decreased over the last decades, mortality due to RA-ILD remained stable (15, 19) resulting in a 3–10 times higher risk of death in patients with RA-ILD compared to patients with RA without lung involvement (14, 20). RA-ILD not only increases the risk of all-cause and respiratory mortality, but also seems to be associated with elevated risk of cancer-related mortality (22) with pulmonary malignancy being the most common cancer-related cause of death in patients with RA, especially if ILD is present (22–24). The incidence of lung cancer is higher in patients <60 years with rheumatic disease-associated ILD (RD-ILD) than patients without rheumatic disease (25) and the incidence of lung cancer in RA-ILD is comparable to idiopathic pulmonary fibrosis (IPF) (26) but how these data apply to RA is unclear. Last, a trend towards a mortality reduction is associated with the early diagnosis of RA-ILD at HRCT and with the use of immunosuppressive therapy (27), while it has been demonstrated that diagnostic delay in RA-ILD diagnosis leads to increased mortality (28).

Risk factors and prognostic factors of RA-ILD

Established risk factors for RA-ILD are summarized in Table 1 and include demographics such as older age, male sex, obesity, and smoking history, along with the presence of respiratory comorbidities (22, 29). In addition, RA disease features, such as longer disease duration (13), high disease activity (22) and serum autoantibodies, in particular rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) significantly increase the risk of developing ILD. Furthermore, novel emerging biomarkers seem to play a prognostic role (27, 29) while genetic risk factors such as gain-of-function MUC5B promoter variant rs35705950 increase the risk of ILD in patients with RA and are associated with the usual interstitial pneumonia (UIP) pattern at HRCT (30) apart from being associated with IPF (31). Additionally, single-nucleotide polymorphisms (SNPs) in TERT, TOLLIP, and FAM13A loci have also been associated with pulmonary fibrosis in patients with RA (32).

While time-dependent decline in lung function correlates with mortality in RA-ILD (13, 33), other prognostic factors include older age, male sex, smoking habit, or the presence of comorbidities (13, 34) such as RA disease activity and the use of systemic glucocorticoids (13, 34). Additional poor prognostic features include pleural effusion, short time between RA diagnosis and ILD occurrence (35), as well as the radiologic pattern at HRCT with UIP pattern predicting mortality (13, 33, 36) and correlating with an increased risk of acute exacerbations and lung cancer (36).

Progressive pulmonary fibrosis and RA-ILD

According to the Fleischner Society glossary, fibrosing ILD is defined in the presence of reticular abnormalities, traction bronchiectasis and bronchiolectasis, architectural distortion, and/or honeycombing on HRCT scan (37–39). These radiologic changes reflect the exuberant deposition of extracellular matrix within the

TABLE 1 Established risk factors for ILD occurrence in patients with RA.

Demographics
Older age
Male sex
Smoking history
Comorbidities
Obesity
Previous respiratory disease
RA-associated features
Long disease duration
High disease activity
Seropositivity for RF and/or ACPA
Genetics
MUC5B promoter variant rs35705950

pulmonary interstitium, and may lead to the development of progressive fibrosing ILD in a subset of patients (39).

Progressive pulmonary fibrosis (PPF) has been defined as the progression of at least two domains among clinical and/or functional and/or radiological status, occurring within 1 year, without any alternative explanation, in a patient with an established diagnosis of fibrosing ILD other than IPF (40). One third of patients with RA-ILD develop PPF (12, 41, 42), particularly when a UIP pattern is described at HRCT, although a minority of subjects with these features do not progress (43). PPF is associated with increased mortality and unfavorable outcomes (44) and the antifibrotic drug nintedanib is now recommended in this subset of patients (40), thus making an early diagnosis a major clinical need.

Comorbidities in RA-ILD

Several comorbidities can impact the course of RA-ILD, affecting disease control and leading to impaired quality of life. According to Mena-Vázquez et al. ILD is independently associated with multimorbidity in patients with RA, with the most frequent comorbid conditions being traditional cardiovascular risk factors, depression, and osteoporosis (45).

Among respiratory comorbidities, RA-ILD can be associated with airway disease, including COPD, bronchiectasis and asthma (46). RA-ILD patients with COPD or emphysema have higher mortality risk in different cohorts (47–49). Interestingly, pre-existing COPD has been associated with a higher incidence of ILD in newly diagnosed RA patients (50). Bronchiectasis in RA are associated with increased risk of infections *per se* (46) and in patients treated with biologic disease modifying anti-rheumatic drugs (DMARDs) (51). RA-ILD is a risk factor for pneumonia (51, 52), in particular when associated to an organizing pneumonia pattern, and with daily doses of prednisone exceeding 10 mg. (52) A relevant concern in terms of infections is also represented by COVID-19 (53), since patients with RA are at increased risk of developing severe COVID-19, the risk appearing even higher in those with pre-existing ILD (54, 55).

Sleep disorders are frequently associated with RA. A recent meta-analysis has shown that the incidence of obstructive sleep apnea syndrome (OSAS) is 29.8% among RA cohorts, however with a significant heterogeneity, and high BMI is the principal risk factor (56). Although the epidemiology of sleep disorders is still blurred in RA-ILD, it is reasonable to consider OSAS as a significant complication in this subgroup of patients due to its relevance in other ILDs, including IPF, and can cause an extremely poor sleep quality that correlates with poor quality of life (57, 58). Thus, OSAS and prolonged oxygen desaturation during sleep have been associated with a worse prognosis in IPF, both in terms of mortality and clinical progression. (59)

Pulmonary hypertension associated to interstitial lung disease is an established clinical entity, owing to class III World Health Organization (WHO) classification (60). However, pulmonary arterial hypertension (PAH, i.e., class I WHO) can represent a rare complication patients suffering from RA (60, 61). Also, the prothrombotic effect associated to chronic inflammation increases the risk of venous thromboembolism (62), and chronic thromboembolic pulmonary hypertension should be taken into account when approaching to the differential diagnosis of pulmonary hypertension in patients with RA and RA-ILD. Interestingly, the dominating cause of pulmonary hypertension may change over time, making the diagnostic and therapeutic process more challenging (63).

Traditional and novel biomarkers in RA-ILD

Biomarkers are measurable indicators of biologic and pathologic processes (64), and include well-established serum autoantibodies used in routine clinical or research settings in addition to RF and ACPA and non-autoimmune markers of lung damage. Table 2 summarizes the main established and investigational biomarkers in RA-ILD.

Rheumatoid factors (RF)

RF is represented by immunoglobulins, mainly IgM but also IgG and IgA, directed towards the constant (Fc) portion of another immunoglobulin (101); serum RF is positive in up to 80% of patients with RA, albeit with lower specificity (101) since non-rheumatic conditions (e.g., infective endocarditis, hepatitis B and C, primary biliary cholangitis, lymphoma) and rheumatic diseases other than RA (e.g., Sjogren's syndrome, cryoglobulinemia) manifest different degrees of RF positivity (102). RF can be tested with different laboratory methods, including latex fixation test, Waaler-Rose reaction, and enzyme linked immunosorbent assay (ELISA) (103), with the latex fixation test and Waaler-Rose reaction capable of detecting only IgM-RF, while immunoassays can also identify IgG and IgA isotypes, possibly increasing the diagnostic sensitivity (104, 105).

RF positivity is an established risk factor for ILD development in patients with RA (65–67). It has been demonstrated that the prevalence and incidence of RA-ILD correlates with serum titers of RF (68) and high-titer RF is associated with an increased risk of progression and elevated mortality in patients with RA-ILD (69), along with a more aggressive form of RA with a higher risk of erosions (70). Moreover, signs of advanced fibrosis at HRCT (including honeycombing) have been associated with RF seropositivity in patients with RA-ILD (69).

In contrast to IgG and IgM RF isotypes, IgA-RF correlates with more severe articular disease, development of bone erosions, and increased prevalence of extra-articular manifestations including ILD (71, 72) with a higher prevalence of UIP pattern at HRCT (73). Despite this preliminary evidence, the clinical significance of different RF isotypes needs to be further explored in longitudinal studies.

Anti-citrullinated protein antibodies

Serum ACPA are associated with an increased risk of ILD in patients with RA (74) in a titer-dependent manner (75). Also, the prevalence of ILD at disease onset is higher among subjects with high ACPA titers (76). There is also a direct correlation between ACPA and disease severity in terms of clinical presentation (i.e., symptoms, signs, presence of respiratory insufficiency), worse lung function, and extent of ILD on HRCT (77). In a meta-analysis by Zhu and colleagues, ACPA status predicted ILD in RA and was significantly associated with an increased risk of fibrosing ILD (78) at degrees correlating with ACPA titers (77). Since signs of fibrosis at HRCT are an established

TABLE 2 Established and candidate biomarkers for RA-ILD; the proposed mechanistic links and setting of use are specified for all markers.

Biomarker	Pathogenic and/or clinical association(s)	Availability
Autoantibodies		
Rheumatoid factor (65–73)	Incidence and progression of ILD in RA correlate with RF titers; fibrosing ILD and UIP (especially IgA-RF)	+ (+/− isotypes)
ACPA (74–81)	Incidence and severity of ILD in RA correlate with ACPA titers; fibrosing ILD, UIP (especially ACPA repertoire expansion), NSIP (secretory ACPA)	+ (Repertoire for research purposes)
anti-CEP-1 (82)	Positive association with ILD in non-smokers	Research
anti-citrullinated Hsp90 (83)	Positive association with ILD	Research
Anti-PAD2 (84)	Negative association with ILD	Research
Anti-PAD3/4XR (85)	Positive association with ILD in non-smokers	Research
Anti-CarP (86)	Positive association with ILD at increasing titers	Research
Anti-MAA (87)	Positive association with ILD (IgA and IgM)	Research
Anti-class I (88)	Negative association with ILD	Research
Anti-MICA (88)	Positive association with ILD	Research
Antisynthetase (89–91)	Positive association with ILD, especially NSIP; ASSD overlap vs RA misdiagnosis	+
Cytokines		
IL-4 (92)	Increased in patients with RA-ILD	Research
IL-11 (93, 94)	Correlates with ILD severity and disease activity	Research
IL-13 (95)	Correlates with the extent of fibrosis	Research
IL-18 (96)	Increased in patients with RA-ILD	Research
IL-33 (93, 94)	Correlates with ILD severity	Research
Circulating factors with immunologic implication		
KL-6 (97–100)	Correlates with lung damage	+

risk factor for PPF (40), patients with RA testing positive for ACPA could be at higher risk for PPF development and may warrant a closer monitoring of lung changes.

ACPA formation against different citrullinated peptides and epitope spreading, which is the development of immunity against self-antigens release during autoimmune responses (79), are established mechanisms in the pathogenesis of RA (80). As such, as RA progresses, the ACPA repertoire (i.e., the number of different autoantigens and specific moieties recognized by ACPA) expands. This phenomenon has been associated with an increased risk of fibrosing ILD, lower lung volumes and DLCO, and higher prevalence of UIP pattern at HRCT (81). This is relevant considering that such functional and radiological features can predict PPF and suggests that analyzing the ACPA repertoire during the disease course may help individuating patients with RA-ILD at high risk of PPF.

Among autoantibody subtypes, patients testing positive for serum ACPA with secretory components have more frequently a nonspecific interstitial pneumonia (NSIP) pattern at HRCT, in contrast to what is commonly seen in RA-ILD (73).

Novel autoantibodies in RA-ILD

Among the non-classical autoantibodies putatively correlated with ILD in patients with RA, anti-citrullinated alpha-enolase peptide 1 (anti-CEP-1) have been identified as a subset of ACPA associated with erosive RA and ILD (82), particularly at high titers (106), and have been proposed for early detection of RA-ILD in at risk non-smoking patients (82). Anti-citrullinated heat shock protein 90 (Hsp90) antibodies are found in a subset of patients with RA-ILD, but not in patients with RA without ILD or in other forms of ILD (83). They are also present in the bronchoalveolar lavage fluid (BALF) (107) while autoreactive Th1 lymphocytes directed towards citrullinated Hsp90 have been detected in the peripheral blood of patients with RA-ILD (108). Peptidylarginine deaminase (PAD) is the most important enzyme causing citrullination (109), as demonstrated for the oral bacterium *P. gingivalis* (110). Autoantibodies against the human PAD isoforms PAD2, PAD3 and PAD4 have been detected in patients with RA (109) and may be useful in the risk stratification for lung disease. Anti-PAD2 antibodies have been described in a subset of patients with RA characterized by milder articular damage, as well as less frequent and less severe extra-articular manifestations, especially ILD (84), whereas anti-PAD4 antibodies correlate with a more aggressive disease (111). A subgroup of patients with RA possesses cross-reactive antibodies towards both PAD3 and PAD4, named anti-PAD3/4XR antibodies, that may predict ILD occurrence, especially in never-smoking patients (85), an association not found for anti-PAD3 or anti-PAD4 antibodies alone. Recent data demonstrate a possible association between double anti-PAD3 and PAD-4 positivity with both ILD and more erosive disease and the authors have hypothesized that such patients might have anti-PAD3/4XR positivity (112). Serum anti-carbamylated proteins antibodies (anti-CarP) have been reported at higher frequency in patients with RA-ILD compared to RA patients without ILD, independent of the smoking status (86). Malondialdehyde-acetaldehyde adducts (MAA) are highly expressed in the lung tissue from patients with RA-ILD, and antibodies against MAA (anti-MAA) have been associated with RA-ILD (87), especially high titers and the IgA or IgM isotypes (87). Furukawa and Colleagues

have described the presence of autoantibodies to human leukocyte antigen (HLA) class I (anti-class I) and HLA class I related chain A (anti-MICA) in a cohort of patients with RA. Notably, higher levels of anti-MICA antibodies and higher values of the anti-MICA/anti-class I ratio were found in patients with RA-ILD, compared to patients without lung involvement (88). Antisynthetase antibodies are directed towards aminoacyl-tRNA-synthetase complex and are mainly found in a cluster of patients with inflammatory myositis, namely the antisynthetase syndrome (ASSD) (113) with NSIP as the most common ILD pattern observed at HRCT (114). In a cohort of patients with RA, the prevalence of serum antisynthetase antibodies was 6%, and ILD occurred more frequently (57%) in seropositive than seronegative (22%) patients. Specifically, anti-PL-7 was the most frequently reported among antisynthetase antibodies, whereas a low prevalence of anti-Jo-1 was observed; this contrasts with what is commonly seen in ASSD cohorts, where anti-Jo-1 is the most common antibody. Furthermore, opposite to RA-ILD with conventional antibodies like RF and ACPA, NSIP was the most frequent pattern at HRCT in antisynthetase antibody-positive subjects with RA (89). The association of antisynthetase antibodies and RA-ILD was confirmed in an independent cohort (90), and a case of anti-EJ and ACPA positive RA with ILD-only onset was also reported (115). Remarkably, ASSD is frequently misdiagnosed and treated as RA, especially when arthritis is the predominant manifestation (91).

Routine laboratory tests

Among tests usually performed in the clinical setting, an unsuspected role has been proposed for serum uric acid, for which higher levels were observed in RA-ILD with a prevailing UIP pattern at HRCT (116). Serum uric acid is already included in the DETECT algorithm for early detection of pulmonary arterial hypertension in patients with systemic sclerosis (SSc) (117). Higher neutrophil and monocyte counts are independent predictors of mortality in RA-ILD, particularly when both are elevated (118).

Other serum biomarkers

Among cytokines, serum titers of IL-4 (92) and IL-18 (96) are increased in patients with ILD, compared to the general RA population while serum IL-13 is increased in patients with RA-ILD and correlates with the extent of fibrosis at HRCT (95). However, such observations warrant further investigation since, as an example, IL-4 is a strict autocrine cytokine and serum levels may not differ even between subjects with IL-4-dependent diseases and healthy controls (119). Both arthritis and ILD severity correlate with the presence and serum concentrations of IL-11 and IL-33, independent of the RF and ACPA status, with the former being also associated with RA disease activity (93, 94). Within the IL23-IL17 axis, Zhang and colleagues reported that lung fibroblasts from patients with RA-ILD express significantly higher levels of the IL-17A receptor (IL-17RA) compared to patients without ILD or IPF (120) while IL-23 contributes to the epithelial-mesenchymal transition in the lung of RA-ILD (121). While the role of IL-17 and IL-23 remains elusive, these results support the use of monoclonal antibodies against IL-17 (e.g., secukinumab, ixekizumab) and IL-23 (e.g., guselkumab, risankizumab, and ustekinumab) which are currently used in spondyloarthritis, psoriasis and psoriatic arthritis, and inflammatory bowel disease for RA-ILD despite being proven ineffective on the articular manifestations of RA (122, 123). Krebs von den Lungen 6 (KL-6, a glycoprotein expressed by type II alveolar cells) serum levels correlate with lung damage in patients with ILD (97) with higher baseline values associated with mortality in RA-ILD, especially with a UIP pattern at HRCT (98). Changes in KL-6 values over time may predict acute exacerbations of RA-ILD (99) to make routine tests a putative screening method for ILD in patients with RA (100). In combination with KL-6, the oncological markers CA 19-9, CA 125, and CEA correlate with the presence and severity of ILD in patients with RA (124) while serum HE4, a biomarker for ovarian cancer, may identify RA cases at risk for subclinical ILD (125). It was demonstrated that serum onco-marker CA 15–3 is a valid alternative to KL-6, with comparable sensitivity and specificity in differentiating fibrosing and non-fibrosing ILD (126). Other proposed molecules involved at different levels in the immune, inflammatory, and fibrotic response characterizing RA-ILD include matrix metalloproteinase 7 (MMP-7), C-X-C motif chemokine ligand 10 (CXCL10) (127), Dickkopf 1 (DKK1) (128), and soluble programmed death 1 (sPD-1) (129). Circulating endothelial progenitor cells (EPCs) are associated with the repair of alveolar damage and are increased in RA-ILD compared to RA patients without lung involvement. However, their levels are lower in comparison to patients with IPF (130). While we acknowledge that observed differences refer to tests performed only for research purposes (67, 131), it should also be noted that non-coding RNAs (132, 133) and metabolomic profiling (134) have also been proposed with promising preliminary results.

Biomarkers in RA-ILD: Unmet needs and research questions

Except for traditional RA autoantibodies (i.e., RF and ACPA), no biomarker is currently used in clinical practice for the screening of RA-ILD, thus, further studies are required. First, it is of critical importance to individuate at baseline (or as early as possible) which patients with RA are at high risk of developing ILD. Second, once RA-ILD is established, there is a need to understand which subjects are likely to develop clinically significant disease or are going to require specific therapies (even in the presence of subclinical disease). Third, since fibrosis and PPF are major concerns in the management of RA-ILD, biomarkers are required for early identification of patients at risk of developing progressive fibrosing ILD. Fourth, there is an urgent need to understand whether antifibrotic therapy can be started only when PPF has established or, vice versa, whether there is any benefit from starting such therapy in patients 'at high risk of PPF'. Fifth, since 'ILD' does not always mean 'fibrosis', biomarkers could help in discriminating different 'treatable traits' when clinical worsening occurs (e.g., progressive fibrosis versus inflammation versus superimposed infection, etc.). Sixth, predictive biomarkers that inform us of therapeutic effects are warranted.

Imaging in RA-ILD

To date, there are neither consensus statements or guidelines / recommendations on radiologic screening and follow-up of

pulmonary involvement in RA, despite HRCT remaining the preferred tool for the identification of lung involvement in RA with a better sensitivity compared to chest X ray at early stages (135). Of importance, HRCT allows to discriminate between inflammatory and fibrotic lesions (136) with prognostic implications (33).

Preclinical thoracic findings

Lung involvement may predate the onset of RA, particularly with ancillary signs suggesting rheumatic involvement including RA-ILD, pleural effusion, pleuritis, bronchiectasis, rheumatoid nodules, pulmonary vascular diseases, and drug-associated lung complications (137).

ILAs, incidental findings involving at least 5% of lung parenchyma at HRCT in individuals in which ILD in not suspected (38) can be the first detectable sign both in patients with early and longstanding RA (138), with the latter having more frequent HRCT abnormalities (139). Gabbay et al. (140) detected ILAs in 44% of RA cases screened for lung involvement while others found HRCT abnormalities in nearly 50% of the patients with no respiratory symptoms. Factors significantly associated with HRCT abnormalities were age older than 40 years, positive tests for IgM-RF, hypoxia at rest, and lung function test evidence of distal airway disease (141). A lower incidence (22%) has been reported in a retrospective study of 293 patients with RA undergoing HRCT; 29% of these manifested progression over 4.4 years, particularly with subpleural distribution and higher baseline ILA extent. HRCT scans were performed for non-pulmonary indications in 46% patients, and ILAs were detected in a considerable proportion (44%) of these subjects. This supports the hypothesis that pulmonary involvement in RA is largely underdiagnosed (142). A 57% progression rate in ILAs has been described in a different study, largely related to past cigarette smoking (143).

ILD patterns at imaging

In patients with RA, UIP is the most common pattern at presentation, followed by NSIP while other types of ILD, i.e., organizing pneumonia (OP), desquamative interstitial pneumonia (DIP) and lymphocytic interstitial pneumonia (LIP), are found less frequently (144, 145). Typical UIP pattern is characterized by heterogenous honeycombing of the pulmonary bases and periphery, peripheral basilar predominant reticular abnormalities, and architectural distortions. However, the presence of anterior upper lobe honeycombing sign, where honeycombing is distributed both in the anterior upper lobes as well as in pulmonary bases, or the presence of exuberant honeycombing sign, where honeycombing is hypertrophic and distributed across multiple layers, are frequently associated with RD-ILDs, including RA-ILD (146, 147). The UIP pattern has been associated with an increased mortality in RA-ILD in different studies (137, 148–150) while Yunt et al. did not report any difference in survival between subjects with definite UIP versus those with possible UIP (137). A recent meta-analysis confirmed that UIP pattern at HRCT, presence of emphysema, and both the occurrence and number of acute exacerbations were associated with increased mortality in RA-ILD (151). Different from UIP, the NSIP pattern is characterized by ground-glass opacities (GGO), fine reticulation or traction bronchiectasis within GGO, and airspace consolidation while honeycombing is rarely present (152). Patients with NSIP develop pulmonary involvement at younger age and longer after RA diagnosis compared to the UIP pattern (153). However, they seem to respond better to immunosuppressive treatment (154, 155) and have a longer duration of articular manifestations and a lower risk of disease progression (155). In terms of natural history, RA-ILD may lead to progressive fibrosis, particularly with UIP (42, 156–159) or a widespread fibrosis (148, 160) with intercurrent acute exacerbations, with over 40% of patients fulfilling the criteria for PPF (161). It has been observed that the UIP pattern at HRCT (9, 10) is *per se* associated to an increased risk of acute exacerbation of pulmonary fibrosis, including fibrotic RA-ILD (162).

While there is no consensus or guidelines on the use and evaluation of HRCT to detect disease progression, visual evaluation is not an ideal tool to estimate the percentage of lung volume containing fibrotic features (40). Despite the absence of universal methods, the quantitative assessment (computer-based quantitative HRCT) of lung fibrosis and progression is a more objective and reproducible method (163, 164), as represented by the MeVis PULMO 3D system using the threshold value of -800HU correlating with both human observers and physiological impairment (165). A different automated quantification system includes the evaluation of lung fibrosis (as the sum of reticulation and traction bronchiectasis) and ILD (as the sum of lung fibrosis, honeycombing, and GGO) scores with a good performance in predicting prognosis in 144 patients with RA-ILD (166). Jacob et al. combined two visual staging systems in a cohort of RA-ILD patients, reaching good prognostic stratification, thus being able to identify a subpopulation of patients with progression characteristics similar to IPF (167).

Lung ultrasonography

Lung ultrasonography (LUS) is emerging as a novel diagnostic approach for ILD (168), with the main pathologic findings being alterations in the pleural line and appearance of vertical artifacts called "B lines." The former lesion is defined by the pleural line becoming irregular and thickened and may appear blurred and fragmented while B lines are vertical hyperechoic laser beam-like artifacts that arise from the pleural line and extend to the end of the screen without fading, erasing A lines, and moving synchronously with the pleural sliding until defining the "interstitial syndrome" (169–171). Several protocols have been proposed for LUS but there is no consensus or guidelines about the ideal examination protocol for ILD. According to different studies, LUS are able to screen for ILD in RA patients with a good sensitivity and specificity (100, 172–176) and Cogliati et al. reported that LUS is a reliable screening tool not only if performed by a trained physician using a standard 72 lines protocol but also if performed by a short-trained physician using a pocket-size lung ultrasound device (173). The presence of B lines has a sensitivity and a specificity, respectively, of 92% and 56% for RA-ILD when LUS is compared to HRCT and this is only slightly reduced (89 and 50%) when an ultrasound pocket device is used and 8 rather than 72 zones are explored (173). Results from a meta-analysis on the use of LUS diagnostic studies on RD-ILD, including RA-ILD, reaffirms the high sensitivity and specificity of LUS. Moreover, of six examined scanning protocols, a simplified method scanning only 14 lung intercostal

spaces showed very high sensitivity and specificity with a short scanning time (177).

The combination of LUS with serum KL-6 demonstrated to increase the correlation with HRCT and disease severity in 150 RA cases with serum KL-6 positively correlating with LUS score and HRCT. Cut-off values of KL-6 and LUS score were 277.5 U/ml and < 5.5, with sensitivity 86.7 and 100%, and specificity 88 and 100%, respectively (100), thus confirming data from a retrospective study on patients with ILD and rheumatic diseases, including RA (178). LUS may be helpful also in the longitudinal follow-up of patients on treatment, as suggested by one case report (179).

Lung function tests in RA-ILD

To date, there are no consensus statements nor guidelines/recommendations on functional screening and follow-up of RA-ILD. However, lung function tests are a reliable and easily accessible tool to detect lung involvement, staging disease severity, and monitor for disease progression.

Due to the systemic manifestations of RA, that can lead to musculoskeletal limitation and major exercise intolerance, lung function tests seem to be a better screening tool compared to clinical evaluation alone. Topcu et al. highlighted that symptom-related patient-reported outcome measures could be used to evaluate health-related quality of life in RA-ILD. However, they may not be very helpful in differentiating 'ILD' from 'non-ILD' causes in patients complaining respiratory symptoms, such as cough or dyspnea (180). On the other hand, concomitant comorbidities and complications due to the systemic disease involvement can represent confounding factors when assessing ILD severity (181).

RA-ILD is typically associated with a restrictive pattern with reduced carbon monoxide diffusing capacity (DLCO) on lung function tests. However, patients with RA can also develop obstructive lung disease, even in association with ILD (182).

Lung function tests can also help predicting the progression of RA-ILD. Lower forced vital capacity (FVC) and DLCO, as well as their decline over a 6-month period are associated to severe disease (159). Also, higher levels of DLCO have been associated with a better prognosis in an observational cohort (160), while DLCO ≤54% predicted has been identified as a cut-off with good sensitivity and specificity to individuate high risk of RA-ILD progression (183).

In another study enrolling 140 RA-ILD patients, most subjects experienced stable or slowly declining lung function. In 5% cases, however, rapid FVC (expressed as % predicted) deterioration was observed, especially in older adults (age > 70 years) with early diagnosis of RA. To note, the lung function trajectory did not go in parallel with RA disease activity (184).

Most RA patients are studied for lung involvement only when suggestive symptoms occur, and pulmonary disease has already evolved. However, since ILA and early ILD are present in asymptomatic patients, in our opinion it is reasonable to screen all subjects with a new diagnosis of RA with lung function tests and thoracic physical examination, looking for velcro-like crackles. Moreover, lung function monitoring and physical examination should be repeated at least once a year during follow-up; prompt radiological evaluation should be obtained in case of impaired baseline lung function tests, abnormal thoracic physical examination, or lung function decline according to recent guidelines on progressive fibrosing ILD (40).

The current clinical practice in the management of RA-ILD

There are significant gaps in the physician knowledge regarding RA-ILD and this is well represented by the underestimated prevalence of ILD in patients with RA (185). Despite the significant burden of RA-ILD, there are no established recommendations for the management of this condition. It is disconcerting that ILD is not mentioned in the latest 2022 European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of RA (186) while the 2021 American College of Rheumatology (ACR) guidelines only advise to pay attention on the role of methotrexate (MTX) in patients with a previous diagnosis of lung or airway disease without addressing ILD (187). At a local level, ILD was included in the Taiwan Society of Rheumatology recommendations for the management of comorbidities and extra-articular manifestations of RA (188), and in the Spanish Societies of Rheumatology (SER), Pneumology and Thoracic Surgery (SEPAR) guidelines for the management of RA-ILD (189, 190). In the aforementioned documents, there is general accordance against the use of MTX and leflunomide (LEF), in favor of rituximab or abatacept (188, 189), despite a recent meta-analysis found that MTX is not associated with the risk of ILD in RA (191). Remarkably, both guidelines are characterized by low quality of evidence. No recommendations or guidelines from international respiratory societies have been specifically directed towards the management of RA-ILD.

The optimal treatment choices and timing for RA-ILD have not been established and limited evidence is currently available. No RCT has investigated the role of immunosuppressants in the treatment of RA-ILD. Despite the lack of evidence, glucocorticoids are often used, and seem to be effective especially in case of NSIP and OP patterns on HRCT (192, 193). Evidence supporting the use of immunosuppressive drugs is mainly derived from large studies investigating ILD associated to systemic sclerosis (194, 195); also, in contrast to IPF, immunosuppressive therapy is safe in patients with RA-ILD also when a UIP pattern is observed (196). Cyclophosphamide (197) and mycophenolate (198) have been used with varying success, despite information on RA-ILD has been often extrapolated from studies investigating heterogeneous populations of patients with ILD associated to different rheumatic diseases (199). In a retrospective study, treatment with either azathioprine, mycophenolate or rituximab was associated with improved pulmonary function at 12 months with no difference among the treatment regimens (200), while in another retrospective study rituximab has shown some efficacy in RA-ILD patients with progressive ILD despite treatment with glucocorticoids and conventional synthetic DMARDs or immunosuppressants (201) Further evidence is required to support the use of specific immunosuppressive drugs in RA-ILD, and a precision medicine approach is warranted to target specific disease pheno- and endotypes.

Concern has been raised towards the use of anti-TNF therapy in patients with RA-ILD, since cases of disease progression and safety issues have been reported but the clinical relevance and prevalence of these observations require further data-based confirmation (202). Biologic DMARDs with targets other than TNF-alpha appear to

be associated with slower rate of progression of lung disease, whereas anti-TNF therapy does not correlate with a risk of ILD worsening (203). Despite the promising role of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in patients with ILD secondary to systemic sclerosis (204), further evidence is required concerning RA. Tocilizumab has demonstrated potential efficacy in maintaining lung function with a good safety profile, in a retrospective cohort of patients with RA-ILD (205). Evidence from a large retrospective registry might encourage the use of rituximab in patients with RA-ILD (206). The RECITAL trial has demonstrated efficacy and safety of rituximab in patients with connective tissue disease-associated ILD, but the study did not include RA-ILD (207). A possible role for Janus kinase (JAK)-inhibitors has been suggested from animal models of ILD associated with arthritis (208) as the JAK2 isoform specifically mediates TGF-beta signaling and the activation of myofibroblasts, and has been advocated in the molecular pathophysiology of RA-ILD (209, 210). However, due to the lack of solid evidence, the use of JAK-inhibitors cannot be encouraged for the treatment of RA-ILD (211, 212). Abatacept has shown promising results in different clinical studies (213–216); the results of the APRIL trial (NCT03084419) which is evaluating change in lung function at 24 weeks in RA-ILD patients treated with abatacept, are still expected. Iguratimod, a novel synthetic DMARD approved in Japan and China, prevents nuclear factor kappa B (NF-kB) migration into the cellular nucleus, thus impairing the transcription of proinflammatory genes and blocking the inflammatory response (217). Iguratimod has been evaluated in a study on 101 RA-ILD patients showing reduction of general inflammation, disease activity, and improvement in lung function (218).

With regard for antifibrotic molecules, these include nintedanib and pirfenidone but only the former is suggested as a therapeutic option in patients with RA ILD who meet the criteria for PPF according to ATS/ERS/JRS/ALAT Guidelines (40). In fact, the INBUILD trial demonstrated the efficacy and safety of nintedanib in patients with PPF other than IPF and significantly reduced the lung function decline at 52 weeks (219); a *post hoc* analysis found significant results in patients with autoimmune disease-related PPF without a specific analysis for RA-ILD (220).

On the other hand, pirfenidone did not achieve the same results and the TRAIL study (NCT02808871), a RCT enrolling patients with RA-ILD to compare pirfenidone to placebo, has been stopped early due to slow recruitment during the COVID-19 pandemic. However, preliminary results seem to suggest the efficacy of pirfenidone in slowing the rate of decline of FVC over time in patients with RA-ILD, although caution in interpreting results is necessary since the study was unpowered (221).

Regarding AE of RA-ILD, no consensus or management guidelines have been published, and, notably, diagnostic criteria are derived from AE in IPF (7). Few retrospective studies have analyzed AE in different RD-ILD (222) and RA-ILD alone (10, 11, 223, 224). In most cases, patients were treated with high doses steroids and best supportive care. One retrospective study failed to demonstrate benefits in term of survival from the use of cyclophosphamide in AE of RA-ILD (223). On the other hand, Ota et al. retrospectively found that the use of high doses of steroids and immunosuppressants (including cyclophosphamide, tacrolimus and cyclosporine) could improve the prognosis in AE of RA-ILD (224). Further studies are necessary to better understand pathologic mechanisms behind AEs in RA-ILD and improve management and prognosis of this severe complication.

Table 3 reports all ongoing RCTs on RA-ILD obtained from a systematic research of different registry trials ([1]ISRCTN registry and EU clinical trials register) on RA-ILD patients or trials on RA patients evaluating ILD among secondary outcomes. Unfortunately, these are based on variable encoded approaches for the diagnosis and management of RA-ILD and underlines the gaps in a uniform approach to this condition.

The management of RA-ILD patients should be not only based on the treatment of ILD itself, but should also address the clinical consequences and comorbidities of RA. With regard to obstructive lung disease, there are no specific guidelines targeting the management in RA patients, and the impact still remains largely unexplored (46). However, smoking cessation programs should be proposed to all patients to reduce risk of death and improve quality of life (225). Patients should be screened for obstructive lung disease and treated accordingly to the current guidelines. The use of conventional DMARDs has been explored both in asthma and in COPD cohorts, and methotrexate may exert a modest steroid-sparing effect (46). As both bronchiectasis (46) and ILD (51, 52) can be associated with an increased risk of lower tract respiratory infections, a multidisciplinary approach including pulmonologists and rheumatologists is warranted for all patients, in order to evaluate the best pharmacologic interventions and reduce the risk of infections (46, 51, 52). Moreover, microbiological sampling should be considered in case of infection, particularly pneumonia, and DMARDs should be suspended and recommenced only once the antibiotic therapy is completed and clinical symptoms have resolved (226). Pneumococcal and annual Influenza vaccinations should be offered to all patients with RA, regardless of the treatment (226, 227), along with SARS-CoV-2 immunization (228, 229). Finally, since treatment with anti-TNF therapy is associated with an increased risk of developing TB, screening and treatment for latent TB should be proposed to all RA patients (226).

Pulmonary hypertension secondary to ILD has been associated to reduced exercise capacity, increased need for supplemental oxygen, worse quality of life and prognosis (230–232). Screening for pulmonary hypertension should be performed in all RA-ILD patients although no recommendation on timing and frequency is available (233). Recently, the INCREASE trial (234) has shown significant improvements in exercise capacity in ILD patients with PH treated with inhaled treprostinil. Clinical worsening also occurred less frequently in the treprostinil group, compared with placebo. The trial also included RD-ILD patients, but subgroup analysis has not been performed, and targeted clinical trials are warranted to confirm these results in specific populations, as is the case of RA-ILD patients. Since subjects with RA-ILD are at higher risk of developing malignancy and in particular lung neoplasms (22, 24), cancer screening should be systematically performed; however, there is no clear indication regarding timing and frequency (24).

In addition to clinical comorbidities, several relevant treatable traits have been identified in ILD and should be addressed in RA-ILD (235), including dyspnea, exercise-induced hypoxemia, and exercise intolerance. In RA-ILD patients, these conditions can be worsened by musculoskeletal involvement due to RA itself. Referral to pulmonary rehabilitation should be considered as an important component of comprehensive patient care (236). On the other hand, in case of end

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TABLE 3 Ongoing randomized clinical trials targeting or including RA-ILD patients.

NCT	Study type	Inclusion criteria	Intervention	Recruiting	Primary outcomes	Secondary outcomes
NCT05246293	Interventional Phase II Open Label Enrolment: 60	- ACR/EULAR 2010 RA classification criteria. - ILD (NSIP, UIP, LIP, OP) at HRCT or a surgical lung biopsy. - 18 years of age or older. - LTBI or TB excluded - Patients must discontinue using the non-permitted medications*	Tofacinib 5 mg BID for 12 months	Yes	AEs [Time frame 52 weeks]	FVC (L) DLCO (mil/min/mmHg) 6MWT Rheumatoid arthritis disease activity according to the SDAI and DAS28
NCT04311567	Interventional Phase IV Single blind (Outcomes Assessor) Enrolment: 48	- Diagnosis of RA according to the ACR/EULAR 2010 criteria within 24 months. - No previous treatment with DMARDs. History of PDN use is allowed but should have been discontinued 2 weeks before baseline measurement. - Active disease with ≥2 painful and ≥ 2 swollen joints in 66/68 joints and CRP ≥2.0 mg/l - Aged 18–80 years	Tofacinib 5 mg BID for 48 weeks vs. Methotrexate 20 mg once weekly for 48 weeks	Yes	Total IDL score of pulmonary abnormalities by HRCT [Time frame 24 weeks]	Extent of ILD pattern by HRCT FVC DLCO 6MWD SpO2 after 6MWT Patient reported outcome of breathing and airway symptoms DAS28-CRP HAQ index DAS remission AEs Patient reported global disease activity Proportion of patients in RA ACR-EULAR Boolean remission CDAI
NCT03084419	Interventional Phase II Open Label Enrolment: 30	- Aged 18 years or over - Diagnosis of RA by 2010 EULAR/ACR criteria - RA-ILD - PF over 14 months**	Abatacept infusions 10 mg/kg fortnightly for the first 4 weeks, then every 4 weeks for a total of 20 weeks	No	FVC [Time frame 28 weeks]	DLCO mMRC K-BILD Semi-quantitative radiological scoring of the ILD SpO2 DAS28 LCQ EQ-5D Respiratory tract infection
NCT03798028	Interventional Single blind (Participant) Enrolment: 250	- 2010 ACR/EULAR classification criteria or the 1987 ACR classification criteria. - Age 18 to 70 years old. - DAS 28 ≥ 3.2 - SDAI>11.0 - CDAI >10.0 - HGB < 90 g/l and/or ILD at HRCT. - Poor response to current treatment.***	UC-MSCs intravenous injection at the dose of 1 × 10^6 cells/kg (single dose) vs. Placebo	No	Blood routine HGB FVC and/or DLCO [Time frame 24 weeks]	Remission rates of ACR 20–50-70 WBC and PLT count FVC DLCO HRCT 6MWD

(Continued)

TABLE 3 (Continued)

NCT	Study type	Inclusion criteria	Intervention	Recruiting	Primary outcomes	Secondary outcomes
NCT04928586	Interventional Phase 4 Open Label Enrolment: 200	Aged 18–80 years. In accordance with the diagnostic criteria of CTD-ILD****	DMARDs + Pirfenidone up to the maximum tolerable dose vs. DMARDs	Yes	FVC DLCO [Time frame 12 months]	FVC, DLCO, 6MWD Dyspnea score HRCT CRP, ESR VAS score AEs
NCT05505409	Interventional Phase IV Open Label Enrolment: 120	- Age ≥ 18 years - CTD diagnostic criteria (RA, IIM, SSc) and UCTD/IPAF classification criteria. - HRCT diagnosis confirmed ILD with corresponding clinical manifestations. - Nonresponding or progressive ILD § - Stable dose of concomitant therapy for at least 4 weeks before the baseline period.	Pirfenidone up to the maximum tolerable dose + glucocorticoid + immunosuppressant vs. Glucocorticoid + immunosuppressant	Yes	FVC [Time frame 6 months]	FEV1%, DLCO%, TLC% PFS 6MWD SpO2 HRCT SGRQ mMRC dyspnea score Clinical deterioration CRP, ERS Inflammatory factors and indicators Primary disease activity AE and SAE FVC% area under the curve Predicators of pirfenidone response in each disease subgroup
NCT00578565	Interventional Phase III Triple blind Enrolment: 123	- Diagnosis of RA according to the revised 1987 American Rheumatism Association criteria - PF (UIP or NSIP subtype) §§ - No change of DMARD treatment within the last 3 months	Rituximab 1,000 mg infusion on each day 1 and 15 with repeat dosing at 6 months.	No	DLCO FVC [Time frame 48 weeks]	Lung Fibrosis Score at HRCT DAS28 Health Associated Quality of Life
NCT02990286	Interventional Phase III Quadruple blind Enrolment: 122	- Age ≥ 18 years - A diagnosis of ILD and NSIP - Patients who did not respond or relapsed or were not able to continue at least one first-line immunosuppressive treatment of ILD ##	Rituximab 1,000 mg infusion (day 1), and 1,000 mg (day 15) + MMF 2 grams daily for 6 months vs. Placebo infusion (day 1 and 15) + MMF 2 grams daily for 6 months	No	FVC% [Time frame 6 months]	PFS Quality of life VAS Cough FVC, DLCO, 6MWT Cumulative doses of corticoids Autoantibodies concentration Biological markers related to lymphocyte B depletion HRCT AE

*Leflunomide, azathioprine, cyclosporine, tacrolimus, cyclophosphamide, and any biologic disease-modifying drug (bDMDARDs) such as anti-TNF therapy, rituximab, tocilizumab, etc. Patients must have a stable prednisone dose of ≤10 mg/PO/day for at least three months. All patients must have stable doses of prednisone during the last three months of follow-up, and the prednisone dose must be ≤10 mg/day. Patients without a prednisone history in the previous three months may also be included in the protocol.

**Progression will be defined as EITHER: a decrease in FVC by at least 5% when comparing two sets of PFTs done in the last 24 months, but with an interval of up to 14 months between the PFTs OR progression of lung fibrosis on a high-resolution CT chest, as reported by a chest radiologist.

***The current treatment refers to receive the medicines (including Leflunomide, Methotrexate, Sulfasalazine, Hydroxychloroquine, Cyclosporine A, and Tacrolimus, alone or in combination for 3 months, and maintain the stable dose of drugs for at least 1 month). More than 3 months and a stable dose for at least 1 month are required if glucocorticoid is used. The dose of glucocorticoid is less than or equal to10mg/day of prednisone.

****The diagnosis of CTD is in line with the international classification standard of rheumatism (including inflammatory myopathy, systemic sclerosis, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, mixed connective tissue disease, undifferentiated connective tissue disease).

(Continued)

TABLE 3 (Continued)

§ Patients with clinical deterioration more than 1 month after diagnosis of ILD history, or poor response or intolerance to glucocorticoids or immunosuppressants treatment, or poor response or intolerance to other antifibrotic drugs (acetyl hemitrine, nidanib, etc.), or effective use of pirfenidone, and exacerbation of clinical symptoms or ILD indicators more than 3 months after withdrawal of the drug. Poor response was defined as no improvement in one of the following:
(1) Symptoms of dyspnea such as cough, chest tightness, breathlessness, shortness of breath after activity, or decreased activity endurance.
(2) the worst decrease in oxygen saturation as measured by SpO2 observed during 6MWD.
(3) There was no improvement in pulmonary ventilation (FVC%) or lung dispersion (DLCO%).
(4) HRCT findings: new onset, fibrosis tendency or density of ILD lesions were not decreased.
Clinical deterioration was defined as meeting one of three criteria:
Clinical deterioration or dyspnea within 4 weeks.
New or worsening radiological abnormalities on chest X-ray or HRCT.

Objective deterioration of pulmonary function tests or gas exchange, defined as meeting at least one of the following criteria:
(1) Start long-term oxygen therapy or increase oxygen supplementation by at least 1 l/min to maintain resting oxygen saturation of at least 90%.
(2) FVC decreased by more than 5% compared with the previously measured value; Or a decrease in DLCO of more than 10% from previous measurements; Or a 20% decrease in 6MWD from previous measurements.
§§ Clinical symptoms consistent with ILD with onset between 3 months and 36 months prior to screening.
Worsening as demonstrated by any one of the following within the past year: (1) > 10% decrease in FVC; (2) increasing infiltrates on chest X-ray or HRCT, or worsening dyspnea at rest or on exertion.
Diagnosis of UIP or NSIP by either of the following: (1) Open or VATS lung biopsy showing definite or probable UIP or NSIP; (2) HRCT scan showing definite or probable UIP or NSIP AND abnormal pulmonary function tests (reduced FVC or decreased DLCO or impaired gas exchange at rest or with exercise) AND insidious onset of otherwise unexplained dyspnea or exertion and bibasilar, inspiratory crackles on auscultation.
FVC > 50% of predicted value at Screening.
DLCO >30% of predicted value at Screening.
A diagnosis of ILD (1) ILD associated with differentiated CTD or IPAF (based on internationally accepted criteria) (2) OR idiopathic ILD.
A diagnosis of NSIP based on: (1) a histological pattern of NSIP (2) OR HRCT findings suggestive of NSIP defined as basal predominant reticular abnormalities with traction bronchiectasis, peri-bronchovascular extension and subpleural sparing, frequently associated with ground-glass attenuation.
##: corticosteroids, azathioprine, cyclophosphamide or other immunosuppressants. For the assessment of clinical response, the absence of response was defined as: either a decrease or an increase, but <10% in % predicted FVC.
ACR/EULAR, American College of Rheumatology / European League Against Rheumatism; RA, rheumatoid arthritis; ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia; LIP, lymphocytic interstitial pneumonia; OP, organizing pneumonia; HRCT, high resolution computed tomography; LTBI, latent tuberculosis infection; TB, tuberculosis (active disease); AE, adverse event; SAE, severe adverse event; FVC, forced vital capacity; 6MWT, 6 minute walking test; SDAI, simplified disease activity index; DAS28, Disease Activity Score Index; DMARDs, disease modifying anti-rheumatic drugs; PDN, prednisone; CRP C, reactive protein; BID, bis in die; SpO2, blood oxygen saturation; 6MWD, 6 minute walking distance; DLCO, diffusion capacity for carbon monoxide; HAQ, index health assessment of physical function index; PF, progressive fibrosis; mMRC, modified Medical Research Council dyspnea scale; K-BILD, Kings Brief Interstitial Lung Disease score; LCQ, Leicester Cough Questionnaire score; EQ-5D, Euro Quality of life 5 dimension; CDAI, Clinical Disease Activity Index; HGB, Hemoglobin; UC-MSCs, human umbilical cord blood mesenchymal stem cells; ACR 20–50-70, American College of Rheumatology 20–50-70; WBC, White blood cell; PLT, platelet; CTD-ILD, connective tissue disease interstitial lung disease; ERS, Erythrocyte Sedimentation Rate; VAS, visual analogic scales; IIM, idiopathic inflammatory myositis; SSc, systemic sclerosis; UCTD, Undifferentiated Connective Tissue Disease; IPAF, interstitial pneumonia with autoimmune features; SGRQ, St. George's Respiratory Questionnaire; FEV1, forced Expiratory Volume in the 1st second; VATS, video-assisted thoracic surgery; MMF, Mycophenolate Mofetil; PFS, progression free survival,

stage disease, a palliative approach is preferable to reduce the burden of symptoms and improve the quality of life (237). Finally, lung transplantation could be considered in selected patients with RA-ILD; no significant differences have been described in terms of survival, acute and chronic rejection, or extrapulmonary organ dysfunction compared to IPF (238, 239). Thus, lung transplant could offer a chance to improve the quality of life in the appropriate patients' subsets (239).

Conclusion

Available data on RA-ILD epidemiology remain unconclusive and heterogeneous for both clinical and research purposes and significant more research efforts are required to finely define incidence, prevalence, and mortality of ILD in the RA population. In particular, one priority is the harmonization of the detection methods since HRCT is the gold standard technique for the diagnosis of ILD. Second, it is essential to define which patients with RA are at increased risk of ILD and, thus, deserve early radiologic investigations as delayed diagnosis is associated with increased mortalityss. Third, the timing, frequency, and the potential role of alternative screening methods, such as lung function tests, serum biomarkers and LUS, also need to be determined (26), likely with the use of biomarkers, including both autoantibodies and non-autoimmune biomarkers. Fourth, the proportion of patients with radiologic ILD who will progress to clinically overt disease is unknown, as is the proportion of patients with radiologic ILD who might benefit from early treatment. Ultimately, efforts are required to imbricate clinical, biological, radiological, and functional risk factors to find reproducible prediction models to estimate the risk and prognosis of ILD in the RA population and to stratify patients with RA-ILD at risk of developing PPF.

Author contributions

AS, AT, and GB: review of relevant papers and manuscript preparation. 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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Myositis interstitial lung disease and autoantibodies

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The aim of this review is to examine and evaluate published literature associated with idiopathic inflammatory myopathies (IIM) and interstitial lung disease (ILD) based on myositis specific autoantibodies (MSA) and the potential clinical significance of each autoantibody subtype for the practicing clinician. The review is a comprehensive search of literature published in PubMed from the year 2005 and onward coinciding with the surge in the discovery of new MSAs. Additionally, we comment on recommended multidisciplinary longitudinal care practices for patients with IIM-ILD with regard to imaging and other testing. Treatment is not covered in this review.

KEYWORDS

myositis, interstitial lung disease, myositis specific autoantibodies, pulmonary fibrosis, narrative review

Introduction

Idiopathic inflammatory myopathies (IIM) are a diverse group of autoimmune inflammatory conditions with multi-organ system involvement. Historically, our understanding of IIM was limited to two broad classifications, dermatomyositis (DM) and polymyositis (PM). The spectrum of IIM has further evolved since the discovery of myositis specific auto-antibodies, yielding new subsets of IIM with distinct clinical, histopathological, and radiologic features aiding in our understanding of the various clinical phenotypes of disease and helping prognosticate organ involvement. Currently, IIM is broadly delineated into dermatomyositis, immune mediated necrotizing myopathy, inclusion body myositis, and overlap syndrome which are further subcategorized on the basis of individual myositis specific autoantibodies. Although they are termed myopathies (often interchangeable with the term "myositis"), they present with varying clinical manifestations. Extra-muscular involvement, including the lungs, skin, joints, and the gastrointestinal tract are among a few organs involved, exemplifying the systemic nature of the disease. Lung involvement can be catastrophic and may lead to mortality. Interstitial Lung Disease (ILD) has been associated with IIM, but it is also recognized that while associated with myositis-specific autoantibodies ILD may be the predominant or sole phenotypic element of the syndrome, with little to no myopathic symptoms present.

Idiopathic inflammatory myopathies are rare diseases that have an extensive range of estimates in determining the incidence and prevalence of IIM whether within the United States and/or worldwide. The determination of incidence and prevalence is multifactorial and may depend on the presentation of patients to specialty centers for accurate diagnosis and continuous monitoring as well as accurate reporting of these diagnoses *via* diagnostic International Classification of Diseases (ICD) codes, which may pose as a challenge with the discovery of new subgroups of IIM and new clinical classifications. As a comparison, Furst et al. determined the adjusted annual incidence of IIM to be 5.8–7.9 per 100,000 person-years, and prevalence ranged from 14 to 17.4 per 100,000 in the United States from the years 2003–2008. Furst et al.

(1) A Swedish study surveying its national registrar estimated the incidence of IIM to be 11 per 1,000,000 person years and prevalence of IIM to be 14 per 100,000. Svensson et al. (2) A Korean population study estimated the incidence of IIM to be 2.9–5.2 per 1,000,000 person-years and prevalence of IIM to be 2.3–4 per 100,000. Cho et al. (3) The above data exemplifies the vast incidence and prevalence rates of IIM and while we were unable to find recently evaluated rates for global incidence and prevalence of IIM, we suspect that national rates may be underestimations of the true incidence and prevalence of disease given the challenging nature of disease presentation, especially when IIM may manifest with extramuscular manifestations of the disease. The global incidence and prevalence of interstitial lung diseases was recently investigated by Kaul et al. in 2022 and they found that the estimated global incidence of ILD ranged from 1 to 31.5 per 100,000 person-years and prevalence ranged from 6.3 to 71 per 100,000 people (4) whereas the global prevalence of ILD-IIM has risen significantly from an estimated 5% in 1974 (5) to 41% (6) of ILD cases as reported in a meta-analysis examining patients over a course of 20 years (7).

IIMs, particularly dermatomyositis, immune mediated necrotizing myopathy, and overlap syndromes are more prevalent in women whereas inclusion body myositis is seen more commonly in men (2, 8–11). A United States cohort assessment found an increasing incidence of IIM occurring in the fifth and sixth decades of life (1).

The clinical manifestations of IIM are heterogeneous and can present with acute, subacute, or chronic symptoms. Typically, myopathic symptoms such as complaints of symmetrical proximal muscle weakness usually evoke clinicians to suspect IIM, however, the initial presentations of IIM can be clinically amyopathic. Accompanying signs and symptoms may vary between the inflammatory myopathy subtypes, such as the presence of dermatological signs and symptoms in dermatomyositis which may include a heliotrope rash, gottron papules, V-sign rash, lateral thigh or holster rash, mechanic's hands, alopecia, and calcinosis; presence of dysphagia in immune mediated necrotizing myopathy and inclusion body myositis, or presence of subtle findings such as atrophy of wrist and finger flexors in inclusion body myositis (12).

The extramuscular manifestations and multi-system organ involvement are particularly important for a practicing clinician to remain cognizant of, as IIM can involve the cardiovascular system, gastrointestinal system, skeletal system, and pulmonary system of which interstitial lung disease is a common manifestation. The signs and symptoms of ILD may present with cough, dyspnea, exercise intolerance, digital clubbing, and signs of pulmonary hypertension such as an accentuated closure of the pulmonic valve on cardiac valve auscultation (13). In IIM-ILD, pulmonary involvement may present in tandem to or subsequently after the myocutaneous manifestations of disease, however, it is of importance to note that pulmonary involvement may be the leading presentation of disease without concomitant myopathic or cutaneous manifestations, therefore, necessitating a high index of suspicion for underlying rheumatologic processes when evaluating ILD as a sole presenting manifestation (14, 15).

Diagnostic evaluation of IIM-ILD entails clinical suspicion from patient history and physical examination in combination with serologic testing (of which negative serologies may not exclude disease), radiologic testing, invasive testing through tissue biopsy, and multidisciplinary evaluations to rule out other conditions. We discuss and comment on individual diagnostic evaluations of IIM-ILD by individual myositis specific auto-antibodies in this review.

Management of IIM-ILD is particularly challenging for patients and clinicians due to the varying clinical presentations of disease and the potential of multi-systemic organ involvement coupled with a paucity of standard treatment regimens which generates variable treatment practices among providers. Additionally, most treatment guidance is from retrospective cohort studies, while only a few randomized controlled studies exist (16). The initial treatment approach usually begins with glucocorticoids, which may or may not help patients in attaining functional improvement, and the chronic use of glucocorticoids is also limited due to its adverse effects and long term complications. The data supporting glucocorticoid use is variable and is mostly based on historical precedent with scant prospective evidence supporting its use (16–18). Subsequent therapy options include immunosuppressive therapy and biologic agents, salvage therapy, and even intravenous immunoglobulins and plasma exchange, which all have varying levels of clinical evidence and benefit which can vary with specific myositis specific autoantibodies (14).

Overall, the development of ILD in patients with IIM portends a poorer prognosis with an increased risk for mortality; clinical outcomes are variable in part due to the unknown response to treatment in individual patients and in part to varying prognosis among individual myositis specific autoantibodies (16). The presence of certain autoantibodies such as anti-MDA5, anti-Jo-1, and anti-Ro-52 have been associated with an increased risk of mortality. Interestingly, while malignancy has been associated with a poorer prognosis in myositis, patients who develop malignancy are at decreased risk of developing ILD (14, 16).

Methods

This comprehensive review aims to analyze and review literature by searching the electronic medical database Pubmed for the following keywords that were chosen due to their established association with our topic of interest: (12, 15, 19, 20) *idiopathic inflammatory myopathy, dermatomyositis (and individual MSA's: anti-MDA5, anti-NXP2, anti-Mi-2, anti-TIF1γ, anti-SAE), immune mediated necrotizing myopathy (and individual MSA's: anti-HMGCR, anti-SRP), inclusion body myositis, and overlap syndrome (and individual MSA's: anti PM/Scl, anti-Ku, anti-RNP and anti-Ro, anti-synthetase antibodies and its entities)* each in combination with *interstitial lung disease, nonspecific interstitial pneumonia, usual interstitial pneumonia, and organizing pneumonia,* from the year 2005 and onward (Figure 1).

Idiopathic inflammatory myopathy classification

First described in the literature by Wagner and Unverricht as early as 1863, dermatomyositis (DM) and polymyositis (PM) criteria were not established until 1975 by Bohan and Peter (21–24). Their criteria focused on the presence or absence of clinical manifestations of muscle weakness, elevation of serum markers of skeletal muscle enzymes, characteristic findings of myopathy on electromyography, select muscle biopsy findings, and the presence of typical cutaneous changes to categorize IIM into DM or PM based "definite," "probable,"

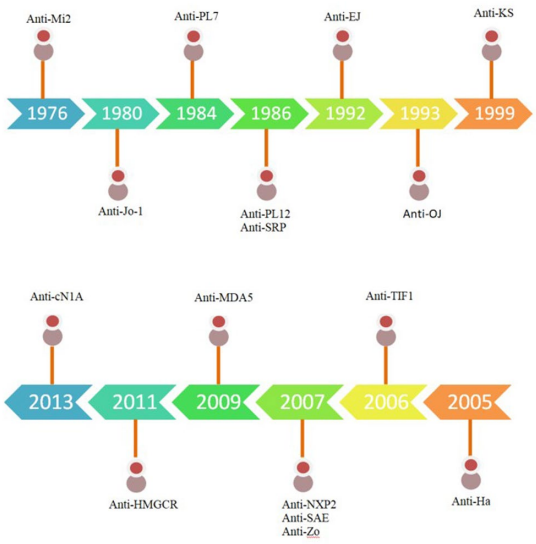

FIGURE 1
Timeline of Myositis specific auto-antibodies. Adapted from Neil J. McHugh and Sarah L. Tansley.

or "possible" diagnoses (23, 24). Over the next few decades, the discovery of myositis specific autoantibodies led to remarkable progress in the understanding of the pathophysiologic processes behind IIM and allowed for the creation of entities and subsets within IIM that better represented individual disease manifestations. Thus, the discovery of myositis specific auto-antibodies ultimately necessitated a reconstruction of the current framework on the approach to IIM and led to the 2017 European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) classification criteria (25). For the scope of this review, we categorize IIM into the following categories: Dermatomyositis (DM), Immune Mediated Necrotizing Myopathy (IMNM), Antisynthetase syndrome (ASynS), and Overlap Myositis (OM). The term "polymyositis" has fallen out of favor recently, with the recognition that this term was often comprised of those with overlap myositis, inclusion body myositis, the antisynthetase syndrome without a rash, or a mimic of myositis, such as muscular dystrophy (26, 27). Thus, polymyositis is not included here. Additionally, inclusion body myositis does not have associated interstitial lung disease and is therefore also not included (14). It must be noted that neither Bohan and Peter nor the ACR/EULAR criteria include pulmonary symptoms as part of the formal classification criteria.

Interstitial lung disease

The reported global prevalence of ILD is likely as high as 41% in patients diagnosed with IIM based on a meta-analysis analyzing 34 studies with a cohort of 10,130 patients over a 20-year period (6). High resolution CT scan (HRCT) is a non-invasive diagnostic modality that is often used to assess pulmonary involvement and is considered the gold standard. Idiopathic interstitial pneumonia can be further classified as idiopathic pulmonary fibrosis which presents with a usual interstitial pneumonia (UIP) pattern or as nonspecific interstitial pneumonia (NSIP) which may mimic interstitial pulmonary fibrosis (28). A diagnosis of UIP can be made with the presence of subpleural or basal honeycombing and by identifying a reticular pattern of fine lines. Additionally, the presence of peripheral traction bronchiectasis represents lung fibrosis and can be used as a prognostic indicator (29). NSIP is the second most common presenting pattern of idiopathic interstitial pneumonia after UIP and can be challenging to distinguish due to features that overlap with UIP patterns, however, the absence of honeycombing, subpleural sparing, and presence of ground glass opacities (GGOs) are more consistent with NSIP (28, 29). A meta-analysis by Ebner et al., determining CT patterns and clinical features to distinguish UIP and NSIP found that in the general population, UIP patterns were more prevalent in elderly male patients with a history of smoking whereas NSIP patterns were seen more often in younger female patients who smoke less often (28). A multi-center retrospective study in 2020 sought to assess organizing pneumonia (OP) patterns based on CT scans in patients with COVID-19 and identified GGOs as the predominant manifestation on imaging followed by variations of mixed abnormalities including GGOs and consolidations with the presence or absence of linear opacities (30).

Up to 25% of patients with symptoms and signs concerning for an autoimmune disease do not meet the classification criteria for connective tissue disease (CTD) as per the American College of Rheumatology, and up to 20% of patients with idiopathic interstitial pneumonias have symptoms and clinical findings suggestive of underlying systemic processes (31). In 2015, the European Respiratory Society/American Thoracic Society developed a task force for "Undifferentiated Forms of CTD-associated ILD" and proposed a research classification of idiopathic pneumonia with autoimmune features (IPAF) to help guide further understanding of these patients (32). The current criteria to diagnose IPAF includes radiological or histopathological evidence of interstitial pneumonia and complete clinical evaluation excluding other etiologies for interstitial pneumonia, and incomplete features of a defined connective tissue disease, in addition to features from a clinical domain, serologic domain, and morphologic domain (32, 33).

There are clear clinical phenotypes with regard to certain MSA's and IIM-ILD manifestations (Figure 2). Similar to previous reviews, our review found all anti-aminoacyl tRNA synthetase (ARS) antibody subtypes and anti-MDA5 antibodies to be associated with an increased risk of ILD relative to other MSA's (34–36). The clinical course of anti-ARS-associated ILD appears to be generally more indolent and chronic with significantly lower rates of rapidly progressive ILD compared to anti-MDA5 (37). Previously, it has been noted that the HRCT pattern most associated with ARS antibodies was NSIP representing approximately two-thirds of cases (35). The patterns on HRCT and restrictive pattern pulmonary function tests (PFTs) are largely consistent across ARS autoantibody subtypes, and non-Jo-1 ARS autoantibodies are associated with later diagnosis, increased pulmonary fibrosis, and worsened prognosis (35).

Additional imaging modalities to screen for ILD include chest x-rays (CXR) and lung ultrasound. CXR is an easily attainable and economical imaging study that has less exposure to ionizing radiation when compared to a HRCT but has an overall decreased sensitivity in detecting ILD in comparison to the HRCT (38). Ultrasound imaging is also easily attainable and equally economical similar to CXR, moreover, it does not pose a risk to ionizing radiation exposure, and point-of-care ultrasounds can be a quick method for bedside

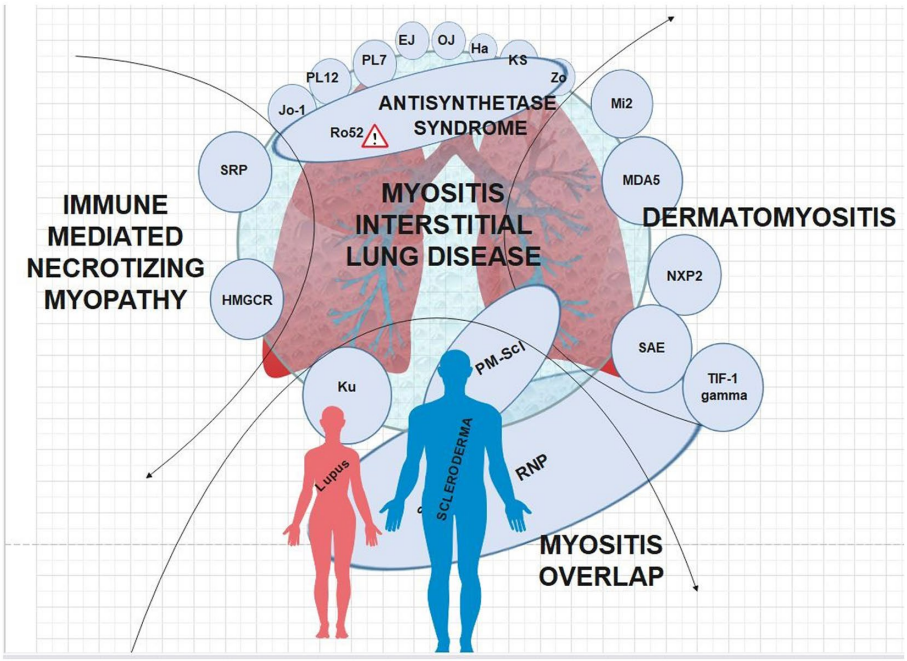

FIGURE 2
MSA's interposed onto the IIM's; caution symbol denotes more severe disease when anti-Ro autoantibodies are present.

assessment of lung parenchyma; however, it is operator dependent. Assessment of ILD through the combined use of CXR and lung ultrasound may decrease the overall exposure of patients to HRCT, therefore, Vizioli et al., compared the accuracy of combined diagnostic testing through CXR and lung ultrasound in comparison to HRCT in a single center study and concluded that lung ultrasound was highly sensitive (92%) but not specific, (79%) whereas, CXR was highly specific (91%) but not as sensitive (48%) in the detection of ILD (38). Consideration of a step-wise diagnostic approach through the use of CXR, lung ultrasound, and PFTs may be beneficial when screening for ILD in IIM.

It is our common practice to initially screen patients for ILD with HRCT and then follow their course with serial PFTs in the absence of serial imaging if they are in a high risk autoantibody group; it should be noted that serial imaging can expose patients to additional radiation and therefore should be considered when pulmonary function testing continues to show worsening of disease but not as a routine yearly screening tool. IIM-ILD is often cared for in the context of a multidisciplinary care team. If the muscle and/or skin disease is clinically significant, the patient may see only a rheumatologist, neurologist and/or dermatologist. Clinically significant interstitial lung disease requires care by a pulmonologist with specialized training. IIM-interstitial lung disease can be present in the context of dermatomyositis, the anti-synthetase syndrome, overlap myositis, or, less frequently, immune mediated necrotizing myopathy.

Dermatomyositis

Dermatomyositis (DM) has been associated with 5 myositis-specific autoantibodies. They include anti-melanoma differentiation associated protein (anti-MDA5), antinuclear matrix protein (anti-NXP-2), anti-Mi-2, anti-transcription intermediary factor 1-γ (anti-TIF1γ), and anti-small ubiquitin like modifier activating enzyme (anti-SAE).

Anti-MDA5

Anti-MDA5 antibodies were first identified in Japanese patients with clinically amyopathic dermatomyositis, per Sato et al. in 2005 (39). Recent literature estimates anti-MDA5 positivity in 10–30% of all DM patients (40). Clinical manifestations of dermatomyositis are variable among certain myositis specific autoantibodies. Cutaneous manifestations can include pathognomonic findings such as Gottron's papules, Gottron's sign, and heliotrope rash; characteristic findings such as shawl sign, V sign, holster sign, nailfold changes, and scalp involvement; or less common and unique findings calcinosis cutis, mechanic's hands, and panniculitis (40).

Some mucocutaneous manifestations are unique to anti-MDA5-associated DM and can present with cutaneous ulcerations in up to 82% of cases with a penchant for developing on existing gottron papules, nail folds, and overlying existing erythematous macules on extensor surfaces. Palmar papules, sometimes referred to as "inverse gottron papules," and panniculitis are also unique findings, and if seen, should incline clinicians to suspect anti-MDA5 positivity. In addition, oral ulcers and diffuse non-scarring alopecia have an associated high prevalence. Moreover, it is thought that this peculiar constellation of findings may be due to underlying vasculopathy (41). Patients with anti-MDA5 can have muscle weakness, however, most patients have mild muscular involvement and often no muscular involvement at all, characterized as clinically amyopathic dermatomyositis (CADM) (12).

Of the 5 myositis specific autoantibodies, anti-MDA5 has been most strongly associated with ILD which portends an increased risk

for mortality (Table 1). Patients with anti-MDA5 may develop features of ILD associated with classic DM or develop the life-threatening rapidly progressive subtype of ILD (RP-ILD). There is an increased prevalence of anti-MDA5 DM in Asian patients in comparison to US and European cohorts (47). The presence of anti-MDA5 is associated with the development of ILD with a reported prevalence ranging from 42 to 100% (41) with an increased predilection for development in Asian cohorts (47).

A review in 2020 compared the features of classic DM with ILD to anti-MDA5 DM with ILD and found that classic DM with ILD is slowly progressive, with a relapsing–remitting course, that clinically manifests with bilateral peribronchovascular ground glass opacities (GGO) or consolidations on CT scan, and nonspecific interstitial pneumonia (NSIP) or organizing pneumonia (OP) on histopathology. In comparison, RP-ILD has an epidemiologic prevalence in Asian countries, is rapidly progressive with a higher mortality rate that clinically manifests with bilateral GGO or consolidation in the posterior and peripheral lungs with the presence of diffuse alveolar damage and microangiopathy on histopathology (48). Intriguingly, the presence of anti-MDA5 antibodies is associated with an increased risk of mortality in Asian patient cohorts. Takada et al. reported a case of a 41-year-old Japanese female with clinically amyopathic dermatomyositis complicated by RP-ILD, and in an effort to increase disease awareness compared the clinical features of DM in Japanese patients with patients in the United States. The study's findings suggest that greater than 90% of Japanese patients develop complications from ILD (of which approximately 80% of patients develop the rapidly progressive subtype), whereas only 50% of American patients with anti-MDA5 develop ILD, with fewer patients developing RP-ILD (49).

A recent multicenter retrospective cohort study of non-Asian patients from European and American centers assessed 149 patients with MDA5 DM of which 72% of patients developed ILD and only 21.5% of patients developed RP-ILD (50), comparatively, fewer patients developed RP-ILD in this cohort compared to the higher incidence of development in Asian cohorts (49, 51). Clinical manifestations also varied in this cohort with 56% of patients exhibiting muscular involvement, whereas Asian cohorts have a higher predilection for amyopathic disease (50). Consistent with our current knowledge of ILD in MDA5, the non-Asian cohort was predominantly found to have NSIP on HRCT, followed by an OP pattern. Of note13% of patients had a UIP pattern on imaging which is a less common pattern seen with MDA5; however, this reflects the diversity of disease manifestations and should remind clinicians to not anchor on the presence or absence of certain findings and to interpret objective data comprehensively (50).

The presence of certain features has been associated with the development of ILD and furthermore, poor prognosis and increased risk for mortality. There is a strong association between MDA5 and the development of cutaneous ulcerations as discussed previously. Intriguingly, the presence of cutaneous ulcers may be indicative of the presence or development of ILD. A retrospective study of 152 DM patients at Stanford University found that a majority of patients with anti-MDA5 antibodies who developed ILD also had cutaneous ulcers (52). While the presence of anti-MDA5 antibodies is associated with increased risk for the development of ILD and consequently increased risk for mortality, Chen et al. (53) the concomitant presence of anti-Ro-52 antibodies is associated with worse outcomes, increased risk of progression to RP-ILD, and decreased rates of survival as evidenced in recent Asian cohorts studies (54–56).

Anti-MDA5-associated dermatomyositis is one of the deadliest and severe ILD phenotypes in the IIMs when present. It may present with hypomyopathic or amyopathic DM. While out of the scope of this review, early and aggressive treatment is imperative; thus, early recognition is paramount, and knowledge of the unique mucocutaneous disease features may be the clinician's first clue to diagnosing the disease.

Anti-NXP2

Anti-NXP2 antibodies, previously reported in the literature as anti-MJ antibodies, are more commonly seen in juvenile dermatomyositis with a reported prevalence ranging from 20 to 25% in comparison to adult cohorts where the reported prevalence is

TABLE 1 Anti-MDA5 and ILD case reports.

Case no	Author year	Antibody	ILD findings	Biopsy	PFT	Age/Sex	Cohort
1.	Sato et al. (2011) (42)	MDA5	B/L lower lung interstitial changes and GGOs on CXR and HRCT RP-ILD	–	FVC: 62%	56/F	Japan $n = 1$
2.	González-Moreno et al. (2018) (43)	MDA5	Peripheral GGO at lung bases RP-ILD	Transbronchial: diffuse alveolar damage	–	54/F	Senegal $n = 1$
3.	Kaenmuang et al. (2021) (44)	MDA5 (6/6) Ro-52 (3/6) Mi-2 beta (1/6)	Subpleural involvement (5/6) GGOs (5/6) RP-ILD (4/6)	Organizing pneumonitis, focal organizing pattern, BOOP	FVC: 62, 58% DLCO: 72, 45%	Age range: 35–63 M (3/6), F (3/6)	Thailand $n = 6$
4.	De Backer et al. (2017) (45)	MDA5	Diffuse subpleural and peribronchial infiltrates and parenchymal consolidations RP-ILD	Transbronchial: diffuse alveolar damage	Restrictive with reduced DLCO	55/M	Belgium $n = 1$
5.	Li et al. (2020) (46)	MDA5 PL-7	Bilateral diffuse ground glass patchy opacities RP-ILD	–	–	27/F	Hispanic/USA $n = 1$

14–25% in the United States adult IIM population and 2–5% in the adult Japanese IIM population (57). Clinical features of dermatomyositis in the presence of anti-NXP2 antibodies can include the development of characteristic cutaneous manifestations, calcinosis cutis (which is prevalent in up to 37% of patients) as well as an increased prevalence of peripheral edema (58). While dermatomyositis is conventionally considered to be a disease to affect proximal muscles and cause proximal muscle weakness, anti-NXP2-associated dermatomyositis has been reported to also affect distal muscles as well causing distal arm and leg weakness. Additionally, these patients can develop symptoms of dysphagia, reflective of significant myopathic involvement (59).

In contrast to anti-MDA5 DM, pulmonary manifestations are relatively scarce, and development of ILD is rare; however, cases do exist (Table 2) (62, 63). A retrospective case series of 7 adult DM patients in France observed pulmonary involvement in 2/7 patients; PFTs of 6/7 patients observed a mean FVC of 90% and a mean DLCO of 56%. HRCT revealed NSIP in one patient, OP in one patient, and normal HRCT in four patients (60). Similarly, in a longitudinal cohort study of anti-NXP2 positive patients in the United States, only 7% of patients developed ILD with a reported mean FVC of 87%, unfortunately, this study did not discuss whether these patients underwent pulmonary imaging (59). The findings reflected in France and the United States are also similarly reflected in a Chinese cohort that identified 17 patients with anti-NXP2 antibodies of which 5 patients developed ILD in a predominantly mixed NSIP + OP pattern on HRCT (64).

Yan et al. performed a retrospective analysis of 33 patients with anti-NXP2 DM over a course of approximately 3 years in which 14/33 individuals developed ILD with 11/14 manifesting features of NSIP and/or OP in lung imaging (65). Interestingly, Kaplan–Meier survival curves did not reveal a statistically significant association between ILD and all-cause mortality (65). In comparison, Li et al. found 21 patients out of 70 patients to have ILD, none developing RP-ILD, in their retrospective 10 year longitudinal cohort study in China (66).

There is an association between anti-NXP2 antibodies and malignancy that was most notably reported in a Japanese cohort of adult patients in which ~37% of patients were found to have malignancy. Their findings were similar to a United States cohort study which found malignancy among ~24% of patients, however, definite associations were not exhibited (67, 68). Moreover, a recent United States cohort study from our cohort at Johns Hopkins and an DM cohort at Stanford determined that patients with anti-NXP2 antibodies are at increased risk of malignancy when compared to the general population (59).

While anti-NXP2 autoantibodies are associated with an increase in malignancy, they do not appear to have an increased association with ILD. This finding supports the observation that malignancy and ILD are inversely proportional to each other and those autoantibodies associated with a higher risk if malignancy have a lower risk of ILD.

Anti-Mi-2

The presence of anti-Mi-2 antibodies in adults ranges from 2 to 38% among dermatomyositis (57). Patients with anti-Mi-2 antibodies predominantly present with the classic cutaneous manifestations of dermatomyositis including heliotrope rash, V sign, shawl sign, gottron papules and gottron sign, additionally, these patients can develop cuticular overgrowths (69). A recent longitudinal cohort study in our center in the United States found that the presence of anti-Mi-2 antibodies is associated with significant and persistent muscle weakness that weakly correlates with elevated creatine kinase levels (70).

Pulmonary involvement is relatively rare in anti-Mi-2 dermatomyositis with multiple cohort studies reporting minuscule lung involvement (71–73). A longitudinal study of anti-Mi-2 patients in the United States found only 3 patients out of 58 developed features of ILD (70). Literature search revealed a case report from the United States of a patient with persistent dry cough and dyspnea who was found to have bibasilar infiltrates on CXR and bilateral patchy ground glass infiltrates on HRCT, with serial imaging revealing of organizing pneumonia, in addition to the development of progressive proximal myopathy in the presence of anti-Mi-2 antibody positivity (74).

While weakness may persist in some Mi-2 + patients, overall, patients who express antibodies to anti-Mi-2 have a favorable prognosis (57, 75). Mi-2 autoantibodies are not generally associated with ILD and thus likely do not require serial PFT and other pulmonary imaging follow-up.

Anti-transcription intermediary factor 1-γ

Anti-TIF1γ typically manifests with more prominent cutaneous manifestations of disease and is less frequently associated with ILD. The reported prevalence of anti-TIF1γ antibodies in adult dermatomyositis ranges from 13 to 31% and is more prevalent in Caucasians as compared to Asians (47, 57). Similar to other autoantibodies, cutaneous manifestations of the disease include gottron papules, heliotrope rash, and V sign, however, these patients are highly photosensitive and can present with unique cutaneous features such as ovoid palatal patches, psoriasis-like skin lesions, palmar hyperkeratosis, and hypopigmented patches overlying telangiectasias (40). In contrast, extracutaneous manifestations of the disease are less common and features of Raynaud's phenomenon,

TABLE 2 Anti-NXP2 and ILD.

Case no	Author year	Antibody	ILD type	ILD findings	Biopsy	PFT	Age/Sex	Cohort
1.	Bermudez et al. (2020) (60)	NXP2	NSIP: 1/6 OP: 1/6	–	–	Mean FVC: 90% ±14% Mean DLCO: 56% +/−17%	Mean age 55 +/− 13 years 5 Female 2 Male	France *n* = 7
2.	Gossez et al. (2015) (61)	NXP2	–	Bilateral consolidations lower lung zones	–	–	41 years/ Female	France *n* = 1

calcinosis, arthritis/arthralgia, and pulmonary involvement are less prevalent (76).

The development of ILD is relatively uncommon with anti--IF1γ antibodies. A retrospective analysis by Harada et al. analyzed 14 patients with anti-TIF1γ positivity out of a pool of 85 patients with DM over a prolonged 18-year course and identified dermatologic manifestations such as erythema, V neck sign, heliotrope rash, and nail fold telangiectasias more frequently present, whereas no patients developed features of ILD on HRCT (77). Intriguingly, patients with anti-TIF1γ positivity have been found to have an increased incidence of developing malignant tumors (78, 79). Patients with anti-TIF1γ and pulmonary involvement should be followed closely for the development of malignancy. Xie et al. reported a case of initial misdiagnosis of interstitial pneumonia with autoimmune features with NSIP on initial HRCT, which was identified to be right lung squamous carcinoma during a one-year follow-up (80).

Anti-TIF1γ autoantibodies do not have a known association with ILD. Alternate diagnoses should be suspected if lung involvement is found in this subset of patients with DM. Again, the intriguing inverse relationship between cancer (common in this DM subset) and ILD (uncommon in TIF1γ positive patients) is noteworthy.

Anti-small ubiquitin like modifier activating enzyme

The frequency of anti-SAE antibody expression in dermatomyositis is approximately 8% (81). Patients typically present with cutaneous manifestations of the disease that precede muscle involvement (81). Extracutaneous manifestations are common, and the development of dysphagia is a frequent finding (81).

While this phenotype is more strongly associated with the dermatologic manifestations of the disease, there have been reports of mild pulmonary involvement. Gono et al., describe two case reports of Asian patients who presented with predominantly skin-related symptoms, found to have preserved pulmonary function on pulmonary function testing, but evidence of peripheral lower lobe lung involvement with subpleural ground glass opacities, more consistent with NSIP (82). In a North American cohort of 9 patients with anti-SAE positivity at the Johns Hopkins Myositis Center, 7/9 patients developed mild features of ILD, with CT findings of multiple peripheral pulmonary nodules (83). Interestingly, Kishi et al., report a case within the pediatric age group of an 8-year-old Japanese girl who presented with juvenile DM with predominantly cutaneous manifestations complicated by non-rapidly progressive ILD (84).

Overall, ILD is generally mild in these patients and improves with treatment (85). Mild ILD that seems to be clinically less significant may be a feature in patients with dermatomyositis and anti-SAE autoantibodies.

Immune mediated necrotizing myopathy

IMNM has been associated with two prototypic autoantibodies: Anti-HMGCR (3-hydroxy-3-methylglutaryl-CoA reductase) and anti-SRP (signal recognition particle).

Anti-HMGCR antibody myopathy was identified in a US cohort of patients with necrotizing myopathy in 2010 (86) and has a reported frequency of approximately 6% (87). Patients may or may not have had exposure to statin medications and clinical manifestations can include severe proximal muscle weakness and extramuscular manifestations are mostly limited to dysphagia (87). Pulmonary involvement is uncommon with anti-HMGCR and a cohort study in China found the presence of anti-HMGCR to be a protective factor against the development of ILD (88).

Similar to anti-HMGCR antibodies, anti-signal recognition particle (SRP) antibodies are relatively rare with a reported prevalence of 4–6% in European cohorts and a slightly higher prevalence in Asian cohorts, up to approximately 13% (87). Clinical manifestations include severe proximal muscle weakness that can lead to severe debilitation, additionally, patients are at an increased risk of developing dysphagia (47).

While anti-HMGCR autoantibodies are not typically associated with interstitial lung disease, the development of ILD has been reported with anti-SRP IMNM. In a retrospective single-center study, 27 out of 60 individuals with anti-SRP IMNM were diagnosed with extra-muscular manifestations of ILD, of which the radiologic presentation of ILD was NSIP (63%), OP (33.3%), and lymphocytic interstitial pneumonia (3.7%) (89). In their cohort, opacities were primarily distributed in the lower lobes and peribronchovascular sites (89). Patients in this cohort were reported to be mostly asymptomatic with slow disease progression; they were classified as having mild to moderate severity; and none of the patients progressed to RP-ILD. Of note, patients in this cohort did not undergo confirmatory diagnostic testing with bronchoscopy or lung biopsy (89). Anti-SRP IMNM has occasionally been associated with severe forms of ILD. In a case report by Qureshi et al. a 40-year-old African American female developed ventilator-dependent respiratory failure and was found to have mildly elevated CK levels and autoantibody positivity for anti-SRP. Interestingly, the patient did not respond to corticosteroids and immunosuppressants ultimately requiring lung transplantation (90). Additionally, a literature search revealed a case report of a 29-year-old male who presented with progressive exertional dyspnea and was identified to have pulmonary arterial hypertension in addition to findings consistent with ILD. Radiographic imaging was initially consistent with an NSIP pattern with diffuse ground glass opacities but rapidly progressed to a UIP pattern with fibrotic and inflammatory changes within a mere 18 months. Ultimately, the patient underwent lung transplantation and histology from the explanted lung revealed mixed features of UIP and fibrotic NSIP (91).

IMNM is a relatively newly understood and recognized subset of IIM in the last two decades. The prototypic associated autoantibodies, anti HMGCR and anti-SRP have different predilection for ILD, with the former having no clear association and the later having a rare association but one that may be severe in nature and can present in a UIP pattern requiring lung transplantation in the most severe cases.

Myositis overlap: anti PM/Scl, anti-Ku, anti-RNP

Myositis overlap is a heterogeneous entity in which patients can share symptoms of multiple distinct connective tissue diseases. Notable myositis overlap autoantibodies include anti-PM/Scl which generally demonstrates clinical features of overlap between

scleroderma (namely Raynaud's phenomenon, telangiectasias and possible skin thickening) and myositis with or without the skin rash of dermatomyositis.

Lung involvement is common in patients with anti-PM/Scl, ranging from 35 to 87%, and has been reported to have better functional outcomes when compared to other groups (92). In a single center study of anti-PM/Scl antibody patients in China, 30 patients were found to be positive for either anti-PM/Scl-75, anti-PM/Scl-100, or both, of which NSIP, UIP, OP, NSIP/OP overlap, and LIP were identified, respectively, in descending order of frequency through either HRCT or lung biopsy; interestingly, ILD was the sole manifesting feature in ~26% of the cohort (93).

Anti-Ku antibodies are myositis associated auto-antibodies and can be identified in patients with myositis as well as in patients with other systemic autoimmune conditions and can present with features of extramuscular involvement, such as ILD. A retrospective study seeking to identify predictive features of ILD found that within their cohort anti-ku antibodies were present in patients who developed ILD at least 12 months after the onset of their myositis, suggesting anti-ku antibodies could be associated with a slow disease progression (94). A study from the Johns Hopkins myositis cohort looking to further describe the phenotype of anti-ku positive patients found that within the cohort, ILD was the presenting feature in only 19% of patients but 56% of patients ultimately developed pulmonary disease (95).

Anti-RNP (ribonuclear protein) antibodies are prevalent in a myriad of systemic diseases such as myositis, mixed connective tissue disease, systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis (96). A study aiming to characterize the pulmonary manifestations among patients with anti-RNP antibodies found that out of a total of 544 patients, ~25% had ILD with NSIP being the predominant radiological finding followed by UIP. Cystic lesions with ground-glass attenuation were identified in a subset of NSIP patients without signs of fibrosis on imaging, identifying an original radiologic pattern termed interstitial cystic lung disease associated with anti-RNP antibody (ICLAR) (97).

Many of the myositis CTD overlap syndromes can present with significant ILD. The practicing clinician must be aware of this potential involvement, and serial monitoring with pulmonary function testing and assessment of patient symptoms including cough and breathlessness should be closely evaluated.

Antisynthetase syndrome

The antisynthetase syndrome is characterized by antibodies directed against an aminoacyl-transfer RNA (tRNA) synthetase (ARAs) and is associated with ILD, myositis, inflammatory arthritis, mechanic's hands, fever, and Raynaud's phenomenon (98). It is generally accepted that the presence of a positive antisynthetase antibody in addition to the presence of two of the following features: ILD, inflammatory myopathy, or inflammatory polyarthritis is classified as anti-synthetase syndrome (34). Alternatively, our group has proposed antisynthetase syndrome criteria that includes positive serologic testing for an anti-tRNA synthetase autoantibody in the presence of any one of the protean symptoms (ILD, myositis, inflammatory arthritis, mechanic's hands, fever, and Raynaud's phenomenon) (15). In a retrospective cohort of 108 patients with anti-synthetase syndrome and ILD, patients had 5 distinct antibodies, anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, and anti-OJ (99). Thirty out of 108 cases received bronchoscopy for transbronchial biopsy to assist in pathological diagnoses, and the remaining cases were diagnosed based on radiological pattern discussions with multi-disciplinary teams (99). Data from this cohort revealed that an OP pattern was seen the most in the EJ + group, NSIP pattern was seen the most in the PL-12 + group, a mixture of OP + NSIP pattern was seen the most in the OJ + group, and UIP was seen the most in the PL-7 + group; all groups had a positive response to steroid therapy (99). In another single-center retrospective study of 84 ILD patients, the NSIP pattern was seen more in the Jo-1, PL-7, and EJ group, OP pattern was seen more in the PL-12 group, and UIP was seen more in the OJ group (100). In a retrospective cohort of 1,194 patients, patients were compared to healthy controls for the presence of anti-Ha, anti-Ks, anti-Zoα, cN1A novel myositis autoantibodies and found that the prevalence of ILD was significantly higher in those with novel myositis antibodies. Radiologic and histologic findings of UIP pattern were less frequently characterized when compared to patients with idiopathic pulmonary fibrosis (101).

Finally, anti-Ro-52 antibodies have been associated with ILD and have been considered to be an independent predictor for complications of ILD. While they may be seen in isolation, they are more often associated with other MSAs, specifically anti-ARS autoantibodies. A prospective observational study in China assessed patients with anti-Ro-52 positivity for the presence of ILD and found that patients with isolated anti-Ro-52 antibodies and non-RP-ILD had an NSIP pattern on radiographic studies whereas patients who developed RP-ILD had an OP pattern on imaging studies (102). Similarly, a retrospective analysis of ILD patients in Italy found that the presence of anti-Ro-52 antibodies could predict the development of ILD. Interestingly, patients in their cohort had statistically significant improvement in DLCO at 5 years from baseline (94).

The antisynthetase antibodies have a strong association with ILD. It must be noted that isolated ILD may be the presenting and sole feature of the illness; thus a high index of suspicion for the antisynthetase syndrome in any patient presenting with an otherwise idiopathic pneumonia, especially in an NSIP pattern, must be present. More often than not, in the antisynthetase syndrome anti-PL12 and anti-PL7 antibodies present with ILD in isolation. The unfortunate nomenclature of "myositis associated autoantibodies" can be confusing to clinicians. Thus attributing these antibodies to a syndromic complex where ILD may be the first or only symptom is an important construct to understand.

Summary

Myositis-specific autoantibodies (MSAs) and Myositis-associated antibodies (MAAs) testing has become commercially available in recent years and is now more accessible worldwide. The diagnostic utility of the MSAs and MAAs in helping to make an accurate diagnosis and assist in the prognosis of myositis-ILD is excellent in the appropriate clinical setting. While anti-MDA5 is associated with the most severe ILD phenotype with respect to rapidly progressive ILD, many other myositis-specific and myositis-associated autoantibodies are found in conjunction with ILD in various frequencies. It is important for the practicing clinician caring for patients with myositis to recognize the significant association with ILD and appropriately triage some patients in higher-risk

autoantibody-associated groups to imaging and serial pulmonary function testing for close follow-up.

Author contributions

SC and LC-S contributed to the conception, writing, and critical review and revision of the manuscript. All authors contributed to the article and 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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Changes in patient-reported outcomes in patients with non-idiopathic pulmonary fibrosis fibrotic interstitial lung disease and progressive pulmonary fibrosis

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Background: Health-related quality of life (HRQoL) captures different aspects of the fibrotic interstitial lung disease (FILD) evaluation from the patient's perspective. However, little is known about how HRQoL changes in patients with non-idiopathic pulmonary fibrosis (IPF) FILD, especially in those with progressive pulmonary fibrosis (PPF). The aim of this study is to clarify whether HRQoL deteriorates in patients with non-IPF FILD and to evaluate the differences in the changes in HRQoL between those with and without PPF.

Methods: We collected data from consecutive patients with non-IPF FILD and compared annual changes in HRQoL over 2 years between patients with PPF and those without. The St George's respiratory questionnaire (SGRQ) and COPD assessment test (CAT) were used to assess HRQoL. Changes in the SGRQ and CAT scores for 24months from baseline were evaluated with a mixed-effect model for repeated measures.

Results: A total of 396 patients with non-IPF FILD were reviewed. The median age was 65 years and 202 were male (51.0%). The median SGRQ and CAT scores were 29.6 and 11, respectively. Eighty-six (21.7%) showed PPF. Both SGRQ and CAT scores were significantly deteriorated in patients with PPF compared to those without PPF (p<0.01 for both). Clinically important deterioration in the SGRQ and CAT scores were observed in 40.0 and 35.7% of patients with PPF and 11.7 and 16.7% of those without, respectively. PPF was significantly associated with clinically important deterioration in the SGRQ score (odds ratio 5.04; 95%CI, 2.61–9.76, p<0.01) and CAT score (odds ratio 2.78; 95%CI, 1.27–6.06, p=0.02).

Conclusion: The SGRQ and CAT scores were significantly deteriorated in patients with non-IPF FILD and PPF. Considering an evaluation of HRQoL would be needed when assessing PPF.

KEYWORDS

interstitial lung disease, progressive pulmonary fibrosis, progressive fibrosing interstitial lung disease, St George's respiratory questionnaire, COPD assessment test, health-related quality of life, 6min walk distance

Introduction

Interstitial lung diseases (ILDs) are a large and heterogeneous group of lung disorders characterized by fibrosis and inflammation of the lung tissue. Various topics of ILDs including genetic variants or the utility of the International Classification of Functioning, Disability, and Health have been discussed and one of the recent hot topics of ILDs were disease progression (1–4). Idiopathic pulmonary fibrosis (IPF) is the symbolic and most frequent disease of fibrotic ILDs (FILDs) and IPF usually shows progression of fibrosis (1). Some FILDs other than IPF also have a progressive phenotype despite treatment (1, 5–10) and have been reported to show similar overall survival to IPF (5, 6). Recently, non-IPF FILDs with a progressive phenotype have been noted as a form of progressive pulmonary fibrosis (PPF) (1).

Studies have used variable definitions of a progressive phenotype, most of which cite a decline in pulmonary function, progression of radiological fibrosis and worsening of respiratory symptoms (1, 5–8, 11). Although these measures are useful to evaluate disease progression, they are not sufficient to assess patients' feelings and functioning.

Health-related quality of life (HRQoL) captures different aspects of ILD from the patient's perspective (12). Although deterioration of HRQoL lacks objectivity in practice, it has been thought to be highly meaningful for patients (13). However, little is known about whether HRQoL deteriorates in non-IPF FILD patients with PPF and whether there is a difference in the changes in HRQoL between those with and without PPF. We think investigating relationships between criteria for PPF and HRQoL lead to identifying PPF in terms of quality of life, shedding light on the significance of HRQoL, and revising the criteria for PPF. The aim of this study is to investigate whether there is a decline in HRQoL in patients with non-IPF FILD. Additionally, the study aims to evaluate and compare the differences in the changes of HRQoL between patients with and without PPF.

Materials and methods

Patient selection

The medical records of consecutive patients with non-IPF FILD who underwent initial evaluation at Tosei General Hospital (Seto, Japan) between January 2008 and July 2015 were retrospectively reviewed. We included patients with non-IPF FILD who had evaluated PPF based on our previous study (5). PPF, which had already been confirmed in the previous study (5), was defined as the presence of at least one of the following at 24 months from the initial evaluation: a relative decline in forced vital capacity (FVC) of at least 10%; a relative decline in FVC of ≥5–<10% with a relative decline in the diffusing capacity of the lung for carbon monoxide (DL_{CO}) of at least 15%; a relative decline in FVC of ≥5–<10% with increased fibrosis on high-resolution computed tomography; and a relative decline in FVC of ≥5–<10% with progressive symptoms. The final diagnoses of non-IPF FILD were categorized as idiopathic non-specific interstitial pneumonia, fibrotic hypersensitivity pneumonitis, connective tissue disease-related ILD, idiopathic pleuroparenchymal fibroelastosis and unclassifiable ILD. Patients who died or underwent lung transplantation within 24 months from the initial evaluation were excluded.

Study design

We collected data on HRQoL and exercise capacity at baseline, 1 year, and 2 years. We compared the annual changes in the HRQoL over 2 years between patients with and without PPF. The baseline data were collected at the initial evaluation of ILD.

The St George's respiratory questionnaire (SGRQ) and COPD assessment test (CAT) were used to assess HRQoL. The SGRQ is a specific questionnaire for respiratory disease and provides three component scores for the domains of symptoms, activity, and impacts, as well as a total score (score range: from 0 to 100, with higher scores indicating greater impairment of HRQoL) (14). The CAT is composed of eight items related to symptoms of respiratory disease and their impact: cough, phlegm, chest tightness, breathlessness, activity limitation, confidence, sleep, and energy. Patients are asked to respond to all items using an identical 0–5 response scale (score range: from 0 to 40, with a score of 0 indicating no impairment) (15). Exercise capacity was evaluated using the 6 min walk test, according to the American Thoracic Society statement (16).

The minimal clinically important difference (MCID) was utilized to evaluate the deterioration of the SGRQ, CAT and the 6 min walk distance (6MWD) with the thresholds of 8 points, 5 points, 7 points, and 7 points for SGRQ symptom, activity, impact, and total scores, respectively (17); 4 points for CAT score (18); and 28 m for 6MWD (19). This study was carried out at a single hospital in compliance with the principles of the Declaration of Helsinki and approved by its institutional review board (IRB No. 1091, August 16th, 2022).

Statistical analysis

The statistical tests used in this study were Fisher's exact test and Mann–Whitney U test to compare categorical and continuous variables, respectively. A mixed-effect model for repeated measures was used to evaluate changes in SGRQ, CAT, and 6MWD over 24 months from baseline. A cumulative distribution function (CDF) plot was generated to visually present the relationship between HRQoL change scores or 6MWD change and PPF. The CDF plots used data from patients with and without PPF. All statistical tests were

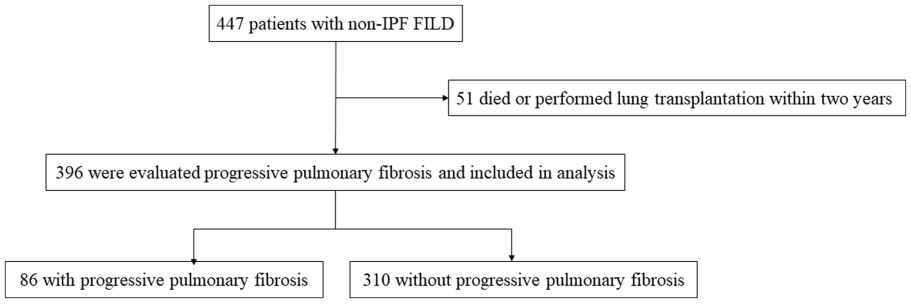


FIGURE 1
Screening and inclusion process for patients in the study. FILD, fibrotic interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

TABLE 1 Patients' baseline characteristics.

	All patients*		PPF				
			yes (n=86)		no (n=310)	p value	
Age, year	65	(60–71)	67	(61–72)	65	(59–71)	0.07
Gender, male	202	[51]	43	[50]	159	[51]	0.90
FVC, %predicted	87.9	(73.5–103.6)	87.7	(74.0–102.3)	87.9	(73.1–103.8)	0.88
DL_{CO}, %predicted	66.5	(52.1–82.5)	68.1	(53.3–84.4)	65.9	(51.7–81.3)	0.68
6MWD, m	560	(494–620)	559	(474–621)	563	(496–620)	0.55
SGRQ total	29.6	(15.0–44.9)	33.4	(15.6–47.5)	28.8	(14.9–42.8)	0.26
SGRQ symptom	37.3	(22.0–54.3)	38.1	(22.7–58.5)	36.8	(21.1–53.2)	0.37
SGRQ activity	36.8	(18.4–59.5)	39.7	(23.4–60.6)	36.5	(18.3–59.5)	0.31
SGRQ impact	21.1	(8.1–36.0)	25.6	(9.1–38.8)	20.1	(8.0–35.8)	0.43
CAT	11	(5–18)	11	(8–19)	11	(5–18)	0.38

Data are presented as median (interquartile range) or number [%]. CAT, COPD assessment test; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; PPF, progressive pulmonary fibrosis; SGRQ, St George's respiratory questionnaire; 6MWD, 6 min walk distance. *N = 396 except for DL_{CO} (n = 384), 6MWD (n = 382), and CAT (n = 263).

two-sided, and a significance level of $p < 0.05$ was used to determine statistical significance. The data were reported using descriptive statistics, such as mean, standard deviation, median, and interquartile range. Results of the statistical tests were reported with the corresponding p-values and confidence intervals (CI) when appropriate. Statistical analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL).

Results

A total of 447 patients with non-IPF FILD were reviewed. Fifty-one were excluded due to death or lung transplantation within 24 months from the initial evaluation. Thus, 396 patients were included in the analysis set (Figure 1). Of these 396 patients, 19 had idiopathic non-specific interstitial pneumonia, 21 had fibrotic hypersensitivity pneumonitis, 163 had connective tissue disease-related ILD, six had idiopathic pleuroparenchymal fibroelastosis and 187 had unclassifiable ILD. Among 163 connective tissue disease-related ILD, 56 were rheumatoid arthritis, 38 were systemic sclerosis, 43 were myositis, 30 were sjögren syndrome, 8 were mixed connective tissue disease, and 4 were systemic lupus erythematosus (including overlap disease). Baseline characteristics are summarized in the Table 1. The median age was 65 years and 202 were male (51.0%). The median 6MWD was 560 meters. The median SGRQ and CAT scores were 29.6 and 11, respectively. Eighty-six (21.7%) showed PPF. Distribution of the baseline SGRQ and CAT scores are shown in Figure 2.

Changes in SGRQ

With regard to HRQoL, the mean change (standard deviation) in the SGRQ score over 2 years from the baseline was 5.8 ± 17.9 in patients with PPF and −9.5 ± 16.4 in those without. The SGRQ score was significantly higher in patients with PPF compared to those without ($p < 0.01$) (Figure 3A). Differences in each component of the SGRQ between patients with and without PPF are shown in Figure 4.

The difference between the baseline SGRQ score and the 2 year SGRQ score was evaluated in 262 patients. Among 86 patients with PPF who evaluated SGRQ at baseline, each number of patients who had evaluated the 2 year changes of SGRQ in each category of the criteria for PPF was 40 in 57 patients met the a relative decline of FVC ≥ 10%, 16 in 17 patients met a relative decline in FVC of ≥5–<10% with a relative decline in DL_{CO} of at least 15%, 15 in 16 patients met a relative decline in FVC of ≥5–<10% with increased

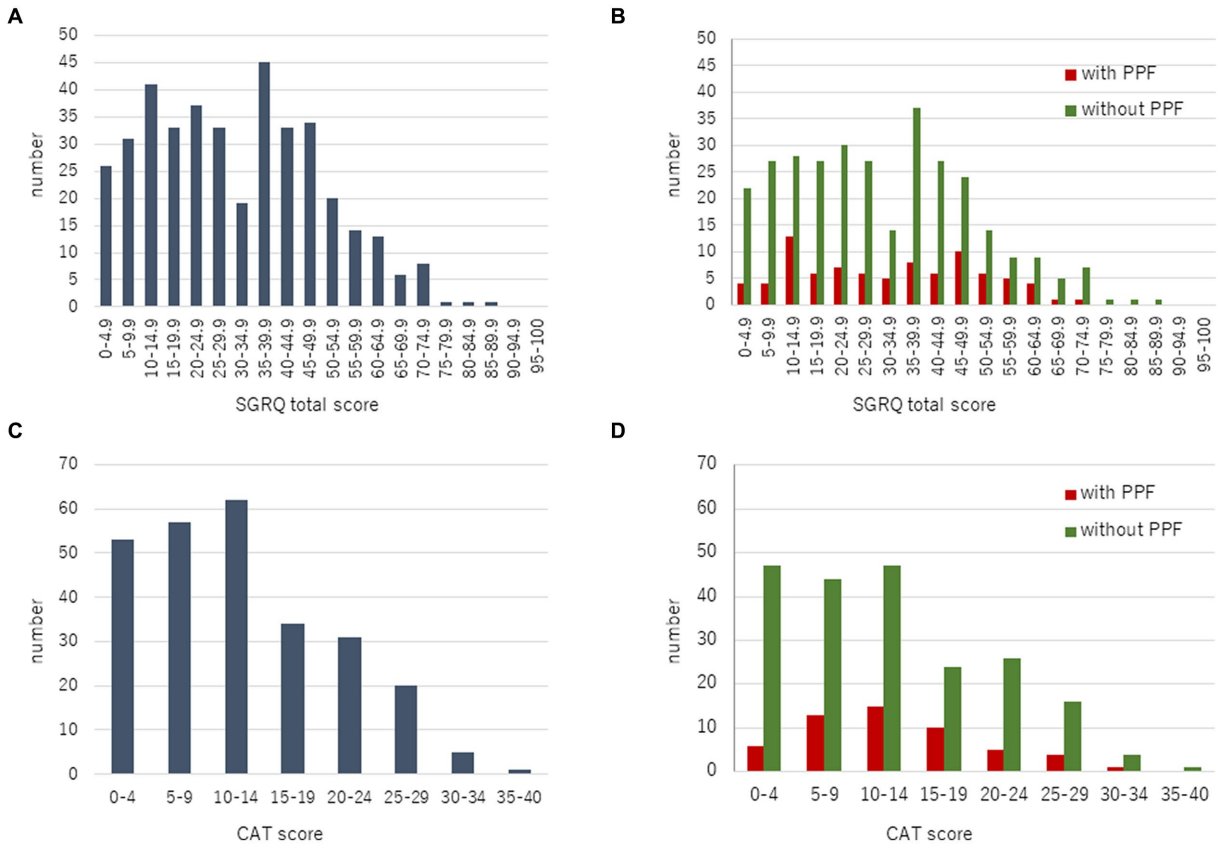
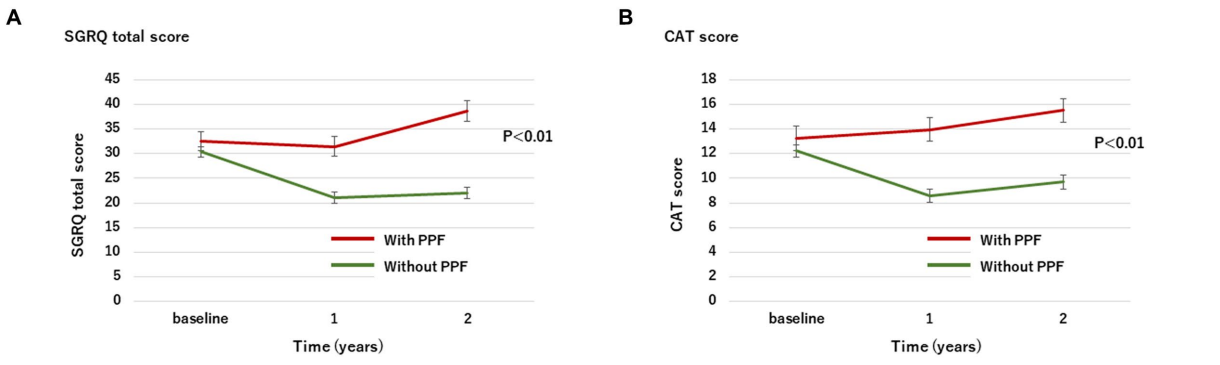


FIGURE 2
Distribution of the baseline SGRQ **(A)** and CAT **(C)** scores in all patients. Comparison of the baseline SGRQ **(B)** and CAT **(D)** scores between patients with and without PPF. CAT, COPD assessment test; PPF, progressive pulmonary fibrosis; SGRQ, St George's respiratory questionnaire.



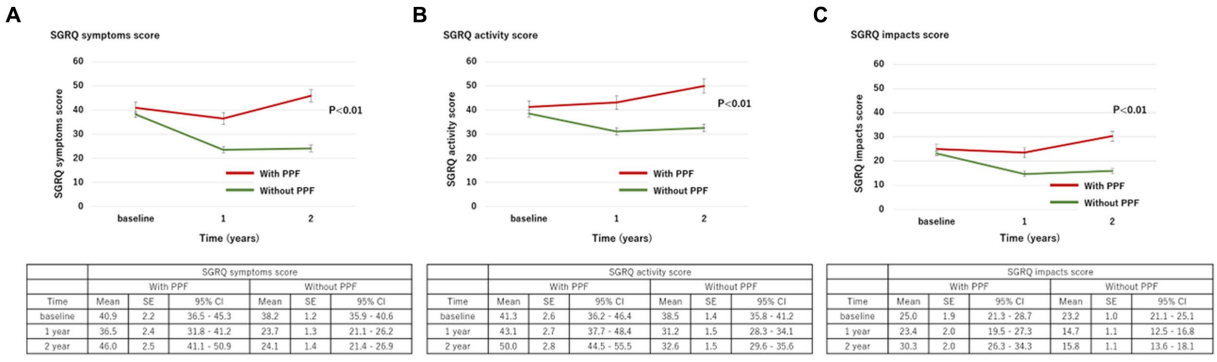
	SGRQ total score					
	With PPF			Without PPF		
Time	Mean	SE	95% CI	Mean	SE	95% CI
baseline	32.5	1.9	28.8 - 36.3	30.4	1.0	28.4 - 32.4
1 year	31.5	2.0	27.5 - 35.5	21.0	1.1	18.9 - 23.2
2 year	38.7	2.1	34.6 - 42.8	22.0	1.2	19.7 - 24.3

	CAT score					
	With PPF			Without PPF		
Time	Mean	SE	95% CI	Mean	SE	95% CI
baseline	13.3	1.0	11.3 - 15.3	12.2	0.5	11.2 - 13.3
1 year	14.0	1.0	12.0 - 15.9	8.6	0.5	7.5 - 9.6
2 year	15.5	1.0	13.6 - 17.4	9.7	0.6	8.6 - 10.8

FIGURE 3
Change in the SGRQ total score **(A)** and CAT score **(B)** over 2 years from baseline. Standard error (SE) is derived from a mixed model for repeated measures. CAT, COPD assessment test; CI, confidence interval; PPF, progressive pulmonary fibrosis; SGRQ, St George's respiratory questionnaire.

fibrosis on high-resolution computed tomography, and 12 in 14 patients met a relative decline in FVC of ≥5–<10% with progressive symptoms.

The CDF plots provide a graphical presentation of the SGRQ change scores in patients with and without PPF (Figure 5A). Changes in the SGRQ total scores were significantly different between patients



	SGRQ symptoms score					
	With PPF			Without PPF		
Time	Mean	SE	95% CI	Mean	SE	95% CI
baseline	40.9	2.2	36.5 - 45.3	38.2	1.2	35.9 - 40.6
1 year	36.5	2.4	31.8 - 41.2	23.7	1.3	21.1 - 26.2
2 year	46.0	2.5	41.1 - 50.9	24.1	1.4	21.4 - 26.9

	SGRQ activity score					
	With PPF			Without PPF		
Time	Mean	SE	95% CI	Mean	SE	95% CI
baseline	41.3	2.6	36.2 - 46.4	38.5	1.4	35.8 - 41.2
1 year	43.1	2.7	37.7 - 48.4	31.2	1.5	28.3 - 34.1
2 year	50.0	2.8	44.5 - 55.5	32.6	1.5	29.6 - 35.6

	SGRQ impacts score					
	With PPF			Without PPF		
Time	Mean	SE	95% CI	Mean	SE	95% CI
baseline	25.0	1.9	21.3 - 28.7	23.2	1.0	21.1 - 25.1
1 year	23.4	2.0	19.5 - 27.3	14.7	1.1	12.5 - 16.8
2 year	30.3	2.0	26.3 - 34.3	15.8	1.1	13.6 - 18.1

FIGURE 4
Change in each component of the SGRQ score (**(A)**, symptoms; **(B)**, activity; **(C)**, impacts) over 2 years from baseline. Standard error (SE) is derived from a mixed model for repeated measures. CI, confidence interval; PPF, progressive pulmonary fibrosis; SGRQ, St George's respiratory questionnaire.

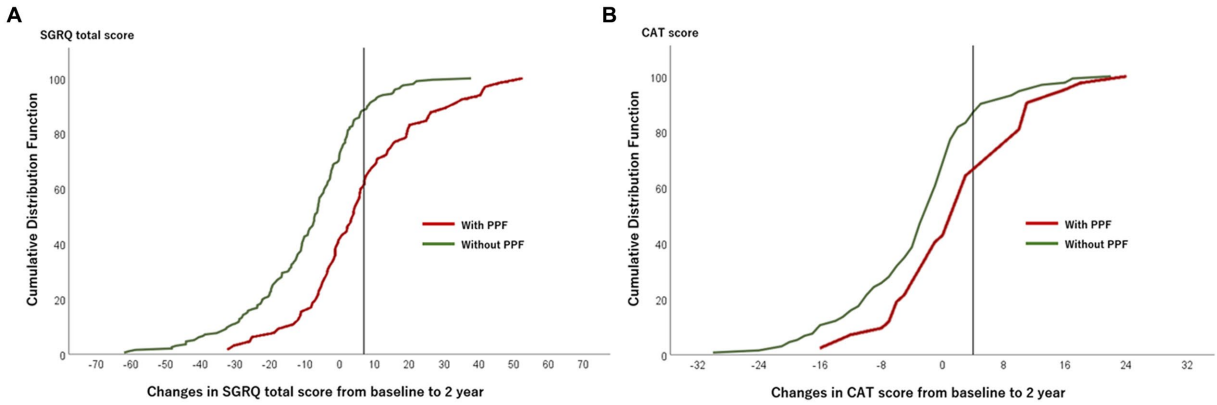


FIGURE 5
Plot of CDF for the SGRQ total score **(A)** and the CAT score **(B)** from baseline to 2 years in patients with and without PPF. The vertical lines show the threshold of the minimal clinically important difference (SGRQ total score, 7 points; CAT score, 4 points). CAT, COPD assessment test; CDF, cumulative distribution function; PPF, progressive pulmonary fibrosis; SGRQ, St George's respiratory questionnaire.

with and without PPF ($p < 0.01$). Clinically important deterioration over 2 years in the SGRQ total score was observed in 26 (40.0%) of 65 patients with PPF and 23 (11.7%) of 197 patients without PPF, respectively. PPF was significantly associated with clinically important deterioration in the SGRQ total score (odds ratio 5.04; 95%CI 2.61–9.76, $p < 0.01$) (Figure 6).

Changes in CAT

The mean change (standard deviation) in the CAT score over 24 months from baseline was 2.0 ± 8.5 in patients with PPF and −3.1 ± 8.6 in those without. The CAT score was significantly higher in patients with PPF compared to those without ($p < 0.01$) (Figure 3B).

The difference between the baseline CAT score and the 2 year CAT score was evaluated in 174 patients. Among 54 patients with PPF who evaluated CAT score at baseline, each number of patients who had evaluated the 2 year changes of CAT score in each category of the criteria for PPF was 24 in 35 patients met the a relative decline of FVC ≥ 10%, 13 in 13 patients met a relative decline in FVC of ≥5–<10% with a relative decline in DL_{CO} of at least 15%, 9 in 9 patients met a relative decline in FVC of ≥5–<10% with increased fibrosis on high-resolution computed tomography, and 8 in 9 patients met a relative decline in FVC of ≥5–<10% with progressive symptoms.

The CDF plots provide a graphical presentation of the CAT change scores in patients with and without PPF (Figure 5B). Changes in the CAT scores were significantly different between patients with and without PPF ($p < 0.01$). Clinically important deterioration over 2 years in the CAT was observed in 15 (35.7%) of 42 patients with PPF and 22 (16.7%) of 132 patients without PPF, respectively. PPF was significantly associated with clinically important deterioration in the CAT score (odds ratio 2.78; 95%CI 1.27–6.06, $p = 0.02$) (Figure 6).

Changes in exercise capacity

With regard to exercise capacity, the mean change (standard deviation) in the 6MWD over 24 months from baseline was −62.2 ± 120.7 in patients with PPF and 22.8 ± 75.6 in those without. The 6MWD was significantly lower in patients with PPF compared to those without ($p < 0.01$) (Supplementary Figure S1).

The CDF plots provide a graphical presentation of the 6MWD change scores in patients with and without PPF (Supplementary Figure S2). The difference between the baseline 6MWD

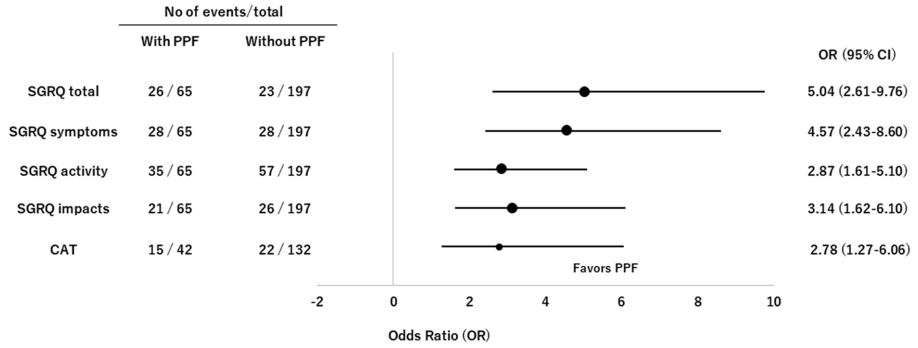


FIGURE 6
Forest plots of odds ratios for deterioration in the SGRQ and CAT scores in patients with non-IPF FILD. CAT, COPD assessment test; CI, confidence interval; FILD, fibrotic interstitial lung disease; IPF, idiopathic pulmonary fibrosis; OR, odds ratio; PPF, progressive pulmonary fibrosis; SGRQ, St George's respiratory questionnaire.

and the 2 year 6MWD was evaluated in 252 patients. Clinically important deterioration over 2 years in the 6MWD was observed in 33 (52.4%) of 63 patients with PPF and 40 (21.2%) of 189 patients without PPF, respectively. PPF was significantly associated with clinically important deterioration in the 6MWD (odds ratio 4.10; 95%CI 2.24–7.51, $p < 0.01$).

Discussion

We evaluated the changes in the SGRQ and CAT scores in patients with non-IPF FILD and PPF compared with those without PPF. Our data showed that both the SGRQ and CAT scores were significantly deteriorated in non-IPF FILD with PPF. The fact that up to 40% of patients with PPF had significant worsening of the SGRQ and CAT scores indicates that majority of patients with PPF do not experience a significant deterioration. On the other hand, only about 15% of patients without PPF had a significant deterioration of the SGRQ and CAT scores indicating that the HRQoL is unlikely to be worsened in patients without PPF. To our knowledge, this is the first study to assess the utility of the SGRQ and CAT scores in non-IPF FILD focused on PPF.

Our results showed that the mean change in the SGRQ total score from baseline to 2 years was about 6 points in patients with non-IPF FILD and PPF. A previous study (the INPULSIS trial) showed that patients with IPF had mean changes of about 4 points in the SGRQ total score in 52 weeks (20). Therefore, non-IPF FILD with PPF may have had a similar impact on the HRQoL to IPF.

The SGRQ is one of the most used tools for assessing HRQoL in patients with IPF (17, 21). Previous studies showed the SGRQ total score had a good correlation with FVC and was associated with prognosis in patients with IPF (21, 22). CAT score is also a valid HRQoL measurement and has a strong correlation with the SGRQ score in patients with IPF (23). The SGRQ and CAT scores have also been validated in patients with connective tissue disease-related ILD (18, 24, 25). Moreover, the CAT score was reported to be associated with poor prognosis in FILD (26). Although several questionnaires are available to evaluate HRQoL in patients with IPF and non-IPF FILD (27), little is known about their utility in patients with non-IPF FILD focused on PPF.

Our study showed that both SGRQ and CAT scores were significantly deteriorated in patients with non-IPF FILD and PPF. However, by using MCID to evaluate the deterioration of HRQoL, it was found that only about 40% of patients with PPF had detectable deterioration, while about 15% of patients without PPF had deterioration. Therefore, the current respiratory function test-based criteria for the progression of ILD has limited value in detecting deterioration in HRQoL. Considering that HRQoL affects prognosis independently of lung function (22, 26) and the criteria for PPF were defined from prognostic factors, HRQoL may be a good candidate for the criteria of PPF. Further studies are needed to determine whether HRQoL should be included in the criteria for PPF.

The present study showed that exercise capacity was also significantly deteriorated in PPF of ILD. Exercise capacity is reported to be a determinant of HRQoL in ILD and is a possible point of intervention. Several reports have shown that the improvement of 6MWD and HRQoL by pulmonary rehabilitation (28), while there are few studies focused on PPF of ILD, and it would be one of the future research topics.

This study has several limitations. First, it is a single-center study from a retrospective clinical cohort in Japan and the sample size for each type of non-IPF FILD was limited. There may be potential diagnostic bias and difficulty of evaluation in each type of non-IPF FILD because of the sample size and the variability of ILD diagnosis between countries. However, all diagnoses were confirmed by multidisciplinary discussion by ILD experts. Second, racial and ethnic differences may exist in patients' perceptions. Prospective validation is needed to clarify these points. Third, it should be noted that we did not evaluate PPF according to the criteria proposed by the guideline in 2022 (1). Finally, we decided the threshold values of changes in the SGRQ and CAT scores and 6MWD based on previous studies (14–16). The optimal thresholds remain controversial and the thresholds applied in this study could have overestimated or underestimated the changes.

In conclusion, our results showed that the SGRQ and CAT scores were significantly deteriorated in patients with non-IPF FILD and PPF. Approximately 40% of patients with PPF experience significant deterioration of HRQoL, while those without PPF are less likely to experience deterioration of HRQoL. Our findings suggest that HRQoL may be a valuable tool for monitoring disease progression in non-IPF FILD patients with PPF, but the current criteria for the progression of non-IPF FILD has limited value in detecting the deterioration in HRQoL. We may need to consider an evaluation of HRQoL when assessing PPF in patients with non-IPF FILD.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by Tosei General Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

RT, TM, and YK designed the study, collected the data, and wrote the original manuscript. RT performed the data analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

YK reports consultant and lecture fees from Boehringer Ingelheim Co., Ltd. and lecture fees from Sekisui Medical Co., Ltd. TF reports grants from Nippon Boehringer Ingelheim Co., Ltd., outside the submitted work. TJ reports lecture fees from Boehringer Ingelheim Co., Ltd., Astra Zeneca Co. Ltd., and Kyorin Co. Ltd.

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.2023.1067149/full#supplementary-material

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