# Long-term evaluation of pulmonary function and survival of patients with interstitial pneumonia with autoimmune features

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## Abstract

### Objective

*Interstitial pneumonia with autoimmune features (IPAF) includes patients with interstitial lung disease with autoimmune features who do not meet criteria for a connective tissue disease (CTD). Previous studies showed a wide variation in the radiologic pattern, pulmonary function and prognosis but there is still limited data on longitudinal outcomes. We aim to describe the long-term pulmonary function, radiological patterns, and survival of IPAF patients and explore a classification based on CTD-like subgroups by using clinical/serologic data.*

### Methods

*Retrospective analysis of IPAF patients who were sub-classified into six CTD-(like) subgroups: systemic lupus erythematosus-like, rheumatoid arthritis-like, Sjögren's syndrome-like, scleroderma, myositis-like, and unclassifiable. Linear mixed-effect models were used to compare the change in percent-predicted forced vital capacity (FVC%), percent-predicted diffusion capacity (DLCO%), and six-minute walk distance (SMWD) over time; and survival in the entire cohort and according to CTD-like subgroups and radiological patterns.*

### Results

*Fifty-nine patients fulfilled IPAF criteria. FVC%, DLCO%, and SMWD remained stable over time. There was no difference between usual interstitial pneumonia (UIP) versus non-UIP radiologic patterns. Thirty-five patients were sub-classified into CTD-like subgroups. Survival decreased from 79% at 60 months to 53% at 120 months in the entire cohort but was similar among CTD-like subgroups and radiological patterns.*

### Conclusion

*Long-term pulmonary function and six-minute walk test remained stable over 36 months in our IPAF cohort. Prognosis and pulmonary function in UIP had similar outcomes compared to non-UIP. Although 40% of IPAF patients could not be sub-classified, our exploratory subclassification stratified 60% of patients into a CTD-like subgroup.*

**Key words**

interstitial pneumonia with autoimmune features, connective tissue diseases, pulmonary function, usual interstitial pneumonia

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## Introduction

Interstitial lung disease (ILD) can be the first or the sole manifestation of an occult connective tissue disease (CTD) (1). The diagnostic work-up and evaluation of patients with ILD can be challenging, and determining the aetiology is important for long-term management (2, 3). Many patients with ILD have a well-defined CTD, but others do not meet rheumatologic classification criteria (4). In prior years, this group of patients has been described as lung-dominant CTD (5, 6) and autoimmune featured ILD (7). More recently, a task force has attempted to group these patients under one term: interstitial pneumonia with autoimmune features (IPAF) (8). However, this approach has the issue of including heterogeneous populations, ranging from patients with features of myositis to others with scleroderma-like features. This distinction is important because the management and prognosis of ILD in these two subgroups may be quite different (9-12). Therefore, the recognition of certain clinical features combined with specific serologic antibodies could help define phenotypes that may suggest a specific CTD. Multiple studies on IPAF have been published in the past few years (13-27) but none have followed this approach. Also, there are few data describing long-term data in IPAF patients (15, 17, 25). Unlike IPF where a pattern of usual interstitial pneumonia (UIP) is associated with significantly worse survival compared to non-specific interstitial pneumonia (NSIP), there is no pattern that has been consistently linked to worse outcome in patients with CTD-ILD, with a possible exception of rheumatoid arthritis (RA)-ILD where UIP has been associated with worse survival compared to NSIP (24, 28, 29). Previous studies have shown that in patients with IPAF, NSIP is the predominant radiologic and histopathologic pattern (14, 18). However, patients meeting IPAF criteria through the clinical and serologic domains may also have a UIP pattern (16). Interestingly, histological UIP pattern observed in IPAF patients has been described as non-typical, with inflammatory findings resembling those of CTD-ILD (30). This is particularly important as these IPAF patients with UIP might have a more favourable prognosis than patients with UIP due to idiopathic pulmonary fibrosis (IPF) and the available therapeutic options might differ significantly.

In this retrospective, single-centre study, we describe the long-term pulmonary function, exercise capacity, radiological patterns, and survival of IPAF patients, and explore a classification based on CTD-like subgroups.

## Materials and methods

We performed an electronic medical chart review of patients with ILD who were evaluated at MedStar Georgetown University Hospital, a tertiary care institution with expertise in scleroderma, from June 2008 to June 2017. We identified 374 patients who were seen in rheumatology and pulmonary clinics. After excluding patients with defined CTDs, IPF, hypersensitivity pneumonitis and drug-induced ILD, 59 met IPAF criteria (8) at the time of record review (Fig. 1). Demographic information represented in Table I was systematically collected. An interdisciplinary team consisting of a senior rheumatologist (VS) with over 30 years of experience and a senior pulmonologist who specialises in ILD (CR) classified the patients at the time of their last follow-up visit into six phenotypes based on the combination of clinical and serologic features: systemic lupus erythematosus (SLE)-like, rheumatoid arthritis (RA)-like, Sjögren's syndrome-like, scleroderma-like, myositis-like, and unclassifiable. Details of this classification can be found in Table S1 of the Supplementary file. None of these patients fulfilled criteria for a specific connective tissue disease. High resolution computed tomography (HRCT) images were blindly reviewed by two experienced board-certified thoracic radiologists (PK and PB). When disagreement occurred, both radiologists discussed the case with the pulmonologist (CR) to reach a consensus. Radiological patterns based on the recent IPF guidelines included NSIP, organising pneumonia (OP), UIP, inconsistent with UIP, and indeterminate pattern (31).

SAS 9.4 (SAS Institute, Cary, North Carolina) was used for the analysis. The

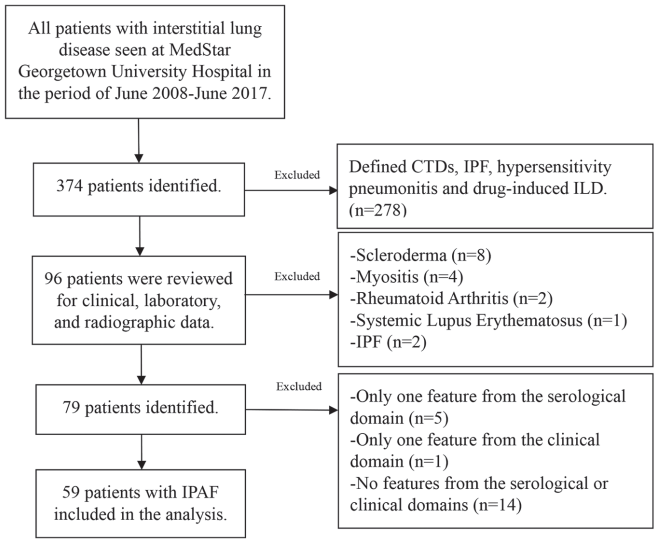


**Fig. 1.** Study diagram. ILD: interstitial lung disease; CTD: connective tissue disease; IPF: idiopathic pulmonary fibrosis; IPAF: interstitial pneumonia with autoimmune features.

**Table I.** Baseline characteristics of patients with IPAF.

| **Demographics** | IPAF n=59 |
|---|---|
| Female, n (%) | 46 (78) |
| Age, mean ± SD* | 59.8 ± 11.4 |
| **Race, n (%)** | |
| African American | 28 (47.5) |
| White | 20 (33.9) |
| Asian | 3 (5.1) |
| Hispanic | 5 (8.5) |
| Other | 1 (1.7) |
| No data | 2 (3.4) |
| **Smoking history, n (%)** | |
| Never | 43 (72.9) |
| Former | 15 (25.4) |
| Active | 1 (1.7) |
| Time from diagnosis (m), mean ± SD* | 36.2 ± 89 |
| Time from first symptom of IPAF (m), mean ± SD* | 55.2 ± 97.7 |
| Dyspnea, n (%) | 52 (88.1) |
| Cough, n (%) | 27 (45.8) |
| **Radiological patterns, n** | 59 |
| NSIP | 9 (15.3) |
| IncUIP | 9 (15.3) |
| OP | 4 (6.8) |
| pUIP | 18 (30.5) |
| UIP | 8 (13.6) |
| IND | 11 (18.6) |
| **Histological diagnosis, n** | 17 |
| NSIP | 7 |
| OP | 4 |
| NSIP+OP | 1 |
| LIP | 1 |
| UIP | 2 |
| IND | 2 |
| FVC%, mean ± SD* | 67.9 ± 19.1 |
| FEV1/FVC, mean ± SD* | 92.8 ± 18.1 |
| TLC%, mean ± SD* | 69.4 ± 17.1 |
| DLCO%, mean ± SD* | 48.7 ± 19.1 |
| 6MWD, metres | 391.8 (99.1) |
| CK, mean ± SD, min - max* | 288.8 ± 1009, 29 – 6708 |
| Aldolase, mean ± SD, min - max* | 8.1 ± 3.8, 2.4 – 21.8 |
| ESR, mean ± SD, min - max* | 49.2 ± 29.7, 4 – 128 |
| CRP, mean ± SD, min - max* | 16.4 ± 27.8, 0.2 – 143 |

IPAF: interstitial pneumonia with autoimmune features; NSIP: non-specific interstitial pneumonia; UIP: usual interstitial pneumonia; inc: inconsistent with; OP: organising pneumonia, p: probable; IND: indeterminate; LIP: lymphocytic interstitial pneumonia; FVC%: percent-predicted forced vital capacity; FEV1: forced expiratory volume in one second; TLC%: percent-predicted total lung capacity; DLCO%: percent-predicted diffusion capacity of the lung for carbon monoxide; SMWD: six-minute walk distance; CK: creatine kinase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; n: number; SD: standard deviation; max: maximum; min: minimum; m: months.
*Age n=59, time from diagnosis n=56, time from first symptom n=58, FVC% n=54, FEV1/FVC n=48, TLC% n=48, DLCO% n=51, CK n=44, aldolase n=33, ESR n=32, CRP n=27.

continuous variables were described with mean and standard deviation; the categorical variables were reported with frequencies and percentages. Linear mixed-effect models were used to compare the change in percent-predicted forced vital capacity (FVC%), percent-predicted diffusion capacity (DLCO%), and six-minute walk distance (SMWD) over time in the entire cohort, according to CTD-like subgroups and radiological patterns. Time from initial diagnosis to death from any cause according to subgroups was evaluated with Kaplan-Meier survival curves and log-rank tests. For a patient who was lost to follow-up, survival time was censored at the last follow-up date. The models were further adjusted for gender, age, race, smoking status, and *prior treatment* (defined as the use of steroid and/or immunosuppressive therapy). Results are presented as hazard ratios (HR) with 95% confidence intervals (CI). The study protocol followed the standard norms of the Helsinki declaration and was approved by our local Institutional Review Board (Natural History of ILD in rheumatic diseases 2016-1207).

## Results

Fifty-nine patients with IPAF were included in the analysis. Forty-six (78%) patients were female and 28 (47.5%) were African Americans (Table I). The mean age at diagnosis was 59.8 years (SD 11.4). Thirty-five out of 59 patients experienced dyspnea as their first symptom and 13 of them developed cough over time. Six out of the 59 patients experienced cough as their first symptom and 5 of those patients developed dyspnea over time. Eighteen patients had other non-respiratory symptoms as their first symptom. Eleven of these patients developed dyspnea and 7 developed cough over time while 6 patients did not develop neither cough nor dyspnea. Table I describes the baseline characteristics of the cohort. Mean follow-up time was 3.1 years (SD 2.7). Table II reviews the features these patients had within the different IPAF domains and shows their associated autoantibodies.
Regarding IPAF domains, 49 (83.1%) patients met the clinical criteria, 56 (94.9%) met the serological criteria, and

**Table II.** IPAF domains in 59 patients with IPAF.

| IPAF domains | n (%) |
|---|---|
| **Clinical domain** | |
| Mechanic's hands | 1 (1.7) |
| Distal digital tip ulceration | 1 (1.7) |
| Inflammatory arthritis/joint stiffness ≥60 min | 24 (40.7) |
| Palmar telangiectasia | 5 (8.5) |
| Raynaud phenomenon | 26 (44.1) |
| Unexplained digital oedema | 10 (16.9) |
| Gottron's sign | 3 (5.1) |
| None | 25 (42.4) |
| **Serological domain*** | |
| *ANA* | 42 |
| ANA≥1:320 titre | 31 |
| ANA nucleolar pattern (any titre) | 12 |
| Anti-centromere pattern (any titre) | 2 |
| RF ≥2x upper limit of normal | 14 |
| Anti-CCP | 9 |
| Anti-dsDNA | 4 |
| Anti-Ro (SSA) | 19 |
| Anti-La (SSB) | 5 |
| Anti-ribonucleoprotein | 10 |
| Anti-Smith | 2 |
| Antitopoisomerase (Scl-70) | 9 |
| Anti-tRNA synthetase | |
| JO 1 | 1 |
| PL7 | 1 |
| PL12 | 0 |
| EJ | 0 |
| OJ | 0 |
| Anti-PM-Scl | 1 |
| Anti-MDA-5 | 0 |
| Other antibodies¶ | 0 |
| **Morphological domain** | |
| Radiological diagnosis** | 13 |
| NSIP | 9 |
| OP | 4 |
| NSIP with OP | 0 |
| Histological diagnosis | 13 |
| NSIP | 7 |
| OP | 4 |
| NSIP with OP | 1 |
| Interstitial lymphoid aggregates with germinal centres | 0 |
| Diffuse lymphoplasmacytic infiltration b | 1 |
| Multicompartment involvement# | 13 |
| Unexplained pleural disease | 3 (5.1) |
| Unexplained pericardial disease | 3 (5.1) |
| Unexplained pulmonary vasculopathy## | 8 (13.6) |
| Unexplained intrinsic airway disease | 1 (1.7) |
| **Domains** | |
| Clinical domain | 49 (83.1) |
| Serological domain | 56 (94.9) |
| Morphological domain | 34 (57.6) |
| Clinical/Serological domain | 46 (78) |
| Serological/Morphological domain | 31 (52.5) |
| Clinical/ Morphological domain | 24 (40.7) |
| All domains | 21 (35.6) |
| **Other characteristics not included in IPAF criteria** | |
| History of weakness | 6 (10.2) |
| Objective weakness | 0 |
| Skin thickening | 8 (13.6) |
| Sicca symptoms | 10 (17) |
| Abnormal nailfold capillaries | 7 (11.9) |
| Alopecia | 3 (5.1) |
| Gastrointestinal reflux | 12 (20.3) |
| Oral/nasal ulcers | 0 |

*The following lists the number of patients who had these tests done. ANA by immunofluorescense n=58, anti-centromere n=32, RF n=46, CCP n=43, dsDNA n=42, Anti-Ro n=52, Anti-La n=51, Anti-RNP n=40, Anti-Smith n=43, Scl70 n=52, JO n=36, PL7 n=7, PL12 n=5, EJ n=5, OJ n=5, Anti-PM-Scl n=7, MDM-5 n=1, Mi2 n=5, Ku n=5, U2 RNP n=3, SRP n=4, KS n=1, Zo N=1, tRS n=1, Th/To n=13, U3RNP n=14, RNA Pol III n=13.
¶ Mi2, Ku, U2 RNP, SRP, KS, Zo, tRS, Th/to, U3 RNP, RNA Pol III
**Three patients had the same radiological and histopathological diagnosis.
# Three patients had two features.
## Right ventricular systolic pressure greater than 45 mmHg on transthoracic echocardiogram or a mean pulmonary artery pressure greater than 25 mmHg on right heart catheterisation.

34 (57.6%) met the morphological criteria. When sub-classifying patients based on clinical and serological features, we identified 35 (59.4%) patients who were grouped into one of the CTD-like phenotypes (Supplementary Table S1). The largest CTD-like group included 21 scleroderma-like patients who had a variety of antibodies and clinical features but did not meet criteria for scleroderma (23). Myositis-like patients (n=4) had some combination of antibodies and clinical findings, but none of them had any muscle weakness on physical exam. There were 4 Sjögren's syndrome-like patients and 5 RA-like patients, none of whom fulfilled criteria for these diseases. There was one SLE-like patient who had photosensitivity and arthritis, but no lupus specific autoantibodies. Interestingly, 24 (40.7%) patients did not have features that could be classified as any of the CTD-like subgroups and were called unclassifiable.

Of the 59 patients, 46 HRCT scans were available for review by our radiologists. The remaining 13 patients had reports available from which their radiologic diagnosis was obtained. The most common diagnoses we found were probable UIP, indeterminate pattern and inconsistent with UIP, which were not included as part of the IPAF radiologic criteria (Suppl. Table S2). Intriguingly, the scleroderma-like subgroup more frequently had probable UIP or UIP rather than NSIP, which is more commonly seen in scleroderma. This was also true for the Sjögren's syndrome-like and myositis-like subgroups. Only 13 patients had NSIP or OP on HRCT. Baseline pulmonary function tests (PFT) according to subgroups can be found in Supplementary Table S3.

Sixty-six percent of the patients had received immunosuppression that included steroids (59.3%), mycophenolate mofetil (39%), azathioprine (15.3%), methotrexate (11.9%), cyclophosphamide (3.4%), rituximab (1.7%), and tacrolimus (1.7%).

### *Linear mixed model analysis for pulmonary function tests*

Adjusted analysis showed that FVC% decreased over time in the entire cohort but the change was not significant

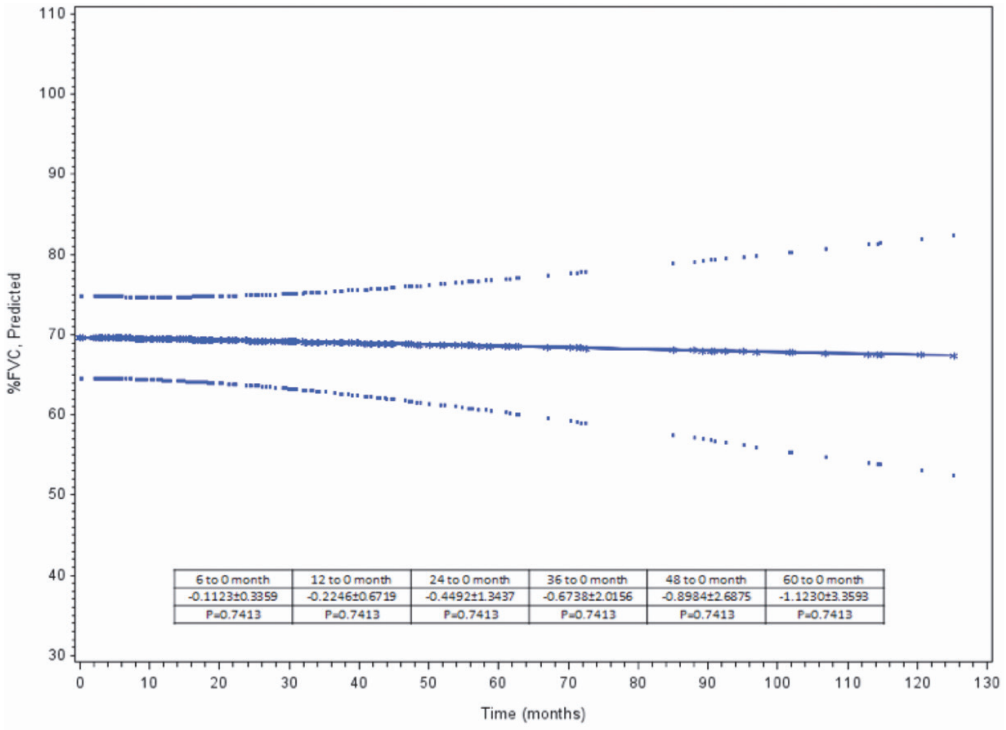


**Fig. 2.** Mixed-effects model estimates for predicted forced vital capacity over time in all patients with IPAF.

over time ($p$=0.8663). No difference in FVC% was found at 6-, 12-, 24-, 36-, 48-, and 60-month follow-up (Fig. 2). Patients with myositis-like phenotype had better FVC% than other subgroups (Fig. 3, $p$<0.04). Patients with OP had a higher FVC% compared to NSIP ($p$=0.0461) and UIP ($p$=0.02). All other pairwise comparisons had no significant difference. No difference was found when stratifying the patients based on the presence of UIP ($p$=0.1819, Fig. 4). DLCO% remained stable in the entire cohort (adjusted analysis, $p$=0.1665) over time. No difference was found at 6-, 12-, 24-, 36-, 48-, 60-month follow-up ($p$=0.1684, Suppl. Fig. S1). No difference was found when stratifying the cohort into CTD-like subgroups. Stratifying the cohort according to the presence of UIP showed no difference between groups ($p$=0.2726, Suppl. Fig. S2). However, patients with UIP had lower DLCO% when directly compared to NSIP ($p$=0.0277).

*Linear mixed model analysis for SMWD*

SMWD remained stable over time (adjusted analysis, $p$=0.1877). The SMWD at 6-, 12-, 24-, 36-, 48-, and 60-month did not differ from baseline ($p$=0.2699). Patients with the myositis-like phenotype had significantly higher SMWD than scleroderma-like patients ($p$=0.0062). No difference was seen among different radiologic patterns (Suppl. Fig. S3) or when patients were stratified according to the presence of UIP.

*Survival analysis*

Overall, 15 patients with IPAF died during the study period. The survival probability of our cohort was 0.98 at 12 months, 0.91 at 24 months, 0.79 at 60 months and 0.53 at 120 months (Suppl. Fig. S4). A Cox proportional regression analysis identified gender, age and smoking history as significant predictors of hazard (Suppl. Table S4). Interestingly, survival according to radiological pattern showed no difference between UIP and non-UIP patients. ($p$=0.8335, Suppl. Fig. S5).

## Discussion

We report a large series of IPAF patients with longitudinal outcomes on their disease course over an average course of 36 months and explore a classification based on CTD-like subgroups. We believe that IPAF includes heterogeneous populations; therefore, defining subgroups could have a potential implication in the diagnosis, treatment and prognosis of a subset of IPAF patients (3, 4). Although several retrospective investigations have been published, there have been limited data on disease progression in IPAF patients (15, 17, 25). To our knowledge, this is one of the largest IPAF studies that reports longitudinal PFTs, SMWD, and survival data and the first study that explores a classification of CTD-like subgroups based on the combination of clinical and serologic features.

Our study includes 59 patients who met IPAF criteria out of a cohort of 374 patients with ILD. Our patients were predominantly females, never smokers and younger (mean age 59.8) than a typical IPF population. This is consistent with the findings of Chartrand *et al*. (25) and Alevizos *et al*. (27) but differs from findings by Oldham *et al*. (21) and Ahmad *et al*. (14) who found patients to be more likely male with a mean age closer to 63. This may be due to the fact that they included patients with previously diagnosed IPF who met IPAF criteria in their cohort (21), whereas our study excluded patients with a multidisciplinary diagnosis of IPF and CTD-ILD based on history, clinical exam and imaging. The serologic domain for IPAF, particularly a strongly positive ANA titre, was most frequently present in our cohort, followed by the clinical and morpholog-

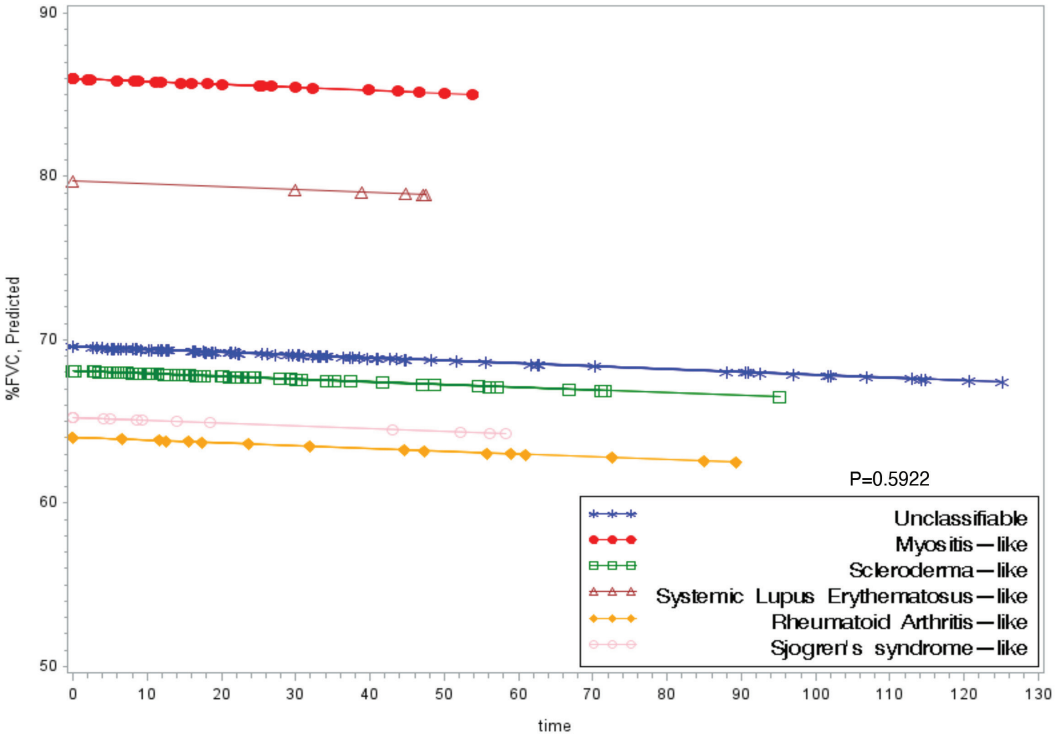


**Fig. 3.** Mixed-effects model estimates for predicted forced vital capacity over time in patients with IPAF according to CTD-like subgroups.

ical domains. The most frequent clinical manifestations were Raynaud's phenomenon (44.1%) and arthritis (40.7%). These observations were similarly seen in other cohorts (14, 21, 24). The most frequent positive serologies were ANA and SSA, which were also seen in other studies (15, 19, 21, 26, 27).

On HRCT, NSIP was seen in less than 20% of our patients. The most common radiological pattern in our cohort was probable UIP (30.5%), even though we excluded patients with a convincing diagnosis of IPF (Table I). As radiological UIP is not part of the IPAF criteria, this demonstrates that most of our cohort fulfilled the serologic and clinical domains (78%). Oldham *et al*. (21) have also reported a large number of patients with UIP, possibly because their study was done in an IPF referral centre. In our study, it is not clear why probable UIP was the most common pattern observed, as NSIP is the pattern typically described in CTD-ILD (32, 33). Surprisingly, only 2 out of 5 patients classified as RA-like had a UIP pattern even though there is a higher prevalence of UIP in RA compared to other CTDs (34). Furthermore, unexplained pulmonary vasculopathy was seen in 13.6% of patients and has been the most common multicompartment feature described in other IPAF populations as well (14, 15). Ito *et al*. attempted to create subgroups based on serology only (19). Our study, on the other hand, incorporated clinical manifestations and serologic studies to help better delineate IPAF sub-groups. Although 40% of the IPAF patients could not be sub-classified, our exploratory subclassification was able to stratify almost 60% of the patients into a CTD-like subgroup. This highlights the complexity associated with subclassifying IPAF patients and their heterogeneity. However, we still feel this subclassification is important not only for diagnostic purposes but for treatment and prognosis, at least, in a subset of patients. Subgrouping IPAF patients is important because treatment of CTD-ILD varies depending on the specific underlying CTD. For instance, the treatment of SLE, Sjögren's syndrome and myositis-related ILD typically involves high doses of corticosteroids plus a steroid sparing agent like azathioprine, mycophenolate mofetil or rituximab (32, 35, 36). Conversely, patients with systemic sclerosis associated ILD usually receive mycophenolate mofetil with low dose or no steroids (35).

This is the first IPAF study that looks at the change in PFTs and SMWD over time based on radiologic diagnosis. Our cohort showed a slow non-significant decline in FVC%, TLC% and DLCO% over 3 years. By stratifying the cohort based on the presence of radiological UIP, these patients had a non-significant lower FVC% and DLCO% over time when compared to non-UIP patients. Kelly *et al*. also published similar results describing a trend towards lower TLC% and DLCO% in IPAF patients with UIP (37). Similarly, Chartrand *et al*. showed stable FVC% over time in IPAF patients (15). Notably, our study shows a similar lung function and survival between patients with UIP and non-UIP which is consistent with recent data from Sebastiani *et al*. (26) but differs from Oldham *et al*. who reported worse survival in IPAF patients with a UIP pattern (21). There is growing evidence that IPAF patients tend to have a longer survival than IPF patients, despite the presence of a UIP pattern (24). UIP represents a frequent pattern in many CTD and previous studies in CTD-ILD, except for RA-ILD, have shown similar survival rates between NSIP and UIP (28, 29). This is an evolving field that requires further investigation.

This distinction between patients with IPAF and those with CTD-ILD and IPF becomes important when considering treatment options. McCoy *et al*.

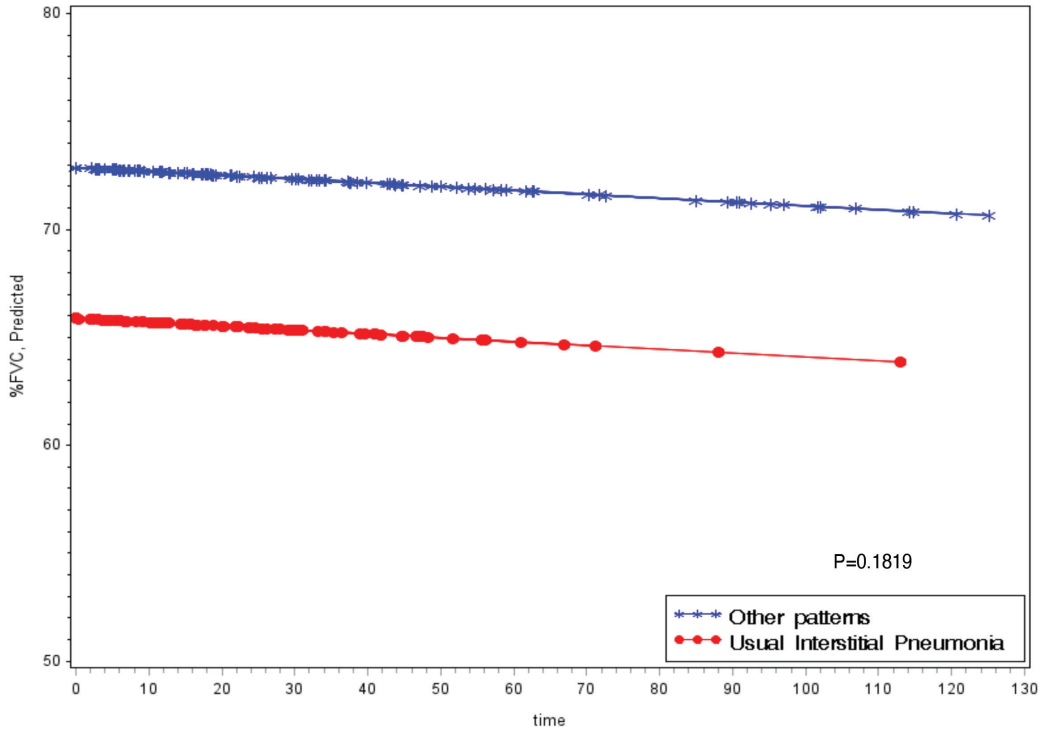


**Fig. 4.** Mixed-effects model estimates for predicted forced vital capacity over time in patients with IPAF according to the presence of radiological UIP.

(38) showed no difference in FVC% and DLCO% between patients treated and those not treated with mycophenolate mofetil (MMF). Benad *et al*. (39) showed that cyclophosphamide and/or rituximab led to improvement of FVC% in 12 patients, and stabilisation in 14 out of 27 severely sick patients with ILD associated with systemic sclerosis, antisynthetase syndrome and Sjögren's syndrome. In our survival and mixed model analysis of FVC% and DLCO%, there was no difference over time, even after adjusting the models for the prior use of treatment. This raises the question if IPAF patients should be started on treatment or not. Further research is warranted, especially taking into consideration our proposed clinical IPAF subgroups in order to tailor the treatment to the CTD that the patient resembles.

The literature on survival in patients with IPAF is limited but actively growing. The majority of retrospective studies have observed worse survival in these patients compared to those with defined CTDs but better survival than patients with IPF (18, 21, 24-26, 37). However, Ahmad *et al*. failed to find a difference, probably due to the short follow-up of the study (14). The survival probability of our cohort was 98.3% at 12 months and 52.8% at 120 months, which is comparable to other studies (18, 28).

Future studies should focus on the prospective data collection of patients with IPAF and should include evaluation and discussion with a multidisciplinary team, including a thoracic radiologist, an ILD specialist and a rheumatologist. Moreover, perhaps the extensive serologic work-up listed in the IPAF criteria should be performed on all patients with a new diagnosis of ILD, although the cost-effectiveness of this intervention needs to be studied. Ito *et al*. described that 12 (12.2%) patients had developed additional characteristics that subsequently led to a diagnosis of a well-defined CTD during follow-up of almost 5 years (19). Currently, there are no guidelines on when patients should be retested or re-examined to monitor for the development of a defined CTD (19). This study has several limitations including its retrospective design and small number of subjects. However, the clinical, demographic, and imaging data were collected prospectively, which decreased the amount of missing data. Furthermore, some of these patients did not have the complete set of serologies listed in the IPAF criteria. This may have caused us to miss a certain subset of this population and may have also prevented further subgrouping. However, previous reports also did not perform all serologic examinations as this approach can be expensive and its significance has not been well-studied (18). Notably, the scleroderma-like subgroup was the most common subgroup in our cohort, probably because our institution is a scleroderma referral centre, but also because scleroderma has the highest frequency of significant ILD of all the CTDs (32). Lastly, no comparisons based on treatment were done, mainly because there is no consensus in the best treatment of IPAF patients. However, we included the variable *prior treatment* in our mixed-model analysis. Our study has several strengths. A multidisciplinary team composed of an experienced rheumatologist and an ILD specialist gave us a high percentage of patients who had criteria in the clinical domain. Chartrand *et al*. (15) also reported the presence of a rheumatologist and their cohort had more features and outcomes similar to CTD-ILD. Our study also presents longitudinal data on important outcomes such as lung function, six-minute walk, and survival and explores a new subclassification that attempts to subgroup a subset of IPAF patients. We believe that our study will add to the accumulating evidence on

IPAF patients and that the sub-classification of patients into CTD-like groups may allow the evaluation of treatments in each subgroup, at least, in a subset of patients.

## Conclusions

Long-term pulmonary function and six-minute walk test remained stable over the course of 36 months in our IPAF cohort. Survival decreased from 79% at 60 months to 53% at 120 months. Prognosis and pulmonary function in UIP patients had similar outcomes compared to non-UIP. Despite using an exploratory sub-classification based on clinical and serologic features, only 60% of the patients were subclassified into CTD-like subgroups which highlights the complexity and heterogeneity of IPAF patients.

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