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Interstitial pneumonia with autoimmune features: evaluation of connective tissue disease incidence during follow-up

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ABSTRACT

Objectives. Among interstitial pneumonia with autoimmune features (IPAF) patients, identifying those at risk to develop a connective tissue disease (CTD) during the disease course is a key issue. The aim of this study was to evaluate the incidence of definite CTD diagnosis in IPAF patients during follow-up.

Methods. We performed a multicentric cohort study of interstitial lung disease (ILD) from 2010 to 2017 in pneumology and immunology departments of tertiary care centers. Patients with a known cause of ILD (including established CTD) at diagnosis were excluded. Among patients with idiopathic ILD and at least three years of follow-up, two groups (IPAF and non-IPAF) were retrospectively analyzed at time of diagnosis.

Results. A total of 249 patients with ILD were enrolled, including 70 IPAF and 179 non-IPAF patients. After a mean follow-up time of 77 ± 44 months, 18/70 IPAF patients (26 %) had a CTD diagnosis – 9 antisynthetase syndrome, 8 systemic sclerosis and 1 overlap myositis – compared with 4/179 non-IPAF patients (2 %). IPAF patients were at higher risk of CTD occurrence at 3 years of follow-up compared to non-IPAF patients (HR 10.1, 95 % CI 3.1- 33.1, $p < 0.01$). IPAF patients progressing to CTD tended to be younger, more often female and have more frequently puffy fingers, capillaroscopy abnormalities and antisynthetase antibodies at diagnosis.

Conclusions. We found that a significant proportion of IPAF patients had associated CTD diagnosis during follow-up. Prospective studies are needed to confirm baseline predictive factors of CTD occurrence in IPAF patients.

Keywords: interstitial pneumonia with autoimmune features, interstitial lung disease, connective tissue disease, antisynthetase syndrome, systemic sclerosis

1. Introduction

Interstitial lung diseases (ILD) are a heterogenous group of diseases characterized by diffuse abnormal deposition of collagen matrices in the pulmonary parenchyma [1,2]. Interstitial lung diseases (ILD) represent a frequent complication of connective tissue diseases (CTD), especially in systemic sclerosis (SSc) (55-65 % of patients), idiopathic inflammatory myopathies (15-35 % of patients) and rheumatoid arthritis (RA) (almost 30 % of patients) [3–6]. ILD remains a cause of significant morbidity and mortality in patients with CTD [7]. As immunosuppressive treatments can improve or stabilize lung function in CTD-ILD patients, early detection of ILD in CTD patients is crucial [8]. ILD can either occur during CTD course or be the first manifestation of CTDs. In idiopathic inflammatory myopathies, ILD concern 10-30 % of patients at the time of diagnosis, and up to 50 % in patients with antisynthetase syndrome (ASS) [9–11]. Therefore, screening patients with ILD for a CTD is a major issue. In some cases, patients with ILD display clinical or serological autoimmune features but fail to meet current international CTD classification criteria. Various definitions have been used to describe these patients in the literature: "undifferentiated connective tissue disease-associated ILD", "autoimmune-featured ILD" and "lung-dominant CTD" [12–14]. Recently, the European Respiratory Society/American Thoracic Society experts proposed a new classification, "interstitial pneumonia with autoimmune features" (IPAF) [15]. While IPAF outcomes have been well studied in the past few years, data regarding CTD occurrence in IPAF patients during follow-up are scarce. In several studies with patients of rheumatology/internal medicine units classified as undifferentiated connective tissue disease, 25-40 % of them had a diagnosis of a definite CTD during follow-up [16,17]. Identifying IPAF patients at risk to develop CTD during follow-up is essential, as they may be best suited to receive immunosuppressive therapies [18].

Therefore, the aims of this study were to assess and compare the incidence of a definite CTD diagnosis during the disease course of IPAF and non-IPAF patients in an idiopathic interstitial pneumonia cohort and to determine factors associated with CTD progression in IPAF patients at the time of ILD diagnosis.

2. Patients and methods

2.1. Patients

We conducted a retrospective multicentric cohort study (NCT04179058) in 3 French tertiary care centers (Nancy, Lille and Metz). Study protocol was approved by the local ethics committee of Nancy University Hospital. A PMSI database research for all patients with a diagnosis of "interstitial lung disease" (i.e. J84.0, J84.1, J84.8 and J84.9 ICD-10 codes) between January 2010 and December 2017 in pneumology and immunology departments were performed and clinical notes were reviewed by an internal medicine specialist (PD) with expertise in rheumatology. Among the 3101 patients screened, patients with a new diagnosis of ILD confirmed by two chest high-resolution computerized tomography (HRCT) 3 months apart and with at least three years of follow-up were included (Fig. 1). Patients with a defined CTD or a known cause of ILD at the time of diagnosis were excluded. Patients with ILD pattern of combined pulmonary fibrosis and emphysema, pleuroparenchymal fibroelastosis or desquamative interstitial pneumonia were excluded. All subjects were enrolled after providing informed consent (all patients received an information document with opposition form, as required by the French legislation). Then, two groups were retrospectively constituted – IPAF and non-IPAF patients – according to 2015 ERS/ATS IPAF criteria definition, irrespective of other ILD diagnoses (idiopathic pulmonary fibrosis, idiopathic non-specific interstitial pneumonia, unclassifiable ILD for example). IPAF diagnosis was considered in the presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) and, exclusion of alternative aetiologies and, absence of criteria of a defined CTD and, at least one feature from at least two domains among clinical domain, serologic domain and morphologic domain (online appendix 1) [15].

2.2. Definitions of CTD

CTDs were defined in accordance with updated international classification criteria as followed: 2010 American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) criteria for RA, 2019 ACR/EULAR criteria for systemic lupus erythematosus (SLE), 2016 ACR/EULAR criteria for Sjögren syndrome (SS), 2013 ACR/EULAR criteria for SSc and 2017 EULAR/ACR criteria for idiopathic inflammatory

myopathies [19–23]. ASS was defined by fulfillment of the 2011 Solomon proposed criteria [5].

2.3. Data collection and definition

A standardized case report form captured demographic, clinical, radiological and laboratory features. IPAF clinical, serological and morphological domains criteria at the time of ILD diagnosis were carefully evaluated retrospectively by an internal medicine specialist (PD) with expertise in rheumatology. HRCT patterns of ILD were determined based on conclusions of multidisciplinary discussion or thoracic radiologists and/or clinicians in medical records. Histopathology patterns of ILD were determined based on pathologists conclusions. The primary outcome measures were CTD incidence after 3 and 5 years of follow-up. Severe ILD at diagnosis was defined as forced vital capacity (FVC) predicted values < 70 % or diffusing capacity of the lung for carbon monoxide (DLCO) predicted values < 50 % [24]. ILD worsening was defined as a decline > 10 % of FVC predicted values or > 15 % of DLCO predicted values at 6 months of initial diagnosis [25]. Pulmonary hypertension (PH) was suspected in case of echocardiographic estimates of systolic pulmonary artery pressure (sPAP) ≥ 35 mmHg. Survival rates without death or lung transplantation were evaluated after 3 and 5 years of follow-up.

2.4. Statistical analysis

Categorical variables were reported as counts and percentages. Continuous variables were described by means with standard deviations (SD) or medians with interquartile range (IQR). Chi-square test or Fischer's exact test for categorical variables and Student's t-test or Mann-Whitney U test for continuous variables were used to compare IPAF and non-IPAF patients, as appropriate. D'Agostino-Pearson normality test was used to evaluate data distribution. Survival curves were generated using Kaplan-Meier method and log-rank test was used to compare survival distributions of IPAF and non-IPAF patients. Statistical analyses were performed using GraphPad Prism. Alpha risk was 5 % for all analyses.

3. Results

Of the 3101 patients with a diagnosis of "interstitial lung disease" according to the hospitals coding systems, we identified 933 patients (30 %) with an idiopathic ILD and 2168 patients (70 %) with a known cause of ILD at baseline (Fig. 1). Two hundred and forty-nine patients with idiopathic ILD were included. Among them, 70/249 patients (28 %) met the 2015 ERS/ATS classification criteria for IPAF at initial diagnosis and 179/249 patients (72 %) did not. A high number of non-IPAF patients had idiopathic pulmonary fibrosis (data not shown). The mean follow-up duration (or ILD duration) of the entire cohort was 71 ± 33 months, with no significant difference between IPAF and non-IPAF patients (77 ± 44 *vs.* 64 ± 25 months, p = 0.13; Table 1). Compared to subjects without IPAF, IPAF patients were younger (mean age 62 ± 13 *vs.* 67 ± 10 years, p = 0.005) and more frequently female (47 % *vs.* 28 %, p = 0.005). No significant differences in body mass index (BMI) and tobacco consumption were observed between IPAF and non-IPAF patients. IPAF patients had more a non-specific interstitial pneumonia (NSIP) HRCT pattern (83 % *vs.* 27 %, p < 0.0001), while patients without IPAF had more a usual interstitial pneumonia (UIP) HRCT pattern (67 % *vs.* 9 %, p < 0.0001). Regarding clinical presentation at ILD diagnosis, we observed a higher prevalence of Raynaud's phenomenon (7 % *vs.* 1 %, p < 0.0001), microangiopathy defined by nailfold capillaroscopy (31 % *vs.* 4 %, p = 0.006), mechanic hands (4 % *vs.* 0 %, p = 0.02), swollen and tender joints (7 % *vs.* 1 %, p = 0.02 and 6 % *vs.* 1 %, p = 0.02, respectively) in patients with IPAF. Antinuclear antibodies (ANA) were more frequently detected in IPAF patients (61 % *vs.* 7 %, p < 0.0001). Anti-Ro52 antibodies (16 % *vs.* 1 %, p < 0.0001), anti-Ro60 antibodies (4 % *vs.* 0 %, p = 0.03), anti-RNP antibodies (6 % *vs.* 1 %, p = 0.03), anticentromere antibodies (6 % *vs.* 0 %, p = 0.007), anti-aminoacyl tRNA synthetase antibodies (31 % *vs.* 7 %, p = 0.0007) and rheumatoid factor (24 % *vs.* 5 %, p < 0.0001) were more prevalent in IPAF patients.

During the follow-up, 18/70 IPAF patients had a CTD diagnosis compared to 4/179 patients without IPAF (26 % *vs.* 2 %, p = 0.0004; Table 2). The median time to CTD onset was similar between IPAF and non-IPAF patients (25 [12-59] *vs.* 29 [12-54] months, p = ns). Of the 18 IPAF patients with a subsequent CTD diagnosis, nine had ASS, eight had SSc and one had overlap myositis (patient with Raynaud's phenomenon, capillaroscopy abnormalities, myositis and ANA positivity without myositis- or SSc-specific autoantibodies). In the group of patients without IPAF, two had a diagnosis of RA, one of

ASS and one of SSc. Initial presentation and further clinical or laboratory features leading to CTD diagnosis during follow-up are described in online supplementary Table S1. In survival analysis, IPAF patients were at higher risk of a definite CTD diagnosis at 3-years (HR = 10.1, 95 % CI 3.1-33.1, p < 0.0001; online supplementary Fig. 1) and 5-years (HR = 9.6, 95 % CI 3.4-27.2, p < 0.0001; online supplementary Fig. 2) of follow-up compared to patients without IPAF. When adjusting survival analysis for age (< 60 or ≥ 60 years) and gender, IPAF patients were still at higher risk of progressing to a CTD at 3-years of follow-up (online supplementary Fig. 3). Next, we compared clinical, serological and morphologic features at ILD diagnosis between IPAF patients with a later diagnosis of CTD during follow-up or not, to study factors associated with CTD progression in IPAF patients (Table 3). Unless non-significant, IPAF patients progressing to CTD were more frequently female (67 % *vs.* 40 %, p = 0.06) and tended to be younger (mean age 58 ± 3 *vs.* 63 ± 2 years, p = 0.1), have more frequently microangiopathy (56 % *vs.* 20 %, p = 0.09), puffy fingers (11 % *vs.* 0 %, p = 0.06), and anti-aminoacyl tRNA synthetase antibodies (50 % *vs.* 25 %, p = 0.1) at the time of diagnosis.

IPAF patients were more symptomatic at the time of ILD diagnosis compared to patients without IPAF (27 % *vs.* 13 % and 12 % *vs.* 5 % patients with functional NYHA class III and IV respectively, p = 0.005; Table 4). The proportion of severe ILD at diagnosis was higher in IPAF patients (64 % *vs.* 33 %, p < 0.0001). IPAF patients received more immunosuppressants than non-IPAF patients (median number of immunosuppressants used 2 [1-3] *vs.* 0 [0-1], p < 0.0001; Table 5). The proportion of patients receiving three or more immunosuppressive drugs during follow-up was higher in IPAF patients (41 % *vs.* 8 %, p < 0.0001). Corticosteroids (89 % *vs.* 23 %, p < 0.0001), azathioprine (40 % *vs.* 15 %, p < 0.0001), cyclophosphamide (20 % *vs.* 6 %, p = 0.002) and mycophenolate mofetil (37 % *vs.* 9 %, p < 0.0001) were more frequently used in IPAF patients compared to non-IPAF patients. If the cumulative risk of death and the cumulative risk of death or lung transplantation were not different between IPAF and non-IPAF patients, the mean time to death and the mean time to death or lung transplantation were shorter in patients without IPAF (mean time 58 ± 17 *vs.* 84 ± 48 months, p = 0.04 and 54 ± 17 *vs.* 84 ± 48 months, p = 0.01, respectively; Table 5). In survival analyses, no statistical difference was observed regarding death or lung transplantation at 5-years of follow-up between IPAF and non-IPAF patients (online supplementary Fig. 4).

DISCUSSION

In this study, we used a multicentric cohort of idiopathic interstitial pneumonia to study CTD occurrence in patients with IPAF during the follow-up. We found that IPAF patients were at higher risk to develop a definite CTD (10-fold higher hazard ratio of progression to a CTD at 3-years and 5-years of follow-up) compared to patients who did not meet IPAF criteria, especially antisynthetase syndrome and systemic sclerosis.

Importantly, IPAF patients had a higher risk of progression to a definite CTD after 3-years and 5-years of follow-up, with a median time to CTD onset of approximately 2 years, even after adjusting survival analysis for gender and age at diagnosis. This finding confirms previously reported data in two retrospective IPAF cohorts. Indeed, Alevizos *et al.* and Ito *et al.* found that 8/50 IPAF patients (16 %) and 12/98 IPAF patients (12 %) had a CTD diagnosis during the follow-up, after a median time of 3.4 years and 4.5 years respectively [26,27]. In a German cohort of 260 patients with idiopathic interstitial pneumonia, 37 patients (14 %) developed CTD during follow-up and ANA positivity and NSIP HRCT-pattern were associated with CTD development [28]. In our cohort, the main CTD occurring during follow-up were ASS and SSc. Our results support the fact that ILD can easily be the presenting manifestation in patients with ASS and SSc or even the initial manifestation in patients with ASS. As proposed in undifferentiated connective tissue disease by Mosca *et al.*, these patients could represent incomplete forms of CTD at initial diagnosis or "early-CTD" [16]. In these cases, evolution to definite CTD usually occurs within the first 5 years of disease [16,17]. One first issue is the use of classification rather than diagnostic criteria for CTD diagnosis. Classification criteria are suitable for clinical trials and research, with high specificity but less sensitivity for the recognition of CTD at the initial course of the disease. Inclusion of antisynthetase antibodies is another major issue of current IPAF criteria. For some authors, ILD patients with NSIP and/or organizing pneumonia HRCT-pattern and isolated antisynthetase antibodies – especially patients with non-Jo1 antisynthetase antibodies in which ILD occurrence without other clinical manifestations is common – who meet IPAF classification criteria should be considered as patients with ASS [29,30]. Recently, Graham *et al.* have demonstrated that IPAF patients with myositis-specific antibodies (MSA) had similar outcomes that patients with idiopathic inflammatory myopathies associated ILD [31]. In our study, we used proposed Solomon classification criteria for ASS to discriminate IPAF patients and patients with ASS at initial diagnosis. It

probably explains the higher frequency of IPAF patients with a diagnosis of ASS during the follow-up compared to previous reported IPAF cohorts in the literature.

Among IPAF patients, identification of predictive factors at time of ILD diagnosis is essential to better evaluate patients at risk to develop definite CTD during the disease course. In a complementary analysis, we identified that among patients with IPAF, female sex, age and specific CTD clinical signs (puffy fingers and microangiopathy on nailfold capillaroscopy) or autoantibodies (anti-aminoacyl tRNA synthetase antibodies) tended to be associated with progression to a definite CTD during the follow-up. The relatively low number of IPAF patients in our cohort possibly explain the lack of results significance and why other specific CTD clinical or serological features – like mechanic hands or scleroderma-specific autoantibodies – were not associated with CTD evolution. This low number of IPAF patients could be partly explained by the different recruitment (more patients with extra-pulmonary signs) and an exhaustive CTD screening in internal medicine units, with a higher proportion of patients with a diagnosis of CTD at the time of ILD discovery.

As described in previous IPAF cohorts, patients with IPAF were younger and with a higher proportion of female in our study [26,27,32–35]. Non-specific interstitial pneumonia HRCT-pattern, Raynaud's phenomenon and presence of antinuclear antibodies were the most encountered IPAF features as previously reported in the literature [26,33–35].

Even if it is well established that long-term outcome of CTD-ILD is better than that of idiopathic pulmonary fibrosis, the long-term prognosis of IPAF remains unclear [36,37]. Oldham *et al.* have reported that a non-UIP HRCT-pattern was associated with improved survival in IPAF patients, similar to patients with CTD-ILD [34]. In a Chinese cohort of idiopathic interstitial pneumonia, Dai *et al.* reported that IPAF patients had worse survival than non-IPAF patients, but better survival than patients with idiopathic pulmonary fibrosis in subgroup analysis [35]. In our study, no survival difference was observed between IPAF and non-IPAF patients, but we did not perform subgroup analysis because of lack of patients. We reported a higher prevalence of severe ILD in IPAF patients at time of diagnosis compared to non-IPAF patients. Patients with idiopathic pulmonary fibrosis were highly represented in non-IPAF patients (patients with idiopathic interstitial pneumonia or unclassified ILD). Idiopathic pulmonary fibrosis patients with severe ILD at diagnosis, especially with low FVC and DLCO predicted values, are at higher risk of mortality in the

first years of follow-up [38]. In our cohort, ILD patients with less than 3 years of follow-up were excluded. This selection bias probably explains the lower percentage of severe patients at ILD diagnosis and the low proportion of death or lung transplant in non-IPAF patients. The inconstant long-term prognosis described in different IPAF cohorts could also reflect the heterogeneity of IPAF patients.

Our study has several limitations. First, data were collected retrospectively with ILD diagnosis between 2010 and 2017. Patients were not systematically evaluated by an internal medicine specialist or a rheumatologist at ILD diagnosis or during the follow-up period, as actually recommended, resulting in some missing data (notably reports of subtle clinical features of autoimmunity) [39]. Furthermore, patients were not systematically discussed during a multidisciplinary discussion. Testing for non-Jo1 MSA is not routine. In our cohort, many patients were not tested for MSA resulting in an obvious results bias. However, the prevalence of specific autoantibodies – notably antisynthetase antibodies – were very similar in previous studies[26,33]. Second, our study was conducted in three different tertiary centers with their own practices regarding patient evaluation and treatment. HRCT-patterns and histopathologic patterns of ILD were not independently reevaluated by expert thoracic radiologists and pathologists for the scope of the study and classification criteria of ILD changed over the study period [40,41]. Third, the relatively small number of CTD (n = 18) observed during the disease course of IPAF patients resulted in a lack of statistical power, especially to identify clinical, serological and morphologic associated factors with CTD occurrence. Indeed, we could not perform multivariable logistic regression analysis to evaluate factors independently associated with progression to definite CTD.

To conclude, we found that a significant proportion of IPAF patients (more than a quarter of patients) had a definite CTD diagnosis during the disease course, mainly ASS and SSc. Currently, there are not consensus guidelines for evaluating CTD in ILD patients. A rheumatologist expertise can be helpful to identify ILD patients with occult CTD. A systematic screening of specific autoantibodies associated with idiopathic inflammatory myopathies and SSc should be considered in case of unexplained ILD. Identifying clinical or serological predictive factors of future CTD occurrence at ILD diagnosis is a key issue in order to not postpone immunosuppressive therapies initiation. This need to be evaluated in large prospective studies.

Data availability statement: the data underlying this article are available in the article and in its online supplementary material.

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Table 1
Clinical, laboratory and radiological features in IPAF and non-IPAF patients

	Total *(N=249)*	IPAF *(N= 70)*	Non-IPAF *(N= 179)*	P-value
Female	83/249 (33)	33/70 (47)	50/179 (28)	0.005
Age at diagnosis (years)	66 ± 11	62 ± 13	67 ± 10	0.005
BMI	28 ± 5	28 ± 5	29 ± 5	0.8
Follow-up (or ILD duration) (months)	71 ± 33	77 ± 44	64 ± 25	0.13
Tobacco	149/249 (60)	35/70 (50)	114/179 (64)	0.06
Lung biopsy	50/249 (21)	12/70 (17)	38/179 (21)	0.6
CT-pattern				< 0.0001
UIP	119/237 (50)[a]	6/69 (9)[b]	113/168 (67)[c]	
NSIP	102/237 (43)[a]	57/69 (83)[b]	45/168 (27)[c]	
LIP	1/237 (0)[a]	1/69 (1)[b]	0/168 (0)[c]	
OP	15/237 (6)[a]	5/69 (7)[b]	10/168 (6)[c]	
Histopathology pattern				0.006
UIP	33/50 (66)	4/12 (33)	29/38 (76)	
NSIP	10/50 (20)	3/12 (25)	7/38 (18)	
LIP	1/50 (2)	1/12 (8)	0/38 (0)	
OP	6/50 (12)	4/12 (33)	2/38 (5)	
Multi-compartment involvement	4/249 (2)	2/70 (3)	2/179 (1)	0.59
Pleuritis	2/249 (1)	1/70 (1)	1/179 (1)	0.48
Pericarditis	2/249 (1)	1/70 (1)	1/179 (1)	0.48
Raynaud's phenomenon	18/249 (7)	18/70 (26)	0/179 (0)	< 0.0001
Nailfold capillaroscopy abnormalities	10/57 (18)[a]	9/29 (31)[b]	1/28 (4)[c]	0.006
Digital tip ulcers or digital ischemia	1/249 (0)	1/70 (1)	0/179 (0)	0.28
Puffy fingers	2/249 (1)	2/70 (3)	0/179 (0)	0.08
Telangiectasia	1/249 (0)	0/70 (0)	1/179 (1)	1
Gottron's sign	1/249 (0)	1/70 (1)	0/179 (0)	0.28
Mechanic hands	3/249 (1)	3/70 (4)	0/179 (0)	0.02
Tender joints	7/249 (3)	5/70 (7)	2/179 (1)	0.02
Swollen joints	5/249 (2)	4/70 (6)	1/179 (1)	0.02
Myalgia	4/249 (2)	0/70 (0)	4/179 (2)	0.58
Muscle weakness	1/249 (0)	1/70 (1)	0/179 (0)	0.28
Xerostomia or xerophtalmia	28/249 (11)	12/70 (17)	16/179 (9)	0.08
Pathologic Schirmer test or salivary flow rate	9/249 (4)	4/70 (6)	5/179 (3)	0.27

Lymphocytic sialadenitis with focus score ≥ 1 foci/mm^2	19/74 (26)[a]	8/30 (27)[b]	11/44 (25)[c]	1
Anemia	26/163 (16)[a]	9/69 (13)[b]	17/94 (18)[c]	0.52
Thrombopenia	1/149 (1)[a]	0/69 (0)[b]	1/80 (1)[c]	1
Leucopenia	1/151 (1)[a]	1/69 (1)[b]	0/82 (0)[c]	0.46
Lymphopenia	7/148 (5)[a]	4/69 (6)[b]	3/79 (4)[c]	0.7
CPK level (IU/l)	116 ± 92	100 ± 82	132 ± 100	0.08
Urea (mg/l)	0.40 ± 0.16	0.40 ± 0.19	0.40 ± 0.14	0.7
Creatinine level (µmol/l)	87.5 ± 33.6	85.7 ± 25.6	88.4 ± 38.0	0.9
Protein C reactive (mg/l)	4 (3-6)	4 (3-6)	3.5 (3-7.4)	0.57
ANA	55/236 (23)[a]	43/70 (61)	12/166 (7)[c]	< 0.0001
Anti-Ro52 Abs	13/234 (6)[a]	11/70 (16)	2/164 (1)[c]	< 0.0001
Anti-Ro60 Abs	3/234 (1)[a]	3/70 (4)	0/164 (0)[c]	0.03
Anti-SSB Abs	0/234 (0)[a]	0/70 (0)	0/164 (0)[c]	1
Anti-dsDNA Abs	2/234 (1)[a]	1/70 (1)	1/164 (1)[c]	0.5
Anti-Sm Abs	1/234 (0)[a]	1/70 (1)	0/164 (0)[c]	0.3
Anti-RNP Abs	5/234 (2)[a]	4/70 (6)	1/164 (1)[c]	0.03
ACA	4/234 (2)[a]	4/70 (6)	0/164 (0)[c]	0.007
Anti-Scl70 Abs	2/234 (1)[a]	1/70 (1)	1/164 (1)[c]	0.5
Anti-PmScl Abs	5/52 (10)[a]	5/36 (14)[b]	0/16 (0)[c]	0.3
Anti-aminoacyl tRNA synthetase Abs	22/124 (18)[a]	17/54 (31)[b]	5/70 (7)[c]	0.0007
Anti-Ku Abs	3/51 (6)[a]	3/36 (8)[b]	0/15 (0)[c]	0.54
Anti-SRP Abs	0/50 (0)[a]	0/36 (0)[b]	0/14 (0)[c]	1
Anti-HMGCR Abs	0/47 (0)[a]	0/34 (0)[b]	0/13 (0)[c]	1
Anti-MDA5 Abs	1/47 (2)[a]	1/34 (3)[b]	0/13 (0)[c]	1
Rheumatoid factor	22/213 (10)[a]	15/62 (24)[b]	7/151 (5)[c]	< 0.0001
Anti-CCP Abs	1/209 (0)[a]	1/59 (2)[b]	0/150 (0)[c]	0.28

Dichotomous variables were represented as n/N (%) and continuous variables as mean ± SD or median (IQR). [a] N≠249 due to missing data. [b] N≠70 due to missing data. [c] N≠179 due to missing data. Abs, antibodies; ACA, anticentromere antibodies; ANA, antinuclear antibodies; BMI, body mass index; CCP, cyclic citrullinated peptide; CT, computerized tomography; dsDNA, doubled strained deoxyribonucleic acid; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; IPAF, interstitial pneumonia with autoimmune features; LIP, lymphocytic interstitial pneumonia; MDA5, melanoma differentiation associated protein-5; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; RNP, ribonucleoprotein; SRP, signal recognition particle; TIF-1, transcription intermediary factor 1; tRNA, transfer RNA; UIP, usual interstitial pneumonia.

Table 2

CTD occurrence during follow-up in IPAF and non-IPAF patients

	Total *(N=249)*	IPAF *(N= 70)*	Non-IPAF *(N= 179)*	P-value
Number of patients with a definite CTD diagnosis	22/249 (9)	18/70 (26)	4/179 (2)	0.0004
Time to definite CTD diagnosis (months)	26 (12-56)	25 (12-59)	29 (12-54)	1
ASS	10/249 (4)	9/70 (13)	1/179 (1)	
SSc	9/249 (4)	8/70 (11)	1/179 (1)	
OM	1/249 (0)	1/70 (1)	0/179 (0)	
RA	2/249 (1)	0/70 (0)	2/179 (1)	

Dichotomous variables were represented as n/N (%) and continuous variables as median (IQR). ASS, antisynthetase syndrome; CTD, connective tissue disease; IPAF, interstitial pneumonia with autoimmune features; OM, overlap myositis; RA, rheumatoid arthritis; SSc, systemic sclerosis.

Table 3
Clinical, laboratory and radiological features in IPAF patients with or without CTD during follow-up

	Total IPAF *(N=70)*	CTD-positive IPAF *(N= 18)*	CTD-negative IPAF *(N= 52)*	P-value
Female	33/70 (47)	12/18 (67)	21/52 (40)	0.06
Age at diagnosis (years)	62 ± 13	58 ± 3	63 ± 2	0.1
CT-pattern				0.51
UIP	6/69 (9)[a]	2/18 (11)	4/51 (8)[c]	
NSIP	57/69 (83)[a]	14/18 (78)	43/51 (84)[c]	
LIP	1/69 (1)[a]	0/18 (0)	1/51 (2)[c]	
OP	5/69 (5)[a]	2/18 (11)	3/51 (6)[c]	
Pleuritis	1/70 (1)	0/18 (0)	1/52 (2)	1
Pericarditis	1/70 (1)	0/18 (0)	1/52 (2)	1
Raynaud's phenomenon	18/70 (26)	6/18 (33)	12/52 (23)	0.53
Nailfold capillaroscopy abnormalities	9/29 (31)[a]	5/9 (56)[b]	4/20 (20)[c]	0.09
Digital tip ulcers or digital ischemia	1/70 (1)	1/18 (6)	0/52 (0)	0.26
Sclerodactyly	0/70 (0)	0/18 (0)	0/52 (0)	1
Puffy fingers	2/70 (3)	2/18 (11)	0/52 (0)	0.06
Telangiectasia	0/70 (0)	0/18 (0)	0/52 (0)	1
Gottron's sign	1/70 (1)	1/18 (6)	0/52 (0)	0.26
Mechanic hands	3/70 (4)	2/18 (11)	1/52 (2)	0.16
Tender joints	5/70 (7)	3/18 (17)	2/52 (4)	0.1
Swollen joints	4/70 (6)	2/18 (11)	2/52 (4)	0.27
Myalgia	0/70 (0)	0/18 (0)	0/52 (0)	1
Muscle weakness	1/70 (1)	0/18 (0)	1/52 (2)	1
Xerostomia or xerophtalmia	12/70 (17)	4/18 (22)	8/52 (15)	0.49
Pathologic Schirmer test or salivary flow rate	4/70 (6)	2/18 (11)	2/52 (4)	0.27
Lymphocytic sialadenitis with focus score ≥ 1 foci/mm^2	8/30 (11)[a]	2/9 (11)[b]	6/21 (12)[c]	1
Anemia	9/69 (13)[a]	2/18 (11)	7/51 (14)[c]	1
Thrombopenia	0/69 (0)[a]	0/18 (0)	0/51 (0)[c]	1
Leucopenia	1/69 (1)[a]	0/18 (0)	1/51 (2)[c]	1
Lymphopenia	4/69 (6)[a]	2/18 (11)	2/51 (4)[c]	0.28
High CPK level	0/70 (0)	0/18 (0)	0/52 (0)	1
Urea (mg/l)	0.40 ± 0.19	0.36 ± 0.13	0.42 ± 0.2	0.44
Creatinine level (mg/l)	9.7 ± 2.9	9.1 ± 1.9	9.9 ± 3.1	0.5

Protein C reactive (mg/l)	4 (3-6)	5 (3-11)	3 (3-6)	0.17
ANA	43/70 (61)	11/18 (61)	32/52 (62)	1
Anti-Ro52 Abs	11/70 (16)	4/18 (22)	7/52 (13)	0.46
Anti-Ro60 Abs	3/70 (4)	1/18 (6)	2/52 (4)	1
Anti-SSB Abs	0/70 (0)	0/18 (0)	0/52 (0)	1
Anti-dsDNA Abs	1/70 (1)	0/18 (0)	1/52 (2)	1
Anti-Sm Abs	1/70 (1)	0/18 (0)	1/52 (2)	1
Anti-RNP Abs	4/70 (6)	0/18 (0)	4/52 (8)	0.57
ACA	4/70 (6)	2/18 (11)	2/52 (4)	0.27
Anti-Scl70 Abs	1/70 (1)	1/18 (6)	0/52 (0)	0.26
Anti-PmScl Abs	5/46 (11)[a]	1/18 (6)	4/28 (14)[c]	0.63
Anti-aminoacyl tRNA synthetase Abs	17/54 (31)[a]	7/14 (50)[b]	10/40 (25)[c]	0.1
Anti-Ku Abs	3/36 (8)[a]	0/8 (0)[b]	3/28 (11)[c]	1
Anti-SRP Abs	0/36 (0)[a]	0/6 (0)[b]	0/30 (0)[c]	1
Anti-HMGCR Abs	0/34 (0)[a]	0/6 (0)[b]	0/28 (0)[c]	1
Anti-MDA5 Abs	1/34 (3)[a]	0/6 (0)[b]	1/28 (4)[c]	1
Rheumatoid factor	15/62 (24)[a]	1/14 (7)[b]	14/48 (29)[c]	0.15
Anti-CCP Abs	1/59 (2)[a]	0/12 (0)[b]	1/47 (2)[c]	1

Dichotomous variables were represented as n/N (%) and continuous variables as mean ± SD or median (IQR). [a] N≠70 due to missing data. [b] N≠18 due to missing data. [c] N≠52 due to missing data. Abs, antibodies; ACA, anticentromere antibodies; ANA, antinuclear antibodies; CCP, cyclic citrullinated peptide; CT, computerized tomography; CTD, connective tissue disease; dsDNA, doubled strained deoxyribonucleic acid; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; IPAF, interstitial pneumonia with autoimmune features; LIP, lymphocytic interstitial pneumonia; MDA5, melanoma differentiation associated protein-5; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; RNP, ribonucleoprotein; SRP, signal recognition particle; TIF-1, transcription intermediary factor 1; tRNA, transfer RNA; UIP, usual interstitial pneumonia.

Table 4
ILD severity at time of diagnosis in IPAF and non-IPAF patients

	Total (N=249)	IPAF (N= 70)	Non-IPAF (N= 179)	P-value
Dyspnea at diagnosis (NYHA classification)				0.005
I	81/246 (33)[a]	18/69 (26)[b]	63/177 (35)[c]	
II	107/246 (43)[a]	24/69 (35)[b]	83/177 (47)[c]	
III	42/246 (17)[a]	19/69 (27)[b]	23/177 (13)[c]	
IV	16/246 (7)[a]	8/69 (12)[b]	8/177 (5)[c]	
Severe ILD at diagnosis	98/238 (41)[a]	42/66 (64)[b]	56/172 (33)[c]	< 0.0001
FVC at diagnosis, % predicted value	86 ± 21	78 ± 3	89 ± 20	0.0003
FEV1 at diagnosis, % predicted value	87 ± 20	77 ± 3	91 ± 19	< 0.0001
DLCO at diagnosis, % predicted value	57 ± 18	52 ± 20	58 ± 16	0.01
6MWT at diagnosis, % predicted value	82 ± 21	71 ± 23	86 ± 20	< 0.0001
Worsening ILD	36/129 (28)[a]	7/64 (11)[b]	29/165 (18)[c]	0.31

Dichotomous variables were represented as n/N (%) and continuous variables as mean ± SD. [a] N≠249 due to missing data. [b] N≠70 due to missing data. [c] N≠179 due to missing data. DLCO, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume; FVC, functional vital capacity; ILD, interstitial lung disease; IPAF, interstitial pneumonia with autoimmune features; 6MWT, 6-minute walk test.

Table 5
ILD outcome and medications used in IPAF and non-IPAF patients

	Total *(N=249)*	IPAF *(N= 70)*	Non-IPAF *(N= 179)*	P-value
Suspected PH on echocardiography	44/249 (18)	15/70 (21)	29/179 (16)	0.36
Death	250/249 (20)	18/70 (26)	32/179 (18)	0.22
Time to death (months)	66 ± 32	84 ± 48	58 ± 17	0.04
Lung transplant	8/249 (3)	0/70 (0)	8/179 (4)	0.11
Death or lung transplant	8/249 (23)	18/70 (26)	40/179 (22)	0.62
Time to death or lung transplant (months)	62 ± 31	84 ± 48	54 ± 17	0.01
Number of immunosuppressants used	1 (0-2)	2 (1-3)	0 (0-1)	< 0.0001
Patients with ≥ 3 immunosuppressants used[a]	43/249 (17)	29/70 (41)	14/179 (8)	< 0.0001
Oral/IV steroids	133/249 (53)	62/70 (89)	71/179 (23)	< 0.0001
Azathioprine	54/249 (22)	28/70 (40)	26/179 (15)	< 0.0001
Cyclophosphamide	25/249 (10)	14/70 (20)	11/179 (6)	0.002
Mycophenolate mofetil	42/249 (17)	26/70 (37)	16/179 (9)	< 0.0001

Dichotomous variables were represented as n/N (%) and continuous variables as mean ± SD or median (IQR). [a] Immunosuppressants used sequentially during follow-up. ILD, interstitial lung disease; IPAF, interstitial pneumonia with autoimmune features; IV, intravenous; PH, pulmonary hypertension.

Figure legend

Fig. 1. Flow chart. Abbreviations: CTD, connective tissue disease; ILD, interstitial lung disease; IPAF, interstitial pneumonia with autoimmune features.

« Interstial lung disease »
PMSI database research

N = 3101

Known cause of ILD:
Infection
Cardiac failure
CTD-ILD
Hypersensitivity pneumonitis
Drug induced ILD
Pneumoconiosis
Lymphangitic carcinomatosis
Sarcoidosis
Familial pulmonary fibrosis

N = 2168

Idiopathic ILD

n = 933

Follow-up < 3 years
Missing data

n = 684

IPAF

n = 70

Non-IPAF

n = 179