Interstitial Pneumonia With Autoimmune Features (IPAF)

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DM seminar

Division

- Background-classification
- ATS statement
- Cohort studies
- Radiological findings
- Treatment

Background-classification

Historical background

- Sir William Osler described *'cirrhosis of the lungs'*

- Hamman and Rich (1944) described four cases of rapidly progressive, diffuse alveolar wall thickening with progressive, diffuse alveolar wall thickening with out identifiable cause, which led to use of the term, Hamman–Rich syndrome for either acute-onset or chronic fibrotic ILD

Historical background

- Subsequently, diffuse pulmonary fibrosis was linked to forms of connective tissue disease (CTD) and other causes, such as exposure to organic or inorganic dusts and pneumotoxic drug reactions, but many forms remained unexplained by any associations
- Terms such as ‘chronic idiopathic interstitial fibrosis’, ‘diffuse fibrosing alveolitis’ or ‘idiopathic pulmonary fibrosis’ were used to designate fibrotic ILD of unknown aetiology, and these disorders were thought to occur as a consequence of alveolar wall inflammation

Diffuse pulmonary alveolar fibrosis[1]

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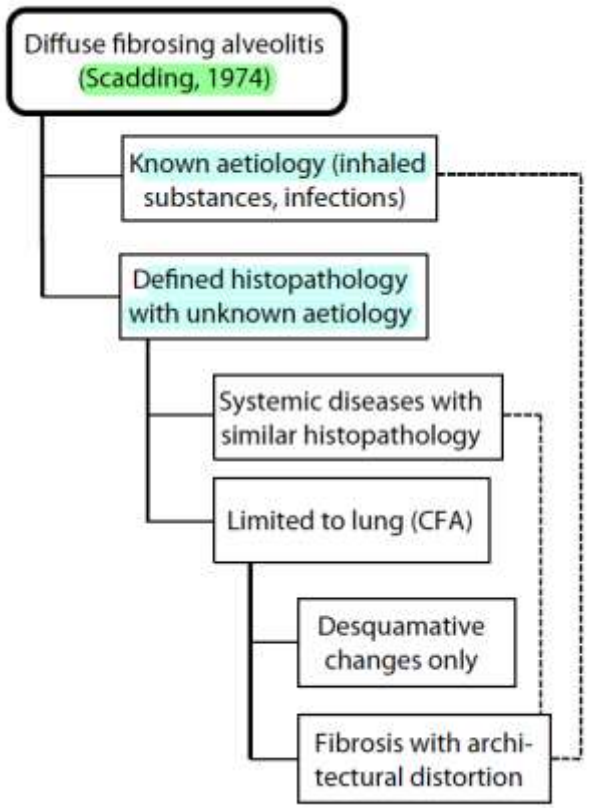


TABLE

DIAGNOSTIC CATEGORIES OF PULMONARY ALVEOLAR FIBROSIS

	Examples and Comment
1. Defined aetiologically	
Inhaled dusts	
Mineral	Asbestos and silica especially liable to cause alveolar fibrosis
Organic	Thermophilic actinomycetes – farmer's lung Avian antigens – bird-fancier's lung Specific antigen-antibody reactions: hence the generic name 'extrinsic allergic alveolitic'
Ingested toxic substances	Paraquat, busulphan
Infections	
Bacterial	*Myco. tuberculosis* – chronic and healed miliary tuberculosis
Fungal	Histoplasma, Coccidioides
Metazoal	Schistosoma, Filaria
?Viral	
Pneumocystis	
2. Defined histopathologically	
As part of a systemic disease with similar histology	
Sarcoidosis	
Histiocytosis X (eosinophilic granuloma)	
Mesodermal dysplasia (tuberous sclerosis)	
As a pulmonary disease	
Fibrosing alveolitis	Most cases can be placed in a range between 'desquamative' and 'mural' histological patterns. A few with unusual features can be appropriately designated. The pulmonary fibrosis associated with scleroderma, and that occurring in a few cases of rheumatoid arthritis, is a predominantly mural fibrosing alveolitis.

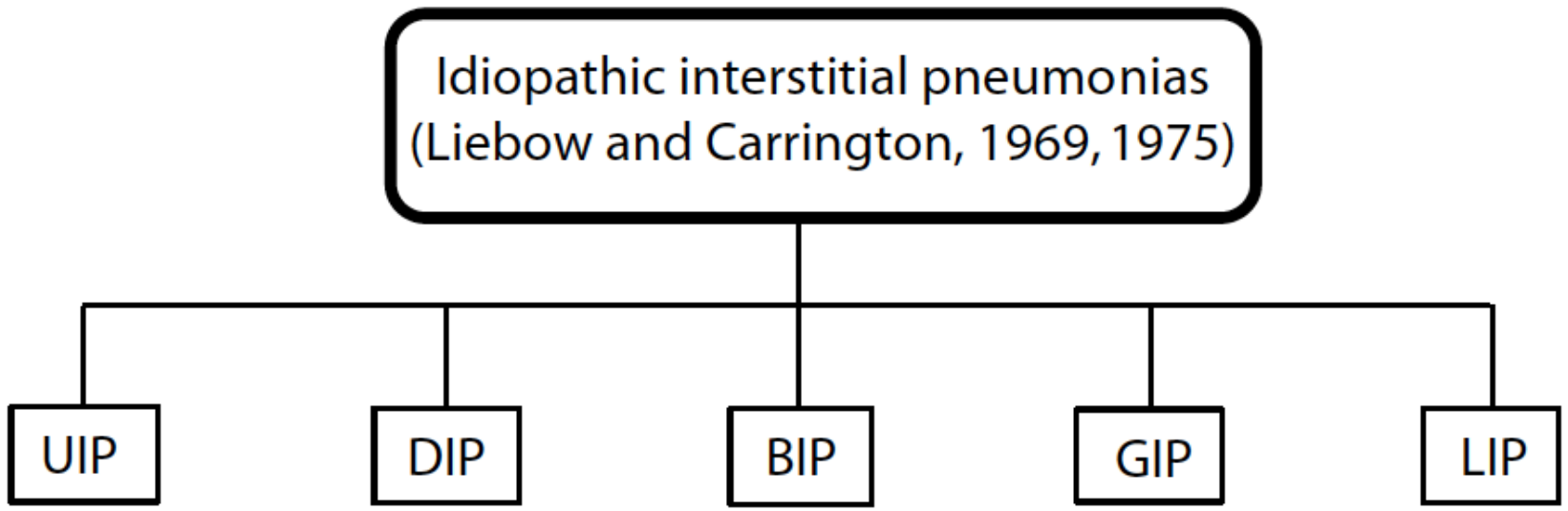
Clinical handbook of interstitial lung diseases

Human Pathology

Alveolar Interstitium of the Lung. Int. Symp., Paris 1974
Prog. Resp. Res., vol. 8, pp. 1–33 (Karger, Basel 1975)

Definition and Classification of Interstitial Pneumonias in Human Pathology[1]

AVERILL A. LIEBOW

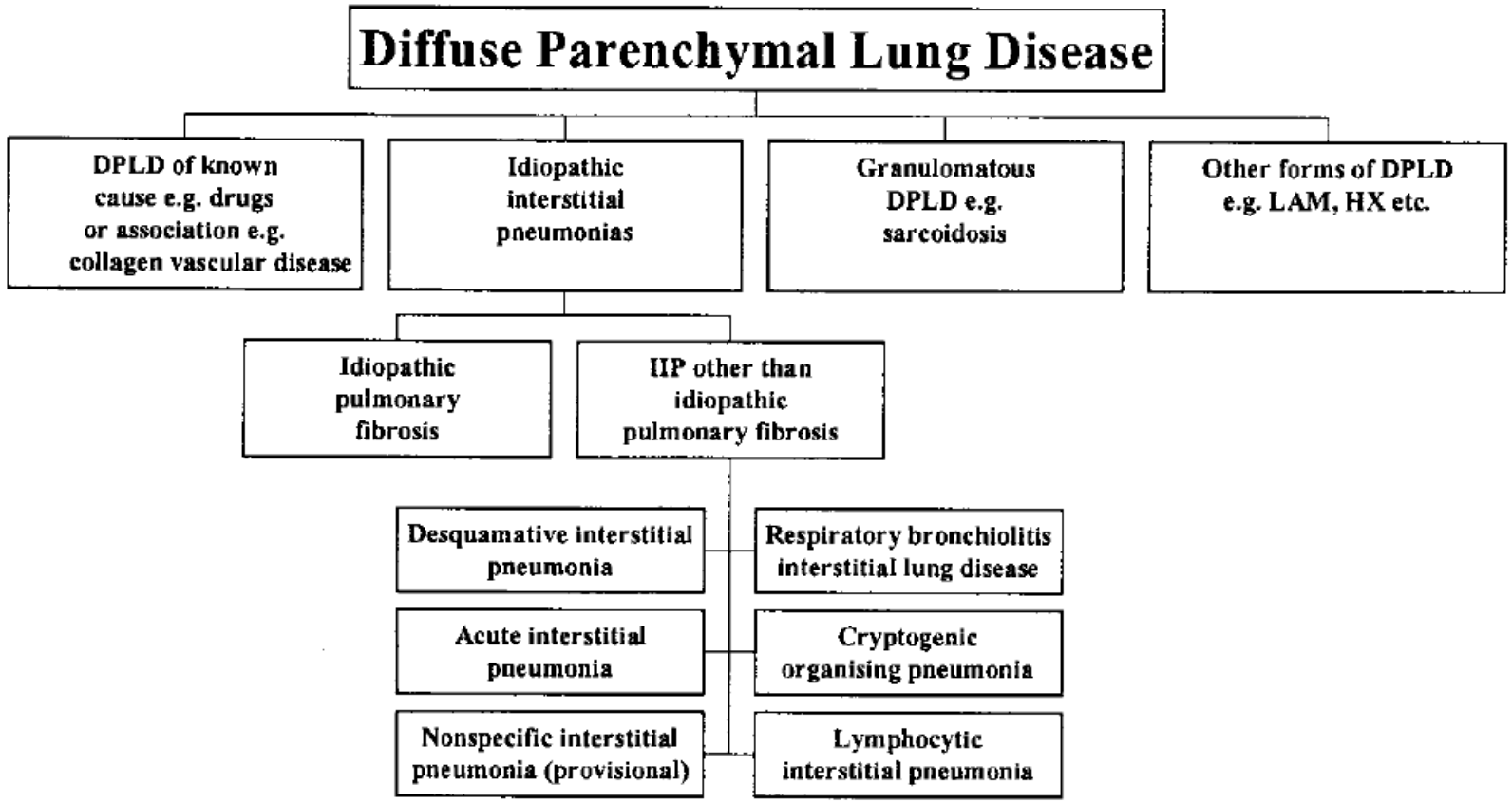


Clinical handbook of interstitial lung diseases

American Thoracic Society

American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias

THIS JOINT STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS), AND THE EUROPEAN RESPIRATORY SOCIETY (ERS) WAS ADOPTED BY THE ATS BOARD OF DIRECTORS, JUNE 2001 AND BY THE ERS EXECUTIVE COMMITTEE, JUNE 2001



An Official American Thoracic Society/European Respiratory Society Statement: Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias

William D. Travis, Ulrich Costabel, David M. Hansell, Talmadge E. K
Christopher J. Ryerson, Jay H. Ryu, Moisés Selman, Athol U. Wells,
Kevin K. Brown, Thomas V. Colby, Harold R. Collard, Carlos Robalo
Marjolein Drent, Rosalind F. Dudden, Jim Egan, Kevin Flaherty, Cor
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Ganesh Raghu, Luca Richeldi, Nicola Sverzellati, Jeffrey Swigris, and
Committee on Idiopathic Interstitial Pneumonias

Major idiopathic interstitial pneumonias
- Idiopathic pulmonary fibrosis
- Idiopathic nonspecific interstitial pneumonia
- Respiratory bronchiolitis–interstitial lung disease
- Desquamative interstitial pneumonia
- Cryptogenic organizing pneumonia
- Acute interstitial pneumonia

Rare idiopathic interstitial pneumonias
- Idiopathic lymphoid interstitial pneumonia
- Idiopathic pleuroparenchymal fibroelastosis

Unclassifiable idiopathic interstitial pneumonias*

*Causes of unclassifiable idiopathic interstitial pneumonia include (*1*) inadequate clinical, radiologic, or pathologic data and (*2*) major discordance between clinical, radiologic, and pathologic findings that may occur in the following situations: (*a*) previous therapy resulting in substantial alteration of radiologic or histologic findings (e.g., biopsy of desquamative interstitial pneumonia after steroid therapy, which shows only residual nonspecific interstitial pneumonia [153]); (*b*) new entity, or unusual variant of recognized entity, not adequately characterized by the current American Thoracic Society/European Respiratory Society classification (e.g., variant of organizing pneumonia with supervening fibrosis) (*79*); and (*c*) multiple high-resolution computed tomography and/or pathologic patterns that may be encountered in patients with idiopathic interstitial pneumonia.

2013

Background

- IIPs are diffuse inflammatory and/or fibrotic lung disorders that are grouped together based on similar clinical, radiologic and histopathologic features
- The diagnosis of IIP requires the exclusion of known causes
- IP-first, and possibly the sole, manifestation of an otherwise occult CTD
- Diagnosis of IIP recommend excluding CTD -assessing for extra thoracic features of CTD, testing for a broad array of circulating autoantibodies, and integrating specific imaging and/or histopathologic features

Fischer A, Antoniou KM, Brown KK, et al, ERS/ATSTask Force on Undifferentiated Forms of CTD-ILD.
An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. Eur Respir J2015;46:976–87.

Background

- 25% of patients with features of a systemic autoimmune disease do not fulfill the American College of Rheumatology (ACR) classification criteria for CTD
- In the absence of a defined CTD, 10– 20% of patients with idiopathic interstitial pneumonia have systemic symptoms and serologic abnormalities suggestive of an autoimmune process
- Experts from different medical specialties have conceptualized this entity as an undifferentiated CTD-associated ILD, lung-dominant CTD, and autoimmune-featured ILD, using different but overlapping criteria and terminology

Fernandes, L., Nasser, M., Ahmad, K., & Cottin, V. (2019). Interstitial Pneumonia With Autoimmune Features (IPAF). *Frontiers in medicine*, *6*, 209

Concept	References	Diagnostic criteria	Main findings
Undifferentiated connective tissue disease associated-ILD, broader definition	Kinder et al. (5)	**Symptoms associated with CTD** At least one of: (1) Raynaud's phenomenon; (2) arthralgias/multiple joint swelling; (3) photosensitivity; (4) unintentional weight loss; (5) morning stiffness; (6) dry mouth or dry eyes (Sicca features); (7) dysphagia; (8) recurrent unexplained fever; (9) gastro-esophageal reflux; (10) skin changes (rash); (11) oral ulceration; (12) nonandrogenic alopecia; (13) proximal muscle weakness; **Positive autoimmune serology** Positive finding of at least one of: (1) ANA; (2) RF; (3) anti-Scl70 antibody; (4) SS-A or SS-B; (5) Jo-1 antibody; (6) ESR (2 times normal), CRP	1. Hypothesis of idiopathic NSIP as a lung manifestation of a UCTD; 2. The majority (88%) of patients previously classified as having idiopathic NSIP had clinical, serologic, radiographic, and pathologic characteristics met the criteria for UCTD.
Undifferentiated connective tissue disease—strict definition	Corte et al. (7)	**Symptoms associated with CTD** At least one of: (1) Raynaud's phenomenon; (2) arthralgias/multiple joint swelling; (3) morning stiffness; (4) dry mouth or dry eyes (Sicca features); (5) proximal muscle weakness **Positive autoimmune serology** Positive finding of at least one of: (1) ANA (high titer); (2) RF (high titer); (3) positive ENA; (4) anti-Scl70 antibody; (5) anti-RNP antibody; (6) anticentromere antibody; (7) SS-A or SS-B; (8) Jo-1 antibody	1. CTD features were not uncommon in IP patients; 2. Less specific diagnostic criteria for UCTD were not useful and associated with a erroneous high prevalence; 3. UCTD diagnosis of was correlated with NSIP histology, without sensitivity or specificity for NSIP, nor association with a survival advantage.

Fernandes, L., Nasser, M., Ahmad, K., & Cottin, V. (2019). Interstitial Pneumonia With Autoimmune Features (IPAF). *Frontiers in medicine*, *6*, 209

Concept	References	Diagnostic criteria	Main findings
Lung dominant-connective tissue disease	Fischer et al. (9)	Four criteria: 1. NSIP, UIP, LIP, OP, and DAD (or DIP if no smoking history), by surgical lung biopsy specimen or suggested by high-resolution CT; 2. Insufficient extrathoracic features of a definite CTD to allow a specific CTD designation; 3. No identifiable alternative etiology; 4. Any one of the following autoantibodies or at least two of the histopathology features: **Autoantibodies** High-titer ANA (>1:320) or RF (>60 IU/mL), Nucleolar-ANA, Anti-CCP, Anti-Scl-70, Anti-Ro, Anti-La, Anti-dsDNA, Anti-Smith, Anti-RNP, Anti-tRNA synthetase (e.g., Jo-1, PL-7, PL-12, and others), Anti-PM-Scl, anticentromere **Histopathology features** Lymphoid aggregates with germinal centers, extensive pleuritis, prominent plasmocytic infiltration, and dense perivascular collagen	Advantages of these criteria: - Objective and measurable; - Nonspecific symptoms, nonspecific inflammatory markers, and low-titer ANA or RF were not included due to its common occurrence in patients without definite CTD; - The term "lung-dominant CTD" was distinct from the idiopathic group of IP and acknowledged a new entity manifested by systemic autoimmunity that could not be designated as a definable CTD; - The diagnosis of lung-dominant CTD provided a framework for research regarding natural history, pathobiology, treatment, and prognosis.
Autoimmune-featured interstitial lung disease (AIF-ILD)	Vij et al. (6)	**Symptoms (one or more of the following)** Dry eyes/dry mouth; gastroesophageal reflux; weight loss; leg/foot swelling; joint pain/swelling; rash photosensitivity; dysphagia; hand ulcers; mouth ulcers; Raynaud phenomenon; morning stiffness; proximal muscle weakness; **Serologic test (one or more positive result of the following)** Antinuclear antibody titer 1:160; rheumatoid factor; aldolase; Anti-Ro antibody; Anti-La antibody; Anti-neutrophil cytoplasmic antibody; Creatine kinase; Anti-double-stranded DNA; Anti-Scl-70; Anti-ribonucleoprotein antibody; Anti-Smith antibody; Anti-cyclic citrullinated peptide antibody; Anti-Jo-1 antibody.	- Demographic profile for gender and age of AIF-ILD group shared similarities with IPF group, but was different from CTD-ILD group; - The most frequent radiological finding in AIF-ILD patients was UIP (62%).

Fernandes, L., Nasser, M., Ahmad, K., & Cottin, V. (2019). Interstitial Pneumonia With Autoimmune Features (IPAF). *Frontiers in medicine*, *6*, 209

ATS statement

An official European Respiratory Society/ American Thoracic Society research statement: interstitial pneumonia with autoimmune features

Aryeh Fischer[1,17,18], Katerina M. Antoniou[2], Kevin K. Brown[3], Jacques Cadranel[4], Tamera J. Corte[5,18], Roland M. du Bois[6], Joyce S. Lee[7,18], Kevin O. Leslie[8], David A. Lynch[9], Eric L. Matteson[10], Marta Mosca[11], Imre Noth[12], Luca Richeldi[13], Mary E. Strek[12,18], Jeffrey J. Swigris[3,18], Athol U. Wells[14], Sterling G. West[15], Harold R. Collard[7,18,19] and Vincent Cottin[16,18,19], on behalf of the "ERS/ATS Task Force on Undifferentiated Forms of CTD-ILD"

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Classification criteria for interstitial pneumonia with autoimmune features (IPAF) [1].

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) AND,
2. Exclusion of alternative etiologies AND,
3. Does not meet criteria of a defined CTD AND,
4. At least one (1) feature from at least two (2) of these domains:

A. Clinical domain	B. Serologic domain	C. Morphologic domain
1. Distal digital fissuring (i.e. 'mechanic hands') 2. Distal digital tip ulceration 3. Inflammatory arthritis or polyarticular morning joint stiffness >60 min 4. Palmar telangiectasia 5. Raynaud's phenomenon 6. Unexplained digital edema 7. Unexplained fixed rash on the digital extensor surfaces (i.e. 'Gottron's sign')	1. ANA, either diffuse, speckled, or homogeneous patterns at >1:320 titer OR ANA nucleolar pattern at any titer OR ANA centromere pattern at any titer 2. RF > 2 × ULN 3. Anti-CCP 4. Anti-dsDNA 5. Anti-Ro (SS-A) 6. Anti-La (SS-B) 7. Anti-ribonucleoprotein 8. Anti-Smith 9. Anti-topoisomerase (Scl-70) 10. Anti-tRNA synthetase (eg, Jo-1, PL-7, PL-12, EJ, OJ, KS, Zo, tRS) 11. Anti-PM-Scl 12. Anti-MDA5 (CADM-40)	1. Suggestive radiology patterns by HRCT: a. NSIP b. OP c. NSIP with OP overlap d. LIP 2. Histopathology patterns or features by surgical lung biopsy: a. NSIP b. OP c. NSIP with OP overlap d. LIP e. Interstitial lymphoid aggregates with germinal centers f. Diffuse lympho-plasmacytic infiltration (with or without lymphoid follicles) 3. Unexplained multi-compartment involvement[a]: a. Pleural effusion or thickening b. Pericardial effusion or thickening c. Intrinsic airways disease d. Pulmonary vasculopathy

HRCT = high-resolution computed tomography scan; ILD = interstitial lung disease; IPAF = interstitial pneumonia with autoimmune features; LIP = lymphocytic interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; RTX = rituximab; SD = standard deviation; UIP = usual interstitial pneumonia.

[a] Either by: thoracic imaging, lung histopathology, right heart catheterization, pulmonary physiology.

Fischer A, Antoniou KM, Brown KK, et al, ERS/ATSTask Force on Undifferentiated Forms of CTD-ILD.
An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. Eur Respir J2015;46:976–87.

Cohort studies

- Chicago cohort-2016
- Denver cohort-2016
- France cohort-2017
- Japan cohort-2018
- Washington chort-2017
- Rochester cohort-2018

Chicago cohort-2016

ORIGINAL ARTICLE
INTERSTITIAL LUNG DISEASES

Characterisation of patients with interstitial pneumonia with autoimmune features

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They applied IPAF criteria to patients with idiopathic interstitial pneumonia and undifferentiated CTD-ILD (UCTD) studied the characteristics of the cohort, compared outcomes to other ILD cohorts and validated individual IPAF domains using survival as an endpoint

Chicago cohort

- University of Chicago & ILD registry from October 2006 to December 2014
- IIP, including IPF, unclassifiable IIP, biopsy-proven idiopathic NSIP and biopsy-proven COP based on ERS/ATS criteria
- ILD diagnosis in a rigorous, multidisciplinary fashion
- UCTD-ILD based on previously proposed narrow criteria
- Anti PM-Scl and anti-CADM (MDA-5) were not done as a routine ILD evaluation
- HRCTs and SLBs were re-reviewed blindly by two chest radiologists and a pathologist

Baseline demographic and clinical characteristics

TABLE 1 Interstitial pneumonia with autoimmune features cohort baseline demographic and clinical characteristics[#]

Age	63.2±11
Sex female	75 (52.1)
Race/ethnicity	
White	102 (70.8)
African-American	25 (17.4)
Hispanic	10 (6.9)
Asian	7 (4.9)
Gastroesophageal reflux	76 (52.8)
Hypothyroidism	28 (19.4)
Diabetes mellitus	17 (11.8)
Coronary artery disease	32 (22.2)
Ever smoker	79 (54.9)
Systemic corticosteroid Use	46 (32.2)
Gastroesophageal reflux therapy	76 (53.2)
Body mass index	30±6.6
Crackles[¶]	125 (89.3)
Clubbing[+]	21 (18.9)
Usual interstitial pneumonia by high-resolution computed tomography[§]	77 (54.6)
Usual interstitial pneumonia by surgical lung biopsy[f]	61 (73.5)
Forced vital capacity in 1 s % predicted	61.9±18.3
Diffusion capacity of the lung for carbon monoxide % predicted	45.3±20.6

Data are presented as mean±SD or n (%). [#]: N=144, unless otherwise stated; [¶]: N=140; [+]: N=111; [§]: N=141; [f]: N=83.

Consort diagram

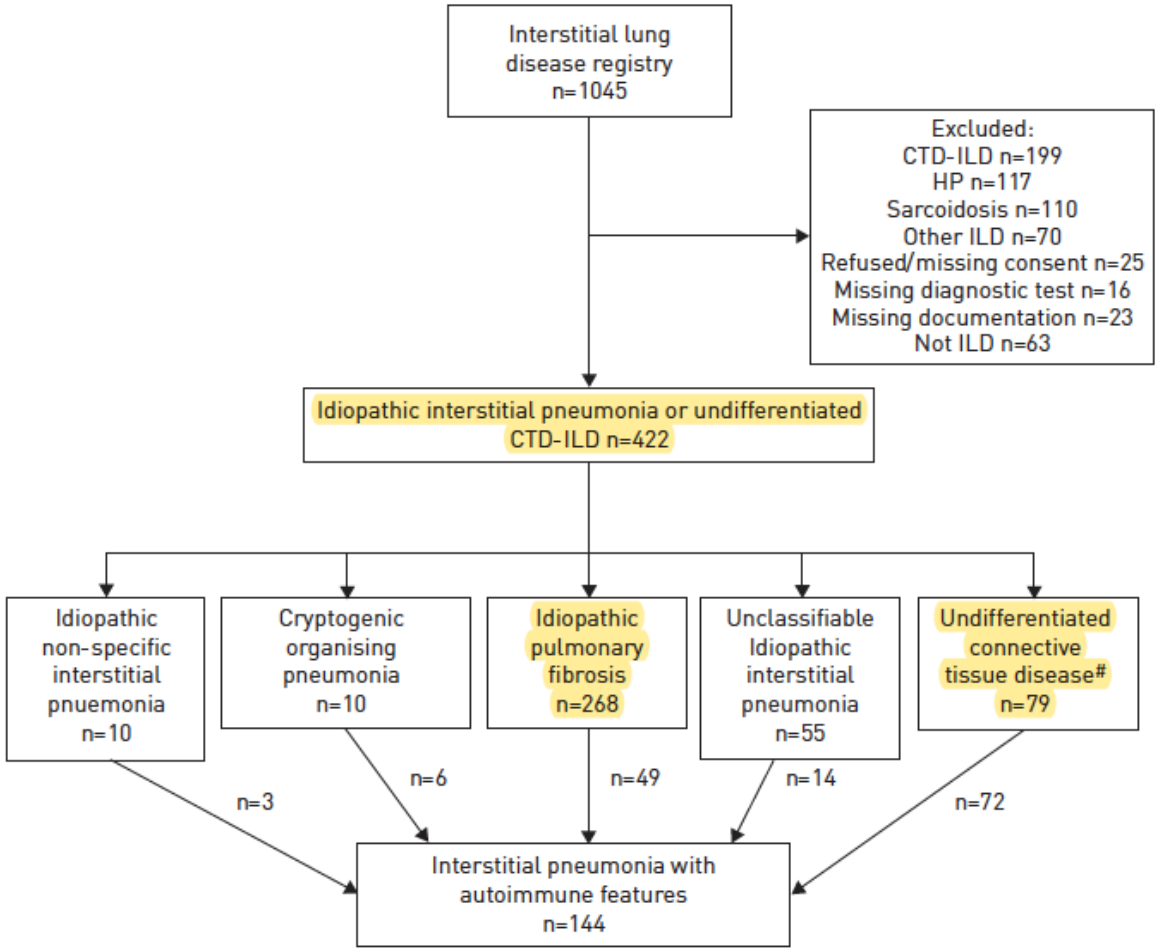

FIGURE 1 Consort diagram. CTD: connective tissue disease; ILD: interstitial lung disease; HP: hypersensitivity pneumonitis; IIP: idiopathic interstitial pneumonia. #: based on narrow criteria as proposed by Corte *et al.* [3].

Interstitial pneumonia with autoimmune-features (IPAF) domains

TABLE 2 Interstitial pneumonia with autoimmune-features (IPAF) domains met by initial diagnosis

Domains met	IPAF cohort	Initial diagnosis			
		NSIP/COP	IPF	UCTD-ILD	Unclassifiable
Subjects	144	9	49	72	14
Clinical and serological	21 (14.6)	0 (0)	3 (6.1)	17 (23.6)	1 (7.1)
Clinical and morphological	12 (8.3)	2 (22.2)	0 (0)	6 (8.3)	4 (28.6)
Serological and morphological	73 (50.7)	7 (77.8)	43 (87.8)	16 (22.2)	7 (50)
All three domains	38 (26.4)	0 (0)	3 (6.1)	33 (45.8)	2 (14.3)

Data are presented as n or n (%). NSIP: nonspecific interstitial pneumonia; COP: crytogenic organising pneumonia; IPF: idiopathic pulmonary fibrosis; UCTD: undifferentiated connective tissue disease; ILD: interstitial lung disease.

TABLE 3 Findings of interstitial pneumonia with autoimmune features by domain[#]

Clinical domain	71 (49.3)
Mechanics hands	15 (10.4)
Distal digital tip ulceration	3 (2.1)
Inflammatory arthritis/polyarticular morning joint stiffness ⩾60 min	25 (17.4)
Palmar telangiectasia	0 (0)
Raynaud's phenomenon	40 (27.8)
Unexplained digital oedema	5 (3.5)
Gottron's sign	7 (4.9)
Serological domain	132 (91.7)
Antinuclear antibody[¶] ⩾1:320[+]	111 (77.6)
Rheumatoid factor[§] ⩾x2 upper limit normal	18 (13)
Anti-cyclic citrullinated peptide[f]	6 (4.7)
Anti-double stranded DNA[##]	7 (7.2)
Anti-Ro Anti (SSA)[¶¶]	23 (16.6)
Anti-La Anti (SSB)[¶¶]	4 (2.9)
Anti-ribonucleoprotein	7 (4.9)
Anti-Smith[++]	2 (1.5)
Anti-topoisomerase (Scl-70)[§§]	4 (3)
Anti-tRNA synthetase[§§]	1 (0.7)
Morphological domain	123 (85.4)
High-resolution computed tomography[ff]	
Nonspecific interstitial pneumonia	45 (31.9)
Organising pneumonia	5 (3.5)
Nonspecific interstitial pneumonia with organising pneumonia overlap	11 (7.8)
Histopathologic pattern[###]	
Nonspecific interstitial pneumonia	19 (22.9)
Organising pneumonia	14 (16.9)
Nonspecific interstitial pneumonia with organising pneumonia overlap	3 (3.6)
Interstitial lymphoid aggregates with germinal centres	11 (13.3)
Diffuse lymphoplasmacytic infiltration	8 (9.6)
Multicompartment involvement[¶¶¶]	
Pleural effusion or thickening (high-resolution computed tomography) or pleuritis (surgical lung biopsy)	18 (12.5)
Pericardial effusion or thickening	2 (1.4)
Intrinsic airways disease	32 (22.2)
Pulmonary vasculopathy	27 (18.8)

Data are presented as n (%). [#]: N=144, unless otherwise stated; [¶]: N=143; [+]: or <1:320 with nucleolar or centromere pattern; [§]: N=138; [f]: N=127; [##]: N=97; [¶¶]: N=139; [++]: N=132; [§§]: N=135; [ff]: N=141; [###]: N=83; [¶¶¶]: not otherwise explained.

- On HRCT, 54.6% of patients demonstrated a UIP pattern
- Of 83 patients biopsied, 61 (73.5%) patients demonstrated a histological UIP pattern

Survival analysis

Survival time was defined as time from diagnostic test to death, transplant, loss to follow-up or end of study period. Survival time was censored on January 1, 2015 or at the time a patient underwent lung transplant or was lost to follow-up

In outcome analysis, 57 (39.6%) of IPAF patients died during the follow-up period and 14 (10.8%) underwent lung transplantation

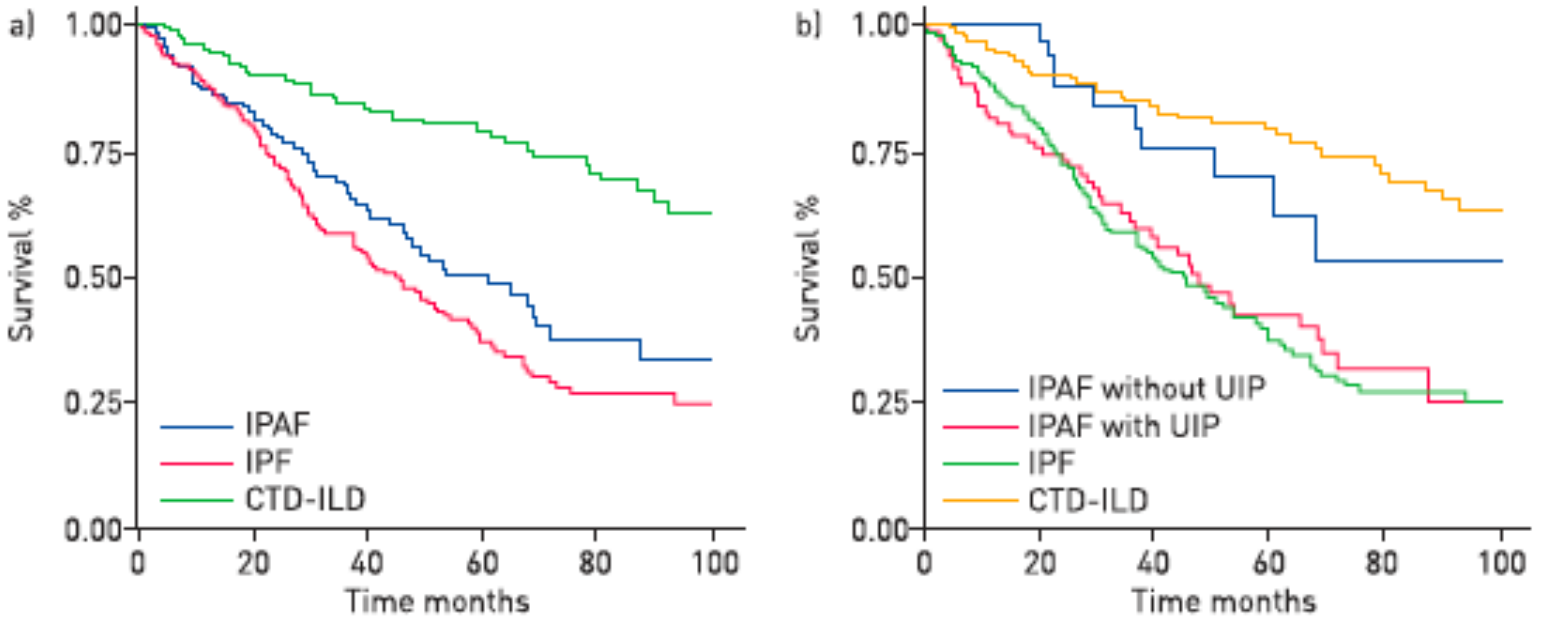

FIGURE 2 Kaplan–Meier survival curves of interstitial pneumonia with autoimmune features (IPAF), idiopathic pulmonary fibrosis (IPF) and connective tissue disease (CTD)-interstitial lung disease (ILD) cohorts. Overall a) IPAF cohort survival was significantly worse than the CTD-ILD cohort ($p<0.001$) and marginally better than the IPF cohort ($p=0.07$). After stratification of the IPAF cohort by the presence of a usual interstitial pneumonia pattern on high-resolution computed tomography and/or surgical lung biopsy b) IPAF patients without usual interstitial pneumonia (UIP) demonstrated survival similar to those with CTD-ILD ($p=0.45$), while those with UIP demonstrate survival similar to those with IPF ($p=0.51$).

Variables predicting survival

TABLE 4 Variables predicting survival in patients with interstitial pneumonia with autoimmune features

Characteristic	Unadjusted[#]		Adjusted[#]	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.06 (1.03–1.08)	**<0.001**	1.05 (1.02–1.08)	**0.001**
Male sex	1.54 (0.91–2.60)	0.11	1.65 (0.92–2.97)	0.09
Hypothyroidism	1.97 (1.05–3.67)	**0.03**	1.08 (0.52–2.22)	0.84
Ever smoker	0.92 (0.54–1.54)	0.74	1.11 (0.60–2.05)	0.74
GER therapy	1.12 (0.66–1.88)	0.67	1.38 (0.79–2.43)	0.26
Chronic systemic corticosteroid therapy	0.82 (0.49–1.38)	0.46	1.39 (0.73–2.63)	0.32
Immunosuppressive therapy[¶]	0.74 (0.47–1.17)	0.2	0.7 (0.35–1.4)	0.31
UIP pattern[+]	2.4 (1.21–4.76)	**0.01**	1.72 (0.83–3.56)	0.14
FVC % predicted	0.99 (0.98–1.01)	0.22	1 (0.97–1.02)	0.76
***D*LCO % predicted**	0.97 (0.96–0.99)	**<0.001**	0.97 (0.95–0.99)	**0.01**
Clinical domain	0.56 (0.32–0.96)	**0.03**		
Raynaud's phenomenon	0.57 (0.29–1.10)	0.09		
Serologic domain	1.89 (0.59–6.06)	0.28		
ANA seropositivity	0.91 (0.51–1.62)	0.75		
Morphological domain	1.31 (0.56–3.06)	0.53		
HRCT features	0.58 (0.34–1.0)	**0.05**		
SLB features	0.36 (0.11–1.18)	0.09		
Multicompartment features	2.01 (1.19–3.38)	**0.009**		

HR: hazard ratio; GER: gastroesophageal reflux; UIP: usual interstitial pneumonia; FVC: forced vital capacity; *D*LCO: diffusion capacity of the lung for carbon monoxide; ANA: antinuclear antibody; HRCT: high-resolution computed tomography; SLB: surgical lung biopsy. [#]: N=143; [¶]: azathioprine n=41, mycophenolate mofetil n=19, tacrolimus n=4, and cyclophosphamide n=2; [+]: based on HRCT or SLB, with SLB serving as final diagnosis when discordant.

Modified IPAF

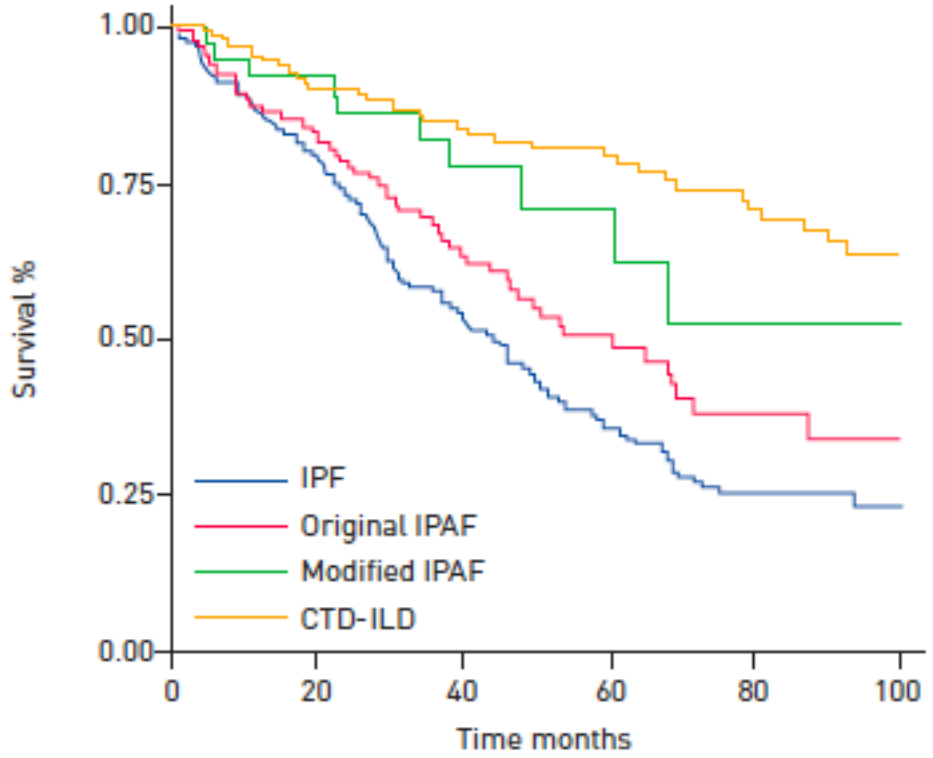

FIGURE 3 Kaplan–Meier survival curves of modified interstitial pneumonia with autoimmune features (IPAF), original IPAF, idiopathic pulmonary fibrosis (IPF) and connective tissue disease (CTD)-interstitial lung disease (ILD) cohorts. Modified IPAF cohort survival was similar to the CTD-ILD cohort (p=0.26), marginally better than the original IPAF cohort (p=0.09) and significantly better than the IPF cohort (p=0.005).

In comparison to the other UCTD-ILD groups

- Patients meeting IPAF criteria -older and smokers
- higher proportion of UIP compared to NSIP
- Similar survival between UCTD-UIP and IPF cohorts
- Survival among IPAF patients with a non-UIP pattern is similar
- Predictors of mortality in the IPAF cohort included age and DLCO, so sex, age, physiology (GAP) scoring system can be validated for IPAF prognostication

Denver cohort-2016

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Respiratory Medicine

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Clinical features and natural history of interstitial pneumonia with autoimmune features: A single center experience

Sandra Chartrand [a], Jeffrey J. Swigris [b, c], Lina Stanchev [c], Joyce S. Lee [c], Kevin K. Brown [b, c], Aryeh Fischer [c, *]

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Methodology

- Retrospective-single center study
- Clinical data collected from EMR between February 2008 and August 2014
- **Objective:** Clinical phenotype and natural history of IPAF cohort
- Myositis -associated and myositis-specific autoantibodies also used
- **Statistical analysis:** Descriptive statistics
- Longitudinal changes in forced vital capacity (FVC)-piecewise linear regression models that considered time as a continuous factor

IPAF n = 56

Age at dx, years (mean ± SD)	54.6 ± 10.3
Age at first follow up, years (mean ± SD)	55.9 ± 10.1
Time between dx and 1st FU, days (mean ± SD)	452 ± 746
Time between dx and 1st PFT, days (mean ± SD)	441 ± 778
BMI, kg/m^2 (mean ± SD)	29.3 ± 5.3
Female, n (%)	40 (71.4)
Ethnicity, n (%)	
Non hispanic	53 (94.6)
Hispanic	3 (5.6)
Race, n (%)	
White	50 (89.3)
Afro-American	4 (7.1)
Asian	1 (1.8)
American Native or Alaskan Native	1 (1.8)
Race, n (%)	
White	50 (89.3)
Other	6 (10.7)
Tobacco status, n (%)	
Never smokers	38 (67.9)
Ever smokers	18 (32.1)
Pack-year (mean ± SD)	21.3 ± 19.8
Expired, n (%)	0 (0.0)
Positive family history of CTD, n (%)	14 (25.0)
Immunosuppressive therapy, n (%)	n = 55
Prednisone	45 (81.8)
Mycophenolate mofetil	42 (76.4)
Azathioprine	20 (36.4)
Cyclophosphamide	13 (23.6)
Tacrolimus	4 (7.3)
Rituximab	2 (3.6)

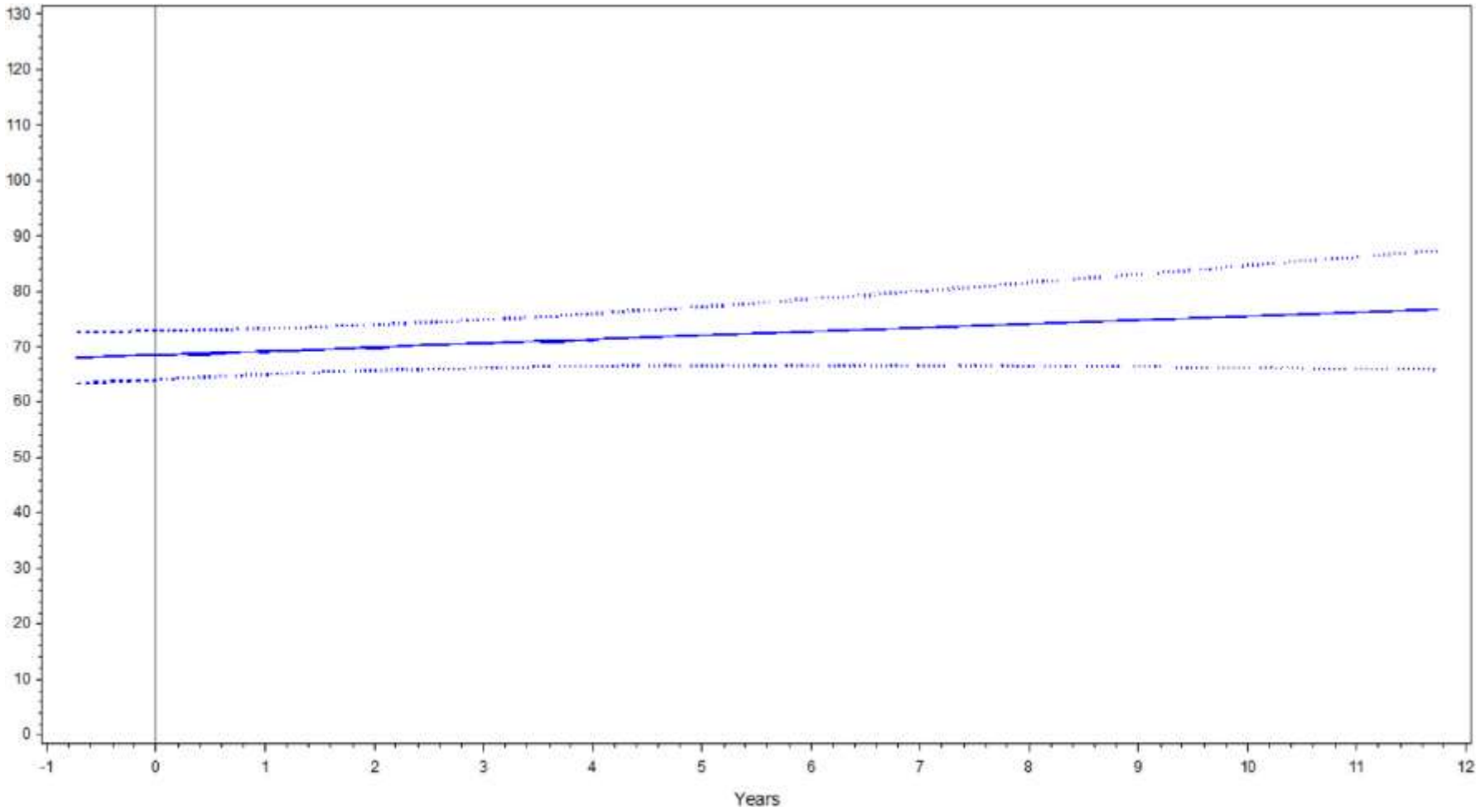
Thoracic HRCT scan, n (%)	
NSIP	29 (51.8)
NSIP + OP	8 (14.3)
UIP	5 (8.9)
LIP	1 (1.8)
OP	1 (1.8)
Undefined	12 (21.4)
Biopsy, n (%)	n = 36
NSIP	12 (33.3)
NSIP + OP	8 (22.2)
UIP	8 (22.2)
OP	3 (8.3)
LIP	1 (2.8)
RB-ILD	1 (2.8)
DAD	2 (5.6)
Undefined	1 (2.8)
Suggestive features of CTD*	19 (52.8)
Other compartment involvement**	7 (19.4)
PFT parameters at baseline, in percent predicted (mean ± SD)	
Forced vital capacity (%FVC)	68.4 ± 16.0
Forced expired volume in 1 s (%FEV1)	72.7 ± 16.3
Diffusion capacity of the lung for CO (%DLCO)	52.2 ± 15.9
Total lung capacity (%TLC)	80.1 ± 13.7

Classification criteria	IPAF patients n (%)
1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) **and**	56 (100.0)
2. Exclusion of alternative etiologies **and**	56 (100.0)
3. Does not meet criteria of a defined CTD **and**	56 (100.0)
4. At least one (1) feature from at least two (2) of these domains:	56 (100.0)
A. Clinical domain (each 1 point)	35 (62.5)
1. Distal digital fissuring (i.e. 'mechanic hands')	16 (28.6)
2. Distal digital tip ulceration	0 (0.0)
3. Inflammatory arthritis or polyarticular morning joint stiffness > 60 minutes	9 (16.1)
4. Palmar telangiectasia	3 (5.4)
5. Raynaud's phenomenon	22 (39.3)
6. Unexplained digital edema	2 (3.6)
7. Unexplained fixed rash on the digital extensor surfaces (i.e. 'Gottron's sign')	10 (17.9)
B. Serologic domain (each 1 point)	51 (91.1)
1. ANA, either diffuse, speckled, or homogeneous patterns at >1:320 titer or ANA nucleolar pattern at any titer or ANA centromere pattern at any titer	27 (48.2)
2. RF > 2 X ULN	6 (10.7)
3. Anti-CCP	6 (10.7)
4. Anti-dsDNA	1 (1.8)
5. Anti-Ro (SS-A)	24 (42.9)
6. Anti-La (SS-B)	3 (5.4)
7. Anti-ribonucleoprotein	9 (16.1)
8. Anti-Smith	5 (8.9)
9. Anti-topoisomerase (Scl-70)	1 (1.8)
10. Anti-tRNA synthetase (eg, Jo-1, PL-7, PL-12, EJ, OJ, KS, Zo, tRS)	20 (35.7)
11. Anti-PM-Scl	1 (1.8)
12. Anti-MDA5 (CADM-40)	0 (0.0)
C. Morphologic domain	55 (98.2)
1. Suggestive radiology patterns by HRCT:	
a. NSIP	32 (57.1)
b. OP	2 (3.6)
c. NSIP with OP overlap	10 (17.9)
d. LIP	3 (5.4)
2. Histopathology patterns or features by surgical lung biopsy:	
a. NSIP	13 (23.2)
b. OP	4 (7.1)
c. NSIP with OP overlap	8 (14.3)
d. LIP	1 (1.8)
e. Interstitial lymphoid aggregates with germinal centers	13 (23.2)
f. Diffuse lympho-plasmacytic infiltration (with or without lymphoid follicles)	6 (10.7)
3. Unexplained multi-compartment involvement[a]:	
a. Pleural effusion or thickening	6 (10.7)
b. Pericardial effusion or thickening	1 (1.8)
c. Intrinsic airways disease	7 (12.5)
d. Pulmonary vasculopathy	17 (30.4)

Modified from: (ref).

[a] Either by: thoracic imaging, lung histopathology, right heart catheterization, pulmonary physiology.

Plot of mixed-effects model estimates for forced vital capacity in percent predicted (FVC%) over time for the entire cohort



Respiratory Medicine 123 (2017) 56–62

Contents lists available at ScienceDirect

Respiratory Medicine

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France cohort-2017

Interstitial pneumonia with autoimmune features: Clinical, radiologic, and histological characteristics and outcome in a series of 57 patients☆

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Methodology

- Retrospective study -Lyon, France January 1st, 2012 to December 31st, 2014
- To assess survival, the overall survival of incident (new) cases in the IPAF cohort was compared to that of incident cases of IPF seen at the same institution over a 3-year period (January 1st, 2012 to December 31st, 2014)
- IPAF score was defined as the cumulative number of IPAFcriteria in each patient
- ILD diagnosis-rigorous

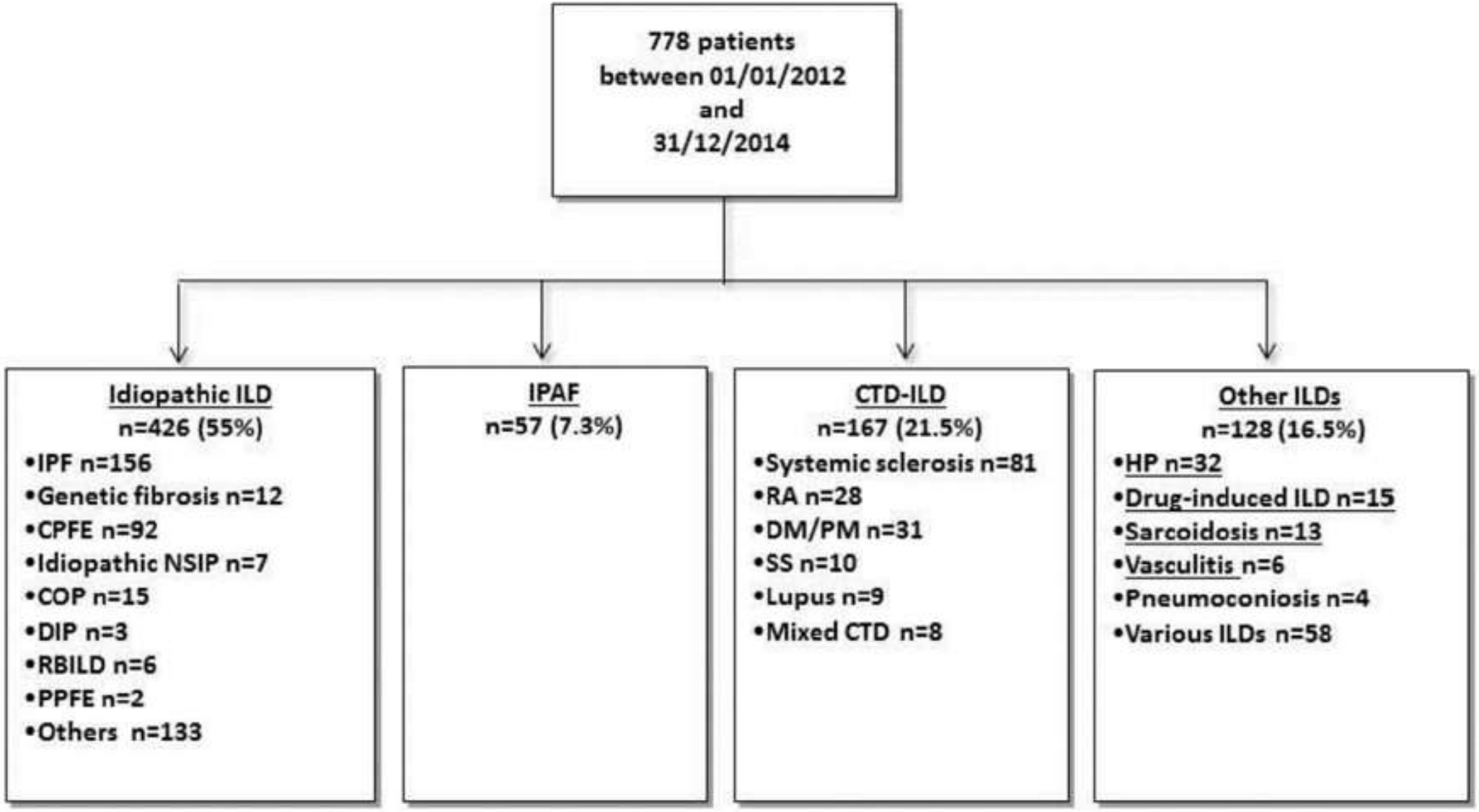


Fig. 1. Study flow chart IPF = idiopathic pulmonary fibrosis; CPFE = combined pulmonary fibrosis and emphysema; NSIP = non specific interstitial pneumonia; OP = organizing pneumonia; DIP = desquamative interstitial pneumonia; RBILD = respiratory bronchiolitis/interstitial lung disease; PPFE = pleuroparenchymal fibroelastosis; CTD-ILD: interstitial lung disease with connective tissue disease; RA = rheumatoid arthritis; DM/PM = dermatomyositis-polymyositis; GS: Gougerot-Sjögren syndrome; HP = hypersensitive pneumonia.

Characteristics and clinical manifestations at the diagnosis of IPAF.

	IPAF (n = 57)[a]
Age, mean (SD)	64.4 (14)
Female, n (%)	28 (49.1)
Tobacco history, n (%)	16 (34)
ILD revealing mode n (%)	
Exertional dyspnea	50 (87.7)
Cough	2 (3.5)
Others	3 (5.4)
Functional tests	
FVC, L (% of predicted)	2.41 (80.2)
FEV1, L (%of predicted)	1.87 (78)
FEV1/FVC	0.78
TLC, L (% of predicted)	3.95 (72)
DLCO (% of predicted)	49.3
KCO (% of predicted)	78
PaO2, kPa	10
BAL	
Ma/Ly/PNN/PNE (%)	49.4/12/29.3/9
Treatment, n (%)	
Anti fibrotic, n (%)	3 (5.4)
Corticosteroid therapy, n (%)	38 (67.9)
Immunosuppressive therapy, n (%)	16 (28.6)

	N (%)
Clinical domain	27 (47.3)
Distal digital fissuring	2 (7.4)
Distal digital tip ulcerations	0 (0)
Inflammatory arthritis or polyarticular morning joint stiffness ≥ 60min	13 (48.1)
Palmar telangiectasia	7 (25.9)
Raynaud's phenomenon	20 (74.1)
Unexplained digital oedema	9 (33.3)
Unexplained fixed rash on the digital extensor surface	3 (11.1)
Serologic domain	53 (93)
ANA ≥ 1:320 titer, diffuse, speckled or homogeneous patterns, ANA nucleolar pattern (any titer), or ANA centromere pattern (any titer)	47 (82.4)
Rheumatoid factor ≥ 2x upper limit of normal	4 (7.5)
Anti-CCP	5 (9.4)
Anti-dsDNA	3 (5.7)
Anti-Ro (SS-A)	5 (9.4)
Anti-La (SS-B)	1 (1.9)
Anti-ribonucleoprotein	0 (0)
Anti-Smith	0 (0)
Anti-topoisomerase (Scl-70)	3 (5.7)
Anti-tRNA synthetase	9 (17)
Anti-Pm-Scl	3 (5.7)
Anti-MDA-5	0 (0)

	N (%)
Morphologic domain	45 (78.9)
Suggestive radiology patterns by HRCT (n = 54)	
NSIP	24 (42.1)
OP	2 (3.5)
NSIP with OP overlap	9 (15.8)
LIP	1 (1.8)
Histopathology patterns or features by surgical lung biopsy (n = 17)	
NSIP	5 (8.8)
OP	2 (3.5)
NSIP with OP overlap	1 (1.8)
LIP	1 (1.8)
Interstitial lymphoid aggregates with germinal centres	6 (10.5)
Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)	7 (12.3)
Multi-compartment involvement (in addition to interstitial pneumonia)	
Unexplained pleural effusion or thickening	1 (1.8)
Unexplained pericardial effusion or thickening	1 (1.8)
Unexplained intrinsic airways diseases (by PFT. imaging or pathology)	5 (8.8)
Unexplained pulmonary vasculopathy	10 (17.5)

- UIP pattern on CT present in 28% of IPAF patients
- CPEF-4
- UIP pattern-3 patients

- Median duration of follow-up -16 months
- 7 patients died. Causes of death in the IPAF cohort were infection (n=3), all of them received immunosuppressive therapy, chronic RF with hypoxemia(n=1), and unknown (n =3)
- Probability of overall survival in IPAF patients was 83.6% at one year compared to 94.8% in IPF patients, with nonsignificant difference between groups (p . 0.05).

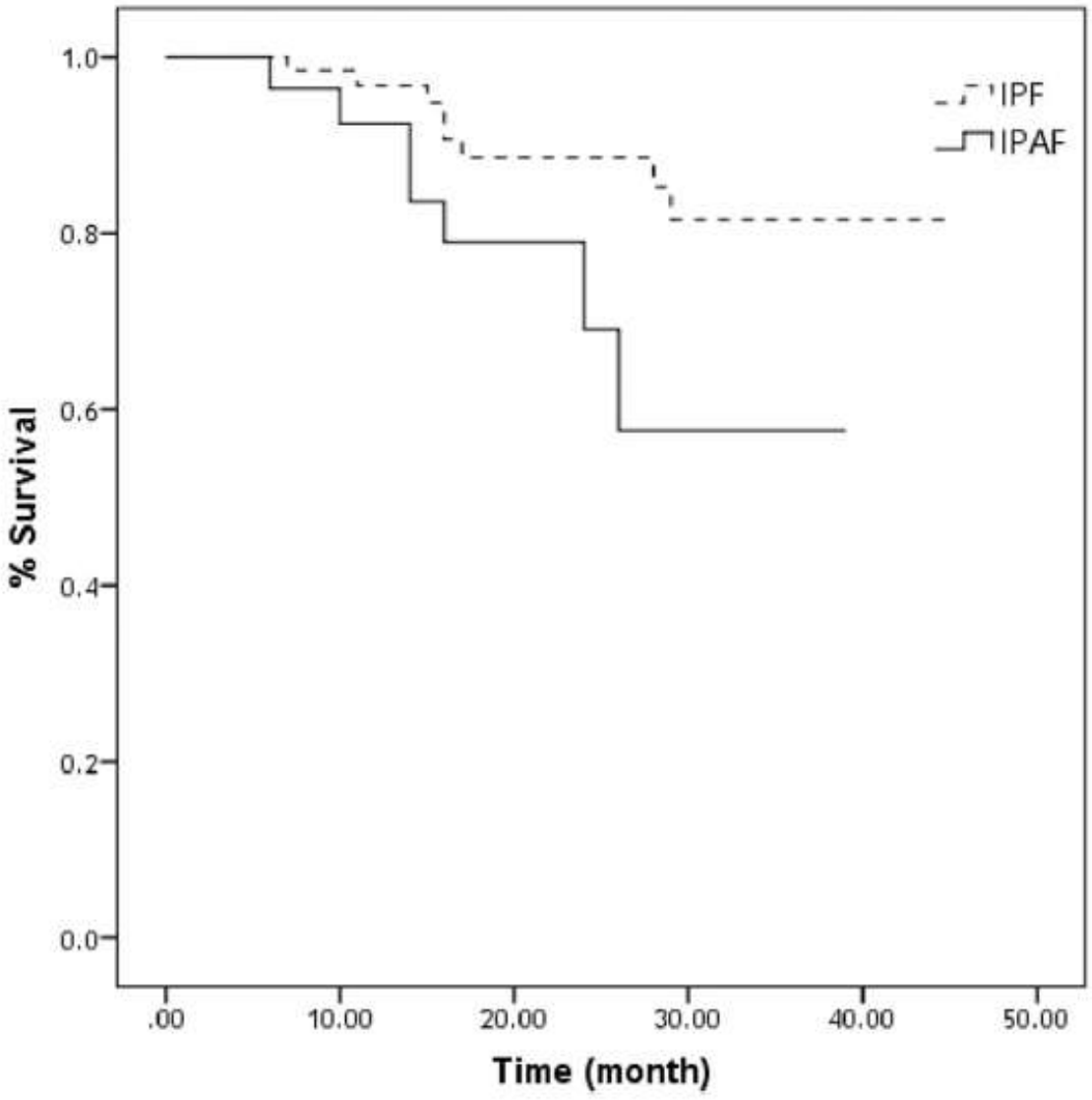
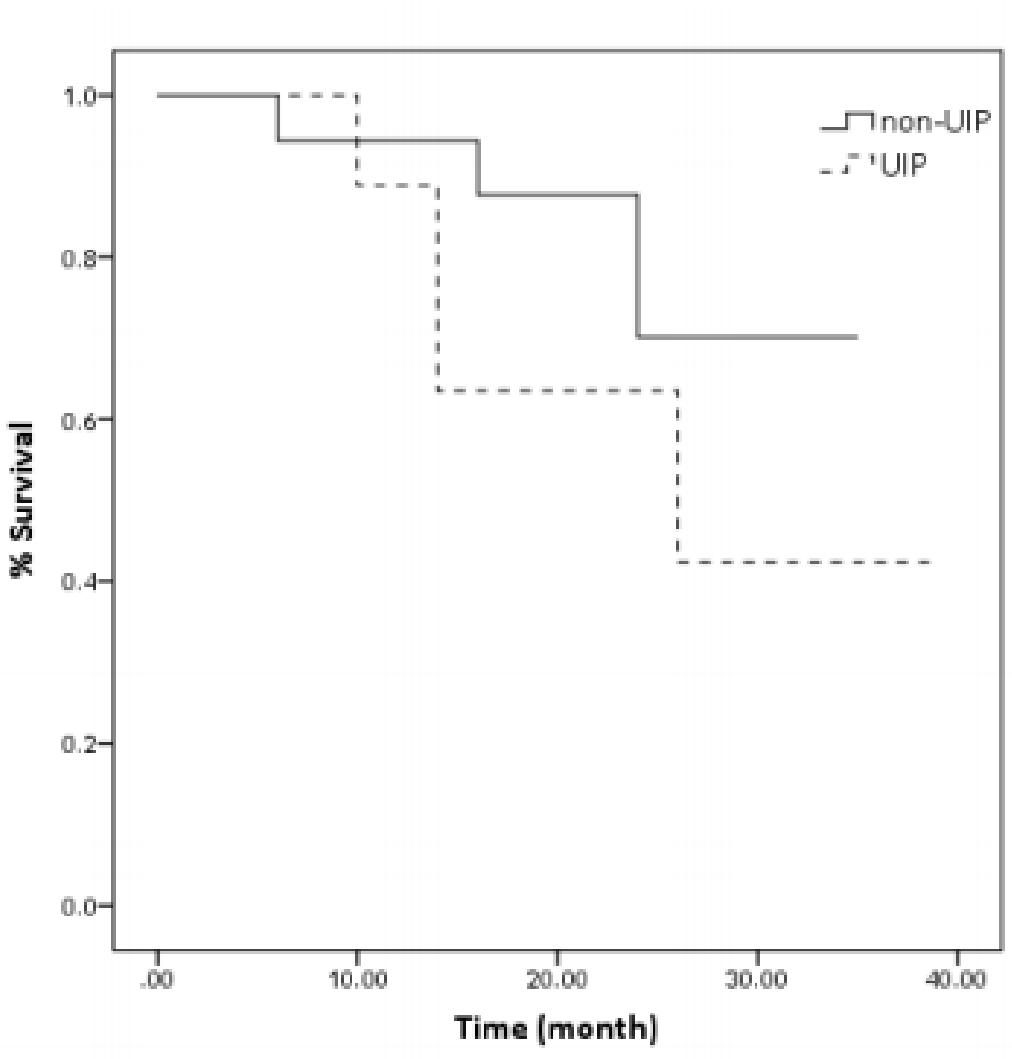


Fig. 3. Kaplan-Meier estimates of overall survival in patients with IPAF and IPF (Log-Rank test, p = 0.05).

Among patients with IPAF, no difference in survival was found between the UIP or NSIP pattern at imaging (p = 0.23 and p =0.73, respectively)



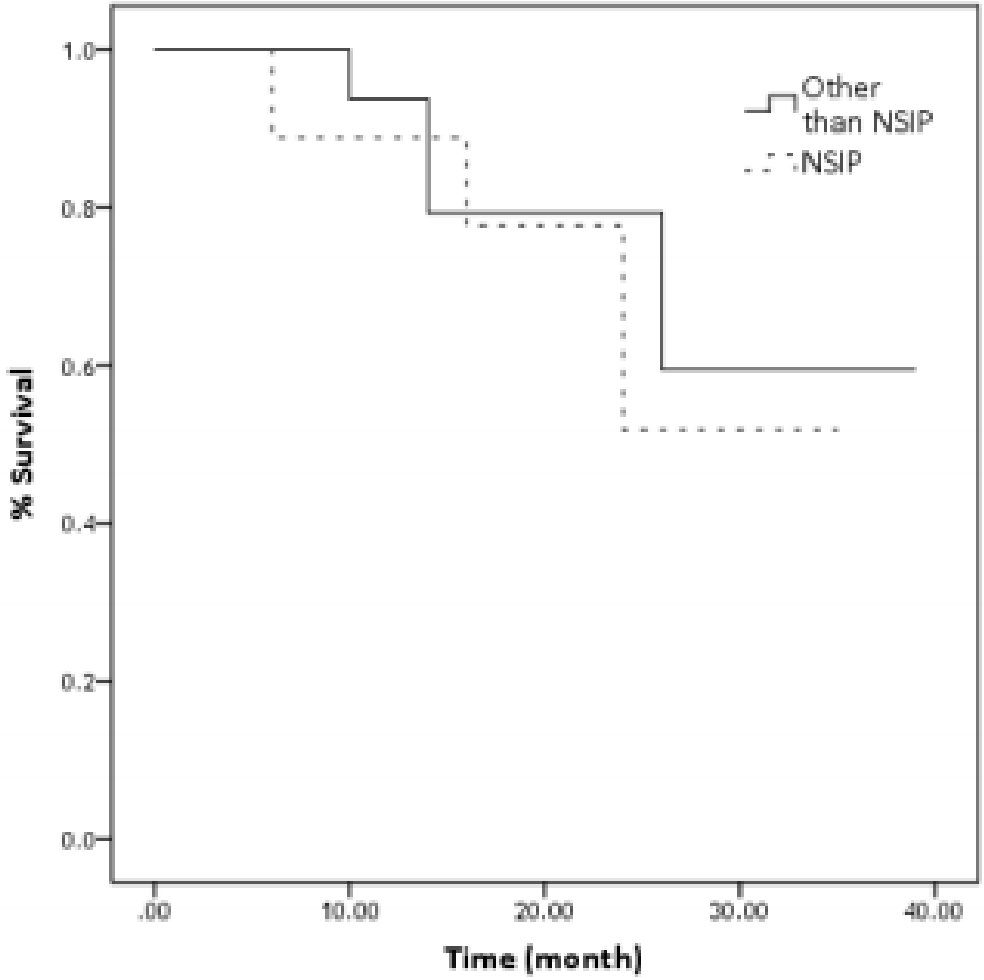


Table 3
Predictive factors of mortality in patients with IPAF (univariate analysis).

	p	odds ratio	IC
Sex	0.282		
History of tobacco smoking	**0.023**	**7.18**	**1.31–39.26**
IPAF score	0.893		
ANA titre	0.886		
HRCT NSIP	0.735		
HRCT UIP	0.244		
Pathology of NSIP	0.778		
Pathology of UIP	0.65		
Pulmonary hypertension	0.17		
FVC	0.316		
DLCO	0.081		
KCO	0.268		
Antifibrotic therapy	0.158		
Corticosteroid therapy	0.097		
Immunosuppressive therapy	0.639		

Text in bold refers to statistically significant results ($p<0.05$).

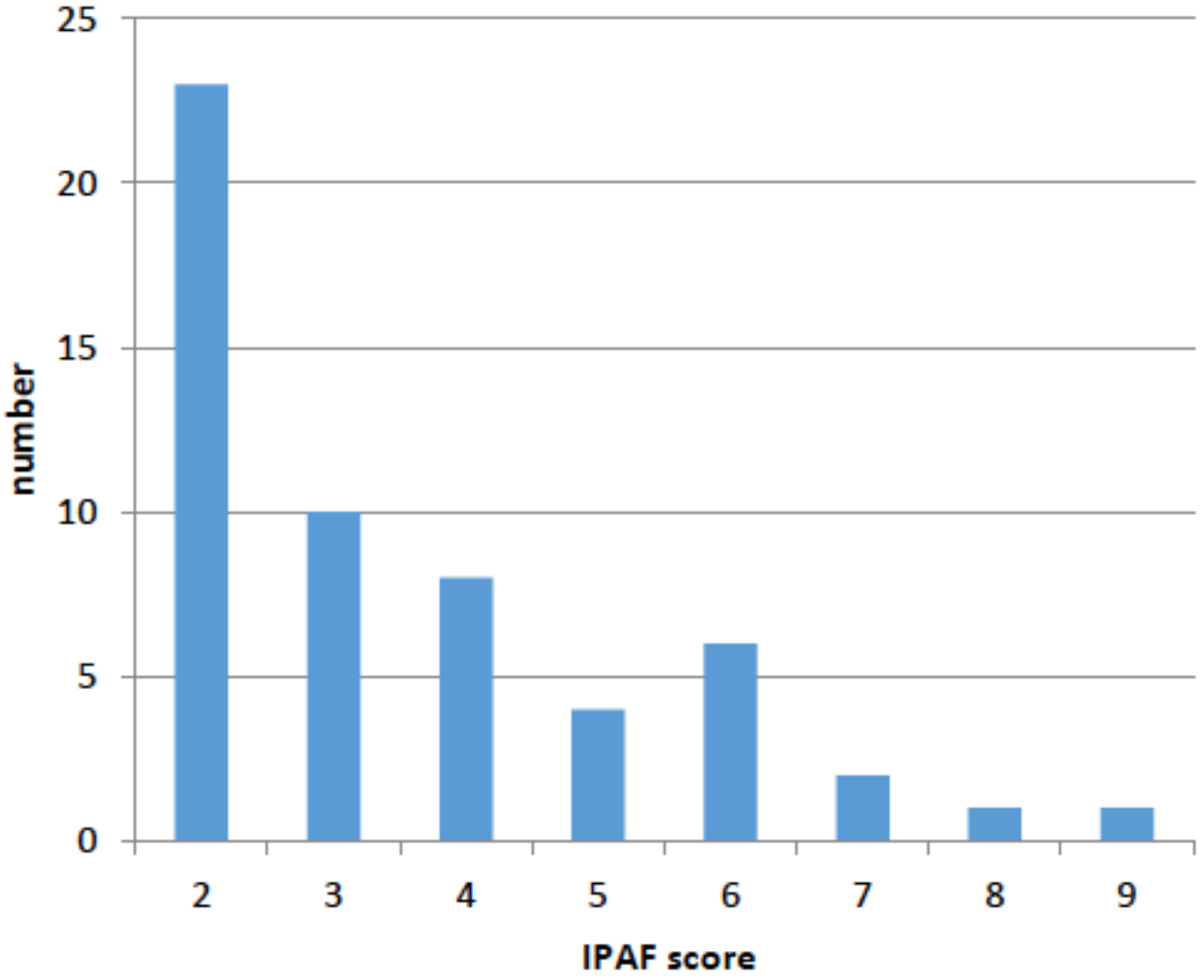


Fig. 2. Distribution of the IPAF score.

IPAF score had no influence on the survival

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Japan cohort-2018

Distinctive characteristics and prognostic significance of interstitial pneumonia with autoimmune features in patients with chronic fibrosing interstitial pneumonia

Katsuhiro Yoshimura[a], Masato Kono[a], Yasunori Enomoto[a], Koji Nishimoto[a], Yoshiyuki Oyama[a], Hideki Yasui[a], Hironao Hozumi[a], Masato Karayama[a], Yuzo Suzuki[a], Kazuki Furuhashi[a], Noriyuki Enomoto[a], Tomoyuki Fujisawa[a], Yutaro Nakamura[a,*], Naoki Inui[a,b], Hiromitsu Sumikawa[c], Takeshi Johkoh[d], Thomas V. Colby[e], Haruhiko Sugimura[f], Takafumi Suda[a]

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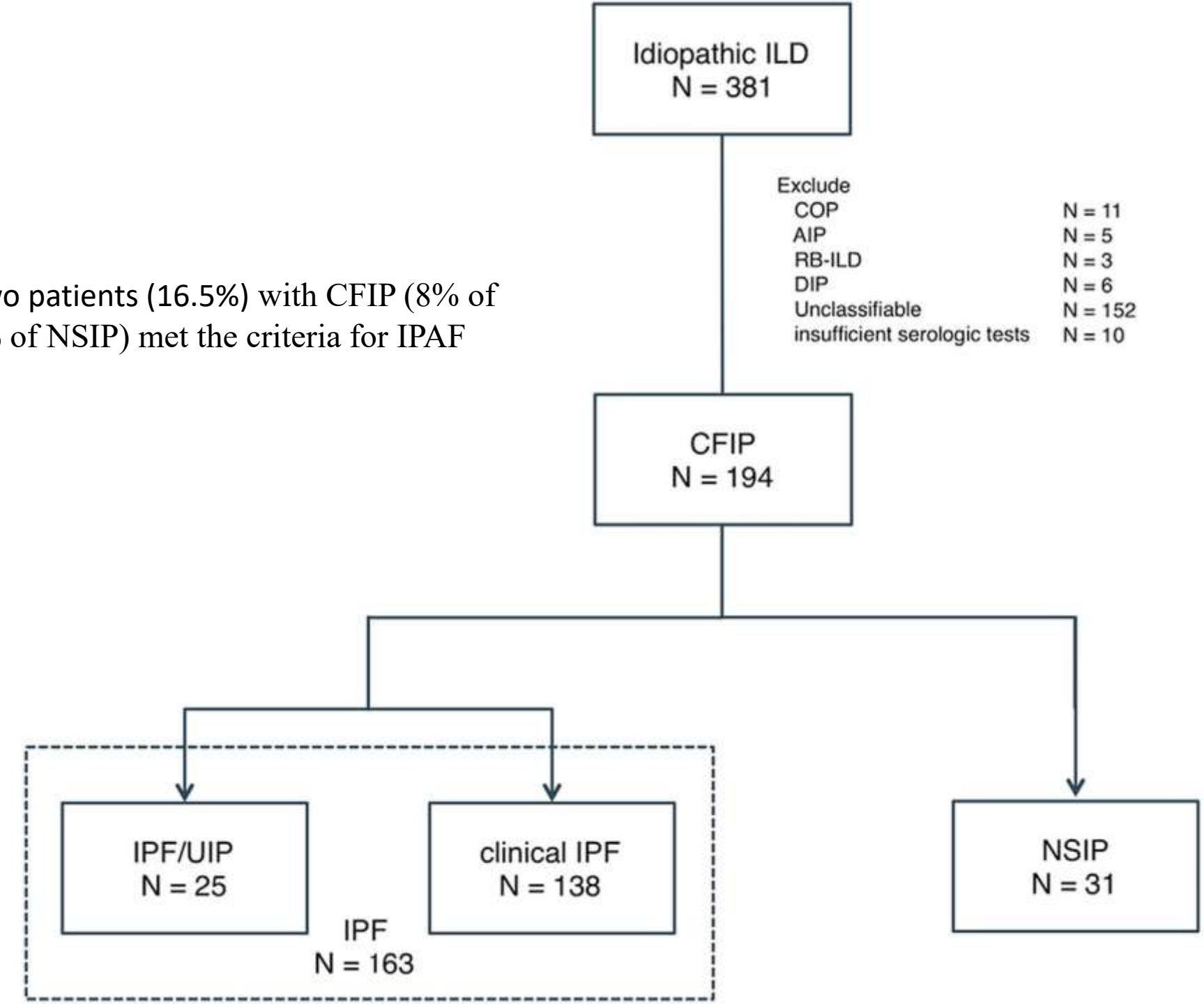
Methodology

- Chronic fibrosing interstitial pneumonia (CFIP)-includes both idiopathic pulmonary fibrosis (IPF) and idiopathic nonspecific interstitial pneumonia (NSIP)
- UIP and NSIP account for approximately 80% of IIPs
- Single-center observational study
- Anti-PM-Scl ,anti-MDA-5 and anti-tRNA synthetase are not done
- Clinical significance of the new IPAF designation, diagnosis of IPAF in terms of both overall survival (OS) and incidence of acute exacerbations (AEs)

Methodology

- 607 patients diagnosed with ILD from January 2000 to December 2015
- Patients with definitive etiology were excluded
- Remaining 381 patients were then screened for types of IIP other than IPF and NSIP, such as cryptogenic organizing pneumonitis (OP), acute interstitial pneumonia, respiratory bronchiolitis- ILD, and desquamative interstitial pneumonia
- 152 patients with unclassifiable IIPs were also excluded
- Finally 194 patients with CFIP were enrolled in the study

Thirty-two patients (16.5%) with CFIP (8% of IPF, 61% of NSIP) met the criteria for IPAF



Characteristics	Total	Non-IPAF	IPAF	*P* - value[a]
	N = 194	N = 162 (83.5)	N = 32 (16.5)	
Age, years	68.7 ± 9.4	69.8 ± 8.3	63.4 ± 12.6	< 0.001
Sex				
Male	155 (79.9)	136 (84.0)	19 (59.4)	0.003
Female	39 (20.1)	26 (16.0)	13 (40.6)	
Smoking status				
Never	43 (22.2)	29 (17.9)	14 (43.8)	0.004
Ever	151 (77.8)	133 (82.1)	18 (56.2)	
Observation periods, years	3.52 ± 3.67	3.11 ± 3.16	5.57 ± 5.15	< 0.001
Surgical lung biopsy	61 (31.4)	39 (24.1)	22 (68.8)	< 0.001
ILD pattern				
IPF	163 (84.0)	150 (92.6)	13 (40.6)	0.015
NSIP	31 (16.0)	12 (7.4)	19 (59.4)	
Laboratory				
LDH, IU/L	238 ± 61	237 ± 59	245 ± 73	0.494
CRP, mg/dL	0.76 ± 1.73	0.81 ± 1.86	0.52 ± 0.80	0.393
KL-6, U/mL	1188 ± 947	1143 ± 861	1440 ± 1330	0.134
Pulmonary function				
FVC, %predicted	77.5 ± 18.5	77.0 ± 18.7	80.4 ± 17.4	0.364
TLC, %predicted	81.4 ± 15.3	80.6 ± 15.8	84.3 ± 13.9	0.393
PaO2 on room air, Torr	79.4 ± 12.9	79.1 ± 13.0	80.5 ± 12.5	0.595
Bronchoalveolar lavage				
Lymphocytes, %	8.3 ± 10.5	8.0 ± 10.1	9.8 ± 12.2	0.420
Neutrocytes, %	2.8 ± 5.6	2.7 ± 5.9	3.0 ± 3.9	0.801
Eosinophils, %	2.0 ± 4.5	2.0 ± 4.7	2.2 ± 3.1	0.829
CD4/CD8 ratio	2.33 ± 2.22	2.56 ± 2.32	1.32 ± 1.31	0.013
Treatment on clinical course				
Corticosteroids	85 (43.8)	67 (41.4)	19 (59.4)	0.079
Immunosupressant	50 (25.8)	40 (24.7)	11 (34.4)	0.275
Pirfenidone	45 (23.2)	37 (22.8)	8 (25.0)	0.820
Long-term oxygen therapy	59 (30.4)	51 (31.5)	8 (25.0)	0.534
None	80 (41.2)	72 (44.4)	8 (25.0)	0.050

Supplementary Table S1. Baseline characteristics of patients with idiopathic pulmonary fibrosis according to IPAF definition.

Characteristics	IPF N = 163	Non-IPAF-IPF N = 150 (92.0)	IPAF-IPF N = 13 (8.0)	*P* - value *
Age, years	70.3 ± 8.1	70.3 ± 8.0	70.2 ± 9.4	0.979
Sex				
Male	140 (85.9)	127 (84.7)	13 (100)	0.218
Female	23 (14.1)	23 (15.3)	0 (0)	
Smoking status				
Ever	28 (17.2)	26 (17.3)	2 (15.4)	1.000
Never	135 (82.8)	124 (82.7)	11 (84.6)	
Observation periods, years	2.86 ± 2.79	2.80 ± 2.78	3.57 ± 2.96	0.340
Surgical lung biopsy	30 (18.4)	27 (18.0)	3 (23.1)	0.709
IPF pattern				
clinical IPF	135 (82.8)	125 (83.3)	10 (76.9)	0.470
UIP/IPF	28 (17.2)	25 (16.7)	3 (23.1)	
Laboratory				
LDH, IU/L	234 ± 53	234 ± 54	234 ± 37	0.949
CRP, mg/dL	0.77 ± 1.69	0.78 ± 1.74	0.67 ± 1.00	0.836
KL-6, U/mL	1100 ± 736	1097 ± 741	1102 ± 712	0.992
Pulmonary function				
FVC, %predicted	77.6 ± 18.7	77.0 ± 18.8	83.6 ± 16.9	0.227
TLC, %predicted	81.1 ± 15.3	80.5 ± 15.9	84.8 ± 10.1	0.462
PaO_2 on room air, Torr	79.0 ± 13.1	79.1 ± 13.3	78.2 ± 11.4	0.835
Bronchoalveolar lavage				
Lymphocytes, %	6.88 ± 7.32	6.9 ± 7.5	6.5 ± 4.1	0.868
Neutrocytes, %	2.60 ± 5.8i6	2.6 ± 6.1	2.3 ± 2.5	0.873

Eosinophils, %	1.99 ± 4.66	1.9 ± 4.7	3.1 ± 4.5	0.475
CD4/CD8 ratio	2.58 ± 2.30	2.62 ± 2.37	2.16 ± 1.42	0.572
Treatment on clinical course				
Corticosteroids	60 (36.8)	59 (39.3)	4 (30.8)	0.768
Immunosupressant	41 (25.2)	37 (24.7)	4 (30.8)	0.739
Pirfenidone	45 (27.6)	37 (24.7)	8 (61.5)	0.008
Long-term oxygen therapy	54 (33.1)	48 (32.0)	6 (46.2)	0.360
None	72 (44.2)	68 (45.3)	4 (30.8)	0.390

Variables were presented as mean ± SD or N (%).

Abbreviations: IPAF, interstitial pneumonia with autoimmune features; IPF, idiopathic pulmonary fibrosis ; UIP, usual interstitial pneumonia.

* Non-IPAF-IPF vs IPAF-IPF

Supplementary Table S2. Baseline characteristics of patients with non-specific interstitial pneumonia according to IPAF definition.

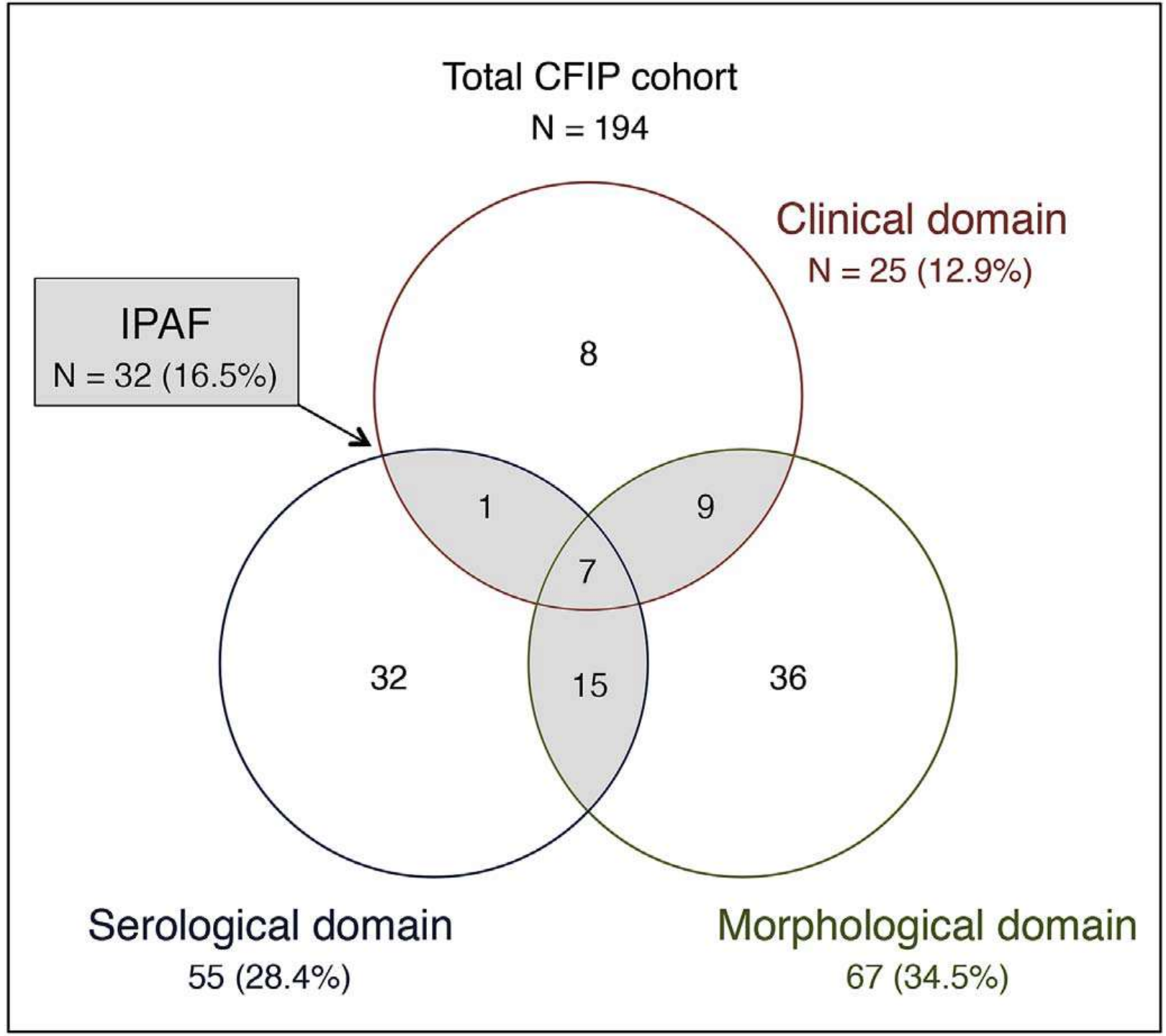
Characteristics	NSIP N = 31	Non-IPAF-NSIP N = 12 (38.7)	IPAF-NSIP N = 19 (61.3)	*P* - value *
Age, years	60.5 ± 11.7	63.3 ± 9.8	58.7 ± 12.6	0.288
Sex				
Male	15 (48.4)	9 (75.0)	6 (31.6)	0.029
Female	16 (51.6)	3 (25.0)	13 (68.4)	
Smoking status				
Ever	16 (51.6)	9 (75.0)	7 (36.8)	0.066
Never	15 (48.4)	3 (25.0)	12 (63.2)	
Observation periods, years	6.98 ± 5.45	7.04 ± 4.88	6.94 ± 5.92	0.962

Surgical lung biopsy	31 (100.0)	12 (100)	19 (100)	1.000
Laboratory				
LDH, IU/L	261 ± 91	275 ± 95.4	252 ± 89.9	0.508
CRP, mg/dL	0.71 ± 1.93	1.23 ± 3.10	0.42 ± 0.64	0.276
KL-6, U/mL	1765 ± 1715	1780 ± 1845	1755 ± 1689	0.973
Pulmonary function				
FVC, %predicted	77.4 ± 18.1	76.8 ± 19.0	77.9 ± 18.0	0.871
TLC, %predicted	83.7 ± 16.5	83.0 ± 16.2	83.9 ± 17.7	0.948
PaO_2 on room air, Torr	81.2 ± 11.9	80.1 ± 9.9	82.0 ± 13.3	0.681
Bronchoalveolar lavage				
Lymphocytes, %	14.0 ± 17.5	18.3 ± 21.6	11.4 ± 14.5	0.313
Neutrocytes, %	3.5 ± 4.5	3.5 ± 4.5	3.4 ± 4.6	0.947
Eosinophils, %	2.2 ± 3.5	3.0 ± 5.2	1.8 ± 2.0	0.390
CD4/CD8 ratio	1.21 ± 1.35	1.89 ± 1.67	0.81 ± 0.98	0.056
Treatment on clinical course				
Corticosteroids	23 (74.2)	8 (66.7)	15 (78.9)	0.676
Immunosupressant	10 (32.3)	3 (25.0)	7 (36.8)	0.697
Long-term oxygen therapy	5 (16.1)	3 (25.0)	2 (10.5)	0.350
None	8 (25.8)	4 (33.3)	4 (21.1)	0.676

Variables were presented as mean ± SD or N (%).

Abbreviations: IPAF, interstitial pneumonia with autoimmune features; IPF, idiopathic pulmonary fibrosis.

* Non-IPAF-IPF vs IPAF-IPF


Total CFIP cohort
N = 194
Clinical domain
N = 25 (12.9%)
IPAF
N = 32 (16.5%)
8
1
9
7
32
15
36
Serological domain
55 (28.4%)
Morphological domain
67 (34.5%)

Proportion of each domain of IPAF.

	Total	Non-IPAF	IPAF	*P* - value[a]
	N = 194	N = 162 (83.5)	N = 32 (16.5)	
Clinical domain	25 (12.9)	8 (4.9)	17 (53.1)	< 0.001
Mechanics hands	5 (2.6)	1 (0.6)	4 (12.5)	0.044
Distal digital tip ulceration	0 (0)	0 (0)	0 (0)	1.000
Inflammatory arthritis or polyarticular morning joint stiffness ≥ 60 min	15 (7.7)	6 (3.7)	9 (28.1)	< 0.001
Palmer talengiectasia	1 (0.5)	0 (0)	1 (3.1)	0.165
Raynaud's phenomenon	8 (4.1)	2 (1.2)	6 (18.8)	< 0.001
Unexplained digital oedema	2 (1.0)	1 (0.6)	1 (3.1)	0.303
Gottoron's sign	2 (1.0)	0 (0)	2 (6.3)	0.027
Serological domain	55 (28.4)	32 (19.8)	23 (71.9)	< 0.001
Antinuculear antibody ≥ 1:320 or < 1:320 with nucleolar or centromere pattern	21 (10.8)	12 (7.4)	9 (28.1)	0.002
Rheumatoid factor ≥ ×2 upper limit normal	22 (11.3)	15 (9.3)	7 (21.9)	0.062
Anti-cyclic citrullinated peptide	3 (1.5)	0 (0)	3 (9.4)	0.004
Anti-double stranded DNA	3 (1.5)	1 (0.6)	2 (6.3)	0.071
Anti-SSA	6 (3.1)	3 (1.9)	3 (9.4)	0.058
Anti-SSB	1 (0.5)	1 (0.6)	0 (0)	1.000
Anti-ribonucleoprotein	0 (0)	0 (0)	0 (0)	1.000
Anti-Smith	0 (0)	0 (0)	0 (0)	1.000
Anti-topoisomerase (Scl-70)	0 (0)	0 (0)	0 (0)	1.000
Anti-tRNA synthetase	2 (1.0)	0 (0)	2 (6.3)	0.027
Morphological domain	67 (34.5)	36 (22.2)	31 (96.9)	< 0.001
HRCT pattern				
NSIP	16 (8.2)	3 (1.9)	13 (40.6)	< 0.001
NSIP with OP	11 (5.7)	7 (4.3)	4 (12.5)	
Histopathologic pattern or features by surgical lung biopsy				
NSIP	31 (16.0)	12 (7.4)	19 (59.4)	< 0.001
Interstitial lymphoid aggregates with germinal centers	11 (5.7)	5 (3.1)	6 (18.8)	0.003
Diffuse lymphoplasmacytic infiltration	28 (14.4)	14 (8.6)	14 (43.8)	< 0.001
Unexplained multicompartment involvement				
Pericardial effusion or thickening	0 (0)	0 (0)	0 (0)	1.000
Pleural effusion or thickening	6 (3.1)	4 (2.5)	2 (6.3)	0.258
Intrinsic airway disease	9 (4.6)	4 (2.5)	5 (15.6)	0.007
Pulmonary vasculopathy	13 (6.7)	4 (2.5)	9 (28.1)	< 0.001

Variables were presented as N (%).

Abbreviations: HRCT, high resolution computed tomography; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia.

[a] Non-IPAF vs IPAF.

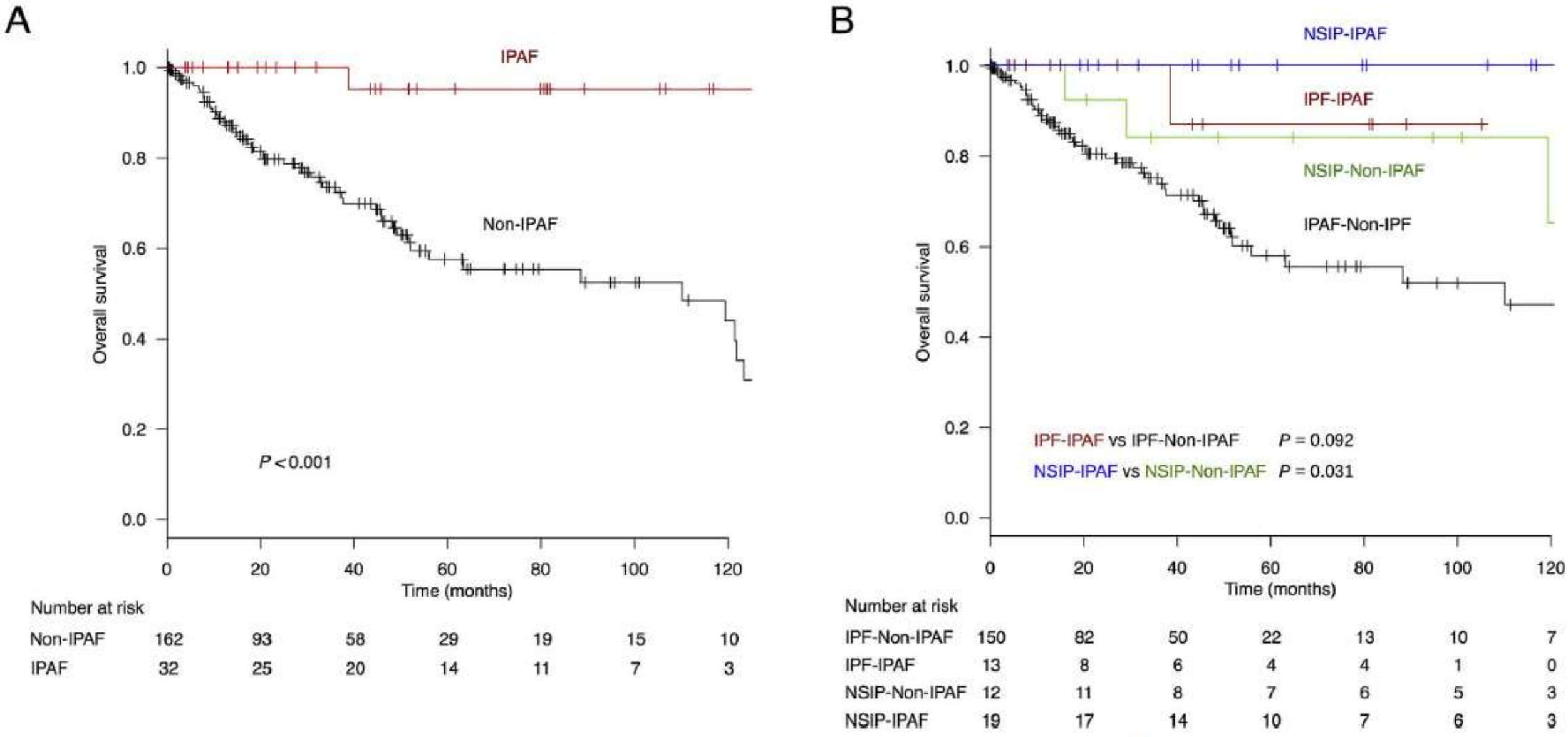
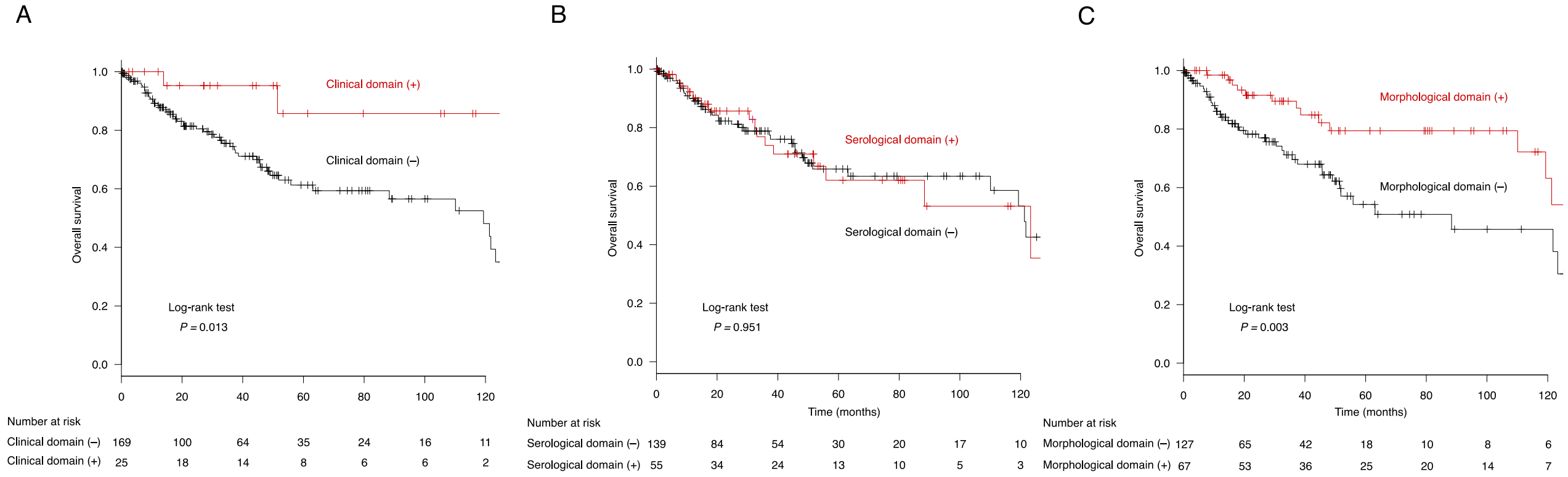


Fig. 3. Overall survival curves in patients with CFIP according to the IPAF diagnostic criteria. Survival curves according to IPAF diagnosis (A), and stratified by both the ILD pattern (IPF or NSIP) and IPAF diagnosis (B) are shown. There were significant differences between the CFIP cohort with and without IPAF ($P < 0.001$, log-rank test) and between the NSIP cohort with and without IPAF ($P = 0.031$, log-rank test). Abbreviations: CFIP, chronic fibrosing interstitial pneumonia; IPAF, interstitial pneumonia with autoimmune features; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia.



Overall survival curves according to the domain of the IPAF diagnostic criteria.

Kaplan-Meier curves for overall survival stratified by the positivity of the clinical domain (A), serologic domain (B), and morphologic domain (C), are shown. There were significant differences between patients with and without IPAF in both the clinical domain and the morphologic domain.

Univariate and multivariate Cox hazards models of overall survival in patients with chronic fibrosing interstitial pneumonia.

Variable	Per unit for hazard ratio	Unadjusted			Adjusted		
		Hazard ratio	95% CI	*P* - value	Hazard ratio	95% CI	*P* - value
Age	1-year	1.057	1.023–1.092	< 0.001	1.050	1.008–1.095	0.021
Sex	Male/female	3.924	1.415–10.88	0.009	1.757	0.500–6.173	0.380
BMI	1-kg/m^2	0.939	0.859–1.027	0.170	–	–	–
Smoking status	Ever/never	2.065	0.932–4.576	0.074	–	–	–
LDH	1-IU/L	0.997	0.992–1.001	0.141	–	–	–
KL-6	1-U/mL	0.999	0.999–1.000	0.485	–	–	–
PaO_2	1-Torr	1.022	0.999–1.044	0.055	1.039	1.015–1.064	0.001
%FVC	1-%	0.985	0.969–1.001	0.065	0.976	0.958–0.994	0.010
Clinical domain	Positive/negative	0.199	0.049–0.822	0.026	–	–	–
Serological domain	Positive/negative	1.019	0.567–1.833	0.951	–	–	–
Morphological domain	Positive/negative	0.400	0.213–0.753	0.005	–	–	–
IPAF diagnosis	Positive/negative	0.064	0.009–0.463	0.006	0.127	0.017–0.952	0.045

Adjusted models were analyzed with "IPAF diagnosis" and covariables which *P* values less than 0.10 at unadjusted model.
Abbreviations: IPAF, interstitial pneumonia with autoimmune features.

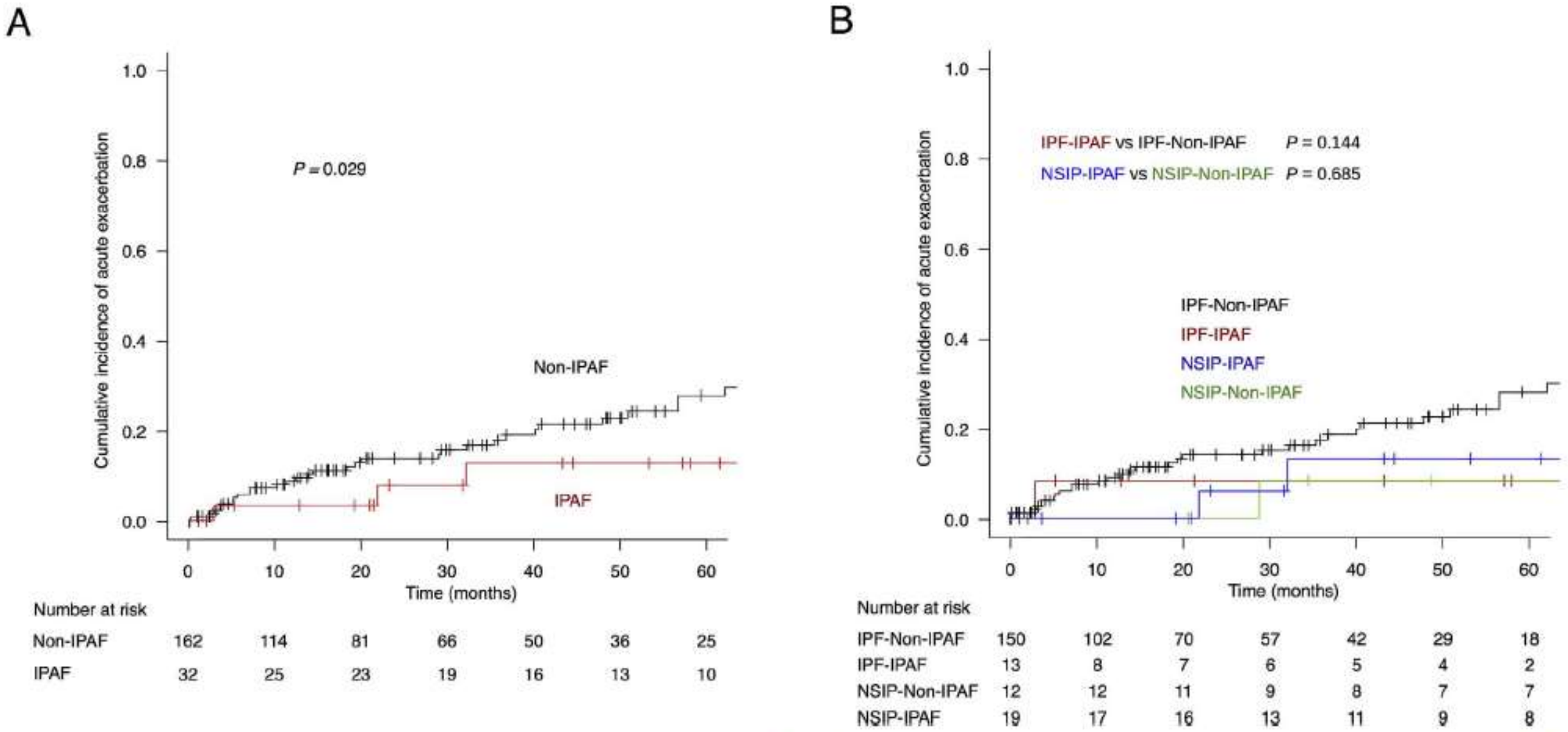


Fig. 4. Cumulative incidence of acute exacerbations in patients with CFIP according to the IPAF diagnostic criteria. Cumulative incidence of acute exacerbations (AEs) according to a diagnosis of IPAF (A), and stratified by both the ILD pattern (IPF or NSIP) and IPAF diagnosis (B) are shown. There was a significant difference between those with and without IPAF in the CFIP cohort ($P = 0.029$, Gray's test). Abbreviations: CFIP, chronic fibrosing interstitial pneumonia; IPAF, interstitial pneumonia with autoimmune features; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia.

Univariate and multivariate Fine-Gray hazards models of cumulative incidence of acute exacerbation in patients with chronic fibrosing interstitial pneumonia.

Variable	Per unit for hazard ratio	Unadjusted			Adjusted		
		Hazard ratio	95% CI	*P* - value	Hazard ratio	95% CI	*P* - value
Age	1-year	1.002	0.973–1.032	0.900	–	–	–
Sex	Male/female	1.708	0.721–4.047	0.220	–	–	–
BMI	1-kg/m^2	1.022	0.935–1.116	0.640	–	–	–
Smoking status	Ever/never	2.493	1.002–6.204	0.049	2.897	1.049–8.002	0.040
LDH	1-IU/L	1.004	1.000–1.008	0.030	1.004	0.998–1.009	0.190
KL-6	1-U/mL	1.000	1.000–1.008	0.150	–	–	–
PaO_2	1-Torr	0.980	0.950–1.012	0.220	–	–	–
%FVC	1-%	0.967	0.951–0.983	< 0.001	0.966	0.947–0.985	< 0.001
Clinical domain	Positive/negative	0.784	0.311–1.979	0.610	–	–	–
Serological domain	Positive/negative	0.495	0.230–1.068	0.073	–	–	–
Morphological domain	Positive/negative	0.918	0.520–1.620	0.770	–	–	–
IPAF diagnosis	Positive/negative	0.303	0.093–0.981	0.046	0.225	0.054–0.937	0.040

Adjusted models were analyzed with "IPAF diagnosis" and covariables remained at unadjusted model.

Abbreviations: IPAF, interstitial pneumonia with autoimmune features.

WASHINGTON CHORT

[Original Research **Diffuse Lung Disease**]

CHEST

Idiopathic Interstitial Pneumonia Associated With Autoantibodies

A Large Case Series Followed Over 1 Year

Bridget F. Collins, MD; Charles F. Spiekerman, PhD; Megan A. Shaw, MD; Lawrence A. Ho, MD; Jennifer Hayes, RN; Carolyn A. Spada, RN; Caroline M. Stamato, MPH; and Ganesh Raghu, MD

- Retrospective cohort study
- UWMC from January 1,2007 to March 31, 2013

Disease Group	Diagnostic Criteria
Interstitial pneumonia with autoimmune characteristics	
IPAF	• Per IPAF criteria, interstitial pneumonia and exclusion of alternate etiologies and does not meet criteria of defined CTD, and one or more features from two or more of three domains ○ Clinical domain: seven extrathoracic features of CTD ○ Serologic domain: specific serum autoantibodies (including ANA ≥ 1:320 diffuse, speckled, or homogenous or any titer nucleolar or centromere pattern) ○ Morphologic domain: certain HRCT image patterns (NSIP, OP, NSIP with OP overlap, LIP) or histopathology pattern/features by surgical lung biopsy (NSIP, OP, NSIP with OP overlap, LIP, interstitial lymphoid aggregates with germinal centers, diffuse lymphoplasmacytic infiltration) or multicompartment involvement (unexplained pleural or pericardial effusion or thickening, intrinsic airway disease[a] or pulmonary vasculopathy)[b]
AI-ILD	• Interstitial pneumonia and exclusion of alternate etiologies and • Positive CTD serology at the UWMC Laboratory (including ANA ≥ 1:80) and • Did not meet IPAF criteria or criteria for specific CTD
CTD-ILD	• Interstitial pneumonia and • Met American College of Rheumatology or other defined/accepted criteria for CTD
IPF[d]	• Per 2011 evidence-based guidelines[c] ○ UIP or possible UIP on HRCT images ○ Exclusion of alternate etiologies: no history of exposures known to be associated with hypersensitivity pneumonitis, no signs/symptoms of CTD • Negative CTD serologies at the UWMC Immunology Laboratory

CTD-ILD group, scleroderma spectrum disease and rheumatoid arthritis were the most common, accounting for 37.1% and 22.9%, respectively

Demographic	IPAF (n = 15)	AI-ILD (n = 20)	CTD-ILD (n = 36)	Lone-IPF (n = 52)	*P* Value[a]
Male	8 (53)	8 (40)	6 (17)	32 (62)	< .01[b]
Age, y	54.6 ± 11.8	62.2 ± 11.7	53.2 ± 13.8	63.2 ± 7.9	< .01[c]
Prior/current smoker	7 (47)	11 (55)	14 (39)	33 (63)	.14
Pulmonary HTN[d]	3 (20)	7 (35)	15 (42)	16 (31)	.48
GER[e]	12 (80)	15 (75)	26 (72)	41 (79)	.89
Initial FVC, mL	2,768 ± 1,208	2,623 ± 810	2,487 ± 910	2,926 ± 881	.17
Initial FVC, % predicted	68.7 ± 20.3	73.4 ± 19.7	71.4 ± 21.2	72.5 ± 16.6	.89
Initial D_{LCO}, mL/mm Hg/min[f]	13.6 ± 5.1	12.4 ± 3.4	12.3 ± 4.6	13.7 ± 4.2	.34
Initial D_{LCO}, % predicted[f]	45.7 ± 15.2	45.9 ± 13.1	45.1 ± 13.5	45.8 ± 12	.96

Values are mean ± SD, No. (%), or as otherwise indicated. GER = gastroesophageal reflux; HTN = hypertension. See Table 1 legend for expansion of other abbreviations.

[a]Overall *P* value for test of association between group and characteristic. Pearson χ^2 test was used for proportions. Analysis of variance was used for means. Post hoc testing was done to compare individual groups if the overall association was statistically significant. For proportions, a Bonferroni correction was applied. For means, the Tukey honest significant difference method was used.

[b]On post hoc test, CTD-ILD differed significantly from IPAF and from Lone-IPF.

[c]On post hoc test, IPAF differed significantly from IPF, CTD-ILD differed from Lone-IPF, and AI-ILD differed from CTD-ILD.

[d]Pulmonary HTN by transthoracic echocardiogram (estimated systolic pulmonary artery pressure > 35 mm Hg or mean pulmonary artery pressure > 25 mm Hg, with capillary normal wedge pressure by right heart catheterization).

[e]Abnormal acid GER by 24-hour pH probe (DeMeester score > 14.7).

[f]Corrected to hemoglobin.

TABLE 4] Patterns of Interstitial Pneumonia/ILD[a]

Pattern of Interstitial Pneumonia	IPAF (n = 15)	AI-ILD (n = 20)	CTD-ILD (n = 36)	Lone-IPF (n = 52)	IPAF/AI-ILD, *P* Value[b]	IPAF/CTD-ILD, *P* Value	AI-ILD/CTD-ILD, *P* Value
	ILD Pattern, %						
UIP[c]	33	75	33	100	.14	.99	.04
NSIP[d]	27	10	34				
Fibrotic	20	5	17				
Cellular	7	5	17				
Other/unclassifiable	40	15	33				

Fisher exact test was used for association between groups (excluding IPF) and ILD pattern (UIP, NSIP, and other/unclassifiable) ($P = .037$). See Table 1 legend for expansion of abbreviations.

[a]All patients had HRCT images determined by histopathology obtained by surgical lung biopsy in 80% of patients with IPAF, 35% of patients with AI-ILD, 41.7% of patients with CTD-ILD, and 75.5% of patients with Lone-IPF.

[b]Pairwise comparisons (with Bonferroni correction).

[c]The definition of UIP pattern from Raghu et al.[2]

[d]The definition of NSIP pattern from Travis et al.[8]

TABLE 5] Analyses of Variance to Assess for Differences in the Mean Change in FVC and D_{LCO} Between 0 and 12 months Among Patients With IPAF, AI-ILD, CTD-ILD, and Lone-IPF

Disease Group	FVC, mL			FVC, % Predicted		
	Mean	95% CI	*P* Value	Mean	95% CI	*P* Value
AI-ILD	−113	−264.0 to 38.0	.70[a]	−2.8	−6.2 to 0.6	.25[a]
IPAF	−58	−232.0 to 116.0		−0.7	−4.6 to 3.3	
CTD-ILD	−11	−123.0 to 102.0		0.2	−2.3 to 2.7	
Lone-IPF	−81	−175.0 to 14.0		−3.0	−5.1 to −0.8	
	D_{LCO} Corrected to Hb, mL/mm Hg/min			D_{LCO} Corrected to Hb, % Predicted		
	Mean	95% CI	*P* Value	Mean	95% CI	*P* Value
AI-ILD	−1.1	−2.0 to −0.3	< .001[b]	−3.9	−7.0 to −0.7	< .001[b]
IPAF	2.4	1.4 to 3.4		6.3	2.6 to 10.0	
CTD-ILD	−0.3	−0.9 to 0.4		−0.7	−3.1 to 1.7	
Lone-IPF	−0.9	−1.5 to −0.3		−2.9	−5.1 to −0.7	

D_{LCO} = diffusion capacity; Hb = hemoglobin. See Table 1 legend for expansion of other abbreviations.

[a]Post hoc tests (Tukey honest significant difference) failed to indicate any pairwise group comparisons as significant.

[b]Post hoc tests (Tukey honest significant difference) showed IPAF significantly different from all other groups in D_{LCO} ($P < .001$) and D_{LCO} percent predicted ($P = .01$).

TABLE 6] Linear Regression to Assess for Differences in the Mean Change in FVC and D_{LCO} Between 0 and 12 Months Among Patients With IPAF, AI-ILD, CTD-ILD, and Lone-IPF

Disease Group	Difference[a] in Mean Change in FVC, mL			Difference[a] in Mean Change in FVC, % Predicted		
	Coefficient	95% CI	*P* Value	Coefficient	95% CI	*P* Value
AI-ILD	0[b]	…	.69	0[b]	…	.28
IPAF	48	−188.0 to 285.0		1.9	−3.5 to 7.3	
CTD-ILD	114	−83.0 to 311.0		3.3	−1.2 to 7.8	
Lone-IPF	37	−143.0 to 218.0		−0.3	−4.4 to 3.9	

	Difference[a] in Mean Change in D_{LCO} Corrected to Hb, mL/mm Hg/min			Difference[a] in Mean Change in D_{LCO} Corrected to Hb, %		
	Coefficient	95% CI	*P* Value	Coefficient	95% CI	*P* Value
AI-ILD	0[b]	…	< .001	0[b]	…	< .001
IPAF	3.6	2.2 to 5.0		10.2	5.2 to 15.2	
CTD-ILD	1.0	−0.2 to 2.1		3.1	−1.1 to 7.3	
Lone-IPF	0.2	−0.9 to 1.3		0.9	−3 to 4.9	

See Table 1 and 5 legends for expansion of abbreviations.
[a]Adjusted for patient age, sex, presence of pulmonary hypertension, and outcome value at initial visit.
[b]Comparison category.

TABLE 7] Analyses of Variance to Assess for Differences in the Mean Change in FVC and DLCO Between 0 and 12 Months Based on Pattern of IP (Regardless of Diagnosis)

	FVC, mL			FVC, % Predicted		
Pattern of IP	Mean	95% CI	*P* Value	Mean	95% CI	*P* Value
UIP	−135	−208 to −63	.003[a]	−3.6	−5.2 to −2.0	.001[a]
NSIP	10	−141 to 161		0.8	−2.7 to 4.2	
Other/unclassifiable	116	−13 to 244		2.4	−0.5 to 5.4	
	DLCO Corrected to Hb, mL/mm Hg/min			DLCO Corrected to Hb, % Predicted		
	Mean	95% CI	*P* Value	Mean	95% CI	*P* Value
UIP	−0.74	−1.26 to −0.22	.04[b]	−2.3	−4.1 to −0.4	.16[c]
NSIP	0.22	−0.80 to 1.25		0.67	−2.9 to 4.3	
Other/unclassifiable	0.48	−0.41 to 1.37		0.67	−2.5 to 3.8	

See Table 1, 2, and 5 legends for expansion of abbreviations.

[a]Post hoc tests (Tukey honest significant difference) showed UIP was significantly different from other/unclassifiable ($P = .002$) and marginally different from NSIP ($P = .053$).

[b]Post hoc tests (Tukey honest significant difference) showed UIP was significantly different from other/unclassifiable ($P = .30$).

[c]Post hoc tests (Tukey honest significant difference) showed no significant differences between any pair of groups.

TABLE 8] Student *t* Tests to Assess for Difference in Mean Change in FVC and D_{LCO} Over 12 Months Between Patients With UIP and Non-UIP Patterns in Each of Three Groups: AI-ILD, IPAF, and CTD-ILD

Change in Pulmonary Function	Non-UIP			UIP			Difference (UIP – Non-UIP)			*P* Value
	No.	Mean	95% CI	No.	Mean	95% CI	Mean	95% CI		
12-mo change in FVC, mL										
AI-ILD	5	−4	−209 to 201	15	−149	−346 to 47	−145	−201 to 491		.38
IPAF	10	−5	−150 to 140	5	−164	−504 to 178	−159	−53 to 371		.13
CTD-ILD	24	33	−80 to 127	12	−98	−318 to 121	−132	−6 to 270		.06
12-mo change in FVC, %										
AI-ILD	5	−1.4	−6.6 to 3.8	15	−3.3	−7.6 to 1.1	−1.9	−7.0 to 10.7		.65
IPAF	10	0.7	−3.0 to 4.4	5	−3.4	−10.9 to 4.1	−4.1	−1.4 to 9.6		.13
CTD-ILD	24	1.7	−0.7 to 4.1	12	−2.8	−7.7 to 2.0	−2.0	−0.1 to 9.2		.06
12-mo change in D_{LCO}, mL/mm Hg/min										
AI-ILD	5	0.0	−1.8 to 1.8	15	−1.5	−2.5 to −0.5	−1.5	0.0 to 3.1		.06
IPAF	10	3.1	1.8 to 4.3	5	1.1	−0.7 to 2.8	−2.0	0.4 to 3.6		.02
CTD-ILD	24	−0.4	−1.3 to 0.4	12	0.0	−1.1 to 1.2	0.5	−1.8 to 0.8		.45
12-mo change in D_{LCO}, %										
AI-ILD	5	0.8	−6.1 to 7.7	15	−5.4	−9.0 to −1.8	−6.2	−0.3 to 12.7		.06
IPAF	10	7.5	2.6 to 12.4	5	3.8	−2.4 to 10.0	−3.7	−3.3 to 10.7		.27
CTD-ILD	24	−1.3	−4.5 to 1.9	12	0.4	−3.6 to 4.4	1.7	−6.8 to 3.5		.51

Rochester cohort-2018

ORIGINAL ARTICLE

Overlap of interstitial pneumonia with autoimmune features with undifferentiated connective tissue disease and contribution of UIP to mortality

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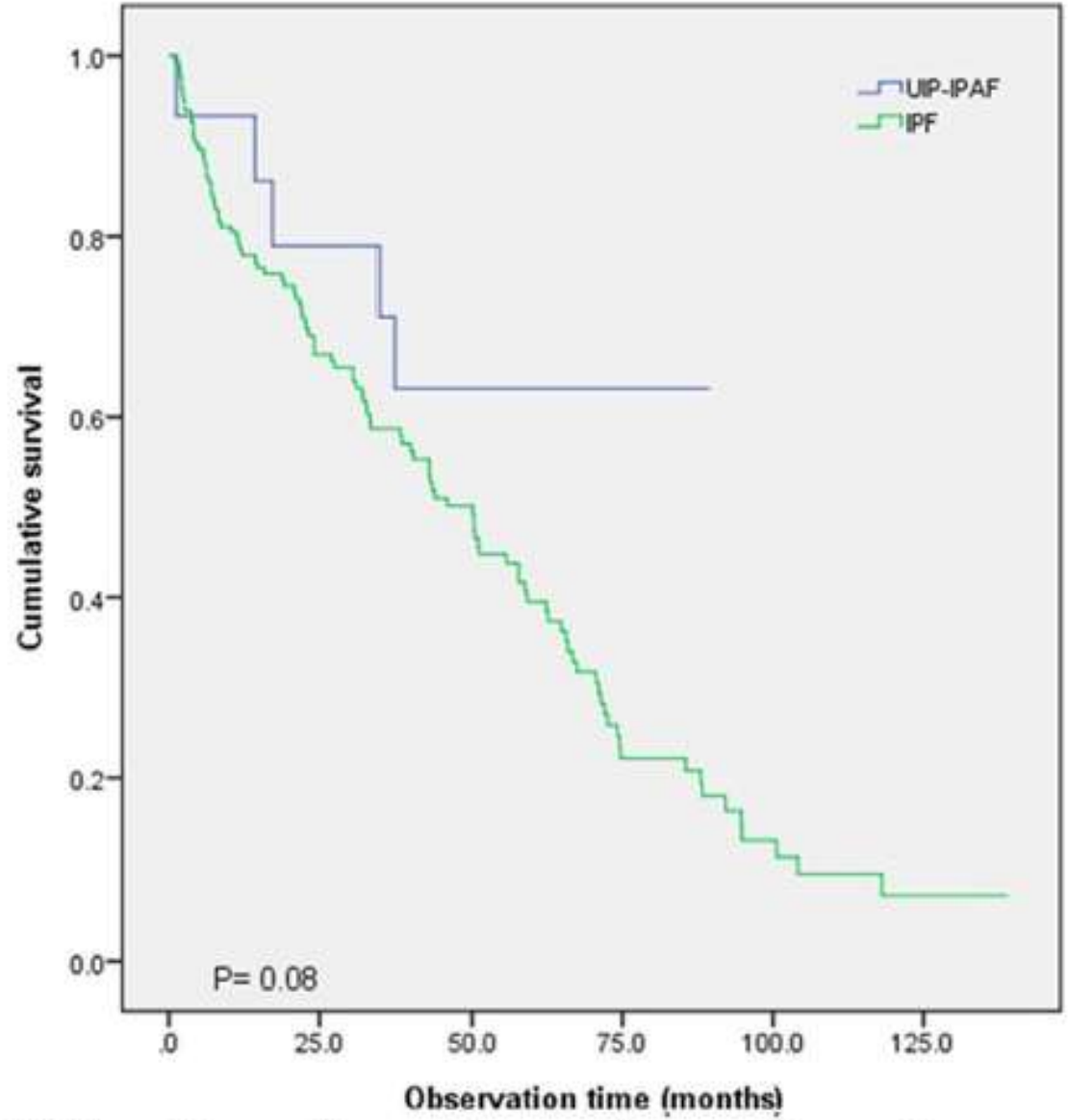
Methodology

- Mayo Clinic Rochester from 1 January 2005 through 31 December 2013
- 111 were confirmed UCTD-ILD diagnoses using the broad definition
- 101 subjects-IPAF non-UIP (N = 82),IPAF-UIP (N =19)
- **Purpose of our study:**
- Incidence of overlap with previously diagnosed UCTD and IPAF and confirm whether differences in survival exist among those with or without UIP features on pathology or computed tomography (CT)

Baseline characteristic (n = 101)	Finding
Age at IPAF diagnosis, (mean ± SD, range)	56.9 ± 14.2 (23–86)
Gender, M/F (%)	61/40 (61/39)
Smoking history, ever/never (%)	31/70 (31/69)
TLC% (mean ± SD, range)	72.2 ± 16.5 (32–127)
FVC% (mean ± SD, range)	69.2 ± 17.9 (25–118)
FEV_1% (mean ± SD, range)	70.1 ± 18.5 (29–113)
DL_{CO}% (mean ± SD, range)	52.2 ± 18.2 (21–108)
Deaths, n (%)	28 (28)
Frequency of positive Clinical Domain findings	N (%)
Distal digital fissuring	11 (10.9)
Distal digital tip ulceration	5 (5)
Inflammatory arthritis/polyarticular morning joint stiffness > 60 min	30 (29.7)
Palmar telangiectasia	7 (6.9)
Raynaud's phenomenon	55 (54.5)
Digital oedema, unexplained	18 (17.8)
Gottron's sign	0
Frequency of positive Serologic Domain findings	N (%)
ANA (titre) (n = 101)	40 (39.6)
ANA >1:320 diffuse, speckled or homogeneous	19 (18.8)
ANA nucleolar (any)	10 (9.9)
ANA centromere (any) (n = 62)	2 (3.2)
RF > 2 × upper limit of normal (n = 89)	16 (18)
Anti-CCP (n = 80)	3 (3.8)
Anti-dsDNA (n = 82)	11 (13.4)
Anti-Ro (SS-A) (n = 101)	36 (35.6)
Anti-La (SS-B) (n = 101)	7 (6.9)
Anti-Smith (n = 101)	7 (6.9)
Anti-ribonucleoprotein (n = 101)	15 (14.9)
Anti-topoisomerase (Scl-70) (n = 101)	6 (5.9)
Ant-tRNA synthetase (Jo-1, PL-7, PL-12, EJ, OJ, KS, Zo, tRS) (n = 101)	1 (1)
Anti-PM-Scl (n = 7)	0 (0)
Anti-MDA-5 (n = 0)	0 (0)

ANA, anti-nuclear antibody; DL_{CO}%, percent diffusion capacity for carbon monoxide; FEV_1%, percent forced expiratory volume in the first second; FVC%, percent forced vital capacity; IPAF, interstitial pneumonia with autoimmune feature; RF, rheumatoid factor; TLC%, percent total lung capacity.



UIP-IPAF	15	10	7	2	0	0
IPF	167	96	56	18	7	2

Fig. 3 Survival was compared between the IPAF patients with UIP pattern ($n = 15$) and the IPF group ($n = 175$). No significant difference was present ($p = 0.08$)

CT findings	*n* (%)
UIP	12 (11.9)
NSIP	65 (64.4)
OP	4 (3.9)
NSIP with OP overlap	4 (4)
LIP	2 (2)
Unclassifiable interstitial fibrosis	14 (13.9)
Histopathology findings (51 undergoing biopsy)	
UIP†	12 (23.5)
NSIP	7 (13.7)
OP	12 (23.5)
NSIP with OP overlap	0 (0)
LIP	0 (0)
Interstitial lymphoid aggregates	0 (0)
Diffuse lymphoplasmacytic infiltrate	8 (15.7)
Other	19 (37.2)
No diagnostic abnormality	3 (5.9)
Unclassifiable	8 (15.7)
Non-specific chronic inflammation	7 (13.7)
Insufficient tissue	1 (2)
Morphological features	
Unexplained pleural effusion	17 (16.8)
Pleural thickening	9 (8.9)
Unexplained pericardial effusion	30 (29.7)
Pericardial thickening	3 (3)
Unexplained intrinsic airway disease	43 (42.6)
Airflow obstruction by PFT or imaging	23 (22.8)
Bronchiolitis	12 (11.9)
Bronchiectasis	8 (7.9)
Pulmonary vasculopathy	39 (38.6)

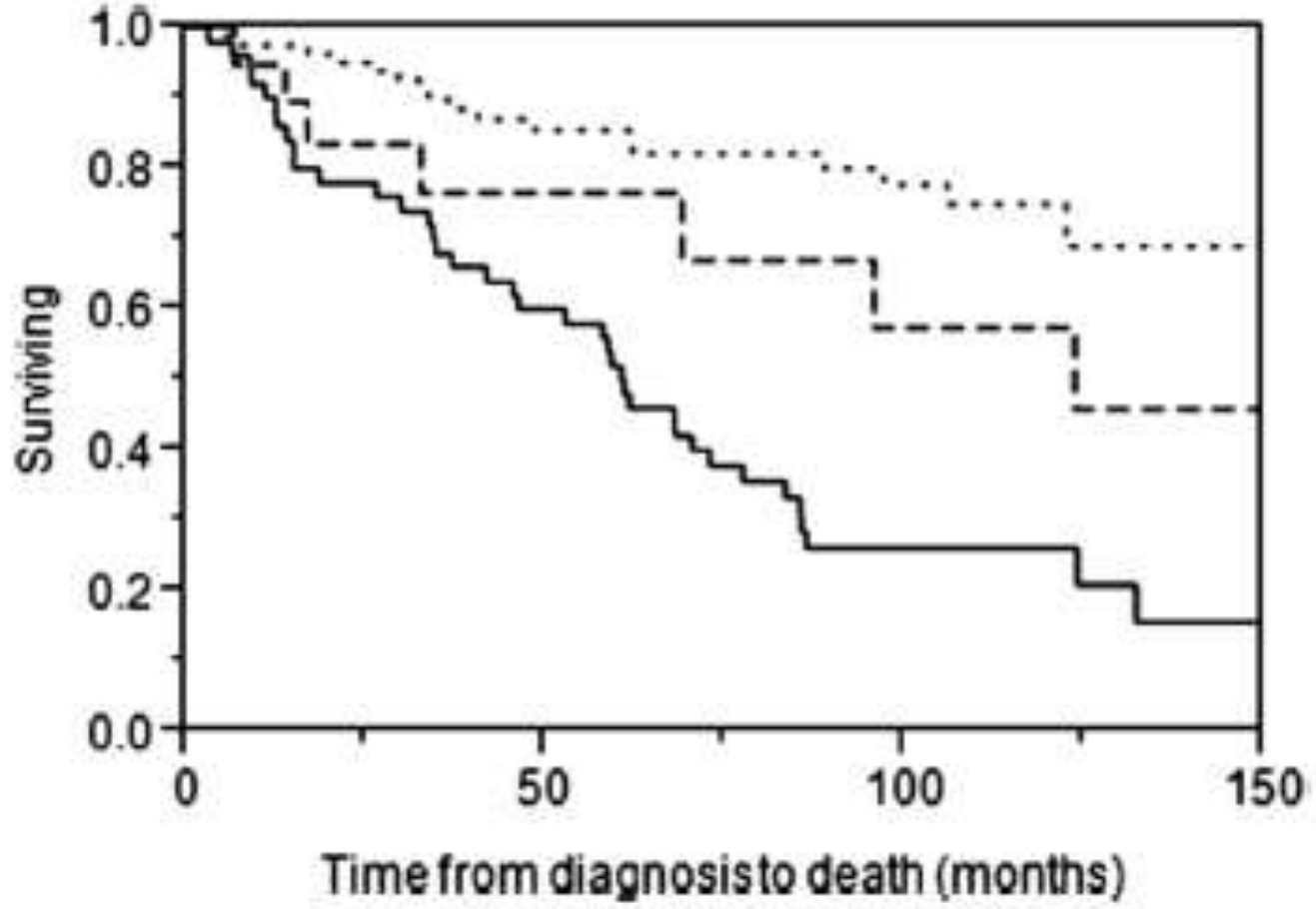


Figure 1 Kaplan–Meier survival comparison between IPAF non-UIP, IPAF-UIP and IPF (log rank $P < 0.0001$) (small dash, IPAF non-UIP; medium dash, IPAF-UIP; solid line, IPF). IPAF, interstitial pneumonia with autoimmune feature; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia.

Lim *et al. BMC Pulmonary Medicine* (2019) 19:120
https://doi.org/10.1186/s12890-019-0868-9

BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

Interstitial pneumonia with autoimmune features show better survival and less exacerbations compared to idiopathic pulmonary fibrosis

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Methodology

- Single institution ILD cohort-305 patients between 2008 and 2015
- 4 groups-IPAF,CTD-ILD,Seronegative IPF, Seropositive IPF
- Clinical characteristics, survival and ILD exacerbation of IPAF patients to the CTD-ILD and IPF groups
- Overall survival (OS) -from the time of enrolment in the cohort until death of any cause

Table 2 Comparison of clinical characteristics between IPAF, CTD-ILD and IPF

	IPAF ($n = 54$)	CTD-ILD ($n = 76$)	Seronegative IPF ($n = 145$)	Seropositive IPF ($n = 30$)	*P*-value
Sex (male) (*n*, %)	19 (35.2)	24 (31.6)	103 (71.0)	22 (73.3)	< 0.001
Mean age (SD)	67.9 ± 10.5	61.6 ± 13.5	71.6 ± 9.5	71.8 ± 8.3	< 0.001
Ever smoker (*n*, %)	15 (27.8)	23 (30.3)	95 (65.5)	20 (66.7)	< 0.001
Smoking pack years	7.0 ± 14.9	11.1 ± 20.4	24.6 ± 23.1	26.7 ± 32.1	< 0.001
ILD pattern from HRCT					< 0.001
UIP	14 (25.9)	35 (46.1)	145 (100)	30 (100)	
NSIP	34 (63.0)	17 (22.4)	0 (0)	0 (0)	
OP	3 (5.6)	5 (6.6)	0 (0)	0 (0)	
NSIP + OP	2 (3.7)	3 (3.9)	0 (0)	0 (0)	
LIP	0 (0)	2 (2.6)	0 (0)	0 (0)	
Emphysema from HRCT (*n*, %)	5 (9.3)	17 (22.4)	45 (31.0)	9 (30)	0.006
Lung biopsy at diagnosis[a]					< 0.001
None	20 (37.0)	33 (43.4)	86 (59.3)	14 (46.7)	
TBLB	13 (24.1)	11 (14.5)	38 (26.2)	12 (40)	
VATS	25 (46.3)	21 (27.6)	18 (12.4)	9 (30)	
FVC, L	2.4 ± 0.7	2.6 ± 0.8	2.5 ± 0.8	2.8 ± 0.9	0.063
FVC (% of predicted)	81.8 ± 17.0	86.2 ± 18.4	80.7 ± 19.1	83.8 ± 17.6	0.225
FEV1, L	1.9 ± 0.6	2.0 ± 0.6	2.0 ± 0.6	2.2 ± 0.7	0.127
FEV1/FVC	82.0 ± 7.7	79.1 ± 9.4	82.1 ± 8.9	79.9 ± 9.6	0.109
TLC, L	3.8 ± 1.2	4.1 ± 1.0	4.4 ± 1.4	4.5 ± 1.3	0.077
TLC (% of predicted)	87.8 ± 21.6	91.1 ± 18.7	91.6 ± 24.5	84.5 ± 19.0	0.434
VC,L	2.4 ± 0.7	2.6 ± 0.8	2.7 ± 0.8	2.8 ± 0.9	0.116
VC (% of predicted)	84.5 ± 17.7	87.4 ± 19.5	80.6 ± 19.2	82.0 ± 18.3	0.224
DLCO (absolute)	10.6 ± 4.4	10.6 ± 3.6	11.4 ± 6.0	9.7 ± 4.4	0.361
DLCO (% of predicted)	62.7 ± 21.0	62.3 ± 18.2	68.5 ± 24.3	57.9 ± 19.0	0.059

Clinical domain (*n* = 17)	
Distal digital fissuring	1 (5.9)
Distal digital tip ulcerations	0 (0)
Inflammatory arthritis or polyarticular morning joint stiffness ≥60 min	13 (76.5)
Palmar telangiectasia	0 (0)
Raynaud's phenomenon	3 (17.6)
Unexplained digital oedema	3 (17.6)
Unexplained fixed rash on the digital extensor surface	0 (0)
Serologic domain (*n* = 49)	
ANA ≥1:320 titer, diffuse, speckled or homogeneous patterns, ANA nucleolar pattern (any titer), or ANA centromere pattern (any titer)	31 (63.3)
Rheumatoid factor > 2x upper limit of normal	14 (28.6)
Anti-CCP	7 (14.3)
Anti-dsDNA	3 (6.1)
Anti-Ro (SS-A)	4 (8.2)
Anti-La (SS-B)	1 (2.0)
Anti-topoisomerase (Scl-70)	1 (2.0)
Anti-ribonucleoprotein	2 (4.1)
Anti-Smith	2 (4.1)
Anti-tRNA synthetase, Anti-Pm-Scl, Anti-MDA-5	0 (0)
Morphologic domain (*n* = 44)	
Suggestive radiology patterns by HRCT	39 (72.2)
Nonspecific interstitial pneumonia	34 (87.2)[a]
Organising pneumonia	3 (7.7)[a]
Nonspecific interstitial pneumonia with organising pneumonia overlap	2 (5.1)[a]
Lymphoid interstitial pneumonia	0 (0)[a]
Histopathologic pattern	12 (22.2)
Nonspecific interstitial pneumonia	0 (0)[a]
Organising pneumonia	4 (33.3)[a]
Nonspecific interstitial pneumonia with organising pneumonia overlap	1 (8.3)[a]
Interstitial lymphoid aggregates with germinal centres	5 (41.7)[a]
Diffuse lymphoplasmacytic infiltration	2 (16.7)[a]
Multi-compartment involvement (in addition to interstitial pneumonia)	11 (20.4)
Unexplained pleural effusion or thickening	5 (45.5)[a]
Unexplained pericardial effusion or thickening	3 (27.3)[a]
Unexplained intrinsic airways diseases	2 (18.2)[a]
Unexplained pulmonary vasculopathy	1 (9.1)[a]

Table 3 Comparison of clinical outcomes between IPAF, CTD-ILD and IPF

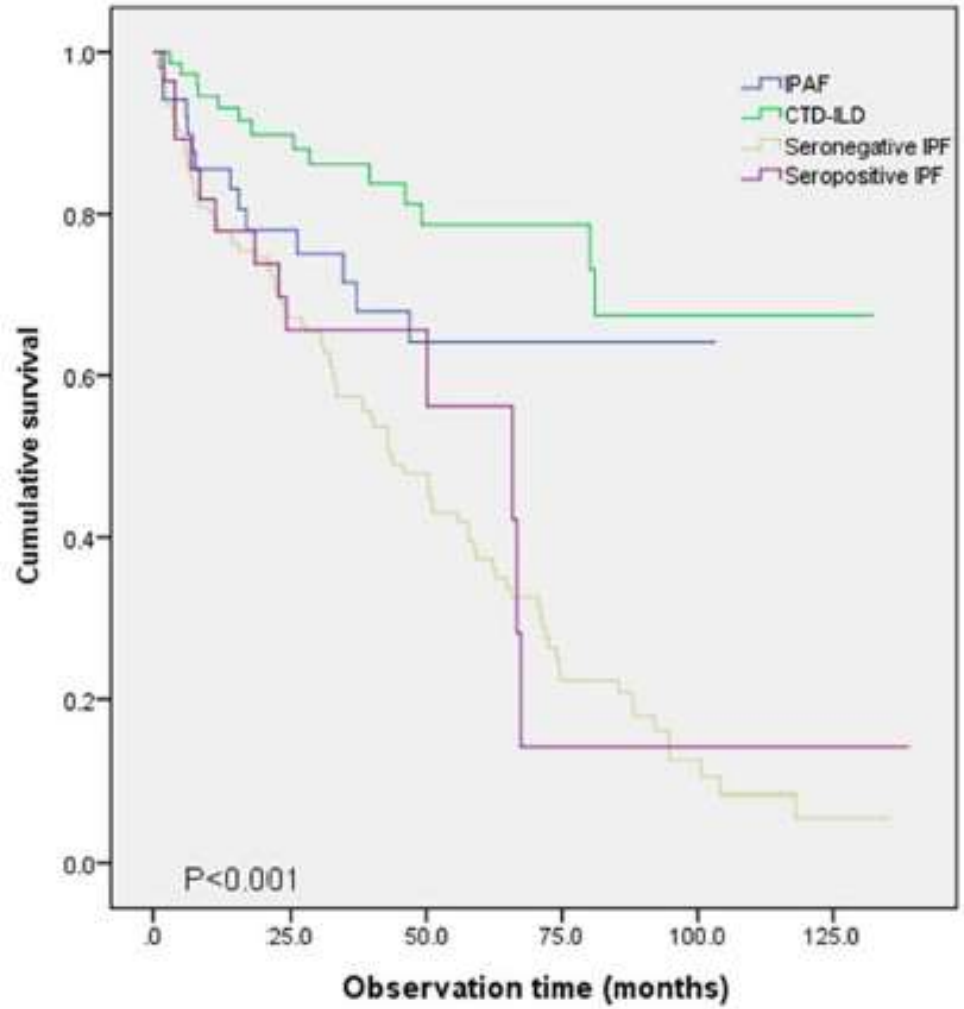
	IPAF ($n = 54$)	CTD-ILD ($n = 76$)	IPF ($n = 175$)	*P*-value*
Total deaths during observation	15 (27.8%)	16 (21.1%)	111 (63.4%)	$< 0.001^{ab}$
Mean survival time (months)	73.3 ± 6.6	104.0 ± 6.7	52.0 ± 3.6	$< 0.001^{ab}$
Time to first exacerbation (mean, months)	29.5 ± 27.5	32.6 ± 29.7	17.3 ± 21.4	0.02^{a}
ILD exacerbations				
Whole observation period	14 (25.9%)	25 (32.9%)	62 (35.4%)	$< 0.001^{b}$
5 yr	11 (21.1%)	19 (25.3%)	56 (33.5%)	0.007^{a}
3 yr	9 (17.3%)	15 (20.0%)	47 (28.1%)	0.026^{a}
1 yr	6 (11.5%)	9 (12.0%)	37 (22.0%)	0.022^{a}

Abbreviations: *CTD-ILD* connective tissue disease-related interstitial lung disease, *ILD* interstitial lung disease, *IPAF* interstitial pneumonia with autoimmune features, *IPF* idiopathic pulmonary fibrosis

*Statistical difference between the three groups

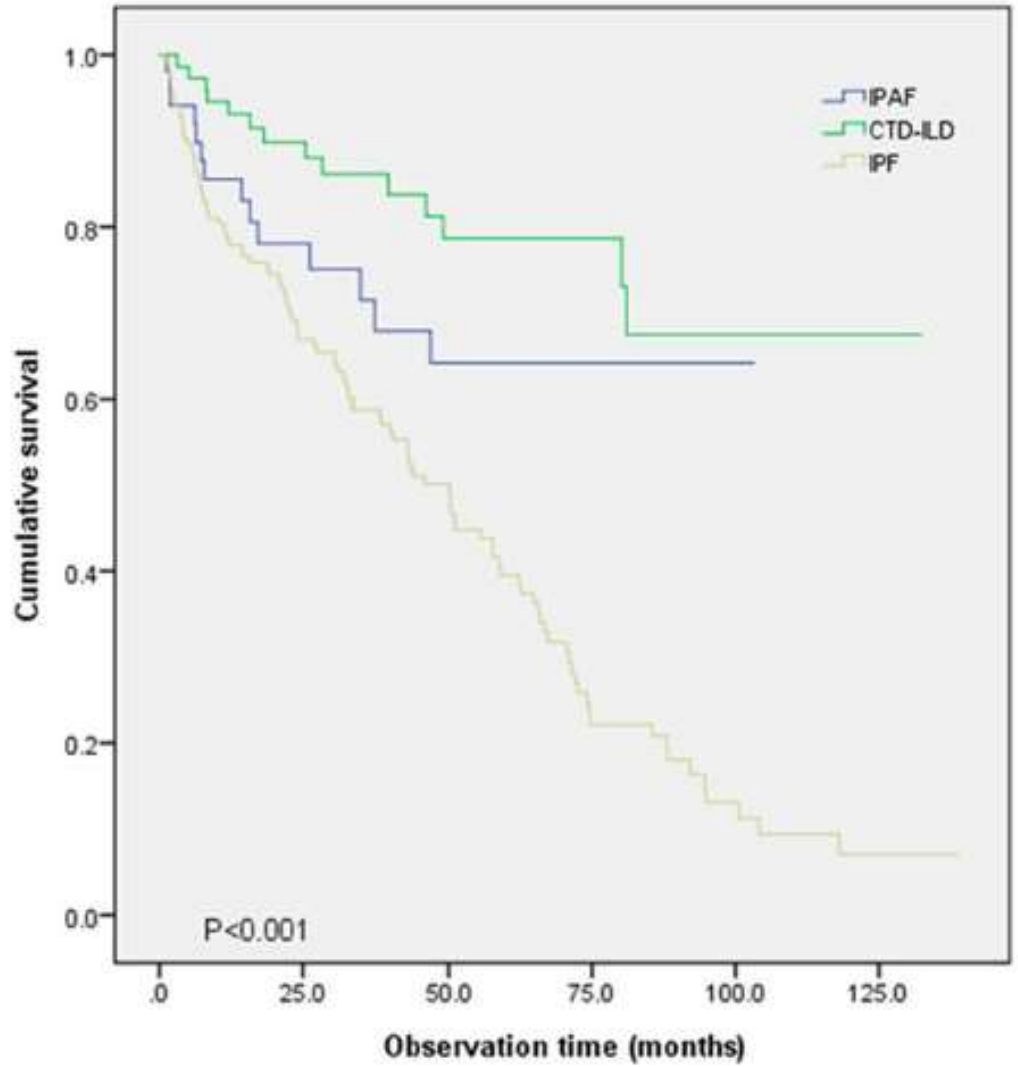
[a]Significant statistical difference between CTD-ILD and IPF

[b]Significant statistical difference between IPAF and IPF



IPAF	51	26	16	6	1	0
CTD-ILD	74	50	30	15	7	2
Seropositive IPF	139	80	49	17	6	2
Seronegative IPF	28	16	7	1	1	0

Fig. 1 Overall survival was compared between the IPAF, CTD-ILD, seronegative IPF and seropositive IPF groups. Statistically significant difference was present between the four groups ($p < 0.001$)



IPAF	51	26	16	6	1	0
CTD-ILD	74	50	30	15	7	2
IPF	167	96	56	18	7	2

Fig. 2 Kaplan-Meier analysis showed that the three groups showed significant difference in survival ($p < 0.001$). The IPF group was taken as a single group, regardless of seropositivity

CT Findings, Radiologic-Pathologic Correlation, and Imaging Predictors of Survival for Patients With Interstitial Pneumonia With Autoimmune Features

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OBJECTIVE. The objective of this study is to determine the CT findings and patterns of interstitial pneumonia with autoimmune features (IPAF) and to assess whether imaging can predict survival for patients with IPAF.

MATERIALS AND METHODS. The study included 136 subjects who met the criteria for IPAF and had diagnostic-quality chest CT scans obtained from 2006 to 2015; a total of 74 of these subjects had pathologic samples available for review within 1 year of chest CT examination. CT findings and the presence of an usual interstitial pneumonitis (UIP) pattern of disease were assessed, as was the UIP pattern noted on pathologic analysis. Analysis of chest CT findings associated with survival was performed using standard univariate and multivariate Cox proportional hazards methods as well as the unadjusted log-rank test. Survival data were visually presented using the Kaplan-Meier survival curve estimator.

RESULTS. Most subjects with IPAF (57.4%; 78/136) had a high-confidence diagnosis of a UIP pattern on CT. Substantially fewer subjects (28.7%; 39/136) had a pattern that was inconsistent with UIP noted on CT. The presence of a UIP pattern on CT was associated with smoking ($p < 0.01$), male sex ($p < 0.01$), and older age ($p < 0.001$). Approximately one-fourth of the subjects had a nonspecific interstitial pneumonitis pattern on CT. Of interest, nearly one-tenth of the subjects had a CT pattern that was most consistent with hypersensitivity pneumonitis rather than the customary CT patterns ascribed to lung disease resulting from connective tissue disease. Most subjects with a possible UIP pattern on CT (83.3%) had UIP diagnosed on the basis of pathologic findings. Focused multivariate analysis showed that honeycombing on CT (hazard ratio, 2.17; 95% CI, 1.05–4.47) and pulmonary artery enlargement on CT (hazard ratio, 2.08; 95% CI, 1.02–4.20) were independent predictors of survival.

CONCLUSION. IPAF most often presents with a UIP pattern on CT and is associated with worse survival when concomitant honeycombing or pulmonary artery enlargement is present.

Keywords: connective tissue disease, CT, interstitial pneumonia with autoimmune features, survival, usual interstitial pneumonitis

DOI:10.2214/AJR.16.17121

TABLE 1: Usual Interstitial Pneumonitis (UIP) Patterns on CT Scans of 136 Patients With Interstitial Pneumonia With Autoimmune Features

CT UIP Pattern	No. (%) of Patients
UIP	70 (51.5)
Possible UIP	19 (14.0)
Inconsistent with UIP	47 (34.6)

TABLE 2: CT Patterns for 136 Patients With Interstitial Pneumonia With Autoimmune Features

CT Pattern	No. (%) of Patients
Usual interstitial pneumonitis	70 (51.5)
NSIP	37 (27.2)
Hypersensitivity pneumonitis	11 (8.1)
NSIP organizing pneumonia	9 (6.6)
Organizing pneumonia	5 (3.7)
Other	4 (2.9)

Note—NSIP = nonspecific interstitial pneumonia.

TABLE 4: Radiologic and Pathologic Correlation for Diagnosis of Usual Interstitial Pneumonitis (UIP)

CT Diagnosis	No. of Patients With Pathologic Diagnosis		Patients With UIP Diagnosis (%)
	Not UIP	UIP	
Inconsistent with UIP	12	12	50.0
Possible UIP	3	15	83.3
UIP	2	30	93.8
Total	17	57	

TABLE 3: Demographic Characteristics of Patients With Interstitial Pneumonia With Autoimmune Features Relative to High-Confidence CT Diagnoses

Characteristic	Pattern Inconsistent With UIP on CT ($n = 47$)	UIP Pattern on CT ($n = 70$)	p
Smoker	19 (40.4)	42 (60.0)	0.041[a]
White race	31 (66.0)	51 (72.9)	0.537
Male	16 (34.0)	41 (58.6)	0.014[a]
Age (y), mean ± SD	59.4 ± 11.5	66.7 ± 9.5	< 0.001[a]

Note—Except where noted otherwise, data are number (%) of patients. UIP = usual interstitial pneumonitis.
[a]Statistically significant.

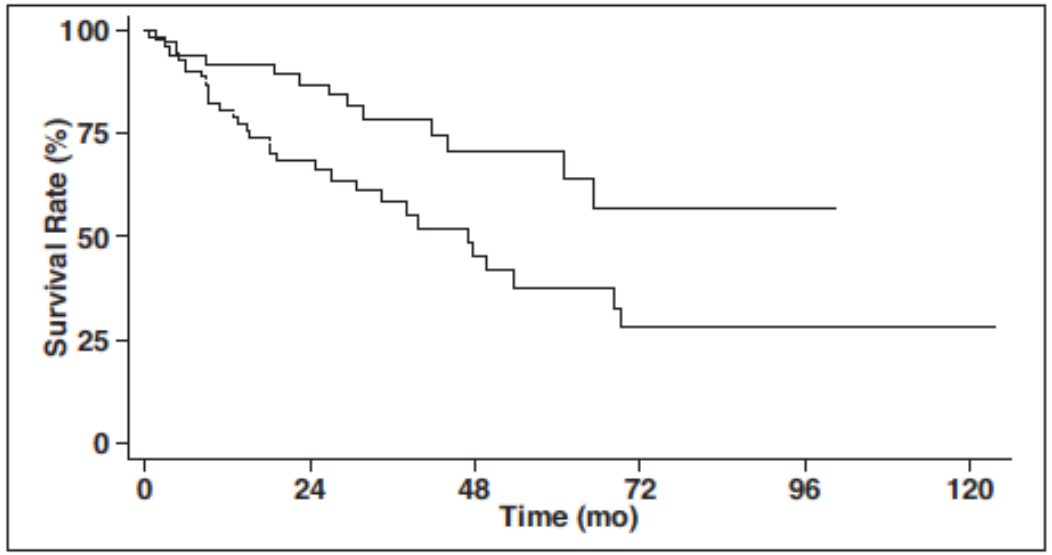

Fig. 4—Survival of patients with interstitial pneumonia with autoimmune features with honeycombing on CT versus those without honeycombing on CT. Kaplan-Meier survival curves show that those with honeycombing on CT (*dashed line*) had significantly worse survival than those without honeycombing on CT (*solid line*) ($p = 0.0092$, log-rank test).

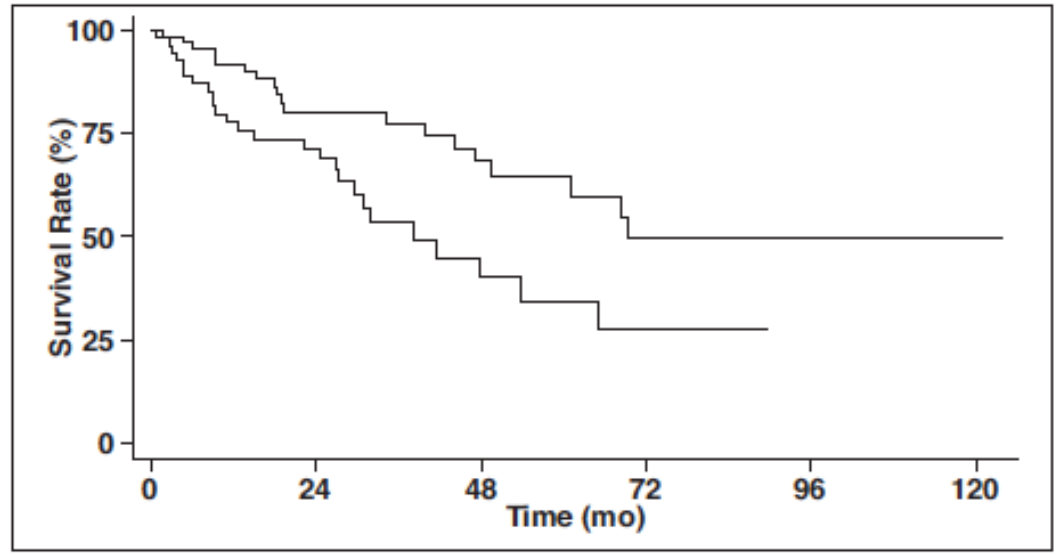

Fig. 5—Survival of patients with interstitial pneumonia with autoimmune features with mosaic attenuation on CT versus those without mosaic attenuation on CT. Kaplan-Meier survival curves show that patients with mosaic attenuation on CT (*dashed line*) had significantly worse survival than those without mosaic attenuation on CT (*solid line*) ($p = 0.0092$, log-rank test).

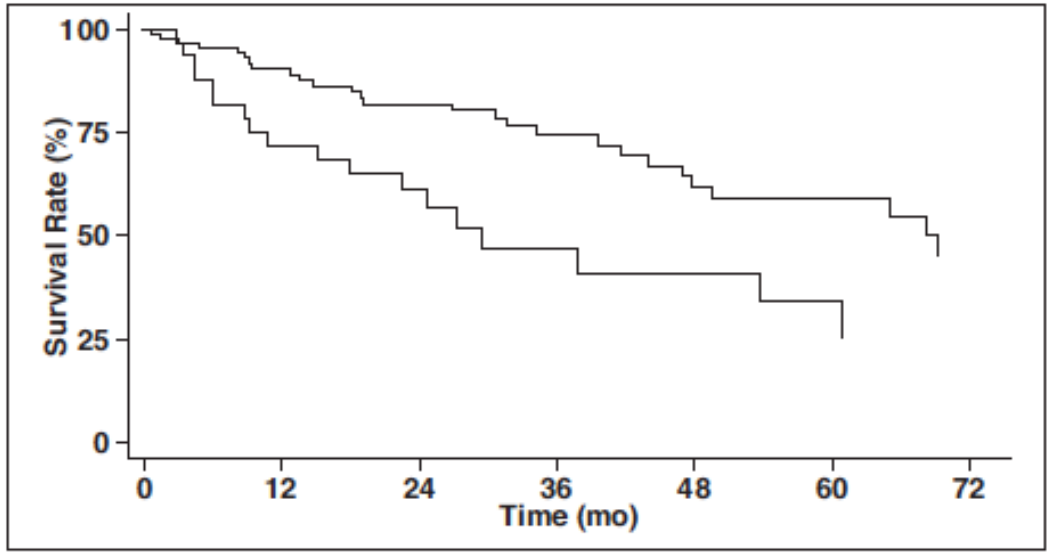

Fig. 6—Survival of patients with interstitial pneumonia with autoimmune features with pulmonary artery enlargement on CT versus those without pulmonary artery enlargement on CT. Kaplan-Meier survival curves show that patients with pulmonary artery enlargement of 3.3 cm or greater (*dashed line*) had significantly worse survival than those with pulmonary artery enlargement of less than 3.3 cm (*solid line*) ($p = 0.0071$, log-rank test).

TABLE 5: Cox Unadjusted and Adjusted Analyses of Prognostic Features Noted on High-Resolution CT Examinations of Patients With Interstitial Pneumonia With Autoimmune Features

Variable	Unadjusted Analysis ($n = 136$)			Adjusted Analysis[a] ($n = 136$)		
	HR	p	95% CI	HR	p	95% CI
Honeycomb pattern	2.60	**0.005**	1.33–5.07	2.17	**0.037**	1.05–4.47
Reticulation (% involvement)	1.04	**0.001**	1.01–1.06	1.01	0.386	0.98–1.05
Multicompartment features						
Mosaic attenuation excluding emphysema[b]	2.17	**0.011**	1.19–3.95	1.79	0.117	0.87–3.70
Pulmonary artery enlargement[c]	2.23	**0.009**	1.22–4.05	2.08	**0.043**	1.02–4.20
UIP pattern[d]						
Possible UIP	0.99	0.982	0.36–2.73			
Definite UIP	1.57	0.172	0.82–2.98			
Mosaic attenuation	1.63	0.102	0.91–2.94			
Ground-glass opacities	0.99	0.968	0.52–1.88			
Axial distribution of fibrosis[e]						
Peripheral	1.40	0.575	0.43–4.56			
Peripheral with subpleural sparing	0.32	0.325	0.03–3.09			
Diffuse	1.29	0.722	0.32–5.17			
Pleural or pericardial effusion or thickening	1.77	0.146	0.82–3.81			

Note—HR = hazard ratio, UIP = usual interstitial pneumonitis. Statistically significant values are shown in **boldface** type.
[a]Adjusted for age, sex, forced vital capacity, diffusing capacity of the lung for carbon monoxide, and presence of clinical domain.
[b]For multicompartment features, with patients with a history of smoking excluded, univariate analysis revealed an HR of 1.83 ($p = 0.047$).
[c]With use of a pulmonary artery diameter cutoff of 33 mm.
[d]Compared with pattern inconsistent with UIP.
[e]Compared with central distribution, bronchovascular distribution, or both.

Therapeutics and Clinical Risk Management

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ORIGINAL RESEARCH

Mycophenolate therapy in interstitial pneumonia with autoimmune features: a cohort study

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management

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Objectives: International experts recently characterized interstitial pneumonia with autoimmune features (IPAF) as a provisional diagnosis for patients with interstitial lung disease who have characteristics of autoimmune disease but do not meet criteria for a specific autoimmune disease. We describe clinical characteristics of IPAF patients and examine responses to mycophenolate as a therapy for IPAF.

Methods: This retrospective cohort included adult patients meeting European Respiratory Society/American Thoracic Society classification criteria for IPAF. Sociodemographic, clinical, and pulmonary function test data were abstracted for patients with and without mycophenolate treatment and followed longitudinally from interstitial lung disease diagnosis for change in pulmonary function test results.

Results: We identified 52 patients who met criteria for IPAF. Of 52 IPAF patients, 24 did not receive mycophenolate and 28 did, with median time to mycophenolate treatment 22 months. Changes in FVC% and percentage predicted lung diffusion capacity for carbon monoxide (D_{LCO}%) between the mycophenolate-treated and untreated groups were not significantly different (FVC% change P=0.08, D_{LCO}% change P=0.17). However, there was a trend toward more rapid baseline decline of both FVC% and D_{LCO}% in the mycophenolate-treated cohort before vs after mycophenolate therapy. The slope of both FVC% and D_{LCO}% values improved after onset of mycophenolate exposure for the treated group, although this finding was not statistically significant.

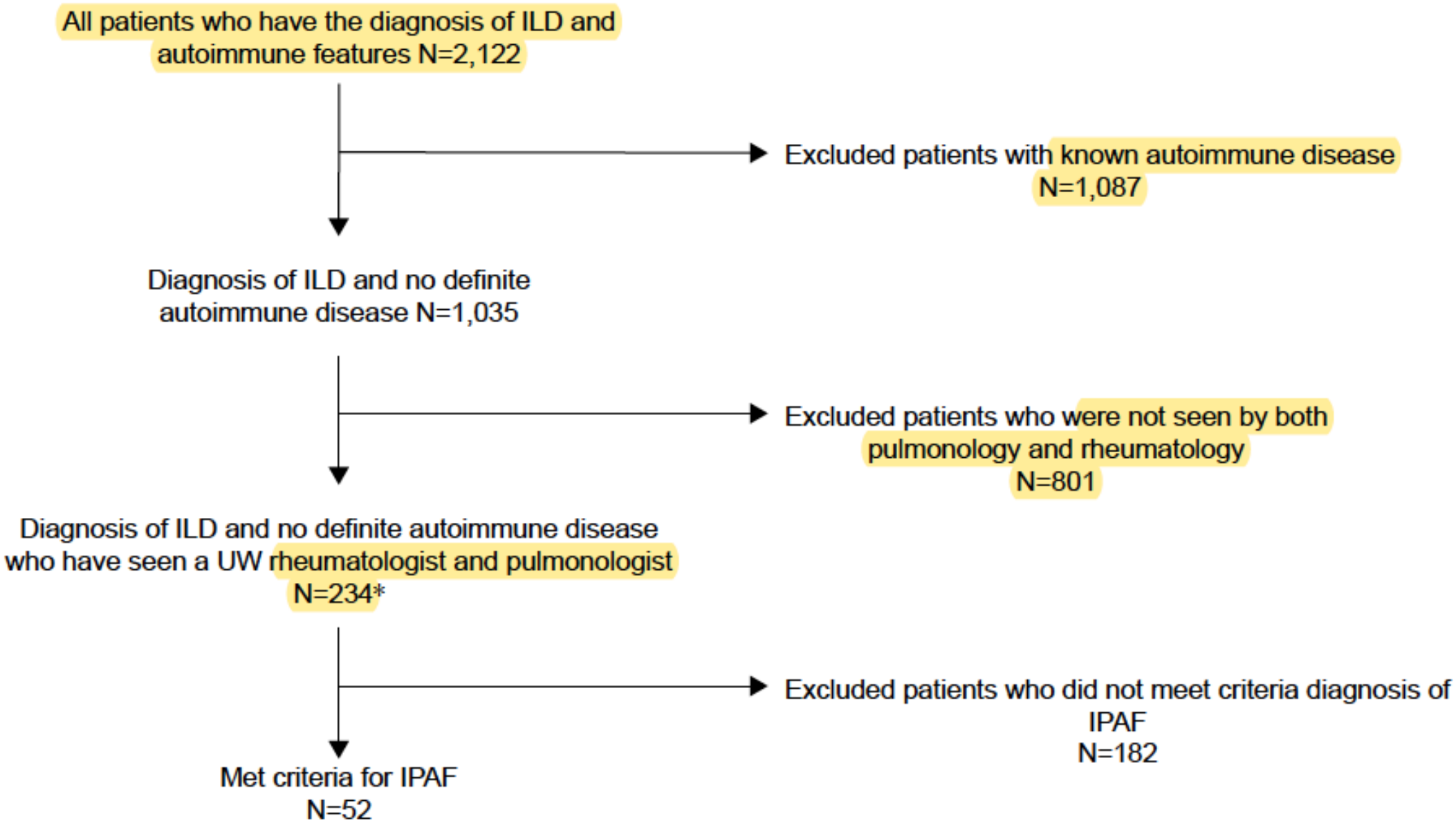

Figure 1 Exclusion and inclusion of patients who met criteria for IPAF diagnosis and saw both pulmonology and rheumatology departments within the University of Wisconsin health system.

Note: *Three patients saw a pulmonologist familiar with rheumatologic disease and were considered to fill both rheumatologic and pulmonary visit requirements.

Abbreviations: ILD, interstitial lung disease; IPAF, interstitial pneumonia with autoimmune features; UW, University of Wisconsin.

Table 1 Baseline demographics and clinical data

	Mycophenolate-exposed	Mycophenolate-unexposed	*P*-value
	n=28 (54%)	n=24 (46%)	
Age, years (mean, SD)	58.68, 12.8	65.38, 12.6	0.06
Male, n (%)	12 (43)	7 (29)	0.31
Female, n (%)	16 (57)	17 (71)	
Tobacco use, ever, n (%)	15 (54)	9 (38)	0.20
Tobacco use, never	12 (43)	15 (63)	
Cardiovascular disease, n (%)#	7 (25)	3 (13)	0.32
Gastroesophageal reflux	24 (86)	12 (50)	0.015*
Malignancy	2 (7)	1 (4)	0.70
Obstructive sleep apnea	6 (21)	3 (13)	0.48
Pulmonary artery hypertension	6 (21)	2 (8)	0.23
Pulmonary embolism	3 (11)	0	0.11
Azathioprine use	9 (32)	7 (29)	0.86
Azithromycin use	15 (54)	4 (17)	0.03*
Cyclophosphamide use	3 (11)	3 (13)	0.66
Hydroxychloroquine use	10 (36)	2 (8)	0.04*
Leflunomide use	1 (4)	2 (8)	0.42
Methotrexate use	1 (4)	2 (8)	0.42
PPI use	26 (93)	14 (58)	0.07
Ranitidine use	13 (46)	12 (50)	0.38
Steroid use	25 (89)	12 (50)	0.02*

Table 1 Baseline demographics and clinical data

	Mycophenolate-exposed	Mycophenolate-unexposed	*P*-value
	n=28 (54%)	n=24 (46%)	
Peak steroid dose (mg), mean, SD	40, 5.3	32, 6.2	0.35
Steroid dose at diagnosis (mg), mean, SD	10, 24.2	7, 21.8	0.66
Hemolytic anemia, n (%)	0	0	
Leukopenia	4 (14)	0	0.07
Lymphopenia	8 (29)	4 (17)	0.35
Thrombocytopenia	6 (21)	1 (4)	0.08
Low complement	0	2 (8)	0.09
Creatinine over double ULN at diagnosis	1 (4)	0	0.38
ESR elevated	18 (64)	15 (63)	0.76
Lymphocytic BAL, n (%)	4 (24)	0	0.25
Eosinophilic BAL, n (%)	3 (18)	3 (50)	
Neutrophilic BAL, n (%)	1 (6)	1 (17)	
Normal BAL, n (%)	9 (53)	2 (33)	
BAL not performed	11	18	
Developed into MPA, n (%)	1 (4)	2 (8)	0.50
Developed into SLE, n (%)	1 (4)	0	

	Mycophenolate-exposed, n (%)	Missing/ unavailable, n	Mycophenolate-unexposed, n (%)	Missing/ unavailable, n	P-value
	28 (54%)		24 (46%)		
Clinical domain					
Digital fissures	0		0		
Digital tip ulceration	1 (4)		0		0.4
Inflammatory arthritis	8 (29)		5 (21)		0.6
Palmar telangiectasia	0		0		
Raynaud's phenomenon	8 (29)		8 (33)		0.7
Digital edema	0		0		
Rash on digital extensor surface	0		0		
Serologic domain					
ANA ≥1:320	21 (78)	1	19 (79)		0.7
Nucleolar/centromere any titer	5 (18)/0		8 (33)/0		0.2
RF double or more ULN/anti-CCP	4 (15)/0	1/11	5 (24)/0	3/16	0.4
Anti-dsDNA	1 (5)	7	2 (14)	10	0.3
Anti-Ro (SS-A)/anti-La (SS-B)	7 (26)/0	1/1	3 (17)/0	6/6	0.6
Anti-ribonucleoprotein	6 (25)	4	0	7	0.03*
Anti-Smith	0	4	0	7	
Anti-topoisomerase	0	15	1 (14)	17	0.2
Anti-tRNA synthetase	1 (4)	18	0	21	0.6

Table 2 IPAF-classification criteria

	Mycophenolate-exposed, n (%)	Missing/ unavailable, n	Mycophenolate-unexposed, n (%)	Missing/ unavailable, n	*P*-value
	28 (54%)		24 (46%)		
Morphologic domain					
HRCT pattern					
NSIP	16 (57)		11 (48)	1	0.4
OP	3 (11)		1 (4)		
NSIP with OP overlap	3 (11)		2 (9)		
LIP	1 (4)		0		
Other	5 (18)		9 (39)		
Lung-biopsy histopathology					
NSIP	4 (21)	9	1 (14)	17	0.2
OP	0		1 (14)		
NSIP with OP overlap	1 (5)		0		
LIP	0		0		
Interstitial lymph aggregates and GC	2 (11)		0		
Diffuse lymphoplasmacytic infiltrate*	1 (5)		0		
Multicompartment involvement					0.3
Pleural/pericardial+	7 (25)/5 (18)		5 (21)/2 (8)		
Intrinsic airway disease	5 (18)		8 (33)		
Pulmonary vasculopathy	6 (21)		2 (8)		
Diagnostic domains met					0.5
Clinical and serological	0		0		
Clinical and morphological	3 (11)		1 (4)		
Serological and morphological	14 (50)		15 (63)		
All three	11 (39)		8 (33)		

Table 3 PFT, 6MWT, and HRCT outcomes

	Mycophenolate-exposed (n=28)			Mycophenolate-unexposed (n=24)			Mycophenolate-exposed vs unexposed (first)
	First mean (SD)	Last mean (SD)	*P*-value	First mean (SD)	Last mean (SD)	*P*-value	*P*-value
PFT							
FVC (%)	68.2 (17.3)	59.3 (17.1)	0.07	79.2 (18.5)	79.2 (0.2)	0.99	0.09
D_{LCO} (%)	53.0 (14.8)	44.9 (16.5)	0.08	62.2 (16.8)	55.4 (17.7)	0.26	0.42
6MWT (feet), mean (SD)	1,044 (359)	969 (412)	0.53	1,057 (340)	1,051 (335)	0.97	0.45
HRCT							
ILD+	23.8 (22.6)	30.4 (27.1)	0.34	22.7 (26.0)	26.6 (29.3)	0.65	0.41
Proportion GGO (%)	0.6 (0.4)	0.5 (0.6)	0.07	0.4 (0.4)	0.3 (0.3)	0.42	0.048*
GGO+ (%)	16.5 (18.0)	16.1 (4.2)	0.95	12.4 (22.2)	11.8 (23.1)	0.93	0.74
Reticulation+ (%)	7.0 (14.3)	14.5 (19.7)	0.11	9.7 (10.8)	12.4 (15.9)	0.51	0.15
Coarseness score	2.4 (1.9)	4.4 (3.3)	0.01*	4.4 (3.9)	5.3 (3.9)	0.44	0.42

Notes: +Global extent; *$P<0.05$.

Abbreviations: D_{LCO}, diffusion capacity of lungs for carbon monoxide; GGO, ground-glass opacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; 6MWT, 6-minute walk test; PFT, pulmonary function test.

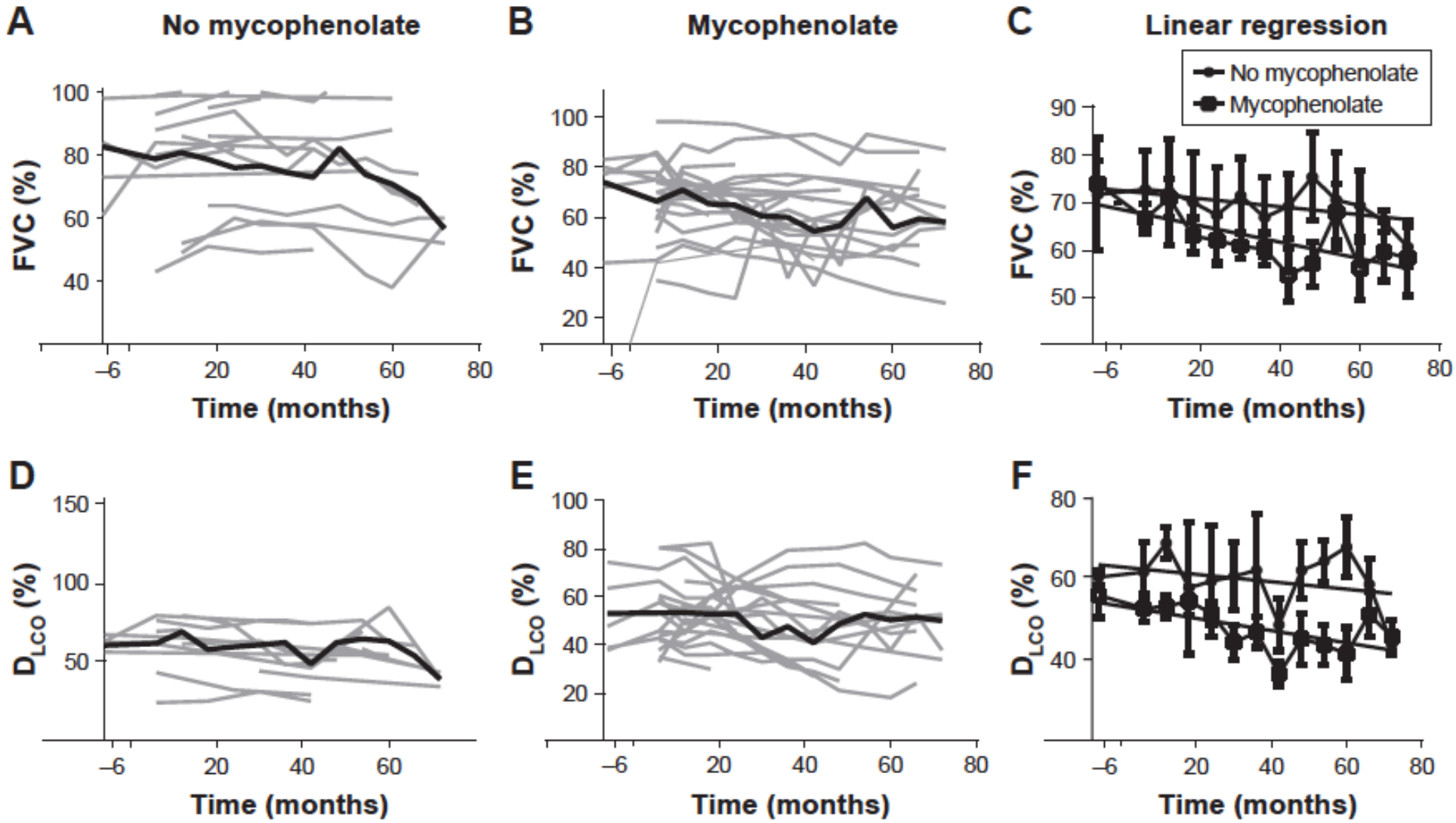

Figure 2 (**A**) Raw FVC% months after IPAF diagnosis in the mycophenolate-unexposed (n=24) group, graphed individually in light gray, with mean is represented by the bold black line. (**B**) Raw FVC% in the mycophenolate exposed (n=27) groups, graphed individually in light gray, with mean represented by the bold black line. (**C**) Linear regression of FVC% months from the date of diagnosis in both the mycophenolate-exposed and unexposed groups. (**D**) Raw D_{LCO}% months after diagnosis date in the mycophenolate-unexposed (n=19) group, graphed individually in light gray, with mean represented by the bold black line. (**E**) Raw D_{LCO}% in the mycophenolate-exposed (n=26) group, graphed individually in light gray, with mean represented by the bold black line. (**F**) Linear regression of D_{LCO}% over time from the date of diagnosis in both the mycophenolate-exposed and unexposed groups.

Abbreviations: D_{LCO}, diffusion capacity of lungs for carbon monoxide; IPAF, interstitial pneumonia with autoimmune features.

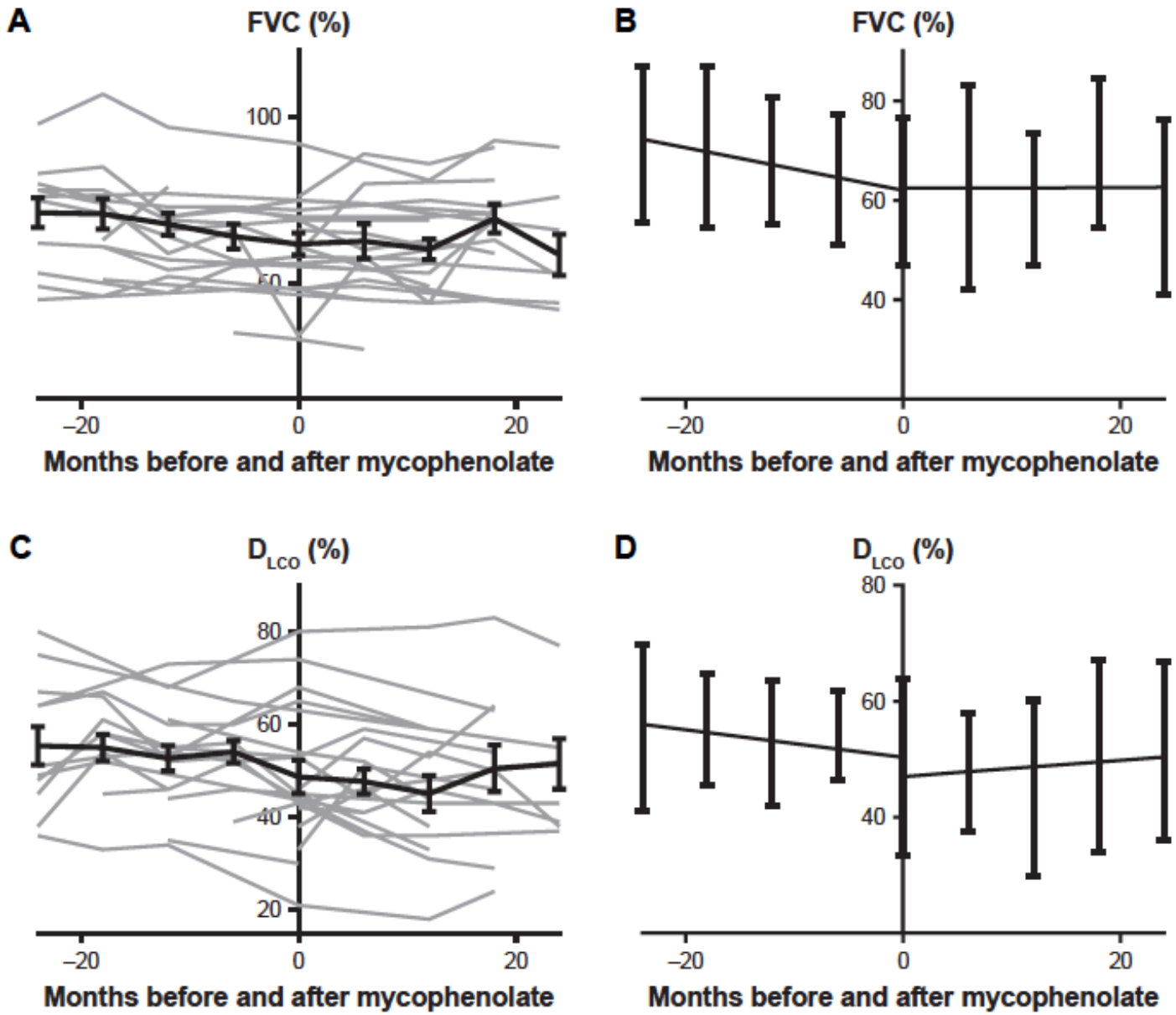

Figure 3 (**A**) Raw FVC% in months before and after mycophenolate exposure among the mycophenolate-exposed. Data graphed individually (n=26) in light gray, and mean with SEM represented with the bold black line. (**B**) Linear regression of FVC% before and after mycophenolate exposure with SD. (**C**) D_{LCO}% before and after mycophenolate exposure, graphed individually (n=26) in light gray and mean with SEM represented with the bold black line. (**D**) Linear regression of D_{LCO}% before and after mycophenolate exposure with SD.

Abbreviations: D_{LCO}, diffusion capacity of lungs for carbon monoxide.

AGORA
RESEARCH LETTER

Cyclophosphamide in steroid refractory unclassifiable idiopathic interstitial pneumonia and interstitial pneumonia with autoimmune features (IPAF)

Methodology

- Retrospective cohort study St Antonius ILD Center between 2011 and April 2016
- 108 ILD cases- excluded 70 patients due to known causes
- 38 patients -unclassifiable IIP and included in the study
- 19 out of the 38 patients –fulfilled IPAF criteria
- All patients were refractory to corticosteroids before initiation of ICPT
- This regimen initially started at 0.5 mg/kg/day, with a maximum of 60 mg corticosteroids and tapered monthly to 0.15 mg/kg/day/

Methodology

- In 6 months A 4-week schedule of ICPT with six cycles and a dose of 15 mg·kg−1 bodyweight was used along with 200 mg of Mesna (sodium 2-mercaptoethane sulfonate)
- Analyses of forced vital capacity (FVC) change were performed in patients treated with at least four cyclophosphamide cycles and with available FVC data at the start, 3–12 months before, and after 6 months and 12 months of therapy (±2 months)

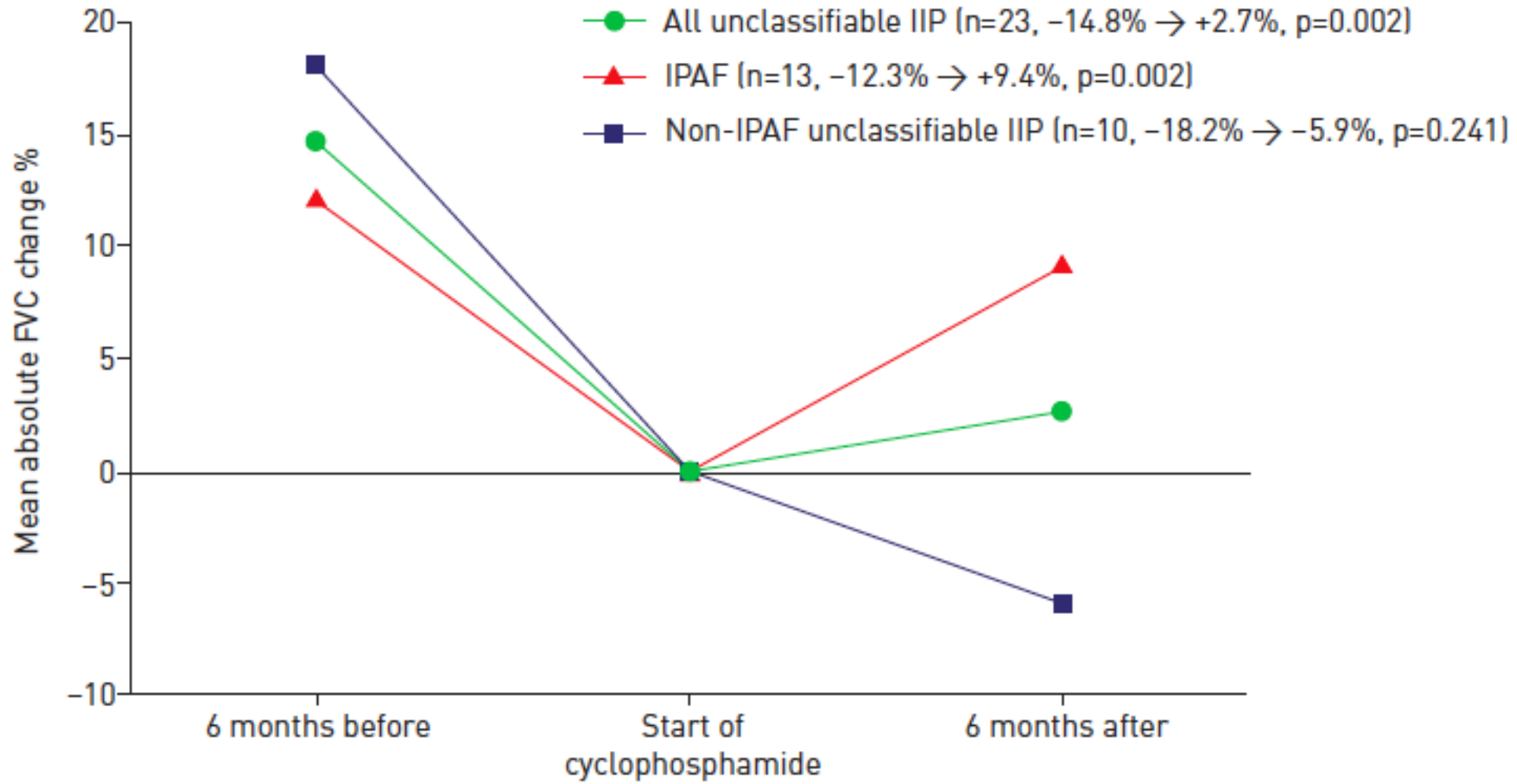

FIGURE 1 Mean percentage absolute forced vital capacity (FVC) change before and after initiation of intravenous cyclophosphamide pulse therapy. IIP: idiopathic interstitial pneumonia; IPAF: interstitial pneumonia with autoimmune features.

Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial

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Lancet Respir Med 2020; 8: 147–57

Published Online September 29, 2019 https://doi.org/10.1016/S2213-2600(19)30341-8

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Summary

Background At present, no approved pharmacotherapies are available for unclassifiable interstitial lung disease (ILD), which is characterised by progressive fibrosis of the lung. We aimed to assess the efficacy and safety of pirfenidone in patients with progressive fibrosing unclassifiable ILD.

Methods We did a multicentre, double-blind, randomised, placebo-controlled phase 2 trial at 70 centres in Australia, Belgium, Canada, Czech Republic, Denmark, Germany, Greece, Ireland, Israel, Italy, Poland, Portugal, Spain, and the UK. Eligible patients (aged ≥18–85 years) had progressive fibrosing unclassifiable ILD, a percent predicted forced vital capacity (FVC) of 45% or higher and percent predicted carbon monoxide diffusing capacity (DLco) of 30% or higher, more than 10% fibrosis on high-resolution CT, and a high-resolution CT from the previous 12 months. Patients were randomly assigned (1:1) to 2403 mg oral pirfenidone daily or placebo using a central validated interactive voice or web-based response system, stratified by concomitant mycophenolate mofetil use and presence or absence of interstitial pneumonia with autoimmune features. Investigators, site personnel, and patients were masked to treatment assignment. The primary endpoint was mean predicted change in FVC from baseline over 24 weeks, measured by daily home spirometry. Secondary endpoints were change in FVC measured by site spirometry, proportion of patients who had a more than 5% or more than 10% absolute or relative decline in percent predicted FVC measured by clinic-based spirometry, change in percent predicted DLco, change in 6-min walk distance (6MWD), change in University of California San Diego-Shortness of Breath Questionnaire (UCSD-SOBQ) score, change in Leicester Cough Questionnaire score, change in cough visual analogue scale, and changes in total and subscores of the St George's Respiratory Questionnaire (SGRQ), all of which were compared with baseline. Additional secondary endpoints included proportion of patients who had non-elective hospitalisation (respiratory and all-cause) and acute exacerbations, and progression-free survival. Efficacy was analysed in the intention-to-treat (ITT) population, which included all randomly assigned patients. Safety was assessed in the safety analysis set, which included all randomly assigned patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, NCT03099187, and is no longer recruiting.

Findings Between May 15, 2017, and June 5, 2018, 253 patients were randomly assigned to receive 2403 mg pirfenidone (n=127) or placebo (n=126) and were included in the ITT analysis set. Analysis of the primary endpoint was affected by intraindividual variability in home spirometry values, which prevented application of the prespecified statistical model.

	Pirfenidone (n=127)	Placebo (n=126)
Age at screening, years	70·0 (61·0–76·0)	69·0 (63·0–74·0)
Sex		
Men	70 (55%)	69 (55%)
Women	57 (45%)	57 (45%)
Race		
White	120 (94%)	123 (98%)
Black	1 (1%)	2 (2%)
Asian	5 (4%)	0
Native American or Alaskan Native	1 (1%)	0
Other	0	1 (1%)
Body-mass index, kg/m²	28·6 (26·5–32·9)	29·3 (26·2–32·7)
Previous surgical lung biopsy	40 (31%)	48 (38%)
Percent predicted FVC	71·0% (59·0–87·3)	71·5% (58·0–88·0)
Percent predicted DLco	44·6% (36·9–53·5)	48·0% (38·4–59·0)
Percent predicted FEV_1	75·0% (62·0–88·0)	76·0% (62·0–92·7)
FEV_1/FVC ratio	0·82 (0·78–0·86)	0·84 (0·78–0·87)
6MWD, m	372·0 (303·0–487·0)	395·0 (325·0–472·0)
Concomitant treatment with mycophenolate mofetil	23 (18%)	22 (17%)
IPAF diagnosis	15 (12%)	18 (14%)
Concomitant treatment with mycophenolate mofetil	6 (5%)	6 (5%)
Unclassifiable ILD diagnosis		
Low-confidence rheumatoid arthritis-ILD	0	0
Low-confidence systemic sclerosis-ILD	0	1 (1%)
Low-confidence undifferentiated connective tissue disease-ILD	3 (2%)	2 (2%)
Low-confidence chronic hypersensitivity pneumonitis-ILD	10 (8%)	9 (7%)
Low-confidence idiopathic non-specific interstitial pneumonia-ILD	4 (3%)	3 (2%)
Low-confidence sarcoidosis-ILD	0	0
Low-confidence myositis-ILD	0	0
Low-confidence other defined ILD	1 (1%)	0
Unclassifiable ILD	93 (73%)	93 (74%)

Data are median (Q1–Q3) or n (%), unless otherwise specified. The sum of some percentages does not equal 100% because of rounding. 6MWD=6-min walk distance. DLco=carbon monoxide diffusing capacity. FVC=forced vital capacity. ILD=interstitial lung disease. IPAF=interstitial pneumonia with autoimmune features.

Table 1: **Demographic and baseline characteristics of the intention-to-treat population (n=253)**

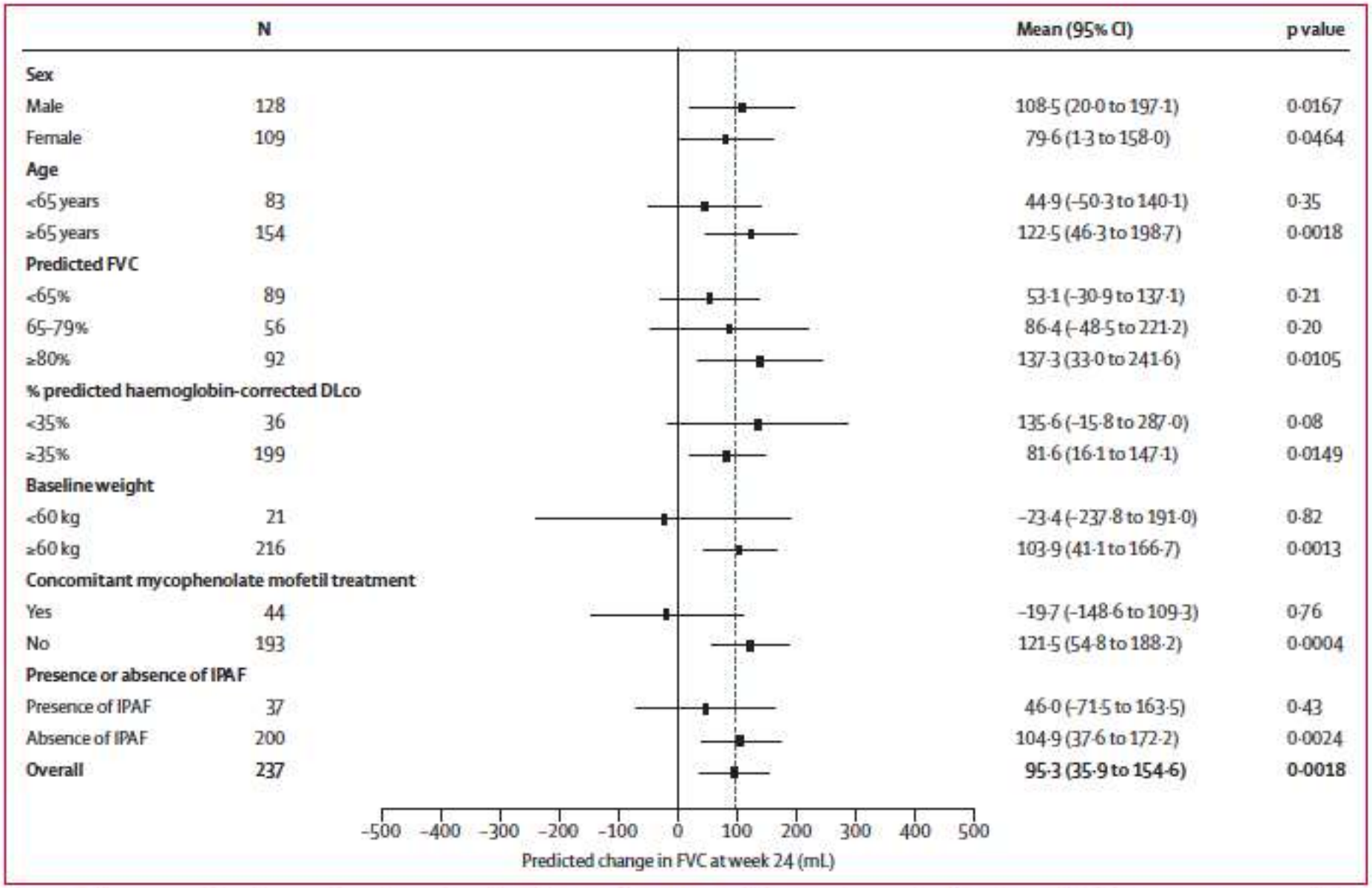

Figure 3: **Subgroup analysis of mean change in FVC from baseline at week 24 measured by site spirometry in all patients who had site spirometry at week 8 (n=237)**

FVC=forced vital capacity. DLco=carbon monoxide diffusing capacity. IPAF=interstitial pneumonia with autoimmune features.

Conclusion

- IPAF patients who have UIP pattern have poor outcomes
- Definition of CTD are dynamic
- CTD diseases definition must includes lung involvement
- IPAF Definition-should be broadened
- Includes sub categories like UIP pattern
- ?useful in management-Require more studies