Interstitial pneumonitis with autoimmune features (IPAF): a good definition?

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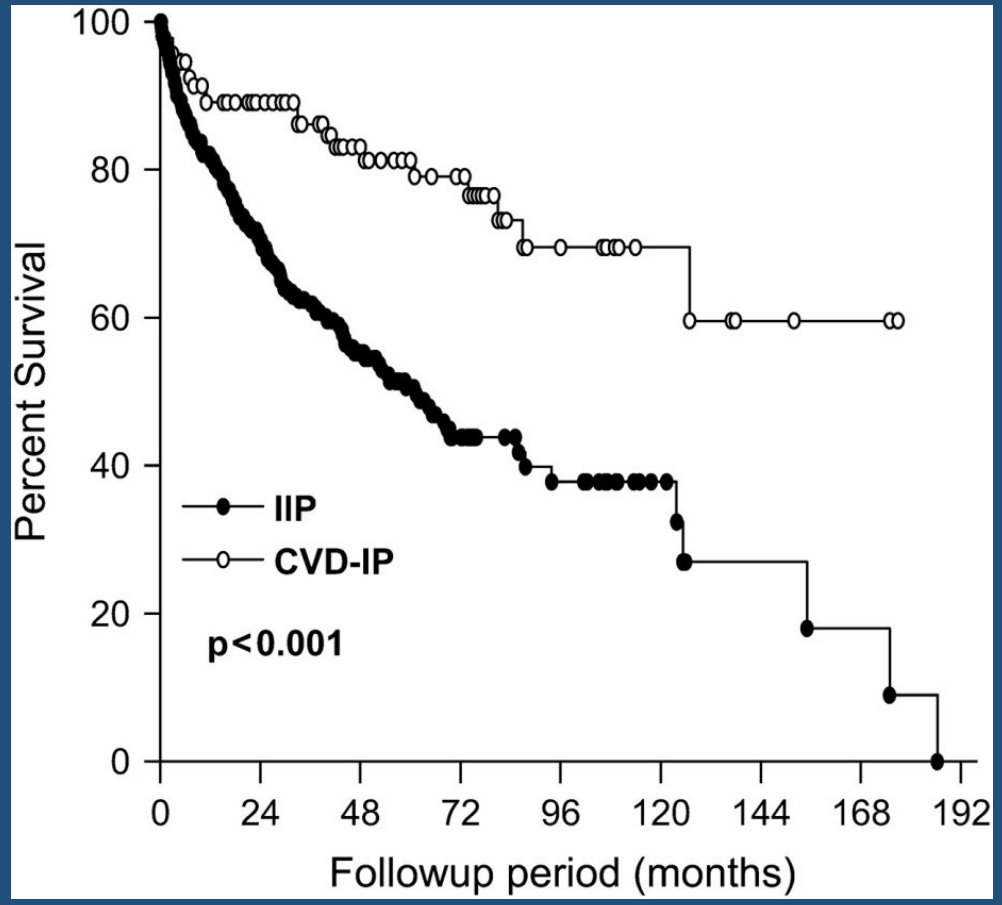
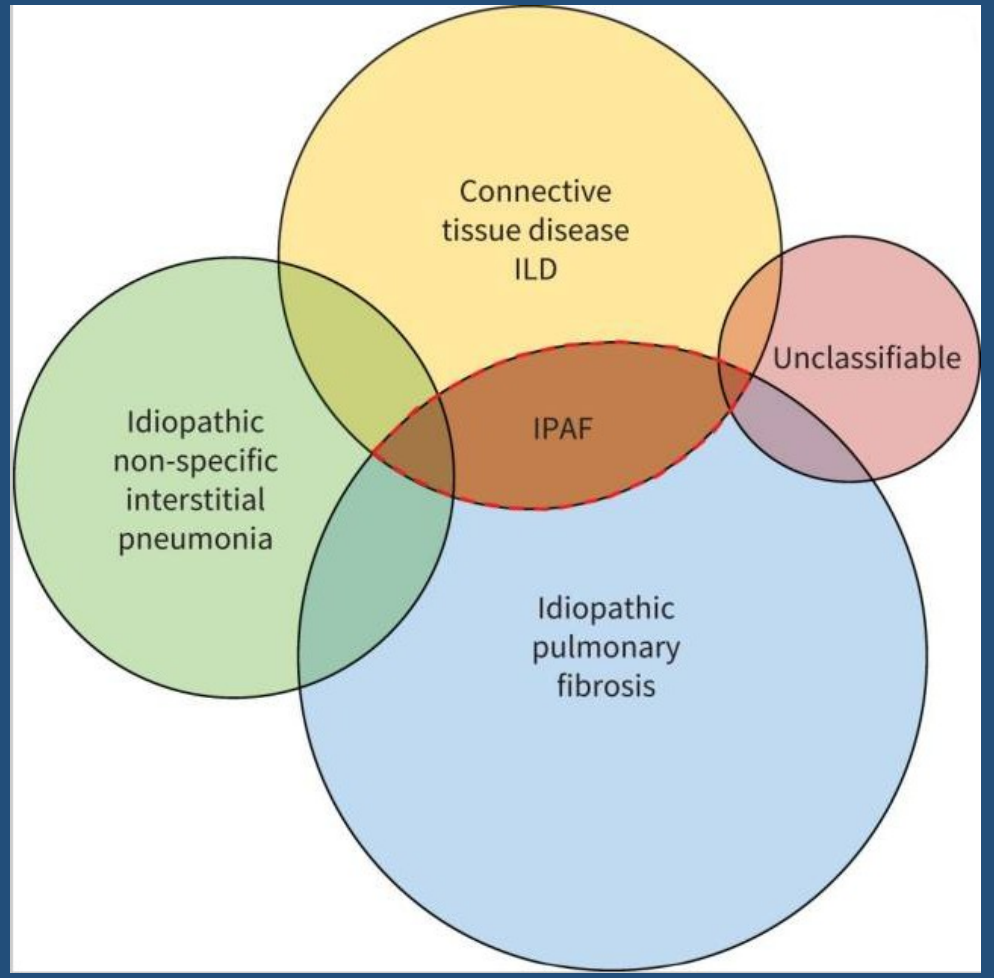
Disclosure

- ER has received speaker/advisory board fees from Boehringer Ingelheim, F. Hoffmann-La Roche and Mundipharma paid into her Institution

A significant proportion of patients with ILD has features suggestive of an autoimmune disease without fitting into defined rheumatological entities



Park et al AJRCCM 2007; 175: 705-711



Mackintosh JA, Wells AU, Cottin V, Nicholson AG, Renzoni EA. Interstitial pneumonia with autoimmune features: challenges and controversies. Eur Respir Rev. 2021 Dec 22;30(162):210177.

IPAF: interstitial pneumonitis with autoimmune features

- Proposed classification criteria:
  - ILD with no alternative cause
  - Incomplete features of a defined CTD
  - At least one feature from at least two of three domains:
    - Clinical
    - Serologic
    - Morphologic

CTD, connective tissue disease; ILD, interstitial lung disease; IPAF, interstitial pneumonitis with autoimmune features

Fischer A *et al. Eur Respir J* 2015;46:976–87

Clinical domain

- Distal digital tip ulceration
- Mechanic's hands
- Inflammatory arthritis
- Palmar telangiectasias
- Raynaud's
- Unexplained digital edema
- Gottron's sign

Serologic domain

- ANA≥1:320 or any titer of anti-nucleolar or ACA
- RF >2 ULN
- Anti-CCP and specific CTD autoantibodies, including myositis specific antibodies:
  - Anti-dsDNA
  - Anti-Ro/anti-La
  - Scl70, Sm, RNP
  - Anti synthetases (Jo1, Pl7, Pl12, EJ, OJ, KS)
  - Anti Pm-Scl, MDA5

Morphologic domain

CT pattern of OP, NSIP, NSIP/OP or LIP

Histologic pattern as above or germinal centers or diffuse lymphoplasmacytic infiltrate

Unexplained multi-compartment involvement

- –Pleural
- –Airways
- –Pericardial
- –Vasculopathy

ACA, anti-centromere antibody; ANA, antinuclear antibodies; CCP, cyclic citrullinated peptide; CT, computed tomography; ENA, extractable nuclear antigen; LIP, lymphocytic interstitial pneumonia; OP, organizing pneumonia; NSIP, nonspecific interstitial pneumonia; LIP, lymphocytic interstitial pneumonia; RF, rheumatoid factor; ULN, upper limit of normal

Clinical domain

- Distal digital tip ulceration
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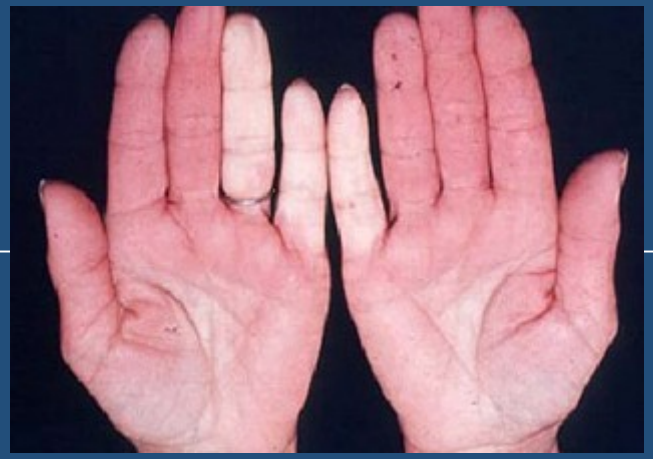
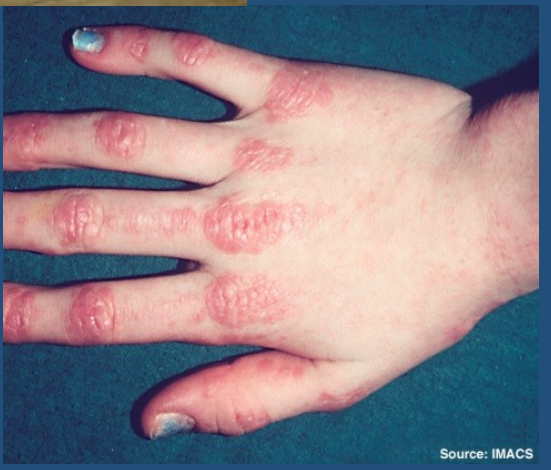
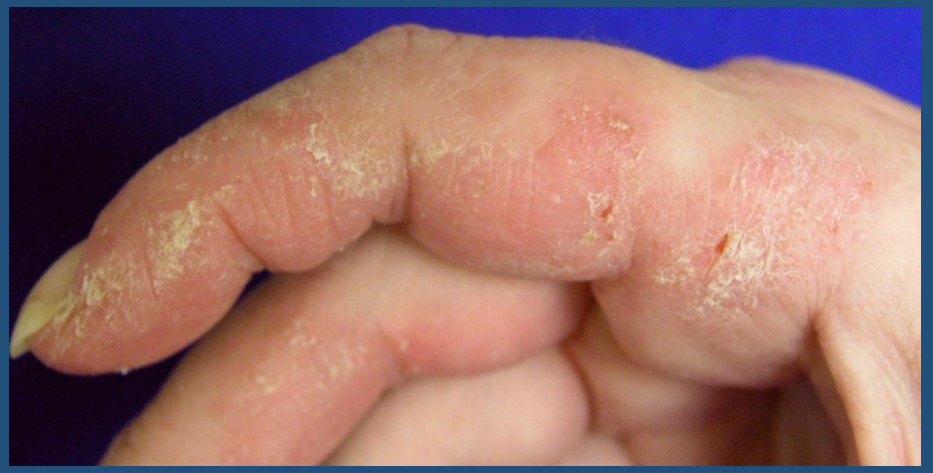






Unresolved issues in the current IPAF criteria

Clinical domain

- When to involve rheumatology and/or immunology in the evaluation of patients meeting IPAF criteria.
- When and how to re-evaluate for a connective tissue disease.
- Inclusion of sicca symptoms, oesophageal dysmotility, proximal muscle weakness and myalgia.
- Clustering in time of autoimmune features.
- Family history of autoimmune disease.
- Role of additional investigations, including nailfold capillaroscopy, salivary gland biopsy, articular radiology and electromyography.

Serological domain

- Inclusion/exclusion of myositis-specific antibodies.
- Inclusion of anti-neutrophil cytoplasmic antibodies.

Morphological domain

- Separation of usual interstitial pneumonia (UIP) from non-UIP – should IPAF criteria be applied differently?
- Specific definitions for the application of multi-compartment involvement.
- Role and indications of lung biopsy in patients with IPAF features.

- UIP

Mackintosh JA, Wells AU, Cottin V, Nicholson AG, Renzoni EA. Interstitial pneumonia with autoimmune features: challenges and controversies. Eur Respir R

Review

Interstitial Pneumonia with Autoimmune Features: Why Rheumatologist-Pulmonologist Collaboration Is Essential

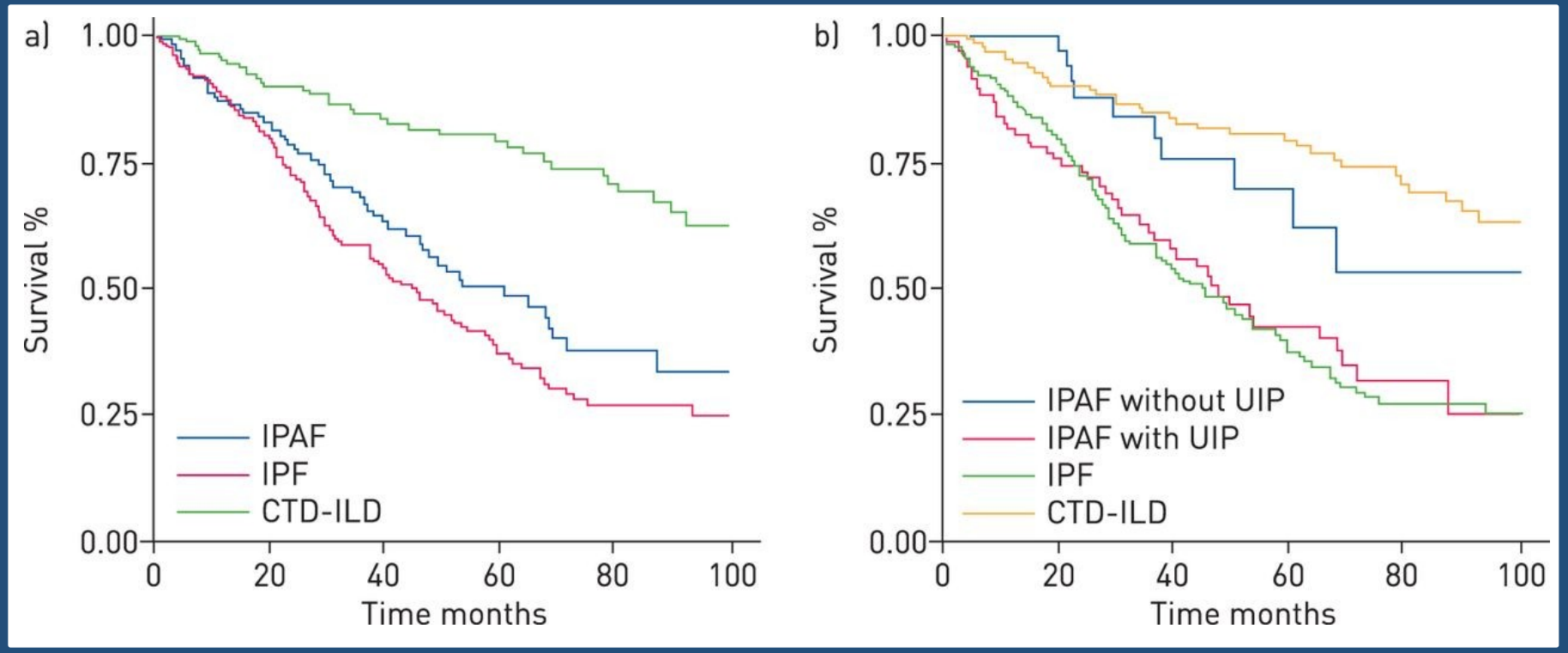
Marco Sebastiani [1], Paola Faverio [2], Andreina Manfredi [1], Giulia Cassone [1], Caterina Vacchi [1], Anna Stainer [2], Maria Rosa Pozzi [3], Carlo Salvarani [1,4], Alberto Pesci [2] and Fabrizio Luppi [2,*]

Table 2. Comparison of retrospectively and prospectively identified interstitial pneumonia with autoimmune features (IPAF) cohorts.

	Oldham et al. [29], 2016	Chartrand et al. [28], 2016	Ahmad et al. [31], 2017	Ito et al. [40], 2017	Dai et al. [41], 2018	Yoshimura et al. [30], 2018	Kelly & Moua [35], 2018	Lim et al. [32], 2019	Alevizos et al. [39], 2019	Kim et al. [37], 2020	Sambataro et al. [34], 2019	Sebastiani et al. [33], 2020
Patients	144	56	57	98	177	32	101	54	50	109	45	52
Study design	Retrospective	retrospective	retrospective	retrospective	retrospective	Retrospective	retrospective	Retrospective	retrospective	retrospective	prospective	prospective
Age, y (mean ± SD)	63.2 ± 11	54.6 ± 10.3	64.4 ± 14	67.5 ± 9	67.6 ± 8.6	63.4 ± 12.6	56.9 ± 14.2	67.9 ±10.5	56 (47–44) [d]	60.6 ± 11.6	66 (59.5–71) [d]	68 (54–82) [d]
Female	52.1	71.4	49.1	58.2	55.9	40.6	39	64.8	60	56	62.2	55.8
Ever smoker	54.9	32.1	34	38.8	19.2	56.2	31	27.8	50	63.3	51.1	63.5
Clinical	49.3	62.5	47.3	NR	20.3	53.1	NR	31.5	38	25.7	62.2	84.6
Serologic	91.7	91.1	93	100 [a]	92.1	71.9	NR	90.7	98	100	48.9	94.2
Morphologic	85.4	98.2	78.9	100 [b]	95.5	96.9	NR	81.5	92	72.5	100	55.8
Clinical and serologic	14.6	2	NR	NR	NR	3.1	4	NR	NR	25.7	NR	NR
Clinical and morphologic	8.3	9	NR	NR	NR	28.1	14	NR	NR	17.4	51.1	NR
Serologic and morphologic	50.7	37.5	NR	100	NR	46.9	26	NR	NR	72.5	37.8	NR
All 3 domains	26.4	52	NR	NR	NR	21.9	36	NR	NR	17.4	11.1	
UIP by HRCT	54.6	8.9	28	0	4.5	NR	11.9	25.9	18	36.7	0	44.2
Underwent SLB, n (%)	83 (57.6)	36 (64.3)	16 (28.1)	17 (17.3)	0 [c]	22 (68.8)	51 (50.5)	NR	40 (80)	NR	NR	2 (3.8)
UIP on SLB, n (%)	61 (73.5)	8 (22.2)	3 (18.8)	3 (17.6)	-	-	12 (23.5)	NR	20 (40)	NR	NR	2 (3.8)
Treatment												
Corticosteroids	32.2	81.8	67.9	17.3	72.3	59.4	NR	NR	NR	84.4	NR	63.5
Antifibrotic	NR	NR	5.4	2	NR	25	NR	NR	0	0	NR	11.5
Outcome												
Death	39.6	0	12.3	27.6	19.8	NR	28	27.8	NR	NR	2.2	28.8
Lung transplant	10.8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Data presented as % unless otherwise stated; NR: not reported; y: years; SD: standard deviation; UIP: usual interstitial pneumonia; HRCT: high-resolution computed tomography; SLB: surgical lung biopsy; [a]: based on study design, inclusion criteria was positive serological evaluation; [b]: based on reported HRCT findings of nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), or NSIP + OP in 98 of 98 subjects; [c]: all histopathology from transbronchial biopsies; [d]: median.

Characterization of patients with IPAF



IPAF patients N=136
52% females; mean age 63.4
54% smoking history

IPAF with UIP: 68%

CTD, connective tissue disease; ILD, interstitial lung disease; IPAF, interstitial pneumonia with autoimmune features; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia

Oldham JM *et al. Eur Respir J* 2016; 47:1767–75

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

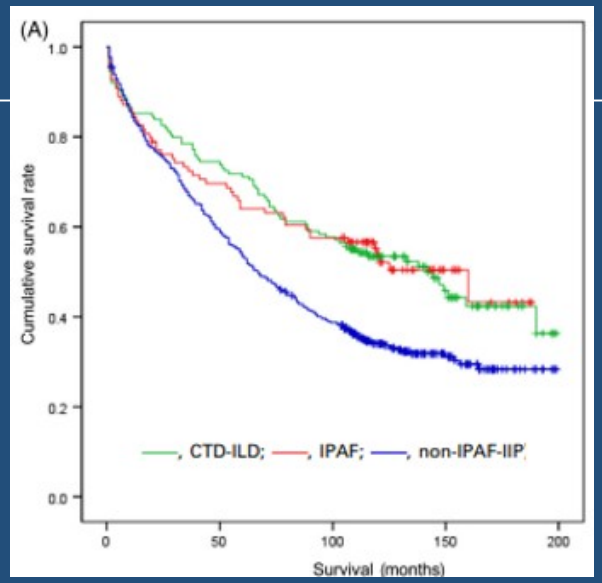
Jonathan H. Chung[1], Steven M. Montner[1], Ayodeji Adegunsoye[2], Cathryn Lee[2], Justin M. Oldham[3], Aliya N. Husain[4], Heber MacMahon[1], Imre Noth[2], Rekha Vij[2], and Mary E. Strek[2]

	Unadjusted (n=136)			Adjusted* (n=136)		
Variable	**HR**	**p-value**	**95% CI**	**HR**	**p-value**	**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^	2.17	**0.011**	1.19 – 3.95	1.79	0.117	0.87 – 3.70
Pulmonary artery enlargement	2.23	**0.009**	1.22 – 4.05	2.08	**0.043**	1.02 – 4.20
UIP Pattern**						
Possible UIP	0.99	0.982	0.36 – 2.73			
Definite UIP	1.57	0.172	0.82 – 2.98			

AJR Am J Roentgenol. 2017 Jun;208(6):1229-1236.

Long-term clinical course and outcome of interstitial pneumonia with autoimmune features

Characteristics	IPAF	Non-IPAF-IIP	CTD-ILD
No. of subjects	109	477	149
Age (years)	60.6 ± 11.6	61.8 ± 8.9	55.8 ± 12.2
Female	61 (56.0)	170 (35.6)	116 (77.9)
Never-smokers	69 (63.3)	157 (32.9)	114 (76.5)
BMI (kg/m^2)	23.7 ± 3.6	24.4 ± 3.0	23.2 ± 3.3
Pattern†			
UIP‡	40 (36.7)	332 (69.6)	64 (43.0)
NSIP	30 (27.5)	37 (7.8)	19 (12.8)
OP	16 (14.7)	35 (7.3)	12 (8.1)
Unclassifiable	23 (21.1)	73 (15.3)	54 (36.2)
PFT			
FEV_1 (% predicted)	81.8 ± 19.4	85.9 ± 19.6	80.6 ± 22.1
FVC (% predicted)	71.5 ± 17.4	75.4 ± 18.6	70.1 ± 18.9
FEV_1/FVC	82.9 ± 9.5	82.1 ± 9.2	85.1 ± 8.3
DL_{CO} (% predicted)	61.5 ± 23.2	69.8 ± 22.3	61.2 ± 19.9
Corticosteroids	92 (84.4)	337 (70.6)	143 (96.0)
With an immunosuppressant	70 (64.2)	254 (53.2)	103 (69.1)
Without an immunosuppressant	22 (20.2)	83 (17.4)	40 (26.8)



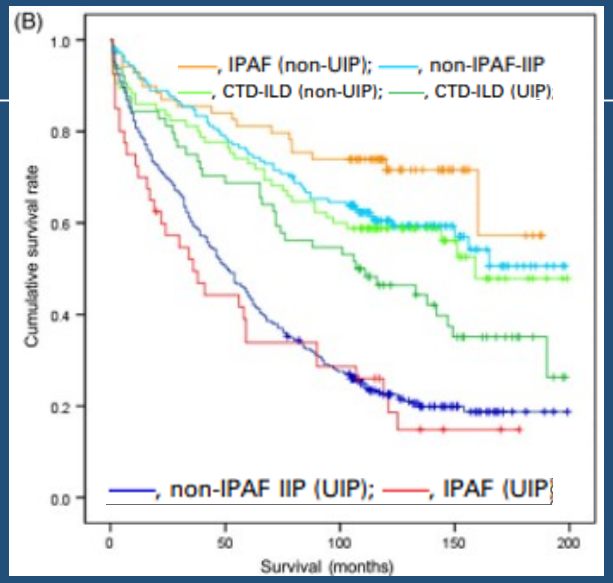
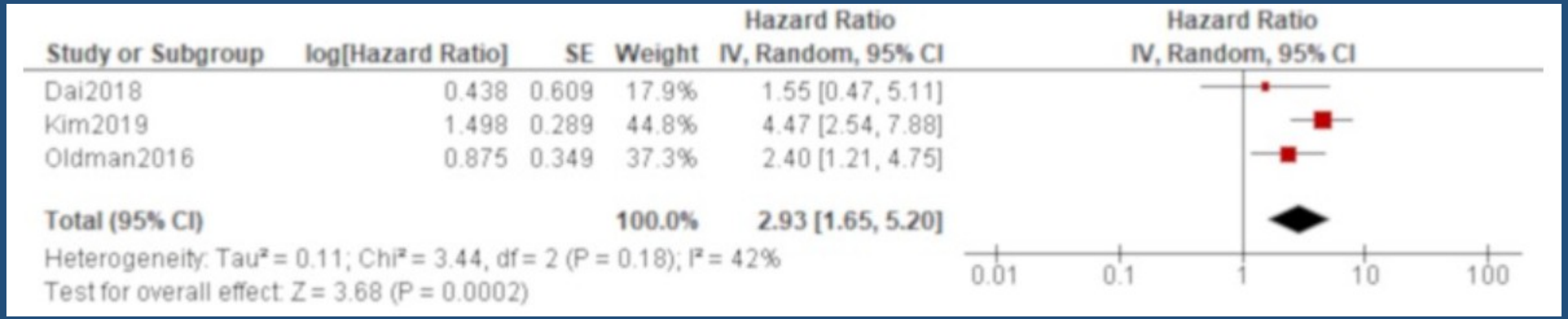


Table 4 Factors predicting mortality in the IPAF cohort, as determined by Cox regression analysis

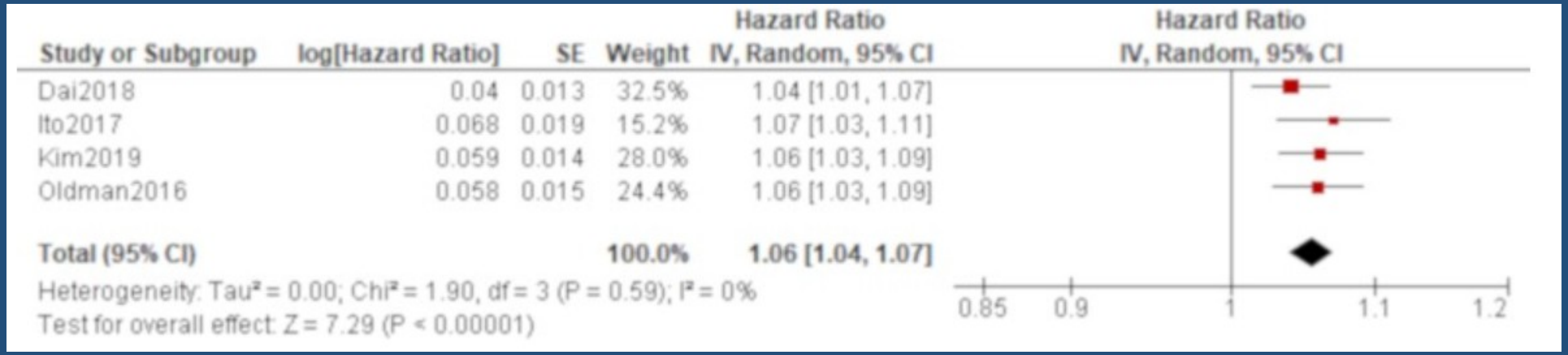
	Univariate		Multivariate	
Characteristics	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.061 (1.032–1.091)	<0.001	1.063 (1.029–1.099)	<0.001
Female sex	0.665 (0.385–1.149)	0.144		
BMI	1.000 (0.920–1.086)	0.992		
Ever-smoker	1.465 (0.842–2.549)	0.177		
UIP pattern	4.473 (2.540–7.877)	<0.001	3.847 (1.991–7.434)	<0.001
PFT				
FVC (% predicted)	0.993 (0.977–1.008)	0.353		
DL_{CO} (% predicted)	0.971 (0.956–0.986)	<0.001	0.961 (0.945–0.978)	<0.001
6MWT				
Distance	0.995 (0.992–0.997)	<0.001		
Lowest SpO_2	0.939 (0.908–0.971)	<0.001		
Use of corticosteroids	0.700 (0.340–1.444)	0.334		
With an immunosuppressant	0.768 (0.438–1.344)	0.355		
Without an immunosuppressant	1.100 (0.565–2.142)	0.780		

Kim HC et al Respirology. 2020 Jun;25(6):636-643.



Forrest plot of the effect of a usual interstitial pneumonia (UIP) pattern on all-cause mortality of IPAF

Kamiya H, Panlaqui OM. BMJ Open. 2019 Dec



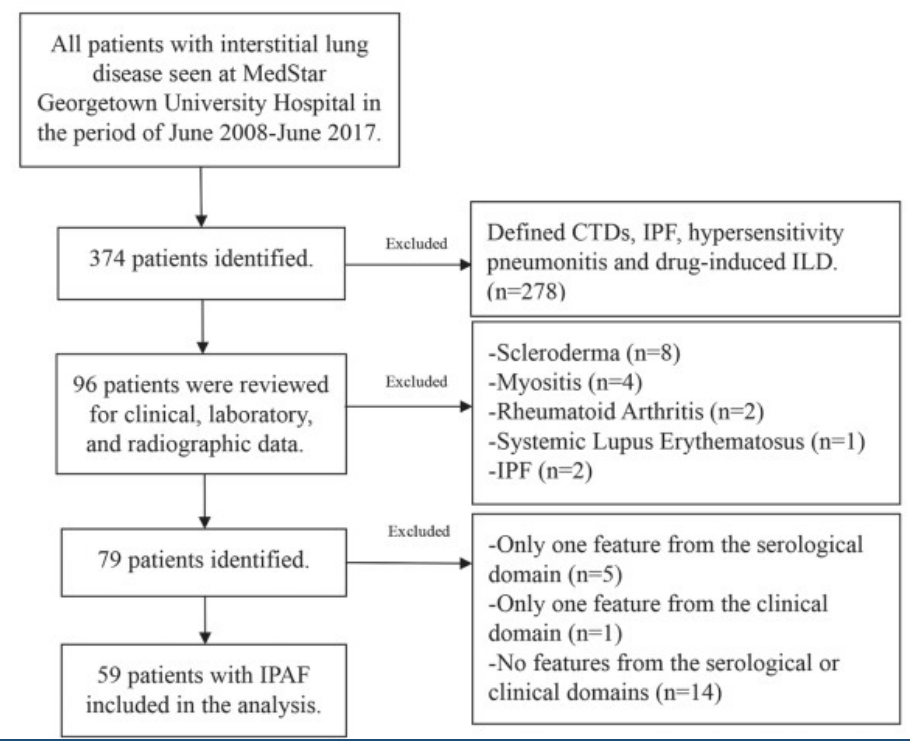
On multivariable analysis, only age remained predictive of mortality

Kamiya H, Panlaqui OM. BMJ Open. 2019 Dec

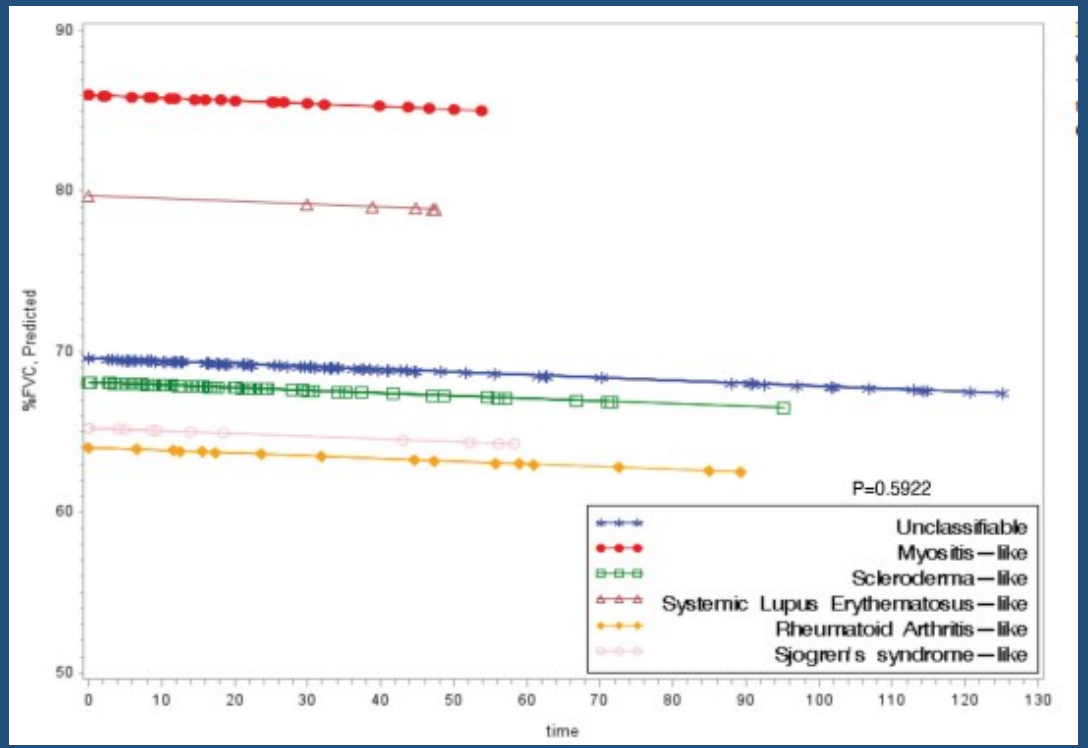
Long-term evaluation of pulmonary function and survival of patients with interstitial pneumonia with autoimmune features

J.A. Huapaya[1], A. Boulougoura[2], J. Fried[3], S. Mesdaghinia[4], B.J. Culotta[5], S. Carson[6], P.J. Bergquist[7], P. Krishnan[7], H. Wang[8], C. Reichner[3], V. Steen[4]

60% of IPAF subdivided into:
-Myositis like
-SSc-like
-SLE Like
-RA-like
-Sjogren-like
-Unclassifiable



- 78% female
- Mean age 59.8 ± 11.4
- FVC 69%; DLCO 49%
- UIP 44.1%; NSIP or OP 22%



Clin Exp Rheumatol. 2023 Jan;41(1):15-23.

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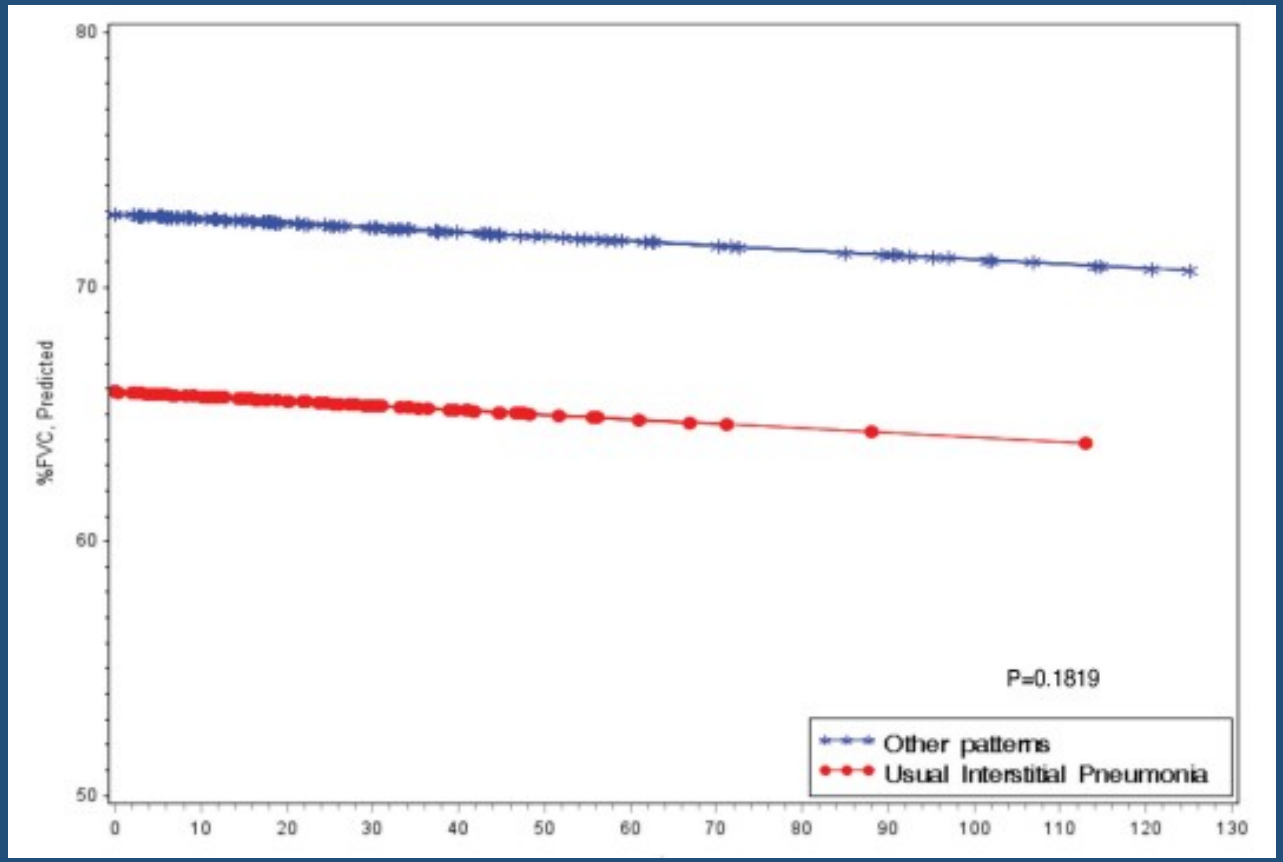
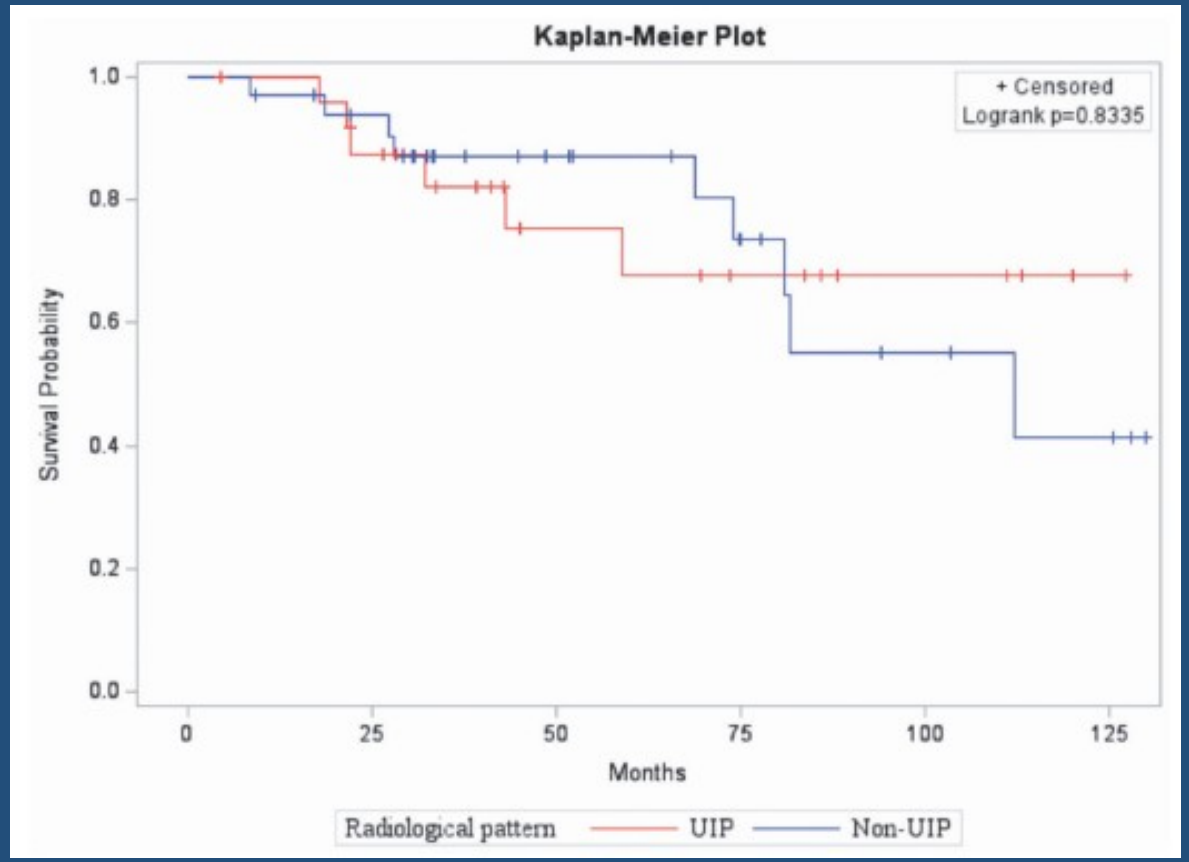


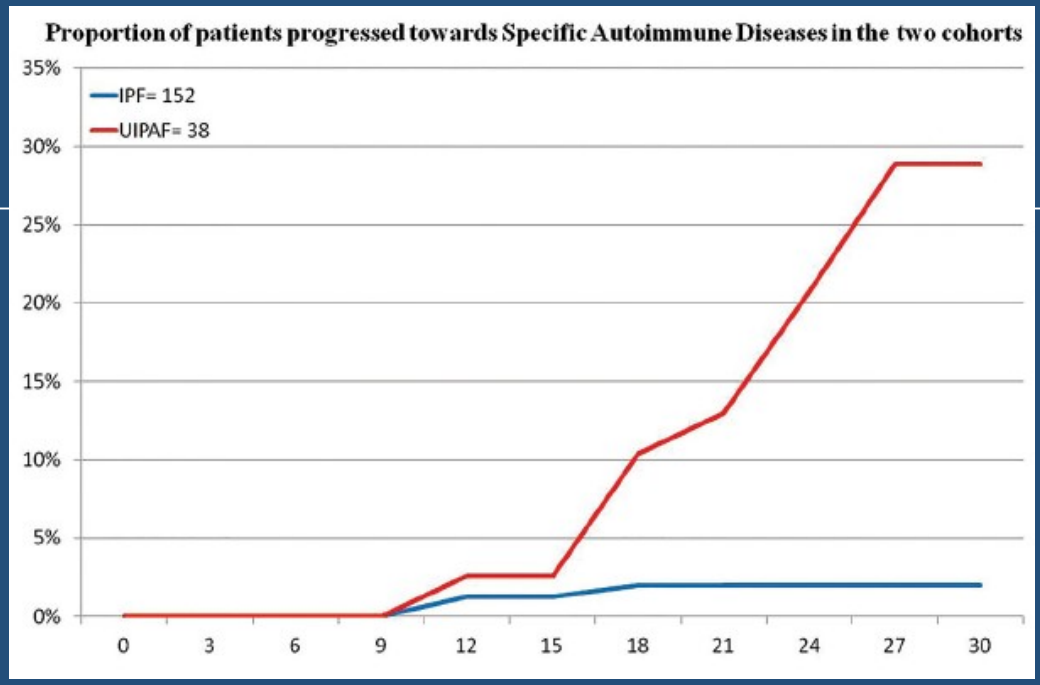


Clin Exp Rheumatol. 2023 Jan;41(1):15-23.

"Usual" interstitial pneumonia with autoimmune features: a prospective study on a cohort of idiopathic pulmonary fibrosis patients

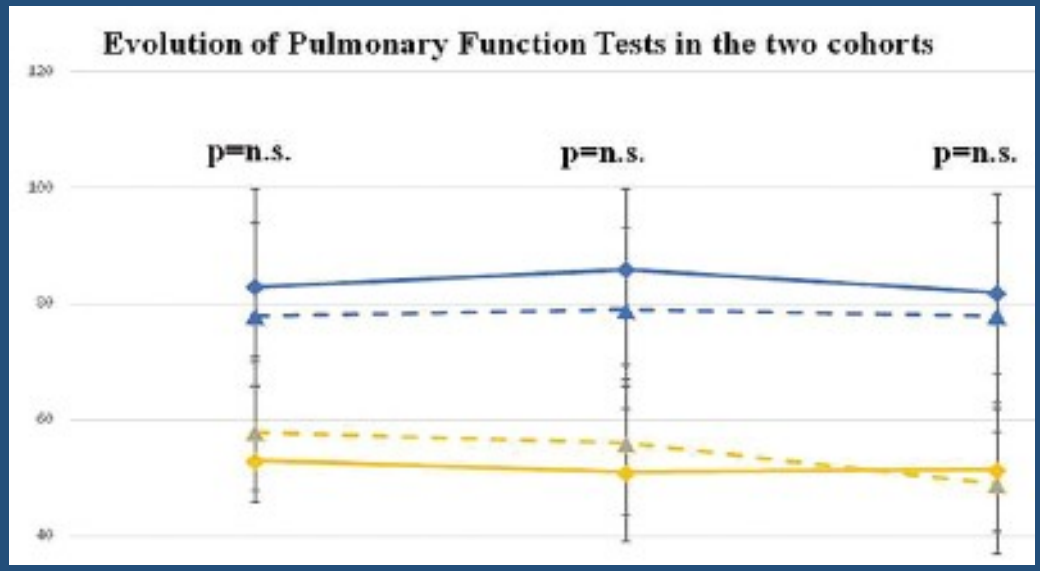
G. Sambataro[1,2], C.A. Ferrara[1], S.E. Torrisi[1], C. Spadaro[1], G. Vignigni[1], A. Vancheri[1], N. Del Papa[3], M. Orlandi[4], M. Colaci[5], L. Malatino[5], S. Palmucci[6], L. Cavagna[7], D. Sambataro[2,5], C. Vancheri[1]

- Prospective study
- Patients with UIP and one IPAF criterion (UIPAF) compared to IPF pts
- All patients reviewed by pulmonologist and rheumatologist; rheumatologist review at least once yearly
- 152 IPF vs 38 UIPAF



6 RA
1SSc
1ASS
1PM
1SLE
1 GPA

1 PM
1 pSS



Clin Exp Rheumatol. 2022 Jul;40(7):1324-

- UIP-IPAF associated with IPF-like survival in most but not all cohorts. In the correct clinical context, UIP-IPAF should be managed as per IPF.

- Not all IPAF-UIPs are equal and demographic & clinical characteristics will impact on prognosis and management

- A proportion (up to a quarter) of patients with IPAF, and of those with UIP and at least one autoimmune feature, will develop CTD on follow up

Sebastiani et al Biomedicines. 2020 Dec 26;9(1):17. Fernandes L, Nasser M, Ahmad K, Cottin V. Interstitial Pneumonia With Autoimmune Features (IPAF). Front Med (Lausanne). 2019 Sep 27;6:209. Alevizos MK et al Rheumatology (Oxford). 2020 Jun 1;59(6):1233-1240. Sambataro G et al *Respir Med.* (2019) 150:154–60. Sambataro et al Clin Exp Rheumatol. 2022.

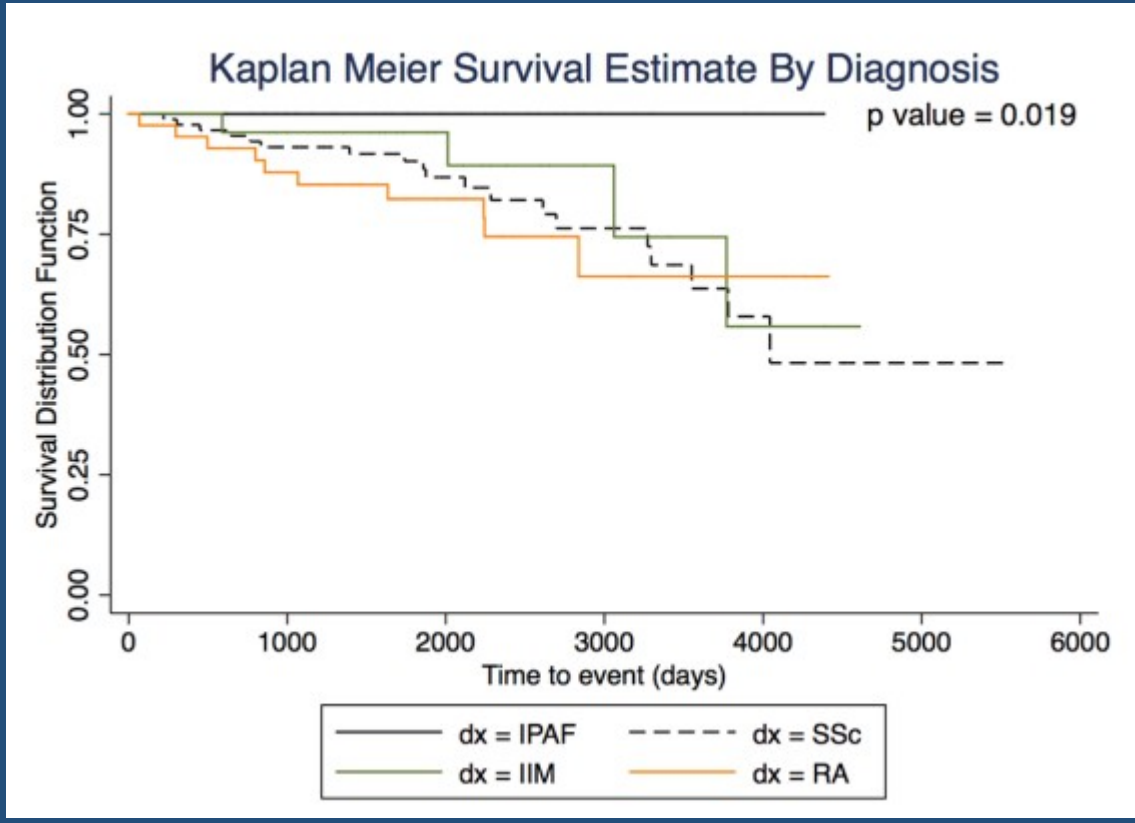
In conclusion

- At the moment, morphological pattern plays a key role in management, with integration of age/gender and other findings on a case by case basis
- Further approaches to tackle heterogeneity before IPAF can be used clinically
- Pragmatically, after considering demographics, smoking history, clinical context, and morphological pattern, manage as per
  - IPF-like IPAF
  - CTD-ILD like IPAF

Thank you, any questions?

Clinical Characteristics and Natural History of Autoimmune Forms of Interstitial Lung Disease: A Single-Center Experience

	SSc-ILD $n=88$	IIM-ILD $n=26$	RA-ILD $n=42$	IPAF $n=56$
Age at diagnosis, years (mean ± SD)	57.3 ± 9.6	54.7 ± 9.6	64.3 ± 10.2	55.1 ± 10.5
Female, *n* (%)	63 (71.6)	18 (69.2)	21 (50.0)	40 (71.4)
PFT parameters at baseline, in percent predicted (mean ± SD)				
FVC%	71.0 ± 15.1	61.5 ± 16.4	74.9 ± 14.3	68.4 ± 16.0
FEV-1%	73.1 ± 15.0	61.8 ± 15.7	76.8 ± 17.1	72.7 ± 16.3
TLC%	87.3 ± 19.5	79.1 ± 20.8	91.5 ± 20.1	80.1 ± 13.7
DLco%	52.3 ± 20.7	49.1 ± 18.3	56.3 ± 17.7	52.2 ± 15.9
Thoracic HRCT scan, *n* (%)				
NSIP	51 (58.0)	14 (53.8)	12 (28.6)	27 (48.2)
NSIP + OP	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
UIP	15 (17.0)	0 (0.0)	19 (45.2)	3 (5.4)



All IPAF patients treated with immunosuppression

After adjusting for diagnosis, age, sex, and FVC, the independent predictors for death in the entire cohort were older age, male sex, and lower FVC

Chartrand S et al Lung. 2019 Dec;197(6):709-713.