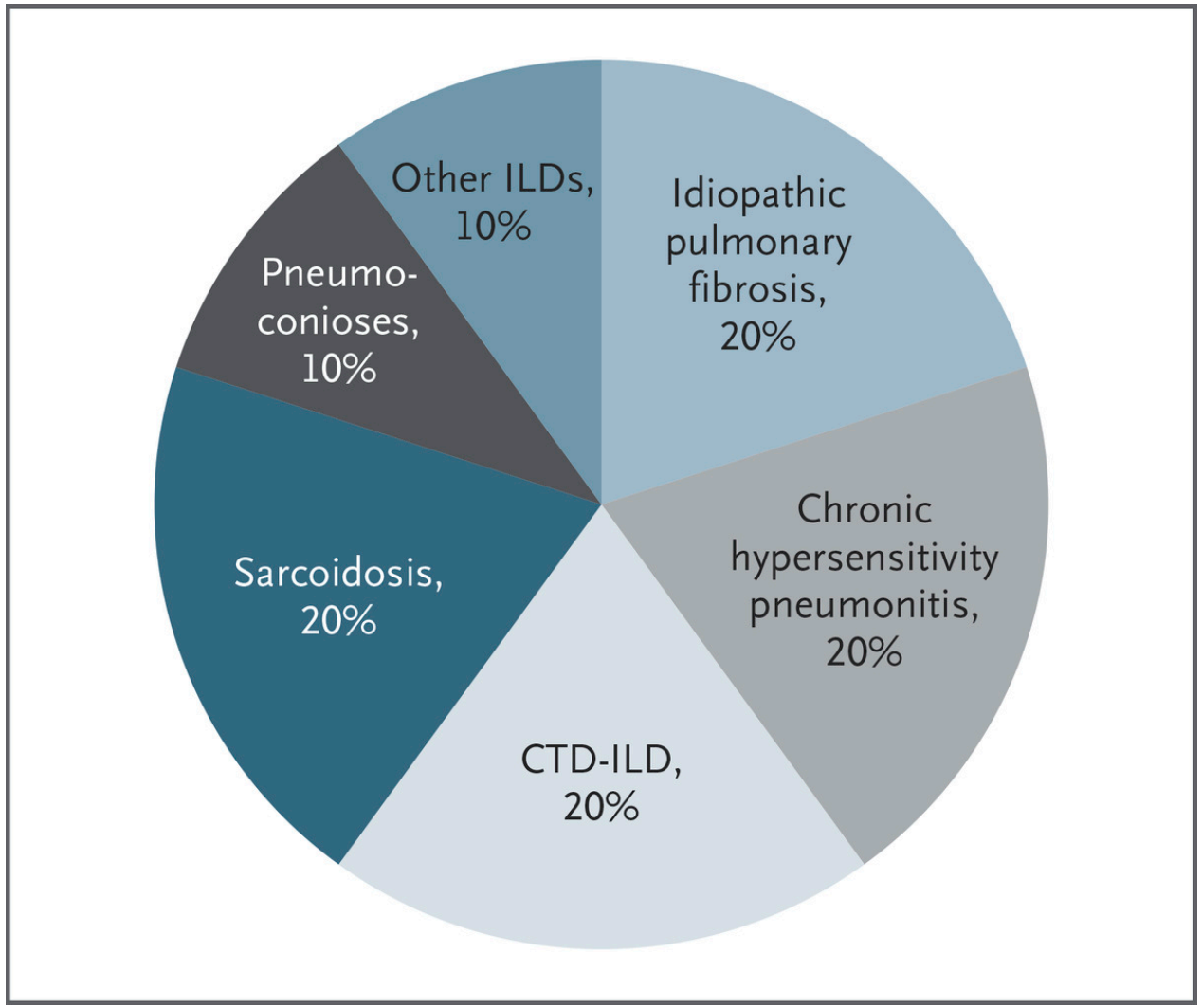
USZ Universitäts Spital Zürich

Interstitielle Pneumopathie mit «autoimmune features» (IPAF)

Christian Clarenbach, Pneumologie

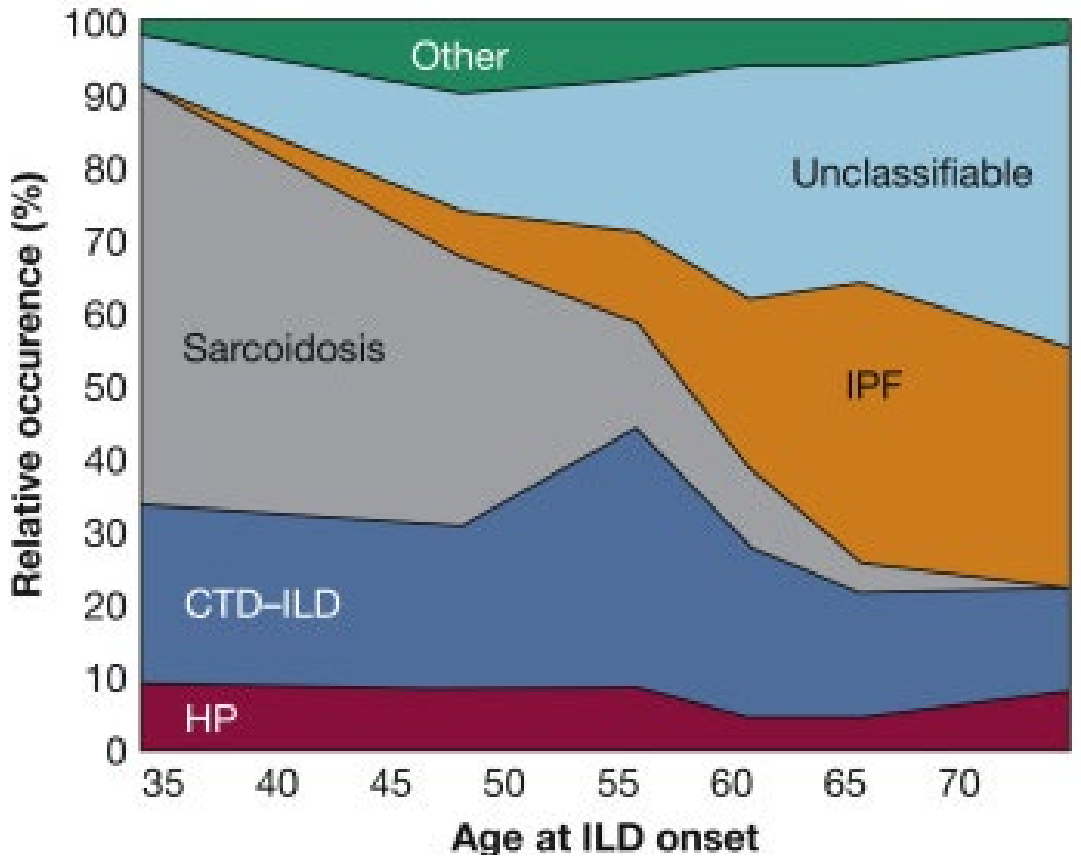
Rheuma-Workshop, 23.09.2021

Relative Verteilung der interstitiellen Lungenerkrankungen

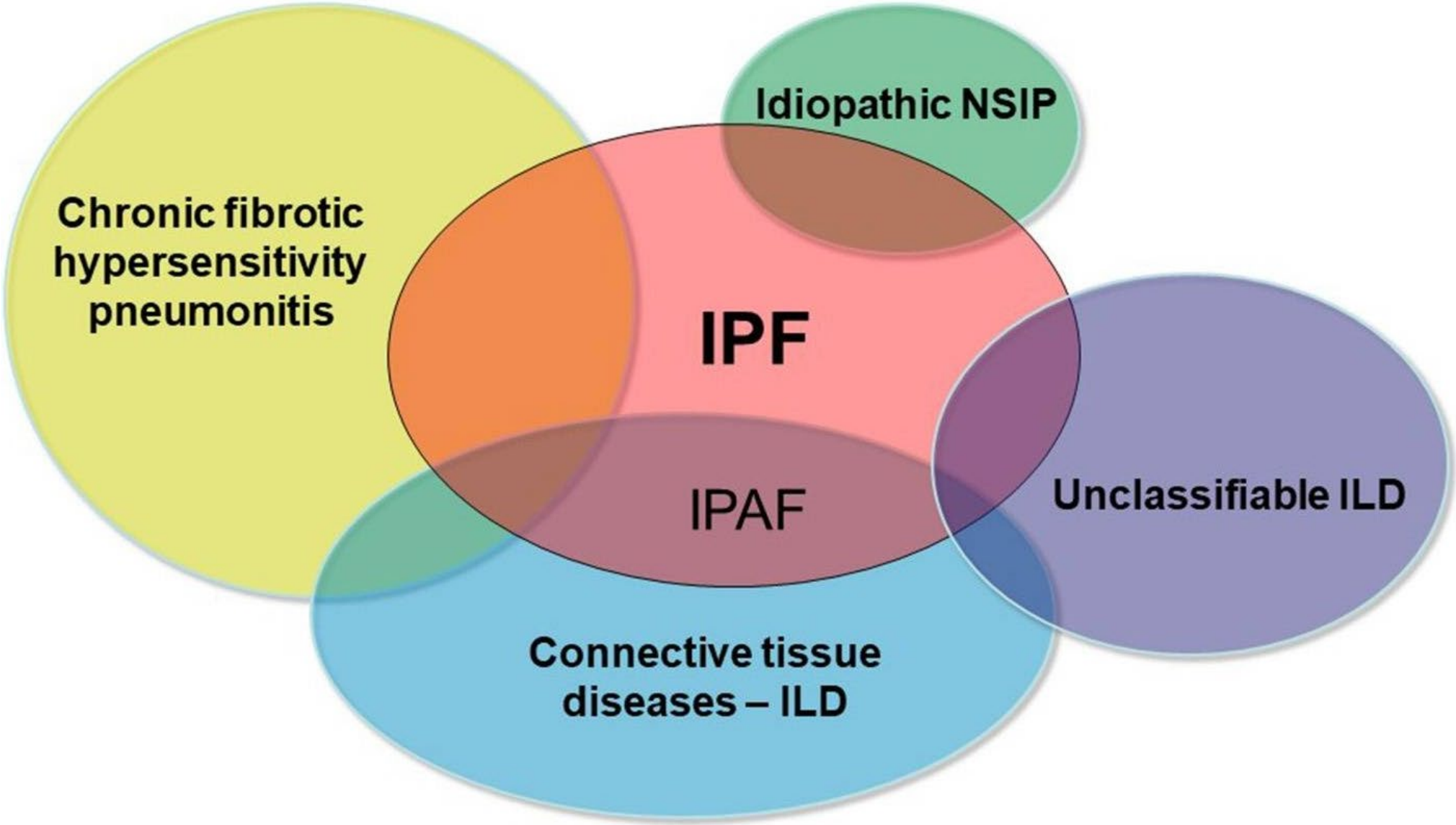


DJ Lederer, FJ Martinez. N Engl J Med 2018;378:1811-1823.

Alter & Diagnose Interstielle Lungenkrankheit



Patterson et al. Chest Volume 151, Issue 4, April 2017, Pages 838-844



Fernandes, Ligia et al. *Frontiers in medicine* vol. 6 209. 27 Sep. 2019, doi:10.3389/fmed.2019.00209

IPAF: Interstitial Pneumonia with Autoimmune Features

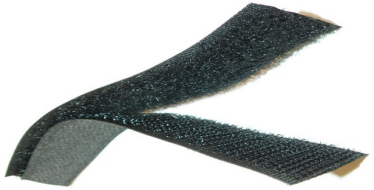
1. Einige Pat. mit interstitieller Lungenerkrankung haben serologische und klinische Hinweise, dass eine rheumatologische Erkrankung vorliegen könnte.
2. Die diagnostischen Kriterien der rheumatologischen Erkrankung werden jedoch nicht erfüllt.
3. IPAF dient als Begriff für diese «graue Zone».

Anamnese & Klinik

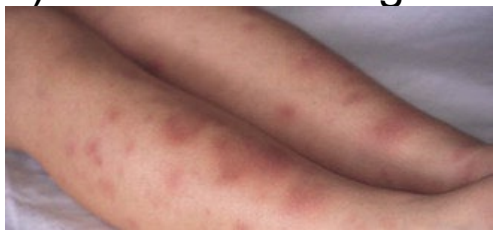
Anamnese

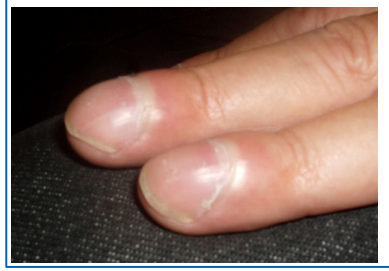
- Belastunsluftnot
- Nicht-produktiver Husten
- Evt. familiäre ILD Fälle

Untersuchung und Labor



- Sklerosiphonie
- Belastungshypoxämie
- Spirometrie (niedrige FVC) und/oder niedrige Dlco
- Bildgebung
- Autoimmunserologie





Anamnese

Exklusion bekannter Ursachen von Pneumopathien (ca. 40%)

- Medikamente
- Beruf (Asbest?)
- Hobbies
- Rheumatologische Erkrankung
- Bestrahlung

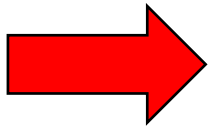


Table 5. Proposed criteria for interstitial pneumonia with autoimmune features (IPAF).

1. Presence of an interstitial pneumonia by HRCT or surgical lung biopsy
2. Exclusion of alternative aetiologies
3. Does not meet criteria for a defined CTD
4. Has at least one feature from at least two of the following domains:

A. Clinical domain	B. Serological Domain	C. Morphological domain
• Distal digital fissuring (i.e., "Mechanic hands") • Distal digital tip ulceration • Inflammatory arthritis *or* polyarticular morning joint stiffness ≥60 min • Palmar telangiectasia • Raynaud's phenomenon • Unexplained digital oedema • Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)	• ANA ≥1:320 titre, diffuse, speckled, homogeneous patterns *or* ANA nucleolar pattern (any titre) *or* ANA centromere pattern (any titre) • RF ≥2 × ULN • Anti-CCP • Anti-dsDNA • Anti-Ro (SS-A) • Anti-La (SS-B) • Anti-ribonucleoprotein • Anti-SmithAnti-topoisomerase (Scl-70) • Anti-tRNA synthetase (e.g., Jo-1, PL-7, PL-12, others are: EJ, OJ, KS, Zo, Ha) • Anti-PM/Scl • Anti-CADM140 (anti-MDA5)	**1. Suggestive radiology patterns by HRCT** • NSIP • OP • NSIP with OP overlap • LIP **2. Histopathology patterns or features by surgical lung biopsy:** • NSIP • OP • NSIP with OP overlap • LIP • Interstitial lymphoid aggregates with germinal centres • Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles) **3. Multi-compartment involvement (in addition to IP):** • Pleural effusion or thickening (not otherwise explained) • Pericardial effusion or thickening (not otherwise explained) • Small airways disease (by PFTs, imaging or pathology) • Pulmonary vasculopathy

Classification criteria of interstitial pneumonia with autoimmune features defined by ERS/ATS

Fallbeispiel einer 50-jährigen Frau

- Seit ca. 1 Jahr zunehmende Belastungsluftnot
- Trockener Husten
- Bilaterale symmetrische Gelenksschmerzen (gross/klein), keine Morgensteifigkeit, keine Schwellungen
- Milde Alopezie

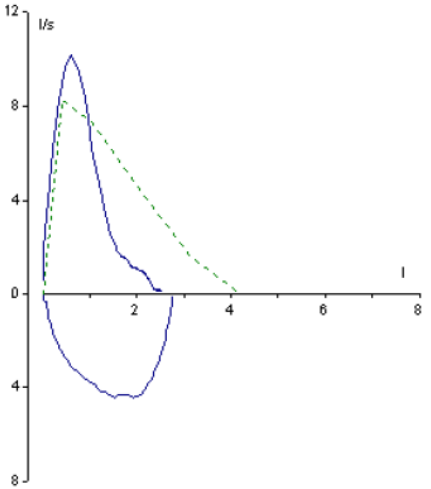
Sonstiges

- Ehem. Rauchgewohnheit 10 PY
- Pleuritis vor 2 Jahren
- Arterielle Hypertonie
- 2 gesunde erw. Kinder

Fallbeispiel einer 50-jährigen Frau

- Bilaterale insp. RGs
- Keine Hautzeichen einer CTD
- Belastungshypoxämie im Gehtest 94 → 88%

- ANA 1:320 (speckled), Anti-dsDNA +



Spirometrie

Parameter	Einheit	Soll	Ist	% Soll
FVCex	l	4.19	2.72	65
FEV1	l	3.27	2.34	72
FEV1/FVCex	%	76	86	113
PEF	l/s	8.27	10.18	123
MEF75	l/s	7.34	9.89	135
MEF50	l/s	4.37	3.17	72
MEF25	l/s	1.62	1.06	66
MEF25-75	l/s	3.38	2.55	76
IVC	l	4.35		
FEV1/IVC	%	76		
ERV	l	1.13		
IC	l	3.43		

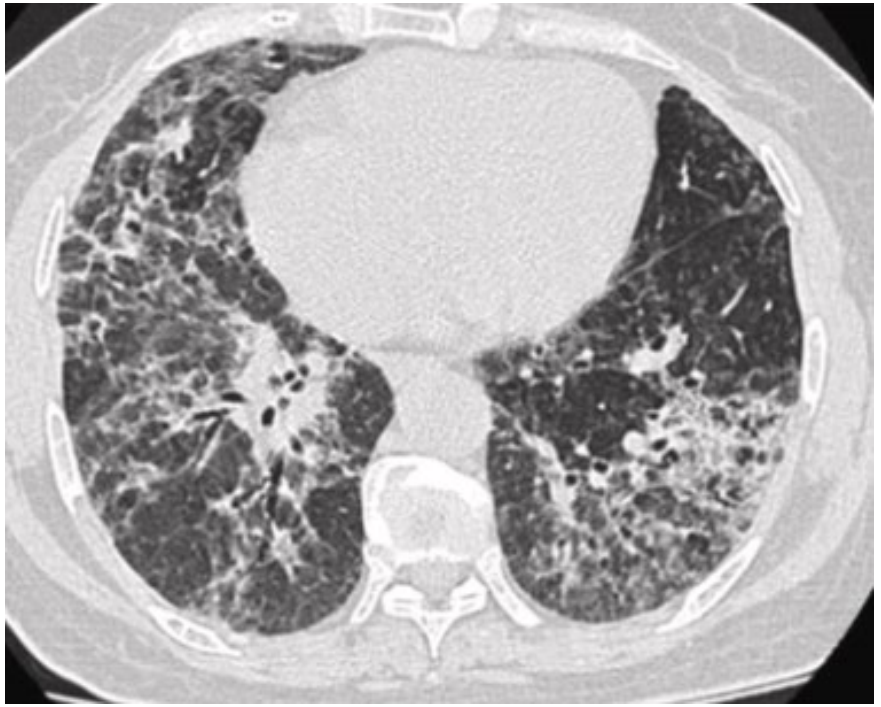


Table 5. Proposed criteria for interstitial pneumonia with autoimmune features (IPAF).

1. Presence of an interstitial pneumonia by HRCT or surgical lung biopsy ✓
2. Exclusion of alternative aetiologies — Keine Medikamente, keine Exposition inhalativ
3. Does not meet criteria for a defined CTD ✓
4. Has at least one feature from at least two of the following domains ✓

A. Clinical domain	B. Serological Domain	C. Morphological domain
• Distal digital fissuring (i.e., "Mechanic hands") • Distal digital tip ulceration • Inflammatory arthritis *or* polyarticular morning joint stiffness ≥60 min ✓ • Palmar telangiectasia • Raynaud's phenomenon • Unexplained digital oedema • Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)	• ANA ≥1:320 titre, diffuse, speckled, homogeneous patterns *or* ANA nucleolar pattern (any titre) *or* ANA centromere pattern (any titre) ✓ • RF ≥2 × ULN • Anti-CCP • Anti-dsDNA ✓ • Anti-Ro (SS-A) • Anti-La (SS-B) • Anti-ribonucleoprotein • Anti-SmithAnti-topoisomerase (Scl-70) • Anti-tRNA synthetase (e.g., Jo-1, PL-7, PL-12, others are: EJ, OJ, KS, Zo, Ha) • Anti-PM/Scl • Anti-CADM140 (anti-MDA5)	**1. Suggestive radiology patterns by HRCT** • NSIP ✓ • OP • NSIP with OP overlap • LIP **2. Histopathology patterns or features by surgical lung biopsy:** • NSIP • OP • NSIP with OP overlap • LIP • Interstitial lymphoid aggregates with germinal centres • Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles) **3. Multi-compartment involvement (in addition to IP):** • Pleural effusion or thickening (not otherwise explained) • Pericardial effusion or thickening (not otherwise explained) • Small airways disease (by PFTs, imaging or pathology) • Pulmonary vasculopathy

Classification criteria of interstitial pneumonia with autoimmune features defined by ERS/ATS

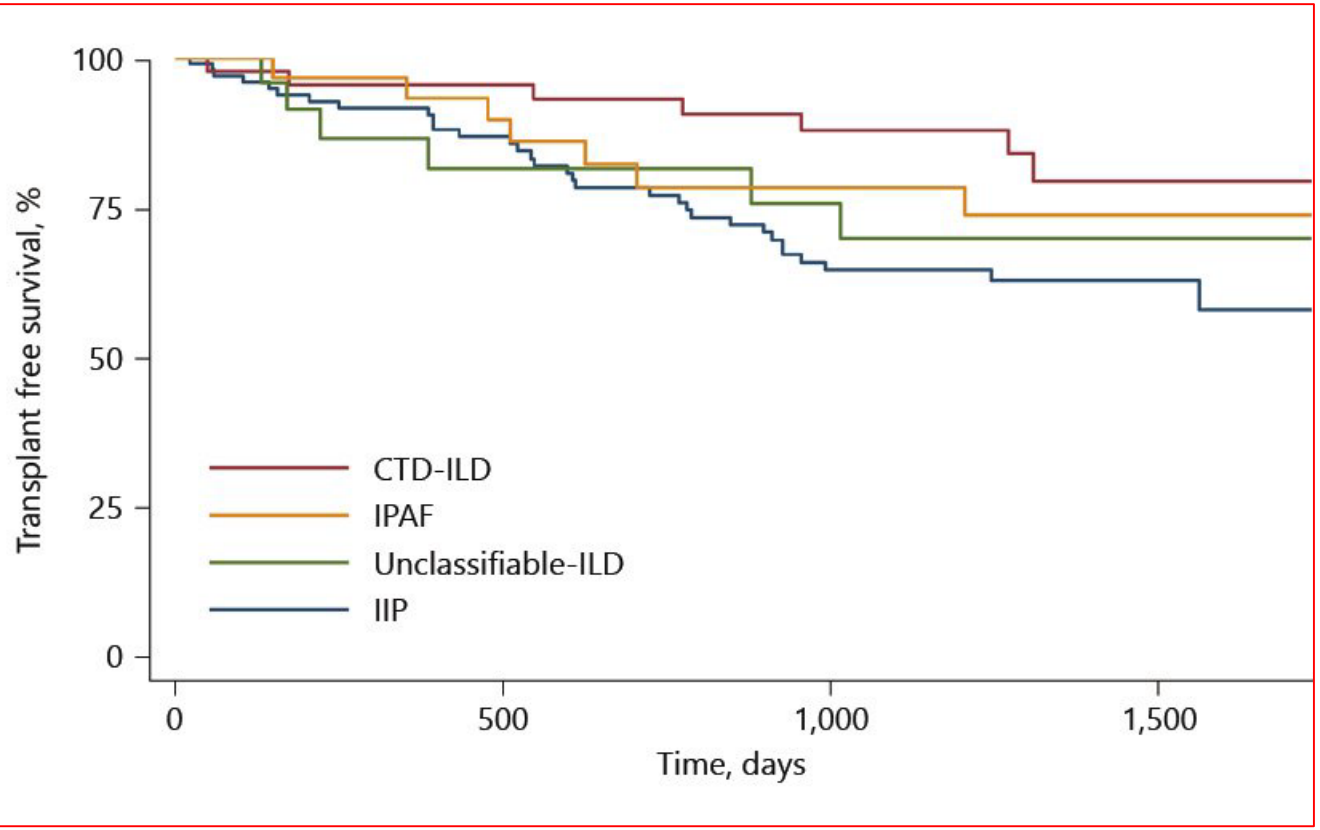
Fallbeispiel einer 50-jährigen Frau

- Initial antibiotische Behandlung bei Vd. a. Pneumonie
- Erneute Überweisung bei zunehmender Luftnot
- Neu Nachweis einer milden Hypoxämie SpO2 92%

Therapie und Verlauf

- 0.75mg/Kg/Tag Prednison initial, im Verlauf weniger
- Nach 3 Monaten Spirometrie verbessert, keine Hypoxämie mehr
- Evaluation steroidsparende Therapie / Antifibrotika

Survival of an Australian Interstitial Pneumonia with Autoimmune Features Cohort



	IPAF (n = 36)	IIP (n = 113)	CTD-ILD (n = 49)	Unclassifiable (n = 30)	Total (n = 228)
Age, years	66.6 (11.9)	72.7 (7.9)*	63.7 (11.8)	71.7 (10.2)	69.7 (10.5)
Male, n (%)	12 (33.3)	84 (74.3)*	17 (34.7)	14 (46.7)	127 (55.7)
Female, n (%)	24 (66.7)	29 (25.7)*	32 (65.3)	16 (55.3)	101 (44.3)
Smoking ever, n (%)	16 (44.4)	60 (53.1)	25 (51.0)	15 (50)	116 (50.9)
Caucasian, n (%)	33 (91.7)	94 (83.2)	36 (73.5)	23 (76.7)	186 (81.6)
Family history ILD, n (%)	3 (8.6)	4 (3.6)	1 (2.0)	2 (6.7)	10 (4.4)
Family history CTD, n (%)	0 (0)	3 (2.7)	4 (8.2)	1 (3.3)	8 (3.5)
Disease duration, years	3.9 (4.7)	2.6 (2.4)	5.3 (6.8)	2.5 (2.7)	3.4 (4.3)
PH, n (%)	6 (16.7)	16 (14.2)	6 (12.2)	3 (10.0)	31 (13.6)
Pulmonary function					
FVC, L	2.2 (0.8)	2.6 (0.9)	2.3 (0.8)	2.4 (0.9)	2.5 (0. 9)
FVC, % predicted	69.8 (19.0)	75.6 (17.4)	73.5 (18.1)	78.9 (21.6)	75.1 (18.7)
DLCO, mL/min/mm Hg	13.0 (4.4)	13.4 (4.6)	13.4 (4.7)	12.5 (3.9)	13.6 (4.7)
DLCO, % predicted	60.0 (18.7)	57.7 (17.4)	60.0 (19.2)	58.4 (18.1)	59.4 (18.3)

Shown as mean (SD) unless stated. IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; CTD-ILD, connective tissue disease-associated ILD; IPAF, interstitial pneumonia with autoimmune features; PH, pulmonary hypertension; FVC, forced vital capacity; DLCO, diffusing capacity for carbon monoxide. * $p < 0.05$ compared with IPAF patients.

Jee A et al. Respiration 2021; 100:853-864. doi: 10.1159/000515396|

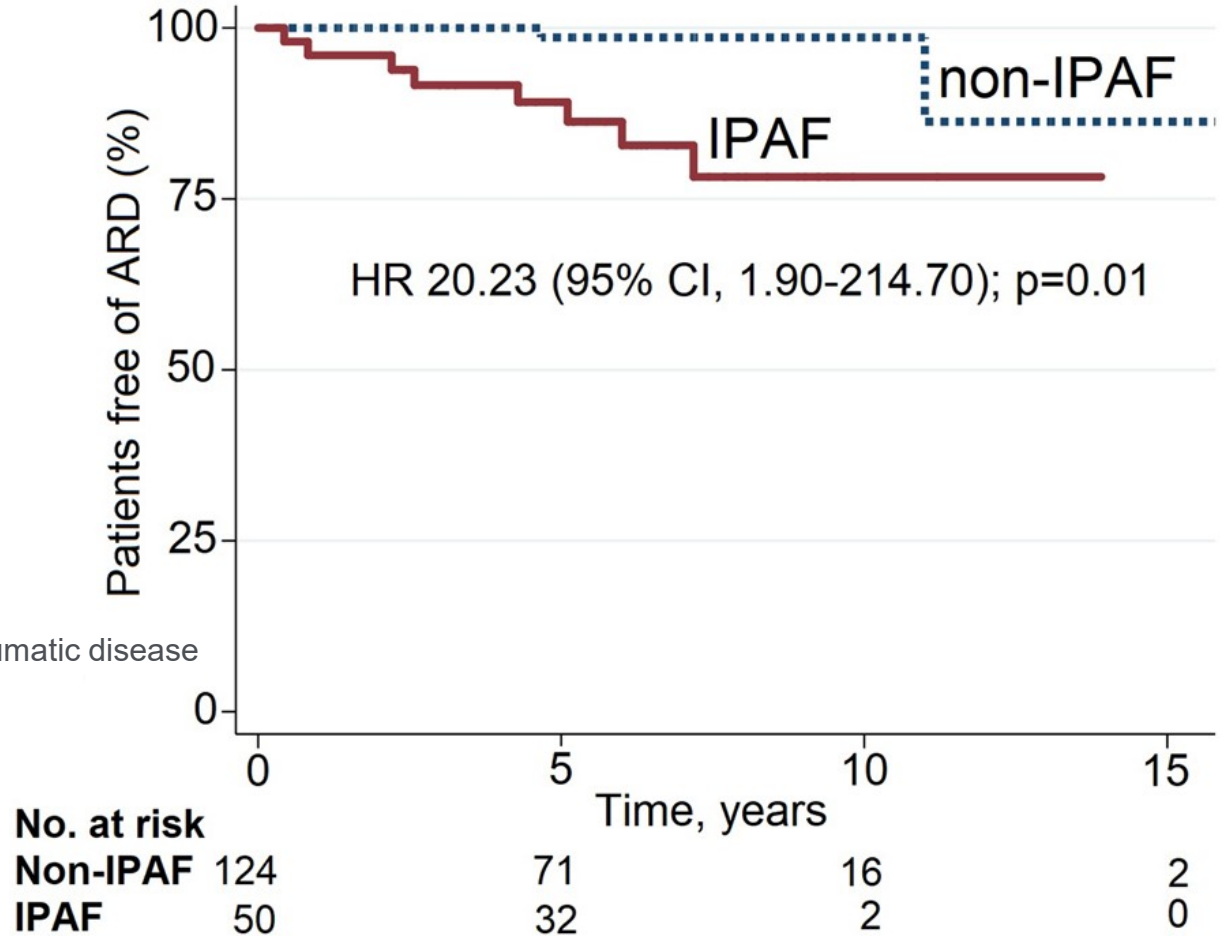
Survival of an Australian Interstitial Pneumonia with Autoimmune Features Cohort

	IPAF (n = 36)	IIP (n = 113)	CTD-ILD (n = 49)	Unclassifiable (n = 30)	Total (n = 228)
Treatment	30 (83.3)	72 (63.7)	42 (85.7)	18 (60)	162 (71.1)
IS	29 (80.6)	23 (20.4)	41 (83.7)	17 (56.7)	110 (48.3)
AF	1 (2.8)	53 (46.9)	4 (8.2)	1 (3.3)	59 (25.9)
Oxygen	12 (33.3)	25 (22.2)	10 (20.4)	6 (20)	53 (23.3)
Outcomes					
Death, n (%)	7 (19.4)	31 (27.4)	7 (14.3)	6 (20)	51 (22.4)
TFS, median months (range)	38.4 (1.0–61.4)	29.9 (0.1–59.1)	40.7 (1.3–60.5)	26.6 (1.1–56.8)	36.4 (0.1–61.4)
PFS, median months (range)	18.7 (1.0–57.3)	13.8 (0.1–58.6)	26.5 (1.3–60.5)	8.4 (1.1–45.8)	16.2 (0.1–60.5)

TFS, transplant-free survival; PFS, progression-free survival; IPAF, interstitial pneumonia with autoimmune features; ILD, interstitial lung disease; CTD, connective tissue disease; IIP, idiopathic interstitial pneumonia; IS, immunosuppression; AF, antifibrotic.

Jee A et al. Respiration 2021; 100:853-864. doi: 10.1159/000515396|

Wie ist das Risiko eine rheumatologische Erkrankung zu entwickeln bei Erstdiagnose einer IPAF?



ARD: systemic autoimmune rheumatic disease

Patienten mit IPAF haben ein 14fach höheres Risiko eine rheumatologische Erkrankung zu entwickeln als sonstige Patienten mit interstitieller Lungenerkrankung

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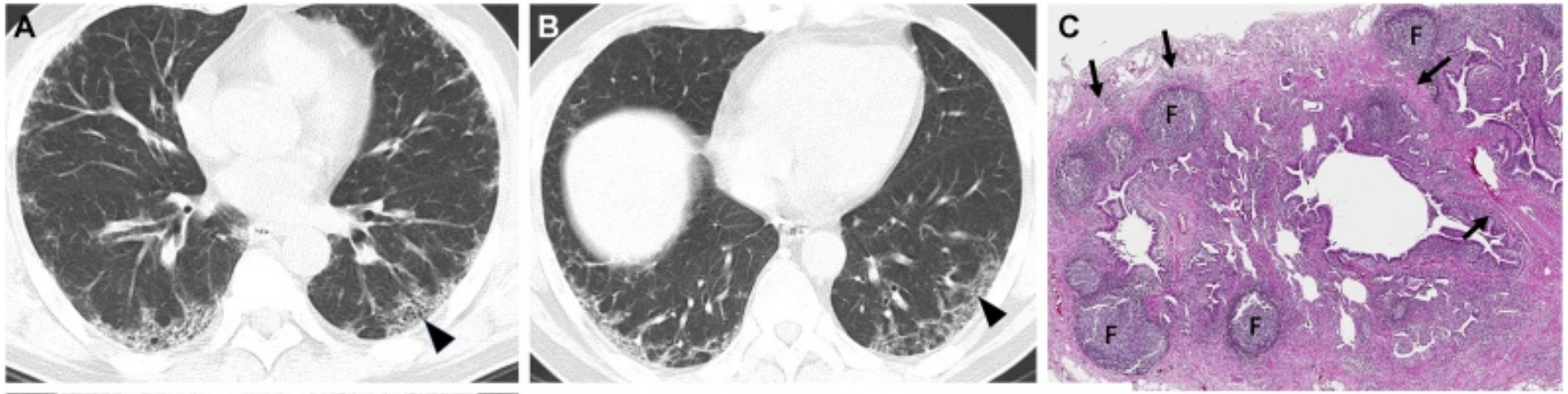
Rheumatology (Oxford), Volume 59, Issue 6, June 2020, Pages 1233–1240

IPAF: Mögliche zeitliche Entwicklung

Vor 4 Jahren



Aktuell

Radiologisch: wie idiopath. Lungenfibrose
Histologisch: lymphoide follikel (wie CTD)

Eur J Radiol Open. 2021; 8: 100311

IPAF in «real life»

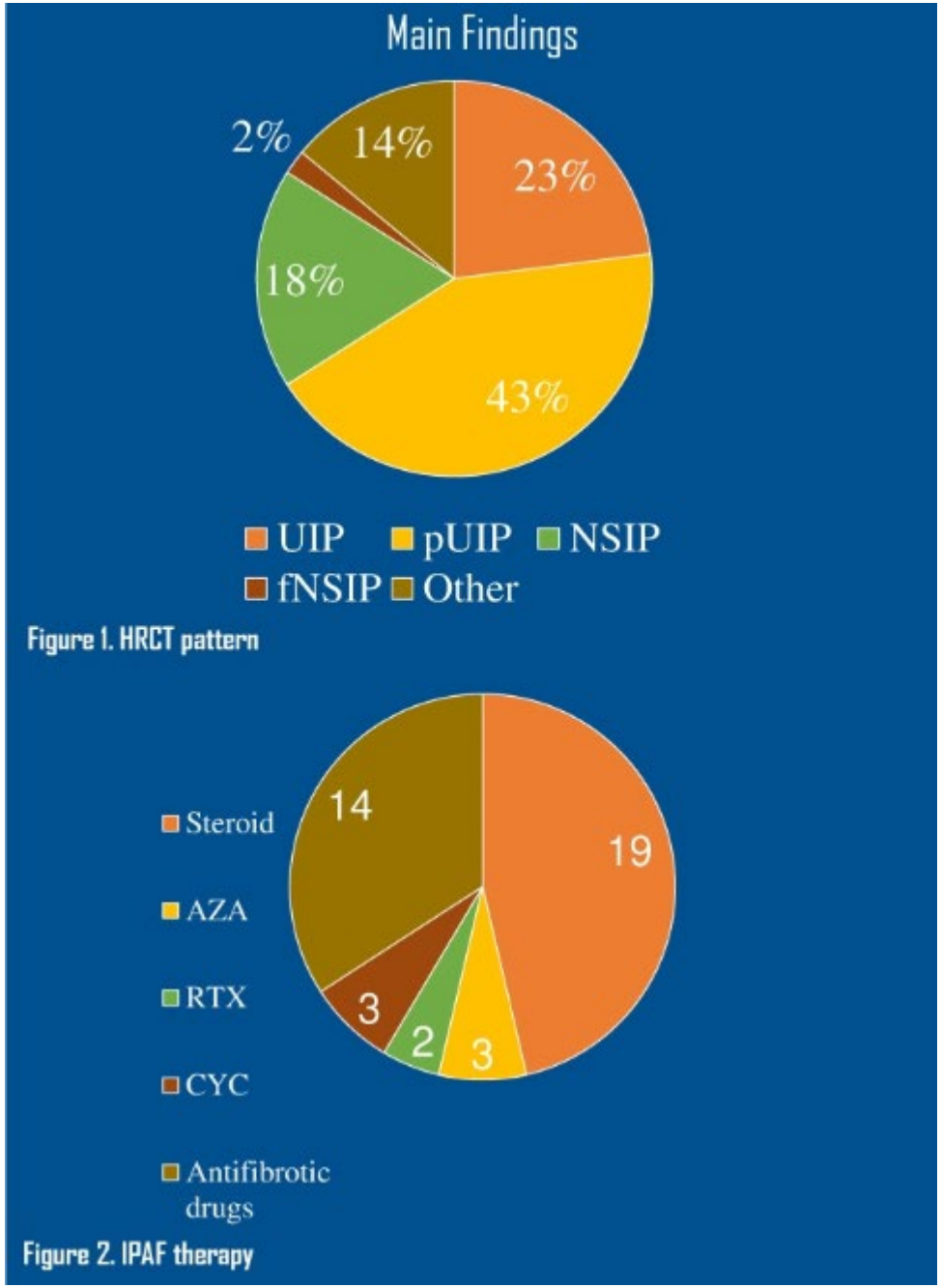


Figure 1. HRCT pattern

Figure 2. IPAF therapy

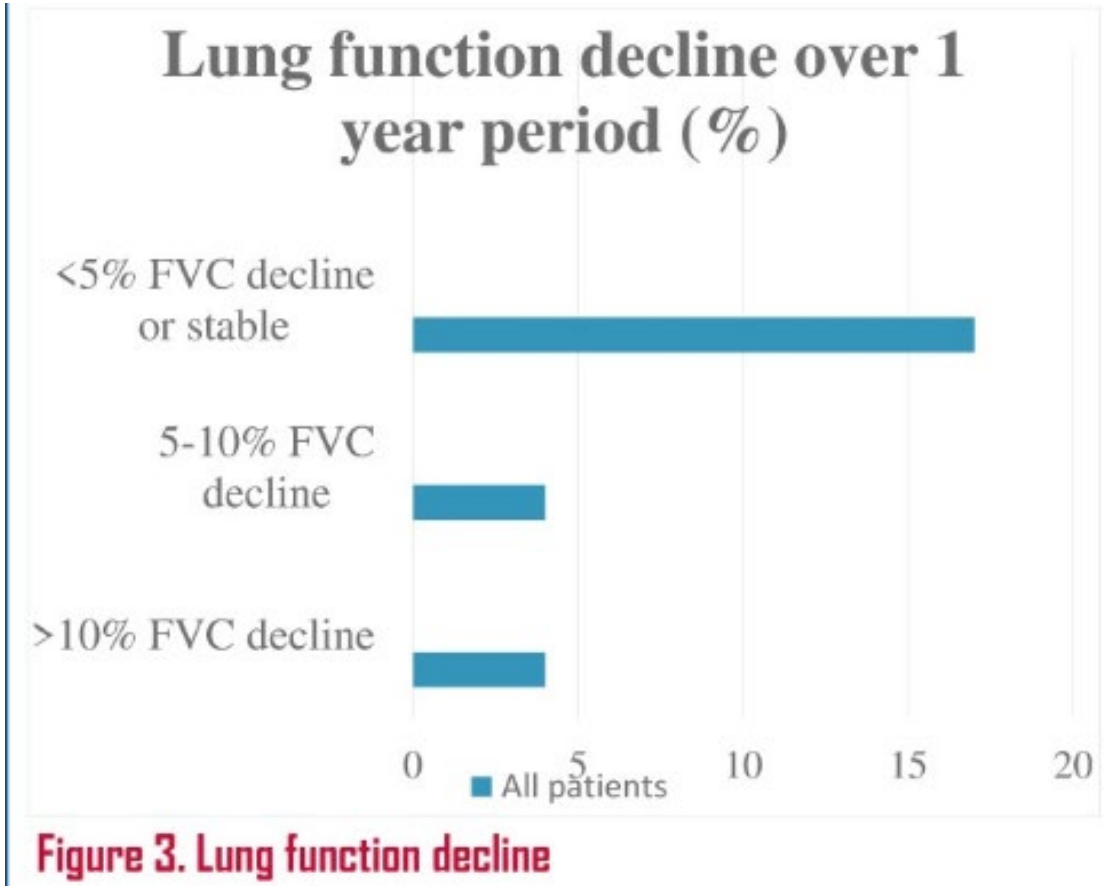
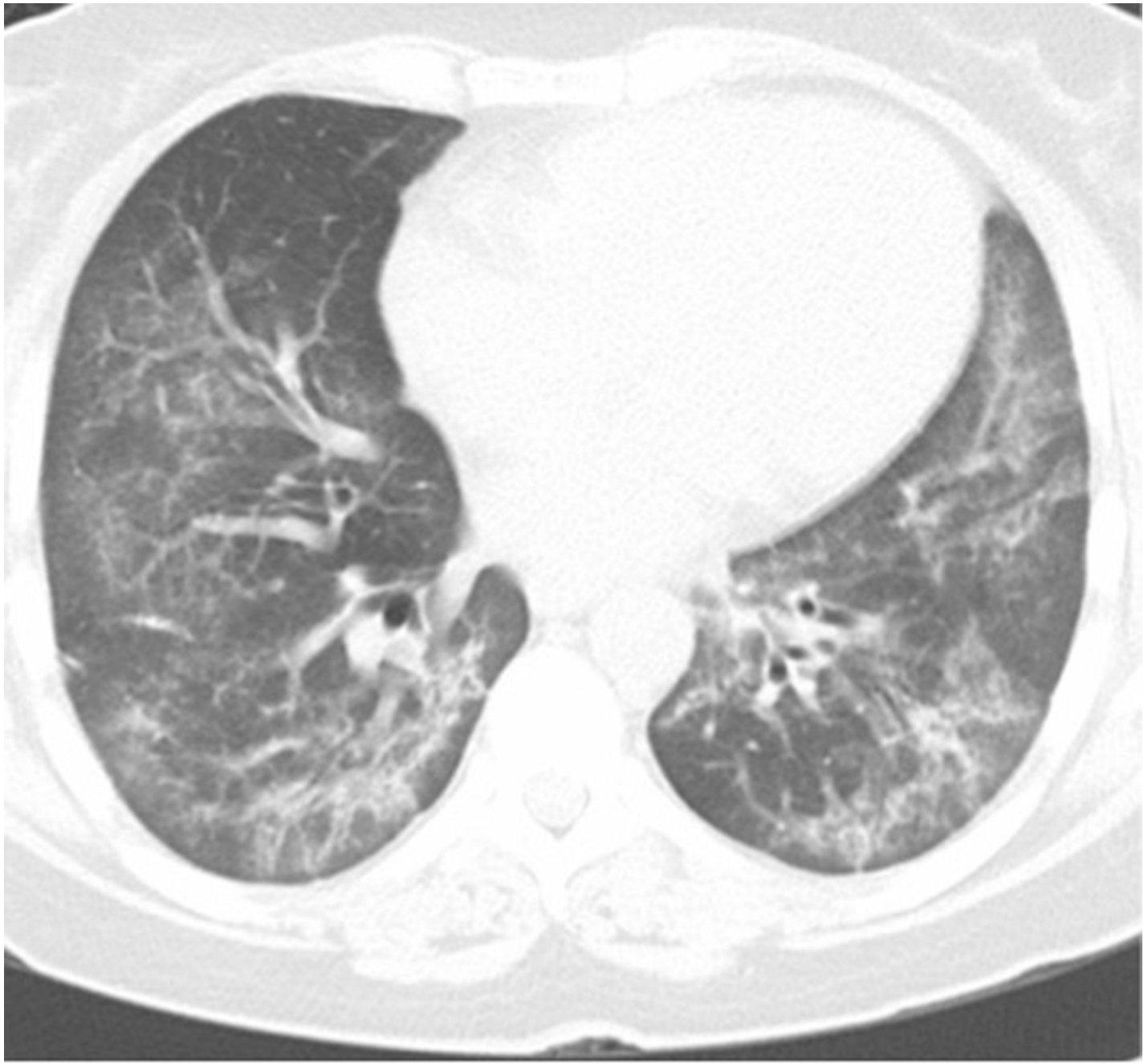
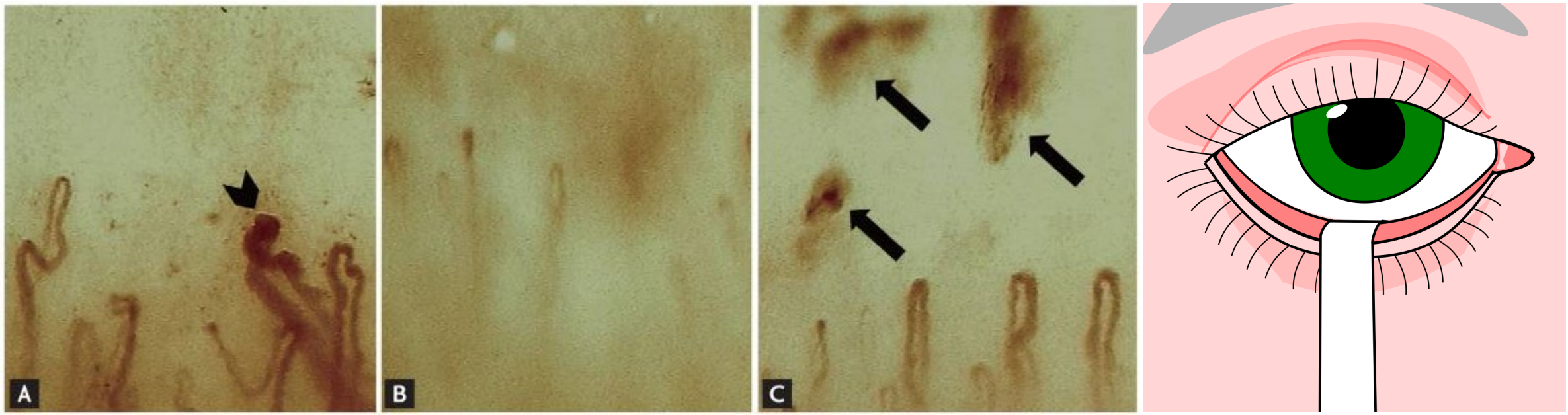


Figure 3. Lung function decline

Nagy et al., ERS 2021; Poster ID 2376

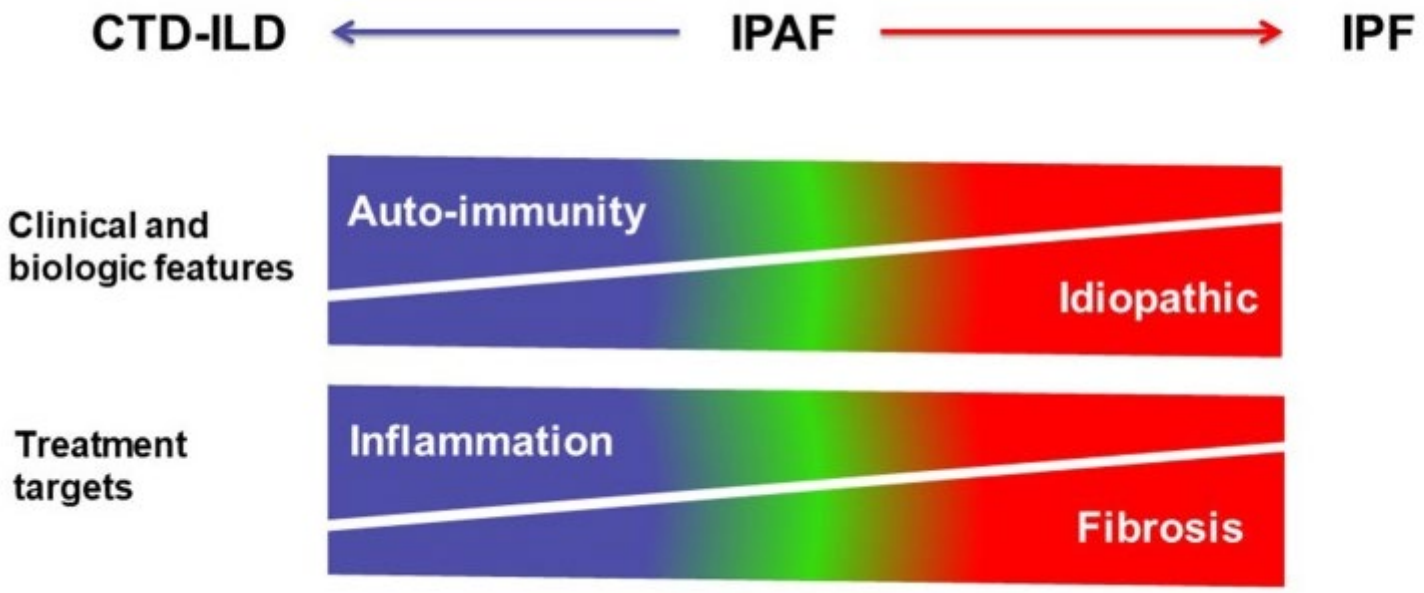


Mögliche Zusatzuntersuchungen



Therapien

1. Anti-inflammatorisch (keine randomisiert kontrollierten Studien)
2. Antifibrotisch (Progressive Fibrotic ILD: PF-ILD)
3. Lunegntransplantation



Fernandes, Ligia et al. *Frontiers in medicine* vol. 6 209. 27 Sep. 2019, doi:10.3389/fmed.2019.00209

Therapeutics and Clinical Risk Management

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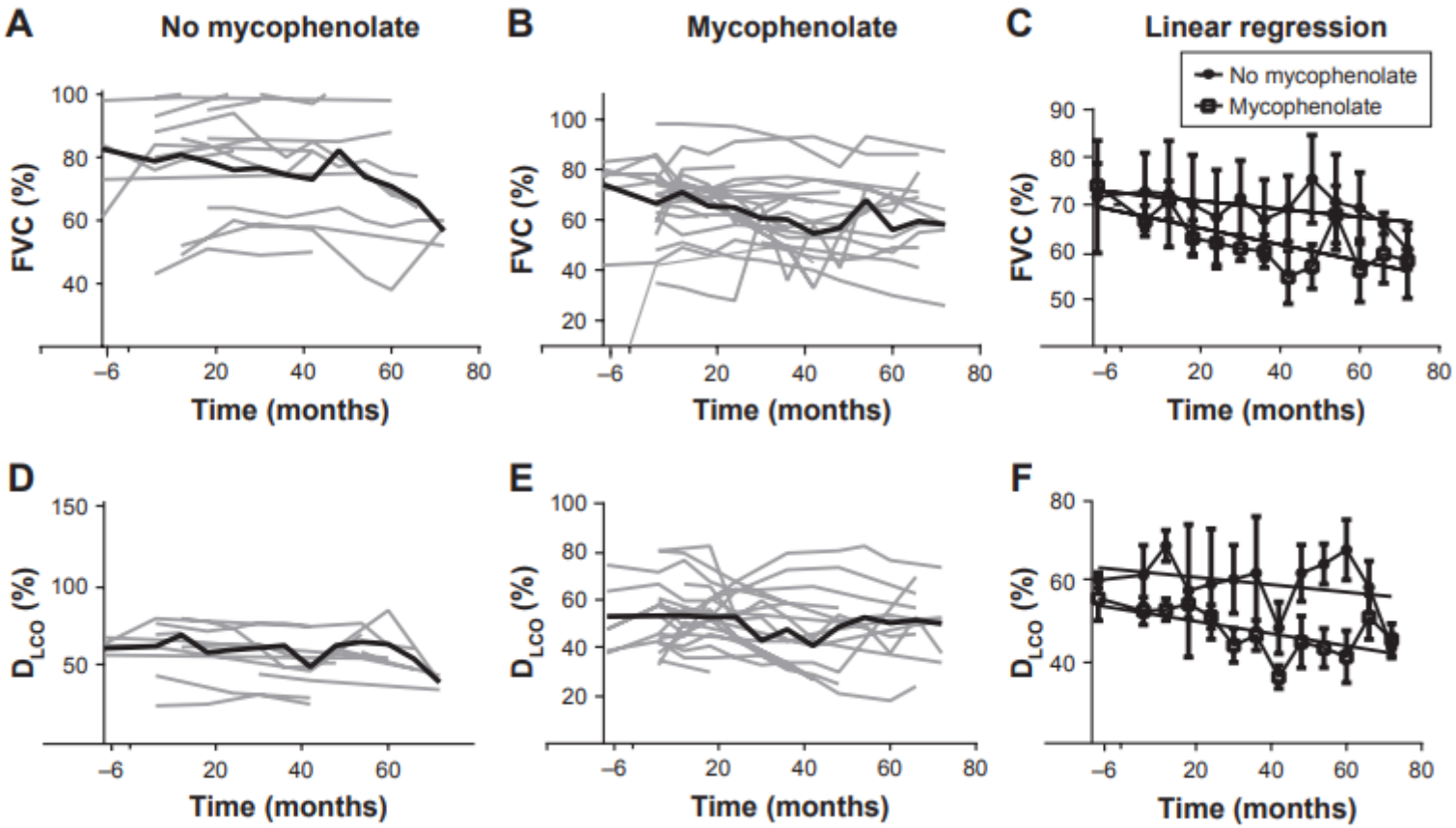
ORIGINAL RESEARCH

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

Retrospektiv
28 IPAF mit MMF
24 IPAF ohne MMF

Fazit:
Möglicherweise progressionsverzögernd



Zusammenfassung

- Möglichst genaue Diagnose anstreben vor Behandlungsbeginn
- Standardisierte pneumologische Abklärung, rheumatologische Untersuchung, Autoimmunserologie
- Multidisziplinäre Besprechung für therapeutisches Management

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Vielen Dank für Ihre Aufmerksamkeit