Πνευμονική ίνωση
γενική επισκόπηση-κλινικοί τύποι

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Disclosure

- …… **no** conflict of interest

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Editorial: Pulmonary fibrosis: One manifestation, various diseases

>200 different types

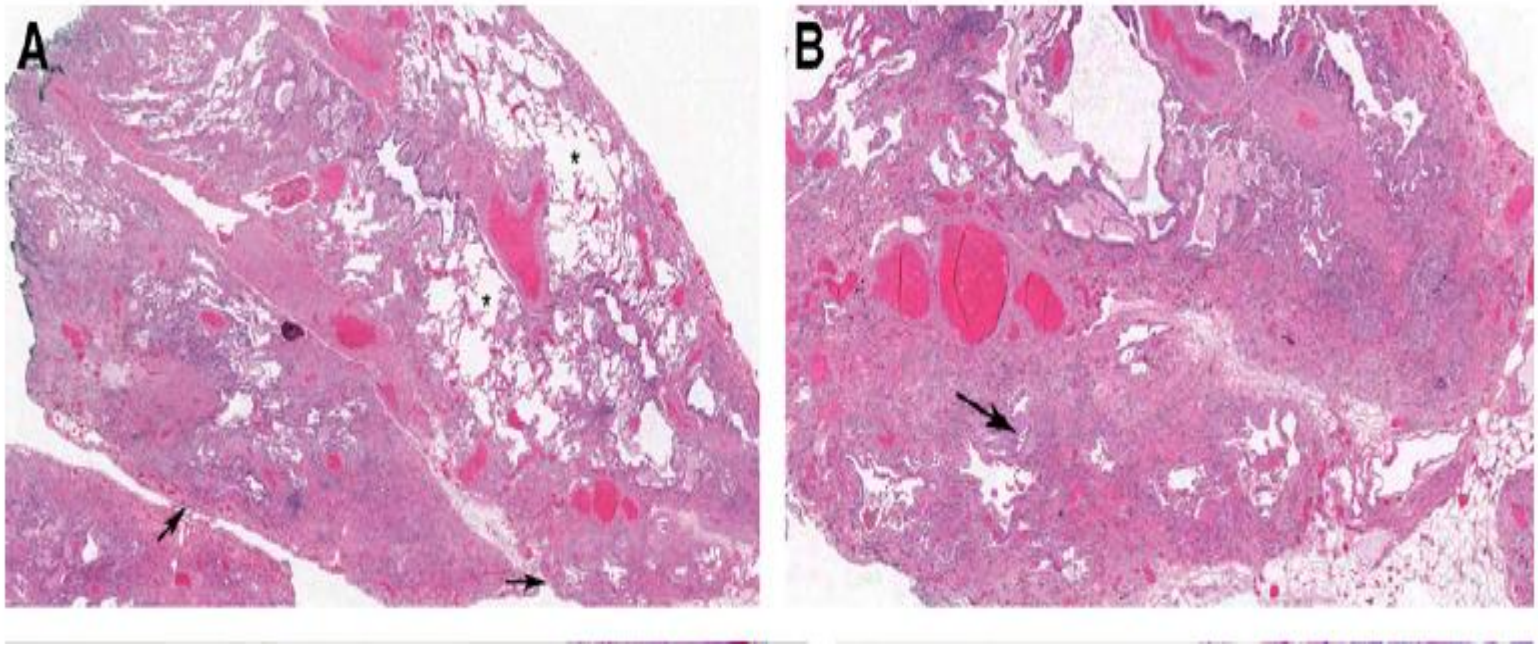
I -PF

- Idiopathic pulmonary fibrosis (I PF)
- chronic
- **fibrosing** interstitial pneumonia of unknown cause that is associated

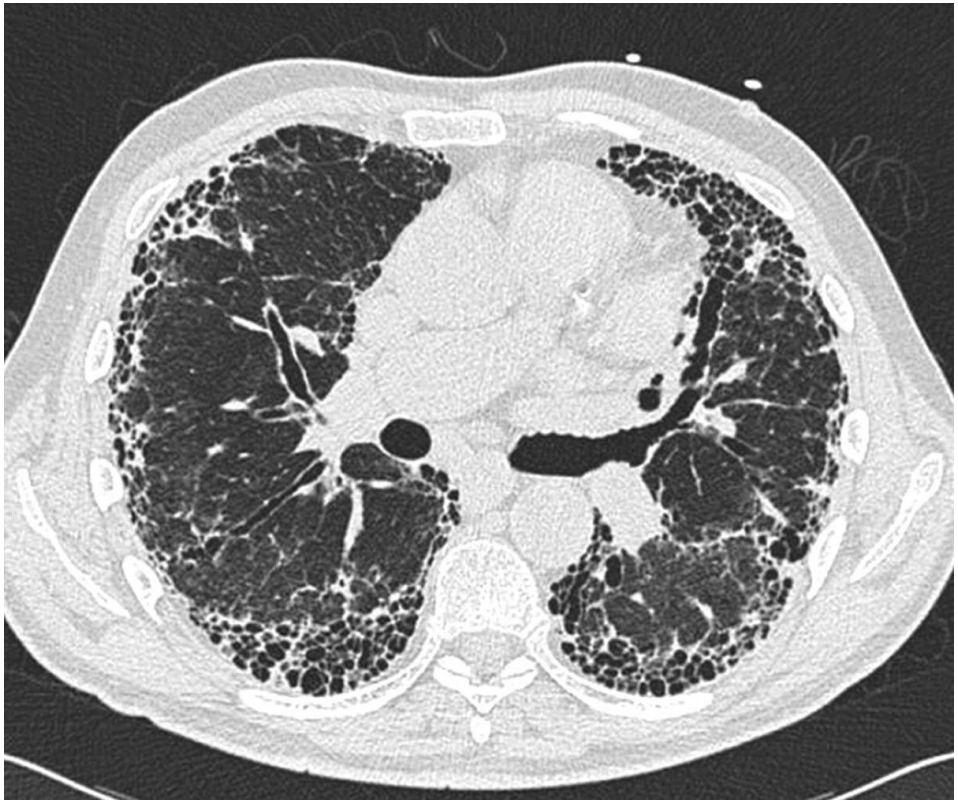
- radiological and histologic features of usual interstitial pneumonia (**UIP**)

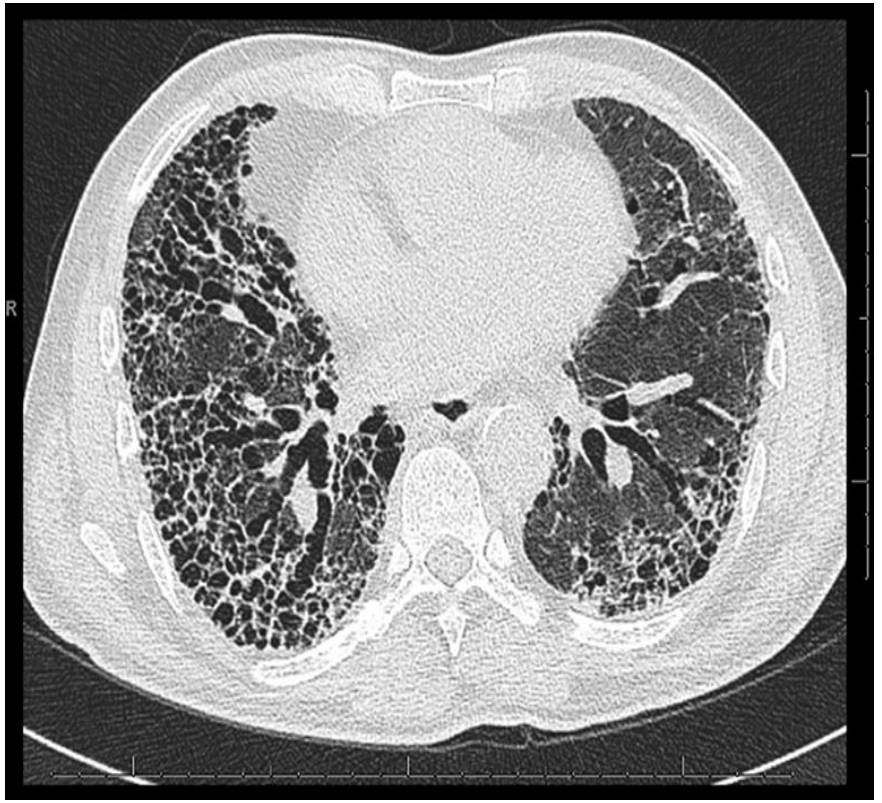
- progressive worsening of dyspnea and lung function
- poor prognosis

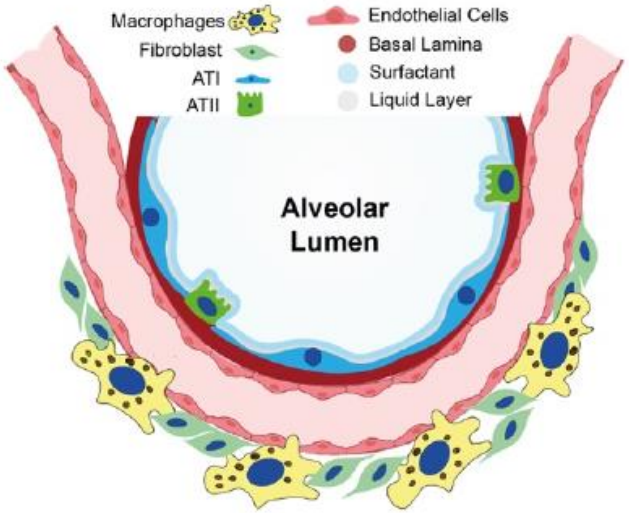
Histo-UIP



HRCT-UIP pattern

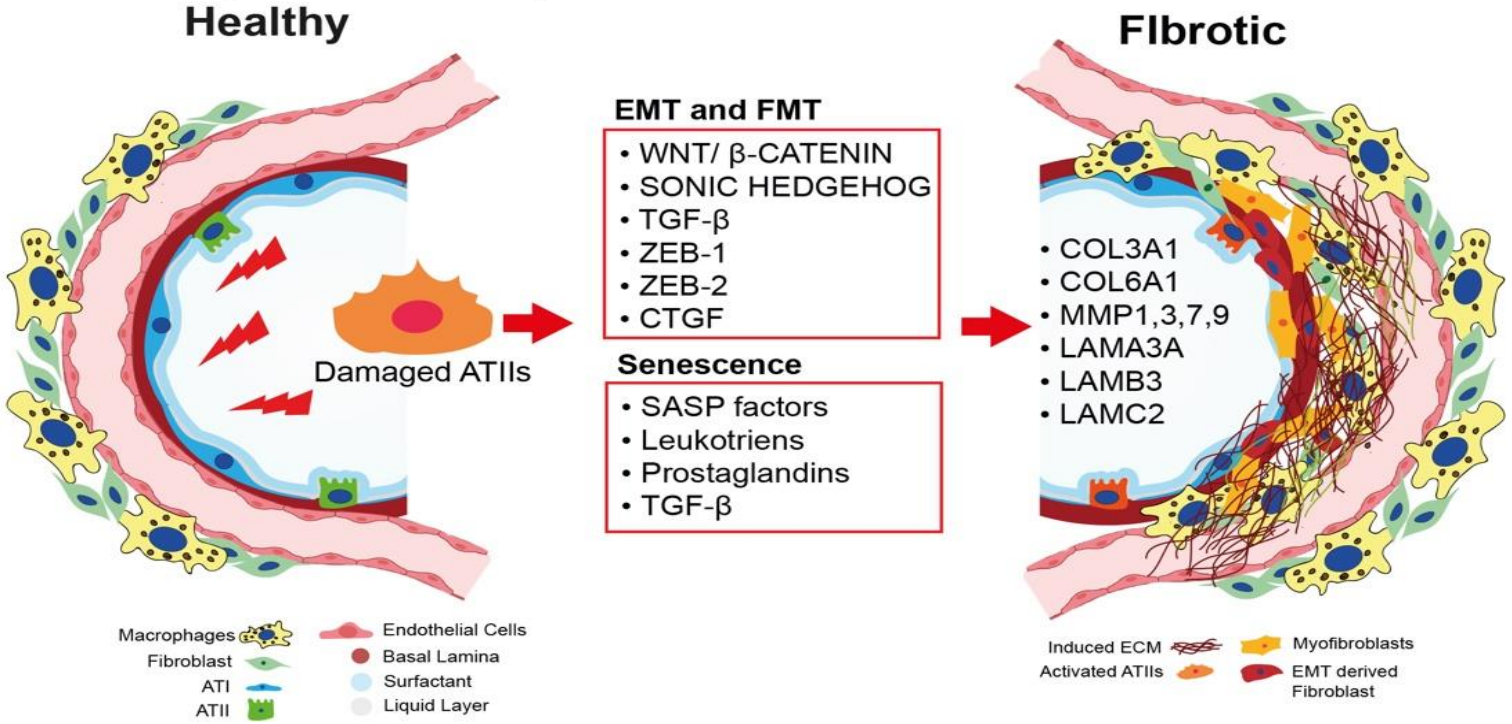






Pathogenesis-PF

Figure 1. Cell composition of the healthy alveolus.



cells, 2022

Incidence and prevalence

TABLE 1 Population-based incidence and prevalence rates for idiopathic pulmonary fibrosis, by region

	Cases per 100 000
Incidence	
Europe	1–9
North America	7–19
Asia	3–13
Australia	10–11
Prevalence	
Europe	10–40
North America	14–59
Asia	5–40
Australia	32–35

Few published studies report incidence and prevalence in South America, and none in Africa. Information from [14, 28–43].

doubling in prevalence between 2000 and 2012 [

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ILD

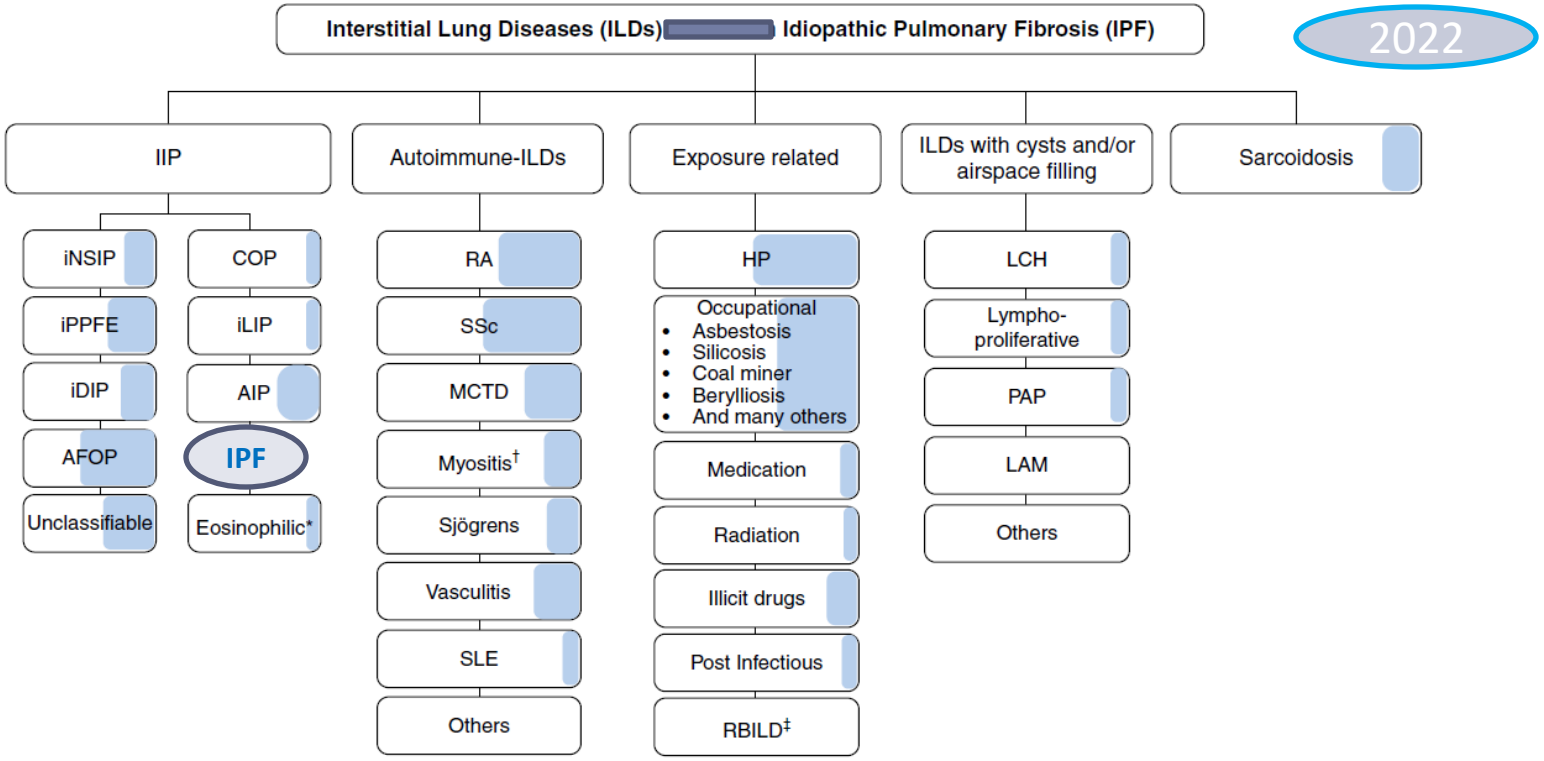
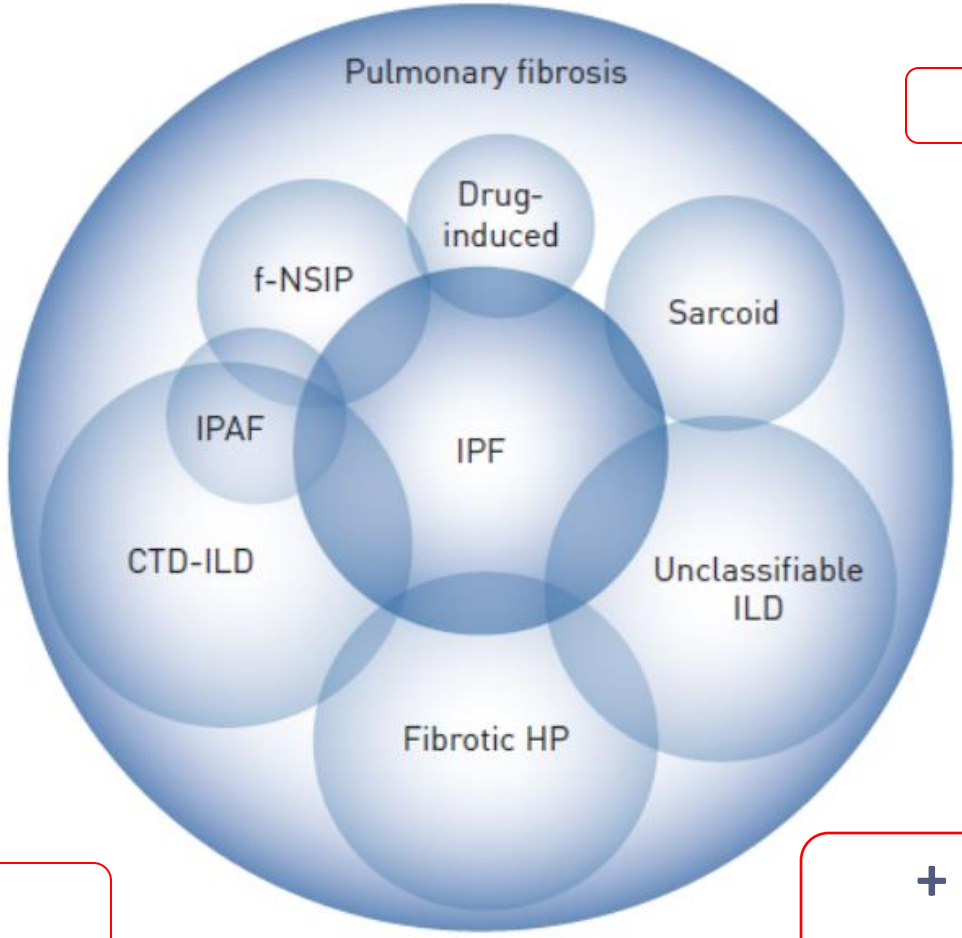


Figure 12. Interstitial lung diseases (ILDs) manifesting progressive pulmonary fibrosis (PPF), developed using consensus by discussion. The

Pulmonary fibrosis > 200 entities



+ Familial PF

+ Radiation

+ Post COVID-19

+ post ARDS syndrom

Histological classification of interstitial pneumonias in CTD

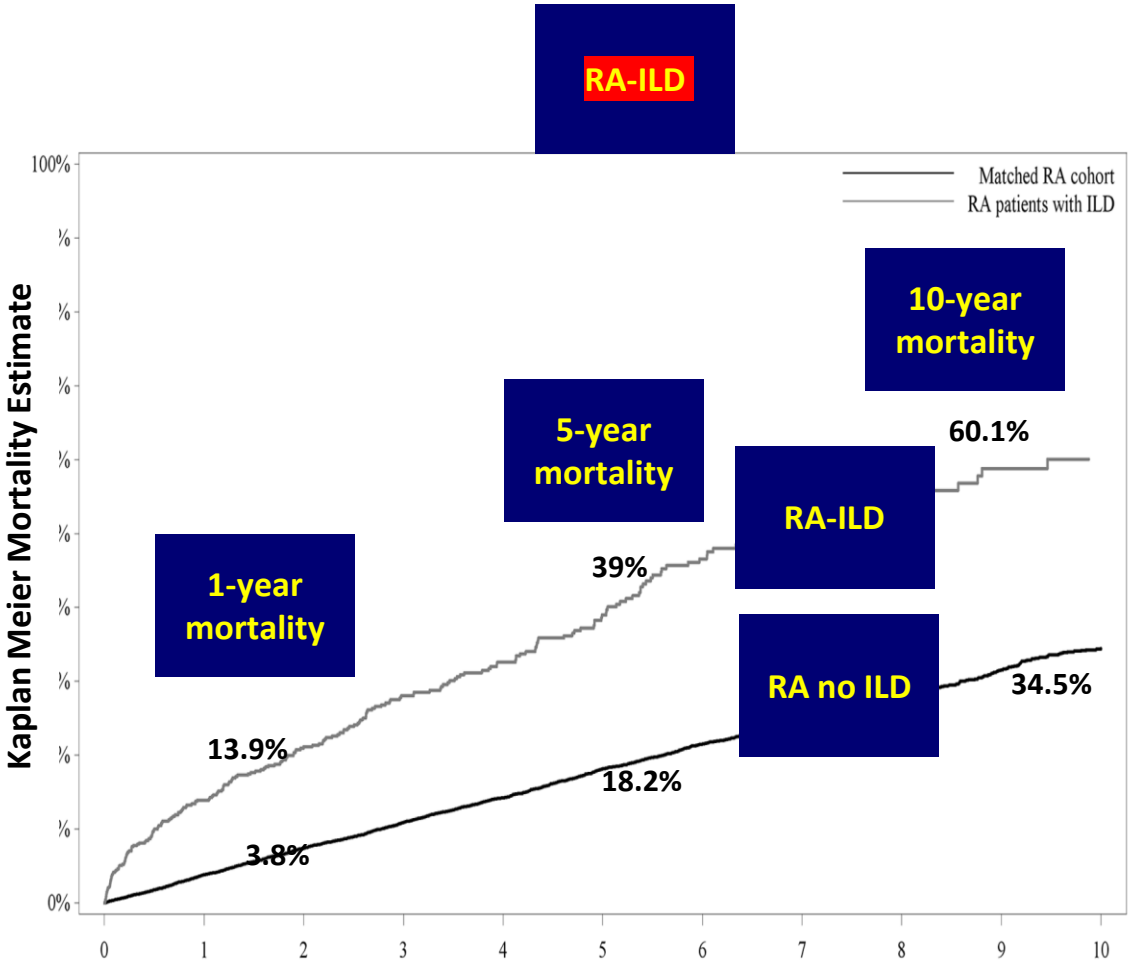
The relative prevalence of histological patterns in IIP in CTDs

Lung pattern	IIP	Rheumatoid arthritis	Systemic sclerosis	SLE	Polymyositis–dermatomyositis	Sjögren syndrome
Usual interstitial pneumonia	+++	++	+	+	+	±
Nonspecific interstitial pneumonia	++	++	+++	++	++	++
Desquamative interstitial pneumonia and/or RB-ILD	+	±	±	±	±	±
Organizing pneumonia	++	+	±	±	++	±
Lymphocytic interstitial pneumonia	±	±	±	±	±	++
Pleuroparenchymal fibroelastosis	±	?	?	?	?	?
Diffuse alveolar damage	+	+	±	+	+	±

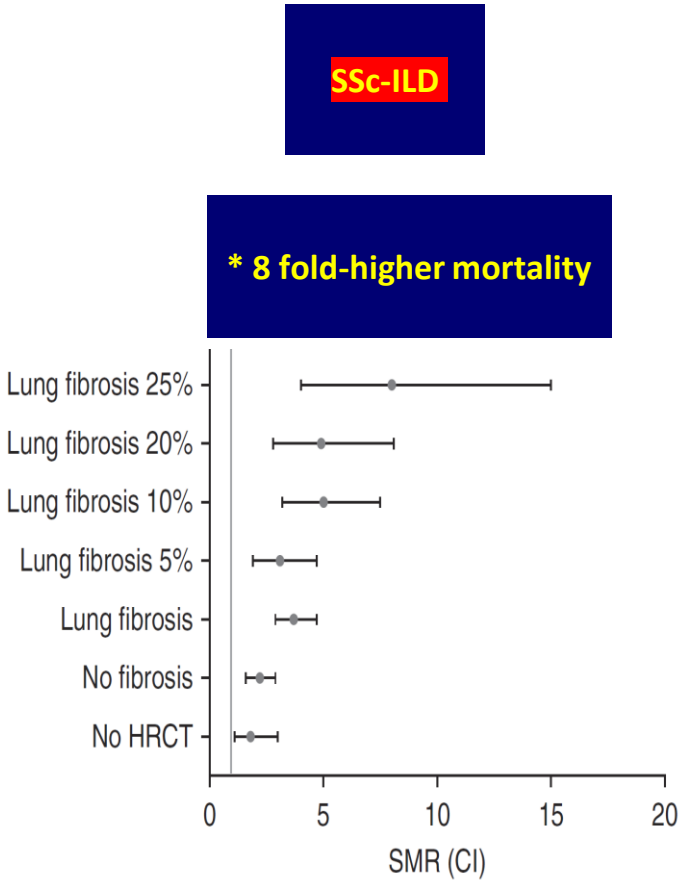
Abbreviations: ?, prevalence unknown; ±, rare; +, infrequent; ++, frequent, but not clearly in the majority of cases; +++, common, clearly in the majority of cases; CTD, connective tissue disease; IIP, idiopathic interstitial pneumonia; RB-ILD, respiratory bronchiolitis-associated interstitial lung disease; SLE, systemic lupus erythematosus.

Wells AU, Denton CP. Interstitial lung disease in connective tissue disease - mechanisms and management. **Nat Rev Rheumatol**. 2014

Is ILD essential in autoimmune diseases?



Hyldgaard et al. Ann Rheum Dis 2017



Hoffmann Vold et al. AJRCCM 2019

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ORIGINAL RESEARCH
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Prognostic Predictive Characteristics in Patients With Fibrosing Interstitial Lung Disease: A Retrospective Cohort Study

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[1]Clinical Center for Interstitial Lung Diseases, Beijing Institute of Respiratory Medicine, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China, [2]Department of Occupational Medicine and Toxicology, Beijing Chaoyang Hospital, Capital Medical

TABLE 1 | Demographics and clinical characteristics of the cohort.

	All	PF-ILD group	Non-PF-ILD group	*p*-value
Number	579	227 (39.21)	352 (60.79)	
Male, *n* (%)	296 (51.12)	121 (53.30)	175 (49.72)	0.399
Age, years (IQR)	62 (55–68)	64 (57–70)	62 (54–68)	0.001
BMI, kg/m^2 (SD)	25.90 (3.31)	25.92 (3.50)	25.89 (3.19)	0.907
Ever smoker, *n* (%)	233 (40.24)	98 (43.17)	135 (38.40)	0.248
Diagnosis, *n* (%)				<0.001
IPF	145 (25.04)	77 (33.92)	68 (19.32)	
CTD-ILD	297 (51.30)	109 (48.02)	188 (53.41)	
FHP	56 (9.67)	16 (7.05)	40 (11.36)	
uIIP	81 (13.99)	25 (11.01)	56 (15.91)	

18-32%

PF Wijsenbeek et al., 2019

TABLE 2 Risk factors for idiopathic pulmonary fibrosis (IPF)

Risk factor	Description	References
Demographic		
Age	Incidence and prevalence of IPF increase with age, and most patients diagnosed with IPF are over 60 years of age.	[4, 15, 30]
Male sex	Men represent ~70% of all patients with IPF in registries and clinical trials. Occupational exposures may account for some of these differences. However, significant gender bias in the diagnosis of IPF has been reported.	[14, 15, 176–178]
Genetic		
Host defence	*MUC5B* promoter polymorphism rs35705950: presence of the minor allele increases disease risk 3-fold in heterozygotes and 7-fold in homozygotes; the gain-of-function variant leads to greater expression of mucin 5B protein and leads to impaired mucociliary clearance, but the link to disease pathogenesis is incompletely understood. *TOLLIP*: three variants in Toll-interacting protein (TOLLIP) have been shown to be associated with IPF susceptibility among individuals of European ancestry; individuals with these variants have decreased expression of TOLLIP.	[51, 54–56]
Telomere maintenance	Variants in telomere maintenance genes (*TERT*, *TERC*, *PARN*, *RTEL1*, *DKC* and *TINF21*) are associated with both familial and sporadic pulmonary fibrosis. These variants lead to telomere shortening and accelerated cellular senescence, which is thought to play a role in abnormal epithelial repair.	[51, 179–181]
Surfactant processing	Rare variants in genes associated with surfactant processing (*SFTPC*, *SFTPA2* and *ABCA3*) can be found in families with pulmonary fibrosis.	[182–184]
Epithelial integrity	A large genome-wide association study of non-Hispanic White subjects identified associations with variants in genes involved in cell adhesion: *DSP* and *DPP9*. These variants are associated with expression of desmoplakin and dipeptidyl peptidase 9, respectively, and may lead to loss of epithelial integrity.	
Fibrotic signalling	*AKAP13:* polymorphism rs62025270 near A-kinase anchoring protein 13 (AKAP13) has been linked with IPF susceptibility. AKAP13 is a Rho guanine nucleotide exchange factor involved in profibrotic signalling pathways.	[57]
Environmental		
Cigarette smoking	Multiple studies have implicated cigarette smoking as a risk factor for IPF.	[62]
Occupational exposures	Work-related exposures to inhaled dust, asbestos, metal and/or wood dust have been linked with IPF risk.	[61, 185]
Air pollution	Exposure to increased levels of air pollution has been linked with increased incidence of IPF and mortality.	[186, 187]

Diagnosis

- Clinical
- Imaging
- Histology

- **Medical history**

  family medical history

  prior medication use

  exposures at home, work and other places

  close attention to signs of CTD

- **antinuclear antibodies**

  C-reactive protein

  erythrocyte sedimentation rate rheumatoid arthritis-associated autoantibodies

  autoantibodies associated with myositis, scleroderma, Sjögren's syndrome and vasculitis

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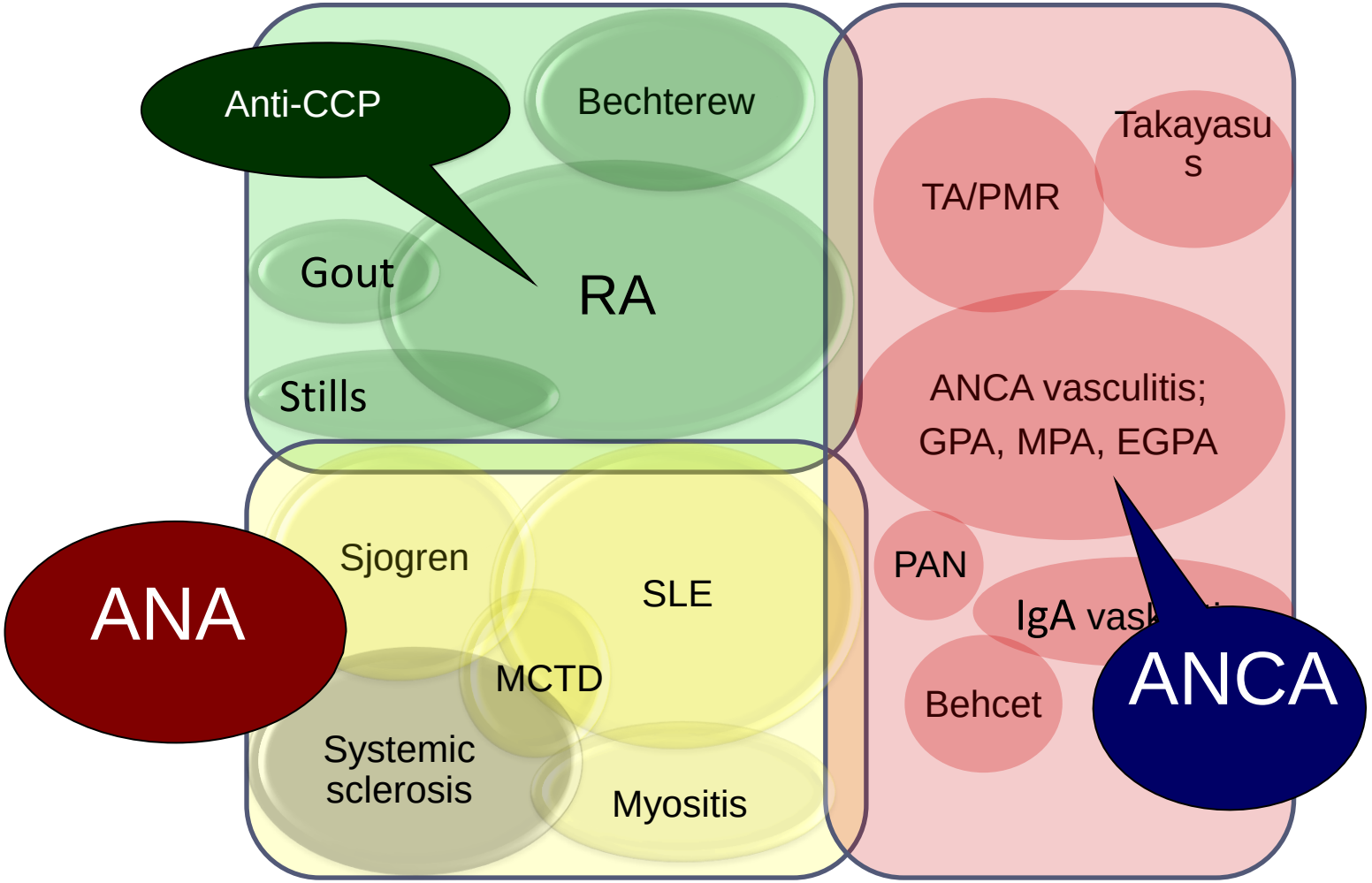
Antibodies


Anti-CCP
Bechterew
Takayasu
s
TA/PMR
Gout
RA
Stills
ANCA vasculitis;
GPA, MPA, EGPA
ANA
Sjogren
SLE
PAN
IgA vas
MCTD
Behcet
ANCA
Systemic
sclerosis
Myositis

Imaging

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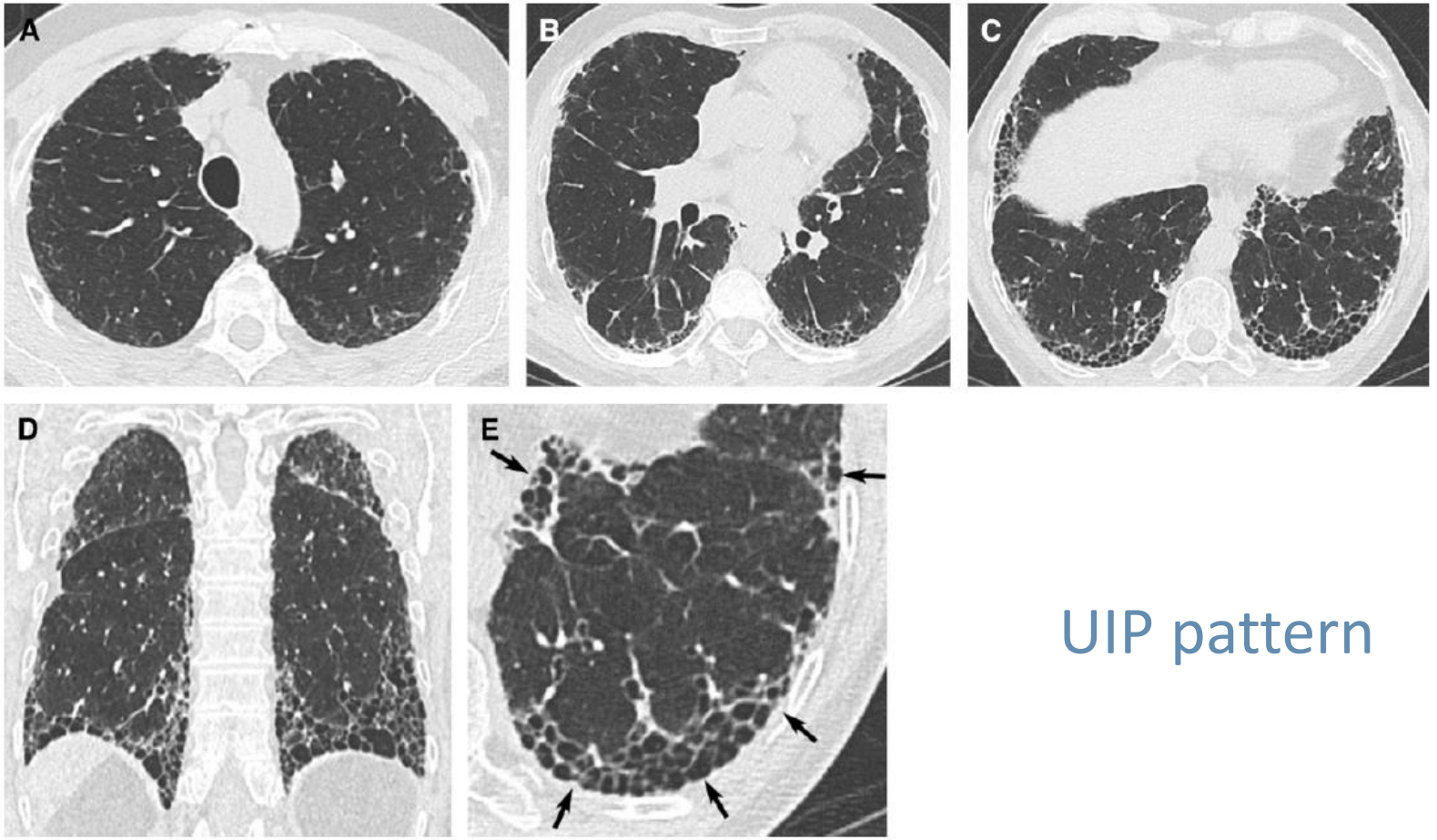
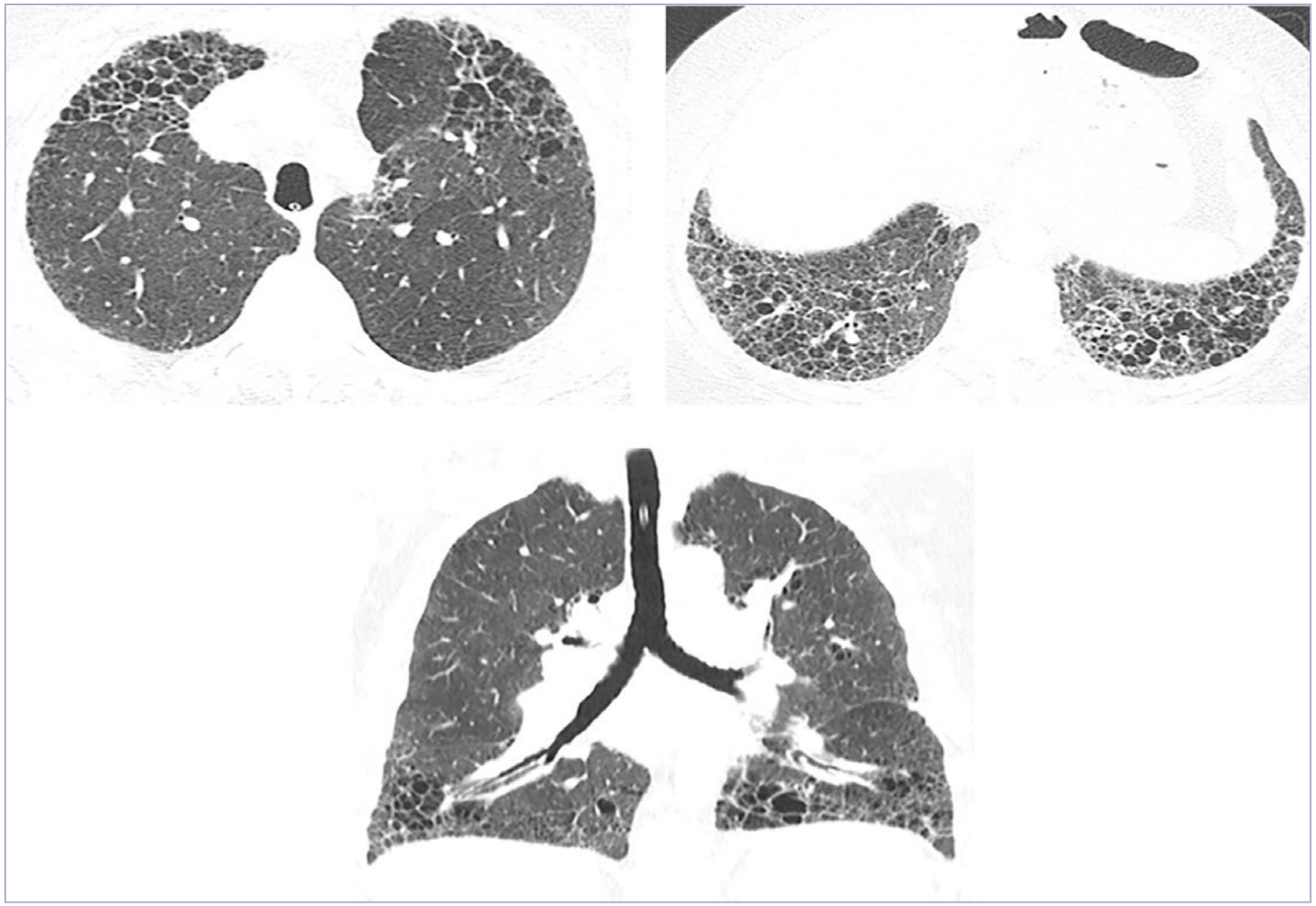
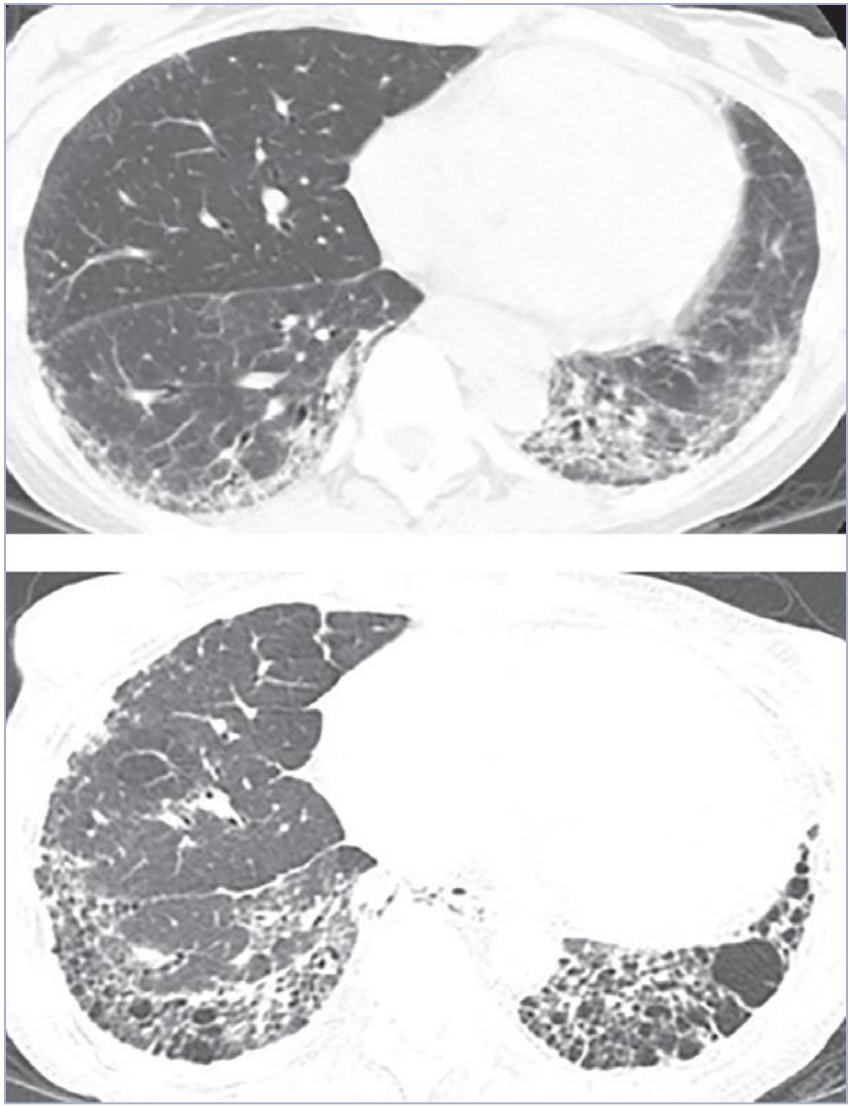


UIP pattern



CTD –UIP DM/Scleroderma overlap

American Journal of Respiratory and Critical Care Medicine Volume 205 Number 9 | May 1 2022



Scleroderma NSIP

PPF

9 years later Scleroderma UIP

American Journal of Respiratory and Critical Care Medicine Volume 205 Number 9 | May 1 2022

Histology?

HRCT is the gold standard for the diagnosis of ILD in CTD patients

- Lung biopsy usually not required

- cryobiopsy
- surgical

- Place for BAL is unclear

Diagnostic algorithm

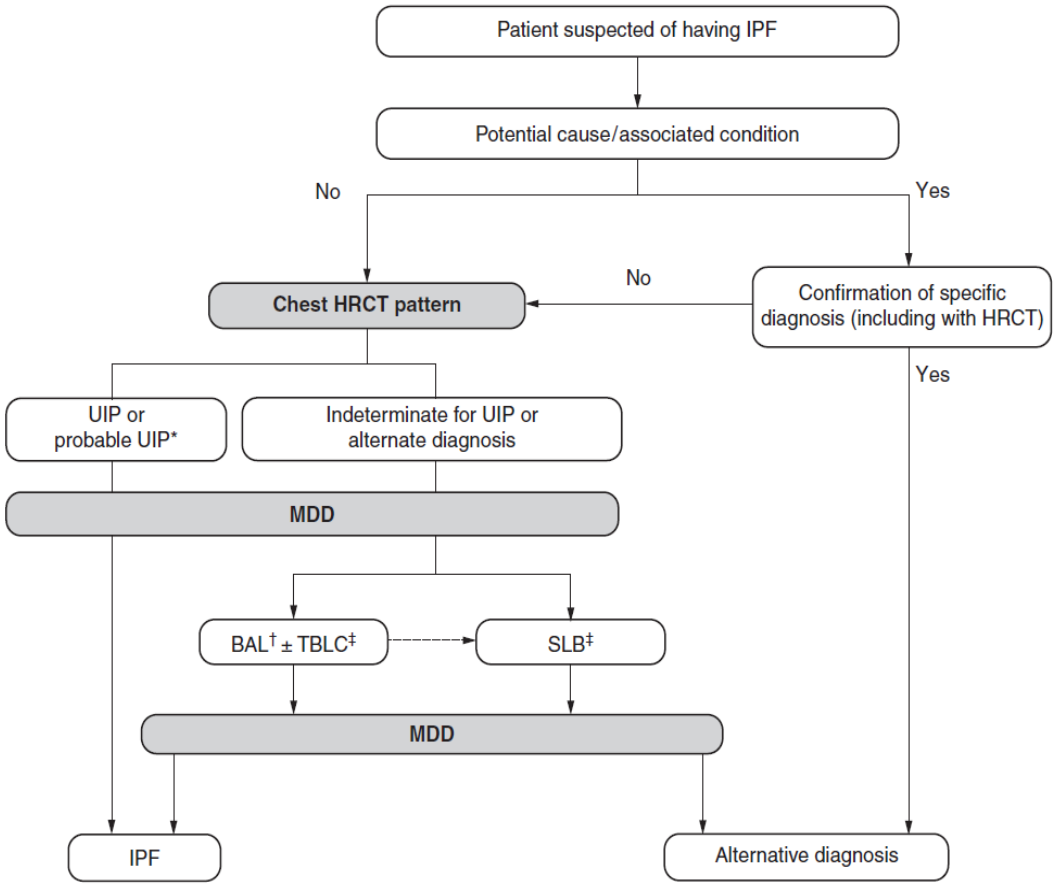


Figure 10 Diagnostic algorithm for idiopathic pulmonary fibrosis (IPF), developed using consensus by discussion. *Patients with a radiological

natural history of PF

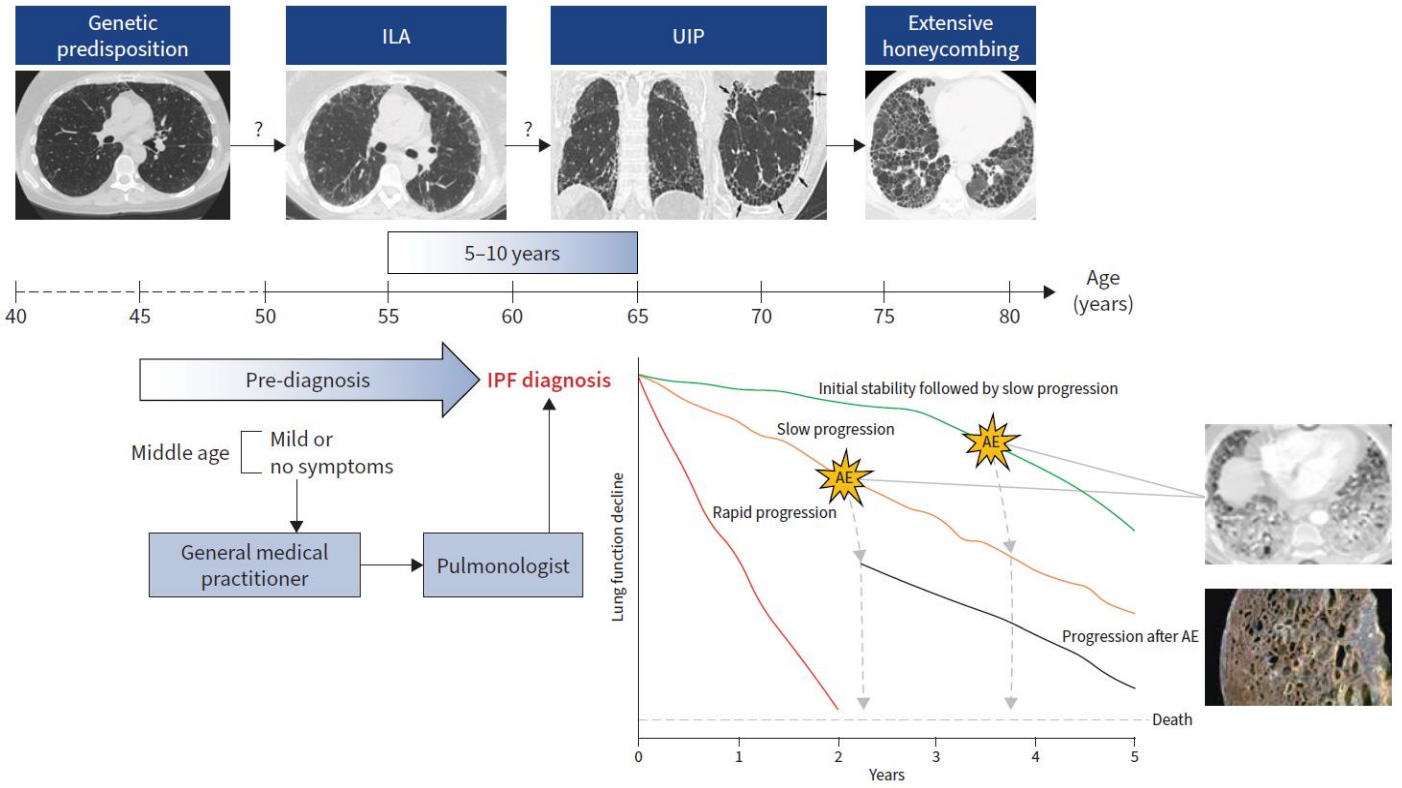


FIGURE 2 Natural clinical course of idiopathic pulmonary fibrosis (IPF). Patients may have evidence of interstitial lung abnormalities (ILAs) on

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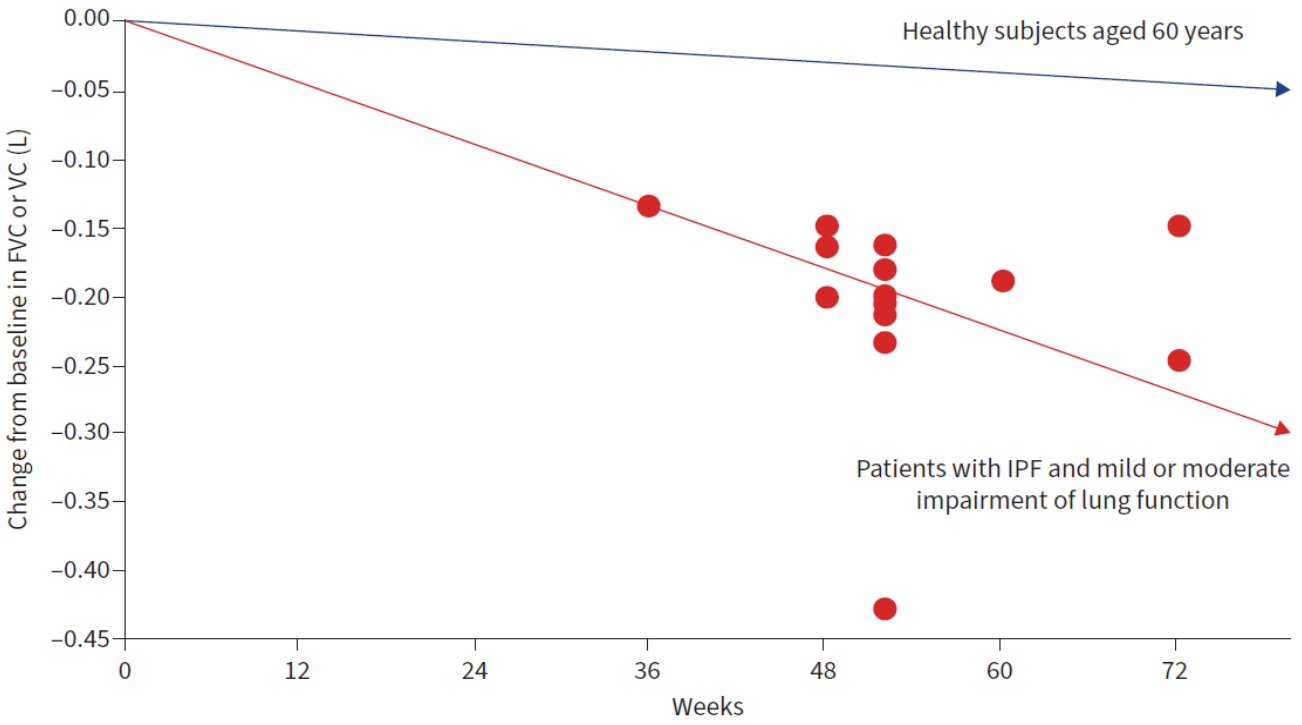

FIGURE 3 Natural course of forced vital capacity (FVC) or vital capacity (VC) decline in patients with idiopathic

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Comorbidities

- Respiratory and nonrespiratory comorbidities
- impact survival

- COPD/Combined pulmonary fibrosis and emphysema (CPFE)
- lung cancer
- pulmonary hypertension

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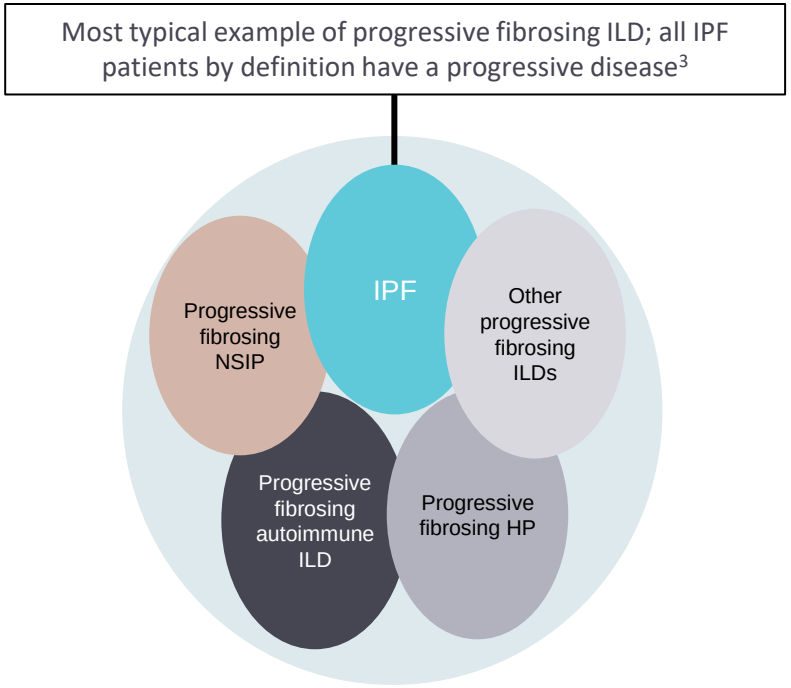
Patients with certain types of fibrosing ILDs have the potential to develop a **progressive phenotype**

- Characterized by **worsening of lung function**, **respiratory symptoms** and **quality of life**, as well as **early mortality**

- Because of the commonalities in clinical behavior and pathogenesis, it has been proposed that fibrosing ILDs with a progressive phenotype may be 'lumped' together for the purposes of clinical research and treatment

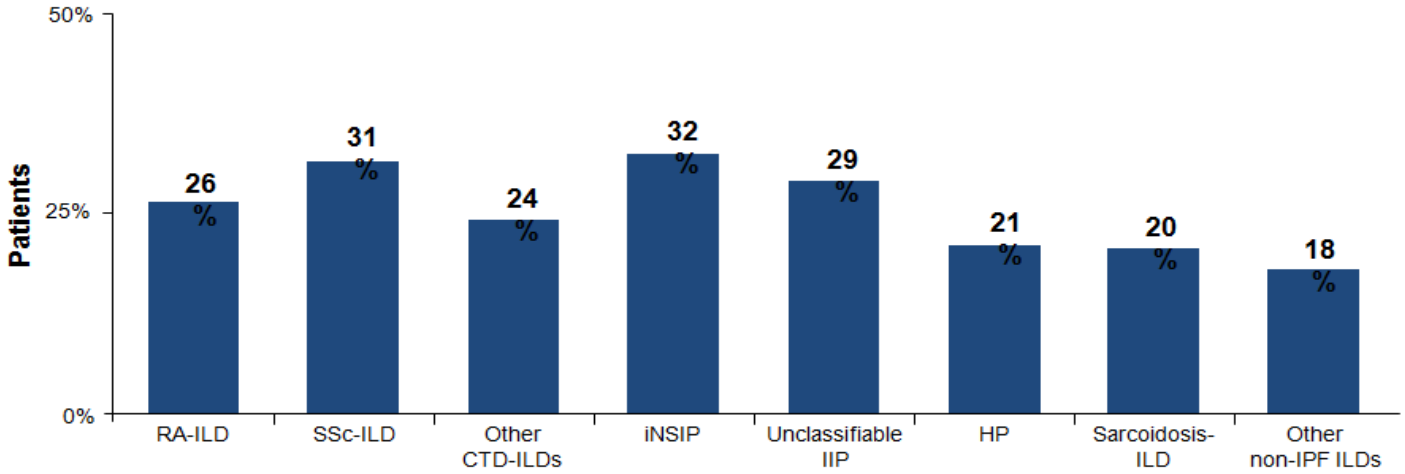
20-30%



HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NSIP, non-specific interstitial pneumonia

1. Cottin V *et al. Eur Respir Rev* 2019;28:180100; 2. Wells AU *et al. Eur Respir J* 2018;51:1800692; 3. Raghu G *et al. Am J Respir Crit Care Med* 2011;183:788–824

Up to one-third of patients with ILDs, including CTD-ILD, develop progressive fibrosing disease



From a survey of 486 physicians who regularly managed ILD patients, it was estimated that 18–32% of patients diagnosed with non-IPF ILD develop progressive fibrosis[1]

1. Wijsenbeek M *et al*. ATS 2018 International Conference. San Diego, USA, May 18–23, 2018; abstract A1678

AMERICAN THORACIC SOCIETY DOCUMENTS

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

Ganesh Raghu, Martine Remy-Jardin, Luca Richeldi, Carey C. Thomson, Yoshikazu Inoue, Takeshi Johkoh, Michael Kreuter, David A. Lynch, Toby M. Maher, Fernando J. Martinez, Maria Molina-Molina, Jeffrey L. Myers, Andrew G. Nicholson, Christopher J. Ryerson, Mary E. Strek, Lauren K. Troy, Marlies Wijsenbeek, Manoj J. Mammen, Tanzib Hossain, Brittany D. Bissell, Derrick D. Herman, Stephanie M. Hon, Fayez Kheir, Yet H. Khor, Madalina Macrea, Katerina M. Antoniou, Demosthenes Bouros, Ivette Buendia-Roldan, Fabian Caro, Bruno Crestani, Lawrence Ho, Julie Morisset, Amy L. Olson, Anna Podolanczuk, Venerino Poletti, Moisés Selman, Thomas Ewing, Stephen Jones, Shandra L. Knight, Marya Ghazipura, and Kevin C. Wilson; on behalf of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax

This official clinical practice guideline was approved by the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax February 2022

Progressive Fibrosing - Interstitial Lung Disease
PF-ILD

- **multifactorial etiology**
- IPF
- connective tissue disease-associated ILD (CTD-ILD),
- Fibrotic hypersensitivity pneumonitis (FHP)
- Unclassifiable idiopathic interstitial pneumonia (uIIP)
- idiopathic non-specific interstitial pneumonia (NSIP)

Cottin et al., 2019

Progressive Fibrosing - Interstitial Lung Disease

PF-ILD

- **HRCT**-documented increase in the extent of PF
- decline in **lung function**
- worsening respiratory **symptoms** and **quality of life**
- high risk of **early mortality** despite available treatments
- clinical course similar to that of idiopathic pulmonary fibrosis (IPF)

Cottin et al., 2018

Radiological Criteria for PPF

- increased traction bronchiectasis and bronchiolectasis,
- new ground-glass opacity with traction bronchiectasis
- new fine reticulation
- increased coarseness of reticular abnormality
- new or increased honeycombing
- increased lobar volume loss

Radiological Criteria for PPF

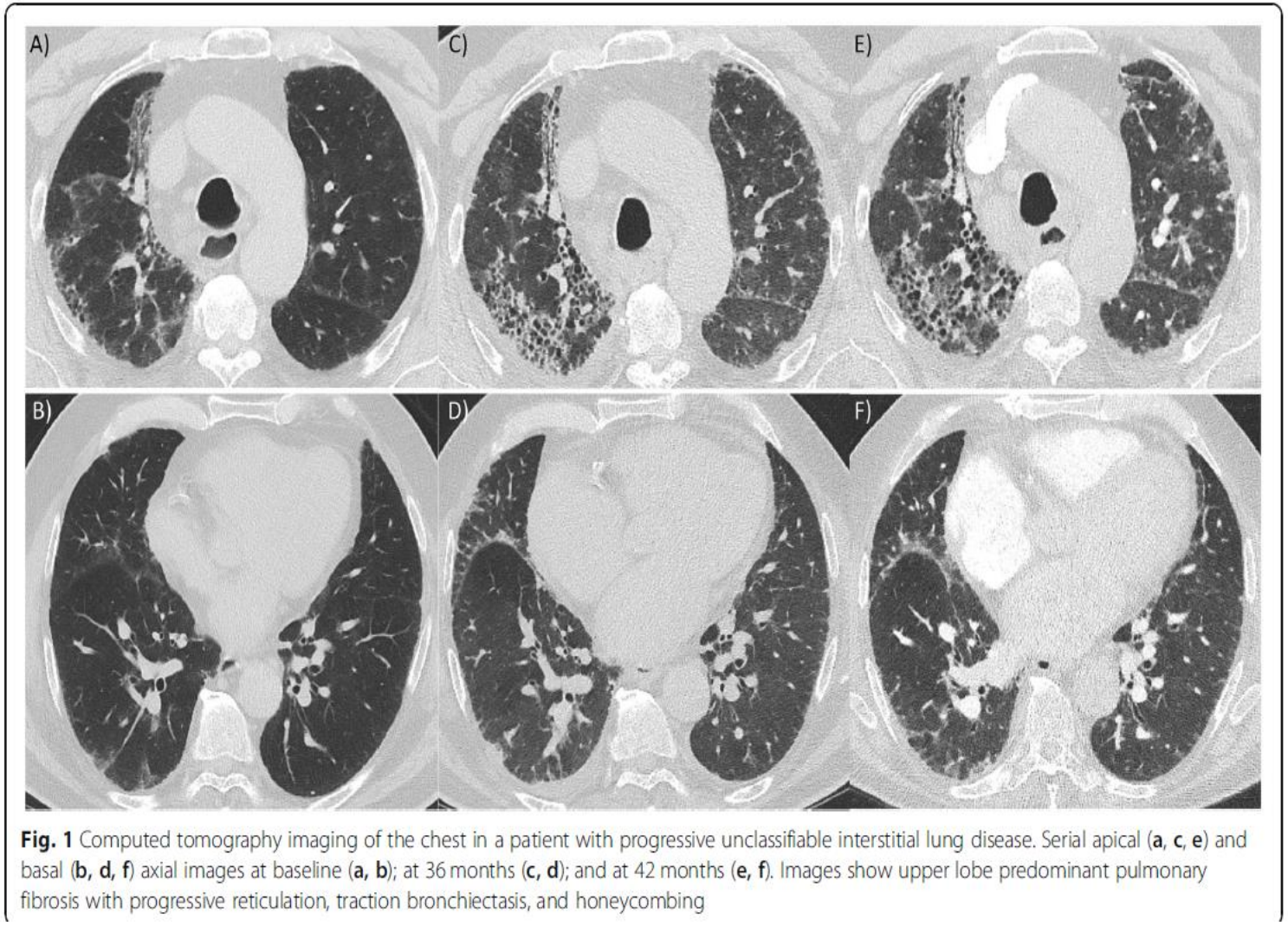


Fig. 1 Computed tomography imaging of the chest in a patient with progressive unclassifiable interstitial lung disease. Serial apical (**a**, **c**, **e**) and basal (**b, d, f**) axial images at baseline (**a, b**); at 36 months (**c, d**); and at 42 months (**e, f**). Images show upper lobe predominant pulmonary fibrosis with progressive reticulation, traction bronchiectasis, and honeycombing

Wong et al., Resp research 2020

Physiological Criteria for PPF

- Absolute decline in FVC of >5%
  within 1 year of follow-up.
- Absolute decline in DLCO (corrected
  for Hb) of >10% within 1 year of follow-up.

WHAT IS PROGRESSION?

STUDY	TIME (months)	LUNG FUNCTION	SYMPTOMS	HRCT
INBUILD Nintedanib[1]	24	FVC ≥ 10% FVC 5-10% and	Worsening or Worsening and	Progression Progression
uILD Pirfenidon[2]	6	FVC ≥ 5%	Worsening	
Relief Pirfenidon[3]	12	FVC ≥ 5%	-	-
TRAIL Pirfenidon[4]	12	FVC ≥ 10% or FVC 5-10% and DLCO ≥ 15%	-	-
Cottin[5]	24	FVC ≥ 10% DLCO ≥ 15%	Worsening	Worsening and FVC 5 – <10%

And what about 6MWT, PROMS, AE, hospitalizations etc.....?

[1]Flaherty et al. NEJM 2019; [2]Maher et al. Lancet Resp. Med. 2019; [3]Behr et al. Lancet Resp. Med. 2021;; [4]Solomon et al. Adv. Therapy 2019; [5]Cottin et al. Diseases. Eur. Respir. Rev. 2018

Prognostic Predictive Characteristics in Patients With Fibrosing Interstitial Lung Disease:

TABLE 4 | Factors associated with 6-year all-cause mortality in the PF-group.

Covariate	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age	1.57 (0.99–2.47)	0.054	1.1 (0.67–1.82)	0.698
Male	1.06 (0.69–1.64)	0.777	–	–
BMI	1.02 (0.65–1.58)	0.944	–	–
Smoking	1.23 (0.80–1.88)	0.347	–	–
FVC% pred	1.13 (0.66–1.95)	0.66	–	–
DLCO% pred	2.30 (1.50–3.45)	<0.001	2.25 (1.45–3.50)	<0.001
Velcro	0.97 (0.63–1.49)	0.88	–	–
Clubbing of fingers	0.77 (0.49–1.22)	0.269	–	–
Hypoxemia	2.24 (1.43–3.50)	<0.001	2.08 (1.31–3.32)	0.002
Hospitalization at baseline	0.90 (0.50–1.61)	0.719	–	–
UIP-like pattern on HRCT	0.23 (1.45–3.45)	<0.001	1.68 (1.04–2.71)	0.034
WBC	1.19 (0.78–1.83)	0.419	–	–
Neutrophils	1.09 (0.71–1.67)	0.697	–	–
Lymphocytes	1.24 (0.81–1.89)	0.33	–	–
Monocyte	1.19 (0.76–1.82)	0.429	–	–

Wang et al., frontiers in Pharmacology, 2022

Progressive Fibrosing Interstitial Lung Disease- **Survival**

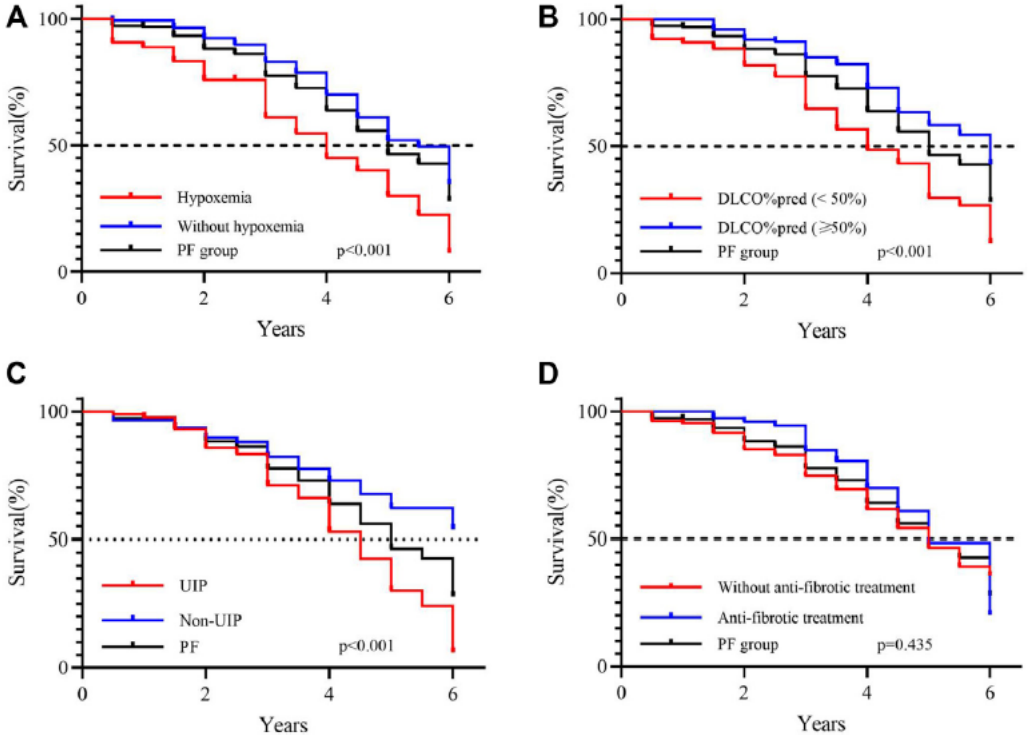


FIGURE 3 | Survival in patients with progressive fibrosing ILD. **(A)** Survival according to with or without hypoxemia at baseline (log-rank test, $p < 0.001$); **(B)** survival according to DLCO% pred at baseline with a 50% threshold (log-rank test, $p < 0.001$); **(C)** survival according to the UIP-like fibrotic pattern on HRCT (log-rank test, $p < 0.001$); **(D)** survival according to with or without anti-fibrotic treatment during observation (log-rank test, $p = 0.435$).

Wang et al., frontiers in Pharmacology, 2022

Diagnosis-Management-Treatment

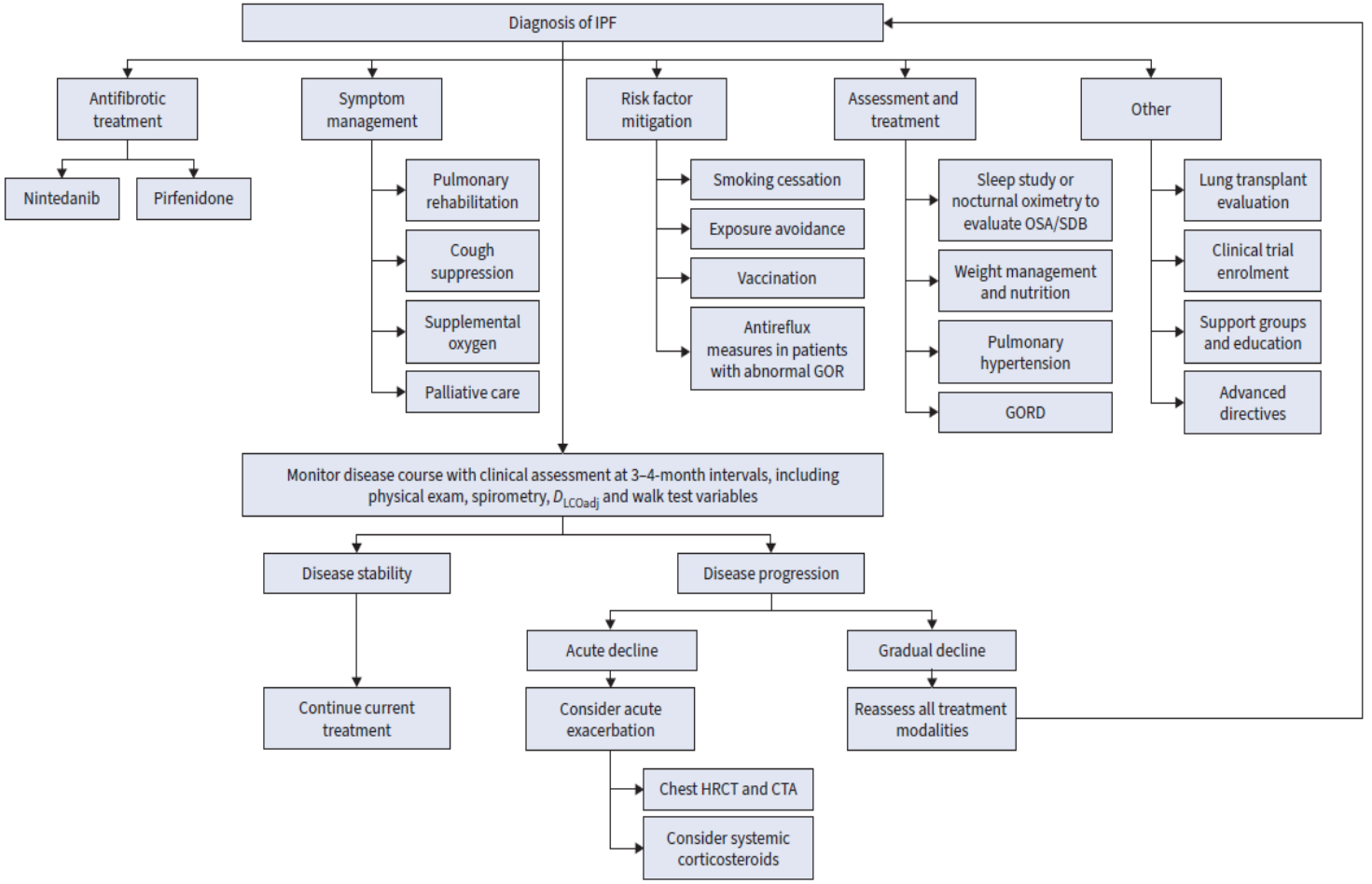
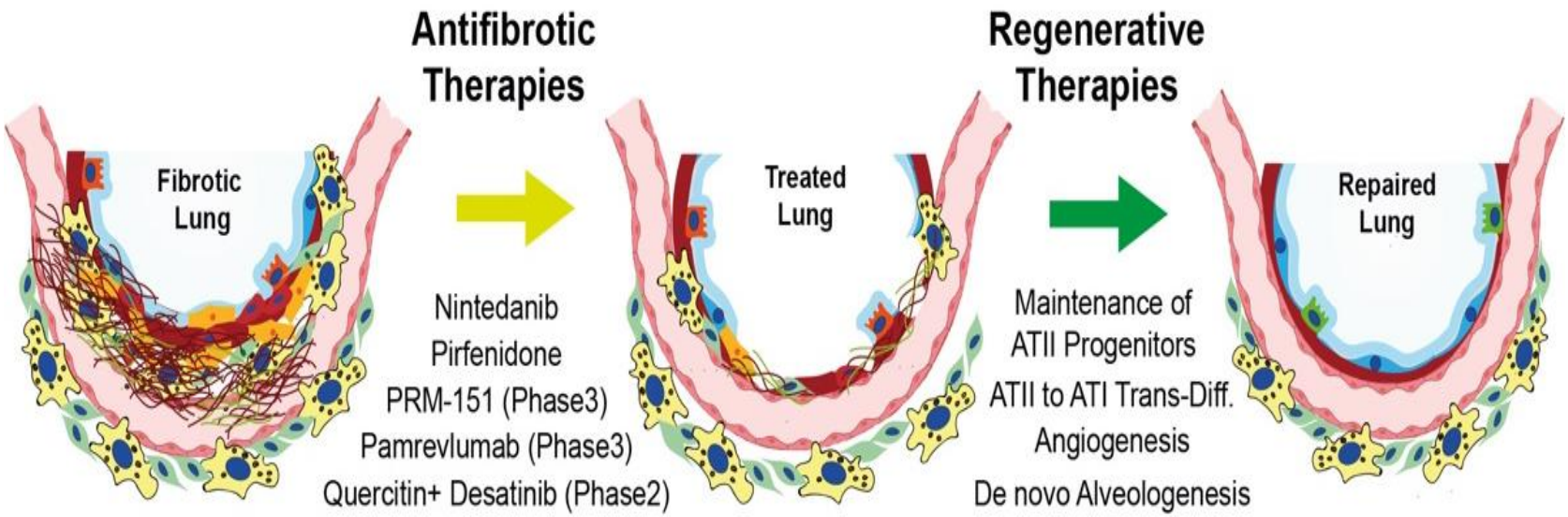


FIGURE 4 Suggested approach to the management of patients with idiopathic pulmonary fibrosis (IPF). Patients with a diagnosis of IPF should be considered for antifibrotic treatment with

2023



Novel therapeutic strategies for IPF treatment

(1) stop fibrosis progression by hampering aberrant ECM deposition and eliminating defective cells (antifibrotic and senolytic drugs) and

(2) bring back the lung to a healthy condition by promoting alveolar regeneration (regenerative therapies).

cells, 2022

ευχαριστώ πολύ για την πρόσκληση και την προσοχή σας