ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ
ΝΟΣΗΜΑΤΩΝ ΘΩΡΑΚΟΣ ΑΘΗΝΩΝ
Η ΣΩΤΗΡΙΑ

Διάμεση Πνευμονοπάθεια Σχετιζόμενη με Ρευματικά Νοσήματα

Λυκούργος Κολιλέκας, MD, PhD
Διευθυντής ΕΣΥ
7η Πνευμονολογική Κλινική
ΓΝΝΘΑ "Η ΣΩΤΗΡΙΑ"

Conflict of interest disclosure

☒ I have no real or perceived conflicts of interest that relate to this presentation.

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Grants/research support:	
Honoraria or consultation fees:	
Participation in a company sponsored bureau:	
Stock shareholder:	
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In Connective Tissue Diseases:

- **All components of the lung can be involved**

	ILD	Airways	Pleural	Vascular	DAH
Systemic sclerosis	+++	–	–	+++	–
Rheumatoid arthritis	++	++	++	+	–
Primary Sjögren's syndrome	++	++	+	+	–
Mixed CTD	++	+	+	++	–
Polymyositis/ dermatomyositis	+++	–	–	+	–
Systemic lupus erythematosus	+	+	+++	+	++

Fischer A. et al. *Lancet 2012*

In Connective Tissue Diseases:

- All components of the lung can be involved
- Interstitial lung disease major cause of morbidity and mortality
- Severity of lung disease usually unrelated to severity of systemic manifestations
- ILD can be the presenting *(forme fruste)* or only manifestation of an underlying CTD in a substantial proportion of patients

Fischer A. et al. *Lancet 2012*
Tzelepis G, et al. Eur Respir J 2008

Classifications of interstitial lung diseases

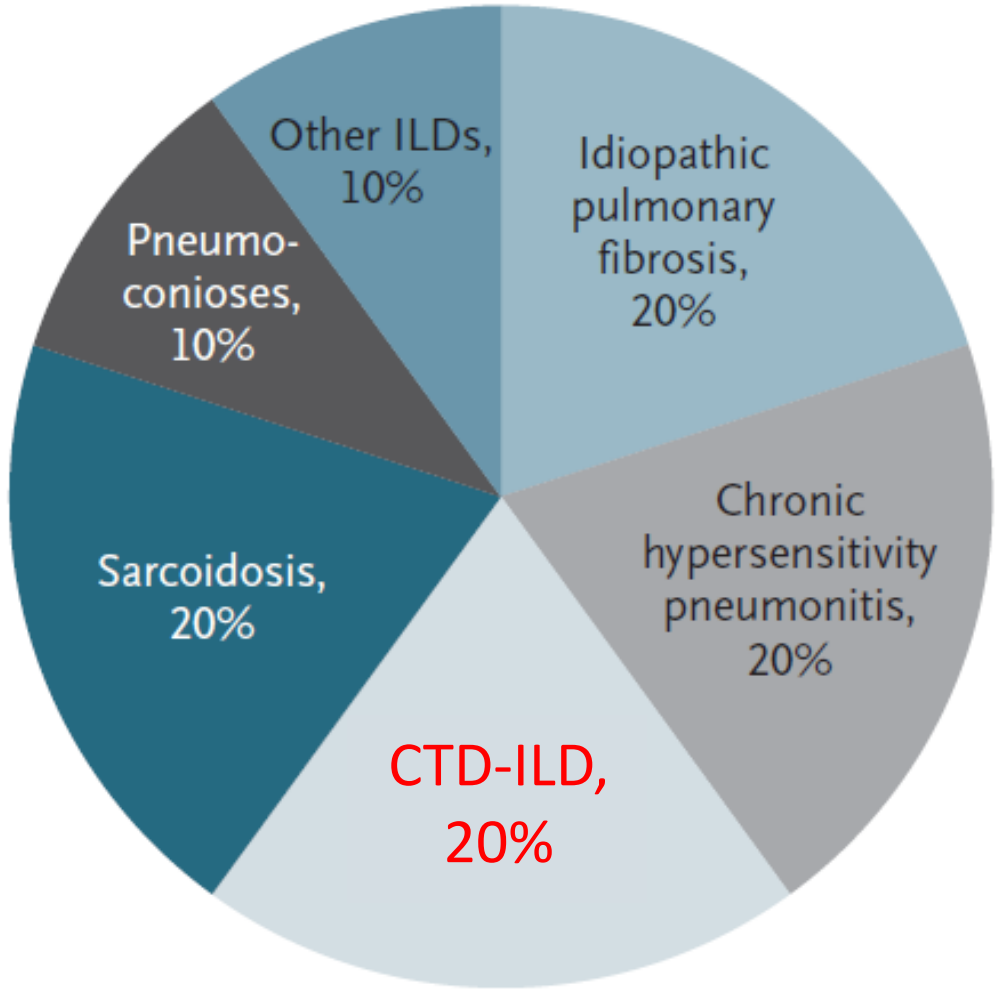
Known causes
- Drugs
- Connective tissue diseases
- Environmental exposures
- Genetics

15%

Idiopathic interstitial pneumonias
- Idiopathic pulmonary fibrosis
- Non-specific interstitial pneumonia
- Respiratory bronchiolitis interstitial lung disease
- Acute interstitial pneumonia
- Desquamative interstitial pneumonia
- Cryptogenic organising pneumonia
- Lymphocytic interstitial pneumonia

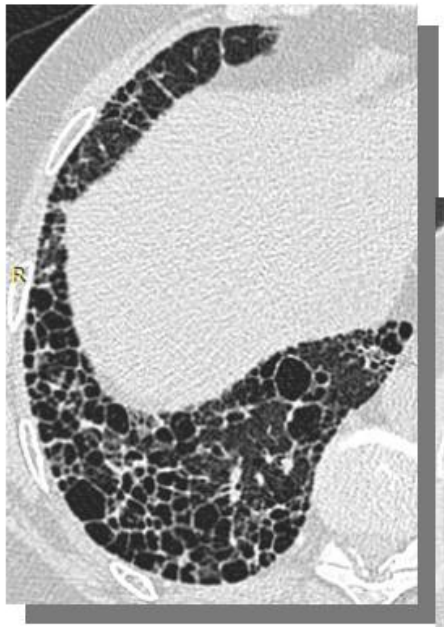
Granulomatous diseases
- Sarcoidosis
- Fungal infection
- Mycobacterial infection
- Diseases associated with environmental exposures (eg, chronic beryllium disease, hypersensitivity pneumonitis)

Other forms
- Pulmonary alveolar proteinosis
- Langerhans' cell histiocytosis
- Eosinophilic pneumonia
- Lymphangioleiomyomatosis
- Pulmonary capillaritis

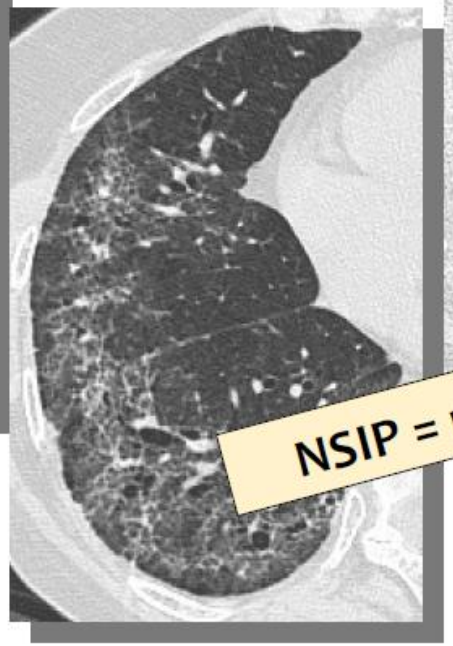


Fischer A. et al. *Lancet 2012*
Lederer DJ. *N EJM 2018*

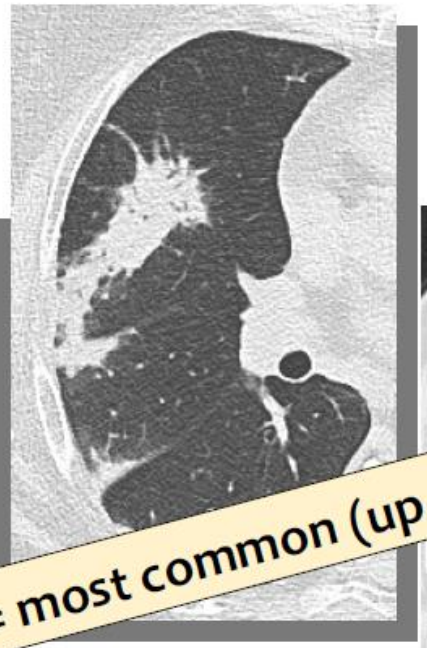
CPFE



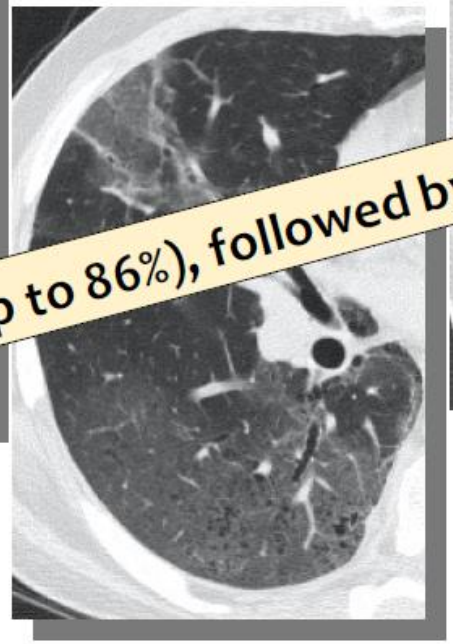
UIP



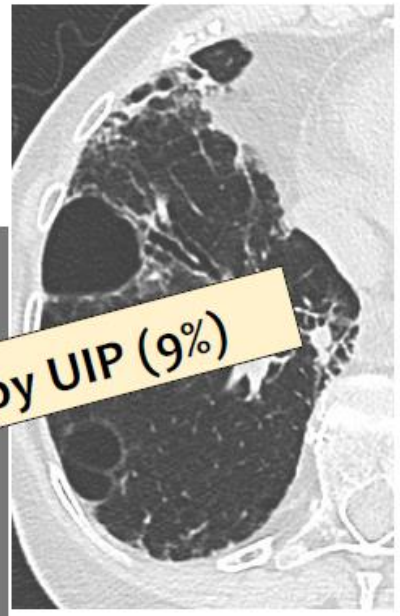
NSIP



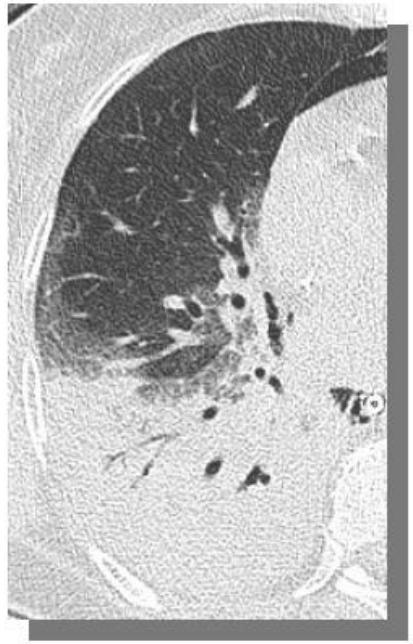
OP



DIP



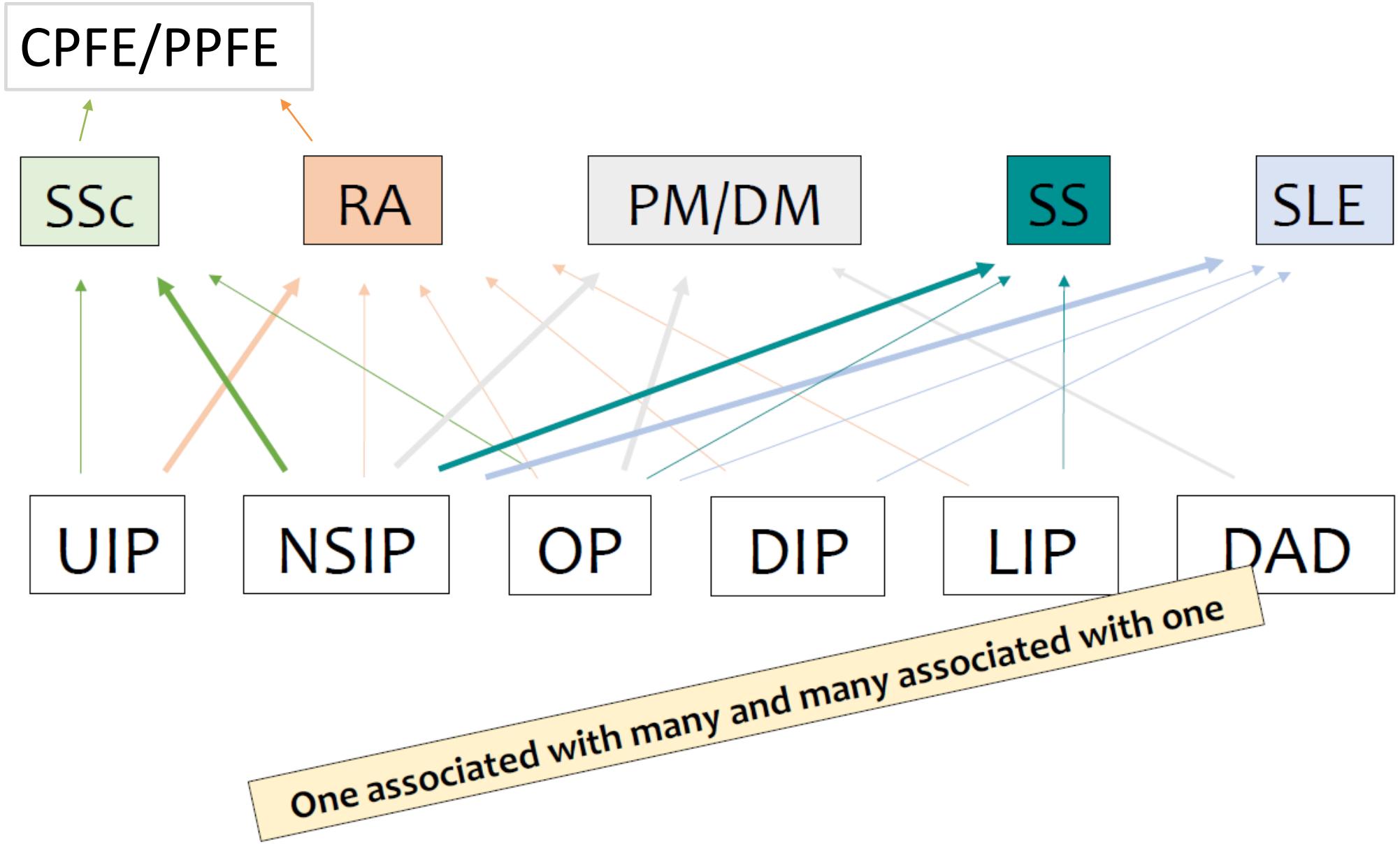
LIP



DAD

NSIP = most common (up to 86%), followed by UIP (9%)

Kim EA, et al. Radiographics 2002
Walsh SL, et al. *Thorax 2014*



Kim EA, et al. Radiographics 2002
Walsh SL. et al. *Thorax 2014*
Palmucci S, et al. *Insights Into Imaging 2022*

Prevalence, imaging patterns and risk factors of interstitial lung disease in connective tissue disease: a systematic review and meta-analysis

Eur Respir Rev 2023

Greta M. Joy[1], Omri A. Arbiv[1], Carmen K. Wong[1], Stacey D. Lok[2], Nicola A. Adderley[3], Krzysztof M. Dobosz[1], Kerri A. Johannson[3] and Christopher J. Ryerson[1,4]

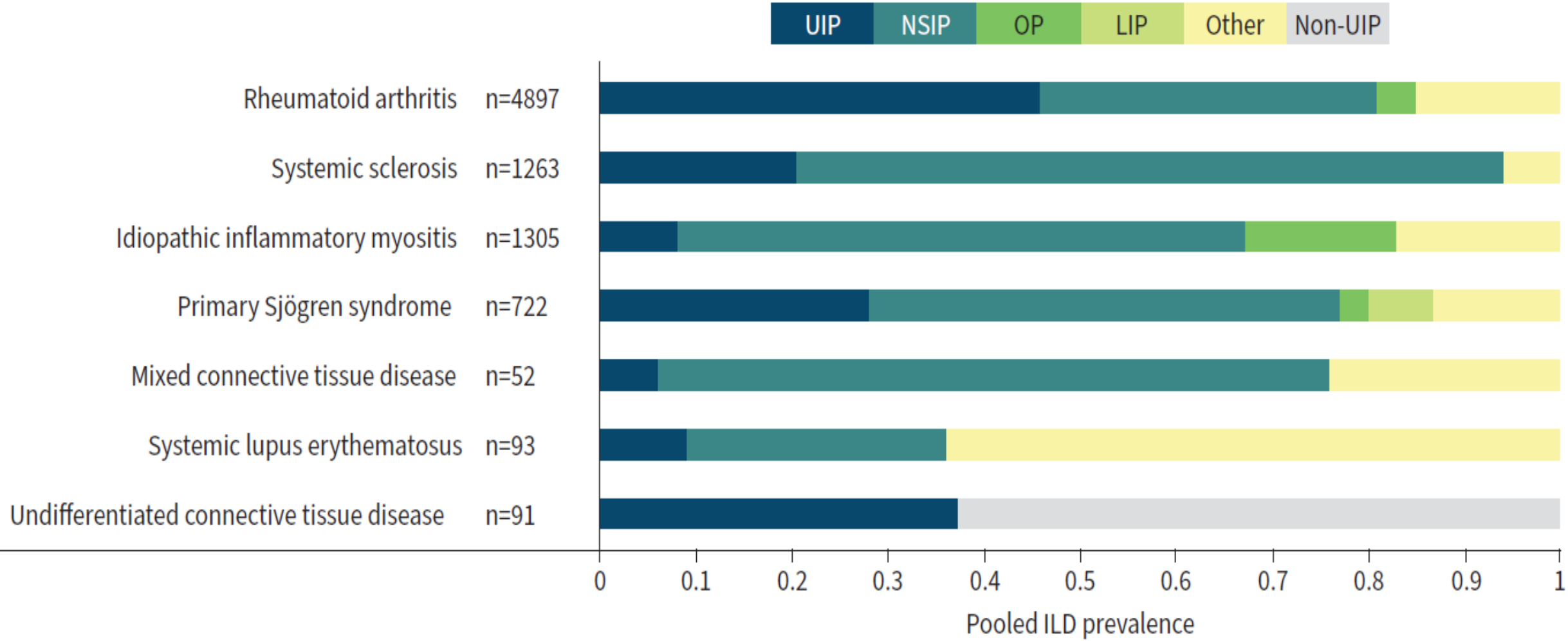


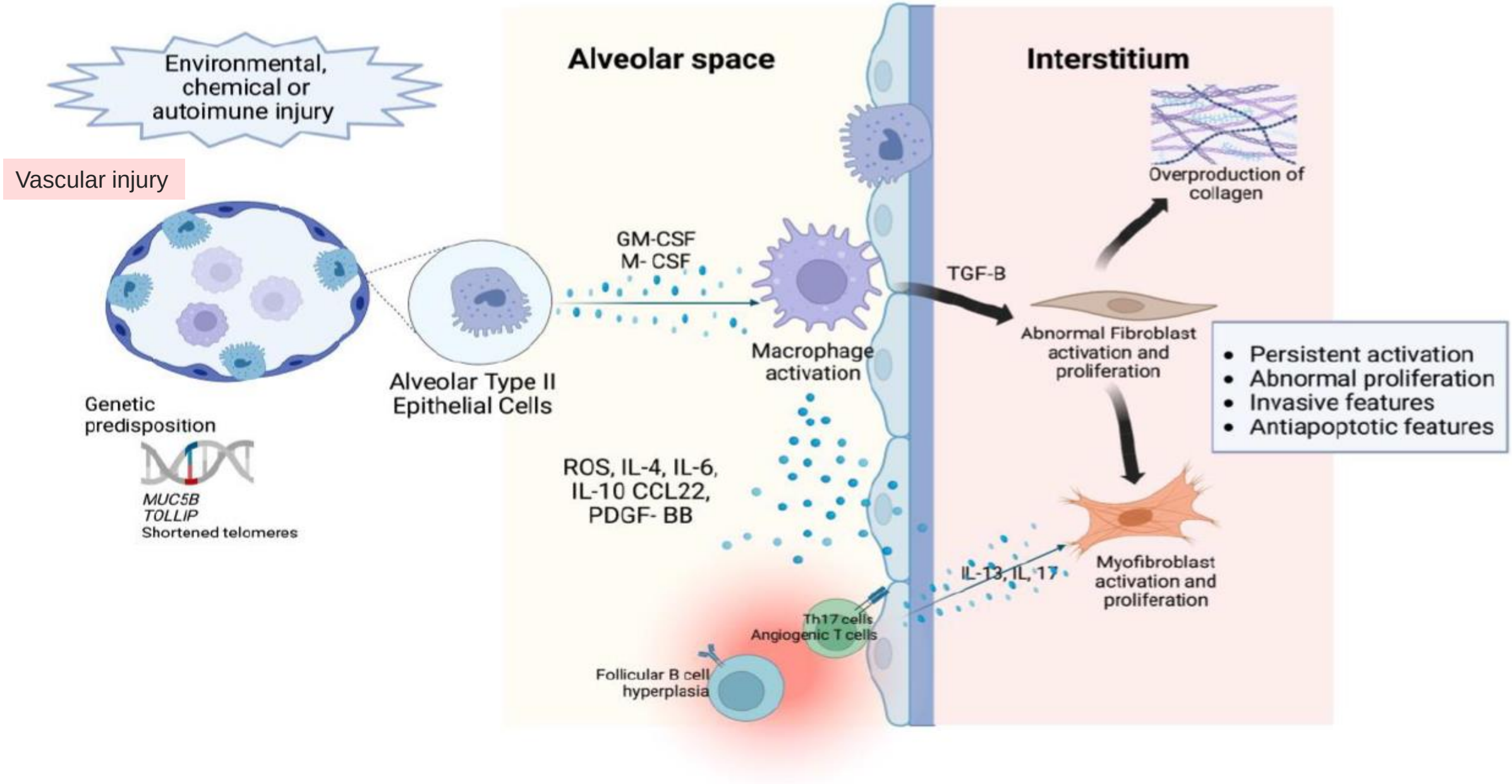
Table 1. Interstitial lung diseases associated with connective tissue diseases

Rheumatic disease	Frequency of ILD (%)
Systemic sclerosis	45 (clinically significant)
Rheumatoid arthritis	20 to 30
Polymyositis/dermatomyositis	20 to 50[a]
Sjögren's syndrome	Up to 25
Systemic lupus erythematosus	2 to 8
Mixed connective tissue disease	20 to 60

ILD, interstitial lung disease. [a]Frequency may be higher based on recent studies.

Castelino FV. et al. *Arthritis Research & Therapy 2010*

Pathogenic Mechanisms in CTD-ILD



Cerro Chiang G. et al. *Int J Mol Sci 2023*

Risk factors for development of interstitial lung disease (ILD)				
	Genetic	Demographic	Clinical	Serologic
RA	MUC5B Promoter polymorphism Telomere mutations	*Older age*# *Older age of RA onset*# *Male sex*# *Longer RA duration*	Morning stiffness Erosive arthritis DAS28 score# BMI >30 $kg \cdot m^{-2}$# *Smoking history*#	*RF positive*# *RF titre*# *Anti-CCP positive*# *Anti-CCP titre*# *ESR*# *CRP* LDH#
SSc		Older age Female sex Black race# Shorter SSc duration	*Diffuse cutaneous subtype*# Higher MRSS Digital ulcers# History of renal crisis GI system involvement# Myopathy Ever smoker (lower ILD)	*Anti-Scl70*# *Anti-centromere absent*# Anti-SSA positive ESR# CRP Hb <13.0 $g \cdot dL^{-1}$
Idiopathic inflammatory myositis		Black race	Polymyositis (lower ILD) Anti-synthetase syndrome Clinically amyopathic Mechanic's hands# Absence of malignancy Arthralgia/arthritis Lateral hip erythema#	Anti-synthetase antibody Anti-Jo1 Anti-PL7/12 Anti-MDA5# ANA Anti-SSA Anti-Ro52 Anti-NXP2, Tiff, Mi2 (lower ILD) ESR# CRP Lower Hb

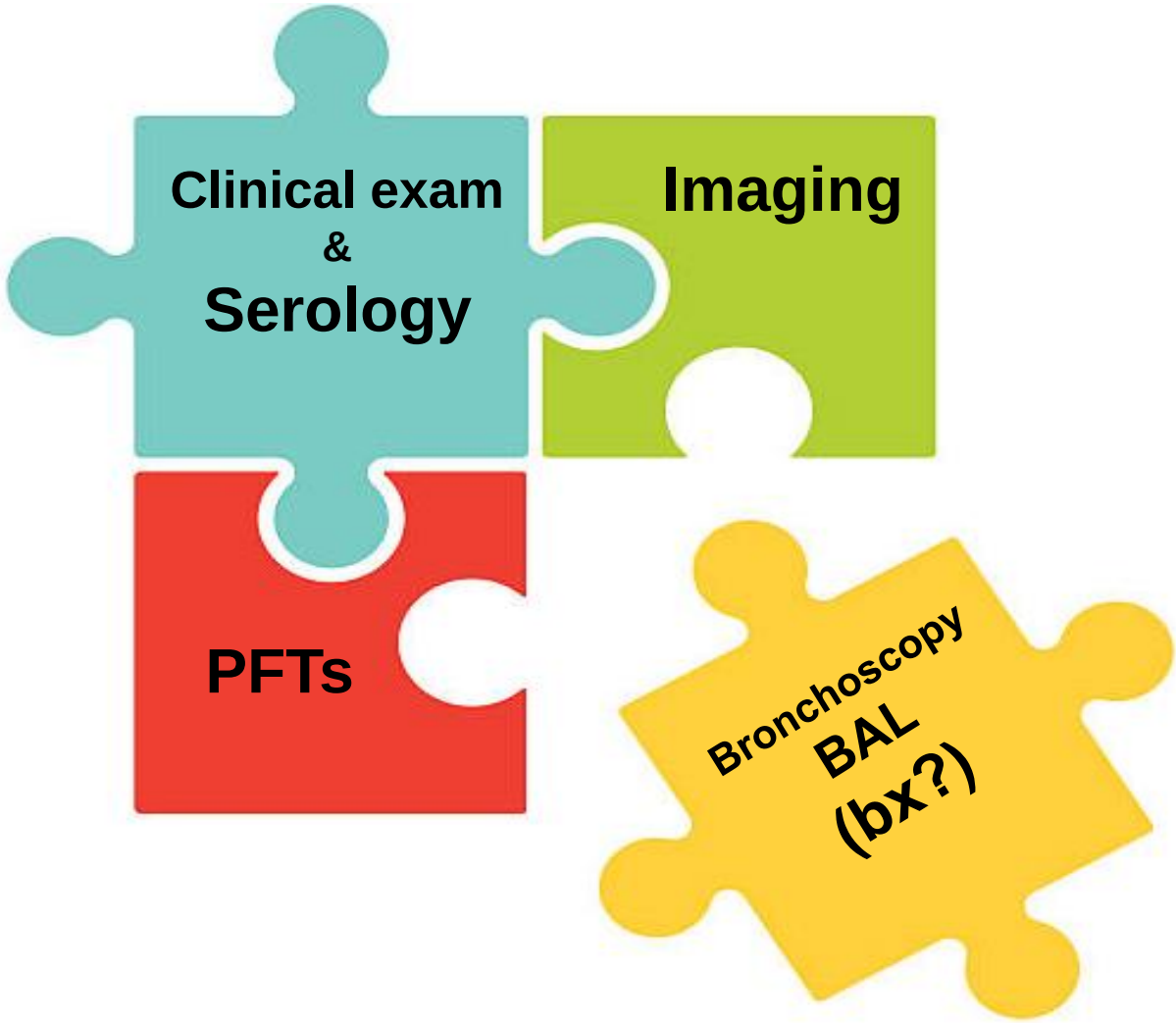
≲ 25% pt with RA-ILD are seronegative

Joy GM. *Eur Respir Rev 2023*

Diagnostic approach of CTD-ILD

Exclusion of other ILD, drug toxicity, infection, cancer

DEFINE CLINICAL PHENOTYPE



Multidisciplinary approach is essential (MDT)

Possible Clinical Scenarios

ILD may be recognized at any point in the natural history of CTD

- ✓ **Most often ILD within the context of an established CTD**
- ✓ **ILD may be the first clinically apparent manifestation of an occult CTD**
  (i.e., ***forme fruste*** presentation)
- ✓ **'Interstitial pneumonia with autoimmune features (IPAF)',**
  as defined by the presence of ILD and features suggestive of – but not diagnostic for – an underlying CTD

Fischer A. et al. *Respiration 2015*

Clinical evaluation

✓ A detailed medical history

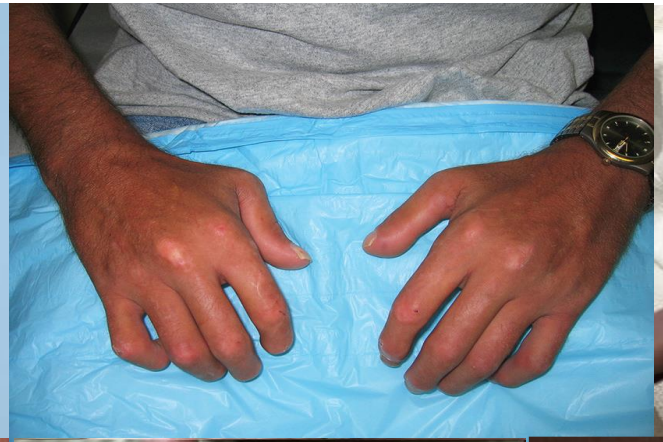
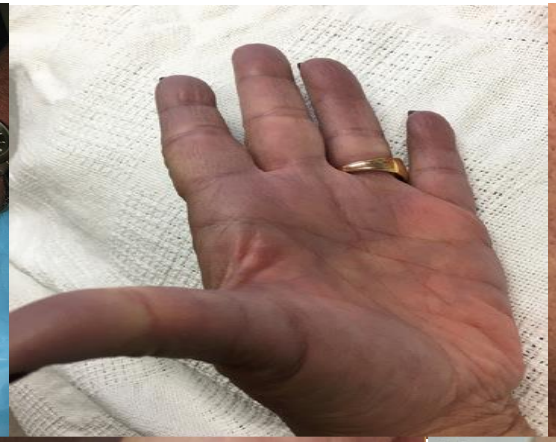
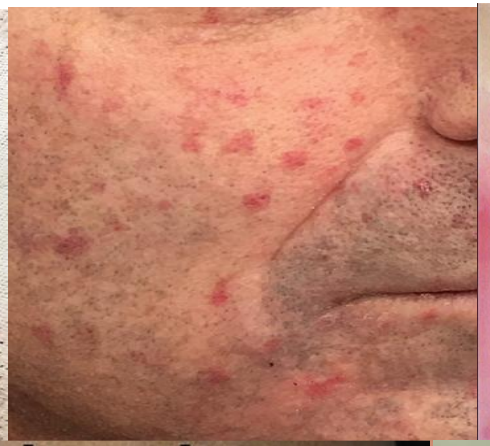
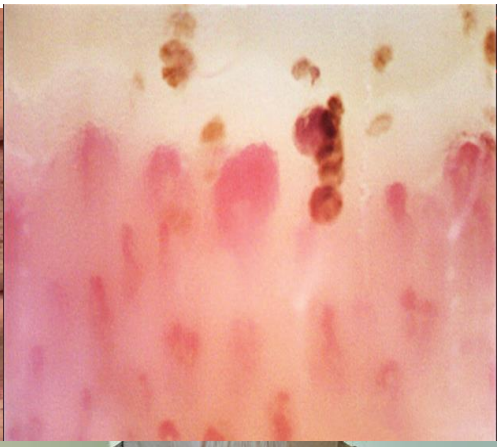
✓ Symptoms

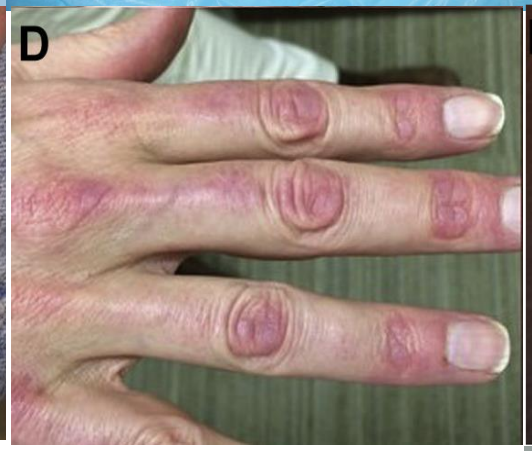
Exertional dyspnea
Cough
Constitutional symptoms
(fever, weight loss, fatigue)

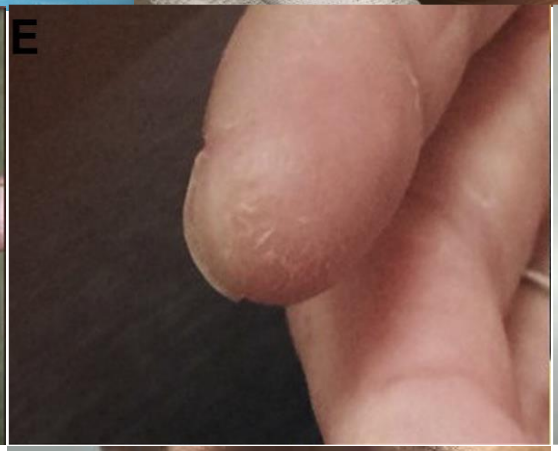
✓ Signs

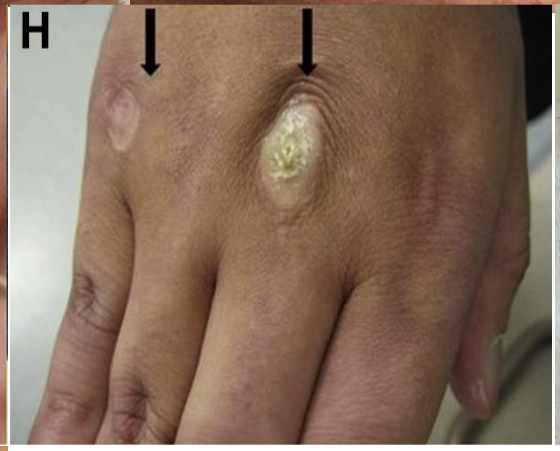
'Velcro' on lung auscultation
Finger clubbing
Signs extrapulmonary involvement

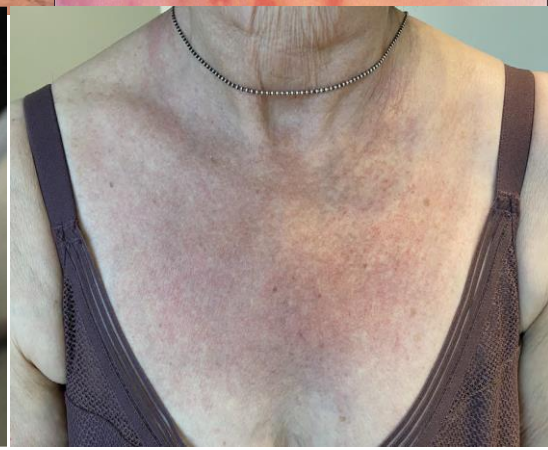
✓ Signs of extrapulmonary involvement








Lab & Serology Panel

first line tests

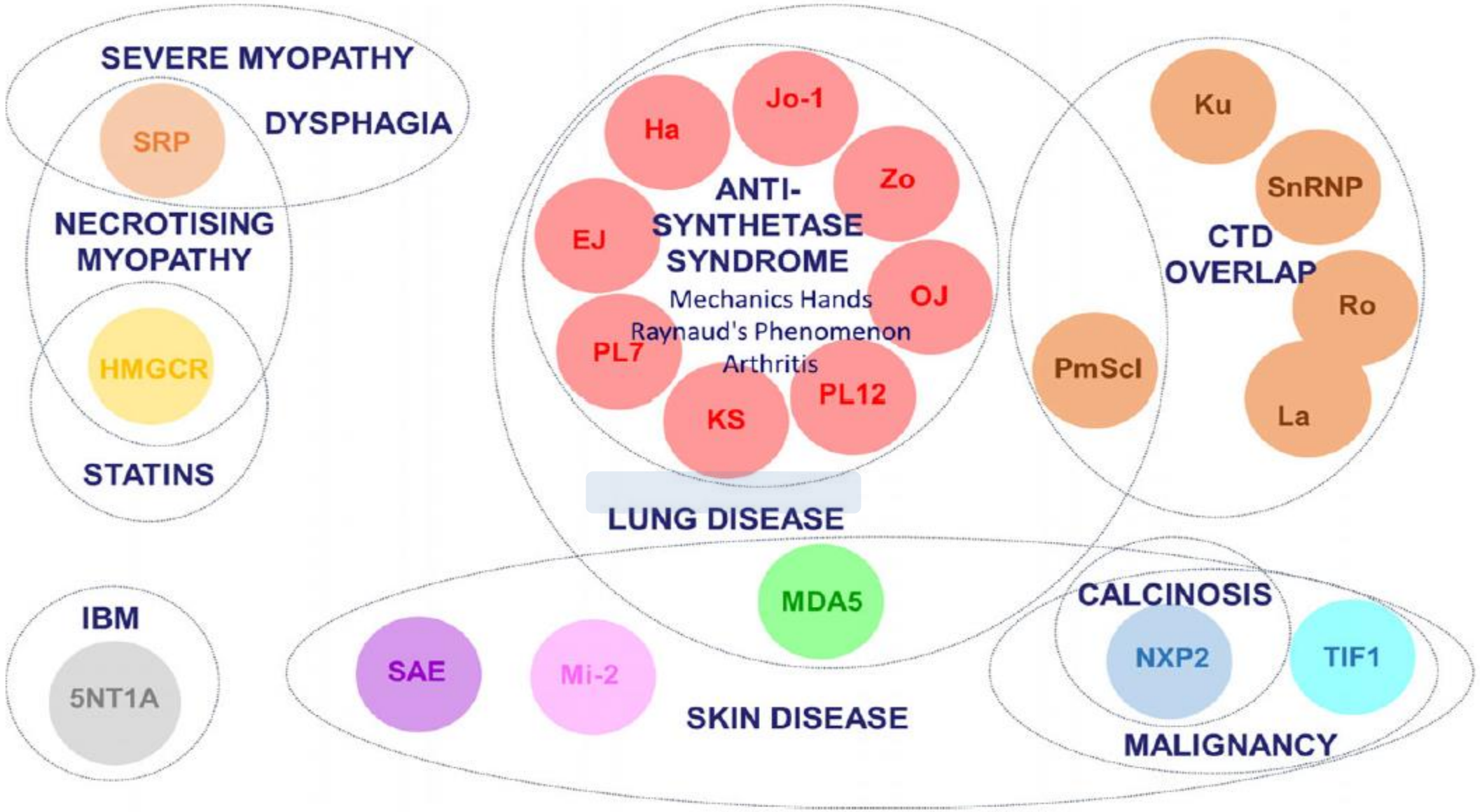
- ***ESR, CRP, CPK, Aldolase***
- **Urine microscopy**

+

- ***RF***
- ***Anti-CCP***
- ***ANA***
- *dsDNA*
- ***Ro***
- *La*
- *Sm*
- ***RNP***
- ***Jo-1***
- ***Scl-70***
- ***ACA***
- ***ANCA***

Papiris S, et al. *Curr Opin Pulm Med 2012*
Tzouvelekis A. et al. *Clin Chest Med 2019*

New era of Myositis Spectrum Antidodies (MSA)



Betteridge Z. et al. *J Intern Med 2016*

Autoantibodies are strongly linked with disease presentation, patterns of lung involvement and clinical outcomes

	RA	SLE	Scleroderma	DM-PM	Sjögren's syndrome	MCTD
Immunofluorescence nuclear pattern						
Homogeneous		+				
Speckled		+	+	+	+	+
Peripheral		+	+			
Nucleolar			+	+		
Specific nuclear antigens targeted in CTDs						
dsDNA		+				
ssDNA		+				
Histones		+				
Sm		+				
U1-RNP		+	+ (PH)			
U3-RNP			+ (ILD, PH)			
U11-RNP			+ (ILD)			
U12-RNP			+ (ILD)			
rRNP		+				
RNP	+	+	+			+
SSA/Ro		+ (ILD)		+ (ILD)	+	
SSB/La		+			+	
Ku		+	+	+ (PH)		
RI		+				
Scl-70			+ (ILD)			
CENP A-E			+ (PH)			
Th/To			+ (ILD, PH)			
RNA-pol-1			+			
RNA-pol-2			+			
RNA-pol-3			+			
Jo-1 (cytoplasmic)				+ (ILD)		
EJ (cytoplasmic)				+ (ILD)		
OJ (cytoplasmic)				+ (ILD)		
PL-7 (cytoplasmic)				+ (ILD)		
PL-12 (cytoplasmic)				+ (ILD)		
KS (cytoplasmic)				+ (ILD)		
Zo (cytoplasmic)				+ (ILD)		
YRS (cytoplasmic)				+ (ILD)		
Mi-2 (cytoplasmic)				+		
SRP				+		
CADM-140 (MDA5)				+ (AIP)		
PM-Scl			+	+		
Non-ANA autoantibodies						
ANCA						
RF	+					
ACPA	+ (↑ILD)					

Papiris S. et al. *Respiration 2015*

HRCT is essential

Suggest diagnosis ⇒
- HRCT pattern of ILD
- ‘Peculiar’ features of the pattern
- Additional findings

Prognostication ⇒
- HRCT pattern
- Extent

Follow-up ⇒
- Progression
- Complications

Walsh SL. et al. *Thorax 2014*
Palmucci S, et al. *Insights Into Imaging 2022*

Lung Function Tests: which parameters to monitor?

- **FVC** - Specific for interstitium - Risk of missing significant ILD or overestimating
  - Variable that most consistently reflects change in SSc-ILD clinical trials, widely validated
  - More repeatable across lung function labs
- **TLC**
- **DLCO** Affected also by pulmonary vasculature (PH), emphysema

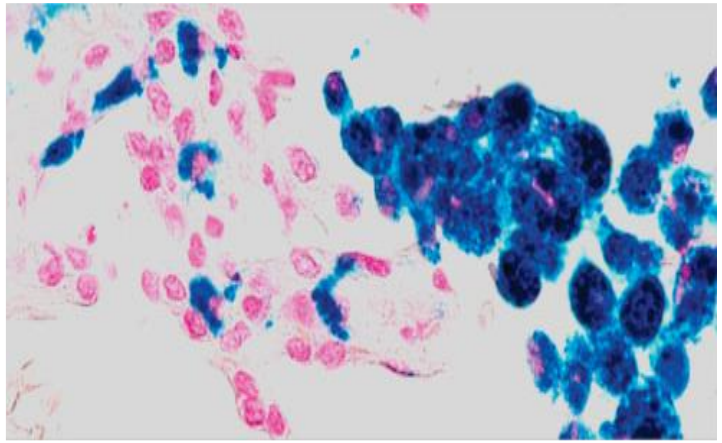
- **Six minute walking test (6MWT)**
- **Dyspnea scales**
- **Arterial blood gas – SaO_2**

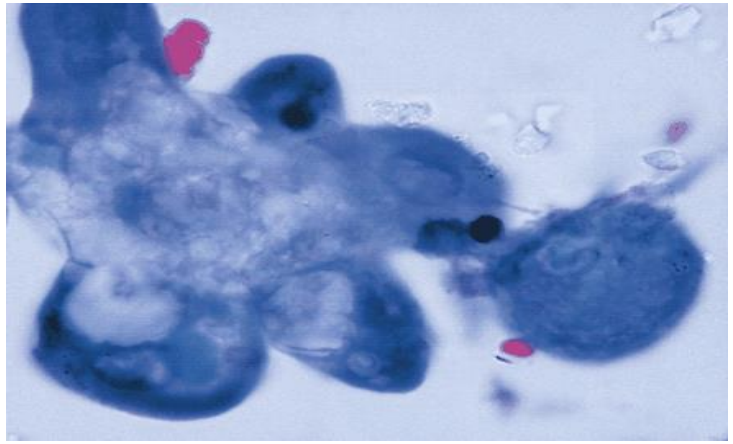
Fischer A. et al. *Lancet 2012*
Jee AS. et al. *Respirology 2022*

Is there any role for bronchoalveolar lavage (BAL)?

- **The routine use of bronchoalveolar lavage (BAL) to solely predict the likelihood of disease progression or response to therapy in CTD-ILD is no longer recommended**

- **BAL may be useful to rule out other processes, such as infection, drug toxicity, diffuse alveolar hemorrhage (DAH) or diffuse alveolar damage (DAD), and for research**





Meyer KC, et al. *AJRCCM* 2012
Fischer A, et al. *Respiration* 2015
Tomassetti S, et al. *Ther Adv Musculoskel Dis 2021*

Lung biopsy (LBx): to do or not to do?

Lung biopsy is generally not required for the diagnosis of CTD-ILD, with HRCT highly specific for discriminating disease pattern in this population.

A surgical lung biopsy may be appropriate in patients with preexisting CTD when

- there are significant concerns for an alternative etiology (e.g., HP or smoking-related lung disease)
- the HRCT is 'atypical' for underlying CTD or suggests malignancy or infection
- the diagnosis of CTD is still unclear

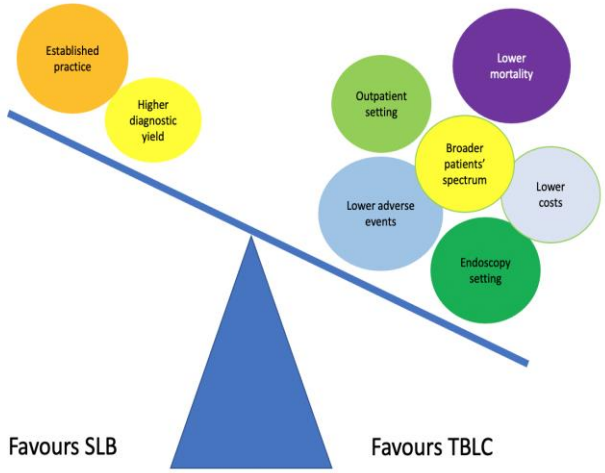
Ultimately, the decision of whether to perform a surgical lung biopsy is individualized, with due consideration for its associated risks and whether its findings will impact management and prognosis

MDT discussion prior to LBx!!!

Fischer A, et al. *Respiration* 2015
Tomassetti S, et al. *Ther Adv Musculoskel Dis 2021*

Lung biopsy: to do or not to do?

- **VATS (Video-Assisted Thoracoscopic Surgery)**
  - **TBCB (Transbronchial Cryobiopsy)**



The availability of **TBLC** in many referral centers as a much safer technique than SLB may allow to obtain from **informative lung tissue** the pivotal information we need to cross the line of **precision medicine** (e.g. proteomics, genetic, molecular studies), with **minimal side effects**

Troy LK, et al. *Lancet Respir Med* 2022
Poletti V, et al. *Expert Rev Respir Med* 2017
Tomassetti S, et al. *Ther Adv Musculoskel Dis 2021*

Monitoring progression of ILD-CTD – General principles

- ✓ Given the heterogeneous disease course of CTD-ILD, accurate prognostication involving staging of ILD severity and assessment of disease progression is important when making treatment decisions

- ✓ An understanding of the natural history of the specific CTD-ILD in question also provides important information

  For example, whilst SSc-associated ILD (SSc-ILD) may follow a relatively indolent course and require only careful monitoring, myositis-associated ILD (IIM-ILD) can progress rapidly, necessitating intensive immunosuppressive therapy

- ✓ Importantly, drug-induced ILD, AE, DAH and infection (including opportunistic infection) should always be considered in the setting of new-onset interstitial changes in CTD

- ✓ Assess comorbid conditions (PH, lung cancer, RF)

Jee AS. et al. *Respirology 2022*

Monitoring progression of ILD-CTD – General principles

- **Lung function evatuation (FVC, TLC, DLCO)**

  (e.g. in SSc-ILD every 3-6 mo for 3-5y, then annualy)

- **HRCT low dose**

- **Clinical evaluation**
- **Six minute walking test (6MWT) (>50m)**

Perelas A, et al. Lancet Respir Med 2020

Jee AS. et al. *Respirology 2022*

Monitoring progression of ILD-CTD

Significant change in lung function

FVC ≥ 10%

DLCO ≥ 15%

Criteria for progressive pulmonary fibrosis

at least two of the following three criteria occurring within the past year with no alternative explanation

worsening of respiratory symptoms

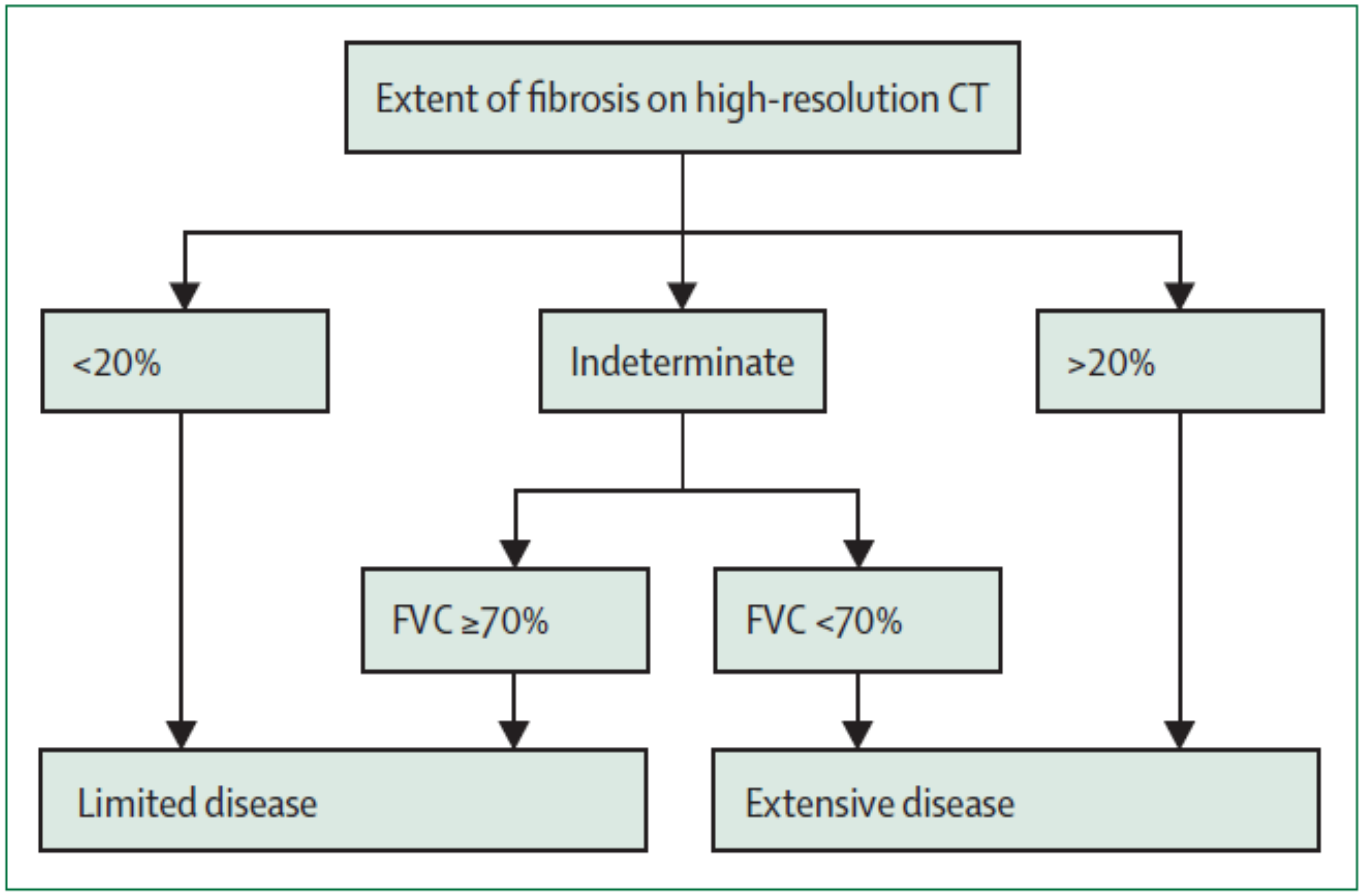
FVC ≥ 5% or DLCO ≥ 10%

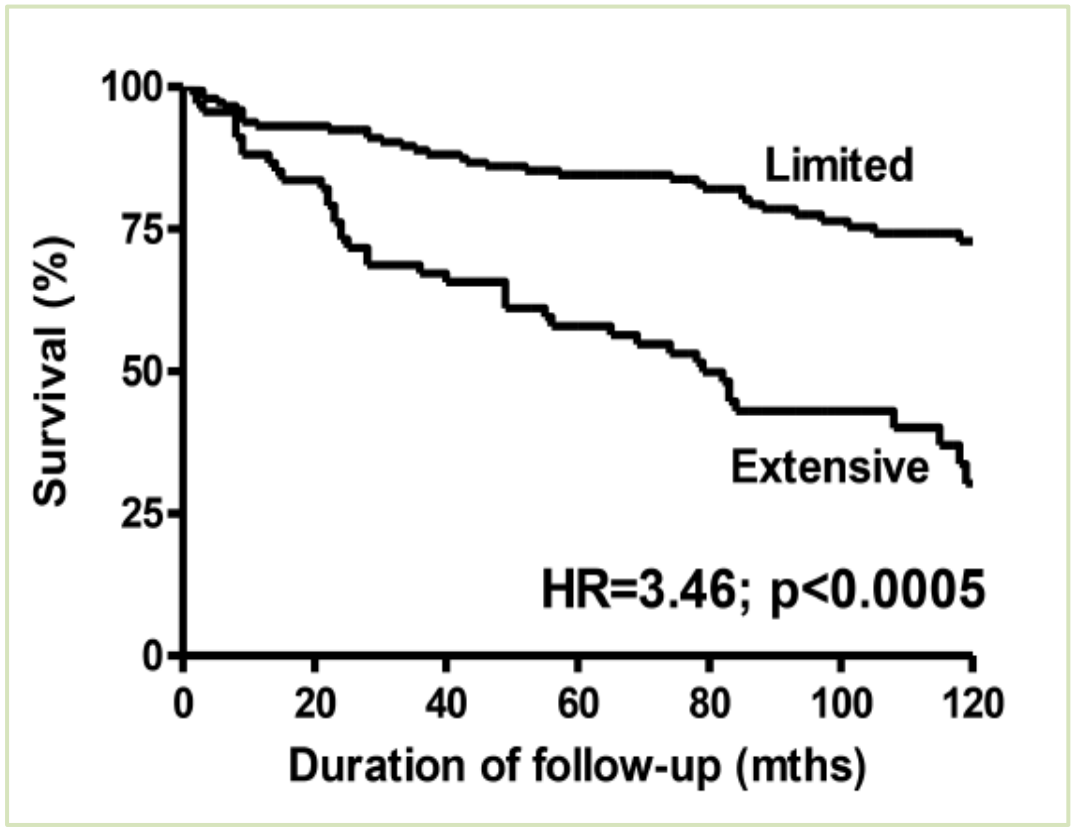
disease progression on HRCT

Goh NS. et al. *Arthitis Rheumatol 2017*

Raghu G, et al. AJRCCM 2022

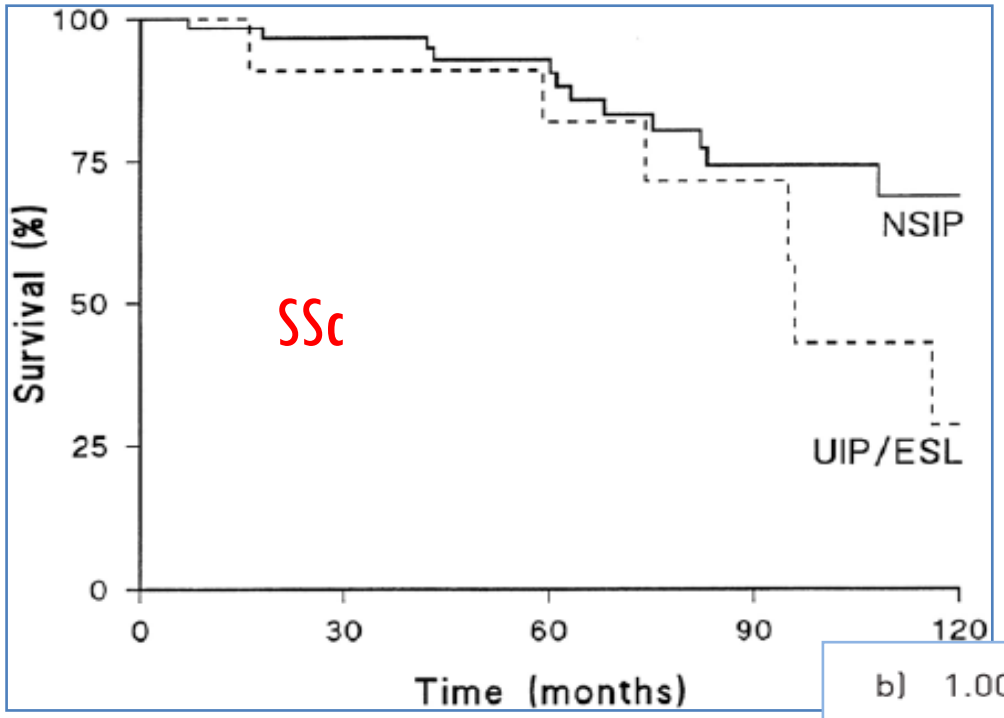
Staging SSc-ILD

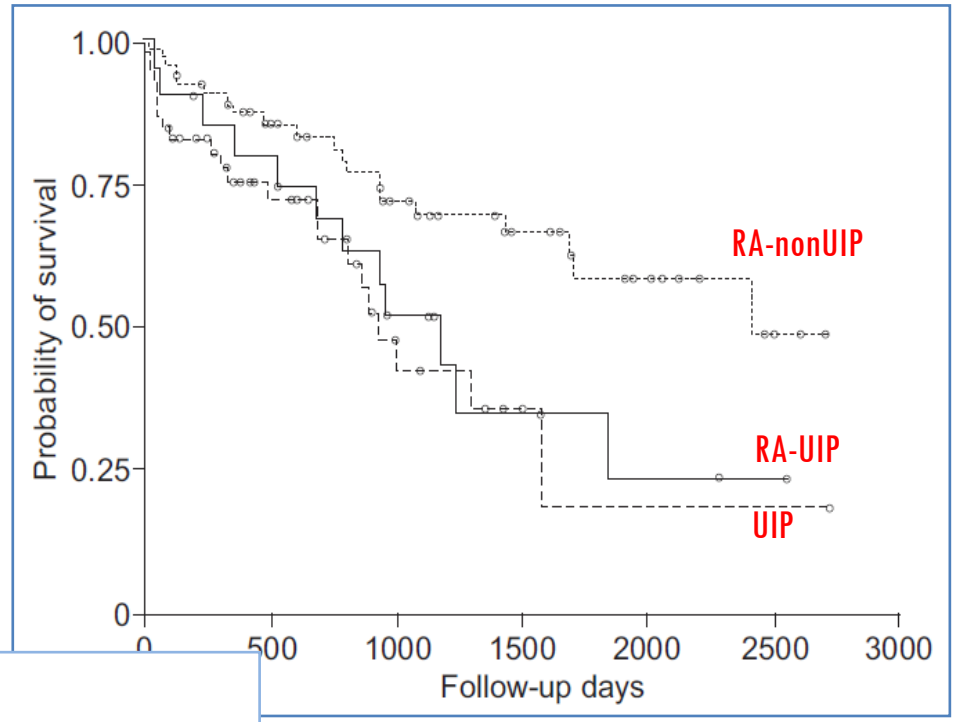


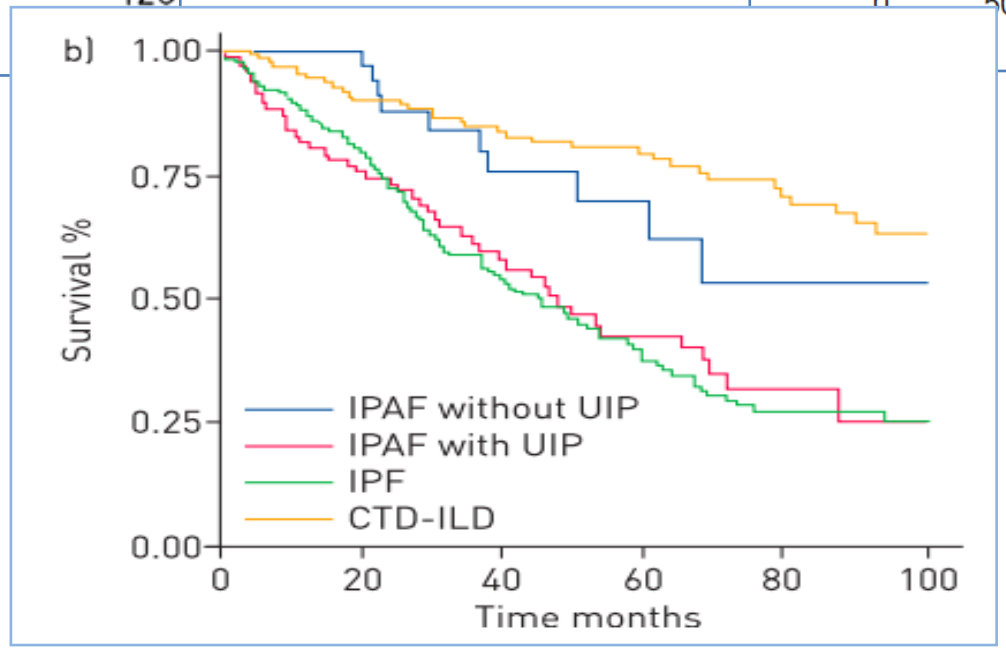


Goh NS. et al. *AJRCCM 2008*

Prognosis of CTD-ILD







Bouros D, et al. *AJRCCM 2002*,
Kim EJ, et al. *Eur Respir J 2010*
Oldham JM, et al. *Eur Respir J 2016*

Conclusions

- ✓ ILDs is a common manifestation of CTD and is often associated with significant morbidity and mortality
- ✓ Integration of clinical, serological, functional and HRCT findings, coupled with ILD-MDT discussion, is key to confirming an accurate diagnosis of CTD-ILD
- ✓ NSIP is the most frequent radiological and histological pattern seen in association with CTD
- ✓ Lung biopsy is generally not required for the diagnosis of ILD-CTD, and should be reserved for cases of major diagnostic uncertainty following ILD-MDT discussion
- ✓ American College of Rheumatology (ACR) Guideline for the Screening, Monitoring, and Treatment of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Disease (autumn 2023)

Ευχαριστώ για την προσοχή σας