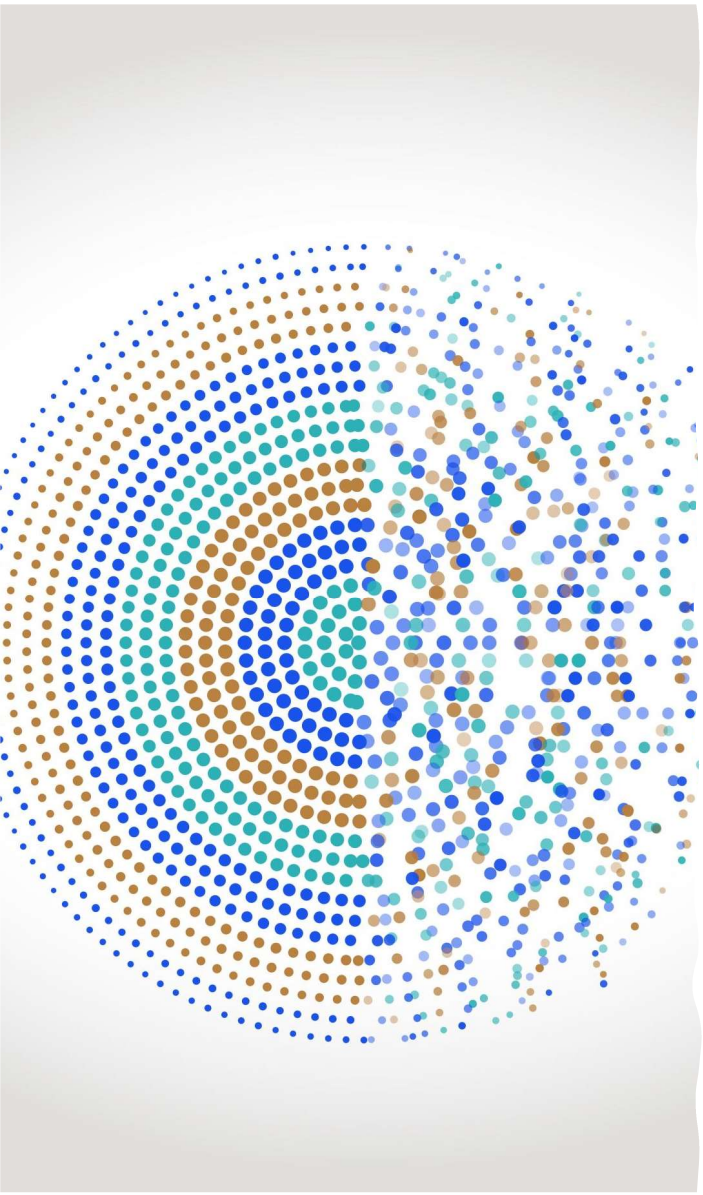

Connective Tissue Disease Related ILD, an Overview

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Disclosures

- I am a site Principal Investigator for clinical trials funded by United Therapeutics

Objectives

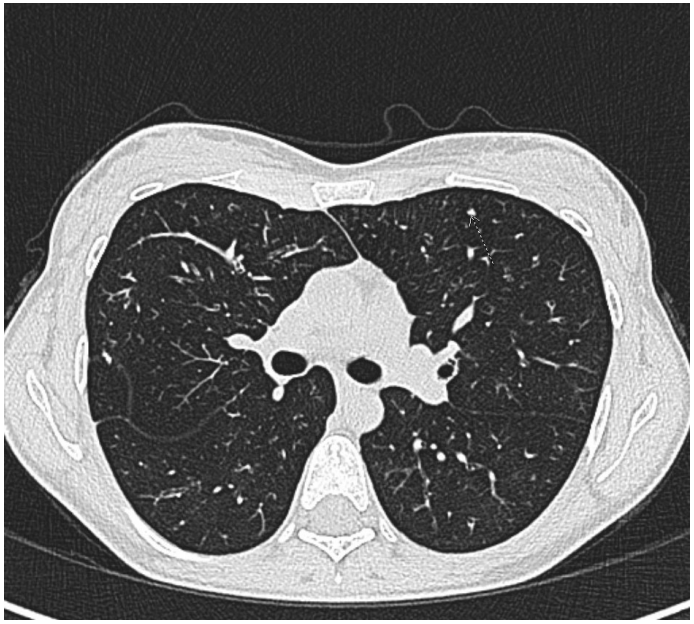
We will review the most common ILD patterns in CTD

We will review the clinical evaluation and diagnostic tests for connective tissue disease related ILD.

We will highlight the most recent clinical trials for management of CTD-ILD

Case 1

35-year-old woman with a diagnosis of seropositive RA since the age of 20, presents to the pulmonary clinic with long standing dyspnea on exertion



	Pred	Actual	Pre %Pred	LLN	A
---- SPIROMETRY ----					
FVC (L)	3.30	*1.61	*48	2.68	
FEV1 (L)	2.76	*0.71	*25	2.24	
FEV1/FVC (%)	83.4	*43.9	*52	73.5	
FEF 25-75% (L/sec)	3.09	*0.22	*7	1.99	
FEF Max (L/sec)	6.45	*2.72	*42	4.93	
Expiratory Time (sec)		9.76			
FEF50%/FIF50% (%)	90-100	8			
TestGrade(ATS)		AA			

Diagnosis?

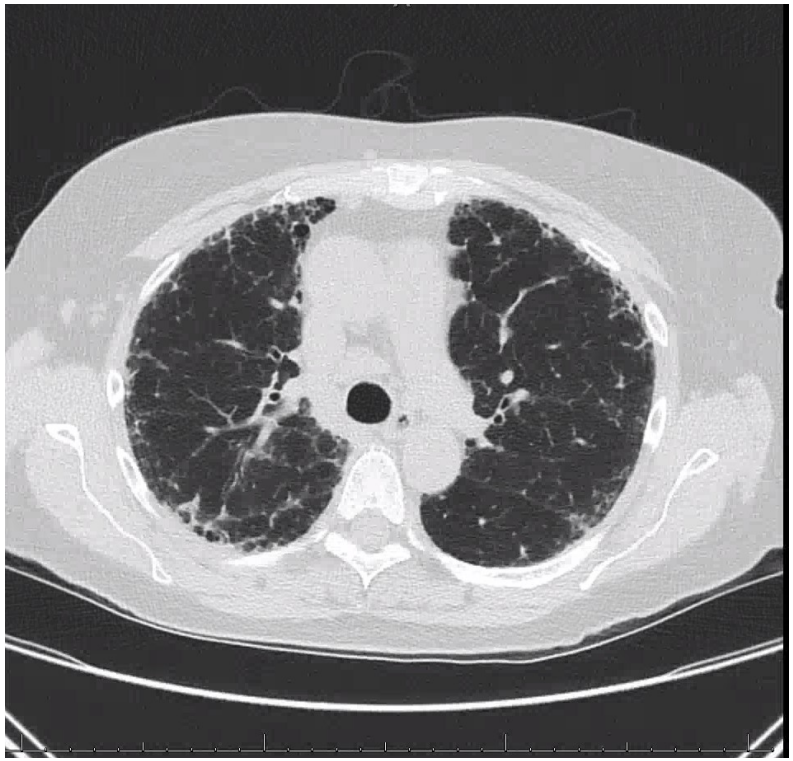
Bronchiolitis Obliterans

Case 2

RA-ILD (UIP pattern)

65-year-old woman with seropositive RA comes in with dyspnea and chronic cough

	Pred	Actual	Pre %Pred	LLN
---- SPIROMETRY ----				
FVC (L)	2.74	*1.52	*55	2.10
FEV1 (L)	2.13	*1.33	*62	1.58
FEV1/FVC (%)	77.75	*88.07	*113	68.40
FEF 25-75% (L/sec)	2.05	1.83	89	0.84
FEF Max (L/sec)	5.27	5.48	104	3.44
Expiratory Time (sec)		6.88		
FEF50%/FIF50% (%)	90-100	52		
TestGrade(ATS)		AA		
---- LUNG VOLUMES ----				
SVC (L)	2.74	*1.81	*66	2.10
IC (L)	2.01	1.51	75	
---- DIFFUSION ----				
DLCOunc (ml/min/mmHg)	21.96	*8.53	*38	14.82
DLCOcor (ml/min/mmHg)	21.96			14.82
VA (L)	4.57	*2.67	*58	3.47



What is the ILD pattern?

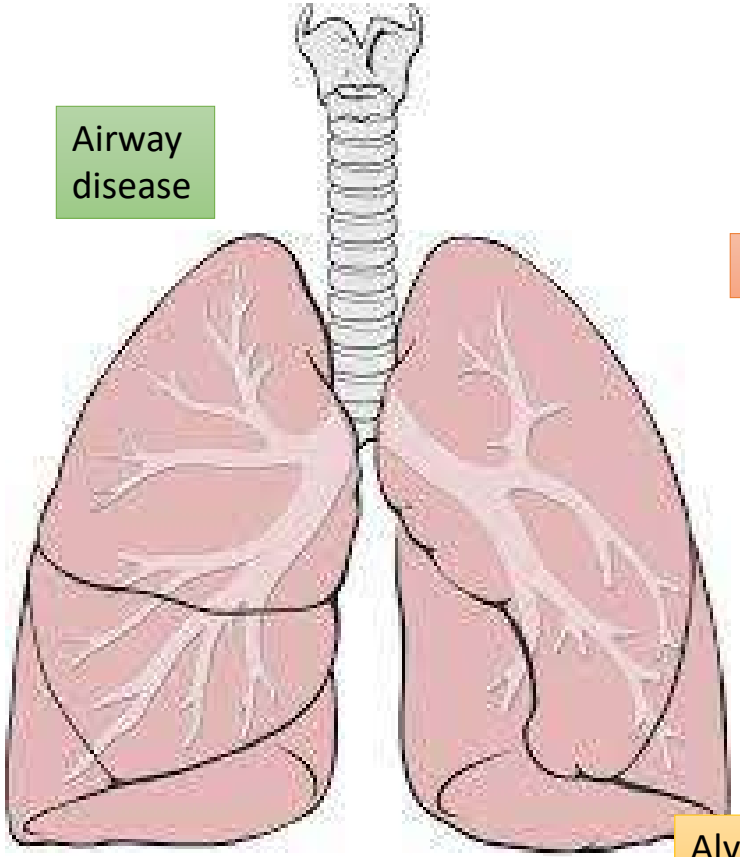
Airway disease

Pleural disease

Diffuse parenchymal disease

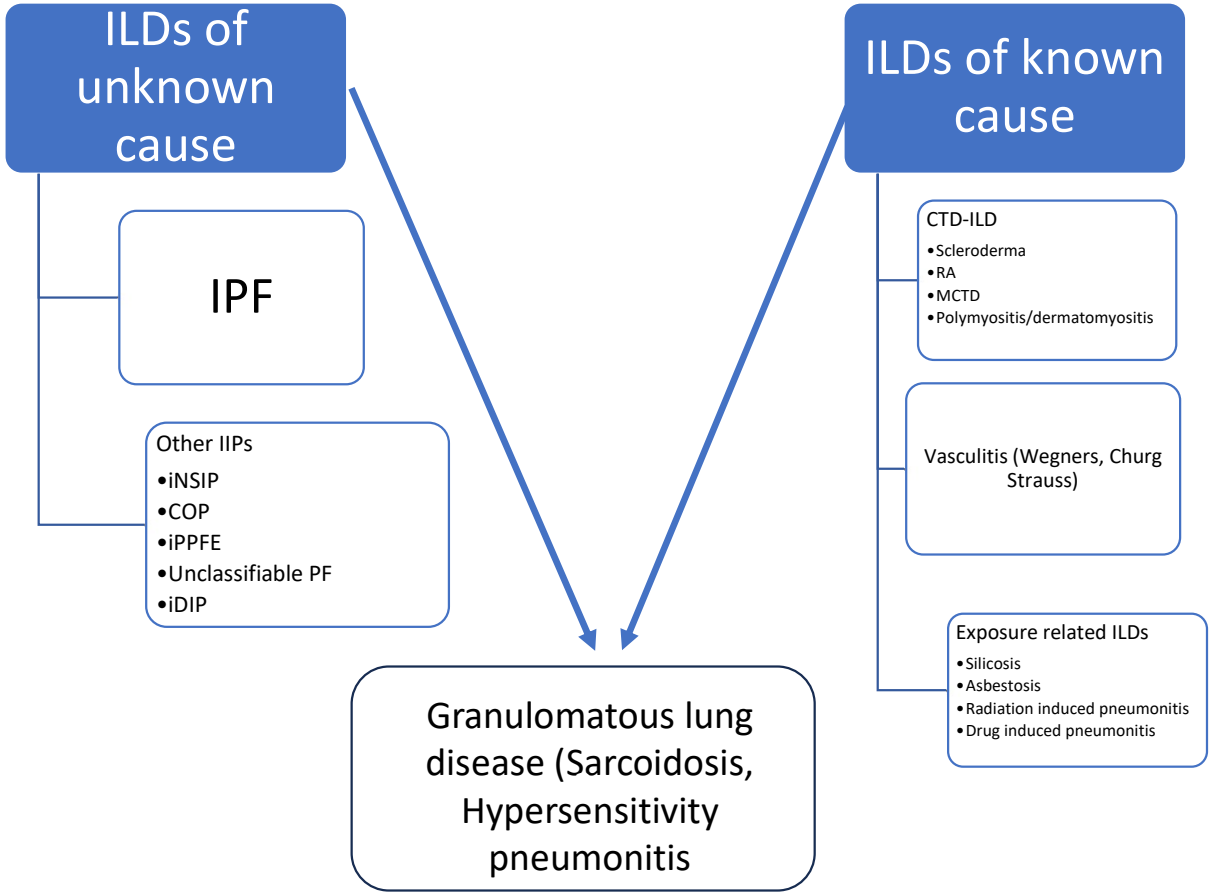
Pulmonary vascular disease

Chest wall disease



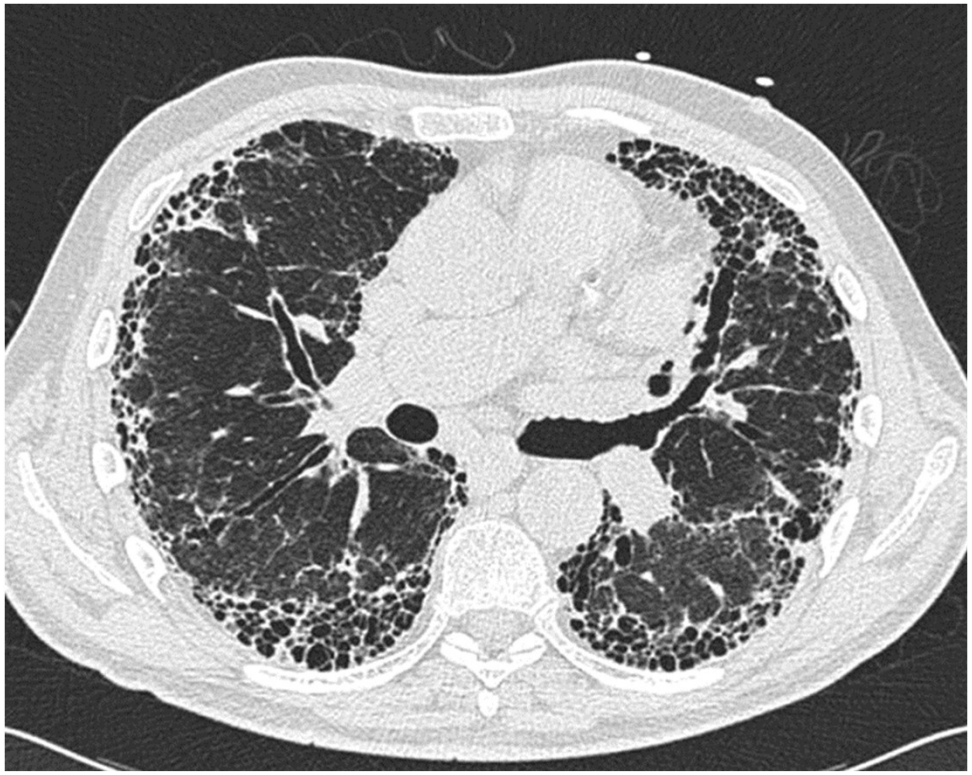
Alveolar hemorrhage

Classification of Interstitial Lung Disease



HRCT

- Inspiratory supine and expiratory supine
- <2 mm axial reconstruction
- “High spatial frequency reconstruction” algorithm
- No IV contrast
- Prone imaging in select cases



Diagnostic criteria for IPF / HRCT

UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
Subpleural and basal predominant; distribution is often heterogeneous*	Subpleural and basal predominant; distribution is often heterogeneous	Subpleural and basal predominant	Features: ◦ Cysts ◦ Marked mosaic attenuation ◦ Predominant GGO ◦ Profuse micronodules ◦ Centrilobular nodules ◦ Nodules ◦ Consolidation
Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis†	Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis	Subtle reticulation; may have mild GGO or distortion (“early UIP pattern”)	Predominant distribution: ◦ Peribronchovascular ◦ Perilymphatic ◦ Upper or mid-lung
	May have mild GGO	CT features and/or distribution of lung fibrosis that do not suggest any specific etiology (“truly indeterminate for UIP”)	Other: ◦ Pleural plaques (consider asbestosis) ◦ Dilated esophagus (consider CTD) ◦ Distal clavicular erosions (consider RA) ◦ Extensive lymph node enlargement (consider other etiologies) ◦ Pleural effusions, pleural thickening (consider CTD/drugs)

*Variants of distribution: occasionally diffuse, may be asymmetrical.
†Superimposed CT features: mild GGO, reticular pattern, pulmonary ossification.

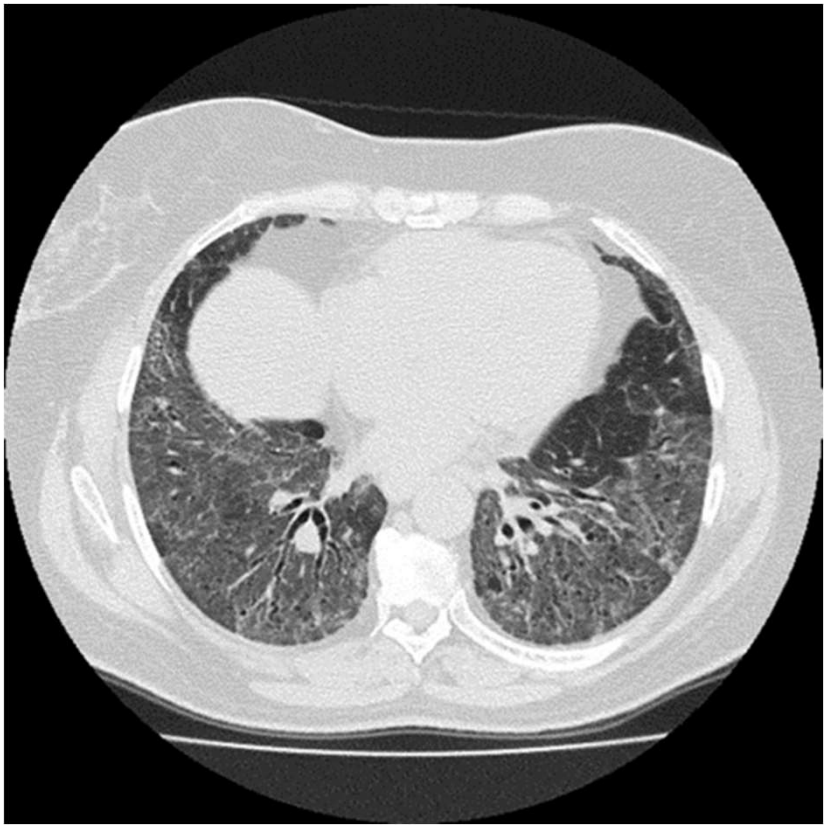
American Journal of Respiratory and Critical Care Medicine Volume 198 Number 5 | September 1 2018

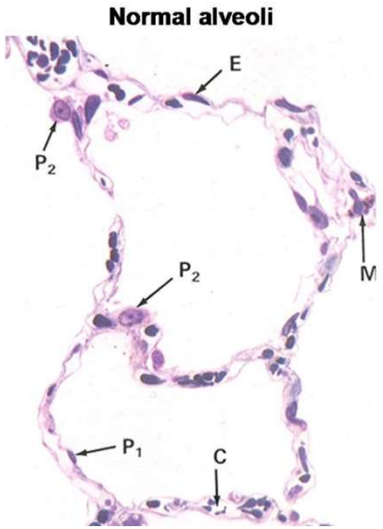
Pulmonary manifestations of CTD

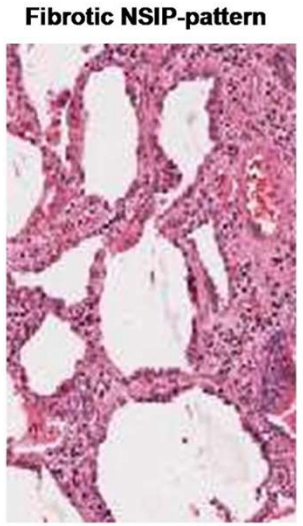
	NSIP	UIP	OP	LIP	DAD	DAH	Airway disease	Pleural disease
RA	++	+++	++	+	+	-	+++	++
SSc	+++	+	+	-	+	-	-	+
PM/DM	+++	+	+++	-	++	-	-	+
Sjogren's	++	+	-	++	+	-	+	+
MCTD	++	+	+	-	-	-	-	+
SLE	++	+	+	++	++	+++	-	+++

Capobianco et al, Radiographics, 2012

NSIP (nonspecific interstitial pneumonia)

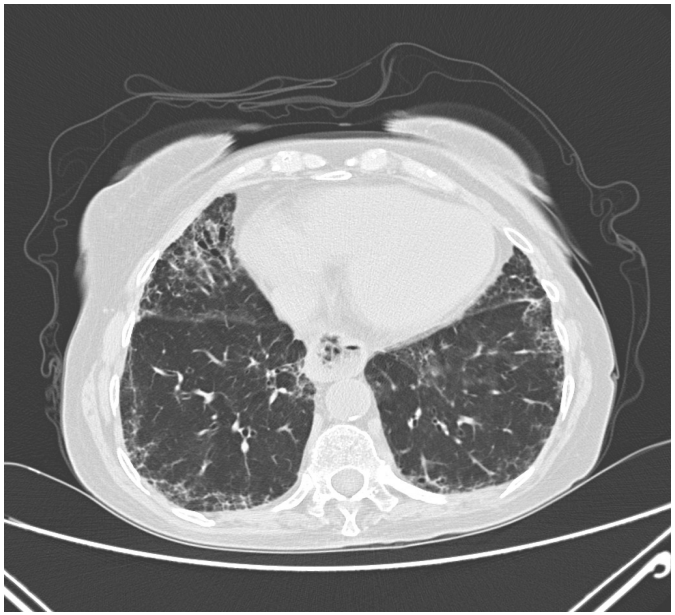


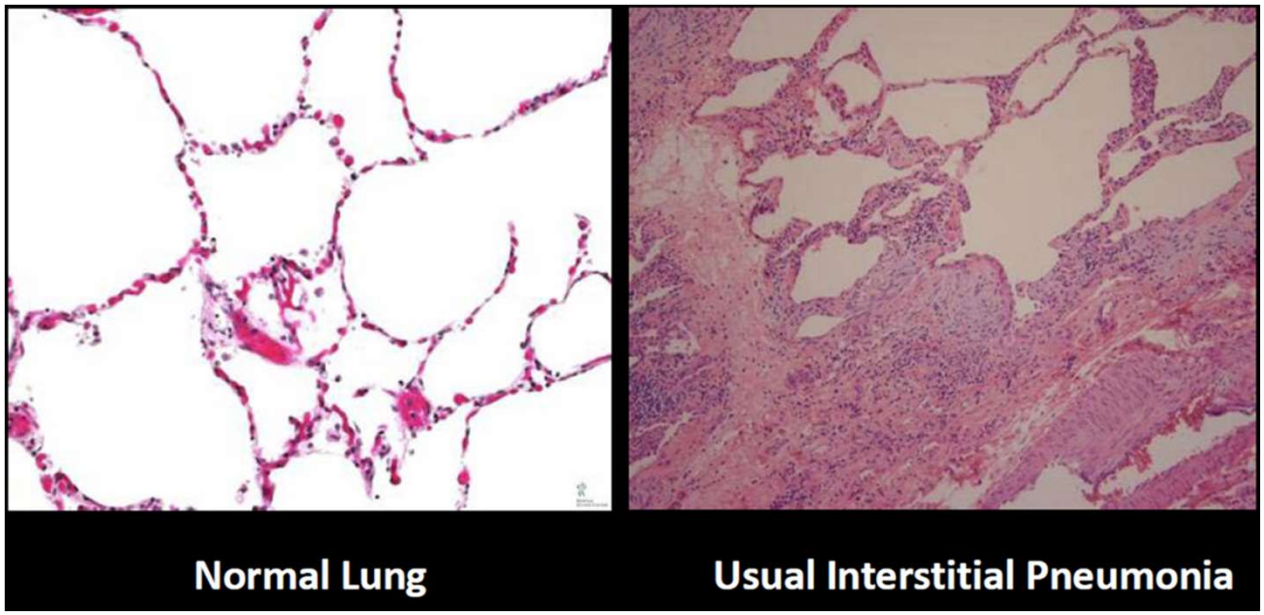




Idiopathic NSIP is extremely rare
Symmetrical and LL Predominant
Ground glass opacities
Traction bronchiectasis
Relative subpleural sparing
Homogenous fibrosis on path

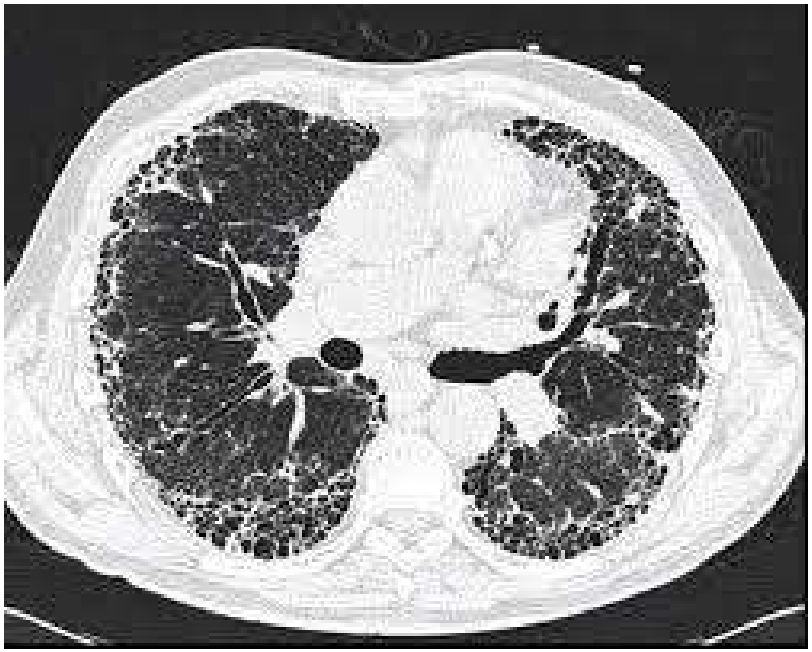
UIP (Usual Interstitial Pneumonia)





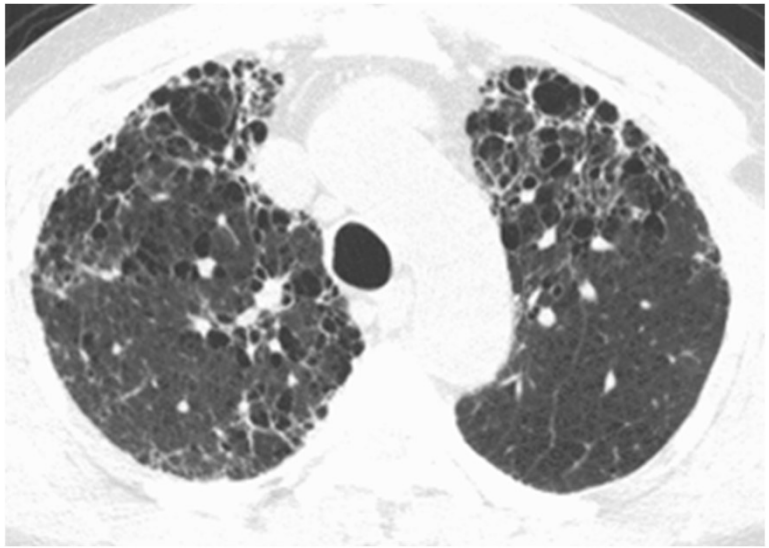
Subpleural and basal predominant
Distribution is often heterogeneous
Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis

Honeycombing and traction bronchiectasis

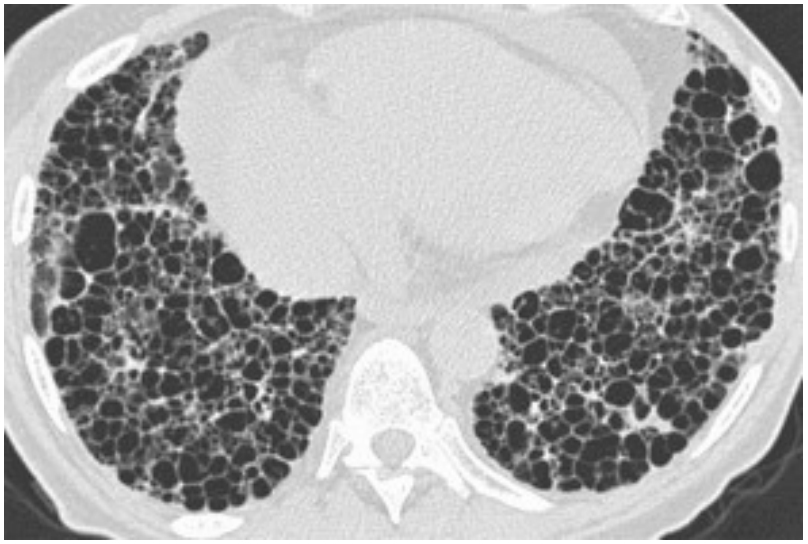


IPF vs CTD-UIP

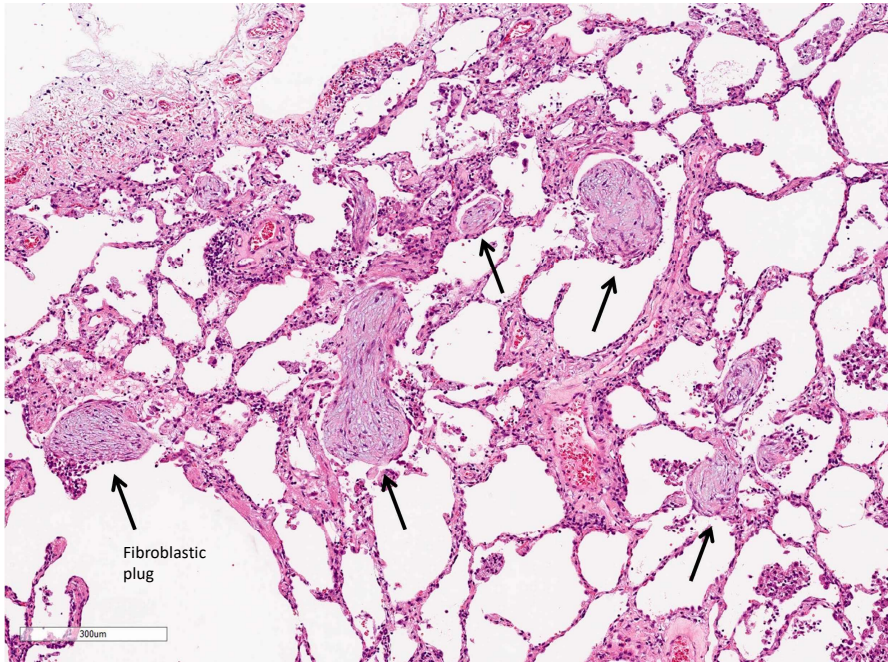
Anterior lobe sign

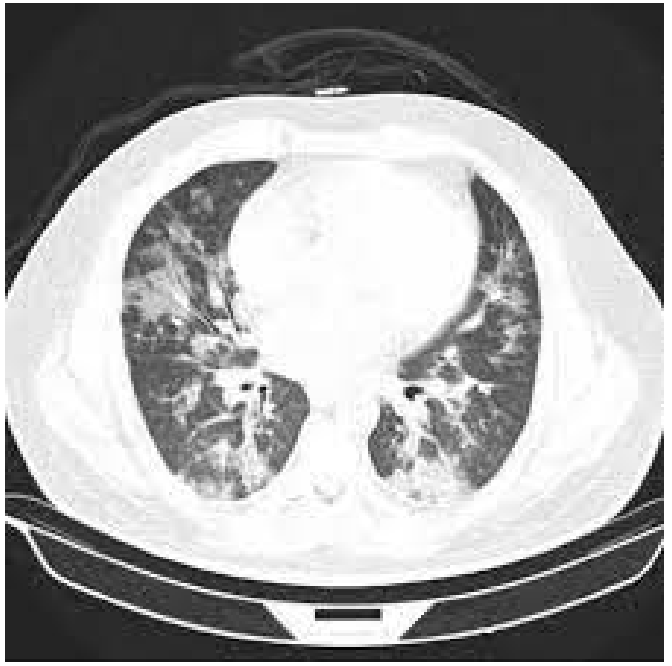


Exuberant Honeycombing



American Journal of Roentgenology. 2018;210: 307-313.
10.2214/AJR.17.18384

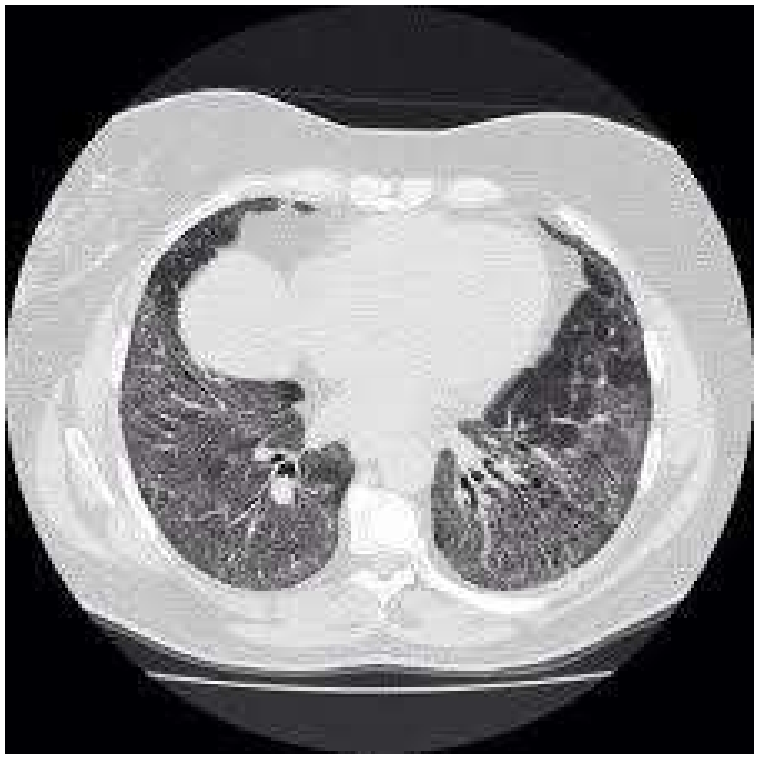


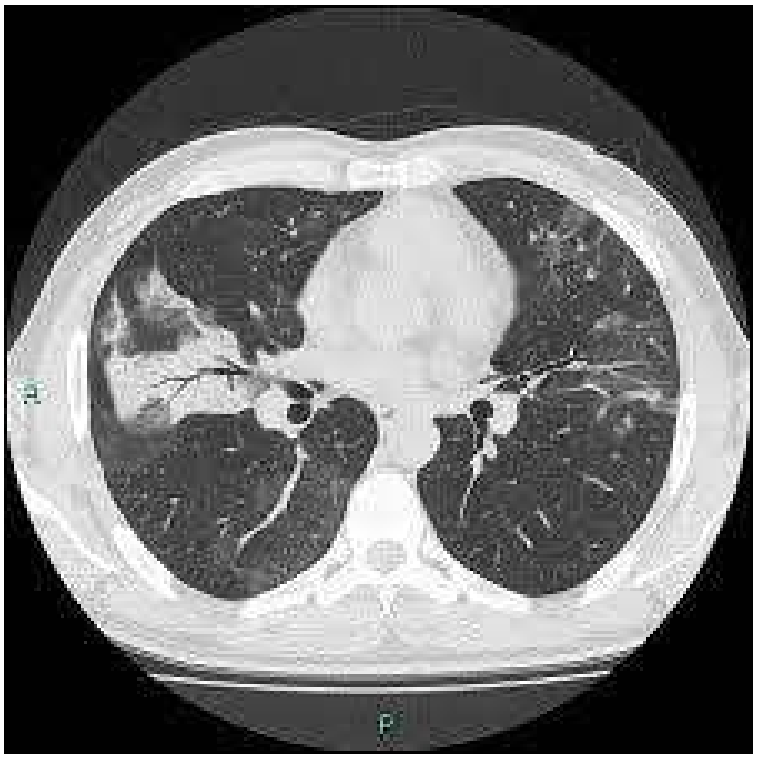


OP: Organizing pneumonia

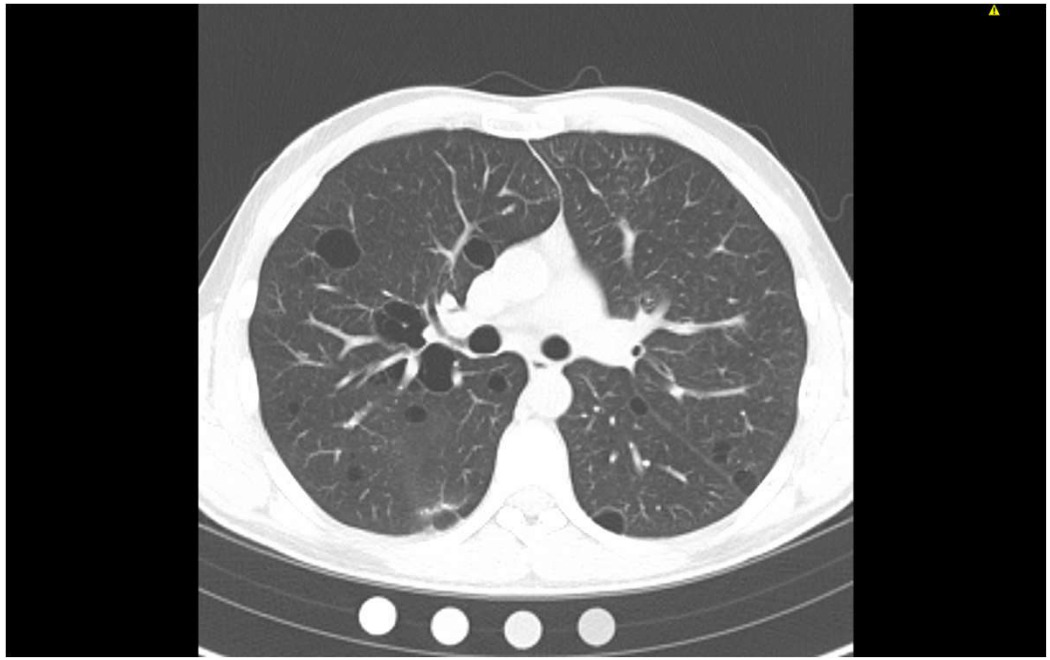
Patchy
Peribronchovascular
Consolidations> Ground glass
Often coexists with NSIP

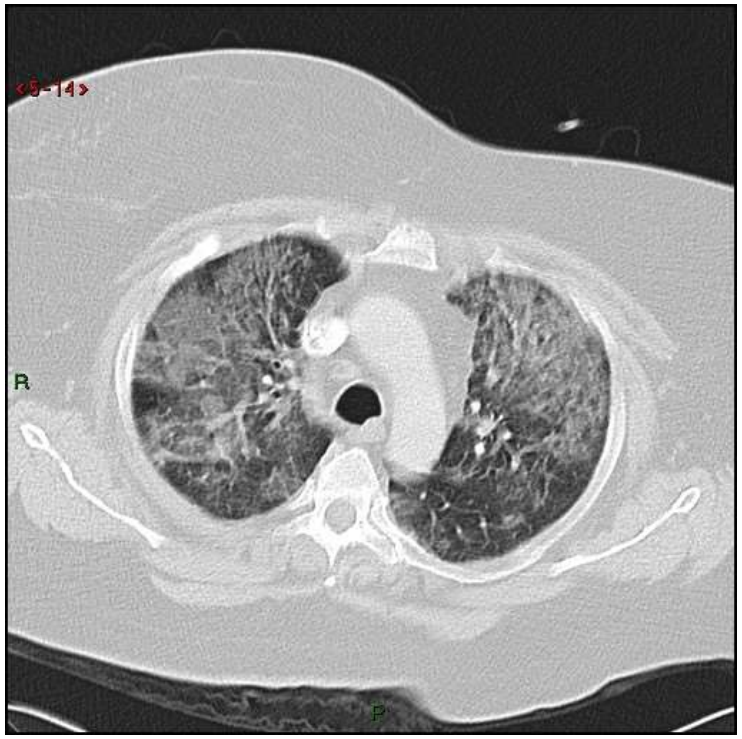
Ground glass vs Consolidations





LIP: Lymphocytic Interstitial Pneumonia





Thin-walled cysts
Ground glass opacities
Pulmonary nodules of variable sizes

How will my patient present?

- Dyspnea and cough
- Abnormal pulmonary physiology and gas exchange
- Abnormal CXR/ chest CT scan

Evaluation

Crackles

Wheezes

Pleural rub

HRCT

Thin cuts

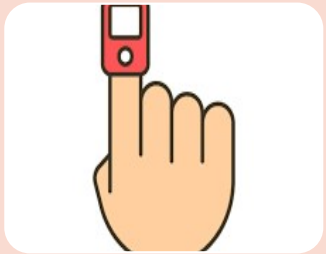
No contrast

Prone/ supine

Inspiratory and expiratory

Spirometry (FVC) suggests restriction

Diffusing capacity

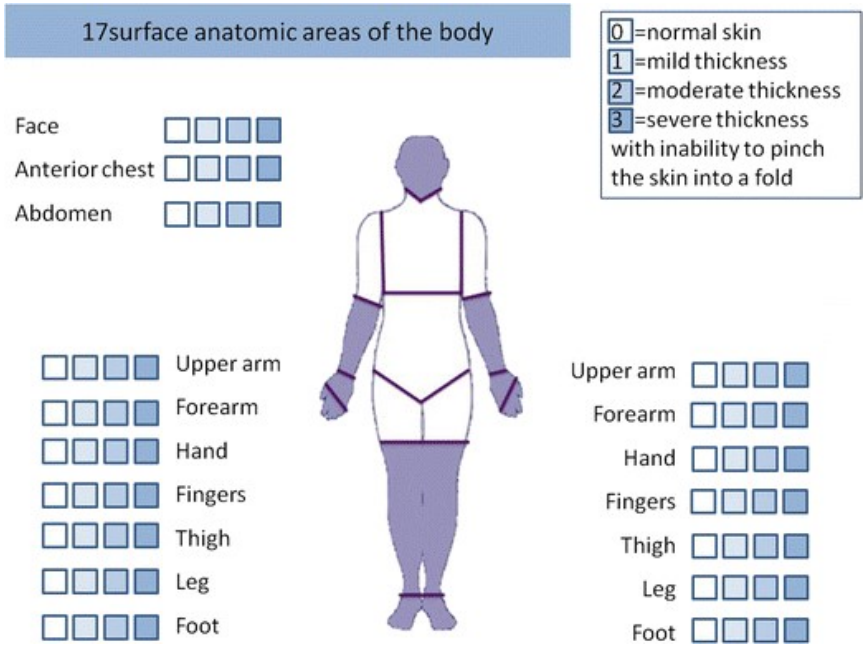


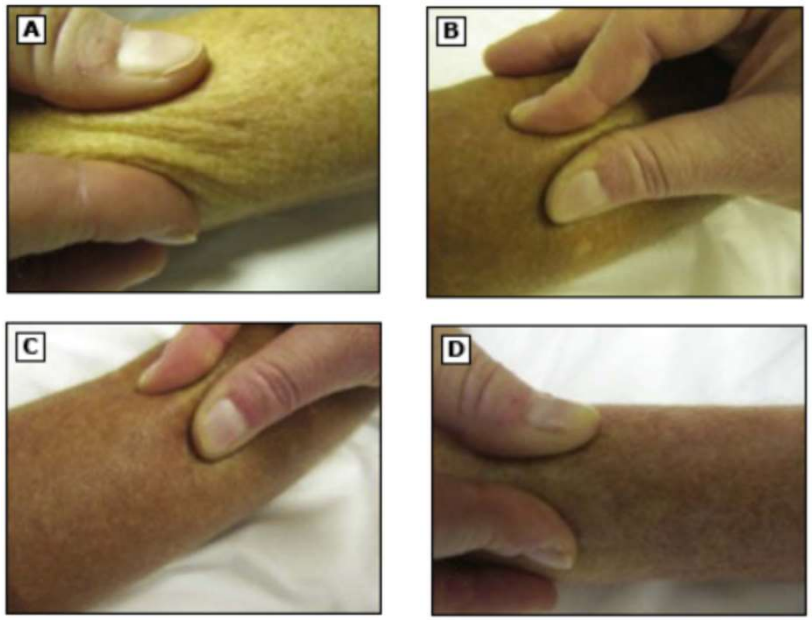
Resting O2 sat

6 min walk

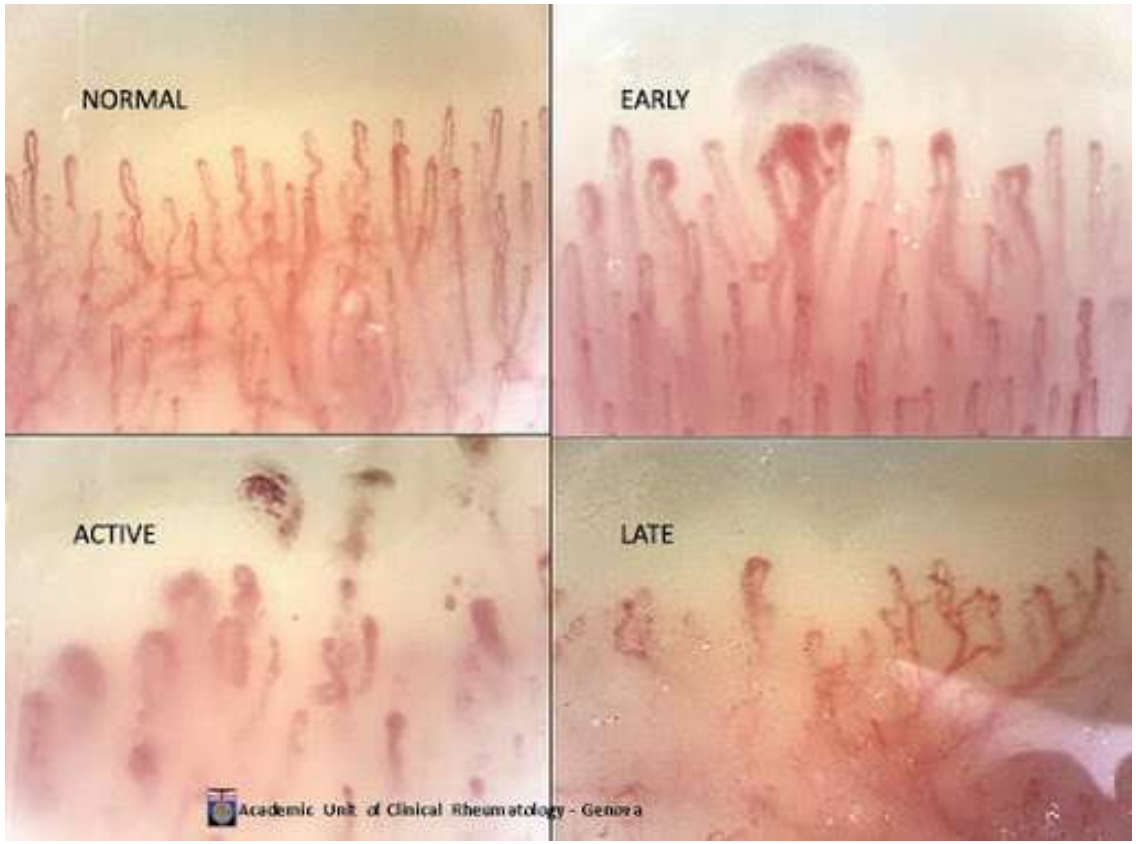
Autoantibodies

Skin disease: Modified Rodnan skin score mRSS



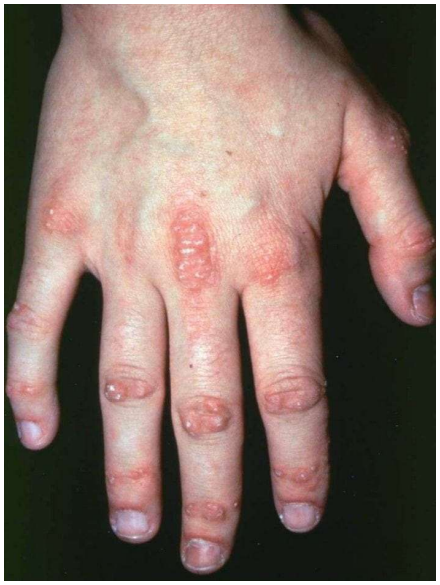


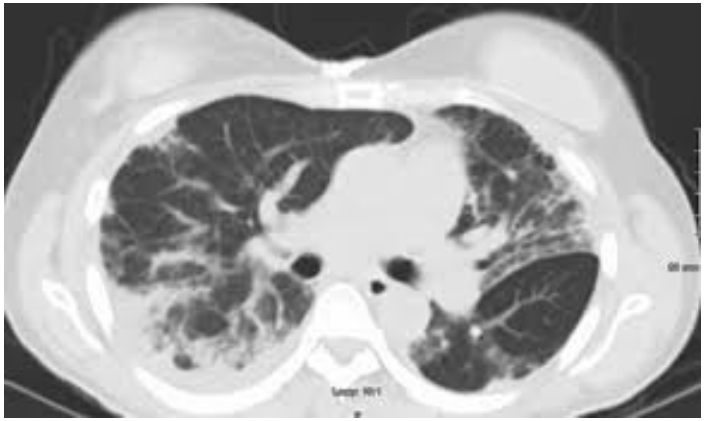
Nailfold capillaroscopy



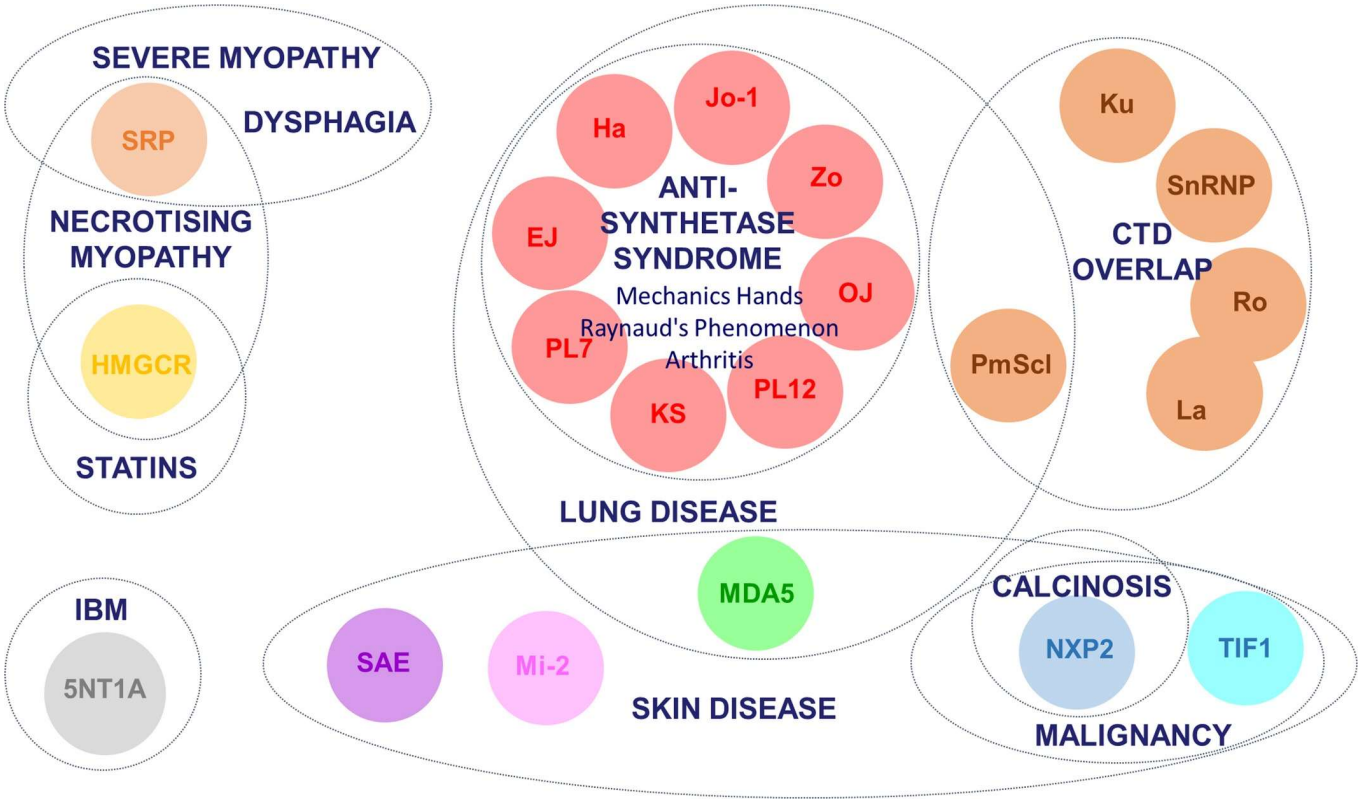
Case

- 44 YO woman identifies as Asian American, presents to urgent care with 2 weeks of breathlessness, chest pain and cough. Normal strength on exam
- What is the most likely abnormality on her autoimmune panel:
  A. Positive SCL-70
  B. Positive ANA
  C. Positive anti MDA-5
  D. Positive Anti-Ro 52



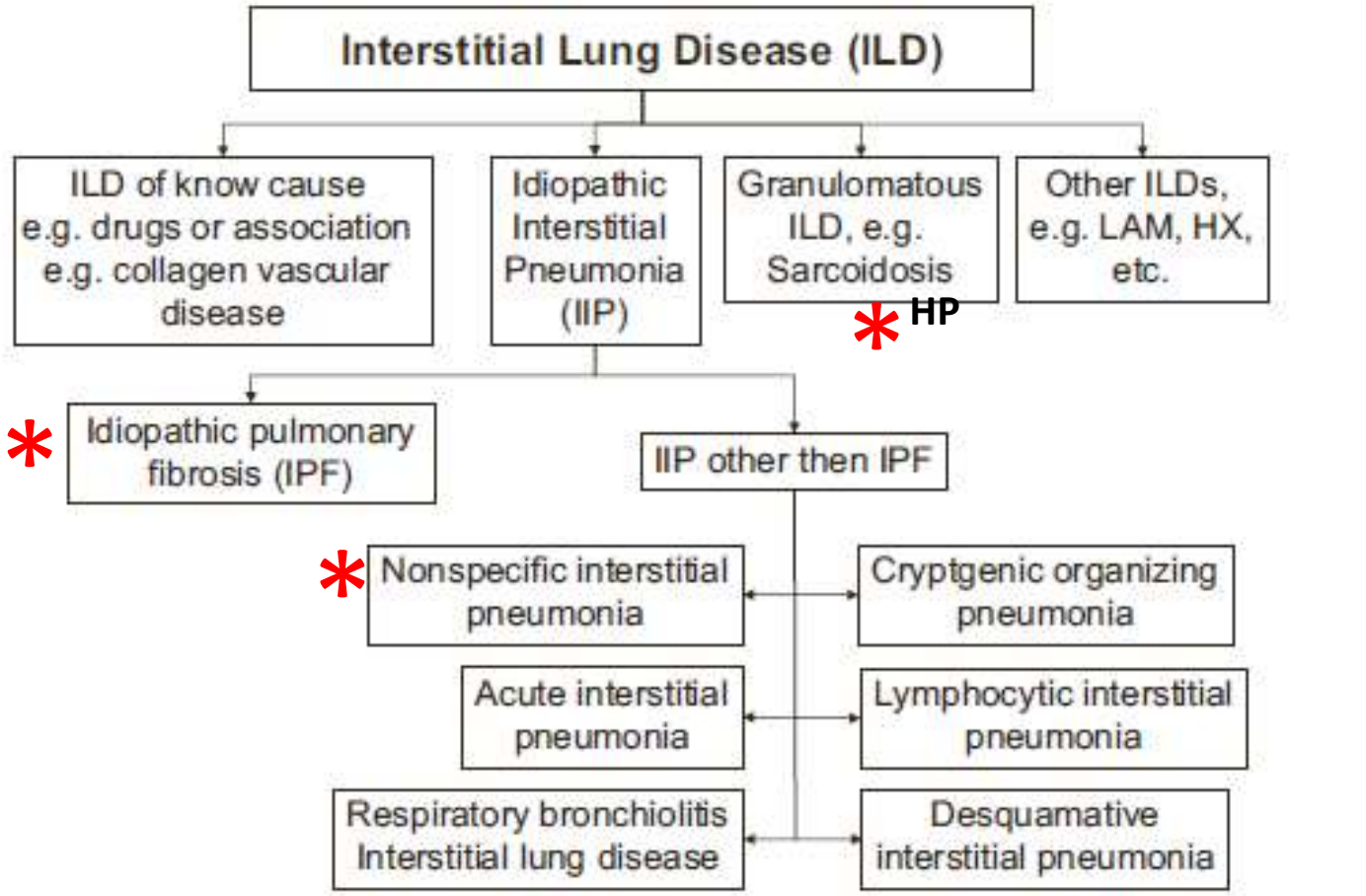


Myositis-specific autoantibodies: an important tool to support diagnosis of myositis



Journal of Internal Medicine, Volume: 280, Issue: 1, Pages: 8-23, First published: 25 November 2015, DOI: (10.1111/joim.12451)

DDx



Behr et al. Clin Chest Med. 2012 Mar;33(1):1-10.

IPAF: interstitial pneumonia with autoimmune features

1. Presence of an interstitial pneumonia by HRCT or SLB *and*
2. Exclusion of alternative etiologies *and*
3. Does not meet criteria for a defined CTD *and*
4. At least one feature from at least two of the following domains:

A. Clinical domain

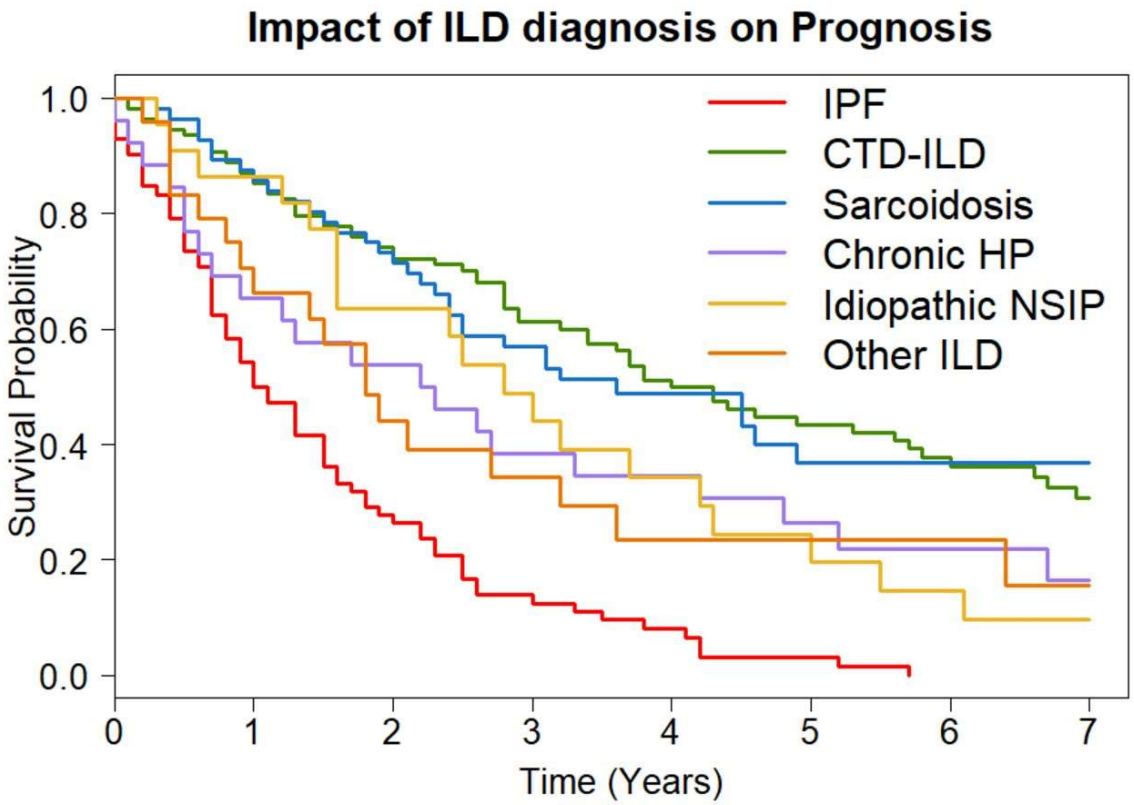
1. Distal digital fissuring (i.e., "mechanic hands")
2. Distal digital tip ulceration
3. Inflammatory arthritis *or* polyarticular morning joint stiffness ⩾60 min
4. Palmar telangiectasia
5. Raynaud phenomenon
6. Unexplained digital edema
7. Unexplained fixed rash on the digital extensor surfaces (Gottron sign)

B. Serologic domain

1. ANA ⩾ 1:320 titer, diffuse, speckled, homogeneous patterns *or*
   a. ANA nucleolar pattern (any titer) *or*
   b. ANA centromere pattern (any titer)
2. Rheumatoid factor ⩾2 × upper limit of normal
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 (e.g., Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS)
11. Anti–PM-Scl
12. Anti–MDA-5

C. Morphologic domain

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 lymphoplasmacytic infiltration (with or without lymphoid follicles)
3. Multicompartment involvement (in addition to interstitial pneumonia):
   a. Unexplained pleural effusion or thickening
   b. Unexplained pericardial effusion or thickening
   c. Unexplained intrinsic airways disease* (by PFT, imaging or pathology)
   d. Unexplained pulmonary vasculopathy



Simon Bax et al. Eur Respir J 2018;52:PA3097

CTD-ILD prevalence

RA	**10-58%**
SSc	**> 65%**
Sjogrens	**25%**
Polymyositis/Dermatomyositis	**23-65%**
SLE	**3-13%**
MCTD	**18-66%**

To treat of not to treat

- Is the ILD progressive?

Table 4. Definition of Progressive Pulmonary Fibrosis

Definition of PPF		
In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation*:		
1	Worsening respiratory symptoms	Q 3 mo
2	Physiological evidence of disease progression (either of the following): a. Absolute decline in FVC ⩾5% predicted within 1 yr of follow-up b. Absolute decline in D_{LCO} (corrected for Hb) ⩾10% predicted within 1 yr of follow-up	Q 3-6 mo
3	Radiological evidence of disease progression (one or more of the following): a. Increased extent or severity of traction bronchiectasis and bronchiolectasis b. New ground-glass opacity with traction bronchiectasis c. New fine reticulation d. Increased extent or increased coarseness of reticular abnormality e. New or increased honeycombing f. Increased lobar volume loss	Q 12 mo

Definition of abbreviations: ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; PPF = progressive pulmonary fibrosis.

*Although it is critical to exclude alternative explanations of worsening features for all patients with suspected progression, this is particularly important in patients with worsening respiratory symptoms and/or decline in D_{LCO} given the lower specificity of these features for PPF compared with FVC and chest computed tomography.

Raghu G, et al. *Am J Respir Crit Care Med*. 2022;205(9):e18-e47. doi:10.1164/rccm.202202-0399ST

Risk factors for progressive CTD-ILD

Disease duration <4 years

Diffuse cutaneous systemic sclerosis

Pulmonary function tests at baseline

FVC <80%

DLCO <80%

HRCT

Interstitial lung disease affecting >20% of the lung

Serology

Anti-topoisomerase I (anti-Scl-70) antibodies

Approach to treatment

ILD pattern

- NSIP/ OP: good response to anti-inflammatory medications
- LIP: Variable response to anti-inflammatory medications
- UIP: Possible response to antifibrotic medication

Extrapulmonary manifestations that also need treatment

Who is driving therapy/ titration: pulmonary or rheumatology?

Monitor treatment response

Scarcity of RCTs outside of SSc-ILD

Landmark clinical trials in CTD-ILD treatment

MMF in SSc-ILD

SLS II trial

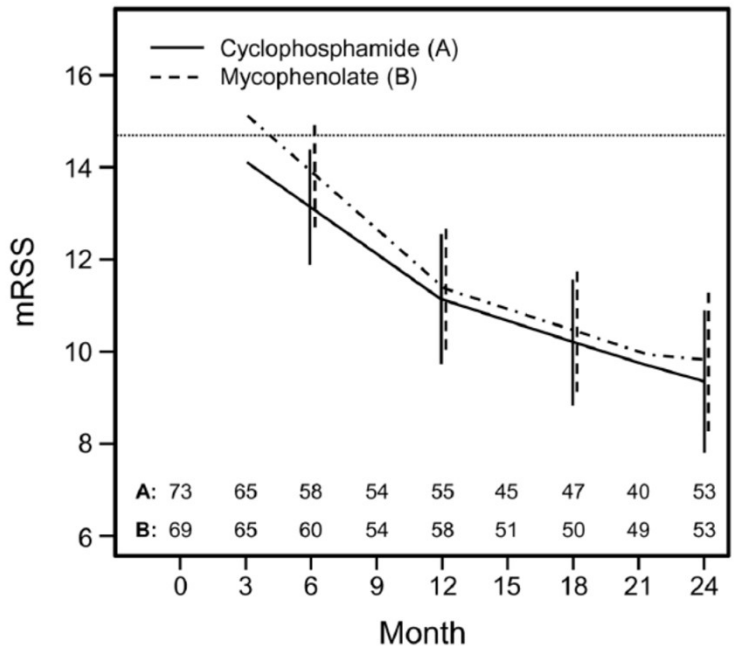
126 patients (63 MMF vs 63 CYC)

24 months

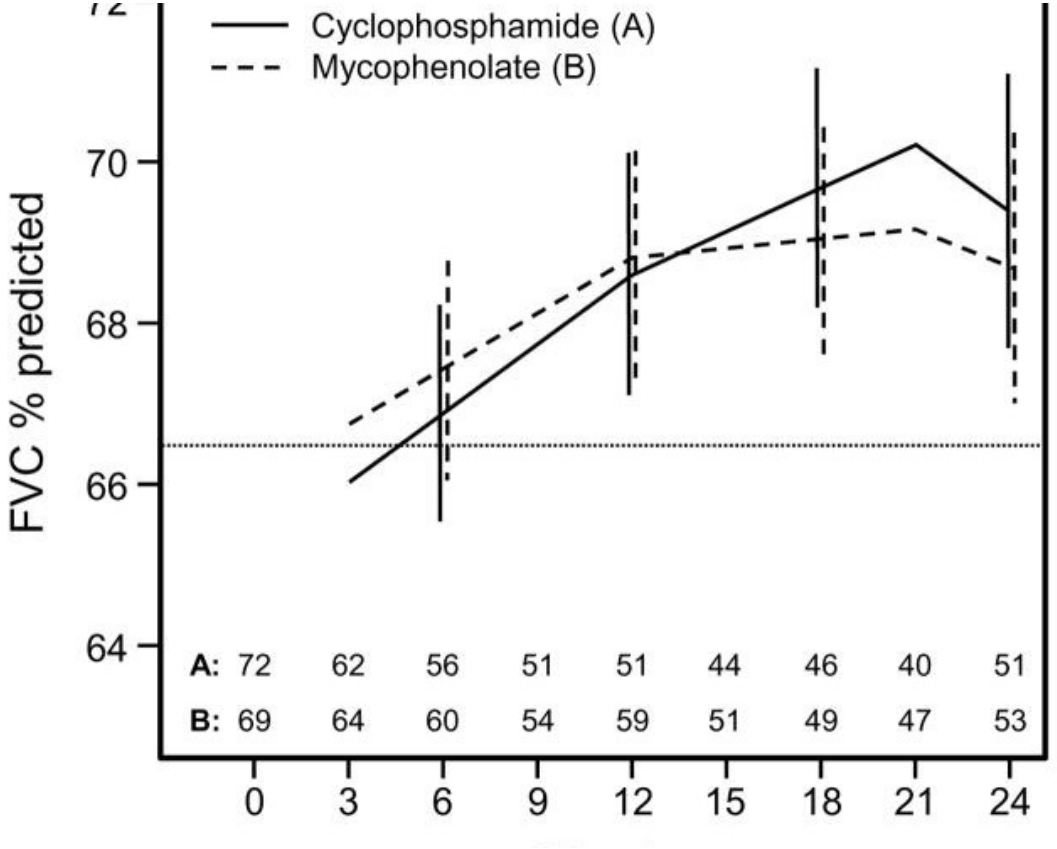
Primary outcome: Change in FVC

Secondary outcomes: mRSS and TDI

MMF vs oral CYC (SLS II Trial)



Less adverse events in the MMF group



Tashkin et al Lan cet Respir Med . 2016

Nintedanib: SENSCIS Trial SSc-ILD

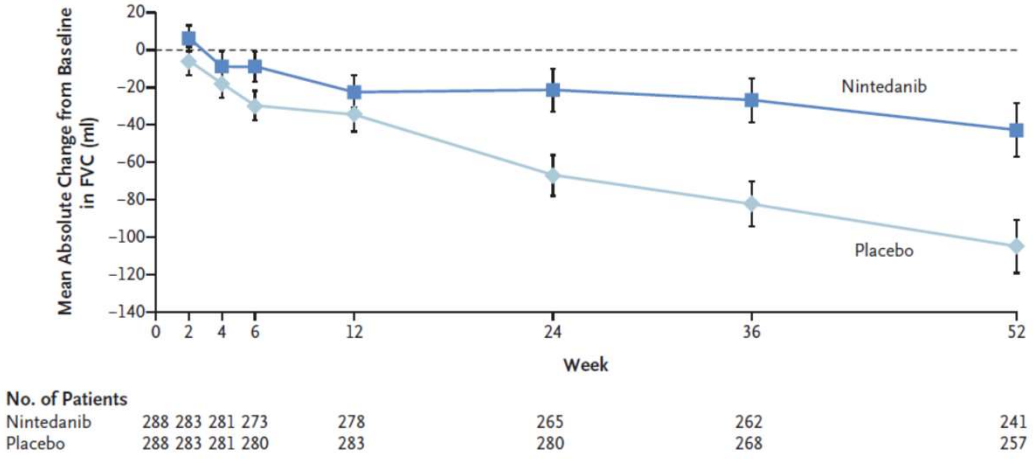
580 Participants, 290 nintedanib vs 290 Placebo

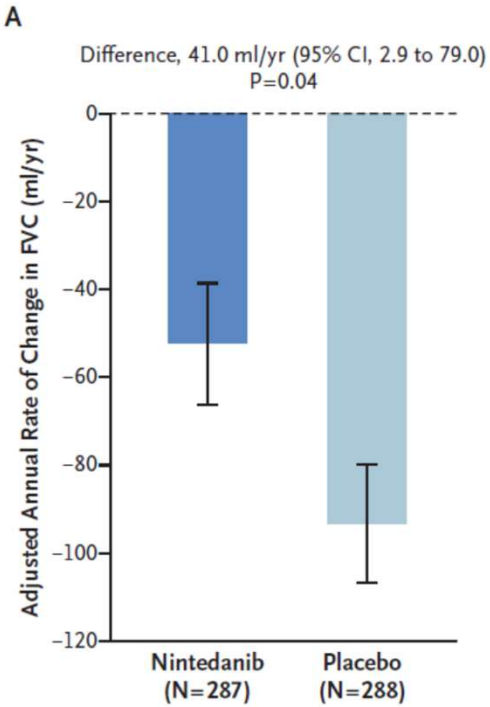
52 weeks

Background treatment with MMF allowed

Primary endpoint: Annual rate of decline in FVC (ml/yr)

Nintedanib in SSc-ILD

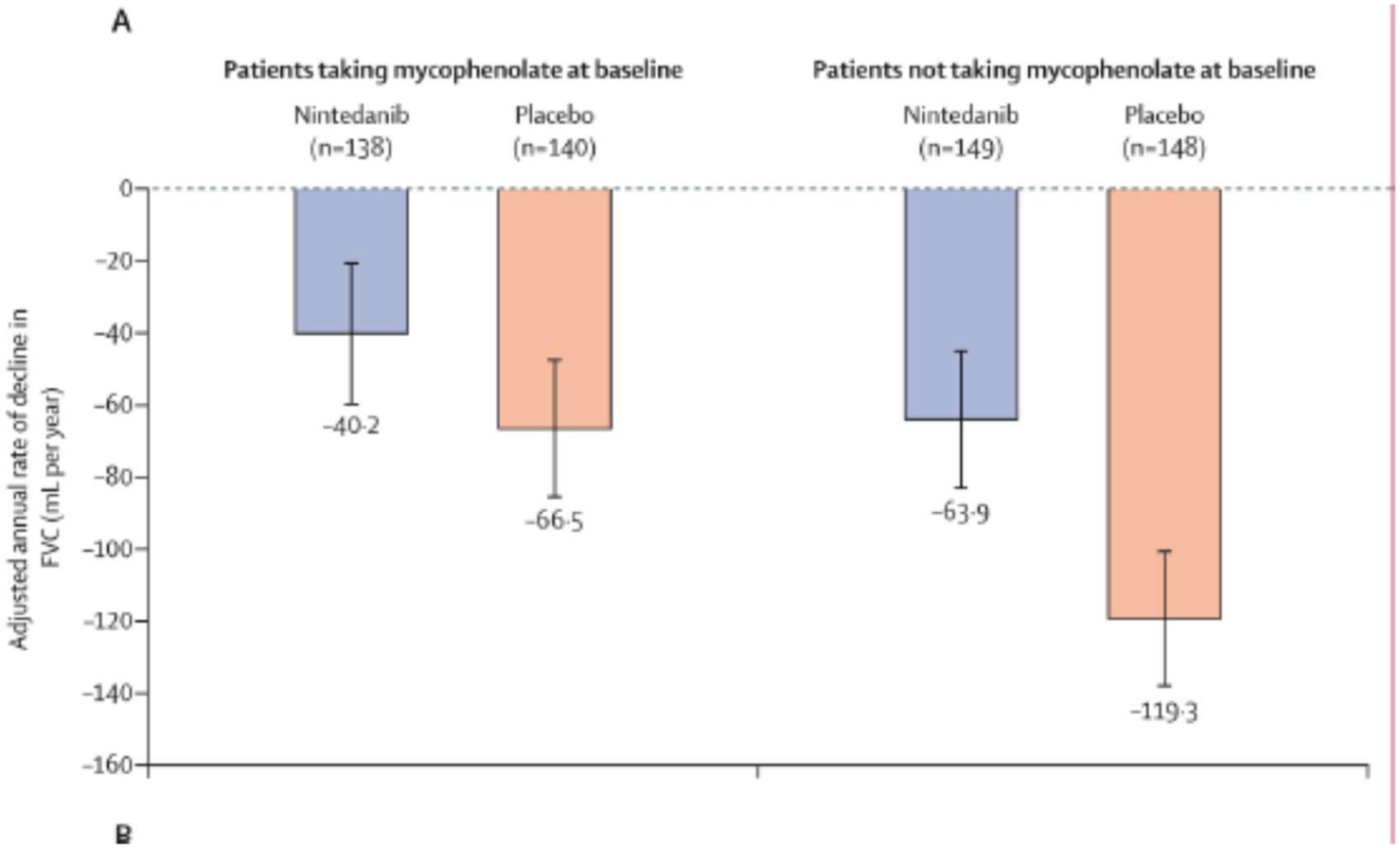




No change in mRSS
Diarrhea in ~ 75% taking nintedanib

SENSCIS trial NEJM 2019

SENSCIS Trial



Nintedanib for PPF

- INBUILD trial
- 663 Participants with PPF, 332 nintedanib vs 331 placebo
- Primary endpoint: annual rate of decline in FVC

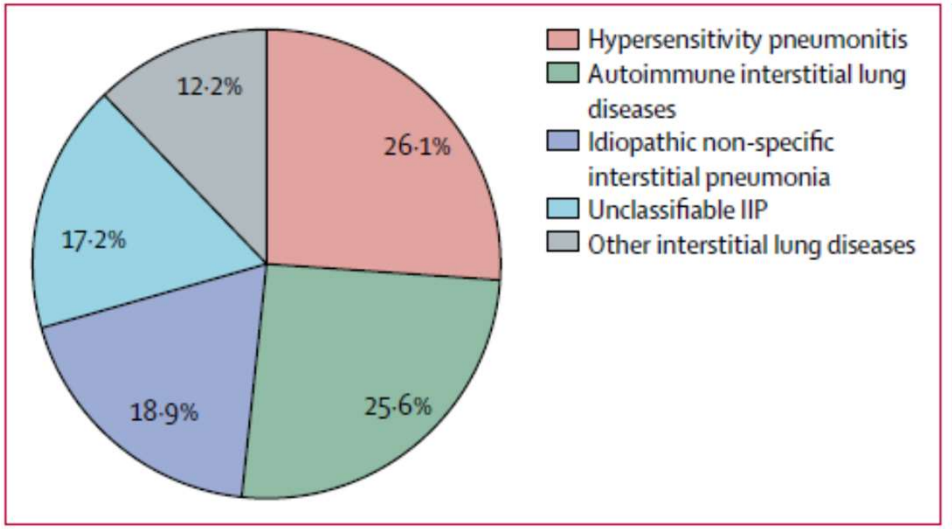
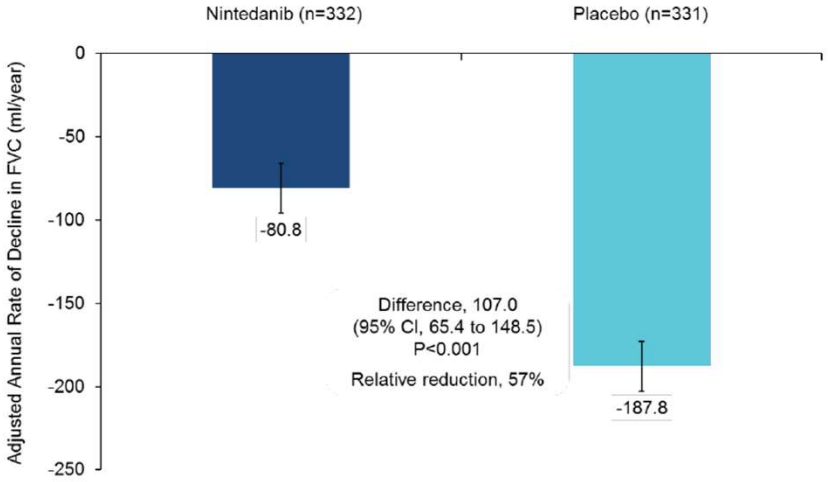


Figure S4A. Between-group adjusted difference in the annual rate of decline in FVC (mL/year) over 52 weeks in the overall population (primary endpoint). The bars indicate the standard error.

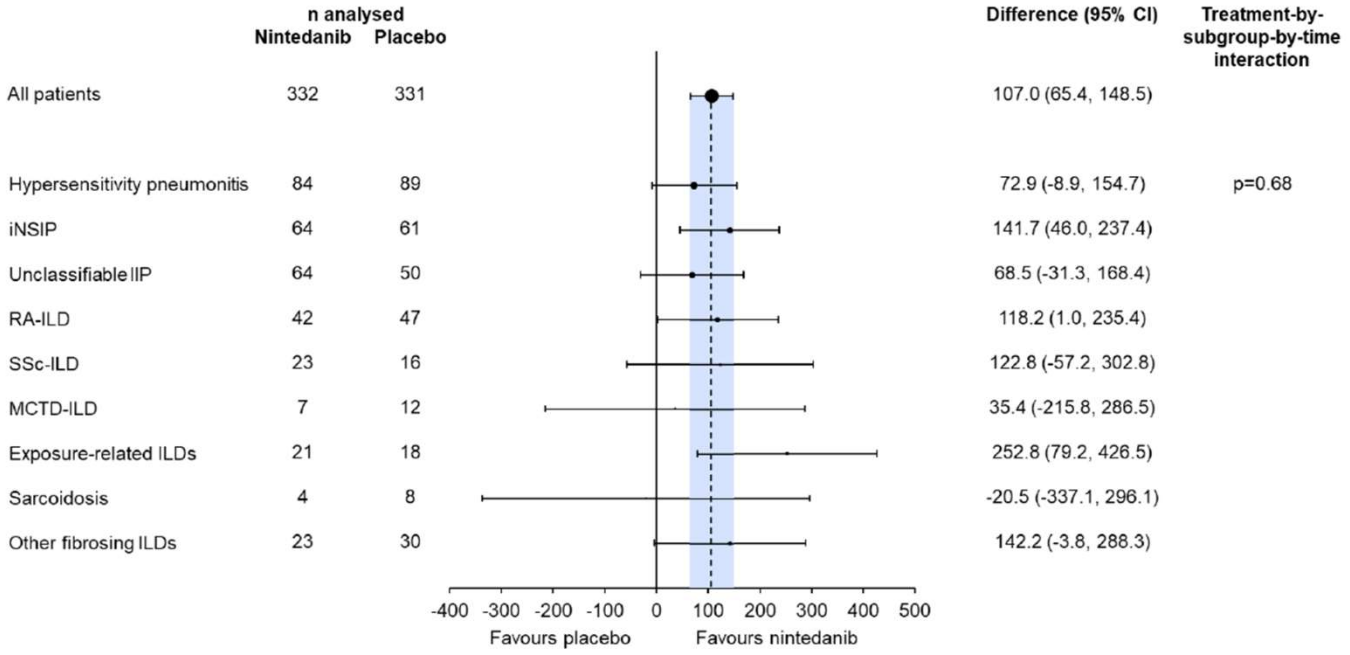


INBUILD trial

Effect is more pronounced in UIP-like disease

This is a post-hoc analysis

Figure S5. Annual rate of decline in FVC (mL/year) in 9 subgroups by ILD diagnosis noted in the case report form (overall population). FVC=forced vital capacity. IIP=idiopathic interstitial pneumonia. ILD=interstitial lung disease. iNSIP=idiopathic non-specific interstitial pneumonia. MCTD=mixed connective tissue disease. RA=rheumatoid arthritis. SSc=systemic sclerosis.



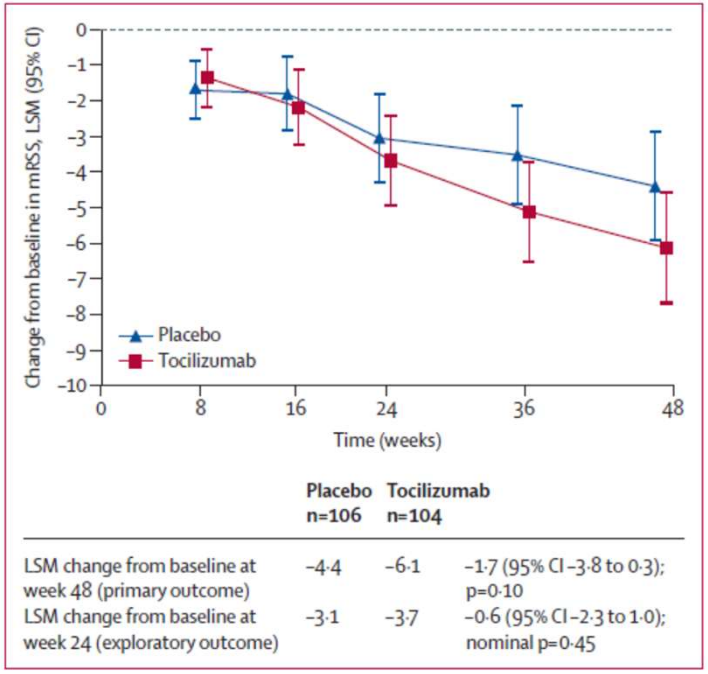
Wells AU, et al. *Lancet Respir Med*. 2020;8(5):453-460. doi:10.1016/S2213-2600(20)30036-9

Tocilizumab in SSc-ILD

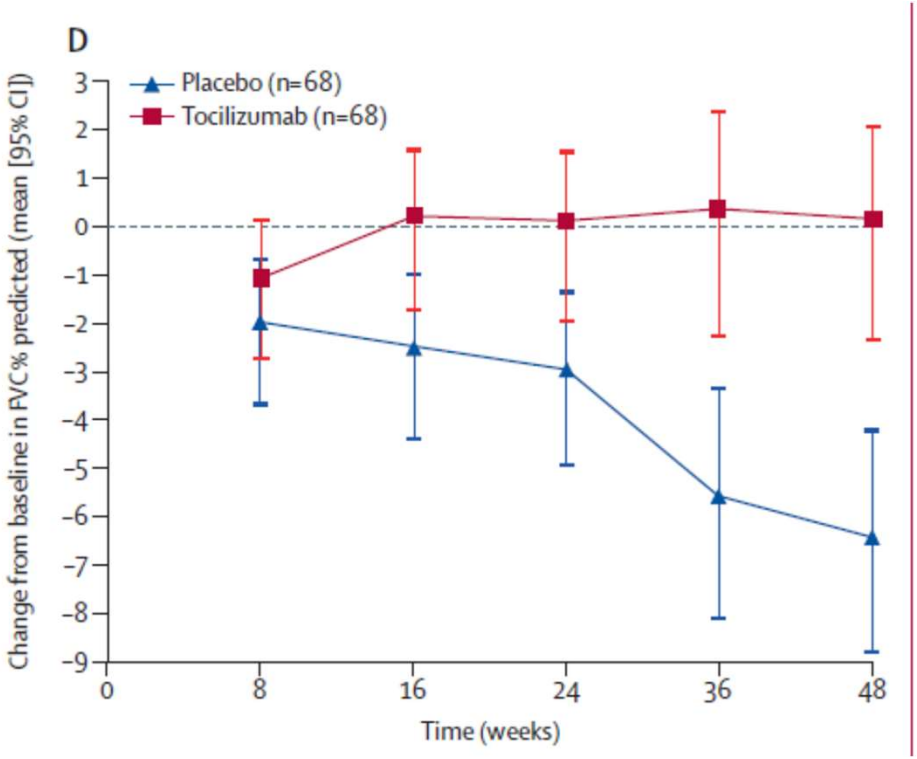
FocuSSced trial
Phase 3, 210 total subjects for 48 Weeks
Treatment group received tocilizumab 162 mg SW weekly for 48 weeks
Primary endpoint: Change in mRSS
Secondary outcome measures includes change in FVC
Background therapy was not permitted
Mean decline in FVC was -14 ml in tocilizumab vs -255 ml in placebo

Khanna et al 2020

Tocilizumab in SSc-ILD



	Placebo n=106	Tocilizumab n=104	
LSM change from baseline at week 48 (primary outcome)	-4·4	-6·1	-1·7 (95% CI -3·8 to 0·3); p=0·10
LSM change from baseline at week 24 (exploratory outcome)	-3·1	-3·7	-0·6 (95% CI -2·3 to 1·0); nominal p=0·45



Khanna et al 2020

Rituximab in SSc-ILD

DESIRES Trial

- SSc (N =56)
- Limited or diffuse disease
- IV rituximab (375 mg/m^2) or placebo once per week for 4 weeks

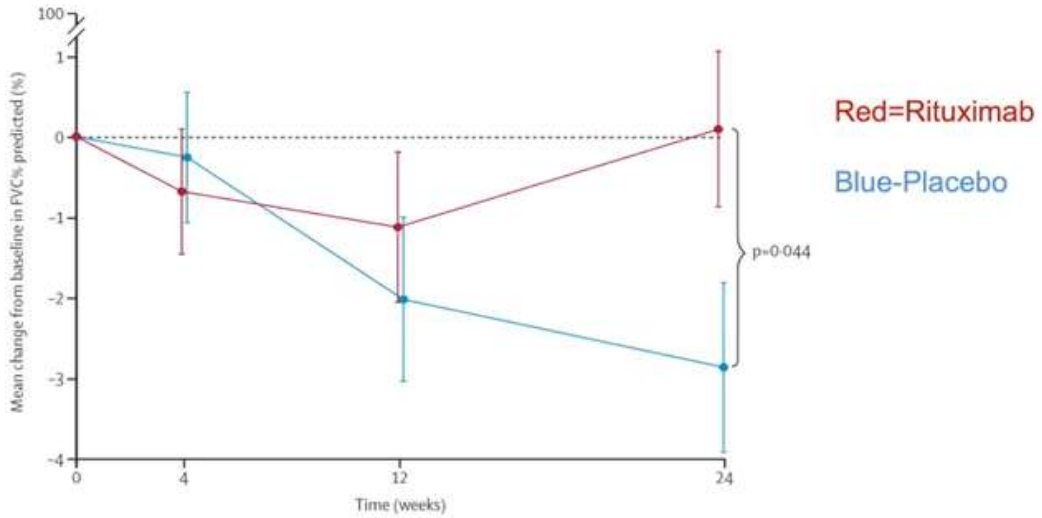
Primary outcome: Change from baseline in mRSS at 6 months

Secondary endpoints : FVC, DLCO, TLC, patient-reported outcomes

Background therapy not permitted

Ebata et.al, lancet rheumatology 2021

DESIRS trial



Significant change in mRSS between the two groups

Ebata et.al, lancet rheumatology 2021

Rituximab for CTD-ILD

- RECITAL trial
- UK. 101 participants 51 Rituximab vs 50 CYC
- 48 weeks
- Primary endpoint change in FVC from baseline
- Secondary endpoint 6 min walk, DLCO, QoL , overall survival

	CYC	Rituximab
Connective tissue disease type		
Idiopathic inflammatory myositis	22 (46%)	22 (45%)
Systemic sclerosis	19 (40%)	18 (37%)
Mixed connective tissue disease	7 (15%)	9 (18%)

Maher TM, et al. *Lancet Respir Med*. 2023;11(1):45-54. doi:10.1016/S2213-2600(22)00359-9

RECITAL Trial

- No difference in secondary outcomes
- Less adverse events in the Rituximab group

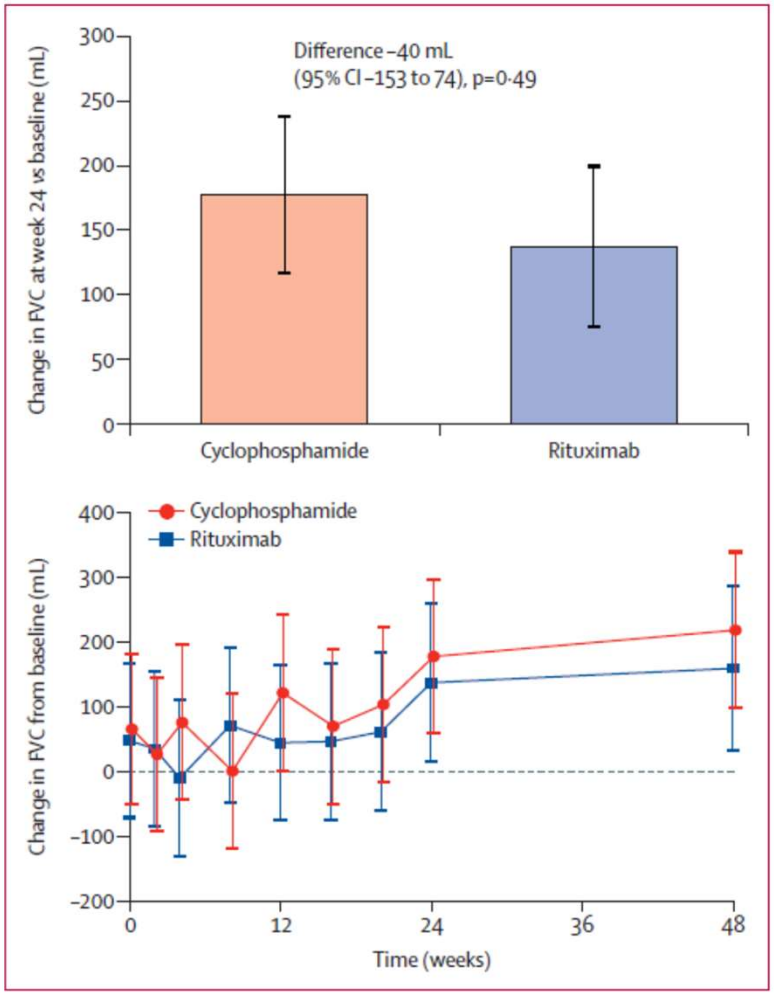


Figure 2: Adjusted rate of change in FVC in the cyclophosphamide and rituximab groups at week 24 (A) and adjusted change in FVC from baseline to week 48 (B)

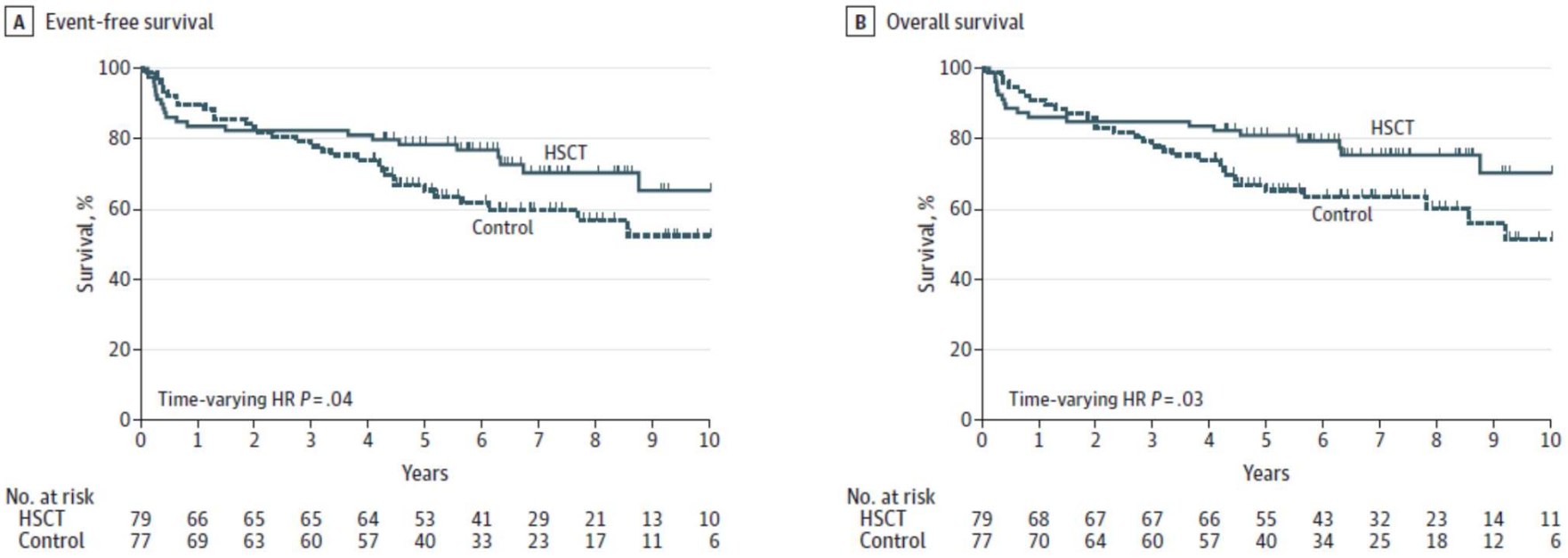
Maher TM, et al. *Lancet Respir Med*. 2023;11(1):45-54. doi:10.1016/S2213-2600(22)00359-9

Original Investigation

Autologous Hematopoietic Stem Cell Transplantation vs Intravenous Pulse Cyclophosphamide in Diffuse Cutaneous Systemic Sclerosis

A Randomized Clinical Trial

Figure 2. Event-Free and Overall Survival During 10-Year Follow-up



ASTIS trial JAMA 2014

ASTIS trial

Early treatment related mortality 10%

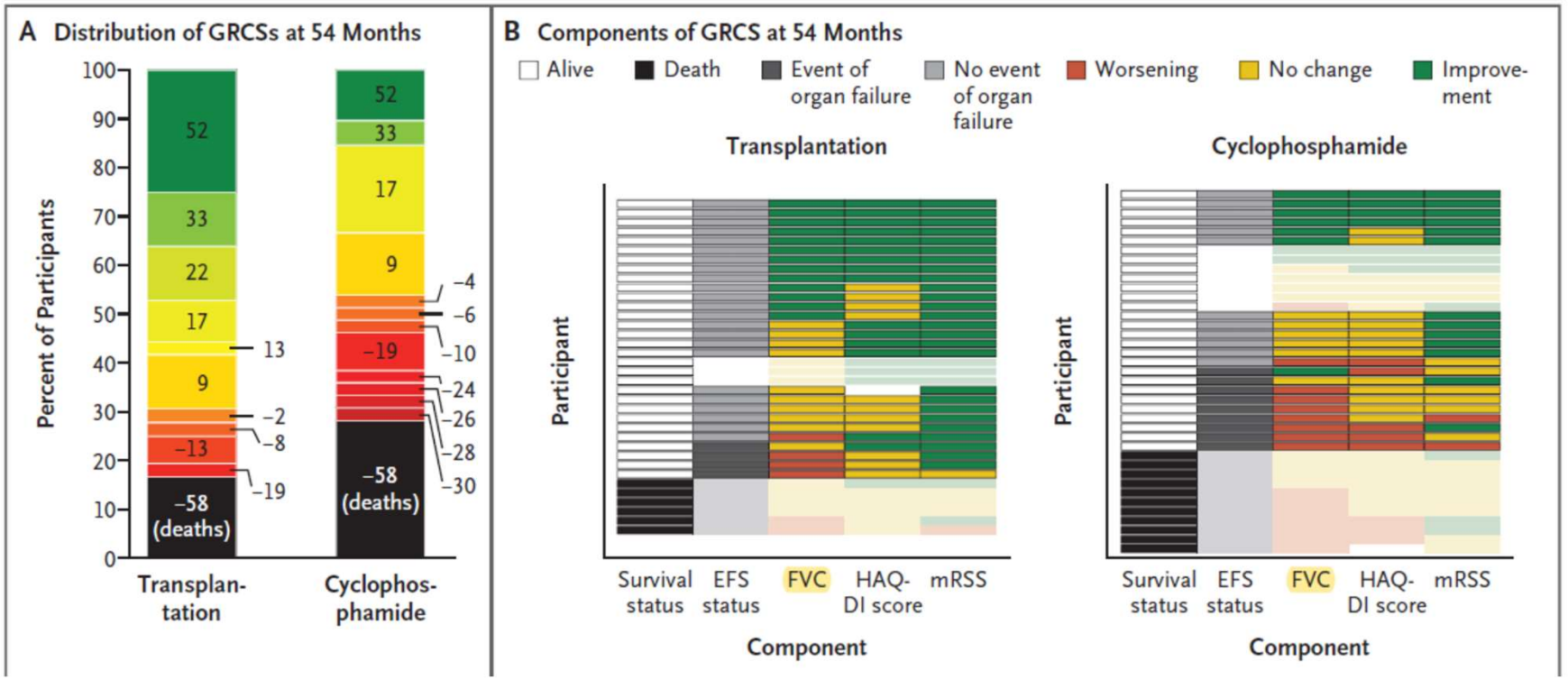
Table 2. Treatment Responses in Clinical Outcome Variables, Change in the Area Under the Time Response Curve From Baseline to 2 Years' Follow-up

Variable	AUC, Mean (SD)		Difference (95% CI)	*P* Value
	HSCT Group (n = 67)[a]	Control Group (n = 64)[a]		
Weight, kg	-0.7 (9.5)	-0.8 (9.6)	-0.2 (-3.5 to 3.1)	.91
Modified Rodnan skin score	-19.9 (10.2)	-8.8 (12.0)	11.1 (7.3 to 15.0)	<.001
Creatinine clearance, mL/min[b]	-12.1 (29.7)	-1.2 (24.1)	10.9 (1.5 to 20.3)	.02
LVEF, % by cardiac echocardiography	-2.2 (14.7)	-1.9 (13.8)	0.3 (-4.7 to 5.2)	.91
Forced vital capacity, % predicted	6.3 (18.3)	-2.8 (17.2)	-9.1 (-14.7 to -2.5)	.004
Total lung capacity, % predicted	5.1 (17.5)	-1.3 (13.9)	-6.4 (-11.9 to -0.9)	.02
Residual volume, % predicted	-4.8 (33.7)	-2.1 (26.9)	2.7 (-7.9 to 13.2)	.62
DLCO, % predicted	-4.7 (13.7)	-4.1 (17.6)	0.6 (-4.9 to 6.0)	.84
HAQ-DI	-0.58 (1.14)	-0.19 (0.79)	0.39 (0.51 to 0.73)	.02
SF-36 score				
Physical component	10.1 (15.8)	4.0 (11.2)	-6.1 (-10.9 to -1.4)	.01
Mental component	3.1 (16.0)	3.4 (17.1)	0.3 (-5.41 to 6.07)	.91
EQ-5D				
Index-based utility score	0.31 (0.50)	0.03 (0.44)	-0.29 (-0.45 to -0.12)	<.001
VAS score	16.9 (44.5)	10.2 (39.7)	-6.7 (-21.33 to 7.87)	.36

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

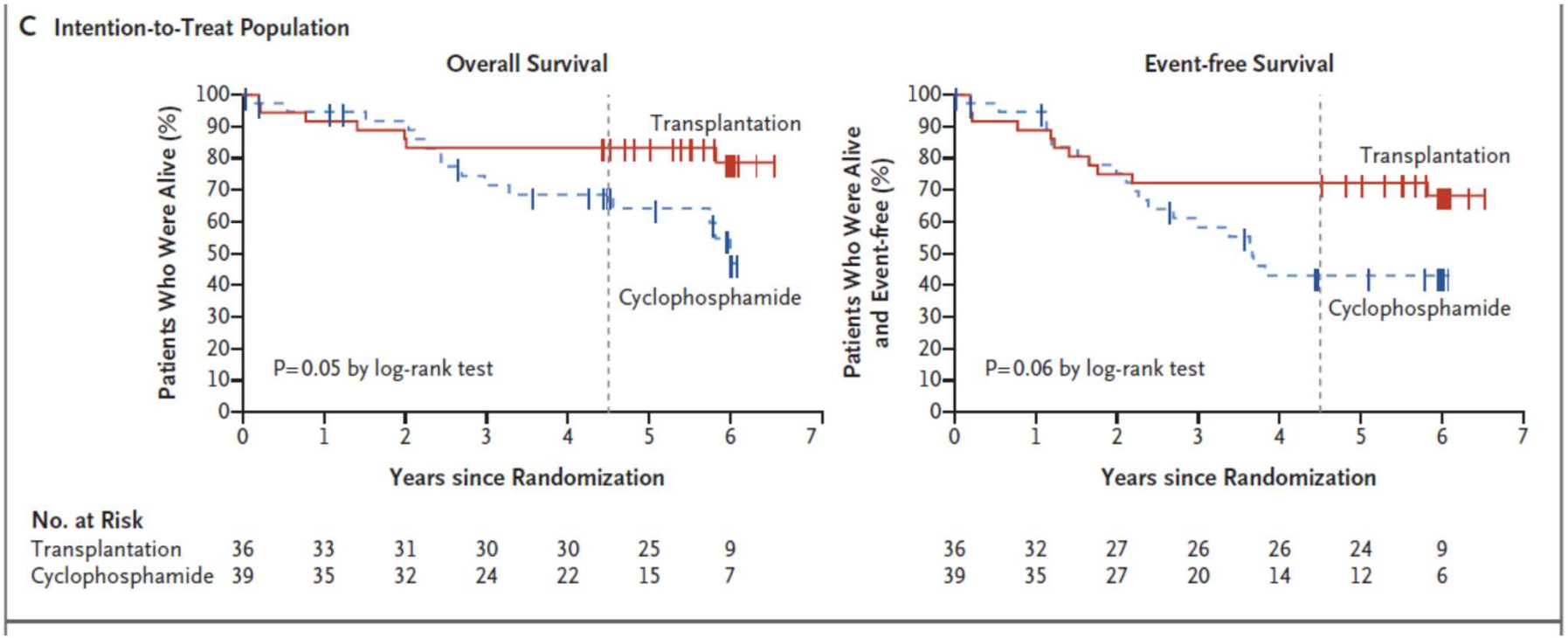
Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma



SCOT trial NEJM 2018

SCOT trial

Treatment related mortality 6%



Non-pharmacological treatments of pulmonary fibrosis

Oxygen therapy

Lung transplant

Pulmonary rehabilitation

Conclusions

Variable forms of interstitial, pleural and vascular pulmonary diseases can be presentations of connective tissue disease.

History and physical exam are key in detecting CTD-ILD

PFTs, HRCT of the chest and an ambulatory oxygen test are important initial tests

Treatment for CTD-ILD should be approached in a multidisciplinary setting