AUTOIMMUNE LUNG DISEASE; SCREENING AND MONITORING MODALITIES, A PULMONOLOGIST'S PERSPECTIVE

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KANSAS INSTITUTE FOR PRECISION MEDICINE
ADVANCING CARE ONE PATIENT AT A TIME
COBRE

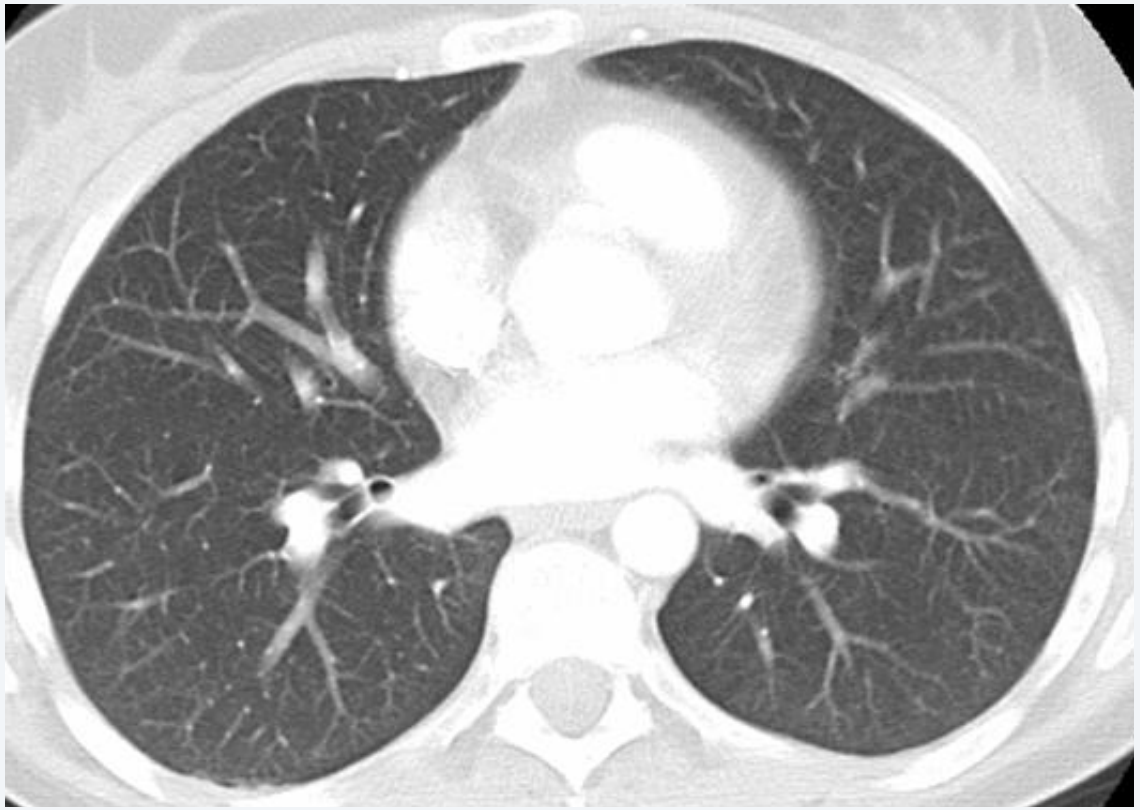
MATSON LAB

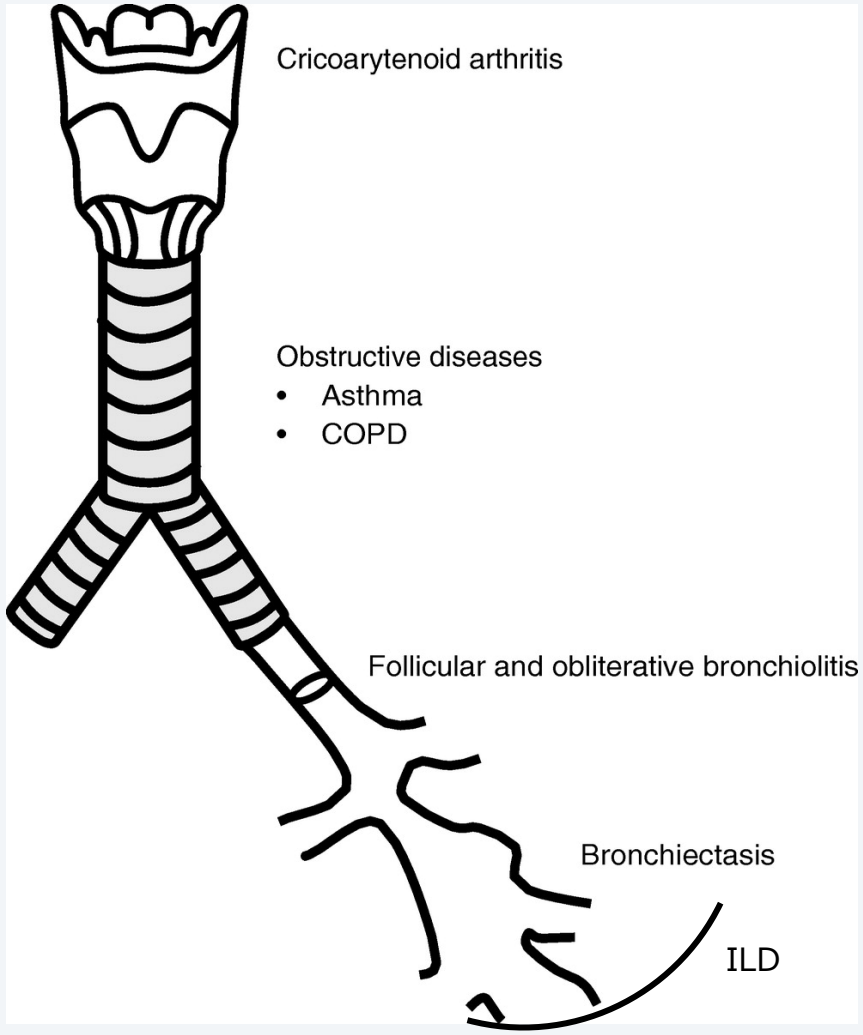
Disclosures

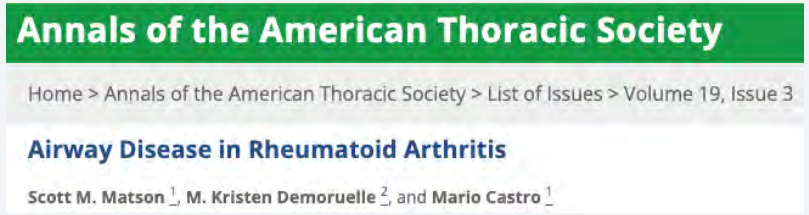
- I have no financial disclosures.

Outline

- Introduction to autoimmune interstitial lung disease, lung-based perspective
- Discussion of screening and modalities
- Implications of treatment post screening- and monitoring modalities for lung disease treatment







Autoimmune Lung Disease

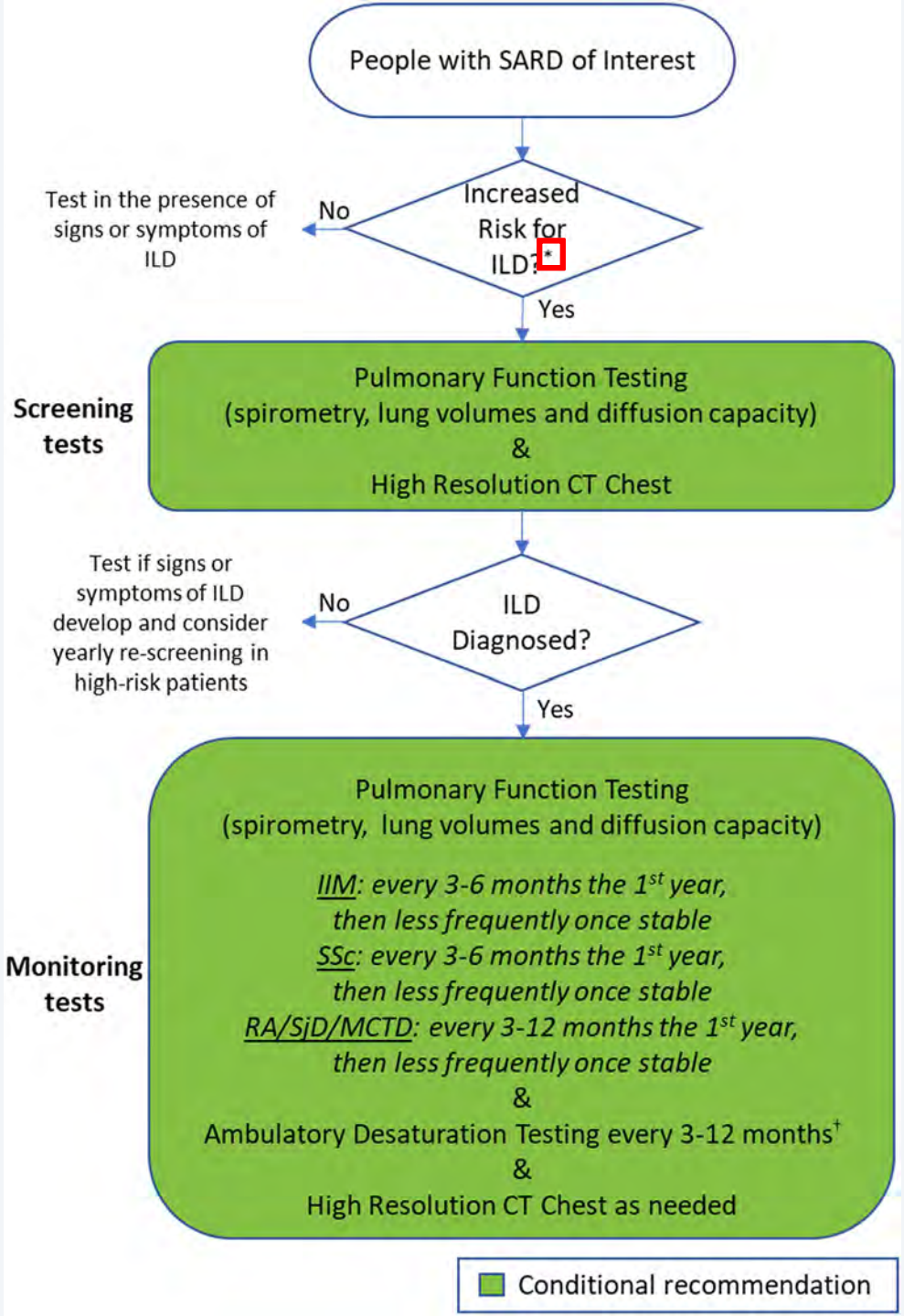
- Under-recognized component of airways disease
  - Asthma in RA or RA-AWD?
- Chicken or Egg
- Treatment and DMARD role?

- **Screening --> Treatment**

Screening in clinical settings vs screening for research settings

What is the purpose of screening in systemic autoimmune disease for lung disease?

- High morbidity and mortality condition where *early intervention* alters the natural history of the disease state



ACR/ACCP SCREENING GUIDELINES

- In SARD of interest – if increased risk for ILD recommend screening with:
- PFTs &
- HRCT

- Yearly rescreening in high-risk patients

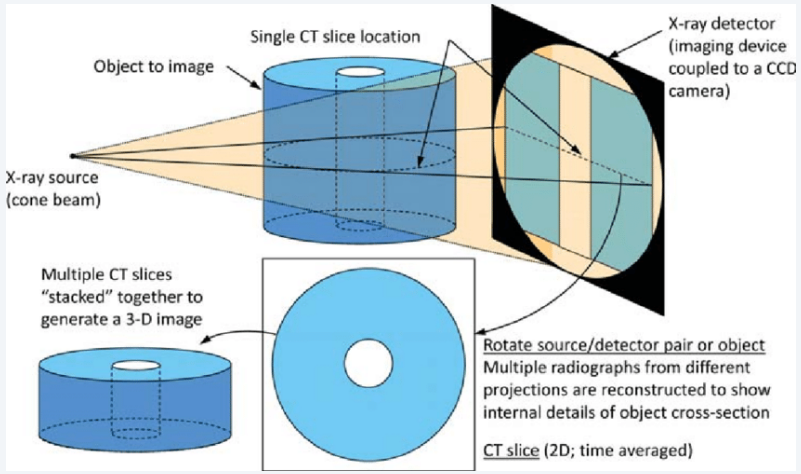
S. Johnson et al, AC&R 2024

Disease	Risk factors
Systemic sclerosis	• Anti–Scl-70 positivity, antinuclear antibody with nucleolar pattern[13] • Diffuse cutaneous subtype, male sex, African American race[14, 15] • Early disease (first 5–7 y after onset) • Elevated acute phase reactants[13, 16]
Rheumatoid arthritis	• High-titer rheumatoid factor, high-titer anti-CCP[17-19] • Cigarette smoking,[20, 21] older age at rheumatoid arthritis onset,[22, 23] high disease activity • Male sex,[22] higher body mass index
Idiopathic inflammatory myopathies	• Anti-synthetase (Jo-1, PL7, PL12, EJ, OJ, KS, Ha, Zo), anti–MDA-5, anti-Ku, anti-Pm/Scl, anti-Ro52 antibody positivity • Mechanic's hands, arthritis/arthralgia, ulcerating lesions[24]
Mixed connective tissue disease	• Dysphagia, Raynaud phenomenon • Other systemic sclerosis clinical or laboratory features
Sjögren disease	• Anti-Ro52 antibody, antinuclear antibody[25, 26] • Raynaud phenomenon • Older age • Lymphopenia

* Increased risk = screening

* These disease features have been identified as placing a person at increased risk for developing ILD; however, the absence of these risk factors does not preclude the development of ILD in patients with these SARDs. Screening for ILD should be performed in shared decision-making with the rheumatologist and patient. As such, screening for ILD should not necessarily be limited only to those with these risk factors. CCP, cyclic citrullinated peptide; ILD, interstitial lung disease; MDA-5, MDA-5 melanoma differentiation-associated protein 5; SARD, systemic autoimmune rheumatic disease.

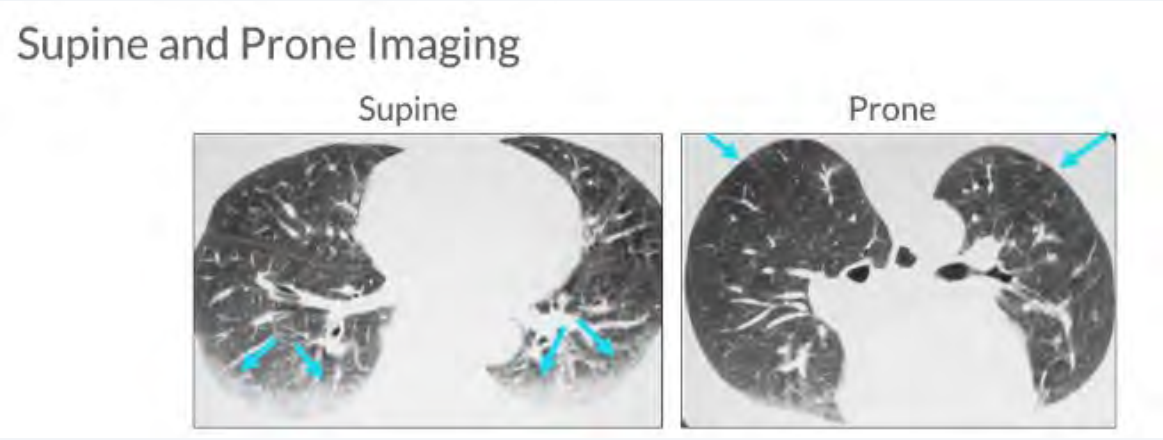

HRCT?



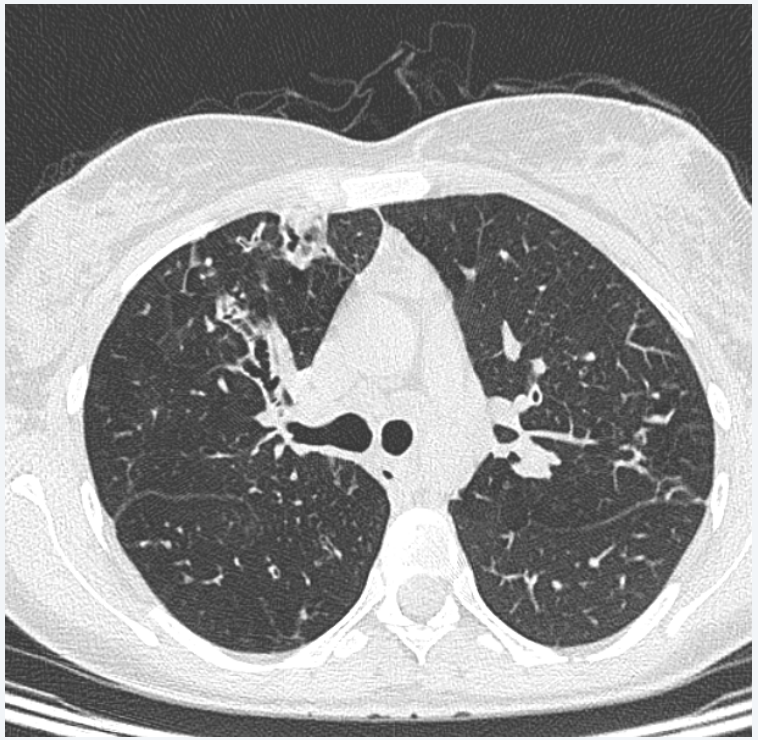
HRCT

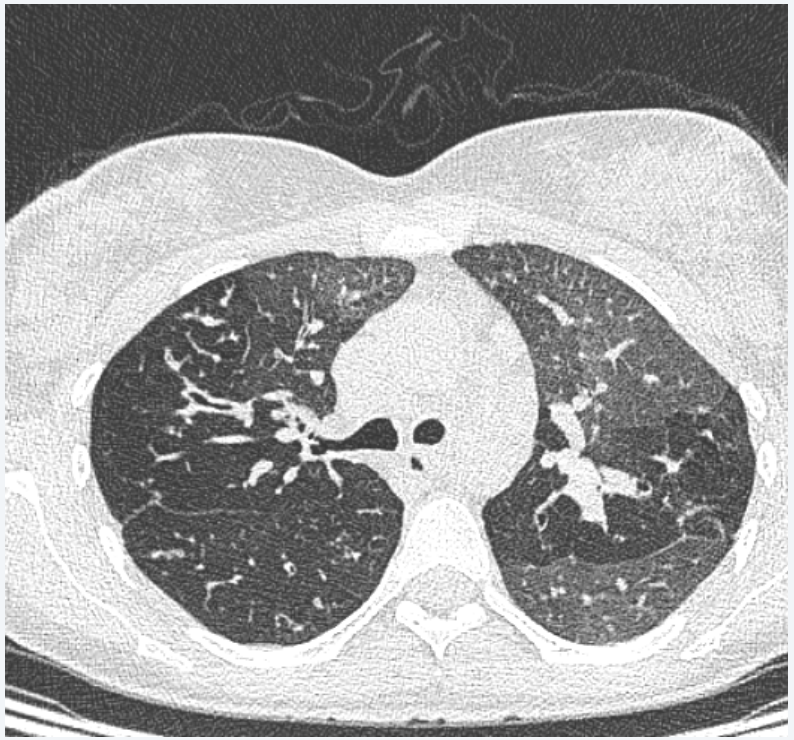
- Protocol to enhance spatial resolution

- Thinner slices (1-2 mm)
- High-resolution reconstruction
- No IV contrast
- Maneuvers (insp, exp, prone, supine)



HRCT vs Standard CT

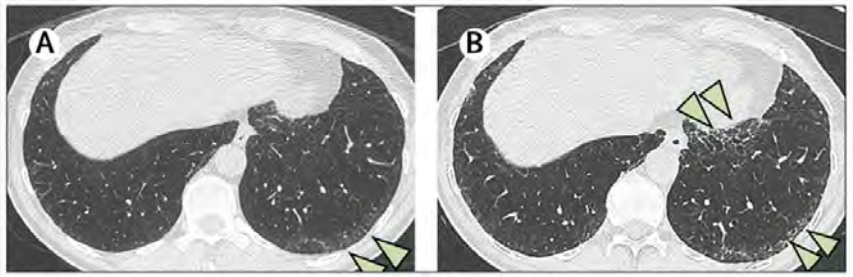




FULL TEXT ARTICLE

Interstitial lung abnormalities detected incidentally on CT: a Position Paper from the Fleischner Society

Hiroto Hatabu Prof, Gary M Hunninghake MD, Luca Richeldi Prof, Kevin K Brown Prof, Athol U Wells Prof, Martine Remy-Jardin Prof, Johny Verschakelen Prof, Andrew G Nicholson Prof, Mary B Beasley MD, David C Christiani Prof, Raúl San José Estépar PhD, Joon Beom Seo Prof, Takeshi Johkoh Prof, Nicola Sverzellati MD, Christopher J Ryerson MD, R Graham Barr Prof, Jin Mo Goo Prof, John H M Austin Prof, Charles A Powell Prof, Kyung Soo Lee Prof, Yoshikazu Inoue Prof and David A Lynch Prof



ILA → ILD

Interstitial lung abnormalities across study populations

	Population-based cohorts				Smoking and lung cancer screening cohorts				
	MESA [11 12 13 14]	Nagano, Japan* [15]	FHS [6 8 9]	AGES-Reykjavik [9]	ECLIPSE [9]	NLST [7 16]	COPDGene [4 9 17]	MILD [18]	DLCST [19]
Study characteristics									
Total number of chest CT scans evaluated	3137	3061	2633	5320	1670	884	9292	692	1990
Prevalence of ILAs	310 (10%)	80 (3%)	177 (7%)	377 (7%)	157 (9%)	86 (10%)	708 (8%)	28 (4%)	332 (17%)
Mean age of those with ILAs (years)	75	62	70	78	64	62	64	60	60
Radiological progression									
Overall progression, follow-up time	NA	46%, 4 years	43%, 6 years	63%, 5 years	NA	20%,2 years	NA	20%, 2 years	NA
Mortality									
Relative risk of death, (hazard ratio [95% CI])	NA	NA	2·7 (1·1–6·5)	1·3 (1·2–1·4)	1·4 (1·1–2·0)	NA	1·8 (1·1–2·8)	NA	2·0 (1·4–2·7)

ILAs=interstitial lung abnormalities. NA=not available.
* Patients participating in a health screening programme from Nagano prefecture, Japan.

Prevalence of clinical ILD in RA

Annals of Medicine

Taylor & Francis
Taylor & Francis Group

Ann Med. 2024 Mar 28;56(1):2332406. doi: 10.1080/07853890.2024.2332406

The prevalence and risk factors of rheumatoid arthritis-associated interstitial lung disease: a systematic review and meta-analysis

Hong-Fei Wang [a,*], Yan-Yun Wang [b,c,*], Zhi-Yu Li [d], Pei-Jie He [e], Shan Liu [f], Qiu-Shuang Li [f,✉]

Table 2.

Subgroup analysis for the prevalence of RA-ILD.

Subgroups	N	Prevalence	95% CI	P	Test (s) of heterogeneity	
					I^2	p value
Overall prevalence ILD criteria	34	18.7%	0.16–0.22	<0.05	96.4%	<0.1
Only HRCT	16	22.7%	0.18–0.28	<0.05	97.1%	<0.1
HRCT and others	11	19.2%	0.14–0.25	<0.05	95.2%	<0.1
Others[b]	7	6.4%	0.04–0.09	<0.05	87.0%	<0.1

[b]Others: ILD diagnosed by chest computed tomography (CT) images, chest X-rays (CXRs), clinical symptoms, pulmonary function test (PFT) results and lung biopsies.

Prevalence of ILD in RA when screened

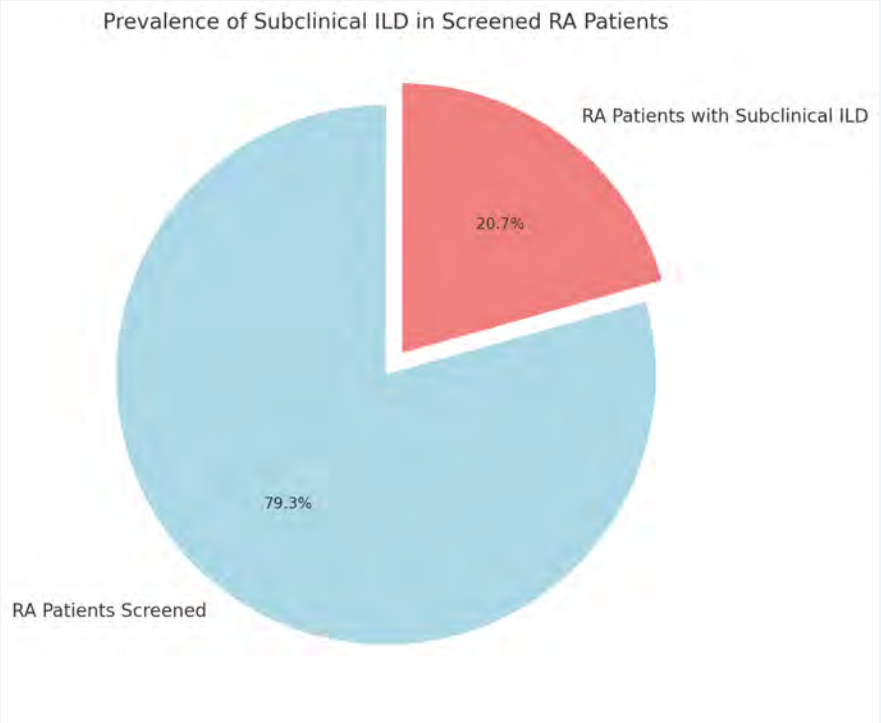
American Thoracic Society
Publisher's Version of Article
Issue Featuring Article
Submissions
American Journal of Respiratory and Critical Care Medicine®

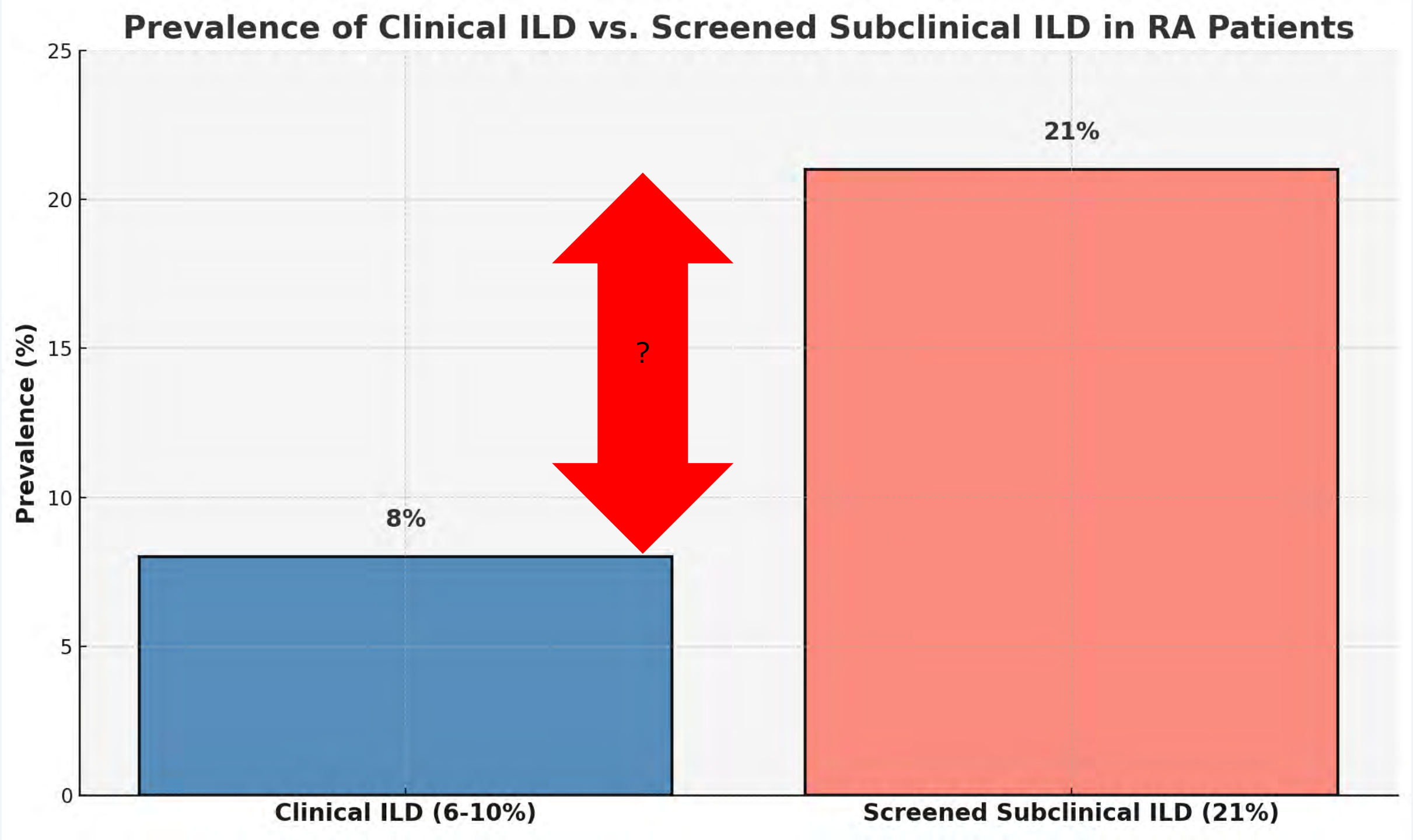
LETTER Am J Respir Crit Care Med. 2021 Dec 7;205(4):473–476. doi: 10.1164/rccm.202109-2087LE

Prospective Identification of Subclinical Interstitial Lung Disease in a Rheumatoid Arthritis Cohort Is Associated with the *MUC5B* Promoter Variant

Scott M Matson [1], Kevin D Deane [2], Anna L Peljto [2], Tami J Bang [2], Peter B Sachs [2], Avram D Walts [2], Christopher Collora [2], Shuyu Ye [2], M Kristen Demoruelle [2], Stephen M Humphries [3], David A Schwartz [2], Joyce S Lee [2,*]

Total Cohort ($n = 184$)	Radiologist-identified Subclinical RA-ILD		
	Present ($n = 38$)	Absent ($n = 146$)	P Value*



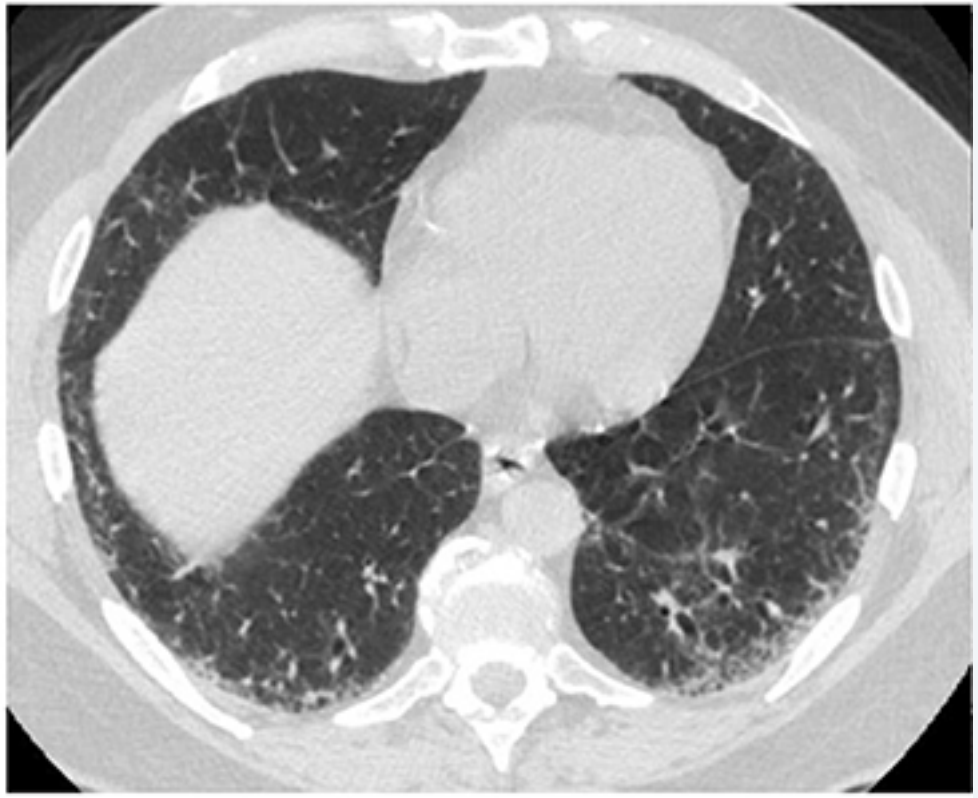

Prevalence of Clinical ILD vs. Screened Subclinical ILD in RA Patients
Prevalence (%)
25
20
15
10
5
0
8%
21%
?
Clinical ILD (6-10%)
Screened Subclinical ILD (21%)

Where you look, you will find…

Table 2. Prevalence of any abnormality on HRCT scans in 188 participants	
Any abnormality	172 (91.5%)
0 abnormalities	16 (8.5%)
Single abnormality	32 (17.0%)
>=2 abnormalities	140 (74.5%)
>=4 abnormalities	72 (38.3%)
Thyroid	
Any abnormality	39 (20.7%)
Nodule	12 (6.4%)
Enlargement	3 (1.6%)
Heterogenous	13 (6.9%)
Calcification	4 (2.1%)
Thoracic inlet/mediastinal	
Any abnormality	66 (35.1%)
Hiatal hernia	23 (12.2)
Patulous esophagus	11 (5.9%)
Esophageal wall thickening	3 (1.6%)
Prominent lymph nodes	15 (8.0%)
Heart	
Any	88 (46.8%)
Coronary artery or other vascular calcification	74 (39.4%)
Lung	
Any	151 (80.3%)
Airways (e.g. thickening, bronchiectasis)	92 (48.9%)
Scarring and/or fibrosis	58 (30.9%)

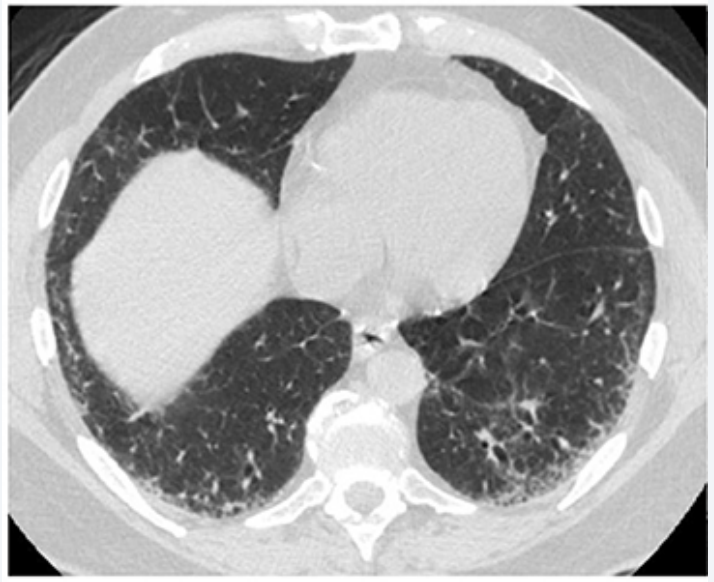
Table 3. Radiologist recommended clinical follow-up based on HRCT scan findings		
Any clinical follow-up recommended by the radiologist	65/188 (34.6%) had >=1 finding	

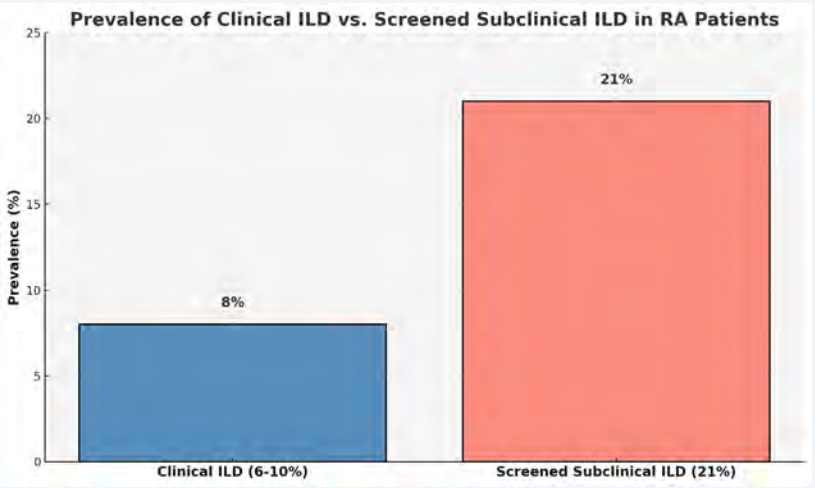
Clinical scenario

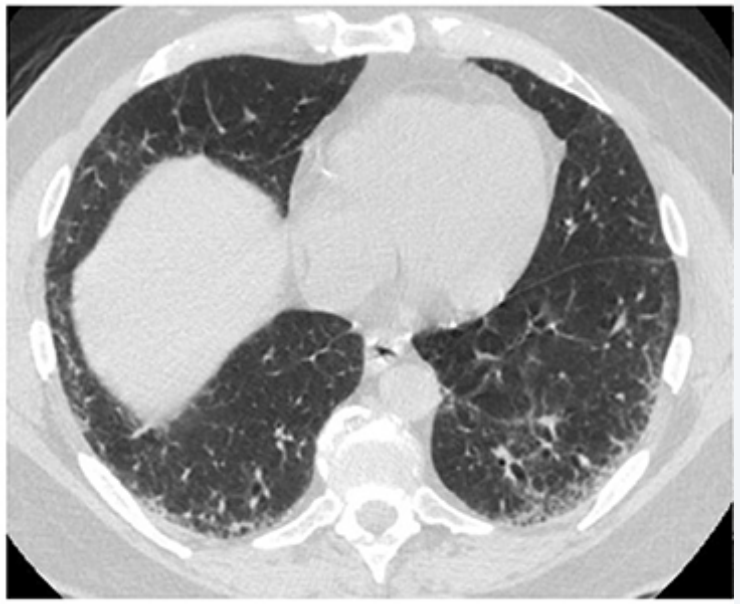


RA patient screened with HRCT and PFTs, found to have this CT scan and FVC% predicted of 89% with DLCO% predicted of 82%

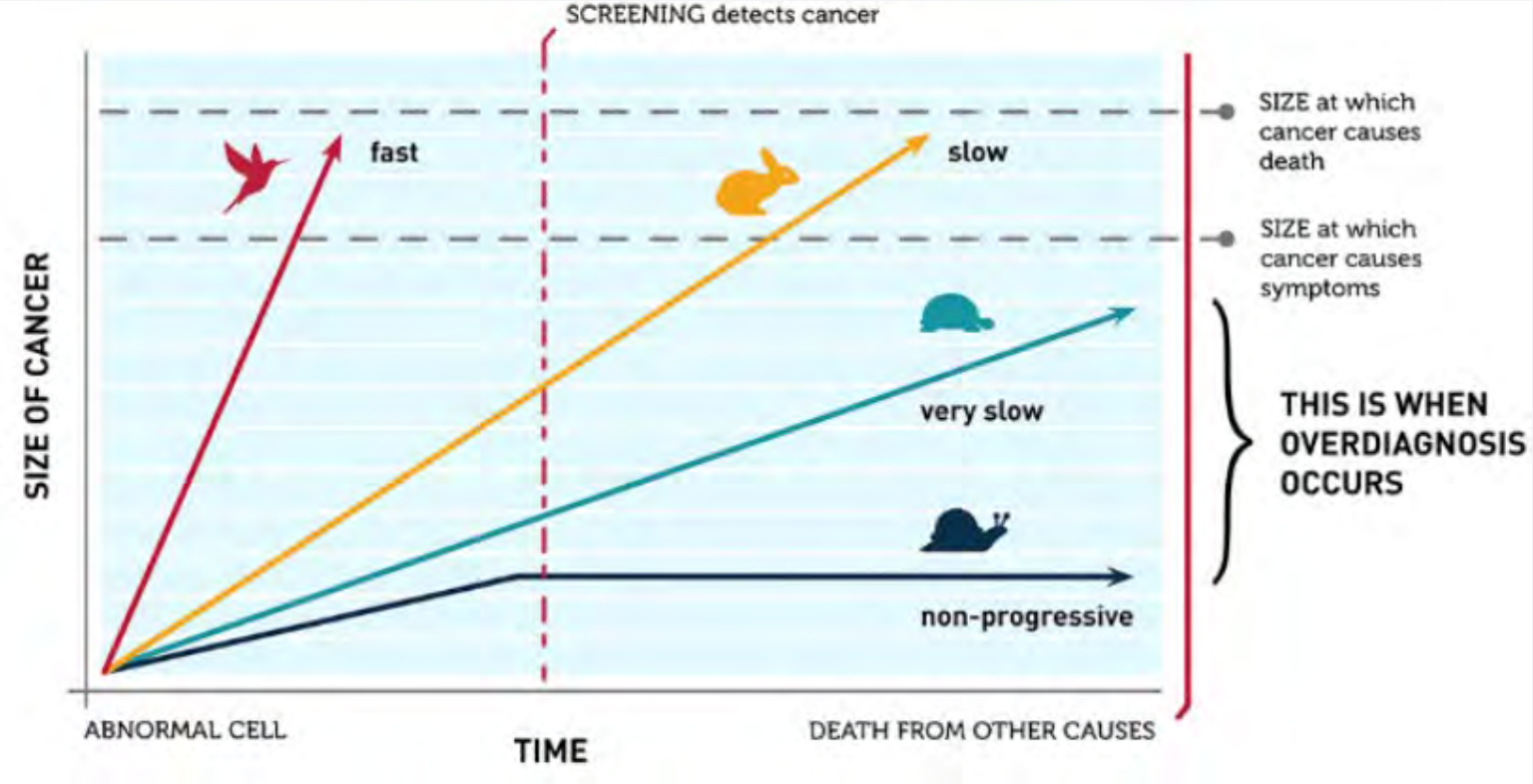
- No symptoms
- Currently joints are well controlled on MTX
- Former smoker

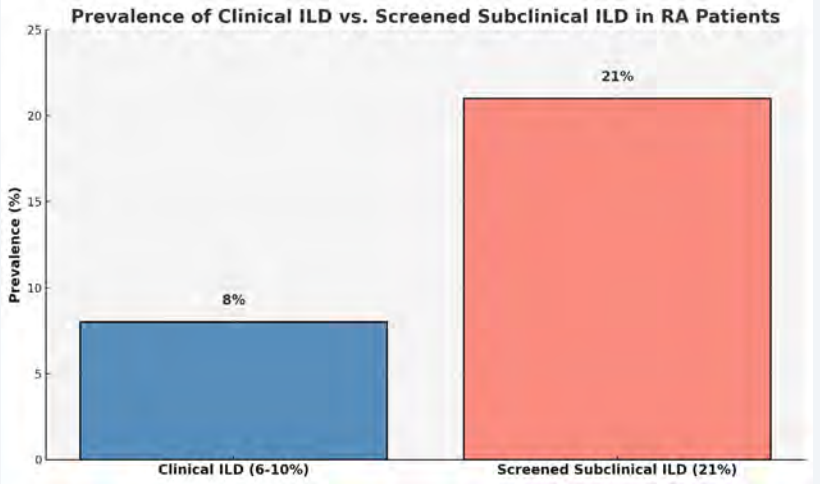



Prevalence of Clinical ILD vs. Screened Subclinical ILD in RA Patients
Prevalence (%)
25
20
15
10
5
0
8%
21%
Clinical ILD (6-10%)
Screened Subclinical ILD (21%)

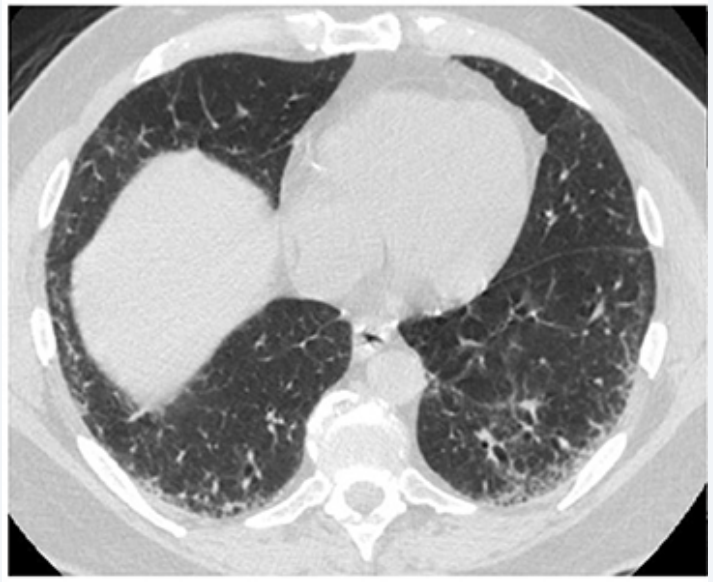


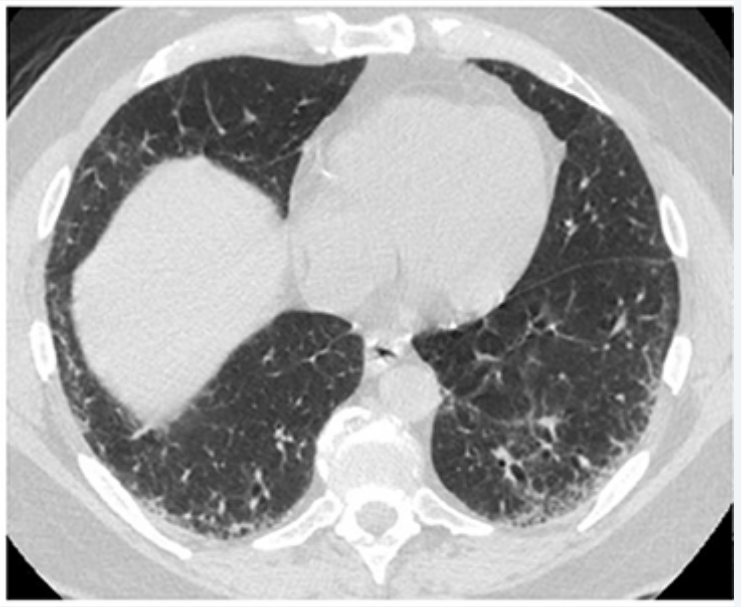
H. Gilbert Welch on cancer screening



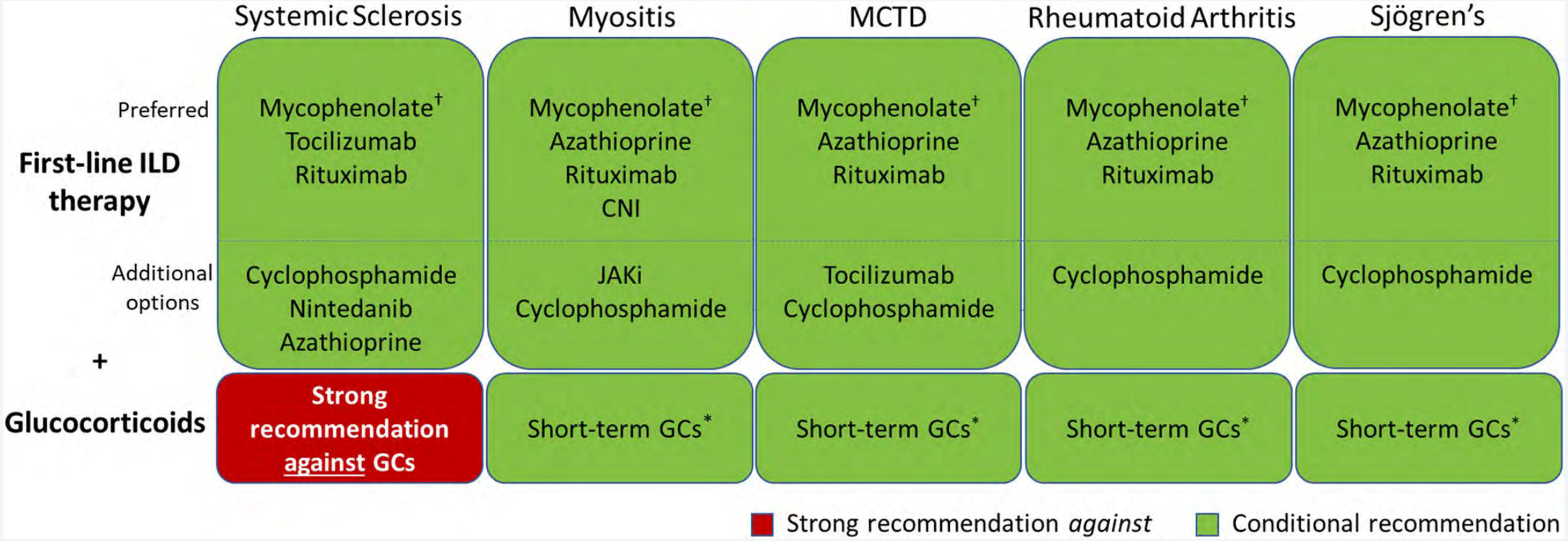


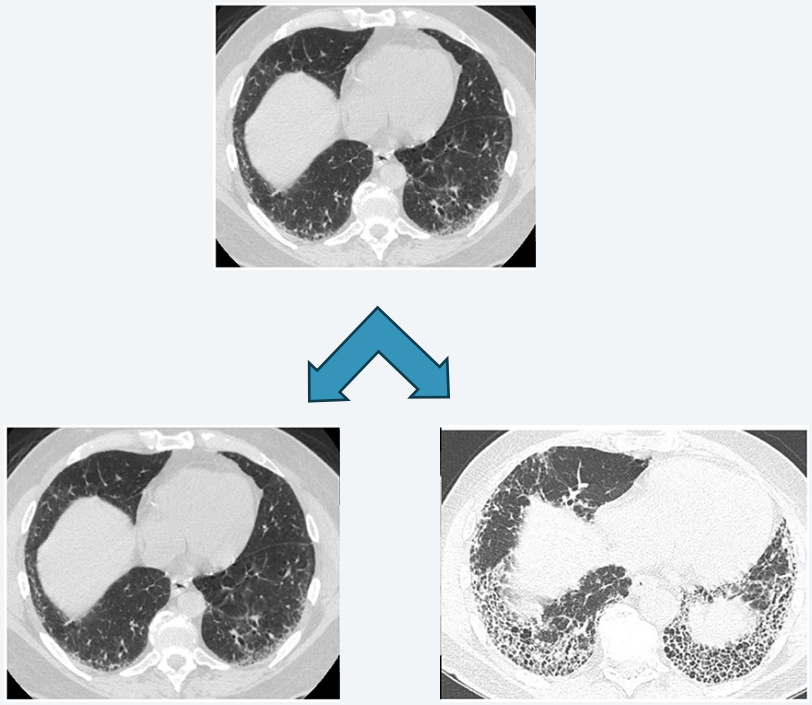
What intervention?





ACR ILD TREATMENT RECOMMENDATIONS





Known unknowns

Is immunomodulation safe for ALL patients with RA-ILD?

What is the role of traditional DMARD therapy (MTX, TNF, etc.) on halting ILD progression to explain the delta? If so, what does changing that regimen mean for RA patients “screened with ILA”

Do antifibrotic drugs alter the natural history of subclinical ILD to clinical ILD progression?

What are the potential harms to those patients who are screened and have altered treatment plans?

Clinical Equipoise

Journal of Thoracic Disease

J Thorac Dis. 2023 May 30; 15(5): 2517–2527. PMCID: PMC10267945
Published online 2023 May 12. doi: 10.21037/jtd-22-1820 PMID: 37324076

Treatment of rheumatoid arthritis-associated interstitial lung disease in a multi-center registry cohort

Veronica Marcoux,[✉1,^] Stacey Lok,[1] Prosanta Mondal,[2] Deborah Assayag,[3] Jolene H. Fisher,[4] Shane Shapera,[4] Julie Morisset,[5] Hélène Manganas,[5] Charlene D. Fell,[6] Nathan Hambly,[7] P. Gerard Cox,[7] Martin Kolb,[7] Andrea S. Gershon,[4] Teresa To,[8] Mohsen Sadatsafavi,[9] Nasreen Khalil,[9] Alyson W. Wong,[9,10] Pierce G. Wilcox,[9] Christopher J. Ryerson,[9,10] and Kerri A. Johannson[6,11,12]

Results

Of 161 patients with RA-ILD, UIP pattern was more common than NSIP (55.9% *vs.* 44.1%). Only 44/161 (27%) patients were treated over median follow-up of 4 years with medication choice appearing unrelated to patient-specific variables. Decline in forced vital capacity (FVC) was not associated with treatment. Patients with NSIP had lower risk of death or transplant, compared to UIP (P=0.0042). In patients with NSIP, there was no difference in time to death or transplant comparing treated to untreated in adjusted models [hazard ratio (HR) =0.73; 95% confidence interval (CI): 0.15–3.62; P=0.70]. Similarly, in patients with UIP, there was no difference in time to death or lung transplant between treated and untreated in adjusted models (HR =1.06; 95% CI: 0.49–2.28; P=0.89).

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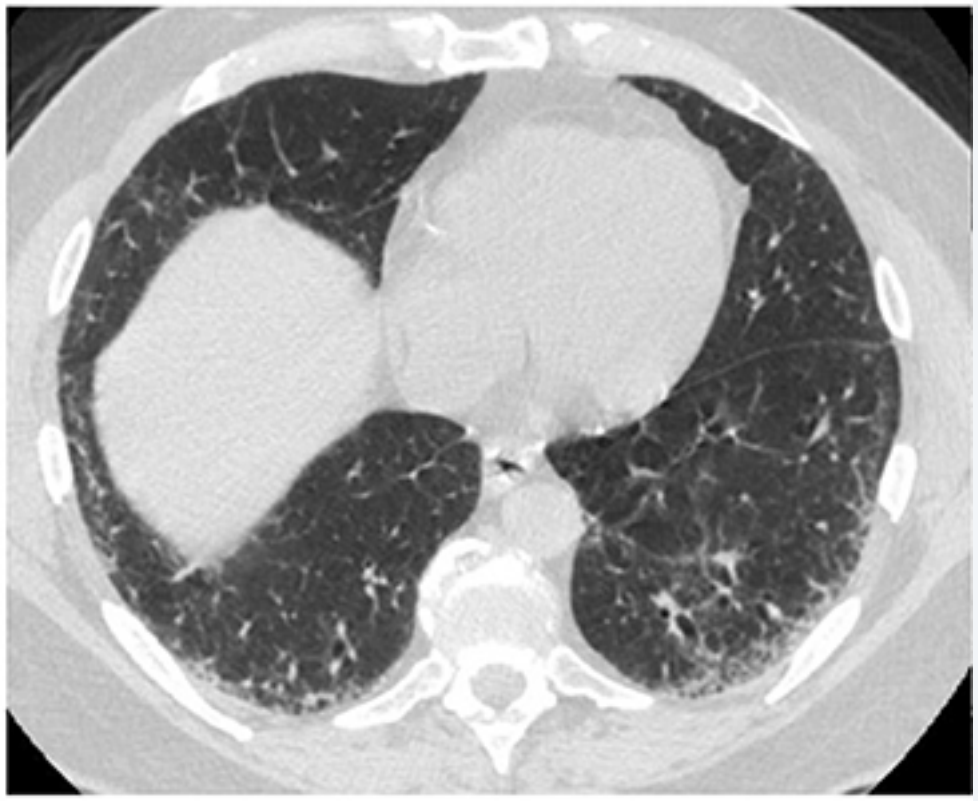
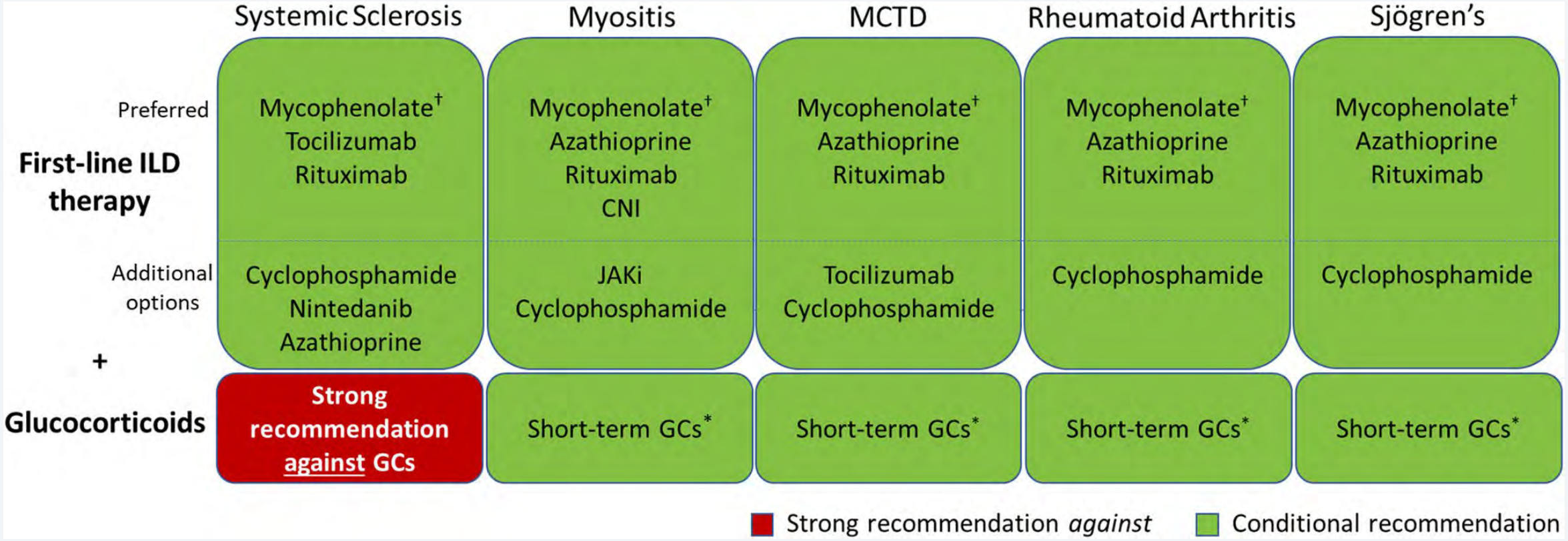
Clinical scenario 2



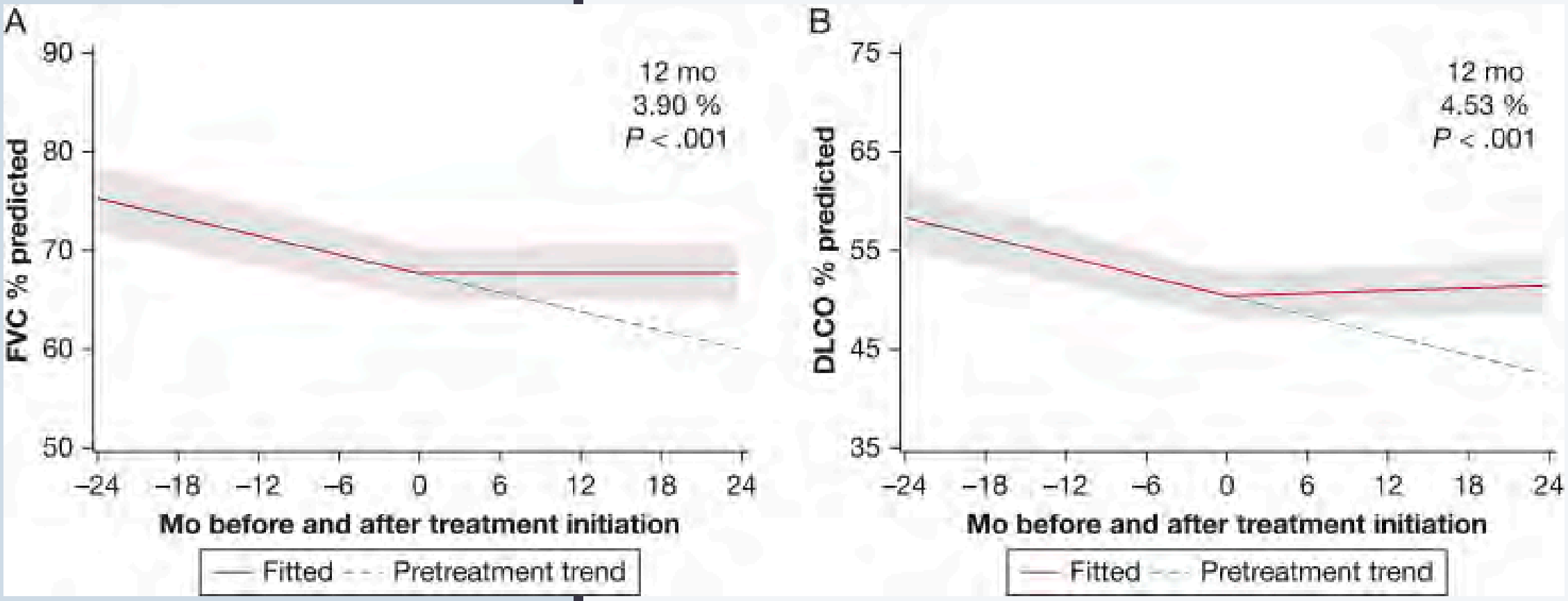
RA patient screened with HRCT and PFTs, found to have this CT scan and FVC% predicted of 73% with DLCO% predicted of 62%

- Cough and dyspnea symptoms
- Currently joints are well controlled on MTX
- Former smoker

ACR ILD TREATMENT RECOMMENDATIONS

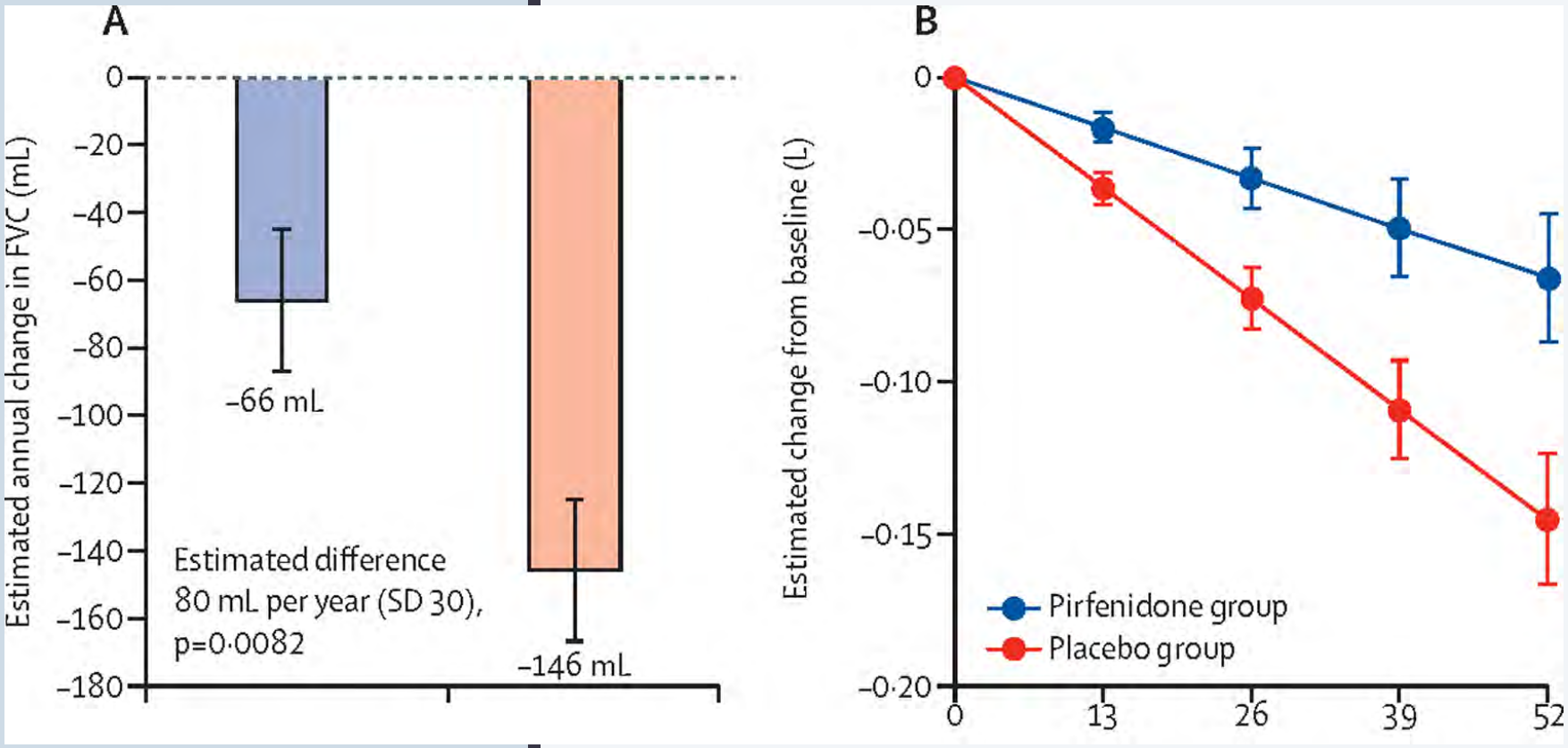


Aza, MMF, RTX, N=212



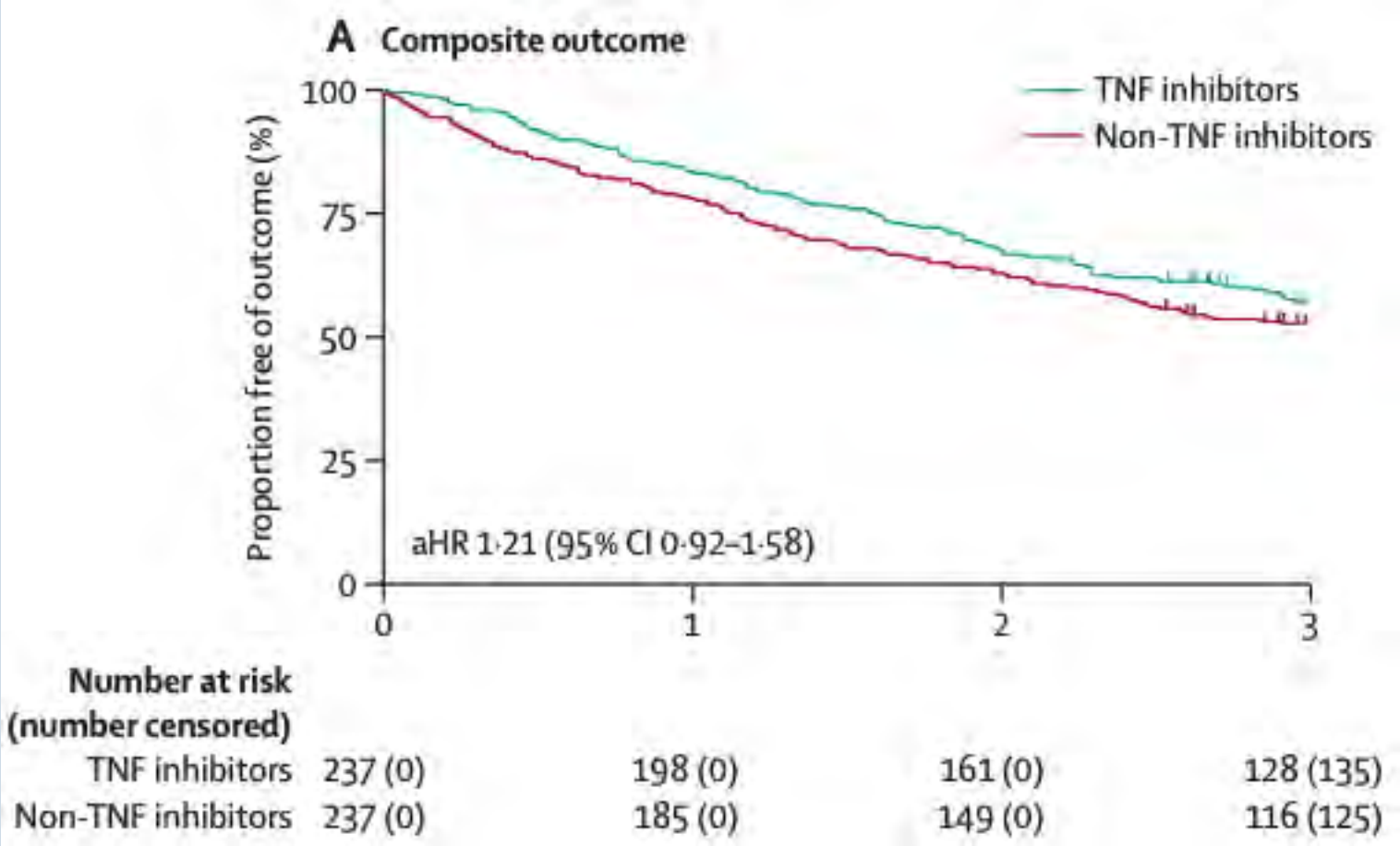
Matson, CHEST 2022

Antifibrotics in RA-ILD



Solomon, TRAIL-1: Lancet Respiratory 2023

TNF inhibitors



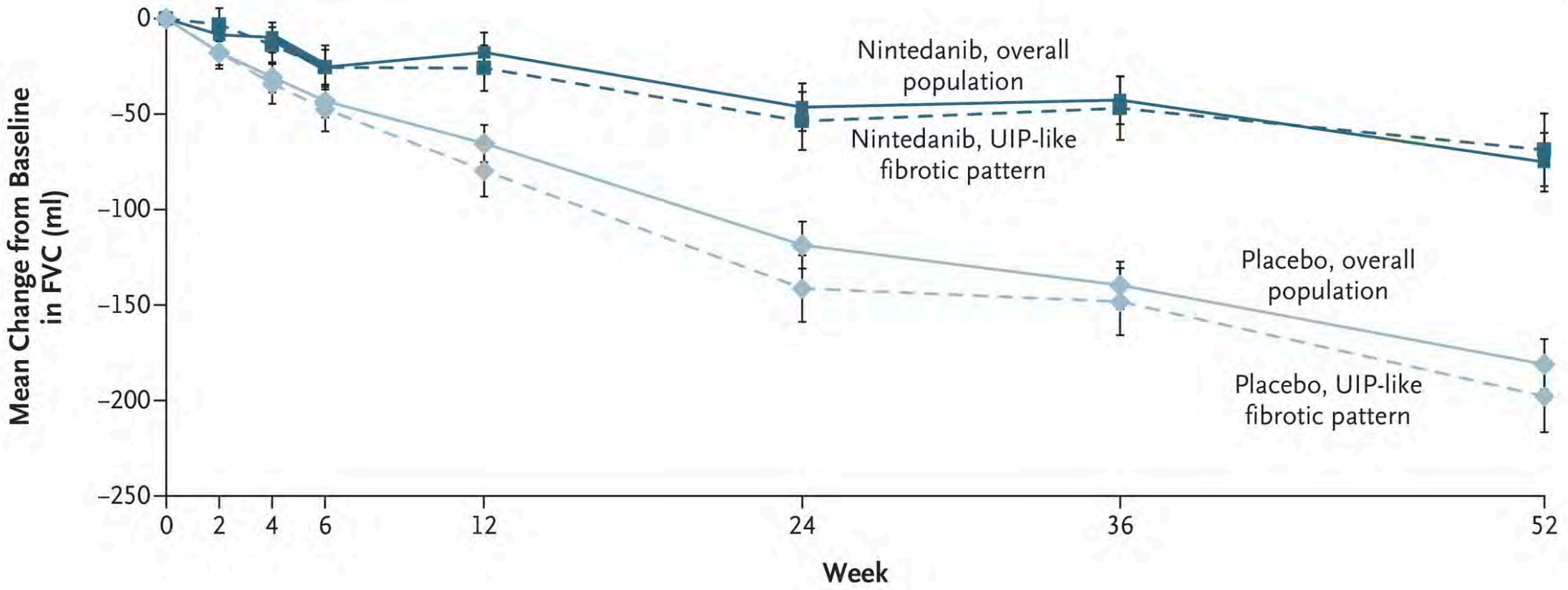
England, Lancet Rheum, 2024

Monitoring, treatment

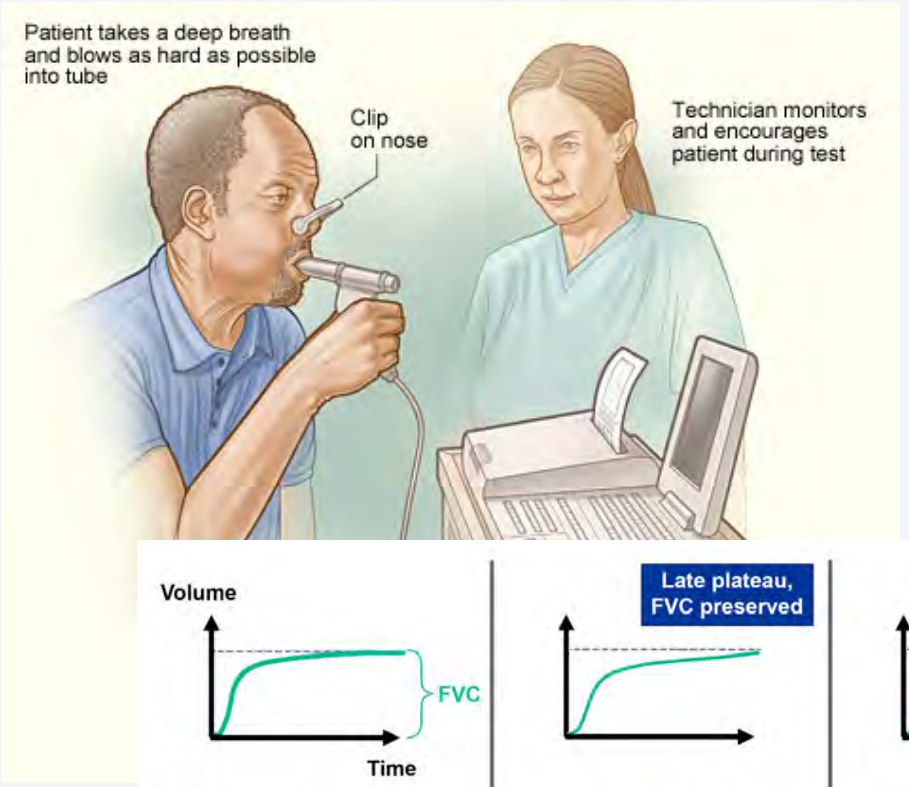
How to define treatment response?

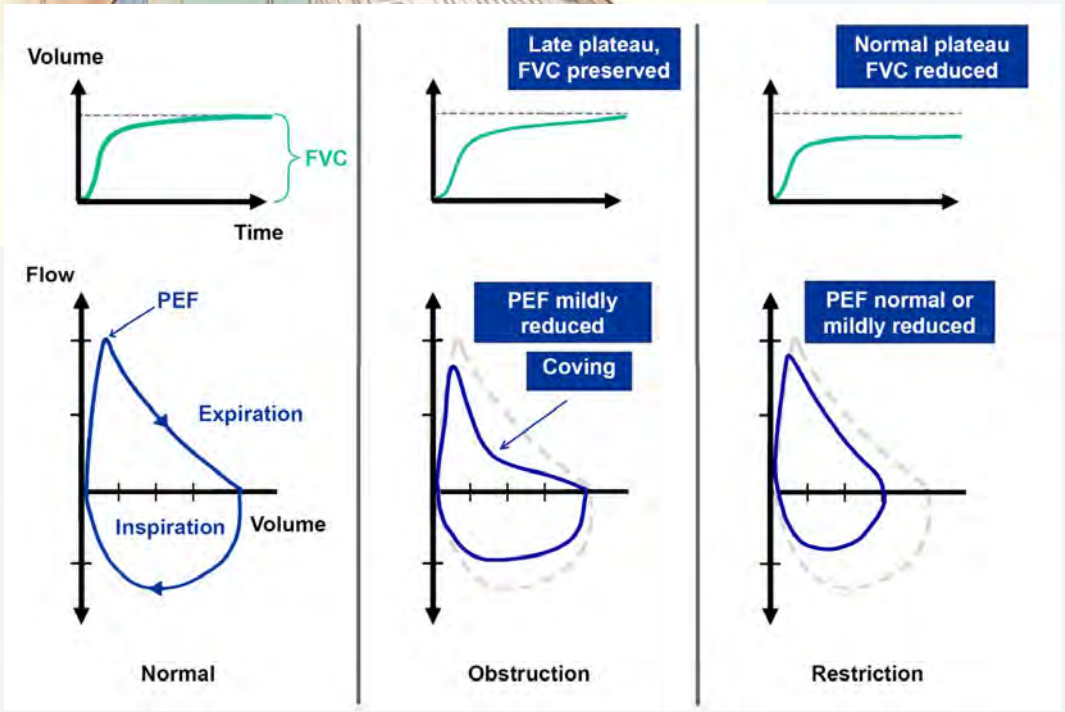
What is FVC?

Treatment switch?



No. of Patients								
Overall population								
Nintedanib	332	326	320	322	314	298	285	265
Placebo	331	325	326	325	320	311	296	274
Patients with UIP-like fibrotic pattern								
Nintedanib	206	203	200	199	193	180	171	160
Placebo	206	202	202	201	197	190	176	162

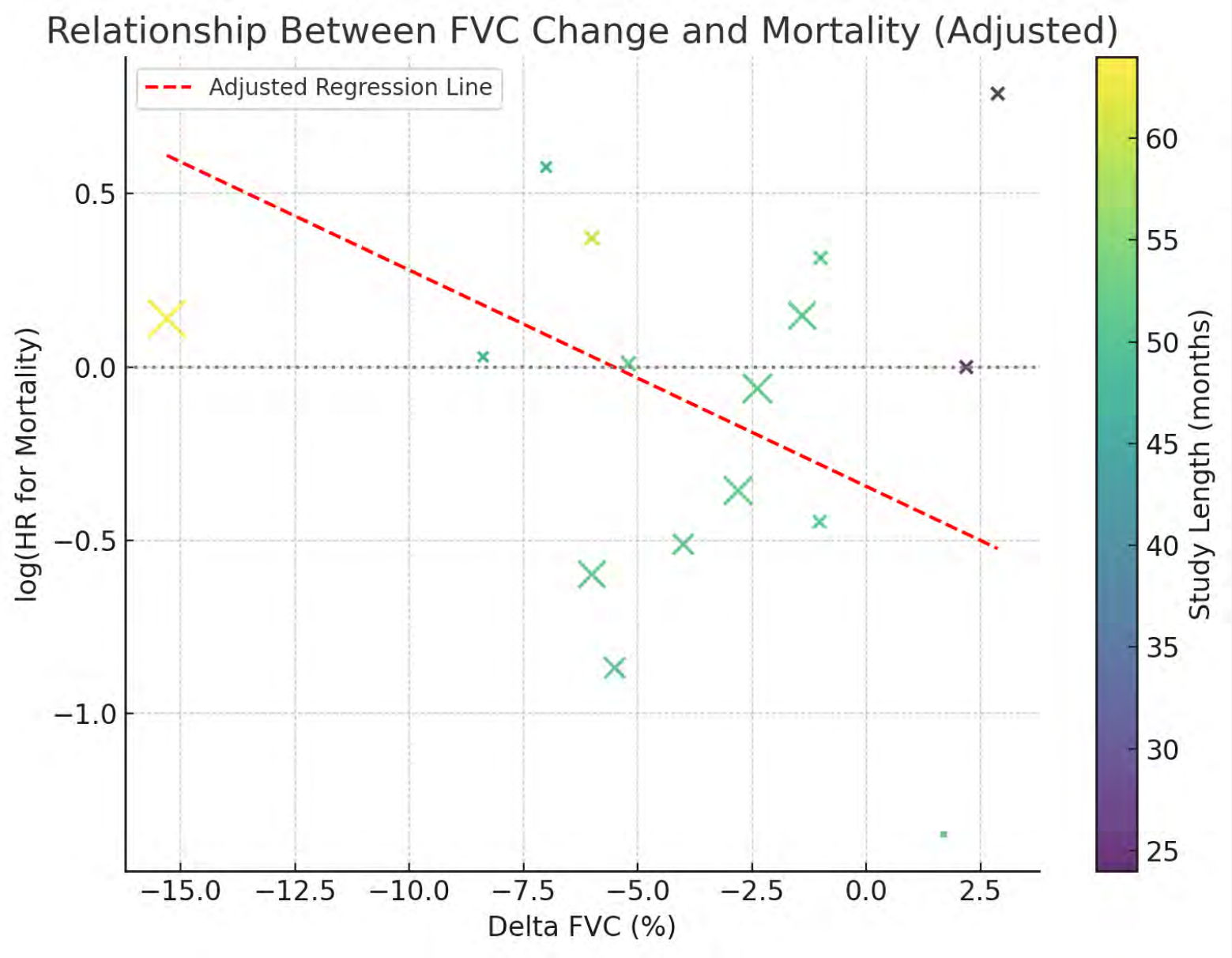




FVC

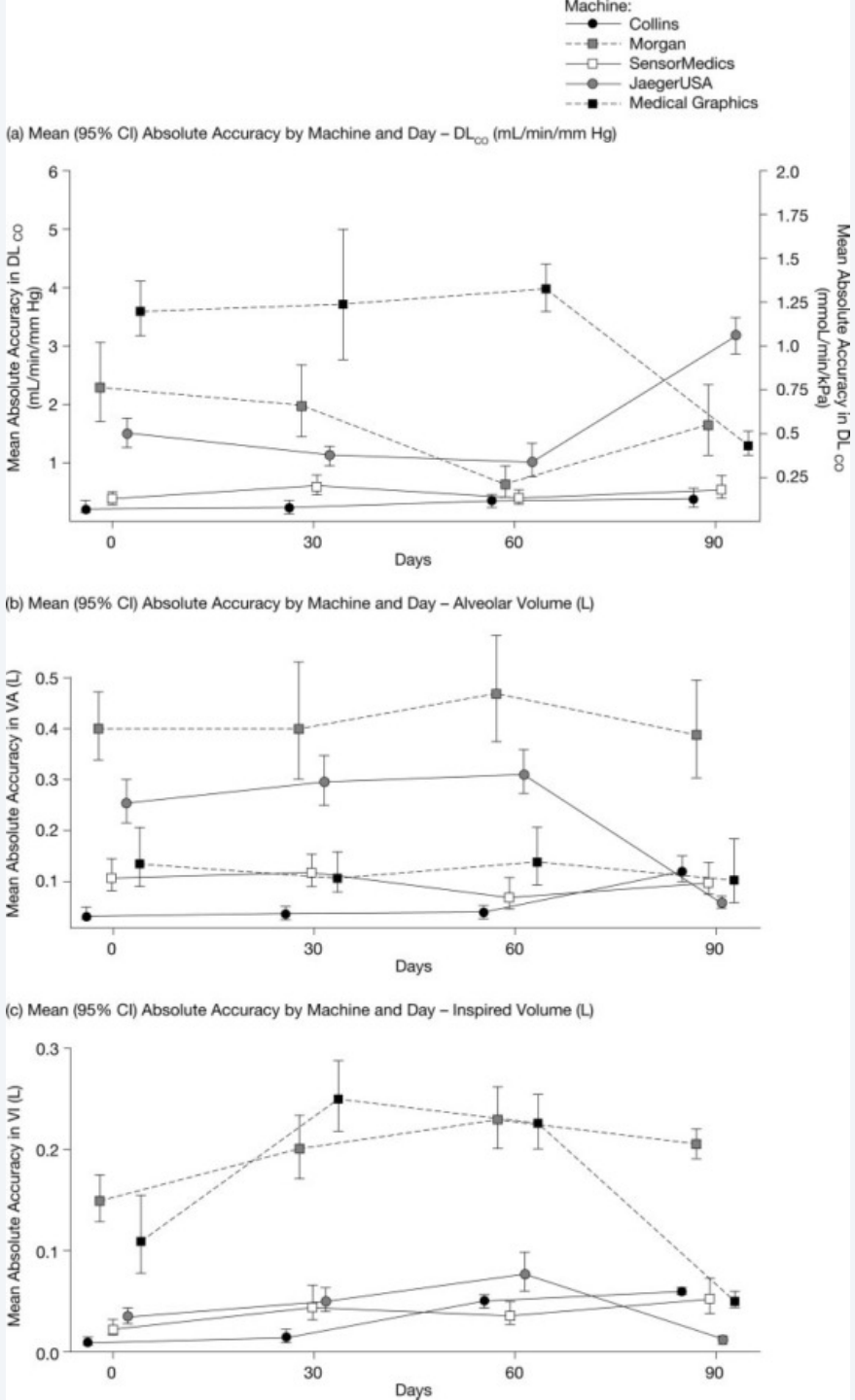
Pulmonary function testing measurement of lung volume

- Effort dependent
- Multiple efforts undertaken, coached by RT, best effort recorded, ATS standards for results



FVC Surrogate

non-statistically significant correlation between FVC change and mortality (-0.062, 95% CI: -0.156, 0.032; p=0.17, R^2 = 0.23). A sensitivity analysis of antifibrotic trials also found no significant association (estimate = 0.009, 95% CI: -0.089, 0.107; p = 0.838, R^2 = 0.017)



CHEST

Volume 132, Issue 2, August 2007, Pages 388-395

Original Research

Pulmonary Function Testing

Instrument Accuracy and Reproducibility in Measurements of Pulmonary Function

Jensen Robert L. PhD [a], Teeter John G. MD [b], England Richard D. MD, PhD [b], White Heather J. DVM [b], Pickering Eve H. PhD [b], Crapo Robert O. MD, FCCP [a]

Autoimmune AWD – screening?

Prevalence of AWD in RA when screened with spirometry

[Diffuse Lung Disease Original Research]

CHEST

Airways Abnormalities in a Prospective Cohort of Patients With Rheumatoid Arthritis

Scott M. Matson, MD; Jiwoong Choi, PhD; Drayton Rorah, DO; Shamir Khan, MD; Anna Trofimoff, BS; Taewon Kim, MS; David H. Lee, MS; Asma Abdolijomoor, BS; Maggie Chen, MD; Imaan Azeem, MS; Linh Ngo, MS; Tami J. Bang, MD; Peter Sachs, MD; Kevin D. Deane, MD, PhD; M. Kristen Demoruelle, MD, PhD; Mario Castro, MD, MPH; and Joyce S. Lee, MD

TABLE 2] Spirometry Features of Cohort Based on Presence of Obstruction (FEV_1 to FVC Ratio < 0.7)

Variable	Obstructed (n = 38; 20.7%)	Nonobstructed (n = 145; 79.3%)	*P* Value
Age, y	61.6 (12.7)	50.0 (19.2)	< **.01**[a]
Male sex	11 (29%)	20 (14%)	.06[b]
History of ever smoking	30 (81%)	60 (42%)	< **.01**[b]
FEV_1, % predicted	76.5 (62.6, 90.4)	100 (90, 110)	< **.01**[a]
FVC, % predicted	95 (82.5, 107.5)	101 (90.5, 111.5)	**.03**[a]
D_LCO, % predicted	79 (64, 94)	89 (76.35, 101.65)	< **.01**[a]
Rheumatoid factor positive[c]	34 (89%)	112 (78%)	.11[b]
Anticyclic citrullinated peptide antibody positive (cyclic citrullinated peptide 3.1)[c]	30 (79%)	122 (84%)	.6[b]
Current methotrexate use	23 (61%)	71 (49%)	.3[b]
RA mean duration, y	13.6 (11.3)	12.7 (11.7)	.6[a]
DAS-28 CRP[d]	2.7 (2.0)	2.6 (1.6)	.9[a]

Prevalence of AWD in RA when screened with radiology

[Diffuse Lung Disease Original Research]

CHEST

Airways Abnormalities in a Prospective Cohort of Patients With Rheumatoid Arthritis

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TABLE 4] Radiologist-Defined Airways Abnormalities

Variable	Radiologist-Determined Airway Abnormality (n = 112)	No Radiologist-Determined HRCT Imaging Airways Abnormalities (n = 71)	*P* Value
Age, y	55.6 (15)	50.63 (14.3)	**.03**[d]
Male sex	25 (22.5%)	7 (9.9%)	< **.01**[h]
History of ever smoking	60 (57.6%)	27 (40.9%)	.2[h]
FEV_1, % predicted	95 (82.5, 107.5)	100 (88.8, 111.3)	< **.01**[a]
FVC, % predicted	99 (89.8, 108.3)	103 (91.1, 114.9)	**.03**[d]
D_{LCO}, % predicted	85 (71.8, 98.3)	90 (77.6, 102.4)	.2[a]
FEV_1 to FVC ratio	0.75 (0.1)	0.8 (0.09)	< **.01**[d]
Rheumatoid factor positive	96 (85.7%)	50 (70.4%)	**.02**[h]
Anticyclic citrullinated peptide antibody positive	95 (84.8%)	57 (80.2%)	.6[h]
Current methotrexate use	63 (58%)	32 (45.7%)	.1[h]
RA duration, y	10.5 (14.75)	9 (14.5)	.4[a]
DAS-28 CRP	2.7 (2.1)	2.5 (1.4)	.5[a]

AWD in RA – quantitative CT analysis

[Diffuse Lung Disease Original Research]

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TABLE 3] Univariate and Multivariate Association Between Shortness of Breath and Cough Severity With Spirometry Obstruction, Radiologist-Determined Airways Abnormalities, Wall Thickness, and Emphysema Percent

Method	UCSD SOBQ	Cough Severity VAS
Spirometry		
Univariate association	β = 3.6, *P* = .3	β = 39.6, *P* = .6
Multivariate association	β = 3.7, *P* = .3	β = 65.3, *P* = .4
Radiologist-defined abnormalities		
Univariate association	β = −4.3, *P* = .1	β = −4.3, *P* = .4
Multivariate association	β = −3.4, *P* = .2	β = −4.9, *P* = .3
Wall thickness percentage		
Univariate association	**β = 2.2, *P* < .01**	β = 2.0, *P* = .09
Multivariate association	**β = 1.8, *P* < .01**	β = 2.0, *P* = .06
Percentage of emphysema		
Univariate association	**β = 1.3, *P* < .01**	**β = 1.1 P = .01**
Multivariate association	**β = 1.3, *P* = .01**	**β = 1.3, *P* = .01**

Bold indicates significant *P* value ($P < .05$). SOBQ = Shortness of Breath Questionnaire; UCSD = University of California, San Diego; VAS = visual analog scale.

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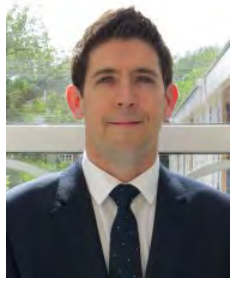


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