Interstitial Lung Abnormalities

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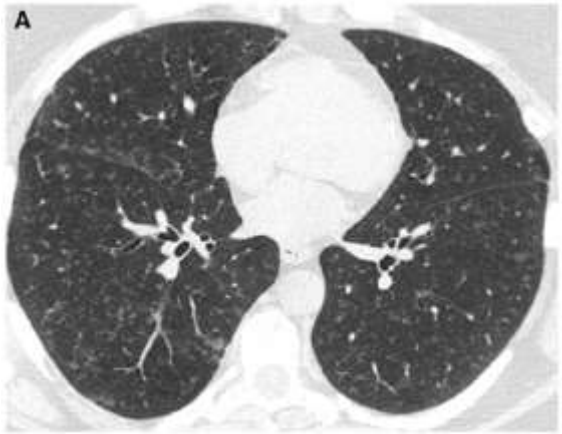
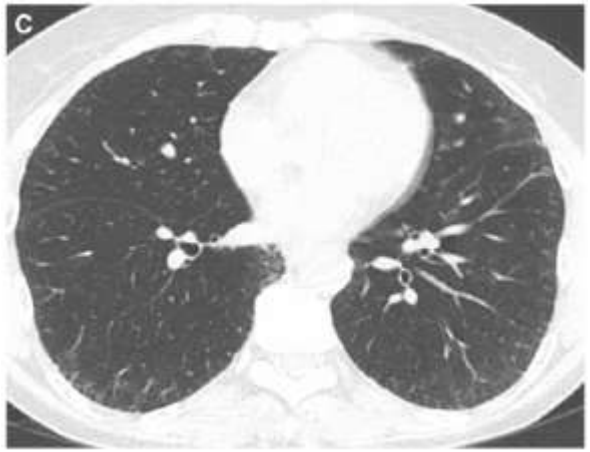
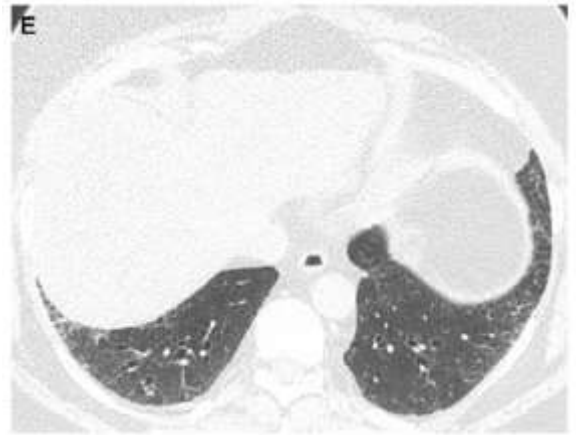
19/07/2025

What constitutes an ILA

" nondependent bilateral parenchymal abnormalities detected on CT, including ground-glass or reticular abnormalities, lung distortion, traction bronchiectasis, and/or honeycombing involving>5% of a lung zone by visual estimate"







The threshold extent of 5% is acknowledged to be arbitrary and subjective and is provided simply to exclude patients with minimal abnormality.

Zones demarcated as upper, middle, and lower by the levels of the inferior aortic arch and right inferior pulmonary vein.

"Nondependent" - parts of the lung that are less influenced by gravity during scan acquisition; this may include abnormalities that are present in dependent locations on supine imaging but persist on prone imaging.

Podolanczuk AJ, Hunninghake GM, et al; Approach to the Evaluation and Management of Interstitial Lung Abnormalities: An Official American Thoracic Society Clinical Statement. *Am J Respir Crit Care Med*. 2025 May 19

What DOES NOT constitute an ILA

- Dependent lung atelectasis
- Unifocal or multifocal linear scarring
- Non-emphysematous cysts, centri-lobular nodularity, and/or features of pleuroparenchymal fibroelastosis, without other CT findings of lung disease
- Findings of heart failure
- Findings of aspiration (e.g., patchy ground-glass, opacities, tree-in-bud nodularity)

Nonemphysematous cysts,
centrilobular nodularity,
features of pleuroparenchymal fibroelastosis can be present but do not contribute to the volume of affected lung needed to satisfy the definition of ILA.

Podolanczuk AJ, Hunninghake GM, et al; Approach to the Evaluation and Management of Interstitial Lung Abnormalities: An Official American Thoracic Society Clinical Statement. *Am J Respir Crit Care Med*. 2025 May 19

What DOES NOT constitute an ILA

Definition of interstitial lung disease for those with ILAs

In a person with CT features of ILAs, at least one of the following criteria must be present to define ILD*

- Symptoms: Any amount of dyspnea and/or cough that a clinician attributes to ILD
- Physiology (any of)
  - Any abnormality in FVC, TLC, or D_{LCO} that a clinician attributes to ILD (defined as a value or *z*-score below the lower limit of normal)
  - Satisfies physiologic criteria for progressive pulmonary fibrosis that a clinician attributes to ILD (9)
- Imaging (any of the following on chest CT)
  - Fibrotic abnormalities (honeycombing and/or reticulation with traction bronchiectasis) involving ⩾5% of total lung volume by visual estimate
  - Progressive fibrotic abnormality on serial chest CT
  - Presence of a major fibrotic ILD pattern on chest CT (i.e., UIP/probable UIP, fibrotic HP, or fibrotic NSIP)
- Pathology: Presence of a major fibrotic ILD pattern (i.e., UIP/probable UIP, fibrotic HP, or fibrotic NSIP)

Podolanczuk AJ, Hunninghake GM, et al; Approach to the Evaluation and Management of Interstitial Lung Abnormalities: An Official American Thoracic Society Clinical Statement. *Am J Respir Crit Care Med*. 2025 May 19

AGES-Reykjavik Study

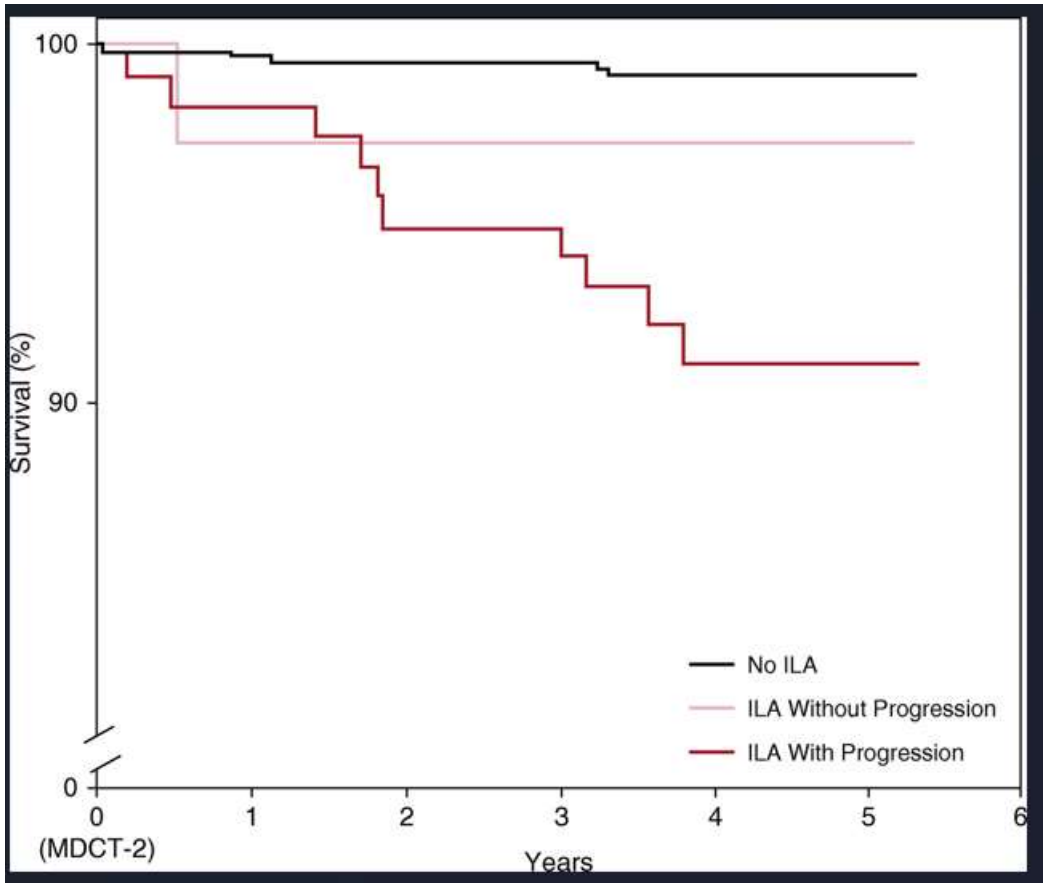
Association between Imaging Features and ILA Progression

	Unadjusted Analysis		Adjusted Analysis*	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Centrilobular nodules	0.2 (0.1–0.4)	<0.0001	0.2 (0.1–0.5)	0.0002
Ground glass†	—	—	—	—
Subpleural reticular markings	5.9 (2.3–15)	0.0002	6.6 (2.3–19)	0.0004
Nonemphysematous cysts	3.1 (1.6–5.9)	0.0005	2.5 (1.3–5.1)	0.009
Lower lobe predominant changes	5.2 (1.8–15)	0.002	6.7 (1.8–25)	0.004
Traction bronchiectasis	5.9 (2.3–14.9)	0.0002	6.6 (2.3–19)	0.0004
Honeycombing‡	—	—	—	—

n= 3,167

median time between CT scans, 5.1 yr; interquartile range, 4.99–5.26 yr)

Putman RK, Gudmundsson G, Axelsson GT, Hida T, et al Imaging Patterns Are Associated with Interstitial Lung Abnormality Progression and Mortality. Am J Respir Crit Care Med. 2019 Jul 15;200(2):175-183.



Araki T, Putman RK, Hatabu H, Gao W, Dupuis J, Latourelle JC, Nishino M, Zazueta OE, Kurugol S, Ross JC, San José Estépar R, Schwartz DA, Rosas IO, Washko GR, O'Connor GT, Hunninghake GM. Development and Progression of Interstitial Lung Abnormalities in the Framingham Heart Study. Am J Respir Crit Care Med. 2016 Dec 15;194(12):1514-1522. doi: 10.1164/rccm.201512-2523OC.

Evolution of definitions

What are interstitial lung abnormalities (ILAs)?

- Incidental identification of non-dependent abnormalities, including ground-glass or reticular abnormalities, lung distortion, traction bronchiectasis, honeycombing, and non-emphysematous cysts
- Involving at least 5% of a lung zone (upper, middle, and lower lung zones are demarcated by the levels of the inferior aortic arch and right inferior pulmonary vein)
- In individuals in whom interstitial lung disease is not suspected

What are not ILAs?

Imaging findings restricted to:

- Dependent lung atelectasis
- Focal paraspinal fibrosis in close contact with thoracic spine osteophytes (figure 2A)
- Smoking-related centrilobular nodularity in the absence of other findings (figure 2B)
- Mild focal or unilateral abnormality (figure 2C)
- Interstitial oedema (eg, in heart failure)
- Findings of aspiration (patchy ground-glass, tree in bud; figure 2C)

Preclinical and clinical identification:

- Preclinical interstitial abnormalities identified during screening of high-risk individuals (eg, those with rheumatoid arthritis, scleroderma, occupational exposure, familial interstitial lung disease)
- Findings in patients with known clinical interstitial lung disease

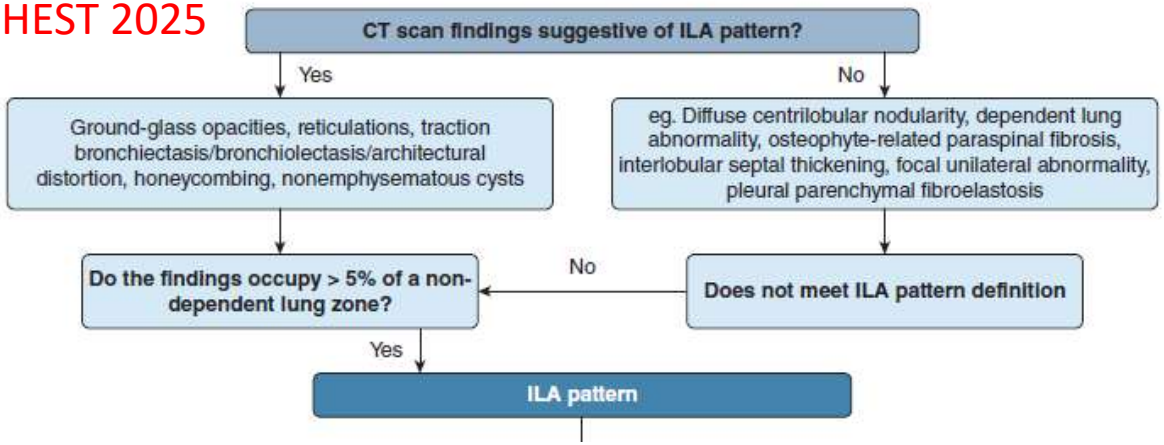
Fleischner Society 2021

ERS 2022

Entity		Population	Diagnostic criteria	Definition
ILA		Only individuals without known or suspected ILD[#]	Clinical-radiological entity	Incidental finding of CT abnormalities affecting more than 5% of any lung zone
Early ILD	Pre-clinical ILD Subclinical ILD	Individuals at risk for ILD Individuals NOT at risk for ILD	Clinical-radiological-pathological entity	Any ILD in asymptomatic patients with preserved lung function
Mild ILD		All individuals	Clinical-radiological-pathological entity	Any clinically significant ILD with minor symptoms and/or trivial PFT abnormalities

ILA: interstitial lung abnormalities; ILD: interstitial lung disease; CT: computed tomography; PFT: pulmonary function test. [#]: abnormalities identified during screening for ILD in high-risk groups (*e.g.* those with rheumatoid arthritis, systemic sclerosis or familial ILD) are not considered as ILA because they are not incidental.

CHEST 2025



Chest CT showing bilateral and nondependent ground-glass opacities, reticular abnormalities, lung distortion, traction bronchiectasis, and/or honeycombing involving ⩾5% of a lung zone*

ATS 2025

- Nonemphysematous cysts, centrilobular nodularity, and features of pleuroparenchymal fibroelastosis can be present but do not contribute to the volume of affected lung needed to satisfy the definition of ILA
- Bilaterality may not be necessary in some high-risk cases (i.e., with a family history of familial pulmonary fibrosis or known ILD-associated genetic variants)
- The need for findings to be incidental and exclusion of high-risk populations has purposefully been removed from the definition
- Mild abnormalities occurring exclusively in dependent locations on supine imaging should be confirmed to persist on prone imaging

The Fleischner Society definition of ILA required findings to be incidental and excluded high-risk populations.

- **ATS definition:**

1) defines ILA independent of pre-test probability : more practical for clinical use.

2) High risk populations: ILAs – prevalent , Inclusion in definition - provides guidance for evaluation and management of these patients.

No data to suggest exclusion,

Simpler to create a relatively broad definition of ILA with consistent evaluation and management algorithms that can be applied to most clinical scenarios

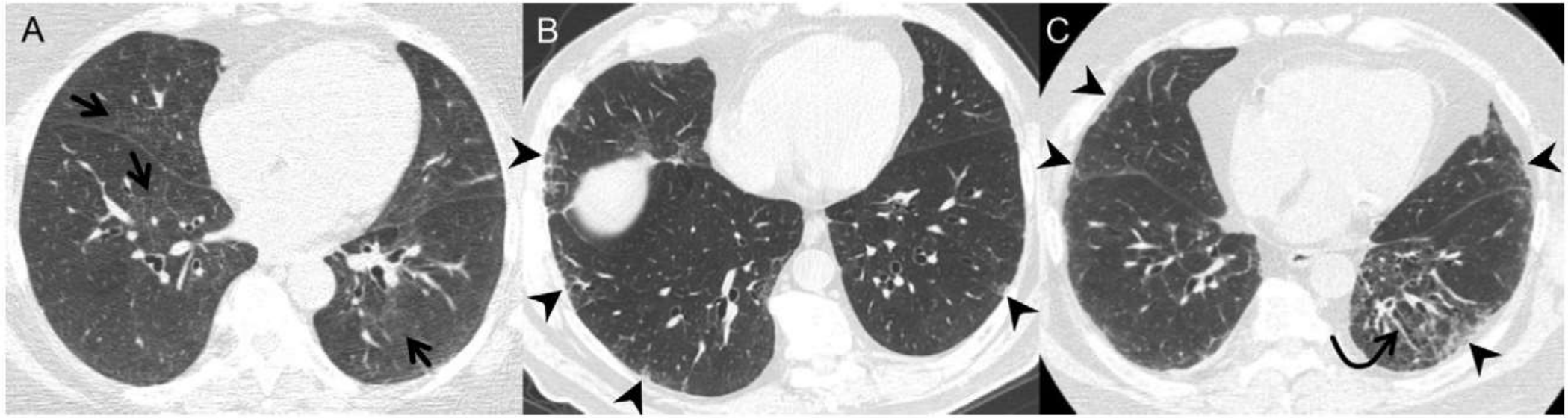
3) Laterality of ILA: Patients with a strong family history or known genetic variants who have unilateral findings may be at risk of future progression to ILD

- .

Subcategories of ILA

- Non-subpleural ILAs (i.e., without predominant subpleural localization)
- Sub-pleural nonfibrotic ILAs (i.e., with predominant subpleural localization and without evidence of fibrosis)
- Sub-pleural fibrotic ILAs (i.e., with predominant subpleural localization and with evidence of pulmonary fibrosis)

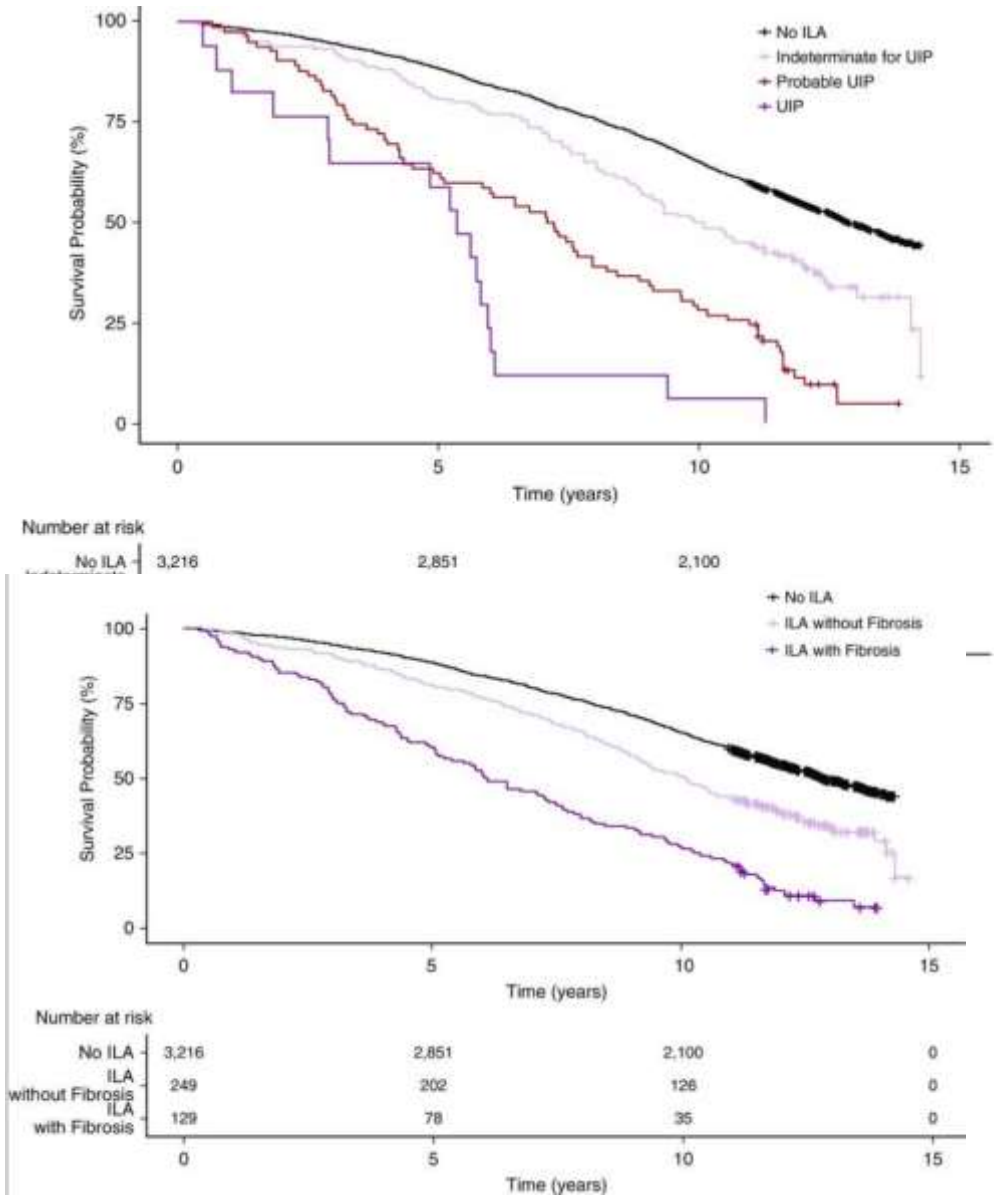
Fibrosis - the presence of architectural distortion with traction bronchiectasis and/or honeycombing and applies to those ILAs that do not meet the extent or pattern criteria for ILD


A
B
C

AGES-Reykjavik Study

Association between Imaging Pattern and Features and Mortality*

	Unadjusted Analysis		Adjusted Analysis†	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Reticular markings	2.0 (1.3–3.1)	0.002	1.6 (1.0–2.5)	0.049
Centrilobular nodules	0.7 (0.6–0.9)	0.01	0.9 (0.7–1.1)	0.3
Nonemphysematous cysts	1.7 (1.3–2.2)	<0.0001	1.4 (1.1–1.8)	0.02
Traction bronchiectasis	2.0 (1.6–2.6)	<0.0001	1.6 (1.3–2.1)	0.0001
Lower lobe‡ predominance	1.5 (0.95–2.5)	0.08	1.1 (0.6–1.7)	0.8
Subpleural location§	2.0 (1.3–3.2)	0.003	1.6 (1.0–2.7)	0.050
ILA without fibrosis	1.3 (1.2–1.4)	<0.0001	1.2 (1.1–1.3)	0.0004
Definite fibrosis	1.9 (1.7–2.1)	<0.0001	1.5 (1.3–1.6)	<0.0001
Indeterminate for UIP	1.6 (1.3–2.0)	<0.0001	1.2 (0.98–1.5)	0.07
Probable UIP pattern	3.3 (2.6–4.2)	<0.0001	1.9 (1.5–2.5)	<0.0001
UIP pattern	6.9 (4.2–11)	<0.0001	4.5 (2.8–7.2)	<0.0001



5,320 participants in total who had completed the baseline CT are included.

Putman RK, Gudmundsson G, Axelsson GT, Hida T, et al Imaging Patterns Are Associated with Interstitial Lung Abnormality Progression and Mortality. Am J Respir Crit Care Med. 2019 Jul 15;200(2):175-183.

Why is ILA significant

Clinical Burden: (I) Prevalence of ILA

- 7-17%
- ~ 60 years
- Progression :

10-70% in 5 years

	Population-based Cohorts				Smoking and Lung Cancer Screening Cohorts				
Parameter	AGES-Reykjavik (9,18)	FHS (6,8,9)	MESA (11–14)	Nagano, Japan (15)	COPDGene (4,9,23)	DLCST (27)	ECLIPSE (9)	MILD (28)	NLST (7,16)
Sample size	5320	2633	3137	3061	9292	1990	1670	692	884
Prevalence of ILA	378 (7)	177 (7)	310 (10)	80 (3)	708 (8)	332 (17)	157 (9)	28 (4)	86 (10)
Age (y)*									
ILA group	78 ± 6	70 ± 12	NA	62 ± 9	64 ± 9	60 ± 5	64 ± 8	60 ± 6	62 ± 5
Non-ILA group	76 ± 5	56 ± 11	NA	54 ± 10	60 ± 9	58 ± 5	62 ± 7	57 ± 6	61 ± 5
Percentage of women (%)									
ILA group	172/378 (46)	89/177 (50)	NA	21/80 (26)	345/708 (49)	136/332 (41)	41/157 (26)	4/28 (14)	27/86 (31)
Non-ILA group	1910/3216 (59)	675/1370 (49)	NA	1243/2981 (42)	2457/5395 (46)	742/1658 (45)	182/528 (34)	185/534 (35)	295/696 (42)
Pack-years of smoking									
ILA group	11 (0–29)†	19 (9–33)†	NA	44 ± 26*	44 (30–64)†	38 ± 13*	43 (30–60)†	NA	60 ± 29*
Non-ILA group	0 (0–16)†	11 (4–23)†	NA	21 ± 13*	40 (30–54)†	36 ± 13*	45 (33–62)†	NA	51 ± 20*
Overall ILA progression (%)	73	43	NA	44	NA	NA	NA	NA	20
Follow-up time (y)	5	6	NA	4	NA	NA	NA	NA	2
Hazard ratio of mortality‡	1.3 (1.2, 1.4)	2.7 (1.1, 6.5)	NA	NA	1.8 (1.1, 2.8)	2.0 (1.4, 2.7)	1.4 (1.1, 2.0)	NA	NA

Note.—Except where indicated, data are numbers of patients, with percentages in parentheses. Adapted, with permission, from reference 2. AGES = Age, Gene/Environment Susceptibility, COPDGene = Genetic Epidemiology of Chronic Obstructive Pulmonary Disease (COPD) Study, DLCST = Danish Lung Cancer Screening Trial, ECLIPSE = Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints, FHS = Framingham Heart Study, ILA = interstitial lung abnormality, MESA = Multi-Ethnic Study of Atherosclerosis, MILD = Multicentric Italian Lung Detection, NA = not available, NLST = National Lung Screening Trial.

* Numbers are means ± standard deviations.

† Numbers are medians, with interquartile ranges in parentheses.

‡ Numbers in parentheses are 95% CIs.

Clinical burden: (II) Progression of ILA

Data from the AGES-Reykjavik Study

n= 3,167

median time between CT scans, 5.1 yr; interquartile range, 4.99–5.26 yr

327 (10%) had ILA on at least one CT scan,

Table 1. Baseline Characteristics of Participants, at the Time of the Second Computed Tomography Scan, Stratified by ILA Status and ILA Progression Status*

	No ILA (*n* = 1,777; 56%) 0	ILA without Progression (*n* = 89; 3%) 1	ILA with Progression (*n* = 238; 8%) 2	*P* Value All	0 vs. 1	0 vs. 2	1 vs. 2
Age, yr	74 ± 5	75 ± 5	76 ± 5	<0.0001	0.4	<0.0001	0.02
Sex, *n* (%)				<0.0001	0.2	<0.0001	0.2
M	704 (40)	42 (47)	131 (55)				
F	1,073 (60)	47 (53)	107 (45)				
Body mass index, kg/m^2	27 ± 4	27 ± 5	28 ± 4	0.06	0.8	0.02	0.4
Pack-years smoking, median, IQR	0 (15)	11 (30)	11 (30)	<0.0001	0.0001	<0.0001	0.7
Smoking status, *n* (%)				<0.0001	0.001	<0.0001	0.5
Never	843 (48)	25 (28)	70 (29)				
Former	751 (42)	48 (55)	138 (58)				
Current	183 (10)	15 (17)	30 (13)				
MUC5B, *n* (%)				<0.0001	0.3	<0.0001	0.0005
GG	1,426 (80)	67 (76)	131 (55)				
GT	335 (19)	20 (23)	98 (41)				
TT	15 (1)	1 (1)	9 (4)				

Definition of abbreviations: 0 = no ILA; 1 = ILA without progression; 2 = ILA with progression; ILA = interstitial lung abnormalities; IQR = interquartile range; *MUC5B* = genotype at the *MUC5B* promoter polymorphism (rs35705950).
Values are *n* (%) or mean ± SD.
*Comparison of categorical variables was done using Fisher exact tests, continuous variables with two-tailed Student's *t* test, and across all three categories comparisons were made using ANOVA.

Putman RK, Gudmundsson G, Axelsson GT, Hida T, et al Imaging Patterns Are Associated with Interstitial Lung Abnormality Progression and Mortality. Am J Respir Crit Care Med. 2019 Jul 15;200(2):175-183.

Data from the AGES-Reykjavik Study

Multivariable Logistic Regression to Assess Factors Associated with ILA Progression, Comparing Those with Imaging Progression with Those without Imaging Progression and Comparing Those with Imaging Progression with Those without ILA on Either Computed Tomography Scan

	Comparison of ILA with Progression with ILA without Progression		Comparison of ILA with Progression with No ILA	
Covariate	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
MUC5B genotype*	2.6 (1.5–4.4)	0.0004	2.9 (2.2–3.8)	<0.0001
Age†	1.08 (1.02–1.1)	0.01	1.08 (1.05–1.11)	<0.0001
Sex‡	0.6 (0.4–1.1)	0.1	0.6 (0.4–0.8)	0.0002
Body mass index§	1.05 (0.99–1.1)	0.1	1.06 (1.02–1.09)	0.001
Pack-years smoking‖	0.99 (0.98–1.01)	0.3	1.01 (1.01–1.02)	<0.0001
Current smoking status¶	1.1 (0.5–2.4)	0.8	1.1 (0.7–1.8)	0.6

Association between Imaging Features and ILA Progression

	Unadjusted Analysis		Adjusted Analysis*	
	OR (95% CI)	***P* Value**	**OR (95% CI)**	***P* Value**
Centrilobular nodules	0.2 (0.1–0.4)	<0.0001	0.2 (0.1–0.5)	0.0002
Ground glass†	—	—	—	—
Subpleural reticular markings	5.9 (2.3–15)	0.0002	6.6 (2.3–19)	0.0004
Nonemphysematous cysts	3.1 (1.6–5.9)	0.0005	2.5 (1.3–5.1)	0.009
Lower lobe predominant changes	5.2 (1.8–15)	0.002	6.7 (1.8–25)	0.004
Traction bronchiectasis	5.9 (2.3–14.9)	0.0002	6.6 (2.3–19)	0.0004
Honeycombing‡	—	—	—	—

Putman RK, Gudmundsson G, Axelsson GT, Hida T, et al Imaging Patterns Are Associated with Interstitial Lung Abnormality Progression and Mortality. Am J Respir Crit Care Med. 2019 Jul 15;200(2):175-183.

Clinical burden: (III) Mortality due to ILA

Table 2. Association Between Interstitial Lung Abnormalities and Mortality

	FHS (N = 2633)		AGES-Reykjavik (N = 5320)		COPDGene (N = 2068)		ECLIPSE (N = 1670)	
Median follow-up time, (IQR), y	4.0 (3.3 to 4.6)		8.9 (6.7 to 9.9)		6.5 (6.2 to 6.7)		2.9 (2.9 to 2.9)	
Mortality, No. (%)								
No ILA	12 (1)		1065 (33)		133 (11)		27 (5)	
ILA	12 (7)		210 (56)		25 (16)		18 (11)	
Mortality difference % (95% CI)	6 (2 to 10)		23 (18 to 28)		5 (−1 to 11)		6 (1 to 11)	
Models	**HR (95% CI)[a]**	***P* Value**	**HR (95% CI)[a]**	***P* Value**	**HR (95% CI)[a]**	***P* Value**	**HR (95% CI)[a]**	***P* Value**
Unadjusted model	7.7 (3.7-16.1)	<.001	1.4 (1.3-1.6)	<.001	1.5 (0.98-2.3)	.08	1.5 (1.1-2.1)	.005
Adjusted model[b]	2.7 (1.1-6.5)	.03	1.3 (1.2-1.4)	<.001	1.8 (1.1-2.8)	.01	1.4 (1.1-2.0)	.02
Plus % emphysema[c,d]	2.6 (1.03-6.7)	.04			1.9 (1.2-3.0)	.007	1.4 (1.03-2.0)	.03
Plus coronary disease[d,e]	2.2 (0.9-5.9)	.10	1.2 (1.1-1.3)	<.001	1.5 (0.9-2.0)	.12	1.7 (1.1-2.4)	.008
Plus cancer history[d,e]	2.6 (1.1-6.2)	.03	1.25 (1.2-1.3)	<.001	1.8 (1.1-2.8)	.008		

Abbreviations AGES, Age Gene/Environment Susceptibility; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; FHS, Framingham Heart Study; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; ILA, interstitial lung abnormality; IQR, interquartile range.

[a] All HRs are for the comparison between participants with and without interstitial lung abnormalities.

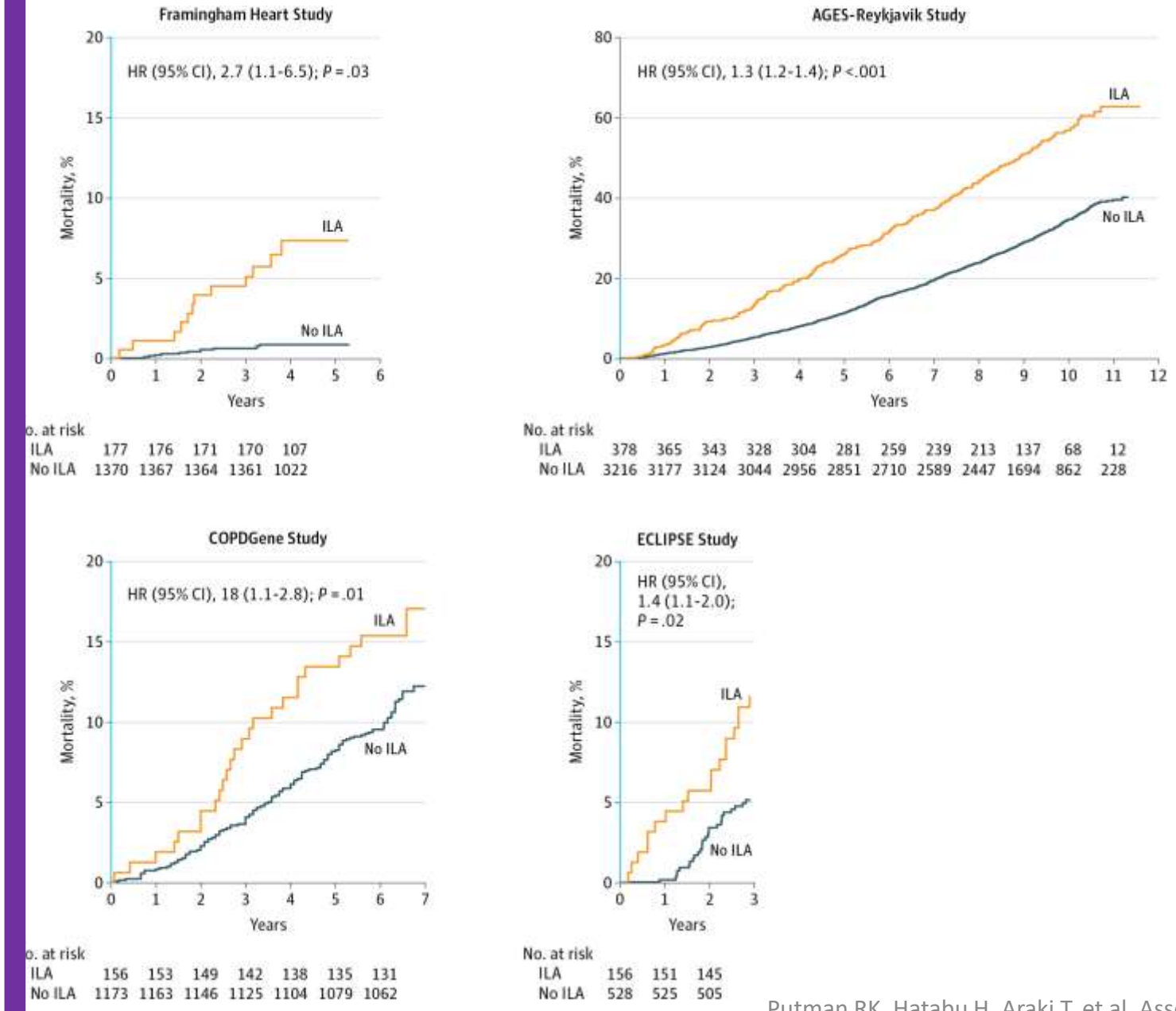
[b] Adjusted HRs include adjustments for age, sex, race, BMI (calculated as weight in kilograms divided by height in meters squared), pack-years of smoking, current or former smoking status, and GOLD stage of COPD (where available).

[c] Adjusted HRs include adjustments for age, sex, race, BMI, pack-years of smoking, current or former smoking status, GOLD stage of COPD, and amount of emphysema (% < −950 Hounsfield units [HU]).

[d] See eTable 4 (Supplement) for variables used in addition to the baseline adjusted model.

[e] Adjusted HRs include adjustments for age, sex, race, BMI, pack-years of smoking, current or former smoking status, GOLD stage of COPD (except in the AGES-Reykjavik where GOLD stage was not available), history of coronary artery disease, and coronary calcium score.

Putman RK, Hatabu H, Araki T, et al. Association Between Interstitial Lung Abnormalities and All-Cause Mortality. *JAMA.* 2016;315(7):672–681. doi:10.1001/jama.2016.0518



Putman RK, Hatabu H, Araki T, et al. Association Between Interstitial Lung Abnormalities and All-Cause Mortality. *JAMA.* 2016;315(7):672–681. doi:10.1001/jama.2016.0518

Table 3. Mortality, Interstitial Lung Abnormalities, and Cause of Death for the AGES-Reykjavik Study

	No. (%)[a]			
	ILA	Indeterminate	No ILA	Overall
No. of participants	378	1726	3216	5320
Deaths				
Total	115 (100)	382 (100)	468 (100)	965
Cardiovascular[b]	48 (42)	161 (42)	204 (44)	413
Cancer[c]	29 (25)	111 (29)	151 (32)	291
Respiratory[d]	15 (13)	22 (6)	20 (4)	57
Pulmonary fibrosis	7	1	0	8
Other	8	21	20	49
Other[e]	23 (20)	88 (23)	93 (20)	204

Abbreviations: AGES, Age Gene/Environment Susceptibility; *ICD*, *International Classification of Diseases*; ILA, interstitial lung abnormality.

[a] Percentages were all rounded to the nearest whole number. Some of the percentages may sum to greater than 100%.

[b] Cardiovascular deaths included the following: *ICD-9* codes 390-459 and *ICD-10* codes I00-I99.

[c] Cancer deaths included the following: *ICD-9* codes 140-239 and *ICD-10* codes C00-D48.

[d] Respiratory deaths included the following: *ICD-9* codes 460-519 and *ICD-10* codes J00-J99.

[e] All causes of death not contained in these *ICD-9* and *ICD-10* codes were included in the category of *other*.

Putman RK, Hatabu H, Araki T, et al. Association Between Interstitial Lung Abnormalities and All-Cause Mortality. *JAMA.* 2016;315(7):672–681. doi:10.1001/jama.2016.0518

(iv) Smokers and Lung cancer screening

Table 1: Major Results of ILA Studies in Large Cohorts

	Population-based Cohorts				Smoking and Lung Cancer Screening Cohorts				
Parameter	AGES-Reykjavik (9,18)	FHS (6,8,9)	MESA (11–14)	Nagano, Japan (15)	COPDGene (4,9,23)	DLCST (27)	ECLIPSE (9)	MILD (28)	NLST (7,16)
Sample size	5320	2633	3137	3061	9292	1990	1670	692	884
Prevalence of ILA	378 (7)	177 (7)	310 (10)	80 (3)	708 (8)	332 (17)	157 (9)	28 (4)	86 (10)
Age (y)*									
ILA group	78 ± 6	70 ± 12	NA	62 ± 9	64 ± 9	60 ± 5	64 ± 8	60 ± 6	62 ± 5
Non-ILA group	76 ± 5	56 ± 11	NA	54 ± 10	60 ± 9	58 ± 5	62 ± 7	57 ± 6	61 ± 5
Percentage of women (%)									
ILA group	172/378 (46)	89/177 (50)	NA	21/80 (26)	345/708 (49)	136/332 (41)	41/157 (26)	4/28 (14)	27/86 (31)
Non-ILA group	1910/3216 (59)	675/1370 (49)	NA	1243/2981 (42)	2457/5395 (46)	742/1658 (45)	182/528 (34)	185/534 (35)	295/696 (42)
Pack-years of smoking									
ILA group	11 (0–29)†	19 (9–33)†	NA	44 ± 26*	44 (30–64)†	38 ± 13*	43 (30–60)†	NA	60 ± 29*
Non-ILA group	0 (0–16)†	11 (4–23)†	NA	21 ± 13*	40 (30–54)†	36 ± 13*	45 (33–62)†	NA	51 ± 20*
Overall ILA progression (%)	73	43	NA	44	NA	NA	NA	NA	20
Follow-up time (y)	5	6	NA	4	NA	NA	NA	NA	2
Hazard ratio of mortality‡	1.3 (1.2, 1.4)	2.7 (1.1, 6.5)	NA	NA	1.8 (1.1, 2.8)	2.0 (1.4, 2.7)	1.4 (1.1, 2.0)	NA	NA

Note.—Except where indicated, data are numbers of patients, with percentages in parentheses. Adapted, with permission, from reference 2. AGES = Age, Gene/Environment Susceptibility, COPDGene = Genetic Epidemiology of Chronic Obstructive Pulmonary Disease (COPD) Study, DLCST = Danish Lung Cancer Screening Trial, ECLIPSE = Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints, FHS = Framingham Heart Study, ILA = interstitial lung abnormality, MESA = Multi-Ethnic Study of Atherosclerosis, MILD = Multicentric Italian Lung Detection, NA = not available, NLST = National Lung Screening Trial.

- In patients with early-stage cancers treated with surgical resection, ILA - associated with a risk of postoperative pulmonary complications such as pneumonia, acute respiratory distress syndrome, respiratory failure, bronchopleural fistula or empyema, prolonged air leakage,and pneumothorax

Table 4 Risk factors associated with PPCs

	Univariate analysis		Multivariate analysis	
Variable	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	0.96 (0.88–1.06)	0.427		
Sex, male	2.47 (1.35–4.55)	**0.004**		
Smoking history (current & former)	2.25 (1.25–4.07)	**0.007**		
ASA classification ≥3	1.79 (1.10–2.93)	**0.019**	1.91 (1.14–3.21)	**0.014**
BMI	1.15 (1.05–1.29)	**0.003**	0.86 (0.78–0.95)	**0.004**
Hemoglobin	1.18 (0.95–1.46)	0.066		
Squamous vs. others	2.54 (1.33–4.84)	**0.005**		
ILA	1.07 (1.02–1.12)	**0.009**	1.91 (1.02–1.13)	**0.004**
Emphysema index	1.04 (1.01–1.07)	**0.010**		
Extent of surgery				
Segmentectomy & Wedge resection & Lobectomy	Reference		Reference	
Pneumonectomy & Bilobectomy	4.61 (1.65–12.8)	**0.004**	4.46 (1.54–12.9)	**0.006**

ASA: American Society of Anesthesiologists; *BMI*: body mass index; *CI*: confidence interval; *ILA*: interstitial lung abnormality; *OR*: odds ratio; *PPCs*: postoperative pulmonary complications

m Y, Park HY, Shin S, Shin SH, Lee H, Ahn JH, Sohn I, Cho JH, Kim HK, Zo JI, Shim YM, Lee HY, Kim J. Prevalence of and risk factors for pulmonary complications after curative resection in otherwise healthy elderly patients with early stage lung cancer. Respir Res. 2019 Jul 4;20(1):136. doi: 10.1186/s12931-019-1087-x. PMID: 31272446; PMCID: PMC6610954.

- The incidence of immunotherapy-associated pneumonitis significantly higher in patients with pre-existing ILA than in those without ILA

Among 83 enrolled patients, the incidence of ICI-ILD was 16.9% (14/83). All ICI-ILD cases developed by the third line of treatment. The incidence of ICI-ILD was significantly higher in patients with pre-existing ILA than that in those without ($p = 0.007$). Furthermore, patients with ground glass attenuation (GGA) in ILA had a higher incidence of ICI-ILD than that in those without ($p < 0.001$). In univariate logistic analysis, ILA were significant risk factors for ICI-ILD ($p = 0.005$). Multivariate logistic analysis revealed that only GGA in ILA was a significant risk factor for ICI-ILD ($p < 0.001$).

Nakanishi Y, Masuda T, Yamaguchi K, et al. Pre-existing interstitial lung abnormalities are risk factors for immune checkpoint inhibitor-induced interstitial lung disease in non-small cell lung cancer. Respir Investig 2019;57(5):451–459.

Risk factors for ILA progression

Risk factors: (i) *Age*

- Framingham Heart Study - prevalence of ILA > 70 years - 47%.
- COPDGene study – ILA prevalence increased from 4% in < 60 years to 6% in those > 70 years

Table 1. Baseline Characteristics in the Framingham Heart Study and COPDGene Cohort Stratified by Age Group

	Age Group			
	Age < 60 yr [*Number (%) or Median (IQR)*]	Age ⩾ 60 yr and <70 yr [*Number (%) or Median (IQR)*]	Age ⩾ 70 yr [*Number (%) or Median (IQR)*]	*P* Value*
Framingham Heart Study	1,017 (66)	332 (22)	192 (12)	—
ILA	44 (4)	41 (12)	91 (47)	<0.0001
Sex, F	473 (47)	189 (57)	99 (52)	0.43
BMI, kg/m^2	28 (25–32)	28 (25–32)	28 (25–31)	<0.0001
Pack-years smoking	0 (0–8)	5 (0–20)	8 (0–24)	<0.0001
Current smoking	71 (7)	16 (5)	3 (2)	<0.0001
CAC score†	0 (0–19)	48 (0–270)	246 (40–725)	<0.0001
COPDGene Study‡	272 (29)	410 (44)	246 (27)	—
ILA	10 (4)	10 (2)	14 (6)	<0.0001
Sex, F	128 (47)	171 (42)	97 (39)	0.09
BMI	27 (23–31)	27 (23–31)	27 (24–31)	0.74
Pack-years smoking	41 (32–57)	51 (40–74)	56 (39–76)	<0.0001
Current smoking	148 (54)	111 (27)	26 (11)	<0.0001
CAC score†	2 (0–102)	86 (3–291)	193 (29–543)	<0.0001
African American race	85 (31)	59 (14)	19 (8)	<0.0001
GOLD stage				0.01
2	114 (38)	131 (30)	88 (34)	
3	99 (33)	138 (31)	95 (37)	
4	84 (28)	172 (52)	77 (30)	
Percent emphysema (<−950 HU)§	7 (2–23)	16 (5–29)	16 (7–26)	0.004

Definition of abbreviations: BMI = body mass index; CAC = coronary arterial calcium; COPDGene = Genetic Epidemiology of Chronic Obstructive Pulmonary Disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HU = Hounsfield units; ILA = interstitial lung abnormalities; IQR = interquartile range.

**P* values represent the between-group differences. In the Framingham Heart Study, *P* values are from generalized estimating equations to adjust for familial correlation. In the COPDGene Study, *P* values are from Fisher exact tests for categorical variables and Kruskal-Wallis tests for continuous variables.

†The CAC score is calculated using the Agatston scoring method (24). There were 158 COPDGene participants missing a CAC score in this subset.

‡All COPDGene participants in this subset had a GOLD grade ⩾ 2 for chronic obstructive pulmonary disease.

§Percent emphysema is calculated as the percentage of the lung below −950 Hounsfield units. There were 37 COPDGene participants missing percent emphysema in this subset.

Presence of ILA associated with increased levels of growth differentiation factor 15, a biomarker of aging.

Table 2. Association of Aging Biomarkers with ILA in the Framingham Heart Study

Biomarker	Unadjusted Odds of ILA		Adjusted Odds of ILA*		Adjusted Odds of ILA†	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
GDF15, ln	12.2 (7.8–19.2)	<0.0001	3.2 (1.7–5.9)	0.0002	3.4 (1.8–6.4)	0.0002
TNFR, ln	8.0 (4.8–13.1)	<0.0001	2.4 (1.3–4.3)	0.004	3.1 (1.6–5.8)	0.0004
IL-6, ln	2.3 (1.9–2.8)	<0.0001	1.8 (1.4–2.2)	<0.0001	1.8 (1.4–2.4)	<0.0001
CRP, ln	1.5 (1.3–1.7)	<0.0001	1.5 (1.3–1.8)	<0.0001	1.7 (1.3–2.0)	<0.0001
Insulin, ln	1.4 (1.1–1.9)	0.01	1.6 (1.1–2.2)	0.01	1.7 (1.4–2.0)	0.01
HGBA1C, 1%	1.5 (1.2–1.9)	0.0003	1.2 (0.9–1.5)	0.16	—	—
Cystatin-C, 0.1 mg/L	1.3 (1.2–1.5)	<0.0001	1.1 (1.0–1.2)	0.21	—	—
IGFBP1, ln	1.3 (1.1–1.5)	0.0006	1.0 (0.8–1.3)	0.79	—	—
IGF1, ln	1.0 (1.0–1.0)	0.02	1.0 (1.0–1.0)	0.37	—	—
IGFBP3, ln	1.0 (1.0–1.0)	0.13	1.0 (1.0–1.0)	0.66	—	—

Definition of abbreviations: CI = confidence interval; CRP = C-reactive protein; GDF15 = growth differentiation factor 15; HGBA1C = Hb A1C; IGF = insulin-like growth factor; IGFBP = IGF binding protein; ILA = interstitial lung abnormalities; ln = natural log transformed; OR = odds ratio; TNFR = tumor necrosis factor α receptor II.

*All models are adjusted for age, sex, body mass index, current smoking, smoking pack-years, and familial correlation. Each biomarker is included in its own model. ORs depict an ln increase in biomarkers, as noted.

†Additionally adjusted for coronary arterial calcium score and adjudicated clinical coronary heart disease.

Sanders JL, Putman RK, Dupuis J, Xu H, Murabito Jmet al The Association of Aging Biomarkers, Interstitial Lung Abnormalities, and Mortality. Am J Respir Crit Care Med. 2021 May 1;203(9):1149-1157.

Data from the AGES-Reykjavik Study

Multivariable Logistic Regressi
Those with Imaging Progressio
with Imaging Progression with

Covariate	Comparisc IL OR (			
MUC5B genotype*	2.6 (			
Age†	1.08 (			
Sex‡	0.6 (			
Body mass index§	1.05 (			
Pack-years smoking‖	0.99 (0.98–1.01)	0.3	1.01 (1.01–1.02)	<0.0001
Current smoking status¶	1.1 (0.5–2.4)	0.8	1.1 (0.7–1.8)	0.6

ILA progression is more likely in older individuals
The increased risk of mortality in those with ILA persists independent of age: suggests that ILA remains clinically relevant in older patients.

				alysis*
				P Value
Nonemphysematous cysts	3.1 (1.6–5.9)	0.0005	2.5 (1.3–5.1)	0.009
Lower lobe predominant changes	5.2 (1.8–15)	0.002	6.7 (1.8–25)	0.004
Traction bronchiectasis	5.9 (2.3–14.9)	0.0002	6.6 (2.3–19)	0.0004
Honeycombing‡	—	—	—	—

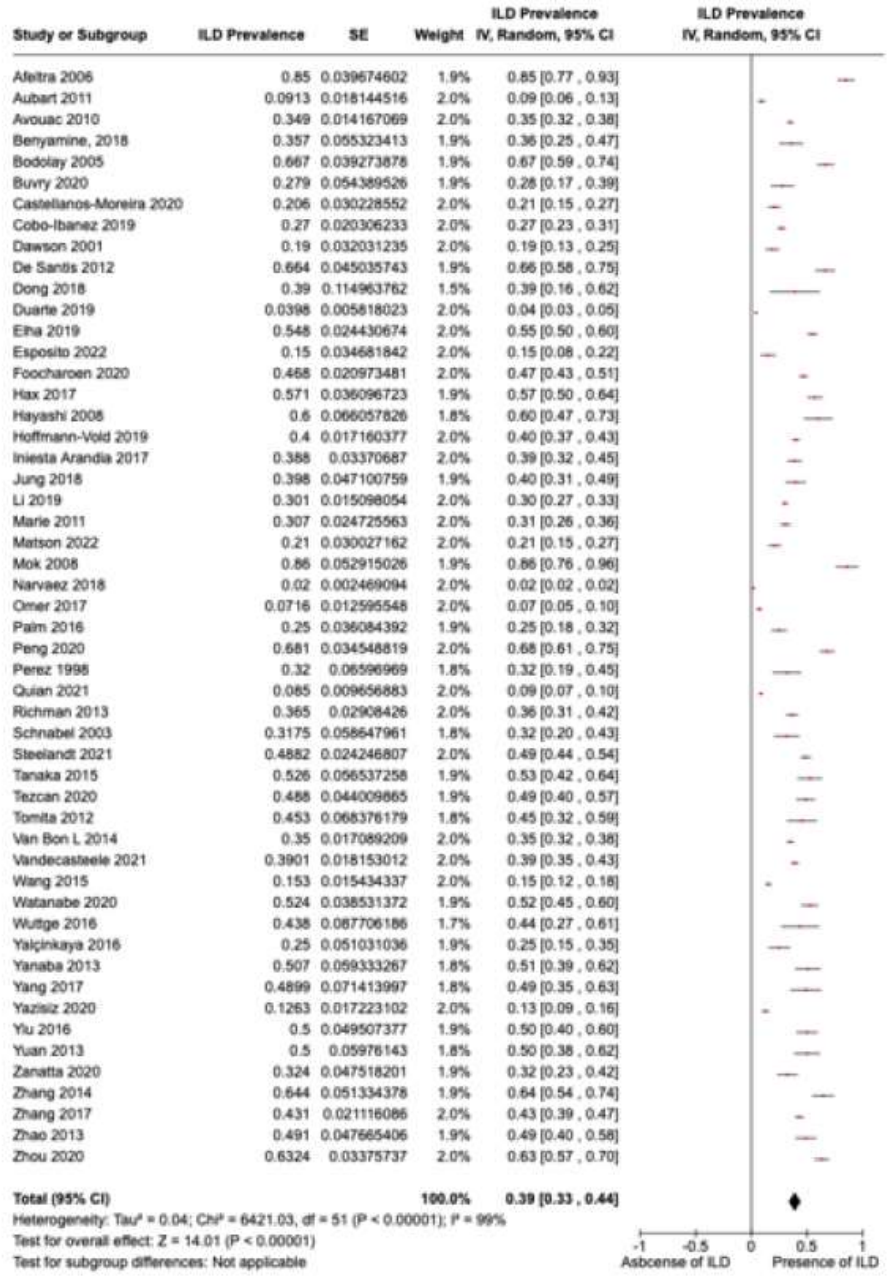
Putman RK, Gudmundsson G, Axelsson GT, Hida T, et al Imaging Patterns Are Associated with Interstitial Lung Abnormality Progression and Mortality. Am J Respir Crit Care Med. 2019 Jul 15;200(2):175-183.

Risk factors (ii) *Connective Tissue Disease*

721 studies screened : 52 studies selected

Author	Year	No. Participants	ILD (%)	Type of CTD	Mean Age	Type of CT
Matson	2022	184	21.00%	RA	56.4 (44.2-66.6)	HRCT
Dong	2018	18	39.00%	RA	52 (47-57)	HRCT
Perez	1998	50	32.00%	RA	57.9 ±1.5	HRCT
Esposito	2022	106	15.00%	RA	63 (55-71)	HRCT
Afeltra	2006	81	85.00%	MCTD	57±12.5	HRCT
Zhao	2013	110	49.10%	pSS	55.5 (14.2)	HRCT
Zhang	2017	550	43.10%	RA	61 ±13	HRCT
Zhang	2014	87	64.40%	pSS	55.2 (37–69)	HRCT
Zanatta	2020	97	42.30%	SSc	55.4 (±12.4)	HRCT
Yuan	2013	70	50.00%	DM/PM	55.5 (15.4) /50.4 (15.4)	HRCT
Yiu	2016	102	50.00%	SSc	58 (15)	HRCT
Yanaba	2013	71	50.70%	SSc	NA	HRCT
Yalçinkaya	2016	72	25.00%	SSc	44.9 ±12.7	HRCT
Wuttge	2016	32	43.80%	SSc	NA	HRCT
Watanabe	2020	168	52.40%	DM/PM	59 (44±67)	HRCT
Wang	2015	544	15.30%	RA	59.60±9.66	HRCT
van Bon L	2014	779	35.00%	SSc	42.4±12.3 / 43.8±11.2	HRCT
Tomita	2012	53	45.30%	SSc	50.4 ±20.8	HRCT
Tezcan	2020	129	48.80%	SSc	NA	HRCT
Tanaka	2015	78	52.60%	DM/PM	54.0 (36 to 65) / 54.5 (19 to 78)	HRCT
Omer	2017	419	7.16%	RA	45.7 ±15.9 years	HRCT
Aubart	2011	252	9.13%	RA	NA	HRCT
Avouac	2010	1132	34.90%	SSc	57 ±14/63 ± 14	HRCT
Benyamine	2018	75	35.70%	SSc	59.29 ±13.98	HRCT
Bodolay	2005	144	66.70%	MCTD	49.18 (29-73)	HRCT
Buvry	2020	68	27.90%	pSS	55 (14.9)	HRCT
Castellanos-Moreira	2020	179	20.60%	RA	59.7 (13.0)	HRCT
Cobo-Ibanez	2019	478	23.40%	DM/PM	47.7 (26.7-62.1)	HRCT
Dawson	2001	150	19.00%	RA	58.9 (10.3)	HRCT
De Santis	2012	110	66.40%	SSc	54.9 (12.6)	HRCT
Duarte	2019	1129	51.70%	RA	63.2±12.4	HRCT
Elha	2019	415	56.40%	SSc	59.6 (13.6)	HRCT
Foocharoen	2020	566	46.80%	SSc	54.6 ±10.8	HRCT
Hax	2017	188	57.10%	SSc	50.9 (13.9)	HRCT
Hayashi	2008	55	60.00%	DM/PM	54 (21-81)/47 (27-70)	HRCT
Hoffmann-Vold	2019	815	40.00%	SSc	53 (14.8)	HRCT
Iniesta Arandia	2017	209	37.60%	SSc	44.2 (16.4)	HRCT
Jung	2018	108	39.80%	SSc	50.1 (13.5)	HRCT
Li	2019	923	30.10%	RA	52.62 ±14.95	HRCT
Marie	2011	348	30.70%	DM/PM	53	HRCT
Mok	2008	43	86.00%	SSc	47.7 ±13.0	HRCT
Narvaez	2018	3215	0.20%	SLE	37 ±13	HRCT
Palm	2016	144	25.00%	pSS	52 (14)	HRCT
Peng	2020	182	68.10%	DM	49.6 (13.3)	HRCT
Quian	2021	834	85.10%	pSS	48.4±12.7	HRCT
Richman	2013	274	36.50%	RA	NA	HRCT
Schnabel	2003	63	31.75%	DM/PM	53.5 (46.5-66.5)	HRCT
Steelandt	2021	425	48.82%	SSc	6.42 (14.46)	HRCT
Vandecasteele	2021	722	39.01%	SSc	54 (14)	HRCT
Yang	2017	49	48.99%	DM/PM	44(13)/5 (17)	HRCT
Yazisiz	2020	372	12.63%	pSS	60.6 ±11.9	HRCT
Zhou	2020	204	63.24%	SSc	52.8 ±12.9	HRCT

Podolanczuk AJ, Hunninghake GM, et al; Approach to the Evaluation and Management of Interstitial Lung Abnormalities: An Official American Thoracic Society Clinical Statement. *Am J Respir Crit Care Med*. 2025 May 19



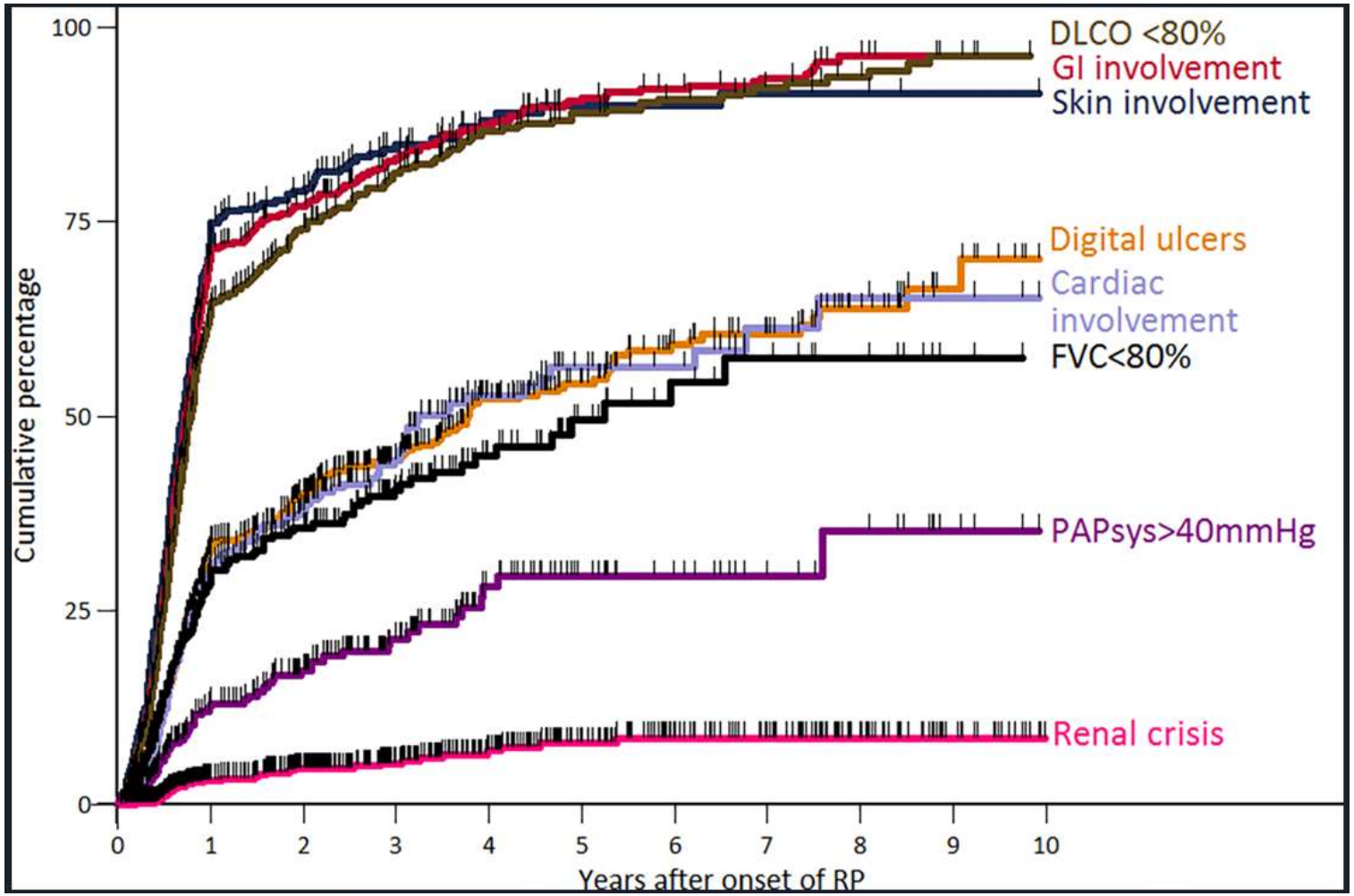
On aggregation by meta-analysis, the estimated prevalence of ILAs/ILD was 40% (95% CI, 33–43%)

Prevalence of ILA according totype of CTD on subgroup analysis

CTD	No of studies included	Prevalence, 95% CI
Rheumatoid arthritis	13	23% (17–29)
Systemic Sclerosis	22	45%; (42–49)
Sjogren's Syndrome	5	39% (18–59)
Dermatomyositis/ Polymyositis	10	44%; (37–52)

Podolanczuk AJ, Hunninghake GM, et al; Approach to the Evaluation and Management of Interstitial Lung Abnormalities: An Official American Thoracic Society Clinical Statement. *Am J Respir Crit Care Med*. 2025 May 19

Duration to development of ILA in CTDs



In 695 SSc patients who had a baseline visit within 1 year of RP onset,
The incidence of non-RP manifestations

FVC<50% predicted –
2% (95%CI 1–5) within the first year in
12% (95%CI 6–23) during the 10-year follow up

Jaeger VK, Wirz EG, Allanore Y, Rossbach P, et al; EUSTAR co-authors. Incidences and Risk Factors of Organ Manifestations in the Early Course of Systemic Sclerosis: A Longitudinal EUSTAR Study. PLoS One. 2016 Oct 5;11(10):e0163894.

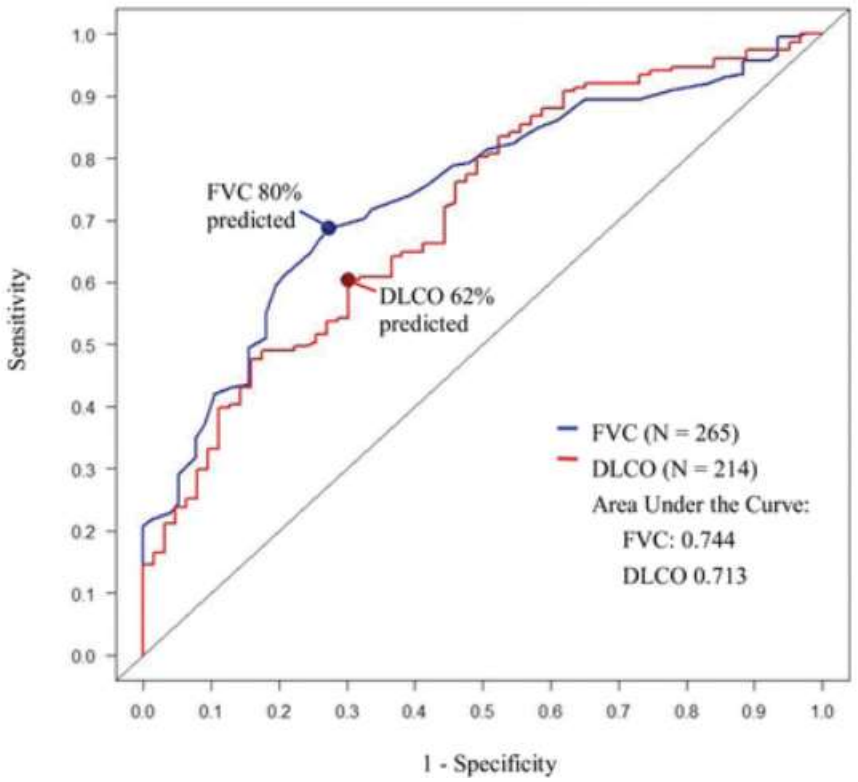
- A baseline chest HRCT scan to screen for ILAs/ILD in adults with CTDs that are associated with an increased risk of ILD.
- New pulmonary involvement in a patient with CTD - initiation or escalation of immunomodulatory therapy
- Screening may identify such pts (For every 1,000 patients with a high-risk CTD, ~ 400 may be found to have ILAs/ILD)

Why not just PFT?

Performance of Forced Vital Capacity and Lung Diffusion Cutpoints for Associated Radiographic Interstitial Lung Disease in Systemic Sclerosis

Kimberly Showalter, Aileen Hoffmann, Gerald Rouleau, David Aaby, Jungwha Lee, Carrie Richardson, Jane Dematte, Rishi Agrawal, Rowland W. Chang and Monique Hinchcliff

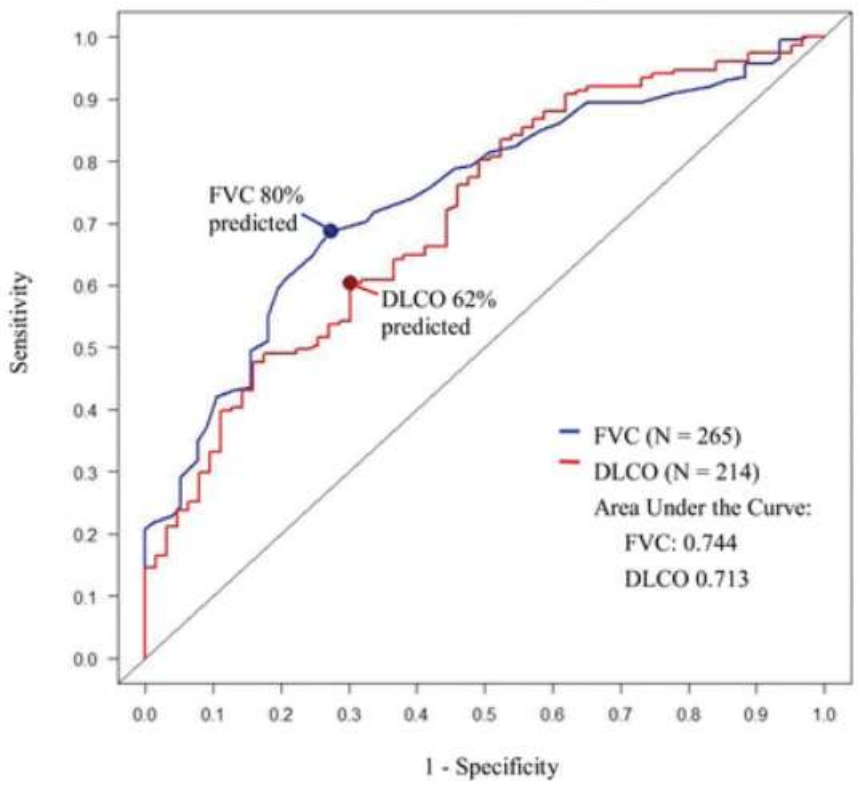
The Journal of Rheumatology November 2018, 45 (11) 1572-1576; DOI: https://doi.org/10.3899/jrheum.171362



404 patients enrolled in
Northwestern Scleroderma Registry

265 patients with ≥ 1 HRCT and ≥ 1
PFT –
265 with FVC values, 214 with DLCO

Why not just PFT?



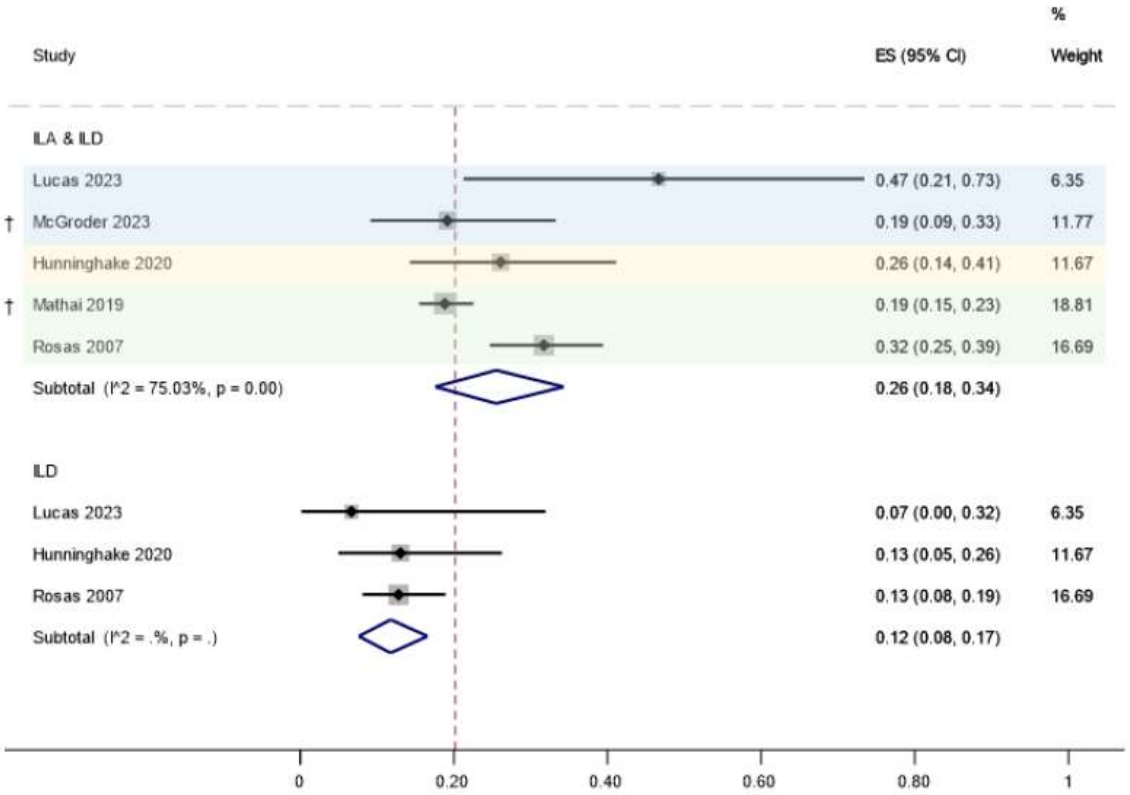
Variables	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Entire cohort				
FVC % predicted, n = 265				
< 80 (conventional and optimal)	0.69	0.73	0.86	0.49
DLCO % predicted, n = 214				
< 60 (conventional)	0.58	0.70	0.82	0.41
< 62 (optimal)	0.60	0.70	0.83	0.42
< 70 (alternative)	0.80	0.51	0.80	0.52
< 80 (alternative)	0.92	0.32	0.77	0.63
Combination of PFT thresholds % predicted, n = 214				
FVC < 80 and DLCO < 60	0.46	0.81	0.85	0.38
FVC < 80 or DLCO < 60	0.79	0.57	0.82	0.53
FVC < 80 and DLCO < 62	0.49	0.81	0.86	0.40
FVC < 80 or DLCO < 62	0.80	0.56	0.81	0.53
FVC < 80 and DLCO < 65	0.53	0.78	0.85	0.41
FVC < 80 or DLCO < 65	0.82	0.46	0.78	0.52
FVC < 80 and DLCO < 70	0.61	0.76	0.86	0.45
FVC < 80 or DLCO < 70	0.87	0.43	0.78	0.57
FVC < 80 and DLCO < 80	0.66	0.73	0.85	0.47
FVC < 80 or DLCO < 80	0.94	0.27	0.76	0.65

Risk factors (iii) *Familial Progressive Fibrosis*

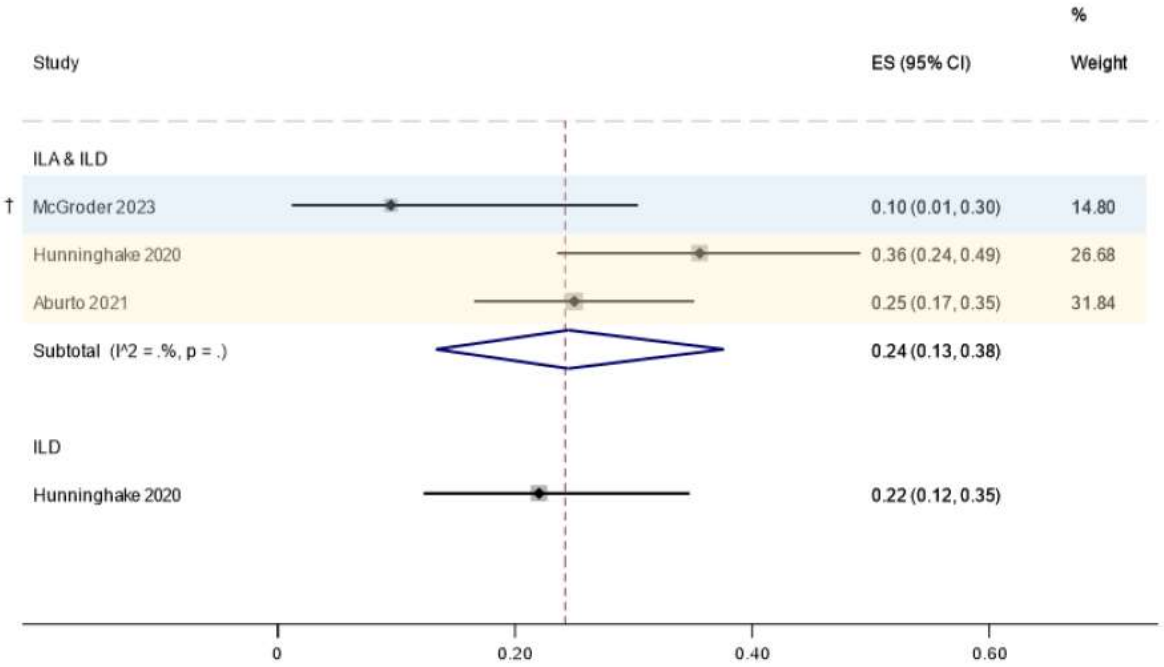
- *FPF – "any fibrotic ILD in at least two blood relative first- or second-degree family members"*
- Presence of familial disease increases the likelihood of a progressive pulmonary fibrosis
- Indicative of a possible (Telomere related gene) TRG or (surfactant related gene) SRG mutation

Borie R, Kannengiesser C, Antoniou K, et al. European Respiratory Society statement on familial pulmonary fibrosis. *Eur Respir J*. 2023;61(3):2201383. doi:10.1183/13993003.01383-2022

Prevalence of ILA/ILD among first-degree relatives of patients with familial pulmonary fibrosis



Prevalence of ILA/ILD among first-degree relatives of patients with IPF and no other known family members with ILD



Podolanczuk AJ, Hunninghake GM, Wilson KC, Khor YH, Kheir F, Pang B, Adegunsoye A, Cararie G, Corte TJ, Flanagan J, Gudmundsson G. Approach to the evaluation and management of interstitial lung abnormalities: an official American Thoracic Society clinical statement. *Am J Respir Crit Care Med*. 2024;209(6):650–668. doi:10.1164/rccm.202401-0121ST

- Chest CT screening for ILA in adults over 50 years of age who have a first-degree relative with familial pulmonary fibrosis (FPF).

For every 1,000 screened, 250 individuals may potentially benefit from early detection, monitoring, or intervention.

- In adults >50 years of age who have a first degree relative with IPF and no other known family members with ILD - smaller evidence base for estimation of prevalence of ILAs/ILD (172 total individuals) vs for first-degree relatives of patients with FPF (1,039)
- 5 years interval of screening – reasonable

Table 1 Comparison of demographic and clinical variables between familial and sporadic PF patients

Variables	Total FPF patients (N = 77)	FPF-DC (N = 57)	FPF-DS (N = 20)	Sporadic patients (N = 50)	Significance of difference
Mean age symptom onset (years)	57.11	57.97	N/A	63.85	**p = 0.012** (FPF-DC vs. sporadic)
Mean age at diagnosis (years)	60.65	61.43	58.45	66.58	**p = 0.012** (FPF-DC vs. sporadic)
Mean age at death or transplant (n = number of deceased or transplanted patients)	N/C	64.58 (n = 36)	73.62 (n = 6)	70.60 (n = 32)	**p = 0.025** (FPF-DC vs. sporadic)
Gender					
Number (%) males Number (%) females	M = 43 (55.8 %) F = 34 (44.2 %)	M = 34 (59.6 %) F = 23 (40.4 %)	M = 9 (45.0 %) F = 11 (55.0 %)	M = 31 (62.0 %) F = 19 (38.0 %)	p = 0.531 (total FPF vs. sporadic)
Current or ever smokers (%)	61/76 (80.3 %)	45/56 (80.4 %)	16/20 (80.0 %)	42/50 (84.0 %)	p = 0.767 (total FPF vs. sporadic)
Number of patients with symptom at diagnosis:					FPF-DC vs. sporadic
Dyspnea	N/C	43 (75.4 %)	N/C	44 (88.0 %)	p = 0.096
Cough		37 (64.9 %)		35 (70.0 %)	p = 0.576
Chest pain		14 (24.6 %)		12 (24.0 %)	p = 0.946
Pneumonia		10 (17.5 %)		7 (14.0 %)	p = 0.617
Hemoptysis		5 (8.8 %)		1 (2.0 %)	p = 0.129
Pneumothorax		2 (3.5 %)		0 (0.0 %)	p = 0.181
Most specific diagnostic test:					
Number of patients (%)					
CXR	4 (5.2 %)	4 (7.0 %)	0 (0.0 %)	0 (0.0 %)	
HRCT	40 (51.9 %)	23 (40.4 %)	17 (85.0 %)	31 (62.0 %)	
Surgical lung biopsy	30 (39.0 %)	28 (49.1 %)	2 (10.0 %)	21 (42.0 %)	
Autopsy	3 (3.9 %)	2 (3.5 %)	1 (5.0 %)	0 (0.0 %)	
Treatments: Number of patients (%)					FPF-DC vs. sporadic
Prednisone	40 (51.9 %)	38 (66.7 %)	2 (10.0 %)	36 (72.0 %)	p = 0.551
Cyclophosphamide	7 (9.1 %)	7 (12.3 %)	0 (0.0 %)	2 (4.0 %)	p = 0.170
Azathioprine	12 (15.6 %)	11 (19.3 %)	1 (5.0 %)	12 (24.0 %)	p = 0.555
N-acetyl cysteine	16 (20.8 %)	13 (22.8 %)	3 (15.0 %)	20 (40.0 %)	p = 0.055
Lung transplant	5 (6.5 %)	5 (8.8 %)	0 (0.0 %)	3 (6.0 %)	p = 0.586

FPF = familial pulmonary fibrosis, FPF-DC = familial pulmonary fibrosis diagnosed because individual developed clinical symptoms of lung disease, FPF-DS = familial pulmonary fibrosis diagnosed because the individual had clinical screening based on family history, N/A = not applicable, N/C = not calculated, % = percentage, CXR = chest X-ray, HRCT = high resolution computerized tomography of chest.

- Increased prevalence in individuals older than the age of 50 years.
- For certain genetic variants- early screening may be needed.
- Recommendation: starting 5 years before the youngest age of diagnosis within the family.

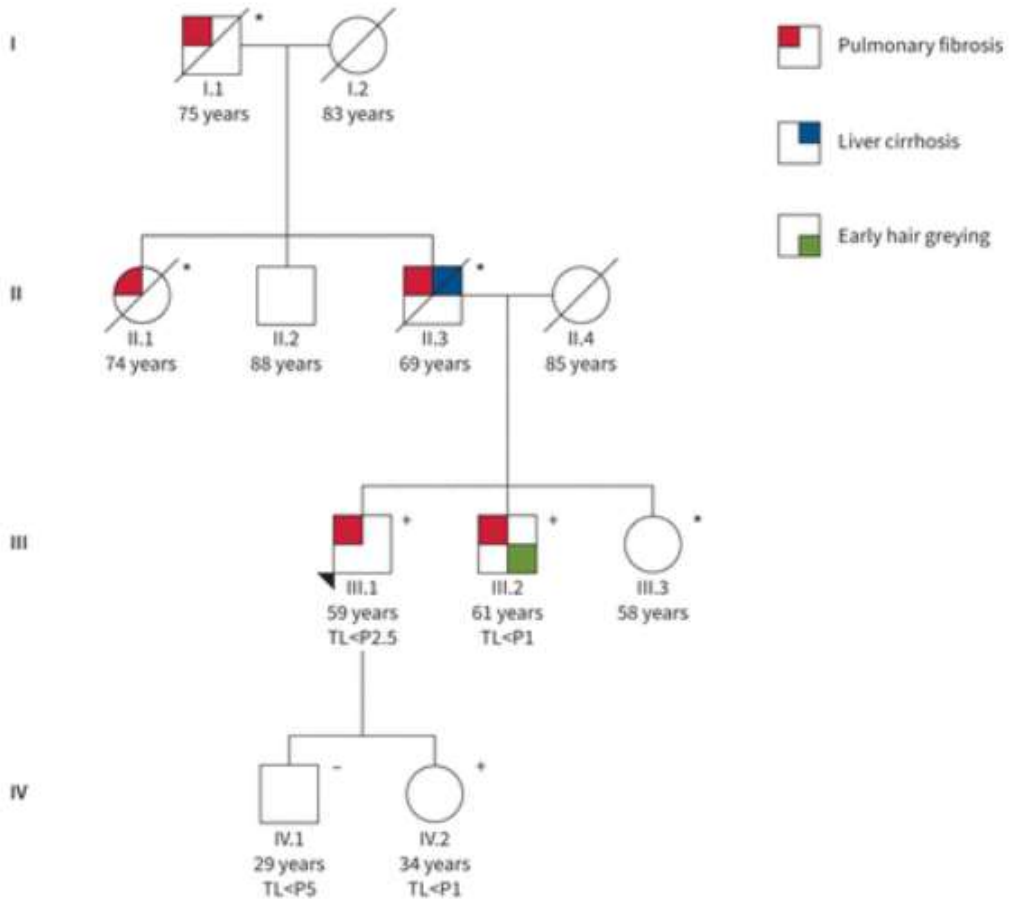
Fernandez et al.: A Newfoundland cohort of familial and sporadic idiopathic pulmonary fibrosis patients: clinical and genetic features. Respiratory Research 2012 13:64.

Anticipation

- The median age at diagnosis of 91 adult patients carrying SRG mutations - 45 years (range 18–72 years)
- In TRG mutation carriers, the median age at diagnosis of ILD is 62 years (range 35–79 years)
- Patients with TRG mutations transmit their short telomeres independently of transmission of the mutation and telomeres shorten at a younger age in subsequent generations
- Genetic anticipation - an earlier and more severe disease with each generation . Age at diagnosis - highly correlated among affected family members of the same generation and decreases over generations by a mean of 6–18 years in FPF

Borie R, Kannengiesser C, Antoniou K, et al. European Respiratory Society statement on familial pulmonary fibrosis. *Eur Respir J*. 2023;61(3):2201383. doi:10.1183/13993003.01383-2022

Representative pedigree of a family with a telomere-related gene mutation associated with pulmonary fibrosis, liver cirrhosis and hair greying, of autosomal transmission with genetic anticipation and telomere shortening. The proband is indicated by an arrowhead. Relatives IV.1 and IV.2 underwent pre-symptomatic screening. Age is indicated. +: carrier of the mutation; −: non-carrier of the mutation; *: unknown genetic status. TL: telomere length; P: percentile.



Borie R, Kannengiesser C, Antoniou K, et al. European Respiratory Society statement on familial pulmonary fibrosis. *Eur Respir J*. 2023;61(3):2201383. doi:10.1183/13993003.01383-2022

Once diagnosed, what next ?

1) Baseline Symptom Assessment

Table 1. Baseline Characteristics of the Participants, According to the Status of Interstitial Lung Abnormalities (ILA).*

Characteristic	Participants without ILA (N=1370)	Participants with Indeterminate ILA (N=1086)	Participants with ILA (N=177)	P Value	
				All Groups	ILA vs. No ILA†
Age — yr	56±11	61±12	70±12	<0.001	<0.001
Female sex — no. (%)	675 (49)	561 (52)	89 (50)	0.48	0.81
Body-mass index	29±6	28±5	28±5	0.08	0.59
Smoking status					
Former smoker — no./total no. (%)	591/1360 (43)	501/1073 (47)	92/175 (53)	0.06	0.03
Current smoker — no./total no. (%)	73/1360 (5)	72/1073 (7)	17/175 (10)	0.09	0.04
Pack-yr — no.	17±16	21±20	26±20	<0.001	<0.001
Respiratory symptoms — no. (%)					
Chronic cough	87 (6)	68 (6)	21 (12)	0.02	0.006
Shortness of breath with minor exertion	117 (9)	143 (13)	31 (18)	<0.001	<0.001
Pulmonary-function testing					
FEV_1 — % of predicted value‡	98±15	98±15	98±17	0.67	0.65
FVC — % of predicted value‡	101±13	103±13	101±15	0.03	0.90
FEV_1:FVC — % of predicted value‡	96±9	95±9	97±9	0.03	0.31
Spirometric restriction — no./total no. (%)§	48/1297 (4)	25/1011 (2)	6/159 (4)	0.25	0.96
Airflow obstruction — no./total no. (%)¶	59/1297 (5)	54/1011 (5)	10/159 (6)	0.48	0.31
Diffusion capacity of carbon monoxide — % of predicted value‖	98±15	97±15	86±14	<0.001	<0.001
Total lung capacity**					
Mean — liters	5.2±1.2	4.7±1.1	4.6±1.2	<0.001	<0.001
Percent of predicted value	88±14	80±16	79±17	<0.001	<0.001
<80% of predicted value — no./total no. (%)	359/1299 (28)	483/981 (49)	81/148 (55)	<0.001	<0.001

* Plus–minus values are means ±SD. Data are missing for patients in the following categories: current and former smoking status, 25 participants (1%); spirometry, 165 participants (6%); diffusion capacity of carbon monoxide, 572 participants (22%); and total lung capacity, 192 participants (7%). The body-mass index is the weight in kilograms divided by the square of the height in meters. FEV_1 denotes forced expiratory volume in 1 second, and FVC forced vital capacity.

† P values for the comparison among all groups and for the comparison between participants with ILA and those without ILA were calculated with the use of general linear models to account for familial relationships in the Framingham Heart Study, as described previously.[17]

‡ Predicted values for FEV_1 and FVC are derived from Hankinson et al.[18]

§ Spirometric restriction was defined as an FVC of less than 80% of the predicted value with an FEV_1:FVC ratio that is more than the lower limit of the normal range.[18]

¶ Airflow obstruction was defined as an FEV_1 and an FEV_1:FVC ratio that are both less than the lower limit of the normal range.[18]

‖ Predicted values for the diffusion capacity of carbon monoxide are derived from Miller et al.[19]

** Quantitative values for total lung capacity were calculated with the use of Airway Inspector (www.airwayinspector.org). Predicted values in this category are based on the guidelines of the American Thoracic Society and European Respiratory Society.[20]

Hunninghake GM, Hatabu H, Okajima Y, Gao W, et al MUC5B promoter polymorphism and interstitial lung abnormalities. N Engl J Med. 2013 Jun 6;368(23):2192-200.

FULL LENGTH ARTICLE · Volume 104, Issue 11, P1712-1721, November 2010 · *Open Archive*

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The radiological patterns of interstitial change at an early phase: Over a 4-year follow-up

Kenji Tsushima [a,b] · Shusuke Sone [a] · Sumiko Yoshikawa [b] · Toshiki Yokoyama [b] · Toshiro Suzuki [b] · Keishi Kubo [b]

Affiliations & Notes Article Info

- 3079 subjects from rural Japan
- LDCT for cancer screening
- honeycombing, interlobular septal thickening (IST), ground glass opacity (GGO), ill-defined subpleural line (IDS), and combined pulmonary fibrosis and emphysema (CPFE)
- Clinical examination
- PFT
- 6MWT

The radiological
Over a 4-year fol

Kenji Tsushima [a,b] · Shusuke

Affiliations & Notes Article I

Table 1 Characteristics of normal and abnormal subjects clarified by low-dose CT scan and HRCT scan.

	(A) Normal subject (n = 2981)	(B) Abnormal subject (n = 80)	P value (A) vs. (B)
Age (years)	53.8 ± 10.3	61.7 ± 9.4	<0.0001
Sex, M/F	1738/1243	59/21	0.002
Smoking history			
No. of subjects (%)	1531 (51.4)	56 (70.0)	<0.0001
Current smokers (%)	969 (32.5)	36 (45.0)	0.014
Pack-year	29.7 ± 9.9	46.0 ± 19.3	<0.0001
Former smokers (%)	562 (18.9)	20 (25.0)	0.110
Pack-year	20.5 ± 12.5	43.7 ± 25.9	<0.0001
Never smokers (%)	1450 (48.6)	24 (30.0)	0.001
Symptoms – no. of subjects (%)			
Chronic cough	428(14.4)	10 (12.5)	0.393
Chronic sputum	532 (17.8)	18 (22.5)	0.177
Shortness of breath	8 (2.7)	12 (14.8)	<0.0001
Physical examinations-no. (%)			
Fine crackles	0 (0)	21 (26.3)	<0.0001
Fine crackles + clubbed finger	0 (0)	4 (5.0)	<0.0001

Data are the mean ± SD. Categorical data (sex, smoking history – number of subjects, symptoms – cough, and sputum) were analyzed by chi-square test. no, number; M, male; F, female.

Baseline Symptom Assessment

- Can assist in distinguishing ILAs from ILD
- Establish a symptom burden at baseline against which changes can be assessed during future follow-up,
- Guide clinical assessment for other causes of abnormal CT findings that may require other specific management approaches.

How?

Visual analogue and numerical scales for cough and dyspnea assessment

Inspiratory crackles +/- : aids in early identification of ILD and should ideally be documented alongside symptom assessment

Hunninghake GM, Hatabu H, Okajima Y, Gao W, et al MUC5B promoter polymorphism and interstitial lung abnormalities. N Engl J Med. 2013 Jun 6;368(23):2192-200.

Table 2. Odds of Having Interstitial Lung Abnormalities on Enrollment High-Resolution Computed Tomography, Based on Self-reported Occupational and Environmental Exposures

Exposure	*n* (%) of Subjects Exposed (*n* = 265)	Univariable			Multivariable*	
		OR (95% CI)	*P* Value	FDR *P* Value	aOR (95% CI)	*P* Value
Dusts						
Grain	44 (16.6)	1.34 (0.60–3.00)	0.4717	0.6119	—	—
Hay	67 (25.3)	1.70 (0.85–3.38)	0.1329	0.3038	—	—
Asbestos	39 (14.7)	1.44 (0.62–3.22)	0.3903	0.5476	—	—
Silica or sand	38 (14.3)	1.04 (0.44–2.46)	0.9330	0.9330	—	—
Mica feldspar	5 (1.9)	2.37 (0.33–16.84)	0.3847	0.5476	—	—
Coal	22 (8.3)	3.33 (1.24–8.99)	0.0177	0.1340	—	—
Rock	34 (12.8)	2.44 (1.06–5.64)	0.0368	0.1472	—	—
Clay or ceramics	27 (10.2)	1.83 (0.72–4.65)	0.2022	0.3801	—	—
Wood	71 (26.8)	2.00 (1.03–3.89)	0.0409	0.1510	—	—
Fiberglass	37 (14.0)	2.04 (0.91–4.61)	0.0851	0.2150	—	—
Cotton	29 (10.9)	1.96 (0.80–4.84)	0.1418	0.3094	—	—
Fumes						
Welding	42 (15.9)	2.60 (1.22–5.53)	0.0138	0.1325	—	—
Metal fume	35 (13.2)	1.82 (0.77–4.29)	0.1707	0.3562	—	—
Ferrous sulfate	9 (3.4)	1.66 (0.35–7.77)	0.5183	0.6547	—	—
Aluminum smelting	9 (3.4)	13.95 (2.44–79.79)	0.0033	0.0528	14.88 (2.67–97.73)	0.005
Plastic	26 (9.8)	2.86 (1.10–7.39)	0.0307	0.1340	—	—
Gases						
Hydrogen sulfide	4 (1.5)	8.85 (0.74–105.7)	0.0845	0.2150	—	—
Sulfur oxide	7 (2.6)	8.52 (1.36–53.29)	0.0223	0.1340	—	—
Nitrogen oxide	8 (3.0)	3.40 (0.70–16.40)	0.1270	0.3038	—	—
Carbon monoxide	33 (12.6)	2.68 (1.13–6.35)	0.0255	0.1340	—	—
Ethylene oxide	9 (3.4)	5.88 (1.19–29.14)	0.0305	0.1340	—	—
Ozone	5 (1.9)	2.66 (0.21–13.33)	0.6294	0.7102	—	—
Elements and metals						
Arsenic	4 (1.5)	4.07 (0.46–36.24)	0.2059	0.3801	—	—
Cadmium	7 (2.6)	1.32 (0.22–8.04)	0.7594	0.8100	—	—
Chromium	10 (3.8)	2.35 (0.56–9.82)	0.2407	0.4126	—	—
Copper	23 (8.7)	3.17 (1.18–8.49)	0.0224	0.1340	—	—
Lead	27 (10.2)	3.73 (1.50–9.25)	0.0049	0.0588	2.91 (1.05–8.05)	0.04
Mercury	14 (5.3)	1.81 (0.52–6.29)	0.3508	0.5432	—	—
Beryllium	4 (1.5)	9.85 (0.84–116.17)	0.0689	0.2149	—	—
Hard metal	14 (5.3)	1.37 (0.37–5.02)	0.6352	0.7102	—	—
Zinc	13 (4.9)	2.19 (0.60–7.95)	0.2305	0.4098	—	—
Nickel	10 (3.8)	1.44 (0.31–6.63)	0.6362	0.7102	—	—
Chemicals						
Acid	22 (8.3)	2.48 (0.91–6.77)	0.0761	0.2149	—	—
Alkali	15 (5.7)	2.93 (0.92–9.35)	0.0699	0.2149	—	—
Ammonia	54 (20.4)	1.23 (0.58–2.61)	0.5812	0.6974	—	—
Detergent	87 (32.8)	1.16 (0.61–2.21)	0.6563	0.7160	—	—
Dyes	18 (6.8)	1.39 (0.43–4.48)	0.5807	0.6974	—	—
Pesticides	59 (22.3)	1.44 (0.70–2.97)	0.3197	0.5115	—	—
Herbicides	46 (17.4)	1.65 (0.72–3.57)	0.2024	0.3801	—	—
Rodenticides	13 (4.9)	1.70 (0.45–6.37)	0.4300	0.5733	—	—
Resins	21 (7.9)	1.06 (0.34–3.37)	0.9175	0.9330	—	—
Formaldehyde	16 (6.0)	2.83 (0.90–8.89)	0.0755	0.2149	—	—
Organic antigens						
Birds	51 (19.3)	3.40 (1.63–7.09)	0.0012	0.0528	3.37 (1.53–7.41)	0.003
Mold	63 (23.8)	2.89 (1.45–5.77)	0.0028	0.0528	3.83 (1.78–8.25)	0.001
Hot tubs	42 (15.9)	0.90 (0.38–2.12)	0.8070	0.8421	—	—
Flooding	21 (7.9)	1.79 (0.63–5.09)	0.2698	0.4466	—	—
Leaking pipes	15 (5.7)	1.69 (0.50–5.68)	0.3926	0.5476	—	—
Basement water	38 (14.3)	0.66 (0.24–1.76)	0.3993	0.5476	—	—

Definition of abbreviations: aOR = adjusted odds ratio; CI = confidence interval; FDR = false discovery rate; OR = odds ratio.
*Each exposure with an FDR-adjusted $P < 0.1$ is included in a multivariable model adjusted for age, smoking status, *MUC5B* genotype, and telomere restriction fragment length, with one exposure included per model.

Exposure history

Supplemental Table E4. Multivariable model with all statistically-significant environmental exposures

n=265 subjects	**OR (CI 95%)**	**P**
Age, per +1 year	2.79 (1.24-6.27)	0.01
Ever Smoker	1.09 (1.04-1.13)	0.0001
MUC5B GT/TT* (vs GG)	1.70 (0.80-3.62)	0.17
TRF length, per +1 kb	0.75 (0.50-1.13)	0.17
Aluminum Smelting	11.52 (1.50-88.33)	0.02
Lead	1.69 (0.51-5.63)	0.39
Birds	2.03 (0.83-4.94)	0.12
Mold	3.22 (1.40-7.41)	0.006

*Each allele with a copy of the *MUC5B* (Mucin 5B) gene promoter polymorphism (rs35705950) is denoted by a T. TRF: telomere restriction fragment; kb: kilobase

336 subjects

a health history and exposure questionnaire

Salisbury ML, Hewlett JC, Ding G, Markin CR, Douglas K, Mason W, Guttentag A, Phillips JA 3rd, Cogan JD, Reiss S, Mitchell DB, Wu P, Young LR, Lancaster LH, Loyd JE, Humphries SM, Lynch DA, Kropski JA, Blackwell TS. Development and Progression of Radiologic Abnormalities in Individuals at Risk for Familial Interstitial Lung Disease. Am J Respir Crit Care Med. 2020 May

(ii) Baseline PFT

- establishing a baseline for future comparison.

Participants without ILA had a mean decrease in FVC of 35 ml (SD ± 44 ml) per year, those with ILA without progression 40 ml (SD ± 44 ml) decrease per year, and ILA with progression had a mean decline of 64 ml (SD ± 51 ml) per year.

Araki T, Putman RK, Hatabu H, Gao W, Dupuis J et alDevelopment and Progression of Interstitial Lung Abnormalities in the Framingham Heart Study. Am J Respir Crit Care Med. 2016 Dec 15;194(12):1514-1522. doi: 10.1164/rccm.201512-2523OC. PMID: 27314401; PMCID: PMC5215030.

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Table 2. Association of ILA Progression with Change in Spirometry Relative to Participants without ILA*

	ILA with Progression Compared with No ILA				ILA with Progression Compared with ILA without Progression			
	Unadjusted Analysis	*P* Value	Adjusted Analysis†	*P* Value	Unadjusted Analysis	*P* Value	Adjusted Analysis†	*P* Value
FEV_1 decline, ml/yr	13 ± 4	0.005	14 ± 5	0.005	9 ± 9	0.3	14 ± 10	0.2
FVC decline, ml/yr	29 ± 5	<0.0001	20 ± 6	0.0005	22 ± 11	0.04	25 ± 11	0.03
FEV_1/FVC, change, %	−0.2 ± 0.07	0.004	−0.06 ± 0.07	0.4	−0.1 ± 0.1	0.3	−0.08 ± 0.16	0.6

Definition of abbreviation: FHS = Framingham Heart Study; ILA = interstitial lung abnormalities.

* *P* values for all analyses, both adjusted and unadjusted, are calculated using general linear models to account for familial relationships in the FHS. No ILA, n = 579; ILA without progression, n = 28; and ILA with progression, n = 72. Values are linear regression coefficients ± SE, representing the additional decline in spirometry in participants with ILA with progression versus the comparison group.

† Adjusted analyses include additional adjustments for age, sex, body mass index, pack-years smoking, and current smoking status.

Araki T, Putman RK, Hatabu H, Gao W, Dupuis J et alDevelopment and Progression of Interstitial Lung Abnormalities in the Framingham Heart Study. Am J Respir Crit Care Med. 2016 Dec 15;194(12):1514-1522. doi: 10.1164/rccm.201512-2523OC. PMID: 27314401; PMCID: PMC5215030.

(iii) HPE analysis

Am J Respir Crit Care Med. 2018 Apr 1;197(7):955-958. doi: 10.1164/rccm.201708-1679LE.

Histopathology of Interstitial Lung Abnormalities in the Context of Lung Nodule Resections

Ezra R Miller [1], Rachel K Putman [1], Marina Vivero [1], Yin Hung [1], Tetsuro Araki [1], Mizuki Nishino [1], George R Washko [1], Ivan O Rosas [1], Hiroto Hatabu [1], Lynette M Sholl [1], Gary M Hunninghake [1]

- Retrospective cohort of 424 patients who had undergone lung nodule resection, had a chest CT scan within 3 months before surgery, and had no history of ILD, at Brigham and Women's Hospital (BWH) (January 2001 - July 2015)
- Radiologically: ILA/indeterminate/No ILA
- Histopath: diagnosis of UIP or other ILDs (e.g., smoking-related ILD) and scored for additional histopathologic findings

Miller ER, Putman RK, Vivero M, Hung Y, Araki T, Nishino M, et al. Histopathology of interstitial lung abnormalities in the context of lung nodule resections. Am J Respir Crit Care Med 2018;197:955–958

Am J Respir Crit Care Med. 2018 Apr 1;197(7):955-9

Histopathology of Interstitia the Context of Lung Nodule

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- Histopath: diagnosis of UIP or other ILDs (e.g., smoking-related ILD) and scored for additional histopathologic findings

Table 1. Characteristics and Analysis of the Lung Nodule Cohort Stratified by Interstitial Lung Abnormality Status

	No ILA (*n* = 257; 61%)	Indeterminate ILA (*n* = 141; 33%)	ILA (*n* = 26; 6%)	*P* Value* All Groups	*P* Value* ILA vs. No ILA
Demographic parameters					
Age at resection, yr, median (IQR)	64 (57–70)	71 (64–75)	73 (63–80)	<0.001	0.002
Sex, female, *n* (%)	148 (58%)	88 (62%)	18 (69%)	0.42	0.30
Race, white, *n* (%)	238 (93%)	126 (89%)	22 (85%)	0.23	0.25
BMI, kg/m^2, median (IQR)	28 (24–31)	27 (24–30)	27 (23–31)	0.54	0.94
Never smoker, *n* (%)	50 (20%)	19 (13%)	3 (12%)	0.08	0.09
Former smoker, *n* (%)	148 (59%)	98 (70%)	21 (81%)	0.08	0.09
Current smoker, *n* (%)	55 (22%)	24 (17%)	2 (8%)	0.08	0.09
Pack-years of smoking, median (IQR)	30 (7–50)	30 (10–50)	28 (19–56)	0.75	0.57
Asbestos exposure, *n* (%)	10 (5%)	15 (13%)	1 (5%)	0.06	1.0
Spirometric parameters					
FEV_1, % of predicted, median (IQR)	89 (68–102)	86 (73–98)	92 (78–104)	0.39	0.32
FVC, % of predicted, median (IQR)	93 (76–106)	88 (77–101)	98 (89–106)	0.13	0.21
FEV_1/FVC, median (IQR)	0.77 (0.69–0.82)	0.76 (0.65–0.83)	0.77 (0.71–0.80)	0.75	0.95
Selected comorbidities					
GERD, *n* (%)	93 (37%)	45 (33%)	13 (50%)	0.24	0.21
History of congestive heart failure, *n* (%)	7 (3%)	10 (7%)	3 (12%)	0.02	0.05
History of connective tissue disease, *n* (%)	15 (6%)	9 (6%)	2 (8%)	0.79	0.67
History of radiation to thorax, *n* (%)	16 (6%)	18 (13%)	0 (0%)	0.03	0.37
History of cancer†, *n* (%)	103 (41%)	69 (49%)	15 (58%)	0.10	0.10
Cancer data					
Malignant biopsy, *n* (%)	202 (79%)	112 (79%)	23 (88%)	0.53	0.31
Stage 2 or greater NSCLC, *n* (%)	51 (20%)	33 (23%)	10 (38%)	0.23	0.08
Histopathologic features					
Fibrosis					
Any fibrosis present‡, *n* (%)	133 (52%)	74 (52%)	19 (73%)	0.11	0.04
Subpleural fibrosis, *n* (%)	43 (17%)	24 (17%)	12 (46%)	0.003	0.001
Peribronchiolar fibrosis, *n* (%)	62 (24%)	32 (23%)	9 (35%)	0.41	0.24
Interstitial fibrosis, *n* (%)	53 (21%)	30 (21%)	9 (35%)	0.27	0.13
Emphysematous fibrosis§, *n* (%)	39 (15%)	24 (17%)	4 (15%)	0.88	1.0
Additional histopathologic features					
Fibroblastic foci, *n* (%)	9 (4%)	4 (3%)	7 (28%)	0.0001	0.0001
Honeycombing, *n* (%)	0 (0%)	0 (0%)	2 (8%)	0.004	0.008
UIP, *n* (%)	0 (0%)	0 (0%)	2 (8%)	0.004	0.008
Respiratory bronchiolitis, *n* (%)	156 (67%)	89 (71%)	17 (71%)	0.70	0.82
Airways disease‖, *n* (%)	126 (51%)	62 (47%)	11 (48%)	0.73	0.83
Smoking-related interstitial fibrosis¶, *n* (%)	21 (8%)	8 (6%)	1 (4%)	0.66	0.70
Pulmonary arterial hypertensive changes**, *n* (%)	213 (83%)	115 (82%)	23 (92%)	0.47	0.39
Atypical adenomatous hyperplasia, *n* (%)	43 (17%)	36 (26%)	9 (35%)	0.02	0.03
Pigment-laden macrophages, *n* (%)	188 (73%)	105 (75%)	20 (80%)	0.82	0.63
Pleural disease††, *n* (%)	18 (7%)	8 (6%)	3 (13%)	0.43	0.41

Miller ER, Putman RK, Vivero M, Hung Y, Araki T, Nishino M, et al. Histopathology of interstitial lung abnormalities in the context of lung nodule resections. Am J Respir Crit Care Med 2018;197:955–958

Table 2. High-Resolution Computed Tomography Findings in At-Risk Subjects

	n = 75
Consistent with early interstitial lung disease	11 (14.7)
Type of interstitial abnormalities	
Intralobular reticular opacities	11 (14.7)
Irregular intralobular septal thickening	9 (12)
Ground glass opacities	3 (4)
Traction bronchiectasis	1 (1.3)
Traction bronchiolectasis	1 (1.3)
Honeycombing	1 (1.3)

Data are expressed as number (percentage).

	Biopsy Normal	Biopsy Abnormal
HRCT Normal	40 (56.4)	21 (29.6)
HRCT Abnormal	5 (7.0)	5 (7.0)

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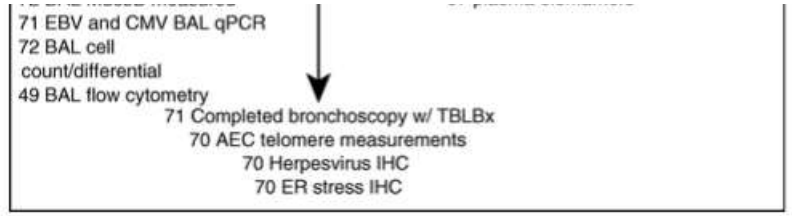

Table 3. Transbronchial Biopsy Histologic Findings

	n = 71
Normal	45 (63.4)
Abnormal	26 (36.6)
Interstitial fibrosis	12 (16.9)
Peribronchiolar fibrosis	15 (21.1)
Chronic inflammation	10 (14.1)
Respiratory bronchiolitis	2 (2.8)
Giant cells/granulomas	6 (8.5)

Data are expressed as number (percentage). Multiple abnormalities could be identified within a single biopsy.

- No differences in total or differential BAL cell counts in at-risk subjects compared with normal control subjects.
- In addition, no differences in lymphocyte subsets were observed in BAL cells compared with normal control subjects or IPF patients (CD4, CD25/FoxP3)

- No evidence to justify routine baseline lung tissue sampling in patients with ILAs to predict outcomes or establish the presence of ILD,
- Lung sampling - an invasive test with potential harms.

Lung tissue sampling: includes surgical lung biopsy and/or bronchoscopy with BAL for cellular analysis with or without transbronchial lung biopsy (including standard forceps or cryobiopsy) for microscopic, histopathologic, and/or genomic classifier evaluation.

(iv) Genetic testing

- MUC5B gene- promoter polymorphism rs35705950 - one of the most significant and well-established genetic risk factors associated with interstitial lung disease (ILD)—especially IPF and FPF
- encodes mucin 5B
- rs35705950 T allele (a gain-of-function variant in the promoter region) leads to overexpression of MUC5B in distal airways.
- GG (homozygous wild-type) : normal genotype
- GT (heterozygous):heterozygous
- TT (homozygous risk variant): homozygous risk

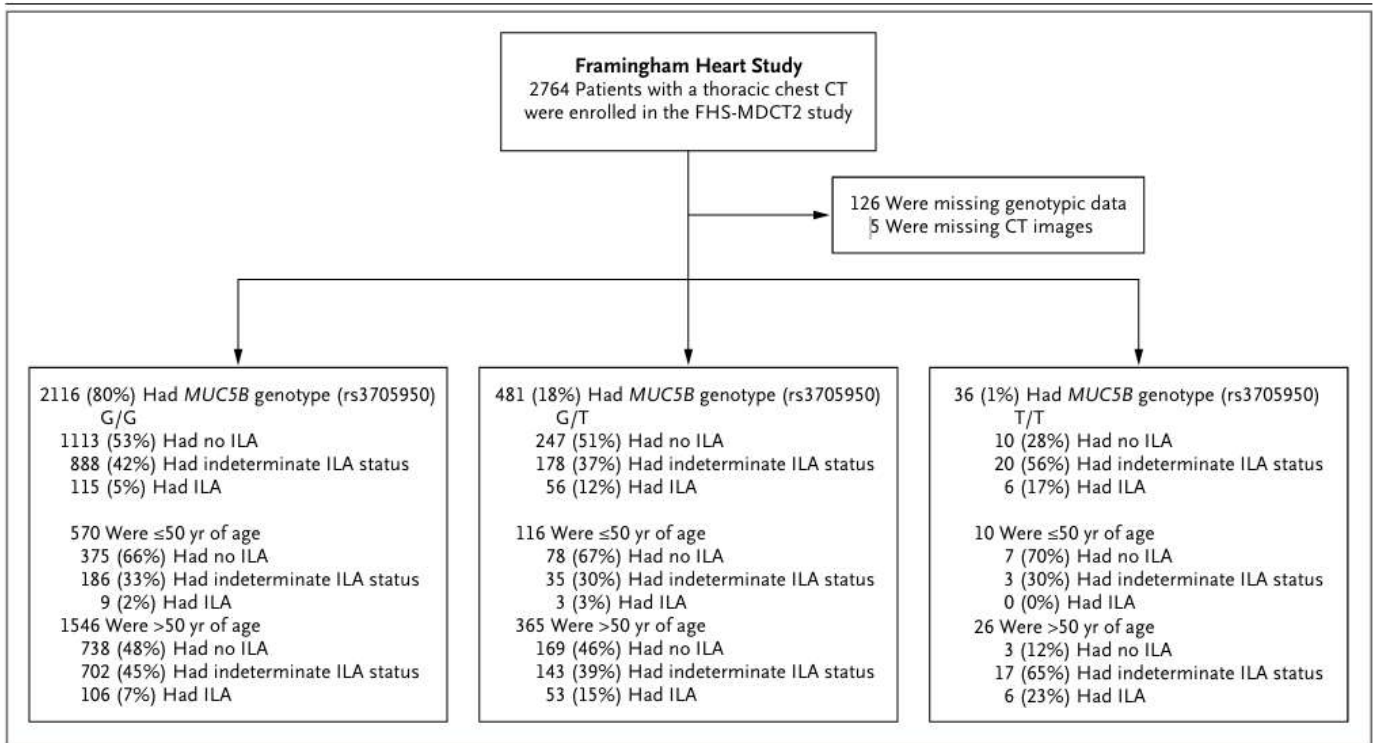

Figure 2. *MUC5B* Genotype According to Lung Abnormality Status and Age Group.

Data from 2633 participants from the Framingham Heart Study are shown according to the *MUC5B* promoter genotype (35705950 G/G, G/T, or T/T), stratified by lung abnormality status and age (≤50 years vs. >50 years). CT denotes computed tomography, FHS-MDCT2 Framingham Heart Study Multidetector Computed Tomography 2, and ILA interstitial lung abnormalities.

Hunninghake GM, Hatabu H, Okajima Y, Gao W, et al MUC5B promoter polymorphism and interstitial lung abnormalities. N Engl J Med. 2013 Jun 6;368(23):2192-200.

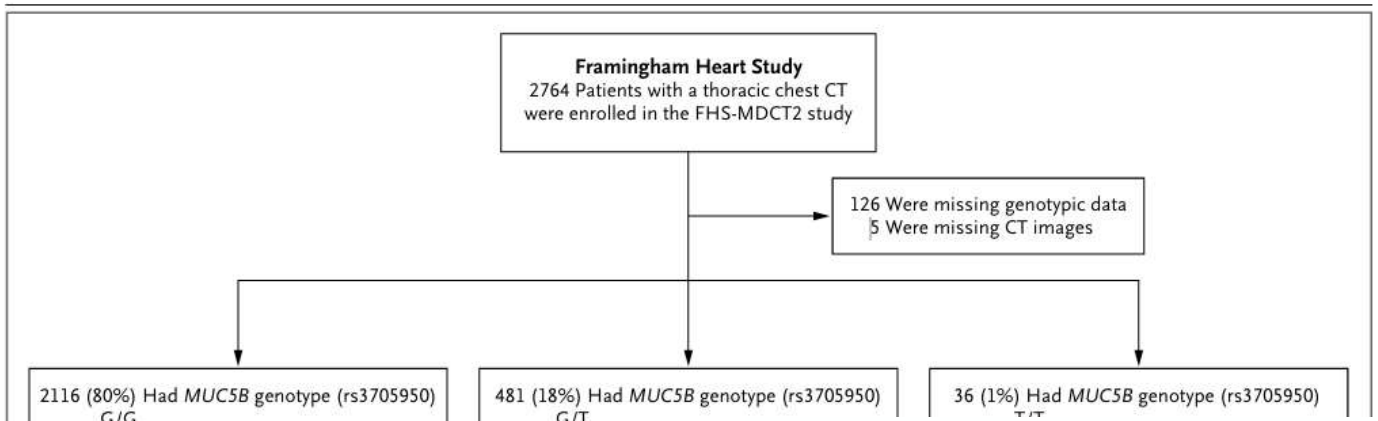

Figure 2. *MUC5B* Genotype According to Lung Abnormality Status and

Data from 2633 participants from the Framingham Heart Study are sho
G/T, or T/T), stratified by lung abnormality status and age (≤50 years vs
Framingham Heart Study Multidetector Computed Tomography 2, and

Table 2. Association between Interstitial Lung Abnormalities and *MUC5B* Genotype in the Framingham Heart Study.*

Status of Interstitial Lung Abnormalities	No. of Patients	*MUC5B* Genotype (rs35705950)			Adjusted Odds Ratio (95% CI)†	P Value	Adjusted Odds Ratio with Covariates (95% CI)‡	P Value
		G/G	G/T	T/T				
		no. of participants (%)						
Absence of interstitial lung abnormalities	1370	1113 (81)	247 (18)	10 (<1)	1.0		1.0	
Presence of interstitial lung abnormalities	177	115 (65)	56 (32)	6 (3)	2.3 (1.6–3.1)	<0.001	2.8 (2.0–3.9)	<0.001
Definite fibrosis§	47	26 (55)	20 (43)	1 (2)	3.0 (1.8–5.0)	<0.001	6.3 (3.1–12.7)	<0.001

* All odds ratios are for the comparison with patients with no interstitial lung abnormalities.
† Odds ratios in this category have been adjusted for familial relationships with the use of multivariate logistic-regression models, as described previously.[17]
‡ Odds ratios in this category have been adjusted for familial relationships and additional covariates, including age, sex, body-mass index, pack-years of smoking, and current or former smoking status.
§ Definite fibrosis is defined as interstitial lung abnormalities limited to those with architectural distortion highly suggestive of a fibrotic lung disease.[15]

Hunninghake GM, Hatabu H, Okajima Y, Gao W, et al MUC5B promoter polymorphism and interstitial lung abnormalities. N Engl J Med. 2013 Jun 6;368(23):2192-200.

Study	Study cohort	Participants	Mean age (SD), years	Follow-up	Comments	Mortality	Respiratory symptom progression	CT imaging progressio
ILA definition:	**Non-dependent patterns of increased lung density including ground-glass, reticular abnormalities, diffuse centrilobular nodules, nonemphysematous cysts and honeycombing or traction bronchiectasis, affecting > 5% of any lung zone**							
Putman 2017	AGES-Reykjavik	377 with ILA	78 (6)	Median 8.3 years (IQR: 4.8-9.6)	**MUC5B promoter polymorphism: Minor allele**	◄►	HR 1.0, 95% CI 0.8–1.3; p=0.95	
	COPDGene	564 with ILA	Non-hispanic white: 64 (10) African American: 55 (8)	Median 5.4 years (IQR: 4.6-6.1)	*Data for mortality evaluation of COPDGene only performed for the non-hispanic white cohort due to small numbers in the African American cohort*	◄►	HR 1.2, 95% CI 0.75–2.0; p=0.41	
Araki 2016	FHS	118 ILA with progression vs 37 ILA without progression	Progression: 65 (11) No progression: 58 (11)	Mean 6.4 years (SD 0.8) Median 6 years (IQR: 0.9)	**MUC5B promoter polymorphism: Minor allele frequency** 5-point scale of serial CT changes: - definite regression - probable regression - no change - probable progression - definite progression		OR 1.5, 95% CI 0.7-3.4; p=0.3 ◄►	
		118 ILA with progression vs 660 no ILA	Progression: 65 (11) No ILA: 49 (10)				**OR 2.8, 95% CI, 1.7–4.4; p=0.0001** ▲	
Putman 2019	AGES-Reykjavik	238 ILA with progression vs 89 ILA without progression	Progression: 76 (5) No progression: 75 (5)	Median 5.1 years (IQR 4.99–5.26)	**MUC5B promoter polymorphism: Minor allele frequency** 5-point scale of serial CT changes: - definite regression - probable regression - no change - probable progression - definite progression		**OR 2.6, 95% CI 1.5-4.4; p=0.0004** ▲	
		238 ILA with progression vs 1777 no ILA	Progression: 76 (5) No ILA: 74 (5)				**OR 2.9, 95% CI 2.2–3.8; p<0.0001** ▲	
ILA definition:	**Presence and extent of specific interstitial features, including ground-glass opacities, intralobular reticular opacities, irregular thickening of interlobular septa, traction bronchiectasis, traction bronchiolectasis, and honeycombing; Categorised as none, early/mild, or extensive**							
Salisbury 2020	Vanderbilt FIP Registry	129 without extensive ILA at enrolment	Not provided Early/mild & extensive ILA: 58.8 (10)	5 years	**MUC5B promoter polymorphism genotypes: GT/TT** ILD events: - Developed clinical ILD or extensive ILA - ILA progression (whole lung visual score)		**MUC5B rates:** - **No event: 29%** ▲ - **ILD event: 40%**	
ILA definition:	**Presence of reticular change with traction bronchiectasis with or without honeycombing (definite PrePF) or by those with reticular change with equivocal traction bronchiectasis and no honeycombing (probable PrePF) using multidisciplinary clinical consensus: radiology core and clinical core**							
Steele 2023	University of Colorado, National Jewish Health, Vanderbilt University (Relatives of familial interstitial pneumonia)	77 with ILA vs 416 without ILA	Not provided Whole cohort: Median 57-58 (IQR 52-66)	Median 3.9 years (IQR 3.5–4.4)	**MUC5B promoter polymorphism genotypes: GT/TT** Dyspnoea assessed using a 5-question assessment and scored as 0-5	◄►	◄►	
						HR 1.69, 95% CI 0.67-4.27, p=0.27	Stated no association, data not presented	

LEGEND

Effect direction: upward arrow ▲= positive association, downward arrow ▼= negative association, sideways arrow ◄►= no change/mixed effects

Statistical analysis method: denoted by arrow colour: **green** = adjusted analyses; **amber** = unadjusted analyses (including those that were unclear); **black** = between-group comparison

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Approach to the evaluation and management of interstitial lung abnormalities: an official American Thoracic Society clinical

Association of *MUC5B* promoter polymorphism with interstitial lung changes after COVID-19: A preliminary observation

Sahajal Dhooria [1,*,#], Amanjit Bal [2,#], Riya Sharma [1], Nidhi Prabhakar [3], Siddhant Arora [4], Inderpaul Singh Sehgal [1], Dharambir Kashyap [2], Mandeep Garg [3], Ashish Bhalla [4], Ashutosh Nath Aggarwal [1], Ritesh Agarwal [1]

▸ Author information ▸ Article notes ▸ Copyright and License information

PMCID: PMC10954098 PMID: 38344913

- 82 consecutive subjects followed up after recovery from severe, COVID-19 pneumonia (January 2021 -February 2022)
- The association of MUC5B with interstitial changes (post-COVID-19 interstitial changes (PCICs)) in the lung, six months after recovery from severe COVID-19 pneumonia.

- 82 consecut … n severe, COVID-19 p …
- The associat … st-COVID-19 interstitial c … r recovery from severe …

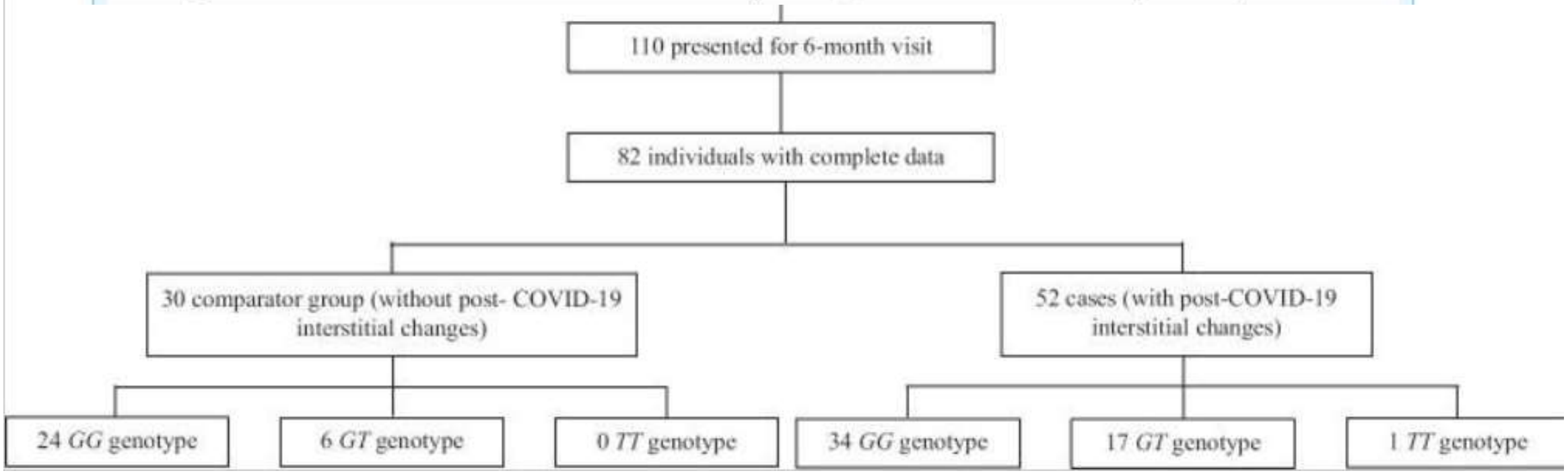
Table. Characteristics of cases and comparator group and logistic regression analyses for factors associated with post-COVID-2019 interstitial lung changes

Parameter	Comparator group (n=30)	Cases (n=52)	P
Age (yr), mean±SD	54.4±12.2	54.6±11.8	0.92
Male sex, n(%)	21 (70)	35 (67.3)	0.8
Smokers, n(%)	7 (23.3)	14 (26.9)	0.72
Comorbid illnesses, n (%)			
Any	27 (90)	42 (80.8)	0.36
Major	26 (86.7)	41 (78.8)	0.38
Others	4 (13.3)	6 (11.5)	1
Parameters during acute illness			
NLR at admission, meadian (IQR)	9.9 (6.3-18.9)	12.9 (7.4-24.7)	0.22
Respiratory support during acute illness			0.05
Oxygen supplementation only, n(%)	29 (96.7)	40 (76.9)	
Mechanical ventilation, n(%)	1 (3.3)	11 (21.2)	
Length of hospital stay (days), mean±SD	9.9±5.5	19±10.8	<0.001
Parameters at six months			
Dyspnoea severity, mMRC scale [median (IQR)]	0 (0-1)	1 (0-1)	0.01
Grade 0	21 (70)	22 (42.3)	
Grade 1	8 (26.7)	20 (38.5)	
Grade 2	1 (3.3)	9 (17.3)	
Grade 3	0	1 (1.9)	
Resting oxygen saturation, mean±SD	98.3±1.1	98.6±1.1	0.38
Forced vital capacity, l, mean±SD	2.72±0.81	2.46±0.61	0.17
Forced vital capacity, % predicted, mean±SD	80.6±11.1	74.7±13.2	0.07
Six-minute walk distance, m, mean±SD	417±109	419±73	0.94
% predicted, mean±SD	88.4±21	89.3±14.4	0.85
Abnormalities on chest CT, n(%)			
Normal	4 (13.3)	0	0.02
Ground-glass opacities	16 (53.3)	42 (80.8)	0.009
Consolidation	1 (3.3)	3 (5.8)	1
Parenchymal bands	7 (23.3)	45 (86.5)	<0.001
Reticulation	1 (3.3)	22 (42.3)	<0.001
Traction bronchiectasis	1 (3.3)	22 (42.3)	<0.001

Dhooria S, Bal A, Sharma R, Prabhakar N, Arora S, Sehgal IS, Kashyap D, Garg M, Bhalla A, Aggarwal AN, Agarwal R. Association of MUC5B promoter polymorphism with interstitial lung changes after COVID-19: A preliminary observation. Indian J Med Res. 2024 Jan 1;159(1):109-113. doi: 10.4103/ijmr.ijmr_137_23

Univariate and multivariate logistic regression analyses for PCICs at six months*

Parameter	OR (95% CI)	*P*	aOR (95% CI)	*P*
Variant genotype at *MUC5B* SNP rs35705950	2.12 (0.73-6.12)	0.17	2.11 (0.72-6.17)	0.17
Age	1 (0.96-1.04)	0.92	1 (0.96-1.04)	0.98
Male sex	1.13 (0.43-2.99)	0.8	1.04 (0.38-2.84)	0.98
Smoking	1.21 (0.43-3.44)	0.72	1.23 (0.42-3.56)	0.7



Dhooria S, Bal A, Sharma R, Prabhakar N, Arora S, Sehgal IS, Kashyap D, Garg M, Bhalla A, Aggarwal AN, Agarwal R. Association of MUC5B promoter polymorphism with interstitial lung changes after COVID-19: A preliminary observation. Indian J Med Res. 2024 Jan 1;159(1):109-113. doi: 10.4103/ijmr.ijmr_137_23.

- The minor MUC5B T-allele appeared at a higher frequency in the cases than in the comparator group [18.3 vs. 10%; odds ratio (OR), 2.01; 95% confidence intervals (CI), 0.76-5.35], but was not significant (P=0.16).
- 75 % with a variant allele (GT /GT) had PCICs at six months vs 58.6 per cent of those without the variant allele (wild-type, GG genotype); P=0.16.
- A variant genotype was significantly associated with subpleural PCICs (OR, 6.36; 95% CI, 1.85-21.85; P=0.003) but not with fibrotic PCICs (OR, 1.73; 95% CI, 0.61-4.94; P=0.31).

Dhooria S, Bal A, Sharma R, Prabhakar N, Arora S, Sehgal IS, Kashyap D, Garg M, Bhalla A, Aggarwal AN, Agarwal R. Association of MUC5B promoter polymorphism with interstitial lung changes after COVID-19: A preliminary observation. Indian J Med Res. 2024 Jan 1;159(1):109-113. doi: 10.4103/ijmr.ijmr_137_23.

(iv) Genetic testing: Telomere length measurement

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(iv) Genetic te measurement

Study	Participants	Size	ILA definition	Intervention	Analysis
Putman 2022	COPDGene, AGES-Reykjavik, Framingham Heart Study	**COPDGene:** 240 with ILA, 2606 without ILA **AGES-Reykjavik:** 163 with ILA, 243 without ILA **FHS:** 44 with ILA, 204 without ILA	Fleischner Society recommendations	**COPDGene and AGES-Reykjavik:** qPCR **FHS:** Southern blot	Unadjusted analysis of lowest quartile and lowest 10th percentile of mean telomere length with mortality Adjusted analyses of qPCR continuous length and shortest quartile with ILA and ILA subtypes Between group (ILA vs no ILA) comparison of telomere length measured by Southern blots
Salisbury 2020	Vanderbilt Familial Interstitial Pneumonia registry	77 with ILA, 259 without ILA	One or more of the following on HRCT: ground-glass attenuation, intralobular reticular opacities, irregular thickening of interlobular septa, traction bronchiectasis, and/or traction bronchiolectasis	Southern blot	Between group (ILA vs no ILA) comparison of telomere length and CT imaging progression Adjusted analyses of continuous telomere length with ILA

Table E17. Baseline telomere length measurement in ILA effect-direction table

Study	Study cohort	Participants	Mean age (SD), years	Follow-up	Comments	Mortality	CT imaging progression
ILA definition:	Fleischner Society criteria						
Putman 2022	AGES-Reykjavik	163 with ILA	AGES-Reykjavik: 78 (6)	Not stated	qPCR: lowest quartile of mean telomere length	◄►	HR 1.2, 95% CI 0.6–2.2; p=0.5
					qPCR: lowest 10th percentile of mean telomere length	▲	**HR 2.0, 95% CI 1.2–3.4; p=0.007**
	COPDGene	240 with ILA	COPDGene: 63 (10)	Not stated	qPCR: lowest quartile of mean telomere length	◄►	HR 0.82 , 95% CI: 0.4–1.7; p=0.6
					qPCR: lowest 10th percentile of mean telomere length	◄►	HR 1.3. 95% CI 0.9–1.8; p=0.14
ILA definition:	Presence and extent of specific interstitial features, including ground-glass opacities, intralobular reticular opacities, irregular thickening of interlobular septa, traction bronchiectasis, traction bronchiolectasis, and honeycombing; Categorised as none, early/mild, or extensive						
Salisbury 2020	Vanderbilt FIP Registry	129 without extensive ILA at enrolment	Not provided Early/mild & extensive ILA: 58.8 (10)	5 years	Southern blot ILD events - Developed clinical ILD or extensive ILA - ILA progression (whole lung visual score) TRF length, kb, mean (SD): - No event: 6.47 (1.04) - ILD Events (ILA progression): 6.26 (0.96) - ILD Events (Clinical ILD or extensive ILA): 6.17 (1.07)		▲ (with shorter telomere length)

LEGEND
Effect direction: upward arrow ▲ = positive association, downward arrow ▼ = negative association, sideways arrow ◄► = no change/mixed effects
Statistical analysis method: denoted by arrow colour: green = adjusted analyses; amber = unadjusted analyses (including those that were unclear); black = between-group comparison

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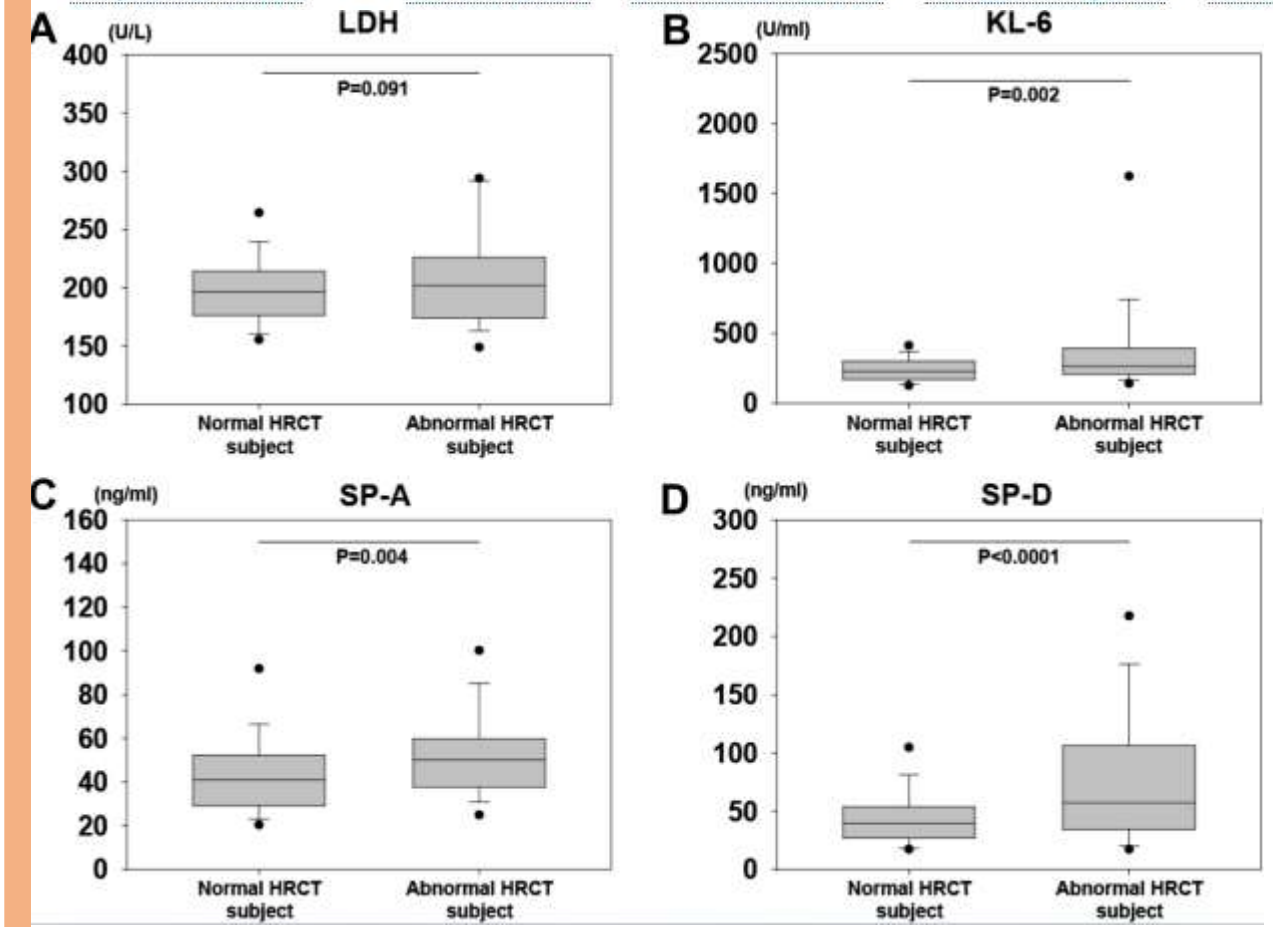
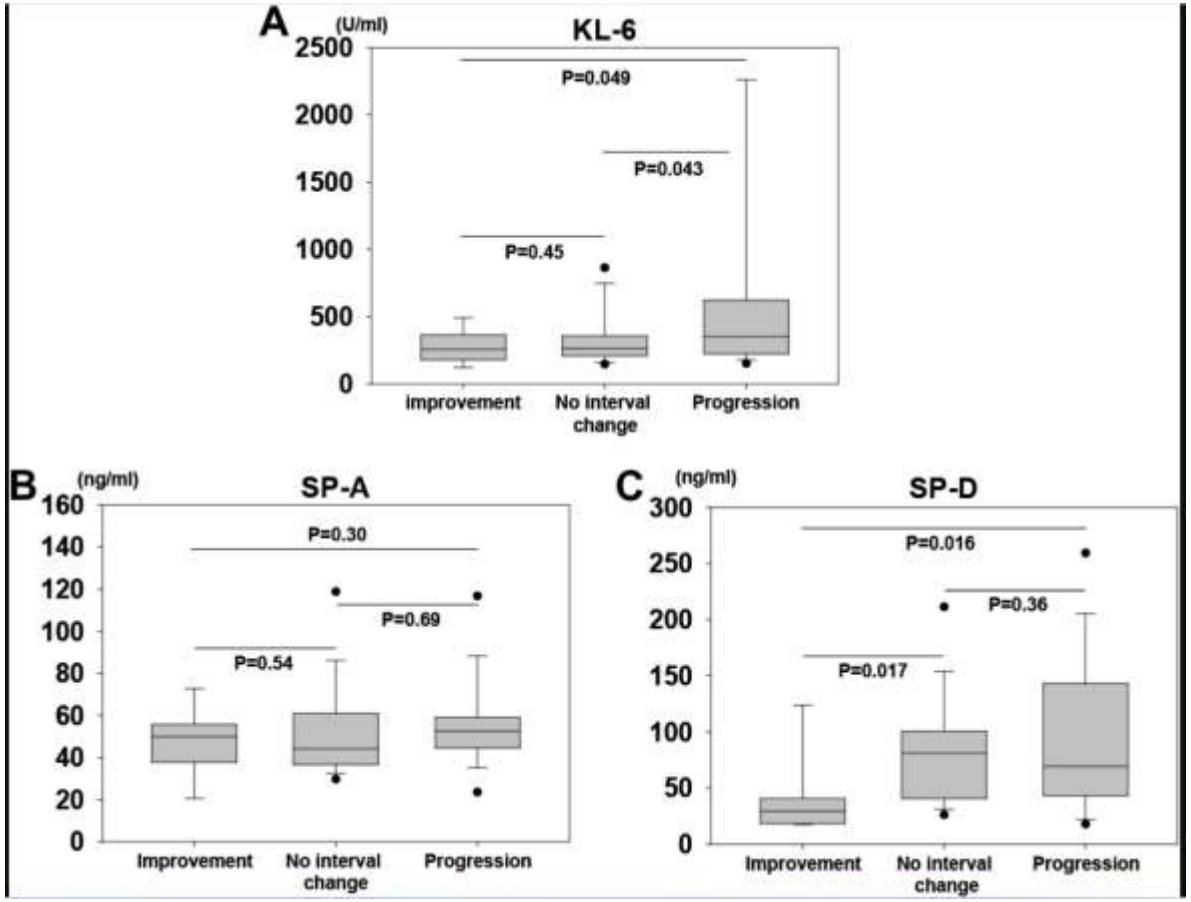
The radiological patterns of interstitial change at an early phase: Over a 4-year follow-up

Kenji Tsushima [a,b] · Shusuke Sone [a] · Sumiko Yoshikawa [b] · Toshiki Yokoyama [b] · Toshiro Suzuki [b] · Keishi Kubo [b]



The identification of interstitial changes using

KL-6 and/or SP-A: sensitivity 64% , specificity 64%,
SP-A and/or SP-D, sensitivity 70%, specificity 64%
KL-6 and/or SP-D , sensitivity 33%, specificity 100%



Serum KL-6 levels in the progression group - significantly higher in comparison to those in the improvement and no interval change groups, respectively (p = 0.049, and p = 0.043).
Serum SP-A levels among the groups: no significant difference observed.
Serum SP-D levels in the improvement group : lower in comparison to no interval change and progression groups, (p = 0.017, and p = 0.016 respectively).

Tsushima K, Sone S, Yoshikawa S, Yokoyama T, Suzuki T, Kubo K. The radiological patterns of interstitial change at an early phase: over a 4-year follow-up. Respir Med. 2010 Nov;104(11):1712-21. doi: 10.1016/j.rmed.2010.05.014. Epub 2010 Jun 9. PMID: 20538446.

(v) Serial CT Scans for longitudinal follow-up

Author	Year	Participants	N	Follow-up	Results
Araki	2016	FHS	1867	Median 4 years	23/53 (43%) of initial ILA progressed 95/1814 (5.2%) of no ILA progressed to ILA over follow-up
Balata	2023	Manchester Lung Health Check	1386	5 years	26/52 (50%) had imaging progression
Buendia-Roldan	2021	MDF lung aging program	817	24+/-18 months	18/80 (22.5%) progression
Chae	2023	Korean Lung Cancer Screening Project/Natl Lung Ca Screening Program	3118	Median 662 days	15/31 (48%) of fibrotic ILA 1/15 (6.67%) of nonfibrotic ILA 2/29 (6.9%) of equivocal ILA
Hino	2021	AGES-Reykjavik	327	At least 5 years	191/327 (58.4%) with progression
Jin	2013	National Lung Screening Trial	884	2 years	16/79 (20.3%) progression 7/19 (36.8%) of fibrotic ILA progression
Lee	2023	Korean health screening cohort	2765	Median 12 years	48/60 (80%) with progression
Mackintosh	2019	Queensland Lung Ca Screening Study (AUS)	256	5 years	1/19 (5.3%) with progression
Park	2023	Self-referral pts for comprehensive health screen in Korea	18118	Median 11.3 years	161/200 (80.5%) of ILA with progression
Patel	2023	Lung cancer screening pts in MA	1699	5.67 +/- 1.59 years	7/15 (46.7%) of progression in pts with initial ILA 7/35 (20%) of indeterminate ILA progressed to ILA
Putman	2019	AGES-Reykjavik	3167	Median 5.1 years	132/284 (40%) with definite progression 106/284 (32%) with probable progression
Rose	2023	CGS-PF study and relatives	192	2 years	15/22 (68%) with progression
Salisbury	2020	FDR of pts with FIP in Vanderbilt registry	336	5 years	13/19 (68.4%) of baseline ILA had progression 6/67 (9%) without baseline ILA progressed to ILA
Tsushima	2010	Japanese rural lung ca screening cohort	3079	4 years	32/73 (43.8%) showed progression
Zhang	2022	Chinese lung cancer screening	155539	Median 4.2 years	25/66 (37.9%) nonsubpleural ILA progressed 198/454 (43.6%) subpleural nonfibrotic ILA progressed 11/16 (68.8%) subpleural fibrotic ILA progressed

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Table E19. Imaging progression (identified by serial chest CT scans) association with mortality effect-direction table

Author	Year	Participants	N	Follow-up	Measurement	Effect	Result
ILAs progressive versus no ILAs (according to serial chest CT scanning)							
Araki	2016	Framingham Heart Study	778	Median 4 years	Association of ILA progression with mortality	▲	HR 3.9, 95% CI 1.3-10.9, p=0.01 OR 4.3, 95% 1.4-13.3, p=0.01
Putman	2019	AGES-Reykjavik	3167	11 years	Association of ILA progression with mortality	▲	HR 1.2 (1.1–1.3), p=0.0004
ILAs progressive versus stable ILAs (according to serial chest CT scanning)							
Araki	2016	Framingham Heart Study	155	Median 4 years	Association of ILA progression with mortality	◀▶	HR 1.6 (95% CI 0.2-12.2), p=0.6 OR 2.0 (95% CI 0.3-14.3), p=0.5
Hino	2021	AGES-Reykjavik	327	5-9 years	Association of ILA progression with mortality	▲	HR 1.68 (95% CI = 1.21–2.34), P < 0.001
Putman	2019	AGES-Reykjavik	3167	11 years	Association of ILA progression with mortality	▲	HR 1.9 (95% CI 1.3–2.8); P = 0.0009

▲ = positive association ▼ = negative association ◀▶ = no effect or mixed effect

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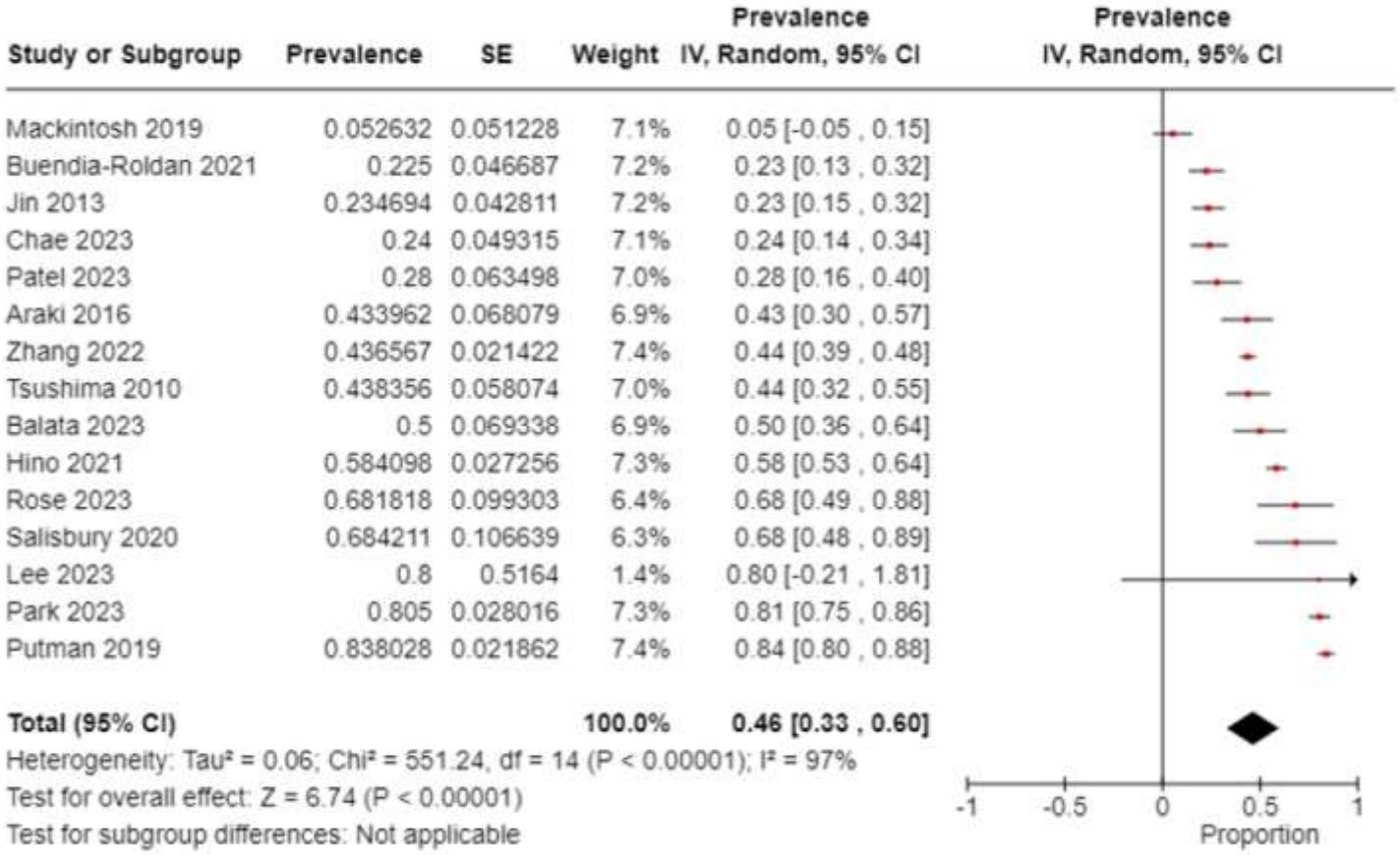
Meta-analysis of prevalence of imaging progression of ILA

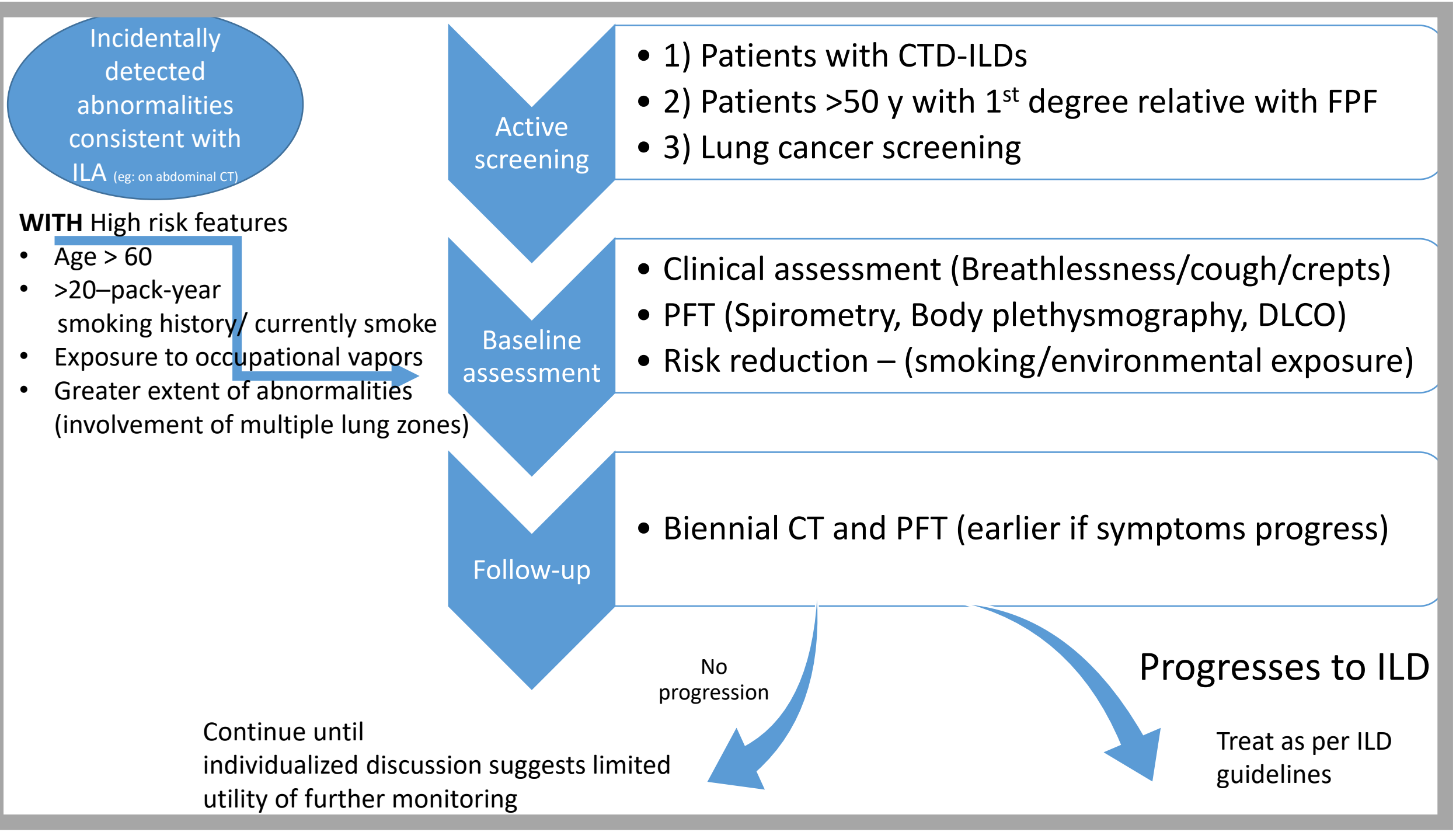


Study or Subgroup	Prevalence	SE	Weight	Prevalence IV, Random, 95% CI
Mackintosh 2019	0.052632	0.051228	7.1%	0.05 [-0.05 , 0.15]
Buendia-Roldan 2021	0.225	0.046687	7.2%	0.23 [0.13 , 0.32]
Jin 2013	0.234694	0.042811	7.2%	0.23 [0.15 , 0.32]
Chae 2023	0.24	0.049315	7.1%	0.24 [0.14 , 0.34]
Patel 2023	0.28	0.063498	7.0%	0.28 [0.16 , 0.40]
Araki 2016	0.433962	0.068079	6.9%	0.43 [0.30 , 0.57]
Zhang 2022	0.436567	0.021422	7.4%	0.44 [0.39 , 0.48]
Tsushima 2010	0.438356	0.058074	7.0%	0.44 [0.32 , 0.55]
Balata 2023	0.5	0.069338	6.9%	0.50 [0.36 , 0.64]
Hino 2021	0.584098	0.027256	7.3%	0.58 [0.53 , 0.64]
Rose 2023	0.681818	0.099303	6.4%	0.68 [0.49 , 0.88]
Salisbury 2020	0.684211	0.106639	6.3%	0.68 [0.48 , 0.89]
Lee 2023	0.8	0.5164	1.4%	0.80 [-0.21 , 1.81]
Park 2023	0.805	0.028016	7.3%	0.81 [0.75 , 0.86]
Putman 2019	0.838028	0.021862	7.4%	0.84 [0.80 , 0.88]
Total (95% CI)			**100.0%**	**0.46 [0.33 , 0.60]**

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 551.24$, df = 14 ($P < 0.00001$); $I^2 = 97\%$
Test for overall effect: $Z = 6.74$ ($P < 0.00001$)
Test for subgroup differences: Not applicable

Podolanczuk AJ, Hunninghake GM, Wilson KC, Khor YH, et al.
Approach to the evaluation and management of interstitial lung abnormalities: an official American Thoracic Society clinical

Proposed algorithm for management of ILA


Incidentally detected abnormalities consistent with ILA (eg: on abdominal CT)
WITH High risk features
Age > 60
>20–pack-year smoking history/ currently smoke
Exposure to occupational vapors
Greater extent of abnormalities (involvement of multiple lung zones)
Active screening
1) Patients with CTD-ILDs
2) Patients >50 y with 1st degree relative with FPF
3) Lung cancer screening
Baseline assessment
Clinical assessment (Breathlessness/cough/crepts)
PFT (Spirometry, Body plethysmography, DLCO)
Risk reduction – (smoking/environmental exposure)
Follow-up
Biennial CT and PFT (earlier if symptoms progress)
No progression
Continue until individualized discussion suggests limited utility of further monitoring
Progresses to ILD
Treat as per ILD guidelines

Thank you