

**Approach to the Evaluation and Management of Interstitial Lung Abnormalities: An
Official American Thoracic Society Clinical Statement**

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Online Data Supplement

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DETAILED METHODS

The project was approved by the American Thoracic Society (ATS). Co-chairs were recruited by the ATS Chief of Guidelines and Documents based upon suggestions from editors of the American Journal of Respiratory and Critical Care Medicine and the leadership of the Assembly on Clinical Problems. Participants were selected by the co-chairs based upon their expertise in ILD clinical care, molecular mechanisms, histopathology, or radiology. A diversity of perspective was sought by considering seniority, geographical location, gender, and ethnicity/race. Two patient representatives were included. A methodology team was assigned to the project, which was led by the ATS Chief of Guidelines and Documents and consisted of three members of the ATS Guideline Methodology Training Program. Participation was contingent upon disclosure and vetting of industry relationships according to the policies and procedures of the ATS.

The co-chairs drafted key clinical questions in a PICO (Population, Intervention, Comparator, and Outcome) format. The questions were discussed, modified, and approved by the full committee. While evidence syntheses were performed by the methodology team to inform each question, the co-chairs led the committee in defining ILAs using consensus by discussion over a series of video conferences.

The evidence syntheses began with systematic searches of Medline via PubMed in October 2023. Results were initially screened based on titles and abstracts, then the full text of potentially relevant publications was reviewed. The bibliographies of selected studies, bibliographies of related systematic reviews, and articles suggested by the committee members were also reviewed. Notably, no studies comparing the intervention versus no intervention were identified for any question; therefore, the study selection criteria were broadened to allow selection of studies without a no intervention group. This change yielded studies to inform the

questions. Data from selected studies were extracted into data tables. The searches, study selection, and data extraction were not performed in duplicate, which was the primary difference between the evidence syntheses and a systematic review.

When data were amenable to weighted pooling, a random effects model was used. For prevalence, generic inverse variance was used to calculate summary estimates. Relative risk (RR) was used to report the summary estimates for other outcomes in which patients with ILA/ILD were compared to patients without ILA/ILD. The accompanying 95% confidence interval (CI) was determined for both measures. Statistical heterogeneity of the pooled results was measured using the I^2 statistic, considering an I^2 value $\geq 50\%$ as significant heterogeneity. In cases of heterogeneity, a stepwise approach was followed: 1) the input data were confirmed, 2) studies were removed from the meta-analysis one at a time to identify which studies contributed to the heterogeneity (i.e., sensitivity analysis), and 3) any responsible studies were compared to the other studies and characteristics that might have contributed to the differing results were sought. If a reason for the differing results was not identified, the outlying studies were excluded. The quality of evidence (confidence in the estimates) was presumed to be low throughout all discussions. This was based upon the observation that all studies were uncontrolled relative to the intervention specified in the PICO questions (i.e., none of the studies had a no intervention group), most studies were small with wide confidence intervals, and heterogeneity was common.

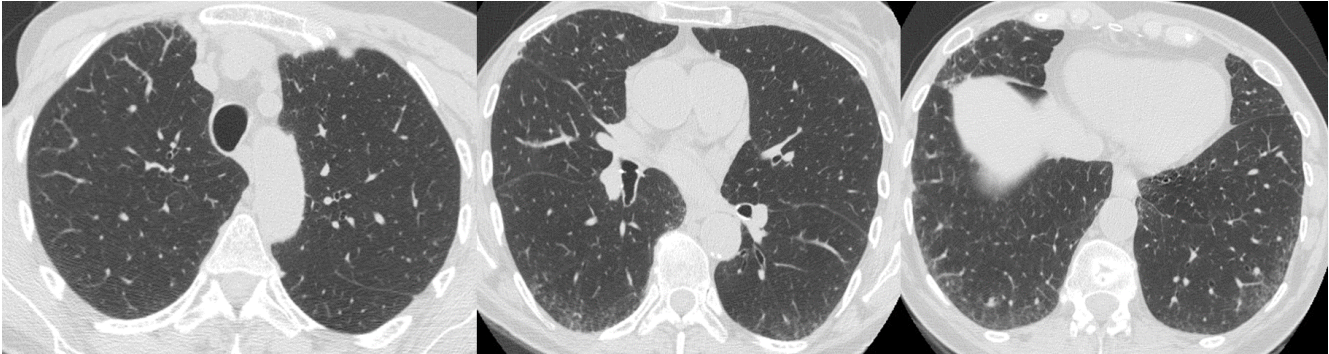
The methodology team provided the committee with a video presentation summarizing the evidence synthesis for each PICO question prior to a meeting of the full committee by video conference. Each meeting began with the opportunity to discuss the evidence synthesis, followed by the co-chairs sharing their opinion on each question, and then a full committee discussion about potential modifications to the suggestions. Following the video conference, the participants

voted to accept or not accept the suggestions. Seventy percent agreement was needed to approve a suggestion. Failure to achieve 70% agreement resulted in no suggestion for or against the intervention.

The initial draft of the manuscript was written by the co-chairs and methodologists, with the latter specifically drafting the evidence summaries. All members of the committee reviewed the manuscript; comments were addressed by the co-chairs and then incorporated into the revised manuscript. The manuscript was redistributed to the full panel for further review and approval, followed by external peer review.

Figure E1. Axial CT images of subpleural nonfibrotic ILA at baseline (A) and follow-up 4 years later (B).

(A)



(B)

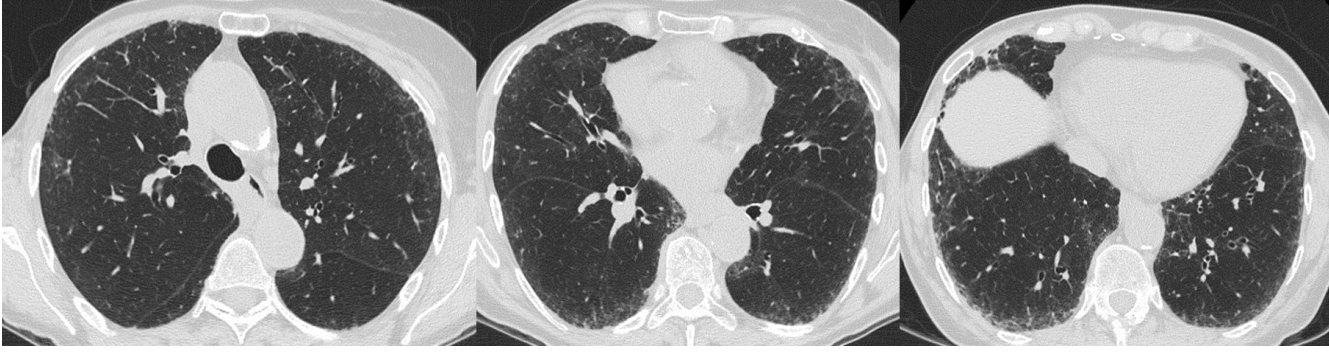
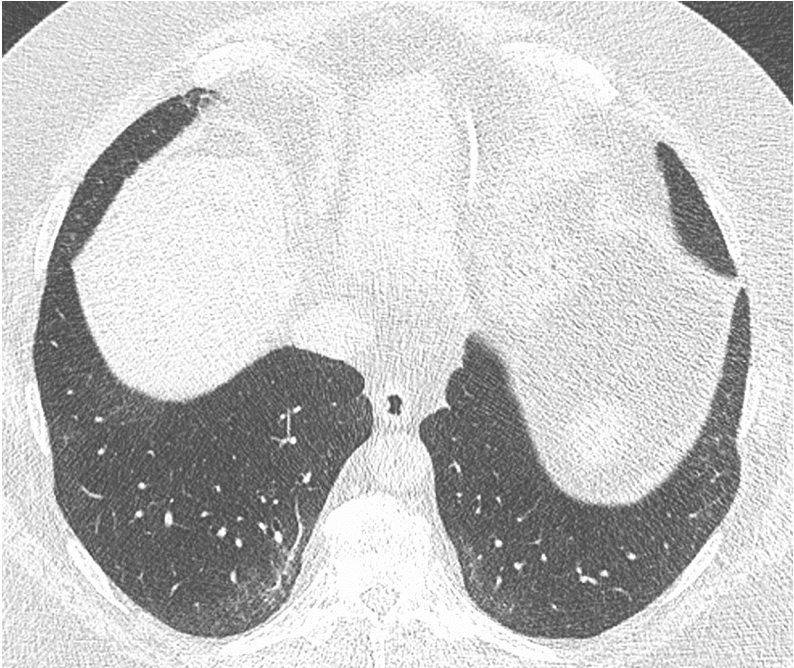


Figure E2 A&B. Axial (A) and coronal (B) CT images demonstrating paraspinal fibrosis that is not considered to be ILA.

(A)



(B)

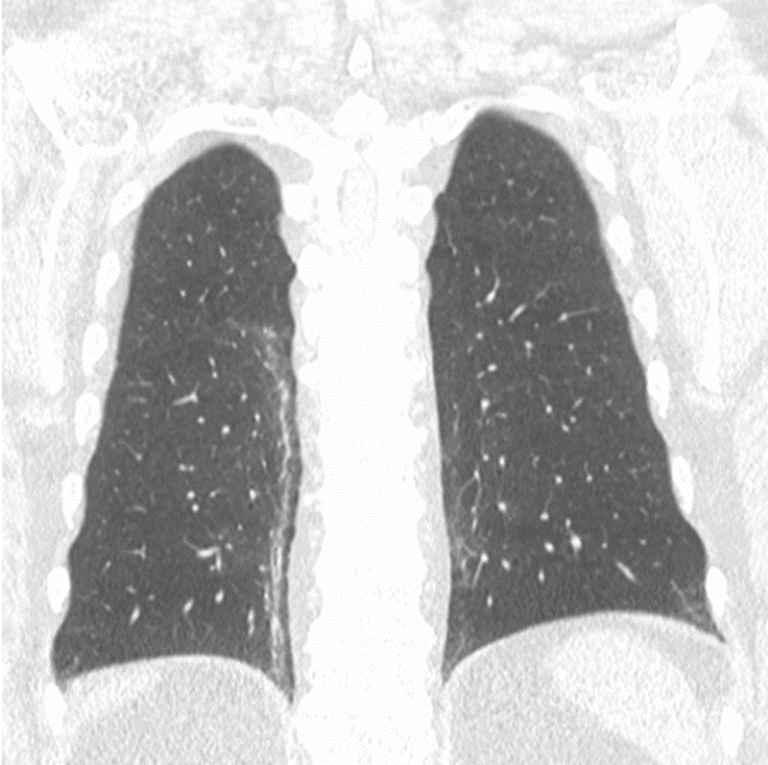
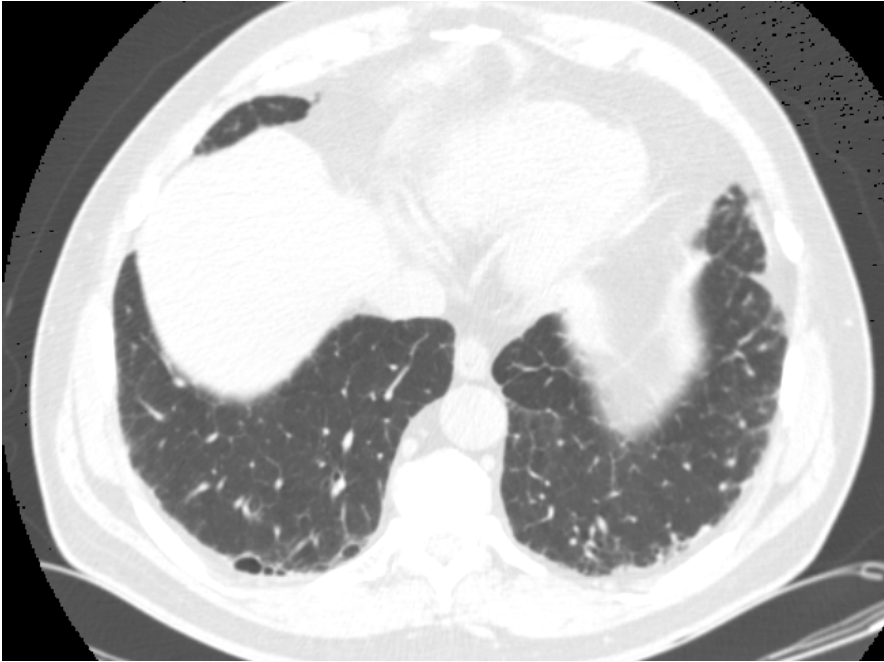
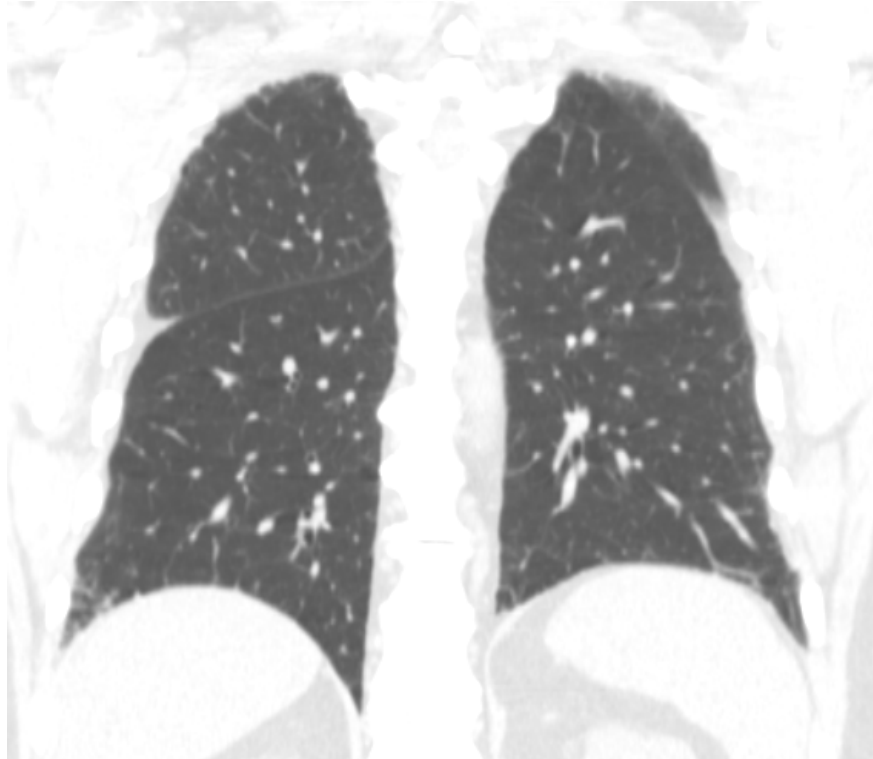


Figure E2 C&D. Axial (C) and coronal (D) CT images demonstrating fibrotic ILA with honeycombing but not meeting criteria for ILD.

(C)



(D)



INTERSTITIAL LUNG ABNORMALITIES ARE CLINICALLY MEANINGFUL (ILA/ILD present versus ILA/ILD absent)

Figure E3. Interstitial lung abnormalities are associated with chronic cough

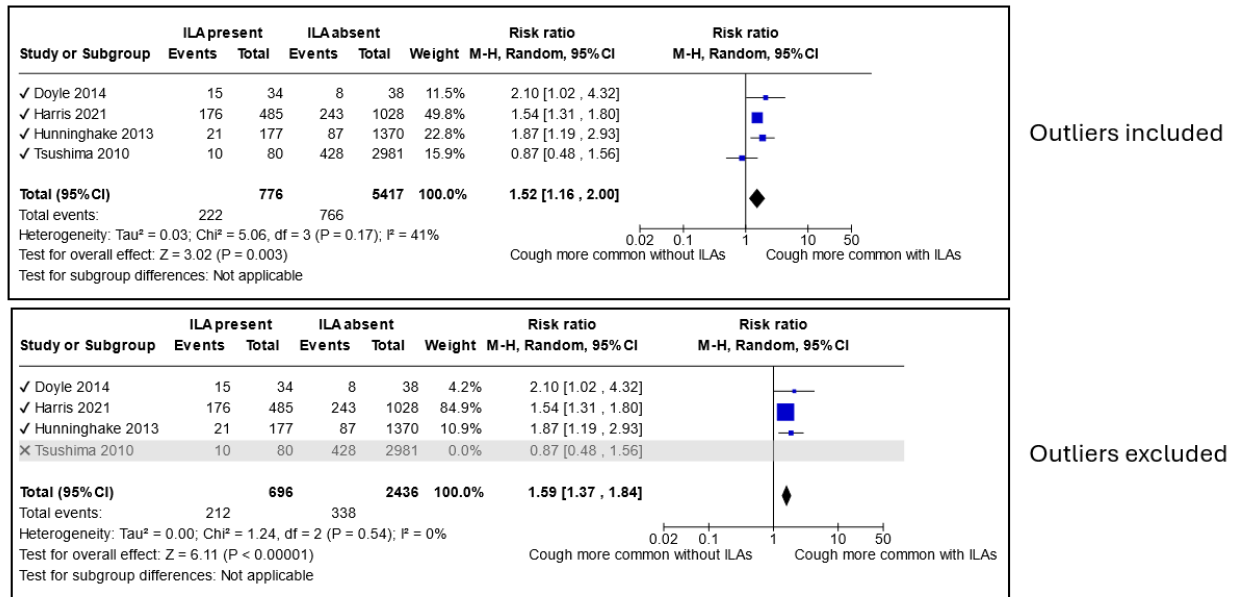


Figure E4. Interstitial lung abnormalities are associated with dyspnea on exertion

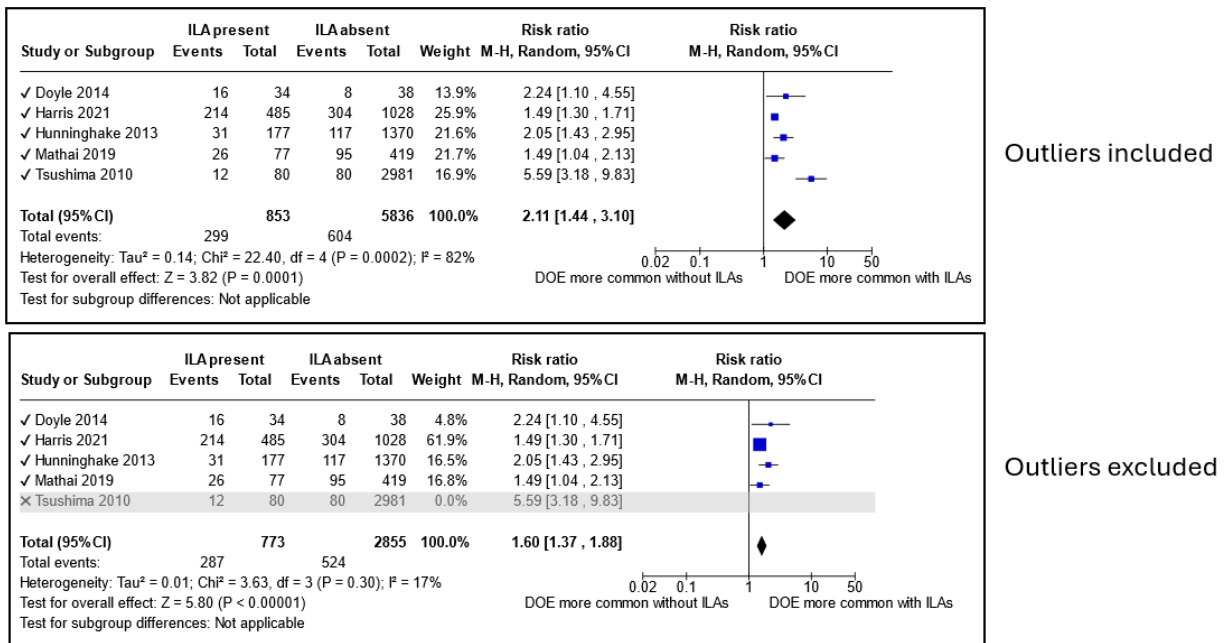


Figure E5. Interstitial lung abnormalities are associated with mortality

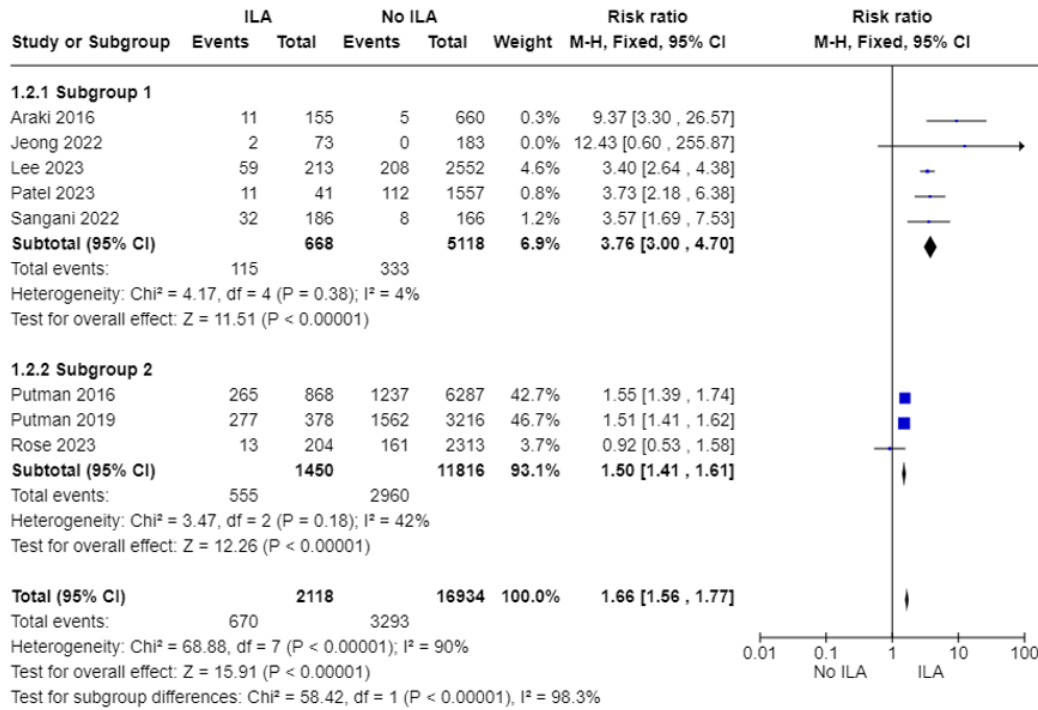


Table E1. Interstitial lung abnormalities are associated with impaired lung function

Author	Year	Participants	Number, n	Measurement	Effect	Result
Forced vital capacity, FVC						
Hata	2022	COPD Gene Study (smokers)	No ILA, n=4,713 TBI-0, n=207 TBI-1, n=267 TBI-2, n=103 TBI-3, n=5	Forced vital capacity (% predicted), stratified by ILA severity [TBI = bronchiectasis / bronchiolectasis index], relative to no ILAs	▲	FVC, median, IQR - TBI-0: -2.8 (-4.3, -1.3), p<0.001 - TBI-1: -2.5 (-3.8, -1.2), p<0.001 - TBI-2: -0.2 (-2.3, 1.9), p=0.86 - TBI-3: -21 (-30, -11), p<0.001 - r ² : 0.65
Buendia-Roldan	2021	Volunteers in a lung aging program	No ILAs = 560 ILAs = 80	Forced vital capacity (% predicted)	◀▶	FVC, mean ± SD - ILAs = 93±17 - No ILAs = 95±15 - p = 0.19
Total lung capacity, TLC						
Hata	2022	COPD Gene Study (smokers)	No ILA, n=4,713 TBI-0, n=207 TBI-1, n=267 TBI-2, n=103 TBI-3, n=5	Total lung capacity (L), stratified by ILA severity [TBI = bronchiectasis / bronchiolectasis index], relative to no ILAs	▲	TLC, median, IQR - TBI-0: -0.4 (-0.6, -0.2), p<0.001 - TBI-1: -0.6 (-0.8, -0.4), p<0.001 - TBI-2: -0.6 (-0.8, -0.3), p<0.001 - TBI-3: -2.3 (-3.2, -1.2), p<0.001 - r ² = 0.45
Diffusion lung capacity, DLCO						
Rosas	2007	Subjects with familial IPF or two or more first-degree relatives with IPF	No ILAs = 53 ILAs = 31	Diffusion capacity for carbon monoxide (% predicted)	▲	DLCO, mean ± SD - No ILAs = 105 ± 2 - ILAs = 97 ± 3 - p = 0.02
Buendia-Roldan	2021	Volunteers in a lung aging program	No ILAs = 560 ILAs = 80	Diffusion capacity for carbon monoxide (% predicted)	▲	DLCO, mean ± SD - ILAs = 87 ± 18 - No ILAs = 102 ± 19 - p = <0.0001
6-minute walk distance, 6MWD						
Rose	2023	COPD Gene Study (smokers)	No ILAs = 2,313 ILAs = 204	Six-minute walking distance (meters)	◀▶	6MWD, meters ± SD - No ILA = 421 ± 128 - ILAs = 415 ± 121 - No ILAs versus ILAs = -5.3 (95% CI -21 to +10.5), p = 0.5

▲ = positive association ▼ = negative association ◀▶ = no effect or mixed effect Green = adjusted analysis; Amber = unadjusted analysis; Black = between group analysis.

Table E2. Interstitial lung abnormalities and lung function decline

Author	Year	Participants	Number, n	Measurement	Effect	Result
Forced vital capacity						
Mackintosh	2019	Queensland Lung Cancer Screening Study (smokers)	No ILAs = 236 ILAs = 20	Change in forced vital capacity (% predicted) from baseline over 2 years	◀▶	FVC change, mean ±SD: - ILAs: -1 ± 4.9 - No ILAs: -4 ± 9.9 - p = 0.316
Rose	2023	CGS-PF (Clinical Genetics and Screening for Pulmonary Fibrosis) study	No ILAs = 51 ILAs = 22	Change in forced vital capacity (% predicted) from baseline over 2 years	◀▶	FVC change, median (IQR): - No ILAs = -3.1 (-6.3 to 0.0) - ILAs = -4.4 (-9.0 to -0.7) - P = 0.2
Balata	2023	Manchester UK Lung Health Check	No ILAs = 1330 ILAs = 54	Change in forced vital capacity (% predicted) from baseline	◀▶	All ILAs, mean ± SD: - year 1: 6.3 ± 12.1 - year 2: 4.3 ± 14.7 - year 5: 0.1 ± 17.1 Fibrotic ILAs, mean ± SD: - year 1: 2.9 ± 9.1 - year 2: -0.8 ± 12.5 - year 5: -3.7 ± 15.0 Non-fibrotic ILAs, mean ± SD: - year 1: 10.2 ± 14.7 - year 2: 7.6 ± 15.4 - year 5: 2.7 ± 18.1 Fibrotic vs. non-fibrotic ILAs = NS
Diffusion capacity						
Rose	2023	CGS-PF (Clinical Genetics and Screening for Pulmonary Fibrosis) study	No ILAs = 51 ILAs = 22	Change in diffusion capacity of carbon monoxide (% predicted) from baseline over 2 years	▲	DLCO change, median (IQR): - No ILAs = 83 (77 to 99) - ILAs = 76 (62 to 84) - p = 0.007

▲ = positive association ▼ = negative association ◀▶ = no effect or mixed effect Green = adjusted analysis; Amber = unadjusted analysis; Black = between group analysis.

Table E1. Interstitial lung abnormalities are associated with mortality

Author	Year	Participants	N	Follow-up	Effect	Result
Hata	2022	COPDGene	5,295	7 years	▲	TBI-0: HR 1.8 (95% CI 1.2 - 2.8), p=0.006 TBI-1: HR 1.1 (95% CI 0.7 - 1.7), p=0.68 TBI-2: HR 3.3 (95% CI 2.2 - 5.0), p<0.001 TBI-3: HR 24.0 (95% CI 8.7 - 67), p<0.001
Kadoch	2018	Patients undergoing pre-TAVR planning	186	2 years	▲	HR 3.29 (95% CI 1.34-8.08), p=0.009
Sanders	2003	FHS and AGES-Reikjavik	7,629	8.8-12 years	▲	FHS: HR 1.95 (1.23 to 3.08), p=0.0042 AGES: HR 1.60 (1.41 to 1.82), p<0.0001
Sangani	2022	Patients who underwent surgical resection for suspicious lung nodules or masses	352	Unclear, maybe 3 years	▲	OR 4.04, 1.74-5.30, p=0.001
Balata	2023	Ever-smokers undergoing lung cancer screening	1,386	5 years	▲	Fibrotic ILA only: HR 3.8, 95% CI 1.7-8.2; p=0.001
Hoyer	2018	Volunteers responding to newspaper ads	1,990	12 years	▲	HR 2.0, 95% CI: 1.4-2.7, P < 0.001
Patel	2023	Pts undergoing lung cancer screening	2,560	5.67 +/- 1.59 years	▲	HR 2.41 (1.57, 3.77); p < 0.001
Rose	2023	COPDGene	4,360	4.9 years	◀▶	HR ILA vs no ILA: 0.9 (0.5-1.5), p=0.6

▲ = positive association ▼ = negative association ◀▶ = no effect or mixed effect Green = adjusted analysis; Amber = unadjusted analysis; Black = between group analysis.

QUESTION 1: SHOULD ADULT SMOKERS UNDERGO CHEST CT SCAN SCREENING TO IDENTIFY ILA/ILD?

Figure E6. Flow of information diagram

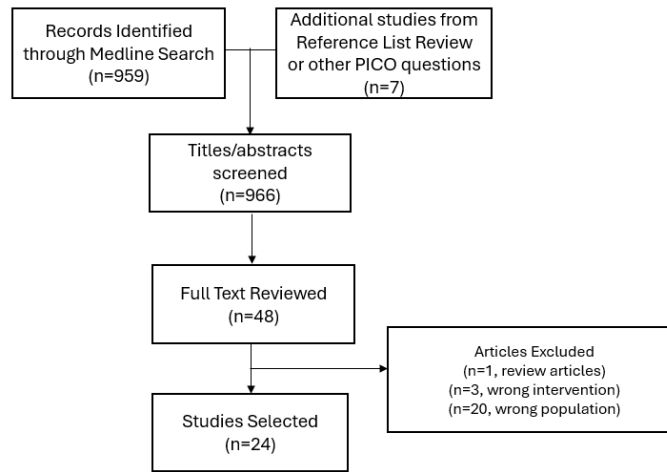


Table E4. Selected studies

Author	Year	Participants	Age	Pack/year	Type of CT
Sverzellati	2011	692	55.5±5.4	at least 20 p-y	LDCT
Ohgiya	2017	349	68.9±10.8	NA	HRCT
Nishino	2015	120	64 (25–90)	20	CT CHEST
Mackintosh	2019	256	65.8 (62.7–69.3)	58.5 (39.8–72.5)	LDCT
Lee	2018	256	63.2 ± 5.4	40.0 ± 21.9	LDCT
Jin	2013	884	61.5 ±5.1	59.9	LDCT
Cho	2022	254	73 (71-76)	0 (0, 30)	CT CHEST
Tseng	2022	208	65.6 (21.4–88.8)	64.9% smokers	CT CHEST
Menon	2022	9,579 phase 1 / 5,277 phase 2	63.4 ± 9.3	43 (32-60)	CT CHEST
Bozzetti	2016	457	63.2±7.4	48.3±24.2	LDCT
Salvatore	2016	951	NA	34.8	LDCT
Tsushima	2010	3079	57.2 ±9.8	20.7 / 29.0	LDCT
Petranovic	2023	475	67.8 ± 10.3	NA (NsclC)	CHEST CT
Araki	2019	484	62 (23-95)	77.3% smokers	CHEST CT
Patel	2023	1699	62.6±6.24	48.5±22.9	LDCT
Washko	2011	2416	64 (56-72)	43.9% smokers	HRCT
Rose	2023	4361	68.4 (8.7)	40.0 (25.5–52.2)	CHEST CT
Hoyer	2018	1990	59.7 (5.0)	37.5 (13.4)	LDCT
Hida	2021	231	69 (40–91)	34.5 (0.0–144.6)	CT CHEST
Hewitt	2022	1853	68.8 (4.8)	40.4 (22.6)	LDCT
Upperton	2023	6650	68.8 (4.8)	32 (22–47)	LDCT
Whittaker Brown	2019	25041	72.6 (6.3)	48 (39-66)	LDCT
Ash	2017	8345	59.9 ± 9.1	44.3±24.9	CT CHEST
Balata	2023	1384	67.5±4.8	46.8±24.6	LDCT

Figure E7. Prevalence of ILA/ILD among smokers (with outliers)

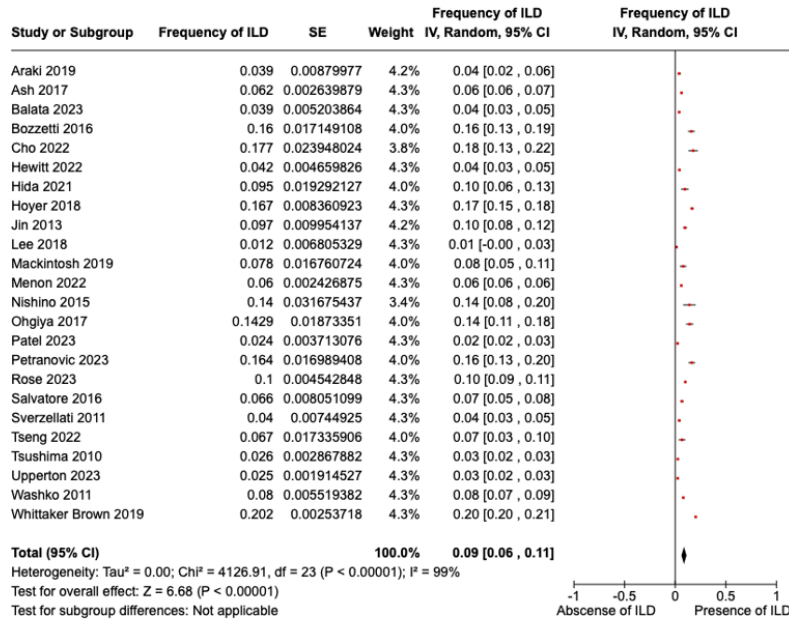
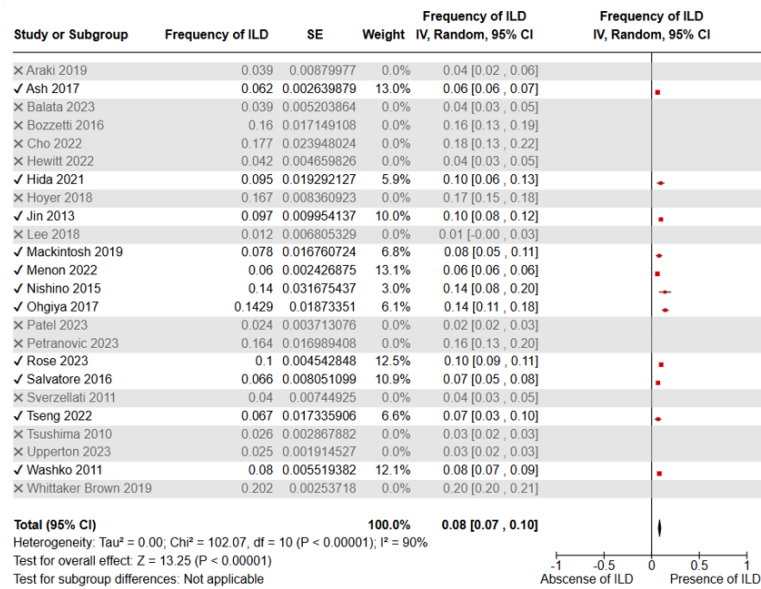


Figure E8. Prevalence of ILA/ILD among smokers (outliers removed)



QUESTION 2: SHOULD ADULTS WITH CONNECTIVE TISSUE DISEASE UNDERGO CHEST CT SCAN SCREENING TO IDENTIFY ILA/ILD?

Figure E9. Flow of information diagram

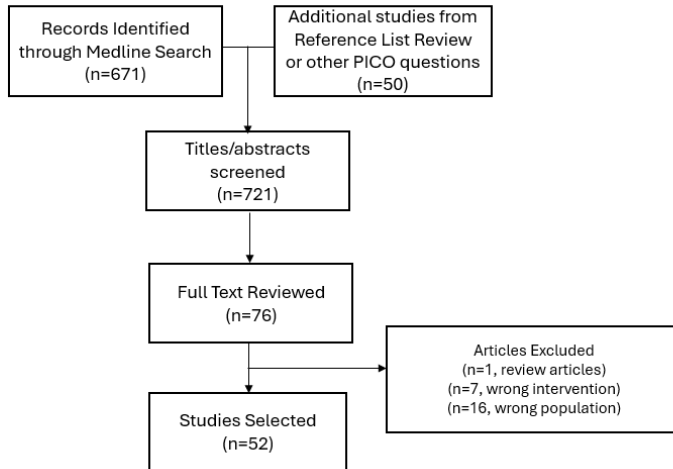


Table E5. Selected studies

Author	Year	No. Participants	ILD (%)	Type of CTD	Mean Age	Type of CT	
Castellano-Moreira	2020	179	20.60%	RA		59.7 (13.0)	HRCT
Matson	2022	184	21.00%	RA	56.4 (44.2-66.6)		HRCT
Cobo-Ibanez	2019	478	23.40%	DM/PM		47.7 (26.7-62.1)	HRCT
Dong	2018	18	39.00%	RA	52 (47-57)		HRCT
Dawson	2001	150	19.00%	RA		58.9 (10.3)	HRCT
Perez	1998	50	32.00%	RA	57.9 ±1.5		HRCT
De Santis	2012	110	66.40%	SSc		54.9 (12.6)	HRCT
Esposto	2022	106	15.00%	RA	63 (55-71)		HRCT
Duarte	2019	1129	51.70%	RA		63.2±12.4	HRCT
Aletra	2006	81	85.00%	MCTD	57±12.5		HRCT
Etha	2019	415	56.40%	SSc		59.6 (13.6)	HRCT
Zhao	2013	110	49.10%	pSS	55.5 (14.2)		HRCT
Foocharoen	2020	566	46.80%	SSc		54.6 ± 10.8	HRCT
Zhang	2017	550	43.10%	RA	61 ± 13		HRCT
Hax	2017	188	57.10%	SSc		50.9 (13.9)	HRCT
Zhang	2014	87	64.40%	pSS	55.2 (37-69)		HRCT
Hayashi	2008	55	60.00%	DM/PM		54 (21-81)/47 (27-70)	HRCT
Zanatta	2020	97	42.30%	SSc	55.4 (± 12.4)		HRCT
Hoffmann-Void	2019	815	40.00%	SSc		53 (14.8)	HRCT
Yuan	2013	70	50.00%	DM/PM	55.5 (15.4)/50.4 (15.4)		HRCT
Iniesta Arandia	2017	209	37.60%	SSc		44.2 (16.4)	HRCT
Yiu	2016	102	50.00%	SSc	58 (15)		HRCT
Jung	2018	108	39.80%	SSc		50.1 (13.5)	HRCT
Yanaba	2013	71	50.70%	SSc	NA		HRCT
Li	2019	923	30.10%	RA		52.62 ± 14.95	HRCT
Yalçinkaya	2016	72	25.00%	SSc	44.9 ± 12.7		HRCT
Marie	2011	348	30.70%	DM/PM		53	HRCT
Wuttige	2016	32	43.80%	SSc	NA		HRCT
Muk	2008	43	86.00%	SSc		47.7 ± 13.0	HRCT
Watanabe	2020	168	52.40%	DM/PM	59 (44±67)		HRCT
Nanaez	2018	3215	0.20%	SLE		37 ± 13	HRCT
Wang	2015	544	15.30%	RA	59.60±9.66		HRCT
Palm	2016	144	25.00%	pSS		52 (14)	HRCT
van Bon L	2014	779	35.00%	SSc	42.4±12.3 / 43.8±11.2		HRCT
Peng	2020	182	68.10%	DM	50.4 ± 20.8		HRCT
Tomita	2012	53	45.30%	SSc	NA		HRCT
Tezcan	2020	129	48.00%	SSc	NA		HRCT
Tanaka	2015	78	52.60%	DM/PM	54.0 (36 to 65) / 54.5 (19 to 78)		HRCT
Quian	2021	834	85.10%	pSS		48.4±12.7	HRCT
Omer	2017	419	7.13%	RA	45.7 ± 15.9 years		HRCT
Richman	2013	274	36.50%	RA		NA	HRCT
Aubart	2011	252	9.13%	RA	NA		HRCT
Schnabel	2003	63	31.75%	DM/PM		53.5 (46.5-66.5)	HRCT
Avouac	2010	1132	34.90%	SSc	57 ± 14/63 ± 14		HRCT
Steele	2021	425	48.82%	SSc		6.42 (14.46)	HRCT
Benyamine	2018	75	35.70%	SSc	59.29 ± 13.98		HRCT
Vandecasteele	2021	722	39.01%	SSc		54 (14)	HRCT
Bodily	2005	144	66.70%	MCTD	49.18 (29-73)		HRCT
Yang	2017	49	48.99%	DM/PM		44(13)5 (17)	HRCT
Buvry	2020	68	27.90%	pSS	55 (14.9)		HRCT
Yazici	2020	372	12.63%	pSS		60.6 ± 11.9	HRCT
Zhou	2020	204	63.24%	SSc		52.8 ± 12.9	HRCT

Figure E10. Prevalence of ILA/ILD among patients with connective tissue disease (with outliers)

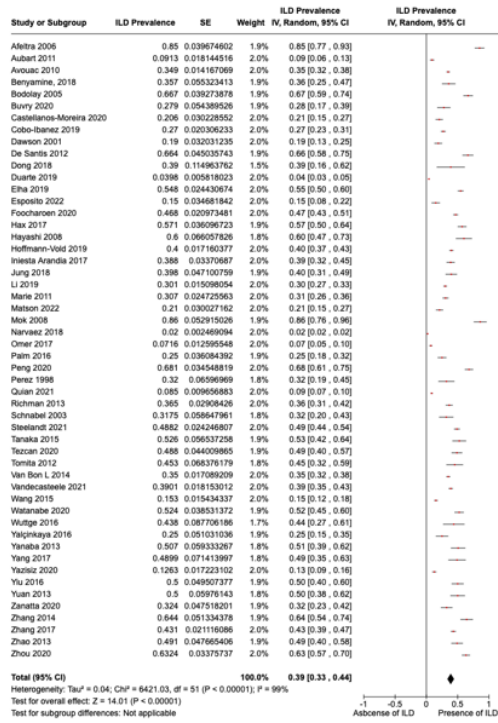


Figure E11. Prevalence of ILA/ILD among patients with connective tissue disease (outliers removed)

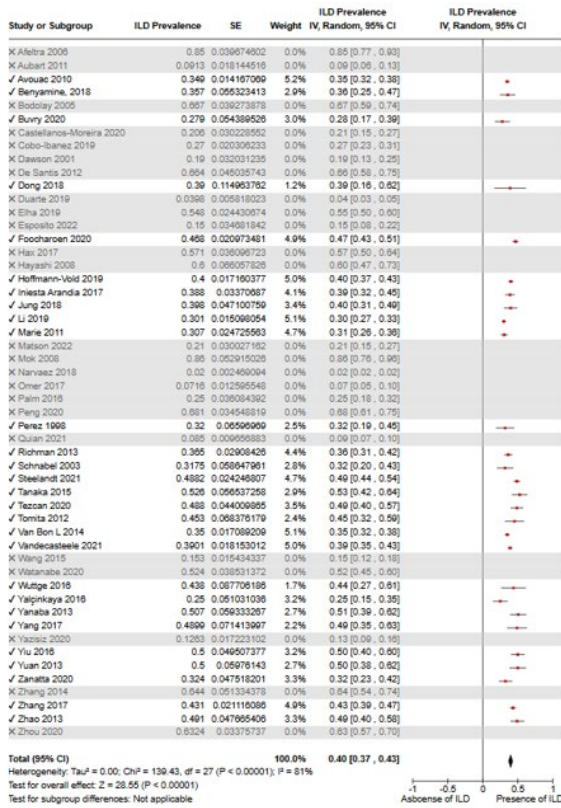


Figure E12. Prevalence of ILA/ILD among patients with Rheumatoid Arthritis

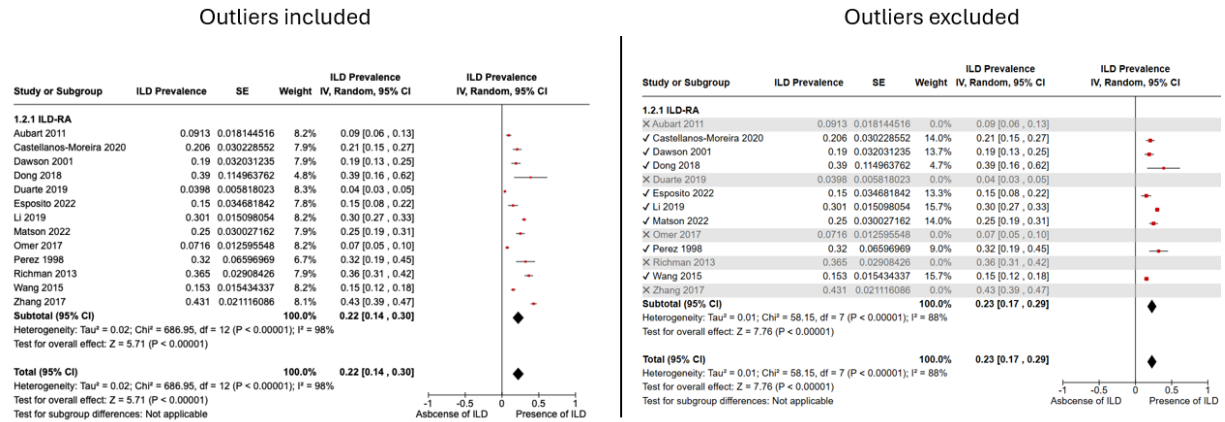


Figure E13. Prevalence of ILA/ILD among patients with Systemic Sclerosis

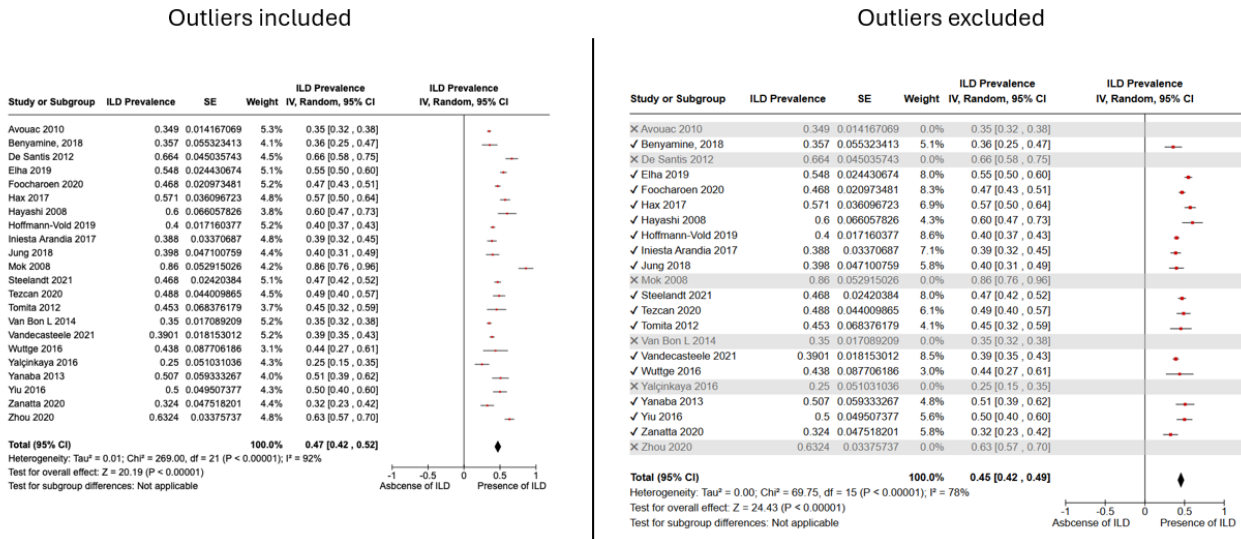


Figure E14. Prevalence of ILA/ILD among patients with Sjogren's Syndrome

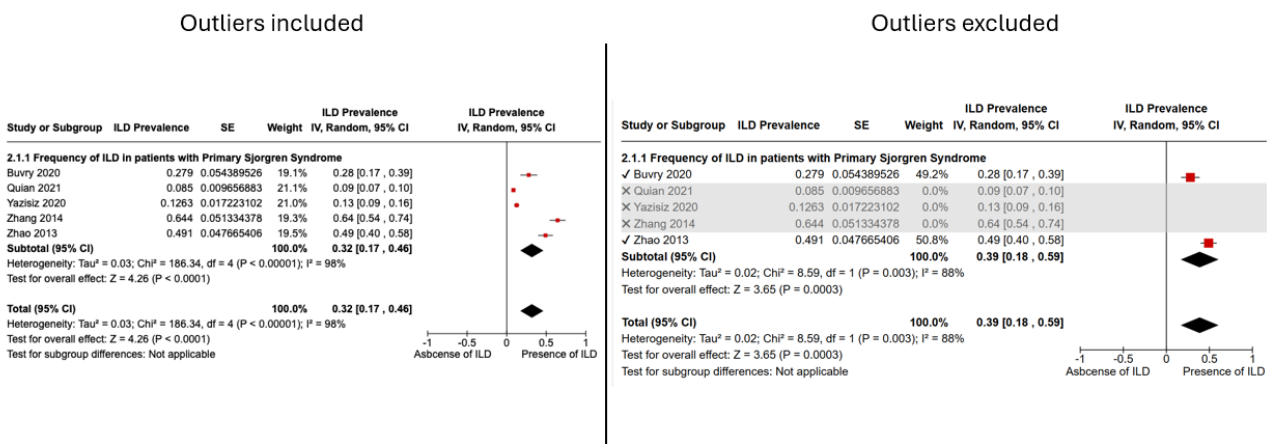
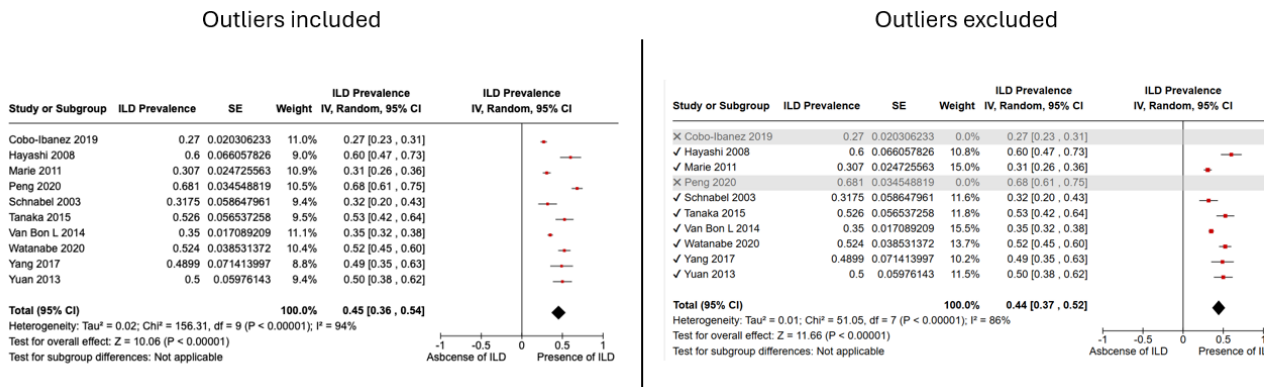


Figure E15. Prevalence of ILA/ILD among patients with Inflammatory Myositis



QUESTION 3: SHOULD ADULTS WITH A FIRST-DEGREE RELATIVE WITH PULMONARY FIBROSIS UNDERGO CHEST CT SCAN SCREENING TO IDENTIFY ILA/ILD?

Figure E16. Flow of information diagram

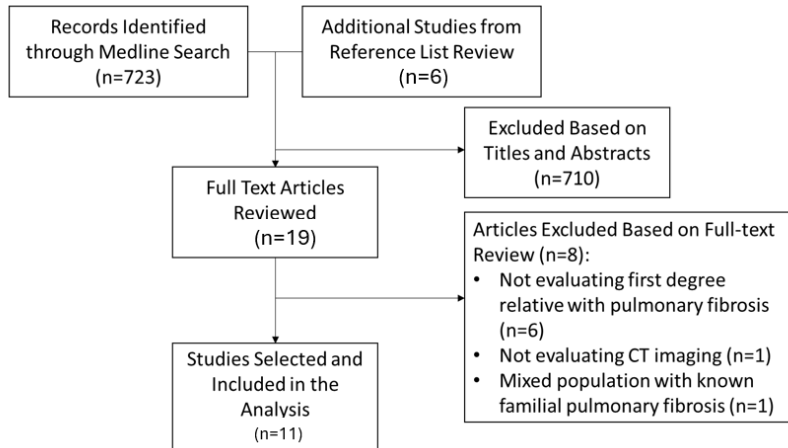


Table E6. Selected studies

Study	Participants	Size	Intervention	Analysis
Steele 2005	Web recruitment with 3 assessment sites: National Jewish Medical and Research Center, Vanderbilt University, Duke University Medical Center	722 first-degree relatives	HRCT	Prevalence of ILA/ILD Between group (ILA/ILD vs no ILA/ILD) comparison of mortality Adjusted analyses for associated factors of ILA/ILD
Rosas 2007	Clinical Center, National Institutes of Health, Bethesda	164 first-degree relatives	HRCT	Prevalence of ILA, ILD, and ILA/ILD Between group (ILA vs no ILA, ILD vs no ILD) comparison for associated factors of ILA and ILD
Kropski 2015	Vanderbilt Familial Interstitial Pneumonia registry	75 first-degree relatives	Single prone HRCT	Prevalence of ILA Unadjusted analyses for associated factors of ILA
Salisbury 2020		336 first-degree relatives	HRCT	Prevalence of ILA and ILA progression Between group (ILA vs no ILA) comparison of CT imaging progression Adjusted analyses for associated factors of ILA Between group (ILA vs no ILA) comparison for associated factors of ILA progression
Mathai 2019	National Jewish Hospital and Vanderbilt University databases of Familial Interstitial Pneumonia	494 first-degree relatives	HRCT	Prevalence of ILA and fibrotic ILA Between group (ILA vs no ILA) comparison and adjusted analyses for associated factors of ILA
Steele 2023		296 first-degree relatives	HRCT	Prevalence of ILA and ILA progression Incidence of ILA Between group (ILA vs no ILA) comparison and unadjusted analyses of ILA for mortality Between group (ILA/ILD vs no ILA/ILD) comparison of respiratory symptom progression

Aburto 2021	Galdakao University Hospital	92 first-degree relatives (sporadic IPF)	HRCT	Prevalence of ILA, ILD, and ILA/ILD Prediction model for ILA/ILD
Hunninghake 2020	Clinical Genetics and Screening for Pulmonary Fibrosis	105 first-degree relatives (46 familial PF, 59 sporadic IPF)	Single prone volumetric thoracic chest CT at full inspiration	Prevalence of ILA, ILD, and ILA/ILD Between group (ILA vs no ILA, ILD vs no ILD) comparison and adjusted analyses for associated factors of ILA and ILD
Rose 2023		73 first-degree relatives		Prevalence of ILA and ILA progression Incidence of ILA Between group (ILA vs no ILA) comparison of lung function progression Between group (ILA vs no ILA) comparison for associated factors of ILA progression
Lucas 2023	Families identified from Australian IPF Registry	15 first-degree relatives (Familial PF)	HRCT	Prevalence of ILA/ILD
McGroder 2023	Columbia University	98 first-degree relatives (47 familial PF, 51 sporadic PF [21 IPF])	HRCT	Prevalence of ILA Between group (ILA vs no ILA) comparison and adjusted analyses for associated factors of ILA

Figure E17. Prevalence of ILA/ILD among first-degree relatives of patients with familial pulmonary fibrosis

ILA definition

Fleischner Society criteria

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

Absence of symptoms or ILD history with CT changes

† Reported ILA only

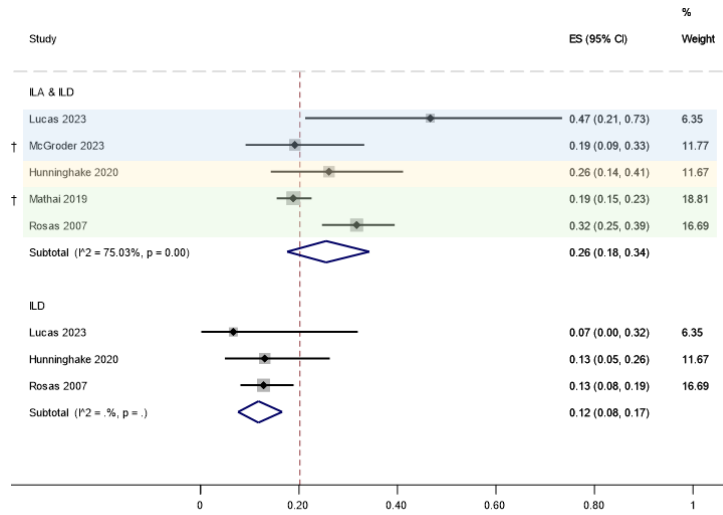


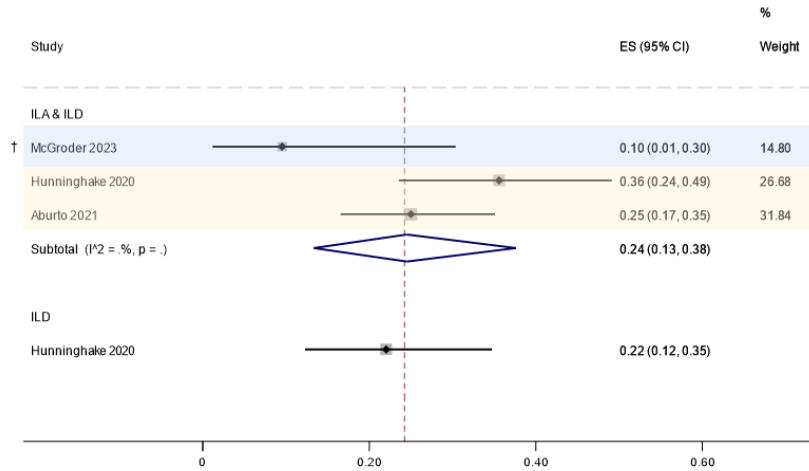
Figure E18. Prevalence of ILA/ILD among first-degree relatives of patients with IPF and no other known family members with ILD

ILA definition

Fleischner Society criteria

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

† Reported ILA only



QUESTION 4: SHOULD ADULTS WITH A FIRST-DEGREE RELATIVE WITH PULMONARY FIBROSIS UNDERGO MUC5B TESTING TO IDENTIFY ILA/ILD?

Figure E19. Flow of information diagram

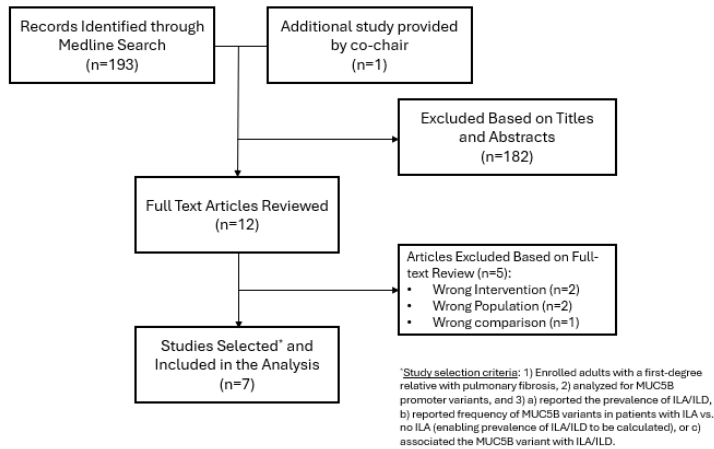


Table E7. Selected studies

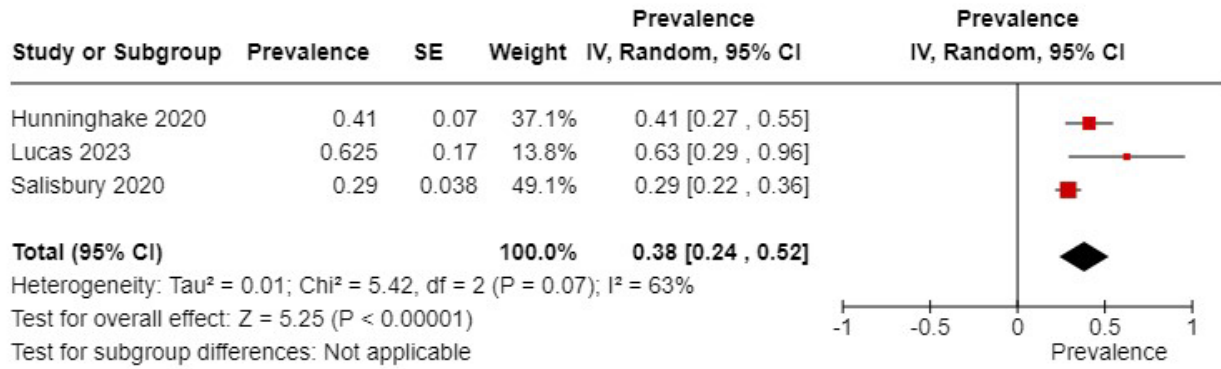
Study	Cohort	Size	Age	Follow-up	Intervention	Analyses
ILA definition: Used the Fleischner Society definition- non-dependent abnormalities, including ground glass or reticular abnormalities, lung distortion, traction bronchiectasis, honeycombing, and non-emphysematous cysts involving at least 5% of a lung zone.						
Hunninghake 2020	Clinical Genetics and Screening for Pulmonary Fibrosis Study (CGS-PF)	With ILAs: 33 No ILAs: 72 With ILD: 19 No ILD: 86	With ILAs: Median 61, IQR 56-67 No ILAs: Median 58, IQR 52-63 With ILD: Median 61, IQR 56-68 No ILD: Median 58, IQR 52-63	2 years	PCR-based detection of the MUC5B promoter minor allele, rs35705950.	Between group comparisons of MUC5B minor allele frequency (ILA vs no ILA, and ILD vs no ILD) Adjusted analysis associating the minor allele MUC5B with the presence of ILAs and ILD.
Lucas 2023	Australian IPF registry	With ILA: 7 With ILD: 22 No ILA or ILD: 8	With ILA: Median 71.6, IQR 56-88 With ILD: Median 69, IQR 49-83 No ILA/ILD: Med 60.8, IQR 47-75	Not stated	PCR-based detection of the MUC5B promoter variant, rs35705950.	Between group comparisons of MUC5B minor allele frequency (ILA vs ILD vs no ILA/ILD)
Rose 2023	Clinical Genetics and Screening for Pulmonary Fibrosis Study (CGS-PF)	With ILA: 22 No ILA: 51	With ILAs: Median 59, IQR 56-65 No ILAs: Median 58, IQR 53-63	2 years	PCR-based detection of the MUC5B promoter variant, rs35705950.	Between group comparisons of MUC5B minor allele frequency (ILA vs no ILA)
McGroder* 2023	Columbia University	With ILA: 13 No ILA: 85	With ILAs: Mean 55.7, SD 10.9 No ILAs: Mean 50.8, SD 7.4	Not stated	PCR-based detection of the MUC5B promoter variant, rs35705950.	Between group comparisons of MUC5B minor allele frequency (ILA vs no ILA) Adjusted analysis associating the minor allele MUC5B with the presence of ILAs.

*McGroder was not included in the following analyses because it did not report prevalence or data from which prevalence could be calculated. However, it demonstrated that the MUC5B promoter variant is associated with ILAs (OR 3.00, 95% CI, 1.08 to 8.39, p=0.03).

ILA definition: 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.						
Salisbury 2020	Vanderbilt University FIP registry	With ILA: 77 No ILA: 259	With ILAs: Mean 58.8, SD 10 No ILAs: Mean 51.6, SD 9.2	5 years	PCR-based detection of the MUC5B promoter variant, rs35705950.	Between group comparisons of MUC5B minor allele frequency (ILA vs no ILA) Between group comparisons of MUC5B minor allele frequency (progressive vs not progressive)
ILA definition: Probable = reticular abnormality, but with traction bronchiectasis that was mild or questionable. Definite = the presence of reticular abnormality with traction bronchiectasis, with or without honeycombing.						
Mathai* 2019	National Jewish Health and Vanderbilt University FIP registries	With ILA: 77 No ILA: 417	All: Mean 57 years, SD 9.6 With ILAs: Mean 65.9, SD 10.1 No ILAs: Mean 55.8, SD 18.7	Not stated	PCR-based detection of the MUC5B promoter variant, rs35705950.	Adjusted analysis associating the minor allele MUC5B with the presence of ILAs and ILD.
Steele* 2023	National Jewish Health and Vanderbilt University FIP registries	With ILA: 44 No ILA: 252	All: Median 57-58 years, IQR 52-66	Median 3.9 years (IQR 3.5-4.4)	PCR-based detection of the MUC5B promoter variant, rs35705950.	Association of the MUC5B minor allele with incident ILAs

*Mathai and Steele were not included in the following analyses because they did not report prevalence or data from which prevalence could be calculated. However, both demonstrated that the MUC5B promoter variant is associated with ILAs: Mathai (OR 2.14, 95% CI 1.0-4.63, p = 0.05) and Steele (OR 1.5, 95% CI 0.82-2.76, p > 0.05).

Figure E20. Prevalence of ILA/ILD among adults with a first-degree relative with pulmonary fibrosis who have the MUC5B promoter variant (rs35705950)



*Rose 2023 was removed because the cohort overlaps with Hunninghake 2020.

Figure E21. Sensitivity and specificity of the MUC5B promoter variant (rs35705950) in predicting ILA/ILD in adults with a first-degree relative with pulmonary fibrosis

	ILA/ILD present	ILA/ILD absent	
MUC5B promoter variant	Hunninghake 2020 – 19 Rose 2023 – 14 (don't count because overlap with Hunninghake 2020) Lucas 2023 – 5 Salisbury 2020 – 41 ----- Total 65	Hunninghake 2020 – 27 Rose 2023 – 21 (don't count because overlap with Hunninghake 2020) Lucas 2023 – 3 Salisbury 2020 – 101 ----- Total 131	196
MUC5B wild type	Hunninghake 2020 – 14 Rose 2023 – 8 (don't count because overlap with Hunninghake 2020) Lucas 2023 – 2 Salisbury 2020 – 36 ----- Total 52	Hunninghake 2020 – 43 Rose 2023 – 30 (don't count because overlap with Hunninghake 2020) Lucas 2023 – 5 Salisbury 2020 – 158 ----- Total 206	258
	117	337	454

Sensitivity = 56%, Specificity 60%

**QUESTION 5: SHOULD ADULTS WITH A FIRST-DEGREE RELATIVE WITH PULMONARY FIBROSIS UNDERGO
TELOMERE LENGTH MEASUREMENT TO IDENTIFY ILA/ILD?**

Figure E22. Flow of information diagram

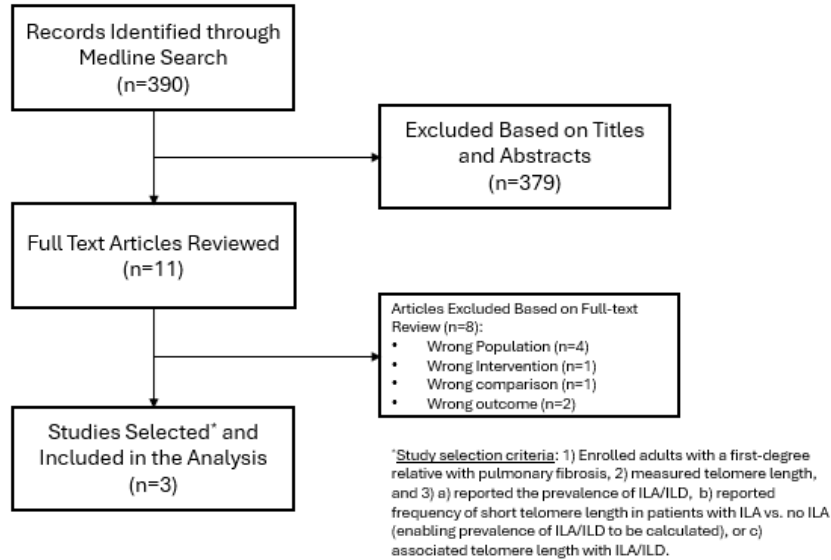


Table E8. Selected studies

Study	Cohort	Size	Age	Follow-up	Intervention	Analysis
ILA definition: Used the Fleischner Society definition- 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.						
Hunninghake 2020	Clinical Genetics and Screening for Pulmonary Fibrosis Study (CGS-PF)	With ILAs: 33 No ILAs: 72 With ILD: 19 No ILD: 86	With ILAs: Median 61, IQR 56-67 No ILAs: Median 58, IQR 52-63 With ILD: Median 61, IQR 56-68 No ILD: Median 58, IQR 52-63	2 years	Telomere length measurement	Between group comparisons of frequency of telomere length <10 th percentile for age (ILA vs no ILA, and ILD vs no ILD) Adjusted analysis associating telomere length <10 th percentile for age with the presence of ILAs and ILD
Rose 2023	Clinical Genetics and Screening for Pulmonary Fibrosis Study (CGS-PF)	With ILA at 0 or 2 yr.: 22 No ILA at 0 or 2 yr.: 51	With ILAs: Median 59, IQR 56-65 No ILAs: Median 58, IQR 53-63	2 years	Telomere length measurement	Between group comparisons of frequency of telomere length <10 th percentile for age (ILA vs no ILA)
ILA definition: 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.						
Salisbury* 2020	Vanderbilt University FIP registry	With ILA: 77 No ILA: 259	With ILAs: Mean 58.8, SD 10 No ILAs: Mean 51.6, SD 9.2	5 years	Telomere restriction fragment length measurement	Between group comparisons of telomere restriction fragment length (ILA vs no ILA) Between group comparisons of telomere restriction fragment length (progressive vs not progressive) Adjusted analysis associating telomere restriction fragment length with disease progression

*Salisbury not included in the following analyses because it reported telomere restriction fragment length, whereas the other studies reported telomere length <10th percentile for age. However, Salisbury demonstrated the telomere restriction fragment length is inversely associated with the risk of ILAs (OR 0.70 per 1-kb increase, 95% CI 0.51-0.97, p=0.03).

QUESTION 6: SHOULD PATIENTS WITH ILA UNDERGO BASELINE SYMPTOM ASSESSMENT?

Figure E23. Flow of information diagram

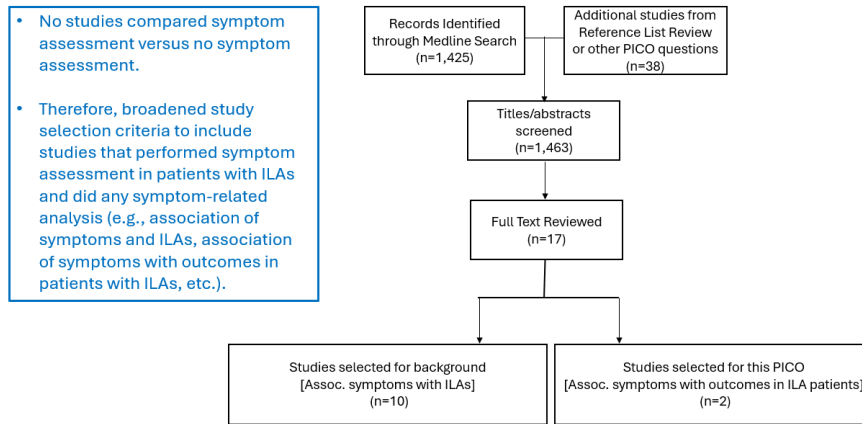


Table E9. Selected studies

Study	Participants	Size	ILA definition	Intervention	Analysis
Balata 2023	Manchester UK Lung Health Check	No ILAs = 1330 ILAs = 54	Incidental finding of nondependent abnormalities involving ≥ 5% of a lung zone	Breathless Visual Analogue Scale (VAS)	Adjusted multivariate analysis of breathless VAS score and mortality in patients with ILAs.
Salisbury 2020	Vanderbilt University database of Familial Interstitial Pneumonia	77 with ILAs 259 without ILAs.	Presence of specific interstitial features, including ground-glass opacities, intralobular reticular opacities, irregular thickening of interlobular septa, traction bronchiectasis, traction bronchiolectasis, and honeycombing.	Questionnaire developed for study (Y/N/No answer): 1) SOB hurrying on level or walking up slight hill? 2) Walk slower than others bc breathlessness? 3) Ever stop to catch your breath? 4) Ever stop to catch your breath after 100 yds? 5) Too breathless to leave house, or dressing?	Across group (no progression vs mild progression vs extensive progression) analysis of annual symptom change and imaging progression

Table E10. Baseline symptom assessment in ILA effect-direction table

Author	Year	Participants	Measurement	Effect	Result
Association of baseline symptoms (cough and dyspnea) with mortality in patients with ILAs					
Balata	2023	Adults in a lung health study.	Adjusted multivariate analysis of breathless VAS score and mortality in patients with ILAs.	▲	Breathless VAS score is associated with mortality in patients with ILAs: HR 1.1, 95% CI 1.0–1.1; p=0.003
Association of baseline dyspnea with imaging progression in patients with ILAs					
Salisbury	2020	Adults with family history of ILD.	Median (IQR) dyspnea score (range 0-5).	◀▶	Baseline dyspnea score the same 0 (0-1) among those with stable ILAs, progressive ILAs, and progressed to extensive ILAs or ILD, although dyspnea increased over time with progression.

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

Green = adjusted analysis; Amber = unadjusted analysis; Black = between group analysis.

QUESTION 7: SHOULD PATIENTS WITH ILA UNDERGO BASELINE PULMONARY FUNCTION TESTING?

Figure E24. Flow of information diagram

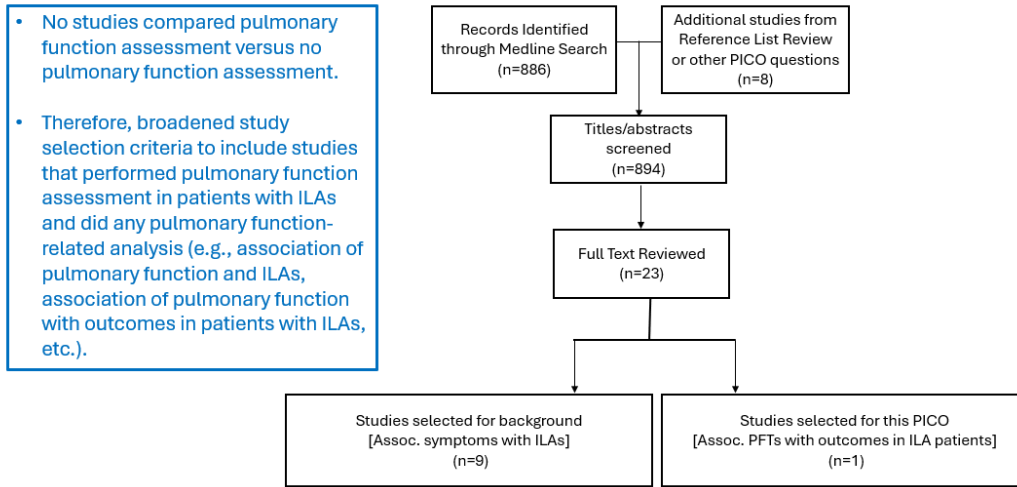


Table E11. Baseline pulmonary function testing in ILA effect-direction table

Study	Participants	Size	Measurement	Effect	Result
Association of forced vital capacity (FVC) with imaging progression in patients with ILAs					
Araki 2016	Framingham Heart Study	No ILAs = 660 Non-progressive ILAs = 37 Progressive ILAs = 118	FVC (ml) in progressive ILAs vs. non-progressive ILAs.	◄►	Baseline FVC associated with progression of ILAs: OR 1.0 (0.93-1.0), p = 0.9

▲ = positive association ▼ = negative association ◄► = no effect or mixed effect

Green = adjusted analysis; Amber = unadjusted analysis; Black = between group analysis.

QUESTION 8: SHOULD PATIENTS WITH ILA UNDERGO BASELINE LUNG SAMPLING FOR HISTOPATHOLOGICAL ANALYSIS?

Figure E25. Flow of information diagram

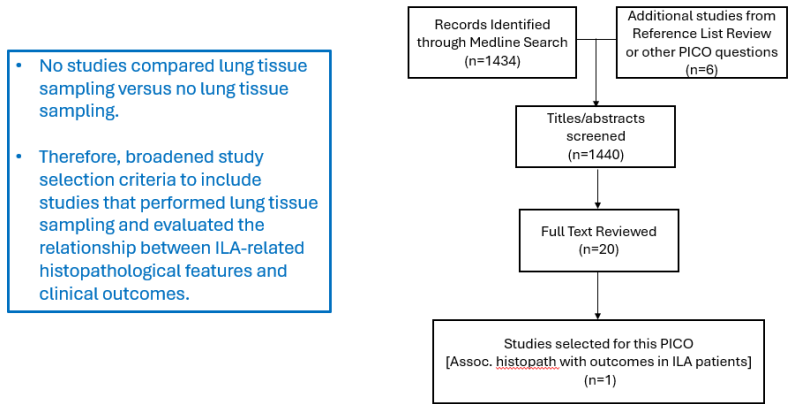


Table E12. Selected studies

Study	Participants	Size	ILA definition	Intervention	Analysis
Miller 2018	Patients who had undergone lung nodule resection, had a chest CT scan within 3 months before surgery, and had no history of ILD	26 with ILAs, 141 indeterminate ILAs, 257 without ILAs	Nondependent changes affecting more than 5% of any lung zone including nondependent ground-glass or reticular abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, and traction bronchiectasis	-Histopathology	-Disease progression -Prevalence of ILAs

Table E13. Baseline lung sampling in ILA effect-direction table

Study	Participants	Length of follow-up	Comparison	Radiographic progression	Effect
Miller 2018	Patients who had undergone lung nodule resection, had a chest CT scan within 3 months before surgery, and had no history of ILD	01/2001-07/2015	Definition of ILAs: Nondependent changes affecting more than 5% of any lung zone including nondependent ground-glass or reticular abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, and traction bronchiectasis	Subpleural fibrosis (OR, 2.1; 95% CI, 1.3–3.1; P = 0.0009), Fibroblastic foci (OR, 4.2; 95% CI, 2.2–8.1; P, 0.0001), Atypical adenomatous hyperplasia (OR, 1.7; 95% CI, 1.1–2.6; P = 0.03)	▲

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

Green = adjusted analysis; Amber = unadjusted analysis; Black = between group analysis.

QUESTION 9: SHOULD PATIENTS WITH ILA UNDERGO BASELINE MUC5B TESTING?

Figure E26. Flow of information diagram

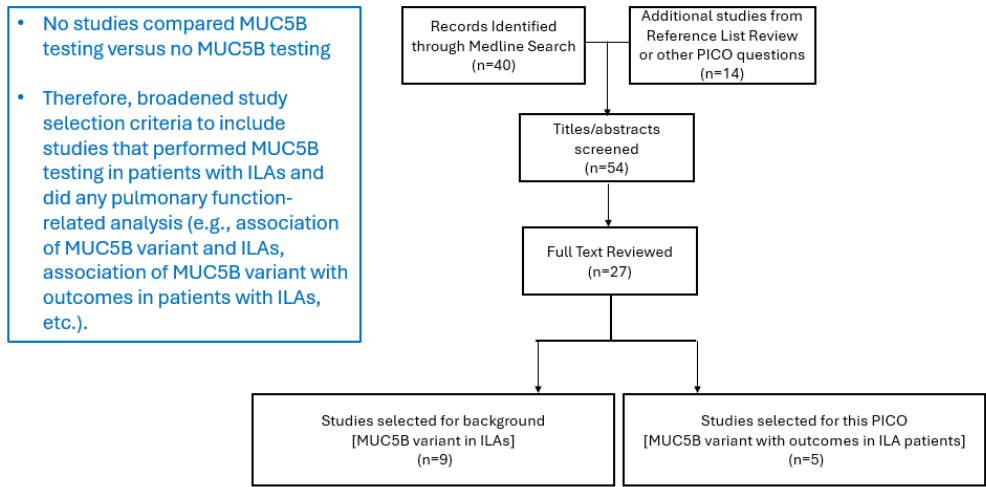


Table E14. Selected studies

Study	Participants	Size	ILA definition	Intervention	Analysis
Araki 2016	Framingham Heart Study	155 with ILA, 660 without ILA	Nondependent changes affecting >5% of any lung zone. These abnormalities included ground glass, reticular abnormalities, diffuse centrilobular nodularity, non-emphysematous cysts, traction bronchiectasis or honeycombing	MUC5B promoter polymorphism genotyping (rs35705950)	Adjusted analyses of MUC5B minor allele and CT imaging progression Between group (ILA with and without progression vs no ILA) comparisons of prevalence of MUC5B minor allele
Putman 2017	COPDGene, AGES-Reykjavik	COPDGene (non-Hispanic white): 485 with ILA, 3667 without ILA COPDGene (African-American): 223 with ILA, 1728 without ILA AGES-Reykjavik: 377 with ILA, 3209 without ILA	Nondependent changes affecting >5% of any lung zone. These abnormalities included ground glass, reticular abnormalities, diffuse centrilobular nodularity, non-emphysematous cysts, traction bronchiectasis or honeycombing	MUC5B promoter polymorphism genotyping (rs35705950)	Unadjusted analysis of MUC5B minor allele with mortality Between group (ILA vs no ILA) comparisons of prevalence of MUC5B minor allele Adjusted analyses of MUC5B minor allele with ILA and ILA subtypes
Putman 2019	AGES-Reykjavik	327 with ILA, 1777 without ILA	Nondependent changes affecting >5% of any lung zone. These abnormalities included ground glass, reticular abnormalities, diffuse centrilobular nodularity, non-emphysematous cysts, traction bronchiectasis or honeycombing	MUC5B promoter polymorphism genotyping (rs35705950)	Adjusted analyses of MUC5B minor allele with CT imaging progression Between group (ILA with and without progression vs no ILA) comparisons of prevalence of MUC5B minor allele
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	MUC5B promoter polymorphism genotyping (rs35705950)	Between group (ILA vs no ILA) comparisons of prevalence of MUC5B minor allele with CT imaging progression Prevalence of MUC5B minor allele in ILA and no ILA Adjusted analyses of MUC5B minor allele with ILA
Steele 2023	National Jewish Hospital and Vanderbilt University databases of Familial Interstitial Pneumonia	296 first-degree relatives	In addition to the definition used as described above, there were assessments by radiological core (based on HRCT) and clinical core (based on history and radiology consensus diagnosis for specific diagnosis)	MUC5B promoter polymorphism genotyping (rs35705950)	Unadjusted analyses of MUC5B minor allele with mortality and respiratory symptom progression Between group (ILA vs no ILA) comparisons of MUC5B minor allele frequency Unadjusted analyses of MUC5B minor allele with ILA

Table E15. Baseline MUC5B testing in ILA effect-direction table

Study	Study cohort	Participants	Mean age (SD), years	Follow-up	Comments	Mortality	Respiratory symptom progression	CT imaging progression
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: 4.8-9.8)	MUC5B promoter polymorphism: Minor allele	◀▶	HR 1.0, 95% CI 0.8-1.3; p=0.95	
	COPDGene	984 with ILA	Non-hispanic white: 64 (10) African American: 55 (8)	Median 5.4 years (IQR: 4.8-6.1)	Data for mortality evaluation of COPDGene only performed for the non-hispanic white cohort due to small numbers in the African American cohort			
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		OR 1.5, 95% CI 0.7-3.4; p=0.3	◀▶
		118 ILA with progression vs 80 no ILA	Progression: 65 (11) No ILA: 49 (10)		5-point scale of serial CT changes: - definite regression - probable regression - no change - probable progression - definite progression			
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 4.59-5.26)	MUC5B promoter polymorphism: Minor allele frequency		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)		5-point scale of serial CT changes: - definite regression - probable regression - no change - probable progression - definite progression			
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. Categorized as none, early/mild, or extensive								
Salisbury 2020	Vanderbilt FIF Registry	129 without extensive ILA at enrolment	Not provided Early/mild & extensive ILA: 59.9 (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

QUESTION 10: SHOULD PATIENTS WITH ILA UNDERGO BASELINE TELOMERE LENGTH MEASUREMENT?

Figure E27. Flow of information diagram

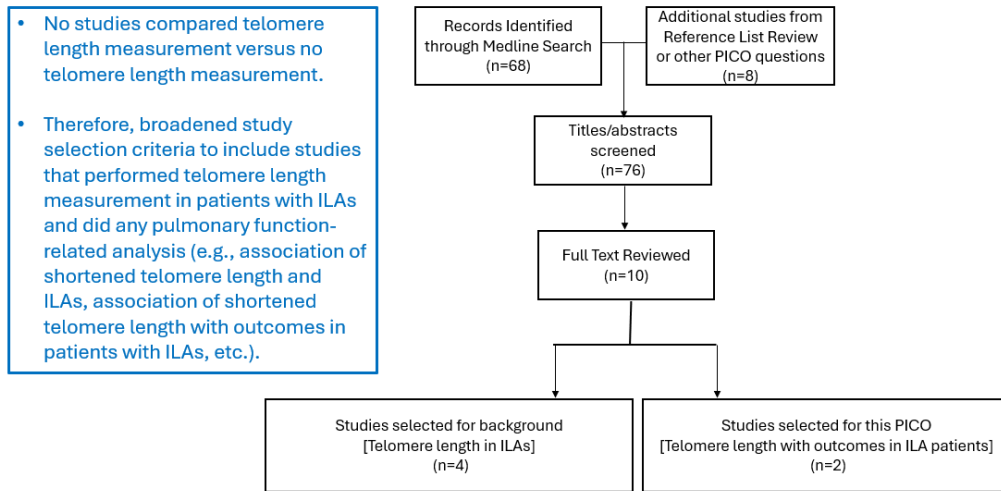


Table E16. Selected studies

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	<u>Fleischner</u> Society recommendations	COPDGene and AGES-Reykjavik: qPCR FHS: Southern blot	Unadjusted analysis of lowest quartile and lowest 10 th 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	Followup	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; Categorized 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)		▲ (with shorter telomere length)
						TLF 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)	
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							

QUESTION 11: SHOULD PATIENTS WITH ILA UNDERGO LONGITUDINAL FOLLOW-UP WITH SERIAL CHEST CT SCANS?

Figure E28. Flow of information diagram

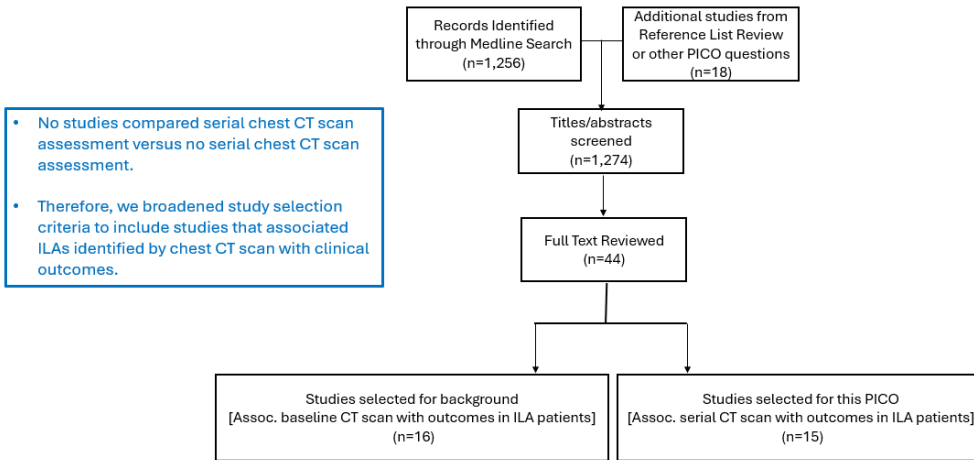
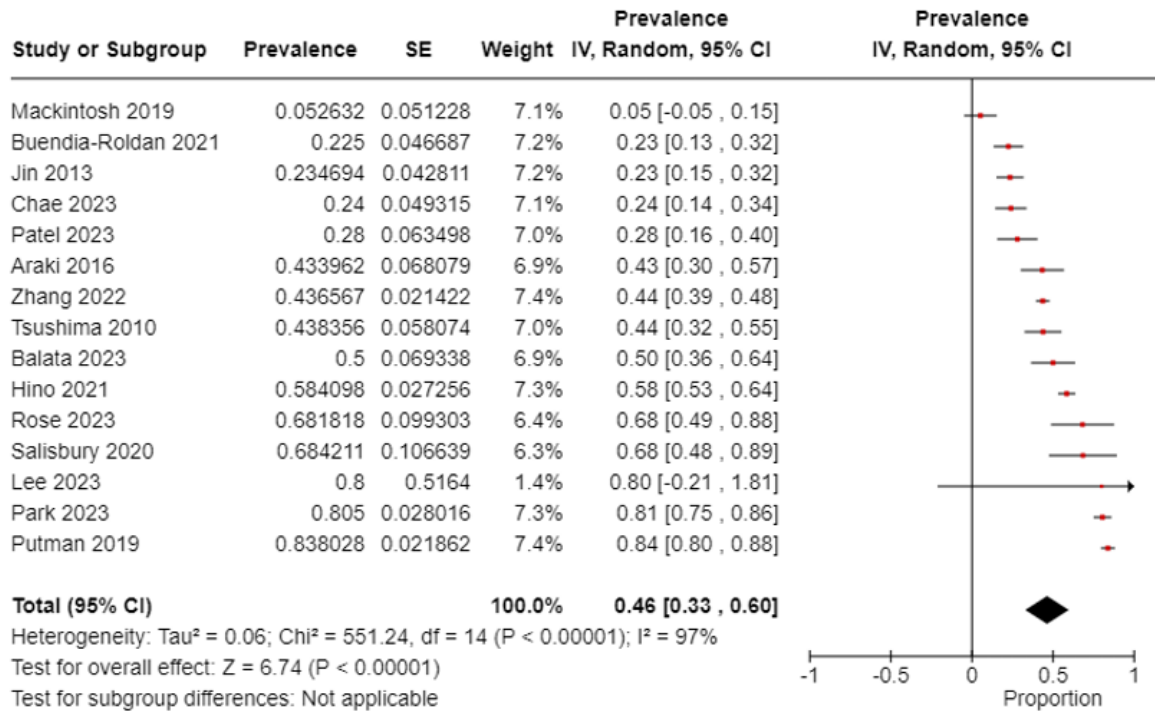


Table E18. Prevalence of imaging progression of ILA

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

Figure E29. Meta-analysis of prevalence of imaging progression of ILA

All studies



Outliers removed

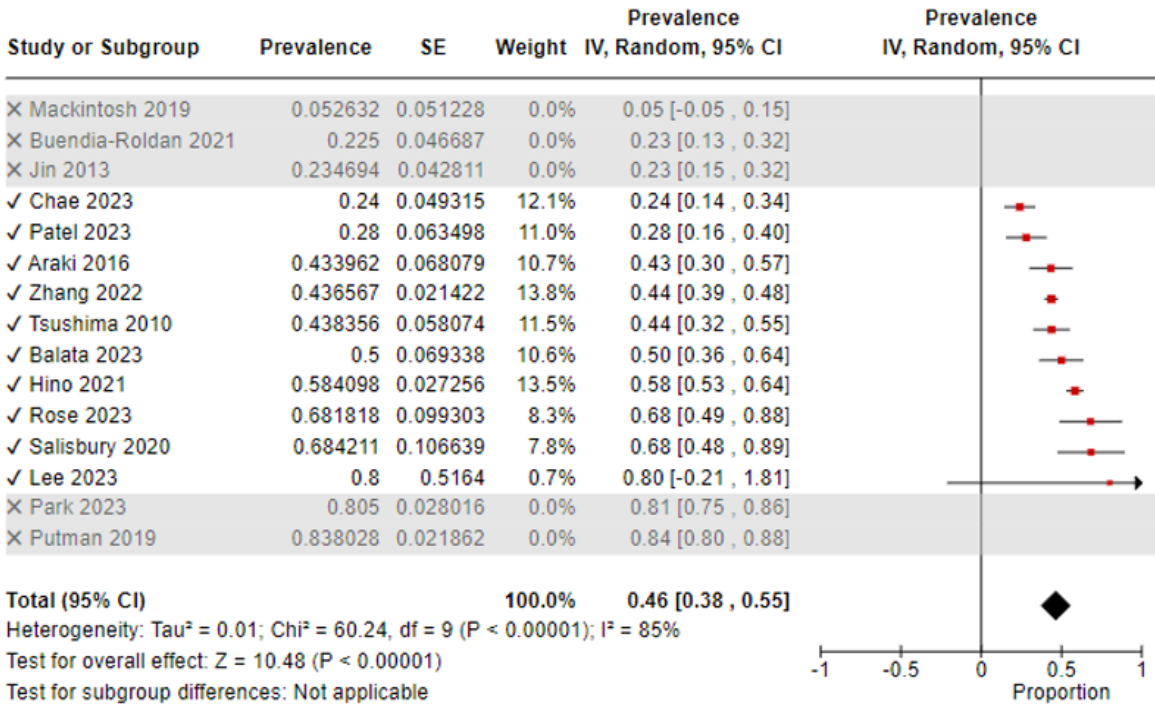


Table E19. Imaging progression (identified by serial chest CT scans) association with mortality effect-direction table

Author	Year	Participants	N	Follow-up	Measurement	Effect	Result
<i>ILAs progressive versus no ILAs (according to serial chest CT scanning)</i>							
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
<i>ILAs progressive versus stable ILAs (according to serial chest CT scanning)</i>							
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

Green = adjusted analysis; Amber = unadjusted analysis; Black = between group analysis.