Interstitial Lung Abnormalities a clinical point of view

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COI

- Speaker's fees from Boehringer Ingelheim, Roche, ERBE, PulmoniX

Interstitial Lung Abnormalities a clinical point of view

- ILA definition and prevalence

ILA definition, prevalence and relevance

Imaging abnormalities on chest CT in research participants without a clinical diagnosis of interstitial lung disease.

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

ILA are present in 7% of individuals undergoing lung cancer screening.

Hatabu et al, ILA Fleischner Position Paper, Lancet Respir Med 2020; 8: 726–37 ,
Putnam R et al, JAMA 2016

Review > Radiol Clin North Am. 2022 Nov;60(6):889-899. doi: 10.1016/j.rcl.2022.06.002. Epub 2022 Sep 3.

Interstitial Lung Abnormality-Why Should I Care and What Should I Do About It?

Andrea S Oh [1], David A Lynch [2]

Affiliations + expand

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Abstract

Interstitial lung abnormalities (ILAs) are specific computed tomography (CT) findings that are potentially compatible with interstitial lung disease (ILD) in patients without clinical suspicion for disease. ILAs are associated with adverse clinical outcomes including increased mortality, imaging progression and lung function decline, and increased lung injury risk with lung cancer therapies. It is expected that identification of ILAs will increase with implementation of lung cancer screening and diagnostic CT imaging for workup of other pathologies. As such, radiologists will play a critical role in the diagnosis and management of ILAs.

ILA definition, prevalence and relevance

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

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

Table: **Interstitial lung abnormalities across study populations**

Hatabu et al, ILA Fleischner Position Paper, Lancet Respir Med 2020; 8: 726–37

ILA mortality for respiratory causes

ILA are more likely to die of RESPIRATORY CAUSES (OR, 2.4 [95% CI, 1.7-3.4]; P < .001) WITH AN INCREASED RATE OF DEATH FROM PULMONARY FIBROSIS.

	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

Putman R et al, JAMA 2016

ILA definition:
When it's NOT ILA

It's not ILAs – clinical criteria for exclusion

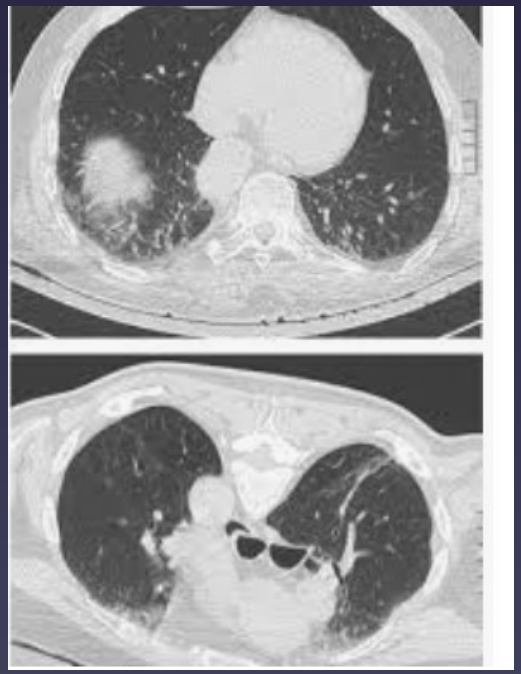
- Abnormalities identified during screening for ILD in high-risk groups (eg, those with rheumatoid arthritis, systemic sclerosis, or familial ILD), NOT INCIDENTAL

- Known ILD diagnosed as clinical-radiological-pathological entity based on current guidelines criteria.

- The term ILAs does not imply the absence of respiratory signs, symptoms, or functional impairment, but when these clinically significant findings are present, ILAs are likely to represent mild ILD rather than subclinical

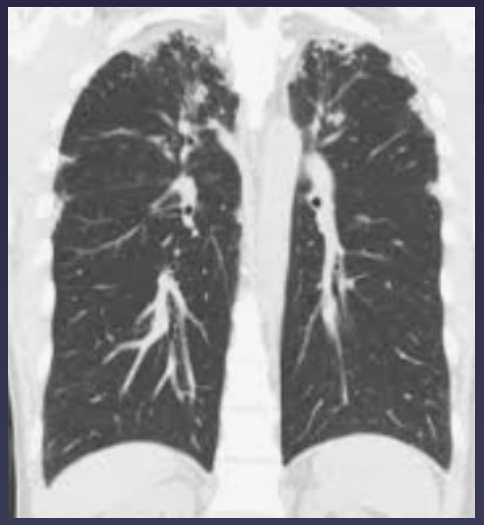
Hatabu et al. ILA Fleischner Position Paper. Lancet Respir Med 2020; 8: 726–37

It's not ILAs – radiologic criteria for exclusion

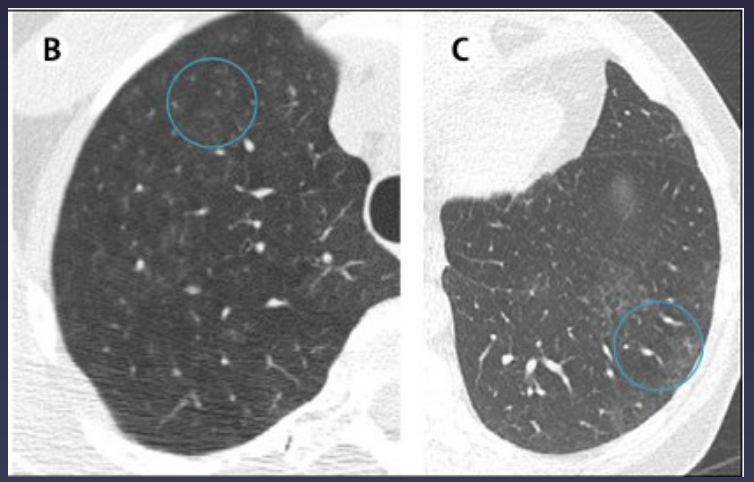


Lung dependent changes

Interstitial edema

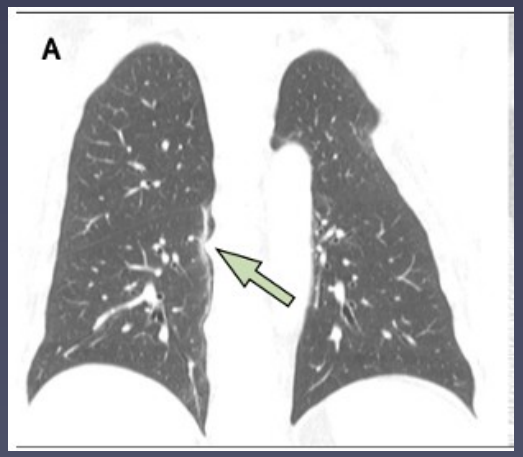


PPFE



Centrilobular nodularity in a heavy smoker.

Unilateral mild focal abnormality
Ggo
Tree in bud (aspiration)



Focal paraspinal fibrosis.

Hatabu et al, LRM 2020


The liquid borders of ILA

The boarders: ILA, early ILD and mild ILD

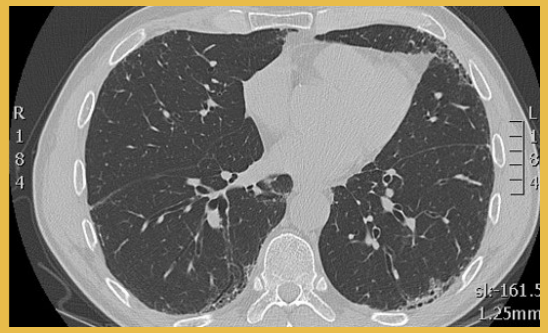
TABLE 1 Simplified definitions

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**	Individuals at risk for ILD	Clinical-radiological-pathological entity	Any ILD in asymptomatic patients with preserved lung function
	Subclinical ILD	Individuals NOT at risk for ILD		
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.

Tomassetti S et al, ERR 2022

ILA

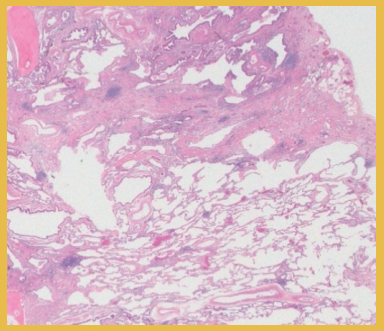


Incidental discovery
FVC 129%, DLco 82%
No symptoms

Tomassetti S et al, ERR 2022

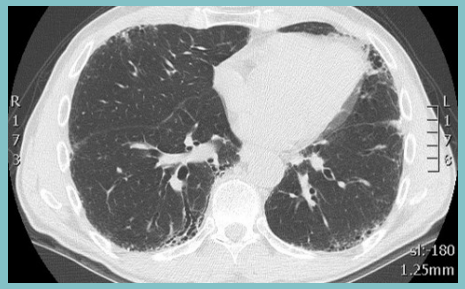
MDT diagnosis: Early IPF

UIP pattern on histology



baseline

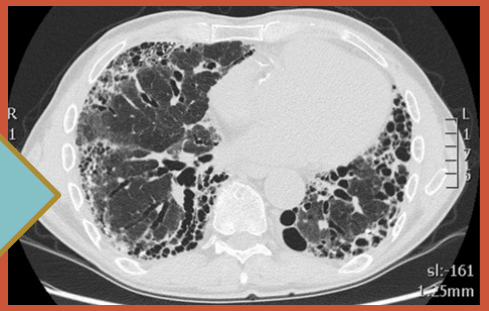
Mild IPF



FVC 122%, DLco 73%, asymptomatic

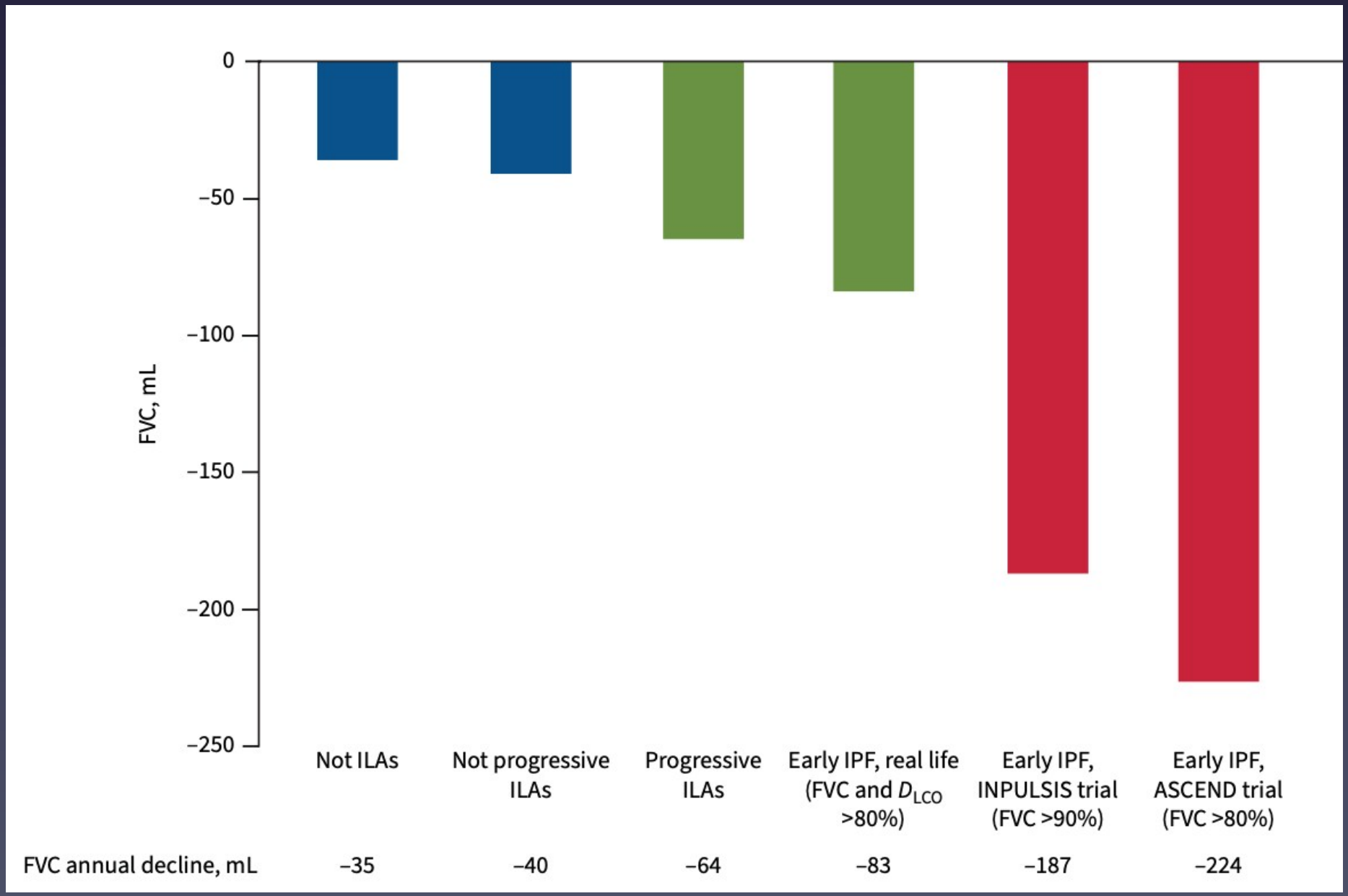
2 years of follow-up

Advanced IPF



FVC 60%, DLco 40&%, symptomatic

7 years of follow-up

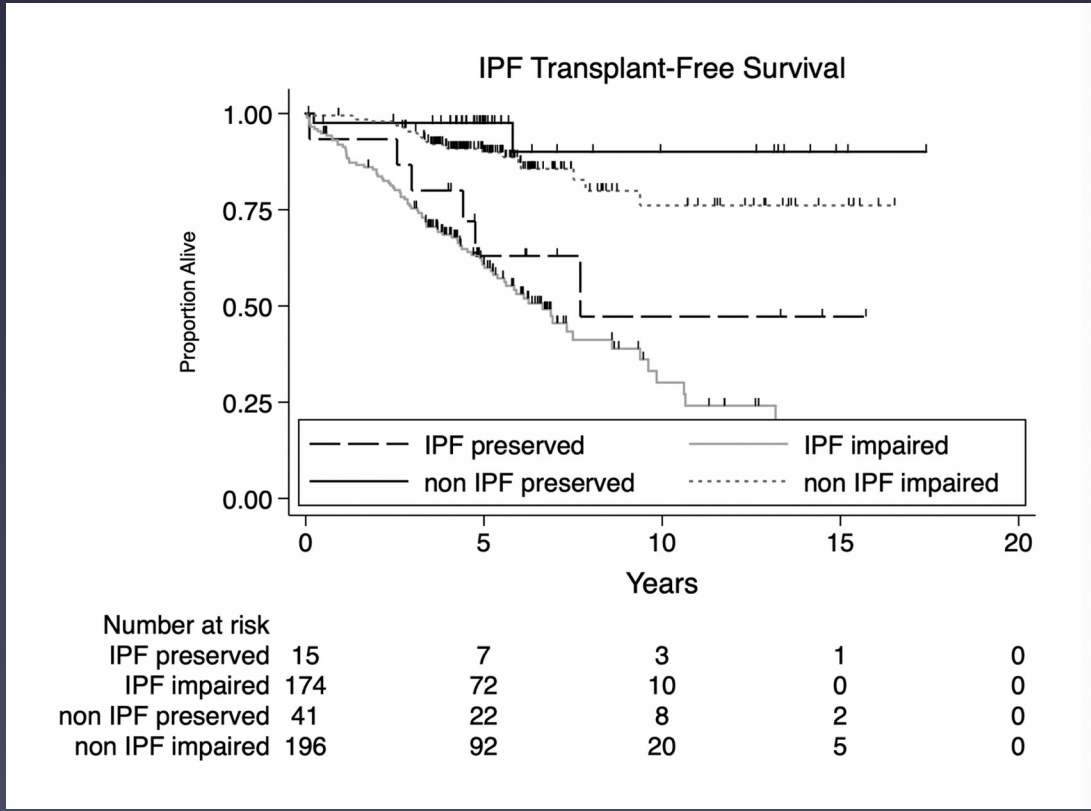


Tomassetti S et al, ERR 2022

Histologic UIP discriminates prognosis of f-ILDs with completely preserved lung function

Preserved LF:

- FVC and DLco >80%, no desat WT
- IPF defined MD and by UIP on TBLC
- NON-IPF included:
  - NSIP, N=68
  - CHP, N= 53
  - SR-ILD, N=42
  - Other fibr, N=74



S Tomassetti, V Poletti et al, unpublished data

ILA clinical features

Clinical features of ILA

Variable	Percent or Median/Means Where Appropriate and Noted						
	Research Subjects with ILA						
	MESA*	Nagano, Japan†	COPDGene‡	MILD§	FHS‖	NLST¶	Patients with IPF**
Demographic parameters							
Age, yr	—	62	64	60	70	62	66
Sex, female, %	—	26	50	14	52	28	41–49
History of smoking, current or former, %	—	70	100	100	62	100	60–72
Respiratory symptoms, %							
Chronic cough, yes	—	13	41	—	12	—	73–86
Chronic shortness of breath, yes	—	15	60	—	18	—	Present in most patients
Physical examination findings							
Fine crackles, %	—	26	—	—	—	—	Present in most patients
Pulmonary physiologic testing							
FVC % predicted	—	113–116	88	101	101	—	68–89
Total lung capacity % predicted	—	—	95	—	79	—	46–78
Diffusion capacity of carbon monoxide, % predicted	—		—	—	86	—	46–61
6-min walk distance, m	—	555–573	403	—	—	—	373–392

Putman RK, AJRCCM 2014

Novel insights on clinical features of ILAs

- ILA in a large health check-up population

(155,539 individuals undergoing low-dose chest CT scans during routine health check-up), 2.1% had ILA

- mean age was 46.1±14.0 years,
- 60.7% male,
- 32.3% smoking history,
- 27.2% comorbidities

Zhang et al, AJRCCM 2021

ILA prevalence increases with age

	Total ILA (N=3,300)
Age (years)	62.1±13.8
<40	113 (3.4)
40-49	543 (16.5)
50-59	855 (25.9)
60-69	712 (21.6)
≥70	1077 (32.6)

Zhang et al, AJRCCM 2021

hiatus ernia and ILA: pathogenetic links versus epiphenomenon of senescence

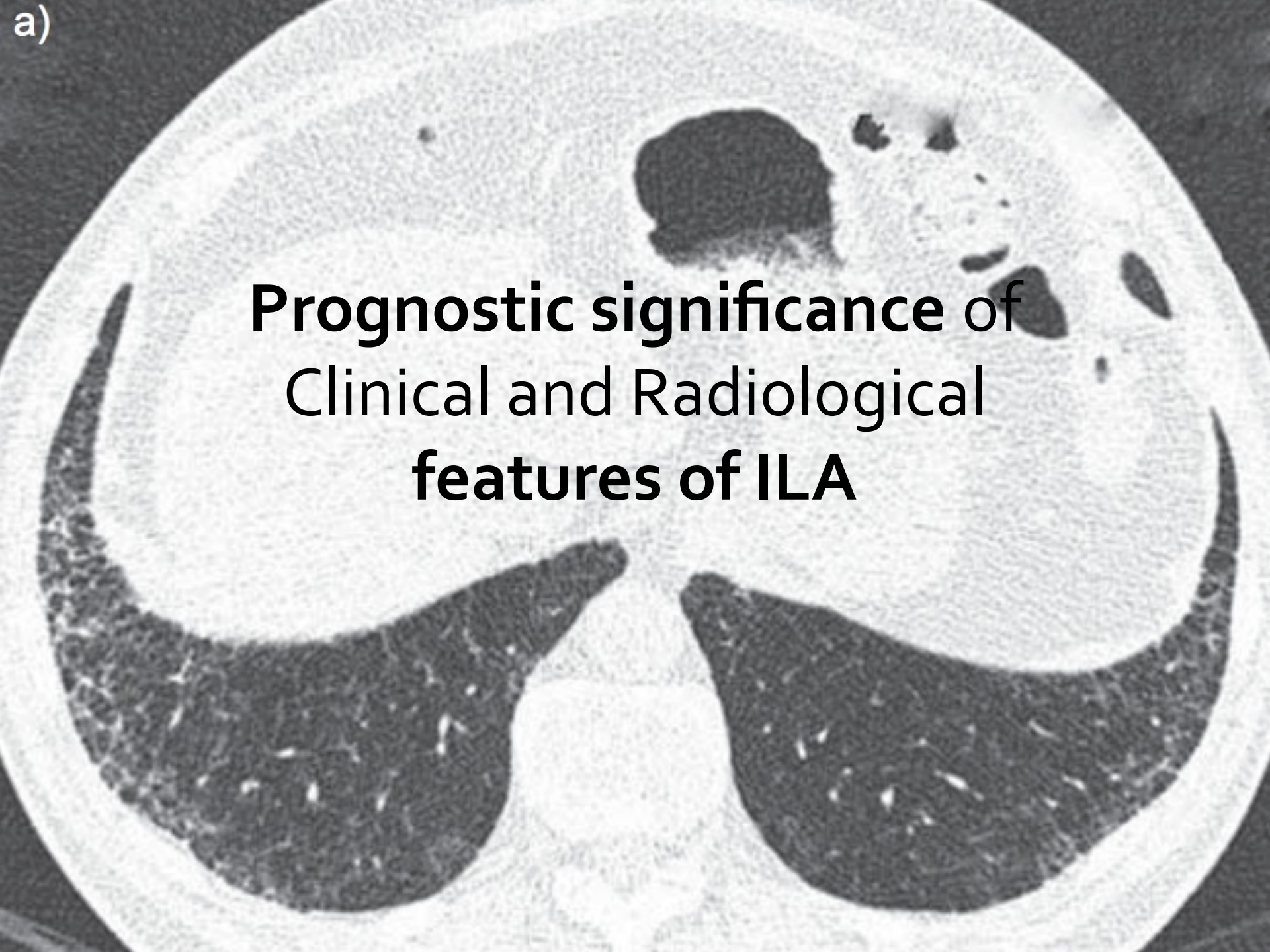
- AGES-Reykjavik study (5000individuals): hiatus hernia was not associated with presence or progression of ILA, but with increased mortality.*
- In contrast in the MESA study hiatus hernia was associated to ILA (OR 1.69) in participants <80 years (OR 1.78), and higher MMP-7 levels in smokers ^

TABLE 1 Association between MESA Exam 5 (2010–2012) hiatus hernia and interstitial lung abnormalities (ILA) from Exam 5 full-lung computed tomography scans (2010–2012) with covariate adjustment

Model	OR for ILA (95% CI)	p-value
Unadjusted	1.69 (1.18 to 2.41)	0.004
Additional adjustment		
Sex	1.66 (1.16 to 2.37)	0.006
Race/ethnicity	1.64 (1.14 to 2.35)	0.007
Smoking status and cigarette pack-years	1.66 (1.15 to 2.39)	0.006
Height and weight	1.56 (1.08 to 2.25)	0.02
Education attainment	1.55 (1.07 to 2.24)	0.02
Age	1.16 (0.79 to 1.69)	0.46

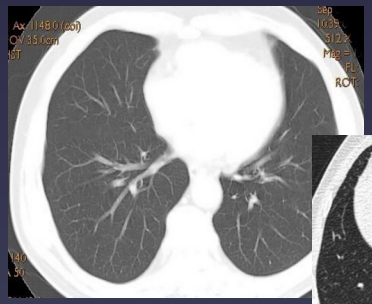
Each covariate adjustment is added to previous row's model.

George et al, ERJ 2023; ^Kim et al. ERJ 2023; *George et al, ERJ 2020

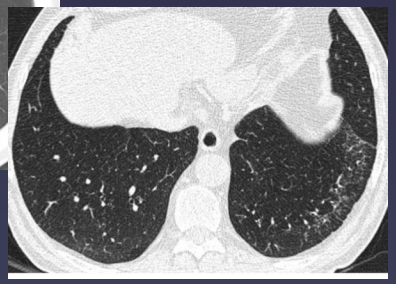


Prognostic significance of Clinical and Radiological **features of ILA**

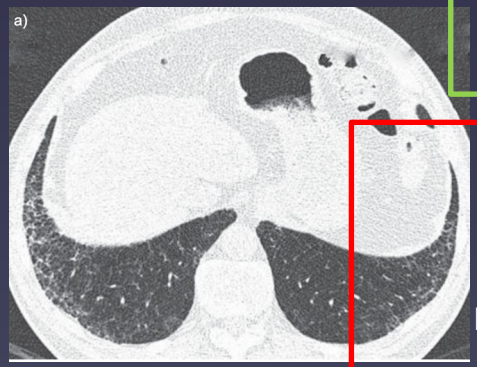
The spectrum of radiological abnormalities



NORMAL



INDETERMINATE (<5%)



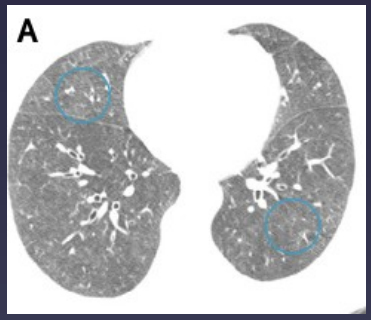
ILA (>5%)

HRCT concordant readings 57%-66%.
Discordant readings involve mainly indeterminate HRCTs 95%-98%.
Discrepancy in ILAs readings is rare (1%-5%).

ILA non fibrotic Kappa 0.3
ILA fibrotic Kappa 0.6
ILA UIP Kappa 1

ILA kappa 0.74
ILA subtypes 0.38

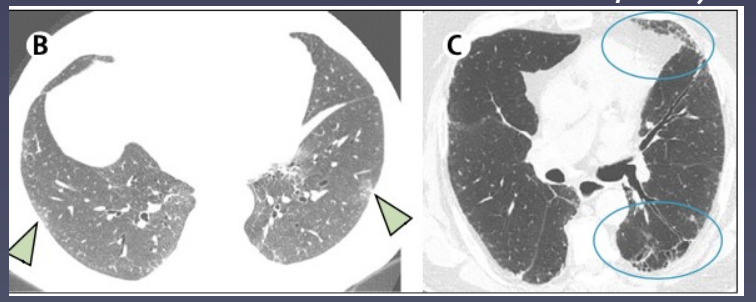
ILA non subpleural



ILA subpleural

48-95%
non fibrotic
(ggo/ret)

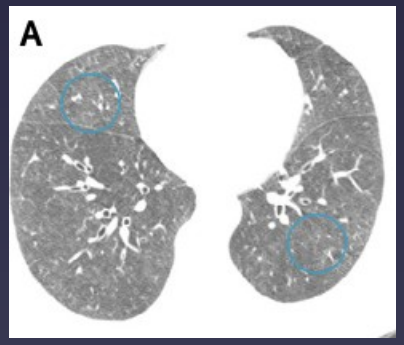
5-30%
fibrotic
(TB/arch distortion/hcc)



Putnam R et al, JAMA 2016;315:672–681; Hatabu et al, LRM 2020; Sverzellati et al, ERJ 2011, Buendian-Roldan...Selman, ERJ 2021; Kim EJR 2022

ILA prognostic subcategories

ILAs with a non-subpleural distribution are usually non-progressive and not associated with increased mortality.



ILA with centrilobular nodules

Progression Adjusted HR 0.2 (95% CI 0.1-0.5), p=0.0002

Mortality Adjusted HR 0.9 (95% CI 0.7-1.1), p 0.3

ILA subpleural

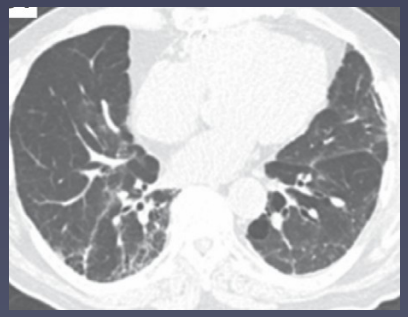
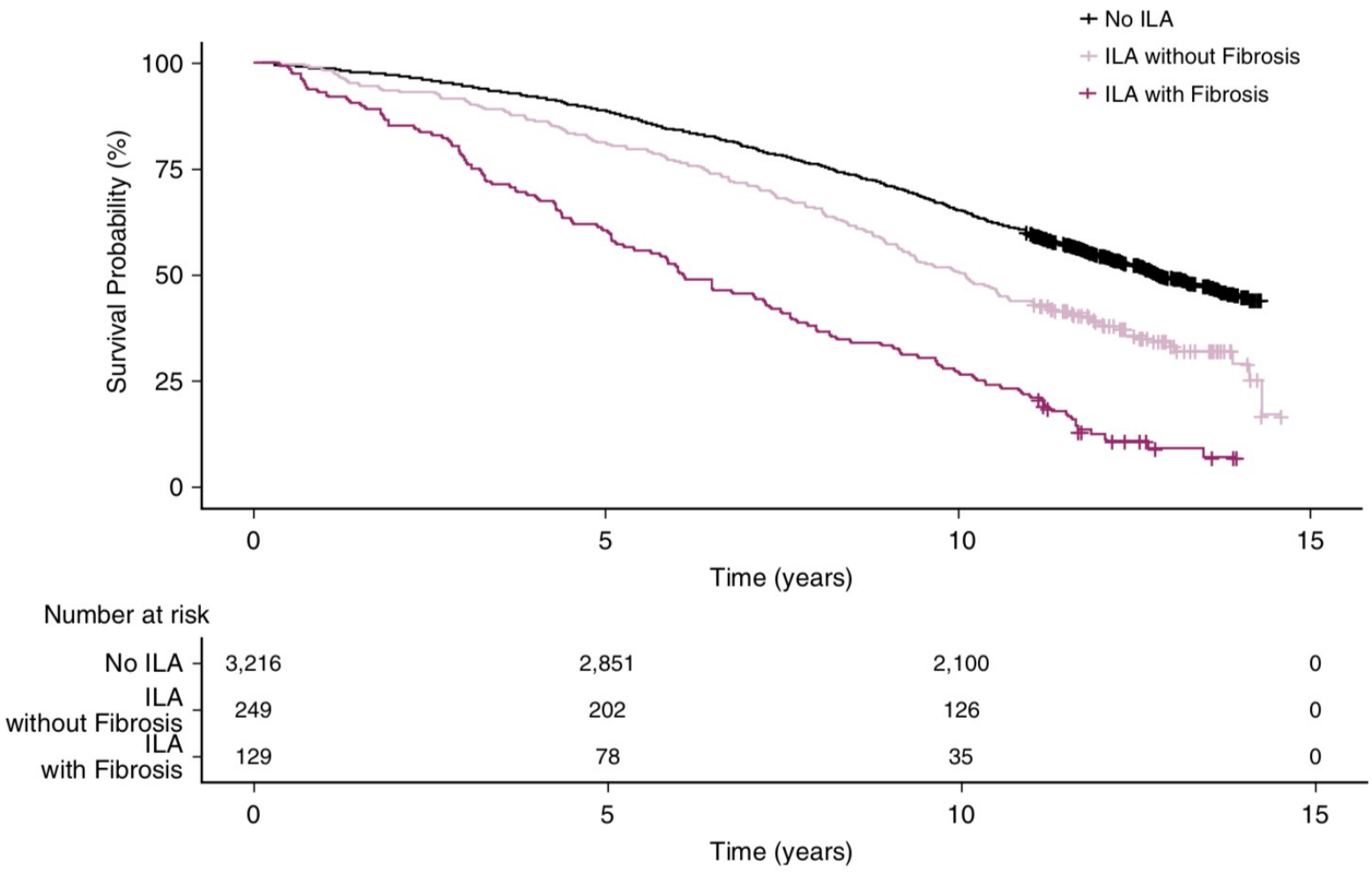


Table 4. Association between Imaging Pattern and Features and Mortality*

	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

Hatabu et al, LRM 2020; Putnam et al , AJRCCM 2019



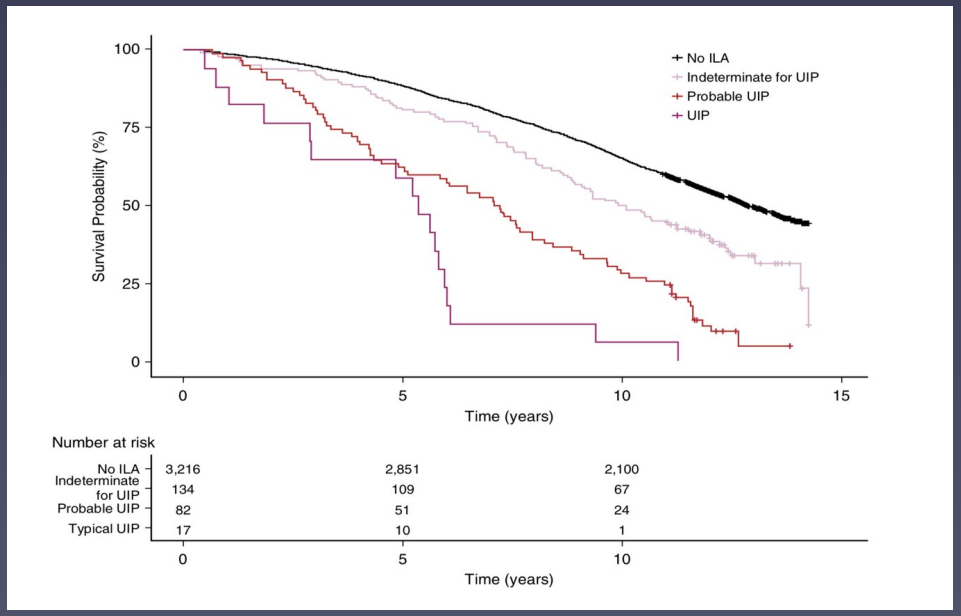
The definite fibrosis pattern was associated with a 70% increase in the risk of death (HR 1,7, 95% CI 1.3-2.1, p<0.0001) and with the highest risk of progression (odds ratio, 8.4; 95% confidence interval, 2.7–25; P = 0.0003).

Putman R et al, AJRCCM 2019

Probable UIP and UIP pattern were associated with an increased risk of death

Table 4. Association between Imaging Pattern and Features and Mortality*

	Unadjusted Analysis		Adjusted Analysis†	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
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



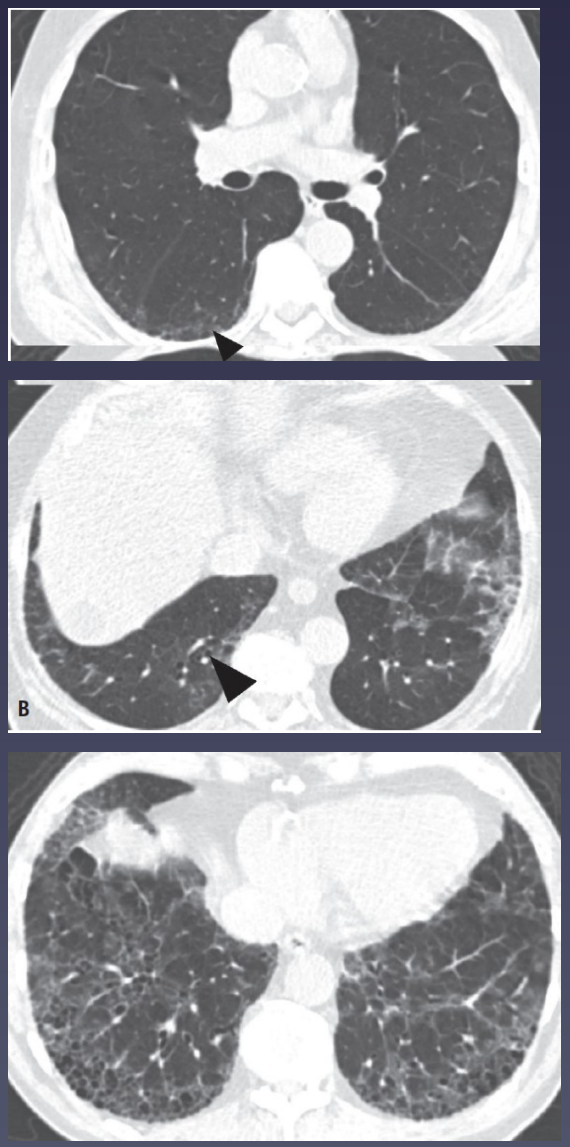
Putman R et al, AJRCCM 2019

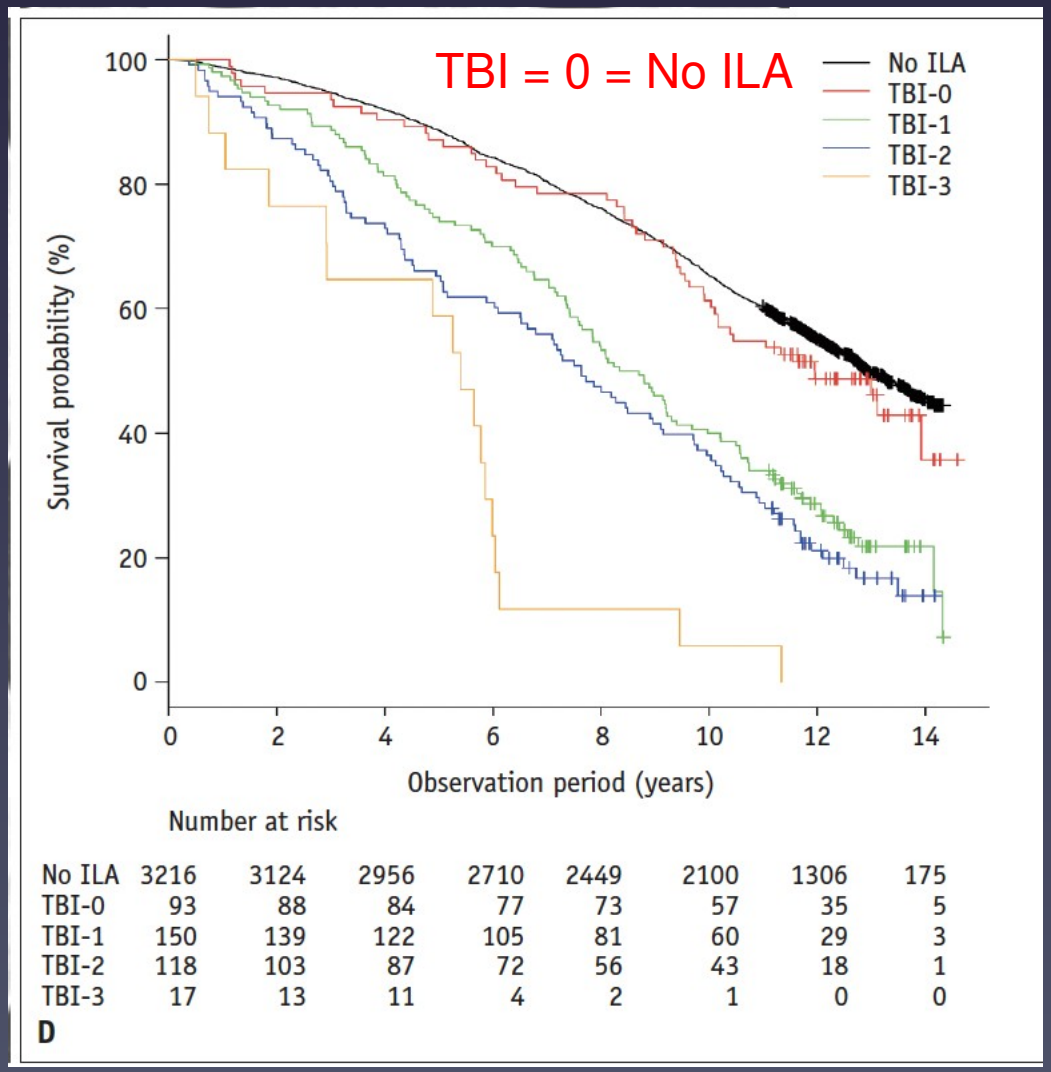
The traction bronchiectasis index (TBI) can stratify the prognoses of patients with ILAs

TBI=1

TBI=2

TBI=3





Hida, EJR 2020; Hino, KJR 2020

› Radiology. 2022 Oct 11;221172. doi: 10.1148/radiol.221172. Online ahead of print.

Prevalence and Long-term Outcomes of CT Interstitial Lung Abnormalities in a Health Screening Cohort

Jong Eun Lee [# 1], Kum Ju Chae [# 1], Young Ju Suh [1], Won Gi Jeong [1], Taebum Lee [1], Yun-Hyeon Kim [1], Gong Yong Jin [1], Yeon Joo Jeong [1]

Affiliations + expand

PMID: 36219115 DOI: 10.1148/radiol.221172

This observational, retrospective multicenter study included patients aged 50 years or older who underwent chest CT at three health screening centers over a 4-year period (2007-2010).

2765 included patients (mean age, 59 years ± 7 [SD]; 2068 men), 94 (3%) had a finding of ILA (35 nonfibrotic and 59 fibrotic ILA) and 119 (4%) had equivocal ILA

Those with fibrotic and nonfibrotic ILA had a higher mortality rate than those without ILA ($P < .001$ and $P = .01$, respectively) over 12 years.

Fibrotic ILA was independently associated with:

- (hazard ratio [HR], 10.3; 95% CI: 6.4, 16.4; $P < .001$),
- development (HR, 4.4; 95% CI: 2.1, 9.1; $P < .001$),
- disease-specific mortality (HR, 6.7; 95% CI: 3.7, 12.2; $P < .001$),
- and all-cause mortality (HR, 2.5; 95% CI: 1.6, 3.8; $P < .001$) compared with no ILA.

Subpleural "non-fibrotic"(=reticular) ILA can be progressive

513 non fibrotic ILA (=bibasal reticulation in the absence of traction bronchiectasis/hcc):

- 186 (36.3%) stable
- 108 (21%) regression
- 219 (42.7%) progressed
  - 54 (24.7% of progressive and 10.5% of the total) newly reticulation
  - 12 (5.5% of progressive and 2.3% of the total) progressed into newly FIBROSIS

Zhang et al, AJRCCM 2021

Individuals with progressive non-fibrotic ILA were significantly older (67.7 ± 12.0 vs. 61.9 ± 9 12.6, *P*<0.0001) and more likely to be former smokers (13.5% vs. 5.6%, *P*=0.0097).

ILA clinical phenotypes by age

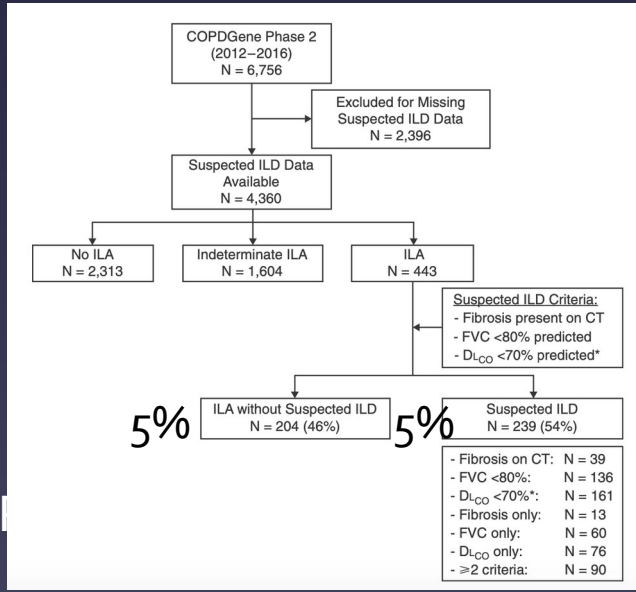
	Total ILA (N=3,300)	Non-fibrotic (N=3,117)	Fibrotic (N=183)	*P* value *
Age (years)	62.1±13.8	61.7±13.7	69.4±12.2	<0.0001†
				<0.0001†
<40	113 (3.4)	109 (3.5)	4 (2.2)	
40-49	543 (16.5)	532 (17.1)	11 (6.0)	
50-59	855 (25.9)	836 (26.8)	19 (10.4)	
60-69	712 (21.6)	665 (21.3)	47 (25.7)	
≥70	1077 (32.6)	975 (31.3)	102 (55.7)	

Zhang et al, AJRCCM 2021

Clinically, when it's not ILA but a suspected ILD the prognosis is worse

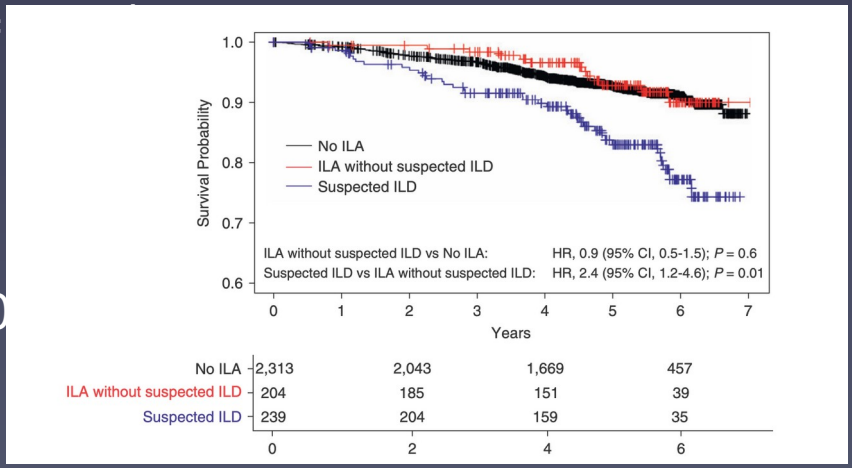
Suspected ILD defined as ILA and at least one additional criterion:

- definite fibrosis on computed tomography,
- FVC less than 80% predicted, or D_{LCO} less than 70% predicted



suspected ILD was associated with
Increased St. George's RQ score [MD], 3.9;
reduced 6MWT (MD, 235 m; P = 0.002),
greater O2 use [OR], 2.3; P = 0.03)
respiratory exacerbations (OR, 2.9; P =
higher mortality (HR, 2.4; P = 0.01)

Risk factors associated with suspected
Black race (OR, 2.0; P = 0.01)
PY smoking history (OR, 1.2; P = 0.000



Rose et al, AJRCCM 2022

TABLE 2 Interstitial lung abnormality (ILA) risk factors for progression and mortality

	ILA progression	Mortality	First author [ref.]
Age, years	OR 1.14 (95% CI 1.11–1.17)		Araki [15]
MUC5B (rs35705950)	OR 2.8 (95% CI 1.7–4.4)		Araki [15]
Progressive ILA		HR 3.9 (95% CI 1.3–10.9)	Araki [15]
HRCT predictors			
Subpleural reticular markings	OR 6.6 (95% CI 2.3–19)	OR 1.6 (95% CI 1.0–2.5)	Putman [31]
Traction bronchiectasis	OR 6.6 (95% CI 2.3–19)	OR 1.6 (95% CI 1.3–2.1)	Putman [31]
Traction bronchiectasis score 1		HR 2.18 (median OS 8.5 years)	Hida [32]
Traction bronchiectasis score 2		HR 2.65 (median OS 7.7 years)	Hida [32]
Traction bronchiectasis score 3		HR 6.8 (median OS 5.4 years)	Hida [32]
Subpleural location	OR 6.6 (95% CI 2.3–19)	OR 1.6 (95% CI 1.0–2.7)	Putman [31]
Lower lobes predominant changes	OR 6.7 (95% CI 1.8–25)	NS	Putman [31]
Indeterminate for UIP		NS	Putman [31]
Probable UIP		OR 1.9 (95% CI 1.5–2.5)	Putman [31]
Definite UIP		OR 4.5 (95% CI 2.8–7.2)	Putman [31]

Traction bronchiectasis score: 0=absence; 1=bronchiolectasis only; 2=mild moderate traction bronchiectasis; 3=severe traction bronchiectasis and/or honeycombing. OR and hazard ratio (HR) on adjusted multivariable analysis. HCRT: high-resolution computed tomography; HR: hazard ratio; NS: nonsignificant when p>0.05; OS: overall survival; UIP: usual interstitial pneumonia.

S Tomassetti et al ERR 2022

Interstitial Lung Abnormalities: An Evolving Entity.

Tomassetti S, Wells A.

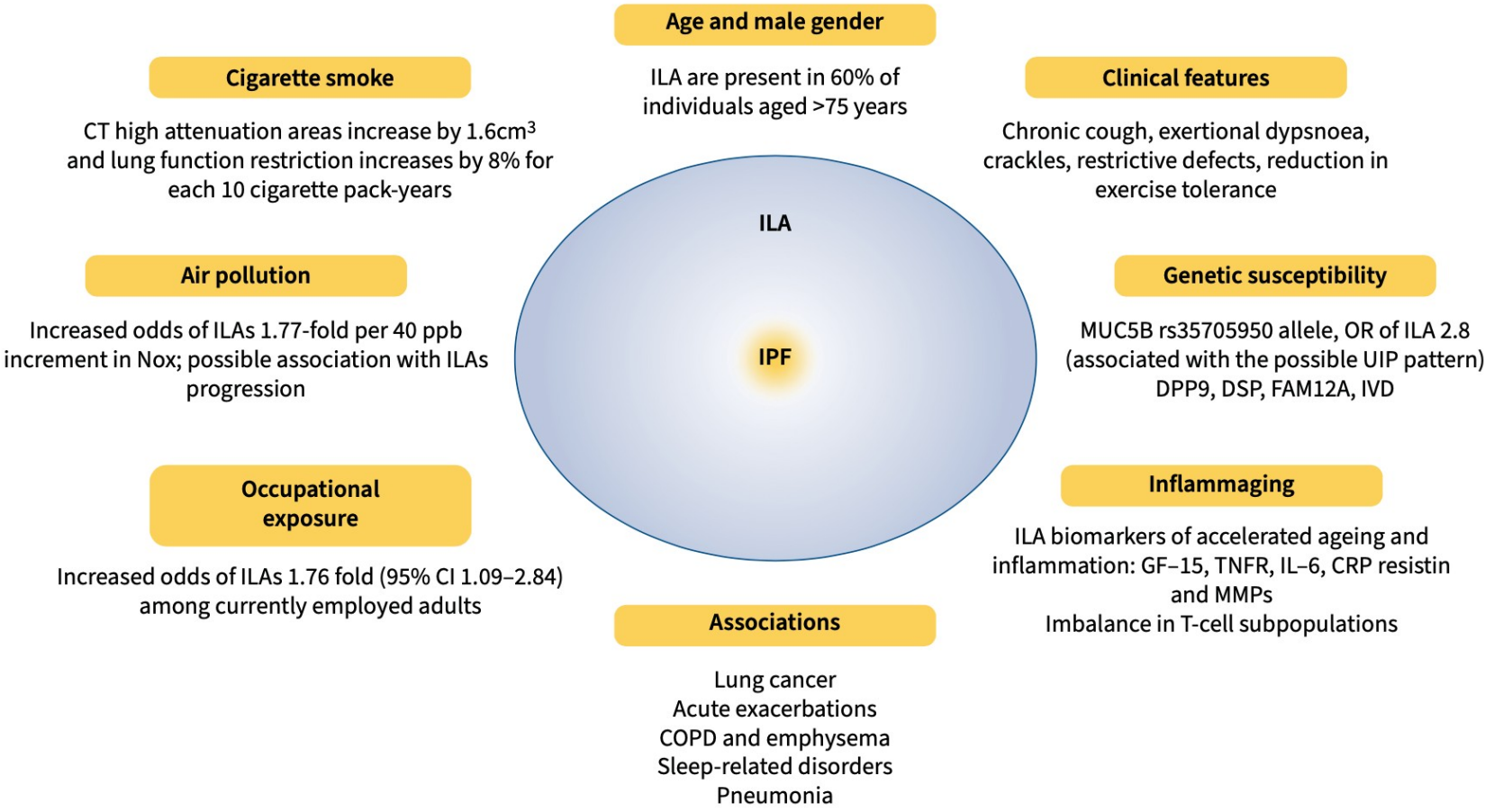
Am J Respir Crit Care Med. 2022 May 10. doi: 10.1164/rccm.202204-0676ED. Online ahead of print.

PMID: 35536727 No abstract available.

Progressive ILA, current understanding:

- Both fibrotic and non fibrotic subpleural (IPF-like distribution ILA) can be progressive.
- In non fibrotic ILA risk factors for progression are older age and smoke.
- In fibrotic ILA fibrosis extent and UIP correlate with prognosis.

Precision medicine:
ILA links with IPF and biologic significance



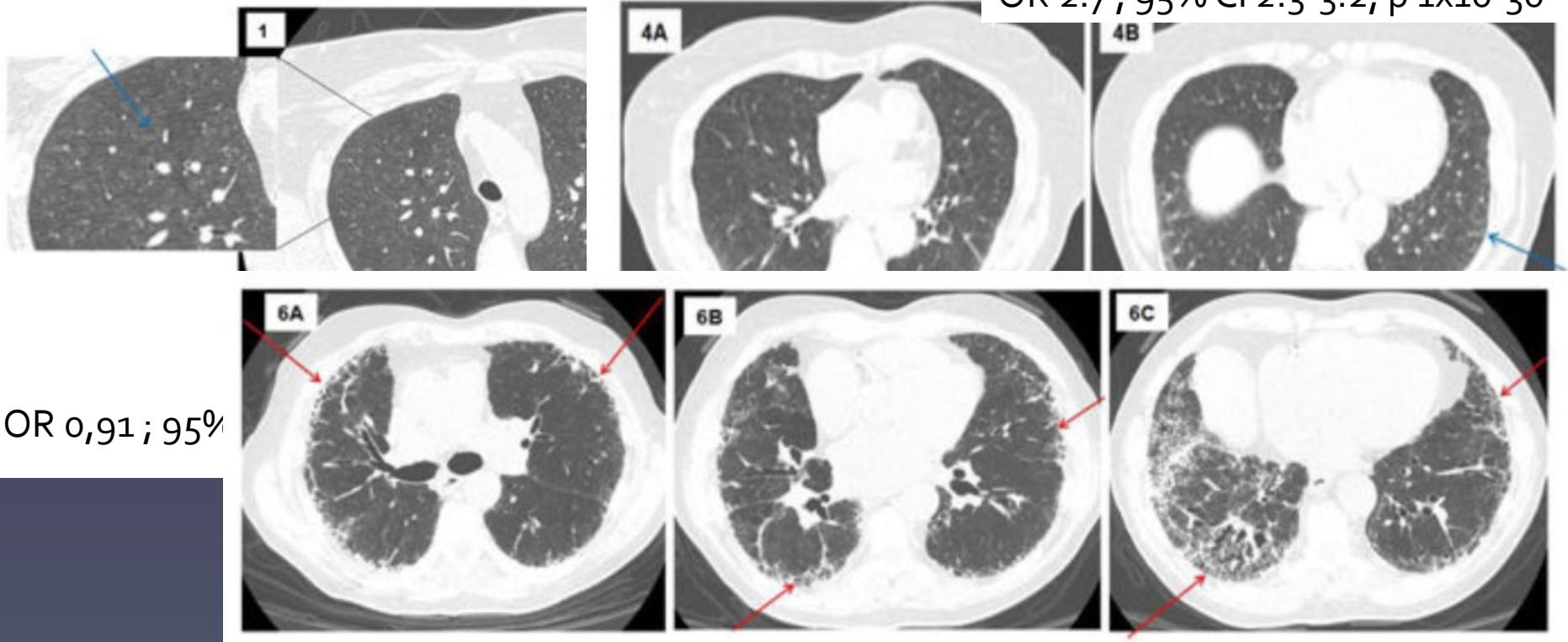
S Tomasetti et al, ERR 2022

MUC5B Is Associated with Specific ILA Subtypes

Putman RK, ERJ 2017

MUC5B genotype is associated with subpleural ILA and a possible UIP pattern, but not with centrilobular abnormalities

OR 2.7 ; 95% CI 2.3-3.2, p 1x10-30



OR 0,91 ; 95%

Fibrotic Radiologic ILD

OR 4.4 ; 95% CI 2.2-9.0, p 4x10-5

Genome-wide significant variants associated with ILA and IPF

Chromosome/ Location	Position	rsID	Risk Allele	Risk Allele Frequency	Nearest Gene	ILA* vs No ILA		Subpleural ILA vs No ILA		Replication in IPF† Cohort	
						Odds Ratio‡ (95% CI§)	P-Value	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value
11p15	1241221	rs35705950	T	0.11	*MUC5B*	1.97 (1.74, 2.22)	3×10^{-27}	2.22 (1.93, 2.55)	2×10^{-29}	4.84 (4.37, 5.36)	1×10^{-203}

* ILA is interstitial lung abnormalities
†IPF is idiopathic pulmonary fibrosis
‡Odds Ratios are per copy of the risk allele
§CI is confidence interval

There was a substantial enrichment of the 12 IPF GWAS loci in our ILA association results:

- ✓ 5 SNPs near *DPP9*, *DSP*, *FAM13A*, *IVD*, and *MUC5B* were significantly associated ($p < 4.2 \times 10^{-3}$) with ILA
- ✓ 2 SNPs at *MAPT* and *LRRC34*, were nominally significant ($p < 0.05$, but did not meet the threshold for significance after adjustment for multiple testing) in association with ILA

Hobbs et al. AJRCCM 2019

ILA biomarkers (CD4+Tcells and inflammaging)

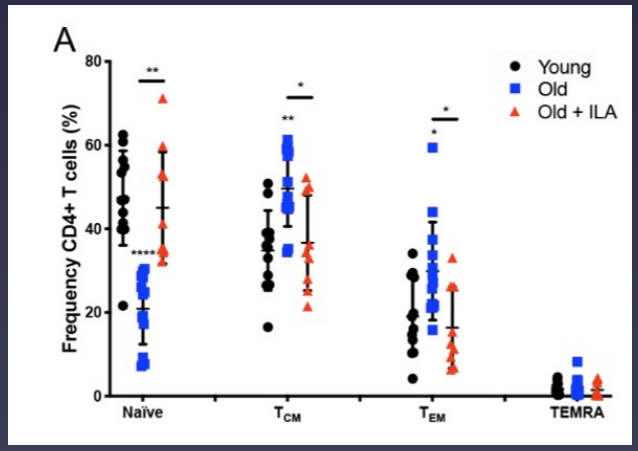
15 individuals with ILA, 21 age-matched controls and 28 healthy young subjects

Basal serum concentrations of biomarkers between groups

Biomarker	ILA n=80	Non-ILA n=80	p value	Corrected p value*
MMP-1 ng/ml (SD)	7 ± 4	6 ± 3	0.02	0.2
MMP-2 ng/ml (SD)	38± 4	37 ± 2	0.53	1.0
MMP-3 ng/ml (SD)	19 ± 11	17 ± 10	0.28	1.0
MMP-7 mcg/ml (SD)	6 ± 4	4 ± 2	0.008	0.09
MMP-8 ng/ml (SD)	4 ± 4	3 ± 3	0.28	1.0
MMP-9 ng/ml (SD)	14 ± 9	12 ± 8.2	0.32	1.0
MMP-12 pg/ml (SD)	30 ± 12	27 ± 10	0.16	1.0
MMP- 13 pg/ml (SD)	357 ± 143	298 ± 116	0.004	**0.04**
IL-6 ng/ml (SD)	15.7 ± 21	11.4 ± 15	0.04	0.4
SP-D ng/ml (SD)	10 ± 11	8 ± 6	0.04	0.4
alfa-Klotho pg/ml (SD)	735 ± 462	519 ± 133	0.99	1.0
Resistin ng/ml (SD)	12 ± 5	9 ± 4	0.0005	**0.006**

*corrected by Bonferroni adjustment; MMP=matrix metalloproteinase; SD=standard deviation; IL=interleukin; SP-D=surfactant protein D.

Buendian-Roldan…Selman, ERJ 2021



CD4+T cells from ILA subjects are highly proliferative and show an excessive functional activity, likely related to the loss of KLRG1 expression, which may contribute to an inflammatory state and the development of ILA.

Machahaua…Selman, Thorax 2021

> Am J Respir Crit Care Med. 2022 Apr 19. doi: 10.1164/rccm.202110-2296OC.
Online ahead of print.

The Proteomic Profile of Interstitial Lung Abnormalities

Gisli Thor Axelsson [1 2], Gunnar Gudmundsson [1 3], Kathrine A Pratte [4], Thor Aspelund [1 5], Rachel K Putman [6], Jason L Sanders [6], Elias F Gudmundsson [5], Hiroto Hatabu [7 8], Valborg Gudmundsdottir [1 5], Alexander Gudjonsson [5], Takuya Hino [8], Tomoyuki Hida [8 9], Brian D Hobbs [6 10], Michael H Cho [6 10], Edwin K Silverman [6 10], Russell P Bowler [4 11], Lenore J Launer [12], Lori L Jennings [13], Gary M Hunninghake [6 8], Valur Emilsson [5], Vilmundur Gudnason [5 1]

287 associations with ILA

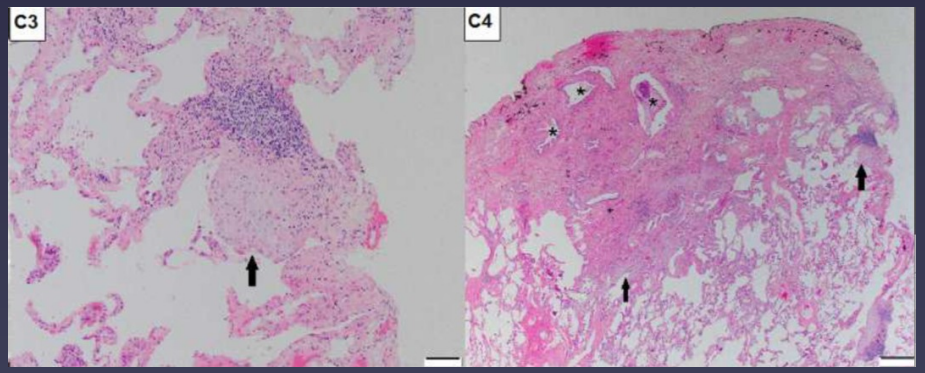
- SFTPB (OR 3.71 [95% CI 3.20-4.30], P 4.28×10-67),
- SCG3AB1 (OR 2.43 [2.13-2.77], P 8.01×10-40)
- WFDC2 (OR 2.42 [2.11-2.78], P 4.01×10-36)

WFDC2 had the strongest associations with ILA progression

Histopathology of ILA, and significance to ILDs development

424 nodule resection , 26 (6%) had ILA, 17 (4%) subpleural distribution

- 4% any fibrosis
- 1.6% fibroblastic foci
- 0.5% honeycombing
- 0.5% UIP pattern



Miller ER et al, Am J Respir Crit Care Med 2018;197:955–958

397 nodule resection , 101 (25%) had interstitial changes, 10% fibrotic

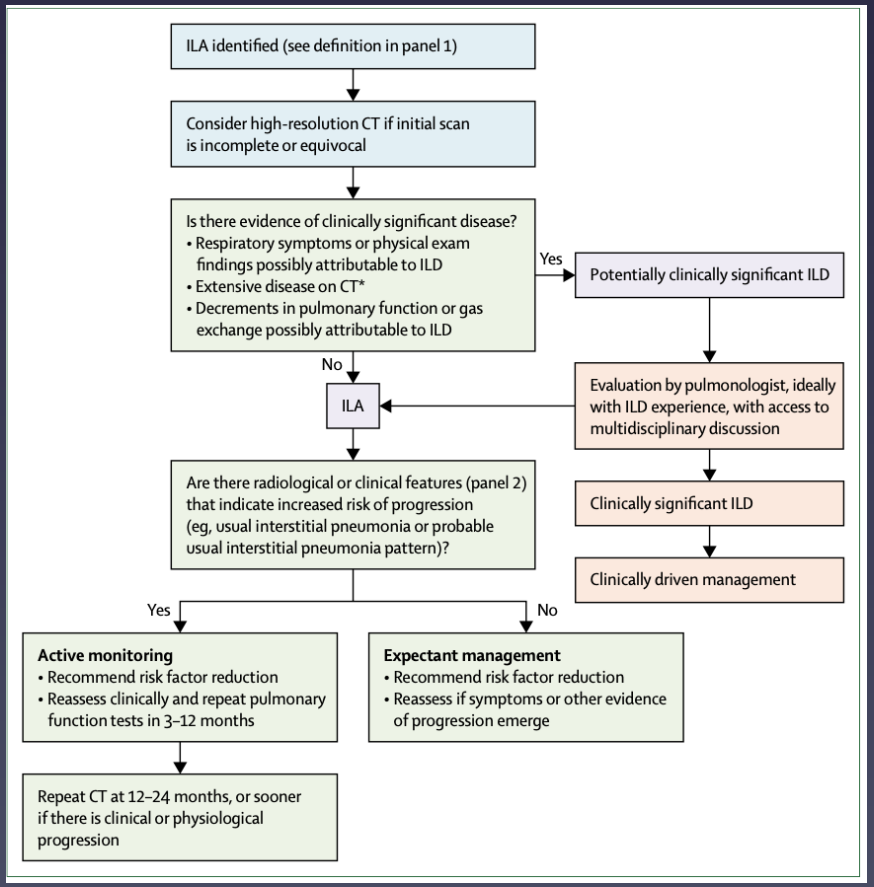
- 7% SRIF
- 1% UIP
- 0.7% NSIP

Hung YP et al, Hum Pathol 2019;86:93–101

ILA biological significance remains a field for research

ILA management

«To date, only minimal evidence exists to support a specific management plan for ILAs.»



Biopsy may tell what this is

Panel 2: Risk factors for progression of interstitial lung abnormalities

Clinical risk factors

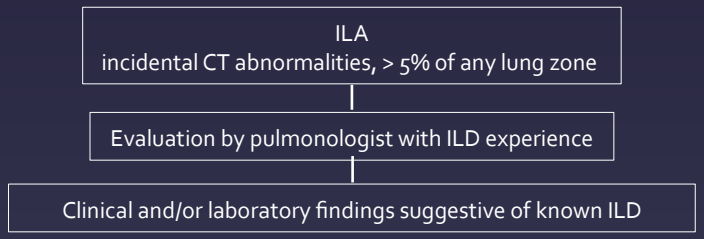
- Cigarette smoking
- Other inhalational exposures
- Medications (eg, chemotherapy, immune checkpoint inhibitors)
- Radiation therapy
- Thoracic surgery
- Physiological or gas exchange findings at lower limits of normal

Radiological risk factors

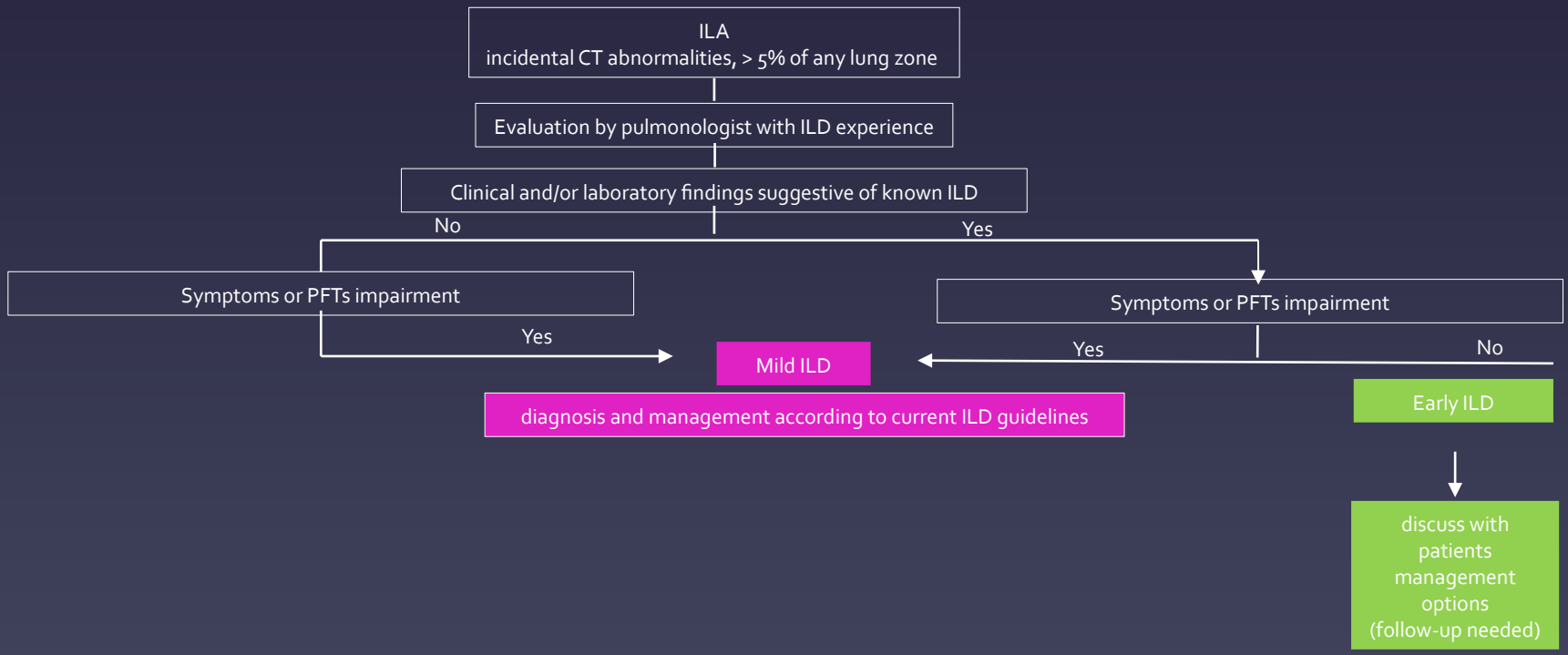
- Non-fibrotic interstitial lung abnormalities (ILAs) with basal and peripheral predominance
- Fibrotic ILAs with basal and peripheral predominance but without honeycombing (ILAs with probable usual interstitial pneumonia pattern)
- Fibrotic ILAs with basal and peripheral predominance and honeycombing (ILAs with usual interstitial pneumonia pattern)

Based on ATS/ERS statement this is IPF

Hatabu et al, Fleischner Soc position paper, LRM 2020



S Tomasetti et al, ERR 2022



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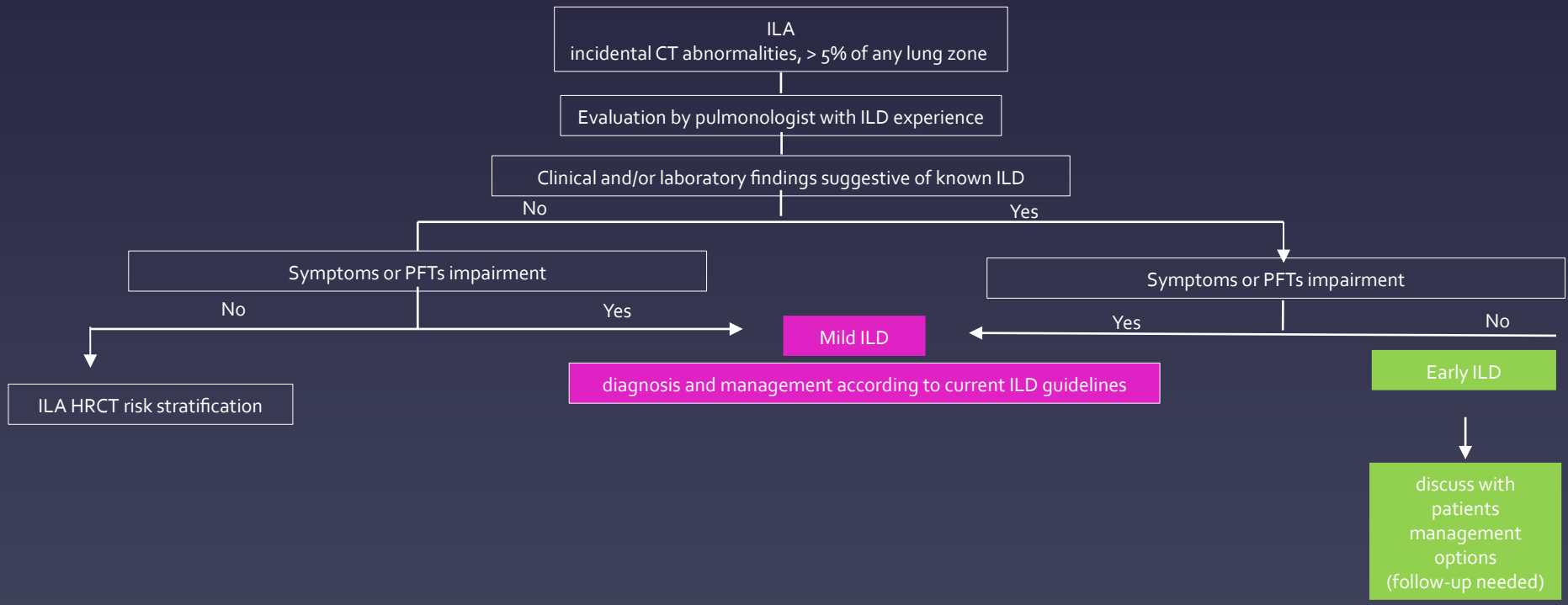

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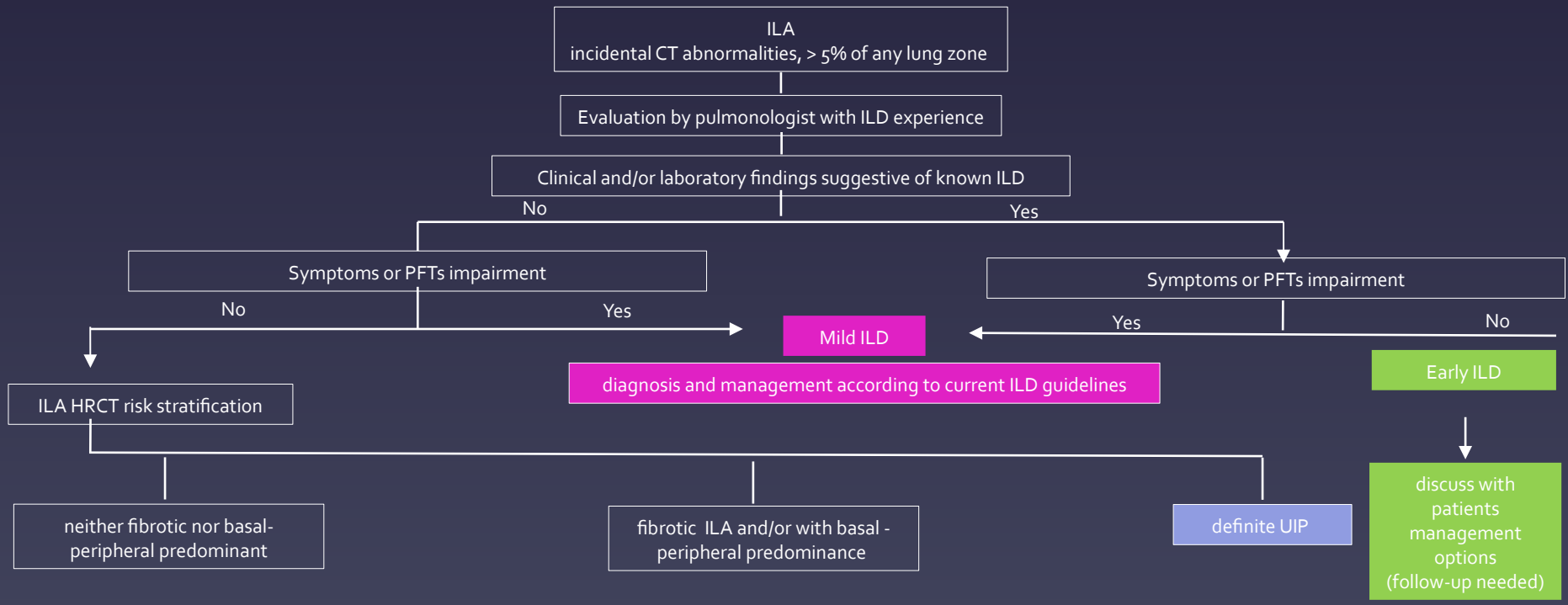
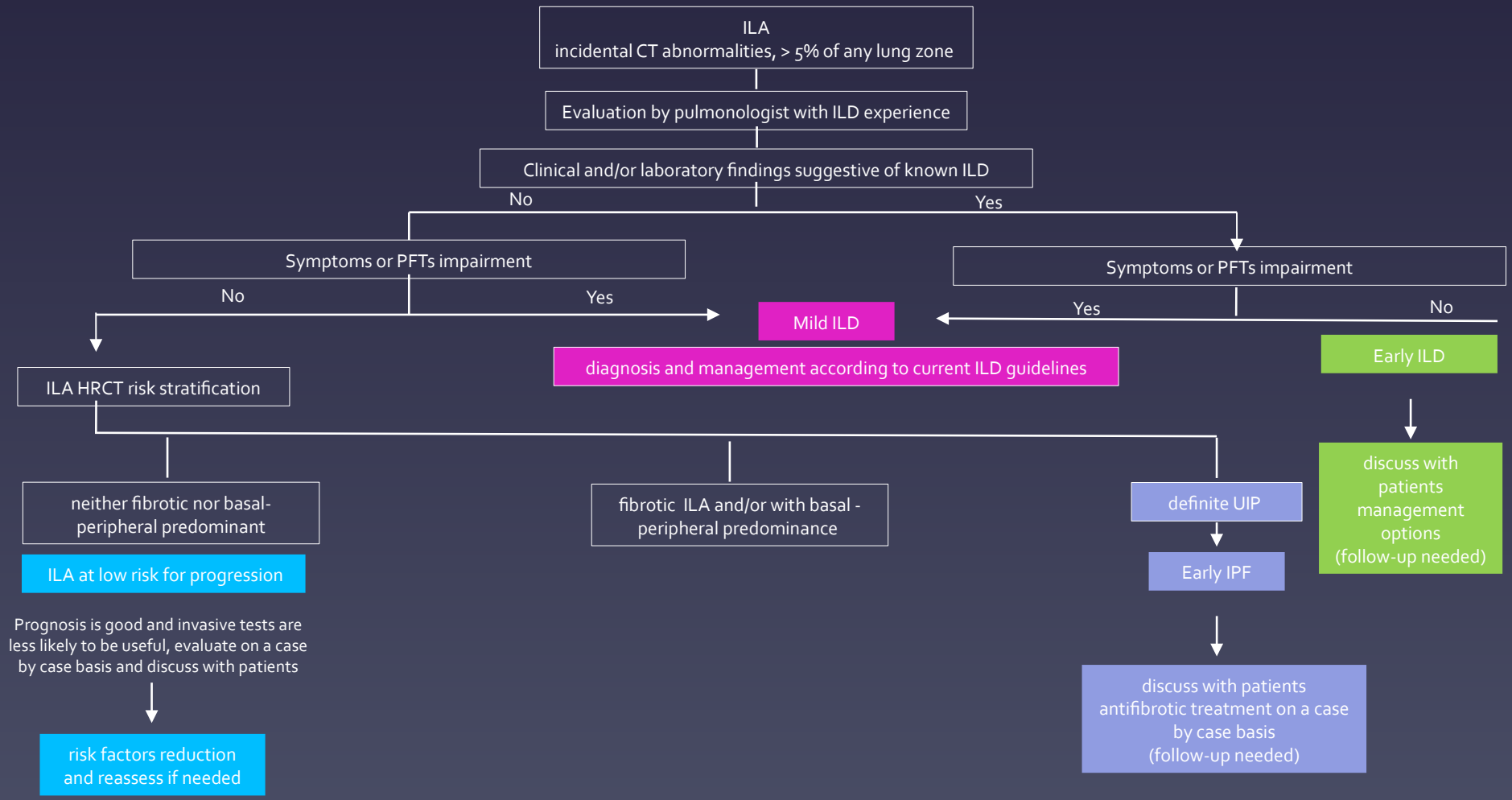
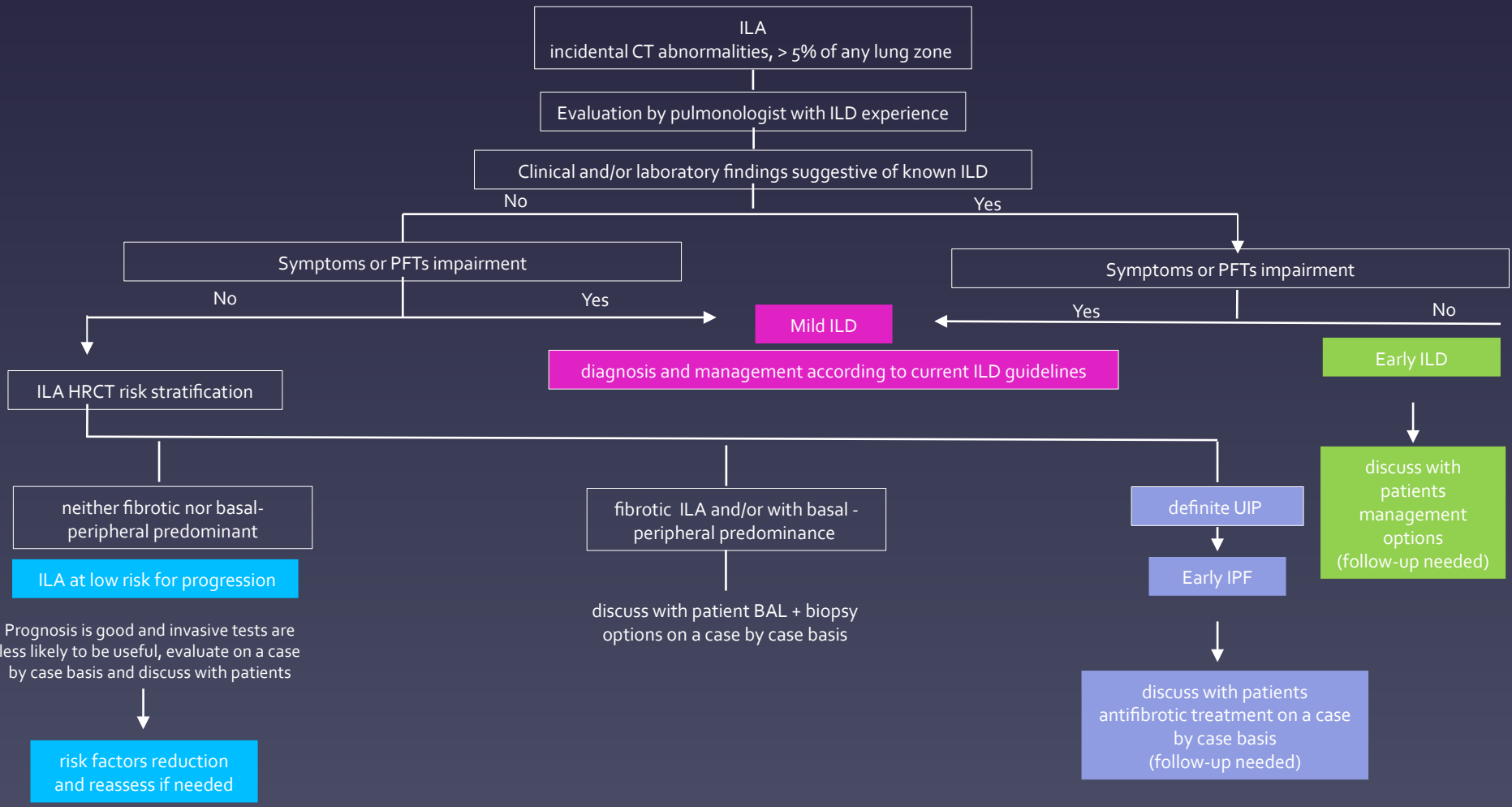


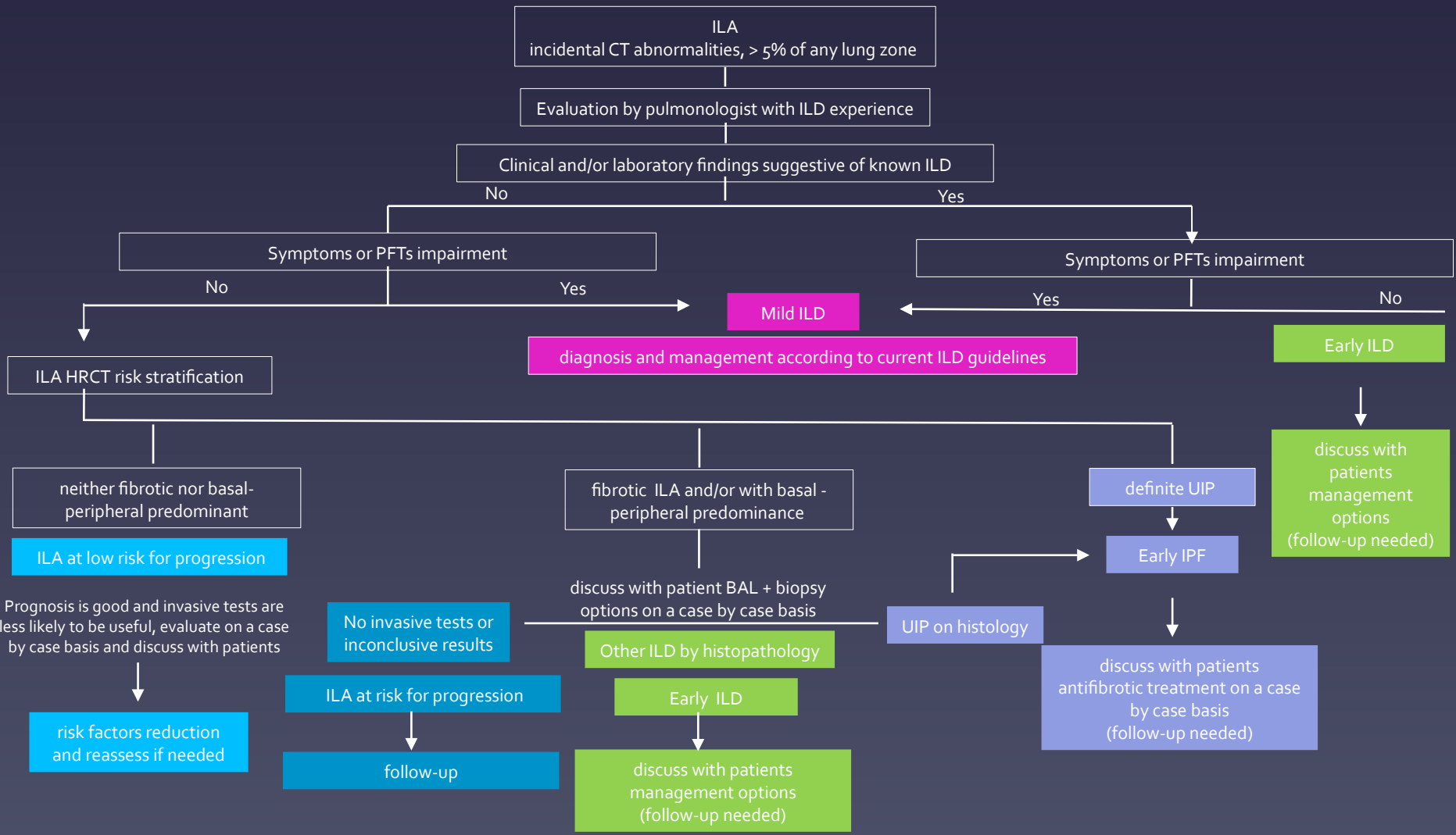
S Tomasetti et al, ERR 2022



S Tomasetti et al, ERR 2022



S Tomasetti et al, ERR 2022



S Tomasetti et al, ERR 2022

CONCLUSION

- ILA is **not** a clinical entity (lack of biologic significance, lack of defined clinical features, unknown pathology, uncertain management).
- ILA is a risk category and ILA subgroups (fibrotic/subpleural = IPF-like features) identify **patients at risk for progression and death** related to pulmonary fibrosis.
- Consensus criteria guiding physicians on when and how further characterize **ILA reclassifying it into known ILD categories** (Early /sub-clinical ILD or mild ILD) are eagerly needed.


Thank You