The Role of Thoracic Ultrasound in Interstitial Lung Abnormalities

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2. Bridging Imaging Gaps: US monitoring between CT scan
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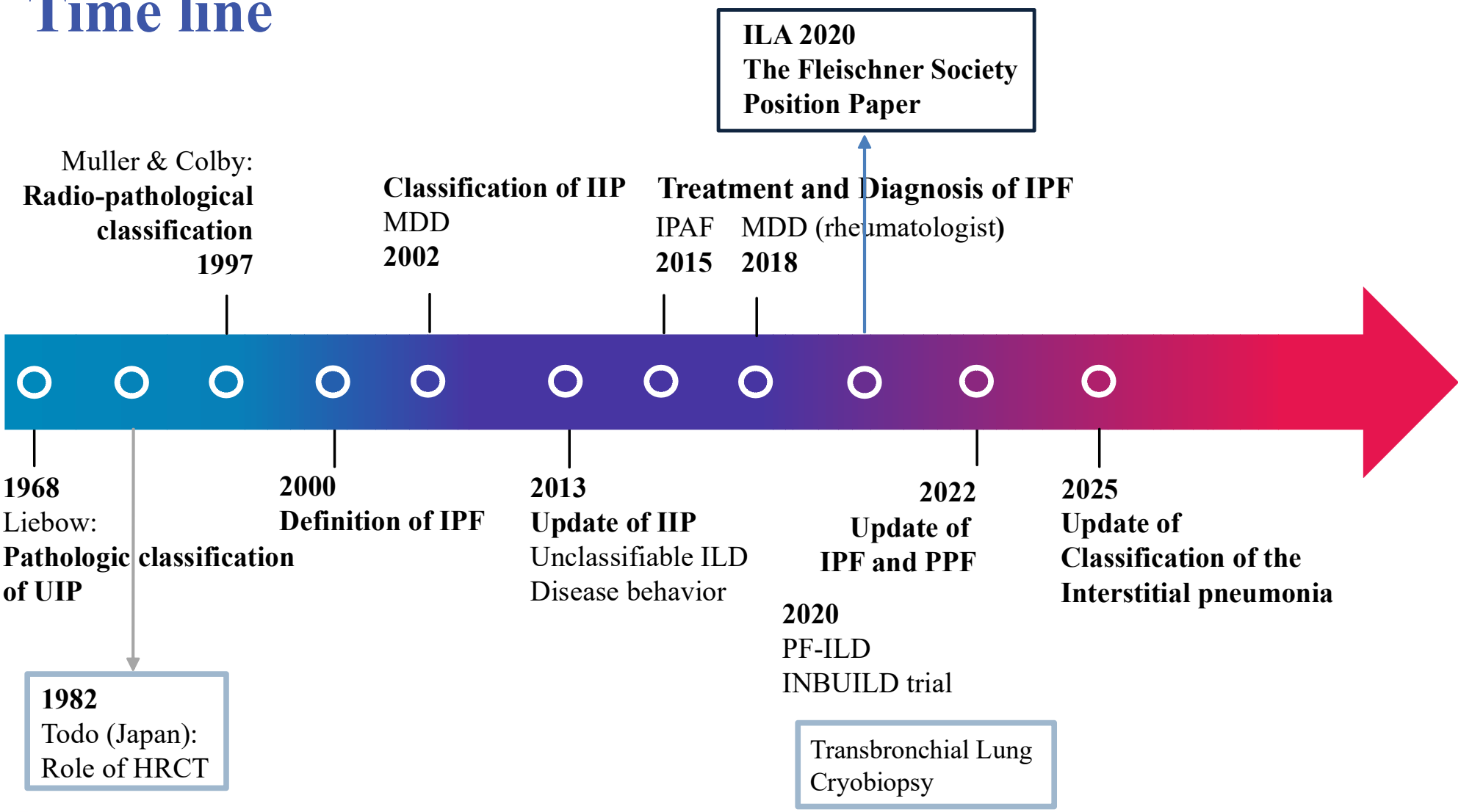
Milestones of ILD classification

Time line



Milestones of ILD classification

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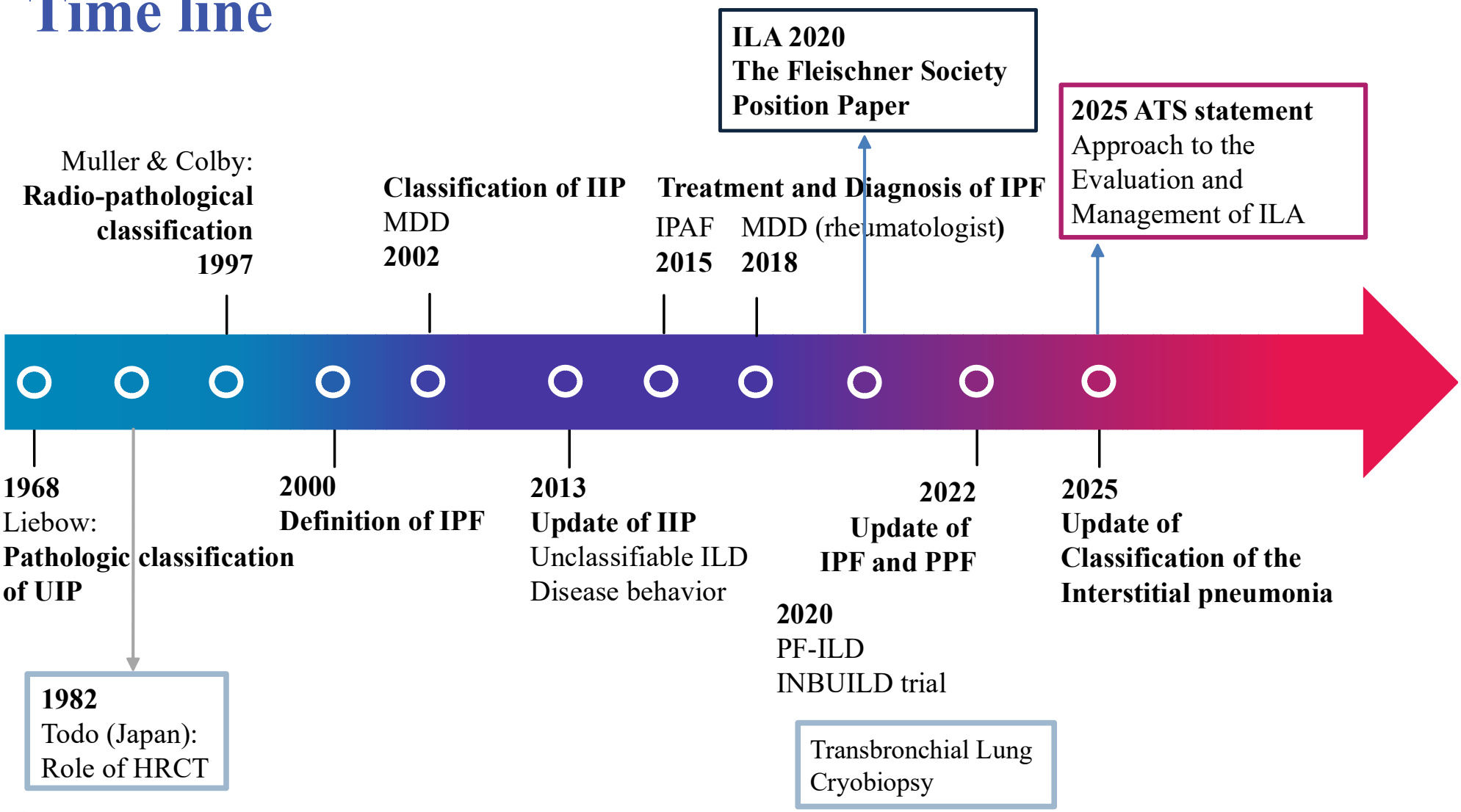
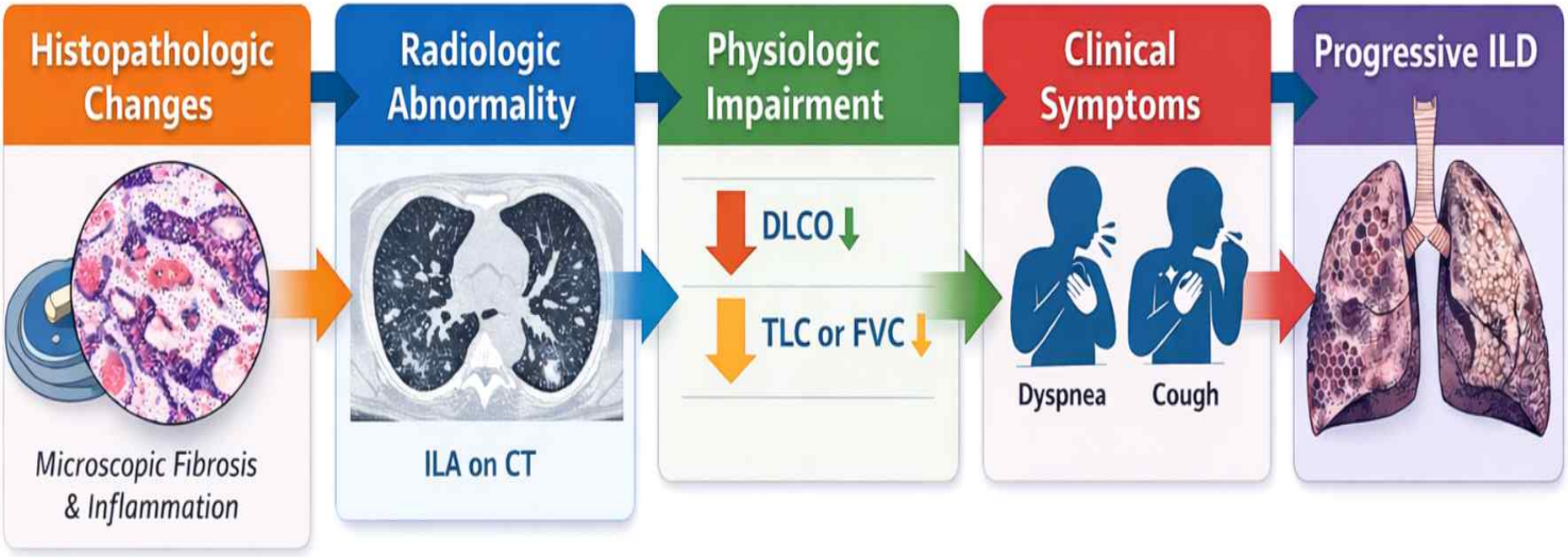


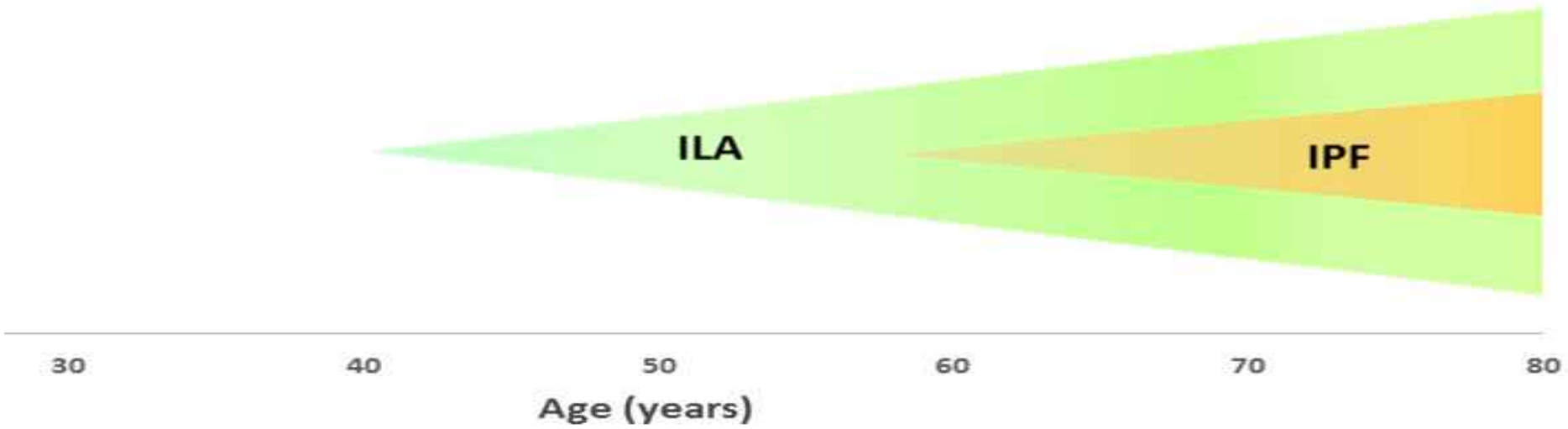
Trajectory of ILD development

- After pathological change (microscopic fibrosis), Imaging abnormalities may represent the earliest detectable manifestation of interstitial lung disease.
- Pathologic fibrosis can be below the resolution of imaging.



ILA and clinical course

	Population	Clinical findings	Diagnostic criteria
ILA	Any (High risk + Incidental)	None	Clinical-radiologic
Early ILD	Any (Pre-clinical – at high risk; Subclinical – Silent ILD)	Asymptomatic with normal PFTs	Clinical-radiologic-pathologic
Mild ILD	Any (established)	Minor symptoms/trivial PFT abnormalities	Clinical-radiologic-pathologic



Analysis of the pathologic findings by ILA status

- A retrospective single-cohort study – 424 patients who had undergone lung nodule resection without ILD diagnosis in Brigham and Women's hospital between 2001 and 2015
- ILA on CT and histopathologic findings were compared

	No ILA (*n* = 257; 61%)	Indeterminate ILA (*n* = 141; 33%)	ILA (*n* = 26; 6%)	*P* Value* All Groups	*P* Value* ILA vs. No ILA
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

AJRCCM 2018; 197(7)

Definition: Interstitial lung abnormality (2020)

- Incidental identification of non-dependent abnormalities (CT finding, not disease), including

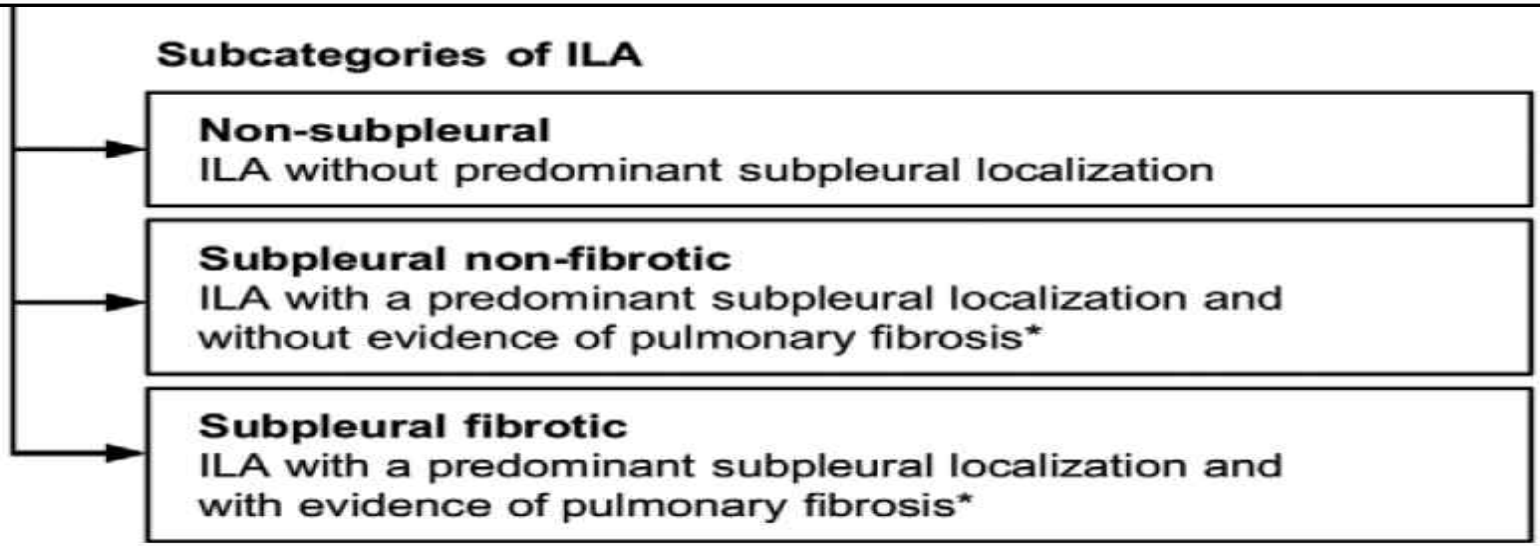
- Ground glass abnormality
- Reticular abnormality
- Lung distortion
- Traction bronchiectasis
- Honeycombing
- Non-emphysematous cysts

- Involving at least 5% of a lung zone
- In individuals in whom interstitial lung disease is not suspected
- Preclinical interstitial lung abnormalities during screening of high risk subjects (e.q. RA, SSc, occupational exposure, familial PF)

Lancet Respir Med 2020;8:726-37

Definition and Subtype of ILAs

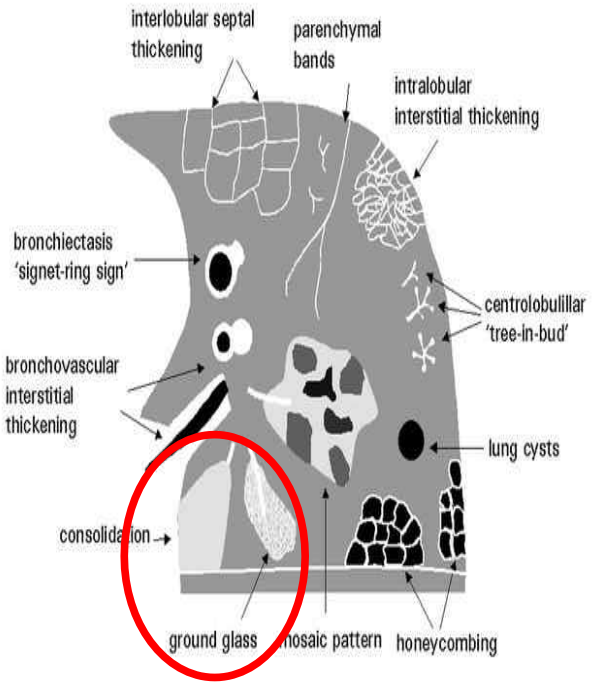
ILA Subtype	Key CT Features	Progression Rates	Key Risk Modifiers
Subpleural fibrotic[1,2,6,15]	traction bronchiectasis, honeycombing	68.8%-89% over 5-8 years; OR-8.4 for progression vs. nonfibrotic	Age, smoking, MUC5B, extent of fibrosis
Subpleural nonfibrotic[1,7]	Ground-glass, mild reticulation, no fibrosis	43.6% over 4.2 years; OR-1.9 if reticulation present	Reticulation, age, smoking
Nonsubpleural[1,8,17]	Nonsubpleural location, no fibrosis	Lower; not well quantified, but <20% over 5 years	Male sex, reduced FVC, age, smoking status, inhalational exposure

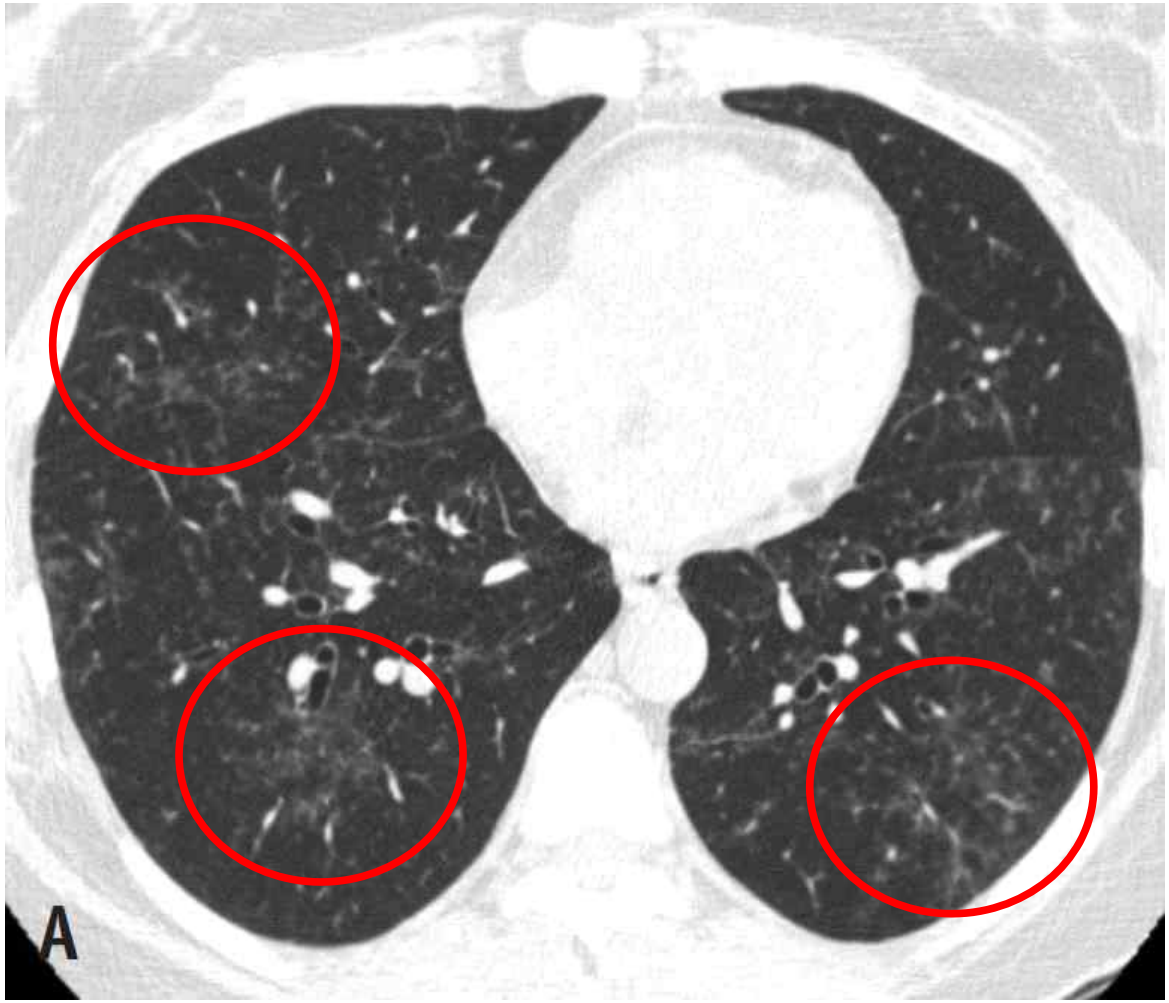


Radiology 2021;301:19-34

Non-subpleural (non-fibrotic) ILA

"Without predominant subpleural localization, Non-fibrotic feature"





Korean J Radiol 2021;22(5):811-828

Subpleural non-fibrotic ILA

"Predominant subpleural location, Without evidence of fibrosis"

Korean J Radiol 2021;22(5):811-828

Subpleural fibrotic ILA

"Architectural distortion with traction bronchiectasis or honeycombing"

Korean J Radiol 2021;22(5):811-828

From Radiologic definition to Clinical Framework : Evolution of ILA (2020→2025)

- The 2020 Fleischner paper – ILA (a radiologic entity) without clinical information
- The 2025 ATS statement – A multidisciplinary (including pulmonology and pathology) clinical framework for evaluation, classification, and management of ILA in real practice

  1) Removal of incidental and high-risk group restrictions

  2) Clear distinction between ILA and ILD

  3) Suggestion of screening, baseline assessment, and follow-up strategies

AJRCCM 2025;211(7):1132-1155

Clinical Relevance of ILAs

ILAs are associated

- Increased respiratory symptoms

  In meta-analyses, ILA have a significantly higher risk of chronic cough (30.5% vs. 13.9%; Risk ratio 1.59) and dyspnea on exertion (37.1% vs. 18.4%; RR 1.60)

- Accelerated loss of lung function (reduction in exercise capacity)

  64mL per year vs. 35mL without ILAs

- Radiologic progression of lung fibrosis

  More than half experience progression of radiologic findings over 5years

- Increased all-cause mortality

  31.6% vs. 19.4%; RR 1.66, 95% CI 1.56-1.77

AJRCCM 2025;211(7):1132-1155

Chest CT screening to identify ILAs/ILD in smokers

- The estimated prevalence of ILAs/ILD: 8% (95% CI, 7-10%)
- Advanced age, smoking(OR 1.7-2.2), and male sex – A common features of IPF
- Screening for ILA in all-smokers: not recommended d/t cost burden, anxiety, undesirable anxiety, radiation exposure, and the need for additional test

❖ However, in the context of lung cancer screening, <u>systematic assessment and documentation of ILAs/ILD</u> are recommended.

(The U.S. Preventive Service Task Recommendation of lung cancer screening – aged 50-80 years who have a 20-pack-year smoking history of current smoke or quit within the previous 15 years) → overlapping risk profiles of ILAs/ILD

AJRCCM 2025;211(7):1132-1155

Chest CT screening to identify ILAs/ILD in CTD

- In meta-analysis, the estimated prevalence of ILAs/ILD (RA, systemic sclerosis, polymyositis, dermatomyositis, anti-synthetase syndrome, mixed CTD, Sjogren's disease or overlap syndrome: 40% (95% CI, 37-43%)
  - Rheumatoid arthritis – 23%; 95% CI, 17-29%
  - Systemic sclerosis – 45%; 95% CI, 42-49%
  - Sjogren's syndrome – 39%; 95% CI, 18-59%
  - Dermatomyositis/Polymyositis – 44%; 95% CI, 37-52%

→ Additional benefit – An indication for the initiation or escalation of immunomodulatory therapy targeting the underlying CTD

❖ <u>We suggest a baseline HRCT to screen for ILAs/ILD in adults with CTD</u>

AJRCCM 2025;211(7):1132-1155

Longitudinal follow-up assessment with serial CT

- The purpose of follow-up imaging is to identify progression to ILD for diagnosis and therapeutic decision
- The prevalence of radiologic progression – 46% (95% CI, 38-55%), and a positive association with mortality (HR 1.9; 95% CI, 1.3-2.8)
- In a previous study, the median time to ILA progression was 3.2 years

❖ We suggest that patients with ILAs undergo a follow-up chest CT 2-3 years after the baseline chest CT

❖ Earlier follow-up (12 month) in some high risks or some clinical contests

❖ No vote, but most committee members agreed follow-up of annual PFT

AJRCCM 2025;211(7):1132-1155

Approach to Evaluation and Management of ILAs

- Detection of ILAs

  1. Screening specific populations (Lung cancer screening, CTD, adults ≥ 50 years with a first-degree relative with FPF
  2. Screening other at-risk populations (A primary relative with IPF and high-risk exposures)
  3. Incidental CT scan

- Identification of ILA and confirmation with HRCT
- Baseline assessment including potential causes, risk factors, and recommendations for symptom assessment & PFT measurement
- Distinction between ILD and ILA
- A multidisciplinary approach including follow-up based on risk assessment and management strategies (smoking cessation, exposure avoidance, and vaccination)

AJRCCM 2025;211(7):1132-1155

Definition of ILD for those with ILAs

The importance of distinguishing between ILA and ILD

1. Simple and Easy application (As defined 2022 international guideline)
2. Progressive abnormalities (not aging)
3. The presence of a major fibrotic ILD pattern

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*

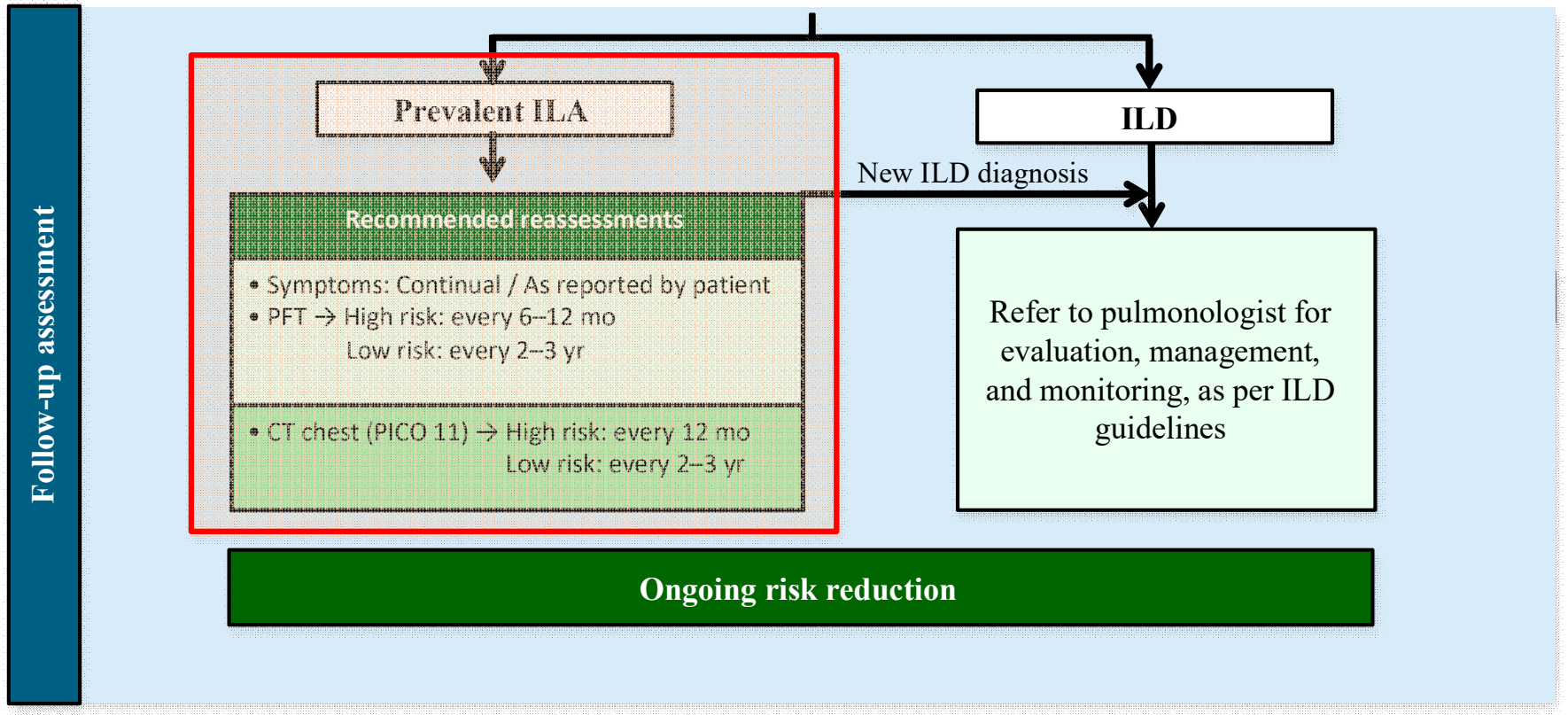
- Symptoms: Any amount of dyspnea and/or cough that a clinician attributes to ILD

- 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 (10)

- 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)

AJRCCM 2025;211(7):1132-1155



Role of Lung Ultrasound in ILA

1. Follow-up assessment before CT scan

→ Bridging imaging gaps: Ultrasound monitoring between f/u of CT scan

2. Adjunct Tool in Clinico-Physiological Mismatch

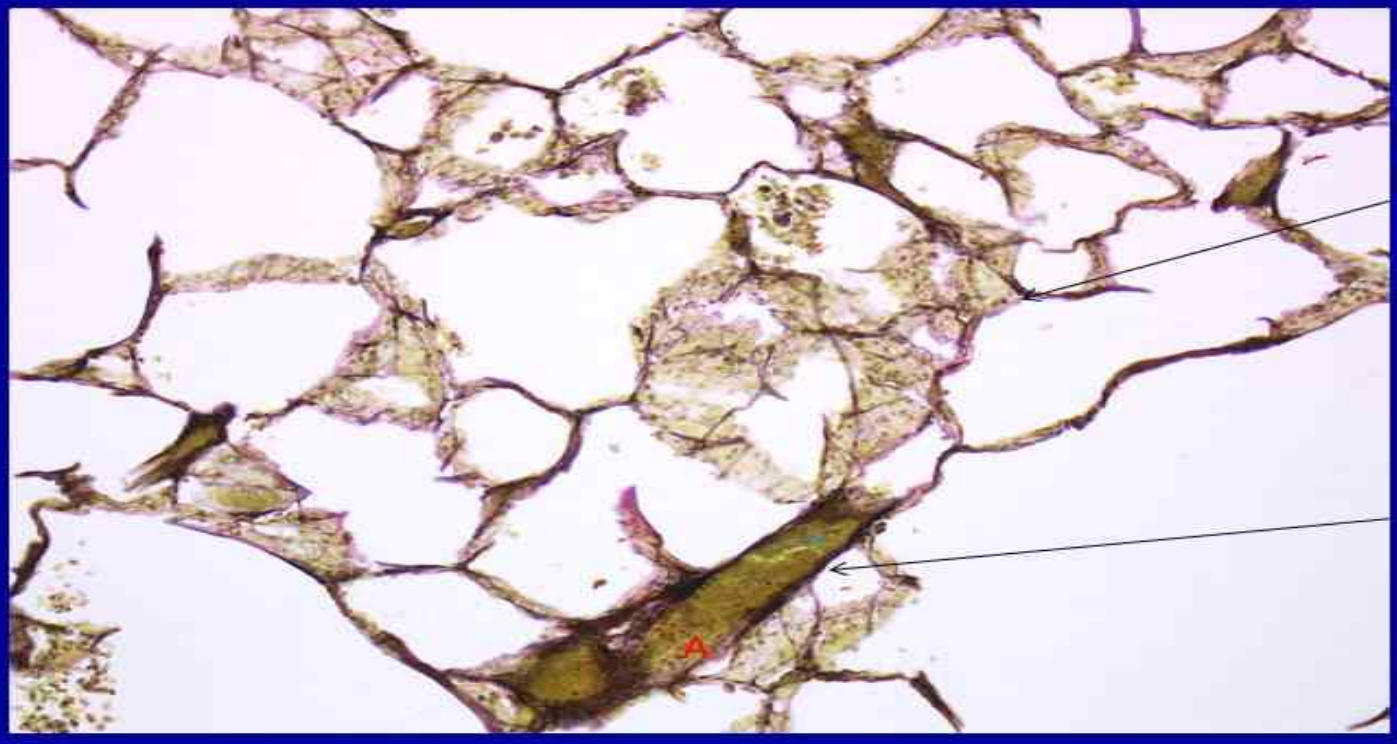
AJRCCM 2025;211(7):1132-1155

Why does fibrosis occur in the subpleural area?

- Collection of venous and lymphatic drainage
- Single faced alveolar walls in the subpleural and paraseptal area

Single-faced alveolar walls and double faced alveolar walls

Single-faced alveolar wall is located along the interlobular septa, blood vessels and bronchus and bronchiole, while double-faced alveolar wall



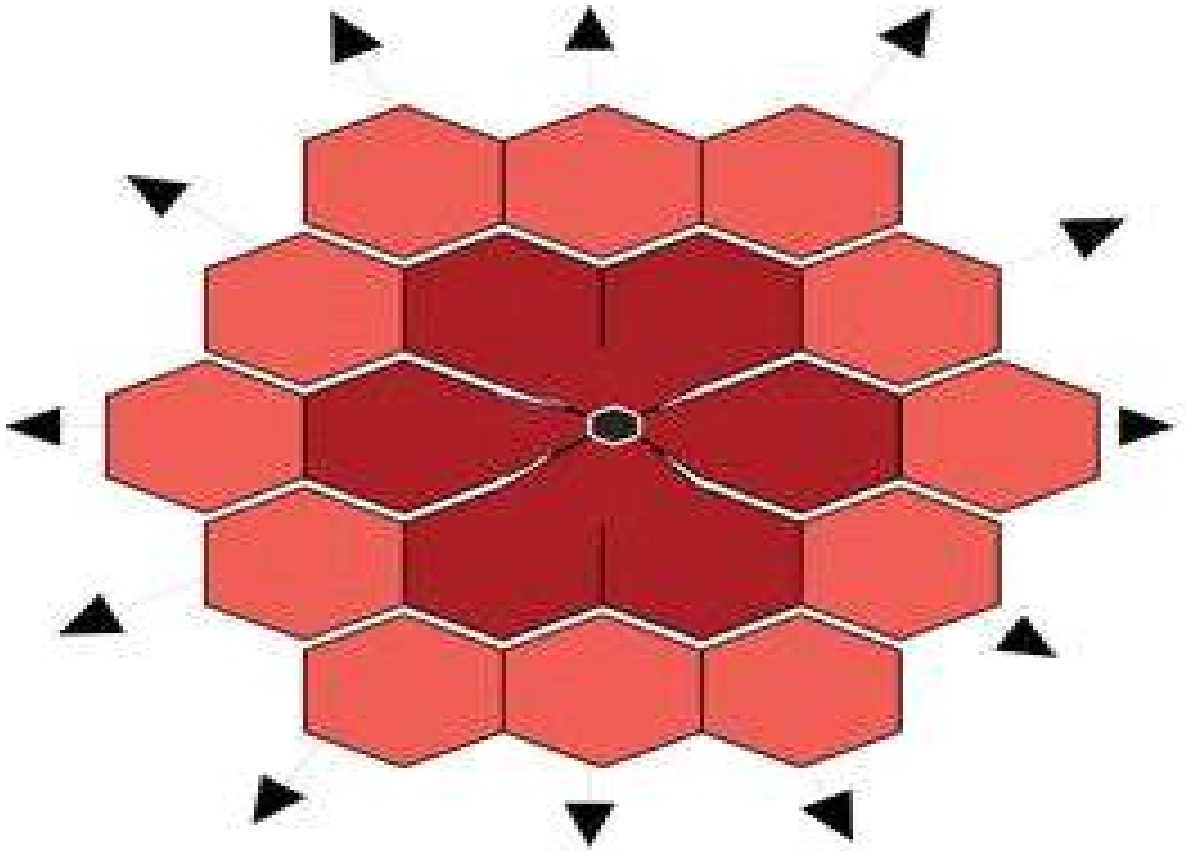
Double-faced alveolar walls (90%)

Single faced alveolar wall (10%)

A; Arteriole

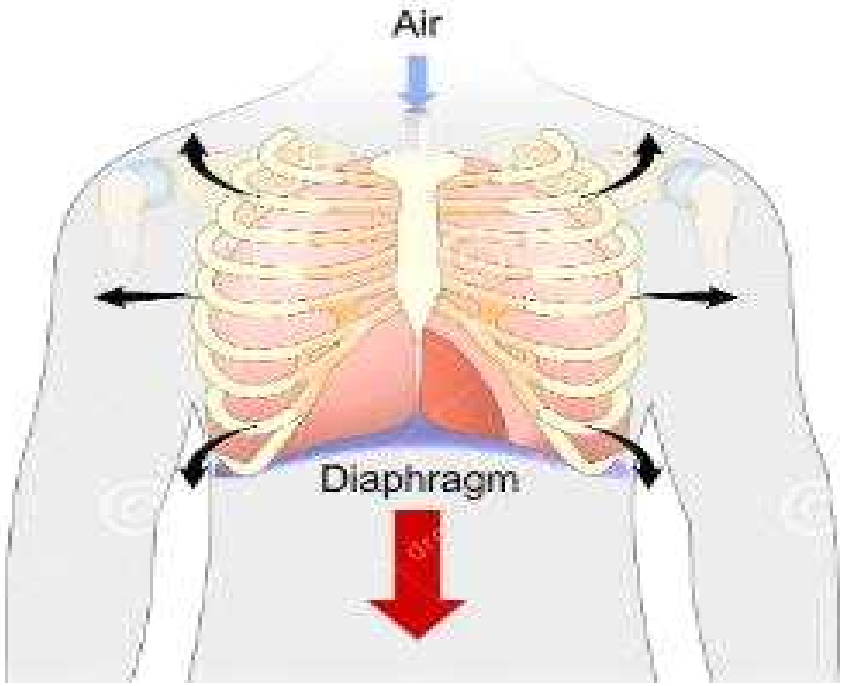
Why does fibrosis occur in the subpleural area?

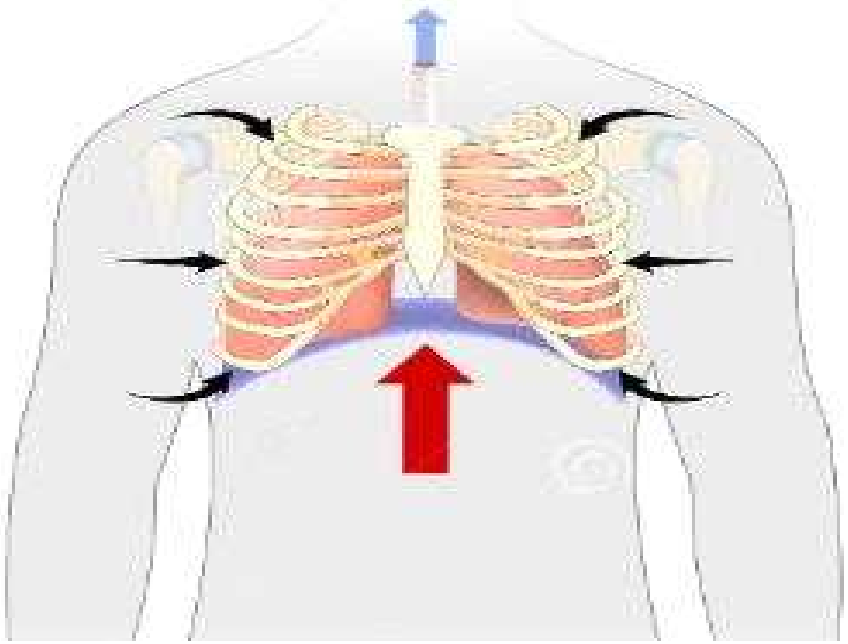
- Collection of venous and lymphatic drainage
- Single faced alveolar walls in the subpleural and paraseptal area



Why does fibrosis occur in the subpleural area?

- Collection of venous and lymphatic drainage
- Single faced alveolar walls in the subpleural and paraseptal area
- Lung movement intensity at the diaphragm
- TGF-β (vulnerable to pressure)





Lung Ultrasound in ILA/ILDs (PRO)

- Lung US can be used in ILA/ILDs because the disease predominantly affects the subpleural region (fibrotic ILD)
- Gold standard: Pathologic Exam ≥ HRCT

  (ILA – radiologic definition)
- Limitations: adverse events of invasive test, radiation exposure of serial CT, cost and accessibility, delayed detection of disease progression d/t long follow-up intervals, and subjective nature of symptoms and variability in PFT results
- Needs: bedside, radiation-free, repeatable tool, and <u>early involvement of a respiratory physician</u>

B-lines & Pleural line abnormalities : Physics and Clinical Significance

- **B-lines**: vertical hyperechoic artifacts from pleural line to screen edge

  → Generated by acoustic impedance mismatch at air-fluid/tissue interfaces

  → Normal lung: ≤2 B-lines per intercostal space

  → ≥3 B-lines per zone = "interstitial syndrome"

  → Reflect subpleural interstitial thickening (edema, fibrosis, inflammation)

  → Key distinction: multiple discrete (early/mild ILD) vs coalescent (advanced fibrosis)

- **Pleural line abnormalities**: Structural alterations of the normally smooth, thin, and continuous pleural line

  → Irregular: subpleural fibrosis and architectural distortion

  → Thickened: fibrotic or chronic involvement

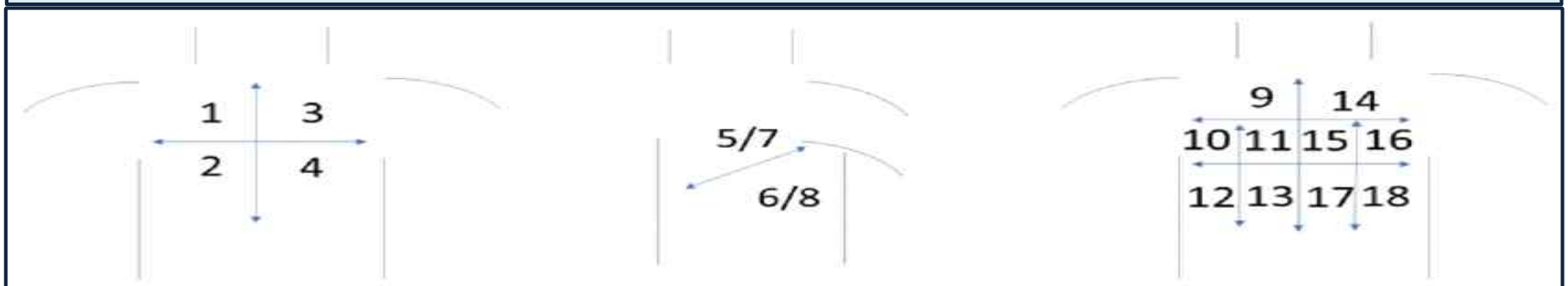
  → Fragmentation: heterogenous or advanced fibrosis

- Reduced or absent pleural sliding: reduced lung compliance or pleural stiffness

Article

Lung Ultrasound in the Screening of Pulmonary Interstitial Involvement Secondary to Systemic Connective Tissue Disease: A Prospective Pilot Study Involving 180 Patients

- A prospective, blinded, multimodal comparative study in Poland between 2019 and 2021
- Rheumatologist (LUS) and Radiologist (HRCT)
- HRCT definition of ILD – bilateral reticulation and/or honeycombing and/or bronchiectasis
- LUS definition of ILD – bilateral B-lines (single or multiple) and pleural line disorder (irregular and coarse or fragmented or blurred)



Parameter	*n* (%)
Gender	
Females	130 (73.9)
Males	46 (26.1)
Rheumatoid arthritis (RA)	22 (12.5)
Eosinophilic granulomatosis with polyangiitis (EGPA)	10 (5.7)
Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA)	25 (14.2)
Myositis	18 (10.2)
Systemic lupus erythematosus (SLE)	25 (14.2)
Systemic sclerosis (SSC)	30 (17)
Sjögren syndrome	46 (26.1)

Lung Ultrasound in the Screening of Pulmonary Interstitial Involvement Secondary to Systemic Connective Tissue Disease: A Prospective Pilot Study Involving 180 Patients

	n	%
LUS		
Pleural line—irregular	34	19.3
Pleural line—coarse	29	16.5
Pleural line—fragmented	18	10.2
Pleural line—blurred	7	4.0
Pleural line—thickened	1	0.6
B-line artifacts—single	28	15.9
B-line artifacts—multiple	17	9.7
B-line artifacts—white lung	4	2.3
Am artifacts	1	0.6
Consolidations < 5 mm	7	4.0
Consolidations > 5 mm	2	1.2
HRCT		
Reticular pattern	29	16.5
Small-nodular pattern	3	1.7
Interlobular septal thickening	5	2.8
Bronchiectasis, changed by inflammation	25	14.2
Cysts	20	11.4
Honeycombing	7	4.0
Ground-glass	8	4.5

		Interstitial Disease in LUS			
		No		Yes	
		n	%	*n*	%
Interstitial disease in HRCT	no	147	99.3	1	0.7
	yes	1	3.6	27	96.4

Lung Ultrasound in the Screening of Pulmonary Interstitial Involvement Secondary to Systemic Connective Tissue Disease: A Prospective Pilot Study Involving 180 Patients

		Interstitial Disease in LUS			
		No		Yes	
		n	%	*n*	%
Interstitial disease in HRCT	no	147	99.3	1	0.7
	yes	1	3.6	27	96.4

- **<u>Correlations between HRCT and LUS</u>**
  - Reticulation (HRCT) – pleural line (irregular/coarse/fragmented) and B-line
  - Septal thickening – white lung pattern
  - Bronchiectasis – pleural abnormalities
  - Honeycombing – small consolidations + white lung + blurred pleural

  → Higher HRCT fibrotic burden → more LUS abnormalities

❖ **LUS demonstrates excellent accuracy for screening ILD in CTD patients, with pleural abnormalities and B-lines as key diagnostic features**

	RR
Pleura	4.82
Pleura	14.40
Pleura	8.32
Pleura	-
Pleura	-
B-line	13.81
B-line	15.72
B-line	-
Am ar	-
Conso	-
Conso	-

scientific reports

OPEN

Lung ultrasound B-line quantification in CTD-ILD: a cross-sectional single-center observational study

- A prospective cross-sectional single-center study in China (117 CTD-ILD – HRCT confirmed)
- LUS – scoring system of B-lines across 12 zone method
- To evaluate correlations between LUS B-lines score and 1) HRCT (Warrick score) and 2) PFT

Each zone scored 0–3: → Total **LUS score = sum of 12 zones (0–36)**

Score	Definition
0	Normal (A-lines or ≤2 B-lines)
1	Multiple B-lines (moderate loss)
2	Coalescent B-lines (severe loss)
3	Consolidation

lung consolidation

mild

HRCT: ground-glass opacity (red arrow)

LUS: discrete B-lines

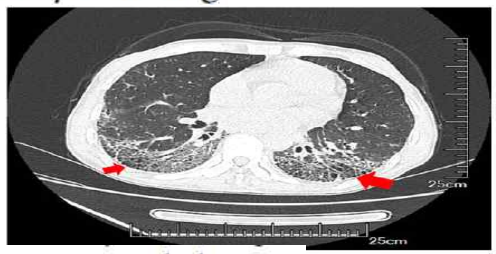
moderate

lung lobular septa

coalescent B-lines

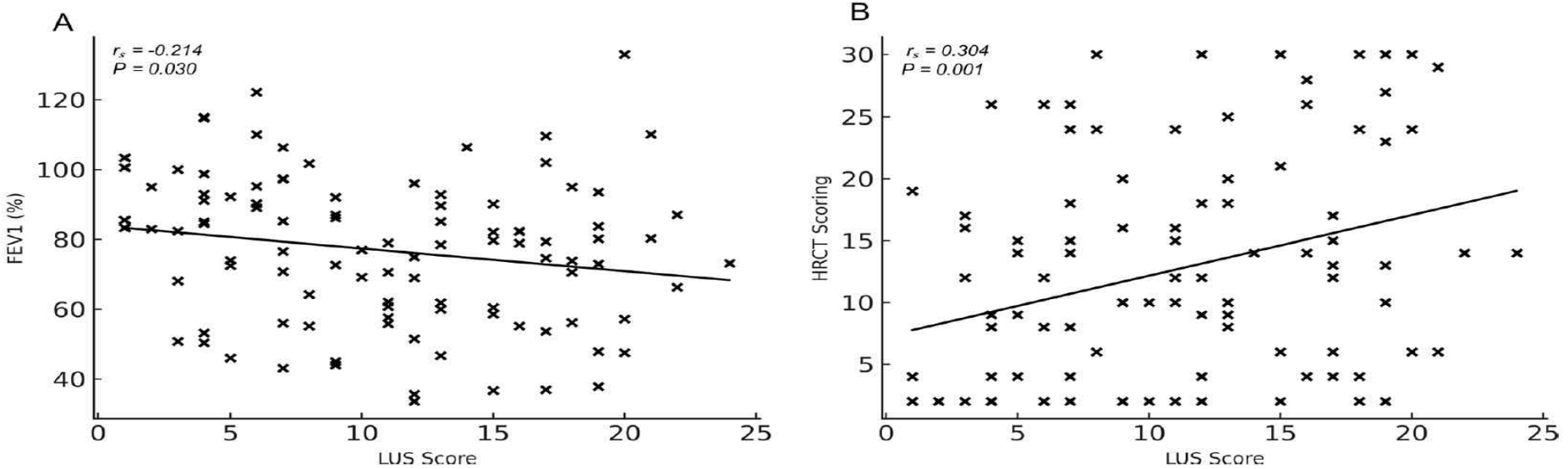
severe

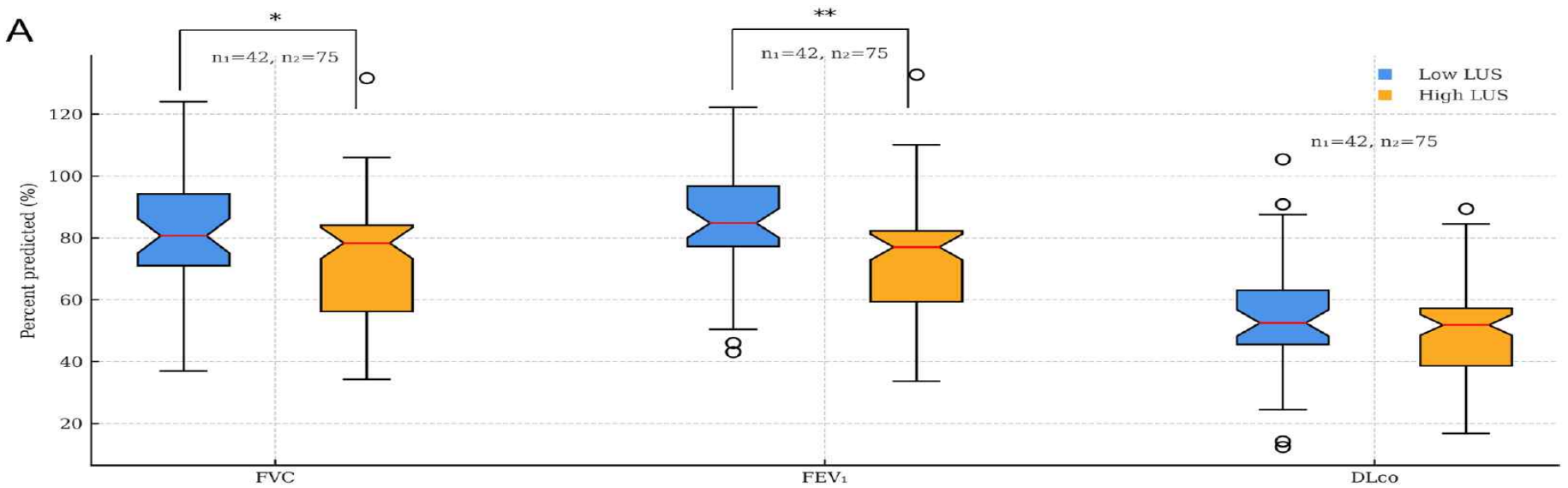
honeycombing



lung consolidation

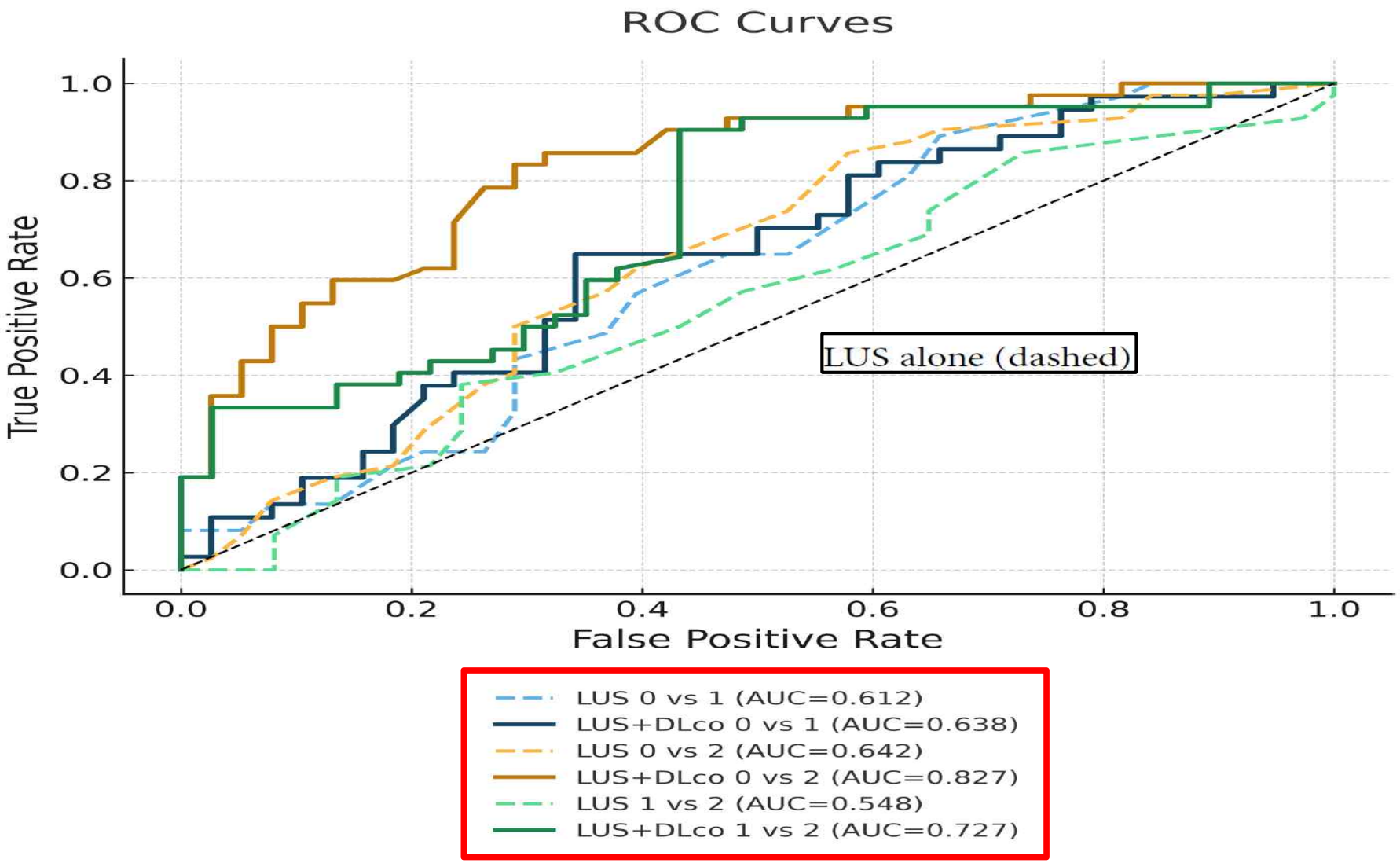
Analysis of the correlation between LUS score and PFT/HRCT





Scientific Reports (2026) 16:6099

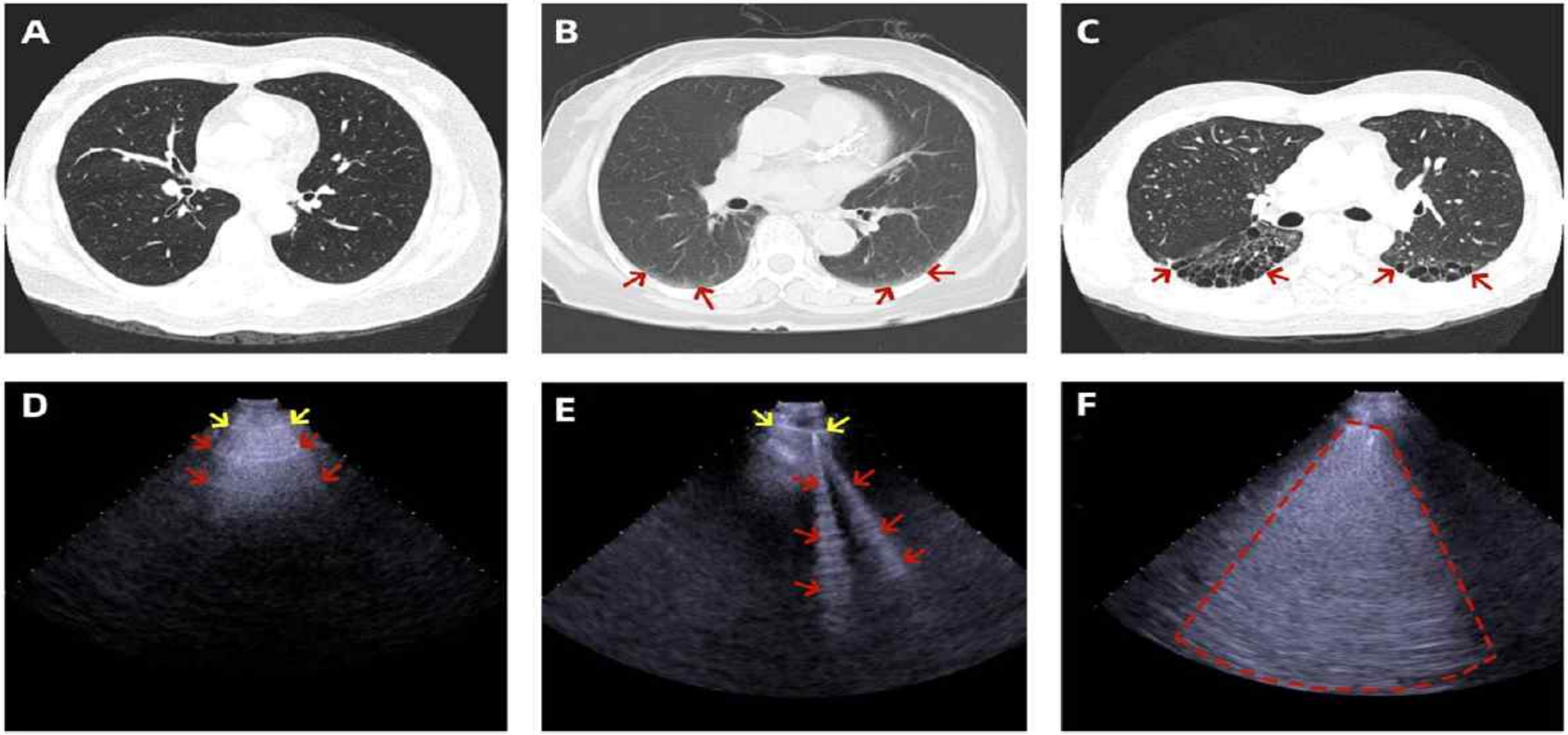
ROC curves comparing LUS alone and the combined LUS + Dlco model for HRCT severity classification



Scientific Reports (2026) 16:6099

Performance of Lung Ultrasound for Monitoring Interstitial Lung Disease

- A prospective longitudinal single-center study in Greece (n= 24 ILD, 6 CTD, 6 CPFE, 3 IPF…)
- Pulmonologist (LUS & PFT), Radiologist (HRCT), Rheumatologist (MDD)
- LUS – total number of B-lines across 56 intercostal space
- To assess the role of LUS in monitoring ILD



J Ultrasound Med. 2022; 41(5):1077-1084

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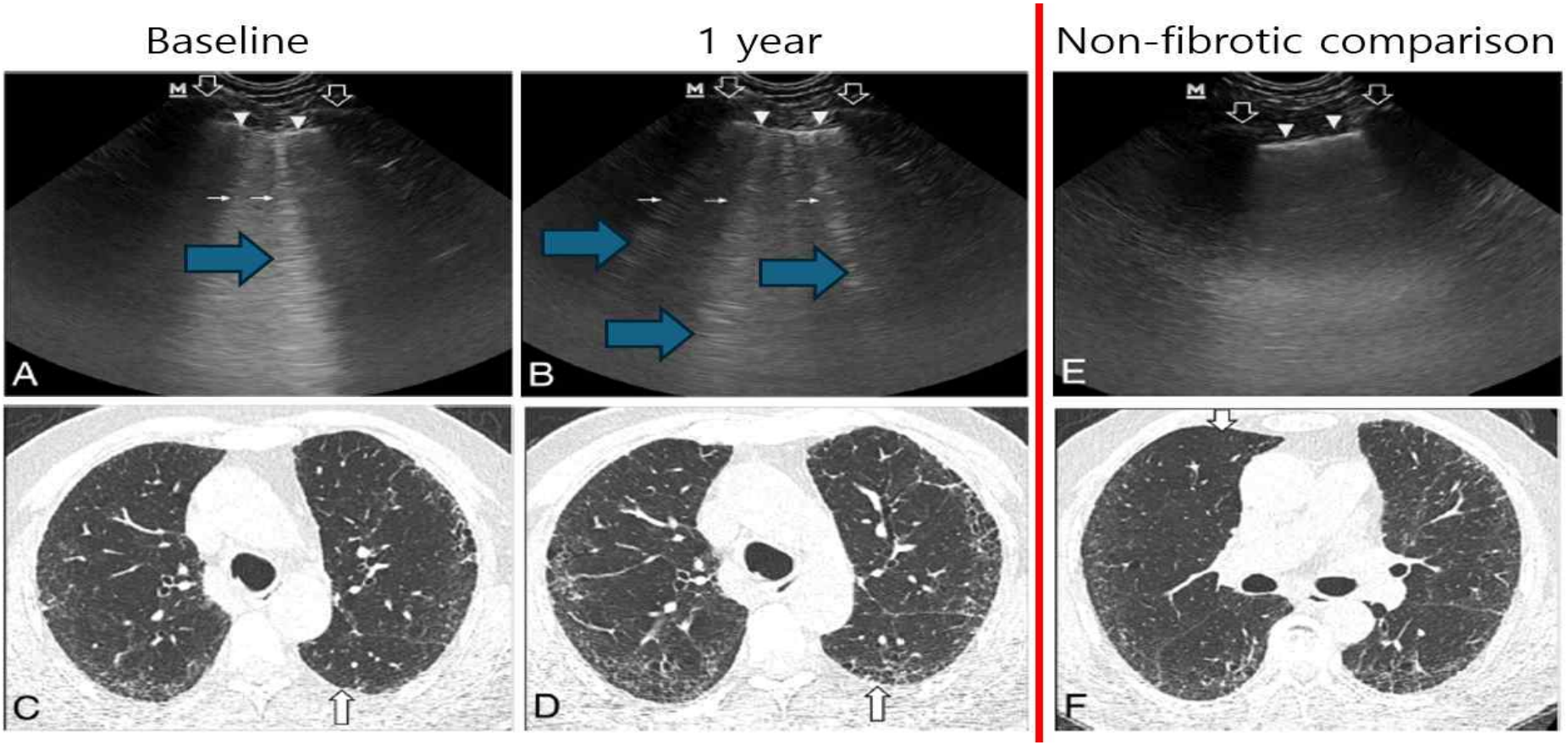

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Performance of Lung Ultrasound for Monitoring Interstitial Lung Disease

Table 3. Univariate Regression Analysis for Association of Lung Ultrasound Scores With Pulmonary Function Tests at 6 Months and 1 Year

Time-Point	Variable	B Value (95% CI)	*P* Value
6 months	VA	−3.717 (−7.368 to −0.067)	.046
	DLCO	−2.635 (−4.736 to −0.534)	<.001
1 year	KCO	−2.367 (−4.483 to −0.251)	.031
	DLCO	−4.245 (−6.605 to −1.885)	.002

VA, alveolar volume; DLCO, diffusing capacity for carbon monoxide; KCO, transfer coefficient of the lung for carbon monoxide.

- Higher LUS score → Worse gas exchange (DLco)
- LUS can reflect disease progression

❖ As monitoring tool, LUS correlates with PFT decline

❖ Limitations – small sample size, single operator, heterogenous ILD population

J Ultrasound Med. 2022; 41(5):1077-1084

Current evidence of LUS in ILA/ILD

- **CTD-ILD screening and adjunct assessment**

  → Most evidence is focused on systemic sclerosis, RA, and inflammatory myopathy

  → In the 2019 meta-analysis, pooled diagnostic performance of LUS for CTD-ILD sensitivity – 0.859 and specificity 0.839 with AUC – 0.934 (a useful adjuntive diagnostic modality compared with /HRCT

- **High consistent correlation with HRCT and lung function**

  → Total B-line burden correlate with HRCT extent/severity

  → Correlation similar to HRCT with several prognostic parameters

- **Early detection of ILD than PFT**

  → LUS may detect subpleural early abnormalities while PFT may be normal or falsely negative in early CTD-ILD

- **Improved assessment with multimodal approach** (LUS + PFT + HRCT, and symptoms) for predicting prognosis (A complementary tool, not a replacement)

Limitations: Lung Ultrasound in ILA/ILDs (CON)

- **Specificity concerns:**

  B-lines not specific to fibrosis (edema, infection, atelectasis)

  Pooled specificity 64-84% across meta-analysis

- **Protocol heterogeneity:**

  Zone numbers vary widely (12 to 72 across studies)

  No standard protocol and cut-off established (study design, not clinical use)

- **Operator dependence:**

  Though reliability is good (Kappa 0.78-0.93), training matters

- **Patient factors;**

  Obesity, subcutaneous edema can impair image quality

- **LUS cannot provide HRCT-like morphological pattern**
- **The evidence mostly based on CTD-ILD**
- **Real practice:** limited time in outpatient settings, no reimbursement, no validated and standardized protocol for the Korean healthcare system, insufficient evidence as a formal test, significant inter-institutional variability or difference, lack of acceptance among clinicians…

Summary

- Updated ILA definition – High risk + Incidental ILA on HRCT
- Potential assessment for progression and Baseline measurement of symptoms and PFT
- Subpleural abnormalities in ILA/ILD
- Role of LUS in ILA: 1) Monitoring After ILA Diagnosis: Tracking Progression of ILA or to ILD
- Role of LUS in ILA: 2) Early Screening and Longitudinal Monitoring of ILA Before CT Detection
- Challenges in real practice
- Adjunctive, Not Independent：as a Complementary Diagnostic Tool

감사합니다