Radiological interpretation of interstitial lung disease (ILD)

15:50-16:40

115年07月19日（日）

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Interstitial lung disease (ILD)

- A heterogeneous group of diffuse parenchymal lung disorders
- Characterized by varying degrees of chronic inflammation, fibrosis, or both, which may progress to respiratory failure.
- Thin-section chest CT: a greater understanding of various ILD manifestations. Increased appreciation of radiologic-pathologic correlation
- Risks associated with surgical lung biopsy have shifted the diagnostic paradigm from a histopathology-based approach to a noninvasive, multidisciplinary approach heavily reliant on imaging.
- The **identification of fibrosis** carries direct prognostic and therapeutic implications. (UIP-centric approach of fibrotic ILD)

HRCT Patterns in Idiopathic Pulmonary Fibrosis

	HRCT Pattern			
	UIP Pattern	**Probable UIP Pattern**	**Indeterminate for UIP**	**CT Findings Suggestive of an Alternative Diagnosis**
Level of confidence for UIP histology	Confident (>90%)	Provisional high confidence (70–89%)	Provisional low confidence (51–69%)	Low to very low confidence (≤50%)
Distribution	• Subpleural and basal predominant • Often heterogeneous (areas of normal lung interspersed with fibrosis) • Occasionally diffuse • May be asymmetric	• Subpleural and basal predominant • Often heterogeneous (areas of normal lung interspersed with reticulation and traction bronchiectasis/ bronchiolectasis)	• Diffuse distribution without subpleural predominance	• Peribronchovascular predominant with subpleural sparing (consider NSIP) • Perilymphatic distribution (consider sarcoidosis) • Upper or mid lung (consider fibrotic HP, CTD-ILD, and sarcoidosis) • Subpleural sparing (consider NSIP or smoking-related IP)
CT features	• Honeycombing with or without traction bronchiectasis/ bronchiolectasis • Presence of irregular thickening of interlobular septa • Usually superimposed with a reticular pattern, mild GGO • May have pulmonary ossification	• Reticular pattern with traction bronchiectasis/ bronchiolectasis • May have mild GGO • Absence of subpleural sparing	• CT features of lung fibrosis that do not suggest any specific etiology	• Lung findings ◦ Cysts (consider LAM, PLCH, LIP, and DIP) ◦ Mosaic attenuation or three-density sign (consider HP) ◦ Predominant GGO (consider HP, smoking-related disease, drug toxicity, and acute exacerbation of fibrosis) ◦ Profuse centrilobular micronodules (consider HP or smoking-related disease) ◦ Nodules (consider sarcoidosis) ◦ Consolidation (consider organizing pneumonia, etc.) • Mediastinal findings ◦ Pleural plaques (consider asbestosis) ◦ Dilated esophagus (consider CTD)

AJRCCM 2022

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

Imaging in interstitial lung diseases (ILD)

- Patterns of abnormality and differential diagnosis of ILD on HRCT
  - Interlobular septal thickening
  - Reticular pattern (reticulation)
  - Cystic pattern and honeycombing
  - Nodular pattern
  - Ground-glass pattern
  - Consolidation
  - Traction bronchiectasis/ bronchiolectasis

Radiological findings of fibrosis

- Reticulation: especially associated with traction bronciolectasis
- Traction bronchiectasis/ bronchiolectasis
- Honeycombing cysts

Normal

Traction bronchiectasis

Honeycombing cysts

The ongoing process of honeycombing formation. There is a spectrum ranging from normal lung tissue (A), through distortion of the secondary lobule with traction bronchiolectasis (B), to end stage cyst formation (C).

Radiological findings other than fibrosis

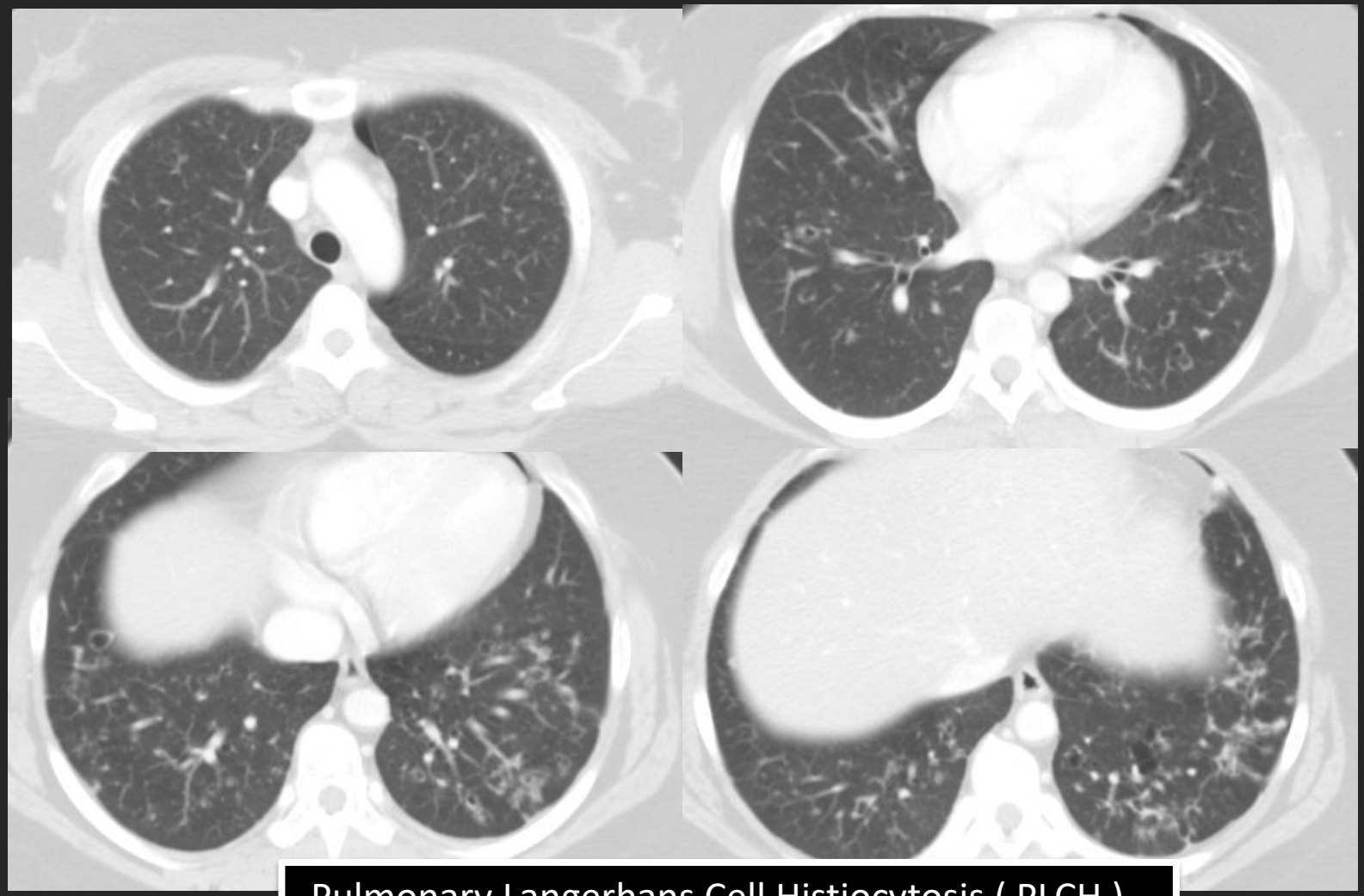
- Ground glass opacities (GGO)
- Consolidation
- Thin wall cysts
- Micronodules (pattern)

Distribution of lung abnormalities

- Upper vs lower lung parenchyma
- Subpleural or subpleural sparing
- Peribronchial
- Centrilobular

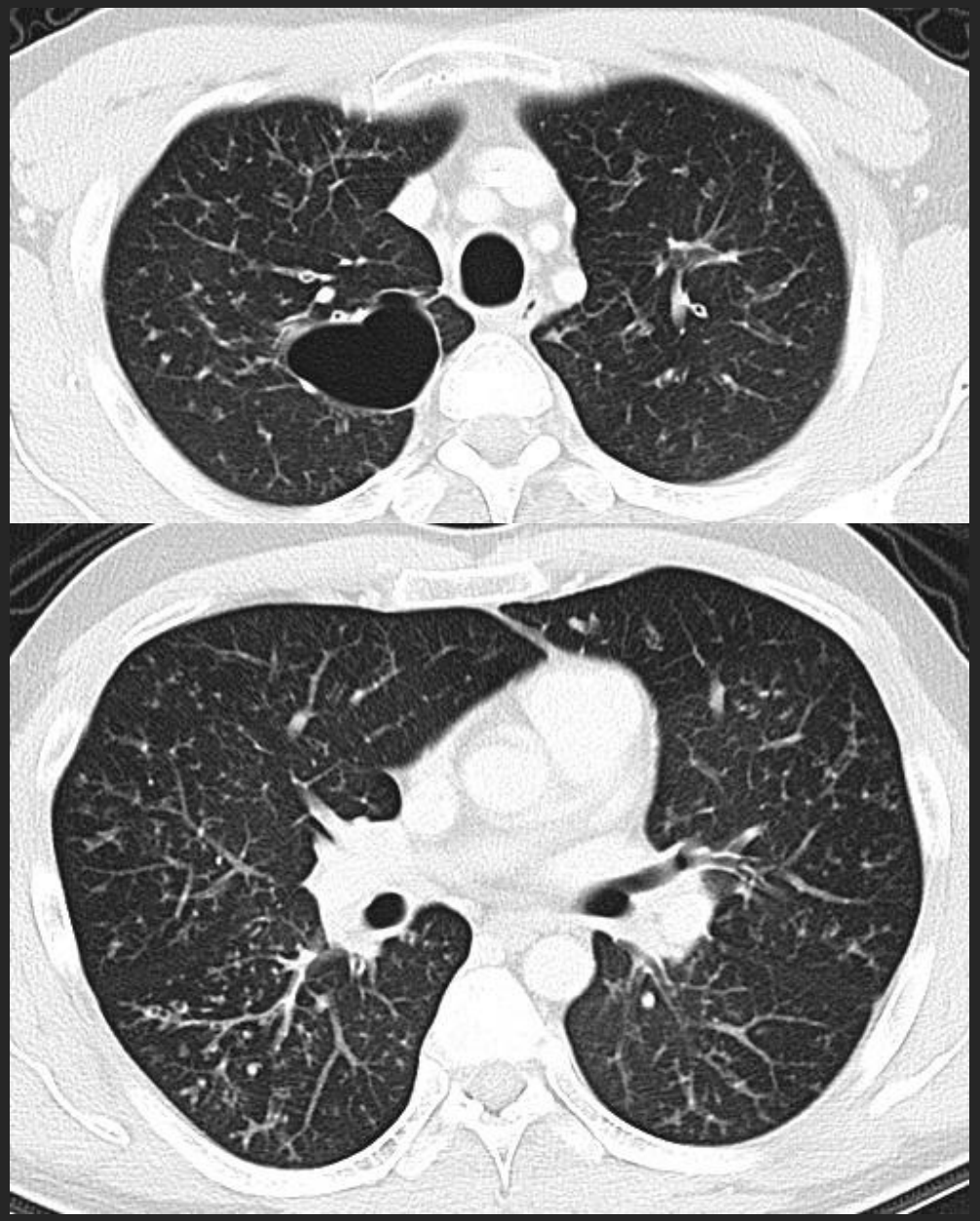
Diffuse nodules, irregular cysts

30 F, non-smoker

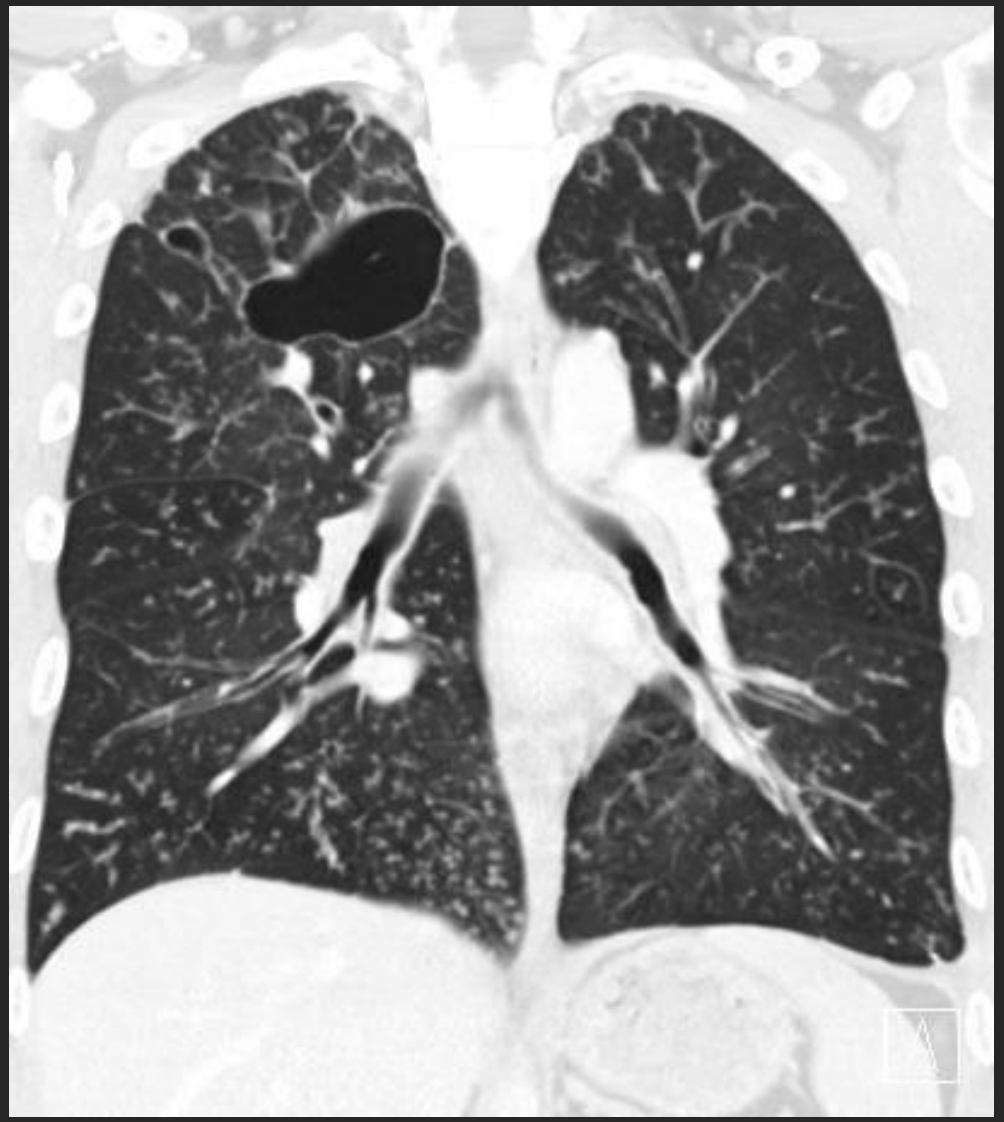


Pulmonary Langerhans Cell Histiocytosis (PLCH)

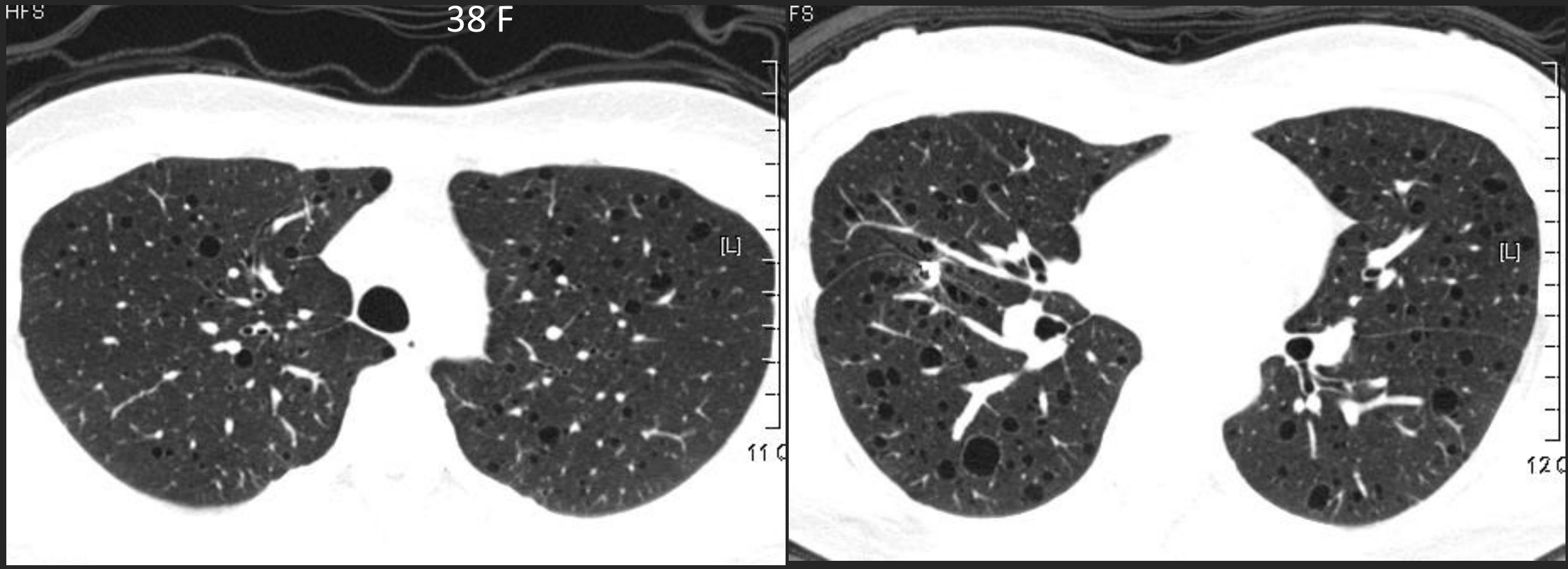
35M



Langerhan Cell Histiocytosis



Thin-wall cysts

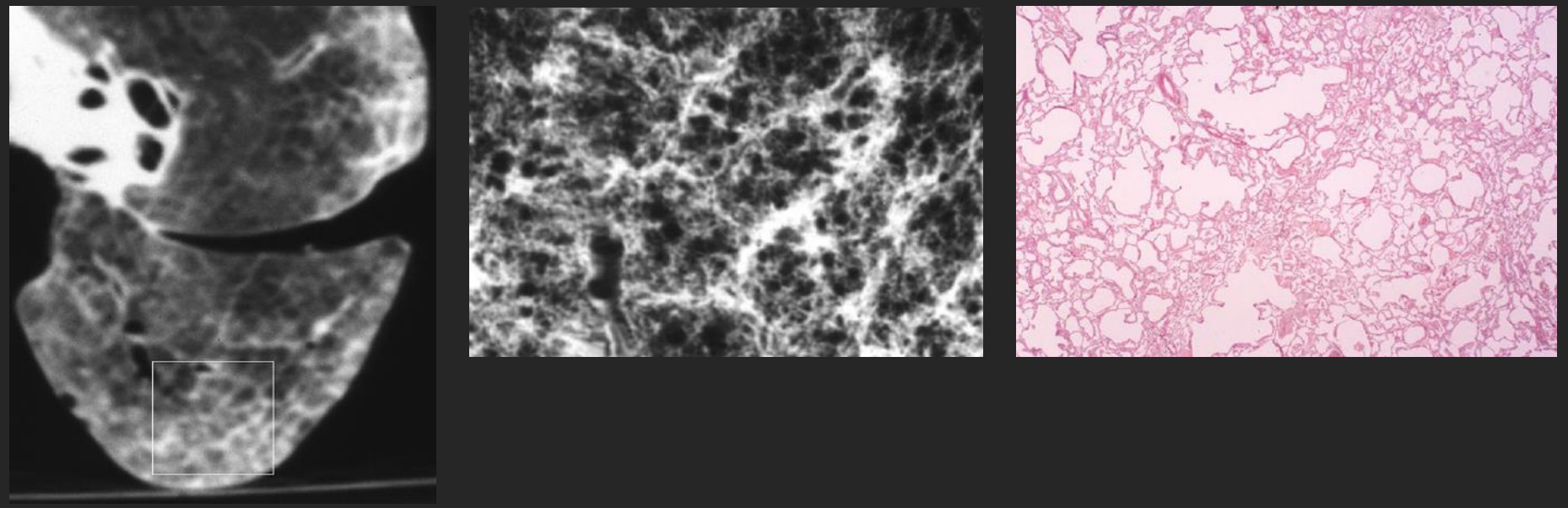


Pulmonary lymphangioleiomyomatosis (LAM)

Honeycombing lung

- Final common feature of end-stage fibrosing ILD
- Cystic dilatation of terminal and respiratory bronchioles consequent to fibrotic destruction of adjacent airspaces, filled with mucin
- Clustered cystic air spaces, typically of comparable diameters on the order of 3-10 mm (occasionally 2.5cm)
- Definable walls, cysts lined up

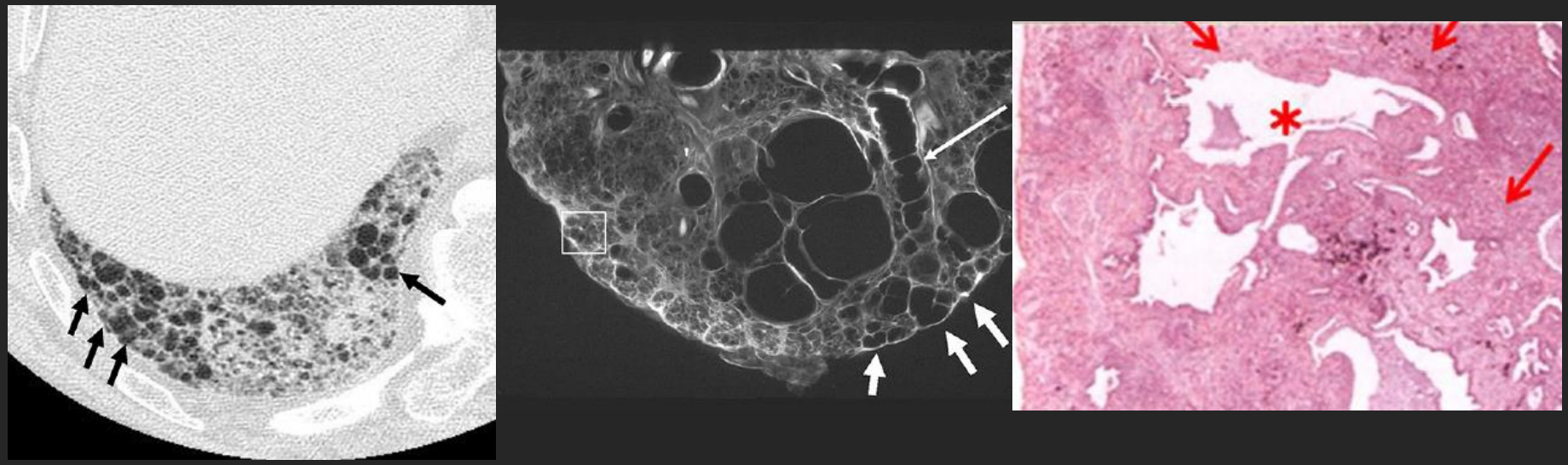
Early stage of fibrosis starts from intralobular opacity



(A) In relatively early stage, fibrosis shows intralobular reticular opacity on CT. (B) Soft X-ray corresponding to the squared area on CT. (C) Scanning micrograph corresponding to the squared area on CT (HE stain; ×8). Admixture of dilatation of terminal airway and periacinar fibrosis correspond to intralobular reticular opacities on CT. If airway dilatation and collapsing of fibrotic alveoli progress, the areas cause honeycombing.

Johkoh T. Euro J Radiol, 2014; 83(1): 27-31. http://dx.doi.org/10.1016/j.ejrad.2013.05.012

CT-pathological correlation of honeycombing



(A) HRCT shows typical honeycombing (arrows) in basal subpleural areas.
(B) Soft X-ray view of post mortem lung inflated and fixed by Heitzman's method. Areas with typical honeycombing (short arrows) are seen in subpleural areas. Note traction bronchiectasis is also seen (long arrows).
(C) Pathologically, honeycombing consists of both collapsing of multiple fibrotic alveoli (arrows) and dilation of alveolar duct and lumen(*).

Johkoh T. Euro J Radiol, 2014; 83(1): 27-31. http://dx.doi.org/10.1016/j.ejrad.2013.05.012

Honeycombing

- Thick walled cystic spaces
- Honeycombing cysts on CT also correlate with foci of traction bronchiolectasis
- Microscopic honeycombing are beyond the resolution of CT and often do not correlate with honeycombing on CT
- Interobserver agreement on CT: only 1/3, when mixed with traction bronchiectasis, large cysts and superimposed paraseptal or centrilobular emphysema

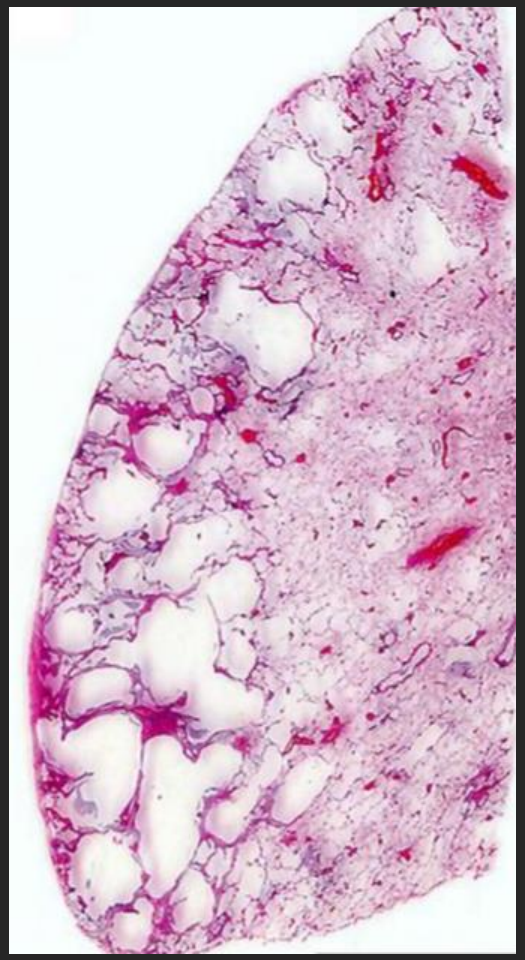
Lynch DA, et al. *Lancet Respir Med* 2017; S2213-2600(17)30433-2

The challenges associated with identification of honeycombing

- CT: Clustered cystic air spaces, cysts of comparable diameters, and cyst diameters typically < 10mm surrounded by well-defined walls.
- Path: Destroyed and fibrotic lung disease containing numerous cystic airspaces with thick fibrous walls. Representing the late stage of various disease, with complete loss of acinar architectures

Airspace Enlargement with Fibrosis

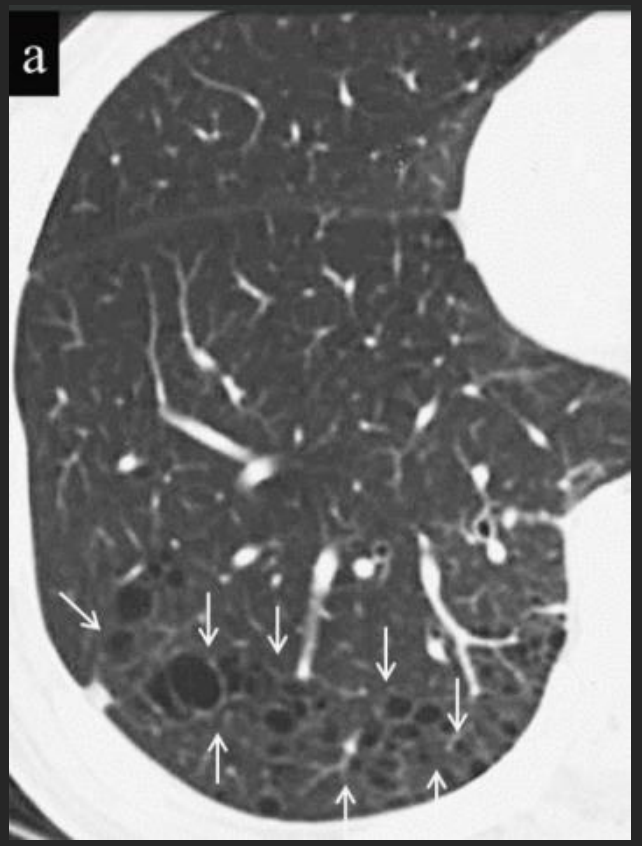
- AEF: smoking related change.
- histological characteristics of AEF differed significantly from UIP, NSIP and CLE.
- multiple cystic lesions with thin walls in the subpleura and deeper parenchyma with tendency of respiratory bronchiolar distribution



Y. Watanabe et al. Euro J Radiol 2015; 84: 986–992

AEF

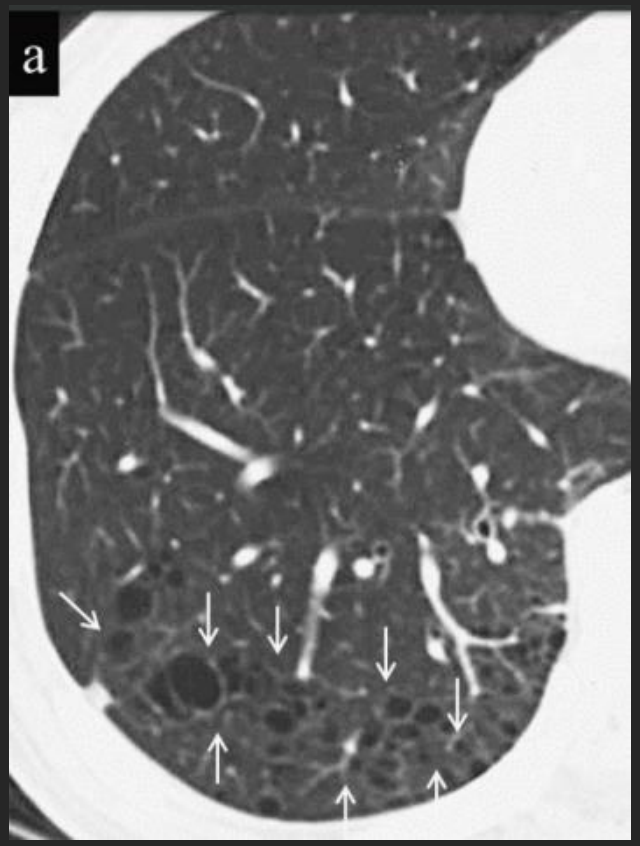
- the histological characteristics of AEF differed significantly from UIP
  - AEF had significantly lower scores for inflammatory cell infiltration than UIP and NSIP, and higher than CLE
  - The score for total intraluminal granulation tissues in AEF was lower than in UIP and NSIP



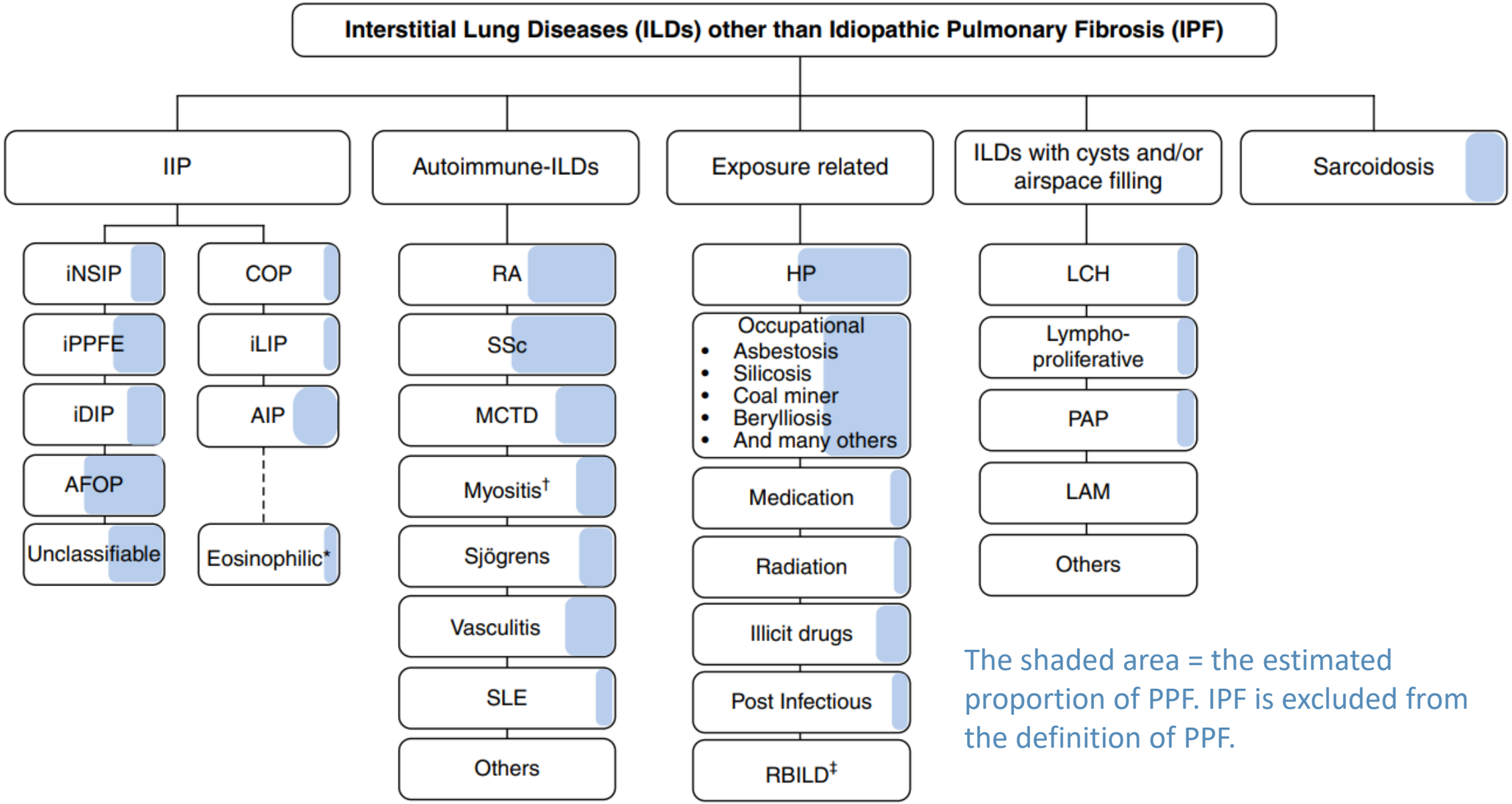
Y. Watanabe et al. Euro J Radiol 2015; 84: 986–992

AEF

- HRCT features of AEF: MTWCs (multiple thin wall cysts), and/or reticular opacities.
- MTWCs might be distinguished from those of honeycomb change.
- MTWCs, these sorts of changes have probably been confused with or interpreted as honeycombing and/ or emphysema.



Y. Watanabe et al. Euro J Radiol 2015; 84: 986–992

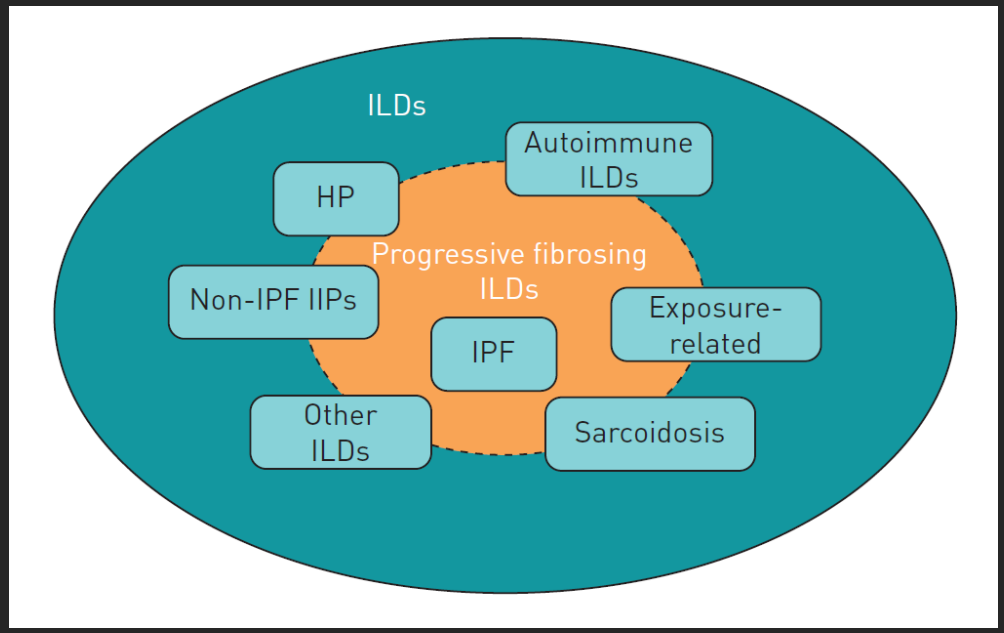


The shaded area = the estimated proportion of PPF. IPF is excluded from the definition of PPF.

Raghu G, et al. Am J Respir Crit Care Med 2022; 205 (9): e18–e47 (May 1, 2022)

Fibrosing ILD

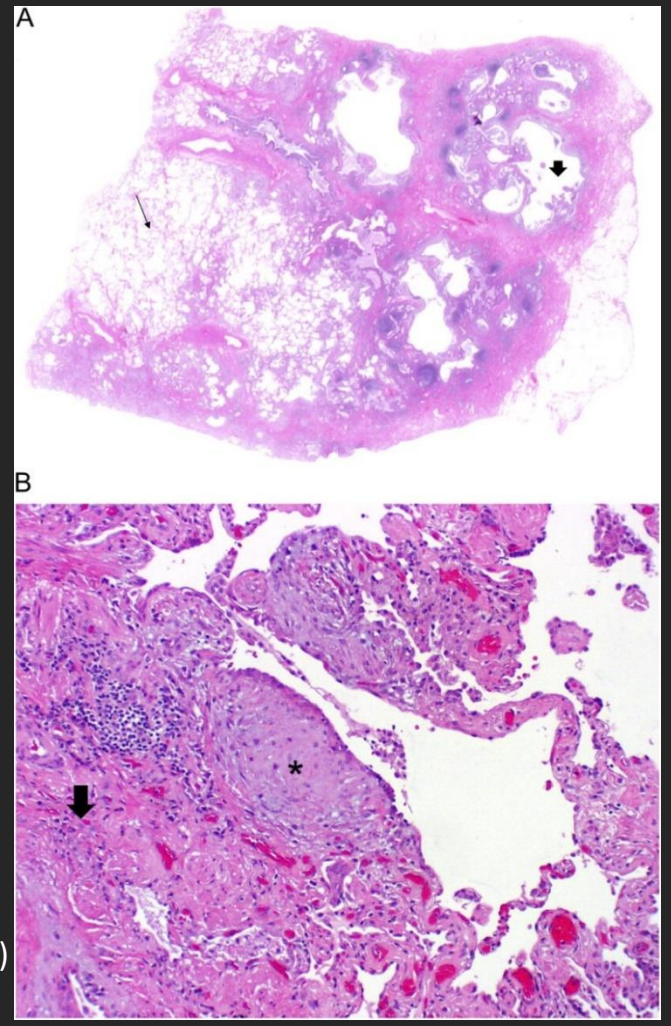
- The most common types of ILD is idiopathic pulmonary fibrosis (IPF).
- Progressive fibrosing ILDs (PF-ILD): to describe ILD in patients who, independent of the classification of the ILD, at some point in time exhibit a progressive fibrosing phenotype.



Cottin V. Eur Respir Rev 2019; 28: 180100

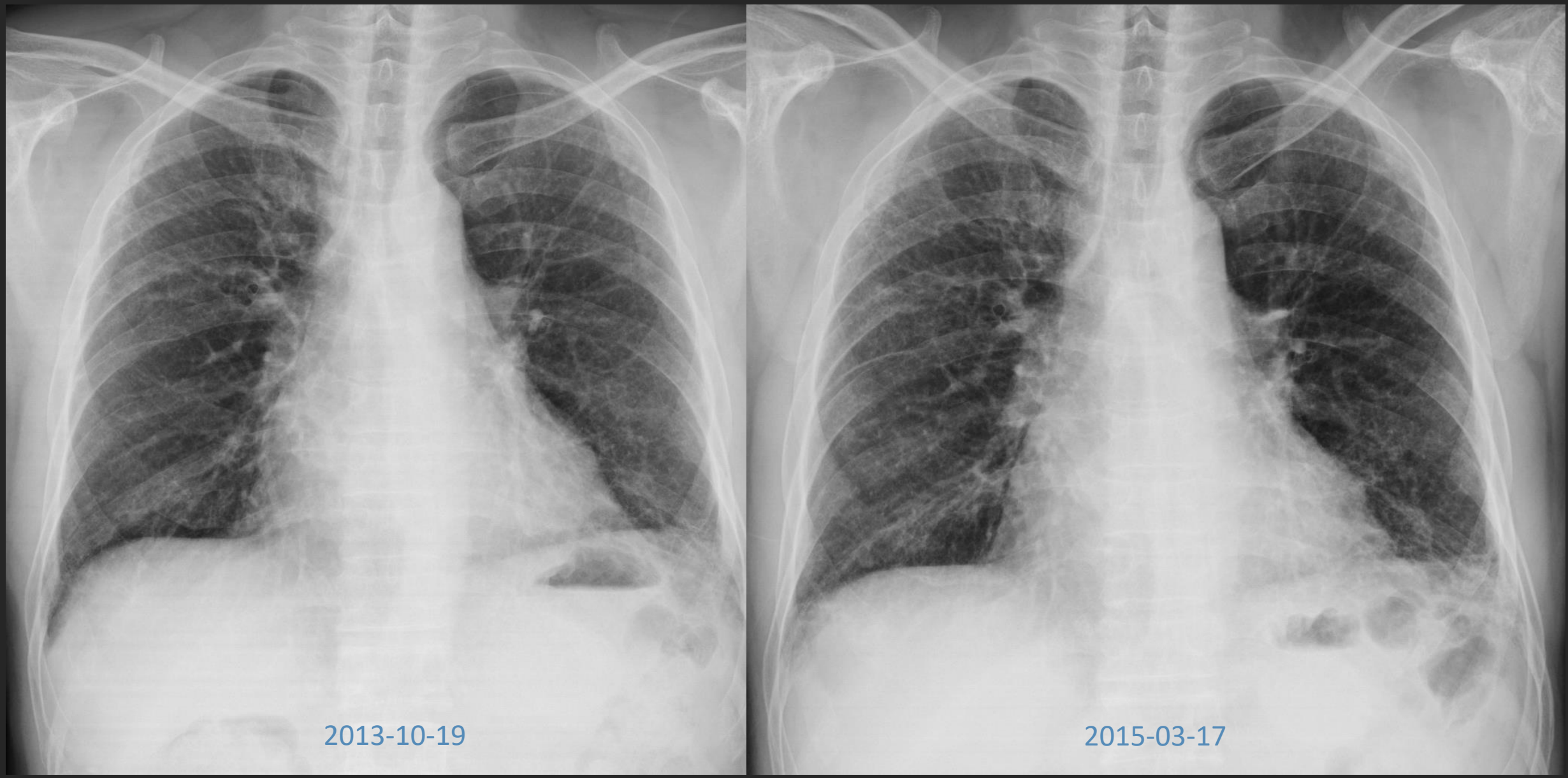
Idiopathic pulmonary fibrosis (IPF)

- A chronic, progressive and fibrotic lung disease
- Altered extracellular matrix and destroyed alveolar architecture
- Decreased lung compliance, disrupted gas exchange
- Respiratory failure and death



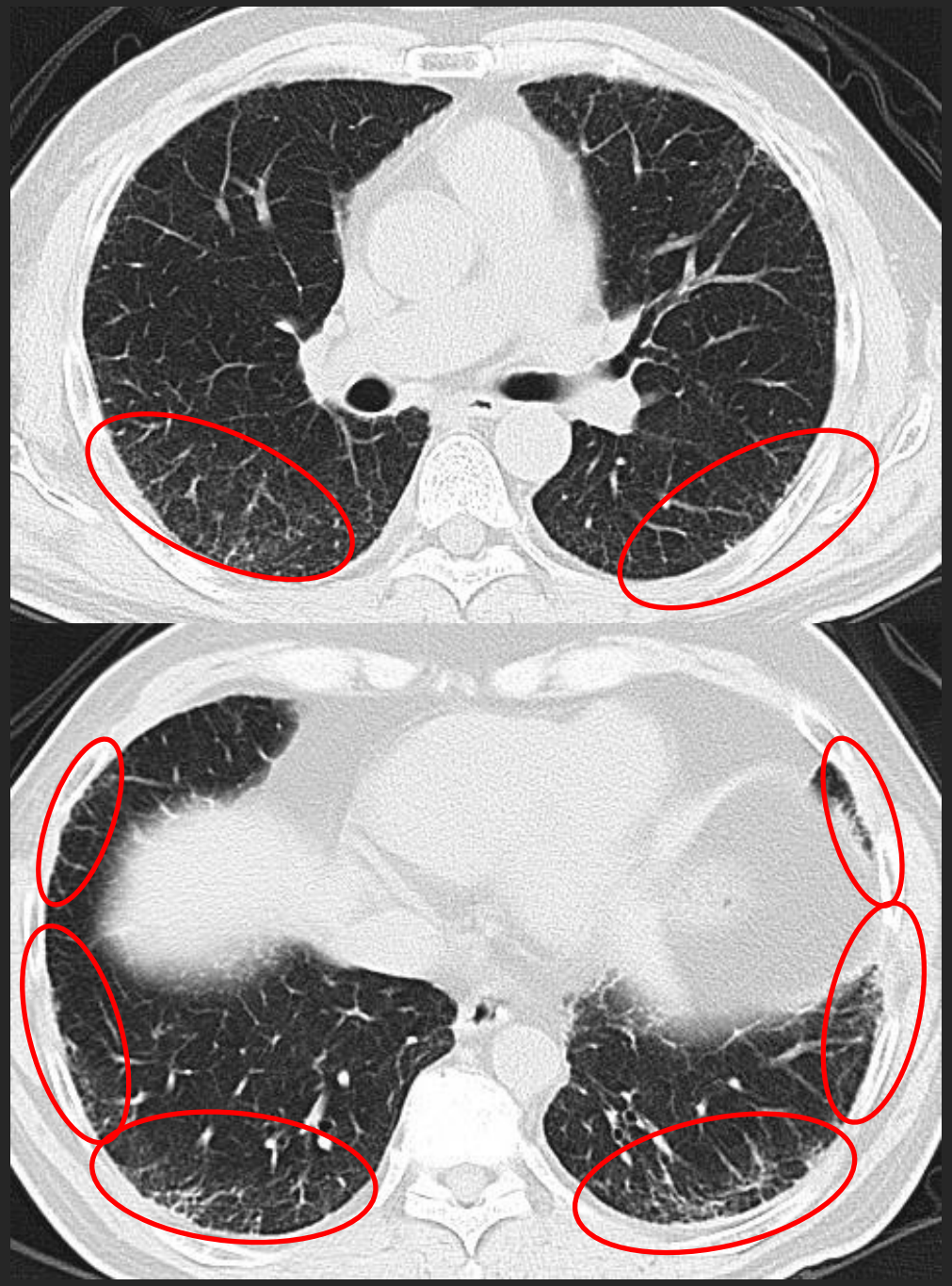
A. Honeycomb space (thick arrow)
Preserved lung tissue region (thin arrow). B. Chronic fibrosis (thick arrow) Fibroblast focus (*)

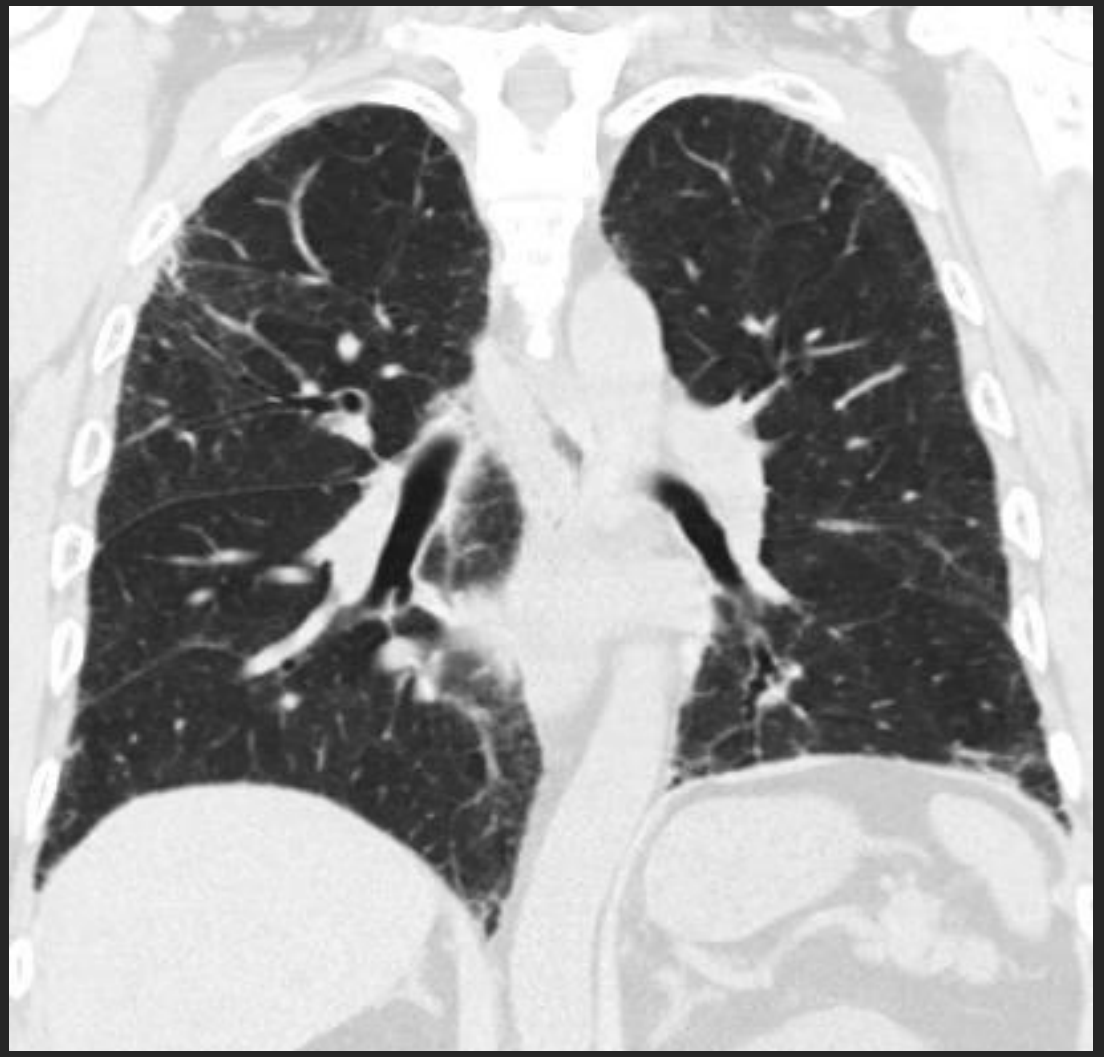
Raghu G, et al. Am J Respir Crit Care Med 2011; 183: 788-824


2013-10-19
2015-03-17

Chest radiographic presentation of ILD

- CXR is usually the first imaging study for pulmonary disease, including IPF
- High suspicious index for CXR findings may lead to the exam of HRCT. Incidental findings on CT ·
- Diagnosis: Typical UIP pattern on HRCT with appropriate clinical setting and scenario, obviating surgical lung biopsy





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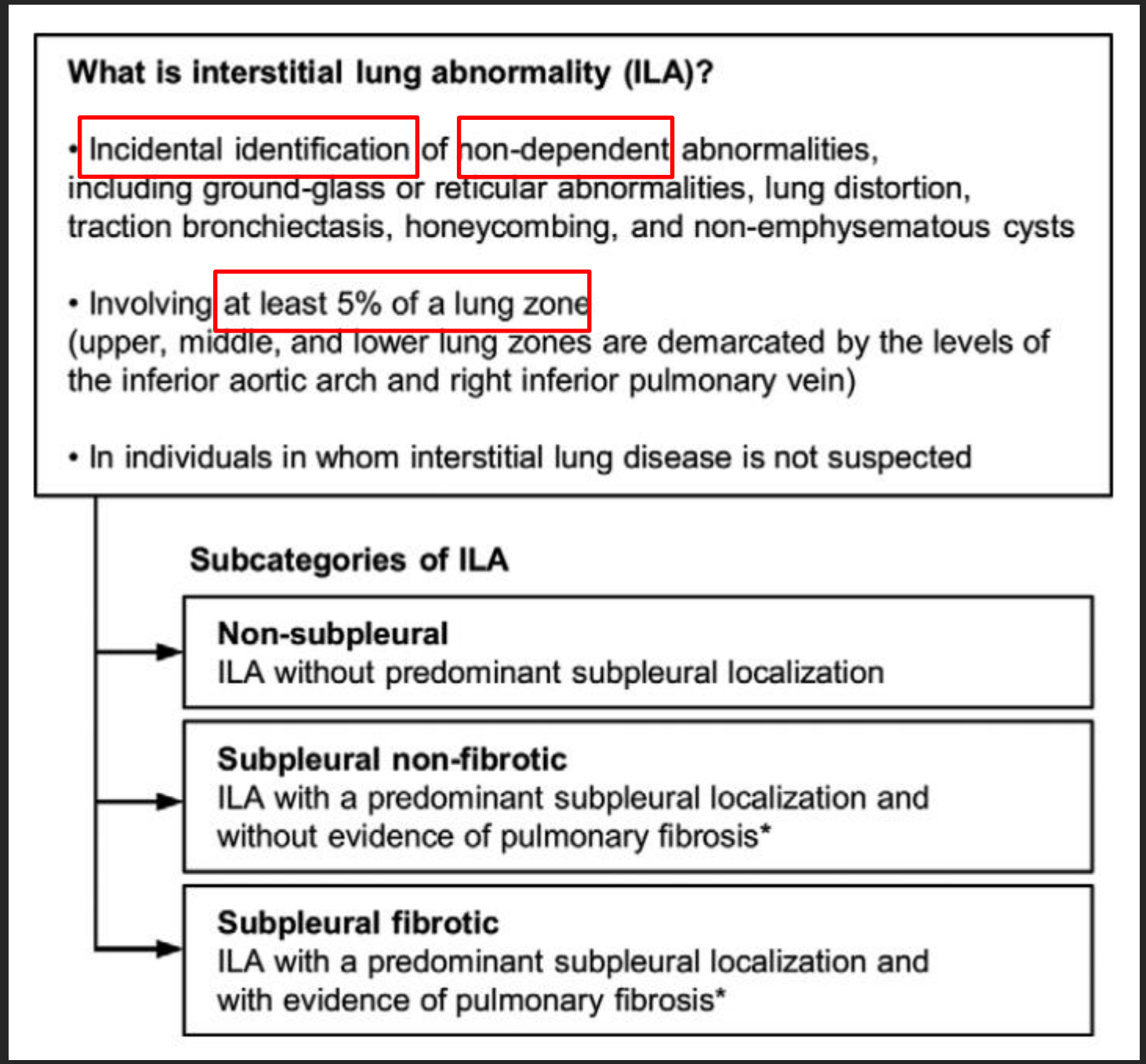
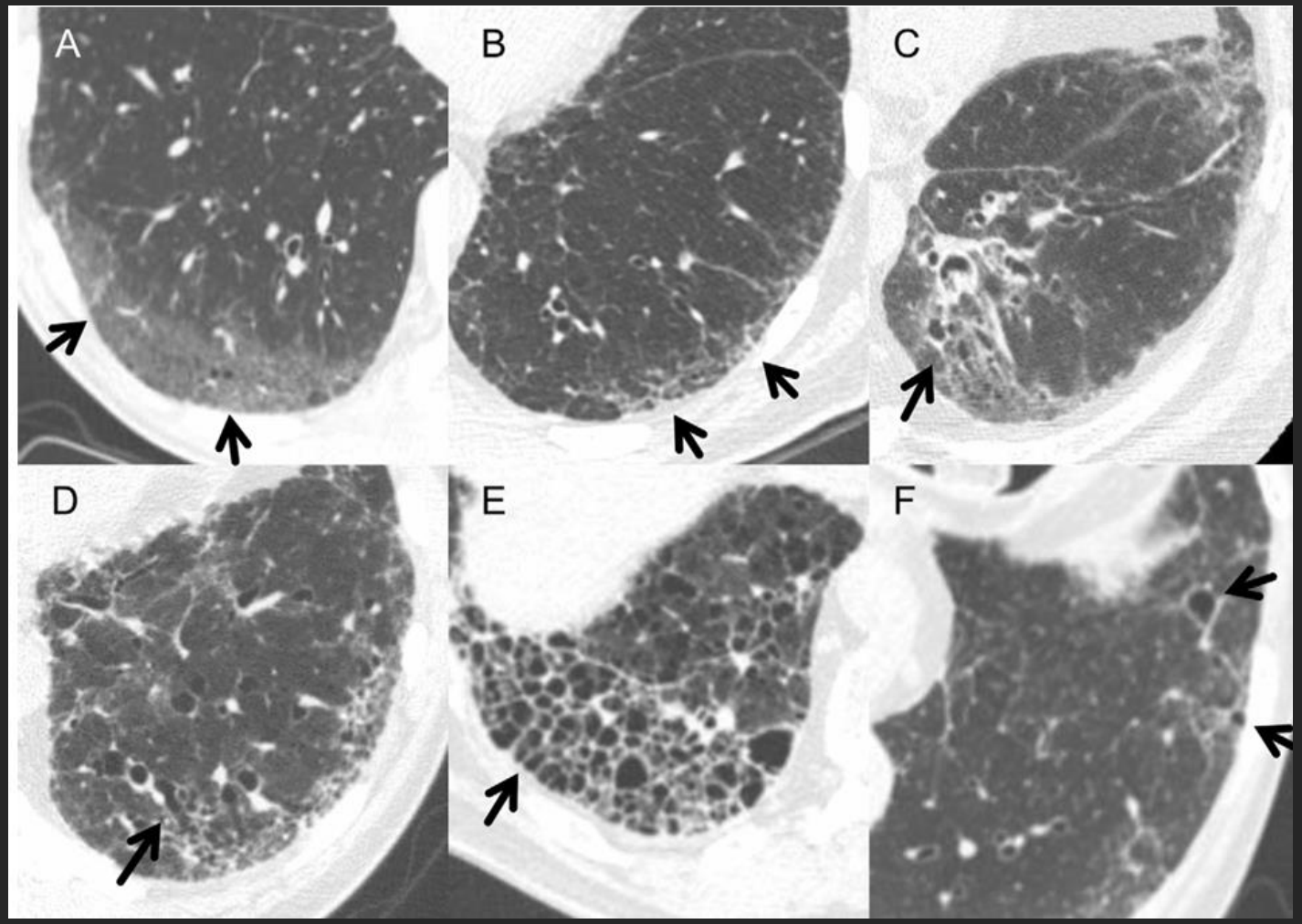


Position Paper from the Fleischner Society

* = Fibrosis is characterized by the presence of architectural distortion with traction bronchiectasis or honeycombing (or both).

Lancet Respir Med 2020;8(7):726–737

Typical findings of ILA



Radiology 2021; 301:19–34

(A) Ground-glass abnormality (arrows) is seen in peripheral lung zone

(B) Reticular abnormality with ground-glass opacity (arrows) is seen in subpleural area

(C) Distortion accompanies ground-glass abnormality and traction bronchiectasis.

(D) Traction bronchiectasis (arrow) is conspicuous in left lower lobe. Ground-glass and reticular abnormalities are also seen in subpleural area.

(E) Honeycombing is demonstrated as appearance of clustered cystic air spaces

(F) Nonemphysematous cysts can be seen as lucencies with well-defined walls (arrows). Surrounding ground-glass and reticular abnormalities are also seen.

Definition of ILA

Table 1. Definition of ILA

Chest CT showing bilateral and nondependent ground-glass opacities, reticular abnormalities, lung distortion, traction bronchiectasis, and/or honeycombing involving ⩾5% of a lung zone*
• Nonemphysematous cysts, centrilobular nodularity, and features of pleuroparenchymal fibroelastosis can be present but do not contribute to the volume of affected lung needed to satisfy the definition of ILA
• Bilaterality may not be necessary in some high-risk cases (i.e., with a family history of familial pulmonary fibrosis or known ILD-associated genetic variants)
• The need for findings to be incidental and exclusion of high-risk populations has purposefully been removed from the definition
• Mild abnormalities occurring exclusively in dependent locations on supine imaging should be confirmed to persist on prone imaging

Definition of abbreviations: CT = computed tomography; ILA = interstitial lung abnormality; ILD = interstitial lung disease.
*Upper, middle, and lower lung zones are demarcated by the levels of the inferior aortic arch and right inferior pulmonary vein, creating a total of six zones (three zones per lung).

Podolanczuk AJ, et al. AJRCCM 2025

Findings Not Considered an ILA

Table 2. Findings Not Considered an ILA

Category	Examples

Extent	• Mild/limited extent
	  ○ Mild focal abnormality (e.g., focal paraspinal [“friction”] fibrosis)
	  ○ Unilateral abnormality (note: unilateral abnormality may be sufficient to characterize as ILA in some populations, e.g., with a family history of familial pulmonary fibrosis)
	• Extensive abnormality that meets the definition of ILD per Table 3

Finding, pattern, etiology	• Dependent lung atelectasis • Unifocal or multifocal linear scarring • Nonemphysematous cysts, centrilobular nodularity, and/or features of pleuroparenchymal fibroelastosis, without other CT findings of lung disease • Findings of heart failure • Findings of aspiration (e.g., patchy ground-glass, opacities tree-in-bud nodularity)

Definition of abbreviations: CT = computed tomography; ILA = interstitial lung abnormality; ILD = interstitial lung disease.

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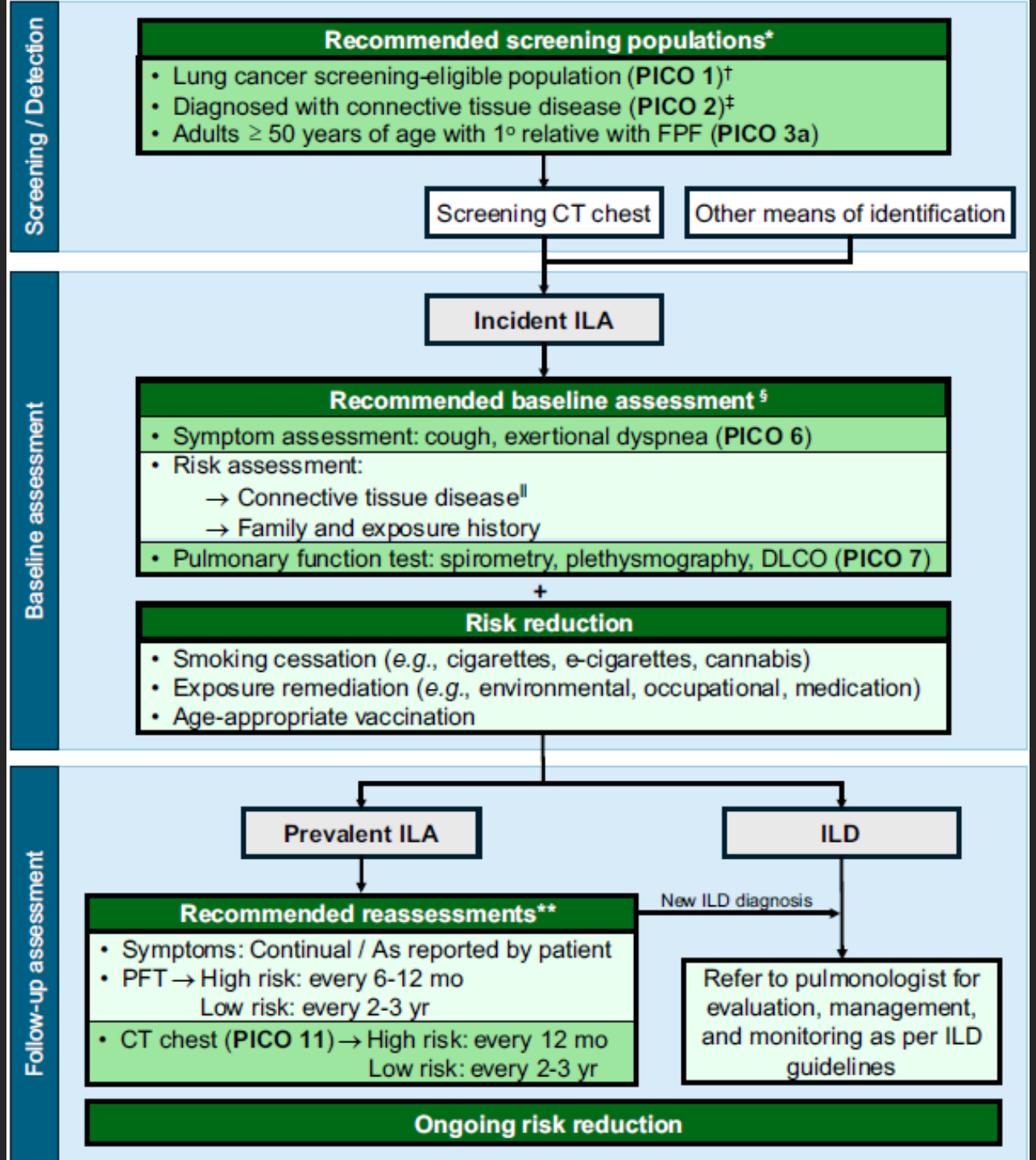
ILD vs. ILA

Table 3. Definition of ILD

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

Definition of abbreviations: CT = computed tomography; HP = hypersensitivity pneumonitis; ILA = interstitial lung abnormality; ILD = interstitial lung disease; NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonitis.
*Further diagnostic workup may be needed to diagnose the specific ILD type. Diagnosis of nonfibrotic ILD requires integration of multiple domains.

Podolanczuk AJ, et al. AJRCCM 2025



population-intervention-control-outcome (PICO) questions

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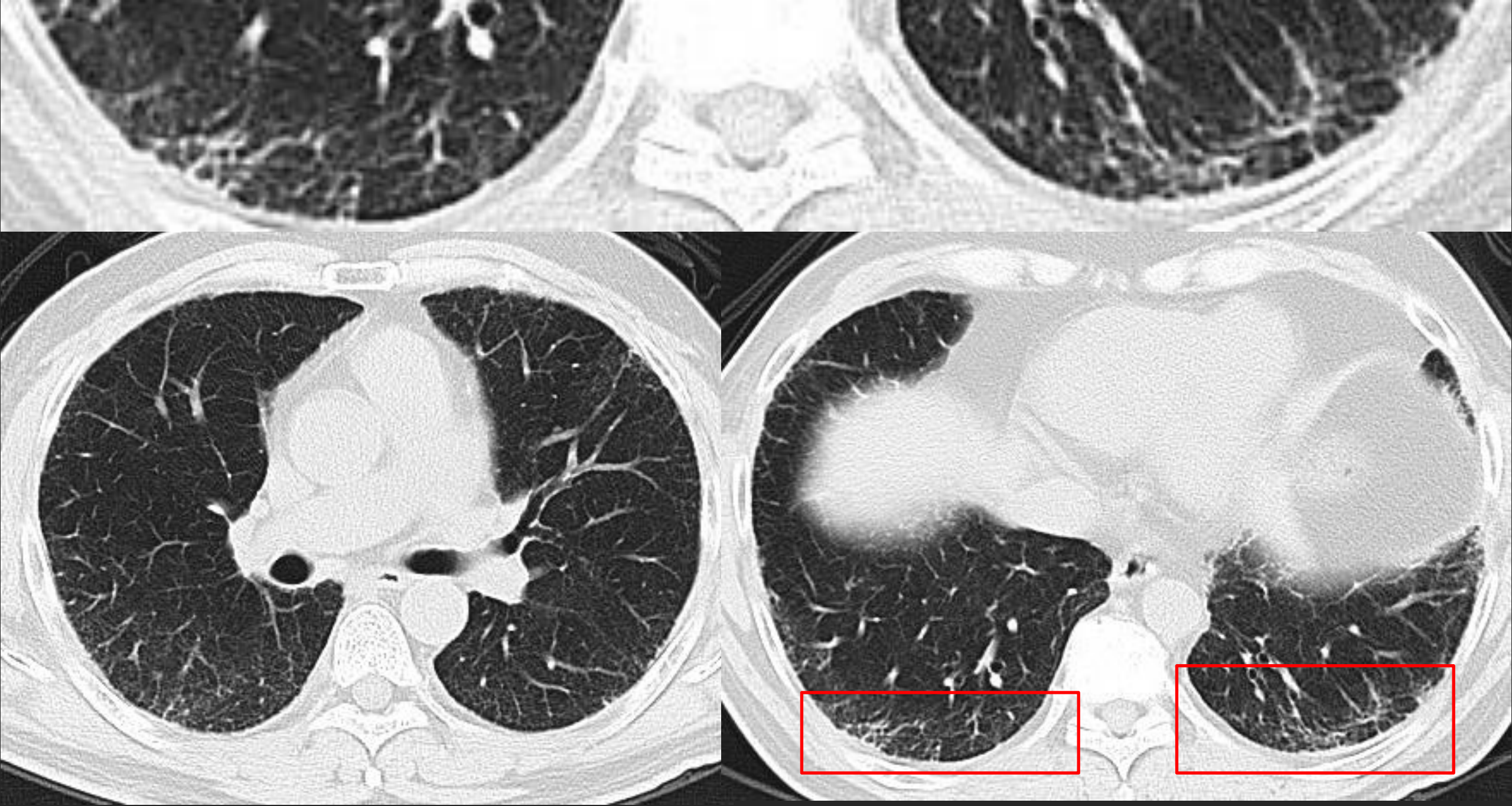
ILA subtypes: key imaging features, progression risks

Table 1 Quantitative Summary of Key Imaging Features, Progression Risk by ILA Subtype, and Risk Modifiers

ILA Subtype	Key CT Features	Progression Rates	Key Risk Modifiers
Subpleural fibrotic[1,2,6,15]	Reticulation, 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

- Subpleural fibrotic ILA, marked by traction bronchiectasis and honeycombing, carries the greatest likelihood of progression and the poorest prognosis

Semin Roentgenology 2025; 61:150959



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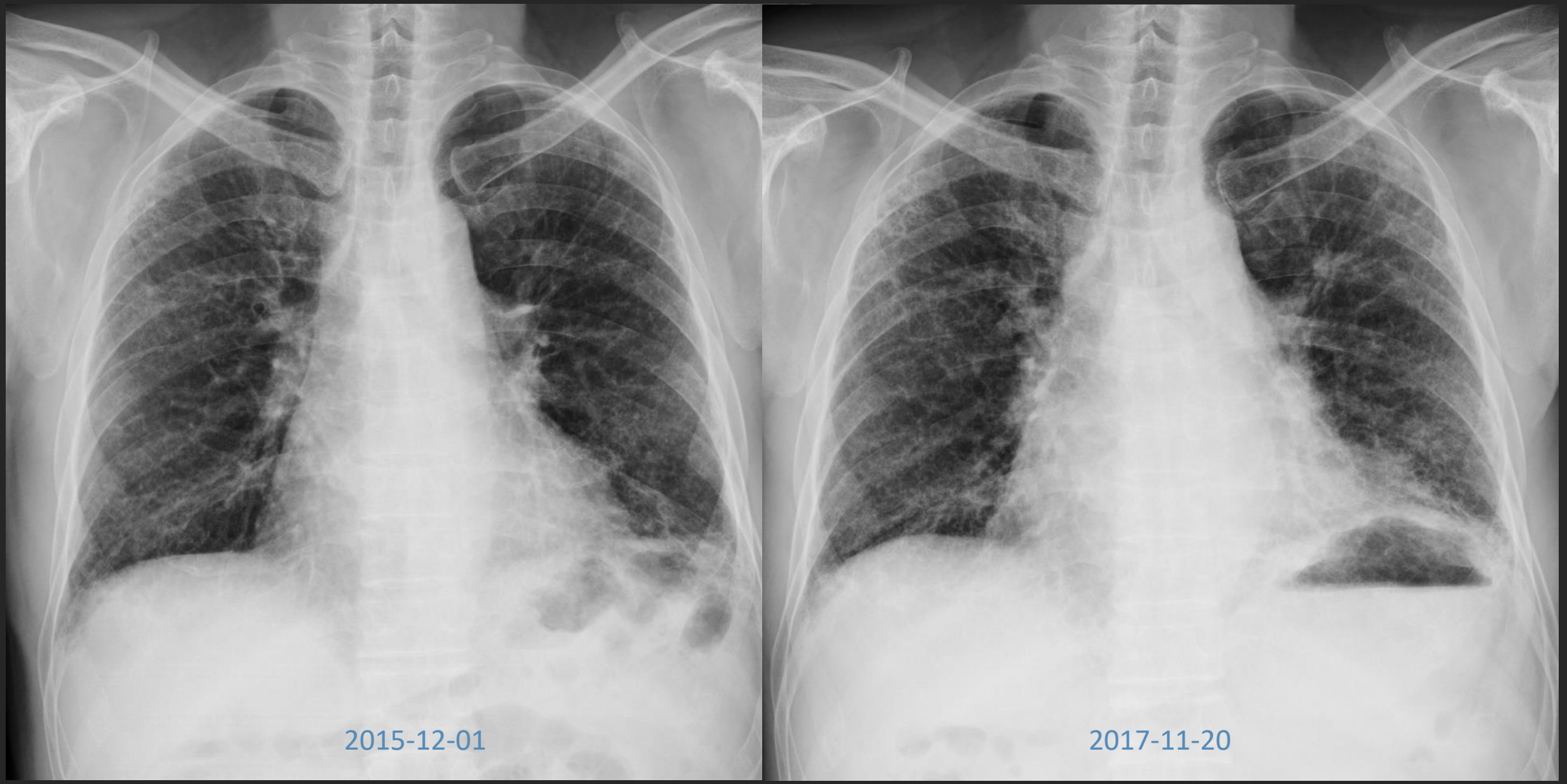
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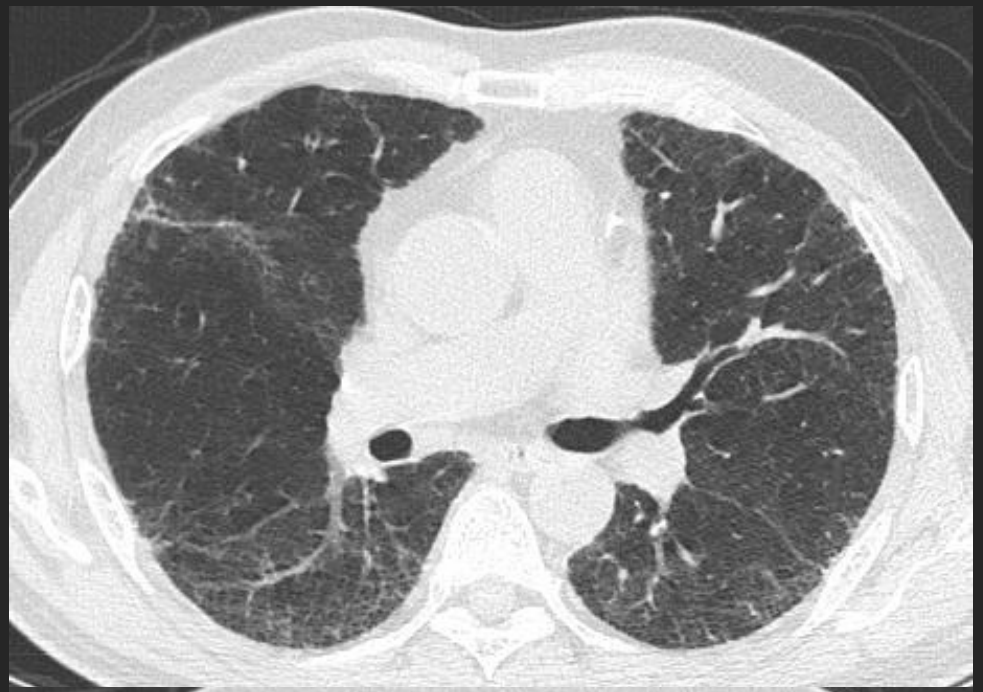

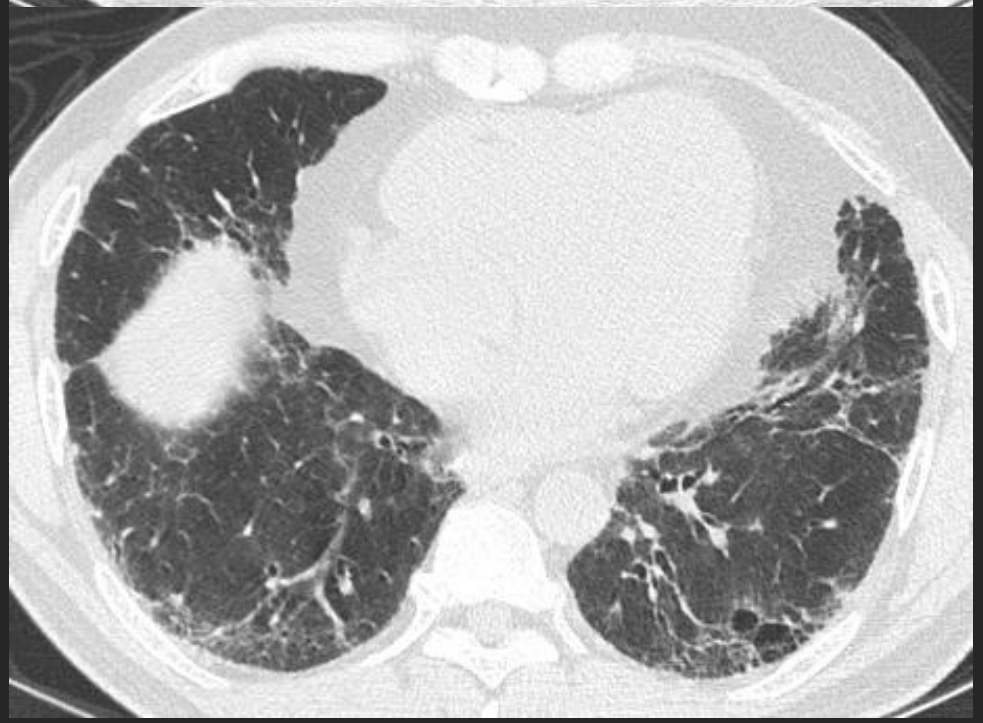

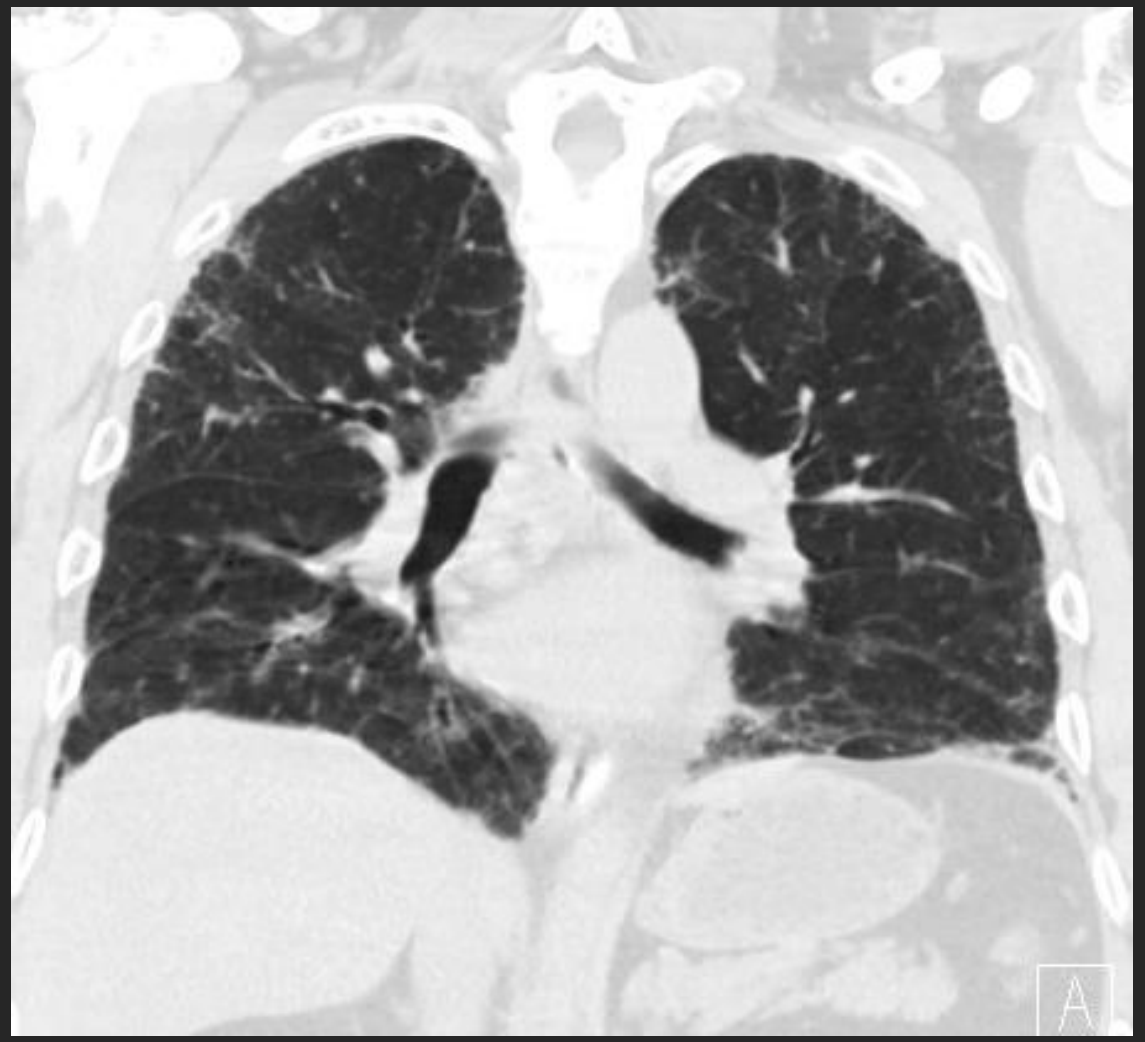

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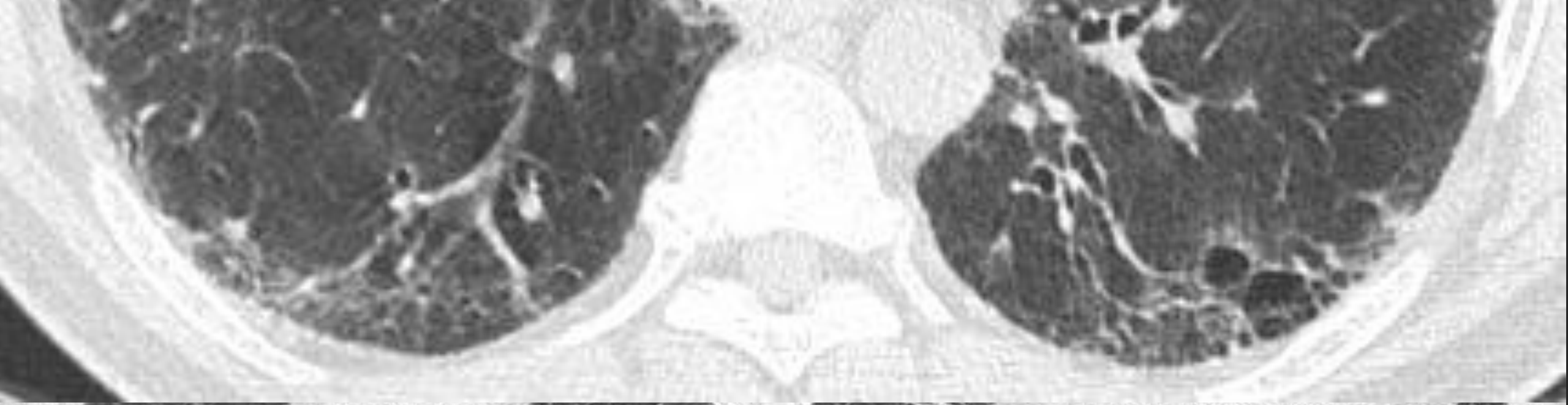

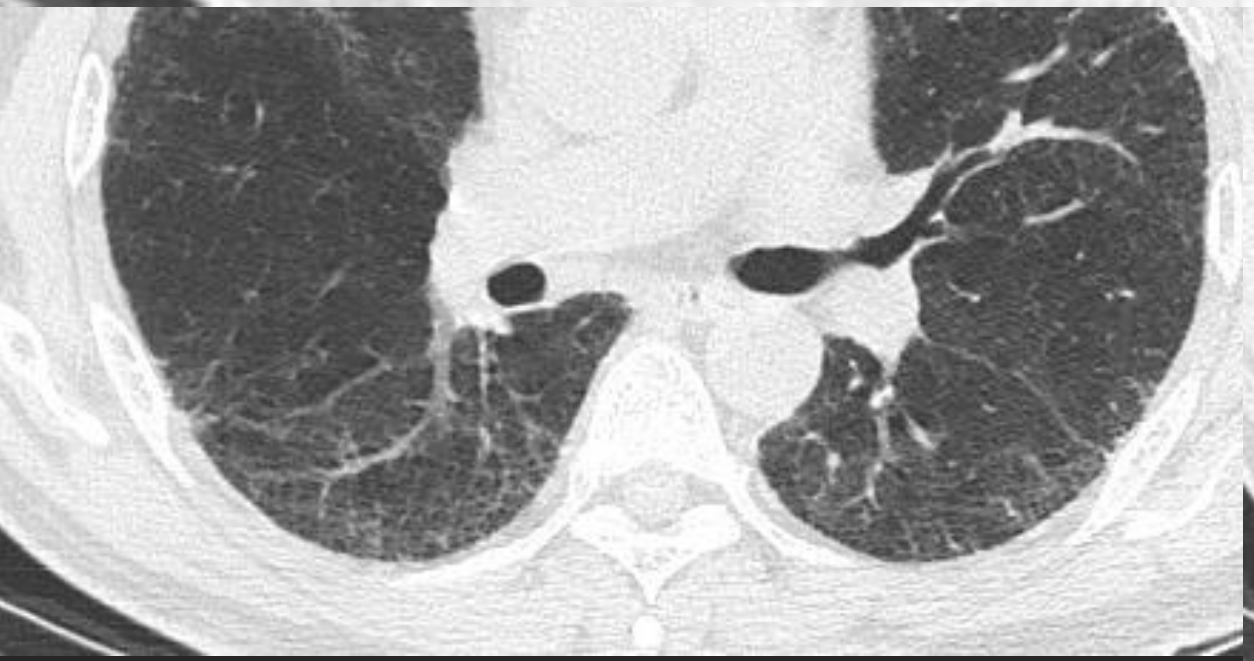

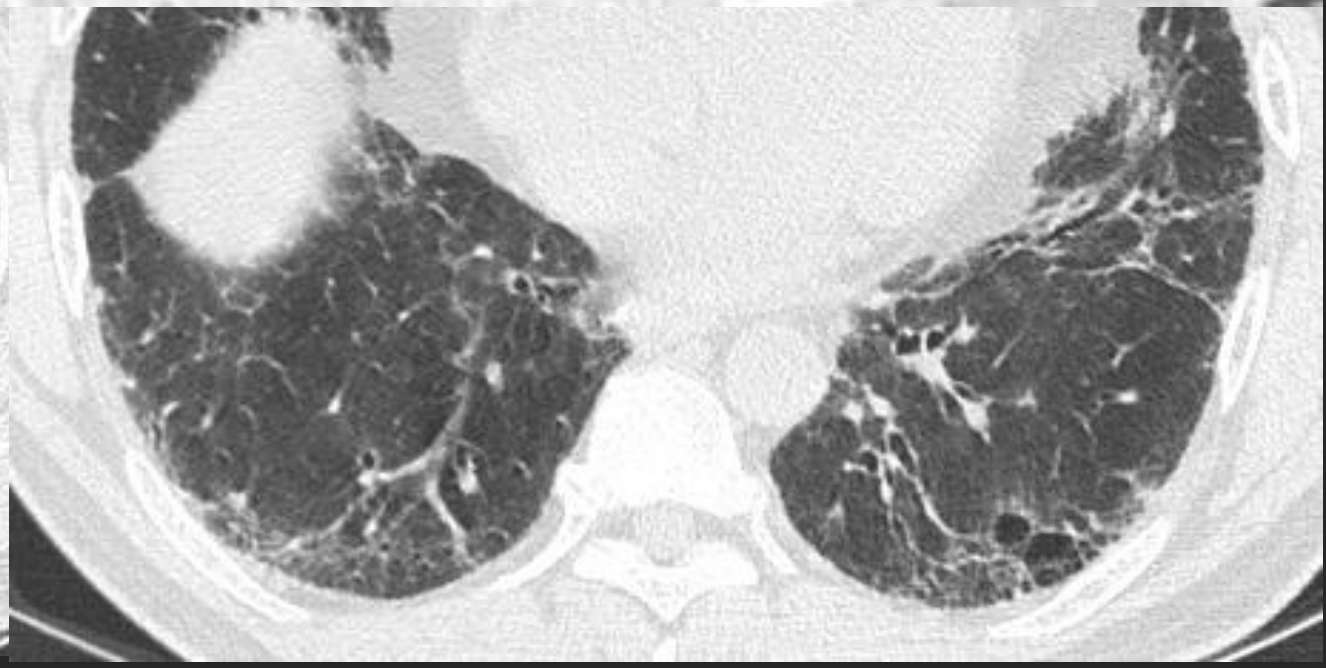

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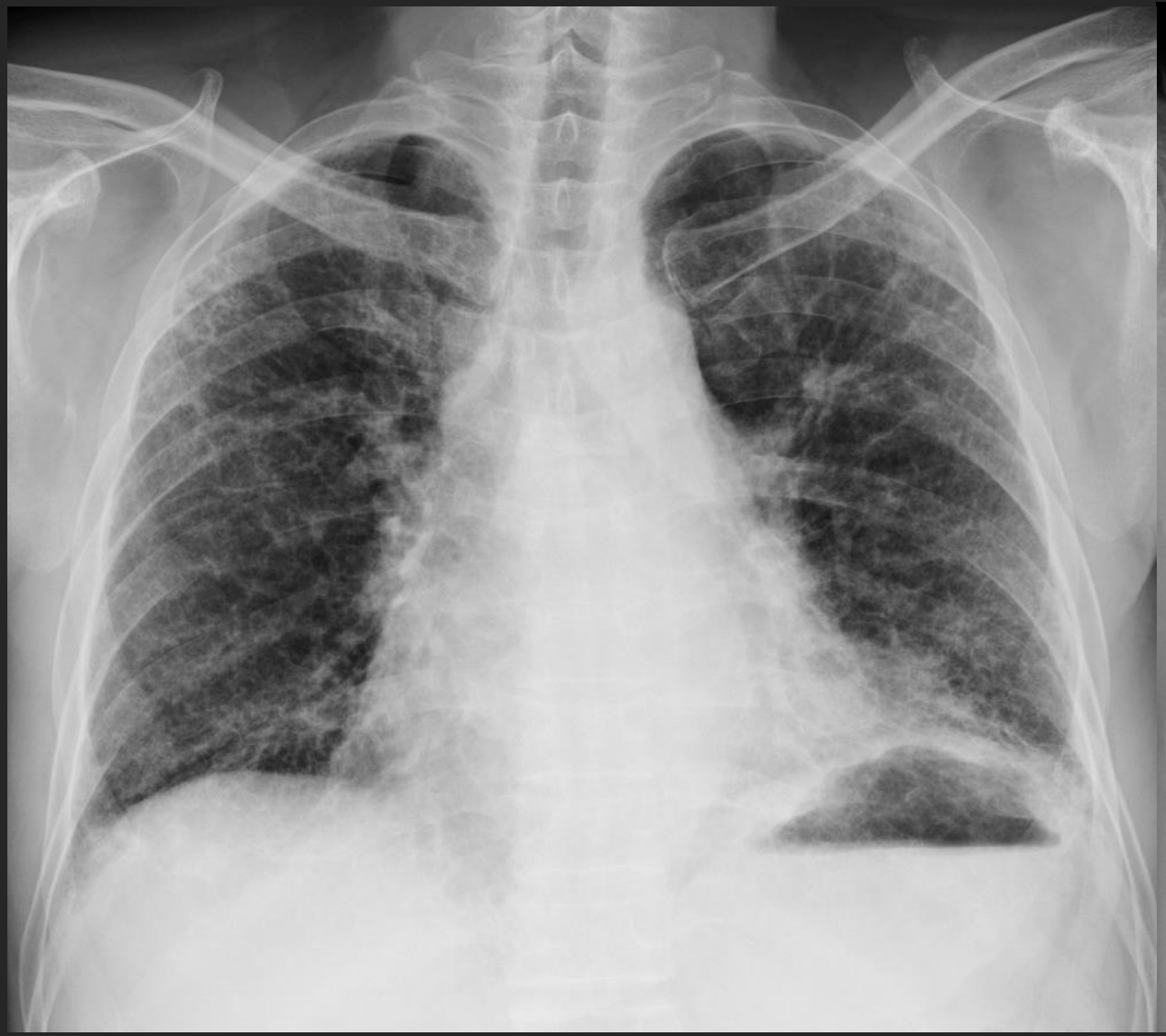

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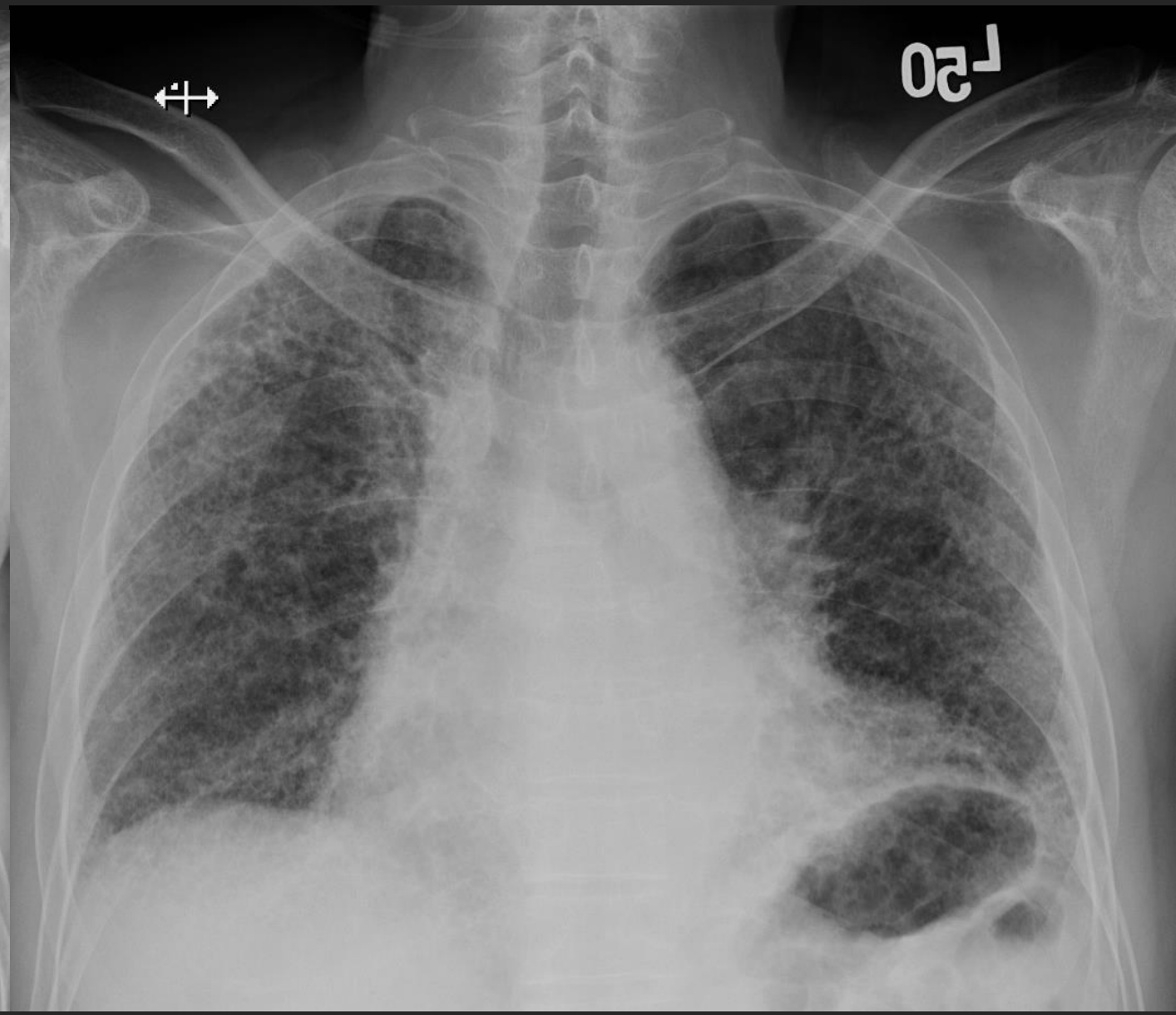

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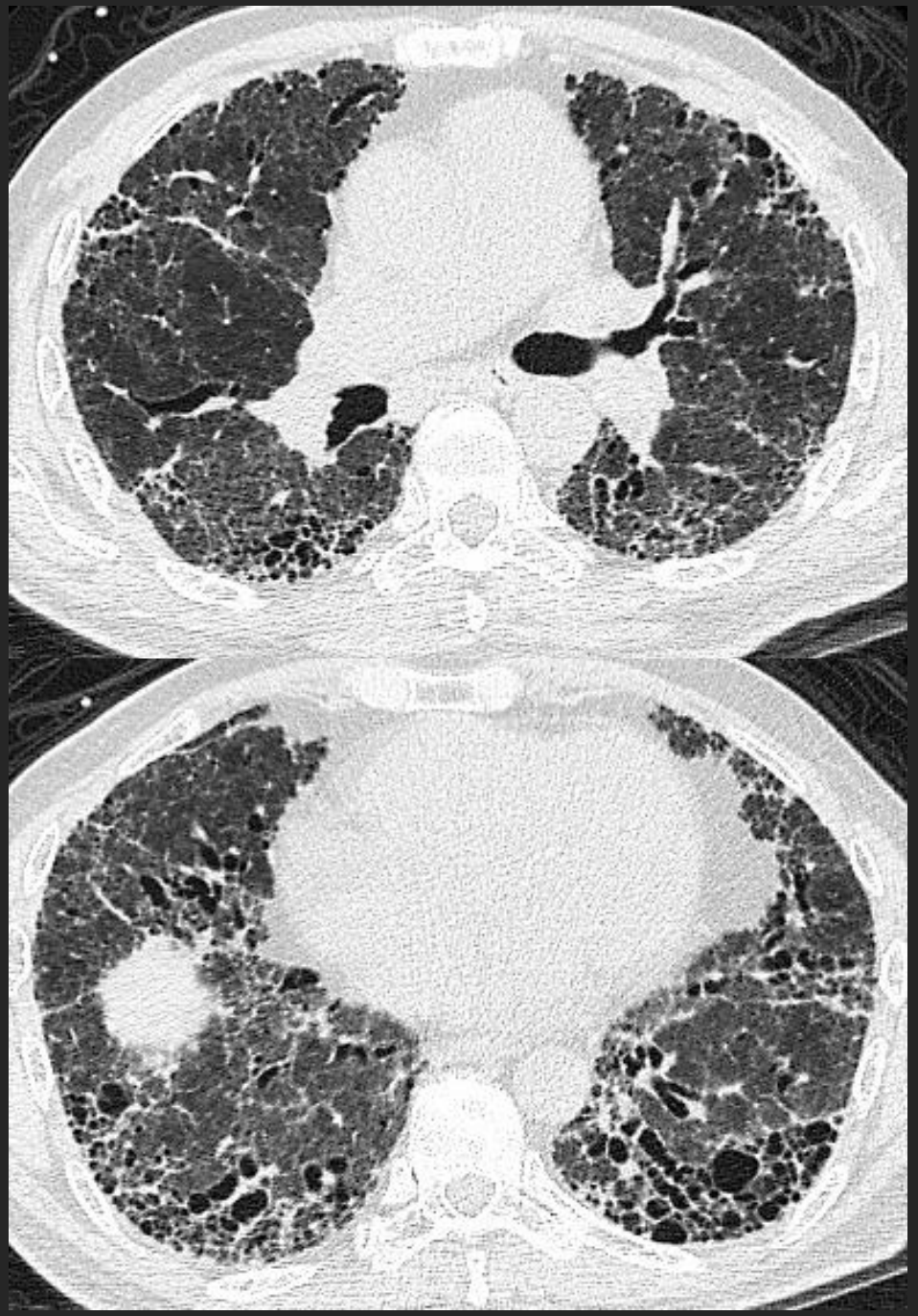
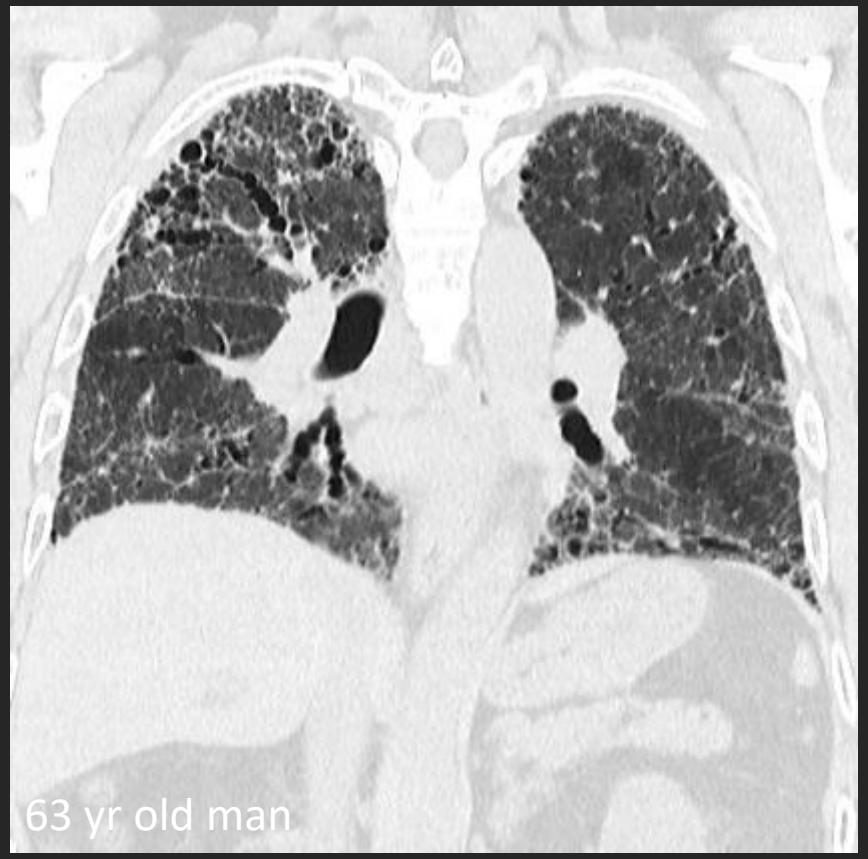


OFEV 150 mg/cap 1# bid since 2018-4-24
But progeressive exertional dyspnea &
irritative cough noted in recent 6 M
FVC 61.2% and DLCO 44.9% on 2018/8/30



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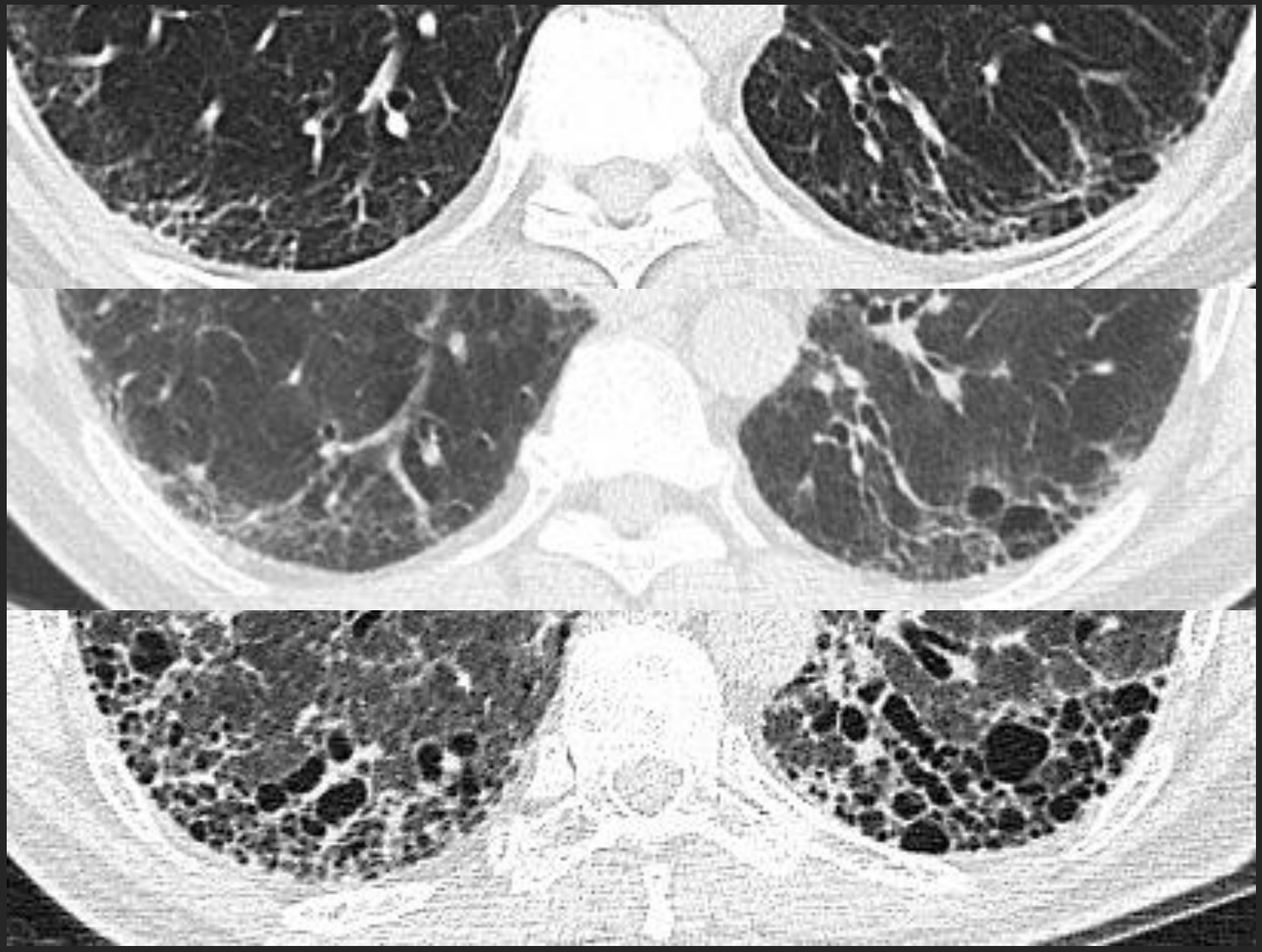
2017-01-25_CT

2019-02-18_CT



Progressive fibrosing ILD (PF-ILD)

- Progressive fibrosis is associated with worsening respiratory symptoms, lung function decline, limited response to immunomodulatory therapies, decreased quality of life and, potentially, early death.
- The commonalities of ILDs that may present a progressive-fibrosing phenotype suggest the potential for a common treatment pathway.

Cottin V, et al. Eur Respir Rev. 2018;27:180076

Progressive fibrosing ILD (PF-ILD)

- Fibrosis (F): the presence of traction bronchiectasis, reticulations with/without honeycombing.
- Progression (P):
  - a relative forced vital capacity (FVC) decline of ≥ 10% in ≤ 24 months or
  - 5%< FVC decline < 10% and progression of fibrosis on HRCT in ≤ 24 months.

Why PPF instead of PF-ILD

- 1) disease progression is the result of PPF beyond the interstitial space in the lung parenchyma;
- 2) disease progression causes a clinical course similar to IPF; and
- 3) PPF is simple and compatible with the broadly used term that is well known and currently used by both clinicians and patients, “pulmonary fibrosis.”

Raghu G, et al. Am J Respir Crit Care Med 2022; 205 (9): e18–e47 (May 1, 2022)

2018

Table 4. High-Resolution Computed Tomography Scanning Patterns

UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
Subpleural and basal predominant; distribution is often heterogeneous*	Subpleural and basal predominant; distribution is often heterogeneous	Subpleural and basal predominant	Findings suggestive of another diagnosis, including: • CT features: ° Cysts ° Marked mosaic attenuation ° Predominant GGO ° Profuse micronodules ° Centrilobular nodules ° Nodules ° Consolidation • Predominant distribution: ° Peribronchovascular ° Perilymphatic ° Upper or mid-lung • Other: ° Pleural plaques (consider asbestosis) ° Dilated esophagus (consider CTD) ° Distal clavicular erosions (consider RA) ° Extensive lymph node enlargement (consider other etiologies) ° Pleural effusions, pleural thickening (consider CTD/drugs)
Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis†	Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis May have mild GGO	Subtle reticulation; may have mild GGO or distortion ("early UIP pattern") CT features and/or distribution of lung fibrosis that do not suggest any specific etiology ("truly indeterminate")	

Definition of abbreviations: CT = computed tomography; CTD = connective tissue disease; GGO = ground-glass opacities; RA = rheumatoid arthritis; UIP = usual interstitial pneumonia.
*Variants of distribution: occasionally diffuse, may be asymmetrical.
†Superimposed CT features: mild GGO, reticular pattern, pulmonary ossification.

Ganesh Raghu, et al. Am J Respir Crit Care Med 2018; 198,(5,): e44–e68,

Guideline of IPF and PPF update in 2022

2022

AMERICAN THORACIC SOCIETY DOCUMENTS

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

Ganesh Raghu, Martine Remy-Jardin, Luca Richeldi, Carey C. Thomson, Yoshikazu Inoue, Takeshi Johkoh, Michael Kreuter, David A. Lynch, Toby M. Maher, Fernando J. Martinez, Maria Molina-Molina, Jeffrey L. Myers, Andrew G. Nicholson, Christopher J. Ryerson, Mary E. Strek, Lauren K. Troy, Marlies Wijsenbeek, Manoj J. Mammen, Tanzib Hossain, Brittany D. Bissell, Derrick D. Herman, Stephanie M. Hon, Fayez Kheir, Yet H. Khor, Madalina Macrea, Katerina M. Antoniou, Demosthenes Bouros, Ivette Buendia-Roldan, Fabian Caro, Bruno Crestani, Lawrence Ho, Julie Morisset, Amy L. Olson, Anna Podolanczuk, Venerino Poletti, Moisés Selman, Thomas Ewing, Stephen Jones, Shandra L. Knight, Marya Ghazipura, and Kevin C. Wilson; on behalf of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax

Am J Respir Crit Care Med Vol 205, Iss 9, pp e18–e47, May 1, 2022

Table 3. High-Resolution Computed Tomography Patterns in Idiopathic Pulmonary Fibrosis

	HRCT Pattern			
	UIP Pattern	**Probable UIP Pattern**	**Indeterminate for UIP**	**CT Findings Suggestive of an Alternative Diagnosis**
Level of confidence for UIP histology	Confident (>90%)	Provisional high confidence (70–89%)	Provisional low confidence (51–69%)	Low to very low confidence (≤50%)
Distribution	• Subpleural and basal predominant • Often heterogeneous (areas of normal lung interspersed with fibrosis) • Occasionally diffuse • May be asymmetric	• Subpleural and basal predominant • Often heterogeneous (areas of normal lung interspersed with reticulation and traction bronchiectasis/ bronchiolectasis)	• Diffuse distribution without subpleural predominance	• Peribronchovascular predominant with subpleural sparing (consider NSIP) • Perilymphatic distribution (consider sarcoidosis) • Upper or mid lung (consider fibrotic HP, CTD-ILD, and sarcoidosis) • Subpleural sparing (consider NSIP or smoking-related IP)
CT features	• Honeycombing with or without traction bronchiectasis/ bronchiolectasis • Presence of irregular thickening of interlobular septa • Usually superimposed with a reticular pattern, mild GGO • May have pulmonary ossification	• Reticular pattern with traction bronchiectasis/ bronchiolectasis • May have mild GGO • Absence of subpleural sparing	• CT features of lung fibrosis that do not suggest any specific etiology	• Lung findings ◦ Cysts (consider LAM, PLCH, LIP, and DIP) ◦ Mosaic attenuation or three-density sign (consider HP) ◦ Predominant GGO (consider HP, smoking-related disease, drug toxicity, and acute exacerbation of fibrosis) ◦ Profuse centrilobular micronodules (consider HP or smoking-related disease) ◦ Nodules (consider sarcoidosis) ◦ Consolidation (consider organizing pneumonia, etc.) • Mediastinal findings ◦ Pleural plaques (consider asbestosis) ◦ Dilated esophagus (consider CTD)

More definite and detailed descriptions of HRCT pattern of IPF including level of confidence and specific relevant diagnosis

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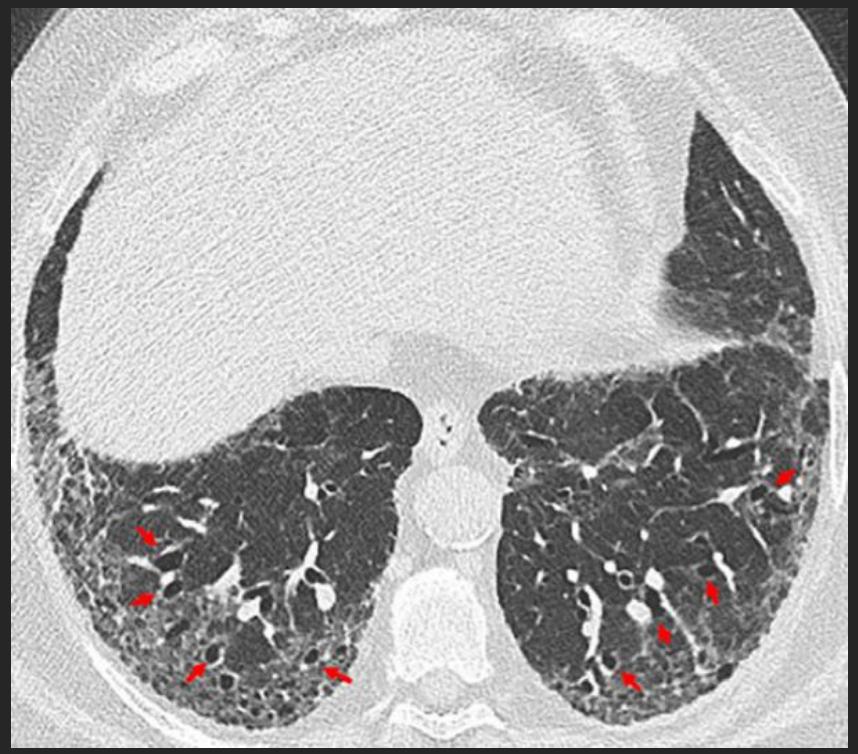
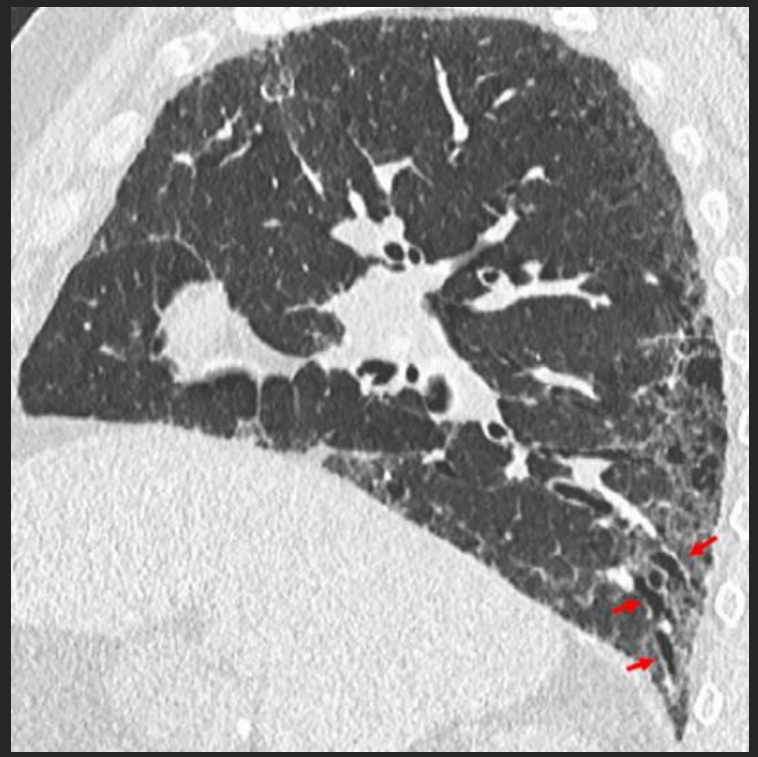
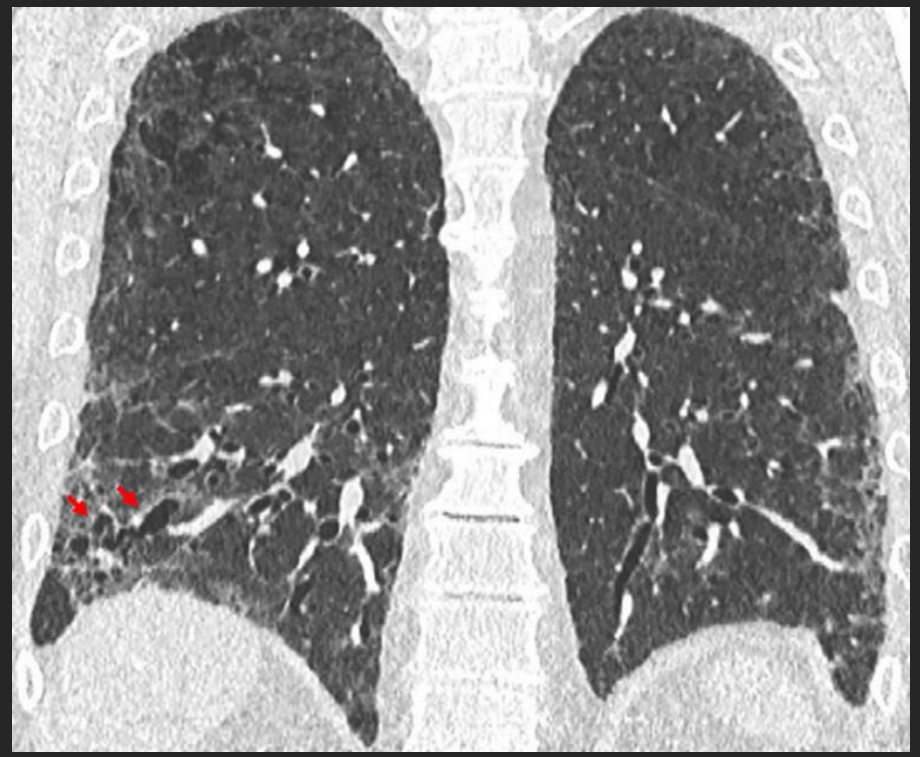
Traction bronchiectasis/bronchiolectasis



probable usual interstitial pneumonia pattern





Traction bronchiectasis/bronchiolectasis represents irregular bronchial and/or bronchiolar dilatation caused by surrounding retractile fibrosis; distorted airways are thus identified in a background of reticulation and/or ground-glass attenuation.

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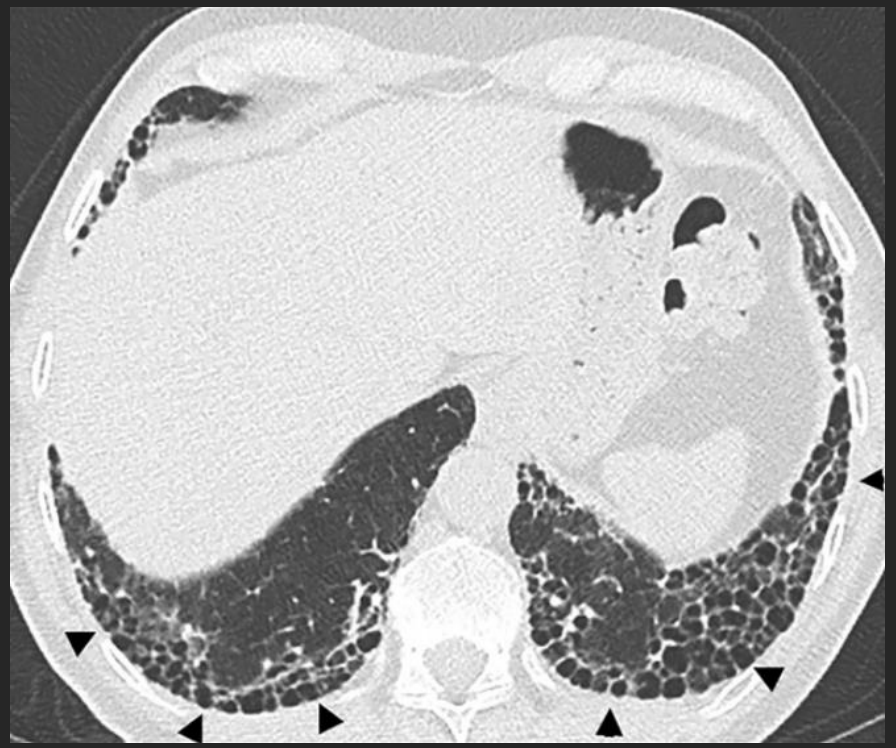
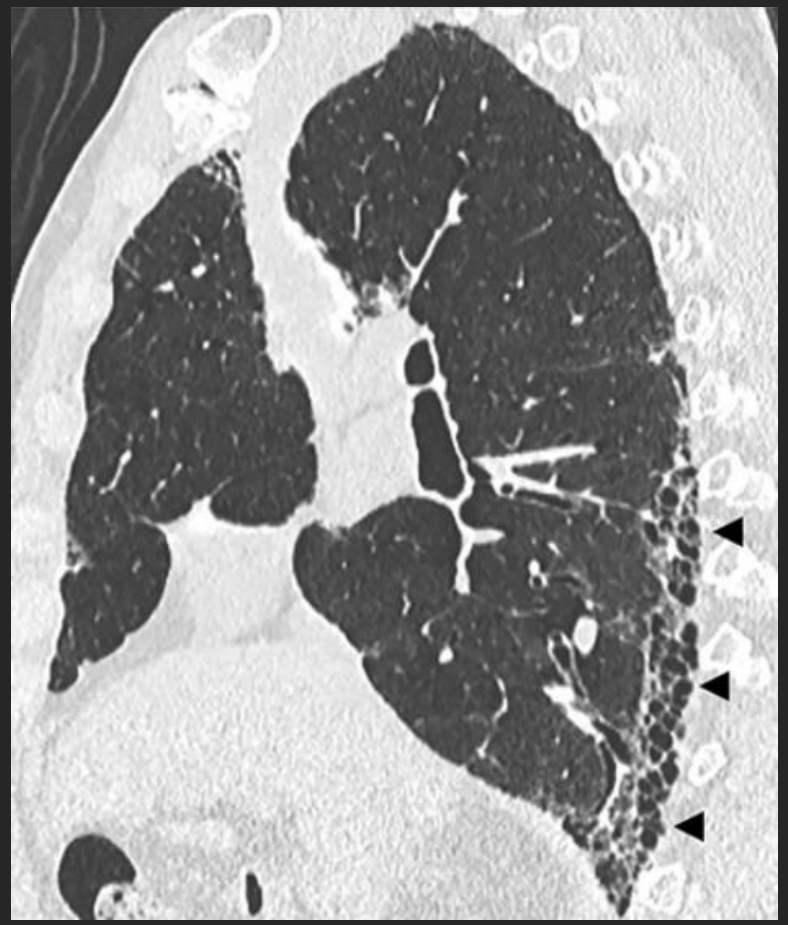
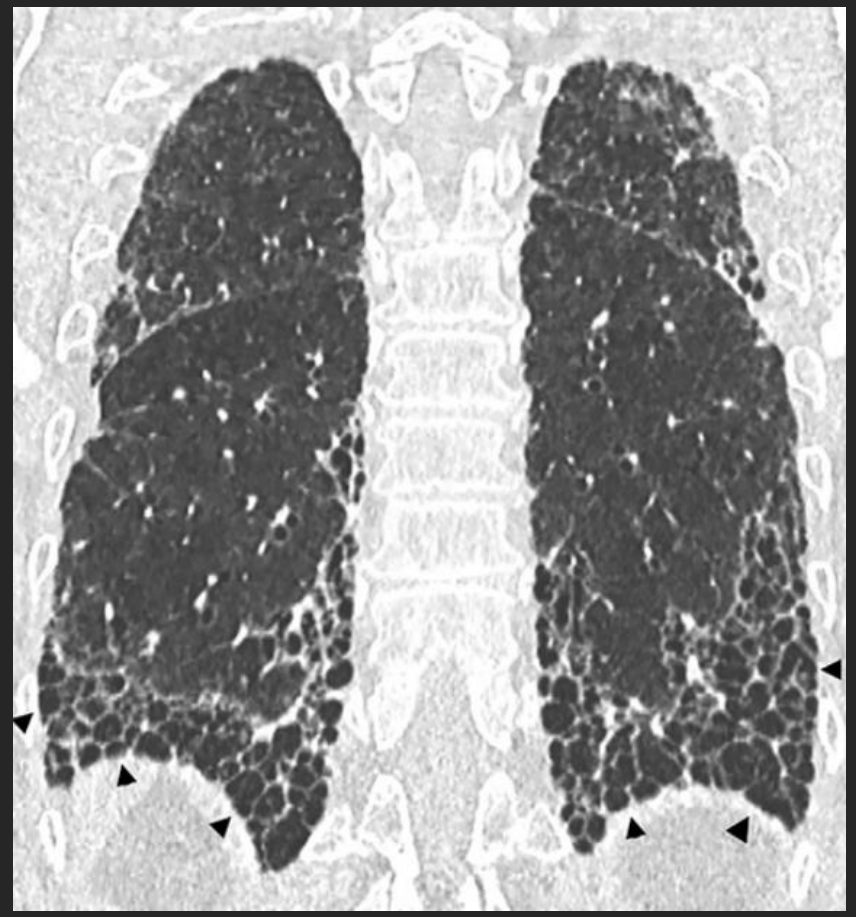
Honeycombing







typical (“definite”) usual interstitial pneumonia

The size and number of cysts often increase as the disease progresses

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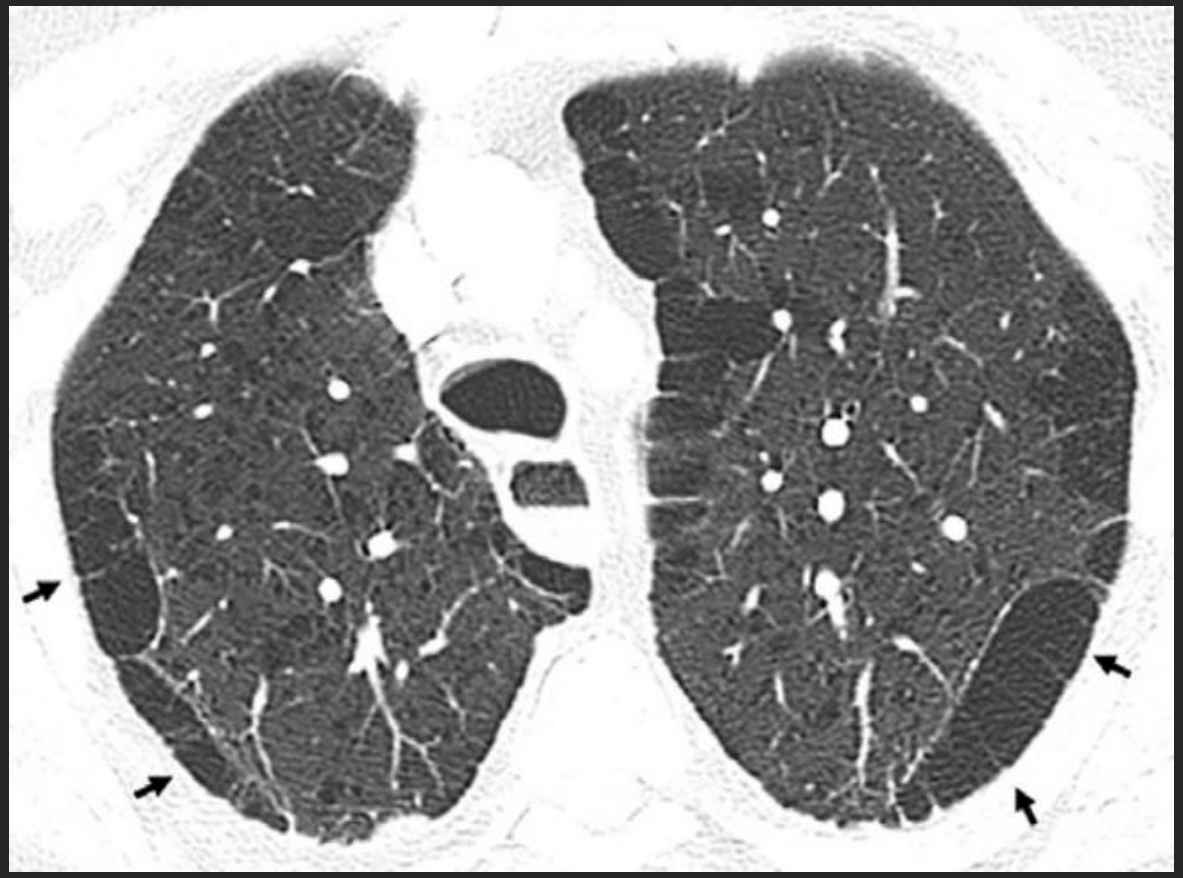
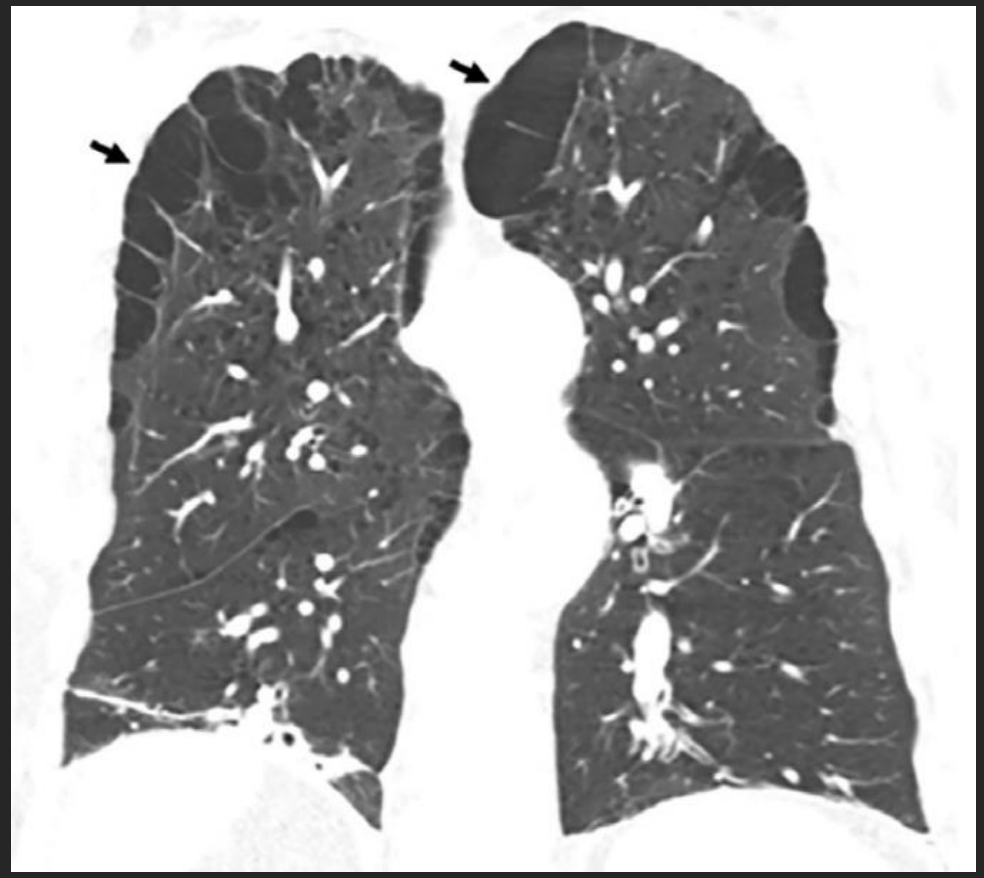
Paraseptal emphysema





Centrilobular emphysema is also present. The subpleural cysts of paraseptal emphysema usually occur in a single layer and are larger than honeycomb cysts (typically .1 cm); they are not associated with other features of fibrosis such as reticular abnormality or traction bronchiectasis

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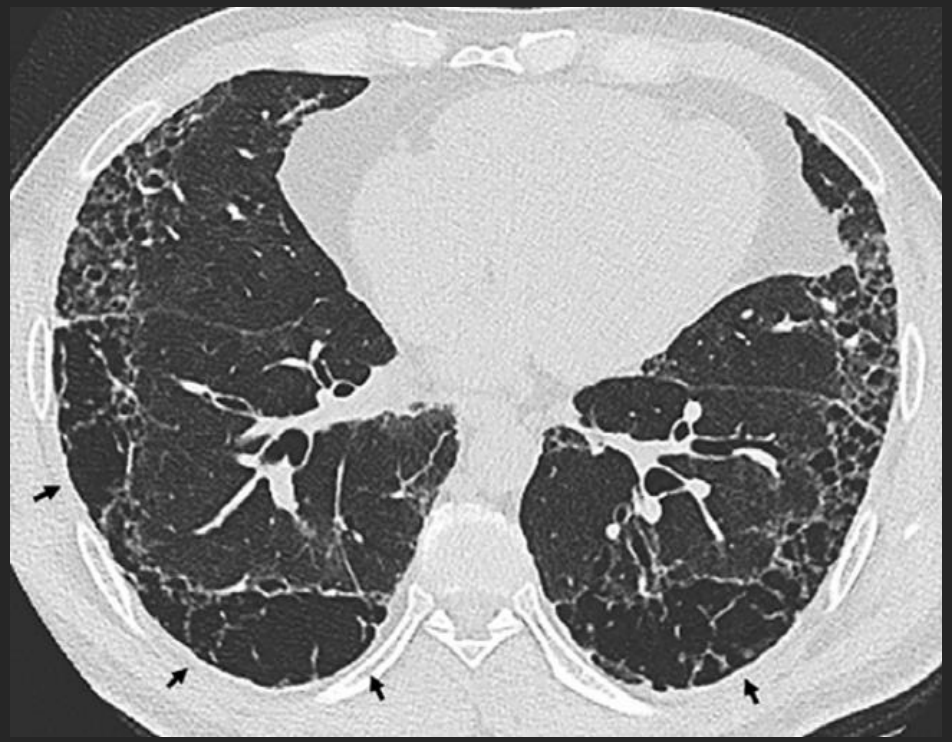
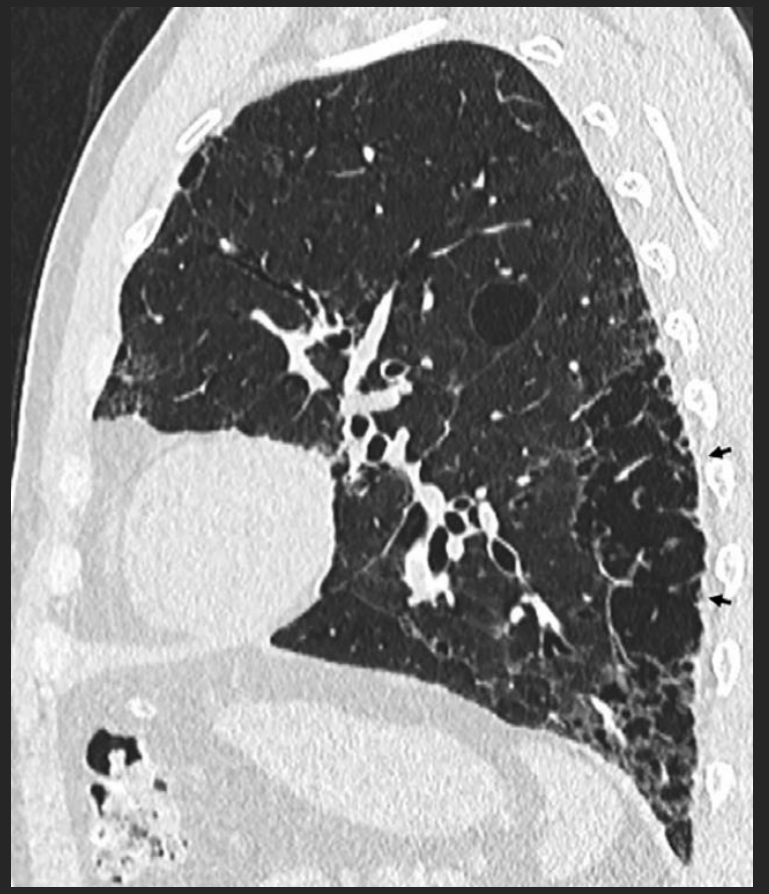
Airspace enlargement with fibrosis (AEF)

smoking-related interstitial fibrosis, in a cigarette smoker





clustered asymmetric cysts that are larger and more irregular than typical honeycomb cysts, without traction bronchiectasis or other signs of fibrosis (arrows). Emphysema is also present. AEF is not regarded as a distinct form of idiopathic interstitial pneumonia but results from the presence of a greater amount of fibrosis than usually described in the classic definition of emphysema.

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IPF diagnosis on the basis of HRCT and biopsy patterns

IPF suspected*		Histopathology pattern†			
		UIP	Probable UIP	Indeterminate for UIP or biopsy not performed	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Probable UIP	IPF	IPF	IPF (Likely)‡	Non-IPF dx
	Indeterminate	IPF	IPF (Likely)‡	Indeterminate§	Non-IPF dx
	Alternative diagnosis	IPF (Likely)‡	Indeterminate§	Non-IPF dx	Non-IPF dx

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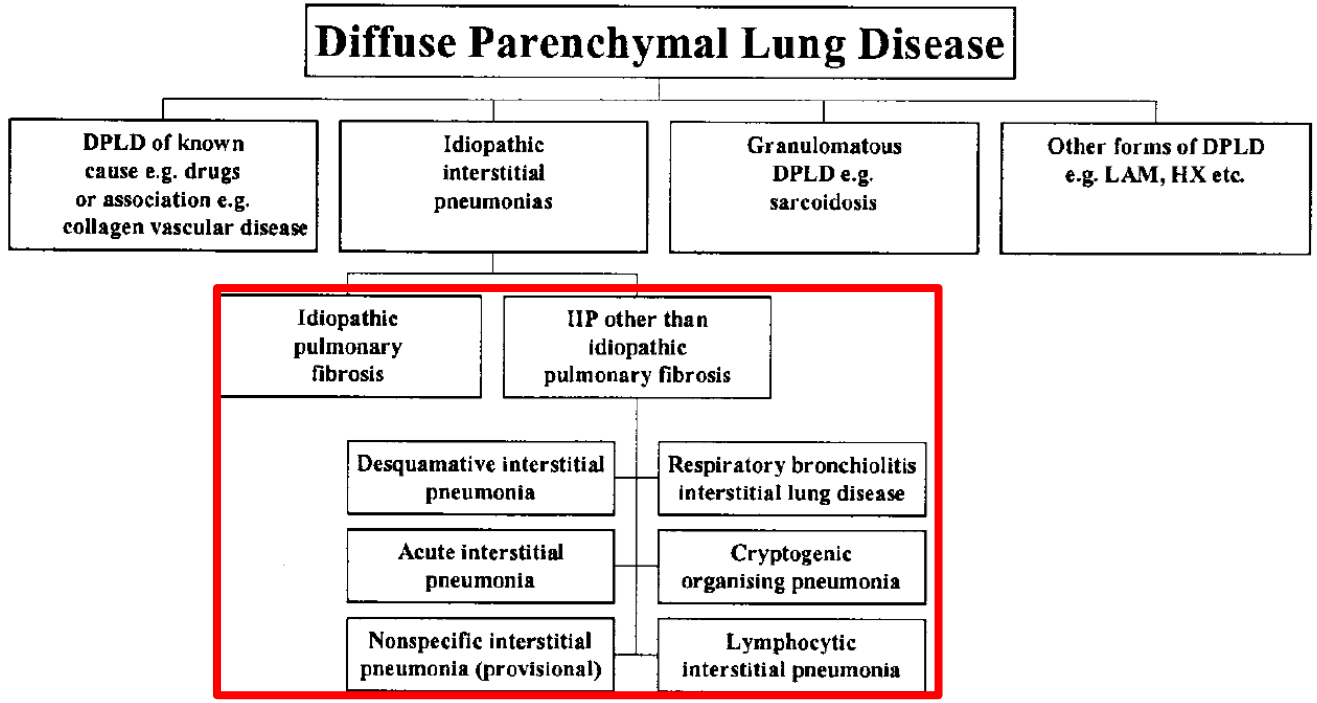
In 2002, seven specific entities using standardised terminology for multidisciplinary gold standard for diagnosis

Focus on idiopathic entities: “Idiopathic” interstitial pneumonia (IIP)

NSIP is a provisional diagnosis.



In 2013, recognition of nonspecific interstitial pneumonia (NSIP) as a major pattern.

Addition of pleuroparenchymal fibroelastosis (PPFE) as an eighth entity.

Subcategorised major idiopathic IPs as chronic fibrosing, smoking-related, and acute/subacute subtypes.

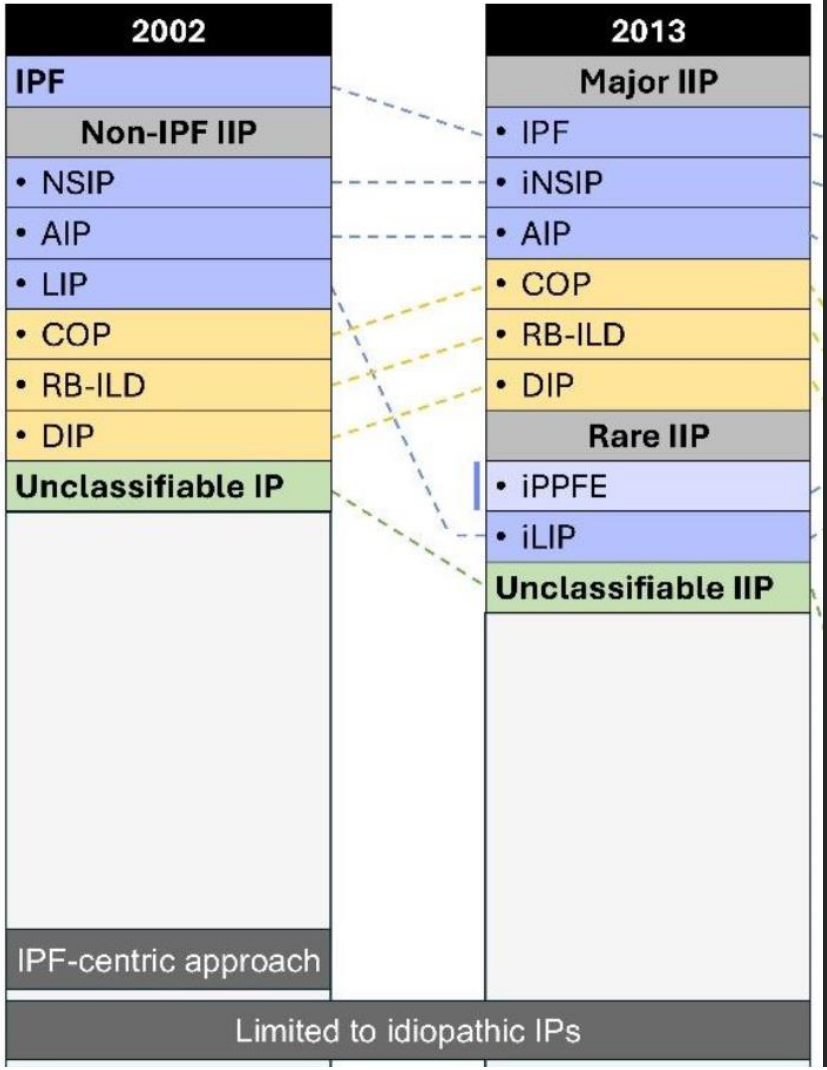


TABLE 2. CATEGORIZATION OF MAJOR IDIOPATHIC INTERSTITIAL PNEUMONIAS

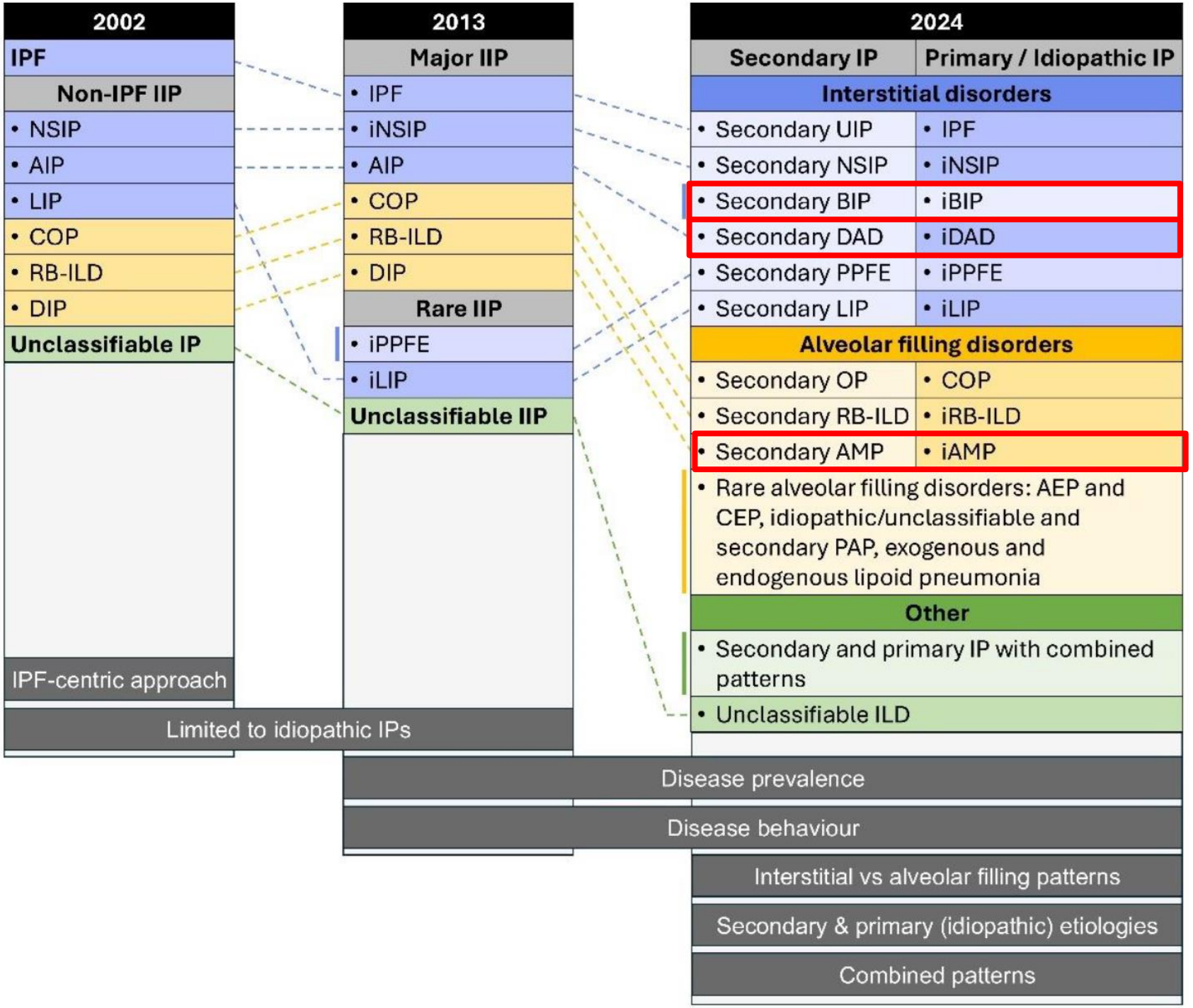
Category	Clinical–Radiologic–Pathologic Diagnoses	Associated Radiologic and/or Pathologic–Morphologic Patterns
Chronic fibrosing IP	Idiopathic pulmonary fibrosis	Usual interstitial pneumonia
	Idiopathic nonspecific interstitial pneumonia	Nonspecific interstitial pneumonia
Smoking-related IP*	Respiratory bronchiolitis-interstitial lung disease	Respiratory bronchiolitis
	Desquamative interstitial pneumonia	Desquamative interstitial pneumonia
Acute/subacute IP	Cryptogenic organizing pneumonia	Organizing pneumonia
	Acute interstitial pneumonia	Diffuse alveolar damage

Recent update including secondary causes.

Bronchiolocentric interstitial pneumonia (BIP) as a major pattern.

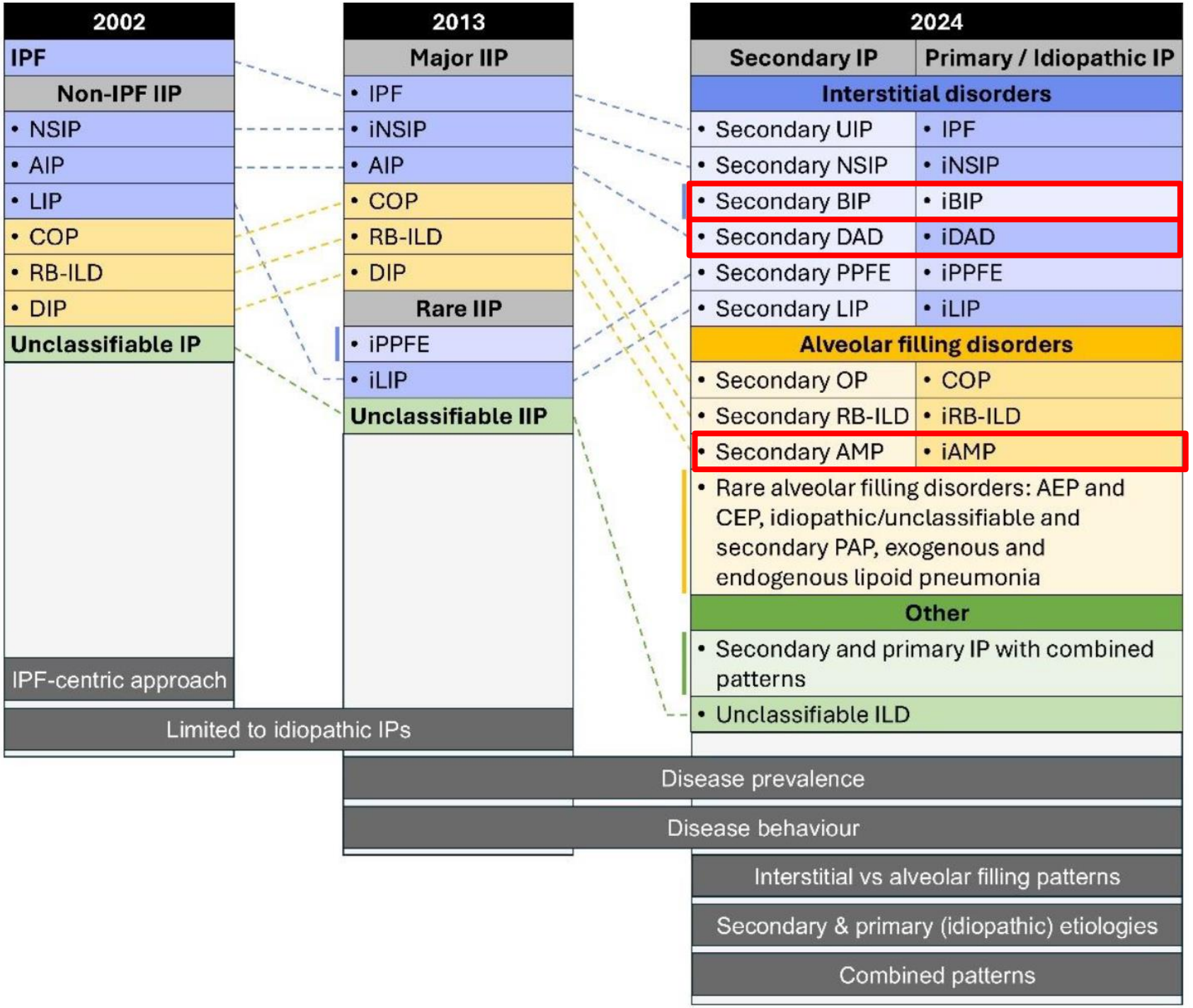
~~Acute interstitial pneumonia~~ became idiopathic diffuse alveolar damage (iDAD)

~~Desquamative interstitial pneumonia~~ became alveolar macrophage pneumonia (AMP)



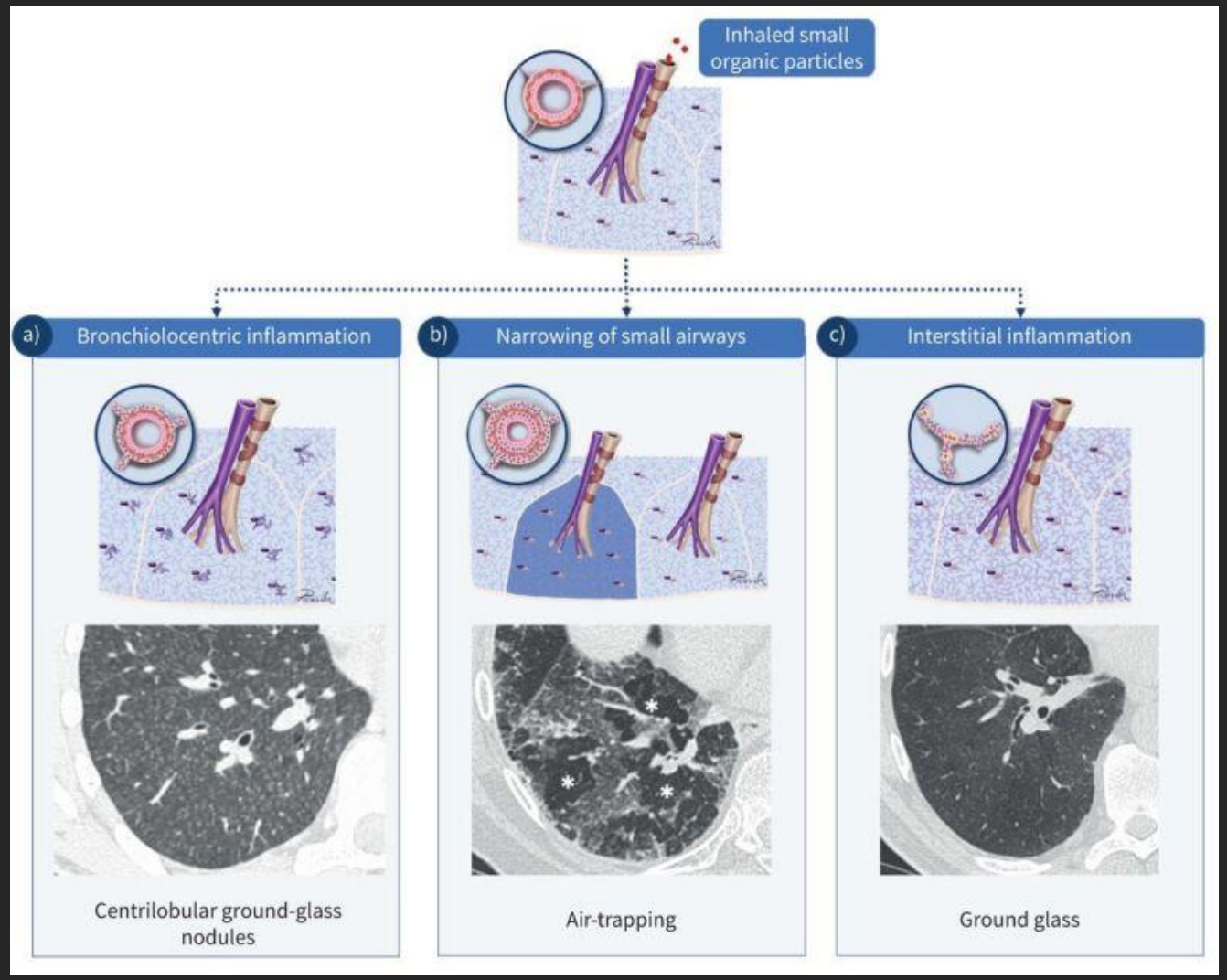
Subclassification of interstitial and alveolar filling disorders, with interstitial disorders further subclassified as fibrotic vs non-fibrotic

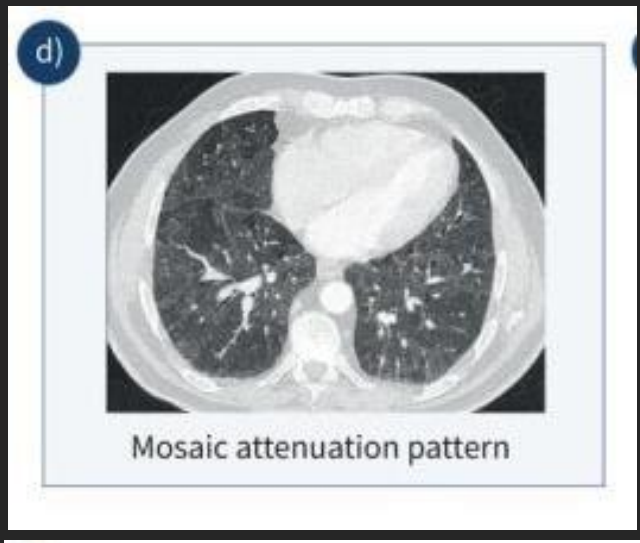
Consideration of diagnostic confidence in patient evaluation and management

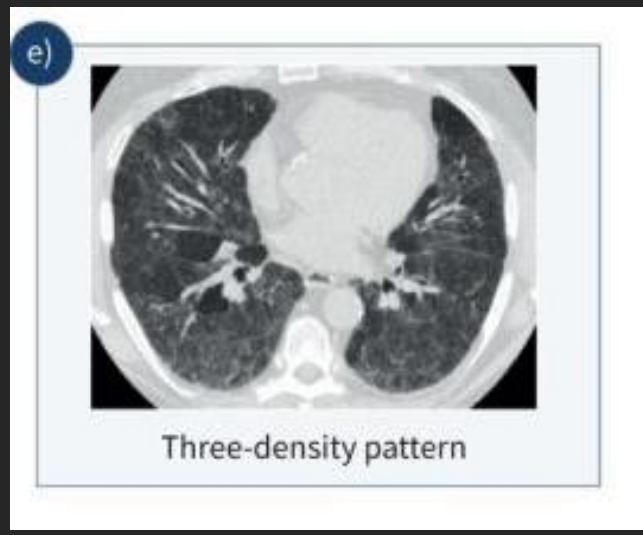


	Morphologic patterns by Pathology and Imaging	Major clinical-radiologic-pathologic diagnoses	
		Secondary	Primary / Idiopathic
Interstitial patterns	**Usual interstitial pneumonia (UIP)**	**Secondary UIP** (*e.g.*, CTD, HP, medications)	**Idiopathic pulmonary fibrosis** (Idiopathic UIP)
	Nonspecific interstitial pneumonia (NSIP)	**Secondary NSIP** (*e.g.*, CTD >>> HP, medications)	**Idiopathic NSIP**
	Bronchiolocentric interstitial pneumonia (BIP)*	**Secondary BIP** (*e.g.*, HP >>> CTD, aspiration, inhalational exposures, medications)	**Idiopathic BIP** *(provisional diagnosis*)*
	Diffuse alveolar damage (DAD)	**Secondary DAD** (multiple causes)	**Idiopathic DAD** (acute interstitial pneumonia)
	Pleuroparenchymal fibroelastosis (PPFE)	**Secondary PPFE** (*e.g.*, IPF, CTD, HP, medications, radiation, transplant [restrictive allograft syndrome, pulmonary infection [post-tuberculosis], occupational)	**Idiopathic PPFE**
	Lymphoid interstitial pneumonia (LIP)	**Secondary LIP** (*e.g.*, CTD, immune deficiency)	**Idiopathic LIP**
Alveolar filling patterns	**Organising pneumonia (OP)**	**Secondary OP** (*e.g.*, CTD, post-infectious, medications, aspiration)	**Cryptogenic OP** (Idiopathic OP)
	Respiratory bronchiolitis-ILD (RB-ILD)	**Secondary RB-ILD** (*e.g.*, smoking >>> CTD, medications, aspiration, hereditary)	**Idiopathic RB-ILD**
	Alveolar macrophage pneumonia† (AMP)	**Secondary AMP** (*e.g.*, smoking >>> CTD, medications, aspiration, hereditary	**Idiopathic AMP**
	Rare alveolar filling disorders	*e.g.*, **Acute and chronic eosinophilic pneumonia**, **pulmonary alveolar proteinosis, lipoid pneumonia** (See **Supplemental Table 1**)	
Other	**Combined pattern**	**Multiple combinations** (*e.g.*, NSIP + OP, UIP + PPFE)	
	Unclassifiable pattern	**Unclassifiable ILD** (multiple undefined patterns)	

HRCT of Hypersensitivity Pneumonitis (BIP spectrum)







European Respiratory Review 2022; 31(163).

Bronchiolocentric interstitial pneumonia (BIP)

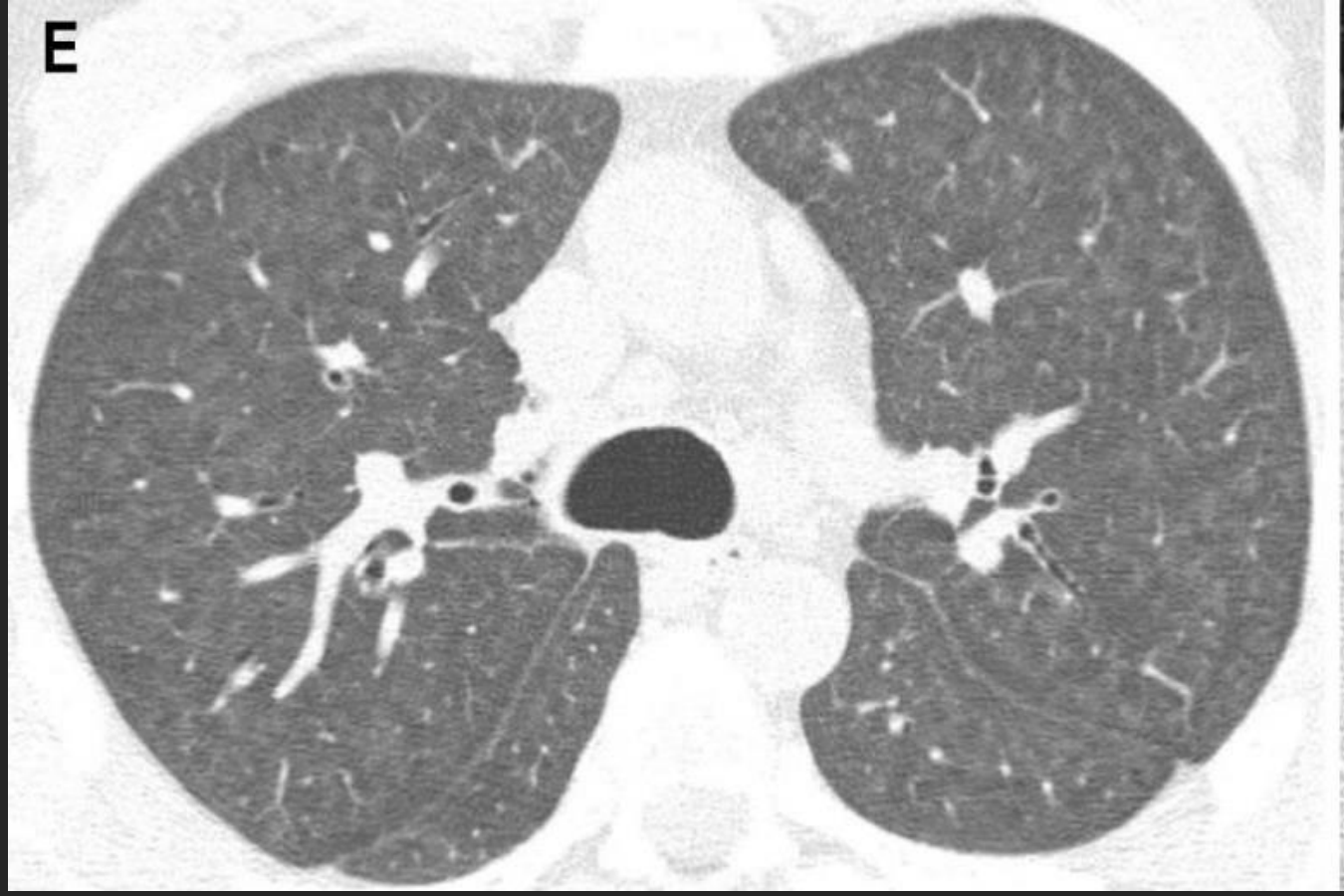
- Many patients with IP have a pattern of airway-centred disease
  - Nonfibrotic and fibrotic HP, Airway-centric/centred disease or fibrosis, Airway-centred interstitial pneumonia, Airway-centred interstitial fibrosis, Bronchiolocentric pattern of IP, Bronchiolocentric pattern of interstitial fibrosis
- The term BIP was originally proposed as a type of IP in 1969
- The 2013 document included bronchiolocentric patterns of IP as a rare histologic pattern. However, such cases were excluded from the category of idiopathic IP as the published data were insufficient to justify formal recognition as an “idiopathic” entity at that time.

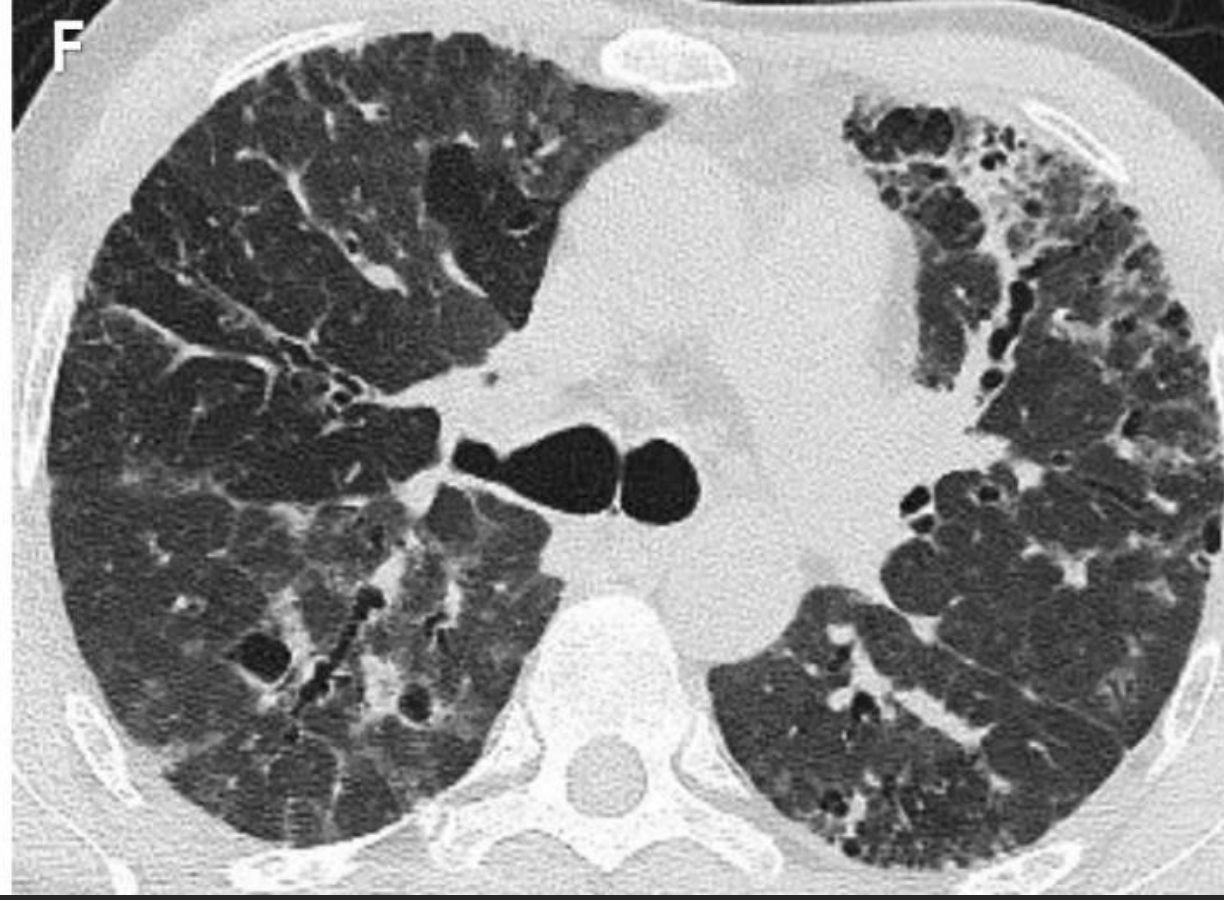
Bronchiolocentric interstitial pneumonia (BIP)

- BIP is recommended as an overarching term to define the histologic and/or radiologic pattern of predominantly airway-centred IP.
  - HP, CTD-ILD, aspiration, and inhalational or medication exposures.
  - Idiopathic BIP is a provisional diagnosis
  - BIP is thus similar to other common interstitial patterns, such as UIP and NSIP, in that all major patterns can occur in a variety of clinical diagnoses.
- CT appearance of BIP is similar to HP, but a substantial percentage of patients with bronchiolocentric patterns of disease on pathology and imaging have a non-HP diagnosis.
  - A study of 645 patients showing 9% of patients with CTD-ILD had an imaging pattern consistent with BIP.

Bronchiolocentric interstitial pneumonia (BIP)

- Non-fibrotic BIP: Pofuse poorly defined centrilobular nodules and ground glass opacities with mosaic attenuation (three density sign) that represents a component of small airway obstruction.
- Fibrotic BIP: Peribronchovascular ground glass opacities, traction bronchiectasis, mosaic attenuation, lobular air trapping and three-density sign. Features can overlap with non-fibrotic BIP.
- The CT features are almost the same as hypersensitivity pneumonia according to 2020 guideline.

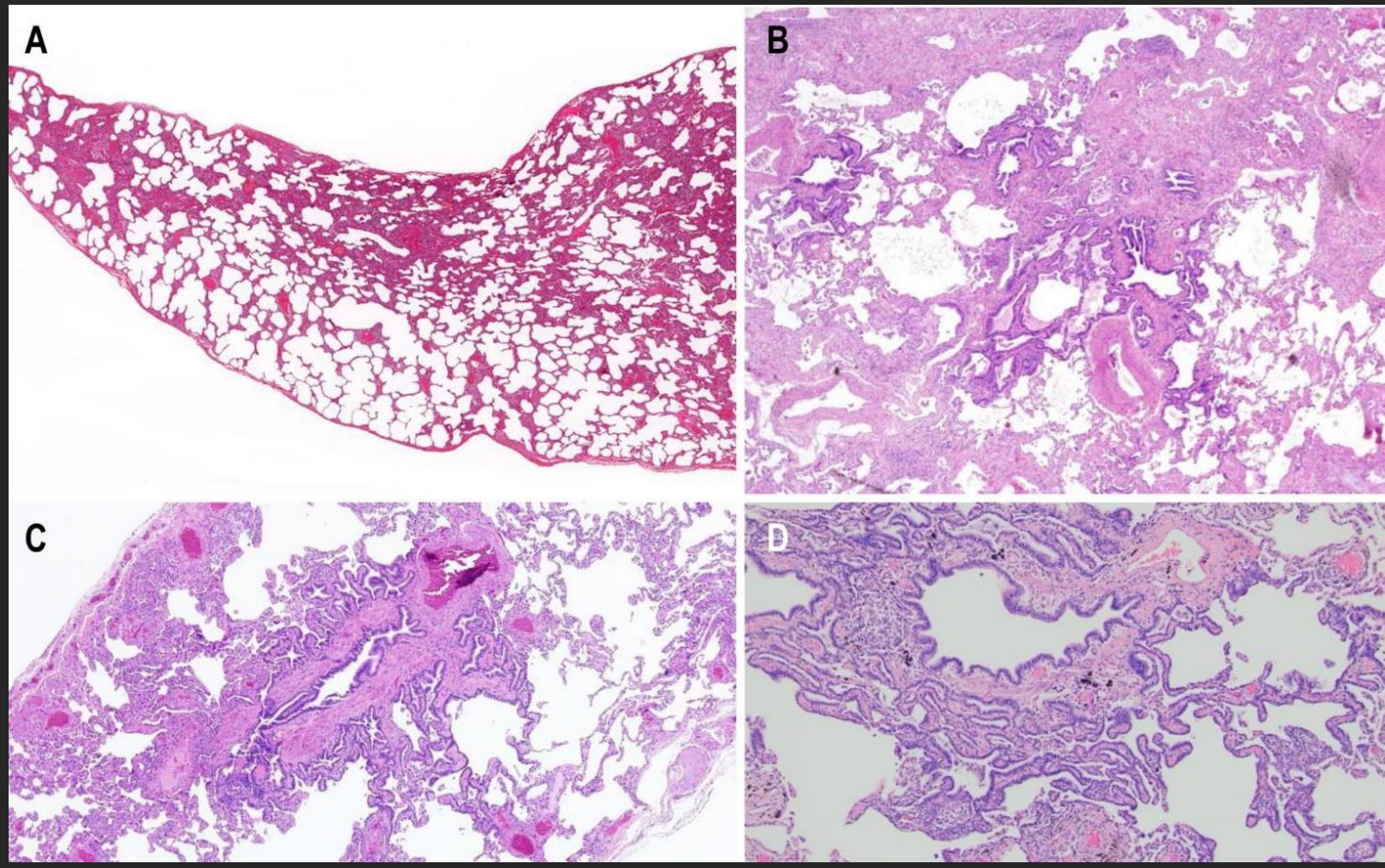




- Non-fibrotic BIP (E) diffuse ground glass centrilobular nodularity without traction bronchiectasis or other signs of fibrosis.
- Fibrotic BIP (F) shows three-density sign, consisting of multiple regions of lung with increased, normal, and decreased density, along with reticulation and traction bronchiectasis.
- This combination of findings would be referred to as a “typical HP” pattern in recent clinical practice guidelines on HP and is instead referred to in this document as a “fibrotic BIP” pattern.

Bronchiolocentric interstitial pneumonia (BIP)

- Non-fibrotic (or cellular) BIP
  - Lymphocyte-predominant inflammation surrounding bronchioles.
- Fibrotic BIP
  - Bronchiolocentric fibrosis (chronic inflammation), often with peribronchiolar metaplasia
- The presence of granulomatous inflammation in a peribronchiolar distribution is highly suggestive of HP as a secondary cause of BIP



Bronchiolocentric interstitial pneumonia (BIP)

- The category of BIP will hopefully allow better categorisation of cases that are not HP and support further studies related to the provisional clinical entity of idiopathic BIP
- HP no longer be used to describe a pattern seen on chest imaging or lung biopsy, and that the term “HP” instead be reserved for the multidisciplinary diagnosis of HP.
  - Similar concept of BIP to HP as UIP to IPF.
  - Many patients with airway-centred patterns cannot be confirmed to have HP even after multidisciplinary review (34% in a recent subgroup analysis of 164 patients with a radiological pattern of “typical HP”)

Bronchiolocentric interstitial pneumonia (BIP)

- Some concerns of the BIP as major IP category
  - Create confusion in the context of relatively recent HP guidelines that describe the above features as defining a “typical HP pattern.
  - “idiopathic BIP” should remain a provisional MDD diagnosis and should not be used if information from multidisciplinary review provides a confident diagnosis of HP or another etiology.
  - Whether there was a need for more evidence and/or greater uptake of BIP term in the literature prior to it being suggested in this document and adopted in clinical practice.
    - Highlights the need for a workshop to further study BIP, similar to the 2008 report on NSIP.

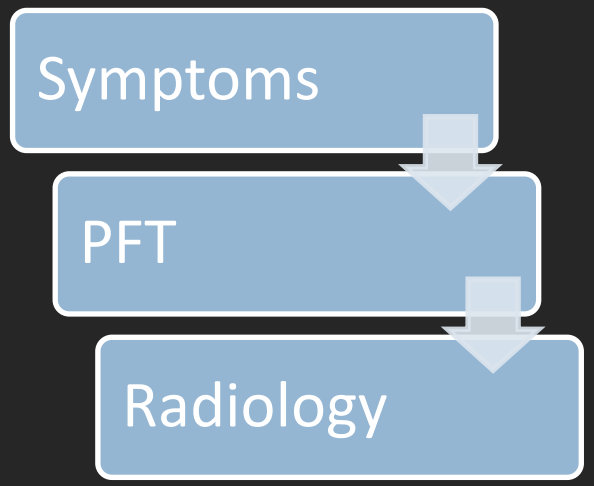


Table 4. Definition of Progressive Pulmonary Fibrosis

Definition of PPF
In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation*:
1 Worsening respiratory symptoms
2 Physiological evidence of disease progression (either of the following): a. Absolute decline in FVC ⩾5% predicted within 1 yr of follow-up b. Absolute decline in D_{LCO} (corrected for Hb) ⩾10% predicted within 1 yr of follow-up
3 Radiological evidence of disease progression (one or more of the following): a. Increased extent or severity of traction bronchiectasis and bronchiolectasis b. New ground-glass opacity with traction bronchiectasis c. New fine reticulation d. Increased extent or increased coarseness of reticular abnormality e. New or increased honeycombing f. Increased lobar volume loss

Definition of abbreviations: ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; PPF = progressive pulmonary fibrosis.

*Although it is critical to exclude alternative explanations of worsening features for all patients with suspected progression, this is particularly important in patients with worsening respiratory symptoms and/or decline in D_{LCO} given the lower specificity of these features for PPF compared with FVC and chest computed tomography.

Raghu G, et al. Am J Respir Crit Care Med 2022; 205 (9): e18–e47 (May 1, 2022)

Progressive pulmonary fibrosis (PPF)

- Definition: radiological and physiological criteria for PPF determined by consensus.
- PPF is defined separately from IPF
- PPF is not a diagnosis (many fibrotic lung diseases can manifest PPF)
- PPF have been associated only with prognosis. Unclear if PPF can identify patients best suited for antifibrotic therapy.
- PPF may beyond the interstitial space (≠ PF-ILD)

Raghu G, et al. Am J Respir Crit Care Med 2022; 205 (9): e18–e47 (May 1, 2022)

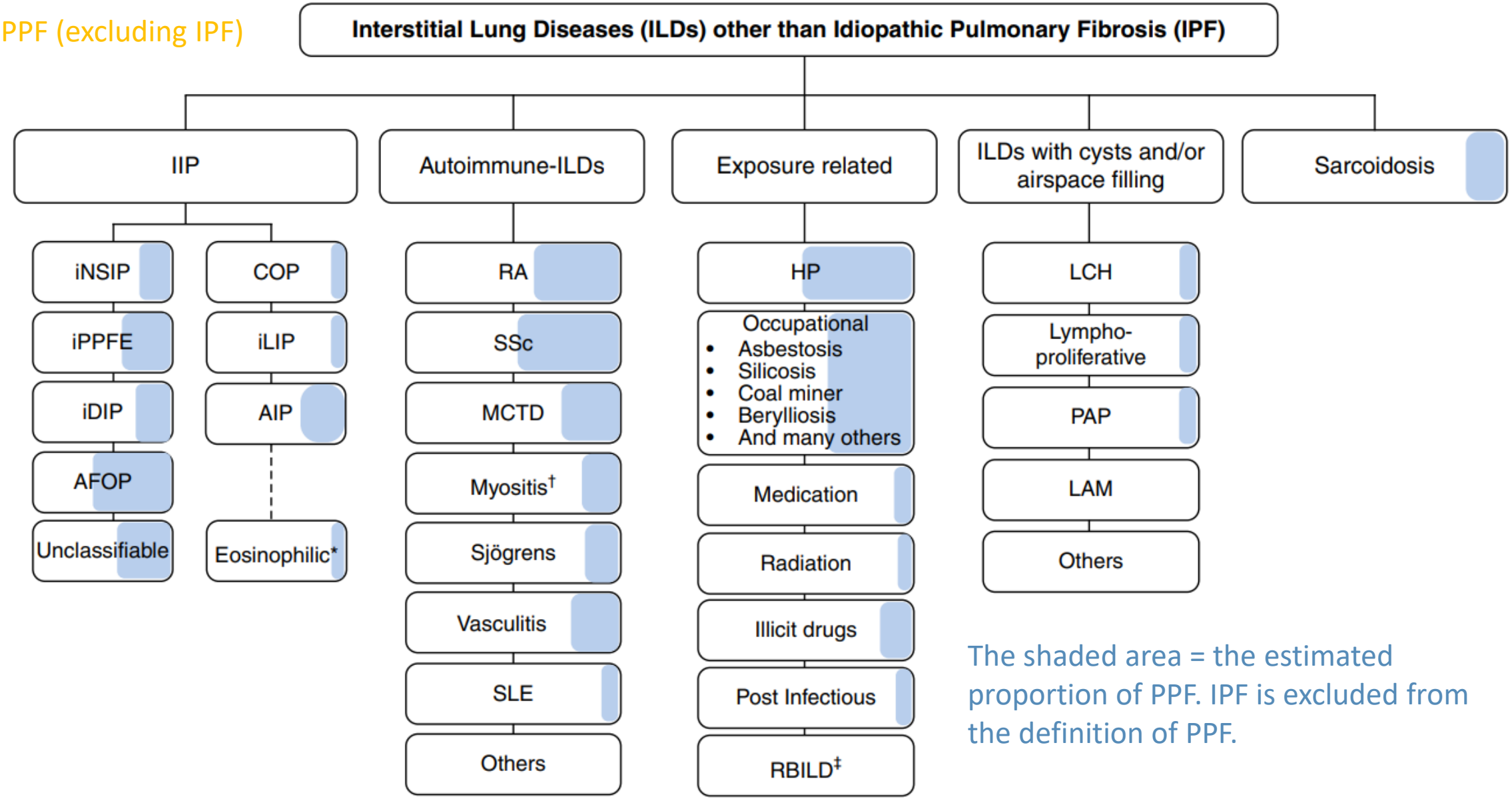
Radiological Criteria of PPF

- Visual determination of progression of pulmonary fibrosis.
- Usually visual assessment on the percentage of lung volume containing fibrotic features in the upper, mid and lower lung zones.
- Increased extent of fibrotic features = progression.
- Increased traction bronchiectasis and bronchiolectasis, new GGO with traction bronchiectasis, new fine reticulation, increased coarseness of reticular abnormality, new or increased honeycombing, and increased lobar volume loss.
- IPF progression: increased UIP pattern extent, HC, traction bronchiectasis/ bronchiolectasis, independent mortality predictor

Radiological Criteria of PPF

- Increased extent or severity of traction bronchiectasis and bronchiolectasis.
- New GGO with traction bronchiectasis.
- New fine reticulation.
- Increased extent or increased coarseness of reticular abnormality.
- New or increased honeycombing.
- Increased lobar volume loss.

PPF (excluding IPF)



The shaded area = the estimated proportion of PPF. IPF is excluded from the definition of PPF.

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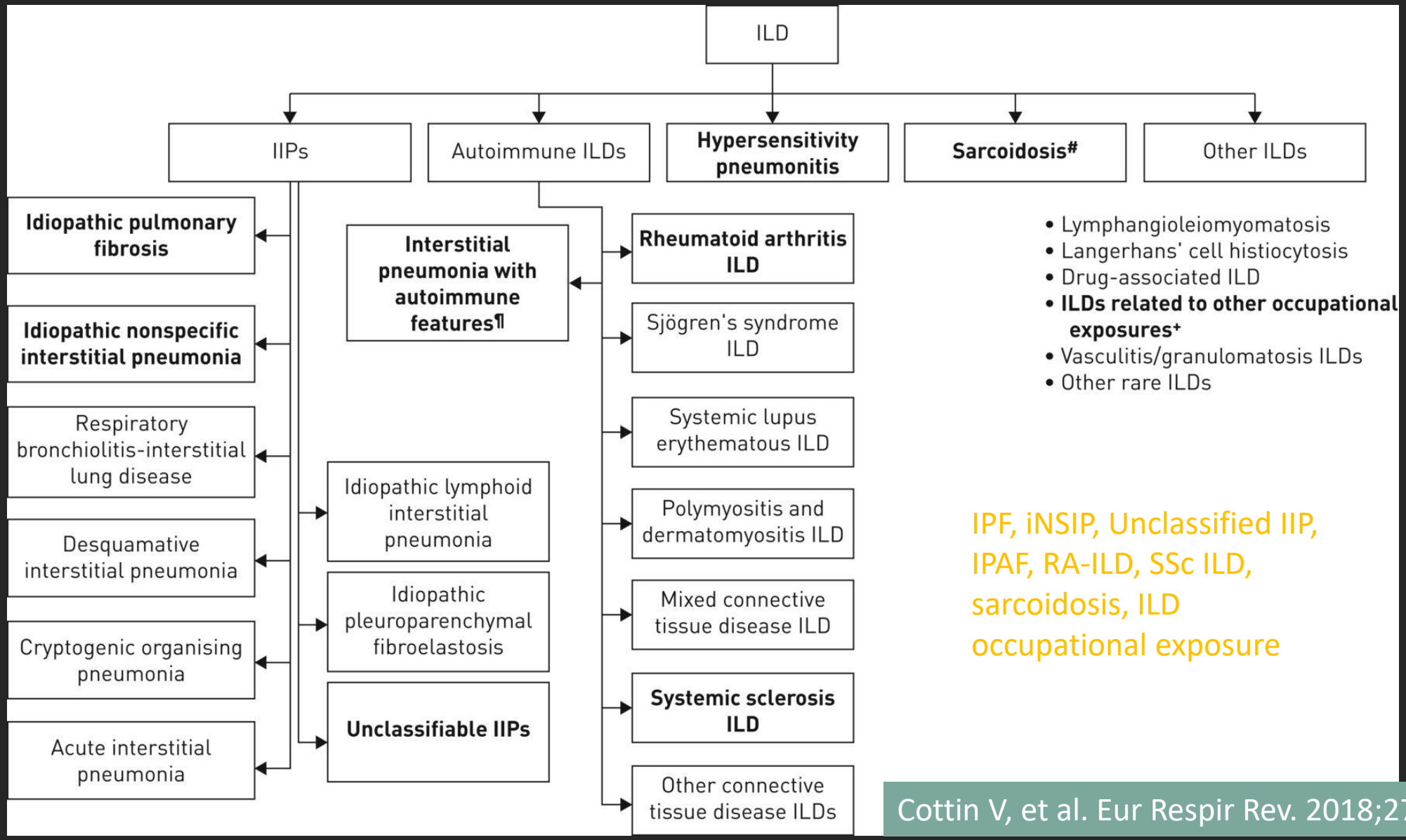
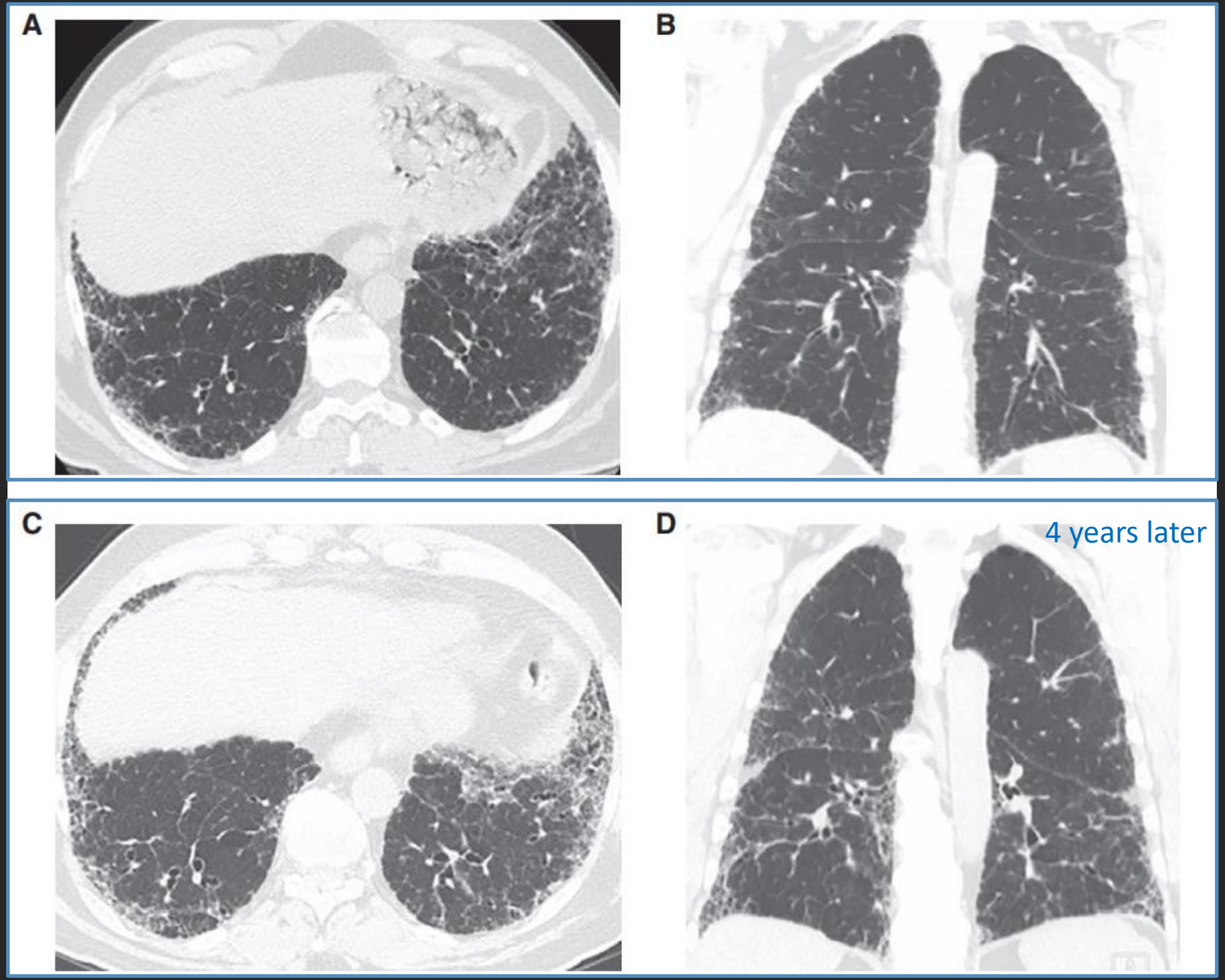
PF-ILD (including IPF)

Fibrosing ILDs with a progressive phenotype



IPF, iNSIP, Unclassified IIP, IPAF, RA-ILD, SSc ILD, sarcoidosis, ILD occupational exposure

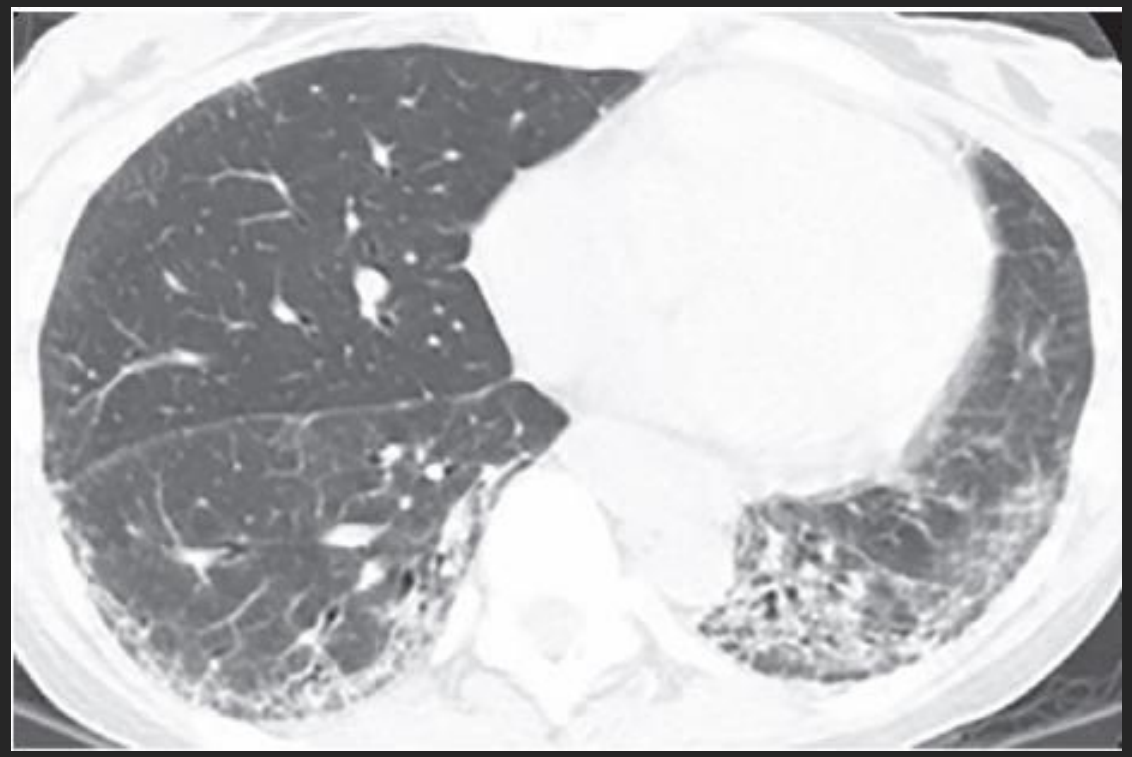
Cottin V, et al. Eur Respir Rev. 2018;27:180076



Progressive pulmonary fibrosis in a patient with IPF (probable usual interstitial pneumonia pattern).

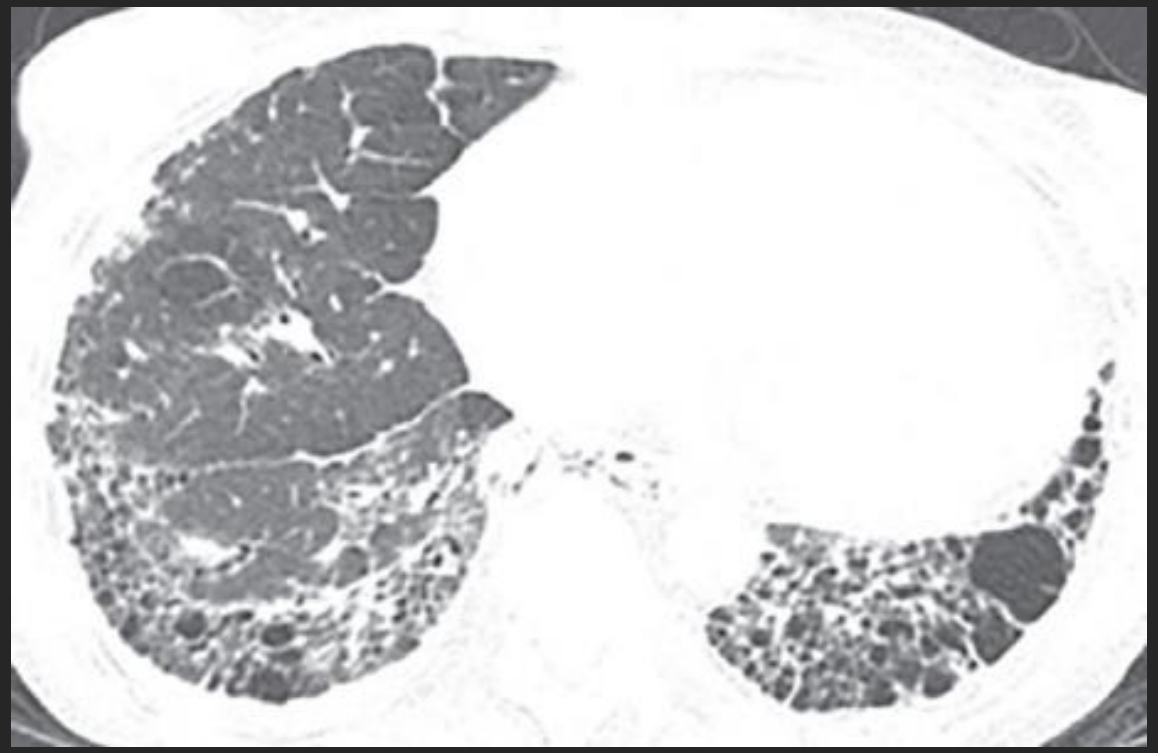
Raghu G, et al. Am J Respir Crit Care Med 2022; 205 (9): e18–e47 (May 1, 2022)

Progressive pulmonary fibrosis due to fibrotic nonspecific interstitial pneumonia (NSIP)



45-year-old woman with scleroderma

lower lung–predominant reticular and ground-glass abnormality with subpleural sparing, typical for NSIP



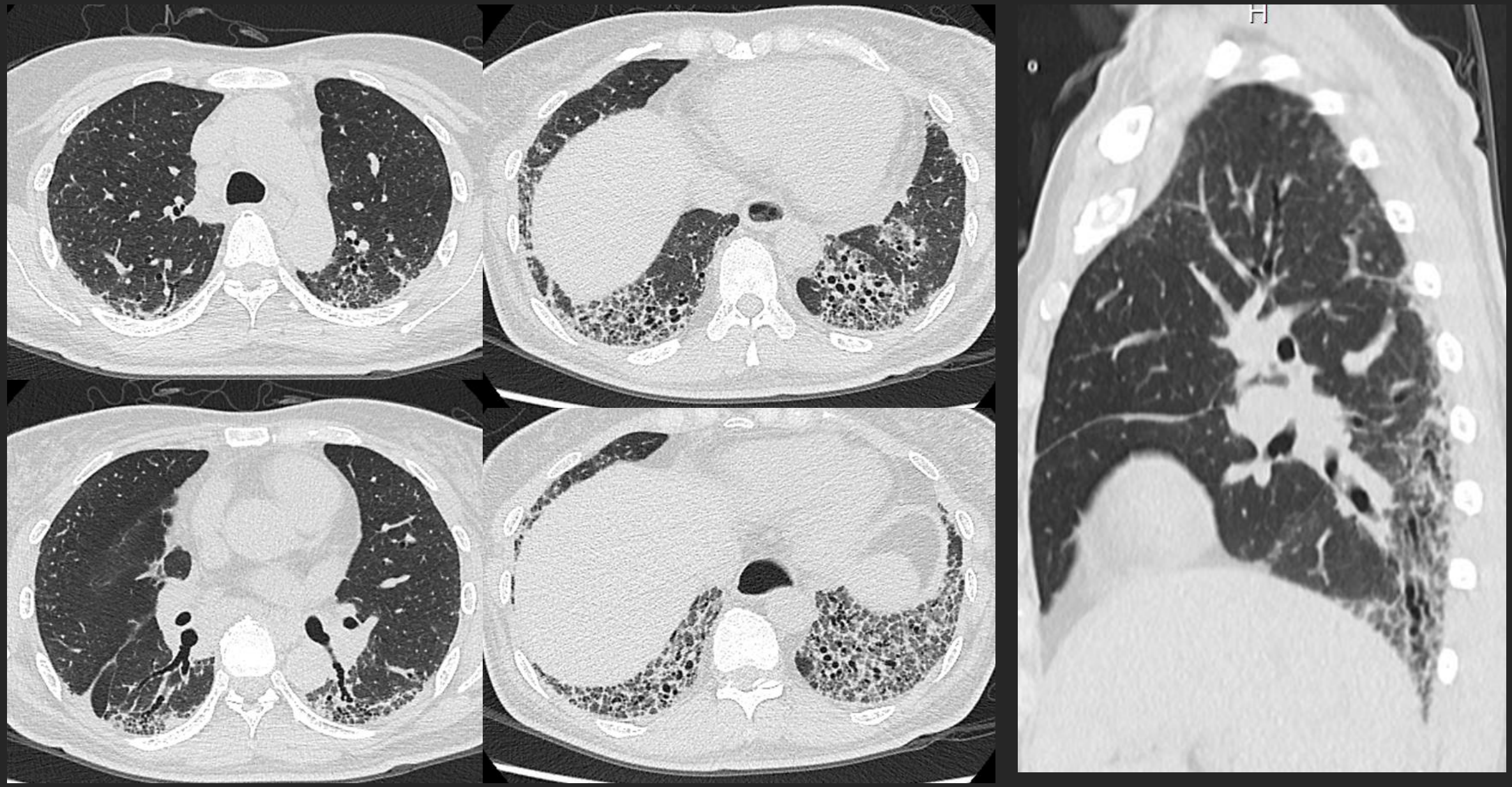
Nine years later

progressed with increased extent of reticular abnormality, increased traction bronchiectasis, and evolution of reticular abnormality to honeycombing. Small bilateral pleural effusions.

Raghu G, et al. Am J Respir Crit Care Med 2022; 205 (9): e18–e47 (May 1, 2022)

46 Female

Dermatomyositis



2026-1-30

ILD

Comprehensive evaluation:
Clinical assessment and PFT
HRCT
Serology
+/– BAL
+/– Biopsy if required

MDD

Diagnosis of a given entity

Working diagnosis of an entity (provisional)

Unclassifiable ILD

Treatment

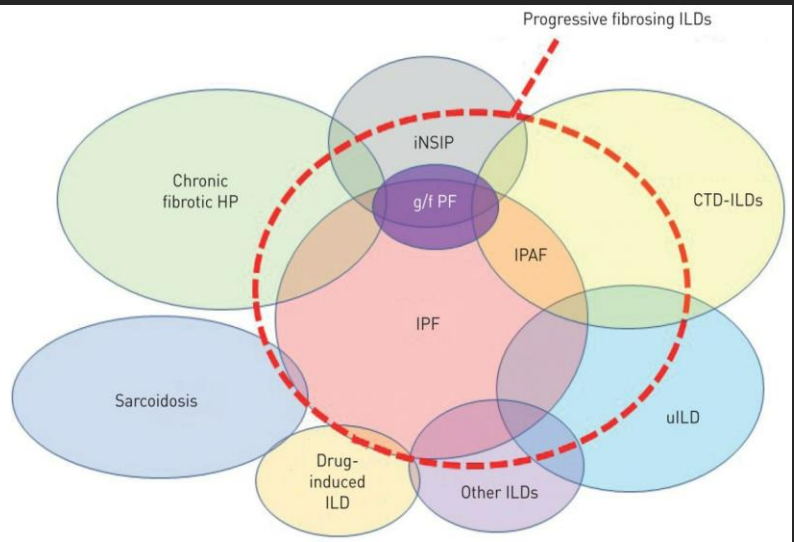
Watch and wait

Disease behaviour

Monitoring of disease progression
(clinical assessment, serial PFTs, follow-up HRCT)

Disease progression = PF-ILD

No disease progression



Cottin V. Eur Respir Rev 2019; 28: 190109

TABLE 1 Proposed criteria that may be used in clinical practice to assess disease progression in fibrotic interstitial lung diseases

Lung function	Rate of decline in FVC (mL·year^{-1})
	Absolute or relative changes in FVC (mL or % predicted)
	Absolute or relative changes in D_{LCO} % predicted
Exercise capacity	Absolute change in 6-min walk test distance
	Change in oxygen saturation nadir during 6-min walk test
	Change in maximal exercise capacity
Symptoms and patient-reported outcomes	Change in symptoms
	Change in everyday life exercise capacity
	Questionnaires on shortness of breath, cough, and/or quality of life
Acute worsening	Acute exacerbation of fibrosis (idiopathic or triggered)
	Non-elective hospitalisation for a respiratory cause
HRCT	Change in the extent or texture of fibrotic features on HRCT
	Change in quantitative fibrosis scores on HRCT[#]
Need for supportive care	Initiation of ambulatory oxygen therapy at exercise
	Initiation of supplemental oxygen therapy at rest, or change in flow of oxygen
Serum biomarkers	None validated
	Not yet applicable in clinical practice

As these criteria are intended to guide individual decisions in clinical practice, they may differ from end-points used in clinical trials [17]. Most clinicians would make management decisions based on a combination of variables. HRCT: high-resolution computed tomography; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide. [#]: not yet routinely available.

Cottin V. Eur Respir Rev 2019; 28: 190109

INBUILD trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

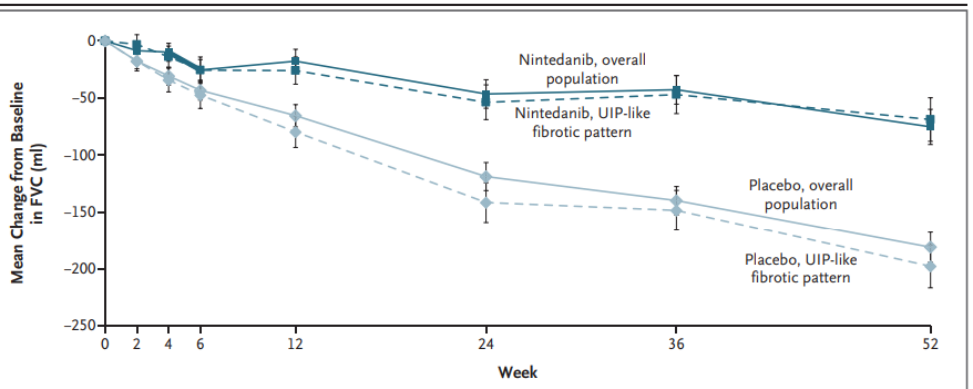
Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

K.R. Flaherty, A.U. Wells, V. Cottin, A. Devaraj, S.L.F. Walsh, Y. Inoue, L. Richeldi, M. Kolb, K. Tetzlaff, S. Stowasser, C. Coeck, E. Clerisme-Beaty, B. Rosenstock, M. Quaresma, T. Haeufel, R.-G. Goeldner, R. Schlenker-Herceg, and K.K. Brown, for the INBUILD Trial Investigators*

ABSTRACT

BACKGROUND

Preclinical data have suggested that nintedanib, an intracellular inhibitor of tyrosine kinases, inhibits processes involved in the progression of lung fibrosis. Although the efficacy of nintedanib has been shown in idiopathic pulmonary fibrosis, its efficacy across a broad range of fibrosing lung diseases is unknown.



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

Figure 2. Decline from Baseline in Forced Vital Capacity (FVC).

Shown is the observed mean change from baseline in FVC over the 52-week trial period in the overall population and in patients with an imaging pattern of usual interstitial pneumonia (UIP) on high-resolution computed tomography in the nintedanib group and the placebo group. The I bars indicate the standard error.

In patients with PF-ILD, the annual rate of decline in the FVC was significantly lower among patients who received nintedanib than among those who received placebo

N Engl J Med 381;18 nejm.org October 31, 2019

INBUILD trial

- Enrolled patients had features of fibrosing lung disease affecting >10% of lung volume on HRCT,
- Progression of ILD within the 24 months
- FVC decline >10%,
- FVC decline 5%~<10% + worsening respiratory symptoms or increased extent of fibrosis (HRCT), or
- + worsening of respiratory symptoms and an increased extent of fibrosis

N Engl J Med 381;18 nejm.org October 31, 2019

The role of HRCT in PF-ILD

- Use of HRCT to diagnose different CTD-ILDs, and to differentiate between stable and progressive disease.
- Serial CT imaging for monitoring disease progression
- HRCT as a prognostic tool
- Disease progression and serial imaging
- Quantitative versus qualitative imaging

Walsh SLF, et al. Eur Respir Rev 2018; 27: 180073

Diagnosis of PF-ILD based on CT

- Change of the extent or texture of fibrotic features on HRCT
- Change in quantitative fibrosis scores on HRCT
- CT evidence of acute worsening (acute exacerbation of fibrosis)

Walsh SLF, et al. Eur Respir Rev 2018; 27: 180073

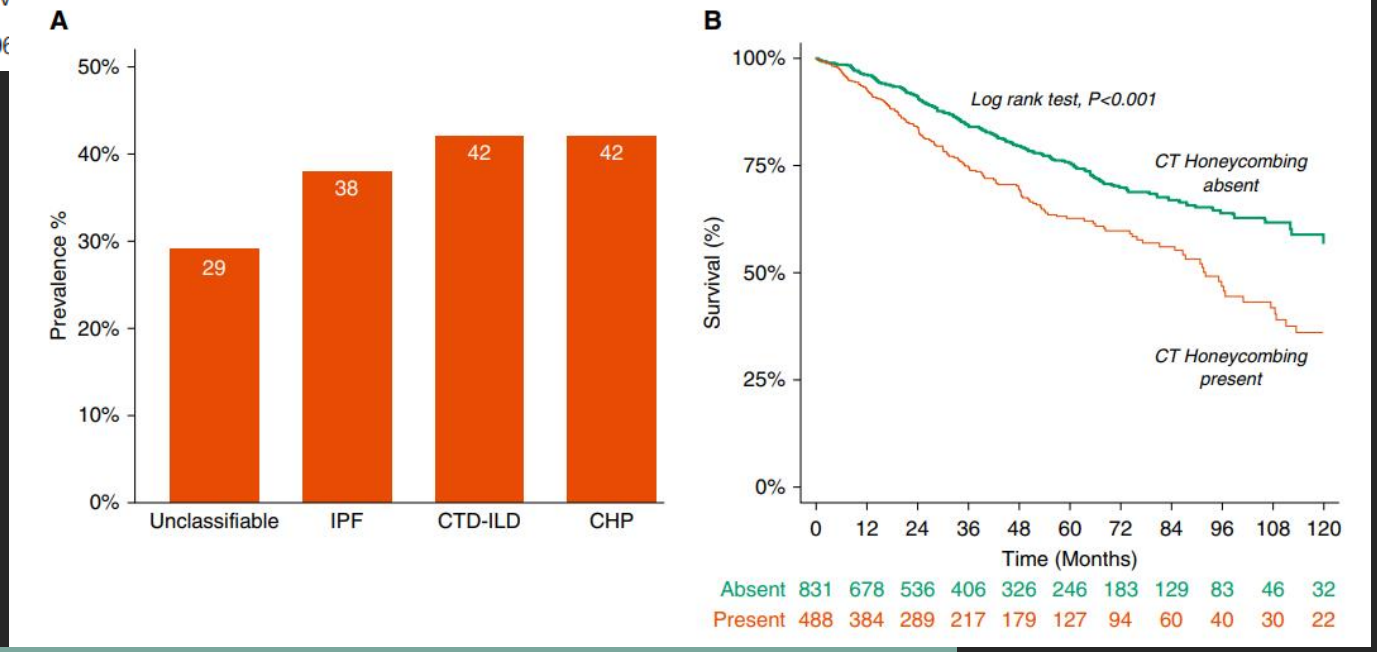
ORIGINAL RESEARCH

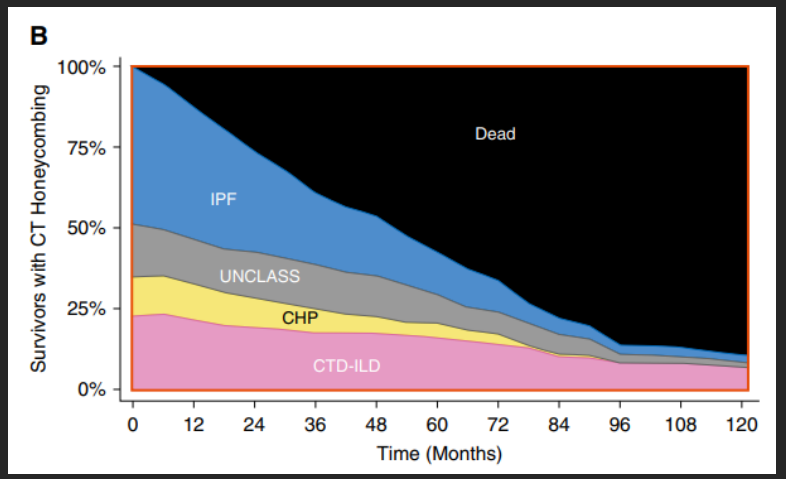
Computed Tomography Honeycombing Identifies a Progressive Fibrotic Phenotype with Increased Mortality across Diverse Interstitial Lung Diseases

Ayodeji Adegunsoye[1], Justin M. Oldham[2], Shashi K. Bellam[3], Steven Montner[4], Matthew M. Churpek[1,5], Imre Noth[6], Rekha Vij[1], Mary E. Strek[1*] and Jonathan H. Chung[4*‡]

[1]Section of Pulmonary and Critical Care, Department of Medicine, [4]Department of Radiology, and [5]Department of Public Health Sciences, The University of Chicago, Chicago, Illinois; [2]Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, University of California at Davis, Davis, California; [3]Division of Pulmonary and Critical Care, Department of Medicine, NorthShore University HealthSystem, Ev

ORCID ID: 0000-0002-7015-96



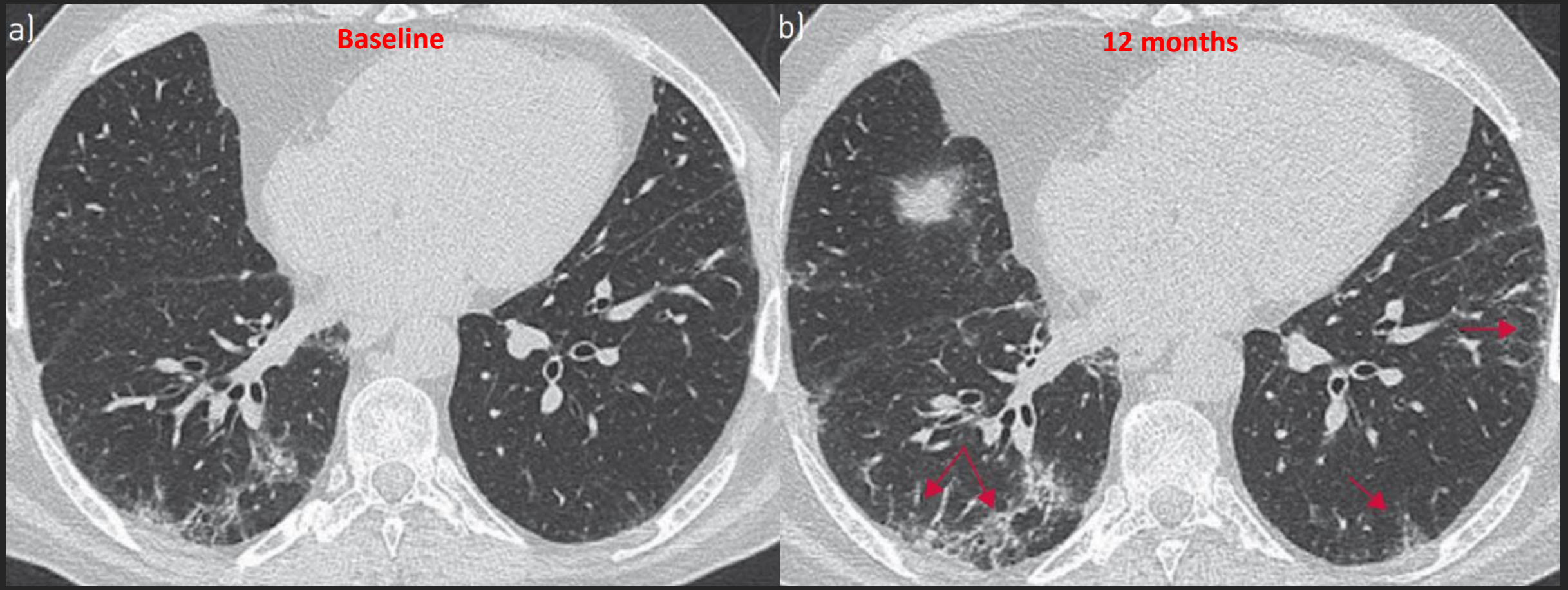


Proportion of survivors for cohort with CT honeycombing (n = 492) stratified by ILD subtype;

Figure 1. (A) CT honeycombing is prevalent across diverse ILD subtypes; (B) Kaplan-Meier analysis demonstrates worsened 10-year survival in participants with ILD and CT honeycombing.

Adegunsoye A, et al. Ann Am Thorac Soc 2019; 16(5); 580–588

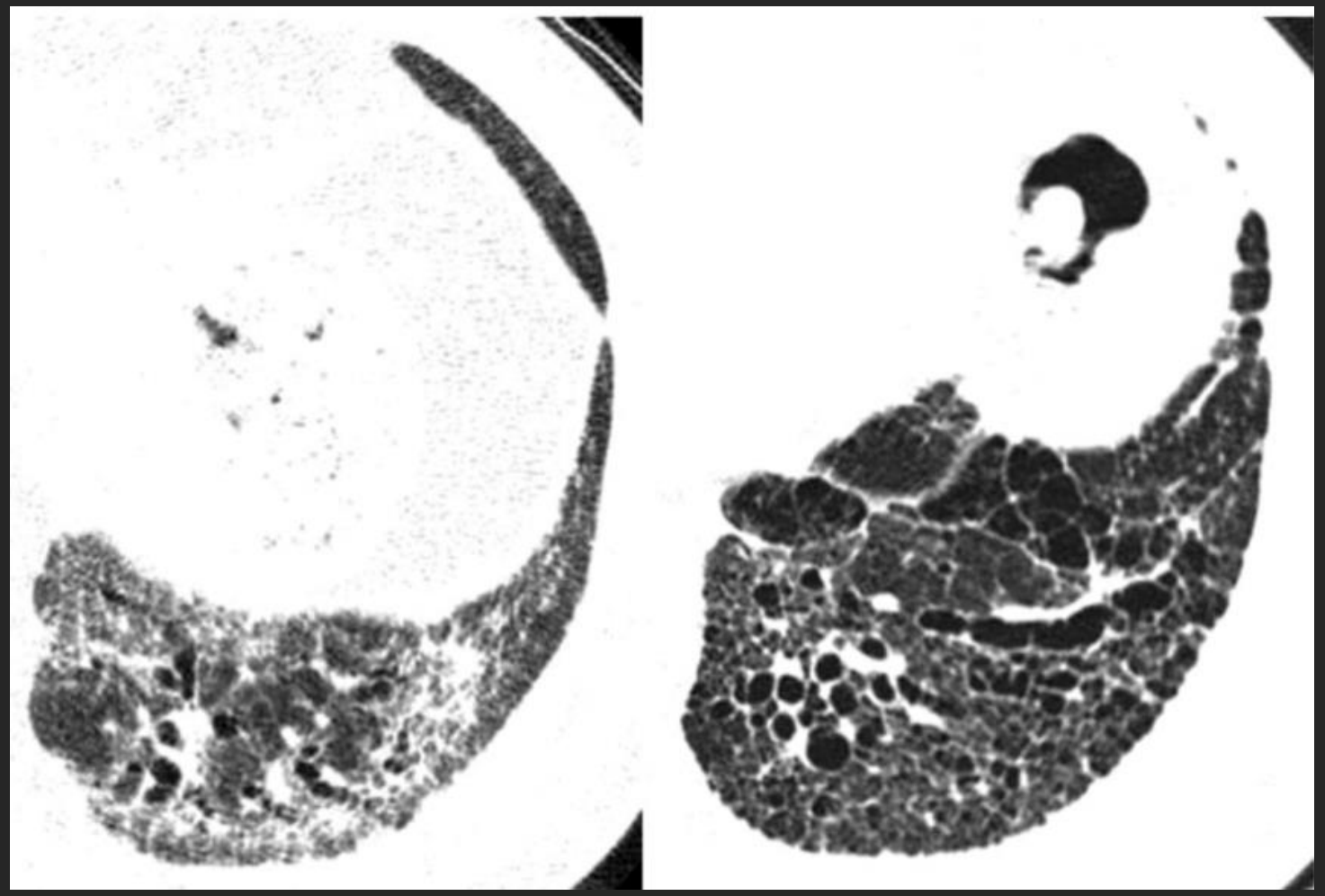
HRCT for monitoring disease progression in IPF



progressive reticulation and traction bronchieolectasis

Robbie H, et al. Eur Respir Rev 2017; 26: 170051
Walsh SLF, et al. Eur Respir Rev 2018; 27: 180073

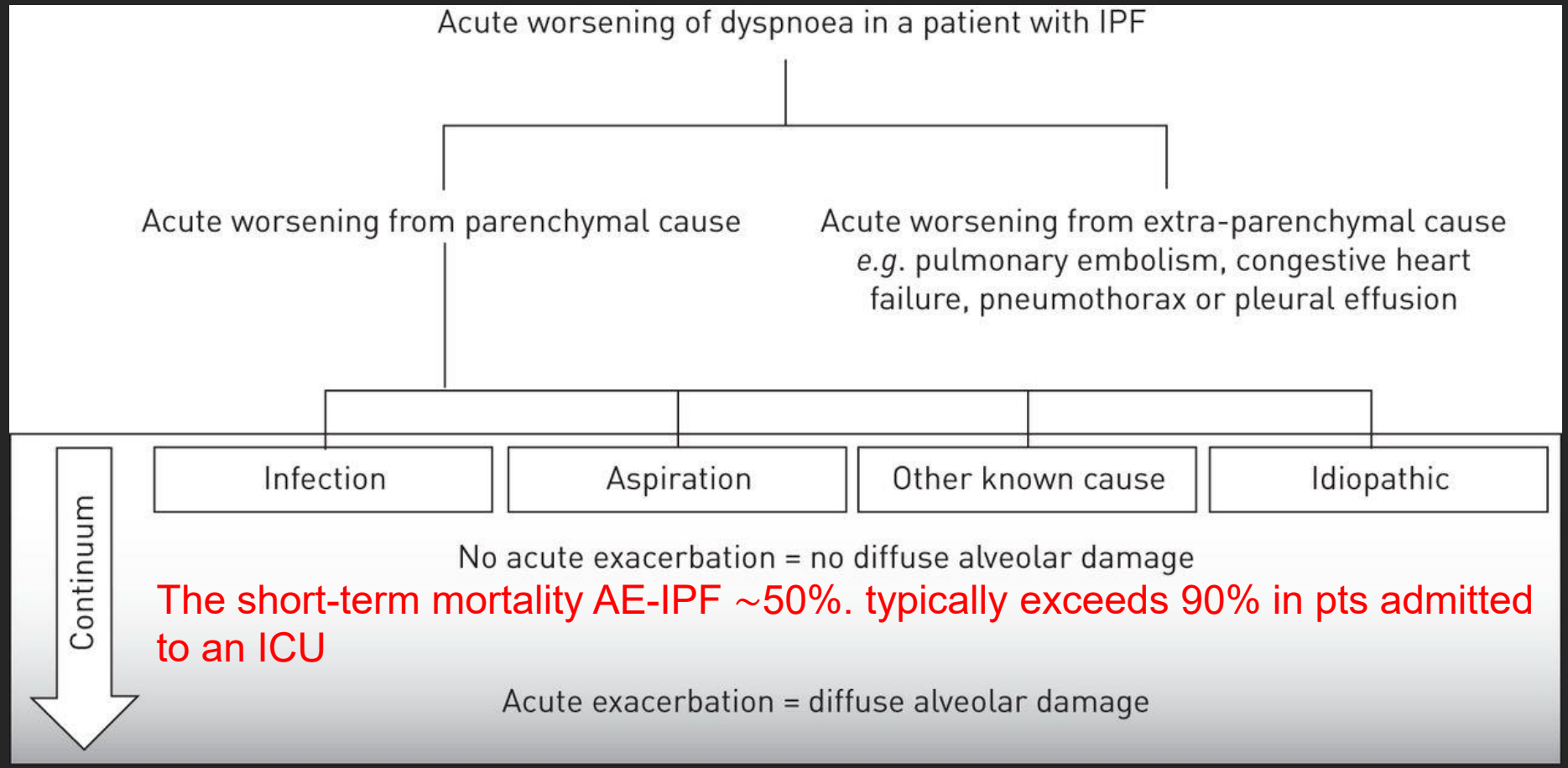
Progression of fibrosis on follow up HRCT



A 57-year-old man with fibrotic NSIP
(A) Initial CT of the left lower lung shows patchy areas of ground-glass attenuation with reticulation and traction bronchiectasis. (B) Follow-up CT scan obtained 60 months later shows a decrease in ground-glass opacity and increase in reticulation and traction bronchiectasis.

Akira M. Ann Am Thorac Soc 2017;14: 432–440

AE-IPF



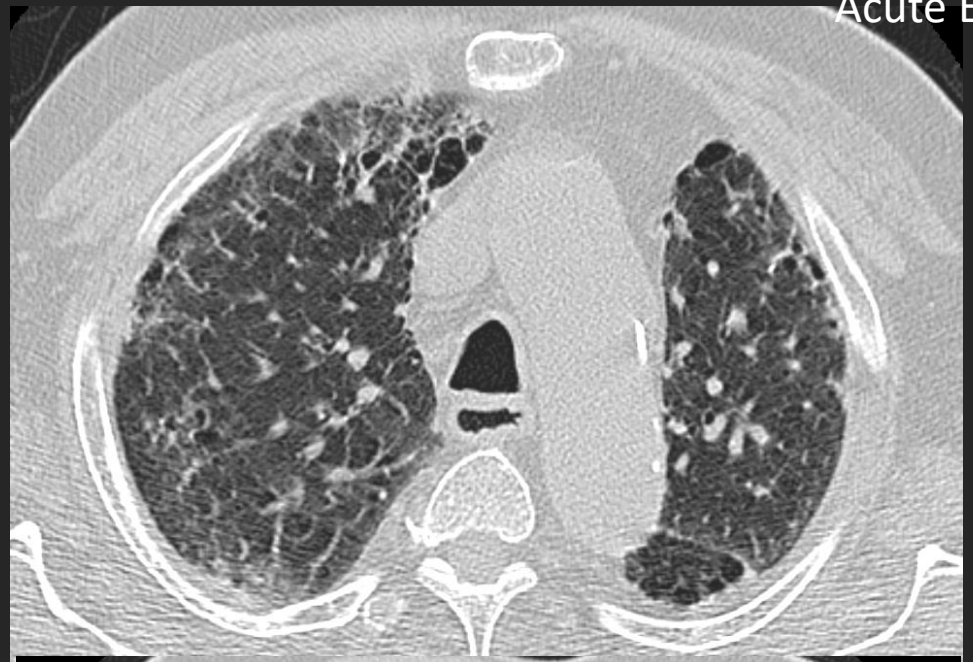
Ryerson CJ, et al. European Respiratory Journal 2015 46: 512-520

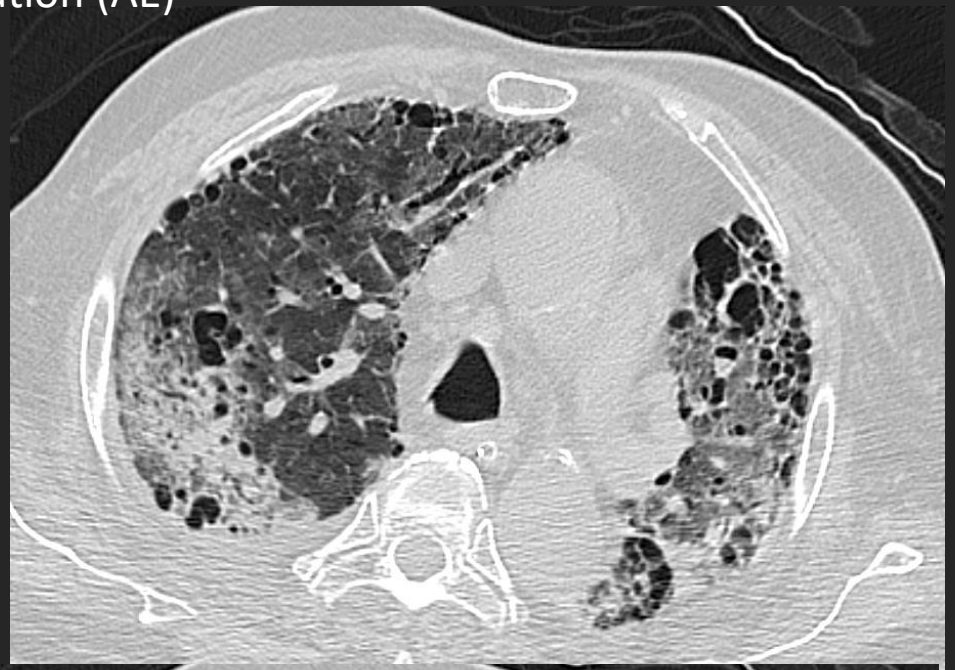
Acute exacerbations of ILD

- Acute, clinically significant respiratory deteriorations characterized by evidence of new, widespread alveolar abnormality
- Acute worsening or development of dyspnea (typically of < 1 month duration).
- CT with new bilateral GGO or consolidation superimposed on a background pattern consistent with fibrosing ILD, and
- deterioration not fully explained by cardiac failure or fluid overload.
- Infection was not an exclusion criterion for an acute exacerbation.

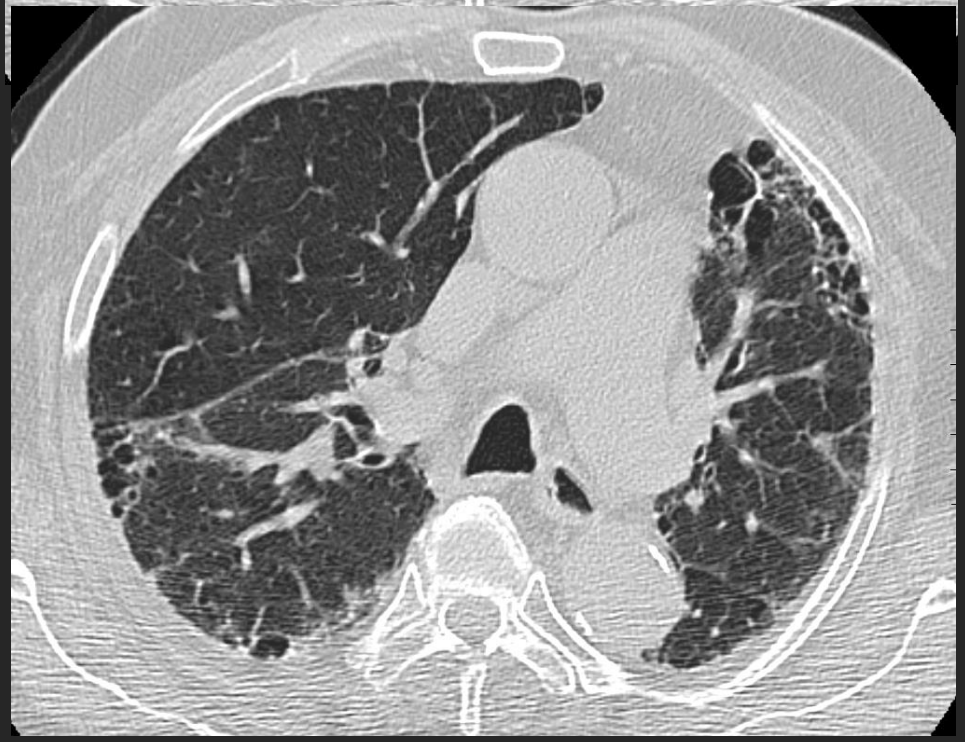
Flaherty KR, et al. N Engl J Med 2019;381:1718-27 (INBUILD)

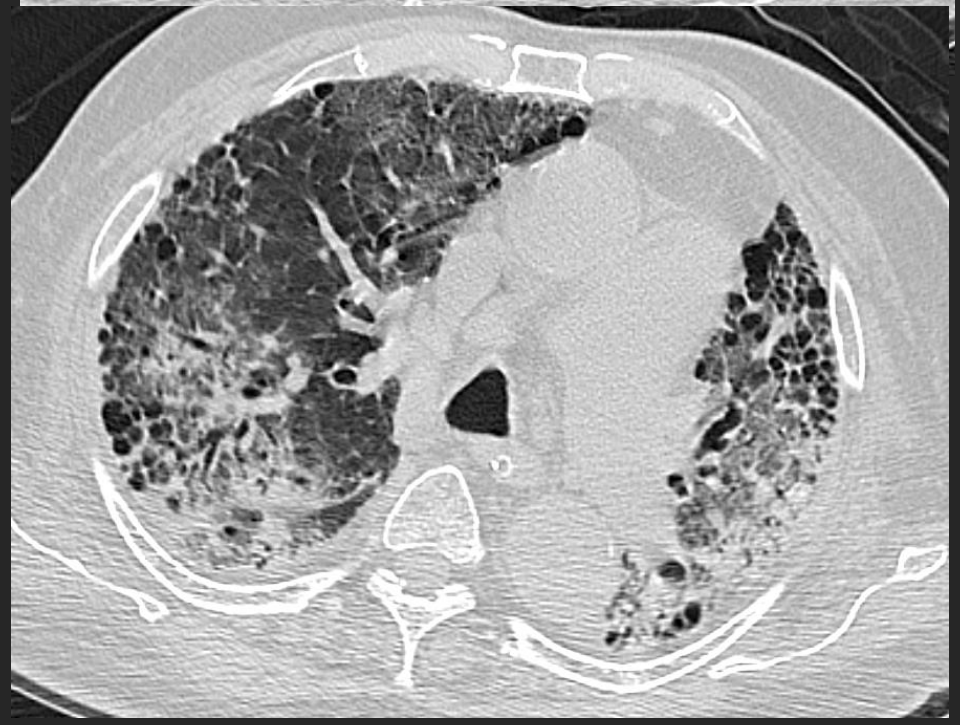
Acute Exacerbation (AE)





2007-01-08

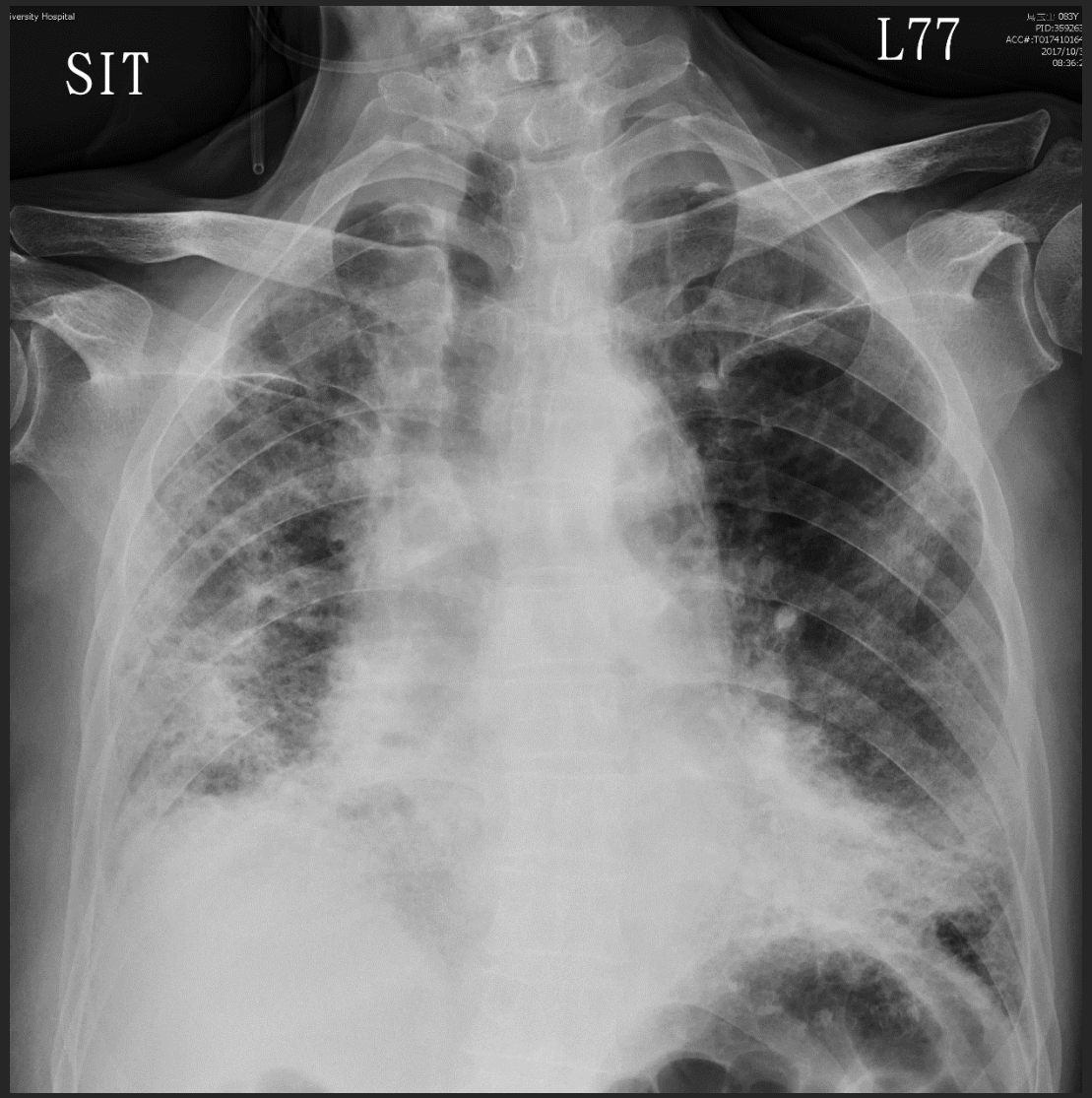




2007-03-06

Case

2017-10-30 ER



Bilateral patchy consolidation and GGO infiltration, more extensive in the right lung and bilateral lower lobes. Atelectasis at the lower lobes, especially RLL.

Fine reticulation and interstitial opacities in both lungs

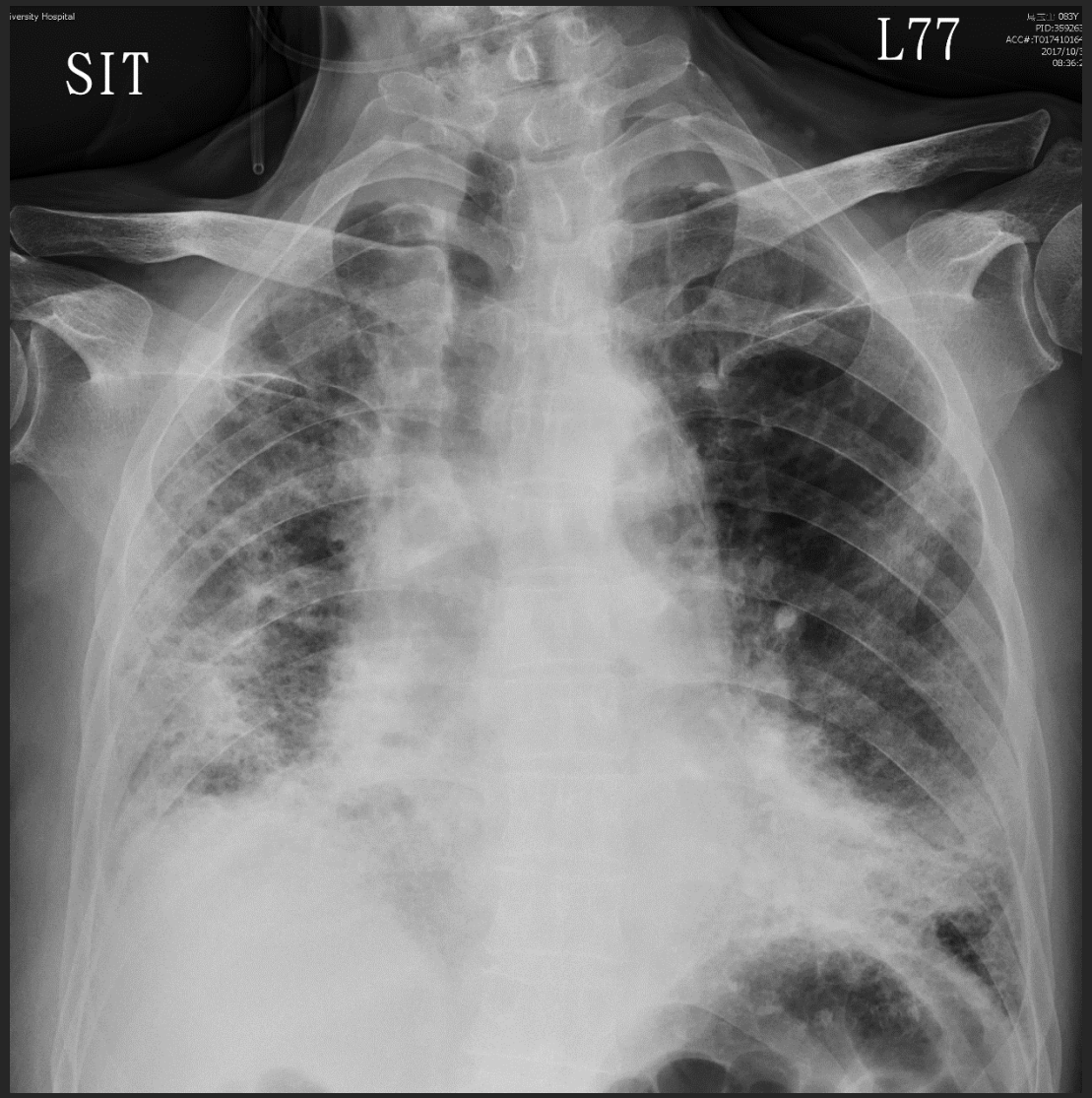
Is it acute, subacute or chronic?

Comparison with prior studies

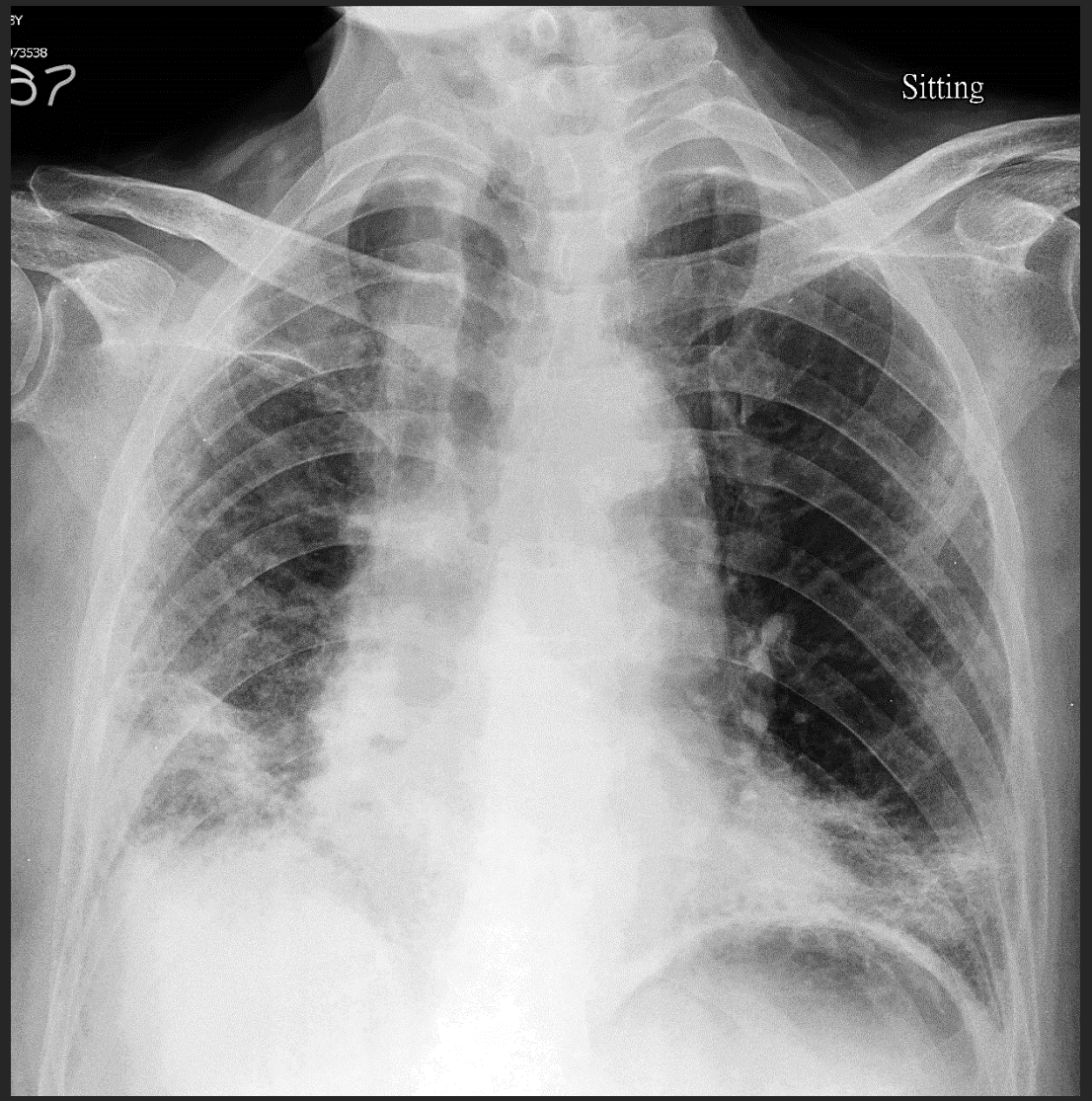
83 year old man, dyspnea worsening since 3 days ago (fever episode) during tappering steroid (1.5# QD) SPO2 at home resting 92-94%, desaturation was found during mild exercise

Case

2017-10-30 ER

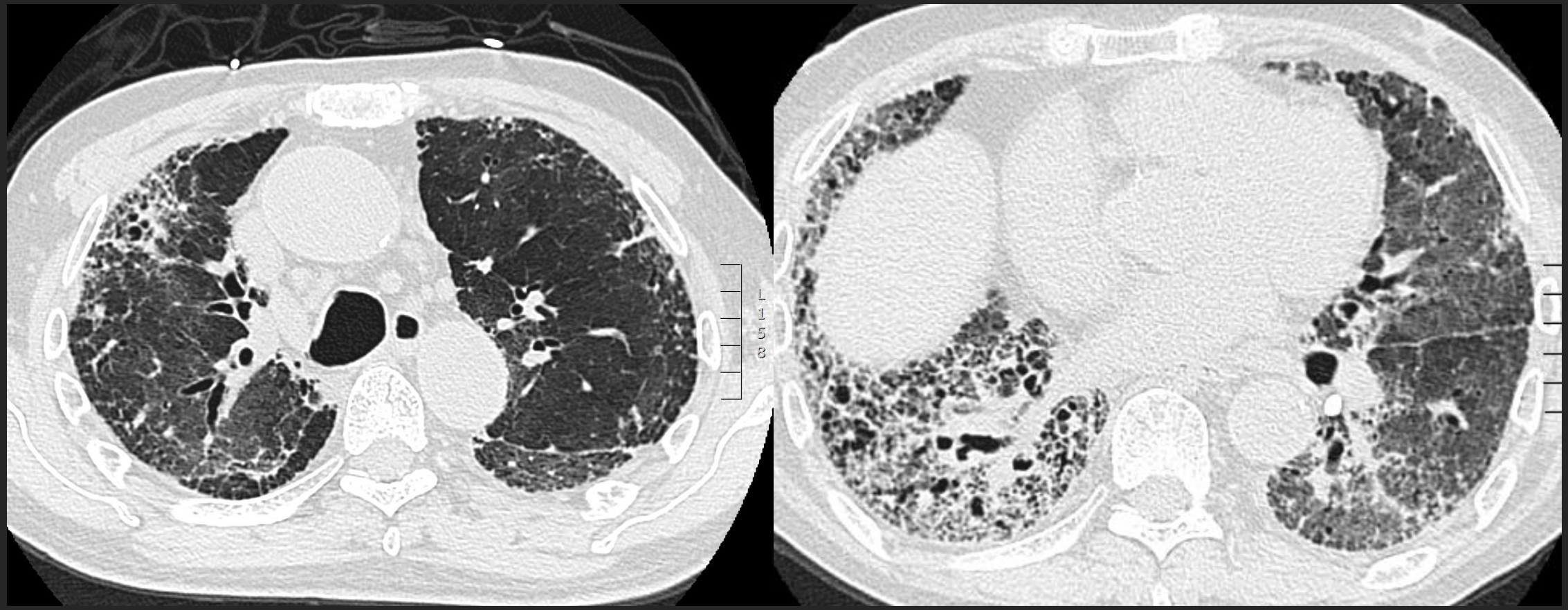


2017-10-19 OPD



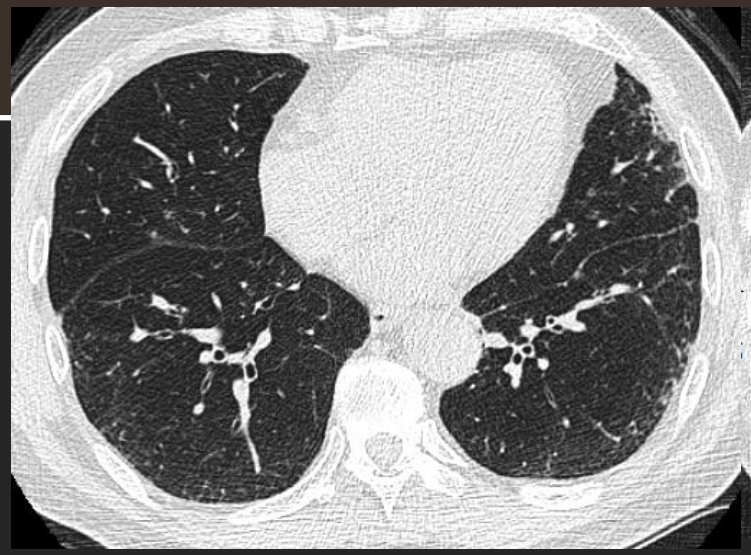
83 year old man, dyspnea worsening since 3 days ago (fever episode) during tapering steroid (1.5# QD) SPO2 at home resting 92-94%, desaturation was found during mild exercise

2017-10-30

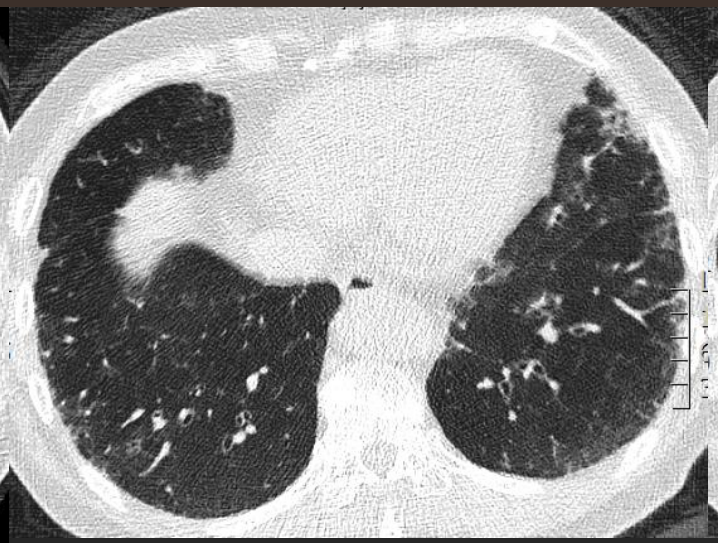


Increased opacity on CXT, compatible with increased GGO infiltration superimposed on the background lung parenchyma showing lung fibrosis (honeycombing, traction bronchiectasis and bronchiolectasis, within one month

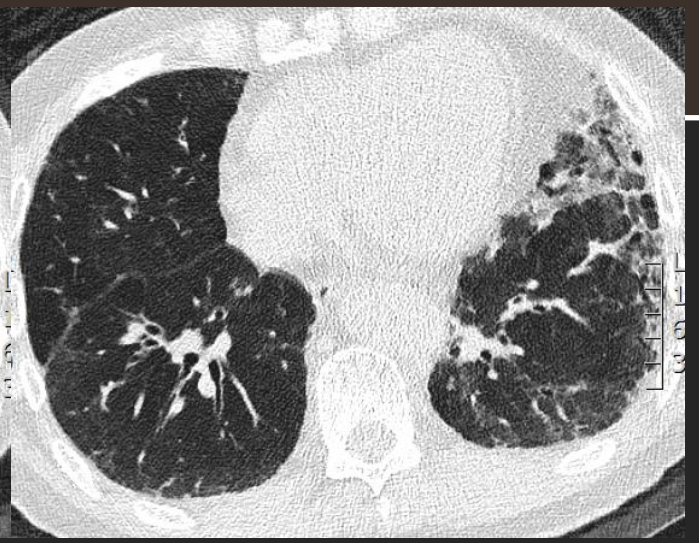
Progression of idiopathic pulmonary fibrosis (IPF)



2010-7-30

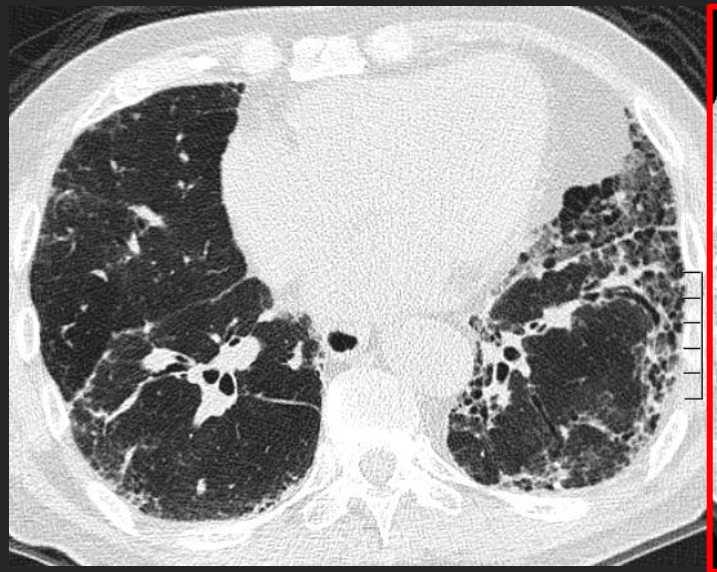


2013-4-10

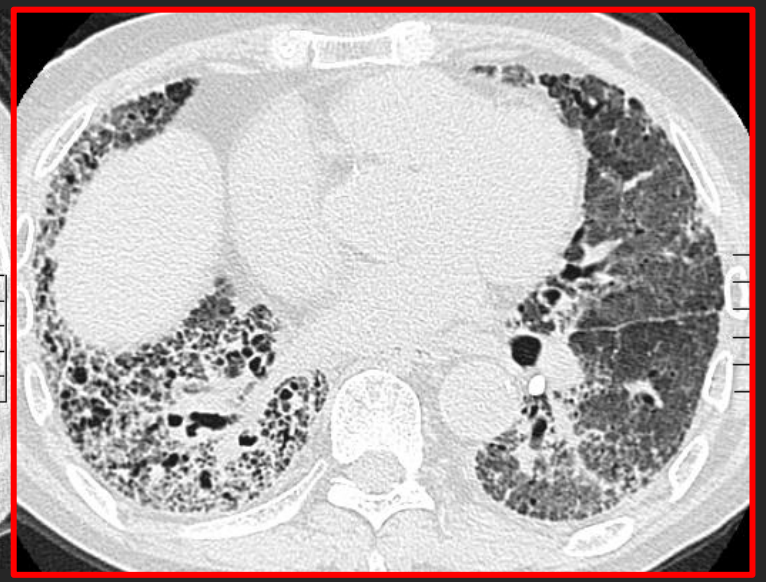


2015-11-4

IPF diagnosed

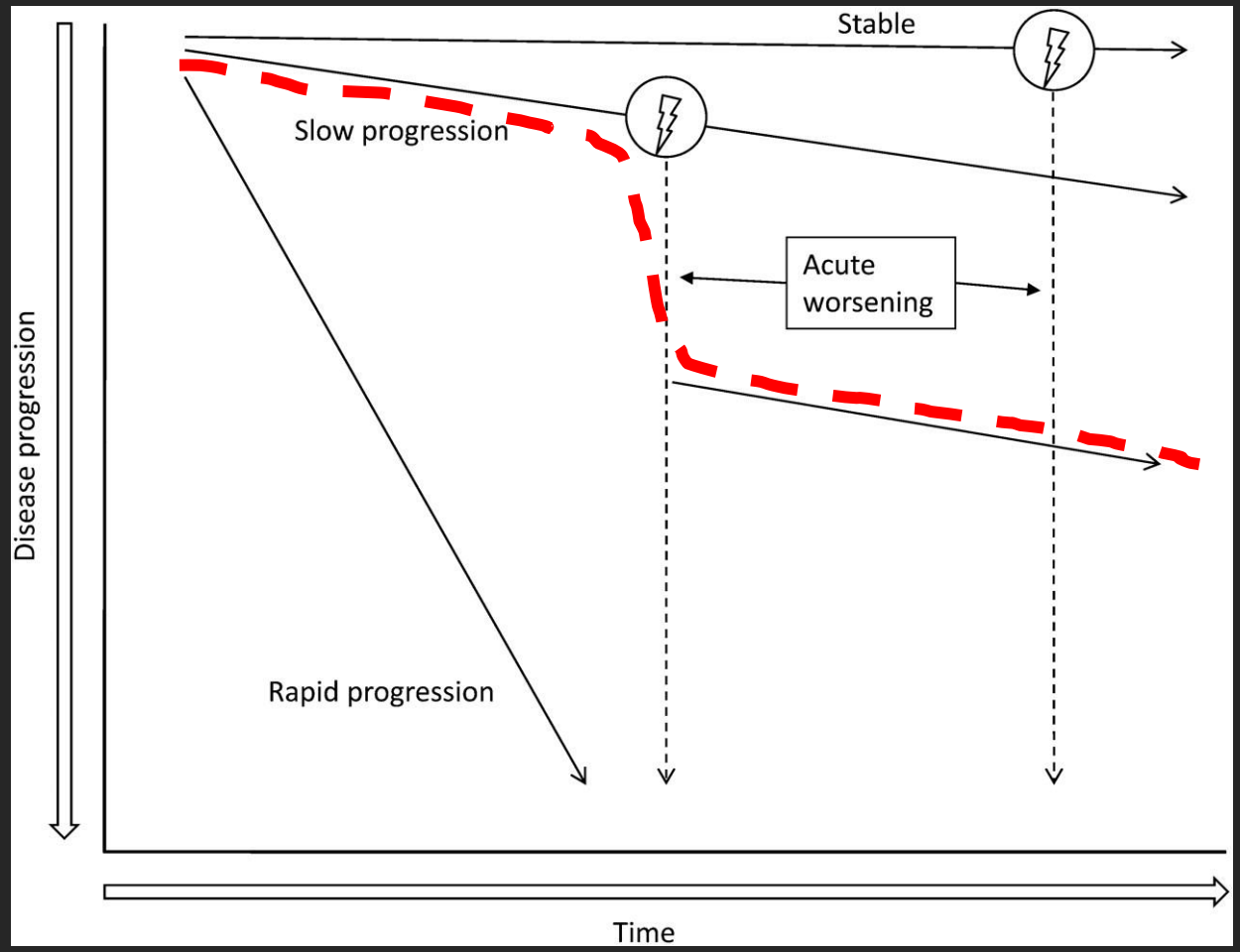


2017-8-2



2017-10-30

Natural history of IPF



Am J Respir Crit Care Med Vol 183. pp 788-824, 2011

Acute exacerbation -ILD

- AE as an acute, clinically significant respiratory deterioration, typically less than 1 month in duration
- together with CT imaging showing new bilateral GGO and/or consolidation
- superimposed on a background pattern consistent with fibrosing ILDs
- no formal strategies to prevent the development of AE, possible approaches include antifibrotic drugs (such as nintedanib and pirfenidone), and minimising exposure to infection, airborne irritants and pollutants

Summary

- Knowing the typical UIP pattern
- Knowing the new classification of ILD
- Identification of fibrotic pattern in ILD
- HRCT is the cornerstone for diagnosis and following up for the severity and progression of fibrosing ILD.
- HRCT findings may be suggestive of pulmonary fibrosis and AE

Thanks for your attention

日月潭 Sun Moon Lake 2019