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CPFE (Combined Pulmonary Fibrosis and Emphysema): a Distinct entity?

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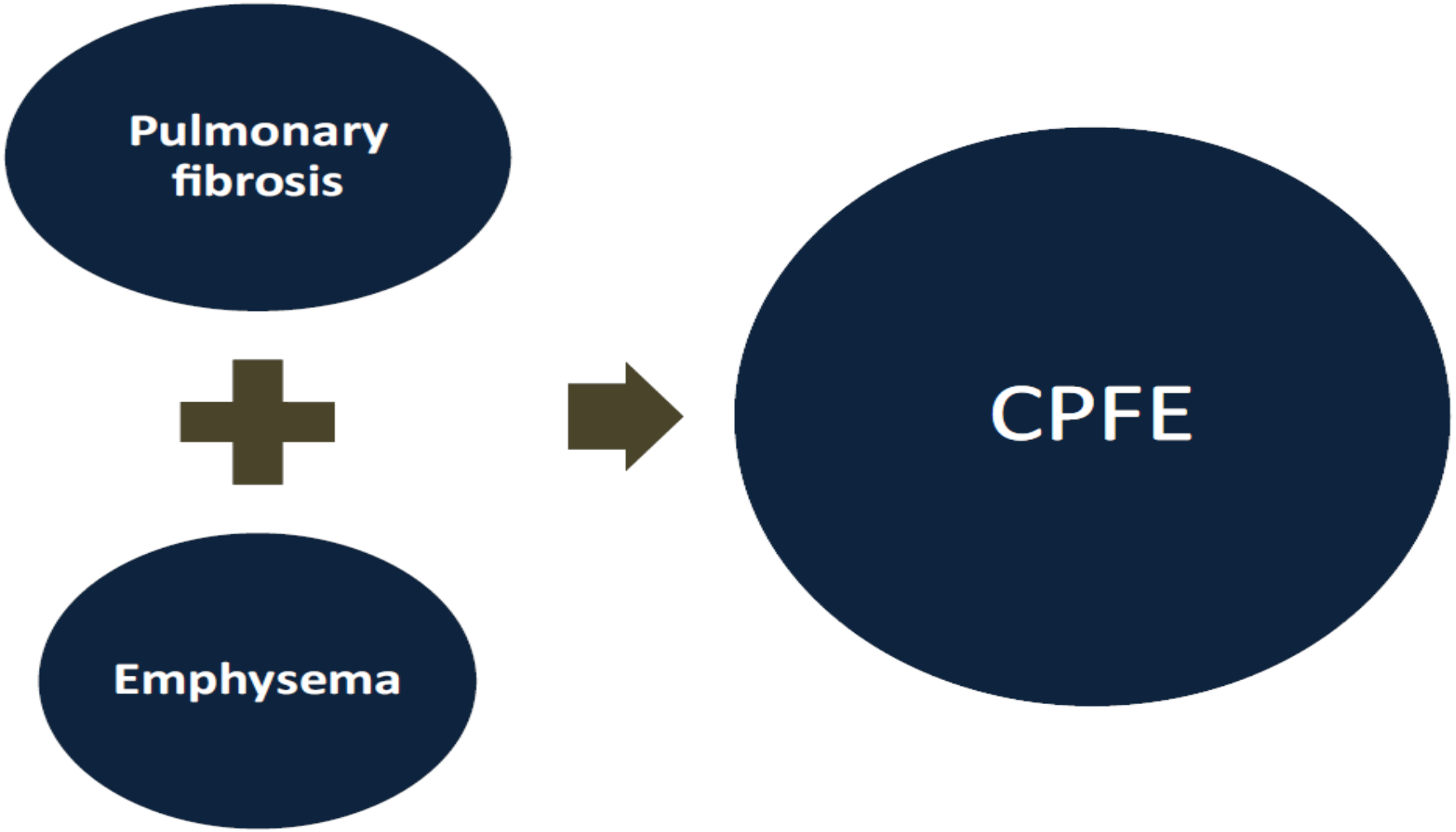
what is the combined pulmonary fibrosis and emphysema

Combined pulmonary fibrosis and emphysema (CPFE) is a lung condition characterized by the presence of both emphysema and pulmonary fibrosis in the same individual. Emphysema is a condition in which the air sacs in the lungs are damaged and lose their elasticity, leading to difficulty in breathing, while pulmonary fibrosis is a condition in which the lung tissue becomes scarred and thickened, making it harder for oxygen to pass into the bloodstream.

In CPFE, the emphysema usually affects the upper lobes of the lungs, while the pulmonary fibrosis affects the lower lobes. This combination of lung diseases is associated with a distinct clinical profile, including a higher prevalence in men, a history of smoking, and a higher incidence of pulmonary hypertension and lung cancer.

The cause of CPFE is not yet fully understood, but it is thought to be related to both genetic and environmental factors. There is currently no cure for CPFE, and treatment usually involves managing symptoms and preventing further lung damage. This may include medications to improve lung function, oxygen therapy, and pulmonary rehabilitation. In severe cases, lung transplantation may be necessary.



The clinical entity of combined pulmonary fibrosis and emphysema (CPFE) is characterized by the admixture of fibrosis and emphysema on high-resolution computed tomography.

Bolaki M et al. Semin Respir Crit Care Med 2020

정의 (KATRD 진료지침)

- 정의: HRCT에서 폐 아래쪽과 흉막하의 폐섬유화와 함께 동반된 상엽에 우세한 폐기종의 존재.
- 폐기종: HRCT에서 확실한 폐기종 즉 1 mm 미만의 얇은 또는 벽이 없는 구획이 명확한 저감쇠 (low attenuation) 구역이 총 폐 용적의 최소 5%를 포함하는 모든 하위 유형 폐기종.
- 폐섬유화: HRCT에서 합당한 소견; 견인성 기관지 확장 (traction bronchiectasis), 벌집모양 (honeycombing), 용적 감소 (volume loss))과 간유리음영 (GGO)이 포함된 경우.

CPFE: A syndrome? A distinct entity?

- recognized as a separate clinical entity and is characterized by progressive worsening of respiratory symptoms, decline of lung function and a high mortality; clinically relevant implications or major pathogenetic significance ??
- Contemporary definition of a syndrome requires greater provenance than the mere recognition of an association, be it between clinical variables or underlying disease processes.

I. Terminology and Definitions

- The contemporary terminology and definition of CPFE:

  - 2005 publication, retrospective study (61 Pts), French multicentric study

- CPFE: the presence of upper-zone–predominant emphysema on HRCT plus a peripheral and basal predominant diffuse parenchymal lung disease with significant fibrosis.

Cottin V. et al. Syndrome for CPFE. AJRCCM. 2022

Summary of Various Definitions Used by Studies to Identify Patients with Combined Pulmonary Fibrosis and Emphysema

Definition for CPFE	Number of Studies	Total Number of Patients with CPFE
No clear definition	3	259
Definitions using radiologic features only		
Definition proposed by Cottin *et al.* (1) as outlined below: i) Diffuse parenchymal lung disease with significant pulmonary fibrosis, defined as all of the following: • Reticulation with peripheral and basal predominance • Honeycombing • Architectural distortion • Minimal ground glass and/or consolidation ii) Areas of decreased attenuation with thin (<1 mm) or no walls that are upper-zone predominant	52	3,426
Minimum disease extent for fibrosis or emphysema required	10	975
Presence of any fibrosis and emphysema that is different than criteria by Cottin *et al.*	22	1,804
Definitions using a combination of domains		
Clinical ILD diagnosis + emphysema on imaging	5	332
Clinical abnormalities (e.g., crackles on auscultation, abnormal gas exchange) + fibrosis and emphysema on imaging	2	55
Airflow obstruction confirmed by spirometry + fibrosis on imaging	2	184

Definition of abbreviations: CPFE = combined pulmonary fibrosis and emphysema; ILD = interstitial lung disease.

Cottin V. et al. Syndrome for CPFE. AJRCCM. 2022

Terminology and Definitions

- Heterogeneity of study populations and criteria used to define CPFE prohibiting direct comparison of different cohorts and validation of key findings.
- Both imaging and histopathologic studies indicate that CPFE can encompass a variety of fibrotic ILDs.
- A potential approach to reconcile these conflicting priorities is to carefully and transparently define CPFE in a manner that reflects the clinical setting and/or research objectives.

II. Primary pathogenic pathways unique to CPFE ?

- Many pathways and pathogenetic mechanisms are shared between fibrosis and emphysema, including gene expression and pathways, gene variants, telomere dysfunction and shortening, alveolar alterations, epigenomic reprogramming, and enzymatic activity, especially matrix metalloproteinases

Main Features Shared by Pulmonary Fibrosis and Emphysema

Domain	Features Shared by Pulmonary Fibrosis and Emphysema
Clustering of pulmonary fibrosis and emphysema	Emphysema on HRCT is more prevalent than expected in IPF and RA-ILD (28) compared with smokers without pulmonary fibrosis Emphysema occurs with a lower pack-year smoking history in IPF, RA-ILD, and SSc-ILD (28, 49, 51) compared with smokers without pulmonary fibrosis Emphysema is more prevalent in patients with nonspecific interstitial pneumonia than in smokers without ILD (223)
Telomere dysfunction and the accelerated aging processes	Gene variants associated with telomere maintenance (90, 91, 99, 231–237) N.B.: Gene variants with opposing effects on risk of IPF or COPD also reported (227–229) Abnormal telomere shortening, cell senescence, mitochondrial dysfunction, and other aging-associated processes (238, 239) Experimental telomere dysfunction results in either pulmonary fibrosis or emphysema (88, 240)
Gene expression and interactome	Shared gene expression and splicing (241, 242) N.B.: Distinct gene expression reported between emphysematous and fibrotic lesions in patients with CPFE (230)
Environmental exposures, smoking, and epigenomic reprogramming	Alterations in cigarette-smoking alveoli (161, 243–246) Epigenetic modifications, including changes in DNA methylation and histone modifications (247, 248)
Mechanical forces	Severe fibrosis may provoke dilation of airway lumens of terminal bronchioles and more visible airways on HRCT (224, 249) Increased risk of progression from probable UIP to UIP in patients with emphysema (225) Clustering of paraseptal emphysema and HRCT pattern of UIP (52, 226)
Enzymatic activity	Exaggerated enzymatic activity of matrix metalloproteinases (250–268) Involvement of fibrocytes (an important source of matrix metalloproteinases) (269–272) Increased elastolytic and neutrophil elastase activity (273–277)
Lung development and lung function trajectories	Hypothesis that abnormal mechanisms early in life may predispose to development of emphysema and fibrosis (as reported for the development of emphysema alone [278, 279])
Experimental models characterized by both emphysema and fibrosis and/or inflammation	Transgenic mice overexpressing platelet-derived growth factor (18) Transgenic mice overexpressing tumor necrosis factor-α (20) Mice deficient in surfactant protein-C (98)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CPFE = combined pulmonary fibrosis and emphysema; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; N.B. = nota bene (note); RA = rheumatoid arthritis; SSc = systemic sclerosis; UIP = usual interstitial pneumonia.

Cottin V. et al. Syndrome for CPFE. AJRCCM. 2022

Primary pathogenic pathways unique to CPFE ?

- CPFE may result from involvement of shared pathways in at least some patients.
  - Are the mechanisms that cause emphysema, IPF, and CPFE different?
- Despite the phenomenon of clustering of emphysema with pulmonary fibrosis, the two diseases will inevitably coexist in some patients as coincidental smoking-related processes.

Primary pathogenic pathways unique to CPFE ?

- The pathogenetic mechanisms leading to the coexistence of emphysema with IPF and other fibrotic ILDs remain unclear.
- It is uncertain whether IPF and non-IPF ILDs are causally linked with emphysema or if they represent different lung disorders running in parallel and sharing some mechanisms.

III. Histopathological or radiologic feature specific for CPFE?

- **Pro**: High prevalence of thick-walled large cysts on HRCT.

  High prevalence of airspace enlargement with fibrosis (AEF)

- **Con**: No histopathological or radiologic feature specific for CPFE

Histopathological Features of Smoking-related Interstitial Fibrosis and Other Patterns of Fibrotic Interstitial Lung Disease in Combined Pulmonary Fibrosis and Emphysema

Pattern of Fibrosis	Distribution	Fibroblast Foci	Honeycomb Change	Interstitial Inflammation
SRIF (5, 23)	Patchy, subpleural, peribronchiolar	Rare	Rare	Absent
DIP (180)	Diffuse	Rare	Absent	Present
UIP, probable UIP (144, 180)	Patchy, subpleural, interlobular septa	Present	Present	Patchy, mild (may be more extensive in areas of honeycombing)
F-NSIP (180)	Diffuse	Rare	Absent	Present
Indeterminate (180, 184)	Patchy or diffuse	±	±	±

Definition of abbreviations: DIP = desquamative interstitial pneumonia; F-NSIP = fibrotic nonspecific interstitial pneumonia; SRIF = smoking-related interstitial fibrosis; UIP = usual interstitial pneumonia.

Cottin V. et al. Syndrome for CPFE. AJRCCM. 2022

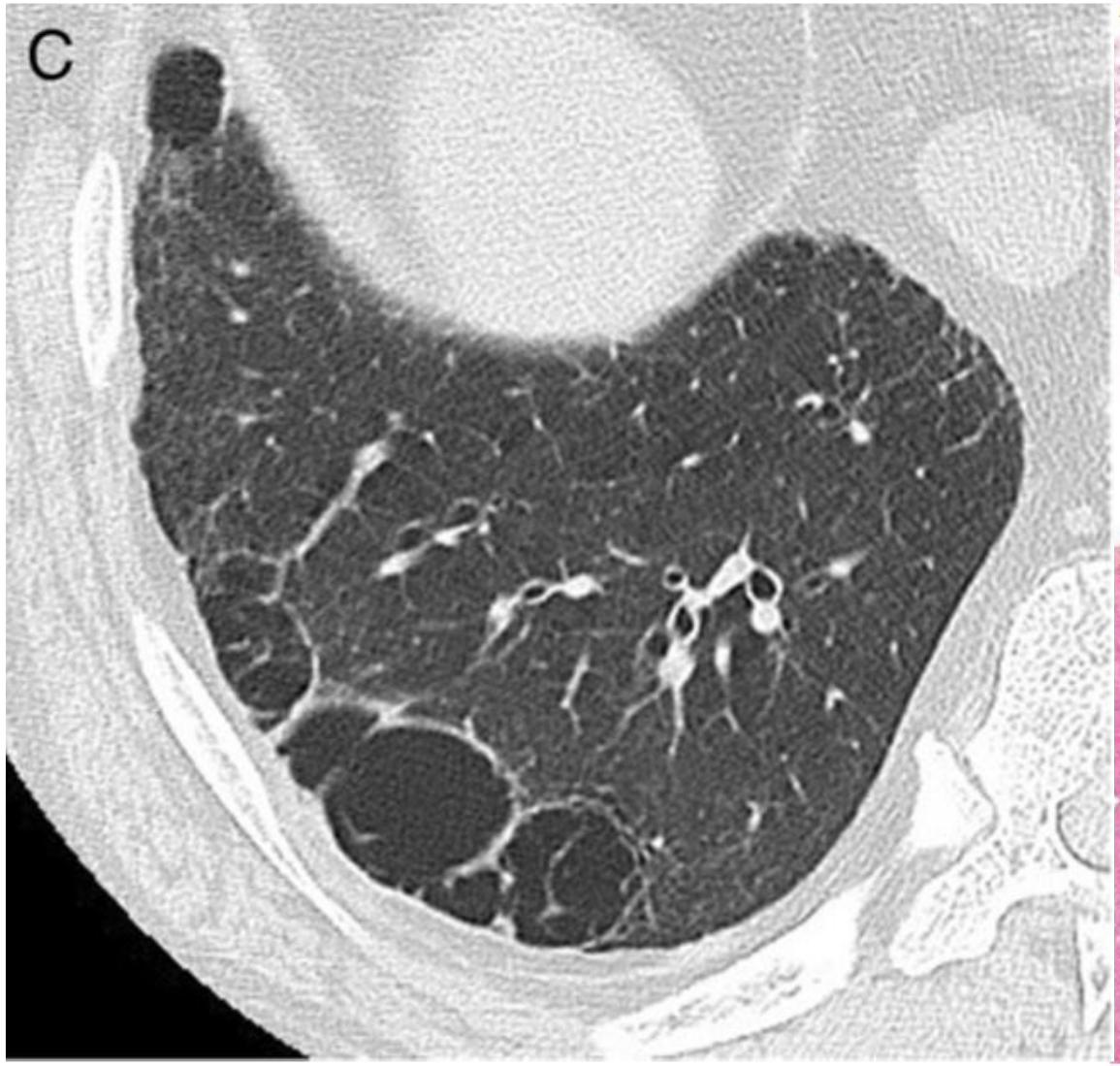
Smoking Related Interstitial Fibrosis (SRIF)

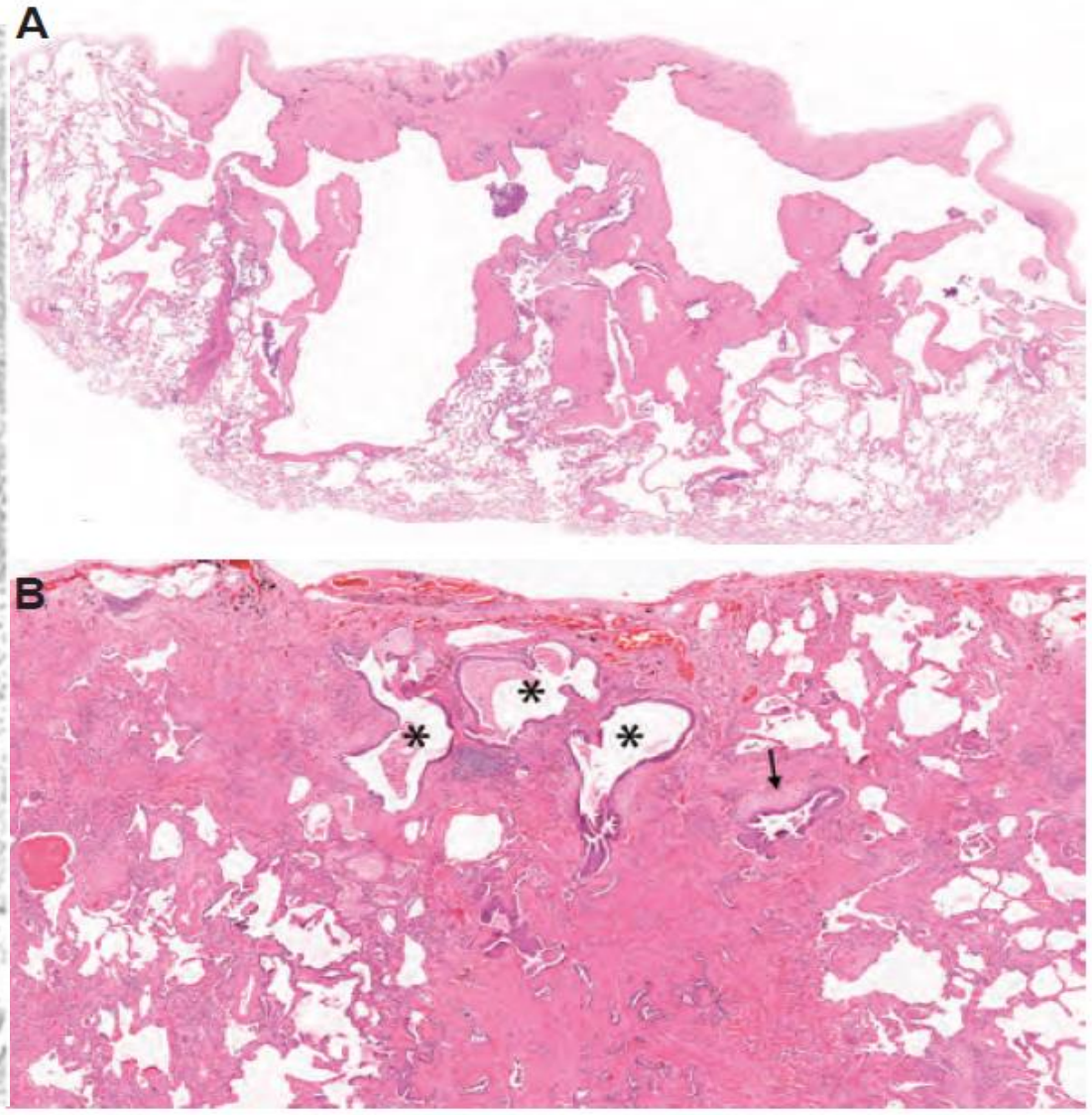
- SRIF: combination of emphysema and usual interstitial pneumonia in middle and lower lobe.
- densely eosinophilic collagen deposited in expanded alveolar septa with preservation of lung architecture and little or no inflammation.
- SRIF may account for the "thick-walled cystic lesions" that are unique to CPFE and distinct from the honeycomb cysts of UIP.

Smoking related interstitial Fibrosis (SRIF)

- SRIF is a common incidental finding in surgical lung specimens, including lung biopsies from patients with other patterns of pulmonary fibrosis.
- Isolated SRIF represents the primary pathological abnormality in a subset of patients with clinical features of ILD in whom it is often combined with RB.
- Attributing pulmonary fibrosis to SRIF in patients with CPFE requires exclusion of other fibrotic patterns, including most importantly UIP.
- LCH is a potentially fibrotic form of smoking-related ILD that may occur in combination with other smoking-related abnormalities, including emphysema, RB, SRIF, and DIP

Thick-walled Cyst: Unique to UIP in CPFE is the presence of thick walled cysts resulting from the combination of emphysema





Histopathological or radiologic feature specific for CPFE?

Thick-walled cystic lesions (TWCL)

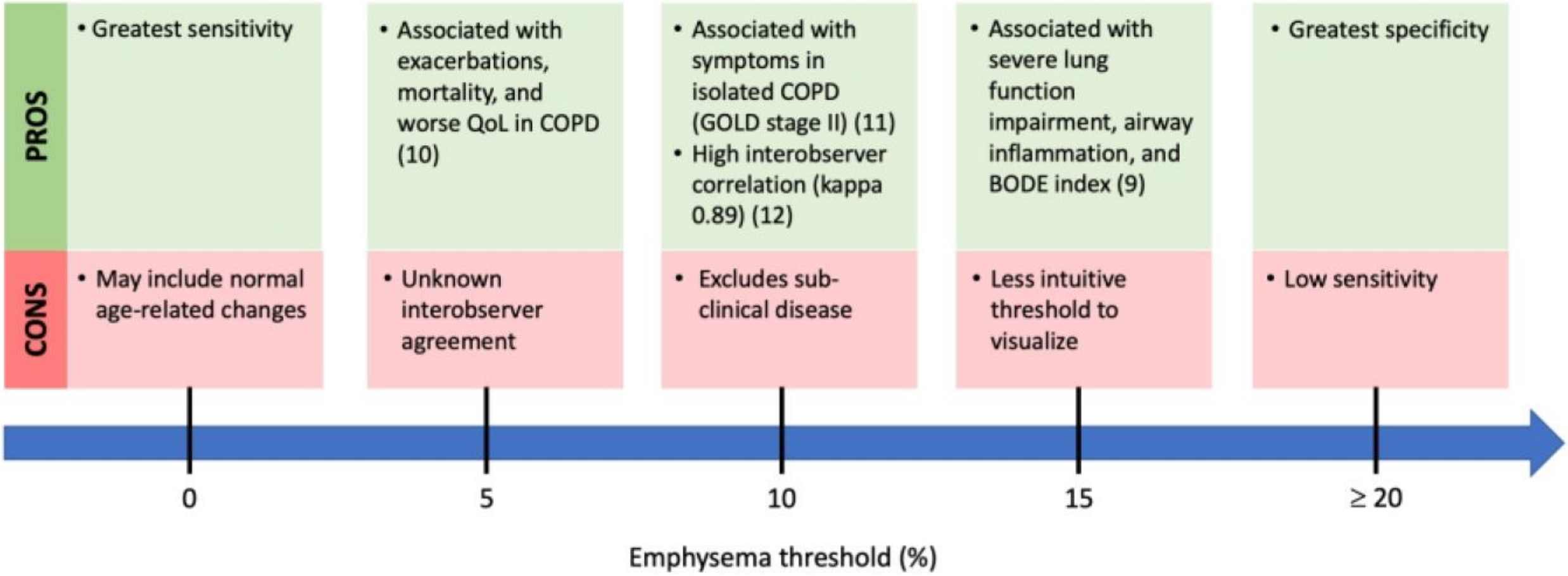
- Expansion of the interlobular septa with collagen fibrosis can make paraseptal emphysema appear as honeycomb cysts.
- Most studies have focused on patients with IPF and/or a UIP pattern on HRCT imaging, although others have included patients with a variety of ILD subtypes and imaging patterns.
- There are no criteria for establishing a diagnosis of CPFE on the basis of histopathological findings alone.

Emphysema Quantification

- Reliable estimation of emphysema extent in patients with established pulmonary fibrosis poses significant challenges.
- Most studies use visual assessment of emphysema by an experienced radiologist, a method that is readily available and has moderate interrater agreement.
- Emphysema thresholds used to characterize a CPFE phenotype on imaging, include: 0%, 5%, 10%, and 15% of total lung volume.

Emphysema Quantification

- Methodology of emphysema quantification is poorly suited to CPFE, because it fails to discriminate between low-density areas due to emphysema and low density due to honeycomb cysts, traction bronchiectasis, or non emphysematous mosaic attenuation due to small airway disease.
- Large multicentered studies are required to determine whether these morphological CPFE subtypes (subtype: paraseptal vs. centrilobular vs. mixed vs. indeterminate) correlate with distinct functional or prognostic disease groups.



Advantages and disadvantages of thresholds used for the minimum extent of emphysema required to be diagnosed with CPFE. GOLD: Global initiative for chronic obstructive lung disease, QoL: quality of life.

Wong A and Cottin V: Ann. ATS; 2020

ILD Quantification

- A minimal threshold extent of lung fibrosis on HRCT imaging has rarely been used in CPFE, despite the clinical importance of fibrotic ILD severity.
- Quantitation of fibrosis extent is confounded by volume loss, with lower lobes sometimes greatly contracted to apparently small areas of fibrosis.
- The concept of a minimal threshold of fibrosis to define CPFE is particularly relevant to lung cancer screening populations.
- when considering CTD-related ILD or fibrotic HP, where ground-glass opacities may reflect inflammation rather than fibrosis, there is no consensus on whether ground glass opacities should be considered as part of CPFE fibrosis extent.

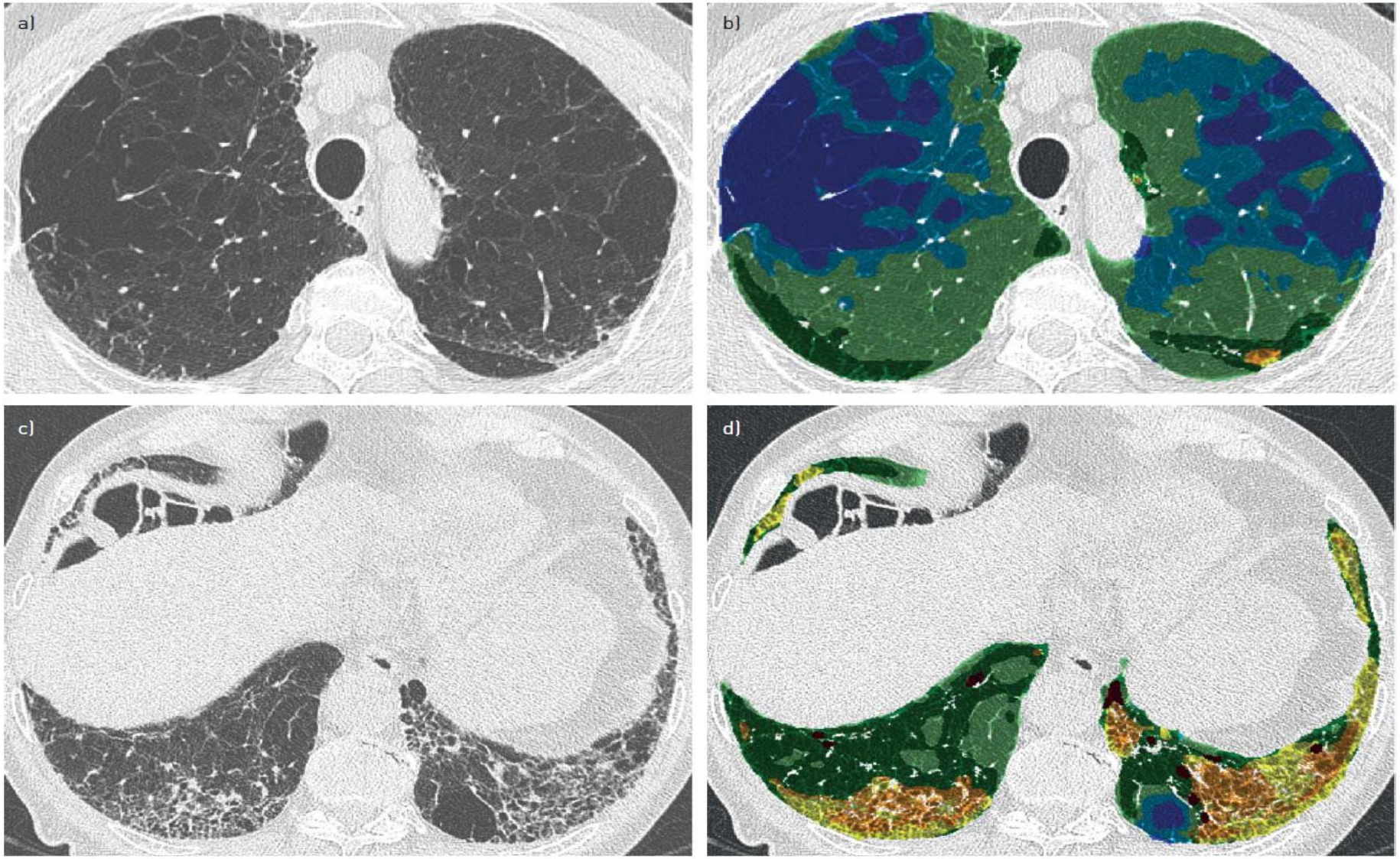


FIGURE (a and c) On visual scoring, 40% of the lung was characterized as emphysema, whilst 31% was identified as interstitial lung disease. The CALIPER overlay images (b and d) outline emphysema (light and dark blue) in the upper lobes, quantified as 23% of lung volume. The sum of ground glass opacities (yellow), reticular pattern (orange) and honeycombing (brown) constitute the extent of total interstitial lung disease, which was quantified as 7.5% of the lung. CALIPER defines light and dark green areas as normal lung

Jacob J et al. ERJ 2017

IV. Complications: PH and Lung Cancer

- **Pro:**

  1. Increased risk of PH compared with IPF for a given extent of fibrosis

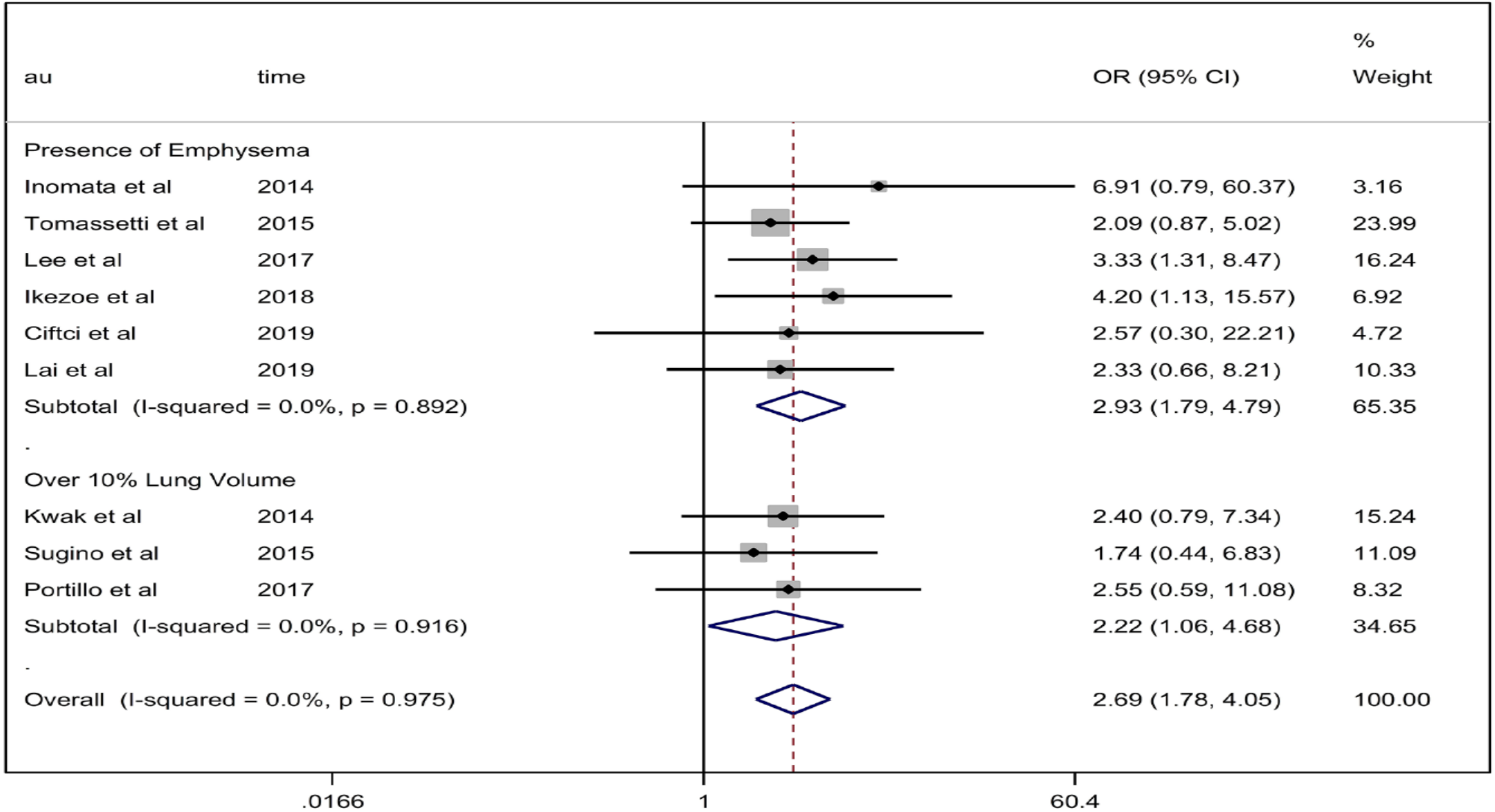
  2. Increased risk of lung cancer compared with IPF or emphysema alone

- **Con:**

The risk of PH is dependent on total extent of fibrosis and emphysema, the quantification of which is challenging

Complications: PH and Lung Cancer

- Automated quantification is challenging when both components are present, hampering the development of imaging criteria and consistency between studies.
- CPFE does not specify extent thresholds for either pulmonary fibrosis or emphysema



Subgroup meta-analysis of the selected studies based on different thresholds of emphysema extent used for CPFE definition.

Chen Q et al. Ther Adv Respir Dis. 2021

V. Mortality

- Pro:

Increased mortality compared with IPF for a given extent of Fibrosis

- Con:

The mortality risk is dependent on total extent of fibrosis and emphysema, the quantification of which is challenging

Variables Associated with Death among Patients with CPFE

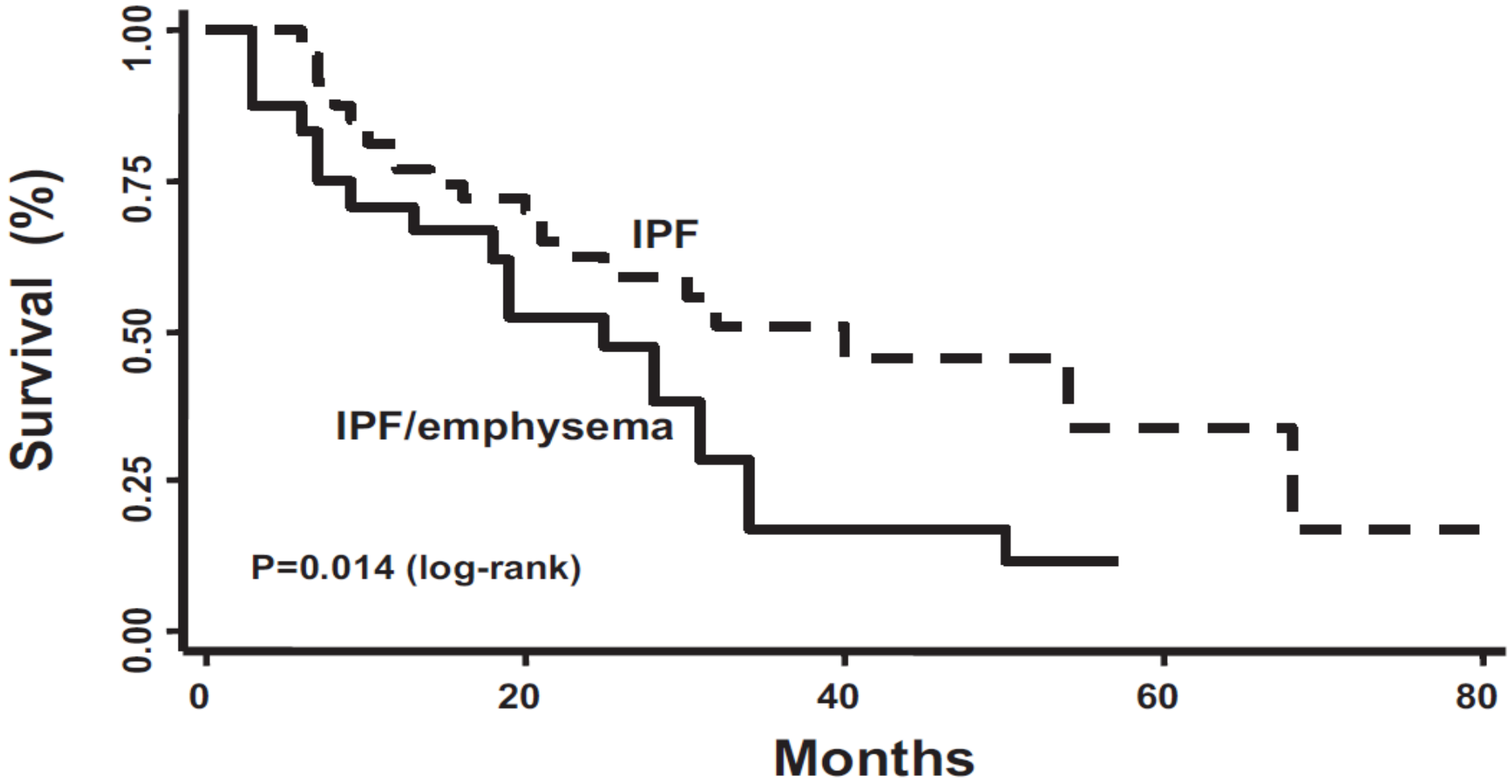
Variable	Association with Increased Mortality	Reference
Demographic	Older age	27
Biologic	Negative antinuclear antibodies	25
	Increased red cell distribution width	220
Physiologic		
D_{LCO}	Lower D_{LCO} %predicted	27, 41, 115, 203, 220, 221
FVC	<50% predicted	32
FEV_1	Decline of ⩾10% over 12 mo	138
CPI	⩾45	119, 188, 220
Oxygen saturation	Oxygen saturation on room air <90%	59
Oxygen requirement	Home oxygen use	203
Complications and comorbidities		
Pulmonary hypertension	Elevated pulmonary artery pressure, right ventricular dysfunction, increased pulmonary vascular resistance, low cardiac index, or main pulmonary artery diameter/ascending aortic diameter ratio (depending on study)	1, 27, 32, 49, 115, 119, 203, 222
Lung cancer	Presence of lung cancer	41, 57, 59, 141, 203, 206, 219
Acute exacerbations	Acute exacerbations of fibrosis	206
Radiologic	Presence of UIP pattern	27, 188
	Presence or extent of honeycombing	27, 41, 203
	Extent of fibrosis (fibrosis score)	59, 221

Definition of abbreviations: CPI = composite physiologic index; UIP = usual interstitial pneumonia.

Relationship Between Prognostic Factors and Mortality by Univariate Analysis

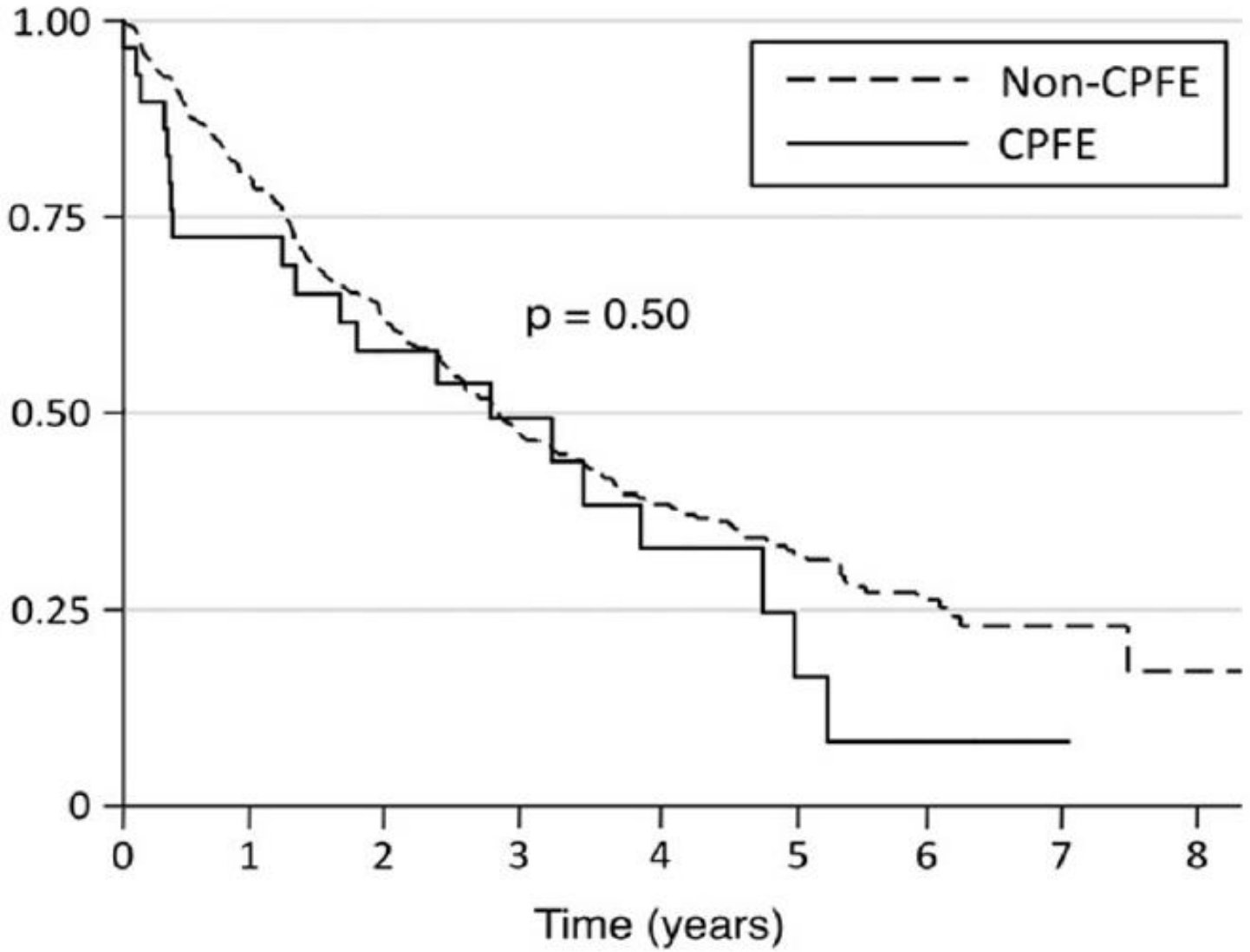
Variables	HR	95% CI	p Value
Male gender	1.84	0.95–3.56	0.069
Emphysema	1.99	1.12–3.53	0.018
HRCT scan fibrotic score	2.18	1.11–4.29	0.023
FVC < 50% predicted	2.45	1.29–4.67	0.006
PAH			
eSPAP > 50 mm Hg	1.13	0.58–2.18	0.71
eSPAP > 75 mm Hg	1.88	1.01–3.48	0.04

Mejia M et al. chest 2009.



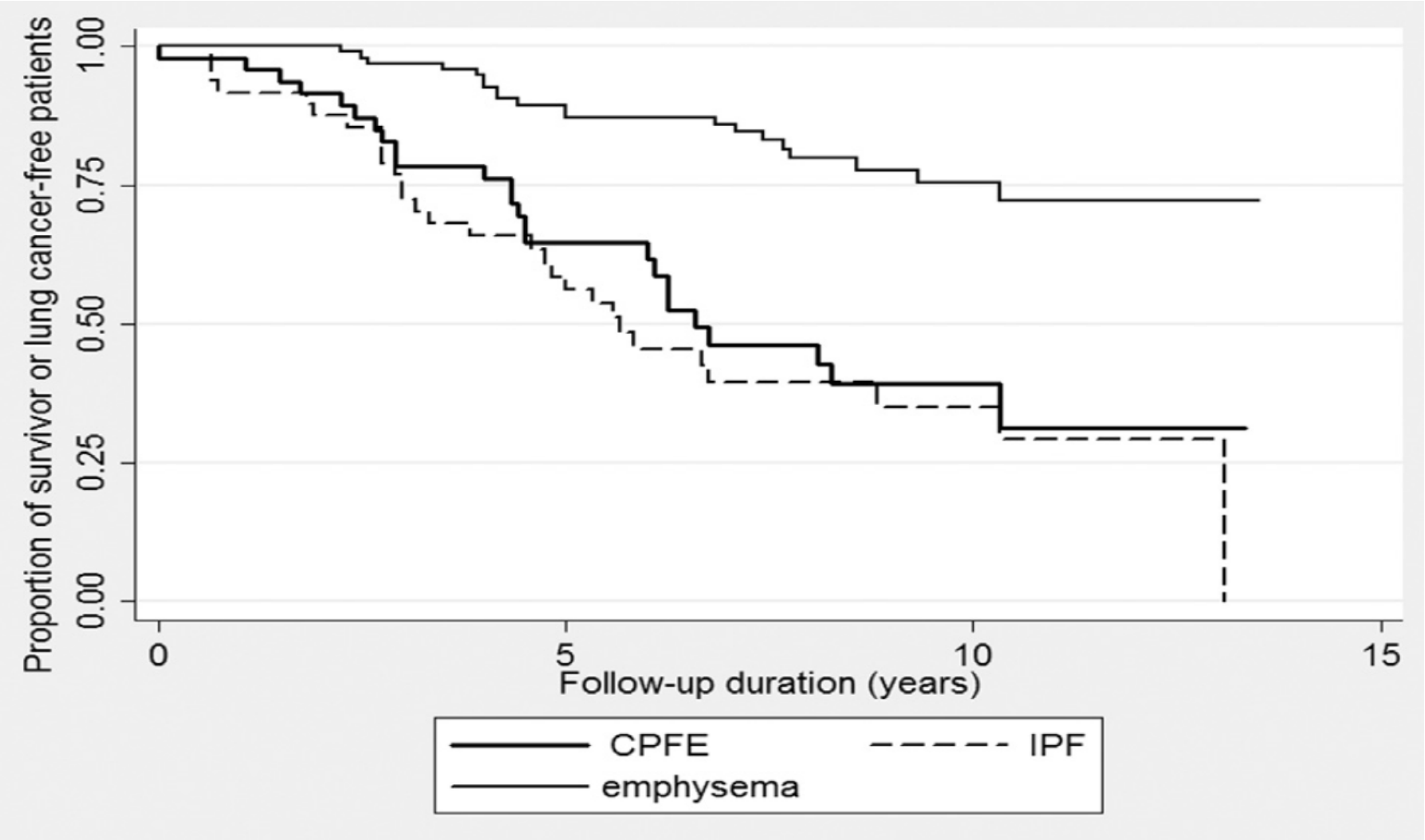
The Kaplan-Meier survival curve for patients with IPF and IPF plus emphysema. Survival time was significantly lower in the group of patients with IPF combined with emphysema (p = 0.01 log-rank test).

Mejia M et al. 2009 chest.



Kaplan-Meier survival curves stratified by CPFE vs non-CPFE.
Survival curves and *P* value represent time to death or transplant.

Ryerson C et al. chest 2013



Kaplan-Meier estimates of time to lung cancer or death among patients with CPFE, IPF and emphysema.

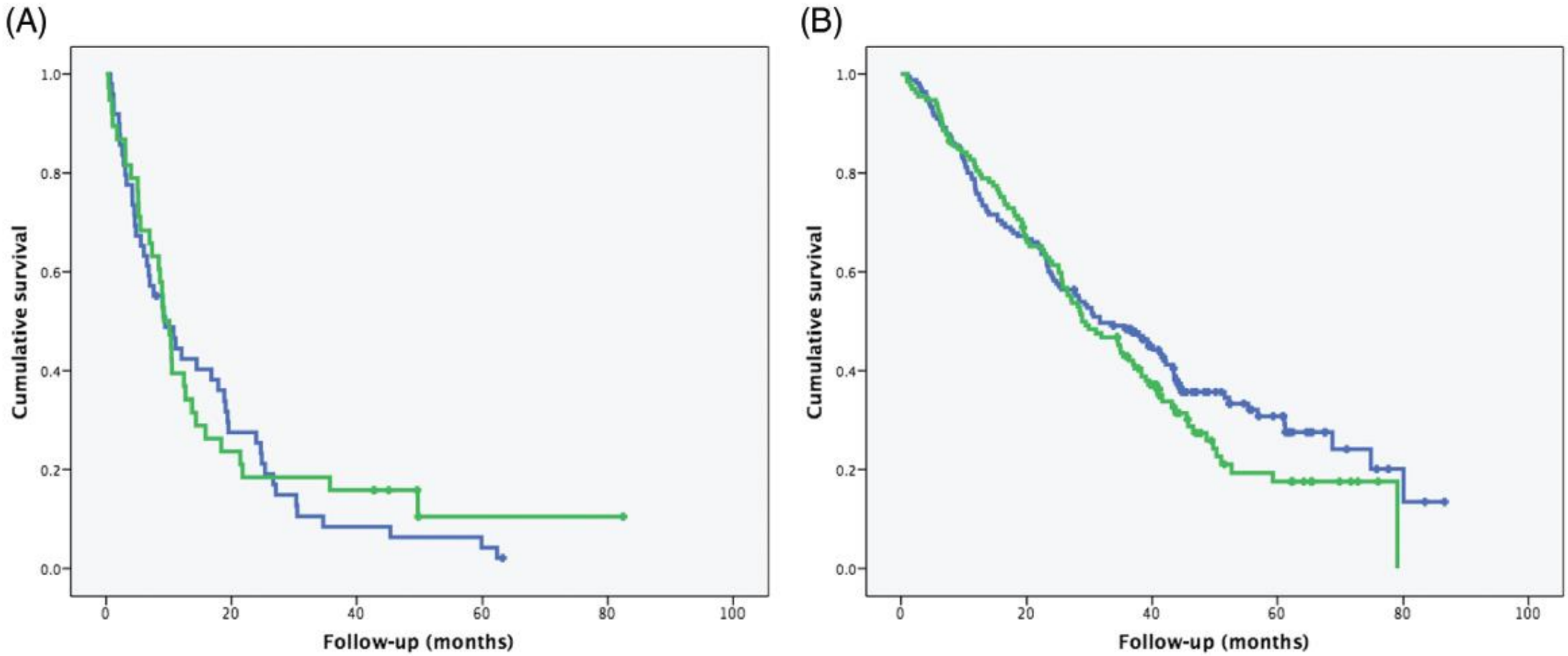
Kwak N et al. Respir Med 2014

The risk of lung cancer development or death in uni- and multivariable analysis

	cHR	95% CI	*p*-Value	aHR	95% CI	*p*-Value
CPFE versus emphysema	3.70	2.03–6.74	<0.001	4.62	2.25–9.47	<0.001
IPF versus emphysema	4.88	2.73–8.74	<0.001	5.28	2.40–11.61	<0.001
CPFE versus IPF	0.76	0.44–1.29	0.310	0.87	0.47–1.2	0.874
Age	1.04	1.01–1.07	0.005	1.04	1.01–1.07	0.018
BMI	1.05	0.97–1.14	0.206			
Number of admission	1.08	0.96–1.22	0.209			
Smoking pack-year	0.99	0.98–1.00	0.114	1.01	0.99–1.02	0.308
FEV_1 (%)	1.00	0.99–1.01	0.423			
FVC (%)	0.98	0.97–0.99	<0.001	0.98	0.97–0.99	0.001
FEV_1/FVC (%)	1.02	1.01–1.03	0.001	1.00	0.98–1.01	0.601

cHR; crude hazard ratio, aHR; adjusted hazard ratio, CI; confidence interval.

Kwak N et al. Respir Med 2014



Kaplan–Meier survival curves for patients across both cohorts with (a) and without (b) a high likelihood of pulmonary hypertension (PHT): combined pulmonary fibrosis and emphysema (CPFE) (green), idiopathic pulmonary fibrosis (IPF) (blue). Log-rank test = 0.72 for patients with a high likelihood of PHT. Log-rank test = 0.21 for patients without a high likelihood of PHT.

Jacob J et al. Respirology. 2017.

Outcome

- Outcomes are worse for a given extent of fibrosis, when there is emphysema in addition to fibrosis (e.g., outcomes are worse in a patient with 10% fibrosis extent and 20% emphysema extent than in a patient with 10% fibrosis extent and no emphysema).

- Risk of mortality and of developing PH does not differ in patients with both IPF and emphysema compared with those with fibrosis alone when adjusting for severity using baseline DLCO or total disease extent on HRCT (e.g., outcomes are comparable in a patient with 20% emphysema extent and 10% fibrosis extent and in a patient with 15% emphysema extent and 15% fibrosis extent)

VI. Monitoring of CPFE

- The strongest argument is that monitoring of disease progression cannot be reliably based on FVC in patients with CPFE: serial FVC trends, generally viewed as the cardinal monitoring measure in IPF, are less reliable in CPFE-IPF, with a lower prognostic significance than in the remaining patients with IPF without emphysema.
- Are there any factors that can monitor PH and lung cancer development?

Main Arguments in Favor of and Against Combined Pulmonary Fibrosis and Emphysema Being a Syndrome

	In Favor of a Syndrome	Against a Syndrome
Pathogeny	Clustering of emphysema and fILD to a greater extent than would be expected from the pack-year smoking history (in patients with IPF, idiopathic nonspecific interstitial pneumonia, rheumatoid arthritis–ILD, and systemic sclerosis–ILD)	No primary pathogenetic pathways unique to CPFE identified
Presentation	High prevalence of thick-walled large cysts on HRCT. High prevalence of airspace enlargement with fibrosis on histopathology	No histopathological or radiologic feature specific for CPFE
Complications and comorbidities	Increased risk of PH compared with IPF for a given extent of fibrosis Increased risk of lung cancer compared with IPF or emphysema alone	The risk of PH is dependent on total extent of fibrosis and emphysema, the quantification of which is challenging
Mortality	Increased mortality compared with IPF for a given extent of fibrosis	The mortality risk is dependent on total extent of fibrosis and emphysema, the quantification of which is challenging
Monitoring	FVC alone is not appropriate to monitor disease progression and a primary endpoint in clinical trials. Consider screening and/or monitoring for PH and lung cancer	—
Diagnosis	Identification of honeycombing and of the UIP pattern is challenging in patients with concurrent emphysema	—

Definition of abbreviations: CPFE = combined pulmonary fibrosis and emphysema; fILD = fibrotic interstitial lung diseases; HRCT = high-resolution computed tomography; IPF = idopathic pulmonary fibrosis; PH = pulmonary hypertension; UIP = usual interstitial pneumonia.

Cottin V. et al. Syndrome fo CPFE. AJRCCM. 2022.

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Is the CPFE a new disease entity?

No, CPFE is not a new disease entity. The term "Combined Pulmonary Fibrosis and Emphysema" was first coined in 2005 to describe a distinct clinical and radiologic phenotype of patients who had both emphysema and pulmonary fibrosis. However, the individual components of CPFE, emphysema and pulmonary fibrosis, have been recognized as separate lung diseases for many years.

Emphysema is a type of chronic obstructive pulmonary disease (COPD), while pulmonary fibrosis is a type of interstitial lung disease (ILD). It is not uncommon for individuals with COPD or ILD to develop both emphysema and pulmonary fibrosis over time, leading to the development of CPFE.

While CPFE is not a new disease entity, it has gained increasing recognition in recent years as a distinct clinical entity with its own unique characteristics and clinical course. Research is ongoing to better understand the underlying mechanisms and optimal management strategies for CPFE.

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