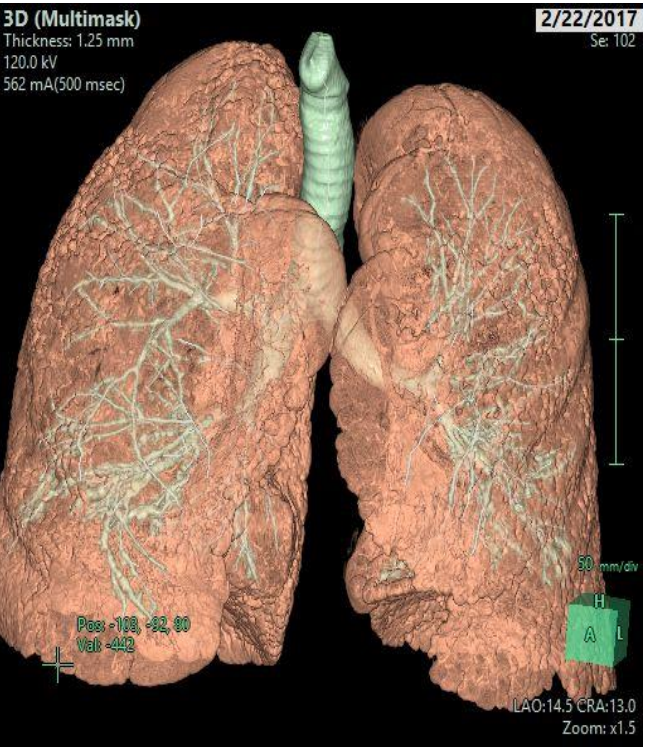
Algorithmic Approach of CTD-ILDs



Argyris Tzouvelekis
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Conflicts of Interest

I have received travel grants and advisory fees from the following companies

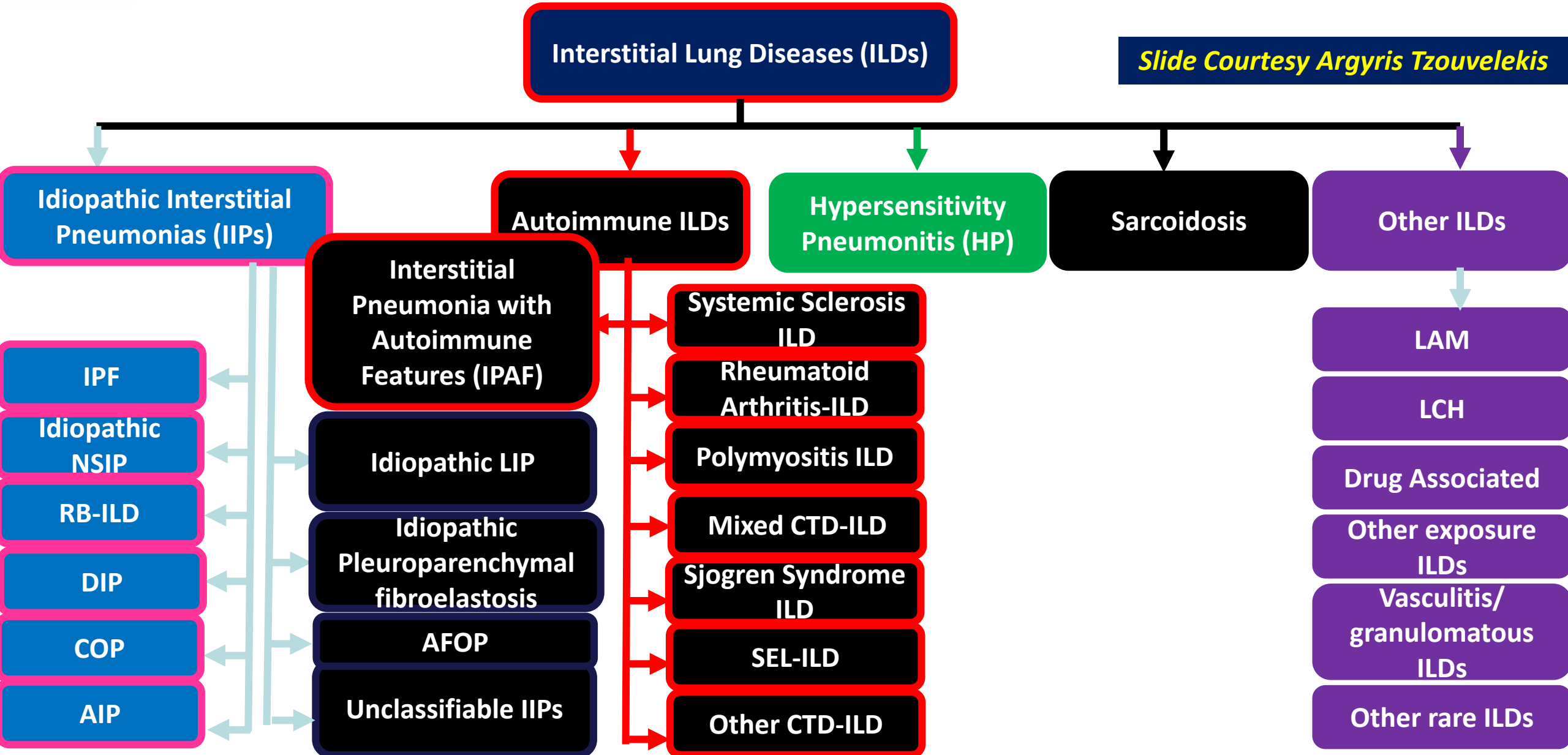
- AstraZeneca
- Boehringer Ingelheim
- Chiesi
- ELPEN
- Roche
- Menarini,
- Pfizer

I am an inventor of two therapeutic patents for the treatment of fibrotic lung diseases, disclosed to Yale University

Introduction

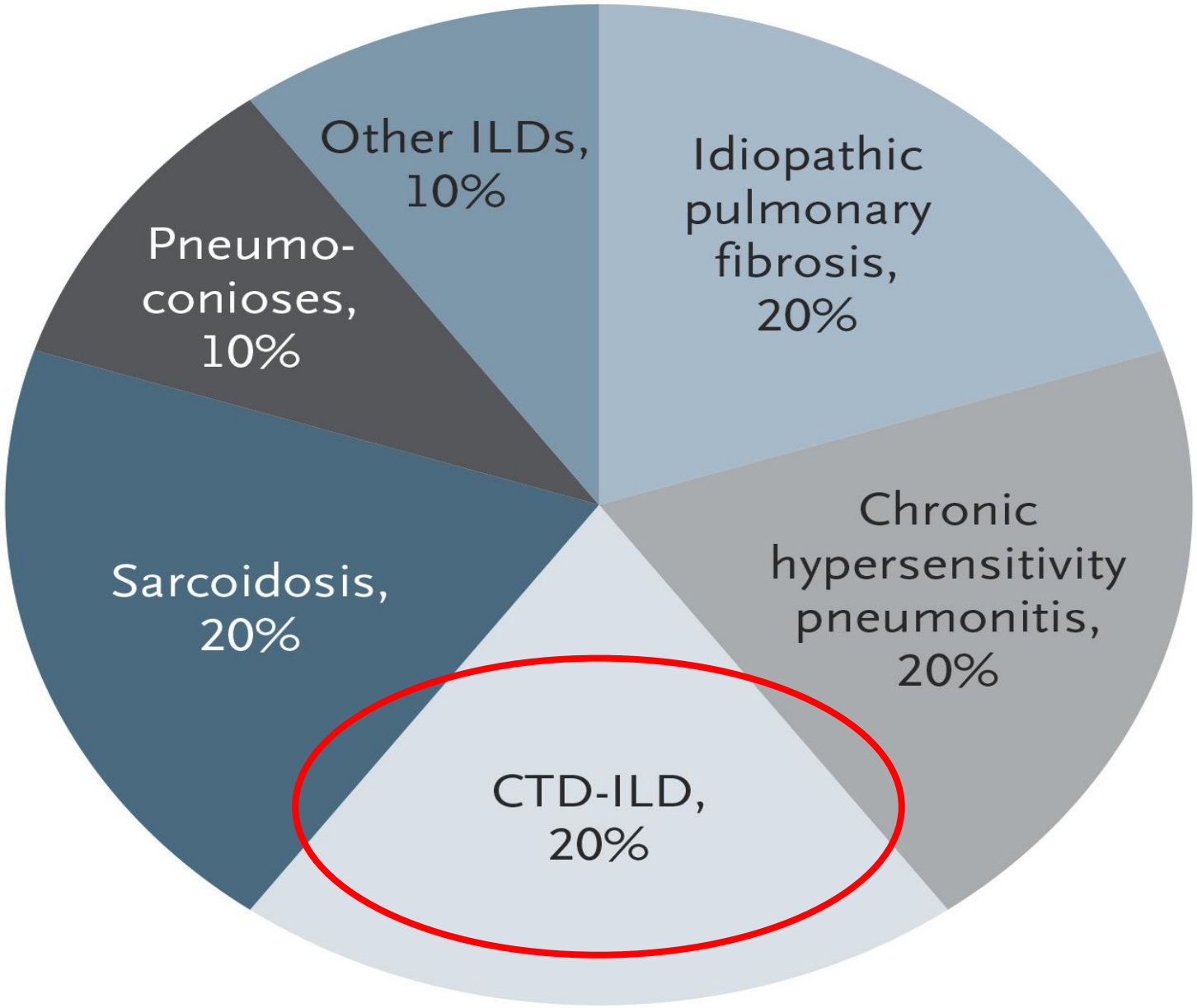
Classification of ILDs

Slide Courtesy Argyris Tzouvelekis



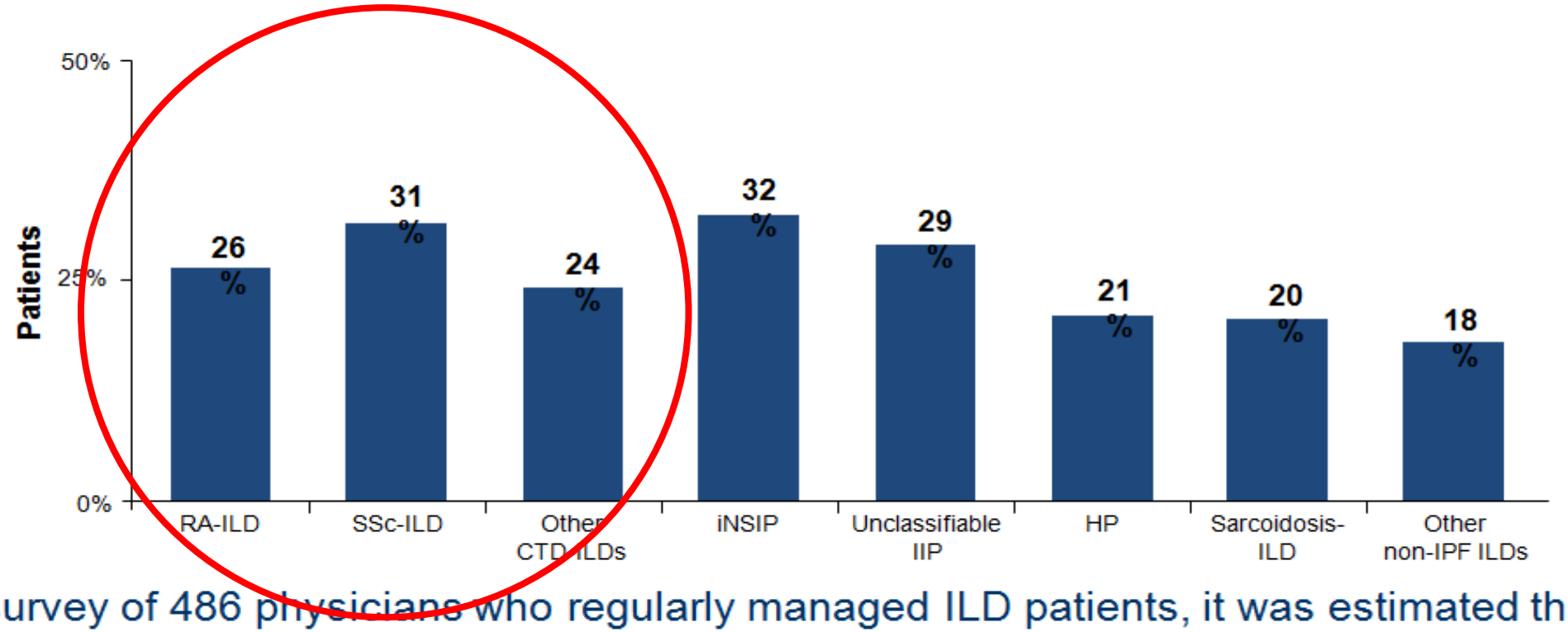
Is it common?

Estimated Relative Distribution of Specific ILDs in the US



NEJM 2018

Up to one-third of patients with ILDs, including CTD-ILD, develop progressive fibrosing disease



From a survey of 486 physicians who regularly managed ILD patients, it was estimated that 18–32% of patients diagnosed with non-IPF ILD develop progressive fibrosis[1]

1. Wijsenbeek M *et al*. ATS 2018 International Conference. San Diego, USA, May 18–23, 2018; abstract A1678

Is it pleiomorphic?

Respiratory involvement in autoimmune diseases

- **Pleomorphic Involvement**

MAIN DIFFERENTIAL DIAGNOSES

- **Direct pulmonary involvement**
- **Indirect**

✓ **Drug induced respiratory involvement?**

✓ **Infection-Immunocompromise?**

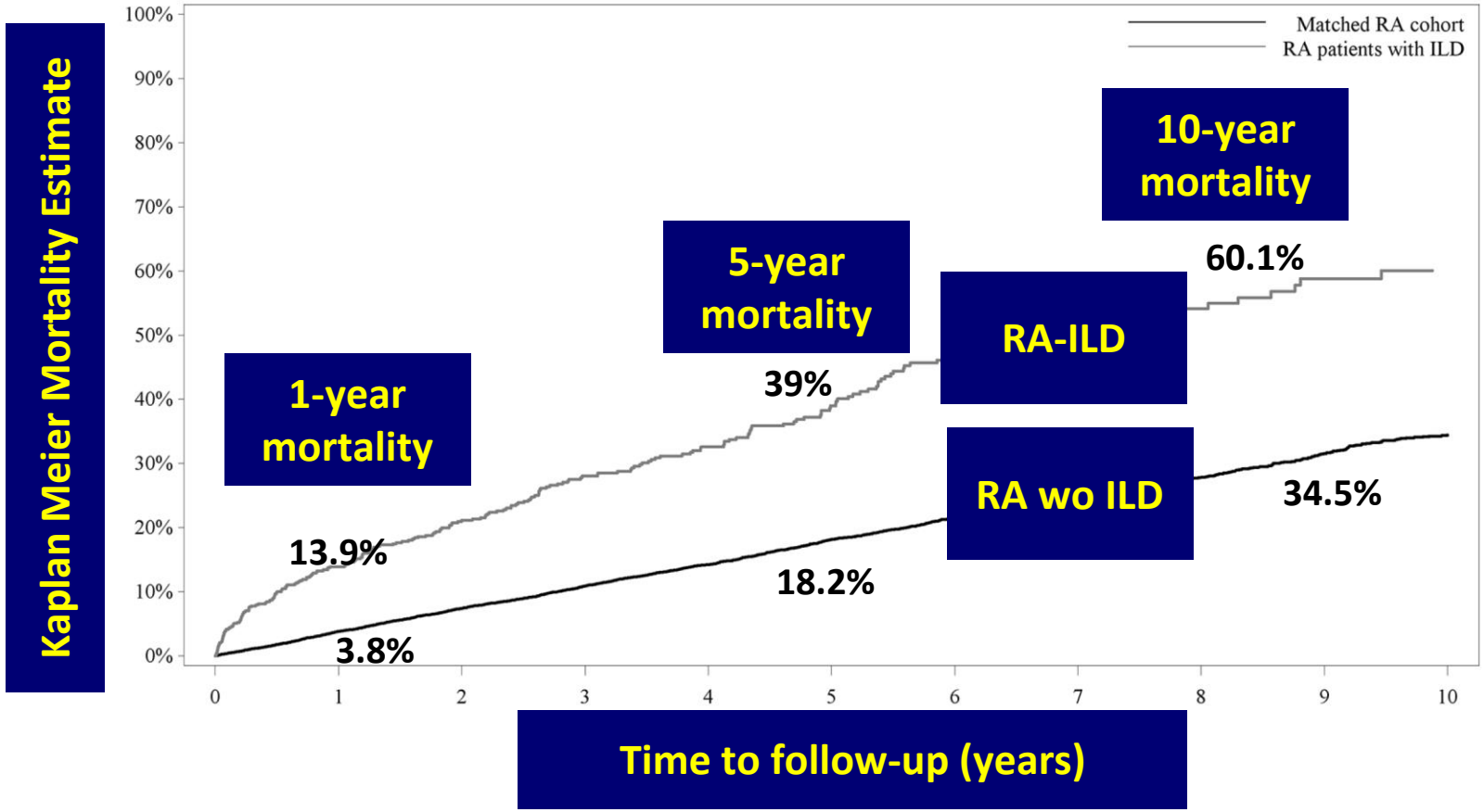
✓ **Comorbidities? (PH-COPD-Lung cancer)**

- **10-15% of cases ILD precedes CTD diagnosis!**

Does it matter?

Is ILD essential?

- **YES!!!!! – MAJOR CAUSE OF DEATH**



Hyldgaard et al. Ann Rheum Dis 2017

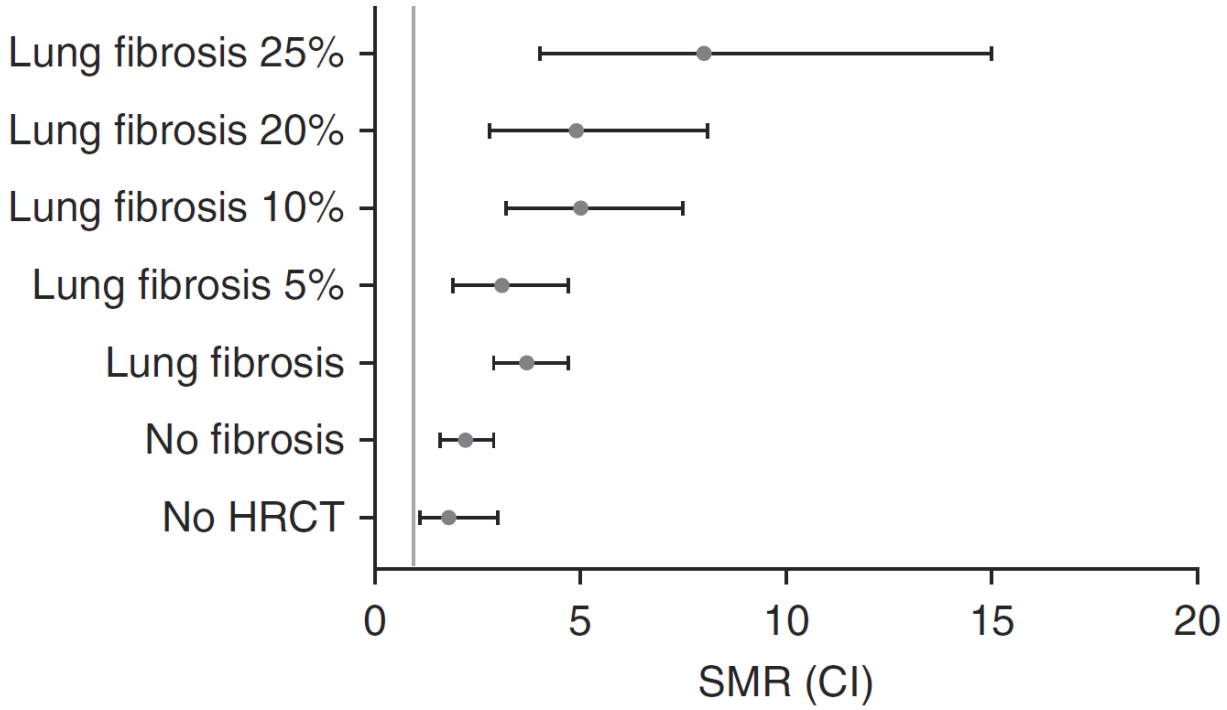
ORIGINAL ARTICLE

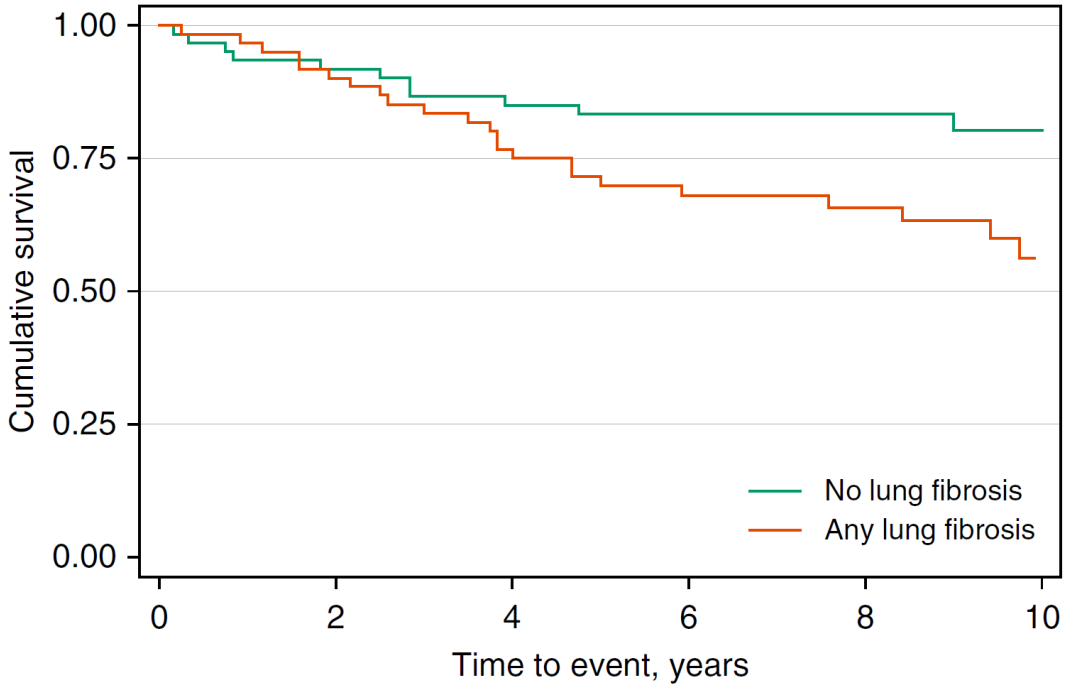
Am J Respir Crit Care Med Vol 200, Iss 10, pp 1258–1266, Nov 15, 2019

Originally Published in Press as DOI: 10.1164/rccm.201903-0486OC on July 16, 2019
Internet address: www.atsjournals.org

Tracking Impact of Interstitial Lung Disease in Systemic Sclerosis in a Complete Nationwide Cohort

***8 mortality rates if Lung fibrosis >25%**





Slower rates of progression in SSc-ILD

Ann Am Thorac Soc Vol 15, No 12, pp 1427–1433, Dec 2018

DOI: 10.1513/AnnalsATS.201806-362OC

Does Systemic Sclerosis–associated Interstitial Lung Disease Burn Out?

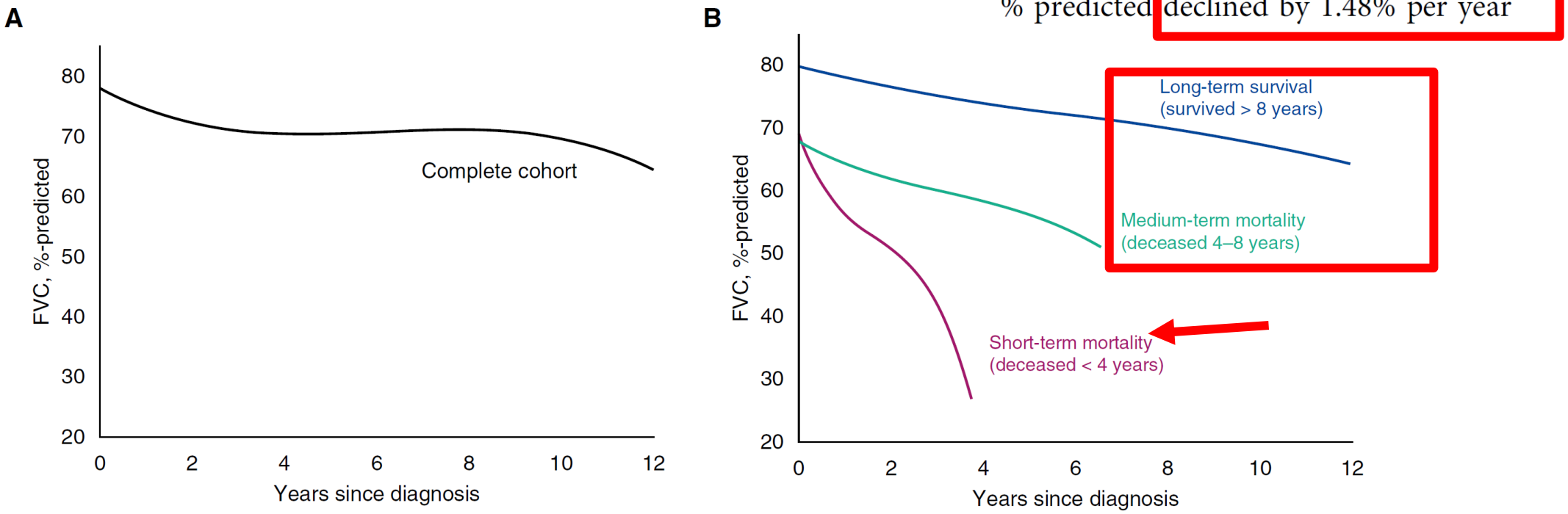
Specific Phenotypes of Disease Progression

Sabina A. Guler[1,2,3], Tiffany A. Winstone[1,2], Darra Murphy[4], Cameron Hague[4], Jeanette Soon[4], Nada Sulaiman[4], Kathy H. Li[5,6], James Dunne[1], Pearce G. Wilcox[1], and Christopher J. Ryerson[1,2]

N=171 SSc-ILD

Rate of Physiological Progression

In the full cohort, FVC % predicted declined on average by 1.06% per year (95% confidence interval [CI], 0.64–1.47%). D_{LCO} % predicted declined by 1.48% per year



Eur Respir J 2010; 36: 116–121
DOI: 10.1183/09031936.00110109

Prevalence and outcome of pulmonary fibrosis in microscopic polyangiitis

G.E. Tzelepis*,#, M. Kokosi*,#, A. Tzioufas*,#, S.P. Toya*,#, K.A. Boki¶, A. Zormpala+ and H.M. Moutsopoulos*,#

TABLE 2 Pulmonary function data in microscopic polyangiitis patients# with or without fibrosis

	Fibrosis	No fibrosis	p-value
FVC % pred	75.4±12.3	79.6±10.9	0.45
FEV_1 % pred	77.0±19.9	71.9±20.4	0.61
FEV_1/FVC	88.3±8.0	78.7±17.5	0.17
TLC % pred	70.6±5.9	82.9±17.1	0.01
$D_{L,CO}$ % pred	55.5±18.0	70.2±19.6	0.16

Data are presented as mean±SD, unless otherwise stated. FVC: forced vital capacity; % pred: % predicted; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; $D_{L,CO}$: diffusing capacity for carbon monoxide. #: there were seven measurements in the fibrotic group and 11 in the non-fibrotic group.

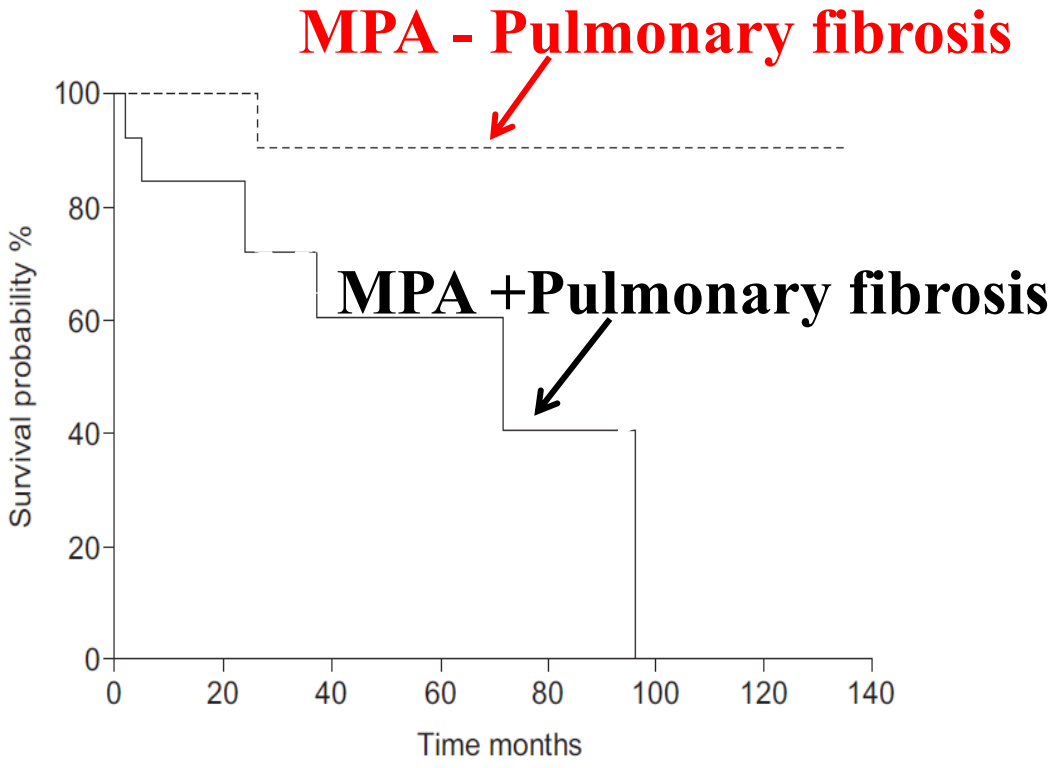


FIGURE 2. Kaplan–Meier survival graph comparing microscopic polyangiitis patients with (——) and without (- - - -) pulmonary fibrosis.

Interstitial lung disease in connective tissue disorders

Aryeh Fischer, Roland du Bois

Lancet

Vol 380 August 18, 2012

	ILD	Airways	Pleural	Vascular	DAH
Systemic sclerosis	+++	–	–	+++	–
Rheumatoid arthritis	++	++	++	+	–
Primary Sjögren's syndrome	++	++	+	+	–
Mixed CTD	++	+	+	++	–
Polymyositis/ dermatomyositis	+++	–	–	+	–
Systemic lupus erythematosus	+	+	+++	+	++

The signs show prevalence of each manifestation (–=no prevalence; +=low prevalence; ++=medium prevalence; +++=high prevalence). ILD=interstitial lung disease. DAH=diffuse alveolar haemorrhage. CTD=connective tissue disease.

Table 1: **CTDs and common pulmonary manifestations**

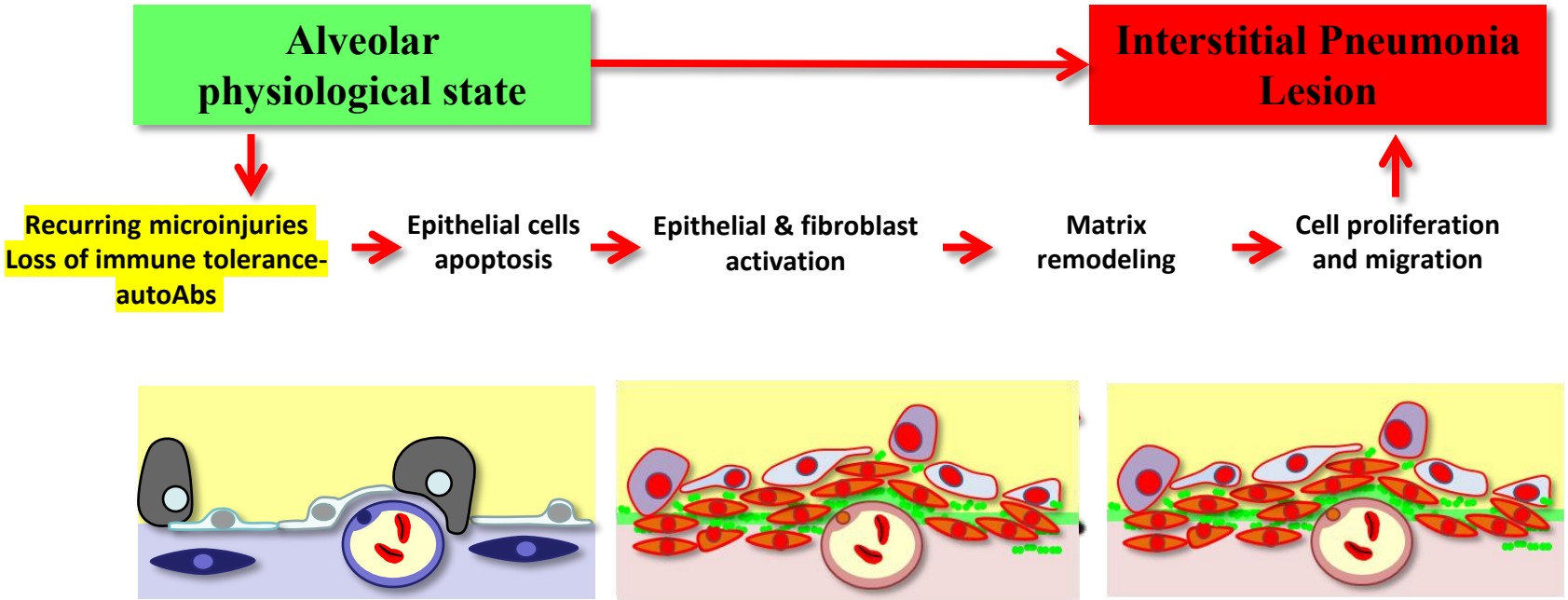
Serology defines PATTERNS of lung involvement

	RA	SLE	Scleroderma	DM-PM	Sjögren's syndrome	MCTD
Immunofluorescence nuclear pattern						
Homogeneous		+				
Speckled		+	+	+	+	+
Peripheral		+	+			
Nucleolar			+	+		
Specific nuclear antigens targeted in CTDs						
dsDNA		+				
ssDNA		+				
Histones		+				
Sm		+				
U1-RNP		+	+ (PH)			
U3-RNP			+ (ILD, PH)			
U11-RNP			+ (ILD)			
U12-RNP			+ (ILD)			
rRNP		+				
RNP	+	+	+			+
SSA/Ro		+ (ILD)		+ (ILD)	+	
SSB/La		+			+	
Ku		+	+	+ (PH)		
Ki		+				
Scl-70			+ (ILD)			
CENP A-E			+ (PH)			
Th/To			+ (ILD, PH)			
RNA-pol-1			+			
RNA-pol-2			+			
RNA-pol-3			+			
Jo-1 (cytoplasmic)				+ (ILD)		
EJ (cytoplasmic)				+ (ILD)		
OJ (cytoplasmic)				+ (ILD)		
PL-7 (cytoplasmic)				+ (ILD)		
PL-12 (cytoplasmic)				+ (ILD)		
KS (cytoplasmic)				+ (ILD)		
Zo (cytoplasmic)				+ (ILD)		
YRS (cytoplasmic)				+ (ILD)		
Mi-2 (cytoplasmic)				+		
SRP				+		
CADM-140 (MDA5)				+ (AIP)		
PM-Scl			+	+		
Non-ANA autoantibodies						
ANCA						
RF	+					
ACPA	+ (↑ILD)					

Papiris S et al. Respiration 2015;90:2-24

Pathogenesis-Pathophysiology

Pathogenesis of CTD-ILD



Slide Courtesy Argyris Tzouvelekis

Pneumocyte type I

Pneumocyte type II

Endothelial cell

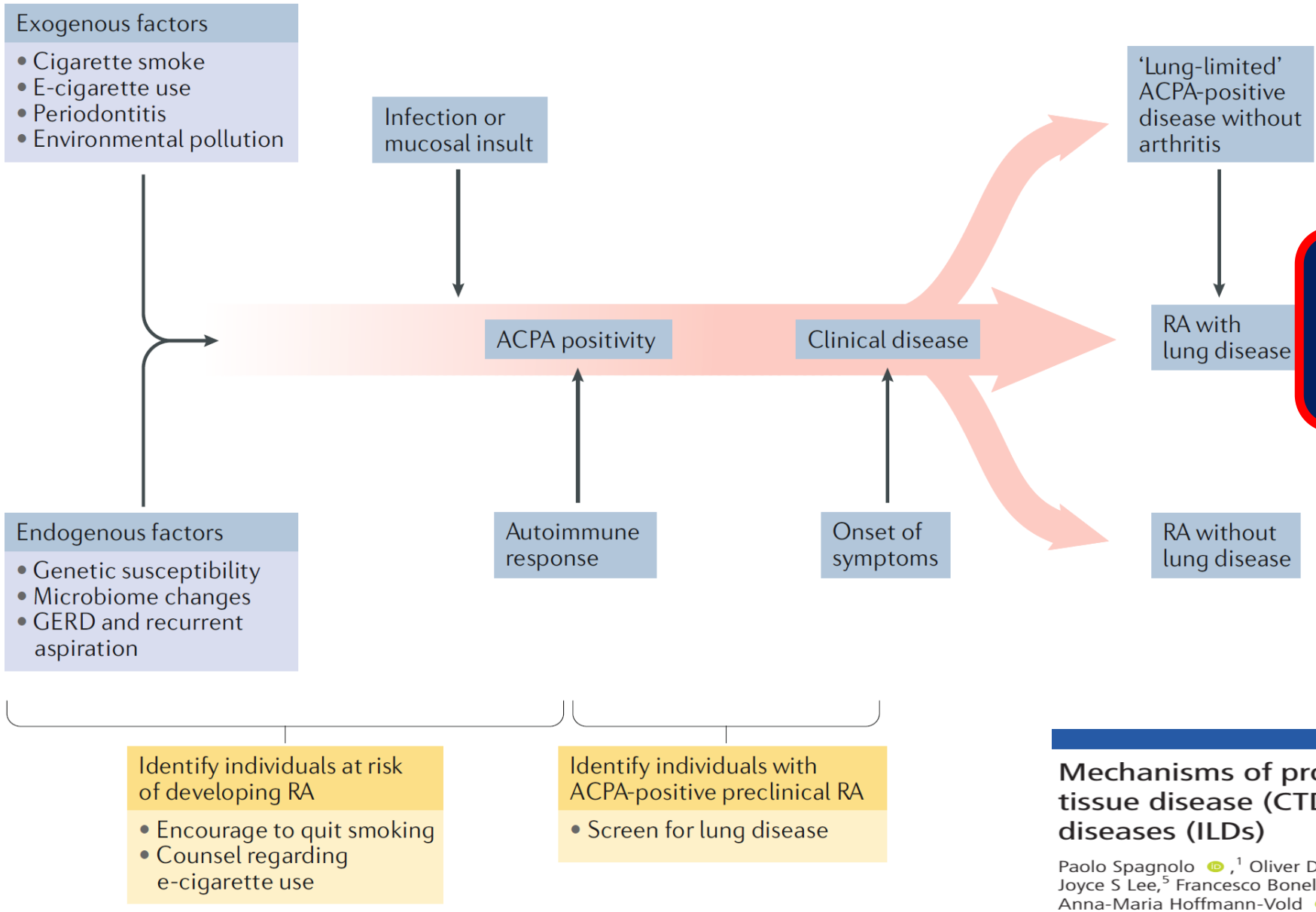
Fibroblast

REVIEWS

Interstitial lung disease in connective tissue disease—mechanisms and management

Athol U. Wells and Christopher P. Denton

NATURE REVIEWS | RHEUMATOLOGY



ACPA antibodies have been found in bronchial washing and sputum of patients with bronchiectasis with and EVEN w/o RA manifestations

NATURE REVIEWS | RHEUMATOLOGY

https://doi.org/10.1038/s41584-019-0275-x

Review

Mechanisms of progressive fibrosis in connective tissue disease (CTD)-associated interstitial lung diseases (ILDs)

Paolo Spagnolo [1], Oliver Distler [2], Christopher J Ryerson,[3] Argyris Tzouvelekis,[4] Joyce S Lee,[5] Francesco Bonella,[6] Demosthenes Bouros,[7] Anna-Maria Hoffmann-Vold [8], Bruno Crestani,[9,10] Eric L Matteson[11]

Spagnolo P, et al. Ann Rheum Dis 2020;0:1–8. doi:10.1136/annrheumdis-2020-217230

Pathogenesis of CTD-ILDs/Vasculitis

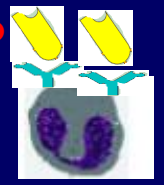
Loss of immune tolerance

Neutrophils

activation

Anti-MPO

MPO



Degranulation

ROS

Fibroblast proliferation

Fibrosis

Elastases

AEC apoptosis –
Loss of alveolar attachment

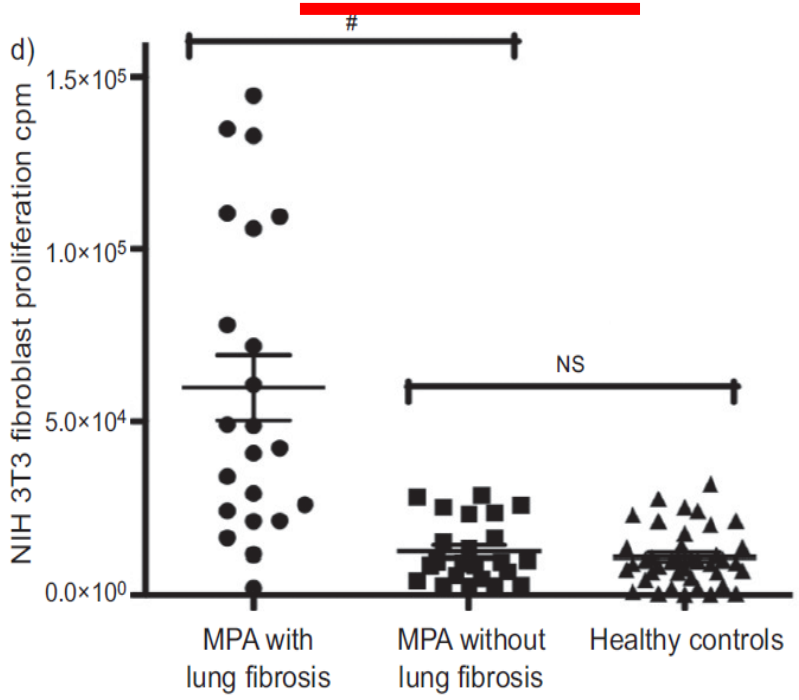
Emphysema

Eur Respir J 2011; 37: 1503–1513
DOI: 10.1183/09031936.00148409

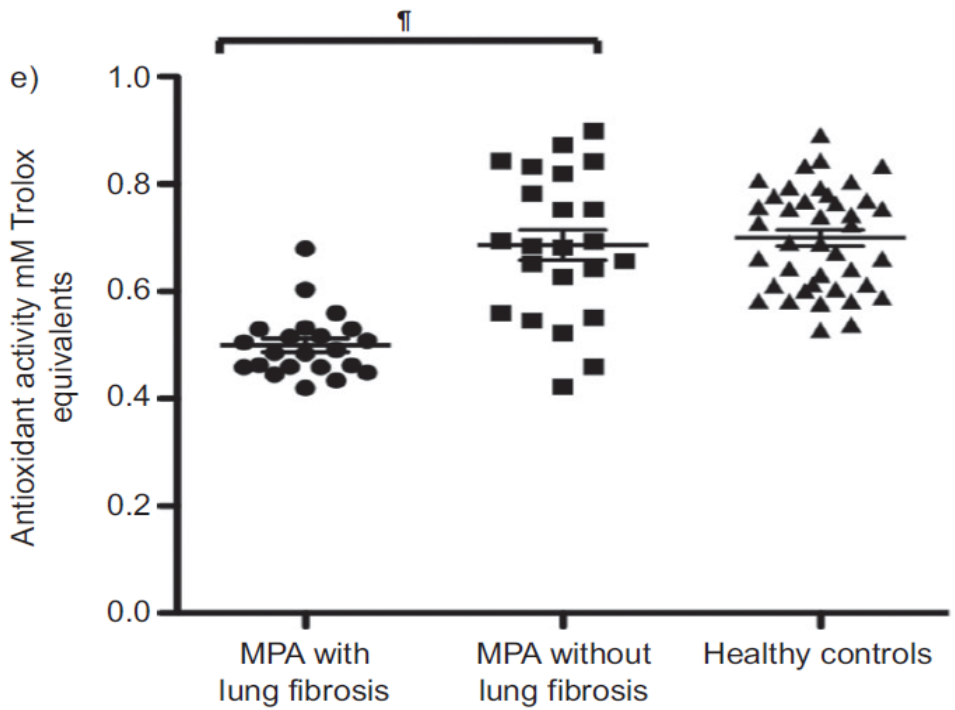
The oxidation induced by antimyeloperoxidase antibodies triggers fibrosis in microscopic polyangiitis

P. Guilpain*,#,f, C. Chéreau*,f, C. Goulvestre*, A. Servettaz*, D. Montani¶, N. Tamas+, C. Pagnoux#,+, E. Hachulla§, B. Weill*, L. Guillevin#,+, L. Mouthon#,+ and F. Batteux*

Increased fibroblast proliferation induced by serum of MPA-PF



Reduced anti-oxidant activity induced by serum of MPA-PF



IPF/UIP vs CTD/UIP
Common genetic background

IPF

Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis

nature genetics

ORIGINAL ARTICLE

A Common MUC5B Promoter Polymorphism and Pulmonary Fibrosis

Max A. Seibold, Ph.D., Anastasia L. Wise, Ph.D., Marcy C. Speer, Ph.D.,*

The NEW ENGLAND JOURNAL of MEDICINE

RA

ORIGINAL ARTICLE

MUC5B Promoter Variant and Rheumatoid Arthritis with Interstitial Lung Disease

This article was published on October 20, 2018, at NEJM.org.

CONCLUSIONS

We found that the *MUC5B* promoter variant was associated with RA-ILD and more specifically associated with evidence of usual interstitial pneumonia on imaging. (Funded by Société Française de Rhumatologie and others.)

Pathophysiology of ILD

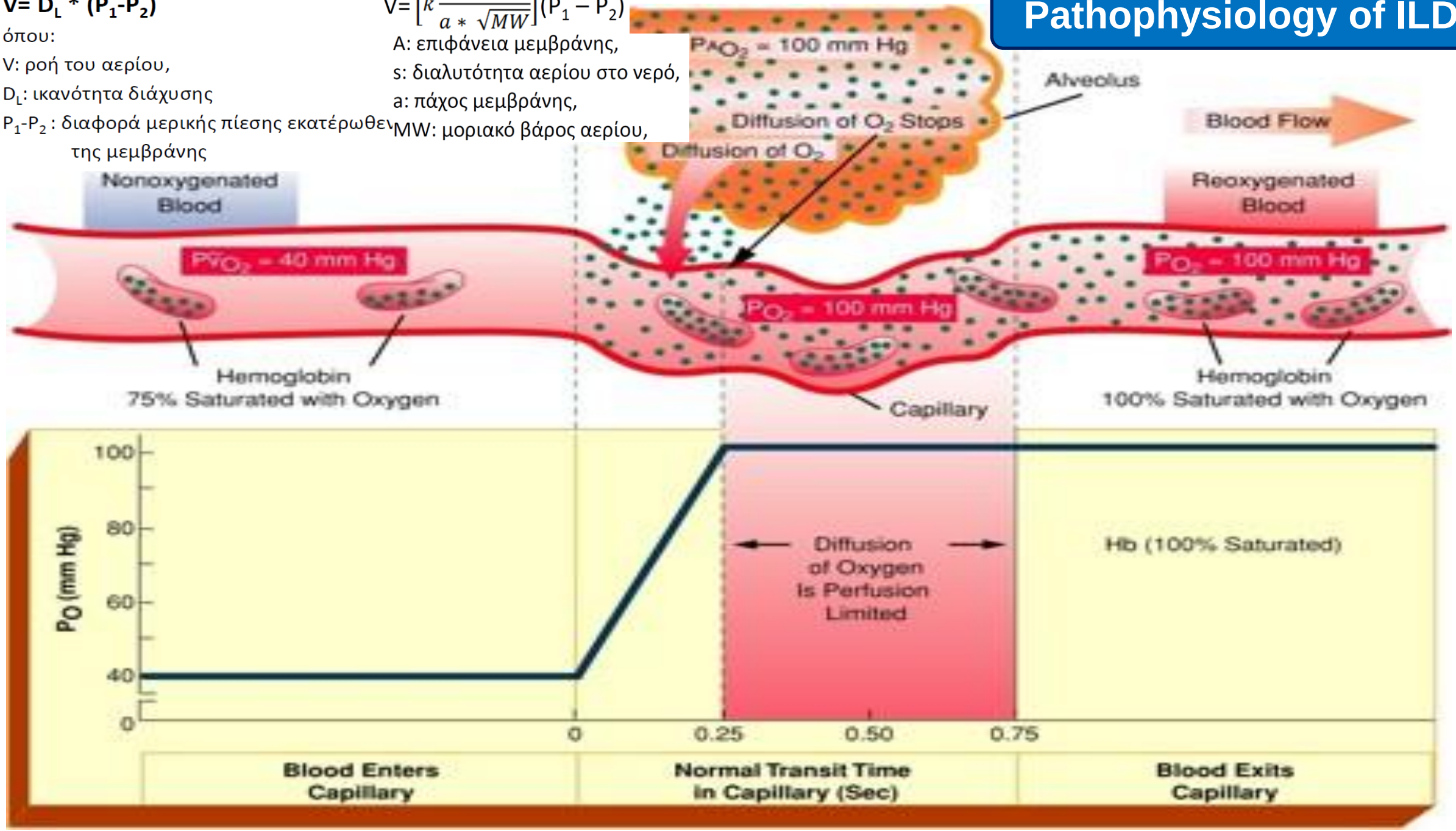
$V = D_L * (P_1 - P_2)$

όπου:

- V: ροή του αερίου,
- D_L: ικανότητα διάχυσης
- P_1-P_2 : διαφορά μερικής πίεσης εκατέρωθεν της μεμβράνης

$$V = \left[k \frac{A * s}{a * \sqrt{MW}}\right](P_1 - P_2)$$

A: επιφάνεια μεμβράνης,
s: διαλυτότητα αερίου στο νερό,
a: πάχος μεμβράνης,
MW: μοριακό βάρος αερίου,



So what do we do?

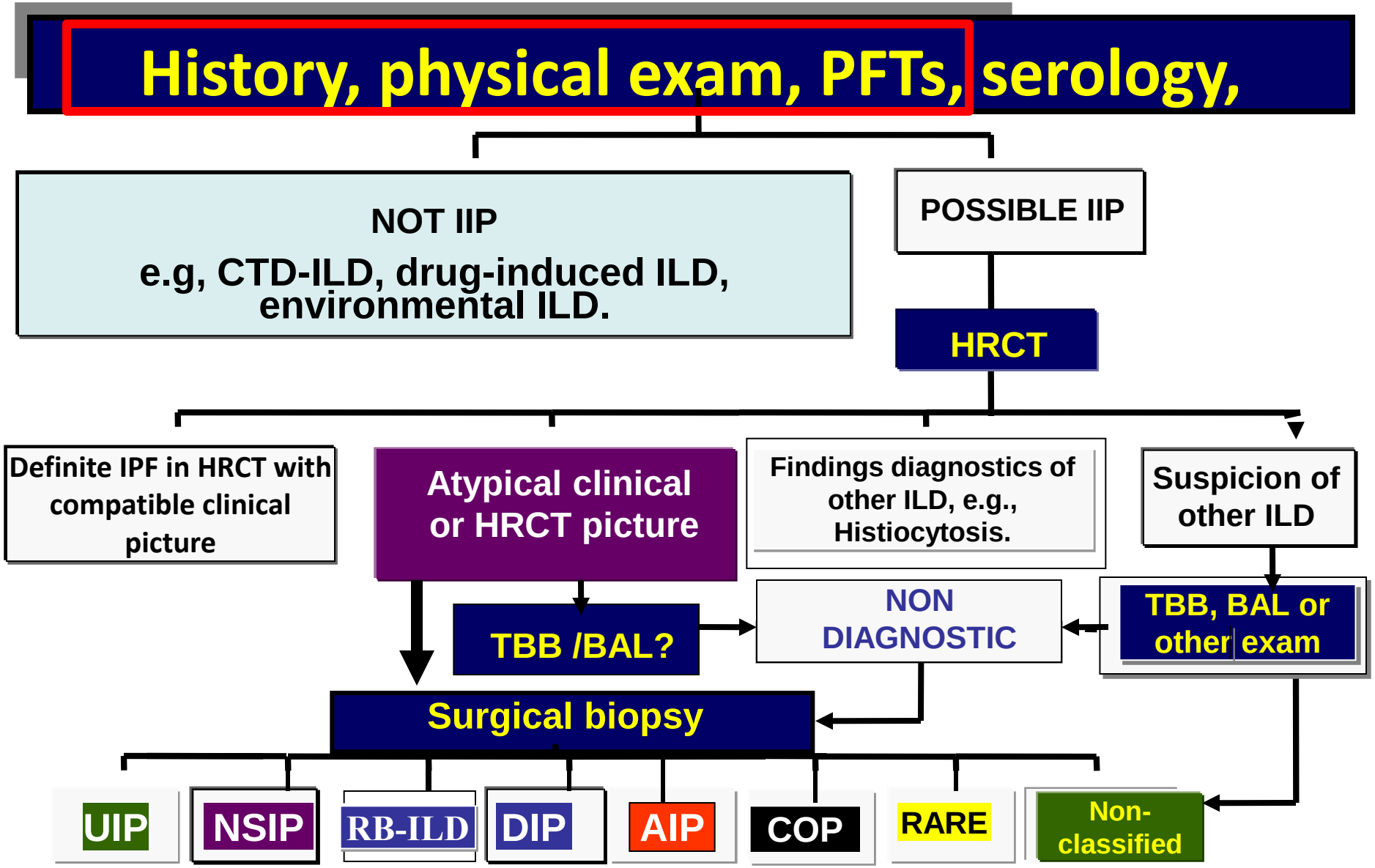
Physical Exam -
Lung function tests/6MWD/Cardiac echo

HRCT – BAL- Biopsy

Treat based on disease behavior

Physical Exam and PFTs

DIAGNOSTIC APPROACH OF CTD-ILDs



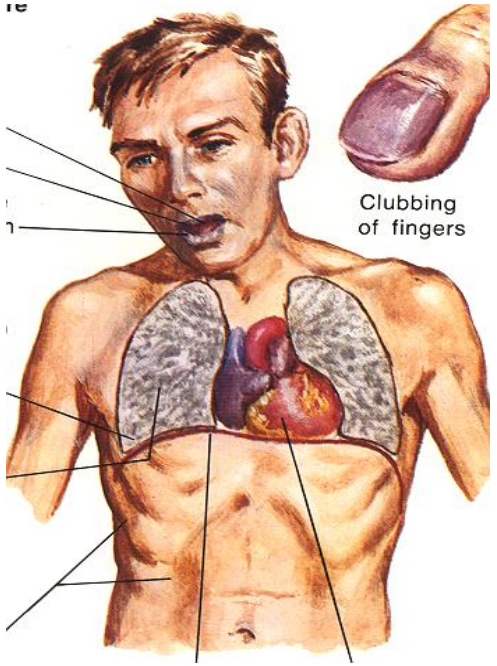
Physical Exam

Eur Respir J 2012; 40: 519–521
DOI: 10.1183/09031936.00001612

EDITORIAL

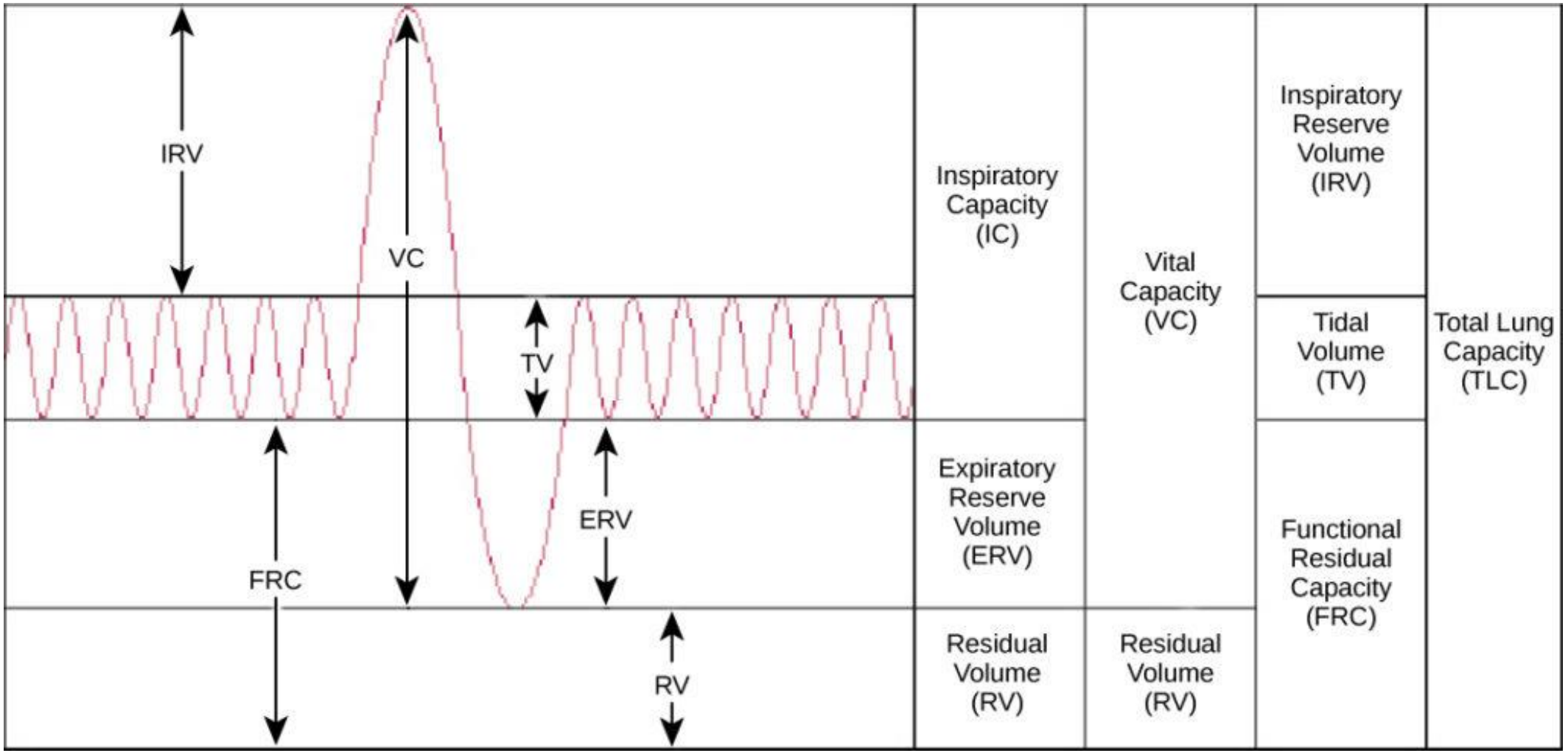
Velcro crackles: the key for early diagnosis of idiopathic pulmonary fibrosis?

Vincent Cottin and Jean-François Cordier



Όγκοι και Χωρητικότητες

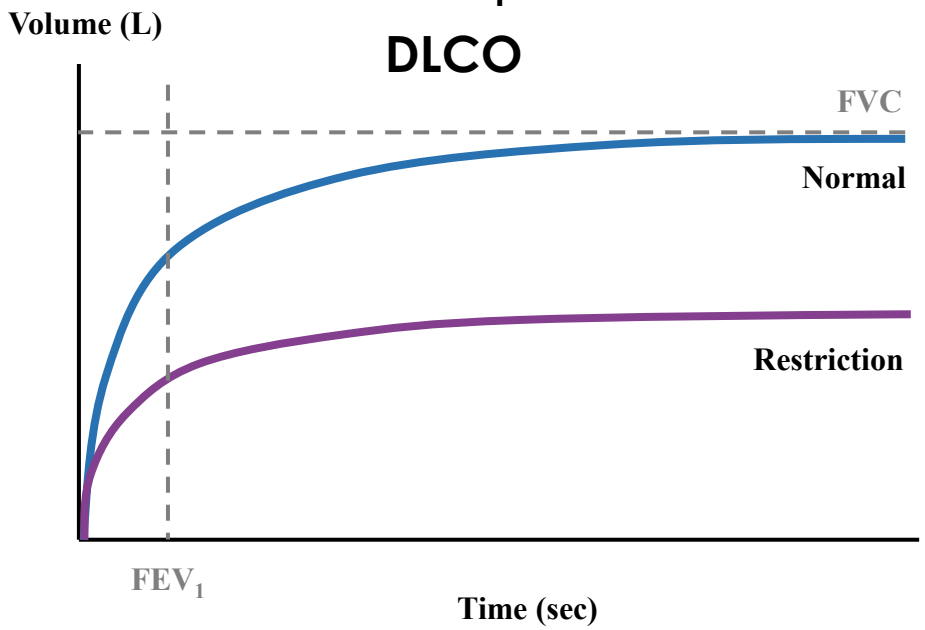
4 όγκοι που σε διάφορους συνδυασμούς μας δίνουν 4 χωρητικότητες



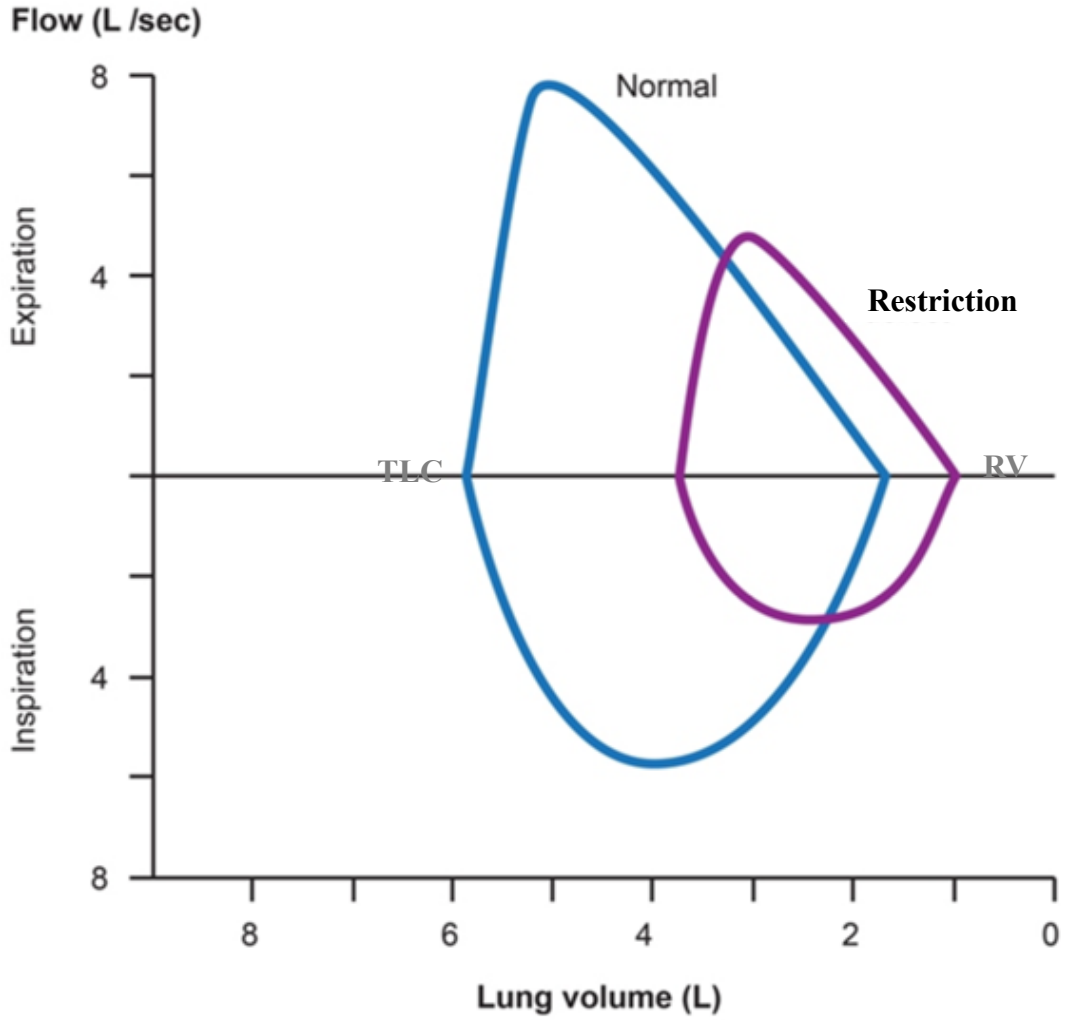
Λειτουργικές Δοκιμασίες-Περιοριστικό πρότυπο ενίοτε μικτό

TLC ↓
FVC ↓
FEV_1 ↓
DLCO ↓

$$\frac{FEV_1}{FVC} = \text{φυσιολογικό}$$

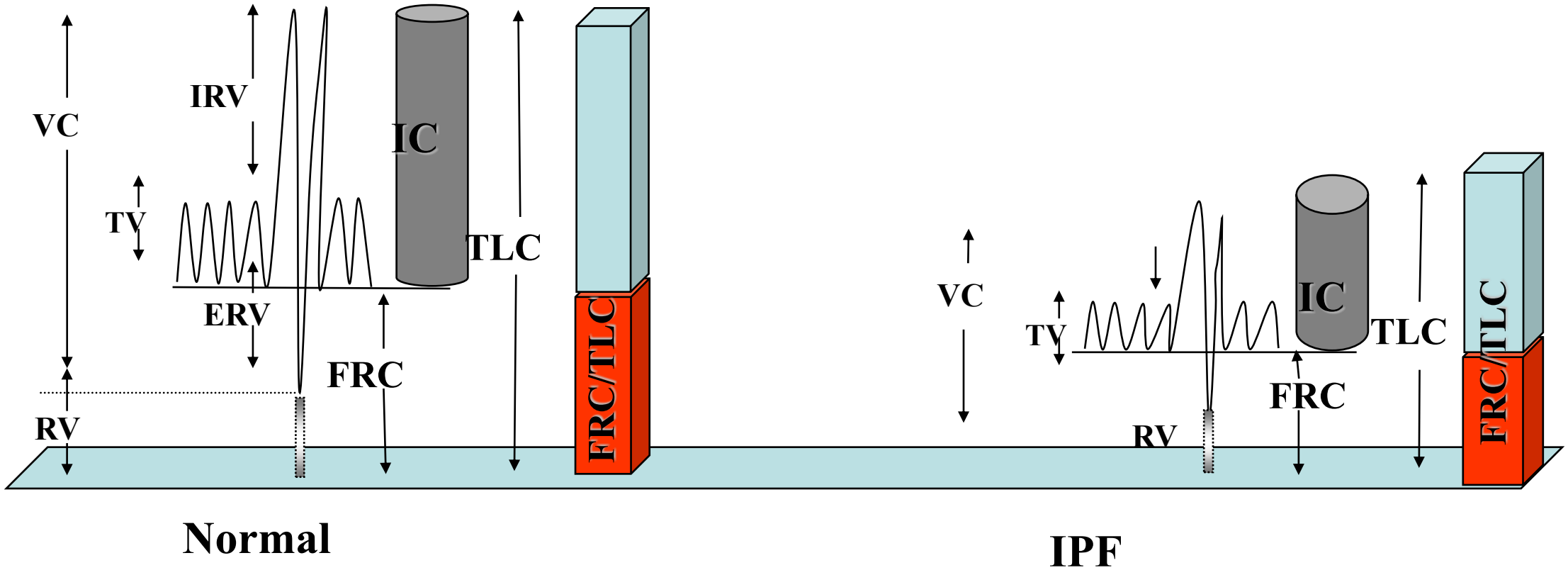


Δεν ανταποκρίνεται στη χορήγηση βρογχοδιασταλτικών.



[6] Jameson *et al.* "Harrison's Principles of Internal Medicine", 20th Edition, Mc Graw Hill Education, 2018
[3] J. D. Zibrak et al. "Interstitial lung disease: raising the index of suspicion in primary care", Primary Care Respiratory Medicine, 2014

Περιοριστικά σύνδρομα – Στατικοί όγκοι



Μέτρηση Διαχυτικής Ικανότητας Πνεύμονα

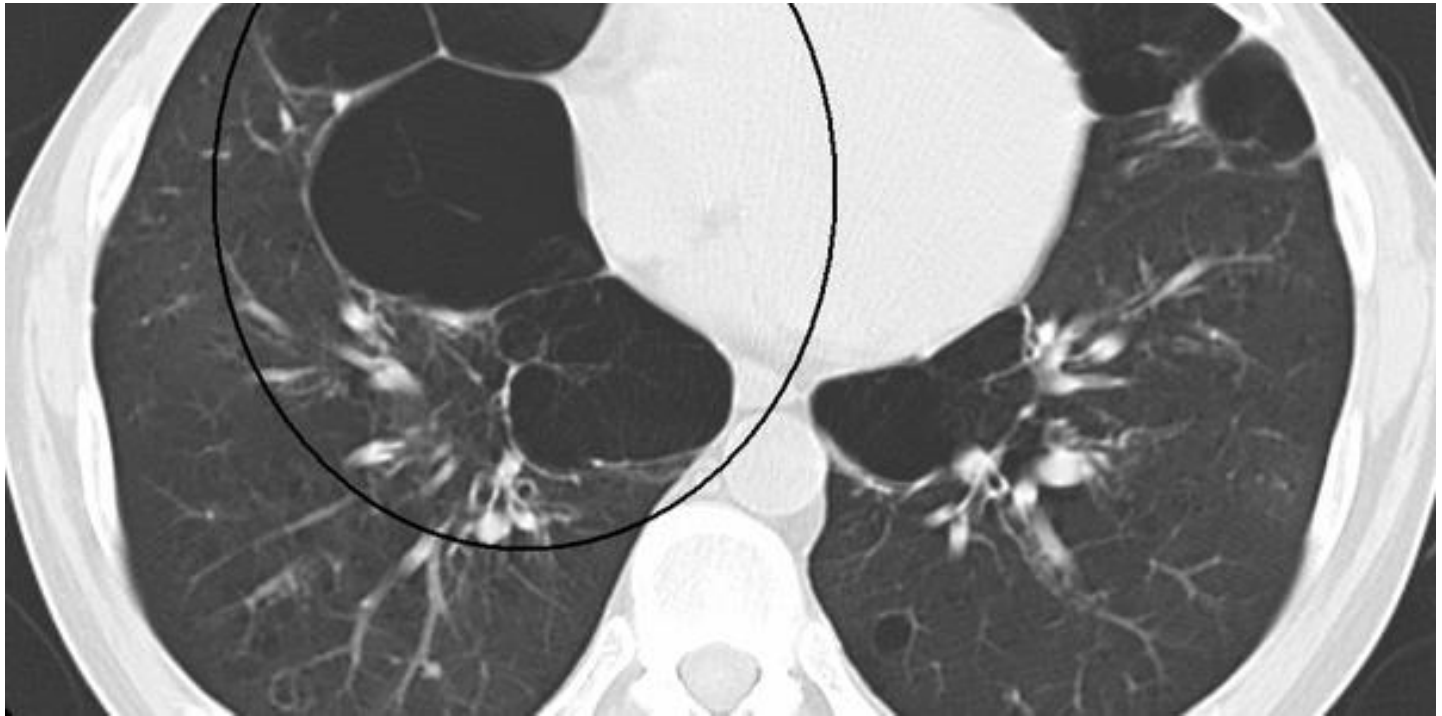
- **O2 – για μέτρηση DLCO – τεχνικές δυσκολίες – V/Q mismatch – διαφορετική τριχοειδική πίεση από φλεβική σε αρτηριακή κυκλοφορία**
- **CO – ιδανικό – 100-200 φορές μεγαλύτερη συγγένεια δέσμευσης με Hgb- δεν επηρεάζεται από αιματική ροή**
- **Μέθοδος μονής εισπνοής (single-breath test) – 3 στάδια**
- **1) Εξεταζόμενος εκπνέει όλο τον αέρα (RV)**
- **2) Βαθιά εισπνοή (TLC) αβλαβούς μίγματος αερίων (0.3% CO, 21% O_2, 10%He, N_2)**
- **3) Απότομη εκπνοή όλου του αέρα (RV)**

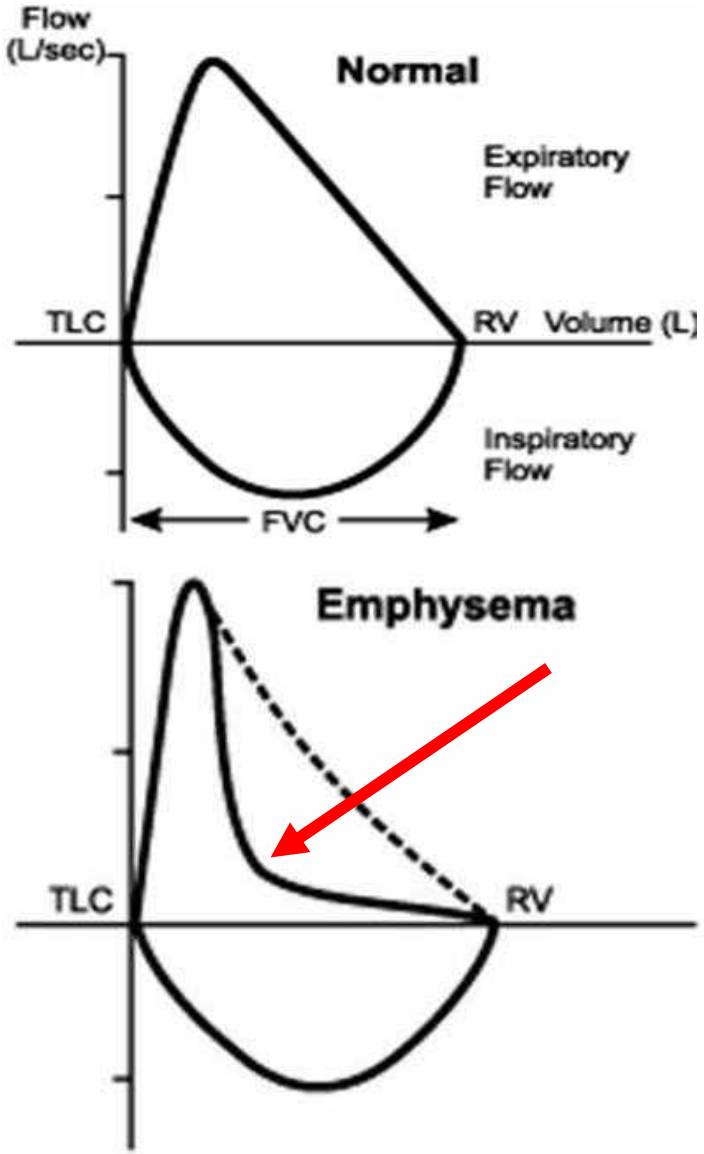
Αποφρακτικά σύνδρομα

FEV1/FVC – ελαττωμένος (<0.70-0.75)

FEV1 – ελαττωμένος ή φυσιολογικός – ανάλογα με βαρύτητα

Μείωση της μέγιστης εκπνευστικής ροής σε σχέση με τον μέγιστο όγκο λόγω αυξημένων αντιστάσεων σύνθλιψης των αεραγωγών κατά την βίαιη εκπνοή απώλειας του υποστηρικτικού ιστού-εμφύσημα – scooping effect ordog-leg appearance of the expiratory limb.

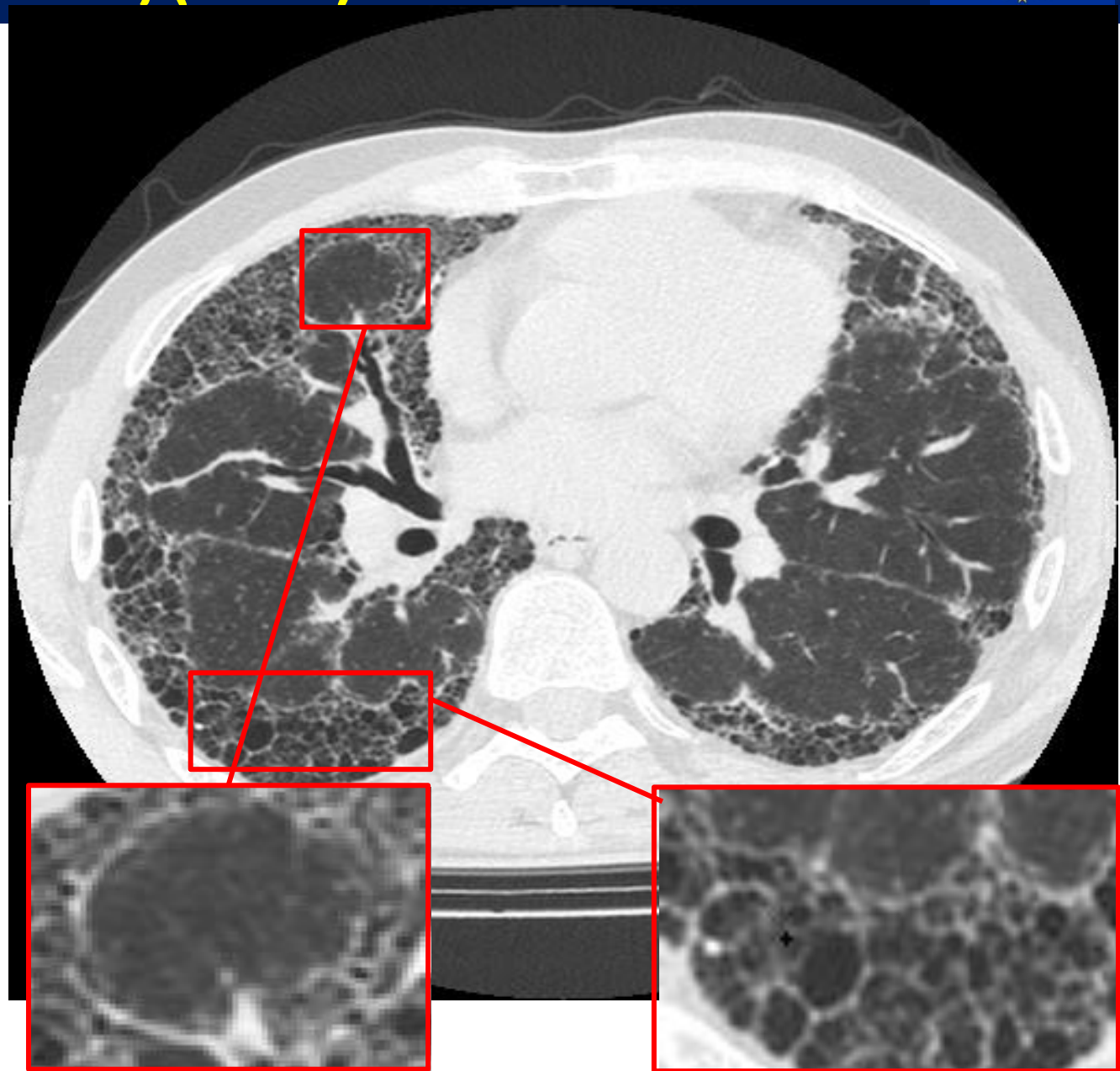




Μικτά πρότυπα- Συνδυασμός Πνευμονικής Ινωσης – Εμφυσήματος (CPFE)

Διατηρημένοι πνευμονικοί όγκοι με ήπια ελάττωση της FEV1 και του λόγου FEV1/FVC με δυσανάλογη ελάττωση της DLCO

- **FVC: 88%**
- **FEV1: 72%**
- **Tif: 70**
- **TLC: 81%**
- **DLCO: 39%**



6MWD- An easy, reproducible,informative biomarker

Six-Minute-Walk Test in Idiopathic Pulmonary Fibrosis

Test Validation and Minimal Clinically Important Difference

Roland M. du Bois[1], Derek Weycker[2], Carlo Albera[3], Williamson Z. Bradford[4], Ulrich Costabel[5], Alex Kartashov[2], Lisa Lancaster[6], Paul W. Noble[7], Steven A. Sahn[8], Javier Szwarcberg[4], Michiel Thomeer[9], Dominique Valeyre[10], and Talmadge E. King, Jr.[11]

[1]National Heart and Lung Institute, Imperial College, London, United Kingdom; [2]Policy Analysis, Inc., Brookline, Massachusetts; [3]Department of Clinical and Biological Sciences, University of Turin, Turin, Italy; [4]InterMune, Inc., Brisbane, California; [5]Ruhrlandklinik and Medical Faculty, University of Duisburg/Essen, Essen, Germany; [6]Vanderbilt University Medical Center, Nashville, Tennessee; [7]Duke University School of Medicine, Durham, North Carolina; [8]Medical University of South Carolina, Charleston, South Carolina; [9]University Hospitals Leuven, Leuven, Belgium; [10]Assistance Publique-Hôpitaux de Paris, Hospital Avicenne, Bobigny, France; [11]University of California, San Francisco, California

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 183 2011

24 m reduction in 6mo means alert

suggesting good construct validity. Importantly, change in 6MWD was highly predictive of mortality; a 24-week decline of greater than 50 m was associated with a fourfold increase in risk of death at 1 year (hazard ratio, 4.27; 95% confidence interval, 2.57–7.10; $P < 0.001$). The estimated MCID was 24–45 m.

Conclusions: The 6MWT is a reliable, valid, and responsive measure of disease status and a valid endpoint for clinical trials in IPF.

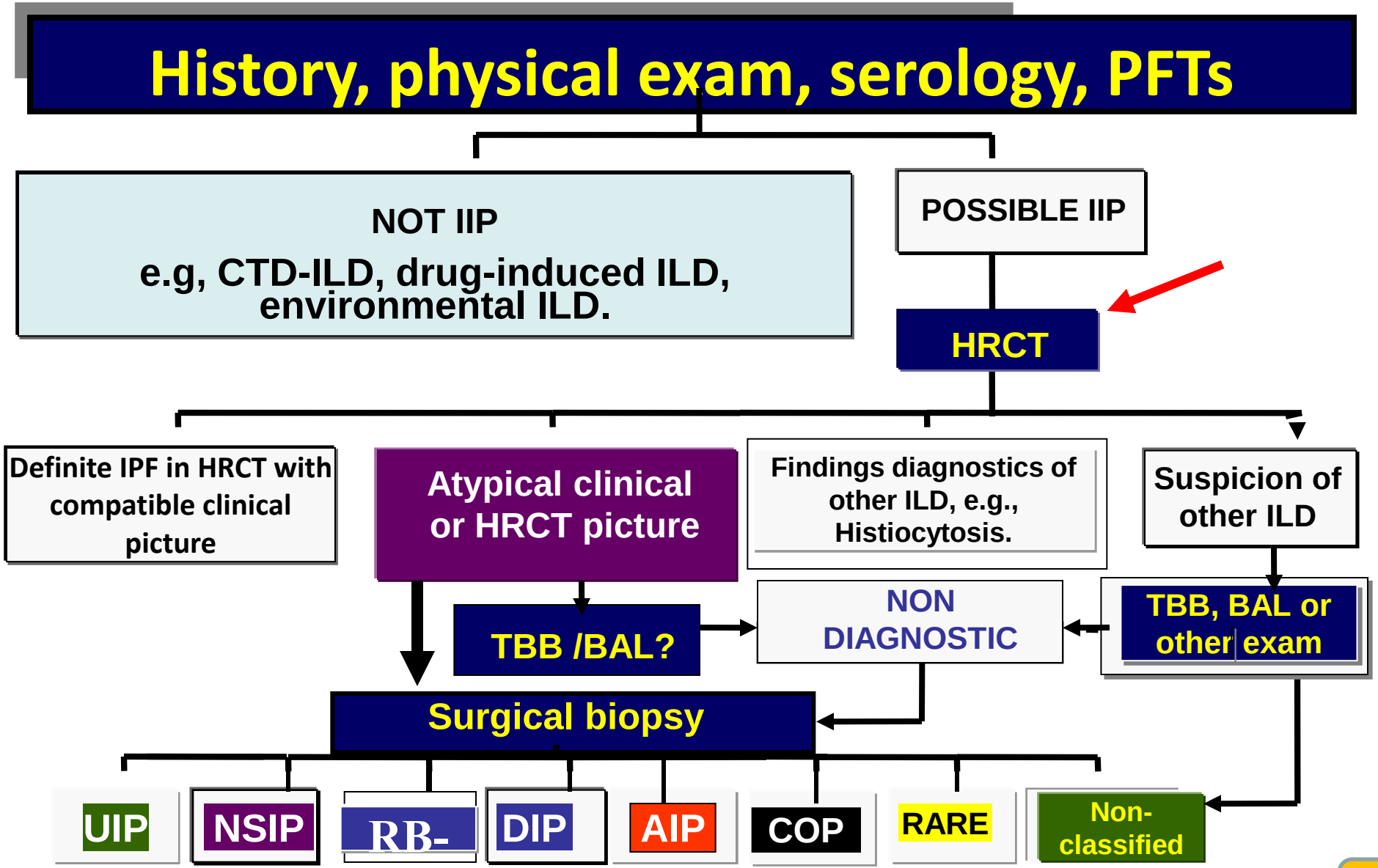
Less than 250 at baseline means alert

TABLE 6. COX PROPORTIONAL HAZARDS MODEL

	Patient Visits (*n*)	Deaths (*n*)	HR (*95% CI*)	*P* Value
Δ6MWT distance, m				
<−50	317	40	4.27 (2.57–7.10)	<0.001
−50 to −26	117	18	3.59 (1.95–6.63)	<0.001
⩾ −25	720	24		
6MWT distance, m				
<250	130	15	2.65 (1.48–4.74)	0.001
250 to 349	255	20	1.54 (0.91–2.60)	0.106
⩾350	823	47		

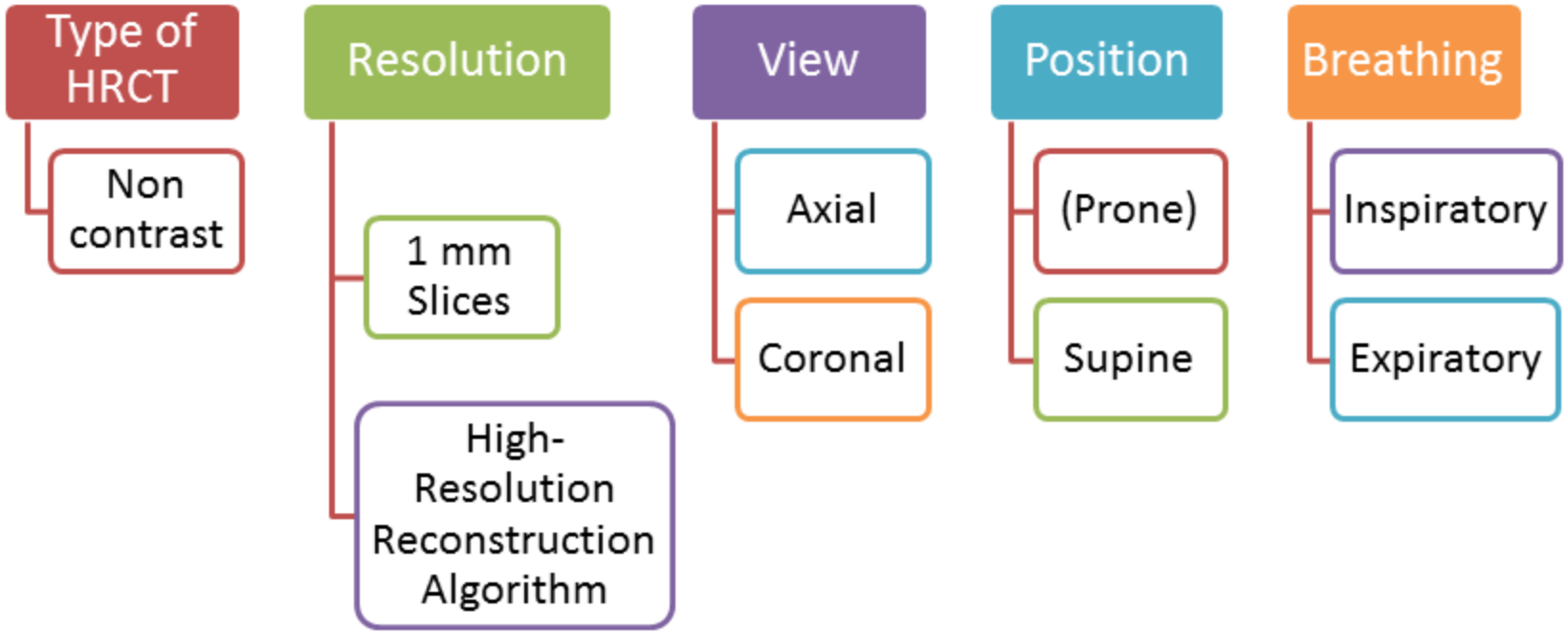
HRCT

DIAGNOSTIC APPROACH OF IIPs

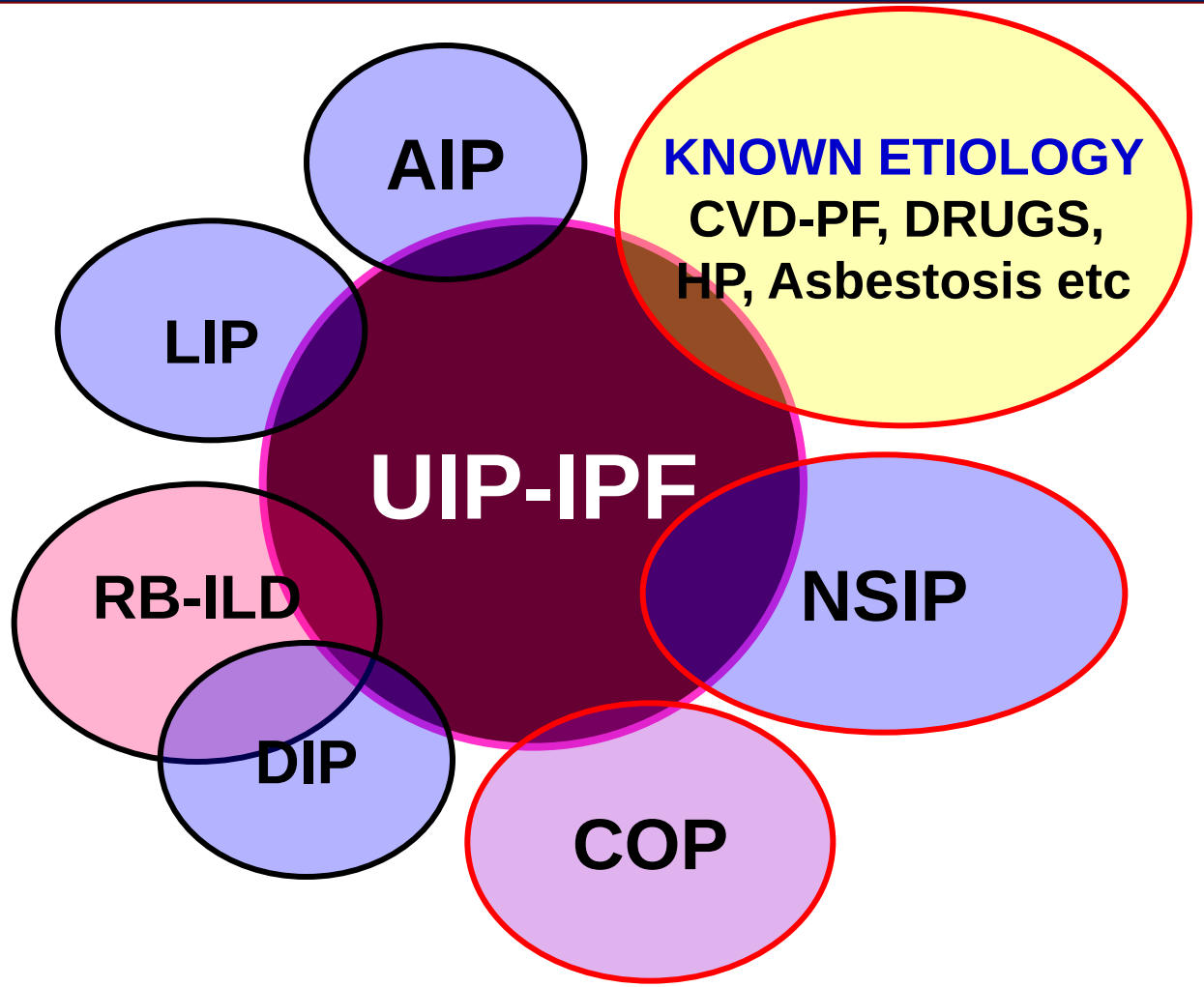


Courtesy Bouros

What are the features of an HRCT?



USUAL INTERSTITIAL PNEUMONIA AND IDIOPATHIC PULMONARY FIBROSIS



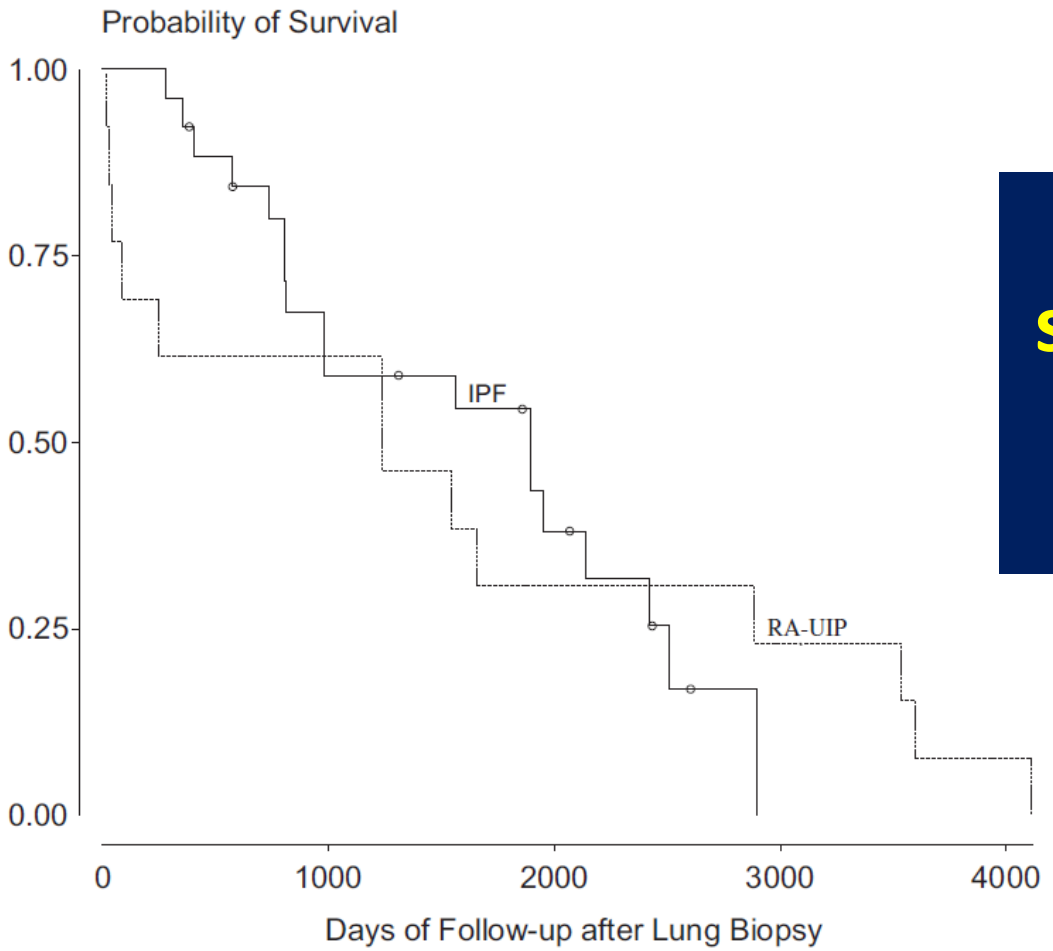
Most UIPs are "IPF", ALL UIPs ARE NOT IPF

ILD patterns in autoimmune diseases

TYPE	SSc	RA	PM/DMM	SLE	MCTD	Sjögren's
UIP	++	++	++	++	+	-
NSIP	+++ 90%	+	+	+	++	++ 25%
OP	+	+	+++ 50%	+	_	-
DAD	+	+	++	++	_	_
DIP	+	+	+	+	_	+/-
LIP	_	_	_	_	_	+++ 20%
DAH / CAPILARITIS	+	+	+	+++	_	_
ILD	+++	++	+++	+	++	+

Slide courtesy of D.Bouros

HRCT pattern defines SEVERITY of lung involvement

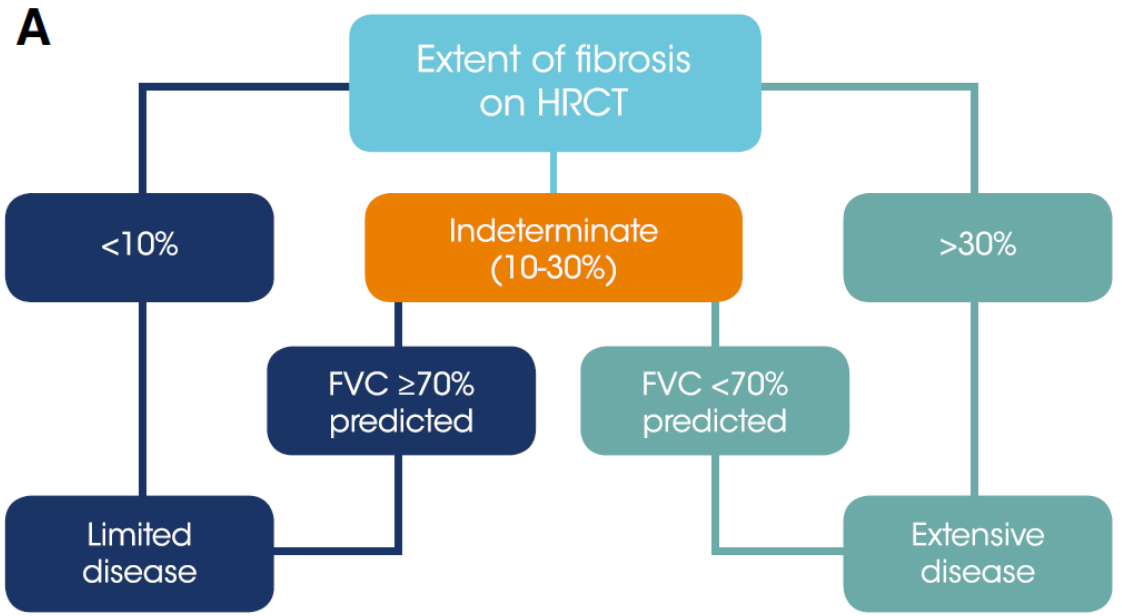


…..and in several cases type of treatment

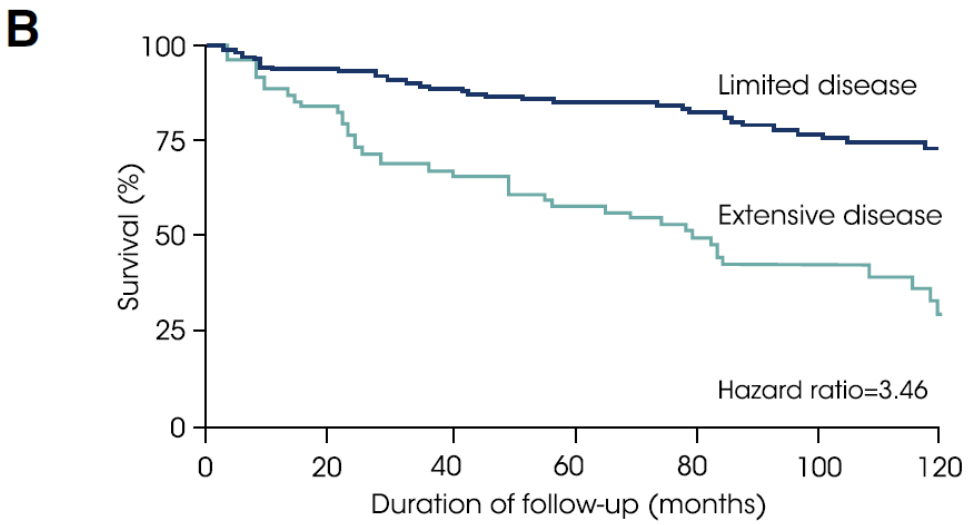
Brown JH et al, Respiratory Medicine 2013

HRCT and functional extent define prognosis

Early identification of anti-fibrotic benefit

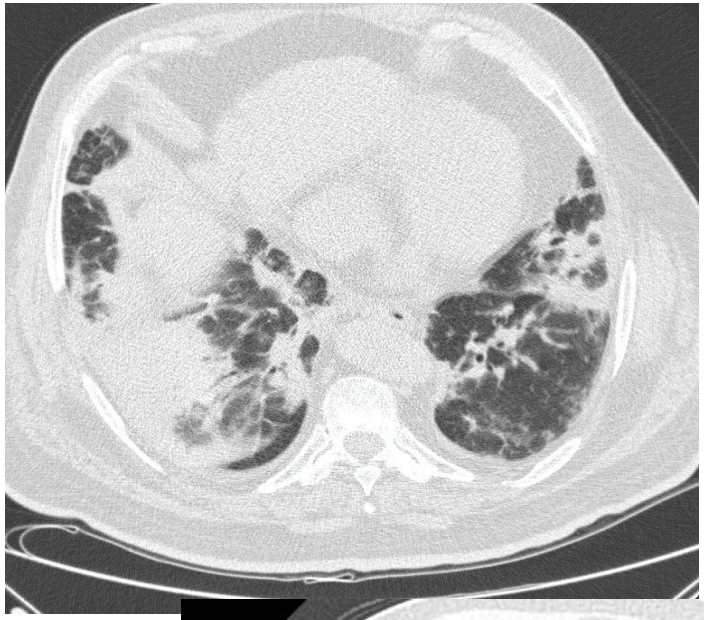


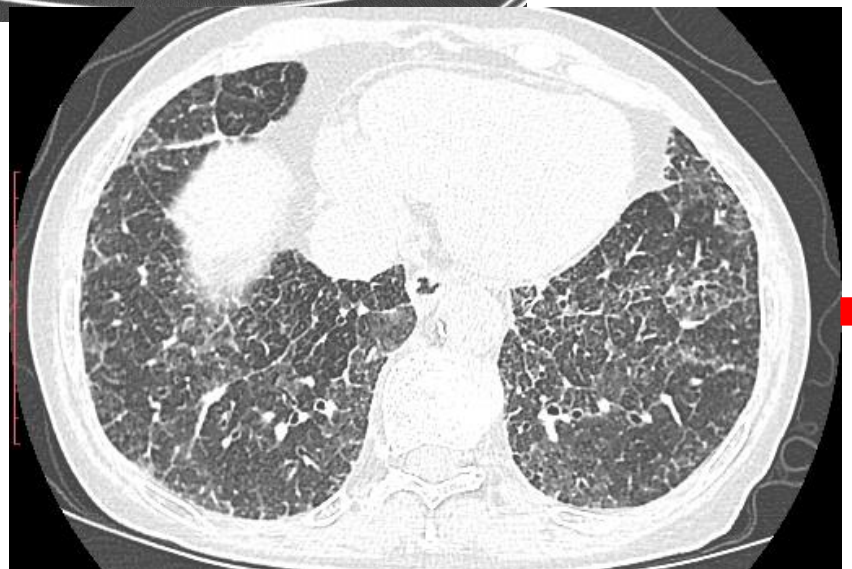
PFTs may be hampered by comorbidities



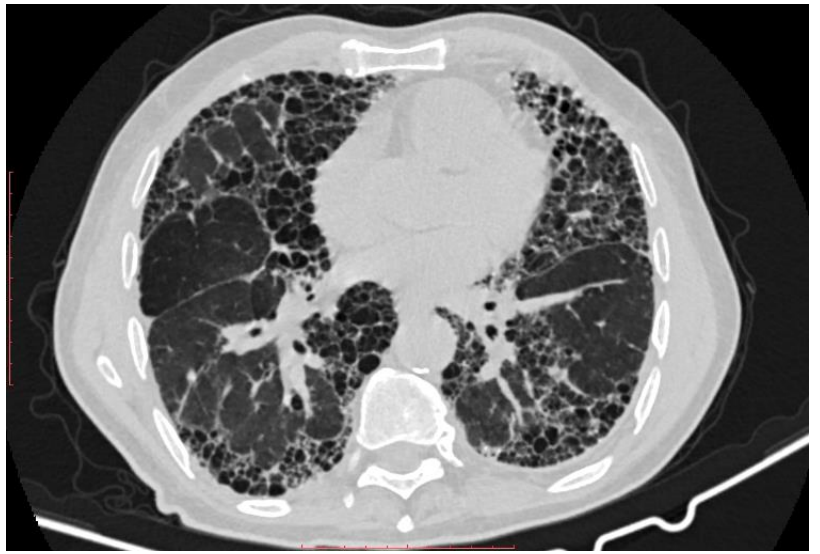
HRCT pattern and “time” dictate treatment

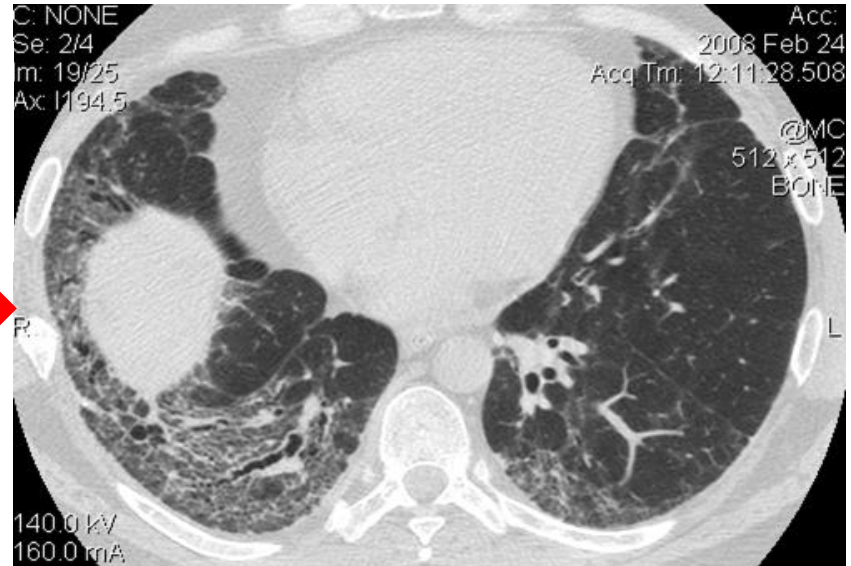
CS+immunomodulation





Anti-fibrotics





DEFINITE UIP PATTERN

Basal

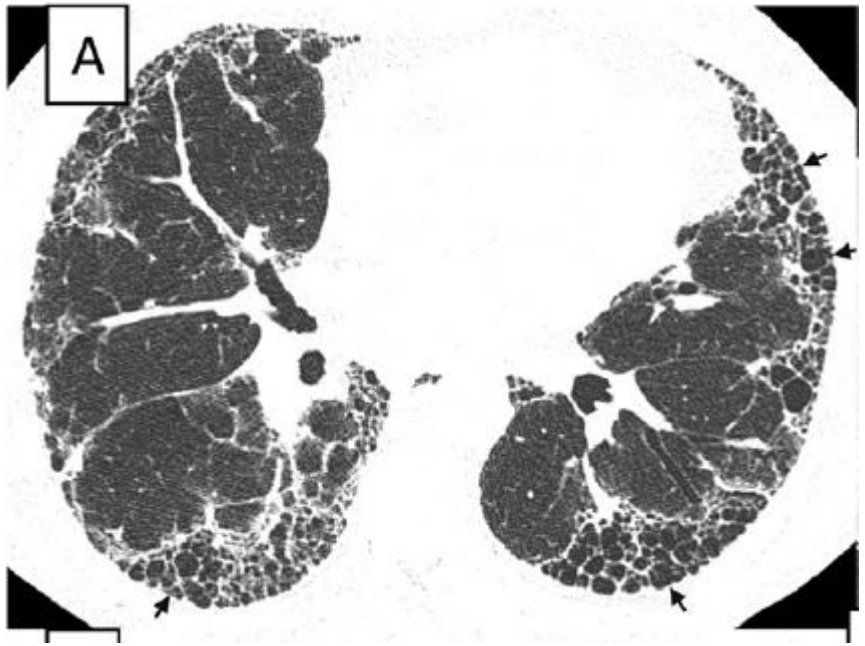
Subpleural

HCM

ATS/ERS 2011

UIP Pattern (All Four Features)

- Subpleural, basal predominance
- Reticular abnormality
- Honeycombing with or without traction bronchiectasis
- Absence of features listed as inconsistent with UIP pattern (*see* third column)



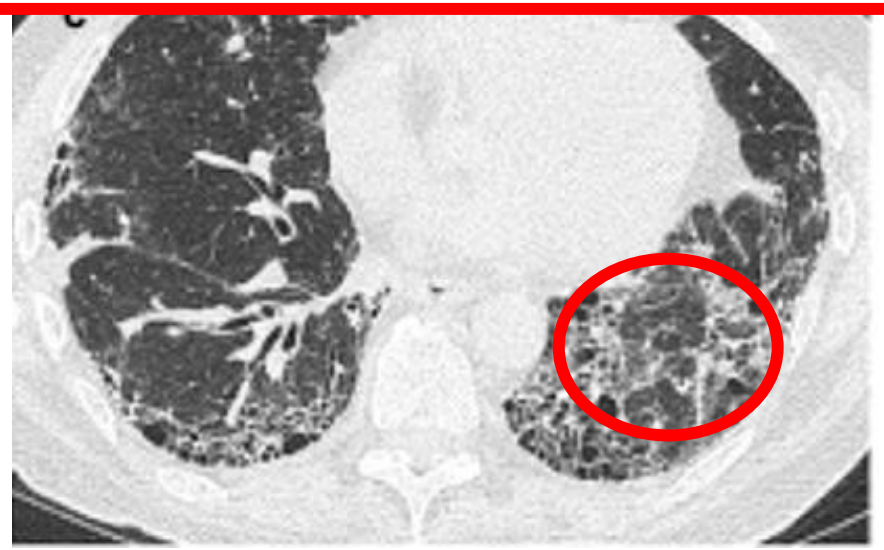
UIP ATS/ERS 2018

Subpleural and basal predominant; distribution is often heterogeneous*

Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis†

More flexible

*Variants of distribution: occasionally diffuse, may be asymmetrical.
†Superimposed CT features: mild GGO, reticular pattern, pulmonary ossification



POSSIBLE BECAME PROBABLE

ATS/ERS 2011

Possible UIP Pattern (All Three Features)

- Subpleural, basal predominance
- Reticular abnormality
- Absence of features listed as inconsistent with UIP pattern (*see* third column)

No HCM

More flexible

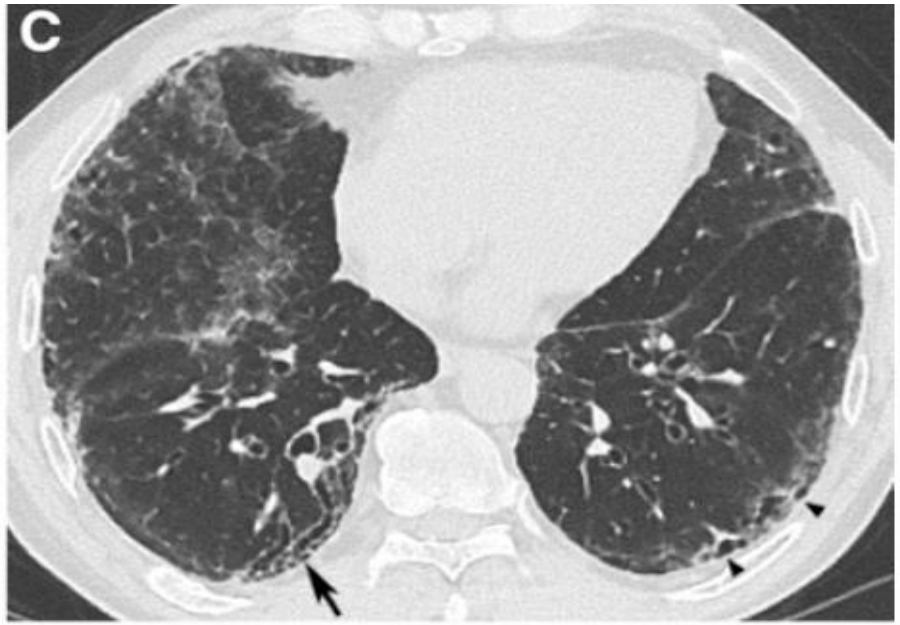
ATS/ERS 2018

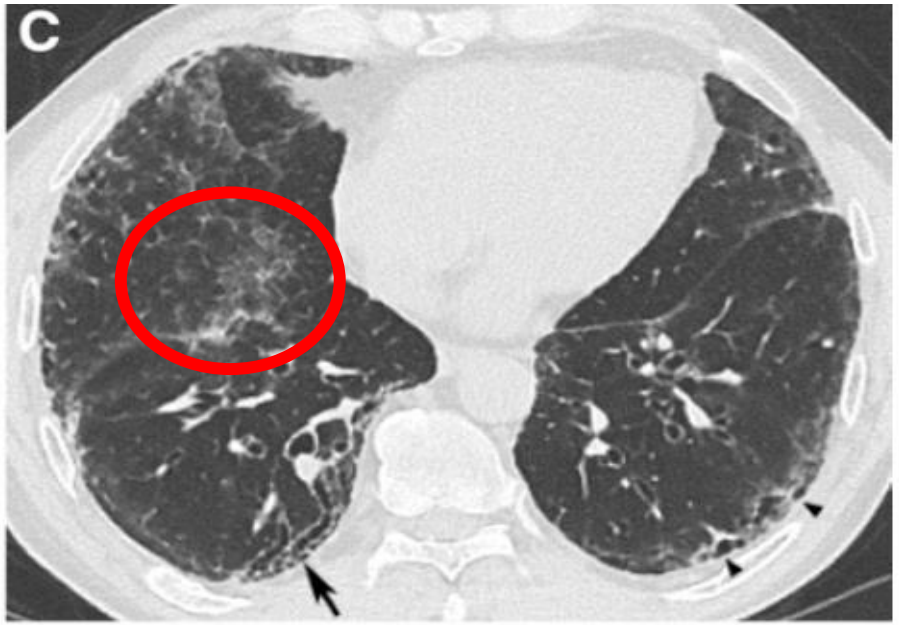
Probable UIP

Subpleural and basal predominant; distribution is often heterogeneous

Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis

May have mild GGO





Indeterminate Pattern

Indeterminate for UIP

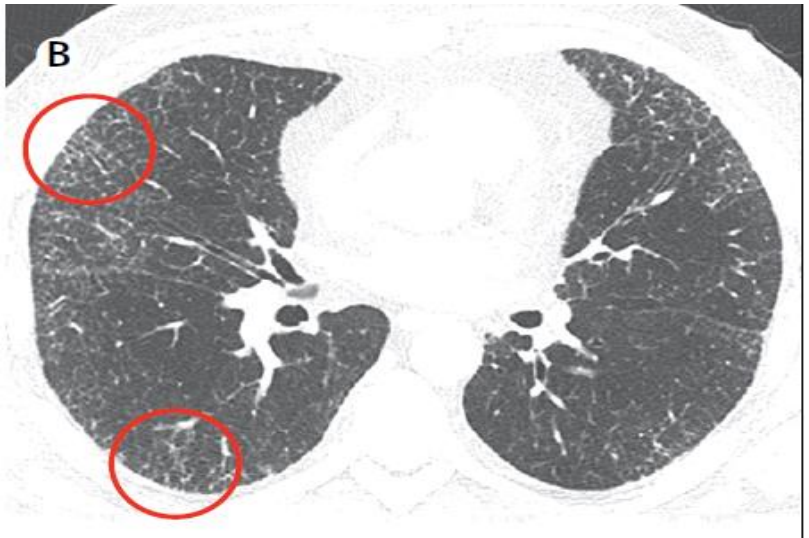
Subpleural and basal predominant

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")

ILA

Early UIP pattern



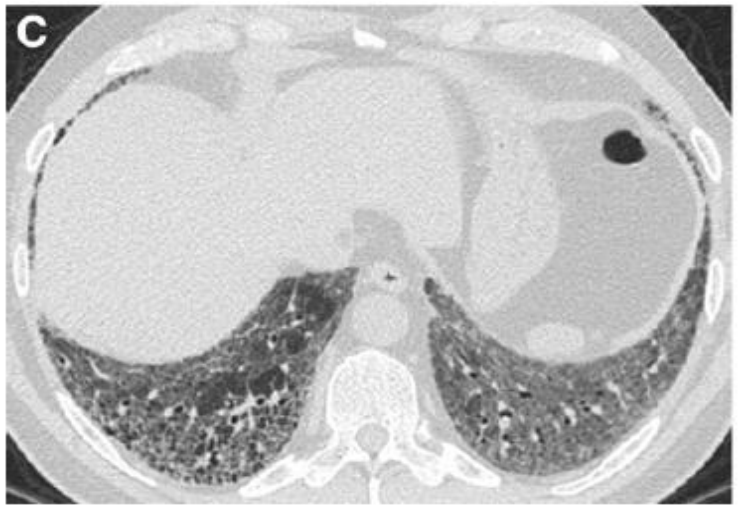
Familial

IPAF

30%

Unclassifiable

Truly indeterminate

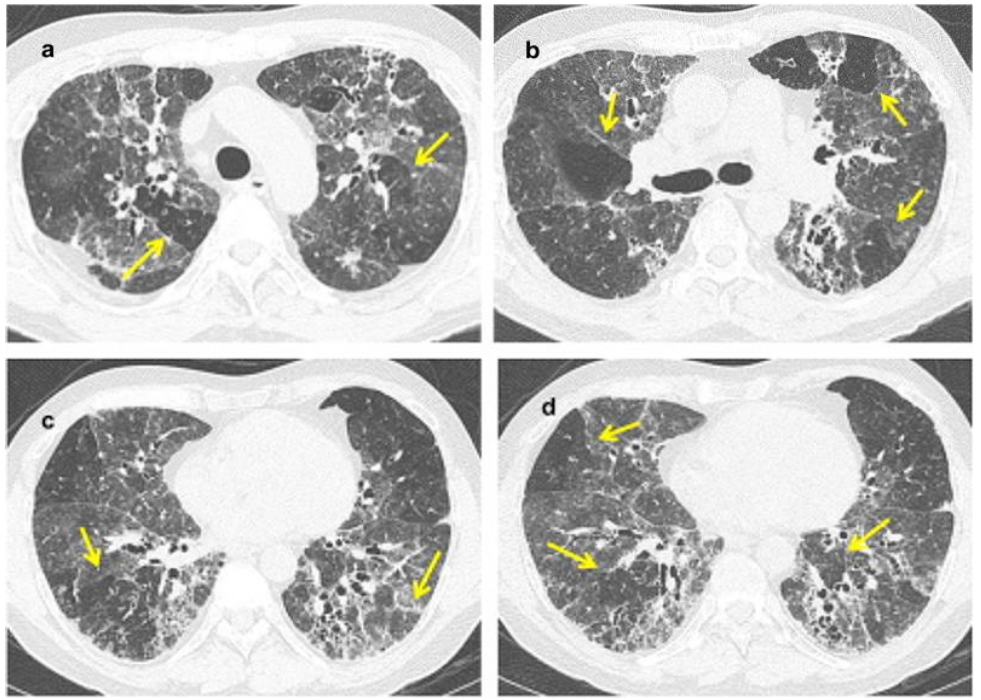


Inconsistent with UIP/Alternative Dx

ATS/ERS 2011

Inconsistent with UIP Pattern (Any of the Seven Features)

- Upper or mid-lung predominance
- Peribronchovascular predominance
- Extensive ground glass abnormality (extent > reticular abnormality)
- Profuse micronodules (bilateral, predominantly upper lobes)
- Discrete cysts (multiple, bilateral, away from areas of honeycombing)
- Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes)
- Consolidation in bronchopulmonary segment(s)/lobe(s)



ATS/ERS 2018

Alternative Diagnosis

Findings suggestive of another diagnosis, including:

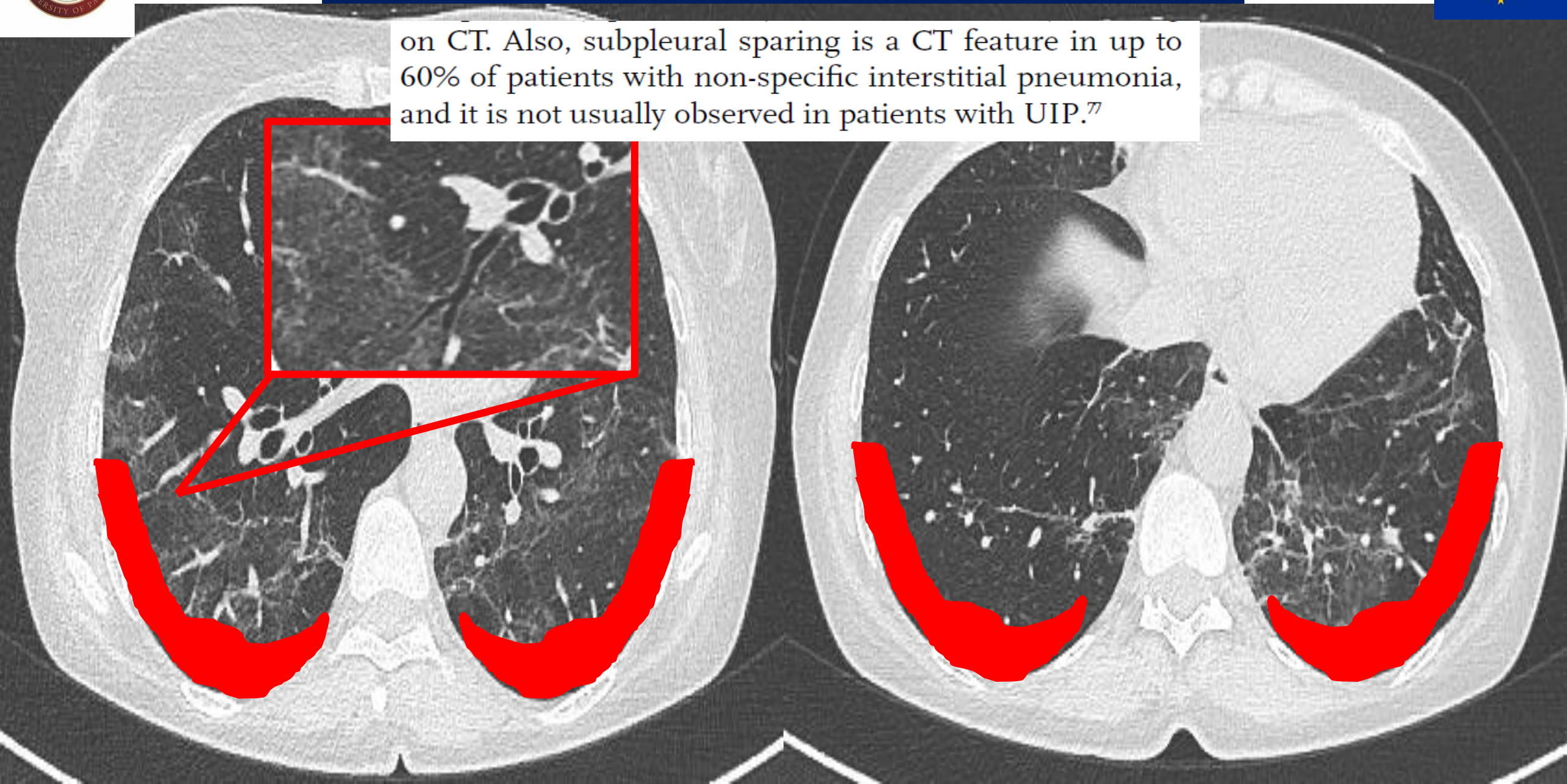
- CT features:
  - Cysts
  - Marked mosaic attenuation
  - Predominant GGO
  - Profuse micronodules
  - Centrilobular nodules
  - Nodules
  - Consolidation
- Predominant distribution:
  - Peribronchovascular
  - Perilymphatic
  - Upper or mid-lung

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

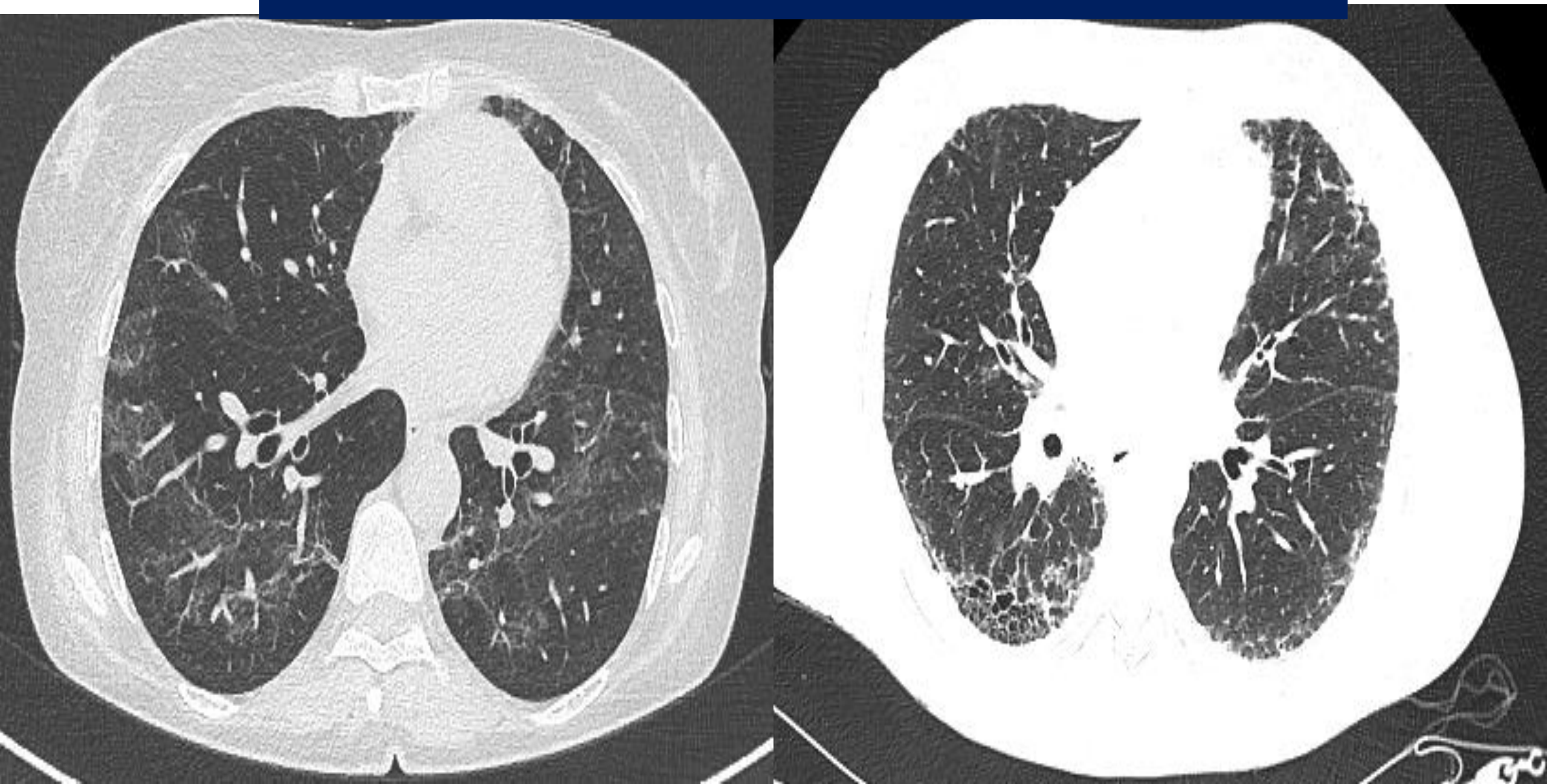
Raghu G, et al. *Am J Respir Crit Care Med*. 2018;198:e44-68.

Feature of Subpleural Sparing

on CT. Also, subpleural sparing is a CT feature in up to 60% of patients with non-specific interstitial pneumonia, and it is not usually observed in patients with UIP.[77]



Feature of Subpleural Sparing



Differential Diagnosis of GGO

Ιστορικό		Κατηγορία	Διαφορική διάγνωση
Ανοσοκατεσταλμένοι	HIV	Ευκαιριακές λοιμώξεις Άλλα	P. jirovechi, ιοί Φαρμακευτική τοξικότητα
	Υπό χημειοθεραπεία	Ευκαιριακές λοιμώξεις Οξεία νόσος πλήρωσης των κυψελίδων Άλλα	PCP, ιοί Πνευμονικό οίδημα (συχνή η υπερφόρτωση υγρών), κυψελιδική αιμορραγία Φαρμακευτική τοξικότητα*
Ανοσοεπαρκείς	Προοδευτική δύσπνοια	Διάχυτες πνευμονοπάθειες Άλλα	NSIP, (C)OP, DIP, RBILD, υποξεία/χρόνια EAA, κυψελιδική πρωτεΐνωση Αδενοκαρκίνωμα με λεπιδική ανάπτυξη
	Οξεία δύσπνοια	Οξεία νόσος πλήρωσης των κυψελίδων	Καρδιακή ανεπάρκεια, μη καρδιογενές πνευμονικό οίδημα, κυψελιδική αιμορραγία, οξεία EAA, AEP

*Η φαρμακευτική τοξικότητα συχνά υποδιαγιγνώσκεται. Μπορεί να προκαλέσει αμιγή, διάχυτη θολή ύαλο με διάφορους τρόπους: NSIP, OP, ηωσινοφιλική πνευμονία, διάχυτη κυψελιδική βλάβη (DAD), πνευμονικό οίδημα λόγω αυξημένης διαπερατότητας (π.χ. gemcitabine, all-trans retinoic

Idiopathic NSIP is not….a final diagnosis

Table 2 Suggested initial evaluation of a patient with possible NSIP

History	Physical Exam
Environmental exposures	Clubbing
Drugs	Crackles
(amiodarone, chemotherapy,	Oral ulcers
TNF inhibitors, nitrofurantoin)	Gottron papules
Antigens	Mechanics hands
(bird proteins, molds,	Sclerodactyly
thermophilic actinomyctes)	
	Laboratory[†]
Family history of ILD	Sedimentation rate or C-reactive protein
Non-pulmonary symptoms	Anti-nuclear antigen
Weight loss	Rheumatoid factor
Morning stiffness	HIV
Sicca symptoms	
Skin changes	
Photosensitivity	
Raynaud's phenomenon	
Muscle weakness	
Arthralgias	

Table 1 Differential diagnosis of idiopathic NSIP

Other ILD (e.g. UIP, RB-ILD, COP)
Toxins/drugs
Rheumatologic diseases
Human immunodeficiency virus
Hypersensitivity pneumonitis
Familial ILD
Miscellaneous[†]

Scleroderma, Sjogren, RA

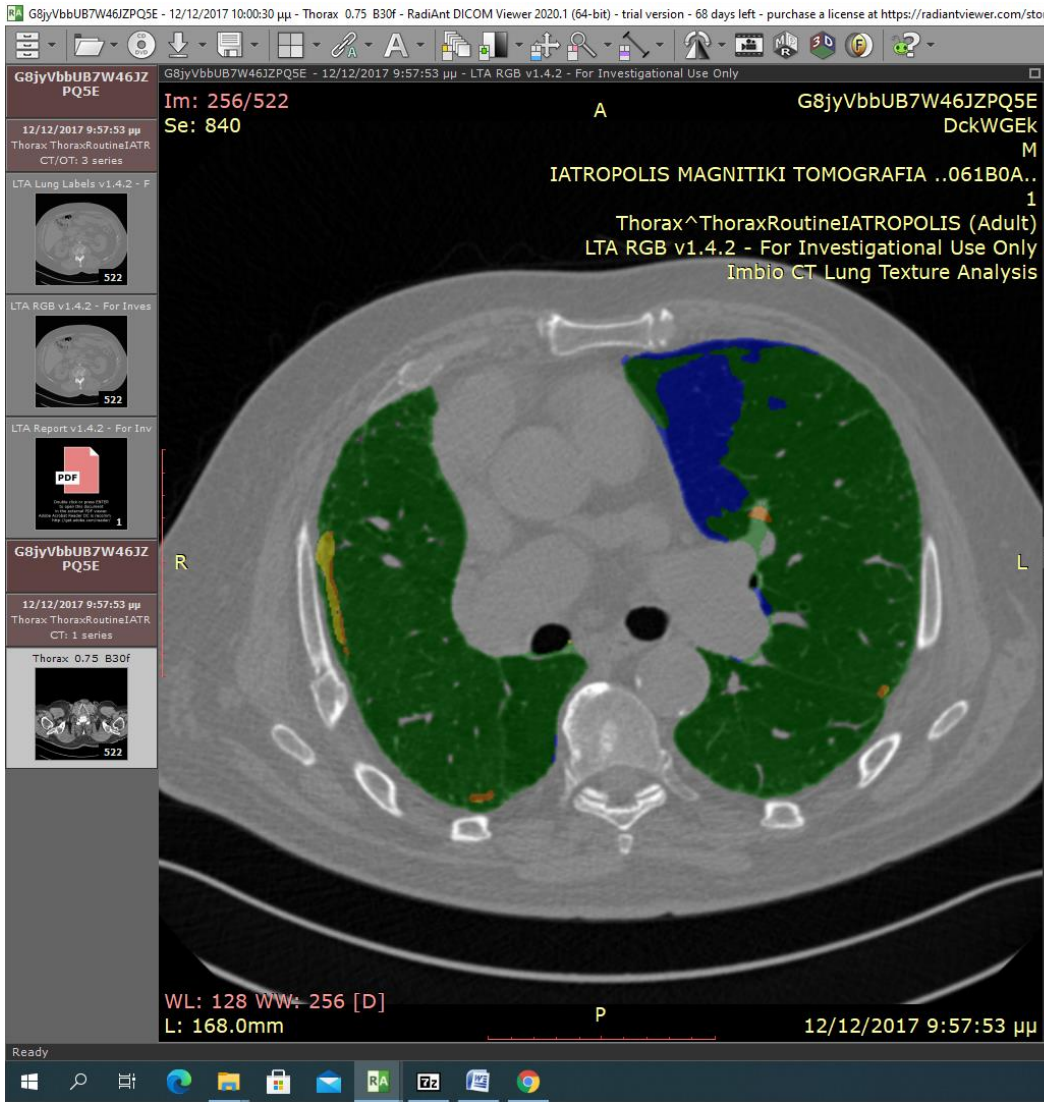
[†]Includes IgG4-related disease, bone marrow transplant associated NSIP.

COP, cryptogenic-organizing pneumonia; ILD, interstitial lung disease; NSIP, non-specific interstitial pneumonia; RB, respiratory bronchiolitis; UIP, usual interstitial pneumonia.

Regardless of the thoroughness of evaluation at initial presentation following the diagnosis of iNSIP, it is known that a subsequent diagnosis of UCTD or CTD may occur at a later date in 9–33% of patients.[30–33]

Respirology (2016) **21**, 259–268
doi: 10.1111/resp.12674

Digital Lung Textural Analysis



WARNING: This report was generated using settings that are characterized for investigational use only.

imbio

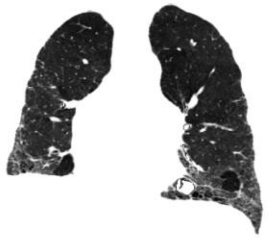
LUNG TEXTURE ANALYSIS

version 1.4.2

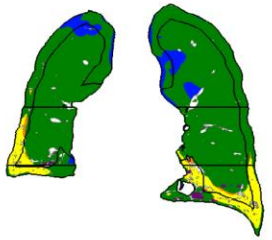
NAME:	G8jyVbbUB7W46JZPQ5E	SEX:	Male	STUDY DATE:	December 12, 2017
PATIENT ID:	DckWGEk	DOB:	Unknown	REPORT DATE:	September 24, 2020
MANUFACTURER:	SIEMENS	MODEL:	SOMATOM Definition Flash	STATION NAME:	CTAWP73210
KERNEL:	B30f	SLICE THICKNESS:	0.8	TUBE CURRENT AVG ($\frac{max}{min}$), KVP:	349 ($\frac{554}{232}$) mA, 140 kV

RESULTS

ORIGINAL CT SCAN

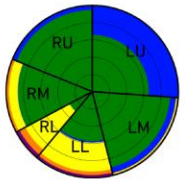


CT SCAN ANALYSIS

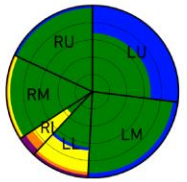


TEXTURE KEY

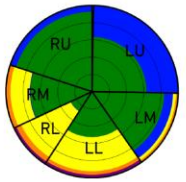
- NORMAL
- HYPERLUCENT
- GROUND GLASS
- RETICULAR
- HONEYCOMB



LUNG TOTAL
5.5 L



LUNG CORE



LUNG RIND

SUMMARY

	NORMAL	HYPERLUCENT	GROUNDGLASS	RETICULAR	HONEYCOMB
TOTAL LUNG	75 %	12 %	10 %	2 %	1 %
Left Lung (3.3 L)	72 %	17 %	9 %	1 %	1 %
Left Upper (T/C/R)	66 % / 68 % / 63 %	34 % / 32 % / 37 %	0 % / 0 % / 0 %	0 % / 0 % / 0 %	0 % / 0 % / 0 %
Left Middle (T/C/R)	91 % / 95 % / 84 %	7 % / 5 % / 10 %	1 % / 0 % / 3 %	1 % / 0 % / 3 %	0 % / 0 % / 0 %
Left Lower (T/C/R)	58 % / 65 % / 53 %	1 % / 4 % / 0 %	34 % / 25 % / 40 %	4 % / 3 % / 4 %	3 % / 3 % / 3 %
Right Lung (2.2 L)	81 %	3 %	13 %	2 %	1 %
Right Upper (T/C/R)	95 % / 97 % / 92 %	5 % / 3 % / 7 %	0 % / 0 % / 0 %	0 % / 0 % / 1 %	0 % / 0 % / 0 %
Right Middle (T/C/R)	86 % / 95 % / 72 %	0 % / 0 % / 1 %	10 % / 3 % / 22 %	3 % / 1 % / 5 %	1 % / 1 % / 0 %
Right Lower (T/C/R)	30 % / 35 % / 27 %	0 % / 0 % / 0 %	58 % / 47 % / 64 %	7 % / 10 % / 6 %	5 % / 8 % / 3 %

T = total, C = core, R = rind, T = C + R

Bronchoalveolar Lavage

Role of bronchoalveolar lavage and lung biopsy

1. Bronchoalveolar lavage cellular analysis – Only in probable/indeterminate
2. Surgical lung biopsy – 10-15% - only in probable/indeterminate
3. Transbronchial lung biopsy – not recommended
4. Transbronchial lung cryobiopsy – not recommended (only in expert centers)
5. Multidisciplinary discussion – always recommended
6. Serum biomarkers – not recommended

POINT:

Should BAL Be Routinely Performed in the Diagnostic Evaluation of Idiopathic Pulmonary Fibrosis? Yes

Athol U. Wells, MD
Maria A. Kokosi, MD
London, England

CHEST

PODCAST

[152#5 CHEST NOVEMBER 2017]

diagnostic surgical biopsy and MDD. The value of BAL is not based on characteristic BAL findings in IPF but on the exclusion of the most frequent differential diagnoses: hypersensitivity pneumonitis (HP), idiopathic nonspecific interstitial pneumonia (NSIP), and ILD associated with occult connective tissue disease (connective tissue disease-interstitial lung disease [CTD-ILD]).

There is indirect evidence that can be cited in support of routine BAL, even in "classic IPF." In a retrospective analysis of 74 patients meeting existing diagnostic criteria for IPF, six patients with a BAL lymphocytosis > 30% were found to have diagnoses of HP or NSIP on further evaluation.[18] The series is difficult to interpret, as

Ohshimo S, Bonella F, Cui A, et al. Significance of bronchoalveolar lavage for the diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2009;179:1043-1047.

Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study

Ferran Morell, Ana Villar, María-Ángeles Montero, Xavier Muñoz, Thomas V Colby, Sudhakar Pipvath, María-Jesús Cruz, Ganesh Raghu

Lancet Respir Med 2013; 1: 685–94

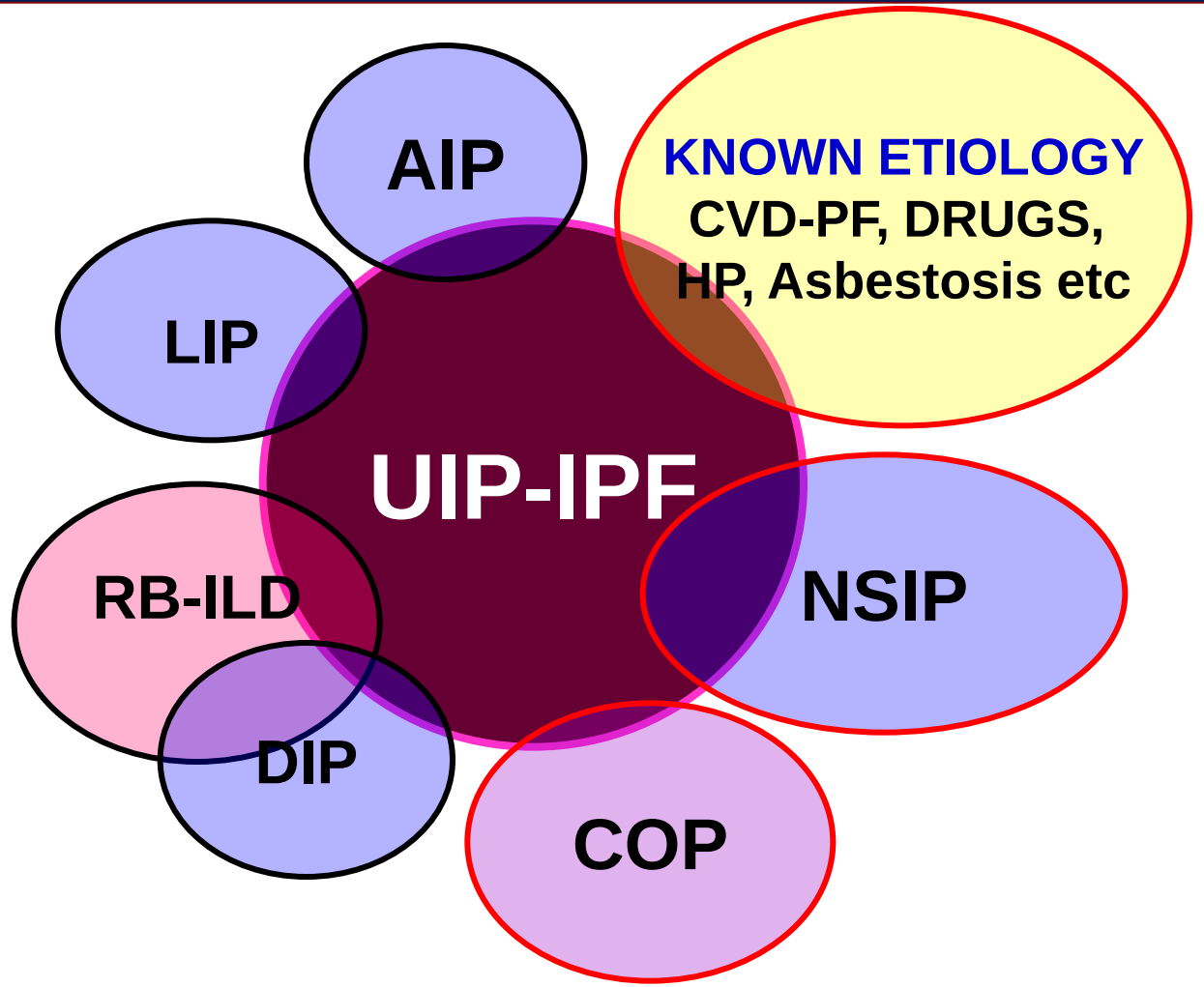
50% of cHP patients were misdiagnosed as IPF

Interpretation Almost half of patients diagnosed with IPF on the basis of 2011 criteria were subsequently diagnosed with chronic hypersensitivity pneumonitis, and most of these cases were attributed to exposure of occult avian antigens from commonly used feather bedding. Our results reflect findings in one centre with recognised expertise in chronic hypersensitivity pneumonitis, and further research and studies at other centres are warranted.

BAL provides us vital information on degree of alveolitis – treatment response

Role of lung biopsy

USUAL INTERSTITIAL PNEUMONIA AND IDIOPATHIC PULMONARY FIBROSIS



Most UIPs are "IPF", ALL UIPs ARE NOT IPF

Do we really need lung biopsy?

In-Hospital Mortality after Surgical Lung Biopsy for Interstitial Lung Disease in the United States

2000 to 2011

John P. Hutchinson, Andrew W. Fogarty, Tricia M. McKeever, and Richard B. Hubbard

Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, United Kingdom

Am J Respir Crit Care Med Vol 193, Iss 10, pp 1161–1167, May 15, 2016

Measurements and Main Results: We estimated there to be around 12,000 surgical lung biopsies performed annually for interstitial lung disease in the United States, two-thirds of which were

What This Study Adds to the Field: In a large national dataset, in-hospital mortality after elective lung biopsy was 1.7% but significantly higher in nonelective procedures. (16.0%). sex, increasing age, and comorbidity were associated with increased risk.

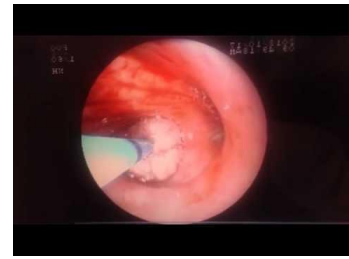
Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study

*Lauren K Troy, Christopher Grainge, Tamera J Corte, Jonathan P Williamson, Michael P Vallely, Wendy A Cooper, Annabelle Mahar, Jeffrey L Myers, Simon Lai, Ellie Mulyadi, Paul J Torzillo, Martin J Phillips, Helen E Jo, Susanne E Webster, Qi T Lin, Jessica E Rhodes, Matthew Salamonsen, Jeremy P Wrobel, Benjamin Harris, Garrick Don, Peter J C Wu, Benjamin J Ng, Christopher Oldmeadow, Ganesh Raghu, Edmund M T Lau, on behalf of the Cryobiopsy versus Open Lung biopsy in the Diagnosis of Interstitial lung disease alliance (COLDICE) Investigators**

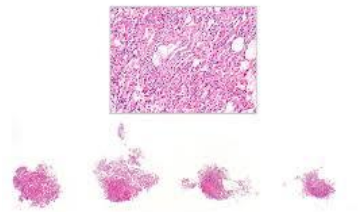
Lancet Respir Med 2019

Published Online

September 29, 2019



N=65 patients
Cryo and Surgery
K-Agreement-0.7



Interpretation High levels of agreement between TBLC and SLB for both histopathological interpretation and MDD diagnoses were shown. The TBLC MDD diagnoses made with high confidence were particularly reliable, showing excellent concordance with SLB MDD diagnoses. These data support the clinical utility of TBLC in interstitial lung

Prognostic value of transbronchial lung cryobiopsy for the multidisciplinary diagnosis of idiopathic pulmonary fibrosis: a retrospective validation study

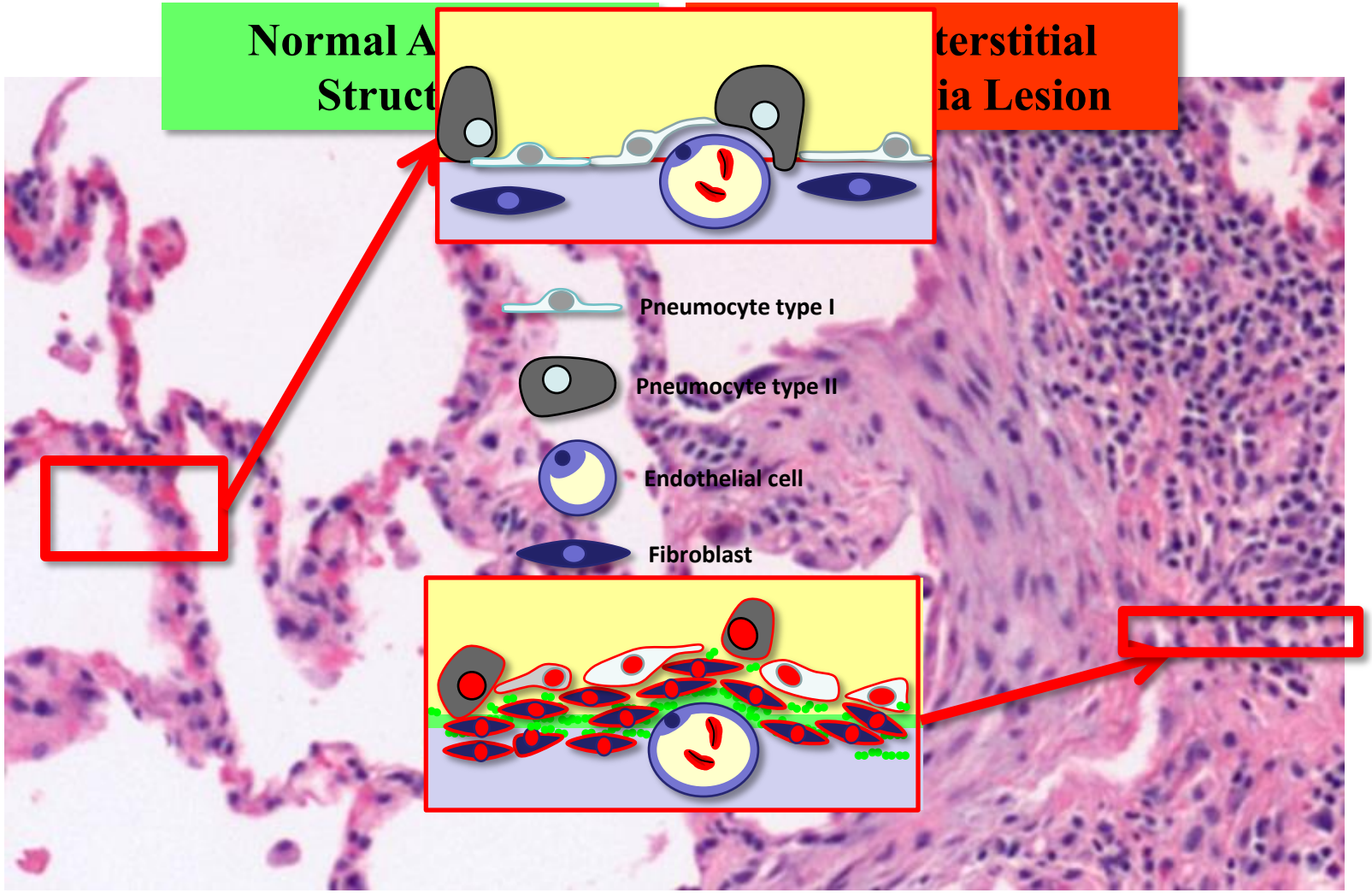
Lancet Respir Med 2020; 8: 786–94

Sara Tomassetti, Claudia Ravaglia, Athol U Wells, Alberto Cavazza, Thomas V Colby, Giulio Rossi, Brett Ley, Jay H Ryu, Silvia Puglisi, Antonella Arcadu, Martina Marchi, Fabio Sultani, Sabrina Martinello, Luca Donati, Carlo Gurioli, Christian Gurioli, Paola Tantalocco, Jurgen Hetzel, Alessandra Dubini, Sara Piciucchi, Catherine Klersy, Federico Lavorini, Venerino Poletti*

N=426 patients
Non-UIP cases
IPF 68% 5-yr survival
Non-IPF 93% 5-yr survival

Interpretation TBLC makes an important diagnostic contribution in interstitial lung disease, on the basis of the prognostic distinction between idiopathic pulmonary fibrosis and other interstitial lung diseases when TBLC findings are included in multidisciplinary diagnosis.

Fibrosis – Heterogeneous-Subpleural-FF



AJRCCM: 100-YEAR ANNIVERSARY
Progress in Interstitial Lung Disease American Journal of Respiratory and Critical Care Medicine Volume 195 Number 9 | May 1 2017

Rationale behind the change
94% of HRCT possible cases had UIP histology pattern

Diagnosis of idiopathic pulmonary fibrosis with high-resolution CT in patients with little or no radiological evidence of honeycombing: secondary analysis of a randomised, controlled trial

Lancet Respir Med 2014; 2: 277–84

Ganesh Raghu, David Lynch, J David Godwin, Richard Webb, Thomas V Colby, Kevin O Leslie, Juergen Behr, Kevin K Brown, James J Egan, Kevin R Flaherty, Fernando J Martinez, Athol U Wells, Lixin Shao, Huafeng Zhou, Patricia S Pedersen, Rohit Sood, A Bruce Montgomery, Thomas G O'Riordan

Interpretation In the appropriate clinical setting, for patients with possible usual interstitial pneumonia pattern on high resolution CT, surgical lung biopsy sampling might not be necessary to reach a diagnosis of idiopathic pulmonary fibrosis if high-resolution CT scans are assessed by experts at regional sites familiar with patterns of usual interstitial pneumonia and management of idiopathic interstitial pneumonia.

Pulmonary hypertension
A medical condition associated with an elevated pressure (hypertension) in the pulmonary arteries.

Cricoarytenoiditis
Inflammation of the cricoarytenoid joint (a synovial joint located between the arytenoid and cricoid cartilages in the neck), which can occur in rheumatoid arthritis.

Constrictive bronchiolitis
A histopathological term for the bronchiolar (small airway) disorder characterized by fibroproliferative thickening of the bronchiolar walls causing narrowing of the bronchioles.

Follicular bronchiolitis
A bronchiolar disorder associated with bronchiolar narrowing as a result of inflammation and lymphoid hyperplasia of bronchus-associated lymphoid tissue.

Obliterative bronchiolitis
The clinical term used to describe constrictive small-airway bronchiolar diseases that can occur in a variety of clinical contexts, including rheumatoid arthritis; the corresponding histopathological entity to obliterative bronchiolitis is constrictive bronchiolitis.

Pleural effusion
Excessive fluid build-up that happens between visceral and parietal pleura.

Usual interstitial pneumonia
A form of interstitial lung disease associated with a characteristic histopathological pattern on lung biopsy and radiological pattern on chest CT.

Non-specific interstitial pneumonia
A distinct subgroup of interstitial lung disease with characteristic histopathological findings in lung tissue.

Clubbing
A deformity of the fingers and/or toes associated with enlargement of the fingertips and increased curvature of the nails that is associated with a number of lung and other disorders.

RA-ILD

25-60% of RA pts

EUROPEAN RESPIRATORY UPDATE
RHEUMATOID ARTHRITIS AND LUNG DISEASE

Rheumatoid arthritis-associated lung disease

Megan Shaw[1], Bridget F. Collins[2], Lawrence A. Ho[2] and Ganesh Raghu[2]

Eur Respir Rev 2015; 24: 1–16 |

ILD patterns in autoimmune diseases

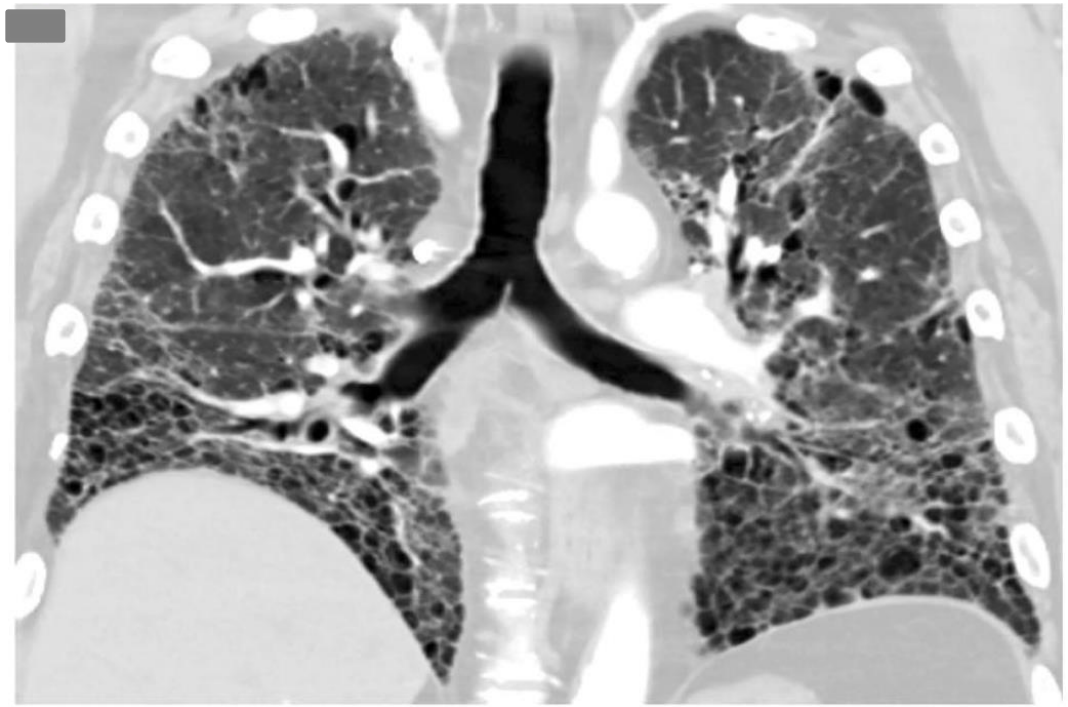
TYPE	SSc	RA	PM/DMM	SLE	MCTD	Sjögren's
UIP	++	++	++	++	+	-
NSIP	+++ 90%	+	+	+	++	++ 25%
OP	+	+	+++ 50%	+	_	-
DAD	+	+	++	++	_	_
DIP	+	+	+	+	_	+/-
LIP	_	_	_	_	_	+++ 20%
DAH / CAPILARITIS	+	+	+	+++	_	_
ILD	+++	++	+++	+	++	+

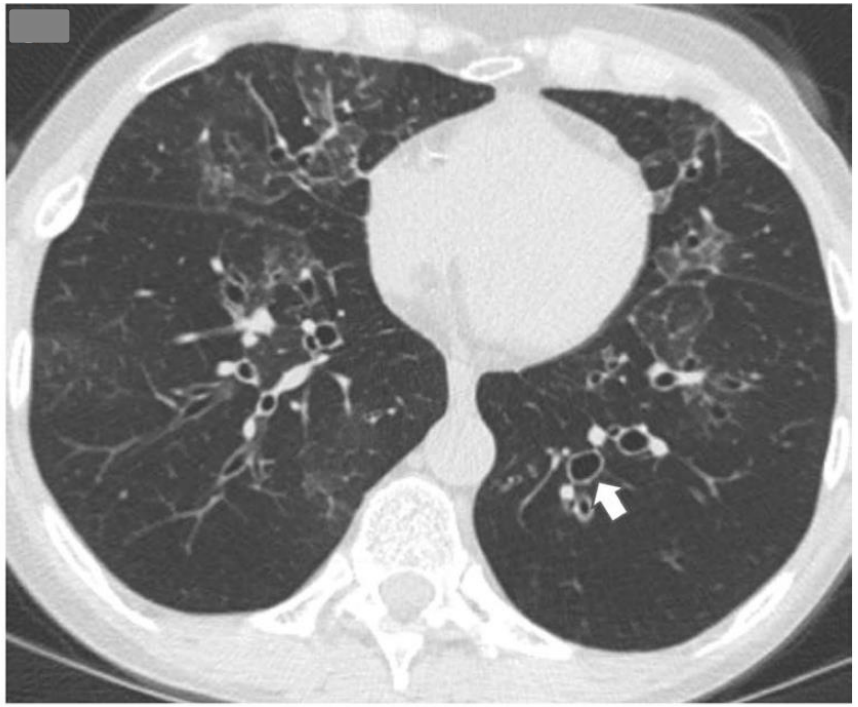
Slide courtesy of D.Bouros

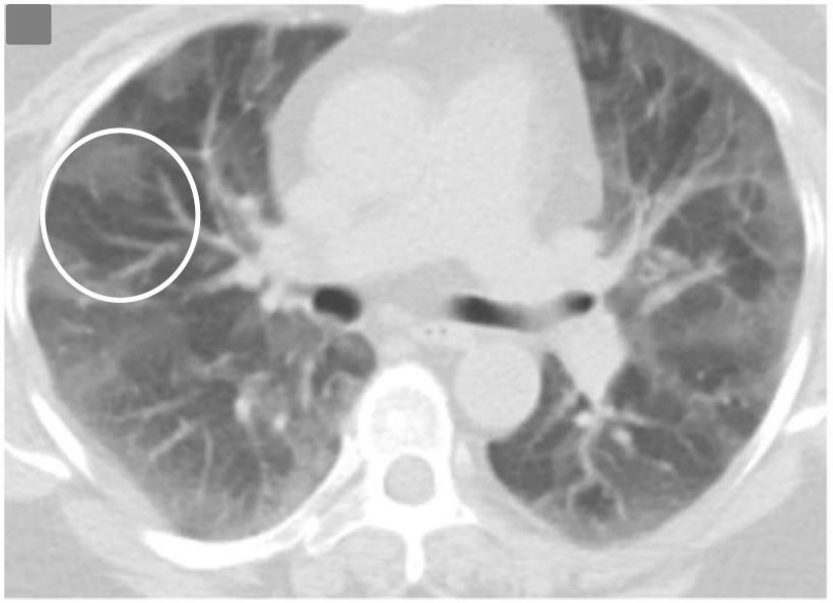
Airway involvement in autoimmune diseases

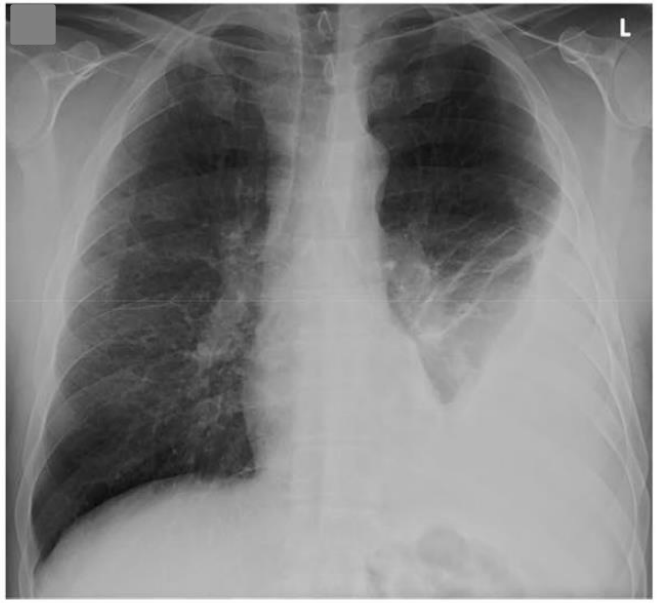
	Rheumatoid arthritis	SLE	DM/PM	Sjögren´s
Bronchitis	++			+
Bronchiectasis	++			±
Follicular bronchiolitis	±			±
Oblit. bronchiolitis	+	±	±	
BOOP/OP	++	±	++	±

Shaw et al. Eur Respir Rev 2015





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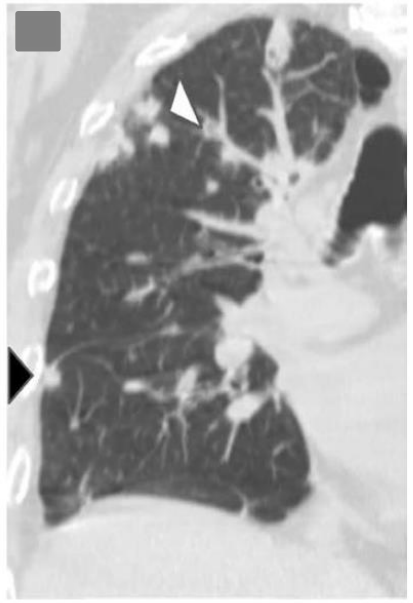


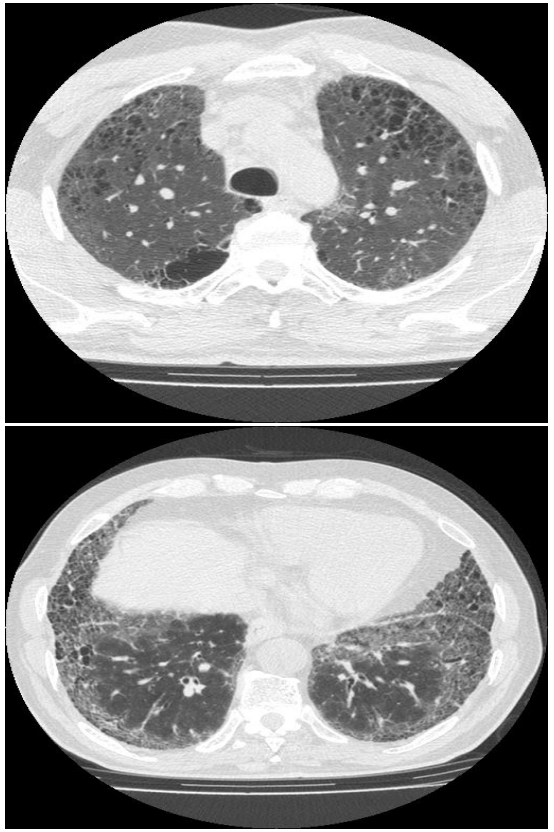
CPFE patterns in autoimmune diseases

Combined Pulmonary Fibrosis and Emphysema Syndrome in Connective Tissue Disease

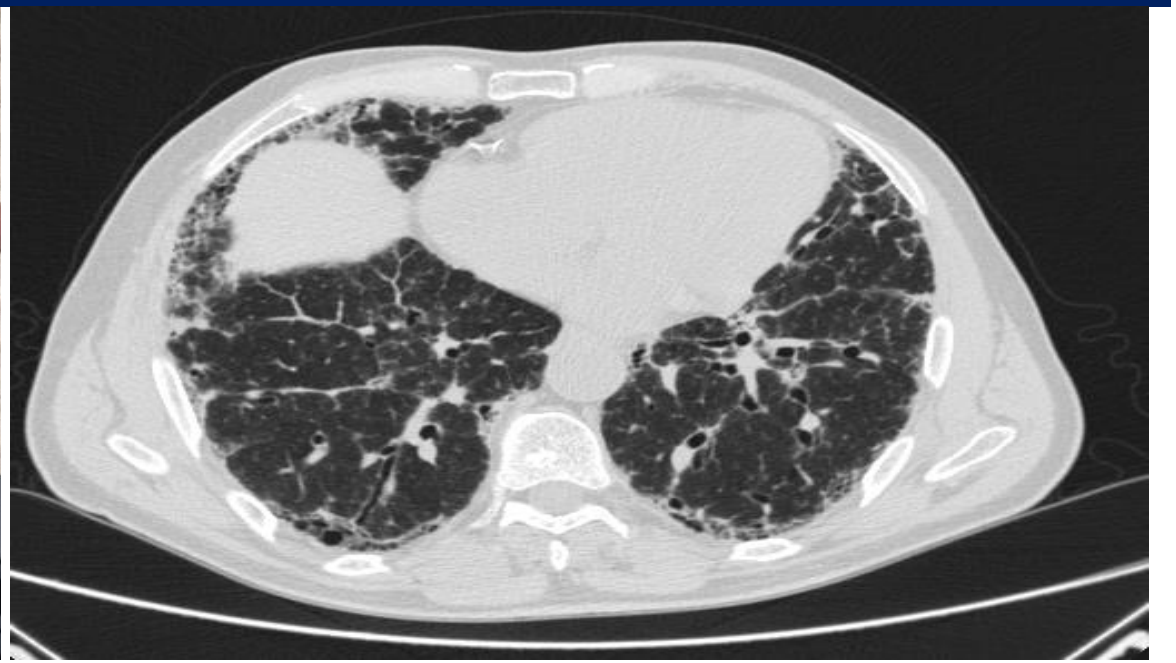
Vincent Cottin,[1] Hilario Nunes,[2] Luc Mouthon,[3] Delphine Gamondes,[4] Romain Lazor,[5] Eric Hachulla,[6] Didier Revel,[4] Dominique Valeyre,[2] Jean-François Cordier,[1] and the Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires

ARTHRITIS & RHEUMATISM
Vol. 63, No. 1, January 2011, pp 295–304
DOI 10.1002/art.30077

CPFE and CTDs – 10%
Younger male (57yrs) , smokers
More common in RA and SSc
Lower emphysema score
Preserved lung volumes- ⇓DLCO



72-yr old, female, non-smoker, dry cough+DOE (mMRC II/IV) the past 9 months –
Morning stiffness, arthralgia past 3 years
Coronary Heart disease, arterial hypertension, hyperlipidemia
Velcro type crackles +



BAL: 28%L,N:13% (-) AFB, (-) fungi,
FVC: 68%, TIF: 73, TLC: 63%, DLCO: 35% (used to be 56% 12 mo ago) under MTX-PZN)
RVSP: 35 mmHg, Serology: ANA: 1/160, RF: 165U/ml, anti-CCPs: 18 (3x)

Definition of Progressive Pulmonary Fibrosis

The presence of <u>at least two</u> of the following three criteria:

1. No alternative explanation for the worsening of respiratory **symptoms**
2. **Physiological** evidence of disease progression, *(Absolute decline in the FVC ≥5% pred OR DLco (corrected for Hb) ≥10% within one year of FU).*
3. **Radiological** evidence of disease progression

Courtesy of Professor Bouros

Lumping rather than splitting

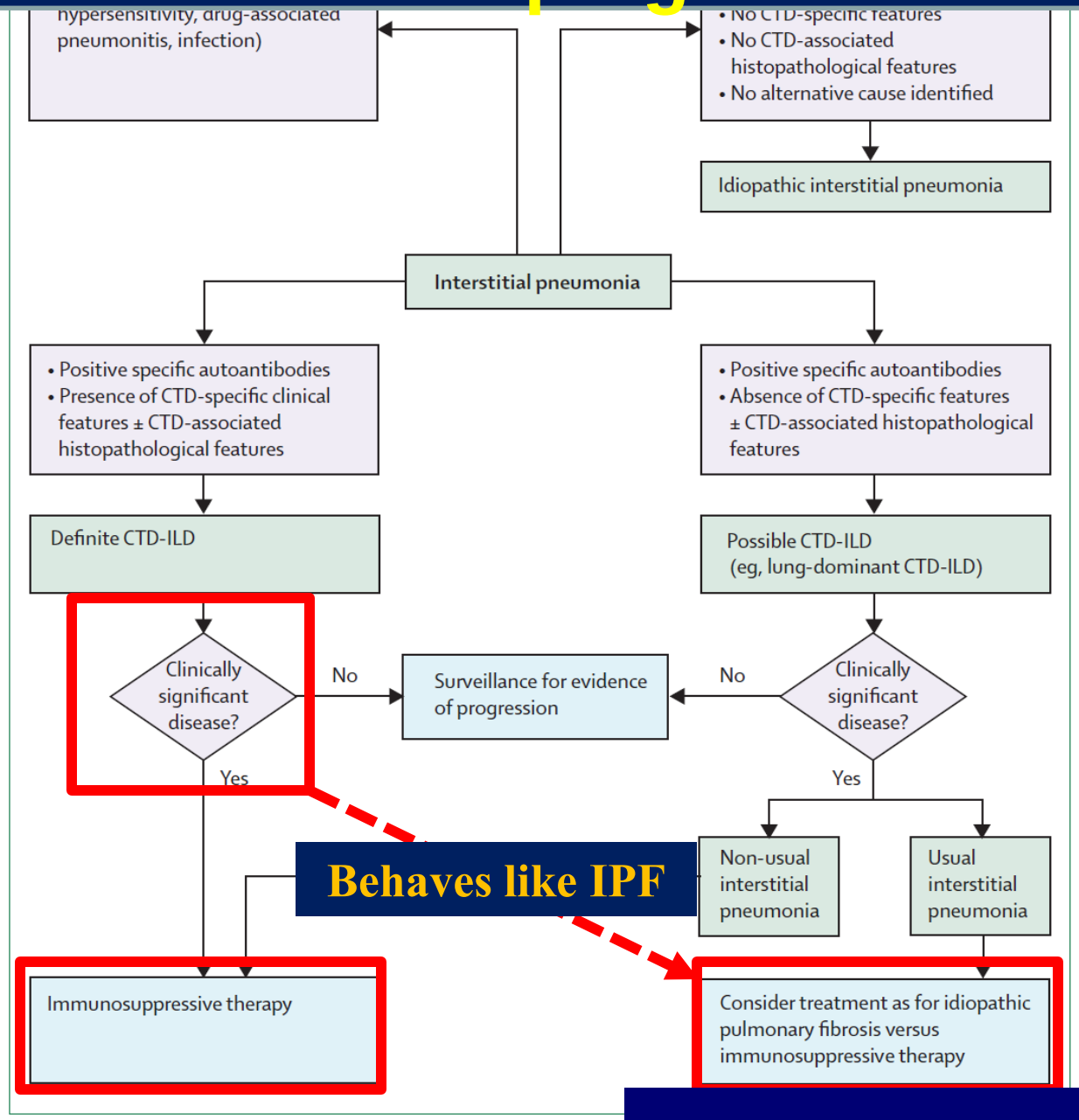
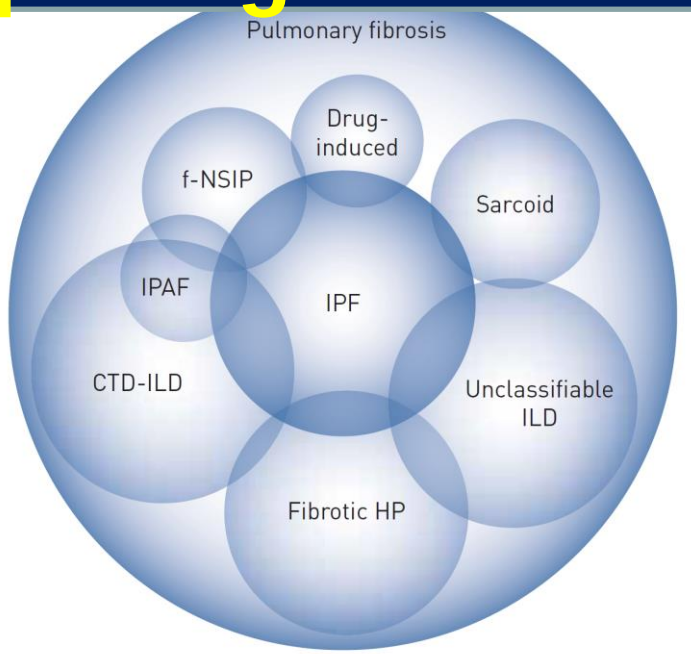


Figure 1: Management schema for interstitial pneumonia in CTD

Fischer et al. Lancet 2012



RA-ILD. Given the shared genetic background between idiopathic pulmonary fibrosis and RA-ILD in general and RA-ILD with a UIP or possible UIP pattern in particular, we would propose that drugs that are known to be effective in treating patients with idiopathic pulmonary fibrosis be evaluated in the treatment of RA-ILD.[41,42]

This article was published on October 20, 2018, at NEJM.org.

Cyclo for induction – MMF for maintenance

Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial

Donald P Tashkin, Michael D Roth, Philip J Clements, Daniel E Furst, Dinesh Khanna, Eric C Kleerup, Jonathan Goldin, Edgar Arriola, Elizabeth R Volkmann, Suzanne Kafaja, Richard Silver, Virginia Steen, Charlie Strange, Robert Wise, Fredrick Wigley, Maureen Mayes, David J Riley, Sabiha Hussain, Shervin Assassi, Vivien M Hsu, Bela Patel, Kristine Phillips, Fernando Martinez, Jeffrey Golden, M Kari Connolly, John Varga, Jane Dematte, Monique E Hinchcliff, Aryeh Fischer, Jeffrey Swigris, Richard Meehan, Arthur Theodore, Robert Simms, Suncica Volkov, Dean E Schraufnagel, Mary Beth Scholand, Tracy Frech, Jerry A Molitor, Kristin Highland, Charles A Read, Marvin J Fritzler, Grace Hyun J Kim, Chi-Hong Tseng, Robert M Elashoff, for the Scleroderma Lung Study II Investigators*

Lancet Respir Med 2016

Published Online
July 25, 2016

These findings support the potential clinical effectiveness of both cyclophosphamide and mycophenolate mofetil for progressive scleroderma-related interstitial lung disease, and the present preference for mycophenolate mofetil because of its better tolerability and toxicity profile

No RCTs for RTX for CTD-ILD

Saunders *et al. Trials* (2017) 18:275
DOI 10.1186/s13063-017-2016-2

Trials

STUDY PROTOCOL Open Access

Rituximab versus cyclophosphamide for the treatment of connective tissue disease-associated interstitial lung disease (RECITAL): study protocol for a randomised controlled trial

Peter Saunders[1], Vicky Tsipouri[1], Gregory J. Keir[2], Deborah Ashby[3], Marcus D. Flather[4], Helen Parfrey[5], Daphne Babalis[3], Elisabetta A. Renzoni[1,6], Christopher P. Denton[7], Athol U. Wells[1,6] and Toby M. Maher[1,6*]

Seminars in Arthritis and Rheumatism 48 (2018) 22–27

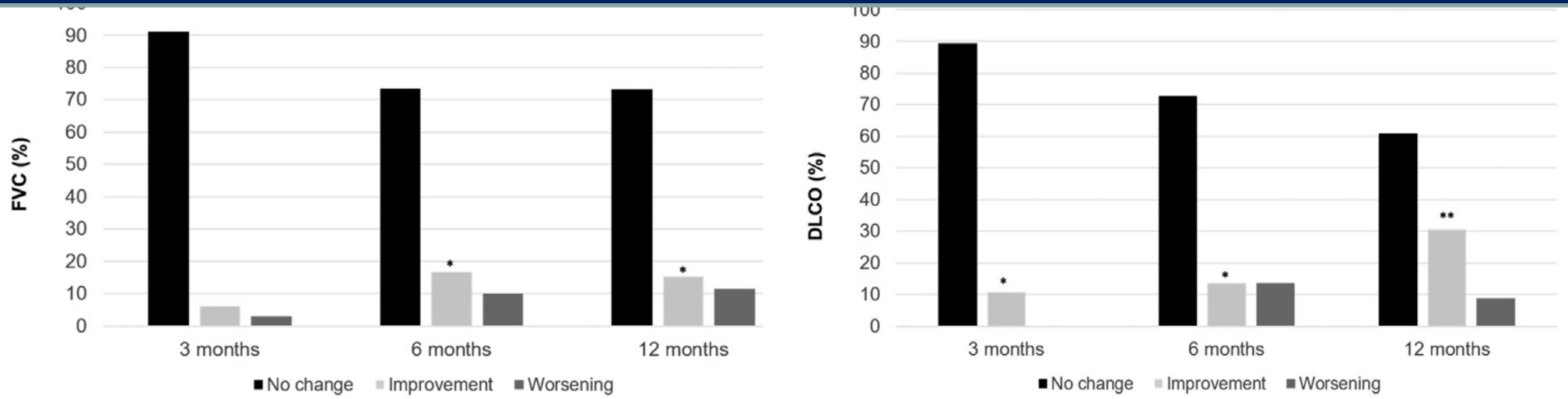
Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Abatacept in patients with rheumatoid arthritis and interstitial lung disease: A national multicenter study of 63 patients

Functional stabilization with abatacept



The NEW ENGLAND JOURNAL of MEDICINE

This article was published on September 29, 2019, at NEJM.org.

DOI: 10.1056/NEJMoa1908681

ORIGINAL ARTICLE

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

INBUILD Trial

- **Inclusion criteria**

✓ **Fibrosing ILD- >10% extent of Fibrosis in HRCT**

✓ **FVC decline >10%**

✓ **FVC decline 5-10% + worsening of symptoms**

✓ **FVC<45%, DLCO 30 – 80%**

✓ **No concomitant RX with MMF, RTX, AZA, CYCLO**

- **35% screening failure**
- **663 patients enrolled**

The NEW ENGLAND JOURNAL of MEDICINE

This article was published on September 29, 2019, at NEJM.org.

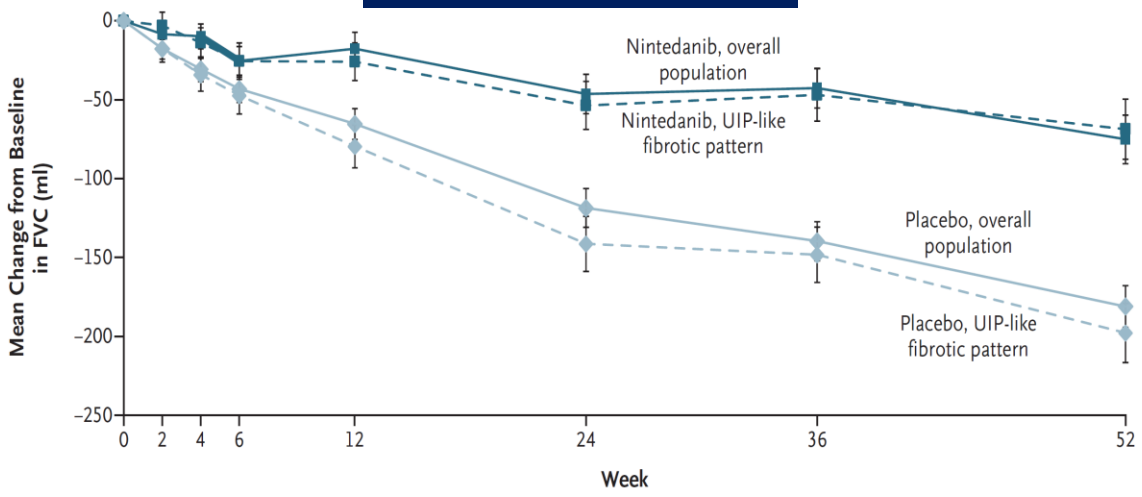
DOI: 10.1056/NEJMoa1908681

ORIGINAL ARTICLE

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

INBUILD Trial

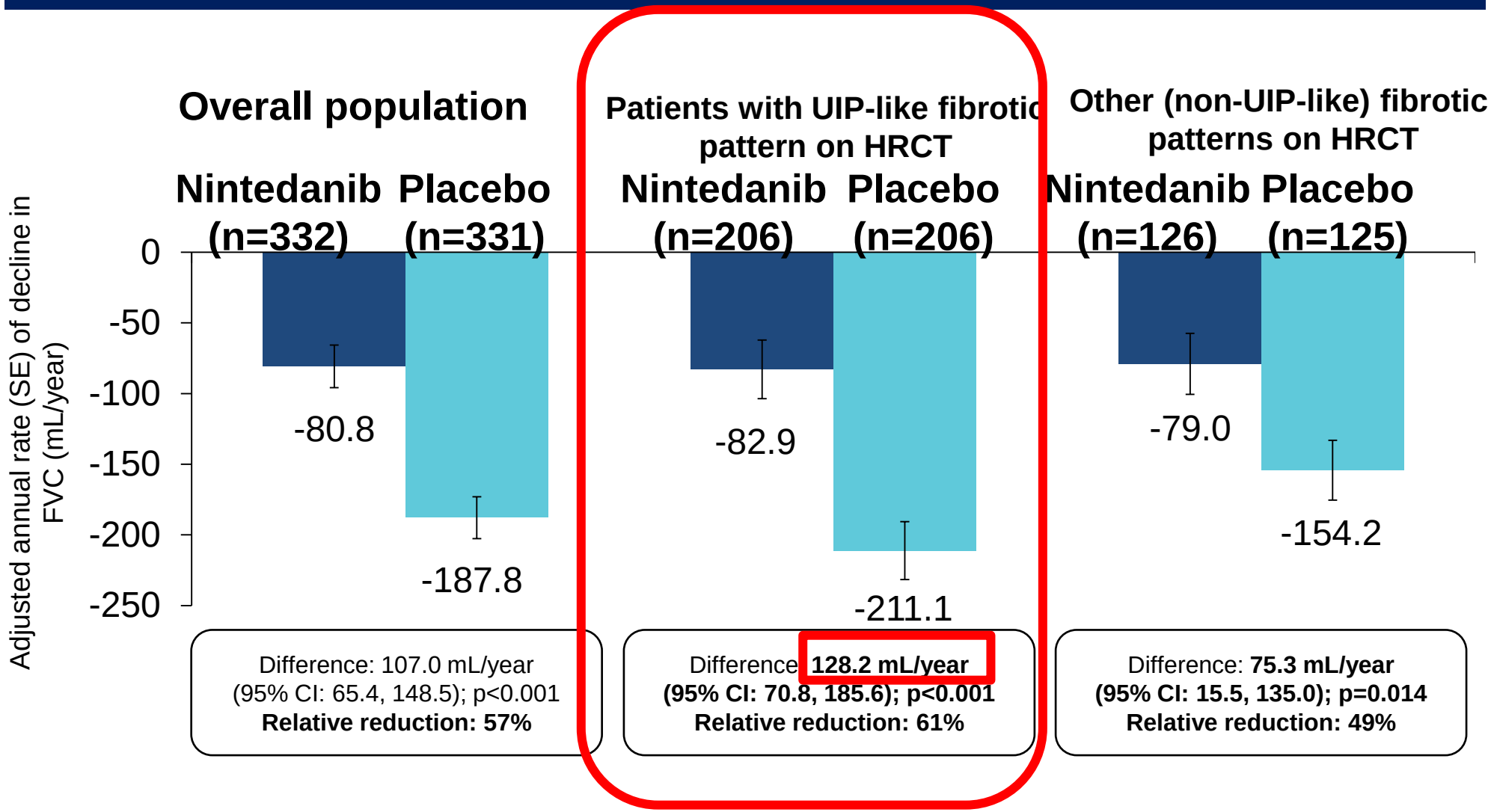
Benefit of 107 ml



RESULTS

A total of 663 patients were treated. In the overall population, the adjusted rate of decline in the FVC was −80.8 ml per year with nintedanib and −187.8 ml per year with placebo, for a between-group difference of 107.0 ml per year (95% confidence interval [CI], 65.4 to 148.5; P<0.001). In patients with a UIP-like fibrotic pattern, the adjusted rate of decline in the FVC was −82.9 ml per year with nintedanib and −211.1 ml per year with placebo, for a difference of 128.2 ml (95% CI, 70.8 to 185.6; P<0.001). Diarrhea was the most common adverse event, as reported in 66.9% and 23.9% of patients treated with nintedanib and placebo, respectively. Abnormalities on liver-function testing were more common in the nintedanib group than in the placebo group.

INBUILD: Annual rate of decline in FVC (mL/year) over 52 weeks in all patients HRCT subgroups



INBUILD: Clinical ILD diagnoses in patients with UIP-like fibrotic pattern on HRCT

	Nintedanib (n=206)	Placebo (n=206)
Hypersensitivity pneumonitis	44 (21.4)	46 (22.3)
Autoimmune ILDs	62 (30.1)	65 (31.6)
Rheumatoid arthritis-associated ILD	36 (17.5)	41 (19.9)
Systemic sclerosis-associated ILD	17 (8.3)	7 (3.4)
Mixed connective tissue disease-associated ILD	4 (1.9)	8 (3.9)
Other autoimmune ILDs	5 (2.4)	9 (4.4)
Idiopathic non-specific interstitial pneumonia	34 (16.5)	37 (18.0)
Unclassifiable IIP	43 (20.9)	34 (16.5)
Other fibrosing ILDs*	23 (11.2)	24 (11.7)

Data are n (%) of patients. ***In the nintedanib and placebo groups, respectively, 14 (6.8%) patients and 14 (6.8%) patients had exposure-related ILDs and 1 (0.5%) and 2 (1.0%) patients had sarcoidosis. IIP, idiopathic interstitial pneumonia.**

Effects of nintedanib in patients with progressive fibrosing RA-ILD in the INBUILD® trial[1]

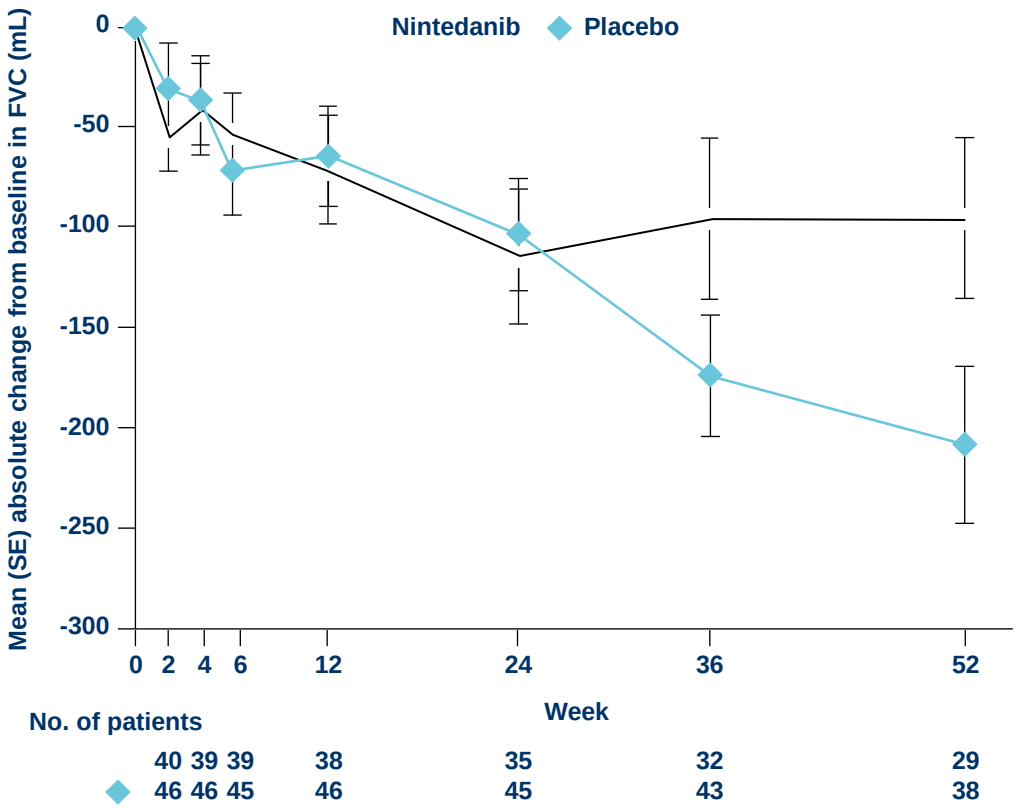
(Kelly C *et al*)

- **INBUILD®[2] enrolled patients with chronic fibrosing ILDs with a progressive phenotype other than IPF (N=663); patients taking stable doses of medications to treat autoimmune rheumatic diseases were eligible to participate This *post-hoc* analysis assessed the efficacy and safety of nintedanib over 52 weeks in the subset of patients with RA-ILD (n=89) in the INBUILD®[2] trial.**
  - **Baseline characteristics were generally similar between the treatment groups:**

Baseline characteristic	Nintedanib (n=42)	Placebo (n=47)
Mean age (years)	66.8	67.0
Male, %	59.5	61.7
Mean time since RA diagnosis (years)	10.1	9.8
Former or current smoker, %	66.7	61.7
bDMARDs, %	26.2	17.0
Non-biologic DMARDs, %	52.4	55.3
Glucocorticoids, %*	76.2	70.2

- **Nintedanib reduced the rate of decline in FVC (mL/year) over 52 weeks in patients with RA-ILD (Figure 1; mean difference 116.7 mL [95% CI: 7.4, 226.1]; *P*=0.037); consistent with the effect observed in the overall INBUILD® trial population[2] (107.0 mL [95% CI: 65.4, 148.5]; *P*<0.001)**
- **Outcomes were further analyzed in subgroups of patients by high sensitivity CRP at baseline (<1 vs ≥1 mg/L and <3 vs ≥3 mg/L) and DMARD and/or glucocorticoid use at baseline (yes/no)**
  - **The effect of nintedanib on the rate of decline in FVC (mL/year) over 52 weeks was consistent between subgroups (treatment x subgroup x time interaction *P*>0.05 for all); however, interpretation of the subgroup analyses was limited by the small number of patients**
- **Patients with RA-ILD treated with nintedanib had more AEs than the placebo-treated group (primarily GI disorders); this safety profile was consistent with the overall INBUILD® population[2]**

Figure 1. Absolute change from baseline in FVC (mL) at week 52 in patients with RA-ILD in the INBUILD® trial[1]



Conclusion: Nintedanib slowed the rate of decline in FVC in patients with progressive fibrosing RA-ILD, with AEs that were manageable for most patients. The efficacy and safety of nintedanib in subjects with RA-ILD were consistent with those observed in the overall INBUILD® trial population

≥20 mg/day prednisone or equivalent

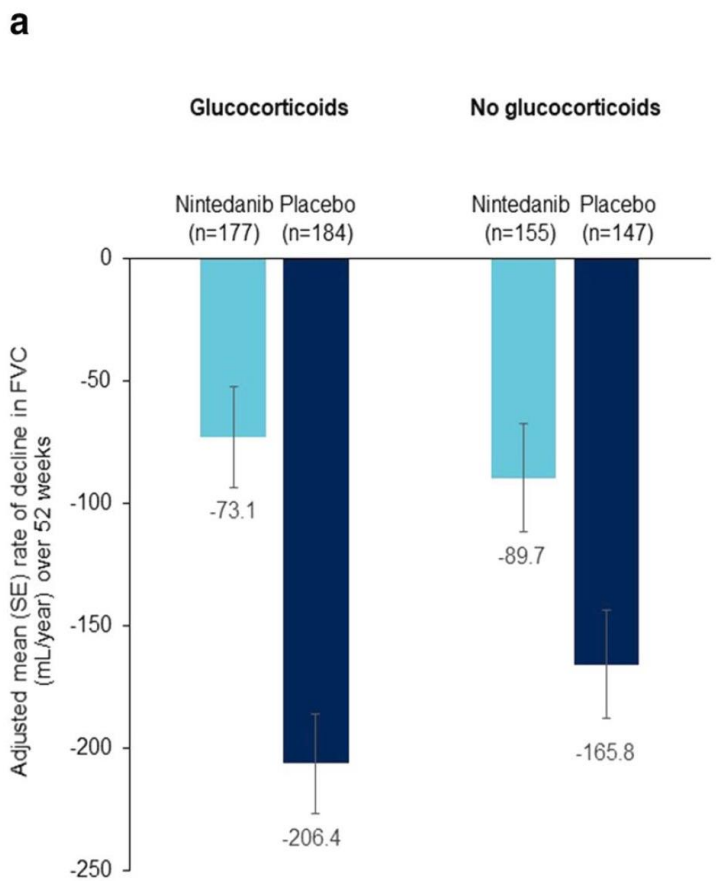
1. Kelly C *et al*. EULAR European Congress of Rheumatology 2021. E-congress, June 2–5, 2021: OP0124; 2 Flaherty KR *et al. N Engl J Med* 2019;381:1718–27

RESEARCH Open Access

Nintedanib and immunomodulatory therapies in progressive fibrosing interstitial lung diseases

Vincent Cottin[1*], Luca Richeldi[2], Ivan Rosas[3], Maria Otaola[4], Jin Woo Song[5], Sara Tomassetti[6], Marlies Wijsenbeek[7], Manuela Schmitz[8], Carl Coeck[9], Susanne Stowasser[10], Rozsa Schlenker-Herceg[11] and Martin Kolb[12] on behalf of the INBUILD Trial Investigators

Cottin *et al. Respir Res* (2021) 22:84
https://doi.org/10.1186/s12931-021-01668-1



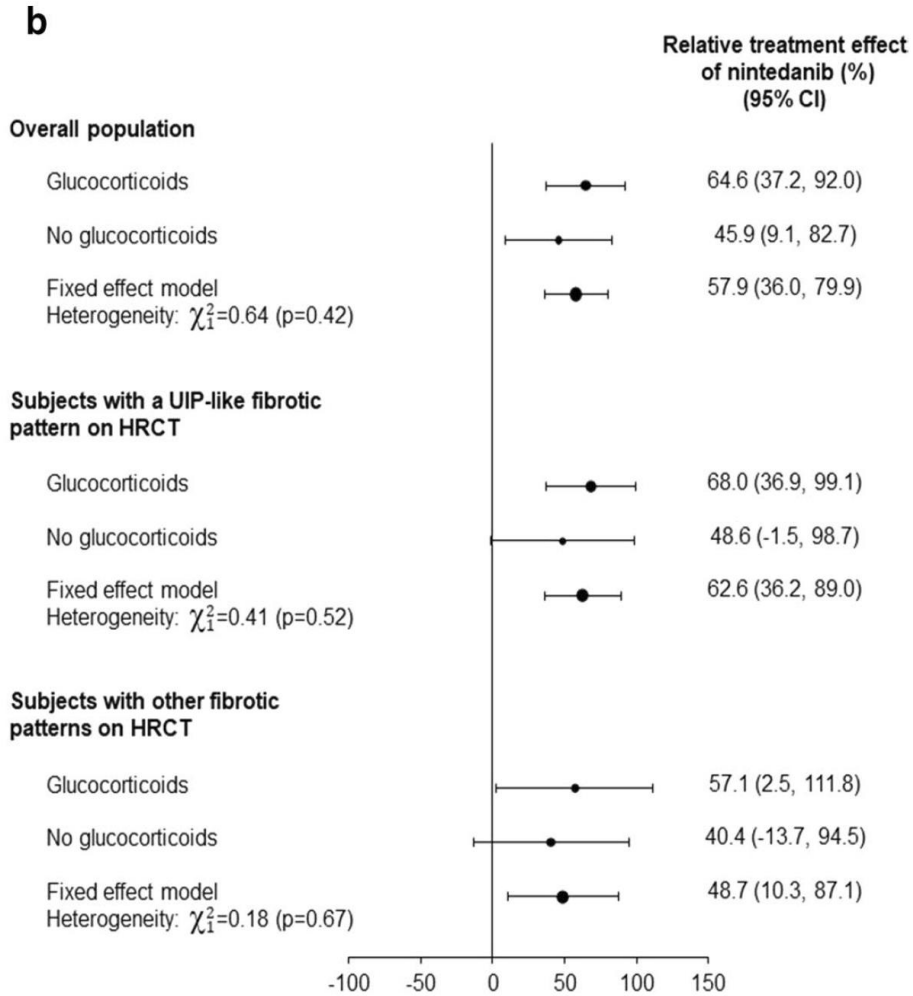
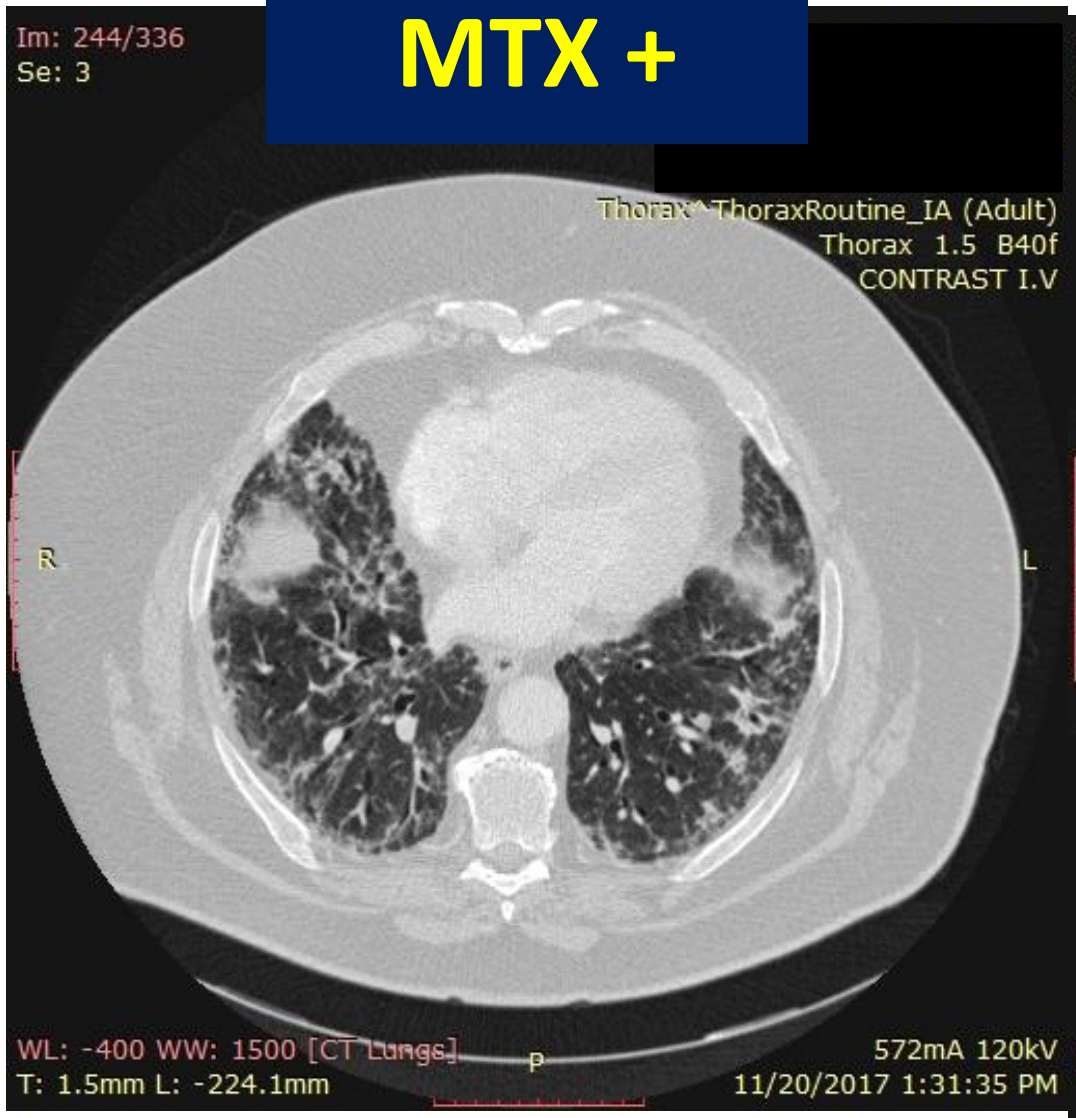


Table 2 Restricted or prohibited immunomodulatory or antifibrotic therapies taken at baseline, during treatment with trial drug and/or following discontinuation of trial drug over 52 weeks by customized drug grouping or preferred name

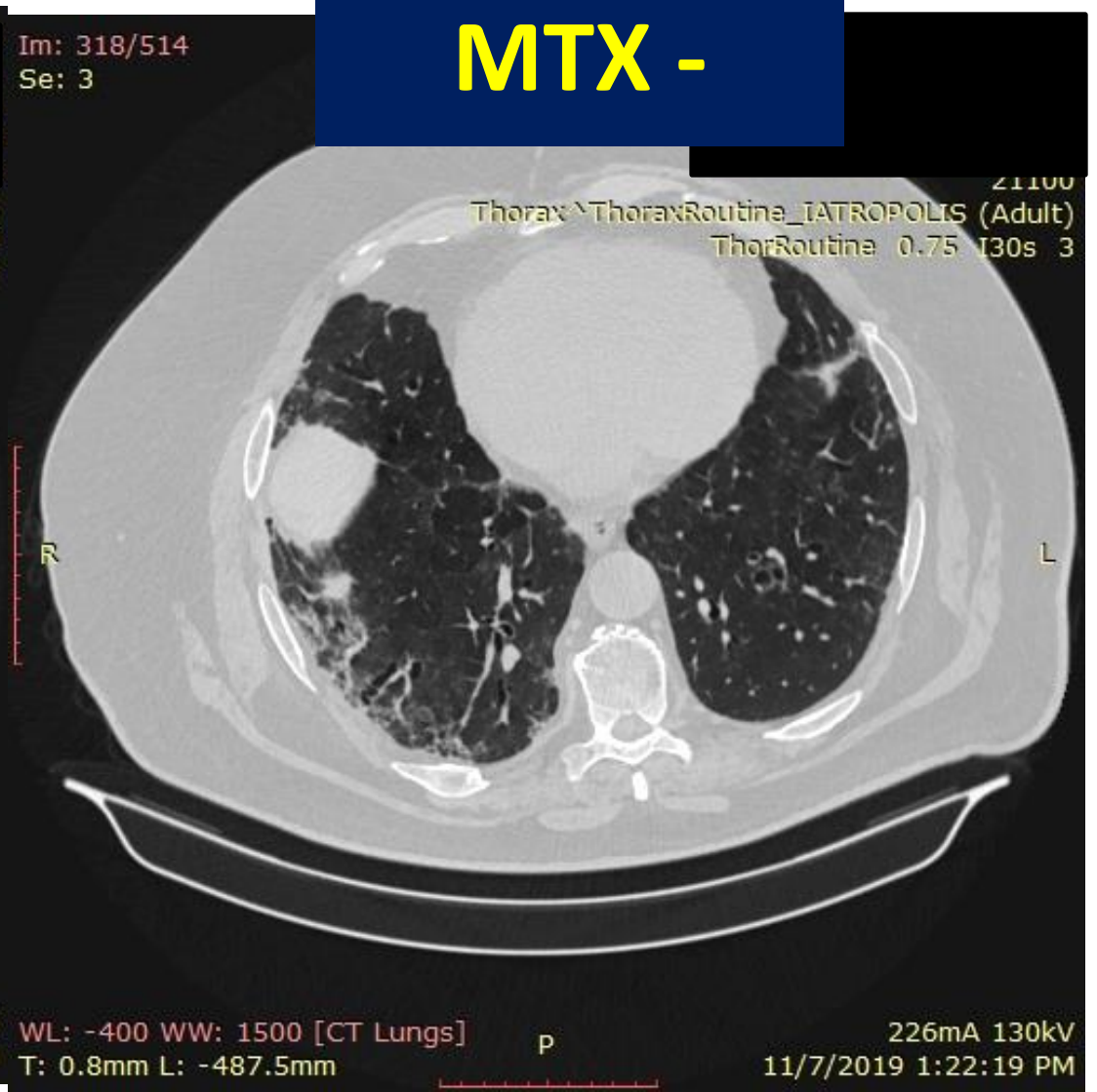
	Nintedanib (n = 332)	Placebo (n = 331)
≥ 1 restricted or prohibited therapy	53 (16.0)	91 (27.5)
Glucocorticoids[a]	44 (13.3)	72 (21.8)
Mycophenolate mofetil	9 (2.7)	9 (2.7)
Azathioprine	4 (1.2)	6 (1.8)
Tacrolimus	4 (1.2)	5 (1.5)
Ciclosporin	1 (0.3)	6 (1.8)
Rituximab	3 (0.9)	2 (0.6)
Cyclophosphamide	0 (0.0)	3 (0.9)
Nintedanib[a]	0 (0.0)	3 (0.9)
Pirfenidone[a]	2 (0.6)	1 (0.3)

74yrs-male-ExSM-RA-MTX-3 yrs-DOE-6mo
650 eos – 35% L-BAL

MTX +

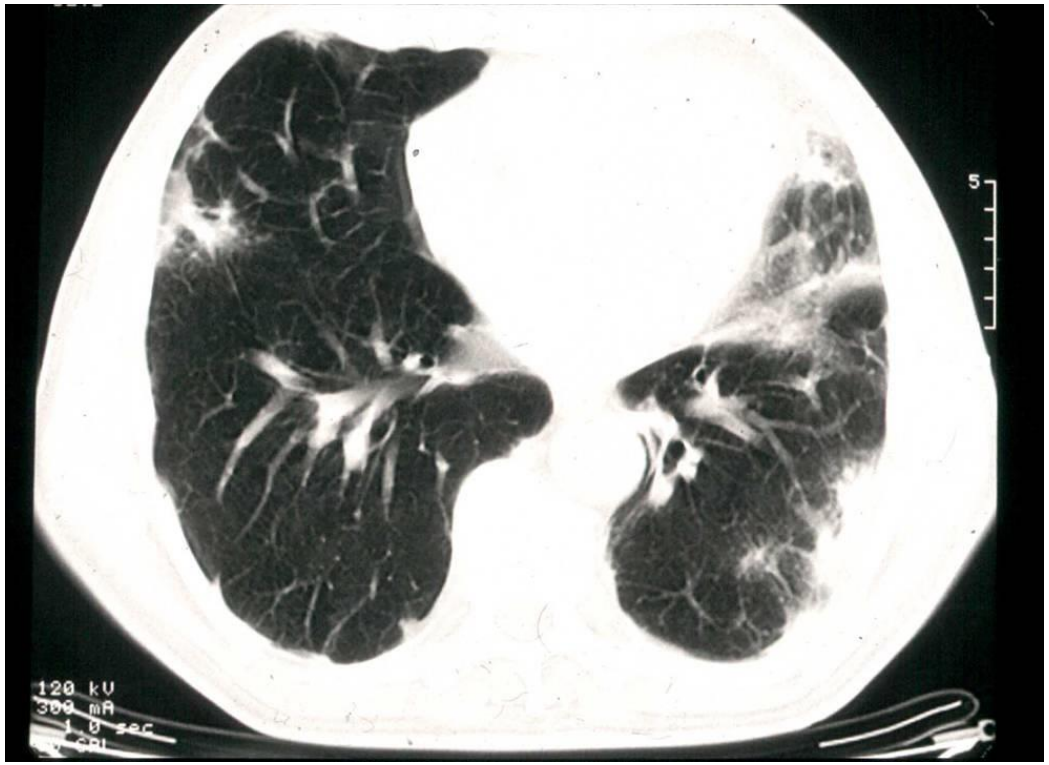


MTX -



Methotrexate Pneumonitis

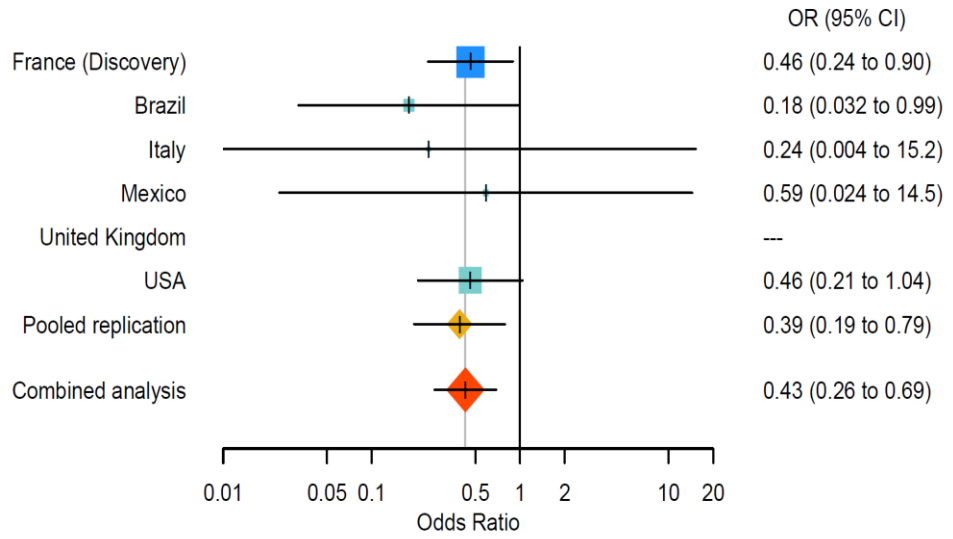
- Prevalence 0.3-7.5%, > 120 cases in literature
- Mostly subacute (progress in weeks), acute, and chronic course also possible
- Cough, dyspnea, fever
- Blood: eosinophilia in 20%
- X-ray: interstitial and interstitial/alveolar
- BALF: mostly CD4 lymphocytosis



Imokawa et al. Eur Respir J 2000; 15: 373

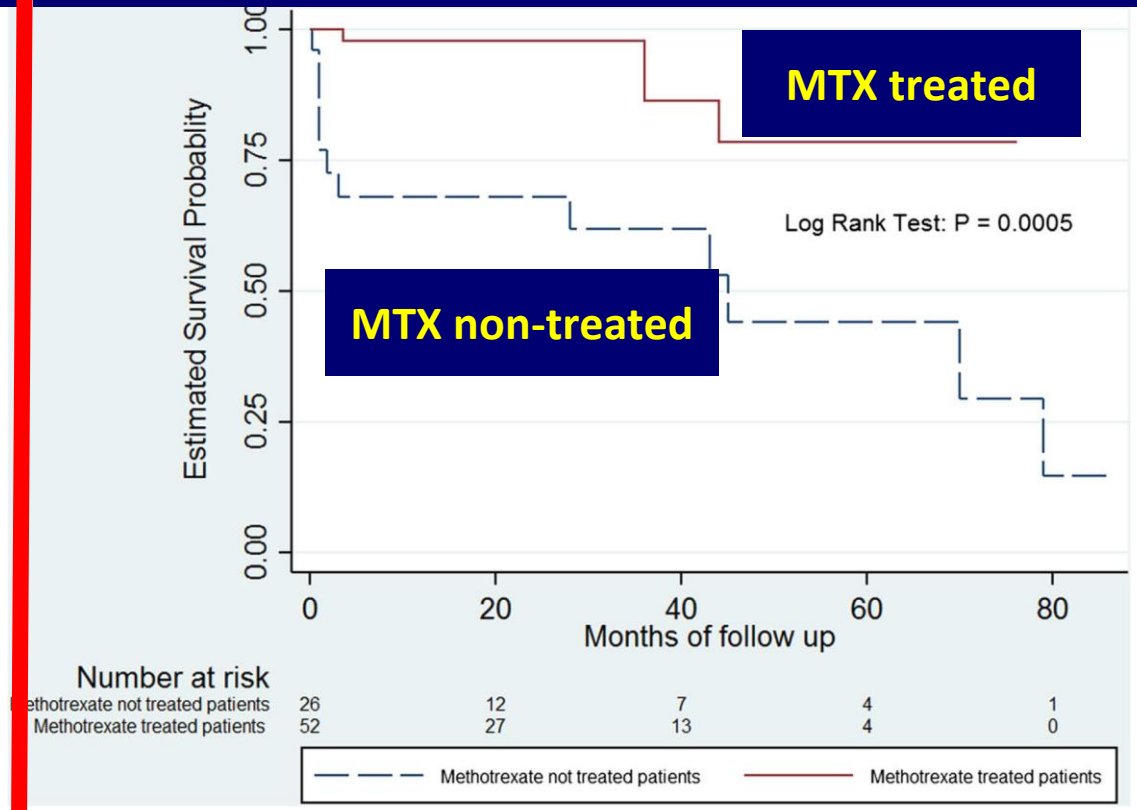
MTX was not associated with RA-ILD

Case control study-410 pts RA-ILD vs 673 pts RA



Dieude et al. Eur Respir J 2020

Retrospective cohort- 78 RA-ILD (52 MTX, 26 noMTX)



Rojas et al. Clin Rheumtol 2017

frontiers in Medicine

Biologic Treatments in Interstitial Lung Diseases

REVIEW
published: 13 March 2019
doi: 10.3389/fmed.2019.00041

Theodoros Karampitsakos[1], Argyro Vraka[2], Demosthenes Bouros[2], Stamatis-Nick Liossis[3] and Argyris Tzouvelekis[2]*

[1] 5th Department of Pneumonology, General Hospital for Thoracic Diseases Sotiria, Athens, Greece, [2] First Academic Department of Pneumonology, Hospital for Thoracic Diseases, Sotiria Medical School, National and Kapodistrian University of Athens, Athens, Greece, [3] Division of Rheumatology, Department of Internal Medicine, Patras University Hospital, University of Patras Medical School, Patras, Greece

Beware of drug induced ILDs/Infections

Scleroderma-ILD

45-90% of SSc pts

Eur Respir Rev 2013; 22: 127, 6–19
DOI: 10.1183/09059180.00005512

EUROPEAN RESPIRATORY UPDATE

Scleroderma lung disease

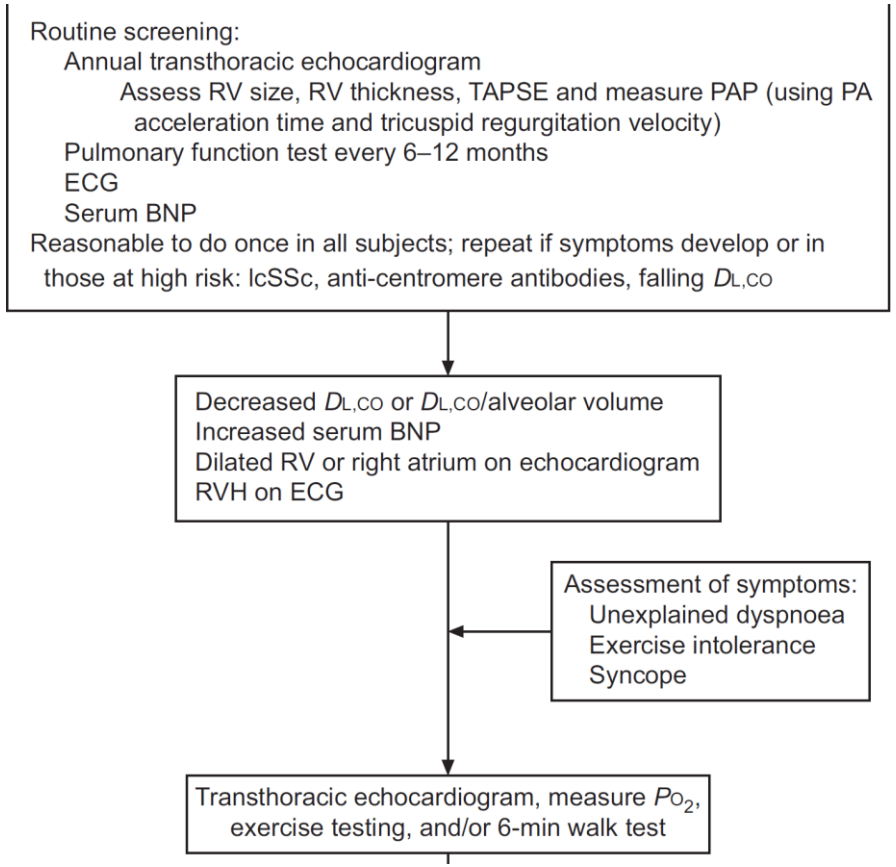
1.ILD (HRCT/PFTS)
2.PH (U/S)

Joshua J. Solomon*, Amy L. Olson*, Aryeh Fischer*, Todd Bull#, Kevin K. Brown* and Ganesh Raghu¶

TABLE 1 Pulmonary involvement in systemic sclerosis

Direct pulmonary involvement
ILD
ILD with PH
PH
Airways disease
Pleural involvement
Indirect pulmonary complications
Gastro-oesophageal reflux and aspiration
Infection
Drug toxicity
Malignancy
Respiratory muscle weakness
Restrictive lung disease from skin involvement
Secondary to cardiac involvement
Combination of direct and indirect pulmonary involvement
Other lung diseases unrelated to systemic sclerosis
COPD/emphysema
Asthma
Pulmonary nodules

ILD: interstitial lung disease; PH: pulmonary hypertension; COPD: chronic obstructive pulmonary disease.

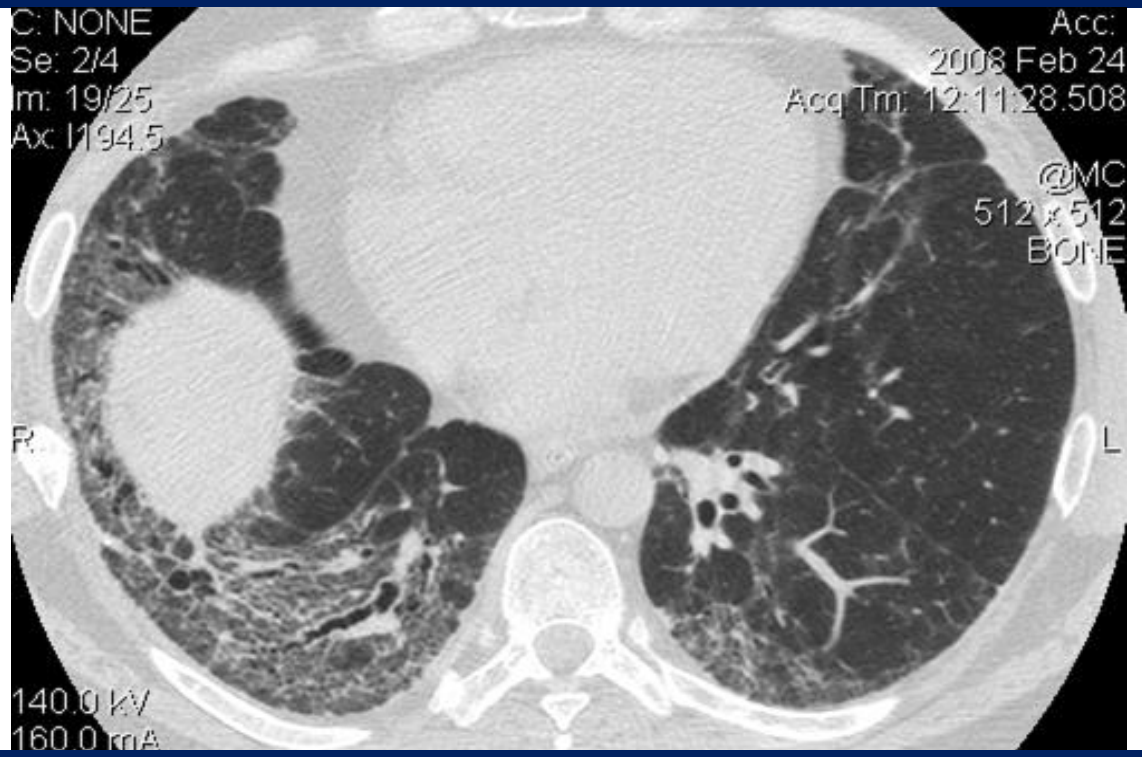


ILD patterns in autoimmune diseases

TYPE	SSc	RA	PM/DMM	SLE	MCTD	Sjögren's
UIP	++	++	++	++	+	-
NSIP	+++ 90%	+	+	+	++	++ 25%
OP	+	+	+++ 50%	+	_	-
DAD	+	+	++	++	_	_
DIP	+	+	+	+	_	+/-
LIP	_	_	_	_	_	+++ 20%
DAH / CAPILARITIS	+	+	+	+++	_	_
ILD	+++	++	+++	+	++	+

Slide courtesy of D.Bouros

40-yrs old, female, non-smoker, DOE (mMRC II/IV)+fatigue the past 9 months – GERD symptoms, medical Hx: unremarkable, Raynaud:+ Velcro type crackles: +



BAL: 24%L,N:13% (-) AFB, (-) fungi,
FVC: 70%, TIF: 86, TLC: 69%, DLCO: 55%
RVSP: 35 mmHg, Serology: ANA: 1/640, antiScl-70: +
GI endocospy: esophagitis

This article was published on May 20, 2019, at NEJM.org.

N Engl J Med 2019;380:2518-28.
DOI: 10.1056/NEJMoa1903076

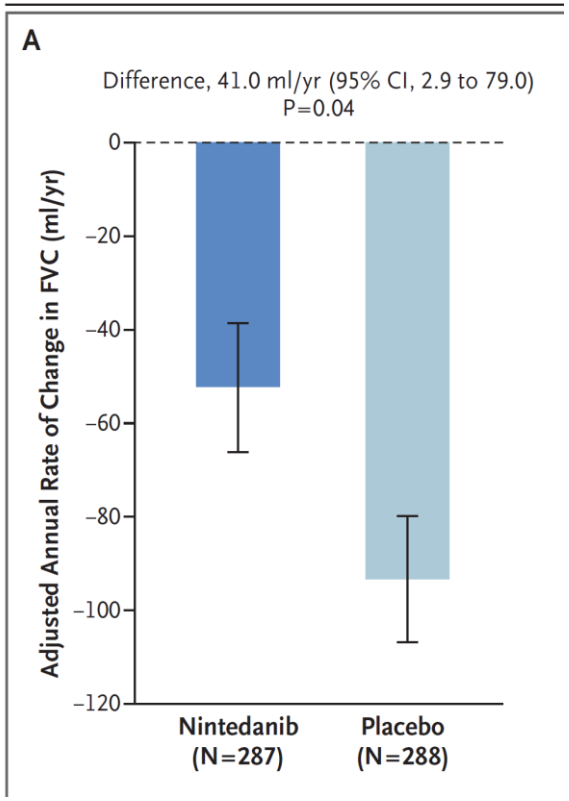
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease

SENSCIS Trial

Benefit of 41 ml



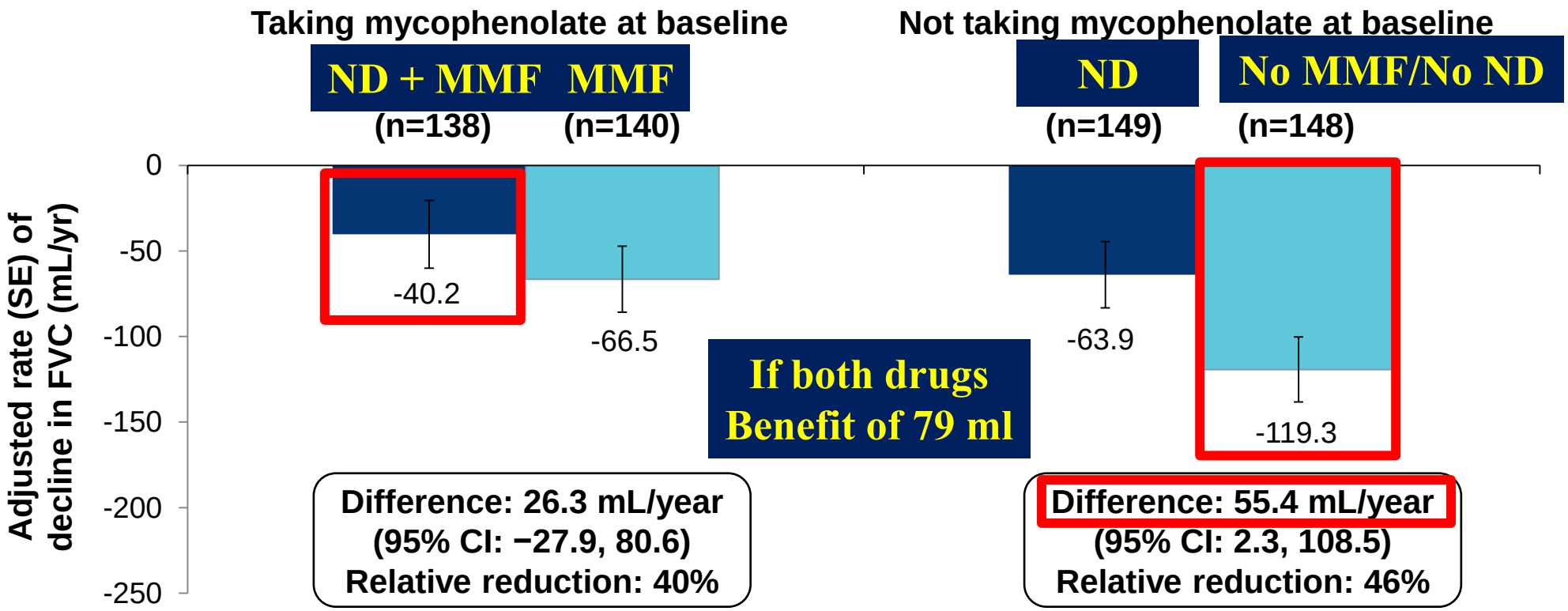
RESULTS

A total of 576 patients received at least one dose of nintedanib or placebo; 51.9% had diffuse cutaneous systemic sclerosis, and 48.4% were receiving mycophenolate at baseline. In the primary end-point analysis, the adjusted annual rate of change in FVC was −52.4 ml per year in the nintedanib group and −93.3 ml per year in the placebo group (difference, 41.0 ml per year; 95% confidence interval [CI], 2.9 to 79.0; P=0.04). Sensitivity analyses based on multiple imputation for missing data yielded P values for the primary end point ranging from 0.06 to 0.10. The change from baseline in the modified Rodnan skin score and the total score on the SGRQ at week 52 did not differ significantly between the trial groups, with differences of −0.21 (95% CI, −0.94 to 0.53; P=0.58) and 1.69 (95% CI, −0.73 to 4.12 [not adjusted for multiple comparisons]), respectively. Diarrhea, the most common adverse event, was reported in 75.7% of the patients in the nintedanib group and in 31.6% of those in the placebo group.

30 to 89% of the predicted value. Patients who were receiving prednisone at a dose of up to 10 mg per day or mycophenolate or methotrexate at a stable dose for at least 6 months before randomization (or both therapies) could participate in the trial. If clinically significant worsening of

Seminal study

Anti-fibrotics plus Immunomodulation…Synergy



Treatment-by-time-by-subgroup interaction p=0.452

DID SENSCIS INCLUDE SLOW-PROGRESSORS?

SCL-ILD-NARROW THERAPEUTIC MARGINS

FVC=2 lt
3% = 60ml

SENSCIS

Identification of the problem

CI, 8.1 to 84.7) (Fig. 2 and Table 2). The adjusted mean annual rate of change in FVC as a percentage of the predicted value at week 52 was –1.4% in the nintedanib group and –2.6% in the placebo group (difference, 1.2 percentage points;

change between 3.0% and 5.3% is the MCID for improvement, and a change of −3.0% to −3.3% is the MCID for worsening (after adjusting for the no-

Am J Respir Crit Care Med Vol 197, Iss 5, pp 644–652, Mar 1, 2018

Originally Published in Press as DOI: 10.1164/rccm.201709-1845OC on November 3, 2017

Reliability and Minimal Clinically Important Differences of FVC
Results from the Scleroderma Lung Studies (SLS-I and SLS-II)

Suzanne Kafaja[1], Philip J. Clements[1], Holly Wilhalme[1], Chi-hong Tseng[1], Daniel E. Furst[1], Grace Hyun Kim[2], Jonathan Goldin[2], Elizabeth R. Volkmann[1], Michael D. Roth[1], Donald P. Tashkin[1], and Dinesh Khanna[3]

Safety Data

Nocebo effect?

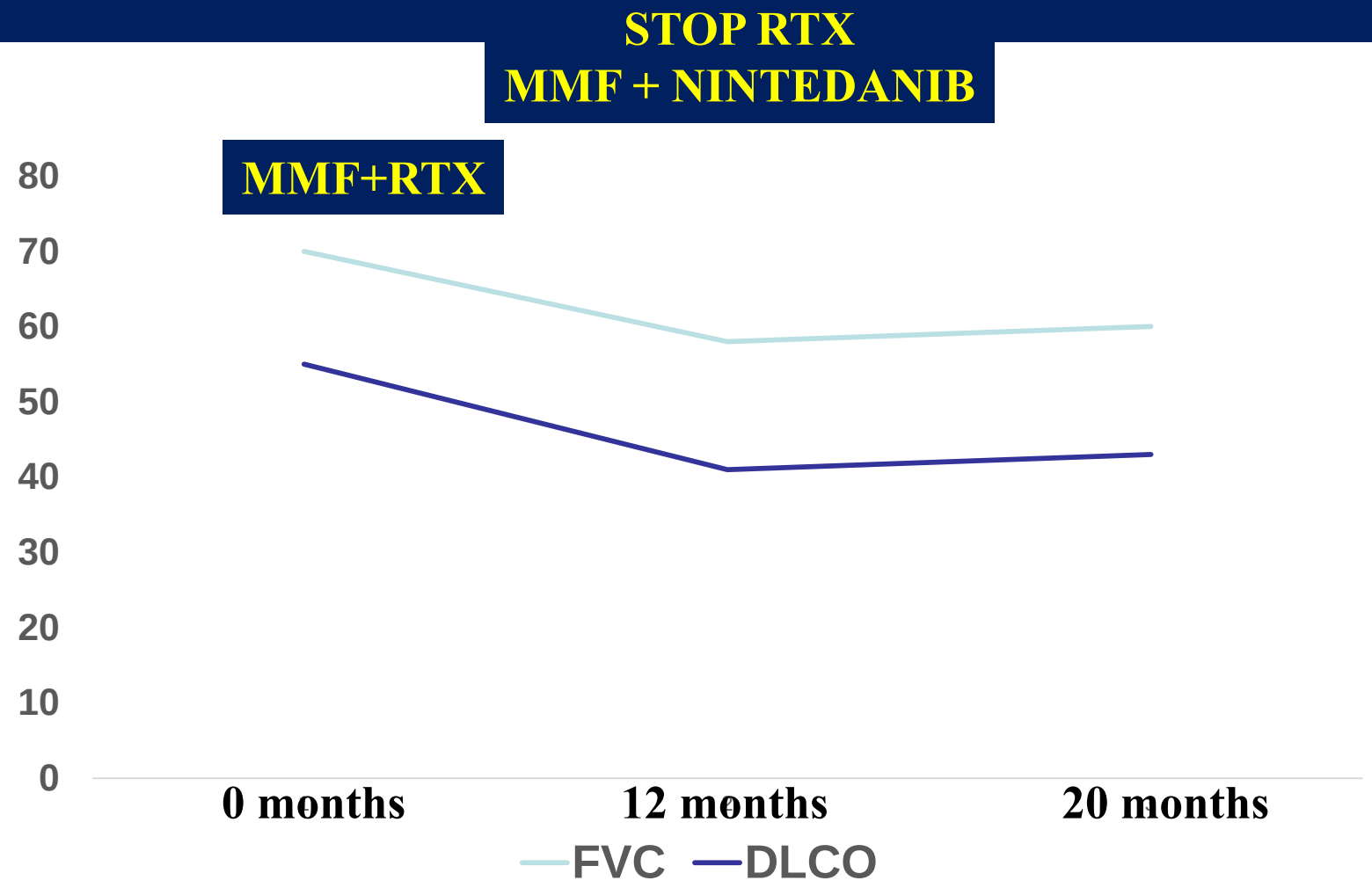
	Nintedanib (n=288)	Placebo (n=288)
Diarrhea	218 (75.7)	91 (31.6)
Nausea	91 (31.6)	39 (13.5)
Vomiting	71 (24.7)	30 (10.4)
Skin ulcer	53 (18.4)	50 (17.4)
Cough	34 (11.8)	52 (18.1)
Nasopharyngitis	36 (12.5)	49 (17.0)
Upper respiratory tract infection	33 (11.5)	35 (12.2)
Abdominal pain	33 (11.5)	21 (7.3)
Fatigue	31 (10.8)	20 (6.9)
Weight decreased	34 (11.8)	12 (4.2)

Adverse events reported over 52 weeks plus 28-day post-treatment period in >10% of patients in either treatment group.
Data are n (%) of patients with ≥1 such adverse event coded based on MedDRA preferred terms.

Commenced on low dose PZN – MMF

6 mo later dyspnea deteriorated – 6MWD: 410m – 95%-87%,

PFTS deterioration- FVC drop 11%, DLCO drop: 14%



Tocilizumab improves FVC in SSc-ILD

Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial

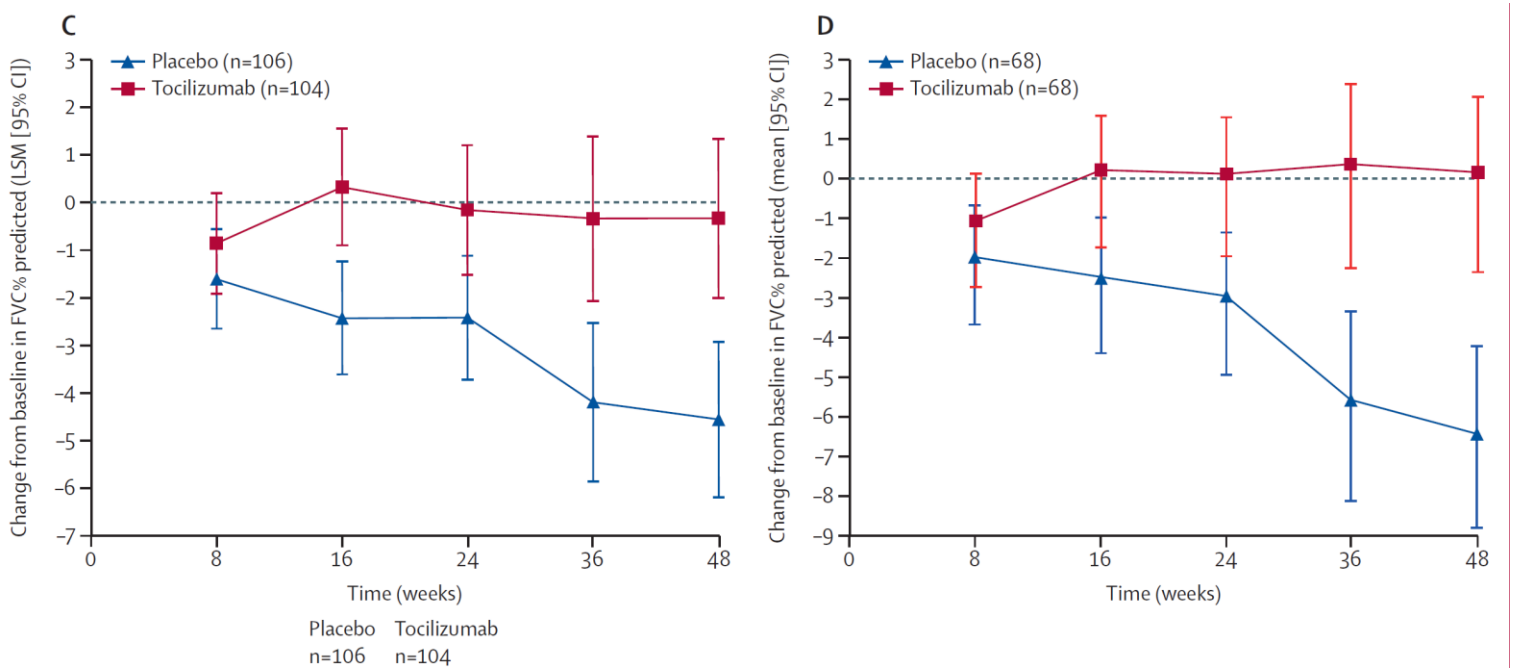
Dinesh Khanna, Celia J F Lin, Daniel E Furst, Jonathan Goldin, Grace Kim, Masataka Kuwana, Yannick Allanore, Marco Matucci-Cerinic, Oliver Distler, Yoshihito Shima, Jacob M van Laar, Helen Spotswood, Bridget Wagner, Jeffrey Siegel, Angelika Jahreis, Christopher P Denton*, for the focuSSced investigators†*

Lancet Respir Med 2020

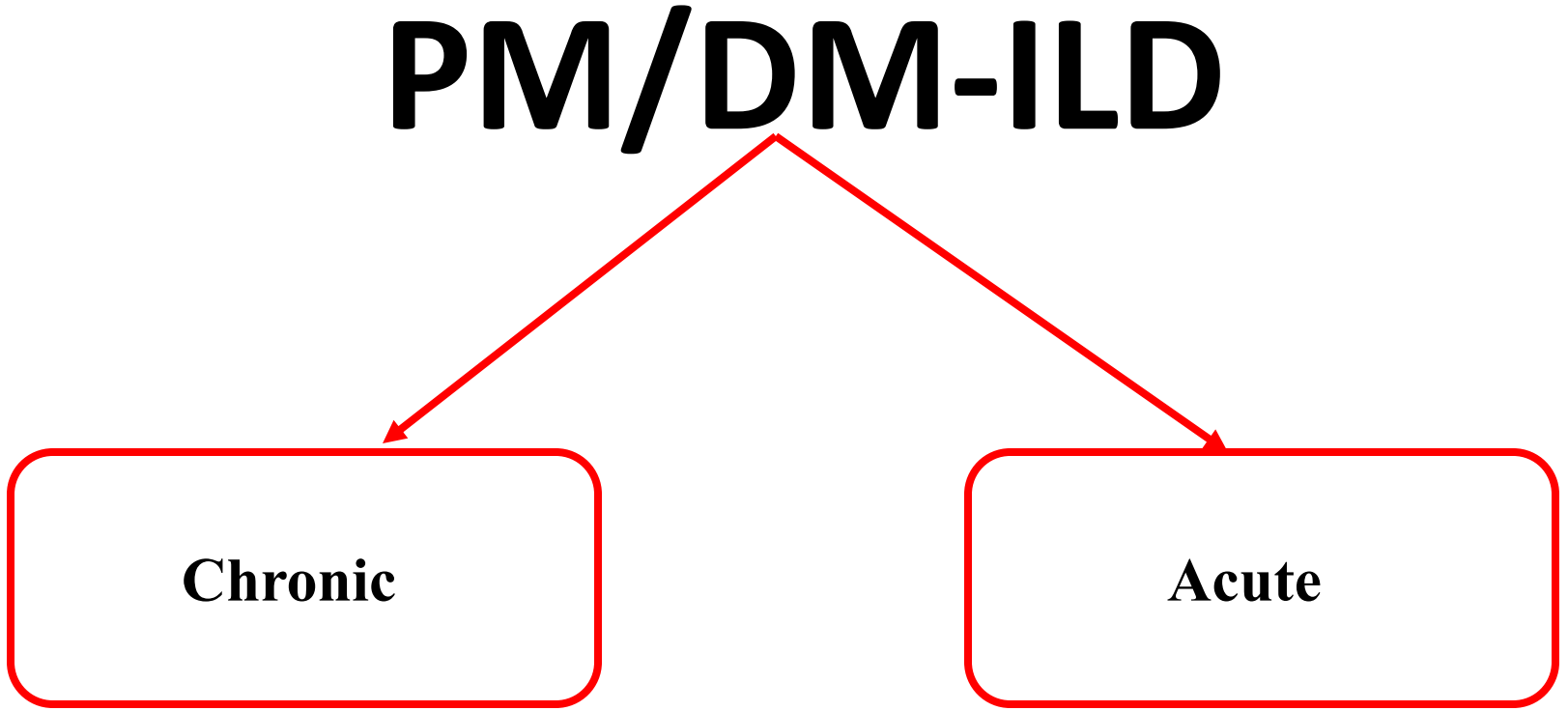
Published Online
August 28, 2020

210 patients, mostly inflammatory component-NSIP

Interpretation The primary skin fibrosis endpoint was not met. Findings for the secondary endpoint of FVC% predicted indicate that tocilizumab might preserve lung function in people with early SSc-ILD and elevated acute-phase reactants. Safety was consistent with the known profile of tocilizumab.



Antibiotic refractory bilateral consolidation in middle age adults (mostly women)



Pulmonary Manifestations in DM/PM

- **Aspiration pneumonia** — **10 - 15%**
  dysphagia
- **Respiratory insufficiency** — **4 - 7%**
  due to alveolar hypoventilation
  (respiratory muscle weakness)
- **Pulmonary Arterial Hypertension** — **10%**
- **Interstitial lung disease** — **up to 60-70%**
  Anti-Jo-1 pos. in 50%
  Histo UIP: bad prognosis (most common)
  Histo BOOP: good prognosis
  Histo DAD: worst prognosis

Idiopathic inflammatory myopathies

Eur Respir Rev 2015; 24: 216–238 |

ARD Online First, published on October 27, 2017 as 10.1136/annrheumdis-2017-211468

2017 European League Against Rheumatism/ American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups

Muscle biopsy available or not
Age of onset = 18-40 or >40 yrs
Muscle weakness
Skin manifestations
Dysphagia/Esophageal Dysmotility
Jo1 + CPK-aldolase
Muscle biopsy features

ILD not included

Box 1 | **The EULAR–ACR classification criteria for adult and juvenile IIMs and their major subgroups**[6,7]

Muscle biopsy available

- Probable idiopathic inflammatory myopathies (IIMs): aggregated score (probability ≥55% and <90%) ≥6.7 and <8.7
- Definite IIMs: aggregated score (probability ≥90%) ≥8.7

Muscle biopsy not available

- Probable IIMs: aggregated score (probability ≥55% and <90%) ≥5.5 and <7.5
- Definite IIMs: aggregated score (≥90% probability) ≥7

Variable	Score	
	Without muscle biopsy	With muscle biopsy
Age of onset of first symptom assumed to be related to the disease ≥18 years and <40 years	1.3	1.5
Age of onset of first symptom assumed to be related to the disease ≥40 years	2.1	2.2
Muscle weakness		
Objective symmetrical weakness, usually progressive, of the proximal upper extremities	0.7	0.7
Objective symmetrical weakness, usually progressive, of the proximal lower extremities	0.8	0.5
Neck flexors are relatively weaker than neck extensors	1.9	1.6
In the legs, proximal muscles are relatively weaker than distal muscles	0.9	1.2
Skin manifestations		
Heliotrope rash	3.1	3.2
Gottron papules	2.1	2.7
Gottron sign	3.3	3.7
Other clinical manifestations		
Dysphagia or oesophageal dysmotility	0.7	0.6
Laboratory measurements		
Anti-histidyl-transfer RNA synthetase (Jo1) autoantibody present	3.9	3.8
Elevated serum levels of one of the following enzymes[a]: creatine kinase, lactate dehydrogenase, aspartate aminotransferase or alanine aminotransferase	1.3	1.4

doi:10.1038/nrrheum.2018.41
NATURE REVIEWS | RHEUMATOLOGY
Published online 12 Apr 2018

Anti-synthetase syndrome

15-30% anti-Jo1

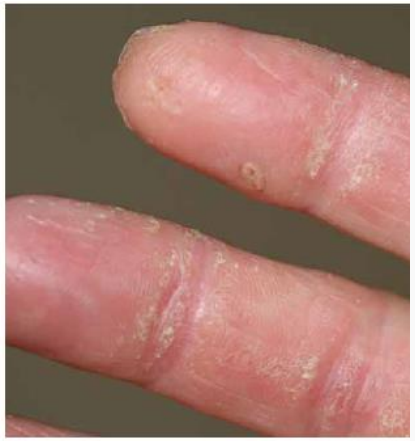
TABLE 3 Proposed criteria for myositis associated with anti-tRNA synthetase antibody

Features the patient must have

Positive serological tests for an anti-tRNA synthetase antibody
Plus one major involvement:
- Evidence of overt or hypomyopathic myositis (elevated CPK levels, myalgia, proximal muscular weakness, positive muscular biopsy, electromyographic triad of myositis or MRI muscular oedema)
- Evidence of ILD according to ATS criteria
- Evidence of articular involvement (symmetrical inflammatory arthralgia or overt arthritis)

Or two minor involvements:
- Unexplained persistent fever
- Raynaud's phenomenon
- Mechanic's hands

ILD included



Myositis Panel

- * Mi-2a Ab
- * Mi-2ß Ab
- * TIF1-Y Ab
- * MDA-5 Ab
- * NXP2 Ab
- * SAE-1 Ab
- * Ku Ab
- * PM Scl-100 Ab
- * PM Scl-75Ab
- * Jo-1 Ab
- * SRP Ab
- * PL-7 Ab
- * PL-12 Ab
- * EJ Ab
- * OJ Ab
- * Ro-52 Ab

Qline Diagnostics

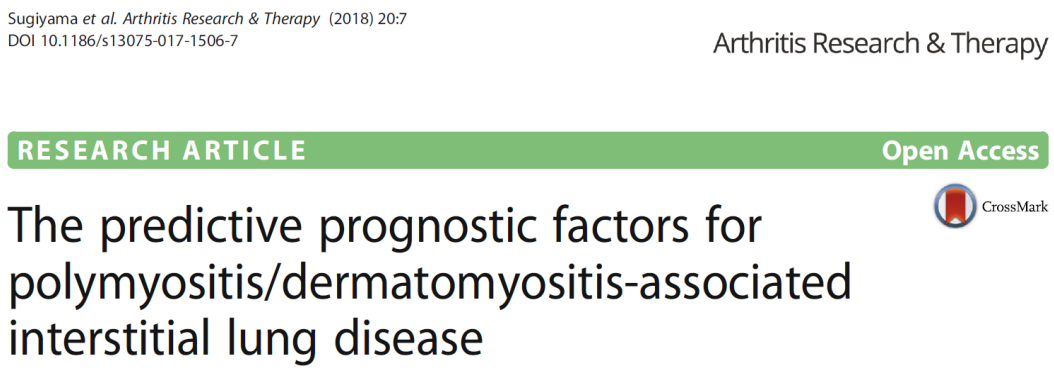
General principles

- ILD may precede muscular signs in 20%
- BAL = Lymphocytosis
- 50% of DM/PM-ILD will die from respiratory failure
- PL7+, PL12+ often isolated ILD
- MDA5 + has 90% mortality
- Amyopathic DM = rapidly progressing ILD
- UIP pattern = worse prognosis
- **ACT TIMELY!!!!!**

Idiopathic inflammatory myopathies and the lung Eur Respir Rev 2015; 24: 216–238 |

Indirect Pulmonary Complications

- Aspiration pneumonia = 35%
- Opportunistic infection = MAC, MTB, PCJ
- Drug Toxicity
- Malignancy = 4-fold increase (1-5%) (TIF1γ)+
- Supra-Ventricular arrhythmias and blocks = 30%



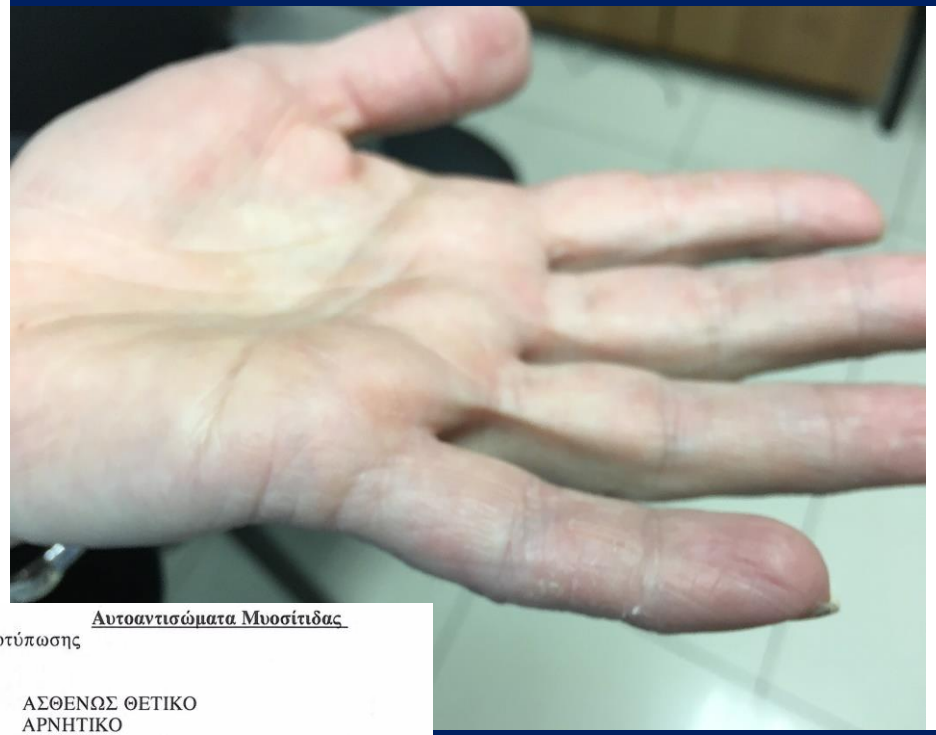
Sugiyama *et al. Arthritis Research & Therapy* (2018) 20:7
DOI 10.1186/s13075-017-1506-7

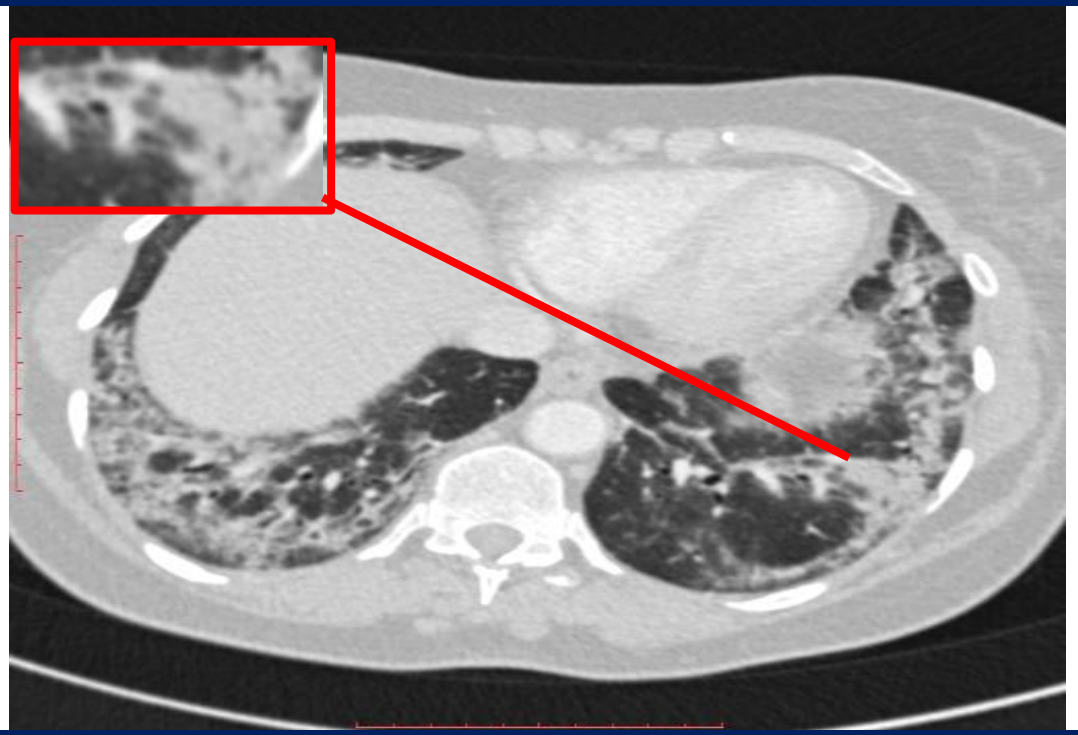
Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

The predictive prognostic factors for polymyositis/dermatomyositis-associated interstitial lung disease

47 yrs old female, non-smoker, DOE (II/IV), dry cough-mild fever-recurrent RTIs past 9 months treated with BDs-antibiotics-NO MYALGIA-history unremarkable – Velcro type crackles +





Αυτοαντισώματα Μυοσίτιδας

Μέθοδος Ανοσοαποτύπωσης

Κατά Αντιγόνων:

Mi-2α	ΑΣΘΕΝΩΣ ΘΕΤΙΚΟ
Mi-2β	ΑΡΝΗΤΙΚΟ
TIF1γ	ΑΡΝΗΤΙΚΟ
MDA5	ΑΡΝΗΤΙΚΟ
NXP2	ΑΡΝΗΤΙΚΟ
SAE1	ΑΡΝΗΤΙΚΟ
Ku	ΑΡΝΗΤΙΚΟ
Pm-Scl 100	ΑΡΝΗΤΙΚΟ
Pm-Scl 75	ΑΡΝΗΤΙΚΟ
Jo - 1	ΑΡΝΗΤΙΚΟ
SRP	ΑΡΝΗΤΙΚΟ
PL-7	ΘΕΤΙΚΟ
PL-12	ΑΡΝΗΤΙΚΟ
EJ	ΑΡΝΗΤΙΚΟ
OJ	ΑΡΝΗΤΙΚΟ
Ro_52	ΘΕΤΙΚΟ

ESR: 75mm/h, CPK: 55mg/dl, aldolase: 10 mg/dl

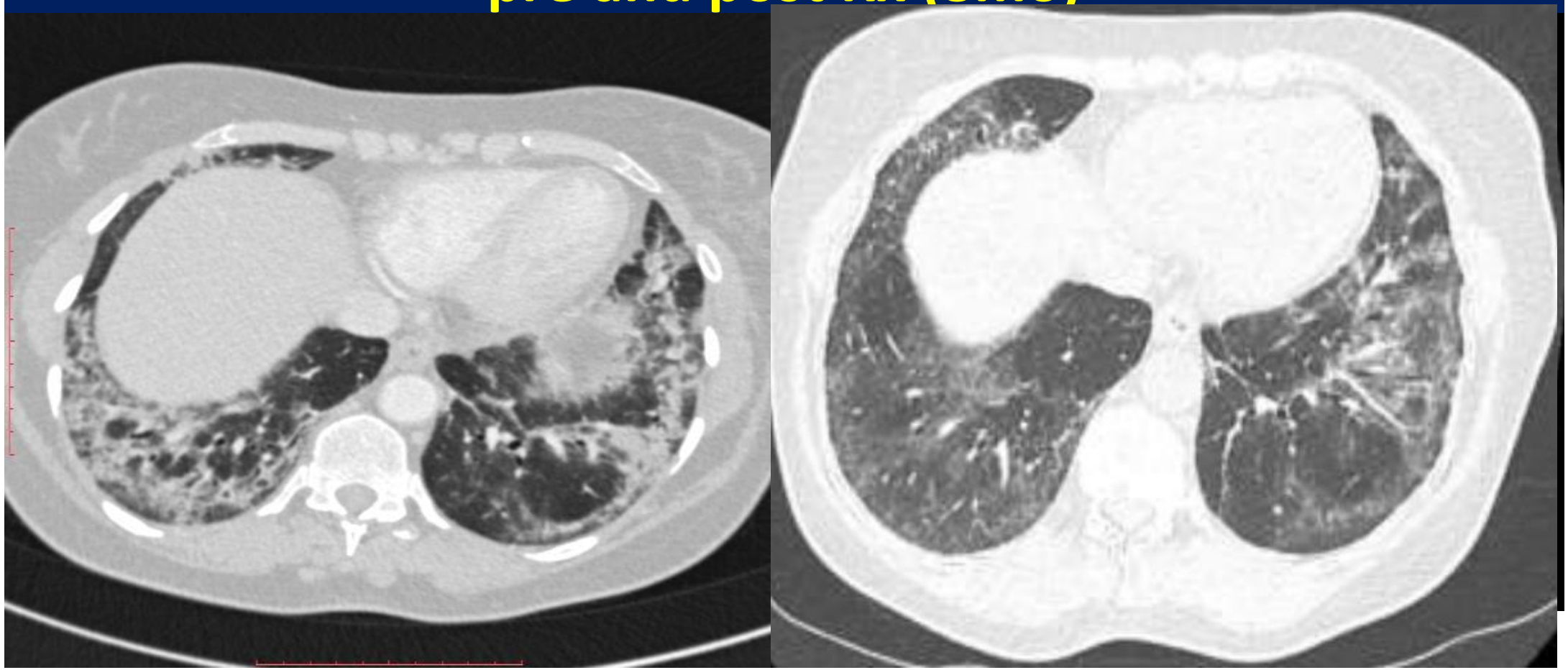
BAL: 30%L, (-) AFB, (-) fungi

FVC: 70%, TIF: 86, TLC: 69%, DLCO: 70%

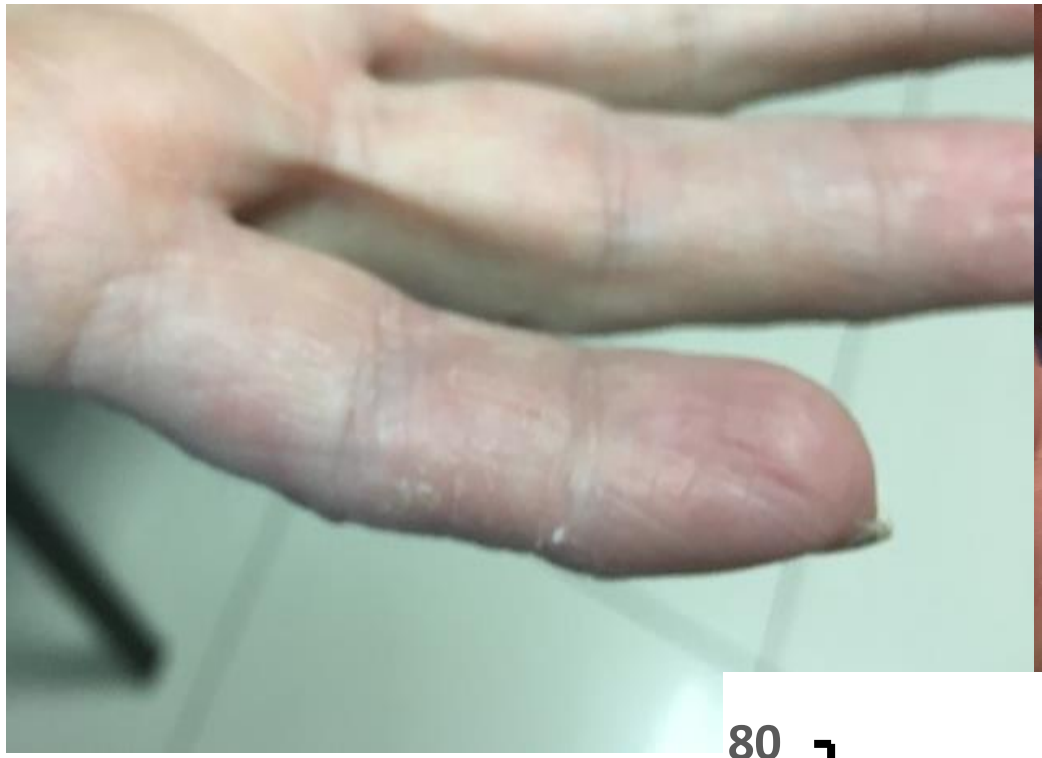
6MWD: 400 M, 98%-92%

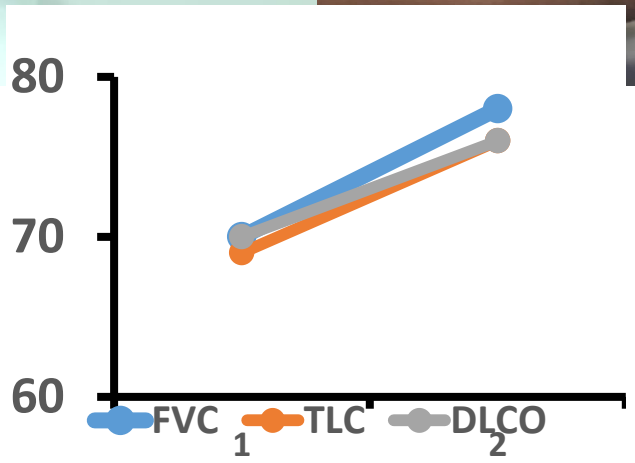
ANA: 1/640, ENA panel: (-), anti-Jo1: (-), anti-PL7: (++), Ro52 : (++),

30 mg prednisolone (gradual tapering to 10 mg) + MMF+TMP/SMX+vaccination pre and post Rx (8mo)

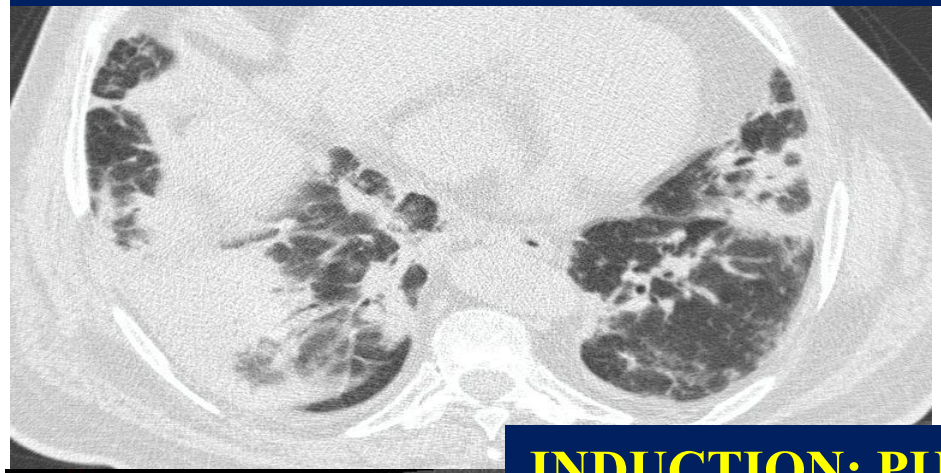


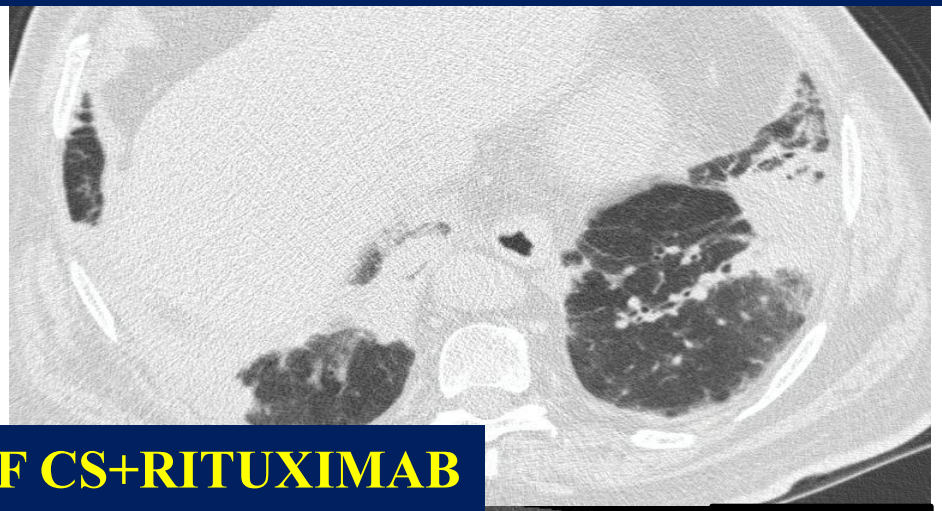
Clinical and functional status



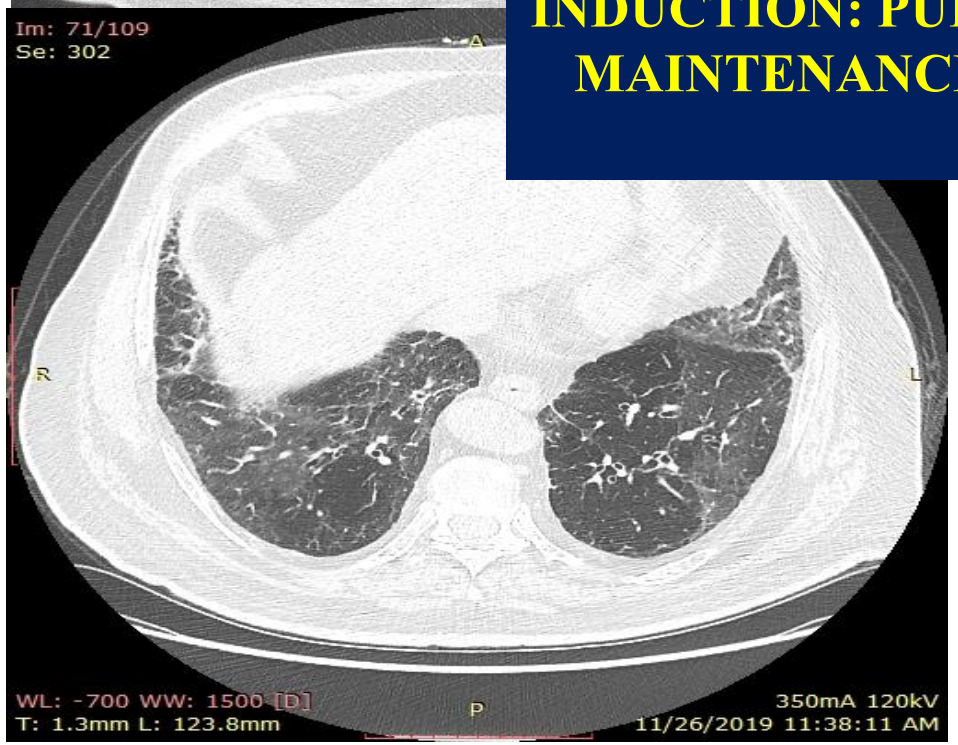


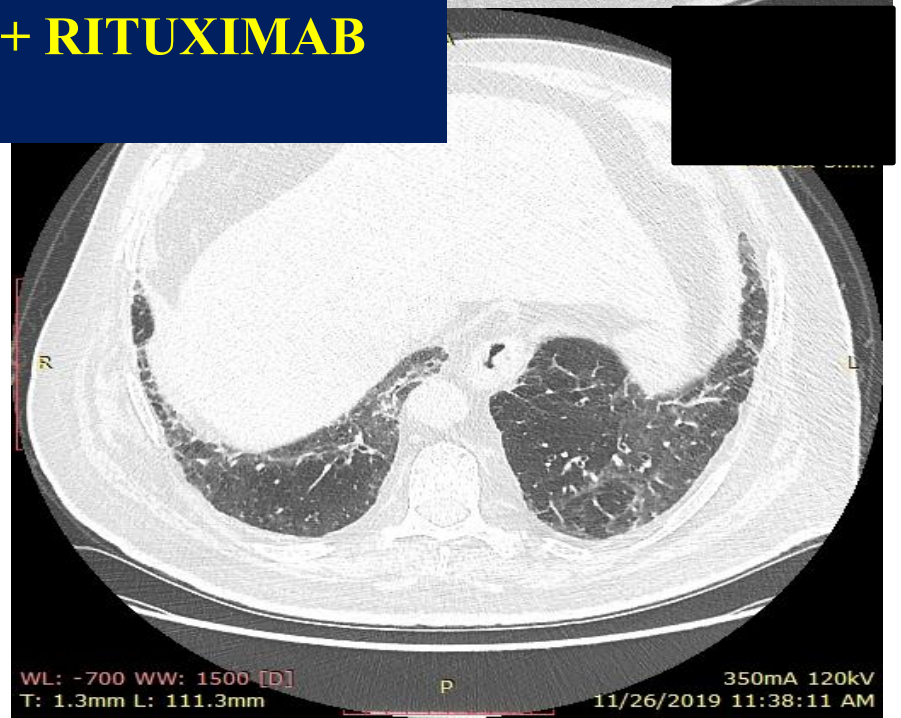
67 yrs old female, smoker, acute onset of dyspnea – Respiratory failure – Antibiotic refractory bilateral OP + PL12, +Ku, +Ro52



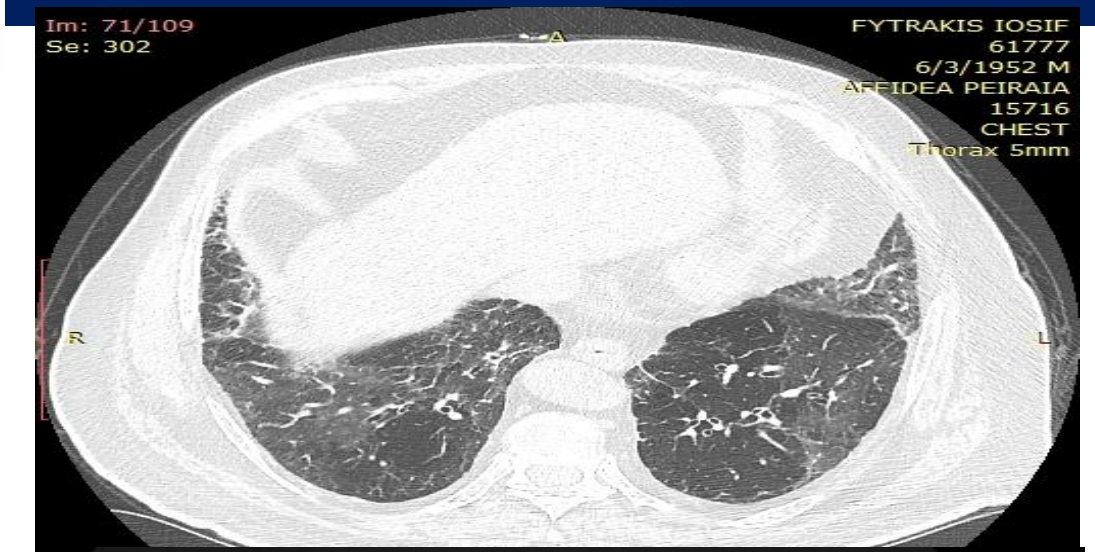


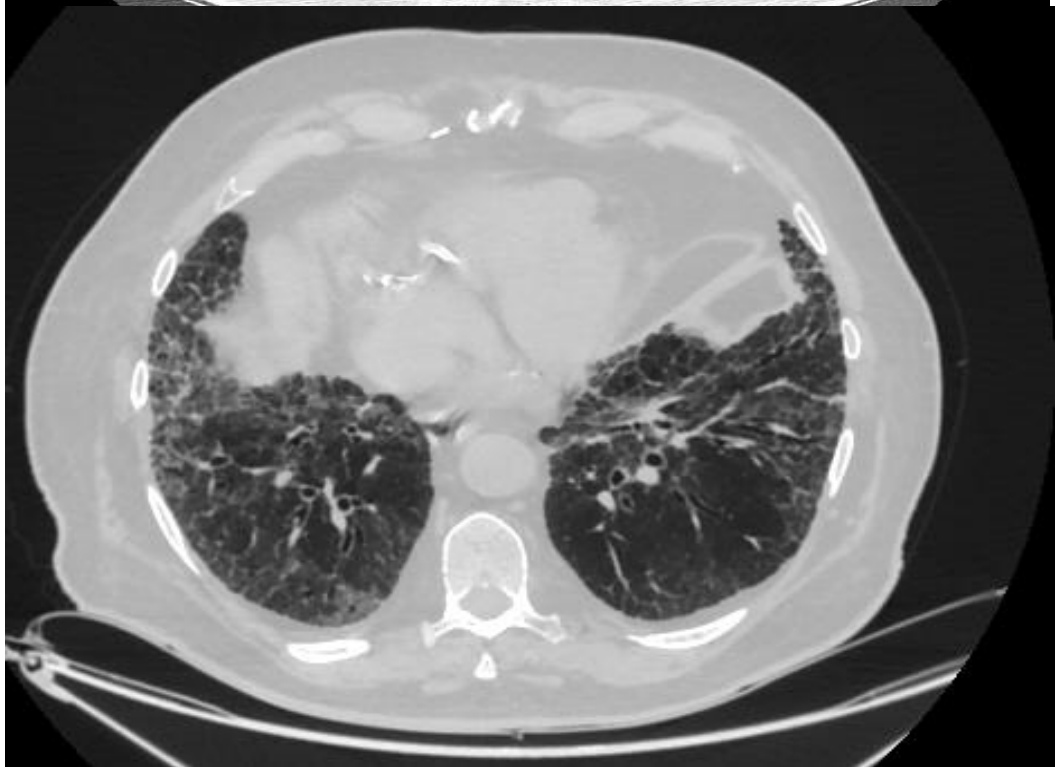
INDUCTION: PULSES OF CS+RITUXIMAB
MAINTENANCE : MMF + RITUXIMAB





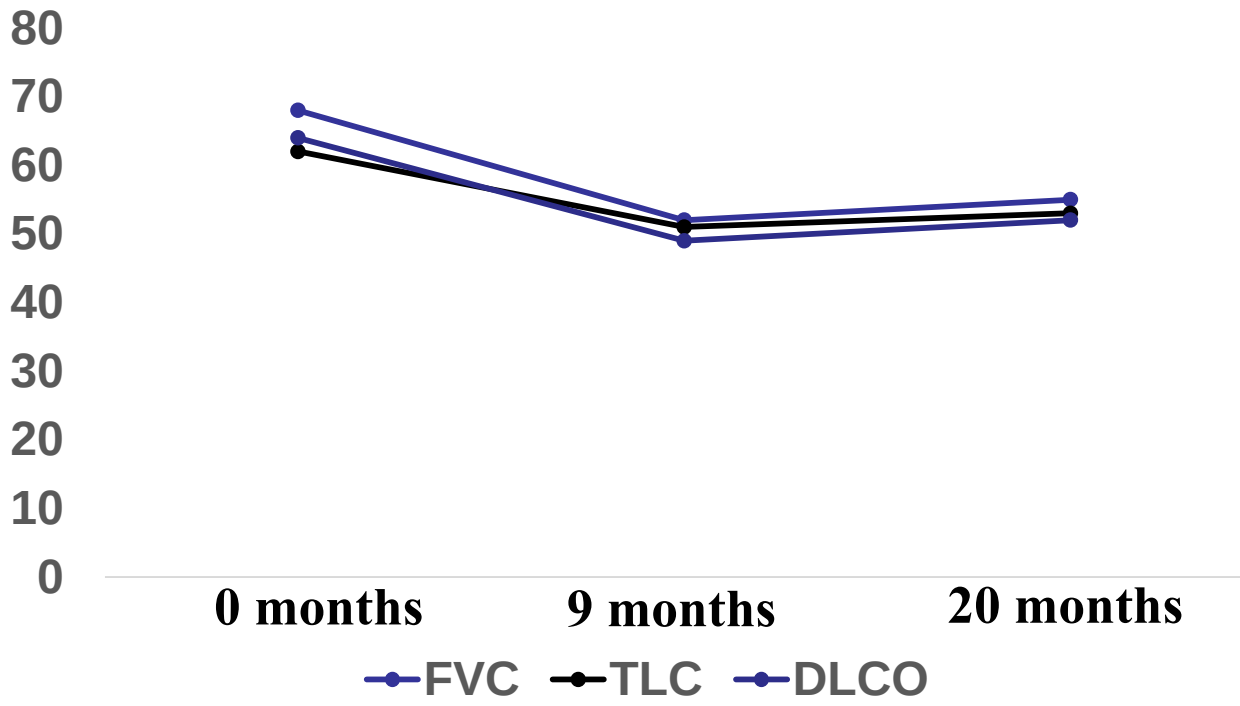
HRCT





PFTs

STOP RTX
MMF + NINTEDANIB



Anti-PL-7 (Anti-Threonyl-tRNA Synthetase) Antisynthetase Syndrome

Clinical Manifestations in a Series of Patients From a European Multicenter Study (EUMYONET) and Review of the Literature

(*Medicine* 2012;91: 206–211)

Disease profile of patients with antisynthetase autoantibodies

Sex ratio – Female/Male	1.7
Age at diagnosis	4th decade
Onset	Acute
Major clinical features	Interstitial lung disease
	Fever
	Raynauds phenomenon
	'mechanic's hands'
Steroid response	Moderate
Mortality (%)	20

Eighteen patients, 15 women, were anti-PL-7 antibody positive. Median follow-up was 5.25 years (interquartile range, 2.8–10.7 yr), and 4 patients died. All patients had myositis (12 polymyositis, 5 dermatomyositis, and 1 amyopathic dermatomyositis), 10 (55.6%) had interstitial lung disease, and 9 (50%) had pericardial effusion. Occupational expo-

Myositis-ILD: Patras cohort

Table 1. Baseline characteristics.

Characteristics	(N,%)
Total number of patients	15
Age median (%95CI)	64.0 (56.3 to 68.7)
Male/ Female	7 (46.7%) / 8 (53.3%)
FVC% predicted ± SD	80.6 ± 20.5
DLCO% predicted ± SD	68.9 ± 25.4
Lymphocytes % in BAL ± SD	29.4± 24.1

Table 2. Most commonly encountered antibodies.

Antibodies	(N,%)
anti-Ro52	8, 53.3%
anti-Jo-1	5, 33.3%
anti-MDA5	4, 26.7%
anti-PL-7	3, 20%
anti-PL-12	2, 13.3%
anti-Ku	2, 13.3%
anti-OJ	2, 13.3%

Specific ILD radiographic features may herald underlying inflammatory myopathies. Incorporation of ILD radiological patterns in the diagnostic criteria of inflammatory myopathies may lead to timely therapeutic interventions and positively impact patients' survival.

Figure 1. Representative HRCT images of two different patients with myositis-ILD.

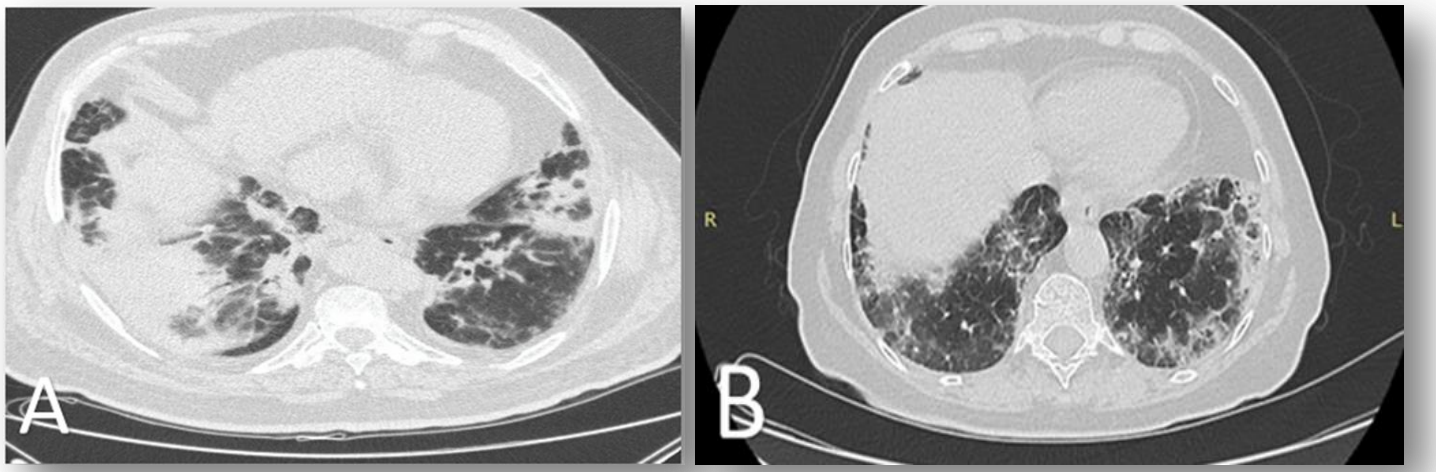
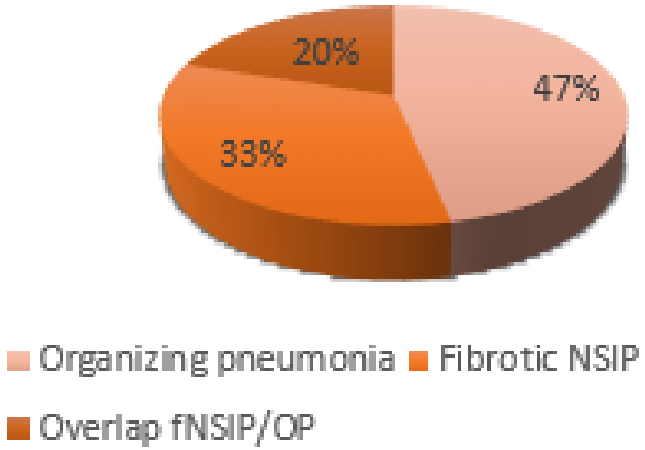


Figure 2. Predominant radiographic pattern.



Miscommunication between Rh and Pm

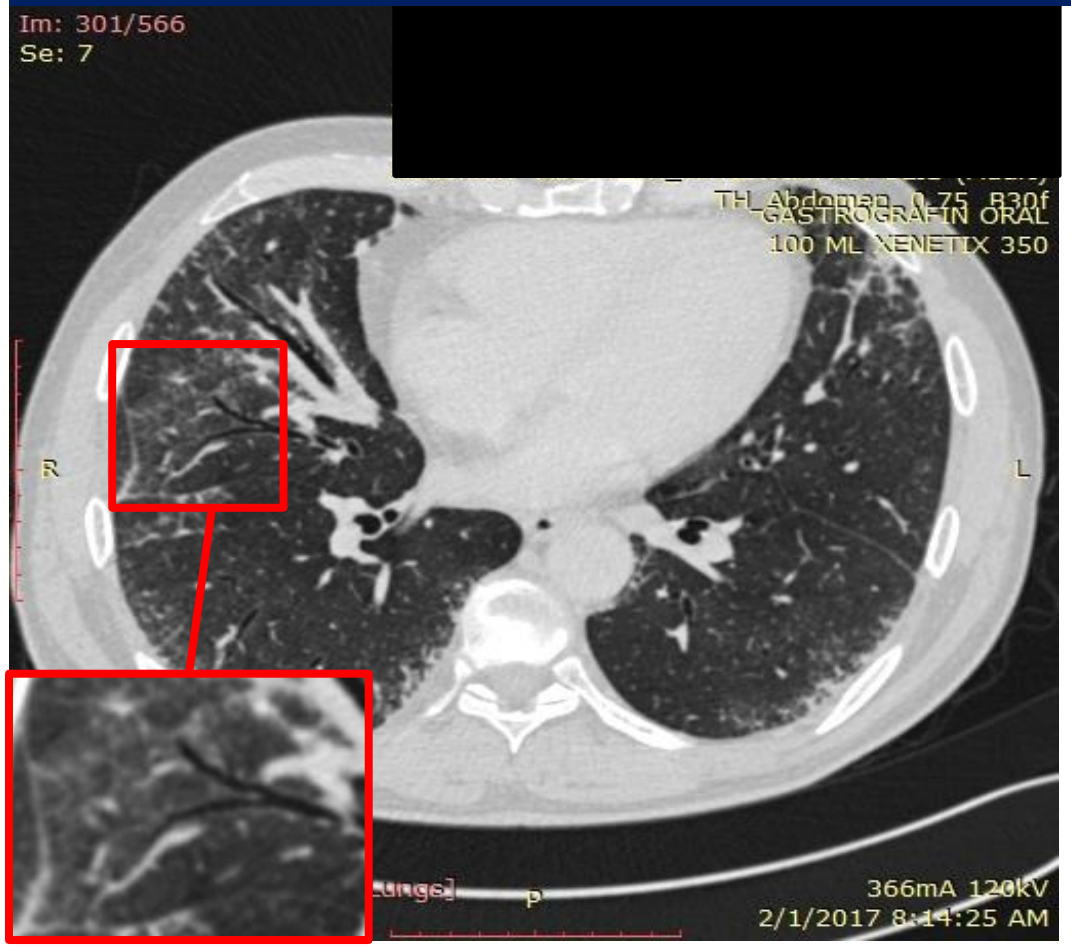
lacking at disease onset. [5]. However, as reported previously [6], in the case of anti-synthetase antibody positivity, the diagnostic scenario may vary with the same patient diagnosed with ASSD if referred to a rheumatologist, or IPAF if referred to a pulmonologist. In fact, a high prevalence of anti-synthetase

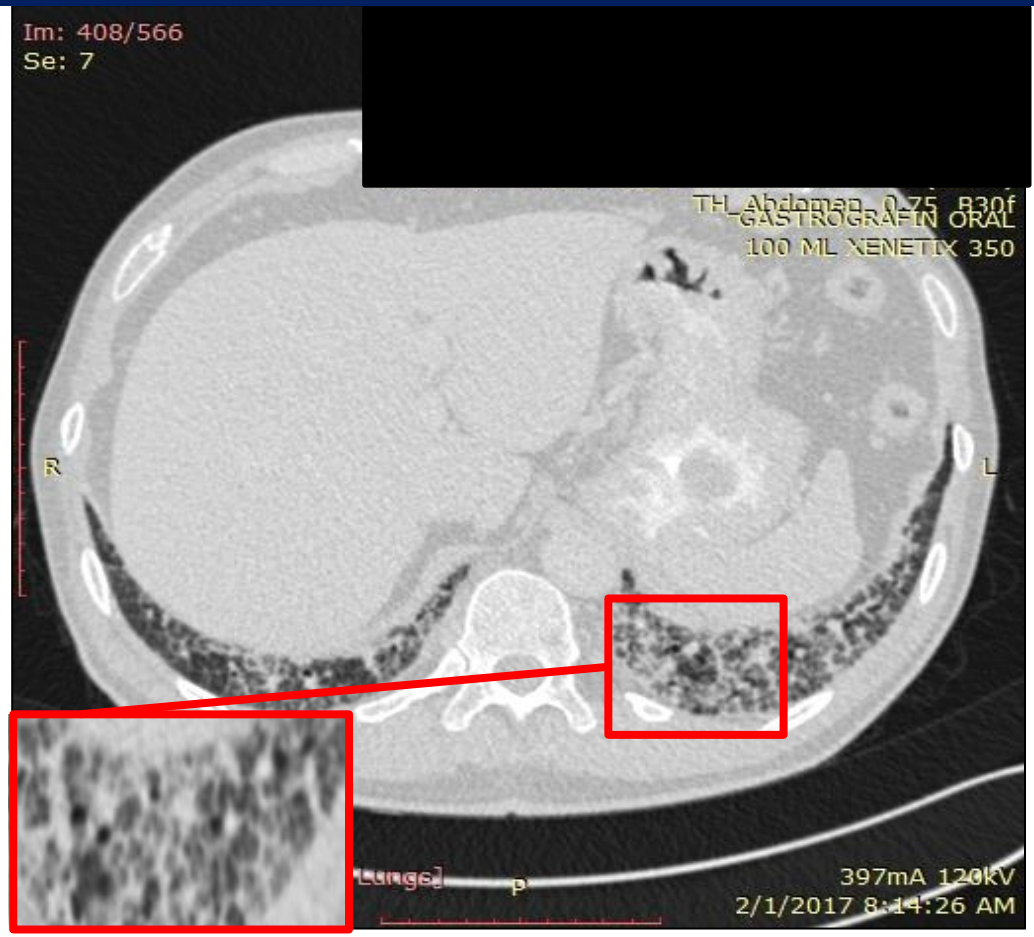
is clear that physicians from the various specialties now need to work together to overcome these problems to improve our understanding about this galaxy of diseases and finally establish shared diagnostic and classification criteria. At present, IPAF criteria have a relevant role in the improvement of our knowledge

Interstitial pneumonia with autoimmune features: a new classification still on the move Eur Respir Rev 2018; 27: 180047

IPAF

60 yrs old male, ex-smoker, history of hypercalciuria, hashimoto,
Non-productive cough, DOE (II/IV) last 6 mo, low-grade fever last 3 days – family doctor - moxifloxacin (WBCs: 17450, CRP: 3.4)- no Raynaud, no arthralgia-myalgia





BAL: 37%L, (-) AFB, (-) fungi
ANA: 1/640, ENA panel: (-), RF: (-)
RVSP: 25 mmHg, 6MWD: 410 m, SaO2: 98% – 88%
VATS biopsy: ?

Indeterminate Pattern

Indeterminate for UIP

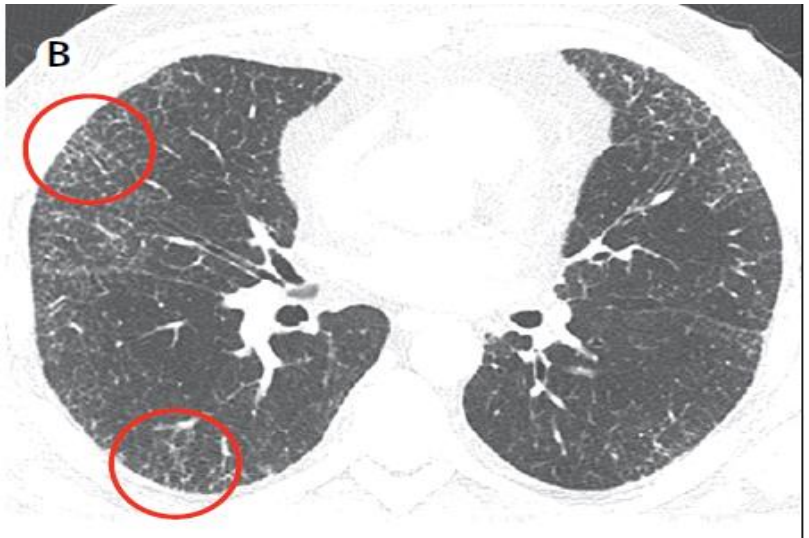
Subpleural and basal predominant

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")

ILA

Early UIP pattern



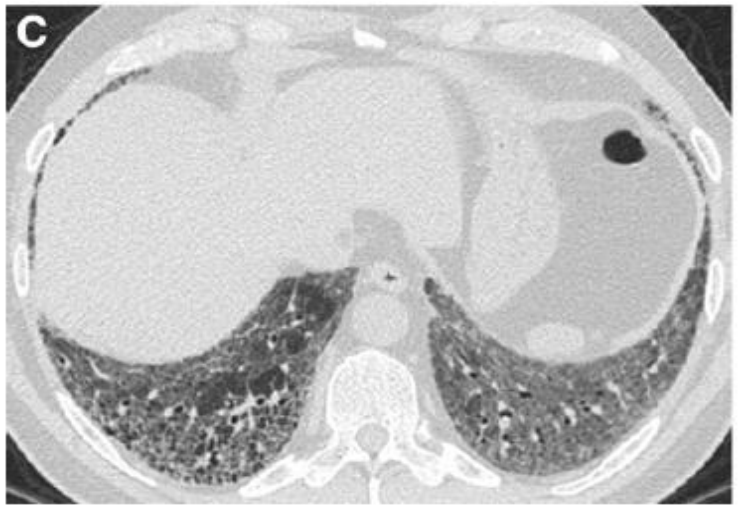
Familial

IPAF

30%

Unclassifiable

Truly indeterminate



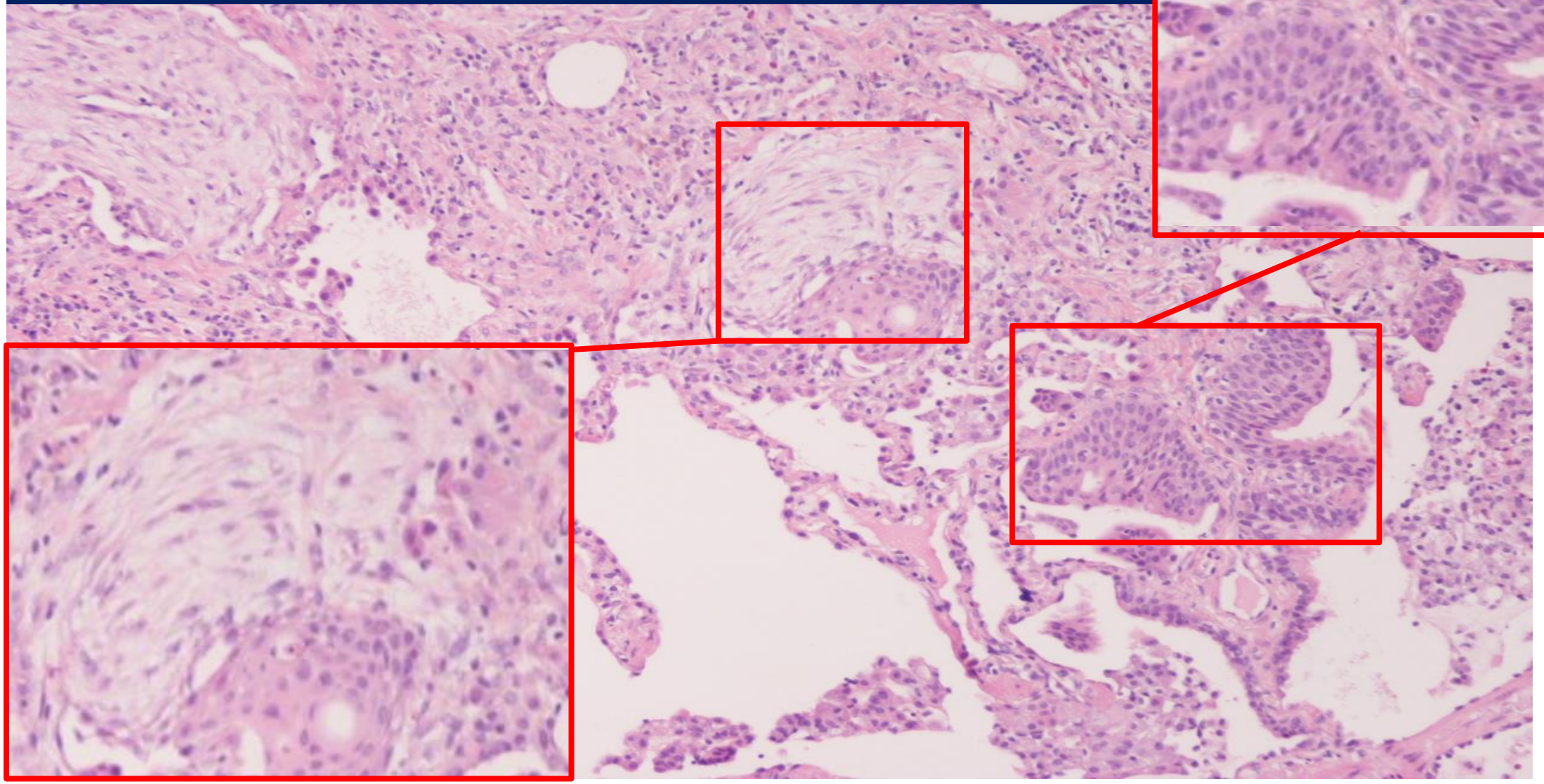
Probable UIP pattern requires biopsy or not?

TABLE 2 Diagnostic components for idiopathic pulmonary fibrosis (IPF)

	ATS/ERS/JRS/ALAT clinical practice guideline [1]	Fleischner white paper consensus statement [2]
Age limit for increased diagnostic confidence	60 years	
HRCT pattern	**UIP** Subpleural and basal predominance Presence of honeycombing with or without peripheral traction bronchiectasis Biopsy not recommended	**Typical UIP** Subpleural and basal predominance Presence of honeycombing with or without peripheral traction bronchiectasis Biopsy not recommended
	Probable UIP Subpleural and basal predominance Presence of peripheral traction bronchiectasis *Biopsy recommended (conditional)*	**Probable UIP** Subpleural and basal predominance Presence of peripheral traction bronchiectasis *Biopsy **not** recommended*
	Indeterminate for UIP Subpleural and basal predominant May have mild GGO or distortion *Biopsy recommended*	**Indeterminate for UIP** Variable or diffuse Features suggestive of non-UIP pattern *Biopsy recommended*
	Alternative diagnosis Findings suggestive of another diagnosis *Biopsy recommended*	**Most consistent with non-IPF diagnosis** Findings suggestive of another diagnosis *Biopsy recommended*

Raghu G, et al. *Eur Respir J*. 2018;52:1801-5.

Histology (I)



IPAF/Unclassifiable ILD

Working diagnosis

An official European Respiratory Society/ American Thoracic Society research statement: interstitial pneumonia with autoimmune features

TABLE 1 Classification criteria for "interstitial pneumonia with autoimmune features"

1. Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) *and*,
2. Exclusion of alternative aetiologies *and*,
3. Does not meet criteria of a defined connective tissue disease *and*,
4. At least one feature from at least two of these domains:
   A. Clinical domain
   B. Serologic domain
   C. Morphologic domain

A. Clinical domain
1. Distal digital fissuring (*i.e.* "mechanic hands")
2. Distal digital tip ulceration
3. Inflammatory arthritis *or* polyarticular morning joint stiffness ⩾60 min
4. Palmar telangiectasia
5. Raynaud's phenomenon
6. Unexplained digital oedema
7. Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)

B. Serologic domain
1. ANA ⩾1:320 titre, diffuse, speckled, homogeneous patterns *or*
   a. ANA nucleolar pattern (any titre) *or*
   b. ANA centromere pattern (any titre)
2. Rheumatoid factor ⩾2× upper limit of normal
3. Anti-CCP
4. Anti-dsDNA
5. Anti-Ro (SS-A)
6. Anti-La (SS-B)
7. Anti-ribonucleoprotein
8. Anti-Smith
9. Anti-topoisomerase (Scl-70)
10. Anti-tRNA synthetase (*e.g.* Jo-1, PL-7, PL-12; others are: EJ, (
11. Anti-PM-Scl
12. Anti-MDA-5

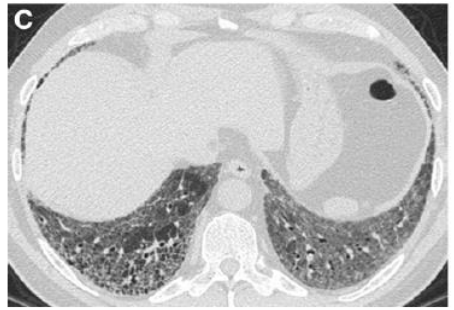
C. Morphologic domain
1. Suggestive radiology patterns by HRCT (see text for descriptions):
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
2. Histopathology patterns or features by surgical lung biopsy:
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
   e. Interstitial lymphoid aggregates with germinal centres
   f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)
3. Multi-compartment involvement (in addition to interstitial pneumonia):
   a. Unexplained pleural effusion or thickening

Interstitial pneumonia with autoimmune features: a new classification still on the move Eur Respir Rev 2018; 27: 180047

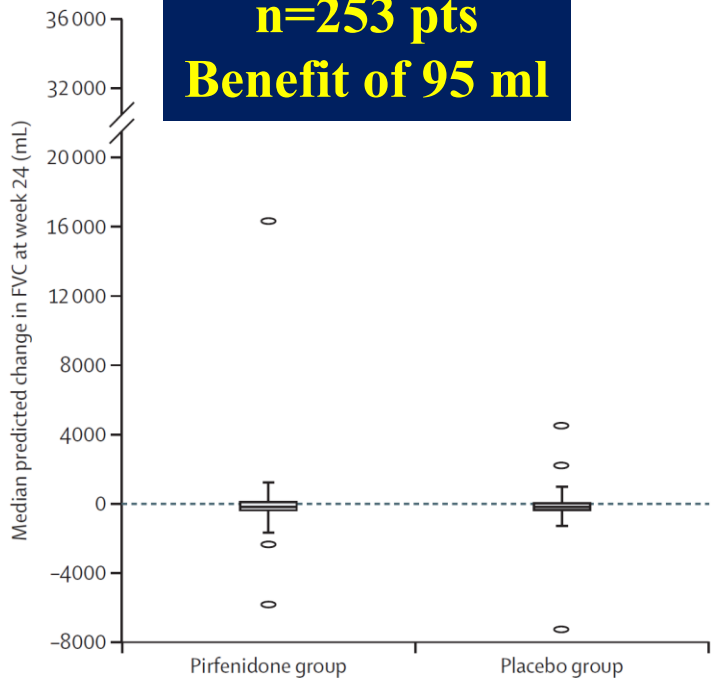
Lancet Respir Med 2019

Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial

Toby M Maher, Tamera J Corte, Aryeh Fischer, Michael Kreuter, David J Lederer, Maria Molina-Molina, Judit Axmann, Klaus-Uwe Kirchgaessler, Katerina Samara, Frank Gilberg, Vincent Cottin



n=253 pts
Benefit of 95 ml

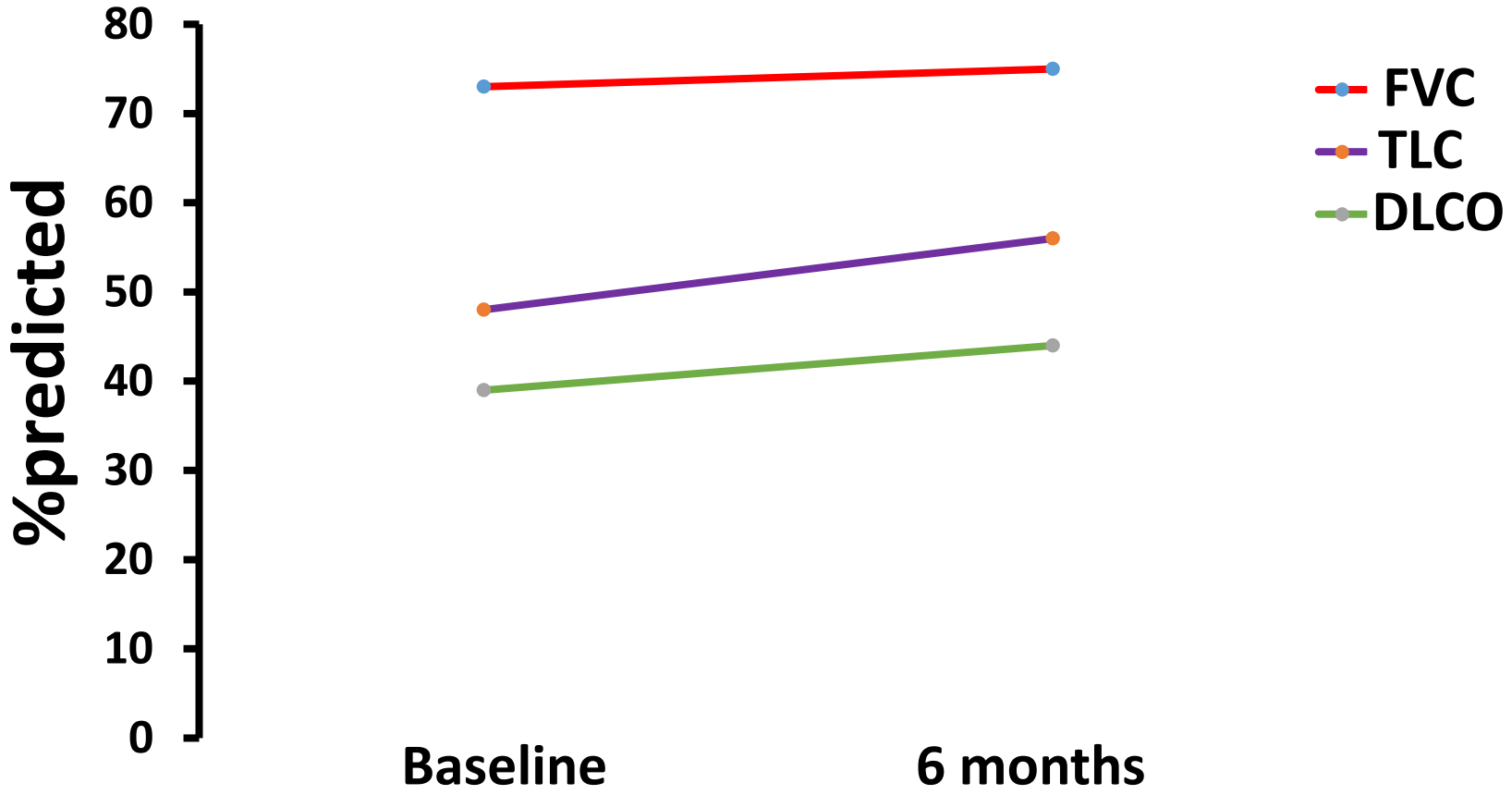


	Pirfenidone (n=127)	Placebo (n=126)	Pirfenidone *vs* placebo	p value*
Predicted FVC change from baseline measured by site spirometry, mL				
Mean (95% CI)	−17·8† (−62·6 to 27·0)	−113·0‡ (−152·5 to −73·6)	95·3 (35·9 to 154·6)	0·002
Median (Q1–Q3)	−7·5 (−185·4 to 112·3)	−125·8 (−238·2 to 2·2)	118·3	..
FVC change from baseline measured by site spirometry, % predicted				
Rank analysis of covariance	..	..	..	0·038
Patients with >5% decline in FVC	47 (37%)	74 (59%)	0·42 (0·25 to 0·69)§	0·001
Patients with >10% decline in FVC	18 (14%)	34 (27%)	0·44 (0·23 to 0·84)§	0·011
DLco change from baseline, % predicted				
Rank analysis of covariance	..	..	..	0·09
Patients with >15% decline in DLco¶	3 (2%)	11 (9%)	0·25 (0·07 to 0·93)§	0·039
6MWD change from baseline, m				
Rank analysis of covariance	..	..	..	0·040
Patients with >50 m decline in 6MWD¶	36 (28%)	35 (28%)	1·03 (0·59 to 1·78)§	0·92

Data are n (%), unless otherwise specified. FVC=forced vital capacity. DLco=carbon monoxide diffusing capacity. 6MWD=6-min walk distance. *p values for secondary endpoints are not adjusted for multiplicity and are provided for descriptive purposes only. †n=118; only patients with a baseline measurement and at least two post-baseline measurements were included in the analysis. ‡n=119; only patients with a baseline measurement and at least two post-baseline measurements were included in the analysis. §Odds ratio (95% CI). ¶Prespecified exploratory outcome.

Low dose OCS – Pirfenidone
Follow-up (6 months)

- **ANA: 1/320, anti-Scl70:++, RF: 10.8, anti-CCPs:-**



“Fatal” limitations of the IPAF/EULAR criteria – miscommunication Rheum-Pulmo

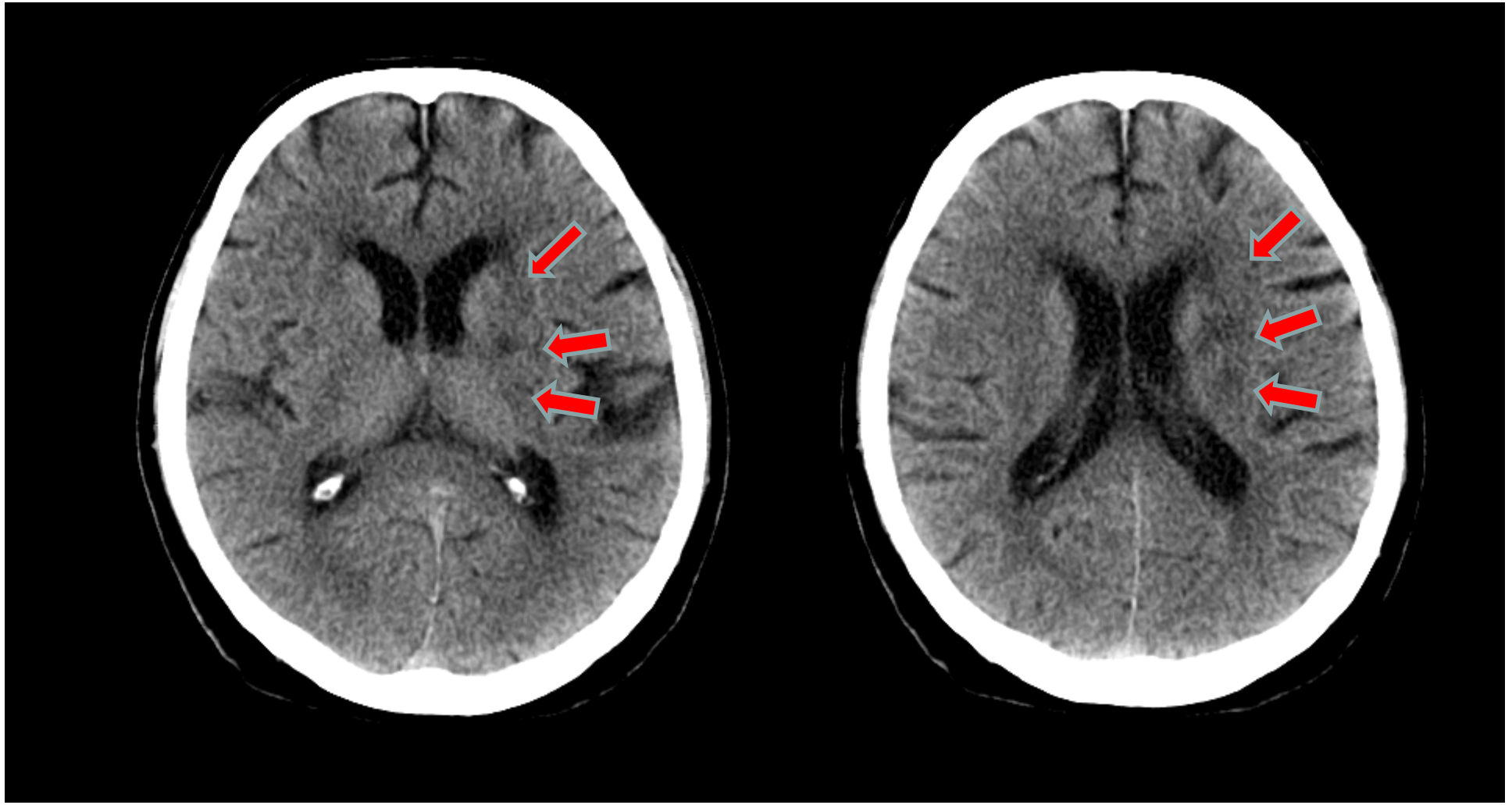
- IPAF criteria contain myositis-specific Abs (MDA5, Jo1)
- Abs= rapidly progressing ILDs that will benefit from aggressive approaches with high-doses of CS and immunomodulation
- No therapeutic guidelines for IPAF
- EULAR 2018 require the presence of 6mo of disease duration – ILD is not included
- 6 mo delays to set firm diagnosis maybe FATAL

Vasculitis associated ILD

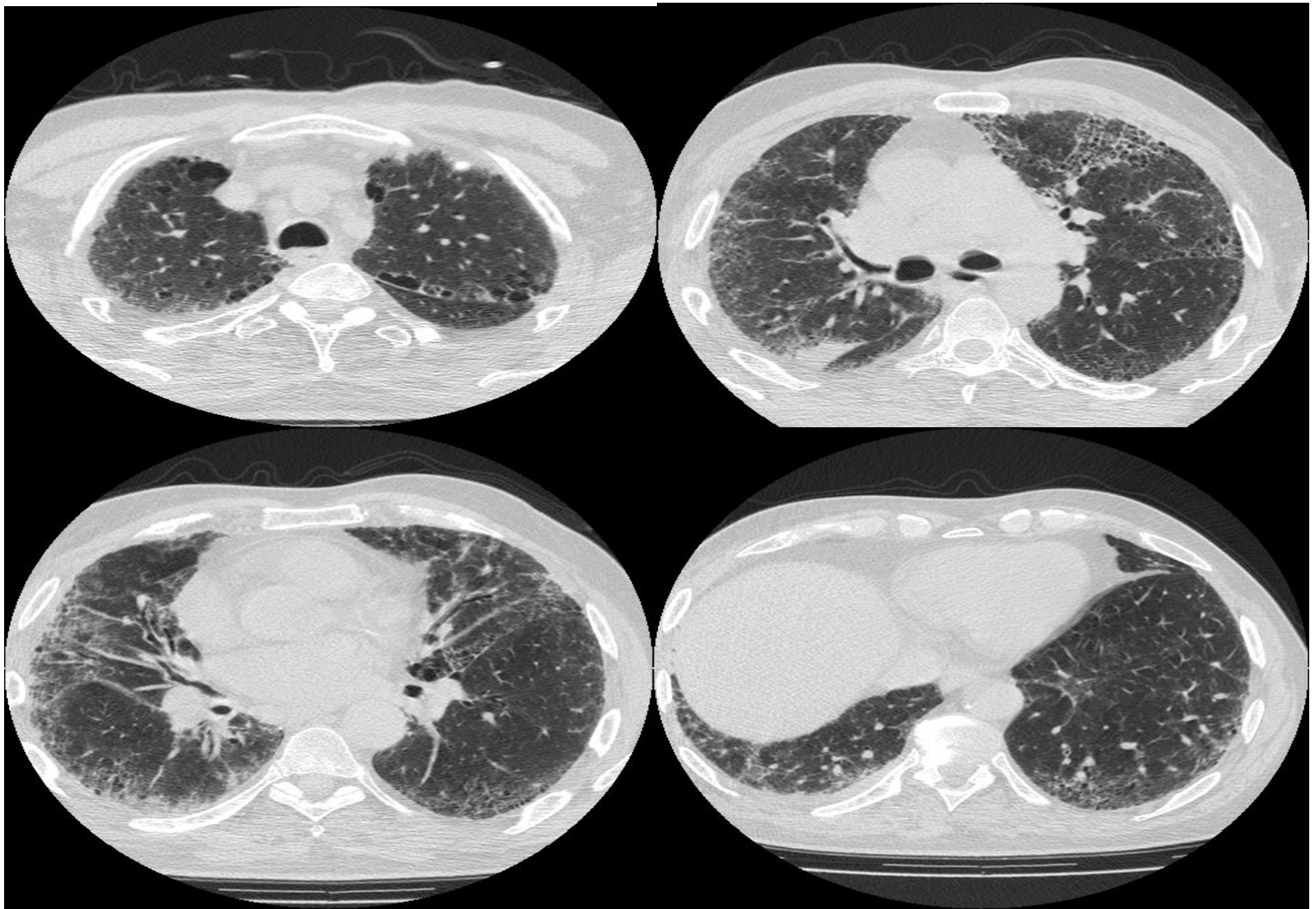
CASE

69-yr old, male, ex-smoker (40 p/yr), BMI=30, farmer, admitted to ER due to mild dyspnoea on exertion (mMRC I) headache, muscle weakness and dysarthria the last 4 hrs.

Brain CT showing multiple ischemia lesions (arrows) in the internal watershed distribution of left internal carotid artery



Day 1



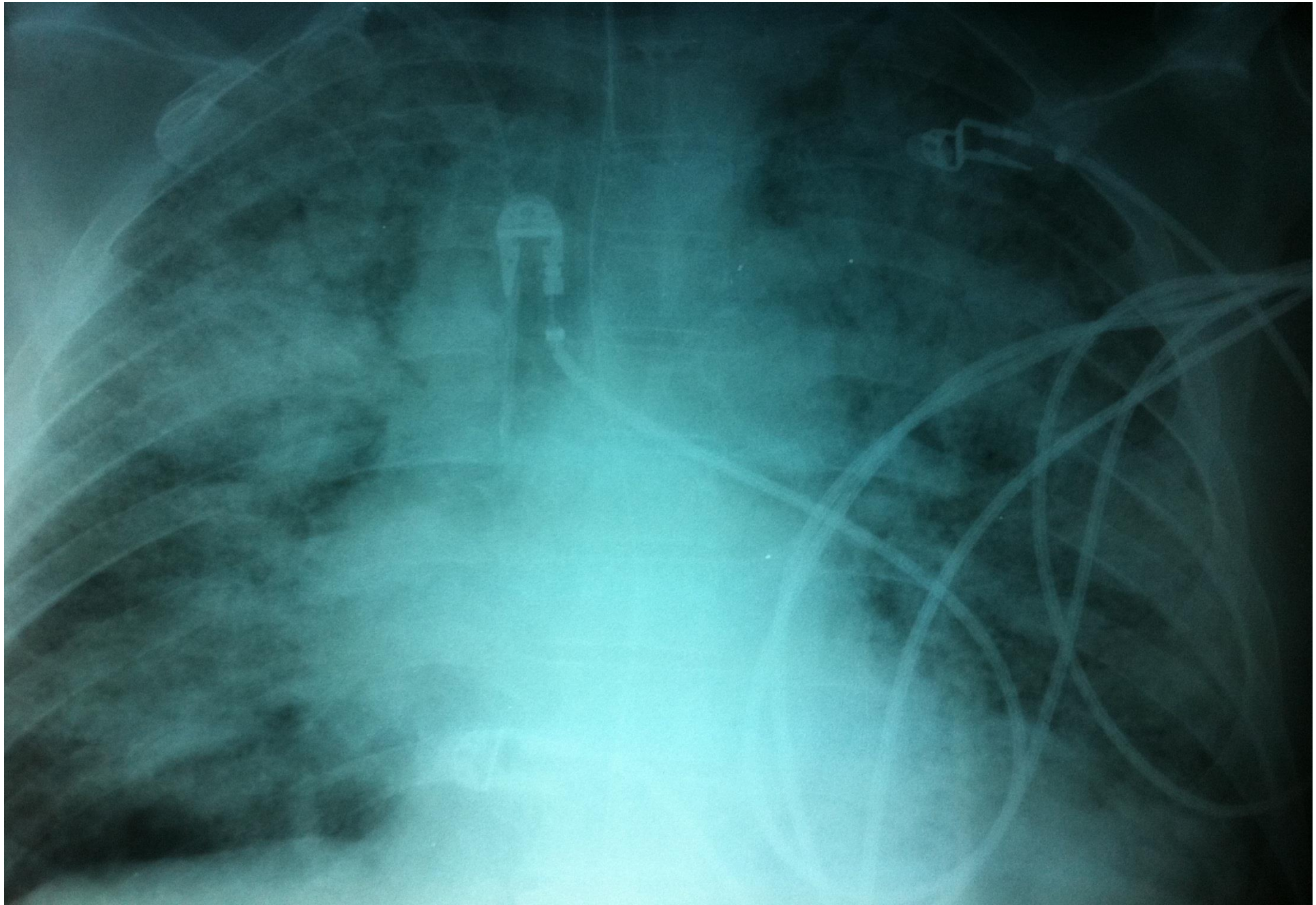
Case follow-up (I)
(day 6)

- **Patient treated with 325 mgr aspirin**
- **Patient developed fever (38_0C) and progressive dyspnea with minimal activity – at rest (mMRC IV/IV). Started on Meropenem 1gr*2/day (GFR=24.6)**
- **ABGs: PO_2: 60 mmHg, PCO_2: 30 mmHg, pH:7.45, FiO2: 21%**
- **Blood cell count: Ht :30,1% Hb: 10,1 g/dL, WBC:6.650, Lymph: 31%, Neu:65%, Eos=180/µl, ESR:55mm/1hr**
- **Routine lab tests:**

  Glucose: 110 mg/dl, U:156 mg/dl, Cr:3,4 mg/dl, Na: 139mmol/L, K: 4,3mmol/L, CRP:2.9 mg/dl

- **24hour urine protein levels: 1400 mg/dl**
- **Microscopic urine analysis: red blood cell renal casts**
- **HRCT: Presented (day 12)**

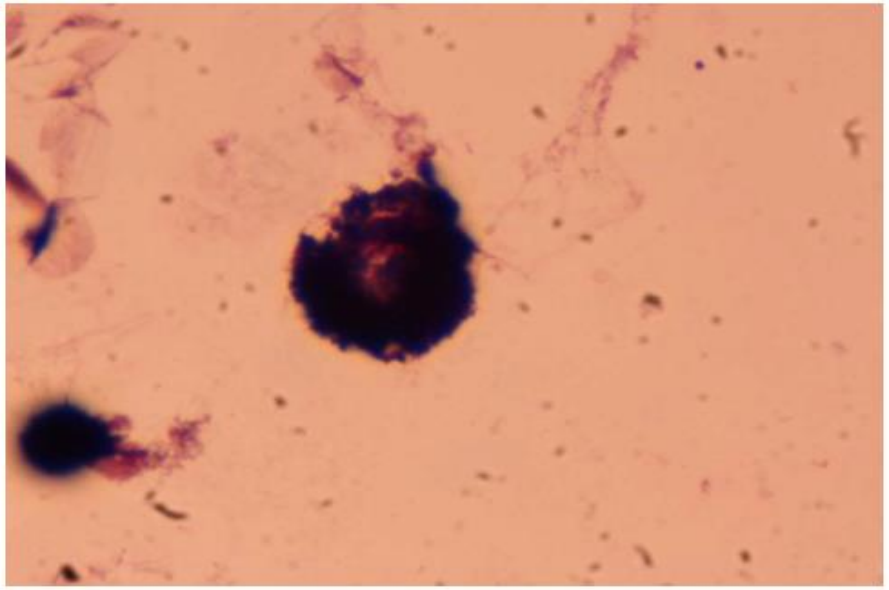
Respiratory Failure - ARDS

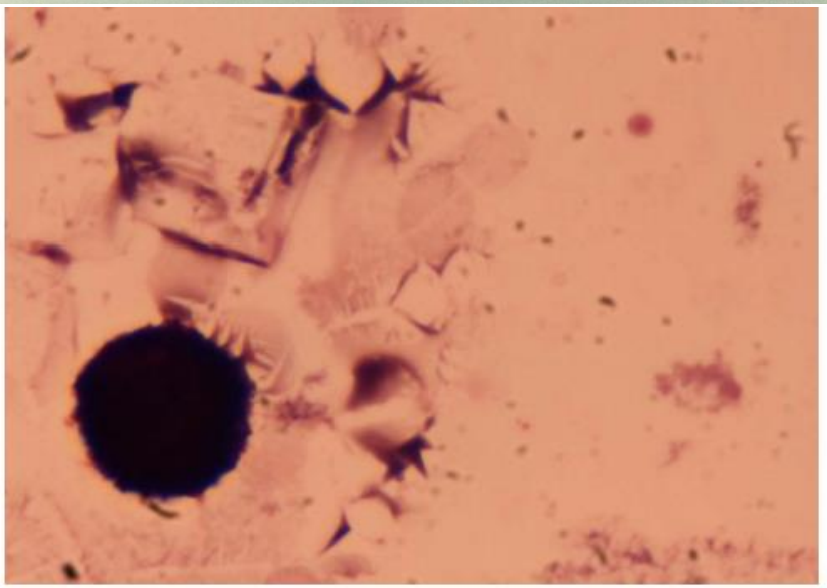


Case follow-up
(day 13)

- **BALF = BLOODY**

- **BALF differential cell count = >40% siderophages**

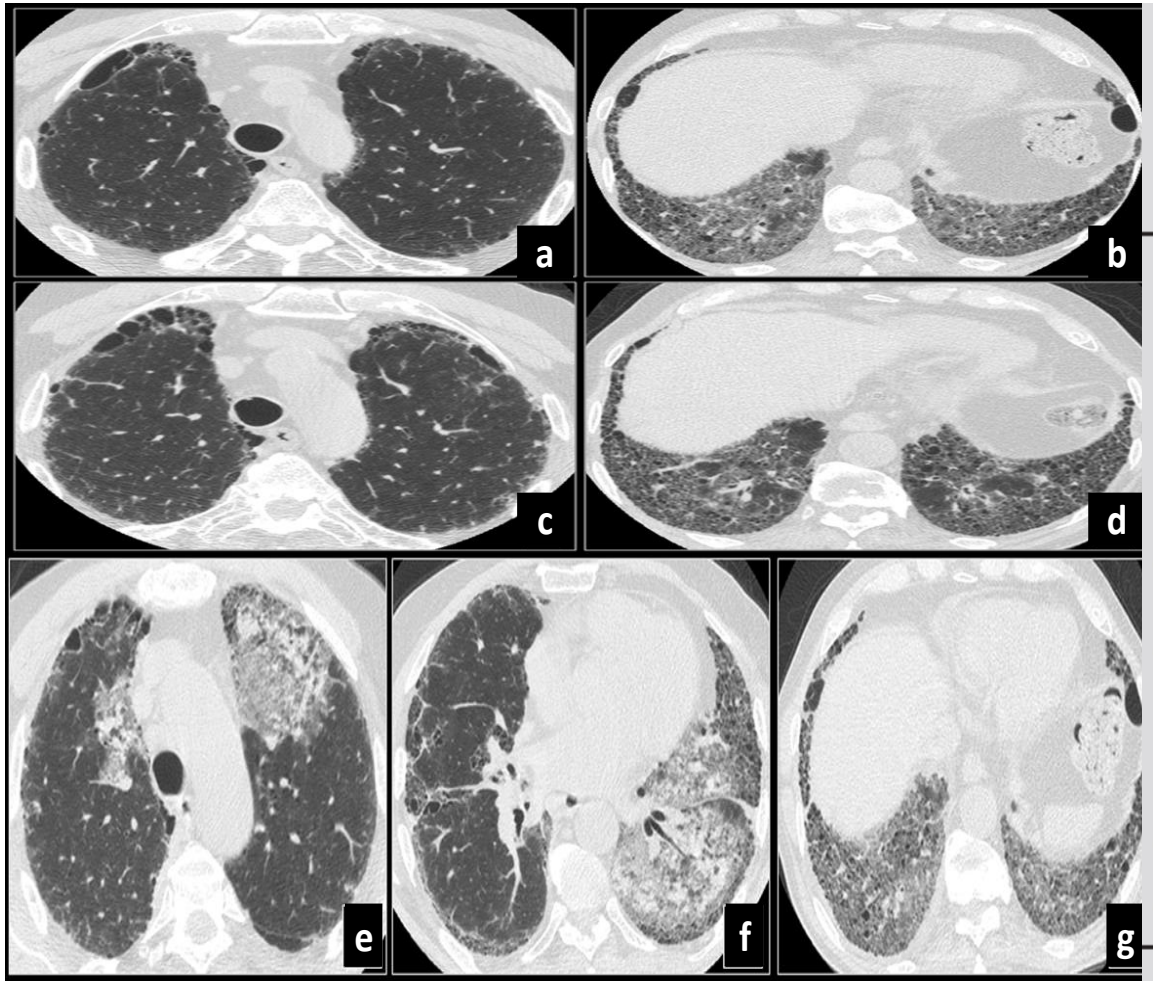




Combined pulmonary fibrosis and emphysema associated with microscopic polyangiitis

Argyris Tzouvelekis*, George Zacharis*, Anastasia Oikonomou#, Andreas Koulelidis*, Paschalis Steiropoulos*, Marios Froudarakis*, Pelagia Kriki¶, Vassilios Vargemezis¶ and Demosthenes Bouros*

EUROPEAN RESPIRATORY JOURNAL



	Time after MPA diagnosis		
	-12 months	0 months	36 months
FEV_1 % pred	69.2	59.6	60.9
FVC % pred	70.1	63.6	67.7
FEV_1/FVC	73.7	70.8	66.2
$FEF_{25-75\%}$ %pred	44	40	33
TLC % pred	73	58.5	53.3
$D_{L,CO}$ %pred	43.4	25.7	30.2
6MWD m	380	NA	370
sP_{pa}# mmHg	25	35	35
P_{a,O_2} mmHg	66	55	60
P_{a,CO_2} mmHg	40	39	46

Eur Respir J 2010; 36: 116–121
DOI: 10.1183/09031936.00110109

Prevalence and outcome of pulmonary fibrosis in microscopic polyangiitis

G.E. Tzelepis*,#, M. Kokosi*,#, A. Tzioufas*,#, S.P. Toya*,#, K.A. Boki¶, A. Zormpala+ and H.M. Moutsopoulos*,#

TABLE 2 Pulmonary function data in microscopic polyangiitis patients# with or without fibrosis

	Fibrosis	No fibrosis	p-value
FVC % pred	75.4±12.3	79.6±10.9	0.45
FEV_1 % pred	77.0±19.9	71.9±20.4	0.61
FEV_1/FVC	88.3±8.0	78.7±17.5	0.17
TLC % pred	70.6±5.9	82.9±17.1	0.01
$D_{L,CO}$ % pred	55.5±18.0	70.2±19.6	0.16

Data are presented as mean±SD, unless otherwise stated. FVC: forced vital capacity; % pred: % predicted; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; $D_{L,CO}$: diffusing capacity for carbon monoxide. #: there were seven measurements in the fibrotic group and 11 in the non-fibrotic group.

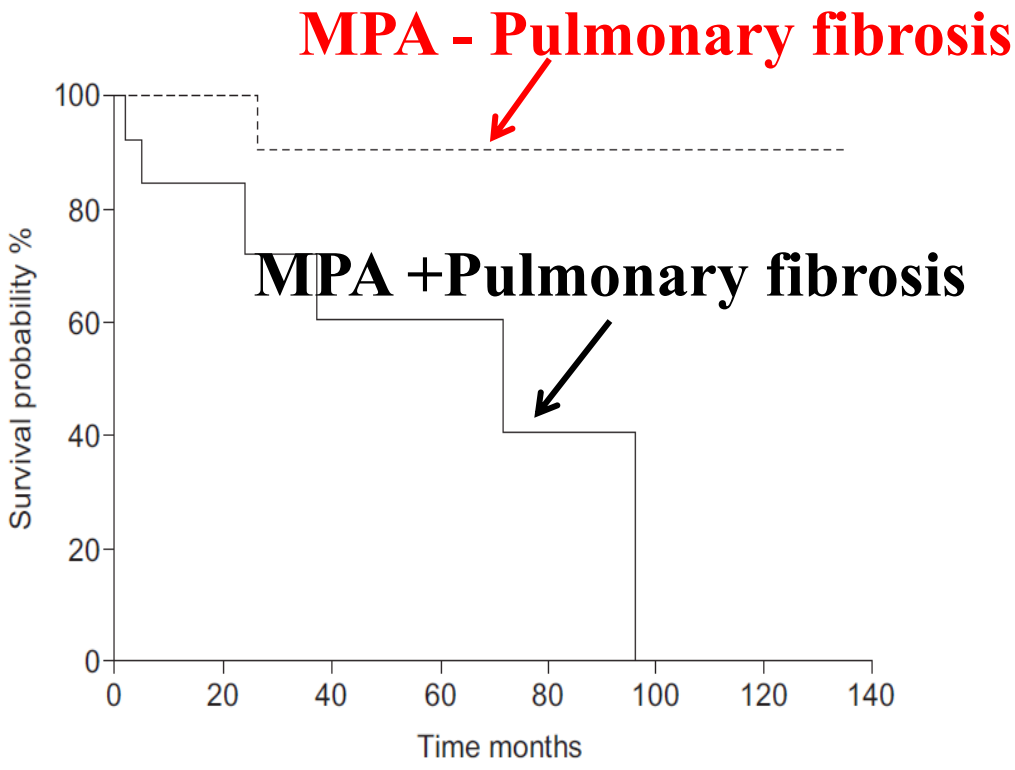
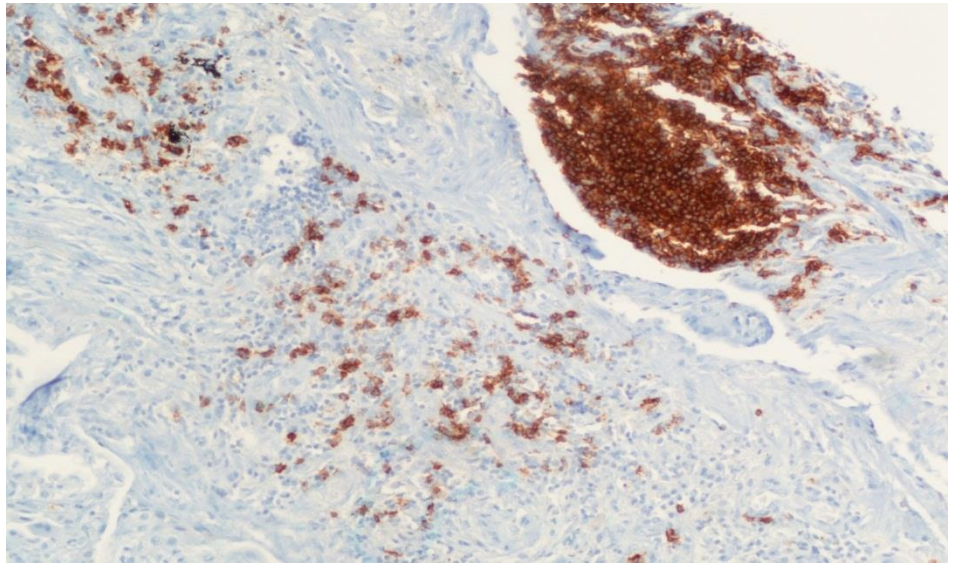


FIGURE 2. Kaplan–Meier survival graph comparing microscopic polyangiitis patients with (——) and without (- - - -) pulmonary fibrosis.

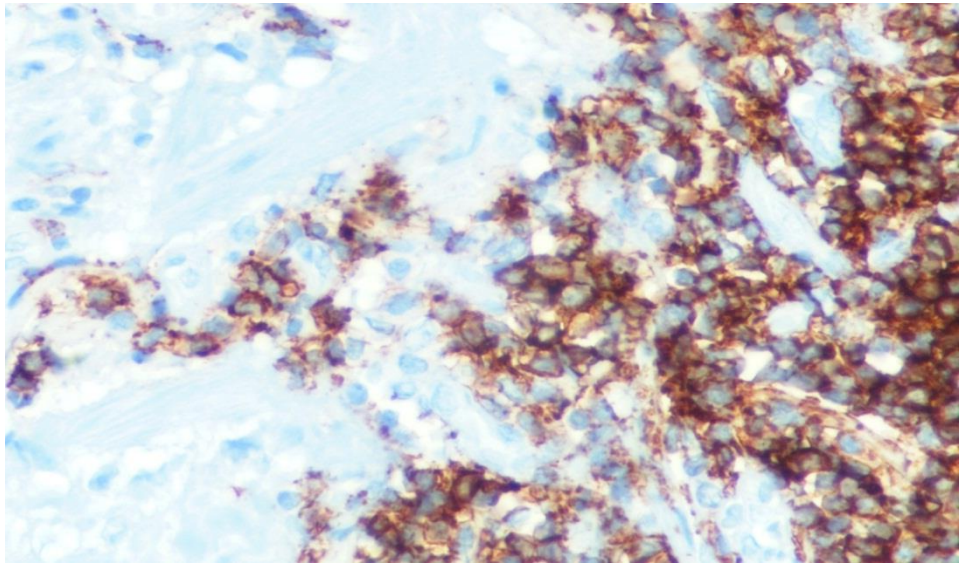
Autoimmunity profile in CPFE patients

Characteristics	CPFE	IPF
Total	40	34
Male	38	29
Age	56 (31-74)	61 (44 – 73)
ANA	17 (42.5%)	11 (32%)
p-ANCA	7 (17.5%)	0
c-ANCA	0	0
anti-scl 70	1 (2.5%)	1 (2.5%)
anti-dsDNA	0	1 (2.5%)
anti-Ro	0	0
anti-La	0	0
Anti-CCPs	2 (5%)	2 (5.8%)
RF	3 (7.5%)	4 (11.7%)
Microscopic Hematuria	7 (17.5%)	0
+ Renal biopsy for necrotizing glomerulonephritis	3 (7.5%)	NA

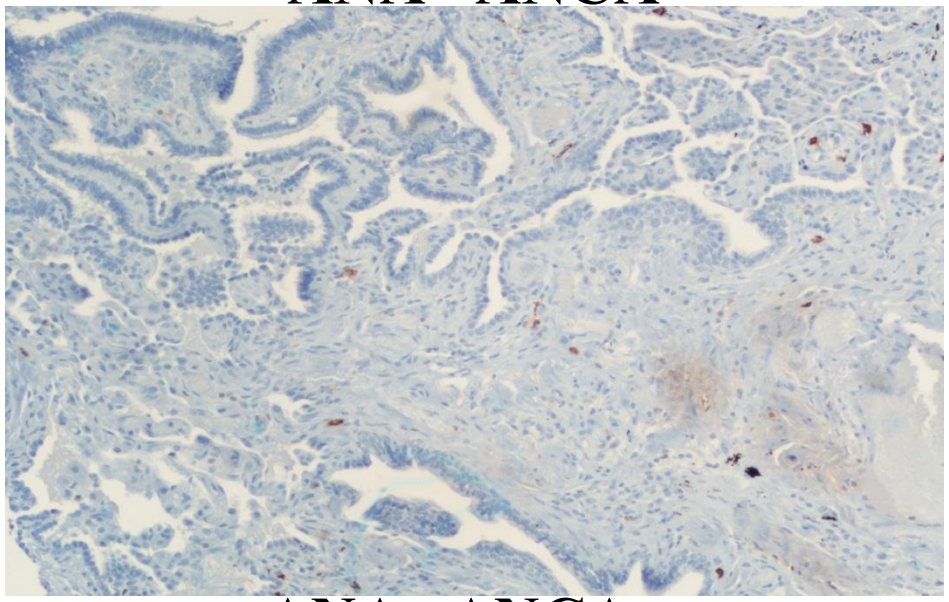
Lymphoid follicles with CD20+ cells in CPFE patients with ANA+ANCA+



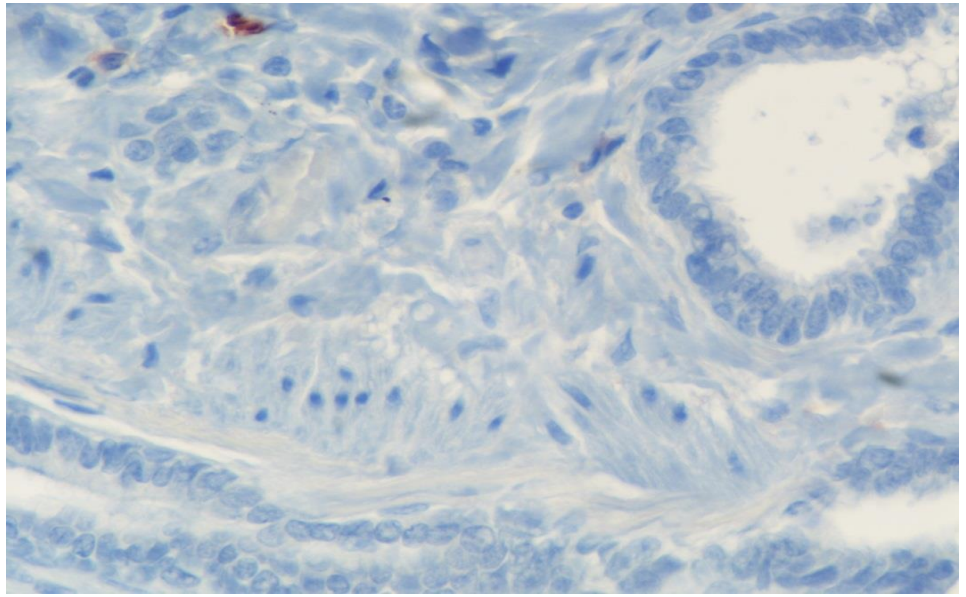
A ANA +ANCA+



B ANA +ANCA+



C ANA –ANCA-



D ANA –ANCA-

Conclusions

Diagnostic algorithm of CTD-ILD

Clinical	Radiology	Pathology
• History • Physical • Laboratory • PFTs	• Chest X-ray • HRCT	• Surgical lung biopsy

Primary care physicians	Pulmonologists Rheumatologist Cardiologists	Pulmonary Radiologists	Pulmonary Pathologists

Multidimensional and multidisciplinary

GOLD STANDARD

Follow-up of CTD-ILD

1. Clinical evaluation (dyspnea, cough)
2. Respiratory function evaluation
3. Every 3-6 months
4. Significant deterioration:
    1. FVC >10% (-3.0% to 3.0%-Clinically meaningful)*
    2. TLco >15%
    3. 6MWT >50 m (24m-MCID**)
5. HRCT annually or symptoms emergence

AJRCCM 2008;177:1248–1254

**Reliability of FVC in SLS-I-II studies-AJRCCM 2017*
*** duBois et al- AJRCCM 2011*

TAKE HOME MESSAGES

- All CTDs can involve the interstitium – 10% prior CTD
- Inflammation = Immunomodulation - beware the acute onset
- Fibrosis = Anti-fibrotics – Nintedanib /Pirfenidone
- Regular routine evaluation for ILD development - HRCT+ PFTs + Cardiac echo (all SSc)- screen for lung cancer
- MDD is mandatory – Treatment specific endotypes

**Volkmann et a- MMF versus placebo in SSc-Arthritis and Rheum-2017*
Fischer et al. MMF in RA-ILD. J Rheum 2013

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Commentary

Endotyping of progressive fibrotic interstitial lung diseases: It is the final destination that matters and not the journey

Argyris Tzouvelekis, Demosthenes Bouros*