2022.06.25

ILD School 2022

Nonspecific Interstitial Pneumonia (NSIP)

Diagnosis and Treatment

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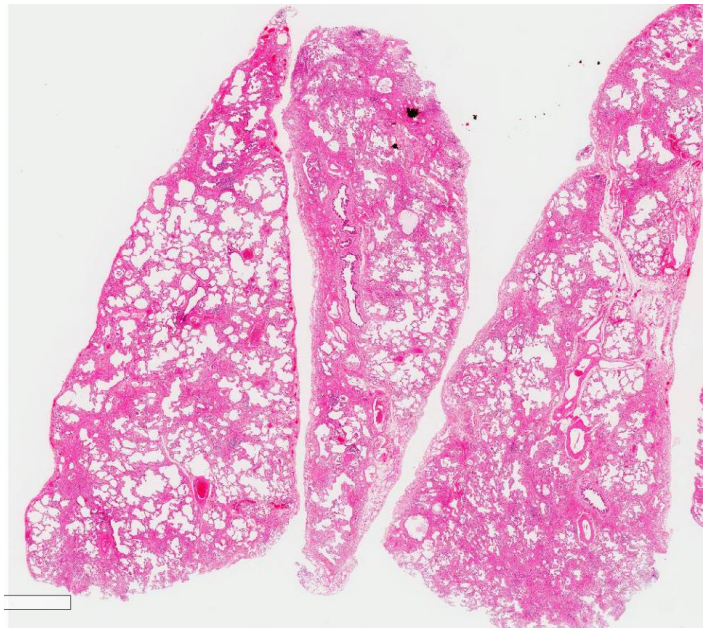
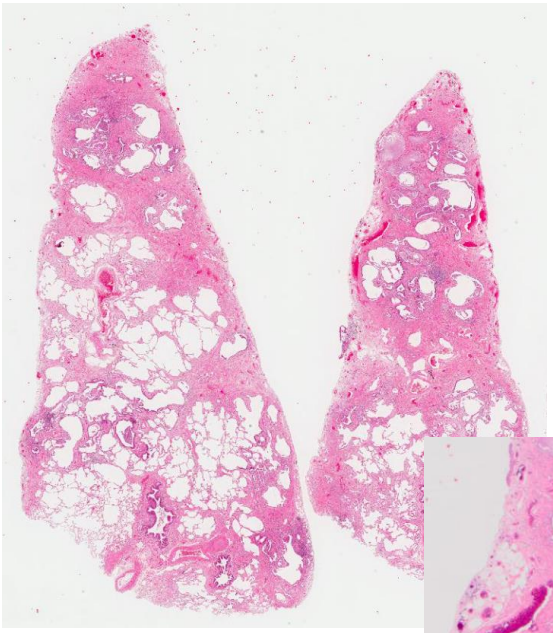
NSIP Pattern (Pathologic features)

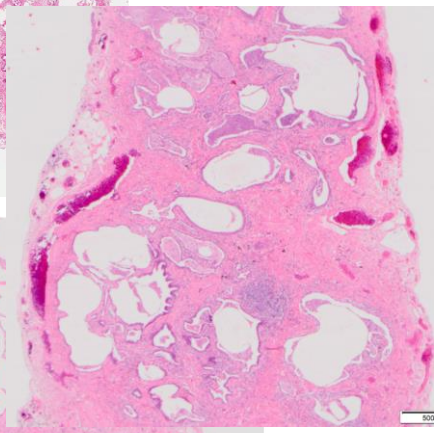
- **Pathologic term**
  - Characterized by an interstitial inflammatory or fibrosing process or both .. [that] appeared temporally uniform within each case (Katzenstein et al.)
  - Contrary to temporally heterogenous process of UIP pattern
  - First viewed as "waste basket pattern'

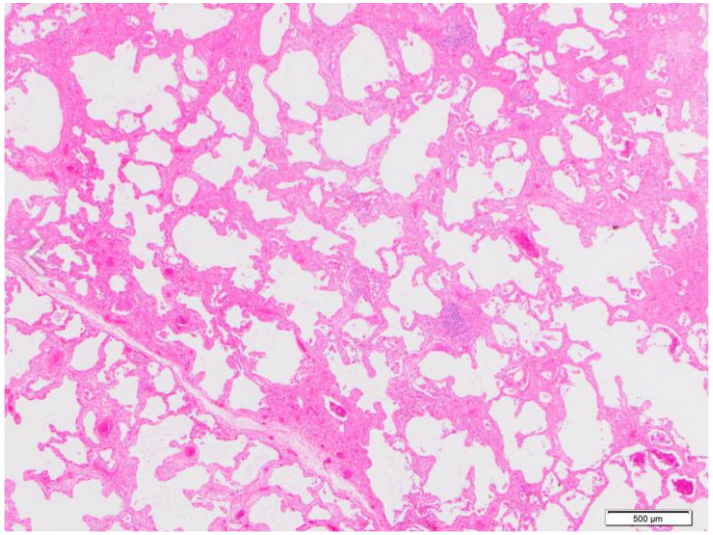
Ketzenstein ALA and Fiorelli RF. *Am J Surg Pathol*. 1994;18(2)
Wells AU and Cottin V. *Curr Opin Pulm Med*. 2016;22

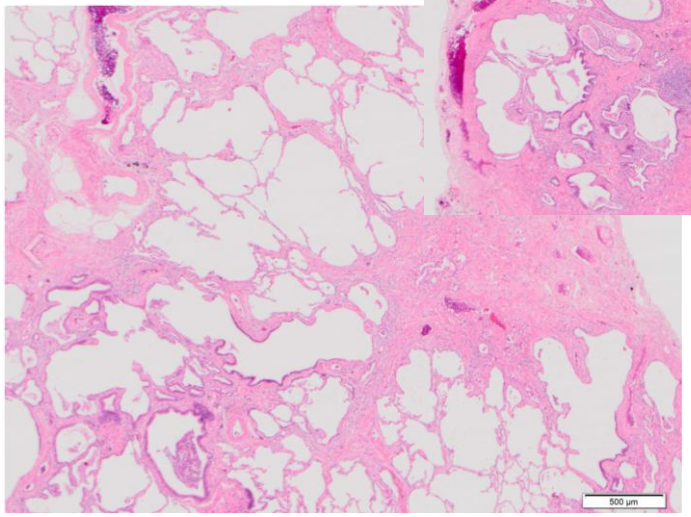
Pathologic Pattern (NSIP vs. UIP)



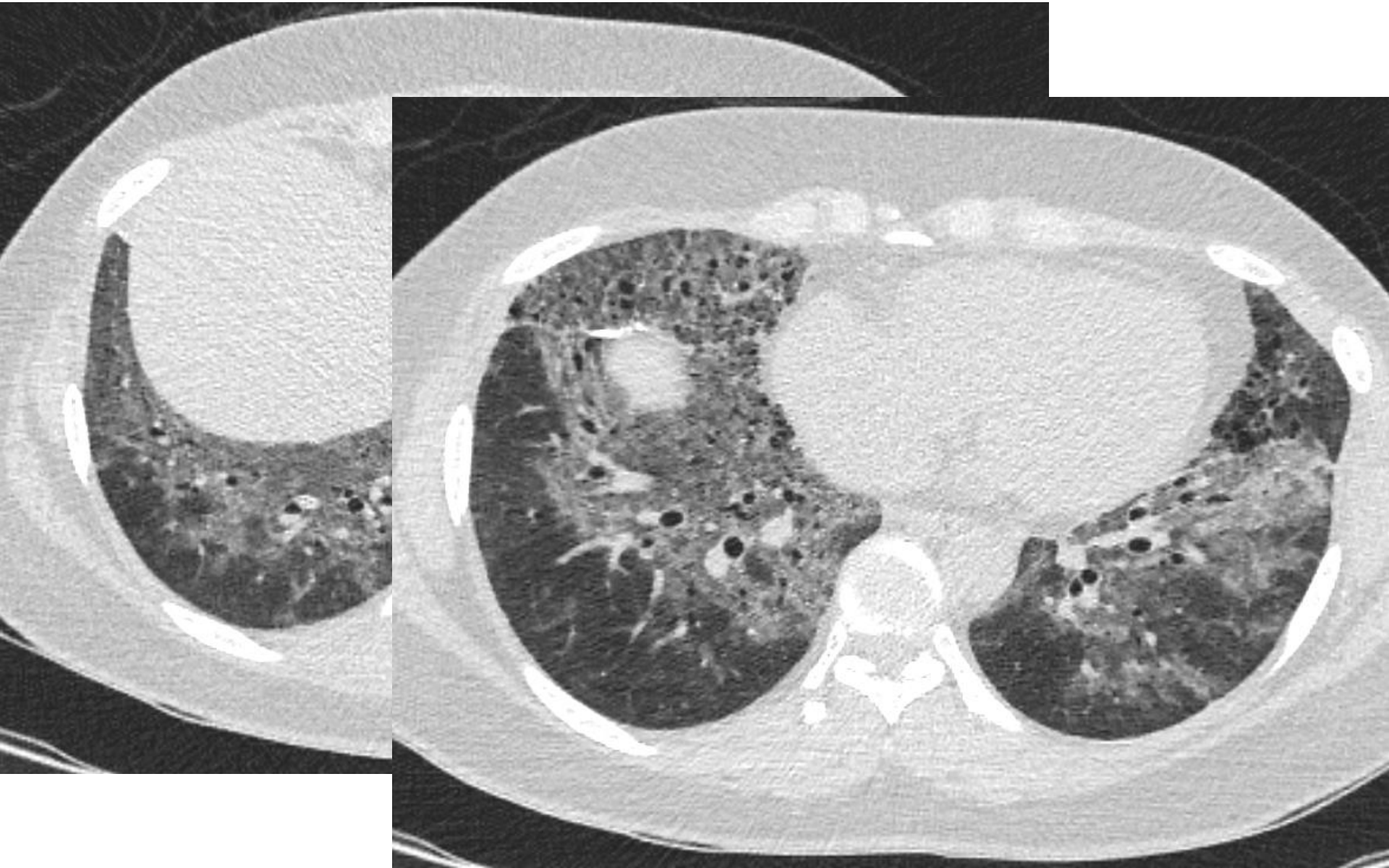








Radiologic Pattern (NSIP)



Historic Classification of IIP

5 Categories

Liebow and Carrington (1969)*: Chronic Forms	
Usual interstitial pneumonia	
Desquamative interstitial pneumonia	
Bronchiolitis obliterans interstitial pneumonia and diffuse alveolar damage	→ Similar to UIP with superimposed BO
Lymphoid interstitial pneumonia	
Giant cell interstitial pneumonia	

Hamman Rich Syndrome → Acute form of UIP

Liebow AA and Carrington CB. *Front Pul Radiol*. 1969

Nonspecific Interstitial Pneumonia/Fibrosis

The American Journal of Surgical Pathology *18(2): 136–147, 1994*

Nonspecific Interstitial Pneumonia/Fibrosis

Histologic Features and Clinical Significance

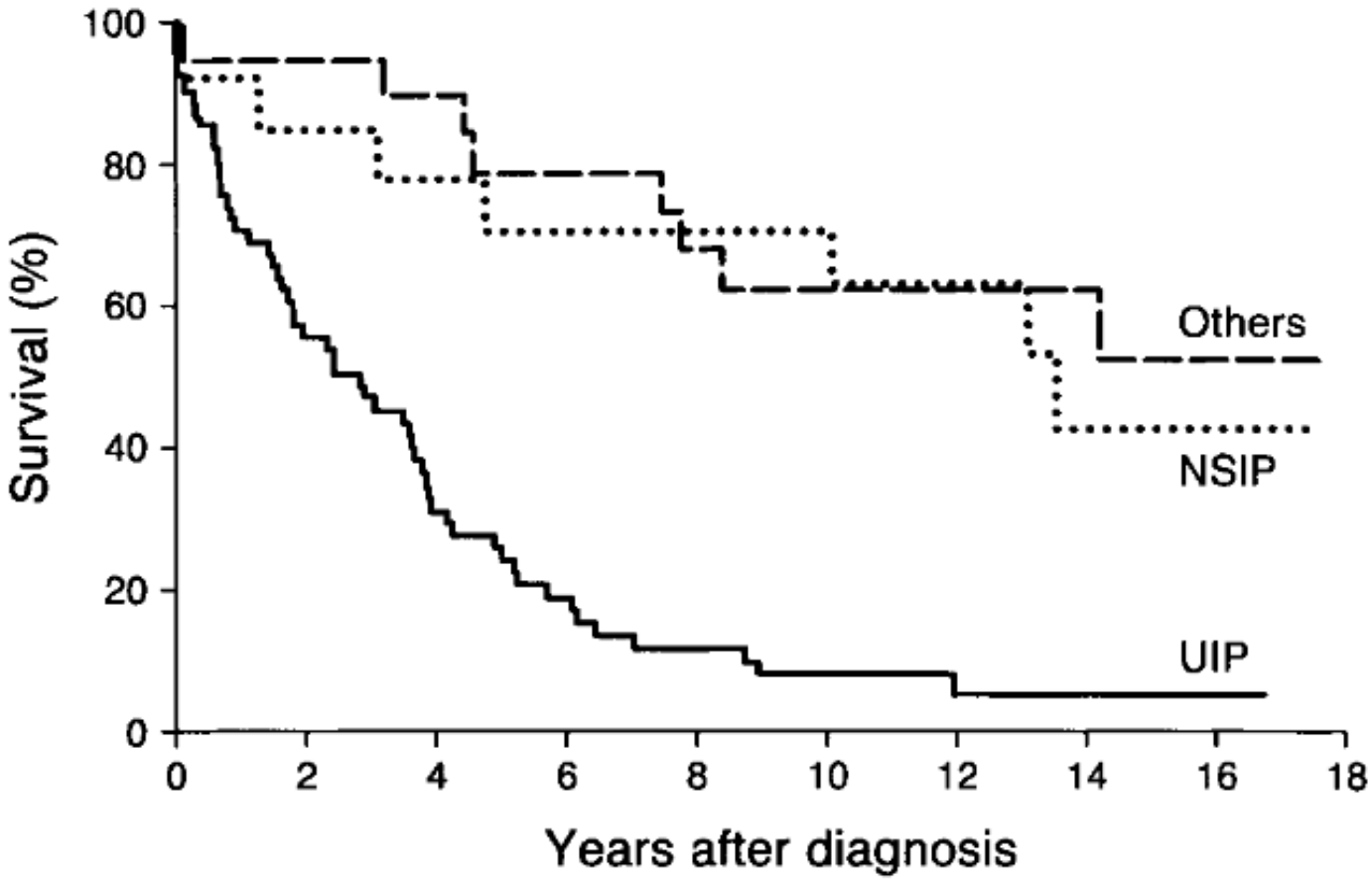
Anna-Luise A. Katzenstein, M.D., and Robert F. Fiorelli, B.S.

drome) (8). It has been our impression that in addition to these entities, a fairly sizeable group of idiopathic interstitial pneumonias cannot be pigeonholed into one of the three main groups, and we have termed these lesions nonspecific interstitial pneumonia or fibrosis. This study was undertaken

showed pure inflammation and no fibrosis. Nonspecific interstitial pneumonia must be separated from the three main forms of idiopathic interstitial pneumonia because of better prognosis and different treatment options. It should not be considered a specific disease, however, because it may have varying etiologies including underlying connective tissue diseases, organic dust or other exposures, and prior acute lung injury; less often, it may reflect a nonrepresentative biopsy of another process.

Katzenstein ALA and Fiorelli RF. *Am J Surg Pathol*. 1994;18(2)

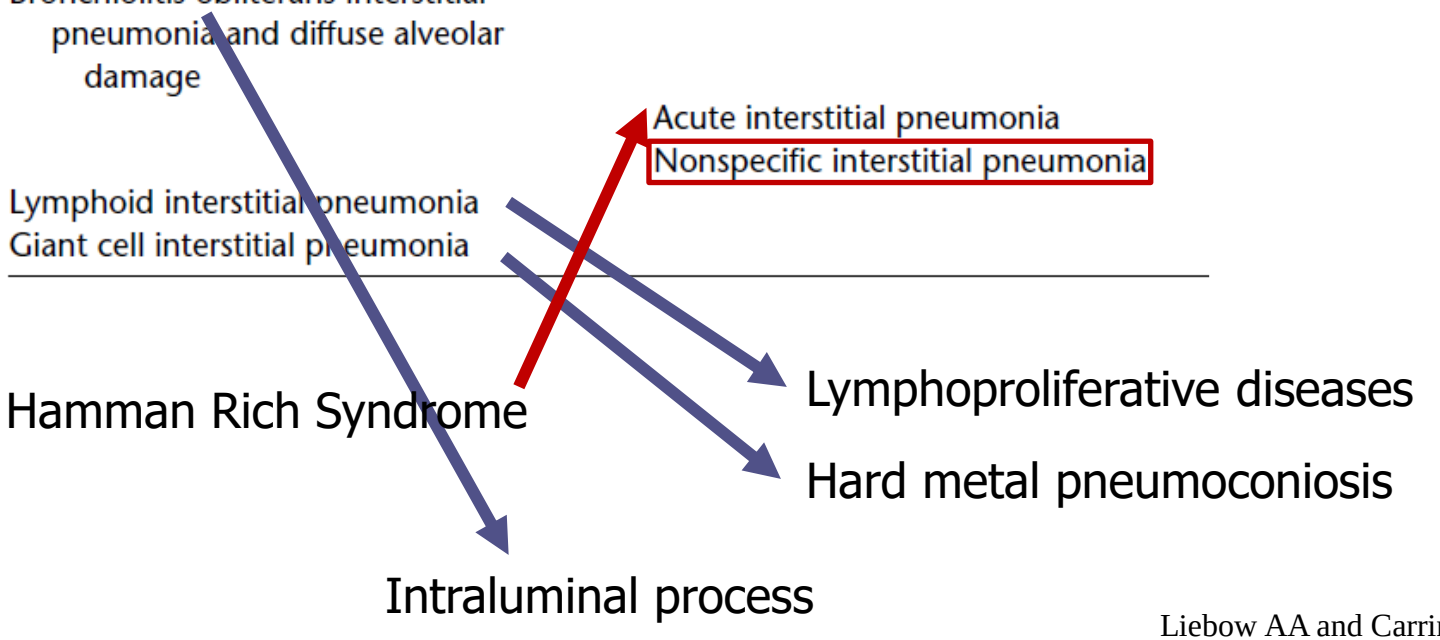
Prognosis of NSIP



Bjoraker JA et al. *Am J Respir Crit Care Med*. 1998; 157

Historic Classification of IIP

5 Categories	4 Categories
Liebow and Carrington (1969)*: Chronic Forms	Katzenstein (1997)†
Usual interstitial pneumonia	Usual interstitial pneumonia
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia/ respiratory bronchiolitis interstitial lung disease
Bronchiolitis obliterans interstitial pneumonia and diffuse alveolar damage	
	Acute interstitial pneumonia
	Nonspecific interstitial pneumonia
Lymphoid interstitial pneumonia	
Giant cell interstitial pneumonia	



Liebow AA and Carrington CB. *Front Pul Radiol*. 1969
Katzenstein AL and Myers JL. *Am J Respir Crit Care Med*. 1998;157

Historic Classification of IIP

5 Categories	4 Categories	5 Categories
Liebow and Carrington (1969)*: Chronic Forms	Katzenstein (1997)†	Müller and Colby (1997)‡
Usual interstitial pneumonia	Usual interstitial pneumonia	Usual interstitial pneumonia
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia/ respiratory bronchiolitis interstitial lung disease	Desquamative interstitial pneumonia
Bronchiolitis obliterans interstitial pneumonia and diffuse alveolar damage		Bronchiolitis obliterans organizing pneumonia
	Acute interstitial pneumonia	Acute interstitial pneumonia
	Nonspecific interstitial pneumonia	Nonspecific interstitial pneumonia
Lymphoid interstitial pneumonia		
Giant cell interstitial pneumonia		

Liebow AA and Carrington CB. *Front Pul Radiol*. 1969
Katzenstein AL and Myers JL. *Am J Respir Crit Care Med*. 1998;157
Muller NL and Colby TV. *Radiographics. 1997;17*

Nonspecific Interstitial Pneumonia/Fibrosis

The American Journal of Surgical Pathology *18(2): 136–147, 1994*

Nonspecific Interstitial Pneumonia/Fibrosis

Histologic Features and Clinical Significance

Anna-Luise A. Katzenstein, M.D., and Robert F. Fiorelli, B.S.

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Katzenstein ALA and Fiorelli RF. *Am J Surg Pathol*. 1994;18(2)

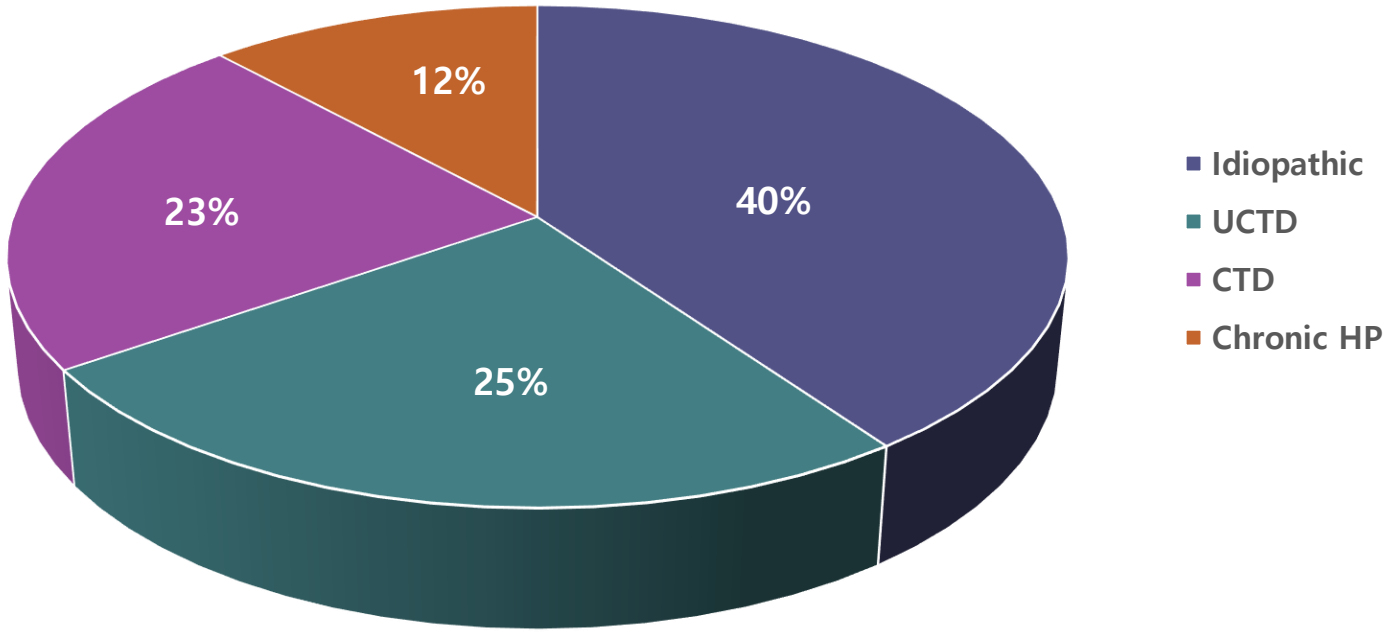
Etiologies of Bx-proven NSIP

- **Idiopathic**
- **Connective tissue diseases**
  - RA, SLE, Polymyositis, SSc, Sjogren's syndrome
- **Environmental exposure**
  - Parrot
- **Drugs**
- **Other possible etiologies**
  - Bird, wood stove, grain dust, coal, paper factory, transfusion, jacuzzi

Katzenstein ALA and Fiorelli RF. *Am J Surg Pathol*. 1994;18(2)

Etiologies of Bx-proven NSIP (Pattern)

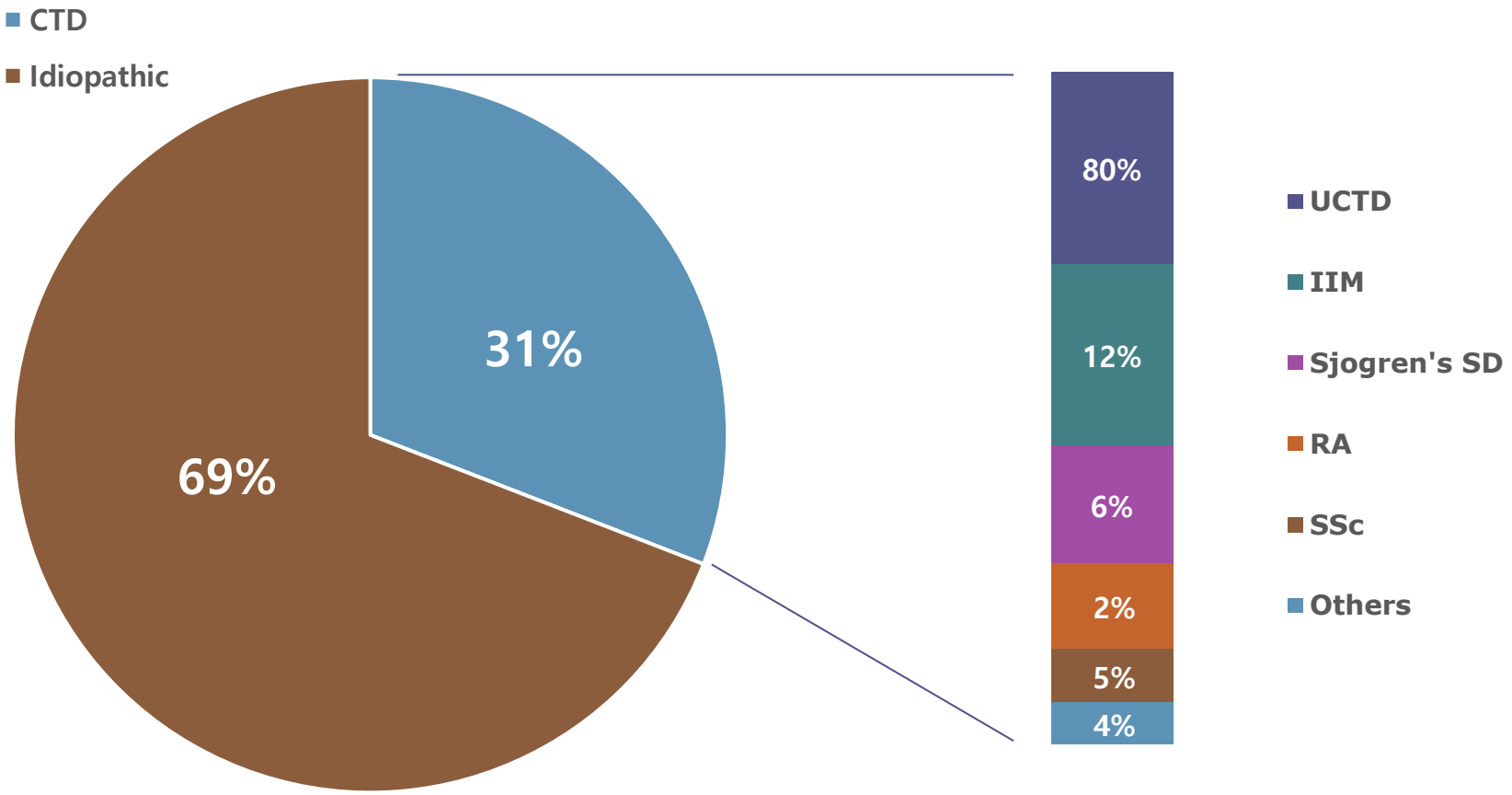
- 127 pathologically proven NSIP cases from single center (France)



Nunes H *et al*. *Eur Respir J*. 2015; 45(3)

Etiologies of Bx-proven NSIP (SMC)

- 204 pathologically proven NSIP cases from single center (SMC)



Cho HK, Chung MP et al. *Ther Adv Respir Dis*. 2022;16

Characteristics of CTD-ILD

Connective Tissue Disease	Pattern of ILD	Estimated prevalence	Occult CTD
Rheumatoid arthritis	UIP NSIP OP	10% (30% subclinical)	Less often
Systemic sclerosis	NSIP UIP	~ 50% (80% subclinical)	Less often
Inflammatory myositis **Anti-synthetase syndrome**	NSIP with OP NSIP OP UIP	40%	Often
Sjogren's syndrome	NSIP UIP LIP	40%	Less often
Interstitial pneumonia with autoimmune features (IPAF)	NSIP OP NSIP/OP UIP	100%	Often

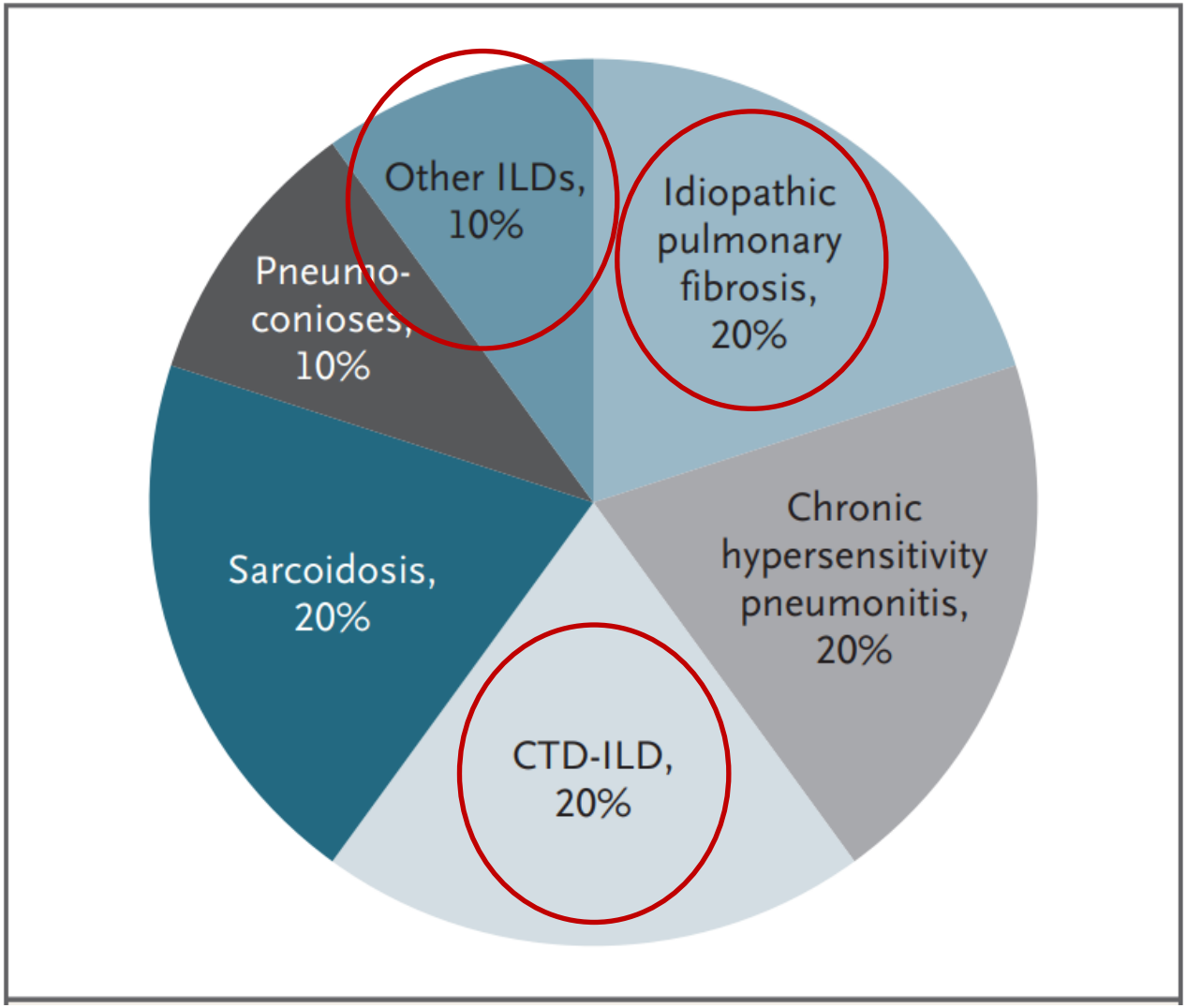
Raghu G *et al*. *Am J Respir Crit Care Med*. 2018;198(5)

Prevalence of Idiopathic Interstitial Pneumonia

	Bjoker et al. (1998)	Nagai et al. (1998)	Travis et al. (2000)	Nicholson et al. (2000)	SMC (2002)	Duchemann et al. (2017)
Total (N)	104	129	101	78	131	848 (Total ILD)
UIP	62 (60%)	50 (39%)	55 (55%)	37 (47%)	56%	68%
NSIP	14 (13%)	24 (19%)	29 (29%)	28 (36%)	24%	14%
COP	4 (4%)	18 (14%)	N/A	N/A	8%	6%
DIP/RB-ILD	10 (10%)	N/A	16 (16%)	13 (17%)	2%	7%
AIP	2 (2%)	N/A	N/A	N/A	7%	N/A
Others	12 (12%)	26 (20%)	N/A	N/A	3%	N/A

Collard HR et al. *JAMA Int Med*. 2003; 163(1):17-29
Zibrak JD and Price D. *Npj Prim Care RP* . 2014; 24

Distribution of ILD (US)



Lederer DJ *et al*. *N Engl J Med*. 2018;378

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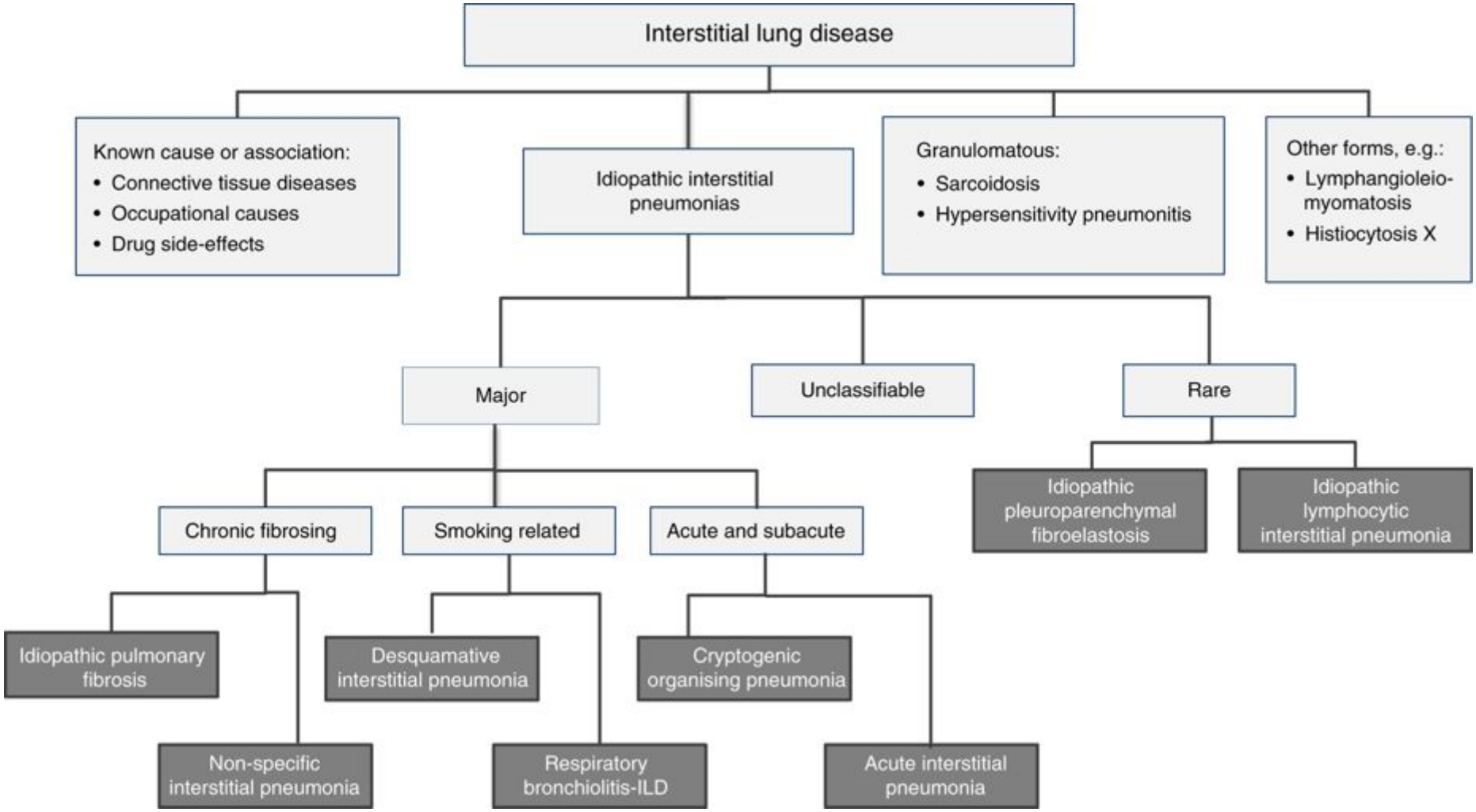
Classification of ILD



Joint statement. *Am J Respir Crit Care Med*. 2002; 165:277-304
Zibrak JD and Price D. *Npj Prim Care RP* . 2014; 24

Significance of CTD in ILD

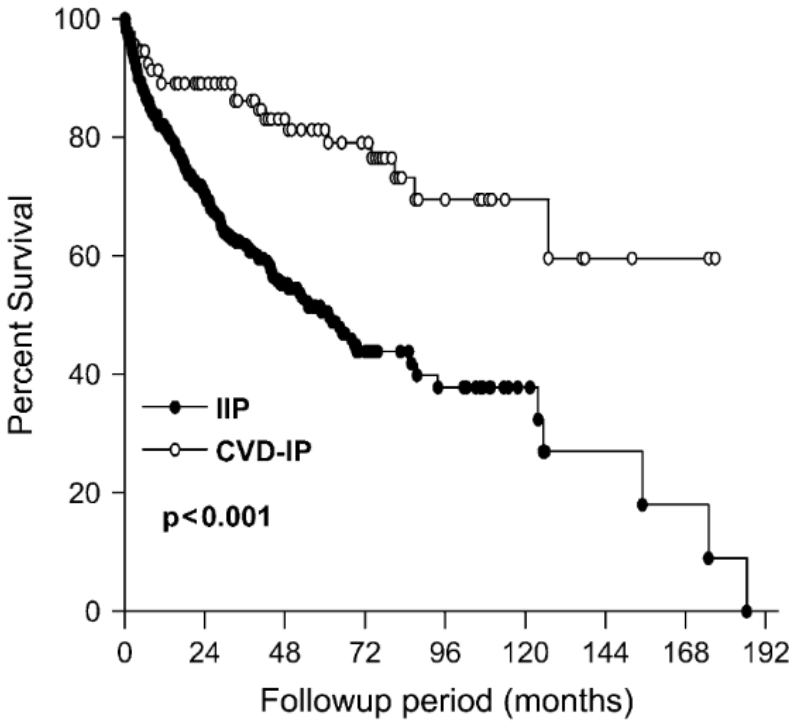
- **Treatment**
  - Different agents and different treatment durations

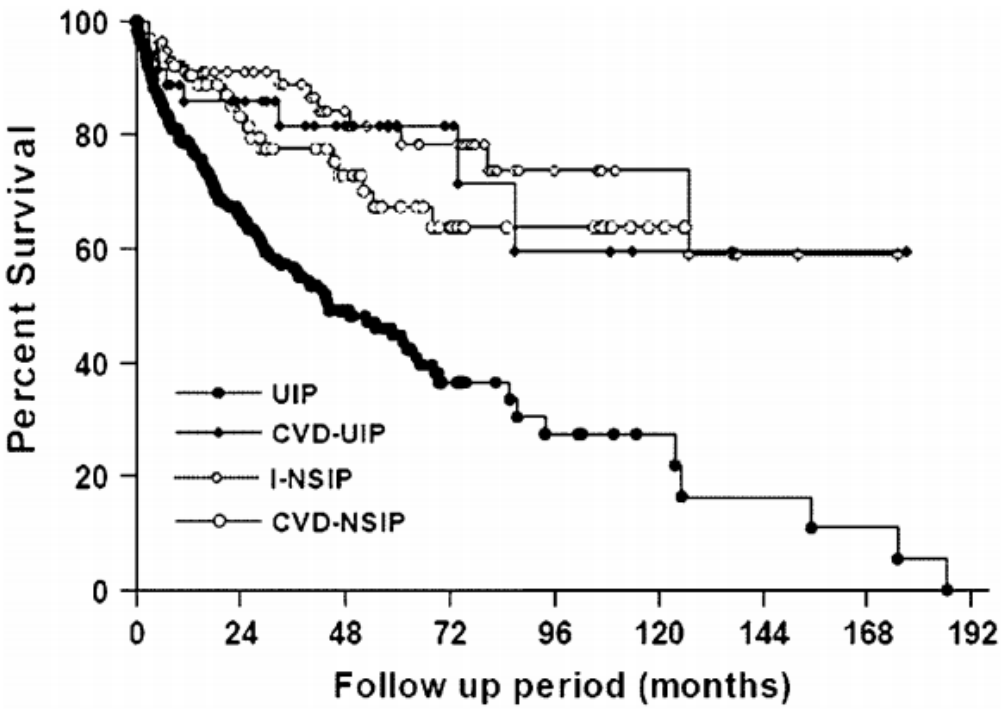
	Type of connective tissue disease					
	SSc	RA	SS	MCTD	PM/DM	SLE
First line treat ment choice for limited CTD	Digital vasculopathy: nifedipine/ iloprost [4]	DMARD	Stimulation of salivary secretions (ssica) Antimalarial agents (extraglandular)	Corticosteroid	Corticosteroid + AZA/MMF	Hydroxychloroquine or chloroquine
First choice for clinical CTD-ILD	CYC 2 mg/kg/day or MMF up to 3,000 mg [36]	High-dose PD MMF	Glucocorticoid, antimalarial agent AZA+ PD	Corticosteroids + cytotoxic drug (CYC)	CYC AZA MMF	Corticosteroid + AZA/MMF
Follow-up interval with PFT/D_{Lco}, chest X-ray or HRCT	Check PFT/D_{Lco}: every 6–12 mo After progression: every 3–4 mo [67]	Initiation of MTX: check chest radiograph within 1 year RA-ILD: PFT/D_{Lco} with HRCT 3–6 mo [21]	NA	NA	Check PFT Stable disease: every 6 mo Progression: every 3–4 mo [21]	NA
Refractory CTD-ILD	Add rituximab (375 mg/m^2) at 4-week interval for 24 weeks [37]	Rituximab	NA	NA	High-dose PDL + CYC	High-dose steroid + steroid-sparing agent (CYC)
Rescue therapy	Lung transplantation [81]	Lung transplantation	NA	NA	NA	NA

Vij R *et al*. *Chest*. 2013; 143
Koo SM *et al*. *KJIM*. 2017;32(4)

Significance of CTD in ILD

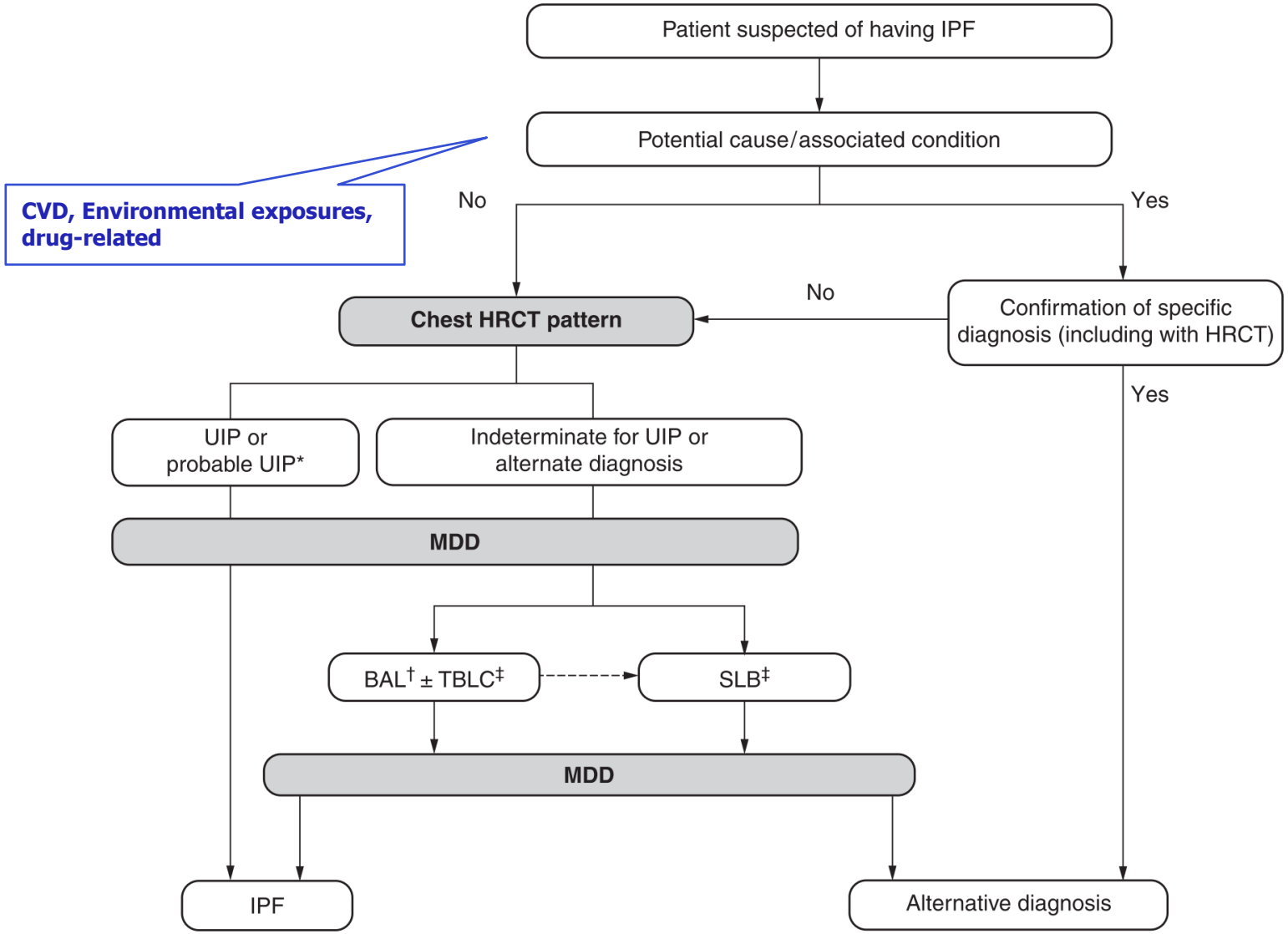
- **Prognosis**
  - Better prognosis compared to IIP





Park JH *et al*. *Am J Respir Crit Care Med*. 2007; 175

Diagnostic Algorithm of ILD



Raghu G *et al*. *Am J Respir Crit Care Med*. 2022; 205(9)

Etiologies or Associated Conditions of NSIP

- **Idiopathic**
- **Connective tissue diseases (CTD)**
  - SSc, Sjogren's syndrome, Inflammatory myopathy, RA, SLE etc.
- **Hypersensitivity pneumonitis (HP)**
- **Infection or immunosuppression**
  - Pneumocystis pneumonia, HIV, HTLV-1
- **Drugs**
- **Lymphoproliferative diseases**

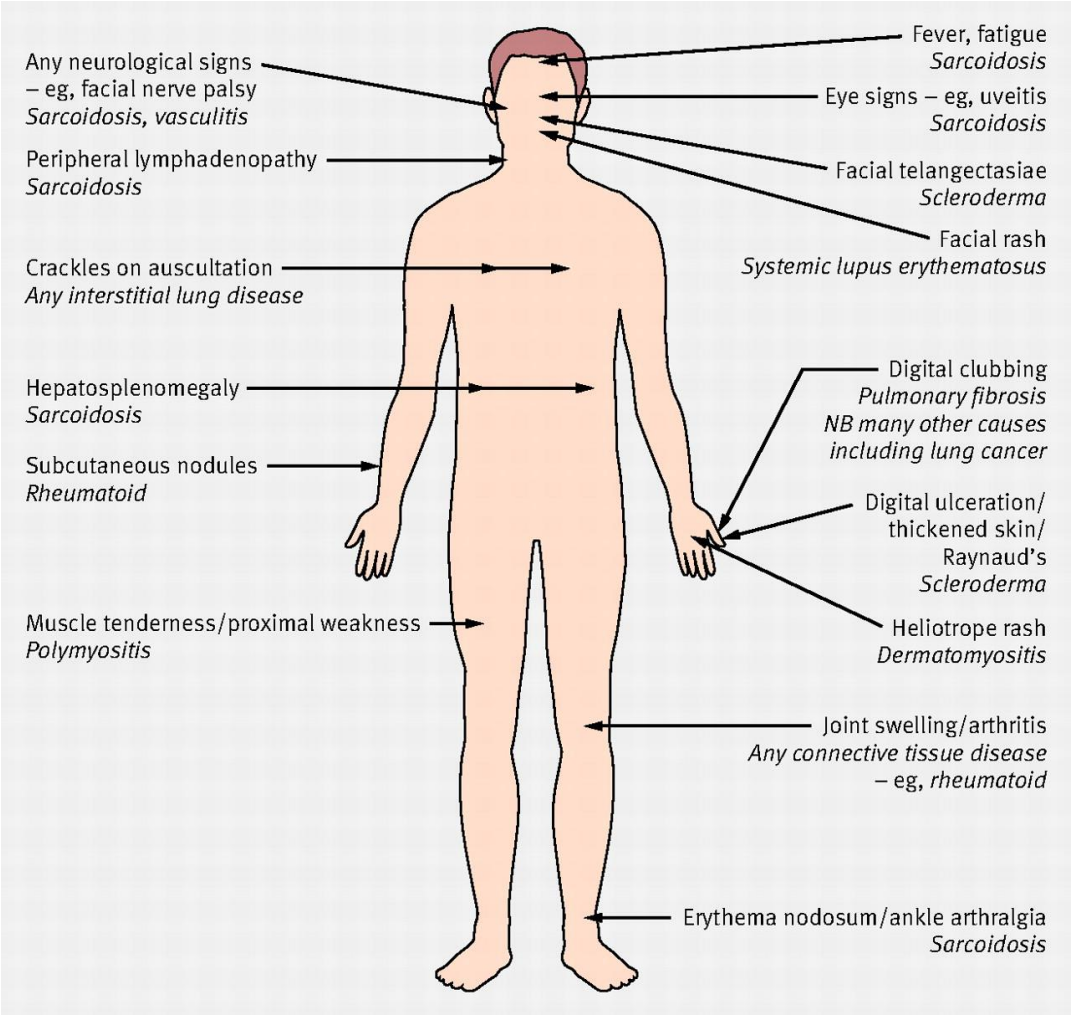
Tomassetti S et al. *Sem Respir Crit Care Med*. 2016;37(3)

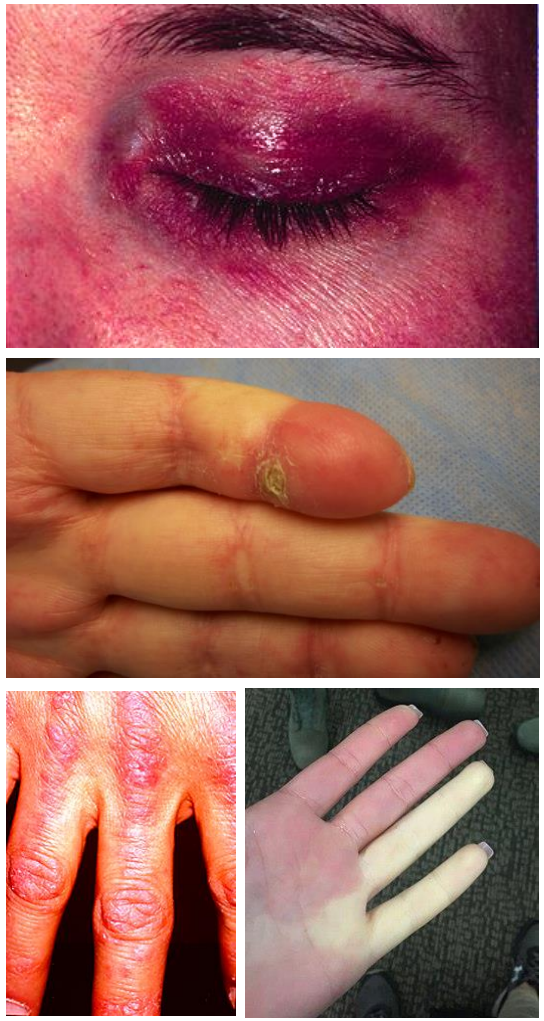
History taking

- **Demographic**
  - Age, gender, family history
- **Onset and types of symptoms**
- **Occupational and environmental factors**
  - Occupation (Specific materials, duration of exposure etc.)
  - Environment (house, frequently visited areas etc.)
- **Smoking history**
  - May be useful for diagnosing smoking related disease
- **Drugs**
  - (Amiodarone, methotrexate, chemotherapy agents etc.)
  - www.pneumotox.com, www.pubmed.gov, www.google.com
- **Symptoms of CTDs**
  - Arthralgia, morning stiffness, dry eye/dry mouth, proximal muscle weakness, paresthesia, alopecia, Raynaud's phenomenon etc.

Broaddus V et al. *Murray and Nadel's Textbook of Respiratory Medicine*. 6th ed. 2016
Longo DL *et al*. *Harrison's Principles of Internal Medicine*. 19th ed. 2013

Physical examination



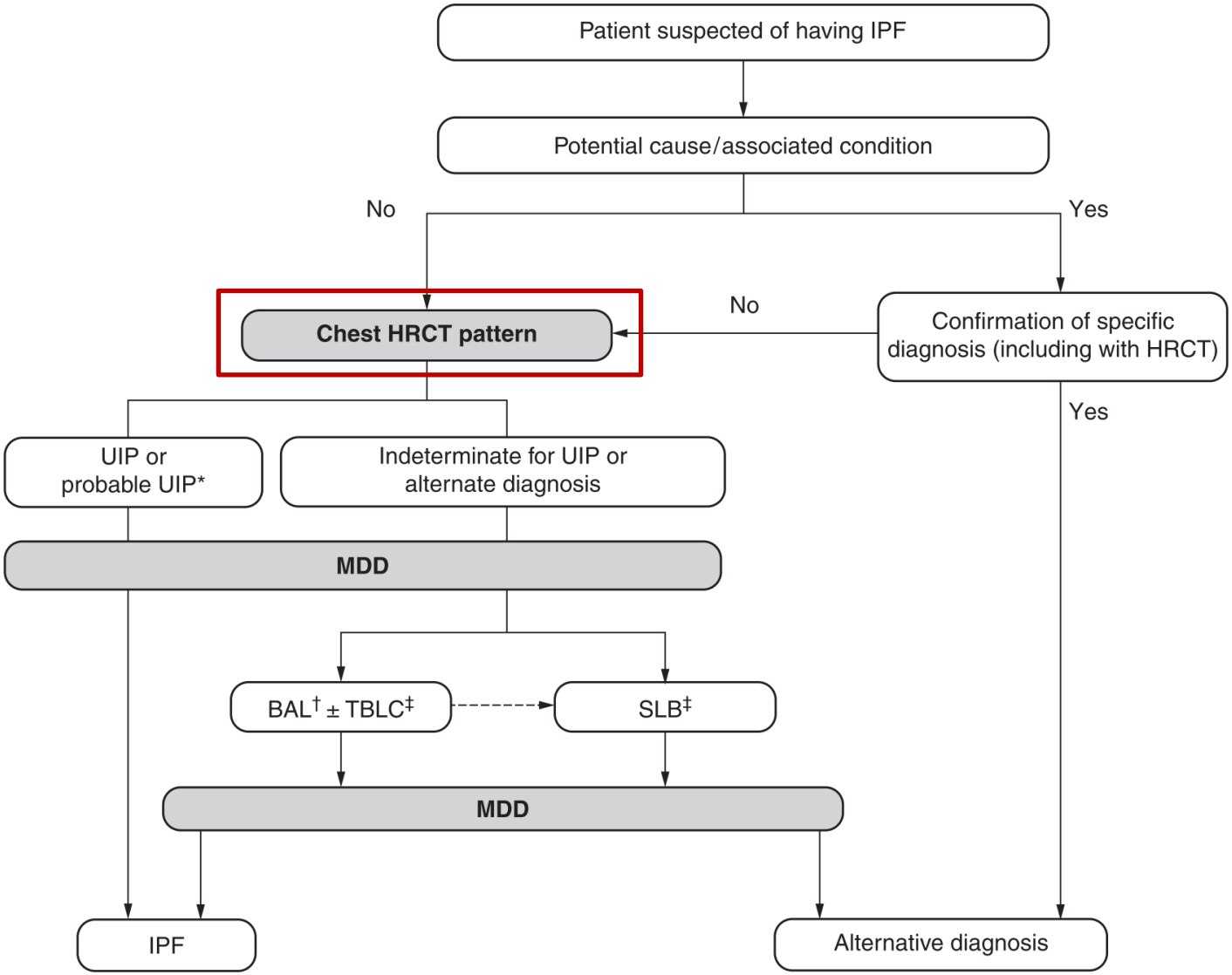


Broaddus V et al. *Murray and Nadel's Textbook of Respiratory Medicine*. 6th ed. 2016
Dempsey OJ *et al*. *BMJ*. 2010;340

Serologic tests

Antibody	Associated connective tissue disease
ANA (>1:320)	Many
RF (>60 IU/mL)	RA, Sjögren's syndrome, SLE
Anti-CCP	RA
Anti-centromere	Systemic sclerosis
Anti-nuclear ANA	Systemic sclerosis
Anti Ro (SS-A)	SLE, Sjögren's syndrome and others
Anti La (SS-B)	SLE, Sjögren's syndrome
Anti-RNP	SLE, MCTD
Anti-dsDNA	SLE
Anti-Smith	SLE
Anti tRNA synthetase	Poly-/dermatomyositis (anti-synthetase syndrome)
Anti-PM-Scl	Systemic sclerosis/myositis overlap
Anti-Th/To	Systemic sclerosis
Anti-U3 RNP	Systemic sclerosis
ANCA panel	Vasculitides
Anti-topoisomerase (Scl-70)	Systemic sclerosis

Diagnostic Algorithm of ILD



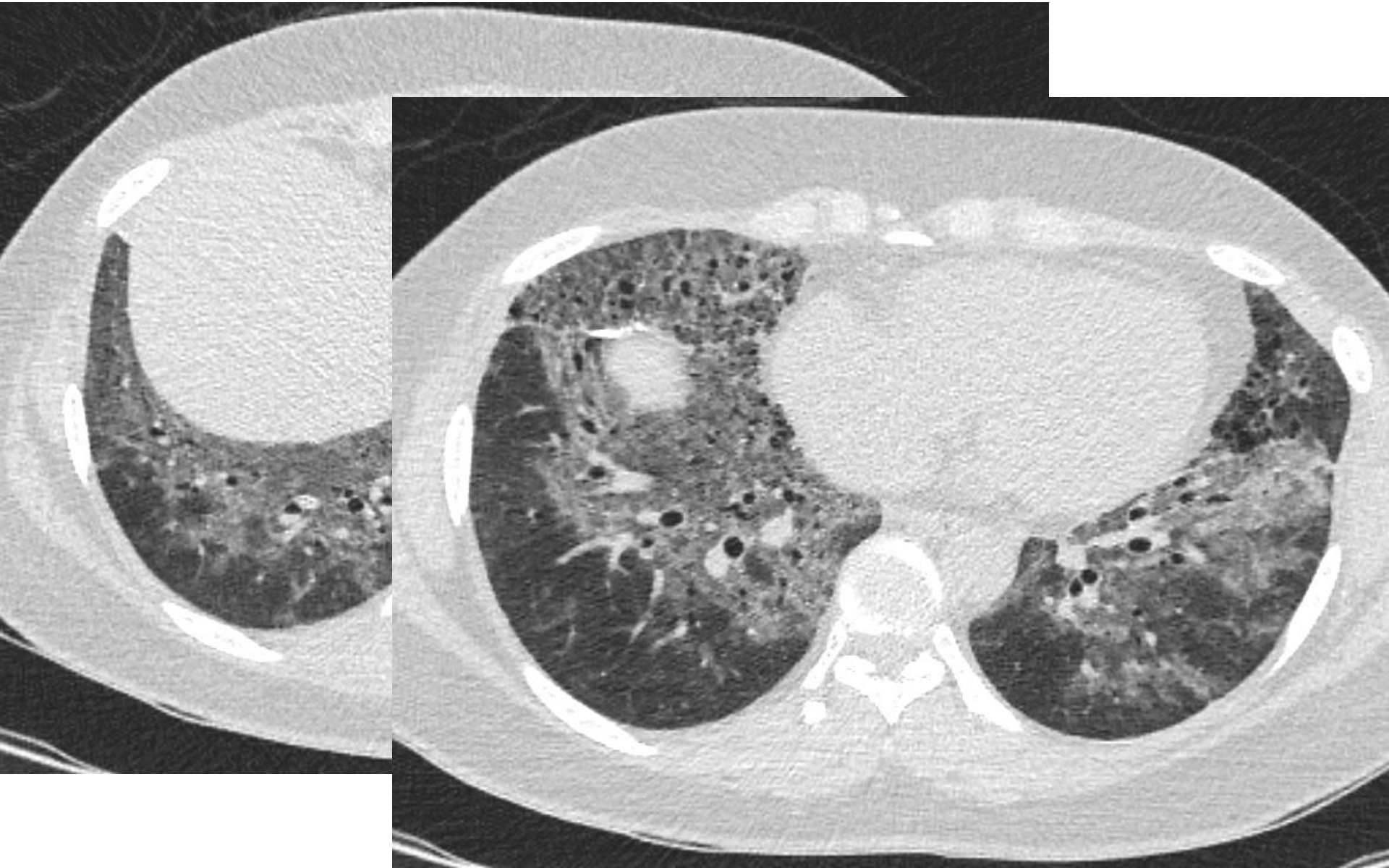
Raghu G *et al*. *Am J Respir Crit Care Med*. 2022; 205(9)

Radiologic pattern (NSIP)

- **Bibasilar predominance**
- **Ground-glass opacities**
- **Reticulation**
- **Traction bronchiectasis**
- **Lobar volume loss**
- **Little or no honeycombing**

Broaddus V et al. *Murray and Nadel's Textbook of Respiratory Medicine*. 6th ed. 2016

Radiologic pattern (NSIP)



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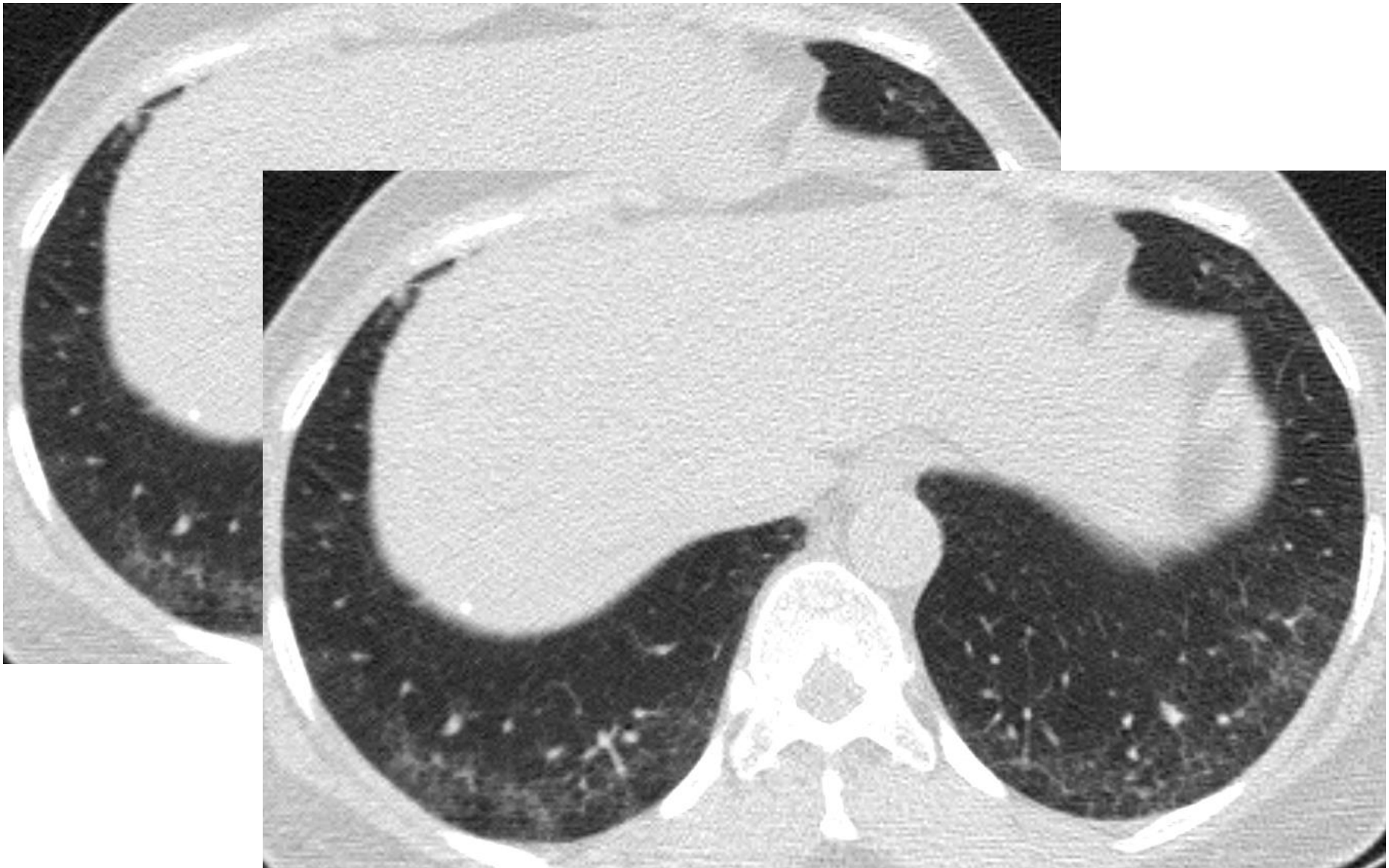

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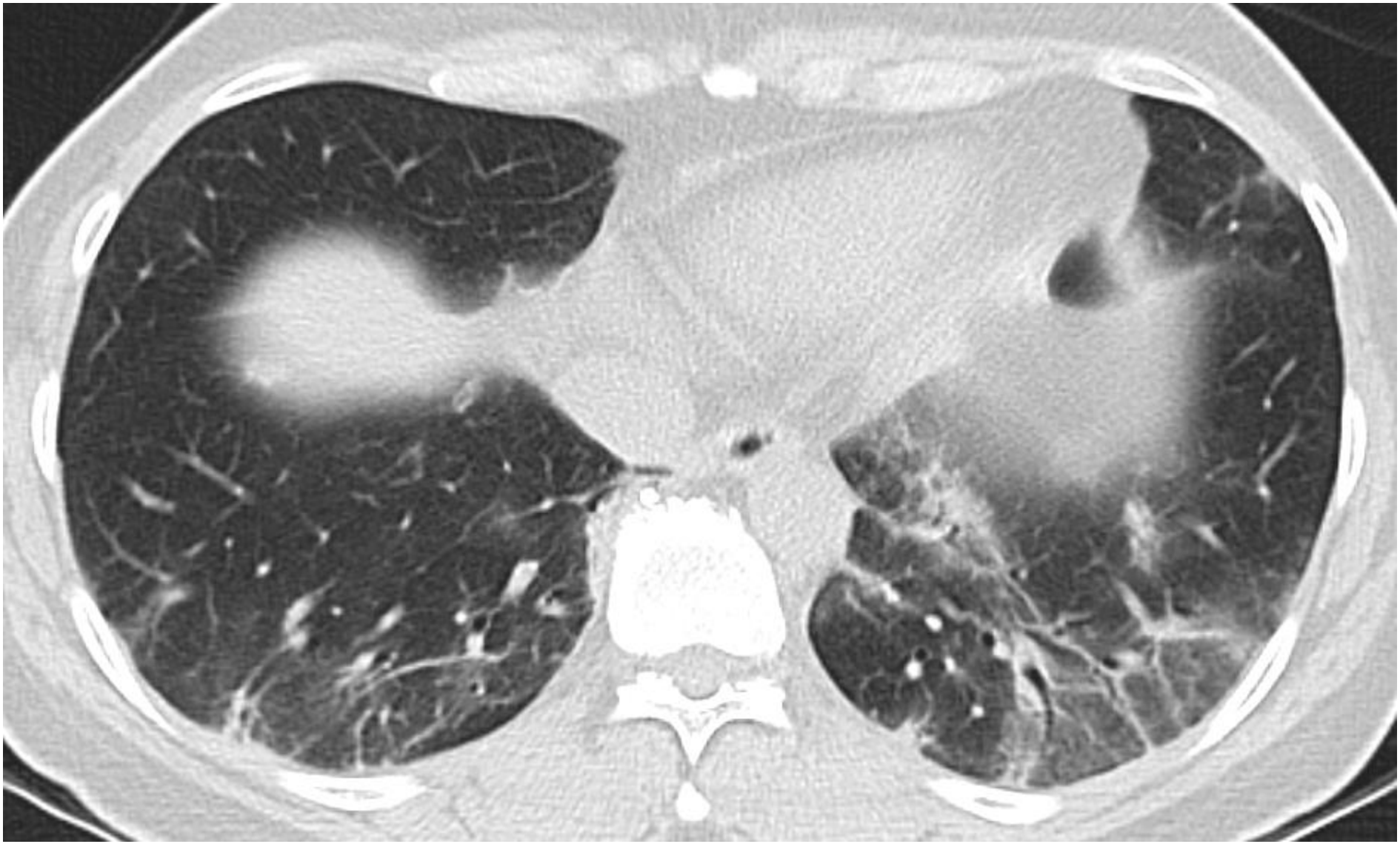

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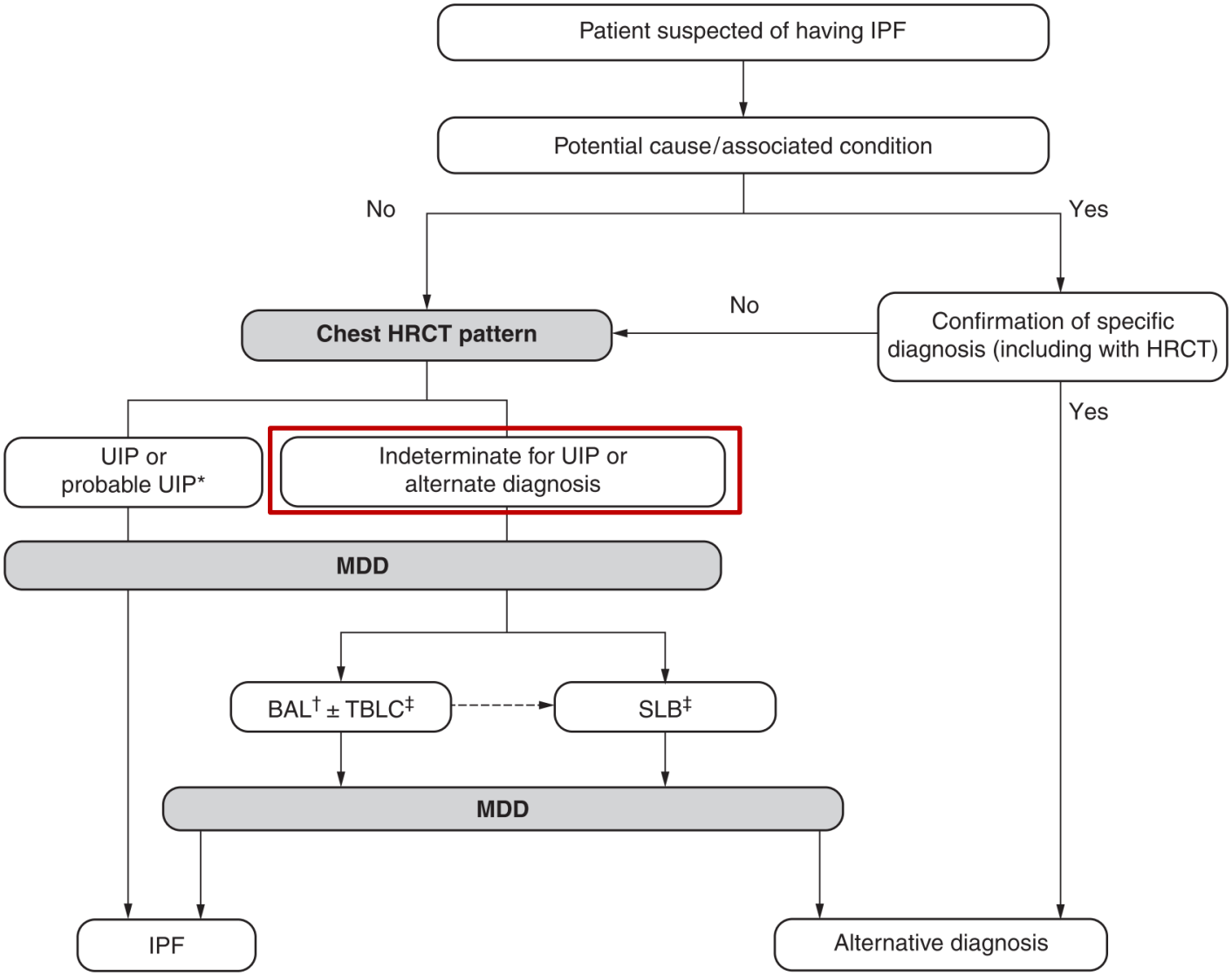


Raghu G *et al*. *Am J Respir Crit Care Med*. 2022; 205(9)

Accuracy of HRCT in UIP

Diagnostic Utility of HRCT

- High PPV of UIP pattern in IPF
  - ✓ Positive predictive value of UIP pattern: 85%~96%
  - ✓ Multicenter (8 special centers) prospective observational study

	Sensitivity	Specificity	Accuracy	Positive Predictive Value
Clinical core	26/33 (79%)	26/30 (87%)	52/63 (86%)	26/30 (87%)
Radiology core	26/30 (87%)	21/22 (95%)	47/52 (90%)	26/27 (96%)
Referring center	37/40 (93%)	5/14 (36%)	42/54 (78%)	37/46 (80%)

Clinical Findings	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
HRCT consistent with IPF	79.6 (43 of 54), 66.5–89.4%	83.8 (31 of 37), 68.0–93.8%	87.8 (43 of 49), 75.2–95.4%	73.8 (31 of 42), 58.0–86.1%
Radiograph consistent with IPF	88.9 (48 of 54), 77.4–95.8%	75.0 (27 of 36), 57.8–87.9%	84.2 (48 of 57), 72.1–92.5%	81.8 (27 of 33), 64.5–93.0%
HRCT consistent with IPF or radiograph consistent with IPF	90.7 (49 of 54), 79.7–96.9%	72.2 (26 of 36), 54.8–85.8%	83.1 (49 of 59), 71.0–91.6%	83.9 (26 of 31), 66.3–94.6%
HRCT consistent with IPF and radiograph consistent with IPF	77.8 (42 of 54), 64.4–88.0%	86.5 (32 of 37), 71.2–95.5%	89.4 (42 of 47), 76.9–96.4%	72.7 (32 of 44), 57.2–85.0%

Hunninghake GW *et al*. *Chest*. 2003;124

Accuracy of HRCT in NSIP

TABLE 1
Combined Results of Four Observers for Sensitivity, Specificity, and Accuracy for a Diagnosis of NSIP at Thin-Section CT

Observations	Sensitivity (%)	Specificity (%)	Accuracy (%)
All observations (n = 212)	70 (59/84)	63 (80/128)	66 (139/212)
"Possible" diagnosis (n = 75)	57 (17/30)	51 (23/45)	53 (40/75)
"Confident" diagnosis (n = 137)	78 (42/54)	69 (57/83)	72 (99/137)
All agree (n = 96)	89 (32/36)	80 (48/60)	83 (80/96)

Note.—Numbers in parentheses are observations.

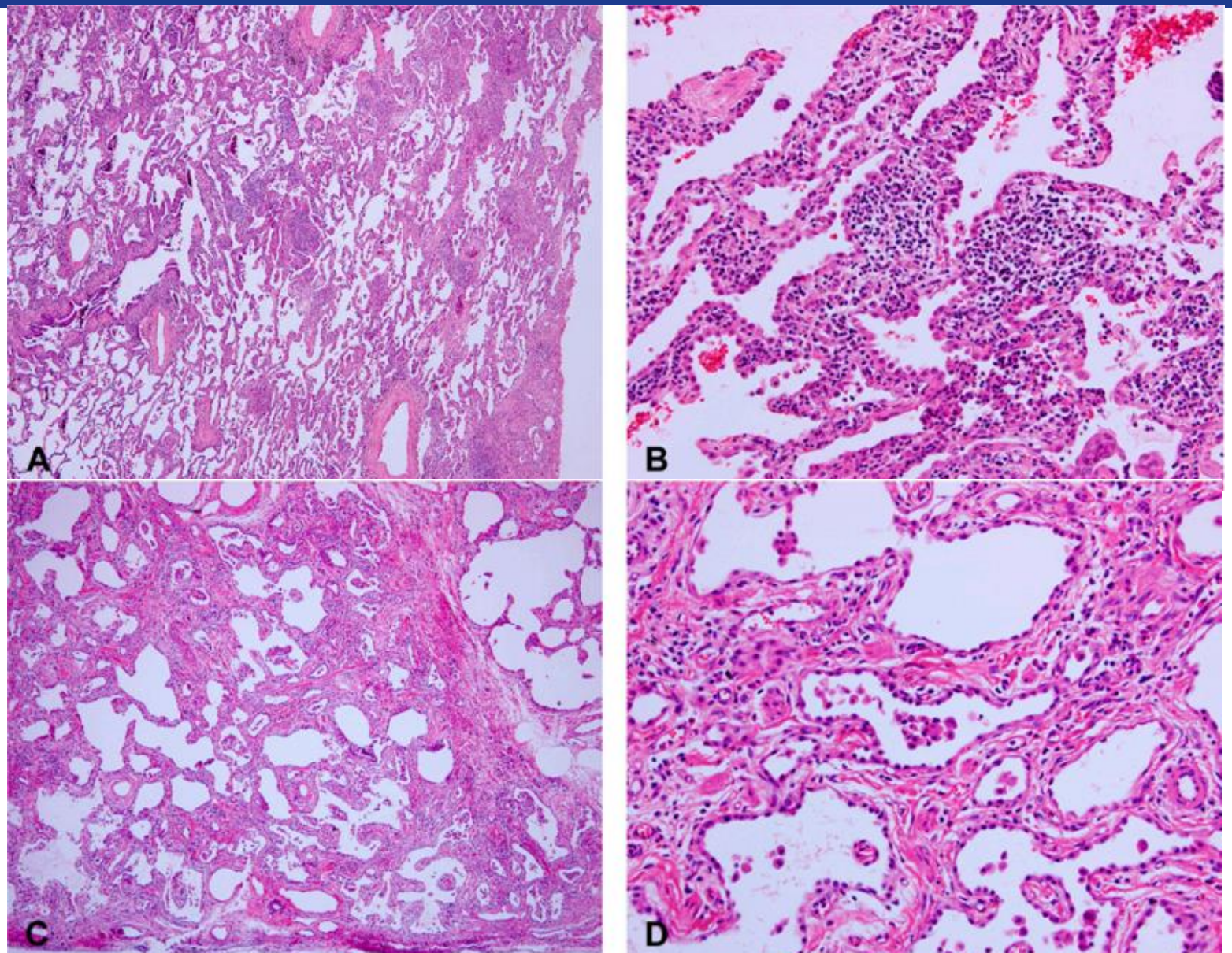
TABLE 2
Correct Diagnoses according to Disease

Disease	Correct Diagnosis*	Diagnosis with High Degree of Confidence	Correct Diagnosis with High Degree of Confidence*
UIP (n = 35)	25.0 (71)	20.5	15.5 (44)
BOOP (n = 24)	19.0 (79)	18.5	15.0 (62)
DIP (n = 23)	14.5 (63)	13.5	8.0 (35)
AIP (n = 20)	13.0 (65)	12.5	11.5 (58)
NIPF (n = 27)	2.5 (9)	1.0	0 (0)
Total (n = 129)	74.0 (57)	66.0	50.0 (39)

Note.—Data are the average of the number of correct diagnoses made by two observers.
* Value in parentheses is the percentage.

MacDonald SL *et al*. *Radiology*. 2001;221
Johkoh T *et al*. *Radiology*. 1999;211

Pathologic Pattern (NSIP)



Etiologies or Associated Conditions of NSIP

특발성 NSIP의 진단을 요약하면 다음과 같다.

1) 아급성 혹은 만성의 경과를 보이는 임상 증상과 제한성 폐기능 장애 소견

2) 흉부 HRCT에서 의심 할 만한 음영의 존재

3) 폐생검에서 조직학적 NSIP 양상

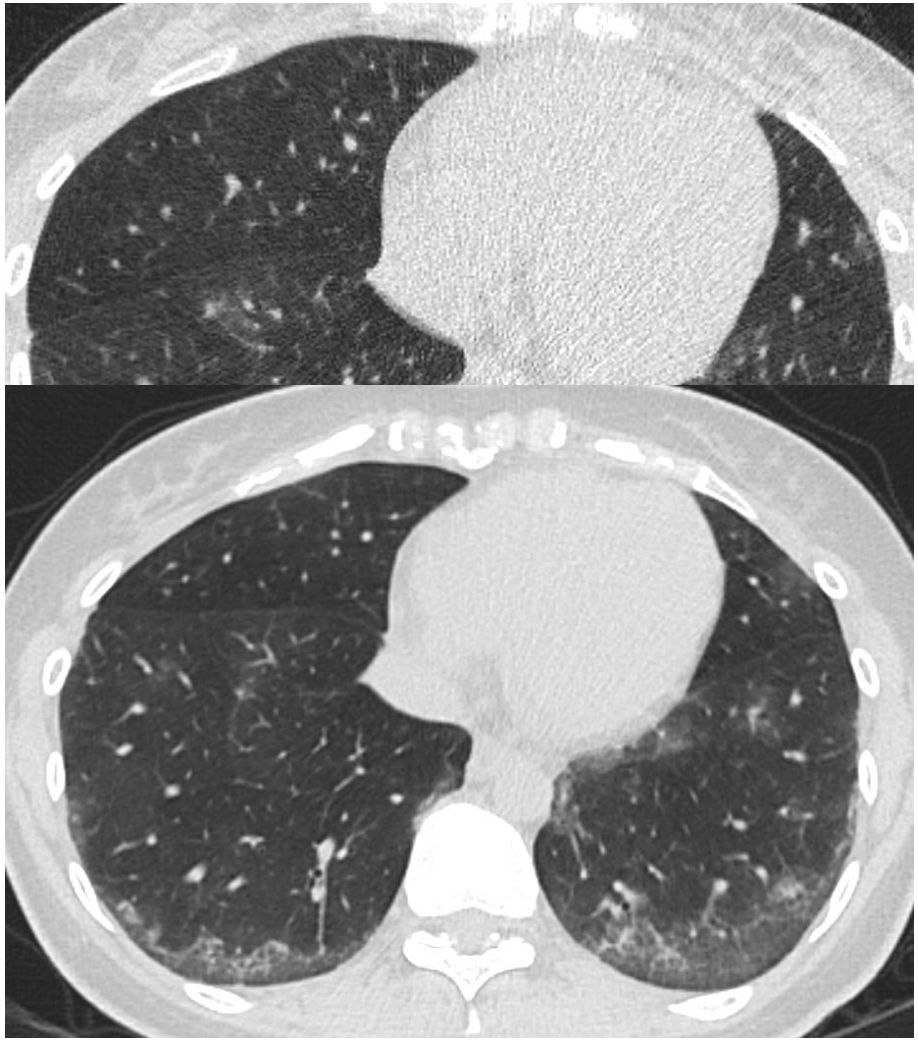
4) NSIP를 보일 수 있는 다른 원인 질환의 배제(특히 결체조직질환과 과민성폐렴)

→ Idiopathic NSIP

Case (I)

- F/29
- CC: Dyspnea (6 months)
- Sx: Cough (10 months)
- Referred from local hospital due abnormal chest CT

- Previously healthy
- Never smoker



Case (I)

- No medication
- No environmental exposure
- Occupation: 초등학교 교사
- Pet: None

- Cough/sputum (+/-)
  Rhinorrhea (-)
  Dyspnea (+) mMRC Gr II
  Orthopnea (-)
  Reflux symptoms (-)

- Arthralgia (-)
  Morning stiffness (-)
  Dry eye/mouth (-/-)
  Proximal muscle weakness (-)
  Raynaud's ph (+)
  Skin thickening (+) hands

- Puffy fingers, both
  Skin color change (face, hands)
  Digital ulcer, Rt 3rd fingertip

Case (I)

- **Serology tests for CTD**

  FANA: 1:320 (Homogenous)

  Rheumatoid Factor (-) / Anti-CCP Ab (-)

  Anti-RNP/ Sm Ab (-)

  Anti-SS-A / SS-B Ab (-/-)

  Anti-centromere Ab (-)

  Anti-Scl-70 (+, > 200.0)

  Anti-ds-DNA (-)

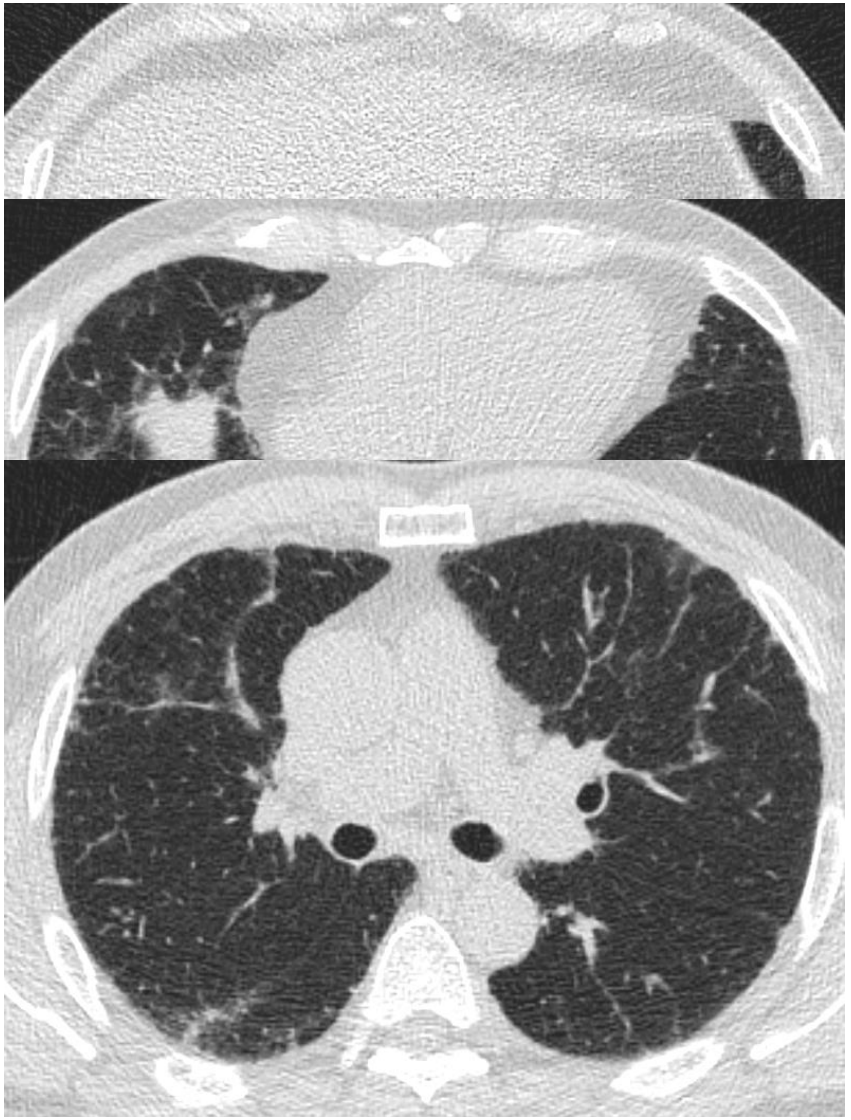
- NCM → Telangiectasia

➡ Diffuse cutaneous SSc-ILD

Case (II)

- M/58
- CC: Dyspnea (1.5 yr) (mMRC II)
- Sx: Sputum (10 yr)

- Known HTN
- Current smoker (1 PPD x 30 yr)
- Abnormal chest radiography for 2 years



Case (II)

- Amlodipine 5mg daily
- No environmental exposure
- Pet: None
- Occupation: 벨트 액세서리 제조 (8년) → 고물상 (5년) → 주차장 관리 (3년)

- Cough/sputum (-/+) whitish

  Dyspnea (+) mMRC Gr II

  Orthopnea (-)

  Reflux symptoms (-)

- Arthralgia (-)

  Morning stiffness (-)

  Dry eye/mouth (-/-)

  Proximal muscle weakness (-)

  Raynaud's ph (-)

- Joint deformity (-)

  Mechanic's hand (-)

  Skin macule or papule (-)

Case (II)

- **Serology tests for CTD**

  FANA: 1:40 (Homogenous)

  Rheumatoid Factor (-) / Anti-CCP Ab (-)

  Anti-RNP/ Sm Ab (-)

  Anti-SS-A / SS-B Ab (-/-)

  Anti-centromere Ab (-)

  Anti-Scl-70 (-)

  Anti-ds-DNA (-)

  ANCA, quantitative (-)

R/O Idiopathic NSIP

R/O IPF

Case (II)

- **Surgical lung biopsy**

1. Lung, R) lower lobe, wedge resection
   - Uniform subpleural, interlobular septal fibrosis
2. Lung, R) middle lobe, wedge resection
   - Subpleural, interlobular septal fibrosis with lymphocytic infiltration, ample of normal lungs

* Temporally uniform fibrosis consistent with NSIP

→ Idiopathic fibrotic NSIP

CONTENTS

Treatment Regimen of CTD-ILD

	Type of connective tissue disease					
	SSc	RA	SS	MCTD	PM/DM	SLE
First line treatment choice for limited CTD	Digital vasculopathy: nifedipine/ iloprost [4]	DMARD	Stimulation of salivary secretions (ssica) Antimalarial agents (extraglandular)	Corticosteroid	Corticosteroid + AZA/MMF	Hydroxychloroquine or chloroquine
First choice for clinical CTD-ILD	CYC 2 mg/kg/day or MMF up to 3,000 mg [36]	High-dose PD MMF	Glucocorticoid, antimalarial agent AZA+ PD	Corticosteroids + cytotoxic drug (CYC)	CYC AZA MMF	Corticosteroid + AZA/MMF
Follow-up interval with PFT/D_{Lco}, chest X-ray or HRCT	Check PFT/D_{Lco}: every 6–12 mo After progression: every 3–4 mo [67]	Initiation of MTX: check chest radiograph within 1 year RA-ILD: PFT/D_{Lco} with HRCT 3–6 mo [21]	NA	NA	Check PFT Stable disease: every 6 mo Progression: every 3–4 mo [21]	NA
Refractory CTD-ILD	Add rituximab (375 mg/m^2) at 4-week interval for 24 weeks [37]	Rituximab	NA	NA	High-dose PDL + CYC	High-dose steroid + steroid-sparing agent (CYC)
Rescue therapy	Lung transplantation [81]	Lung transplantation	NA	NA	NA	NA

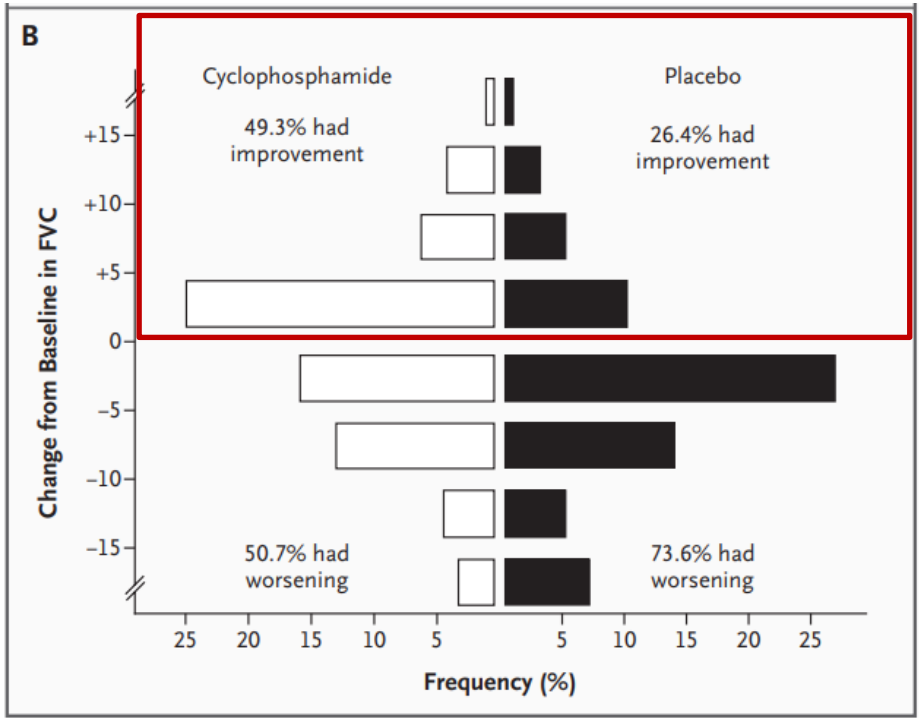
Koo SM *et al*. *KJIM*. 2017;32(4)

Systemic Sclerosis-ILD (SSc-ILD) - CYC

- 158 SSc-ILD patients (13 clinical centers)
- Prospective RCT (1:1 Oral CYC vs. Placebo)
- Outcome: FVC decline at 12 months

Table 2. Change in Values from Baseline to Month 12.*

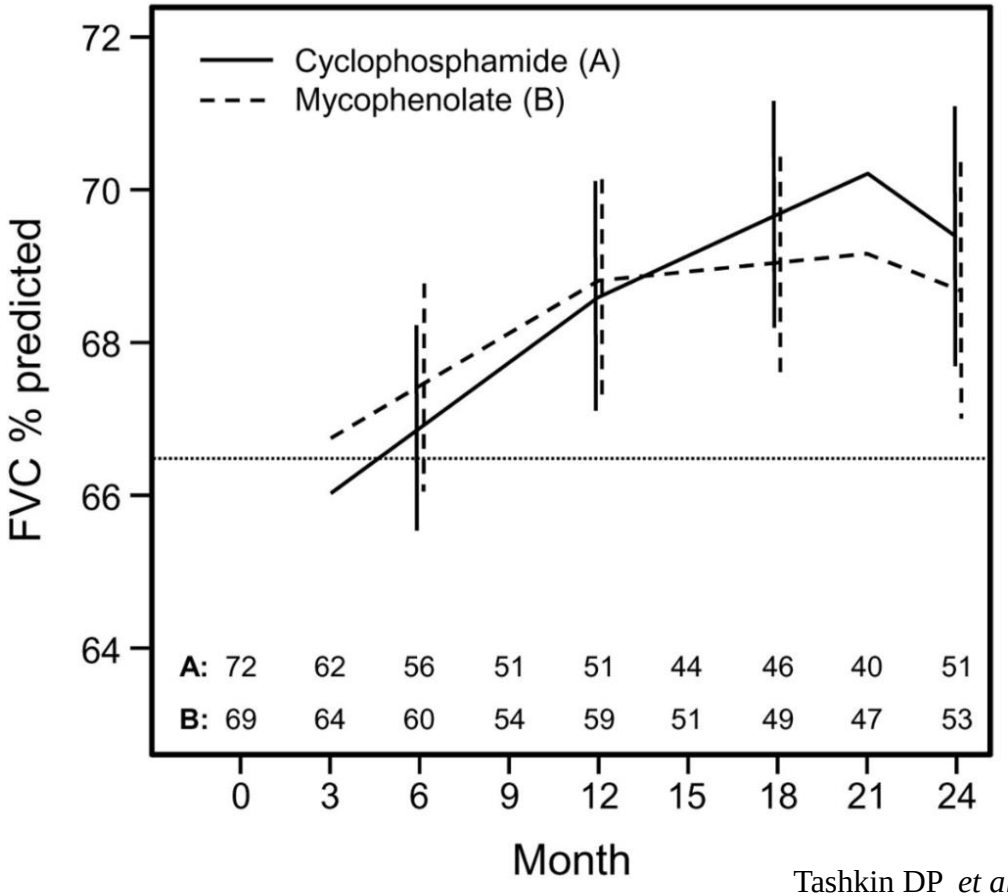
Characteristic	Baseline Value	Value at 12 Mo	Difference
Cyclophosphamide group			
FVC (% of predicted)	67.6±1.3	66.6±1.7	−1.0±0.92†
Total lung capacity (% of predicted)	70.4±2.1	70.5±1.8	−0.3±1.82†
DLCO (% of predicted)	47.2±1.6	42.8±1.7	−4.2±1.16
Score on Mahler Dyspnea Index			
According to baseline instrument	5.6±0.22		
According to transitional dyspnea index (focal score)†		1.4±0.23	
Cough (%)	72.5	66.2	
Score for HAQ disability index	0.94±0.077	0.84±0.08	−0.11±0.05†
SF-36 score			
Physical component	33.0±1.3	33.8±1.3	0.7±1.0
Mental component	48.7±1.2	51.8±1.3	2.9±1.5
Skin-thickness score	15.5±1.3	11.9±1.3	−3.6±0.8†
Diffuse	21.7±10.1	15.9 ±11.0	−5.3±7.4
Limited	6.1±3.6	5.0±4.3	−0.8±2.4
Placebo group			
FVC (% of predicted)	68.3±1.5	65.6±1.6	−2.6±0.9
Total lung capacity (% of predicted)	67.9±1.9	64.7±1.9	−2.8±1.2
DLCO (% of predicted)	47.9±1.7	44.3±2.1	−3.5±1.0
Score on Mahler Dyspnea Index			
According to baseline instrument	5.6±0.42		
According to transitional dyspnea index (focal score)‡		−1.5±0.43	
Cough (%)	55.9	67.2	
Score for HAQ disability index	0.70±0.09	0.86±0.10	0.16±0.06
SF-36 score			
Physical component	35.1±1.4	33.2±1.4	−1.9±1.2
Mental component	50.8±1.4	50.9±1.5	0.1±1.5
Skin-thickness score	14.6±1.4	13.7±1.4	−0.9±1.2
Diffuse	20.2±9.3	19.1±11.2	−1.7±6.9
Limited	5.5±3.4	5.7±4.2	0.2±3.3



Tashkin DP *et al*. *N Engl J Med*. 2006; 354

Systemic Sclerosis-ILD (SSc-ILD) - MMF

- 142 SSc-ILD patients
- Prospective RCT (1:1 Oral MMF vs. CYC)
- Outcome: FVC decline at 24 months



Tashkin DP *et al*. *Lancet Respir Med*. 2016; 4(9)

Treatment of Idiopathic NSIP

- **Systemic corticosteroids**
  - ✓ Retrospective observational studies
  - ✓ Optimal dose or duration: Not known
  - ✓ Initially 0.5~1.0mg/day/kg → gradual tapering (over 1 year, possibly shorter)

- **Immunosuppressive agents**
  - ✓ Cyclophosphamide
  - ✓ Azathioprine
  - ✓ Mycophenolate mofetil
  - ✓ Rituximab for refractory NSIP

- **Other treatment options**
  - ✓ Lung transplantation
  - ✓ Antifibrotic agents

Treatment Outcomes of NSIP Pattern

- Single-center retrospective observational study (SMC)
- 204 patients with Bx-proven NSIP [Idiopathic 141 (69%) vs. CTD 63 (31%)]

	No. (%) or median (IQR)
Initial treatment	
Corticosteroid + azathioprine	94 (46)
Corticosteroids only	52 (25)
Corticosteroid + cyclophosphamide	23 (11)
Azathioprine only	20 (10)
Cyclophosphamide only	6 (3)
No treatment	7 (3)
Other treatments[a]	2 (1)
Duration of treatment, months	17.8 (12.5–19.9)
Treatment outcome ($n = 197$)	
Progression[b]	71 (36)
Relapse[c,d]	47 (24)
Progression or relapse[e]	100 (51)
Mortality	18 (9)

Cho HK *et al*. *Ther Adv Respir Dis*. 2022; 16

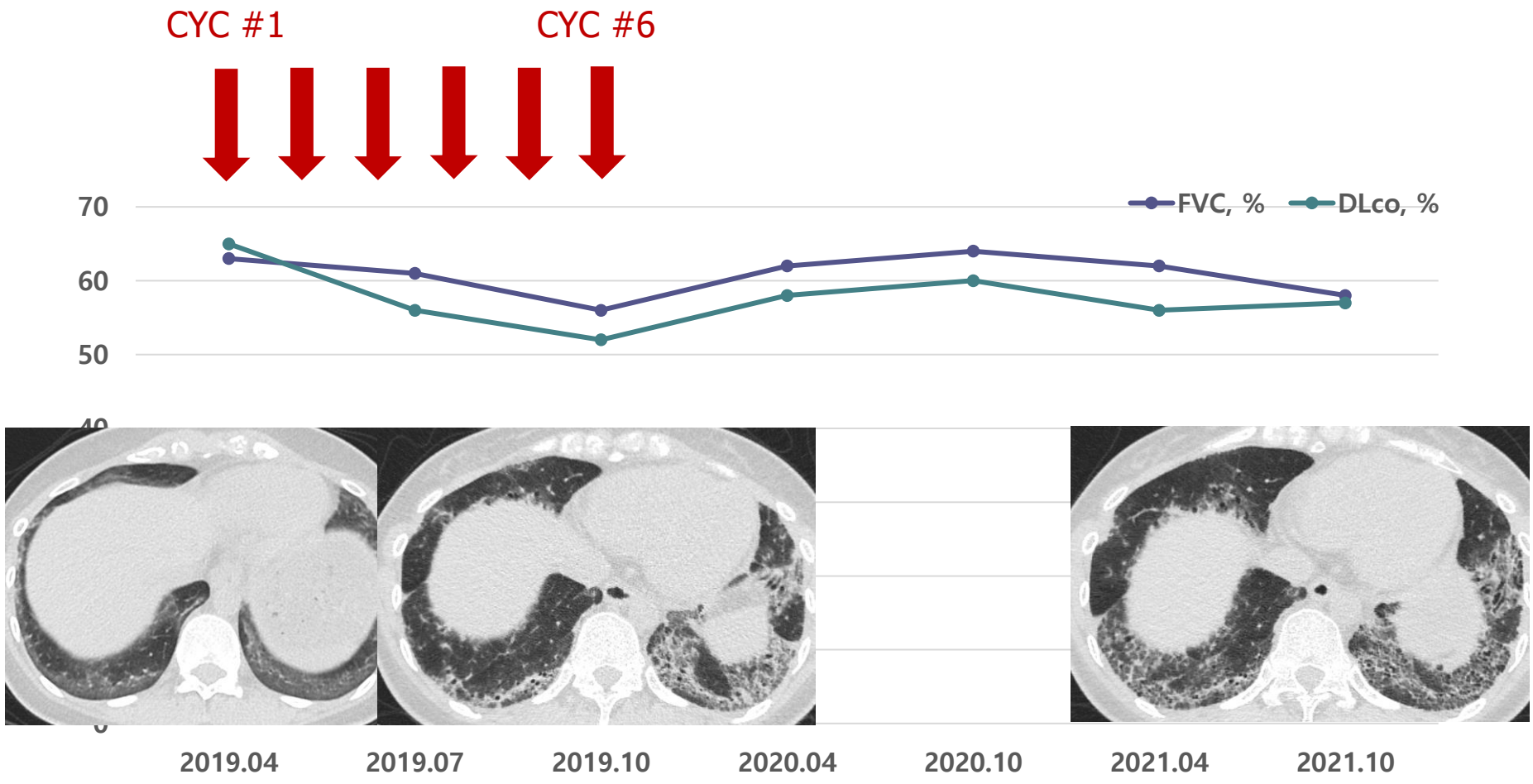
Treatment of Idiopathic NSIP

Clinical course and lung function change of idiopathic nonspecific interstitial pneumonia

Characteristics	Total	Fibrotic NSIP	Cellular NSIP	p-value
Subjects	83	72	11	
Age yrs	54.4±10.1	54.3±10.1	55.4±10.8	0.739
Males/females	27/56	23/49	4/7	0.743
Follow-up period months	56.1±39.0	58.0±40.9	43.4±20.1	0.071
Smoking never/ex/current	57/13/13	51/10/11	6/3/2	0.470
Duration of dyspnoea months	5.7±6.7	5.9±7.0	4.9±4.5	0.666
Antinuclear antibody	46/81 (57)	38/70 (54)	8/11 (73)	0.335
Rheumatoid factor	14/81 (17)	13/70 (19)	1/11 (9)	0.679
Resting P_{a,O_2} mmHg	82.5±14.4	83.4±14.3	77.2±15.0	0.187
Initial PFTs				
FVC % pred	63.6±14.6	63.3±14.9	66.8±13.1	0.594
FEV_1 % pred	71.3±17.1	71.1±17.4	72.5±16.1	0.792
$D_{L,CO}$ % pred	58.9±19.1	58.4±19.9	62.3±13.2	0.532
TLC % pred	72.9±19.1	73.2±20.3	71.1±9.5	0.752
Initial BAL finding %				
Macrophage	51.5±19.6	55.5±17.9	26.6±7.7	<0.001
Lymphocyte	35.3±21.0	30.7±18.0	63.8±15.8	<0.001
Neutrophil	10.3±11.4	10.5±10.7	8.9±16.2	0.714
Eosinophil	2.5±3.8	2.6±4.0	1.7±2.2	0.520
T4/T8 ratio	0.91±0.81	1.00±0.84	0.45±0.37	0.077
Initial treatment				
Initial dose of PD mg	51.5±11.9	51.5±12.0	51.4±12.1	0.980
Combination with CX	62/79 (78)	56/68 (82)	6/11 (54)	0.052
Time to 15 mg of PD months	6.8±7.2	5.7±3.7	12.8±15.5	0.187
Total duration months	17.2±12.1	17.4±12.1	15.8±12.4	0.706

Park IN *et al*. *Eur Respir J*. 2009; 33

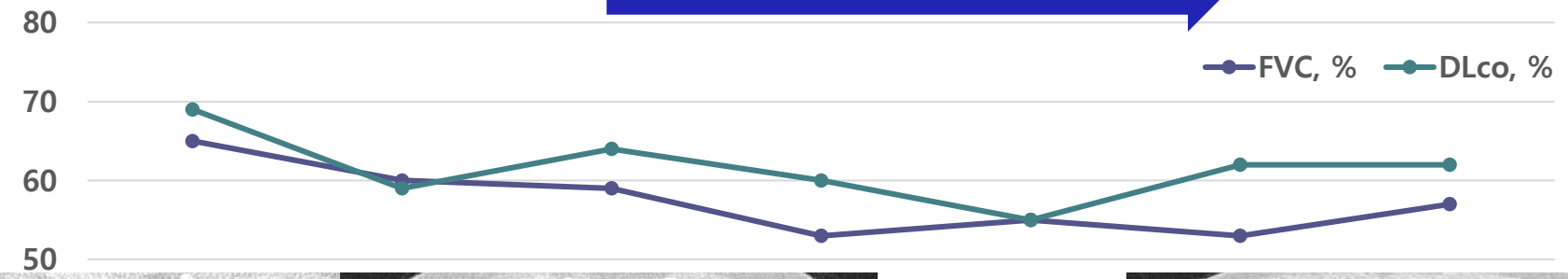
Case (I) – SSc-ILD

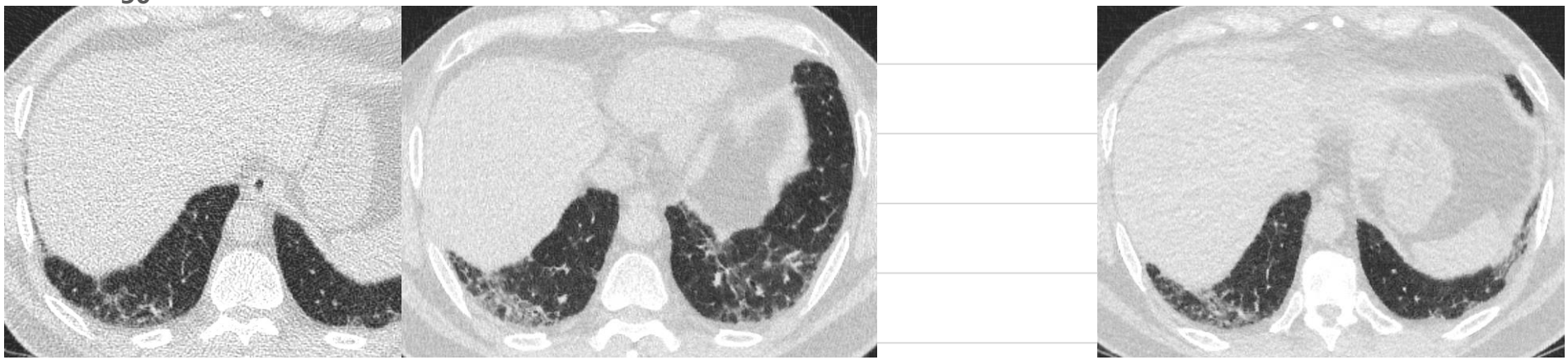


Case (II) – Idiopathic fNSIP

Prednisone (30mg→ tapering)

Azathioprine (100mg)

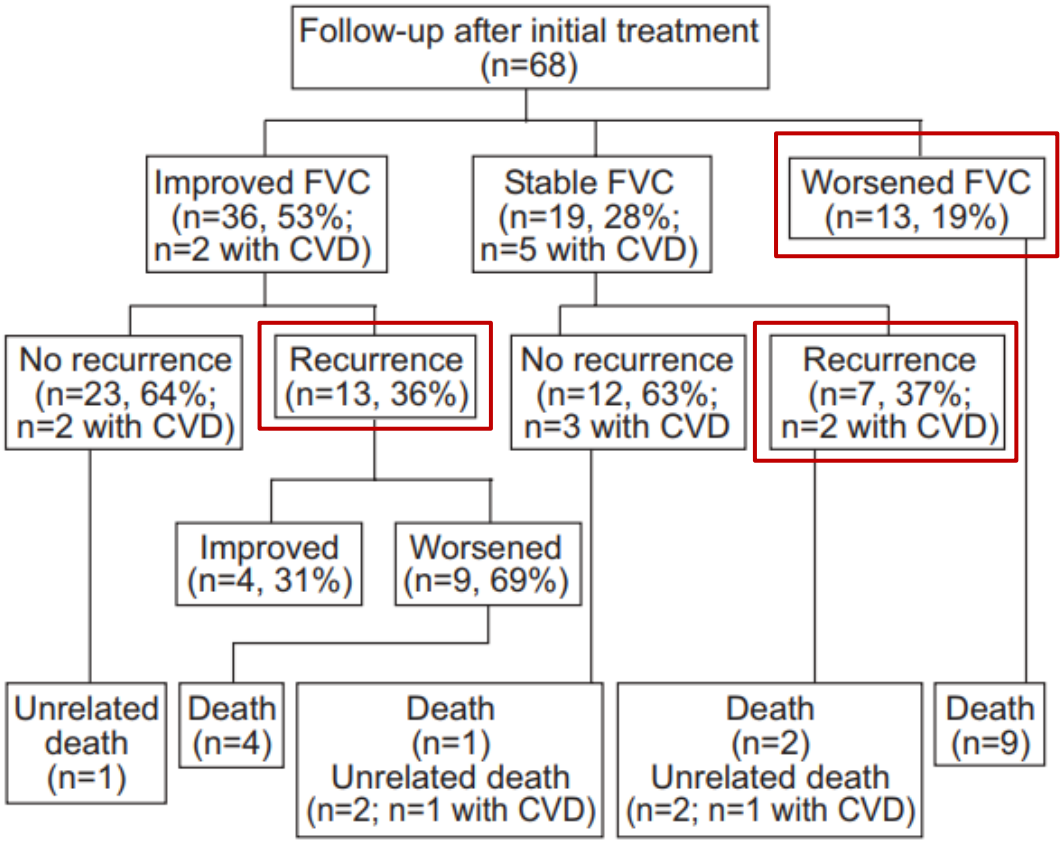




2019.04 2019.07 2019.10 2020.04 2020.10 2021.04 2021.10

Treatment Outcomes of Idiopathic NSIP

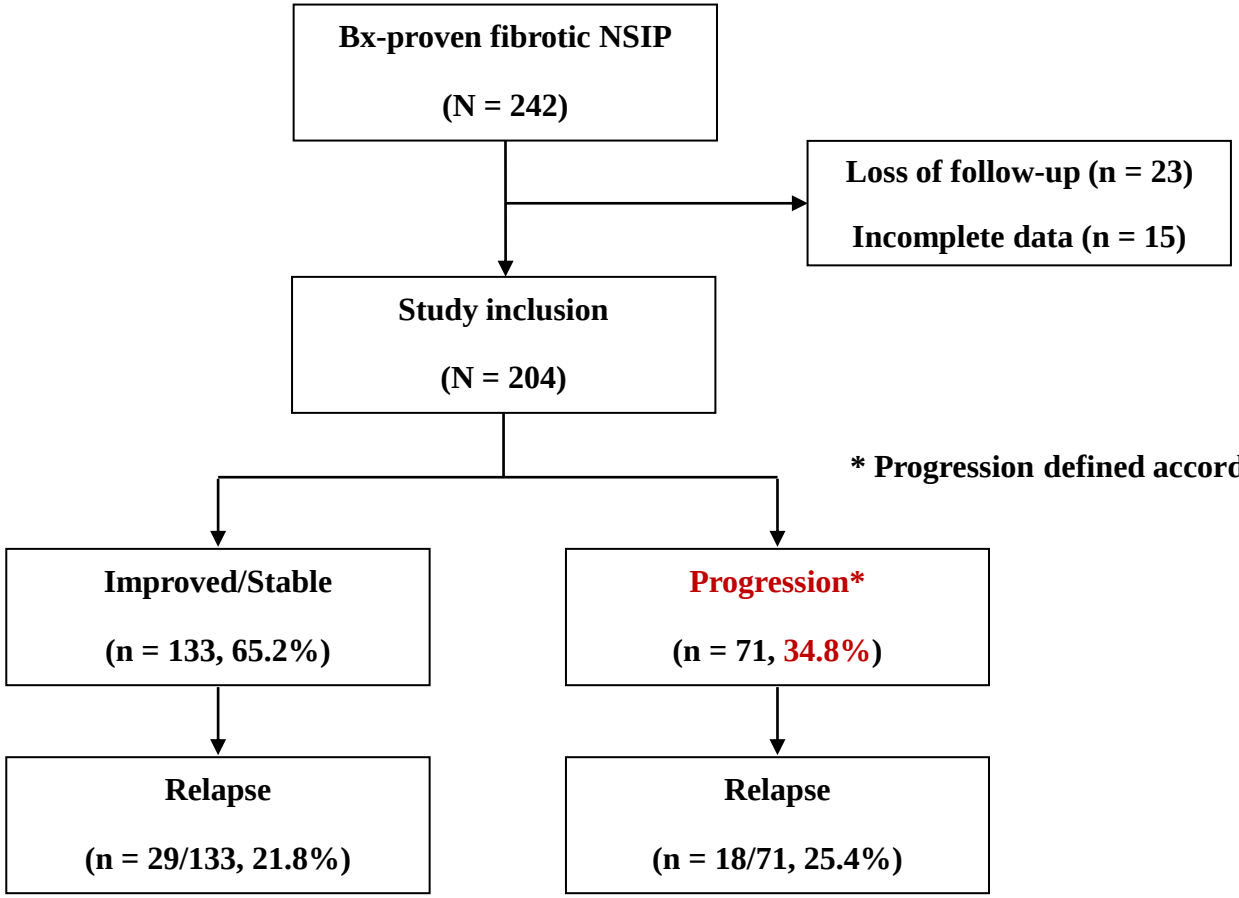
Clinical course and lung function change of idiopathic nonspecific interstitial pneumonia



Park IN *et al*. *Eur Respir J*. 2009; 33

Nonspecific Interstitial Pneumonia (NSIP)

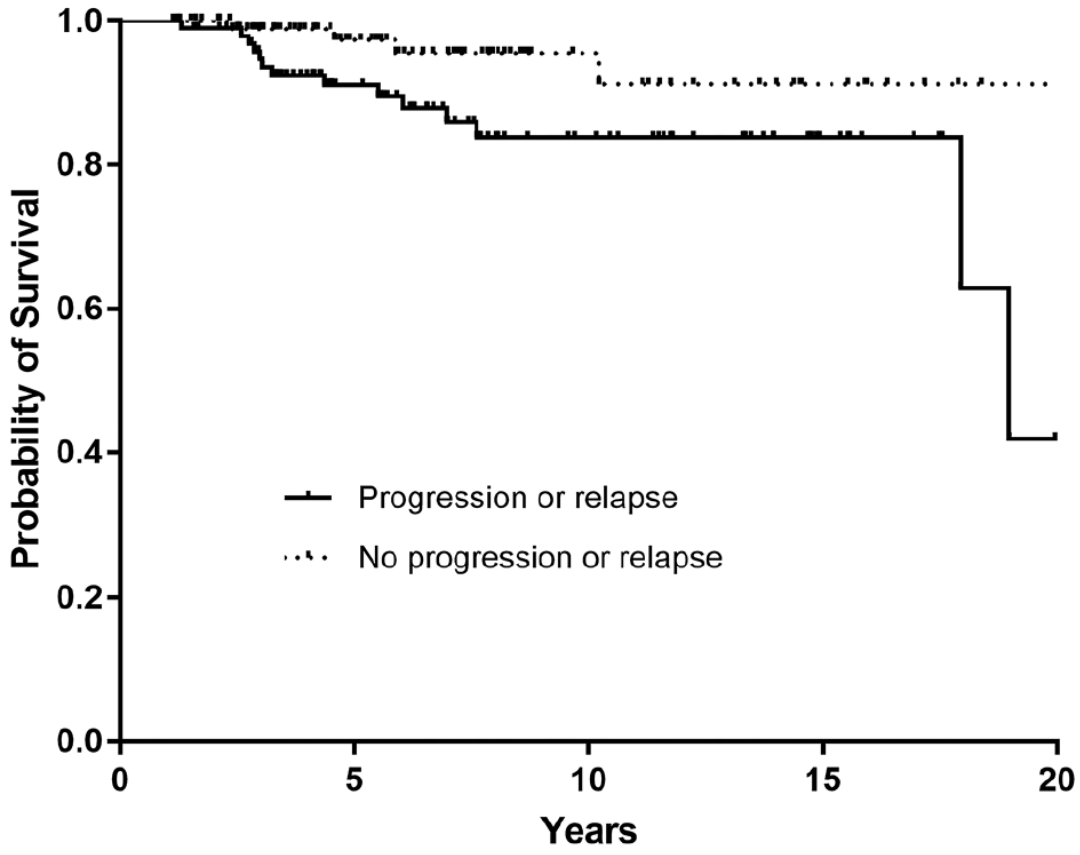
- Single-center retrospective observational study (SMC)
- 204 patients with Bx-proven NSIP [Idiopathic 141 (69%) vs. CTD 63 (31%)]



Cho HK *et al*. *Ther Adv Respir Dis*. 2022; 16

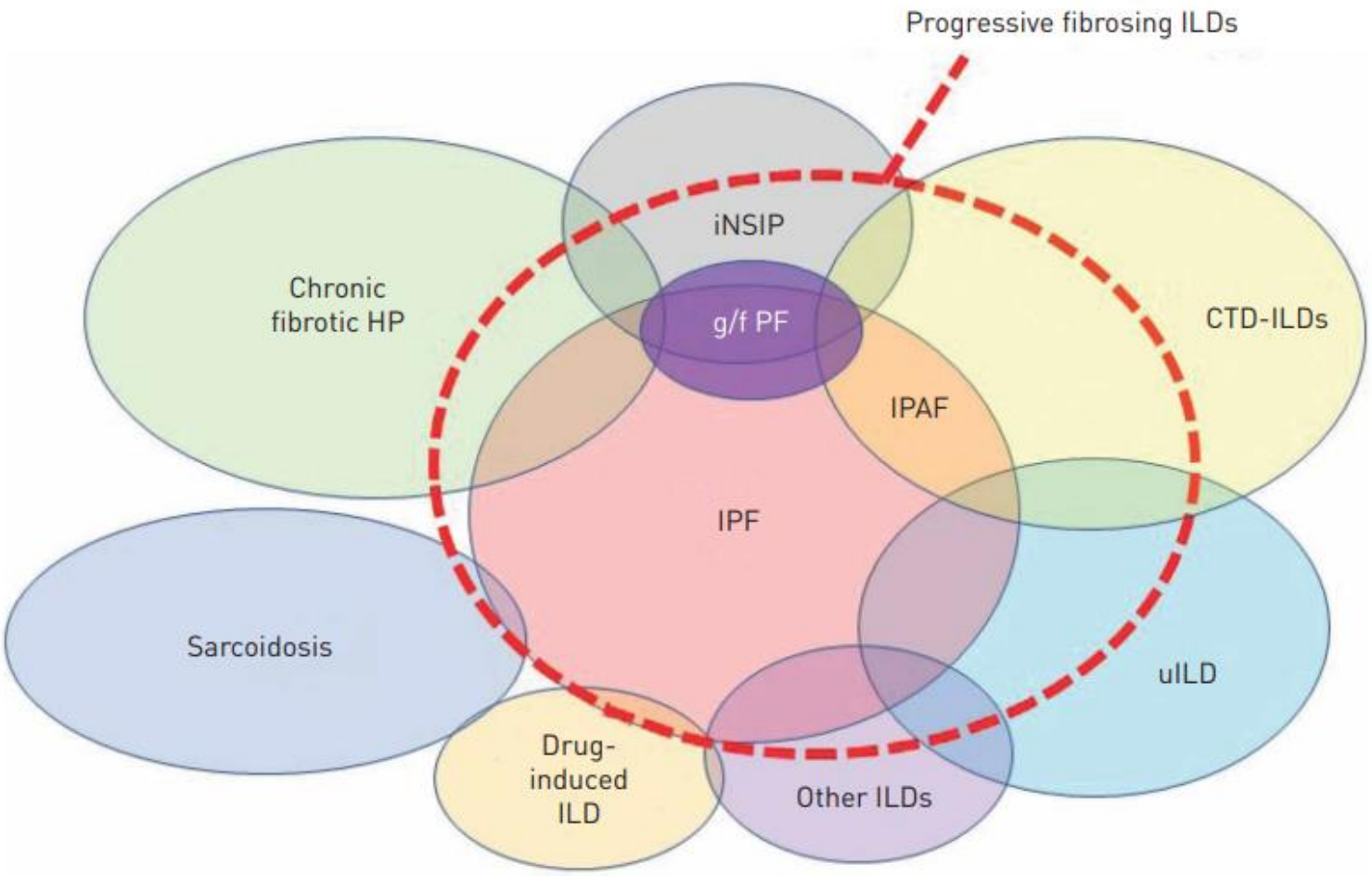
Survival according to Treatment Response

- Single-center retrospective observational study (SMC)
- 204 patients with Bx-proven NSIP [Idiopathic 141 (69%) vs. CTD 63 (31%)]



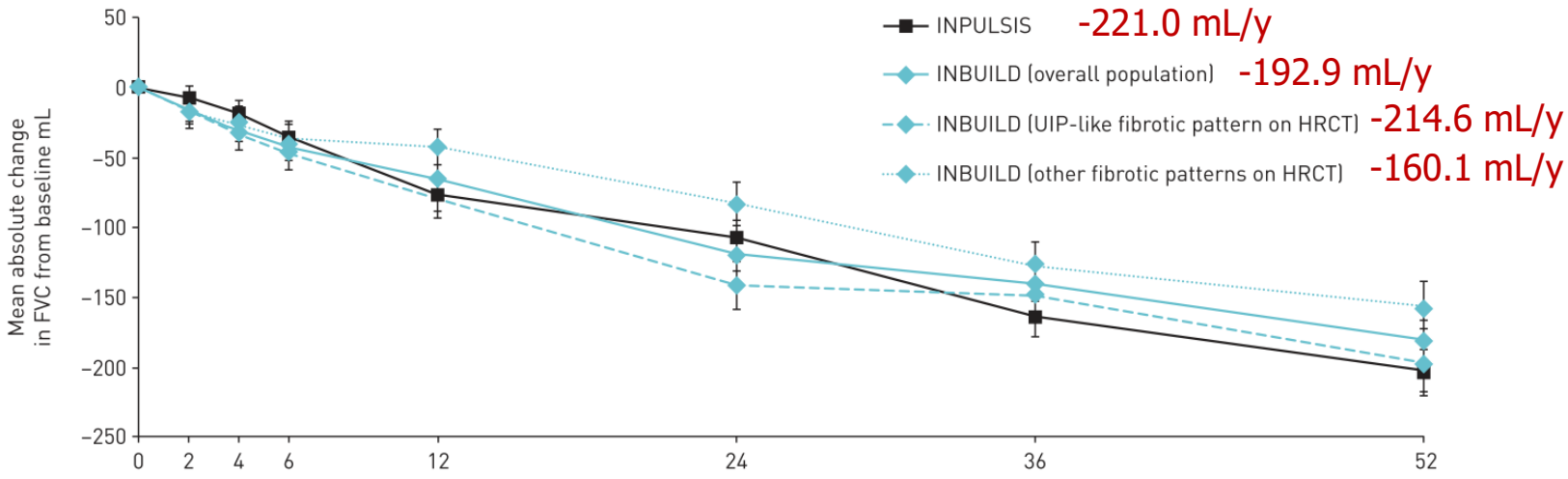
Cho HK *et al*. *Ther Adv Respir Dis*. 2022; 16

Progressive Fibrosing ILD (PF-ILD)



Cottin V. Eur *Respir Rev*. 2019; 28

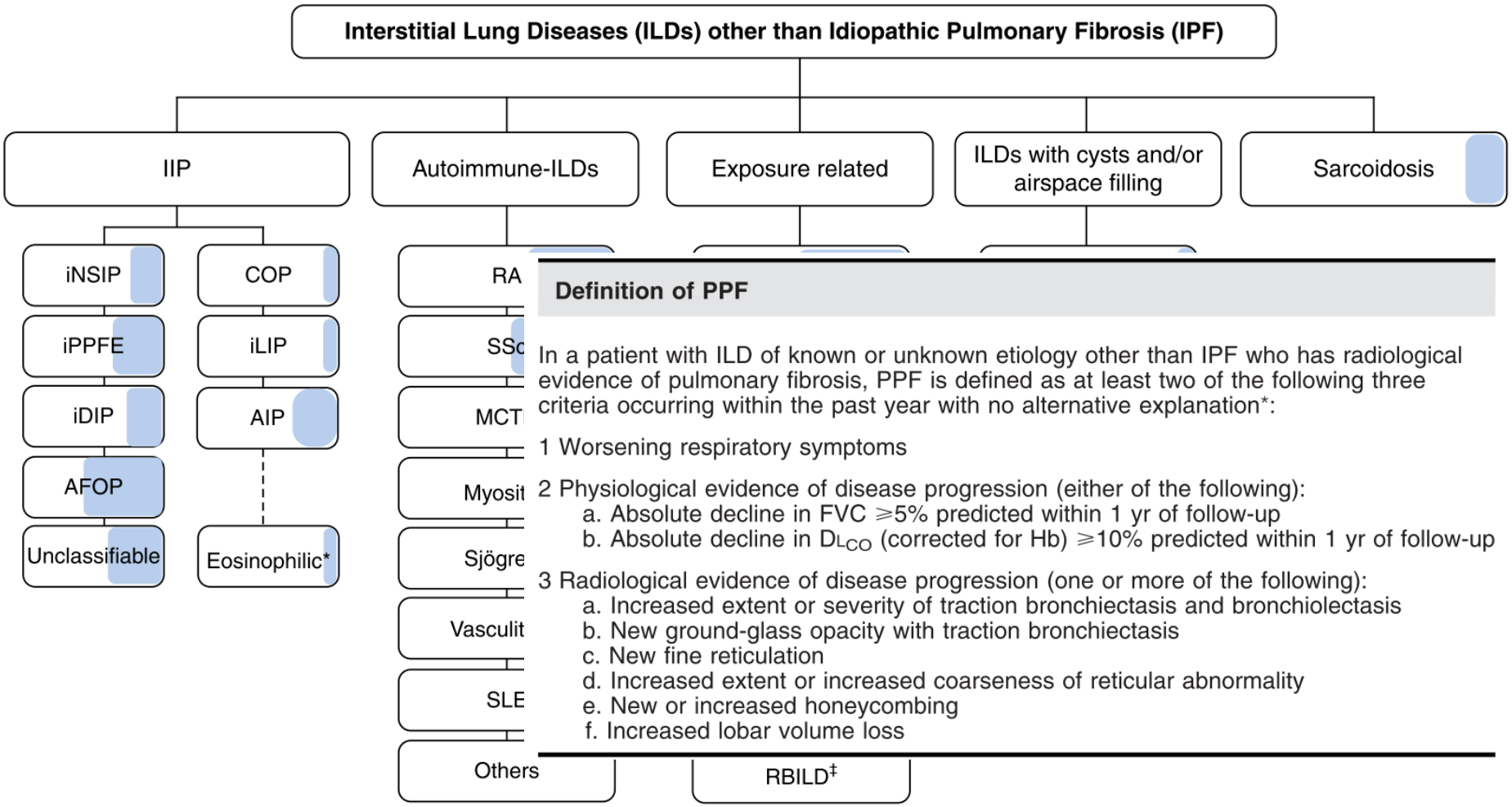
Lung Function in PF-ILD



Number of subjects							
INPULSIS	417	408	407	403	395	383	345
INBUILD (overall population)	325	326	325	320	311	296	274
INBUILD (UIP-like fibrotic pattern)	202	202	201	197	190	176	162
INBUILD (other fibrotic patterns)	123	124	124	123	121	120	112

Brown KK *et al*. *Eur Respir J*. 2020; 55(5)

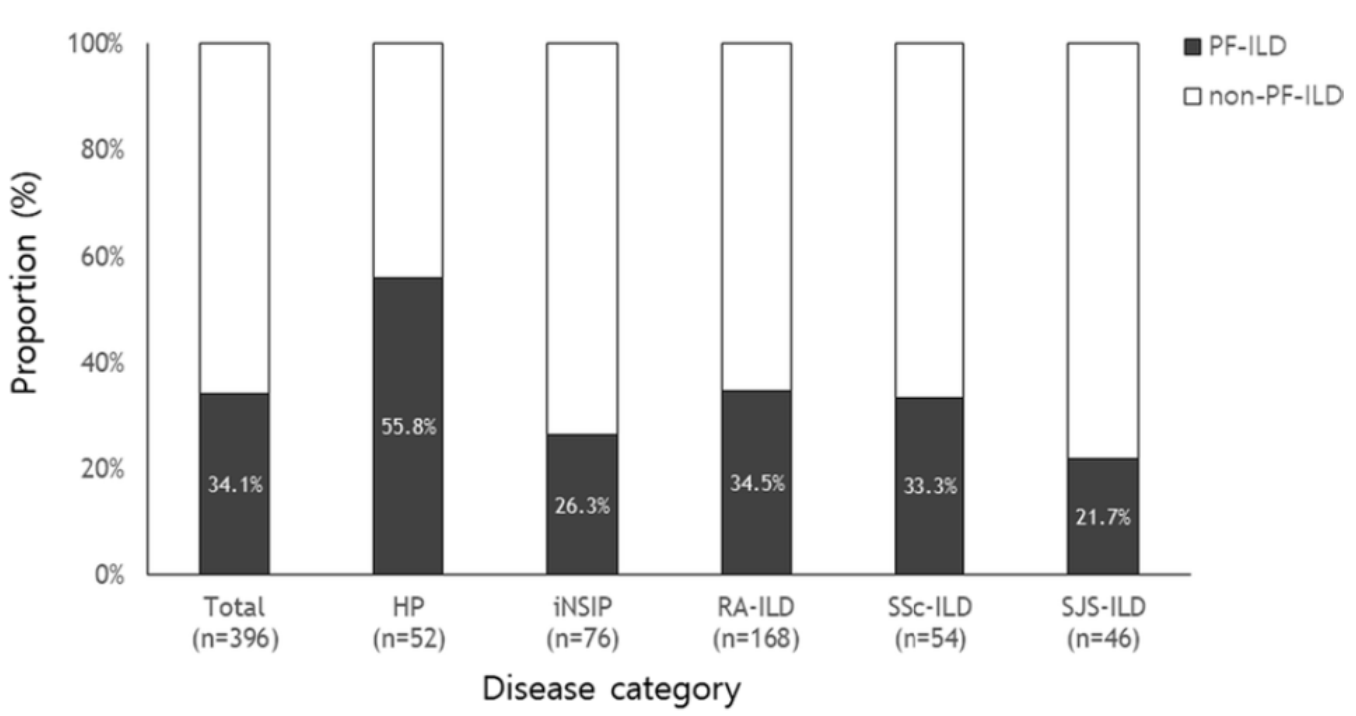
Progressive Pulmonary Fibrosis (PPF)



Raghu G *et al*. *Am J Respir Crit Care Med*. 2022; 205(9)

Progressive Pulmonary Fibrosis/PF-ILD

- 396 Non-IPF ILD patients from single center in Korea
- Definition of PF-ILD: INBUILD criteria



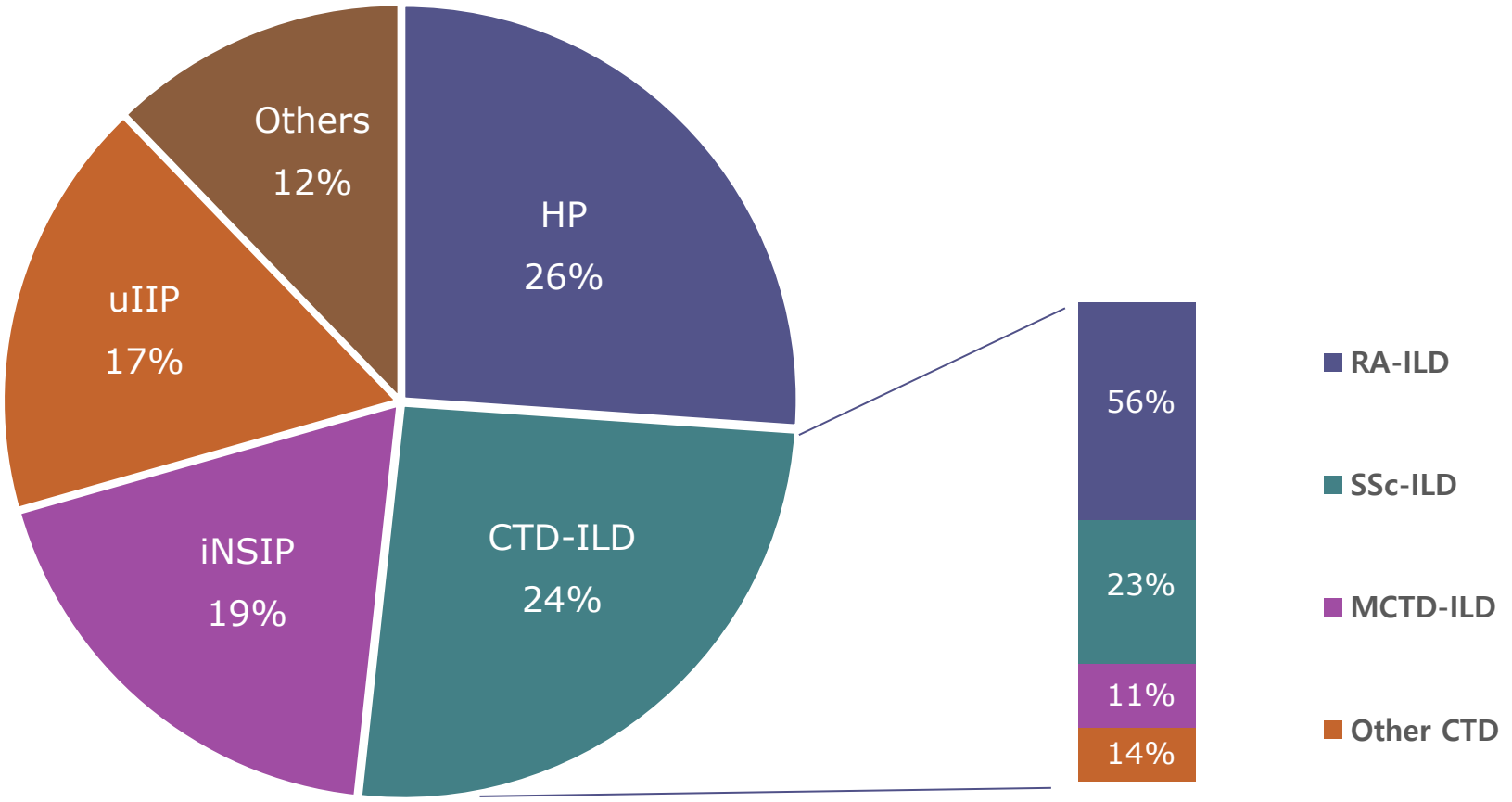
Kwon BS *et al*. *Sci Reports*. 2022; 16

Nintedanib for PF-ILD (INBUILD trial)

- Double-blind placebo-controlled phase 3 trial (15 countries)
- 663 Progressive fibrosing ILD [(HP, CTD-ILD, idiopathic NSIP, uIIP etc.)]
- PF-ILD (Progression within 24 months despite standard treatment)
  - ✓ FVC decline ≥10%
  - ✓ 5% ≤ FVC decline < 10% + Worsening respiratory Sx or Increased fibrosis on CT
  - ✓ Worsening respiratory Sx + increased fibrosis on CT
- Exclusion
  - ✓ AZA, CYC, MMF, Tacrolimus, Rituximab, Cytoxan, Steroid (>20mg)
- Protocol
  - ✓ (1:1 ratio) Nintedanib 150mg bid vs. Placebo for 52 weeks
- Outcome
  - ✓ Annual rate of FVC decline
  - ✓ Change of K-BILD, time till 1st AE, and time till death

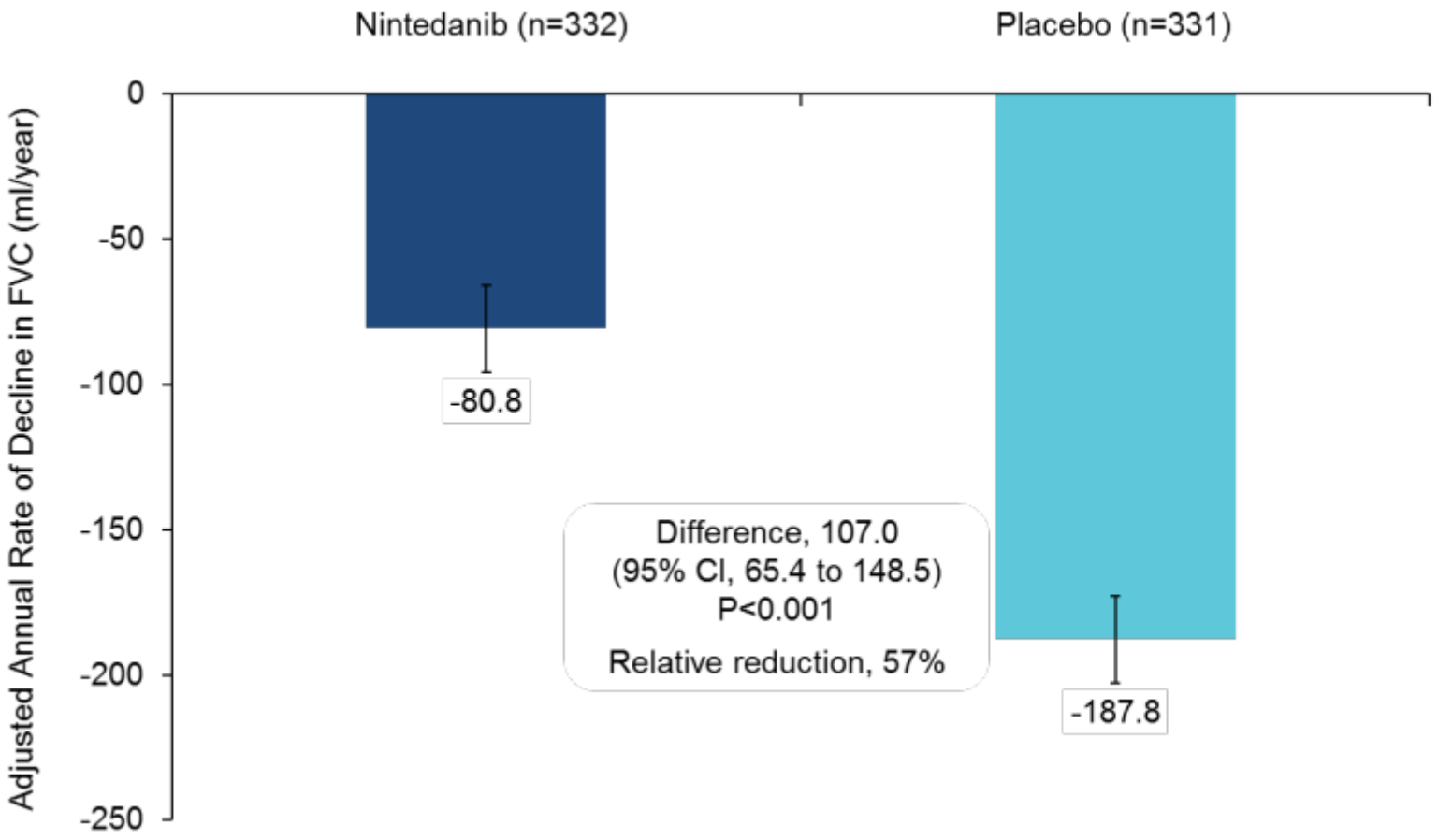
Flaherty KR *et al*. *N Engl J Med*. 2019; 381(18)

Nintedanib for PF-ILD (INBUILD trial)



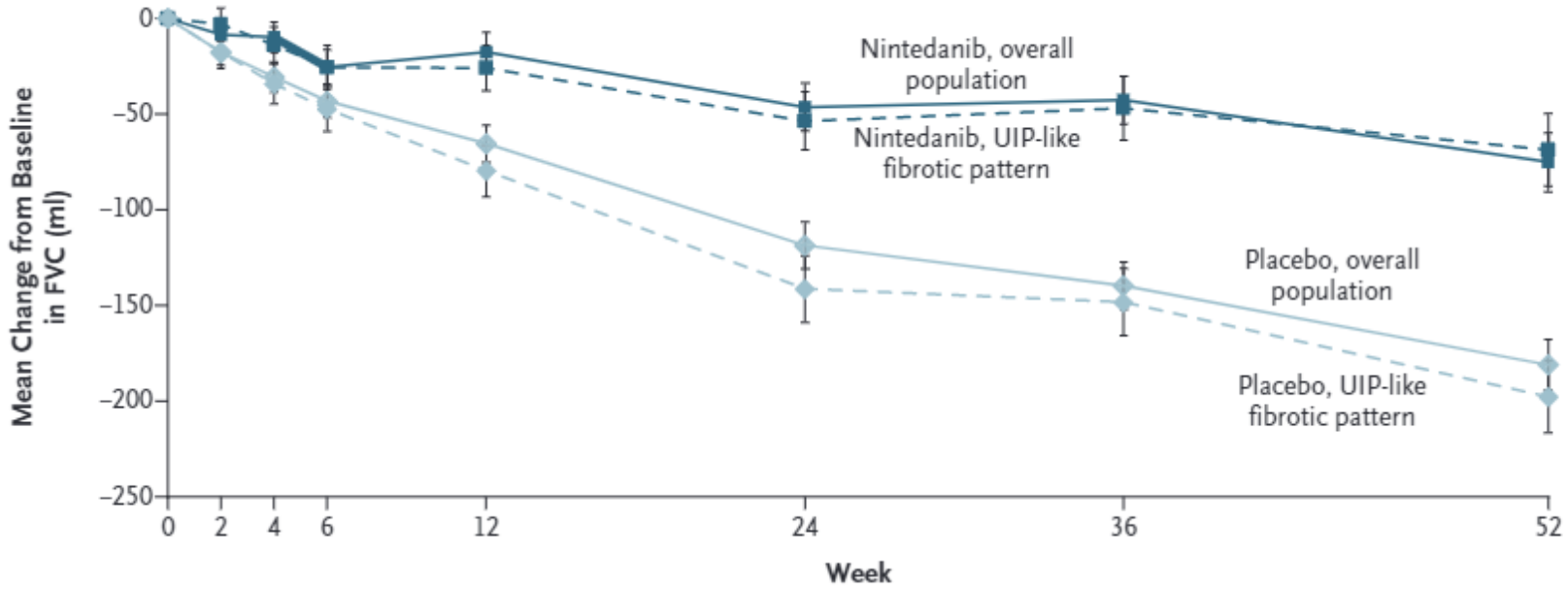
Flaherty KR *et al*. *N Engl J Med*. 2019; 381(18)

Nintedanib for PF-ILD (INBUILD trial)



Flaherty KR *et al*. *N Engl J Med*. 2019; 381(18)

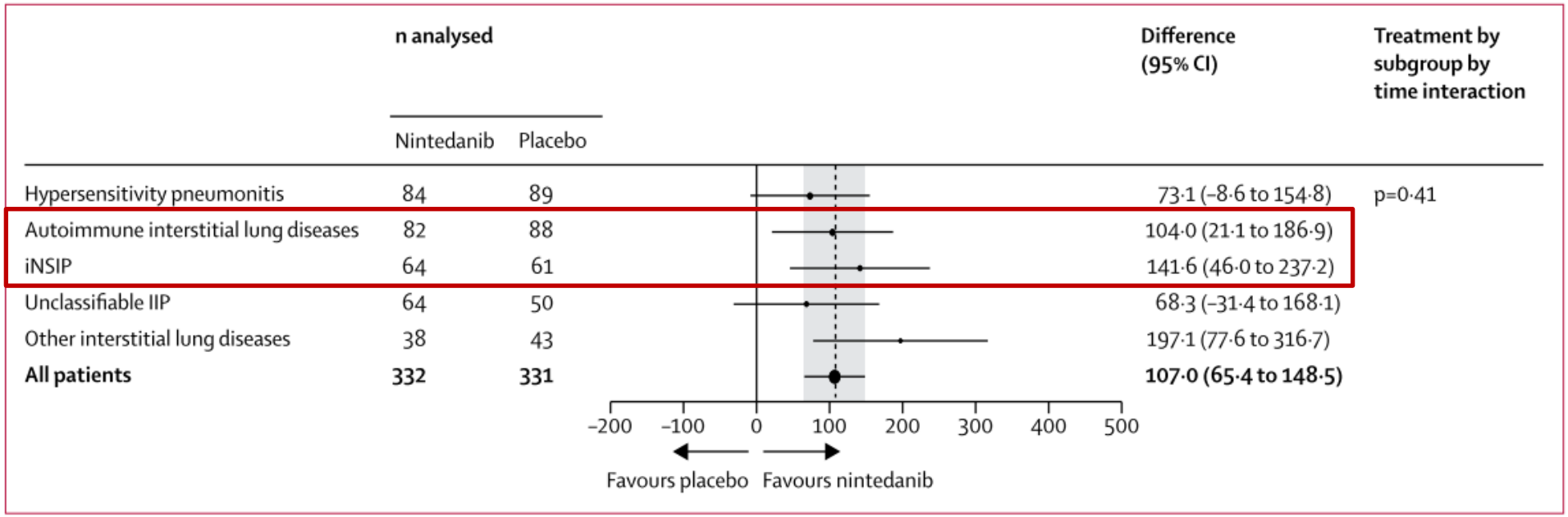
Nintedanib for PF-ILD (INBUILD trial)



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

Flaherty KR *et al*. *N Engl J Med*. 2019; 381(18)

Nintedanib for PF-ILD (INBUILD trial)



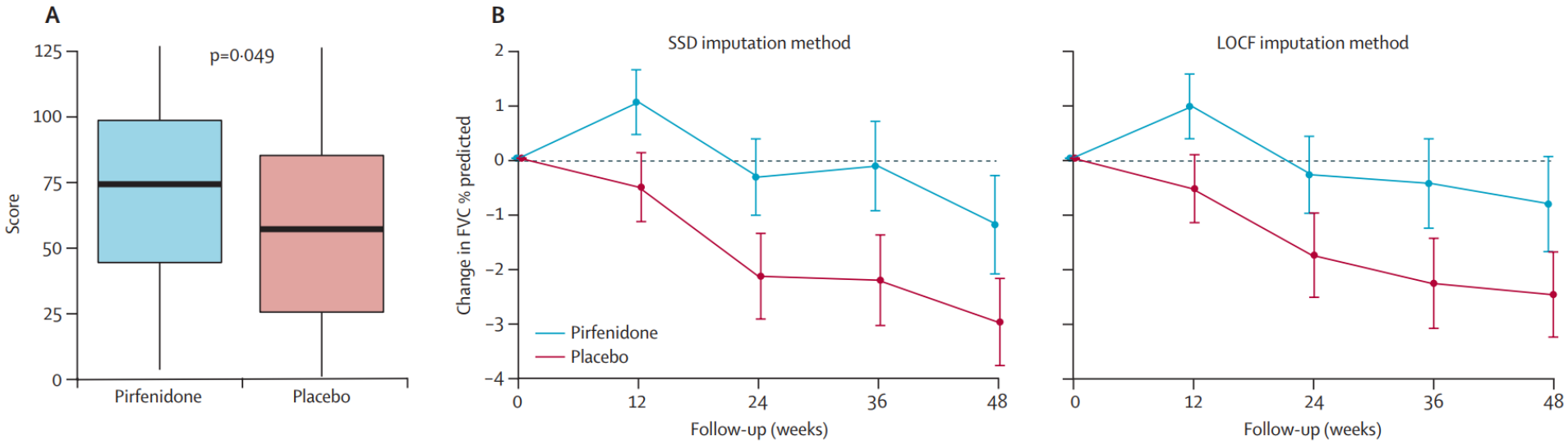
Wells AU *et al*. *Lancet Respir Med*. 2020; 8

Pirfenidone for Progressive fibrotic ILD (RELIEF trial)

- Double-blind placebo-controlled phase 2 trial (RELIEF trial)
- 127 non-IPF lung fibrosis (57 CHP, 37 CVD-ILD, 27 fibrotic NSIP, 6 asbestos-ILD)
- Patients
  - ✓ Annual absolute FVC decline ≥ 5%
  - ✓ CVD-LF, Fibrotic NSIP, Chronic HP, Asbestos-induced lung fibrosis
- Protocol
  - ✓ (1:1 ratio) PFD 2403 mg vs. Placebo
- Outcome
  - ✓ Absolute FVC change (48 weeks)
  - ✓ Change in FVC, DLco, 6MWTD, SGRQ, Adverse event

Behr J *et al*. *Lancet Respir Med*. 2021;9(5)

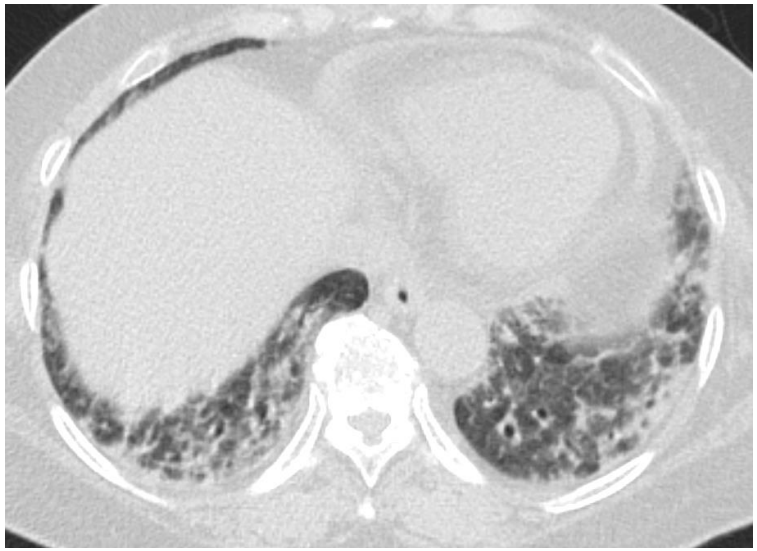
Pirfenidone for Progressive fibrotic ILD (RELIEF trial)

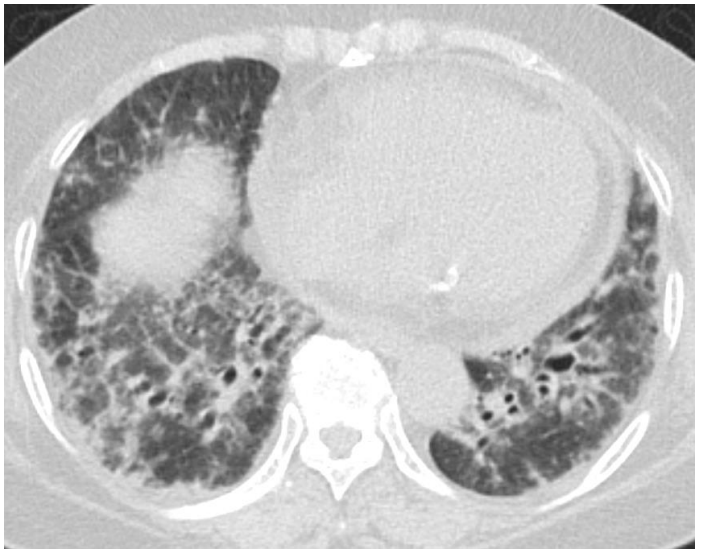


Behr J *et al*. *Lancet Respir Med*. 2021;9(5)

Case (III)

- F/77
- Previously healthy
- Referred from local hospital due pneumonia unresponsive to antibiotics





- TBLB (RLL): Interstitial fibrosis with chronic inflammation favor NSIP
- Anti-SSA (+, > 200), Sicca Sx (+)

→ Sjogren's syndrome associated ILD (NSIP)

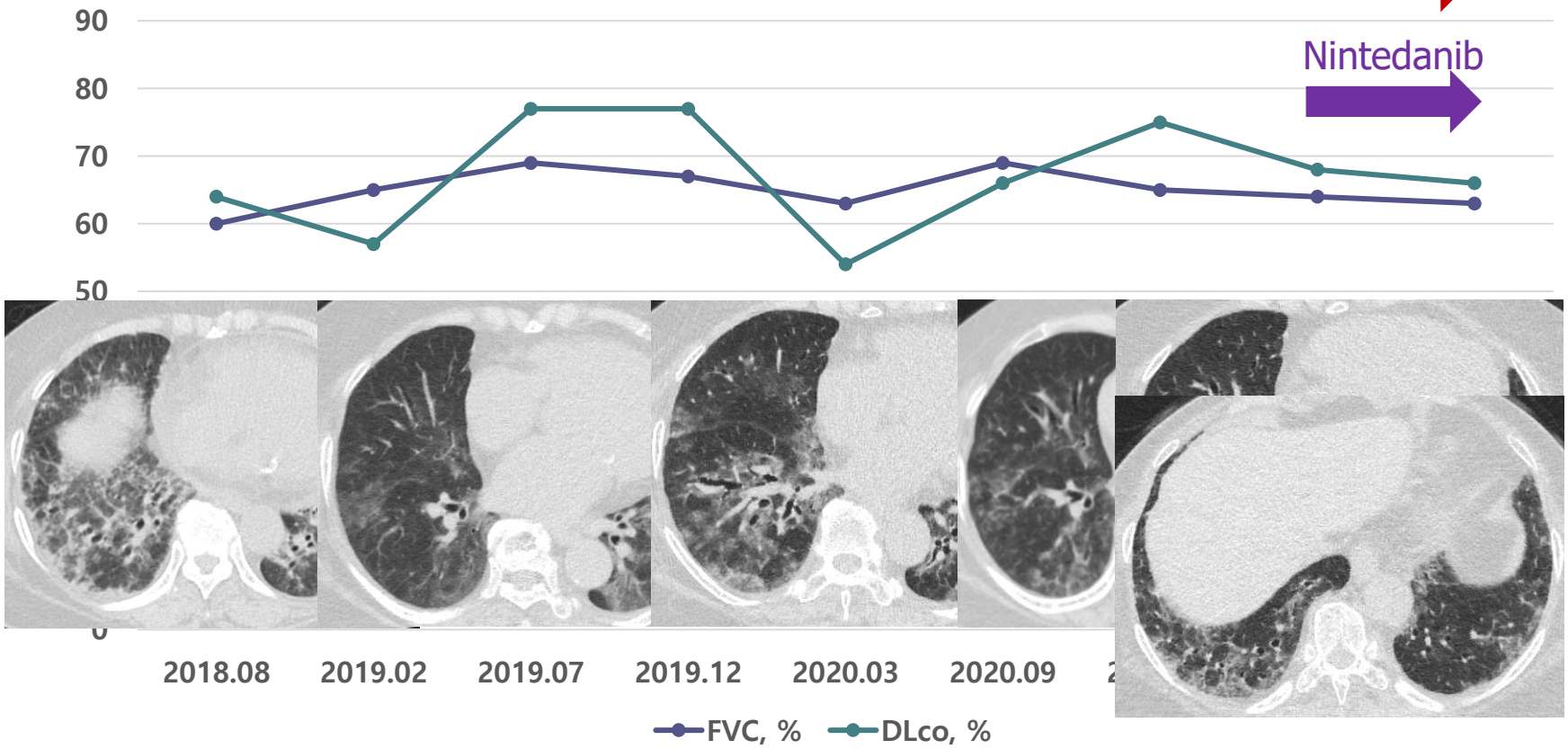
Case (III)

Prednisone (50mg→ tapering)

Azathioprine (100mg)

Prednisone (20mg→ tapering)

Nintedanib



Summary (I)

- **Nonspecific Interstitial Pneumonia (NSIP)**
  - ✓ Pathologic term (Uniform inflammation and fibrosis of interstitium)
  - ✓ Better prognosis than IPF
  - ✓ Various etiologies (most common pattern in most CTD-ILDs)

- **Differential diagnosis of NSIP**
  - ✓ Careful evaluation on etiologies (CTDs, hypersensitivity etc.)
  - ✓ Pathologic confirmation of NSIP pattern (idiopathic)

Summary (II)

- **Treatment of NSIP**
  - ✓ Different treatment regimen for different etiologies (CTDs, hypersensitivity etc.)
    - MMF or CYC in SSc-ILD
    - Steroid is considered as the first line therapy
  - ✓ Idiopathic NSIP
    - Optimal treatment regimen or duration is not known
    - Steroid ± immunosuppressants is usually considered
  - ✓ Progression or relapse is not uncommon (PPF)
    - Antifibrotics (nintedanib or pirfenidone) may be helpful in progressive subtype