자가면역성 간질성 폐렴

Interstitial Pneumonia with Autoimmune Features

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Contents: IPAF

1. Criteria
2. Retrospective Studies
3. Prospective Study

Introduction -1

- Interstitial lung diseases (ILDs) may be associated to connective tissue diseases (CTDs) or other systemic autoimmune diseases (AIDs).
- In some 'autoimmune flavored' ILDs the possible underlying disorder does not fulfill the classification criteria of a given CTD.
- For these patients the term Interstitial Pneumonia with Autoimmune Features (IPAF) has been recently proposed.

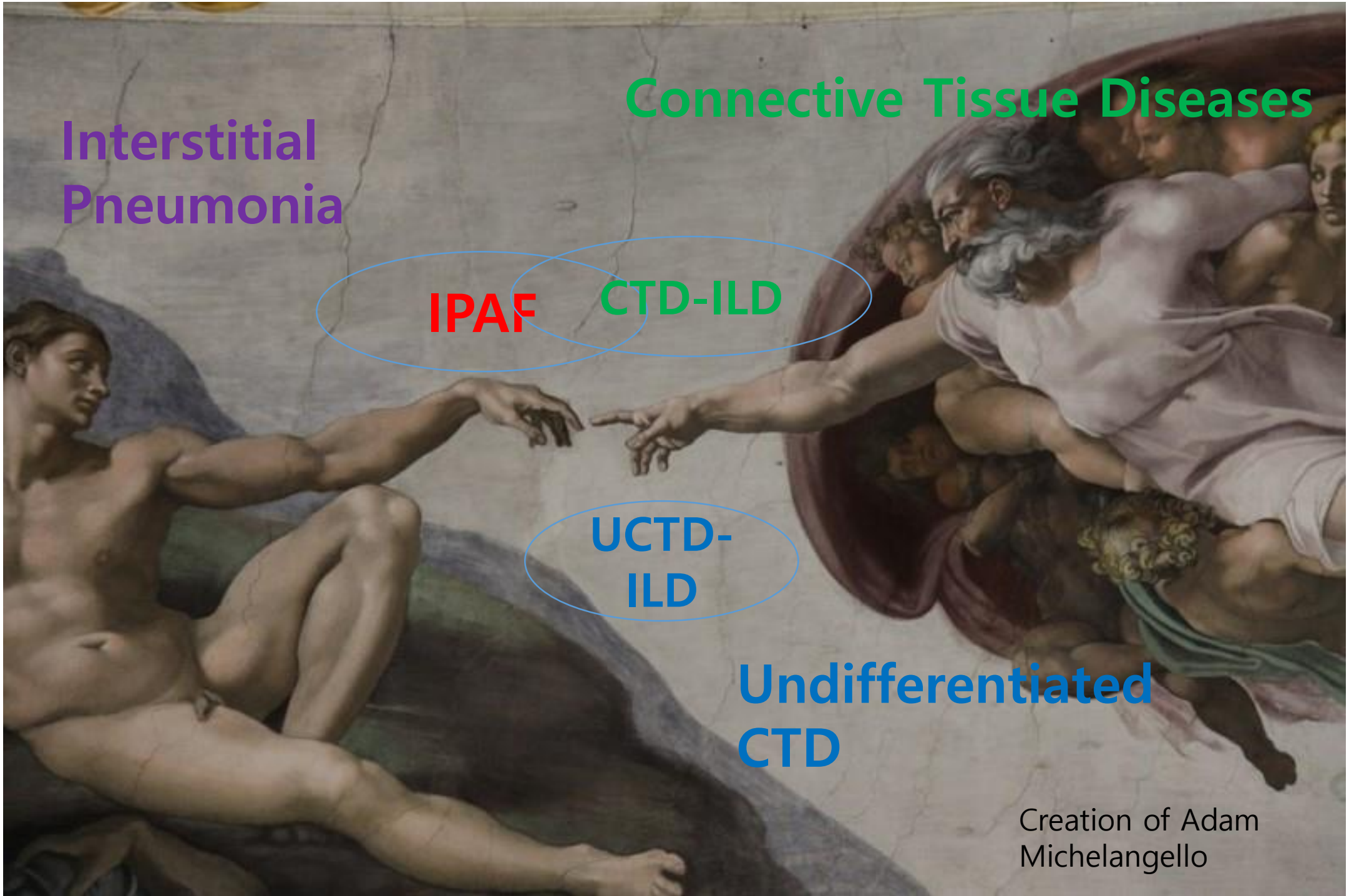
C. Ferri et al. / Autoimmunity Reviews 15 (2016) 61–70

Introduction -2

- IPAF share several clinico-serological features with undifferentiated connective tissue diseases (UCTD), except for ILD that is rarely found in UCTD.
- This difference might be due to pre-selection bias in the patient's referral depending on the presence/absence of clinically dominant ILD.

History of nomenclature

- Lung dominant CTD-ILD
- Autoimmune featured-ILD(AIF-ILD)
- Undifferentiated CTD-associated ILD (UCTD-ILD)
- ILD with features of autoimmunity
- Interstitial pneumonia with autoimmune features (IPAF) – ERS/ATS Taskforce. 2015


Connective Tissue Diseases
Interstitial Pneumonia
IPAF
CTD-ILD
UCTD-ILD
Undifferentiated CTD
Creation of Adam
Michelangello

Why IPAF?

- Poor validation for various criteria
- Various definition of retrospective studies
- Risk assessment
- **Prepare prospective cohort study for natural history**
- Treatment decision

    Immunosuppression vs. antifibrotic therapy

CTD-associated pulmonary manifestations

	SSc	PM/DM	RA	Primary Sjögren's	MCTD	SLE
ILD	+++	+++	++	++	++	+
Airways	-	-	++	++	+	+
Pleural	-	-	++	+	+	+++
Vascular	+++	+	-	+	++	+
DAH	-	-	-	-	-	++

Annals of ATS. 2019. in press

Prevalence and radiologic/histologic pattern

CTD	Prevalence of ILD	Radiological/Histopathological Pattern
SSc	40–75% with clinically significant disease (at least moderate impairment on pulmonary function) [11,31,32] Up to 70% with detectable interstitial changes on HRCT [31]	Most common: NSIP Other: UIP
RA	Detectable on HRCT: 30–60% Clinically evident 10–30% [33]	Most common: UIP Other: NSIP, OP, LIP
IIM	30–50% [34,35]	Most common: NSIP Other: UIP, OP, DAD
SLE	3–11% chronic diffuse interstitial disease [36] Up to 30% with detectable interstitial changes on HRCT Need to distinguish from acute pneumonitis (1–10%) and alveolar haemorrhage (rare)	Most common: NSIP Other: LIP, OP, UIP
SS	10–30% [31] Need to exclude pulmonary lymphoma	Most common: NSIP Other: LIP, OP, UIP
MCTD	20–85% [31]	Common: NSIP Other: UIP

Benefits of immunosuppression in CTD-associated ILD

- **Scleroderma Lung Study I (2007)**

  oral cyclophosphamide
- **Scleroderma Lung Study II(2016, 2017)**

  mycophenolate mofetil vs. cyclophosphamide
- **Mycophenolate, tacrolimus**

  inflammatory myositis–associated ILD
- **Rituximab against SSc**
- ***The results of these studies provide evidence that the use of immunosuppression in CTD-associated ILD may be beneficial.***

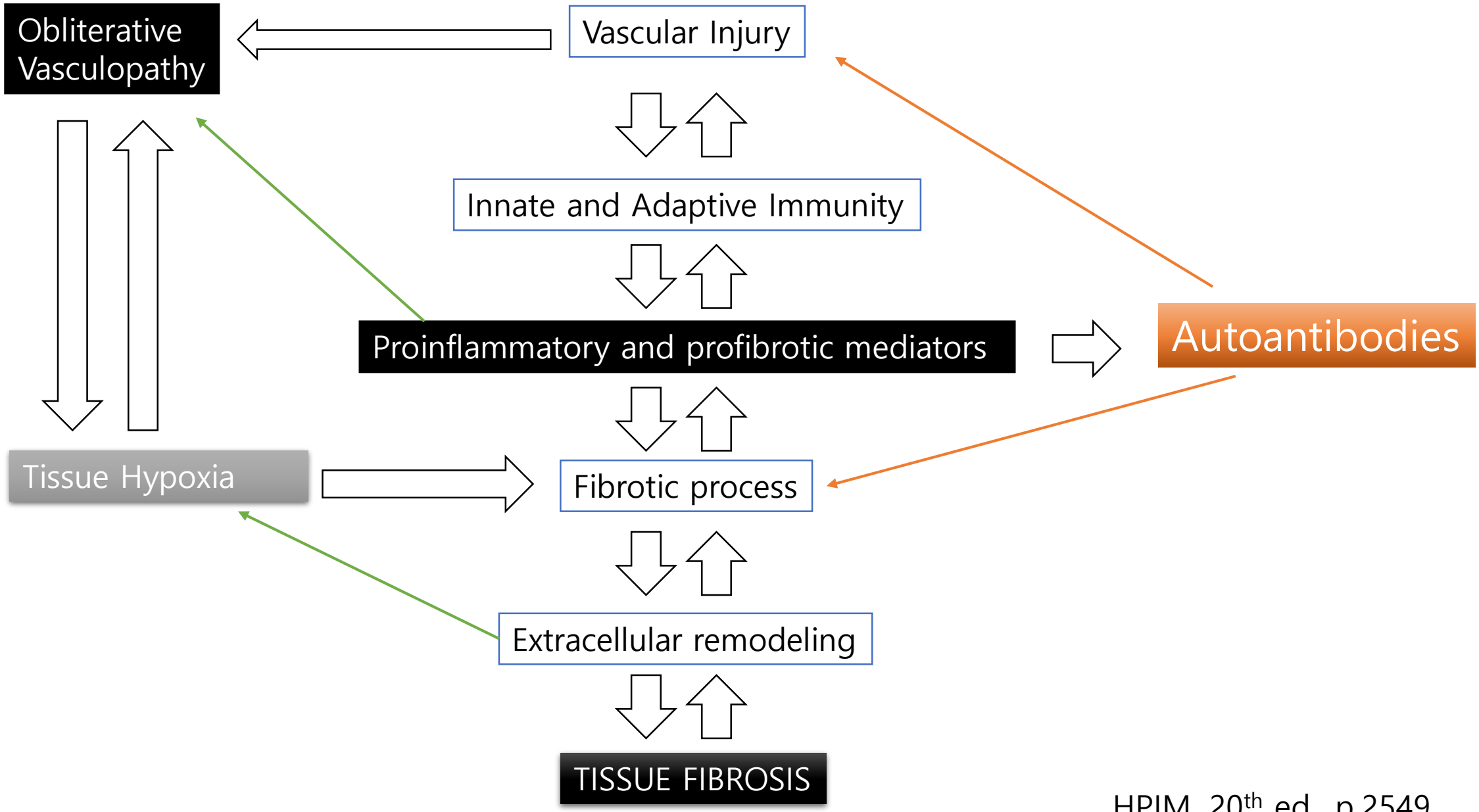
Broad UCTD definition

Clinical findings

- dry eye or mouth, Mouth ulcers
- GERD
- Recurrent FUO
- Weight loss
- Raynaud's phenomenon
- Joint swelling or pain
- Rash;Photosensitivity
- Nonandrogenic alopecia
- Morning stiffness
- Proximal muscle weakness

Laboratory findings

- ANA (any titer)
- Rheumatoid factor
- Anti-Ro
- Anti-La
- Anti-topoisomerase
- ESR (2 X normal)
- CRP



HPIM, 20th ed., p.2549

Evolution of IPAF criteria

- 2002, NSIP into IIP(ATS/ERS)
- idiopathic NSIP

  "the most common histopathologic diagnosis in patients with CTD-associated ILD"

- Early undifferentiated CTD(UCTD)
- Early criteria: Kinder *et al.*; Vij *et al.*; Corte *et al.*
- 2010 Fischer criteria
- Assayag criteria

- 2015 ATS/ERS Criteria

Breakage of Symmetry

- IIP in initiation
- IIP + CTD = CTD-ILD
- IIP – CTD = IIP
- IIP + autoimmune feature – IPAF
- Naming IPAF from “Undifferentiated (forms of) CTD-ILD”
- Identify underlying CTD among IIP!
- boundaries between IIP and CTD-ILD ?

ERJ 2015

Classification criteria for IPAF

1. Interstitial Pneumonia (by HRCT or SLB) and,
2. Exclusion of alternative etiologies and,
3. Does not meet criteria of a defined CTD and,

4. At least one feature from at least two of these domains:

    A. Clinical domain
    B. Serologic domain
    C. Morphologic domain

ERJ 2015

A. Clinical domain

1. Distal digital fissuring (i.e. “mechanic hands”)
2. Distal digital tip ulceration
3. Inflammatory arthritis or polyarticular morning joint stiffness
4. Palmar telangiectasia
5. Raynaud’s phenomenon
6. Unexplained digital edema
7. Unexplained fixed rash on the digital extensor surfaces (Gottron’s sign)

ERJ 2015

Mechanic's hand

Gottron's papules

Eur Respir J. 2015;461;976-987

Sclerodactyly

Digital ulceration

Eur Respir J. 2015;461;976-987

Heliotrope rash

Telangiectasia

KATRD 2018

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

3~8. Anti-CCP; Anti-dsDNA; Anti-Ro (SS-A); Anti-La (SS-B); Anti-ribonucleoprotein; Anti-Smith

9. Anti-topoisomerase (Scl-70)

10. Anti-tRNA synthetase (e.g. Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS)

11. Anti-PM-Scl

12. Anti-MDA-5

ERJ 2015

C. Morphologic domain

1. Suggestive radiology patterns by HRCT

2. Histopathology patterns or features by surgical lung biopsy

3. Multi-compartment involvement (in addition to IP)

ERJ 2015

C1. radiology patterns by HRCT

a. NSIP (Nonspecific Interstitial Pneumonia)

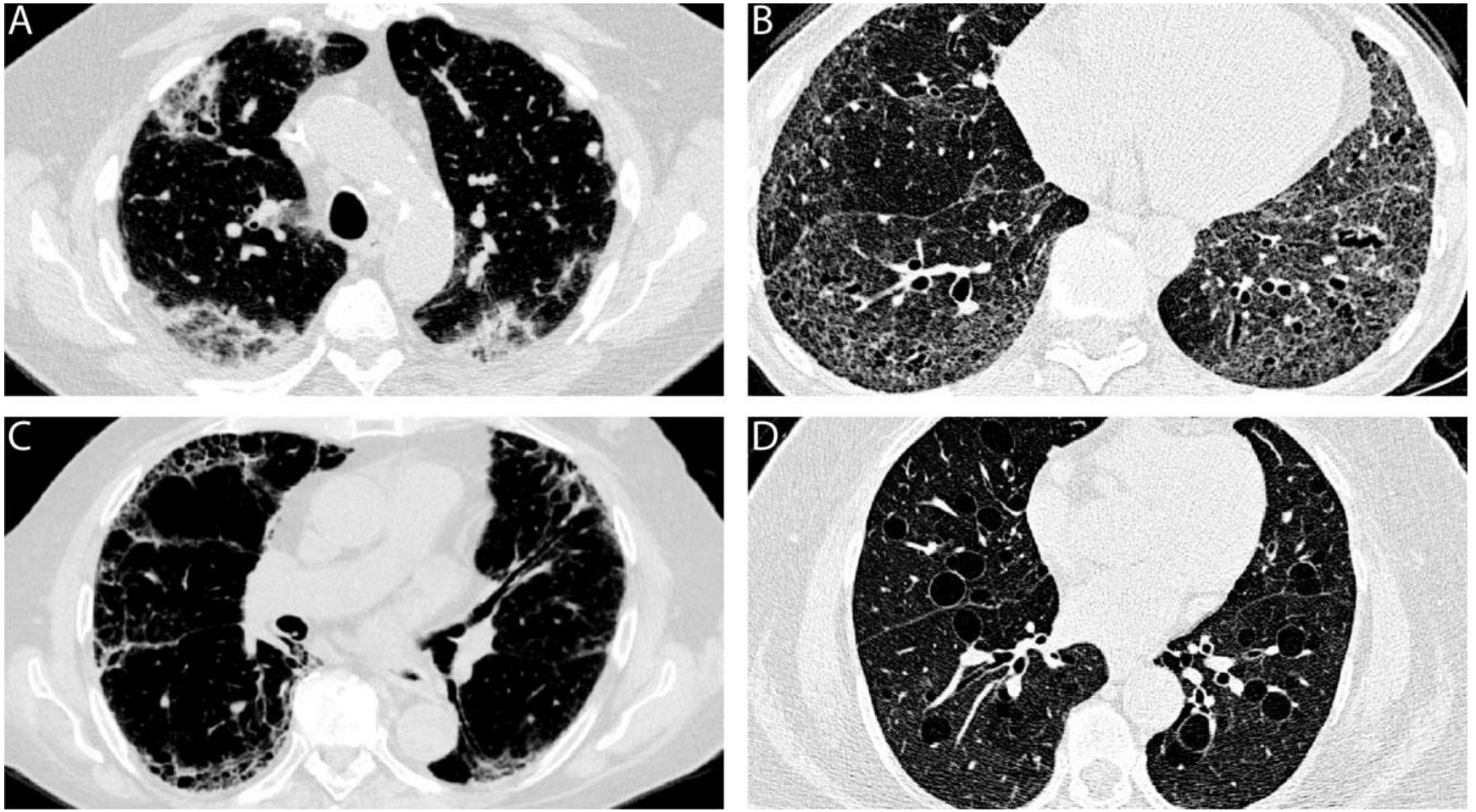
b. OP (Organizing Pneumonia)

c. NSIP with OP overlap

d. LIP (Lymphocytic Interstitial Pneumonia)

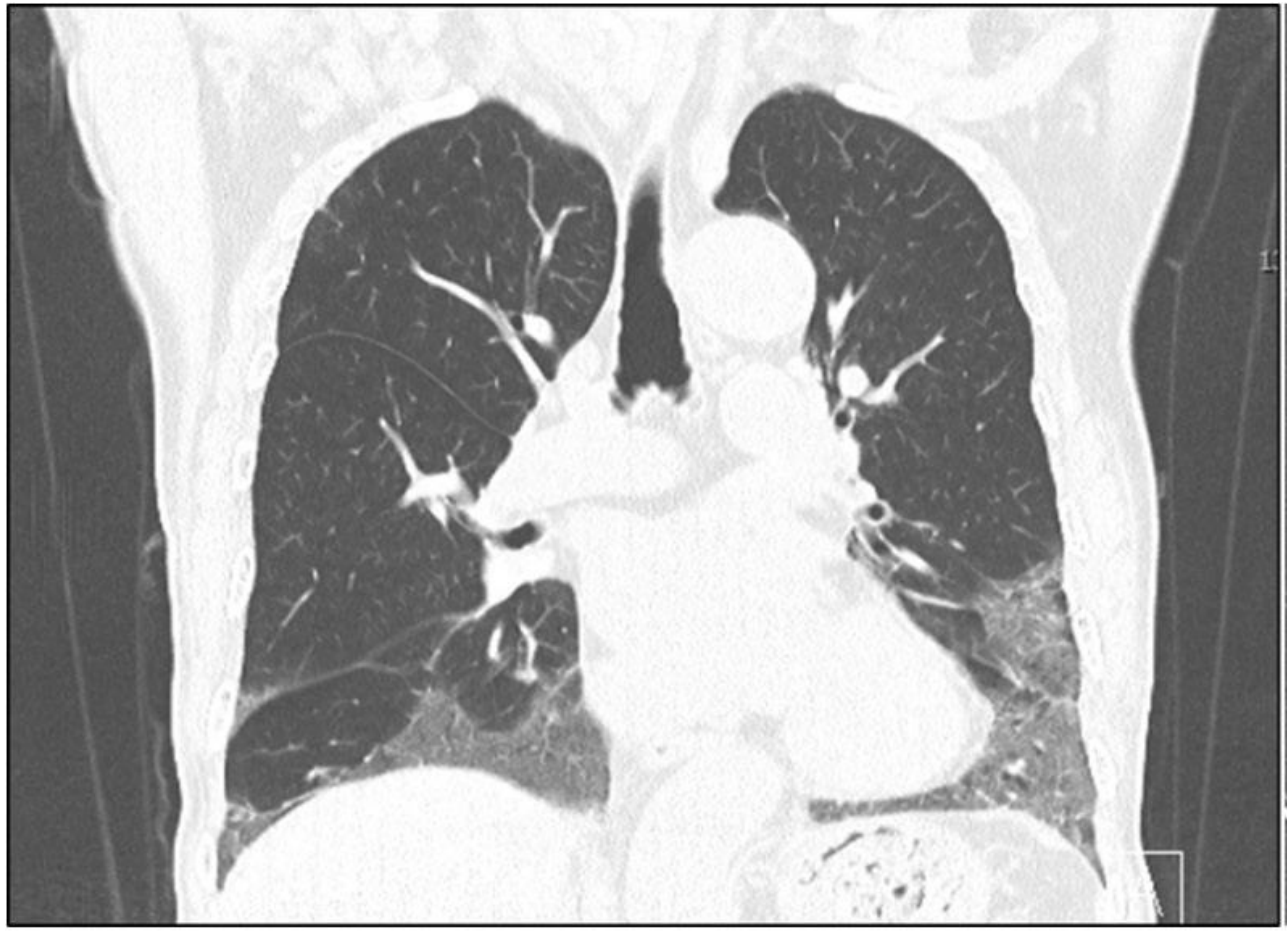
ERJ 2015

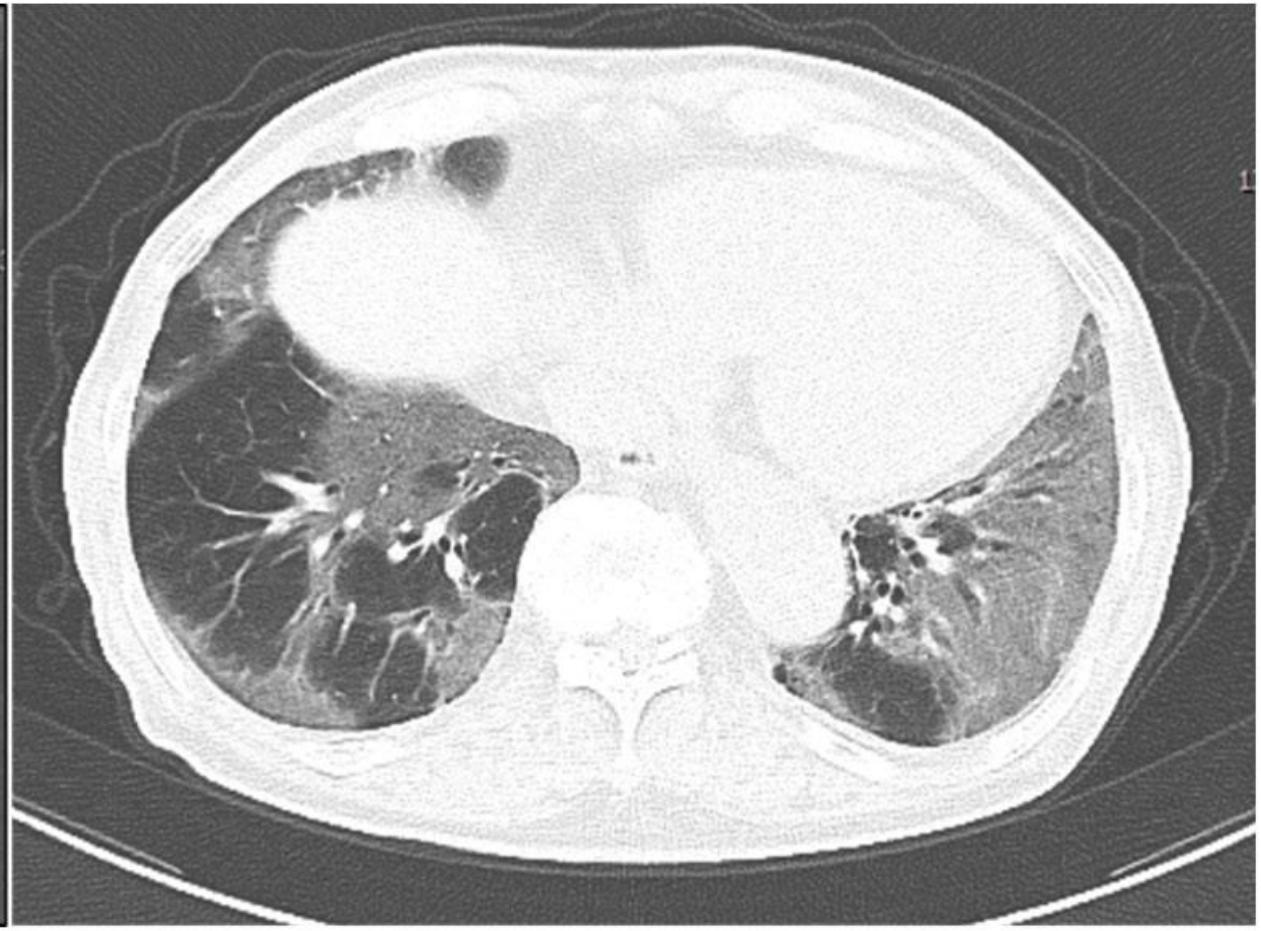
Radiologic IPAF



ARTHRITIS & RHEUMATOLOGY. 2018;70(12):901–1913

NSIP in a patient with systemic sclerosis





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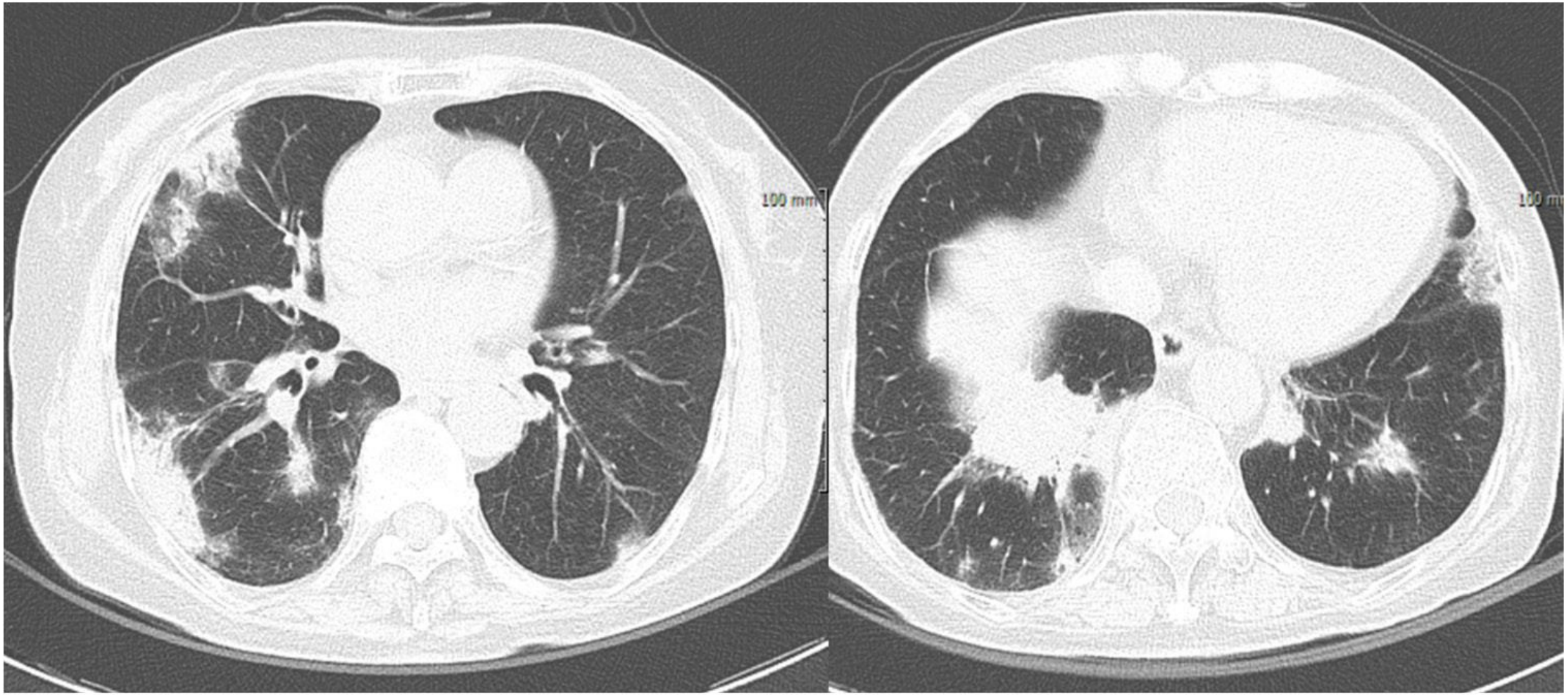
organizing pneumonia in Dermatomyositis



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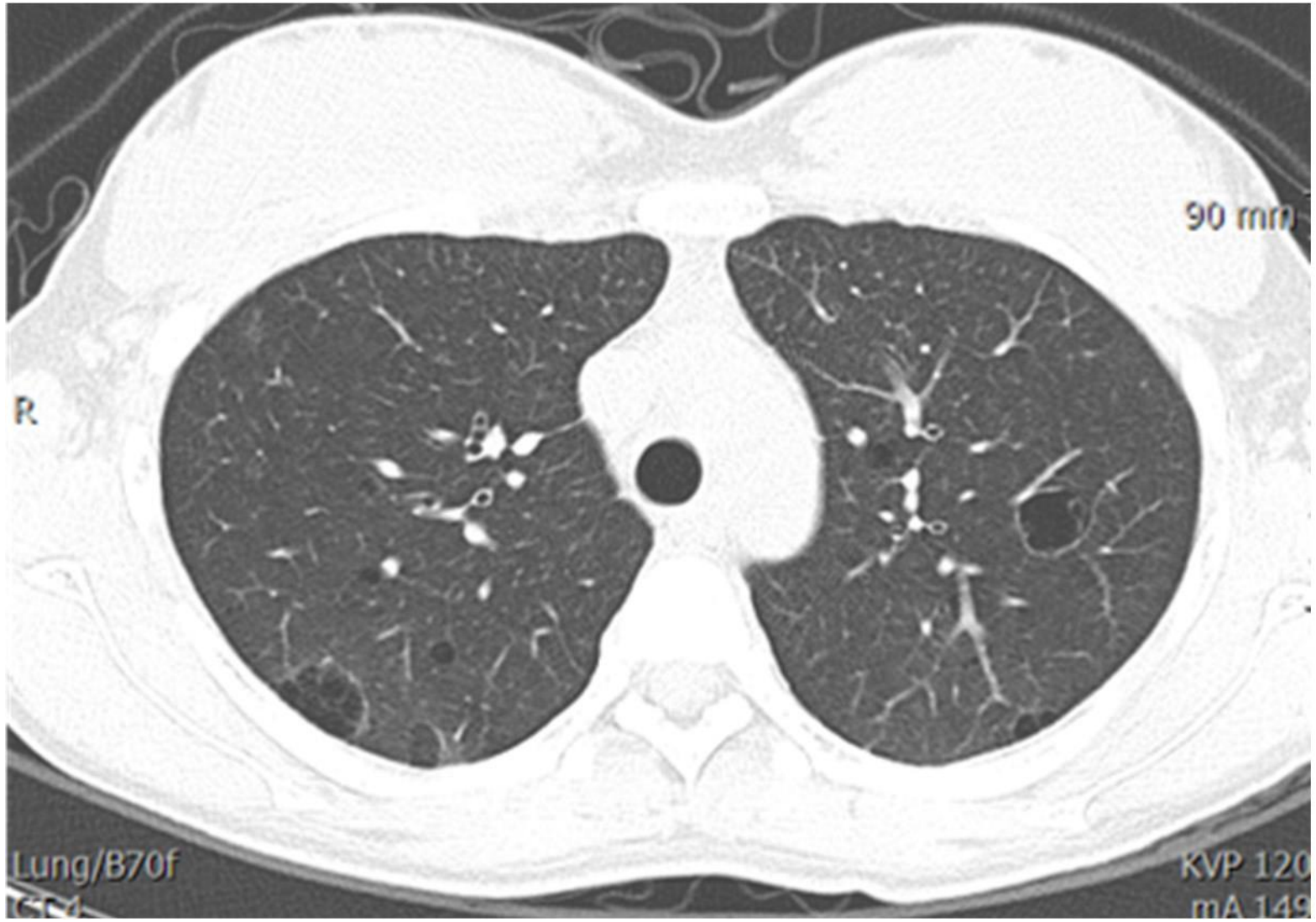
LIP in Sjogren's syndrome



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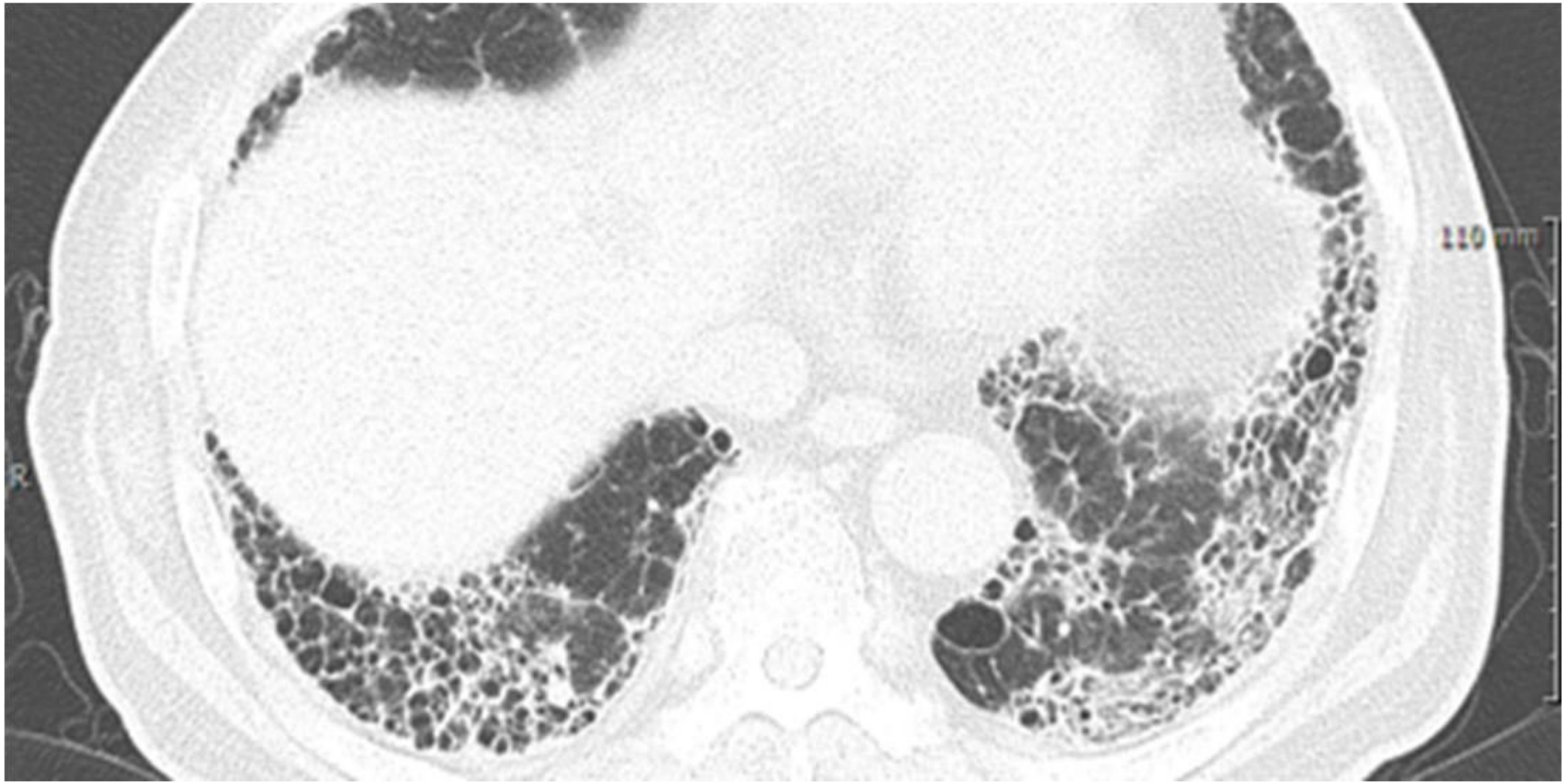
UIP in Rheumatoid Arthritis



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C2. Histopathology (surgical lung biopsy)

a. NSIP

b. OP

c. NSIP with OP overlap

d. LIP

e. Interstitial lymphoid aggregates with germinal centers

f. Diffuse lymphoplasmacytic infiltration

ERJ 2015

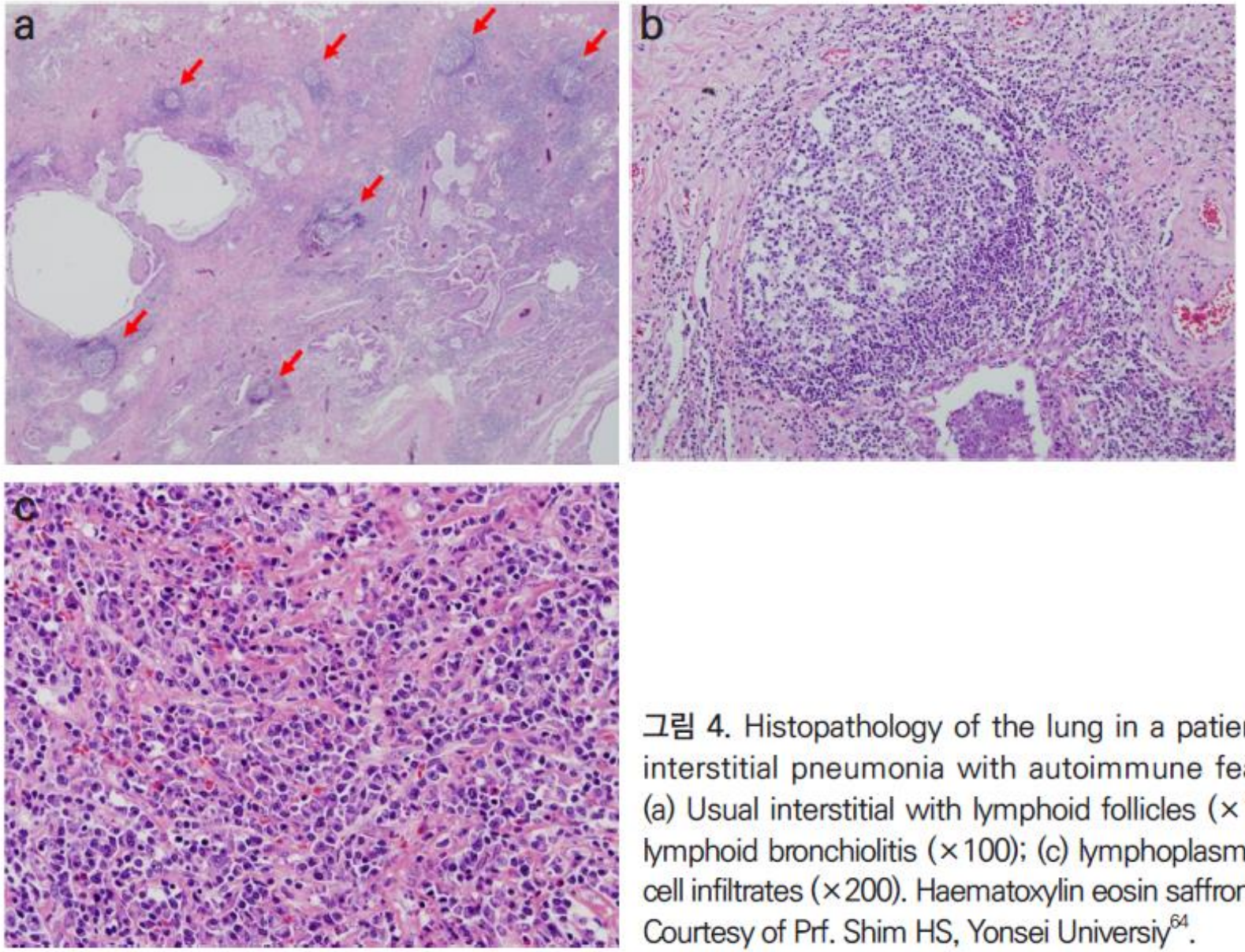


그림 4. Histopathology of the lung in a patient with interstitial pneumonia with autoimmune features. (a) Usual interstitial with lymphoid follicles (×10); (b) lymphoid bronchiolitis (×100); (c) lymphoplasmacytoid cell infiltrates (×200). Haematoxylin eosin saffron (HES). Courtesy of Prf. Shim HS, Yonsei Universiy[64].

C3. Multi-compartment involvement (in addition to interstitial pneumonia)

Unexplained

a. pleural effusion or thickening

b. pericardial effusion or thickening

c. intrinsic airways diseases

d. pulmonary vasculopathy

ERJ 2015

To be diagnosed as having IPAF

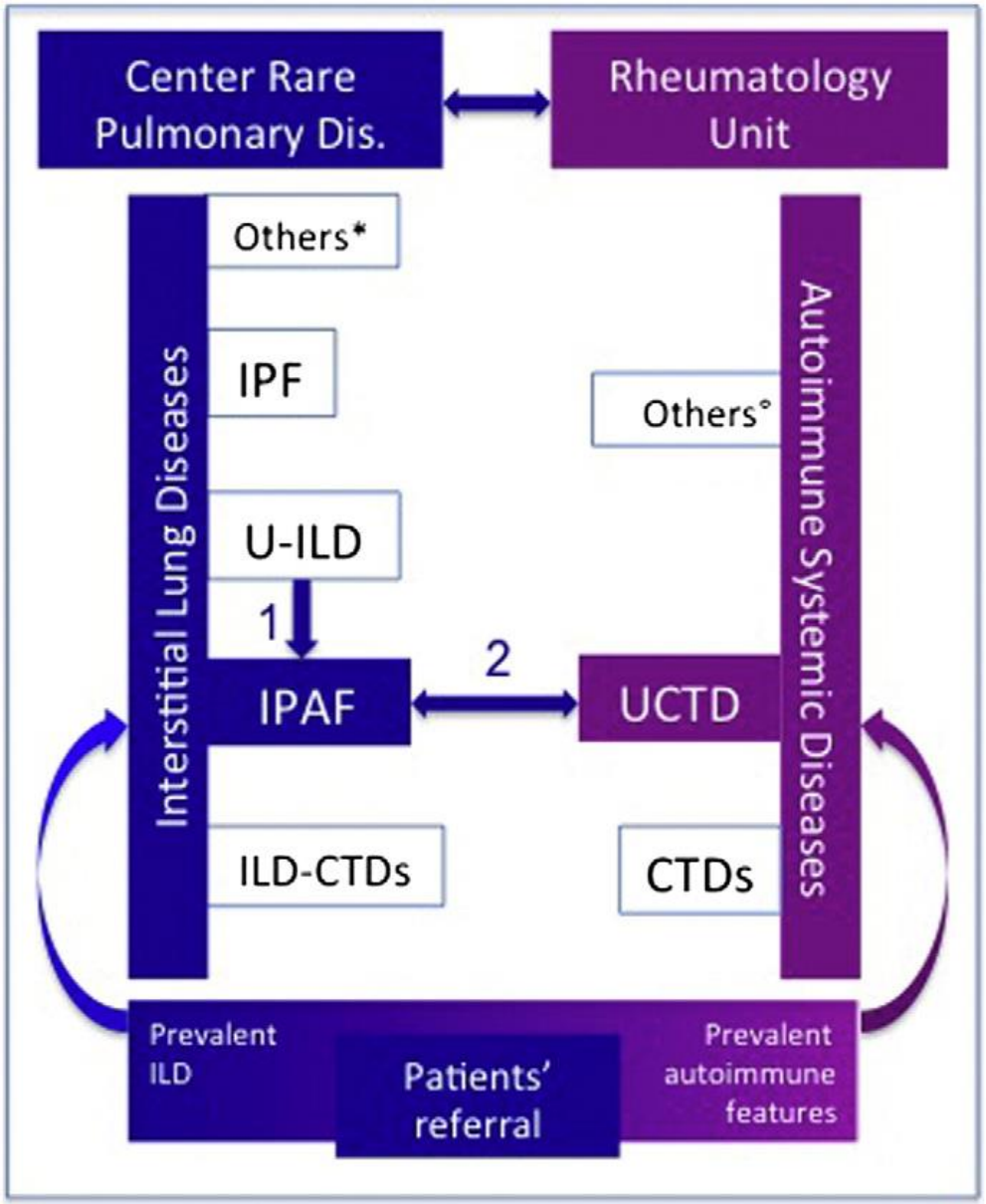
- **NSIP or NSIP+ organizing pneumonia (OP)**

  a (+) serologic finding or

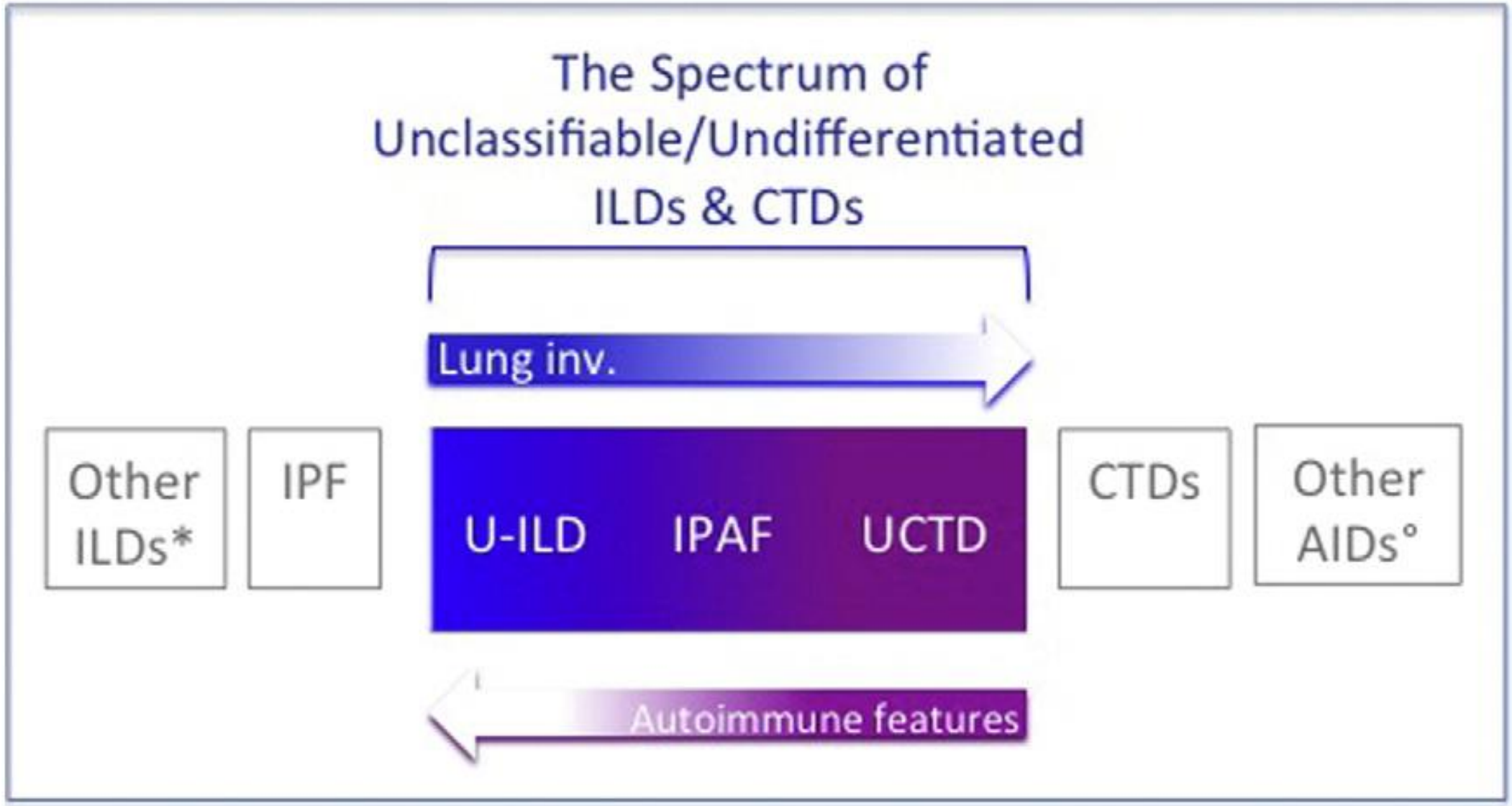
  a (+) clinical feature

- **UIP**

  both a clinical feature and a serologic feature of CTD

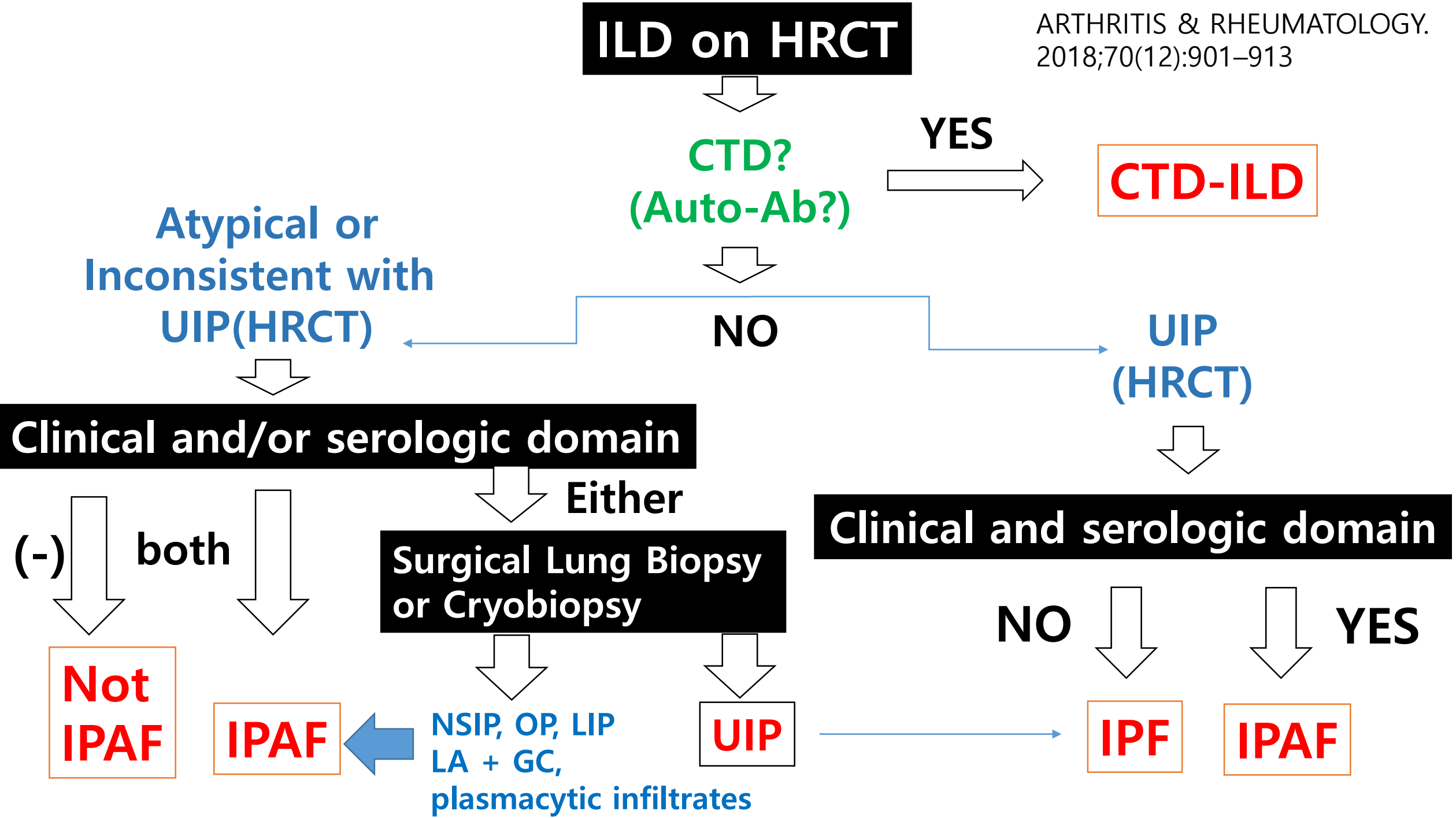


C. Ferri et al. / Autoimmunity Reviews 15 (2016) 61–70



C. Ferri et al. / Autoimmunity Reviews 15 (2016) 61–70

ARTHRITIS & RHEUMATOLOGY.
2018;70(12):901–913



AUTOANTIBODIES

- ILD 진단 시 CTD-ILD 가능성의 감별을 위해 자가항체검사가 필요하다.
- 자가항체가 존재하지만 임상적으로 CTD에 합당하지 않거나 특정 CTD 진단기준에 맞아 떨어지지 않는 경우, 추후에 CTD 관련증상이 발생하기도 하므로 CTD 증상발현 여부에 대한 경과관찰이 필요하다.

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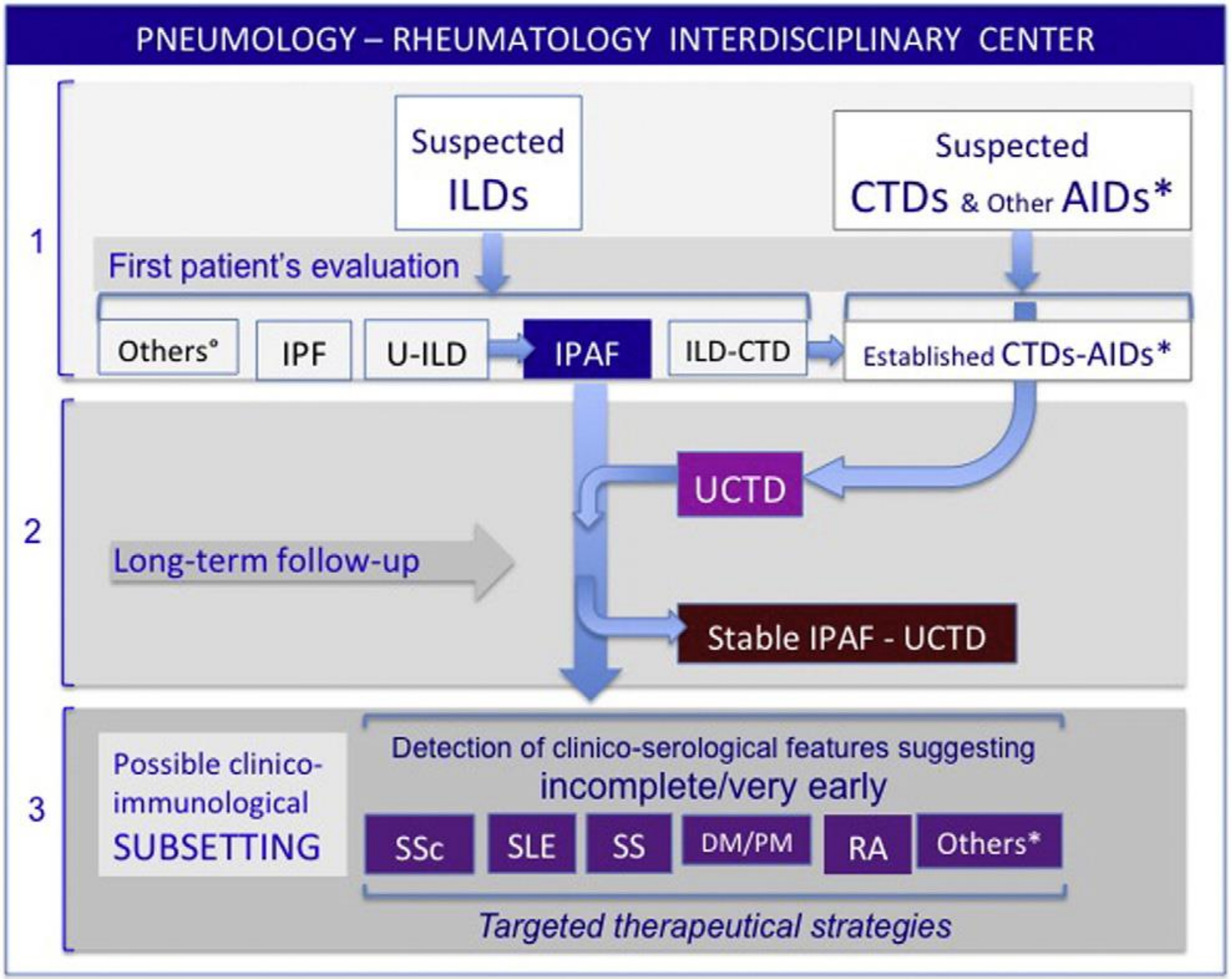

C. Ferri et al. / Autoimmunity Reviews 15 (2016) 61–70

Table 2. Suggested serum serologies in the evaluation of patients with ILD.

Serum Markers of Systemic Inflammation
● erythrocyte sedimentation rate (ESR)
● c-reactive protein (CRP)
Autoantibodies
Anti-neutrophil cytoplasmic antibodies (ANCAs)
● c-ANCA, p-ANCA, atypical p-ANCA
● anti-MPO
● anti-PR3
Rheumatoid arthritis
● anti-CCP
● rheumatoid factor (RF)
SLE and related autoimmune diseases (MCTD, Sjögren's syndrome)
● ANA
● anti-dsDNA
● anti-SS-A (Ro)
● anti-SS-B (La)
● anti-Smith
● anti-RNP
Systemic sclerosis
● anti-Scl-70
● anti-Centromere
Myositis-specific and myositis-associated antibodies
● anti-Jo1 ● anti-PL7 ● anti-PL12 ● anti-EJ
● anti-OJ ● anti-SRP ● anti-Mi-2α ● anti-Mi-2β
● anti-MDA5 ● anti-TIF-1γ ● anti-NXP-2 ● anti-KS
● anti-Zo ● anti-Ku
Muscle Enzymes
● CPK
● aldolase

J. Clin. Med. **2018**, 7, 476

표 2. 자가항체의 종류와 의미[65]

검사	해석
항핵항체검사(ANA)	비특이적이나 역가가 높은 경우 CTD 가능성 높음
류마티스유사인자(rheumatoid factor)	RA에서 상승할 수 있고 다른 CTD에서는 비특이적
Scl-70	전신경화증과 연관
RNP	혼합결체조직질환과 연관
Jo-1	근육염 특이 항체
타 근육염 연관	
Antisynthetase	PL-7, PL-12, EJ, OJ 항체, 모두 ILD와 연관
MDA-5	침식적인 Gottoron's papules와 연관. 심각한 ILD와 연관
PMScl	다발근육염과 경화증과 중첩되는 경우 연관
Ro-52	심각한 ILD와 연관
CPK, Aldolase	근효소로 근염일 때 올라갈 수 있으나, clinically amyopathic dermatomyositis (CADM) 시 정상일 수 있음
SSA, SSB	쇼그렌증후군 연관 항체
Anti-CCP	RA 연관 항체
ANCA	순수한 ILD 연관인 경우는 흔하지 않으나 있을 수는 있음.

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Retrospective IPAF cohorts (1)

	Oldham	Chart-rand	Ahmad	Ito	Dai	Yoshi-mura	Kelly
Patients (= n)	144	56	57	98	177	32	101
Clinical(C)	49.3	62.5	47.3	NR	20.3	53.1	NR
Serologic(S)	91.7	91.1	93	100	92.1	71.9	NR
Morphologic(M)	85.4	98.2	78.9	100	95.5	96.9	NR
C + S	14.6	2	NR	NR	NR	3.1	4
C + M	8.3	9	NR	NR	NR	28.1	14
S + M	50.7	37.5	NR	100	NR	46.9	26
C + S + M	36.4	52	NR	NR	NR	21.9	56

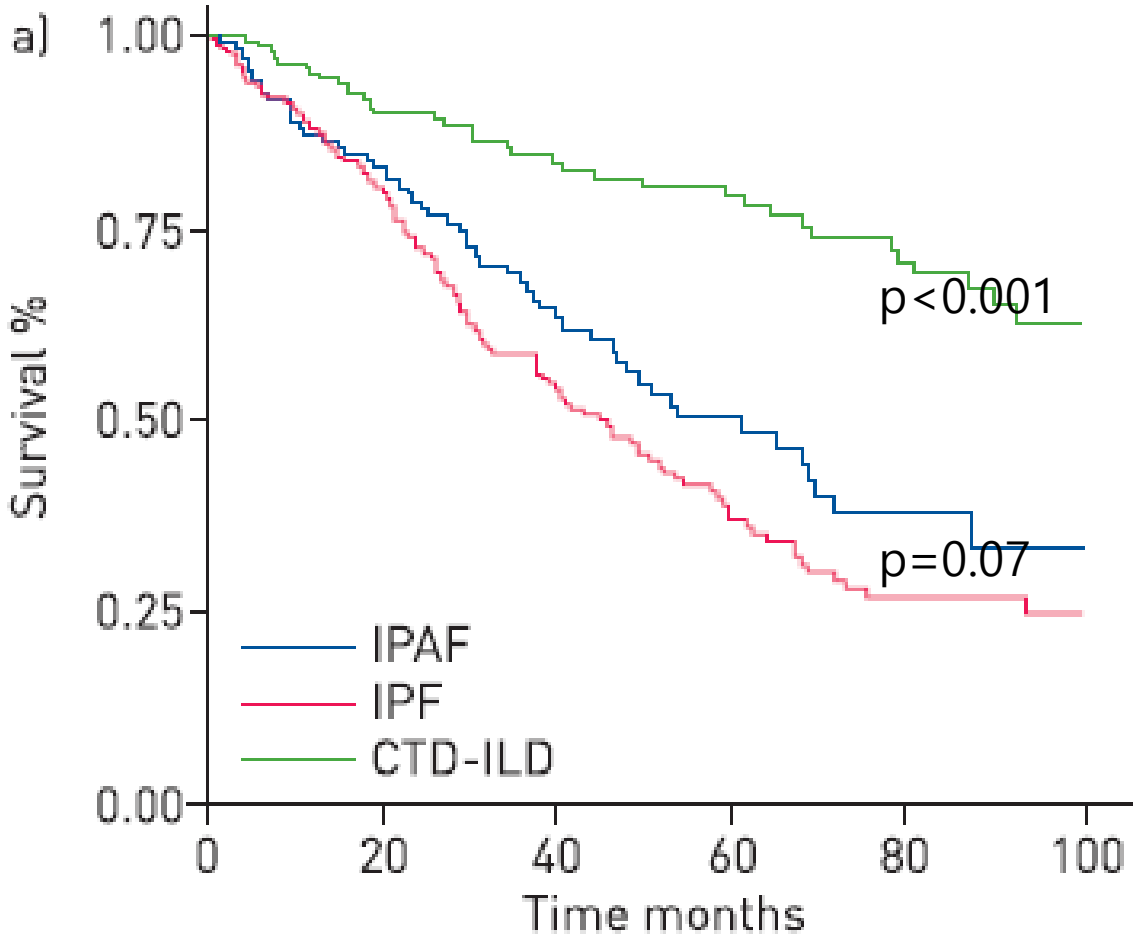
(%)

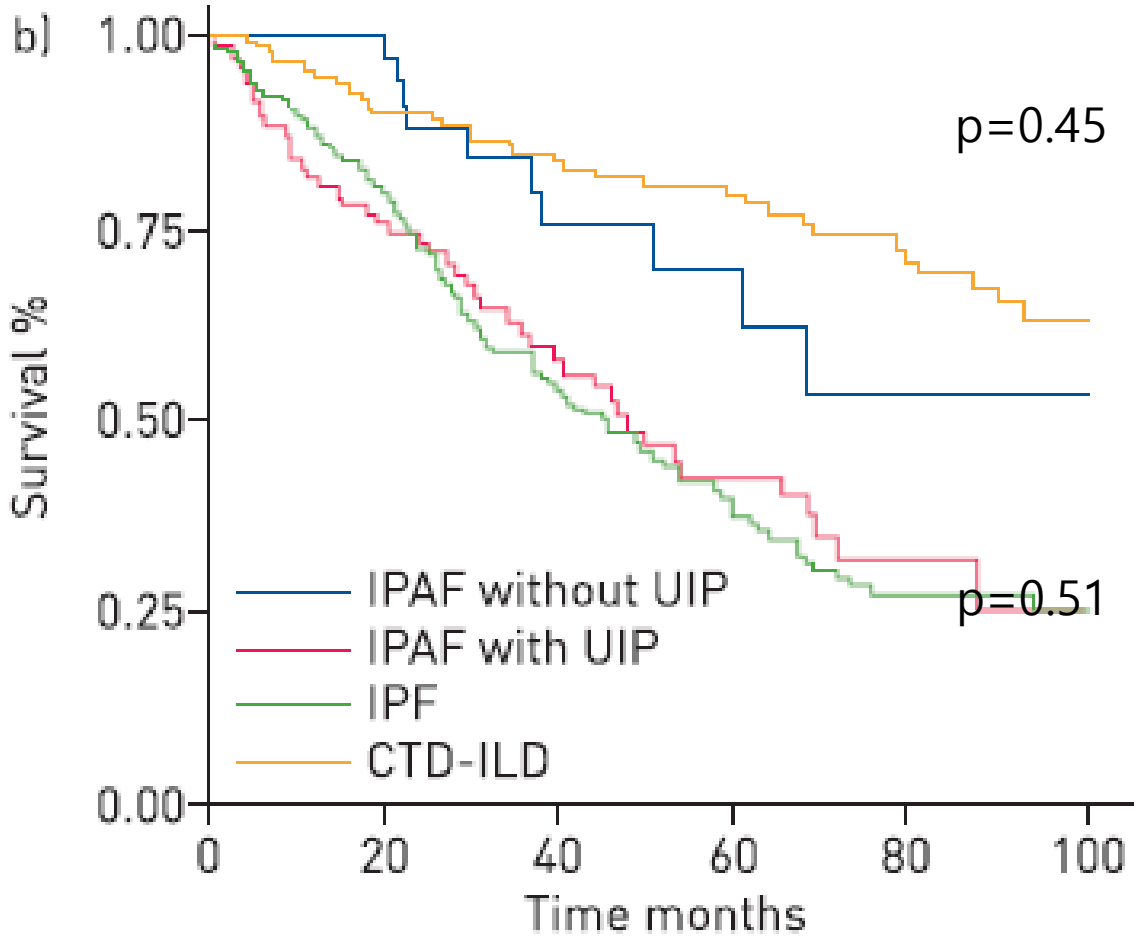
Retrospective IPAF cohorts (2)

	Oldham	Chart-rand	Ahmad	Ito	Dai	Yoshi-mura	Kelly
Most common	UIP	NSIP	NSIP	NSIP	NSIP	NSIP	NSIP
UIP (HRCT)	54.6	8.9	28	0	4.5	NR	NR
SLB, n(%)	83 (57.6)	36 (64.3)	16 (28.1)	17 (17.3)	0	22 (68.8)	51 (50.5)
UIP(SLB), n(%)	61 (73.5)	8 (22.2)	3 (18.8)	3 (17.6)	--	--	12 (23.5)
Steroids	32.2	81.8	67.9	17.3	72.3	59.4	NR
Antifibrotic	NR	NR	5.4	2	NR	25	NR
Transplant	10.8	NR	NR	NR	NR	NR	NR
Death	39.6	0	12.3	27.6	19.8	NR	28

(%)

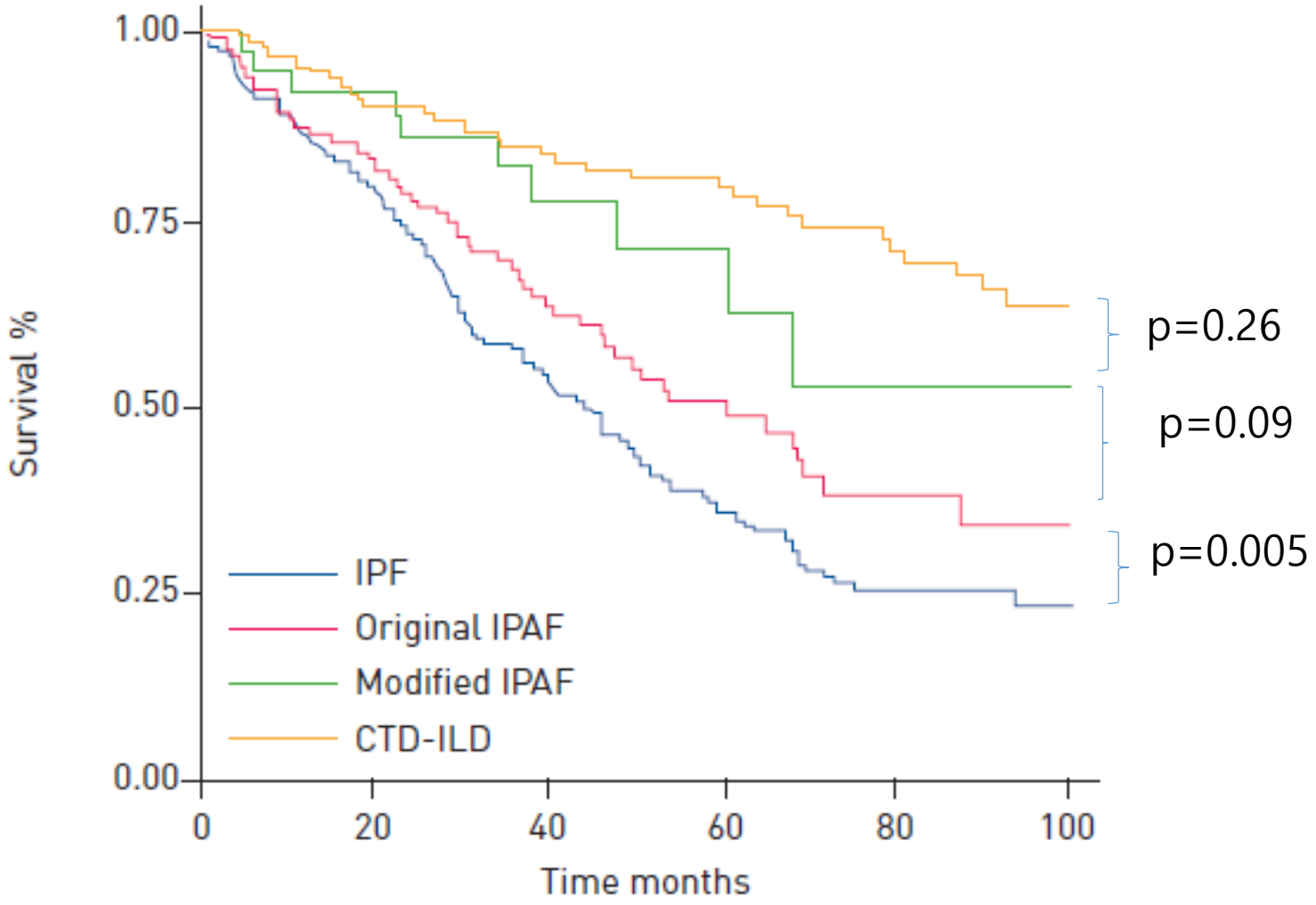
Survival of IPAF, IPF and CTD-ILD





Eur Respir J. 2016 Jun;47(6):1767-75

Survival of **modified** IPAF, original IPAF, IPF and CTD-ILD

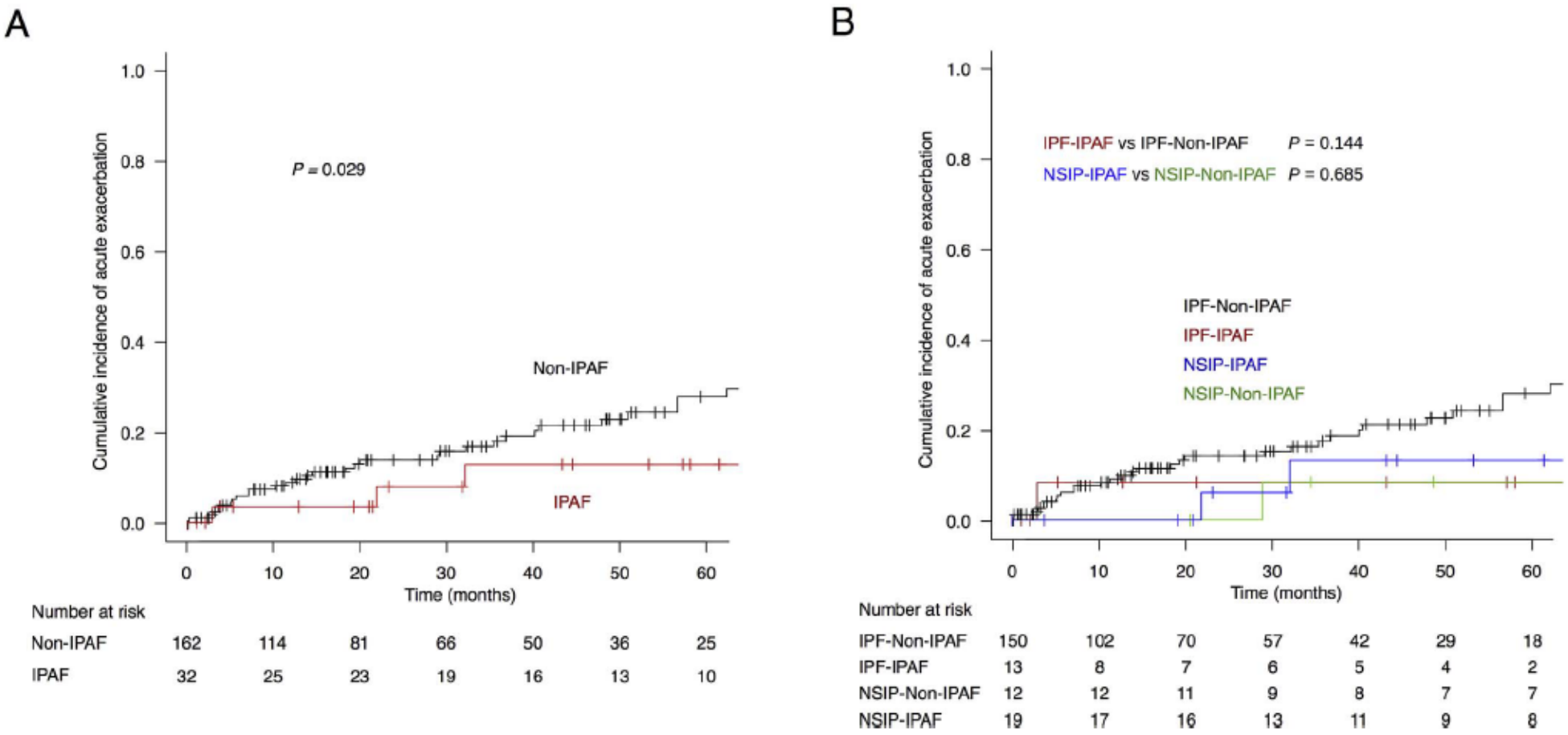


modified IPAF =

(-)multi-compartments

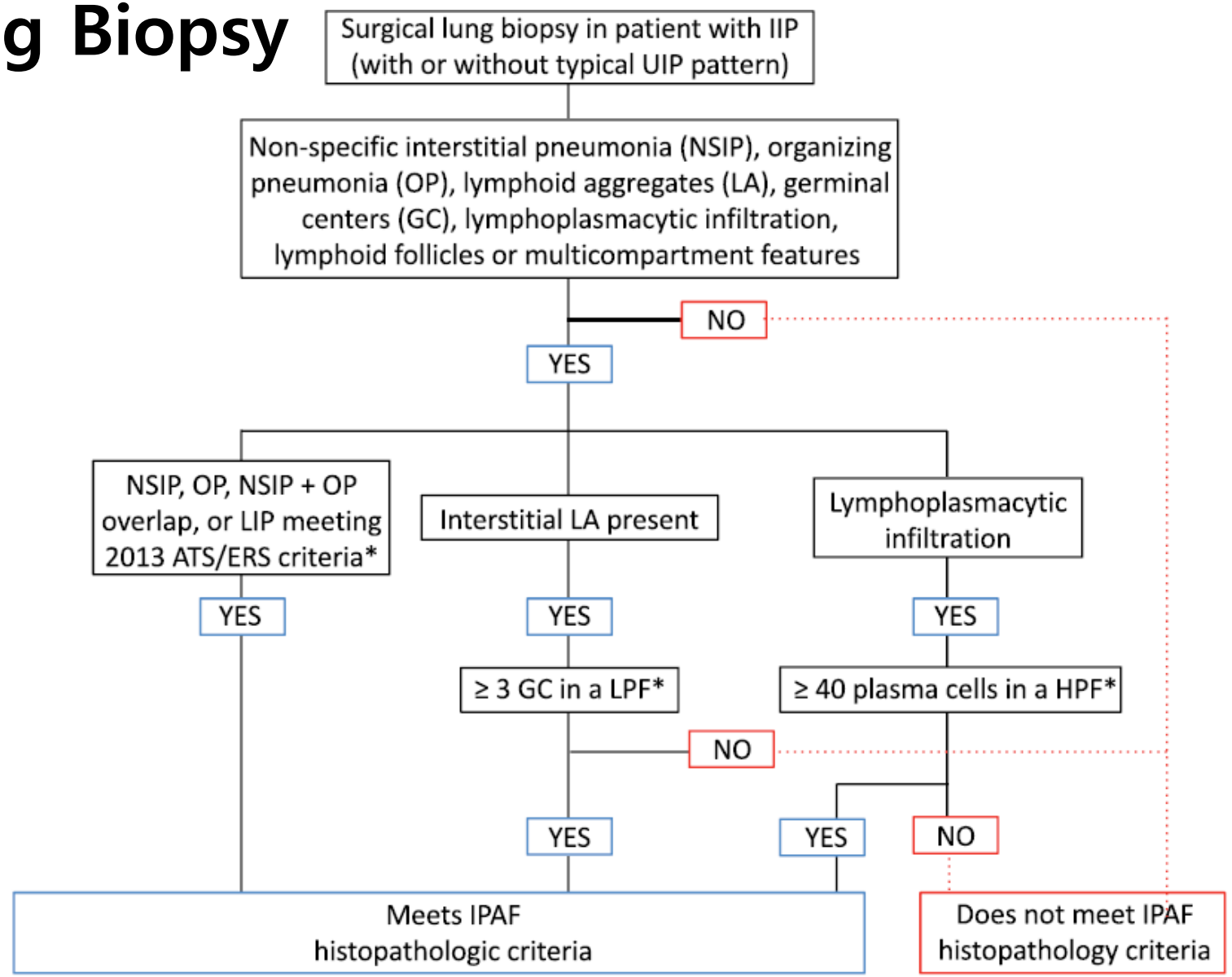
Eur Respir J. 2016 Jun;47(6):1767-75

Acute exacerbations in IPAF in Chronic Fibrosing IP

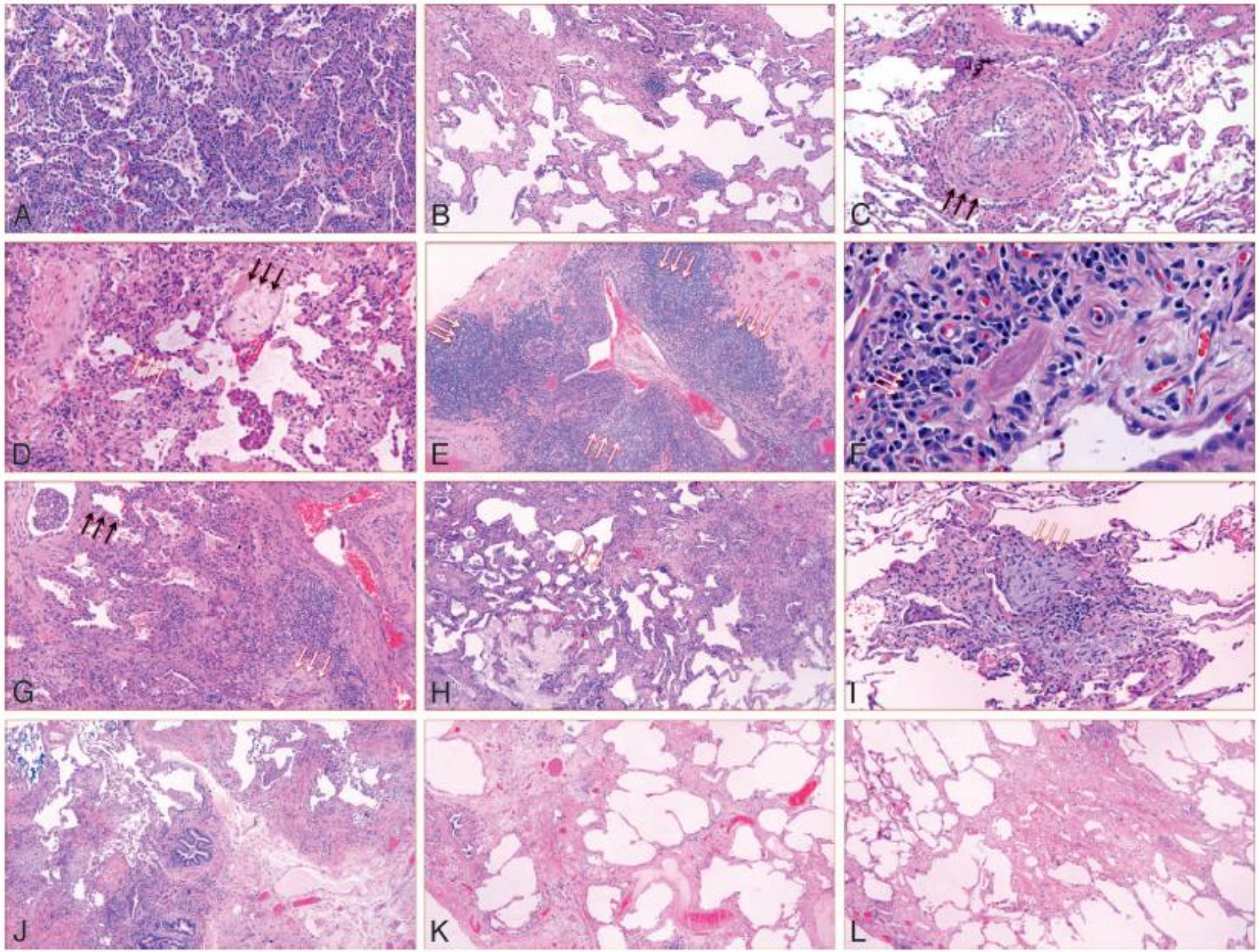


Respiratory Medicine 137 (2018) 167–175

Surgical Lung Biopsy



Arch Pathol Lab Med 2017;141;960-9



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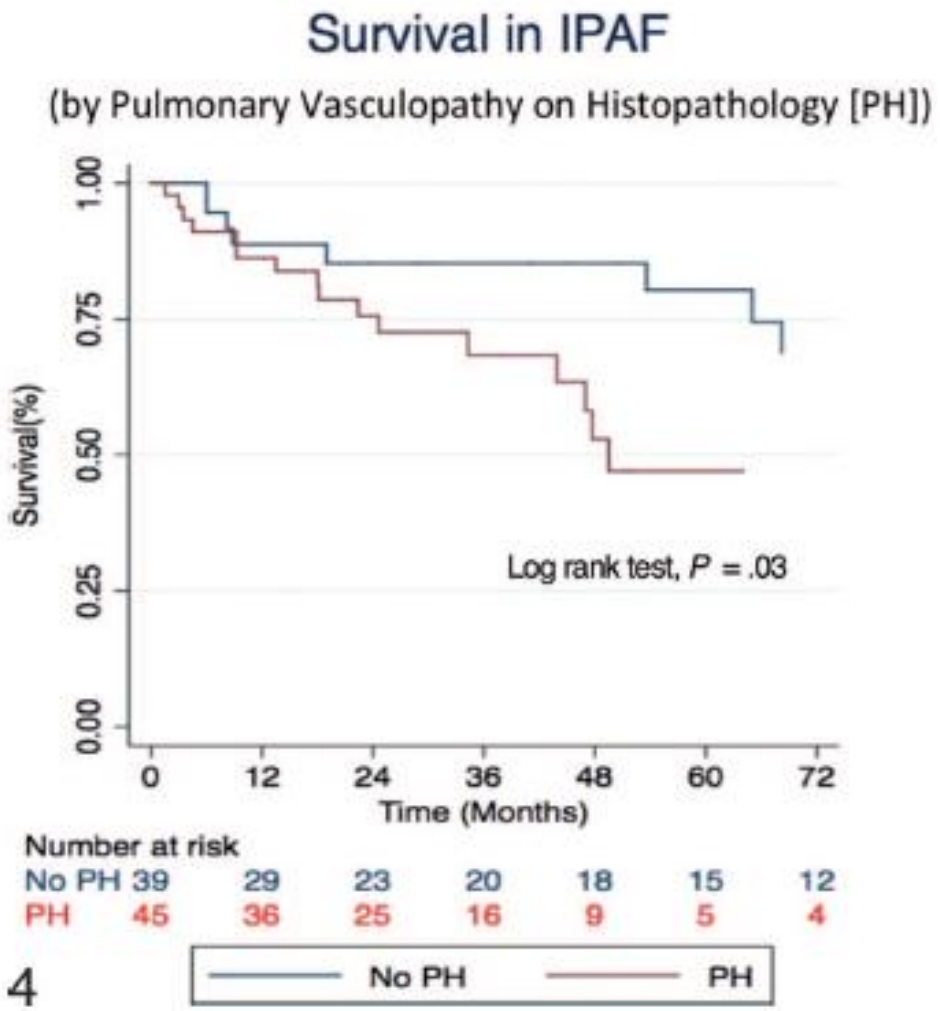

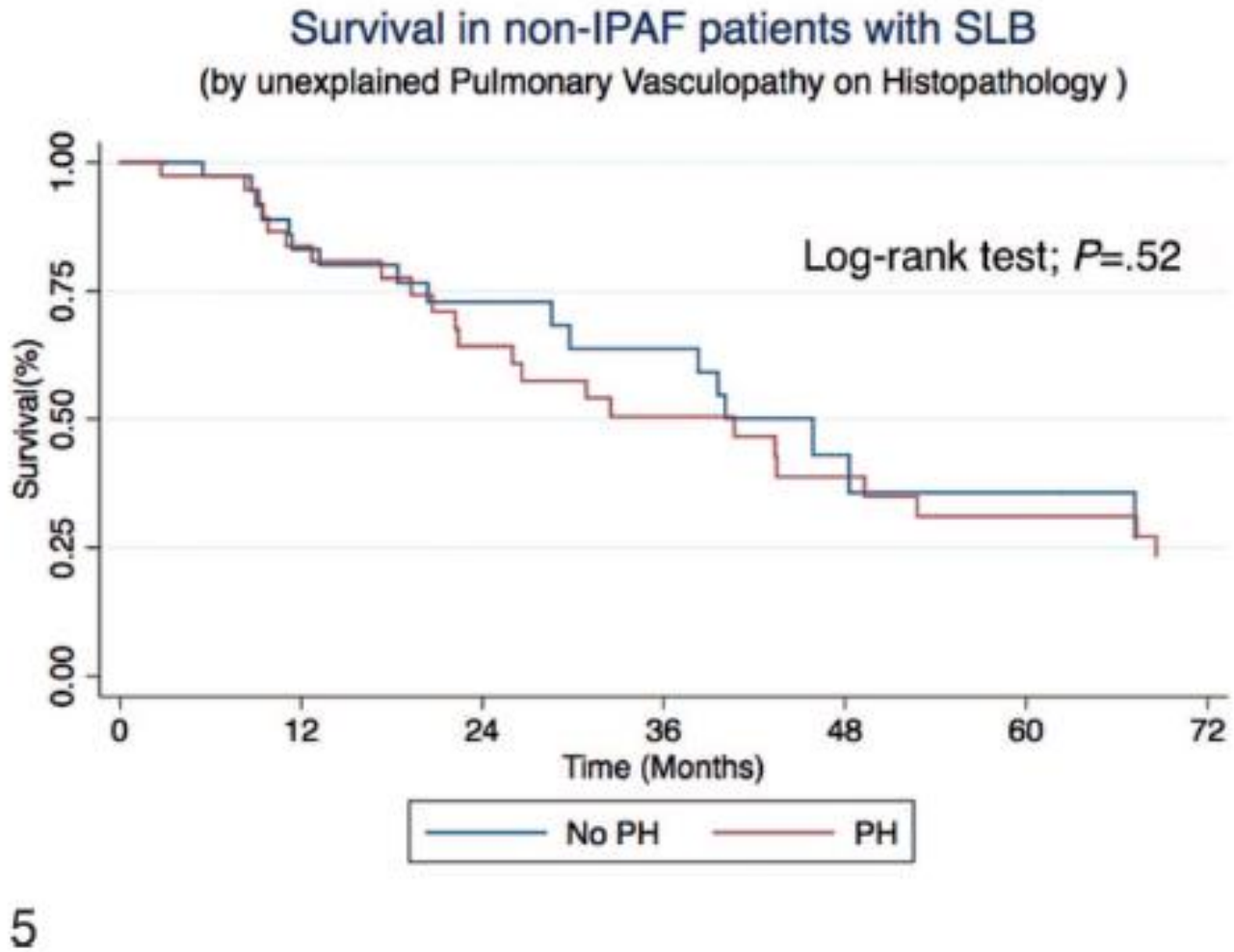

Arch Pathol Lab Med 2017;141;960-9

Pharmacologic management of IPAF

- No RCT, no case-control study with 2015 criteria
- One study: 9 IPAF among 125 CTD-ILD
- Mycophenolate mofetil - improving FVC
- Rituximab against 9 IPAF in Refractory ILD; improving FVC in 4 of 5 patients

Limits of IPAF criteria by ERS/ATS 2015

- Variability in ILD cohorts
- Inclusion of several highly specific CTD antibodies in serologic domain
- Lack of clarity in how multicompartment features

ambiguity

- Extent of germinal centers or lymphoplasmacytic infiltration

  ≥ 3 germinal centers

  ≥ 40 plasma cells

- Multicompartments; unexplained airway disease or unexplained pulmonary vasculopathy
- Smoking history – unexplained?

Fundamental questions

- Natural history and Prognosis
  - Merging to CTD-ILDs or sustained IPAF?
  - IPAF; CTD-like or IIP-like?

- Phenotypes

  Antifibrotic agents vs. immunosuppressants?

Clinical Characteristics of Interstitial Pneumonia With Autoimmune Features (IPAF) - a Multicenter Prospective Cohort Study

- 210 participants

Estimated Study Start Date :	March 18, 2019
Estimated Primary Completion Date :	February 18, 2020
Estimated Study Completion Date :	December 31, 2025

- bronchoalveolar lavage and taking bronchial mucosa samples lung function test
- 6 minute walk test
- use of cough and dyspnea scales
- transthoracic echocardiography
- blood testing
- arterial blood gas and pulse oximetry

Summary

- Construct of IPAF; an important first step for research of patients with IIP and autoimmune features
- Definitions or criteria of IPAF; provisional
- Retrospective data; heterogeneity
- Future studies; natural course by clinical, serologic and morphologic domains – effective treatment.