Interstitial Pneumonia with Auto-immune Features (IPAF)
Pneumopathie interstitielle avec signes auto-immuns (PISA)

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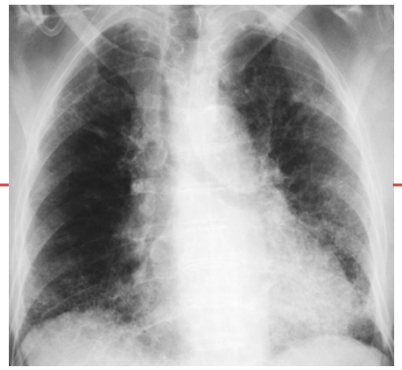
Diagnostic des PID



Contexte
épidémiologique
Signes extra-respi

Clinique

TDM-HR

EFR Biologie Fibroscopie

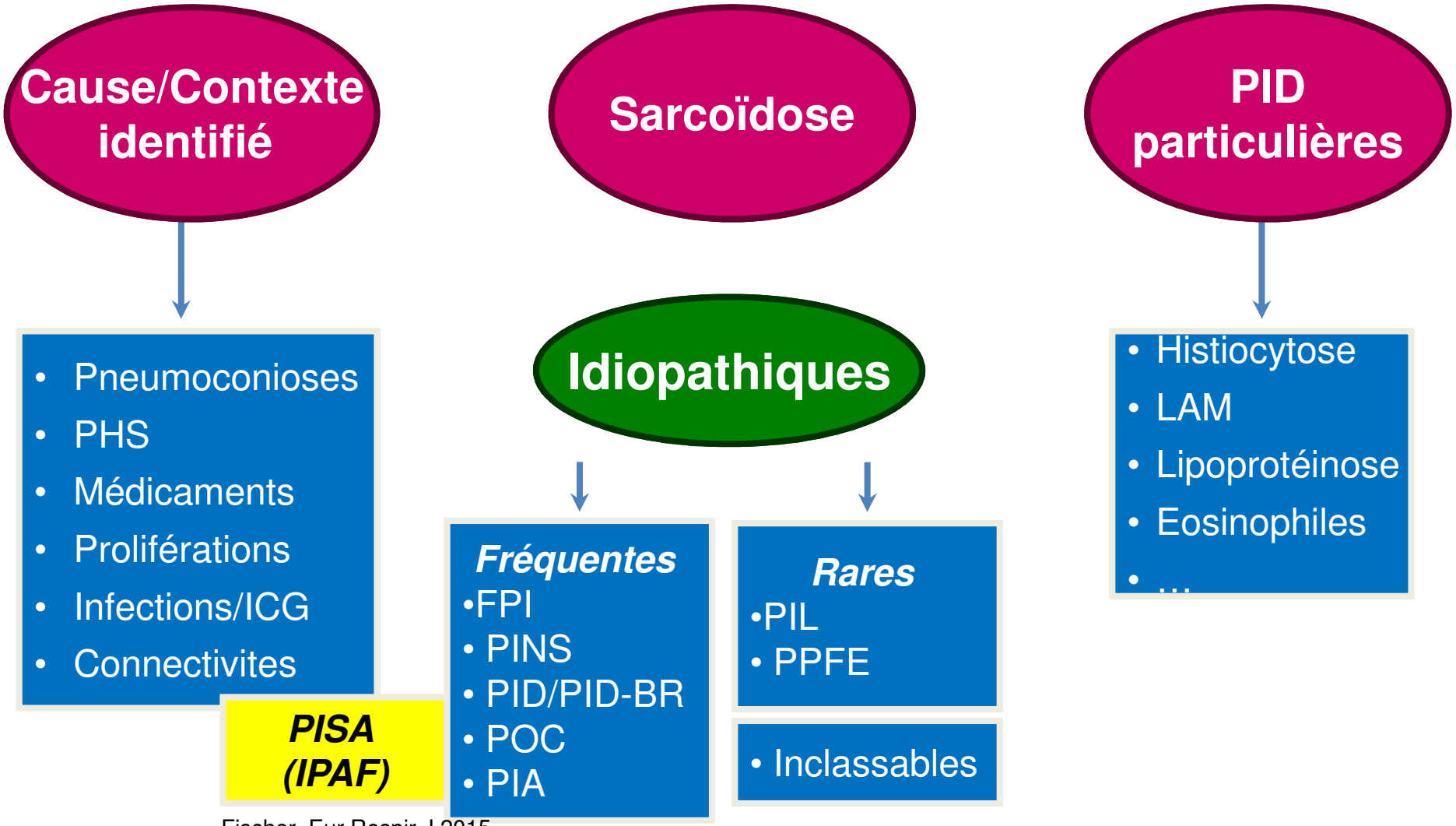
+/-Biopsie Pulmonaire

Si pas trop âgé
Ni trop sévère

Diagnostic
Pronostic
Décision thérapeutique

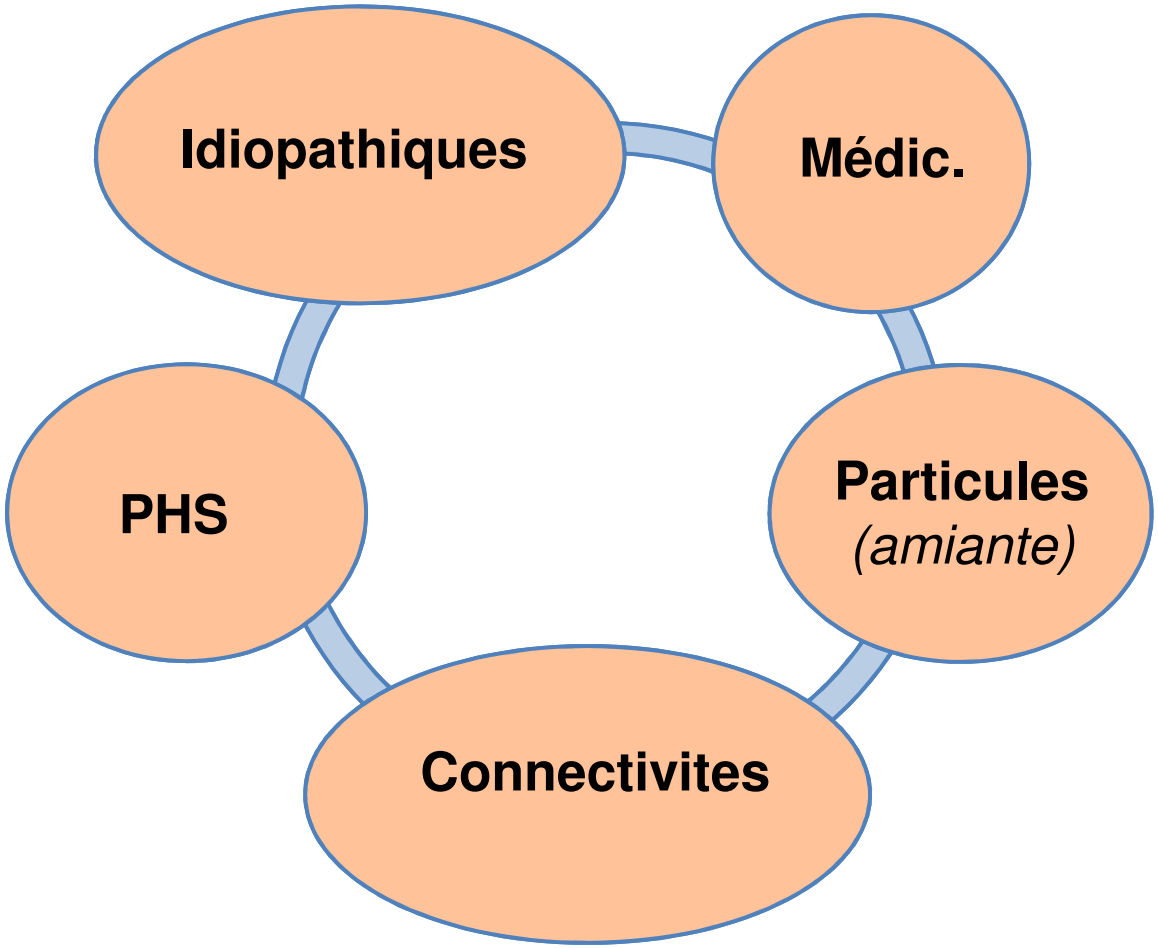
Classification étiologique des PID

(Travis, AJRCCM 2013)



Fischer, Eur Respir J 2015

Grands cadres étiologiques devant une fibrose pulmonaires



Pourquoi rechercher une connectivite

FPI

- Biopsie parfois indiquée
- Contreindication aux CS et immunosuppresseurs
- Traitement anti-fibrosant
- Pronostic médiocre

Connectivite

- Biopsie généralement non indiquée
- Corticoïdes et/ou immunosuppresseurs
- Evolution plus lente
- Pronostic meilleur

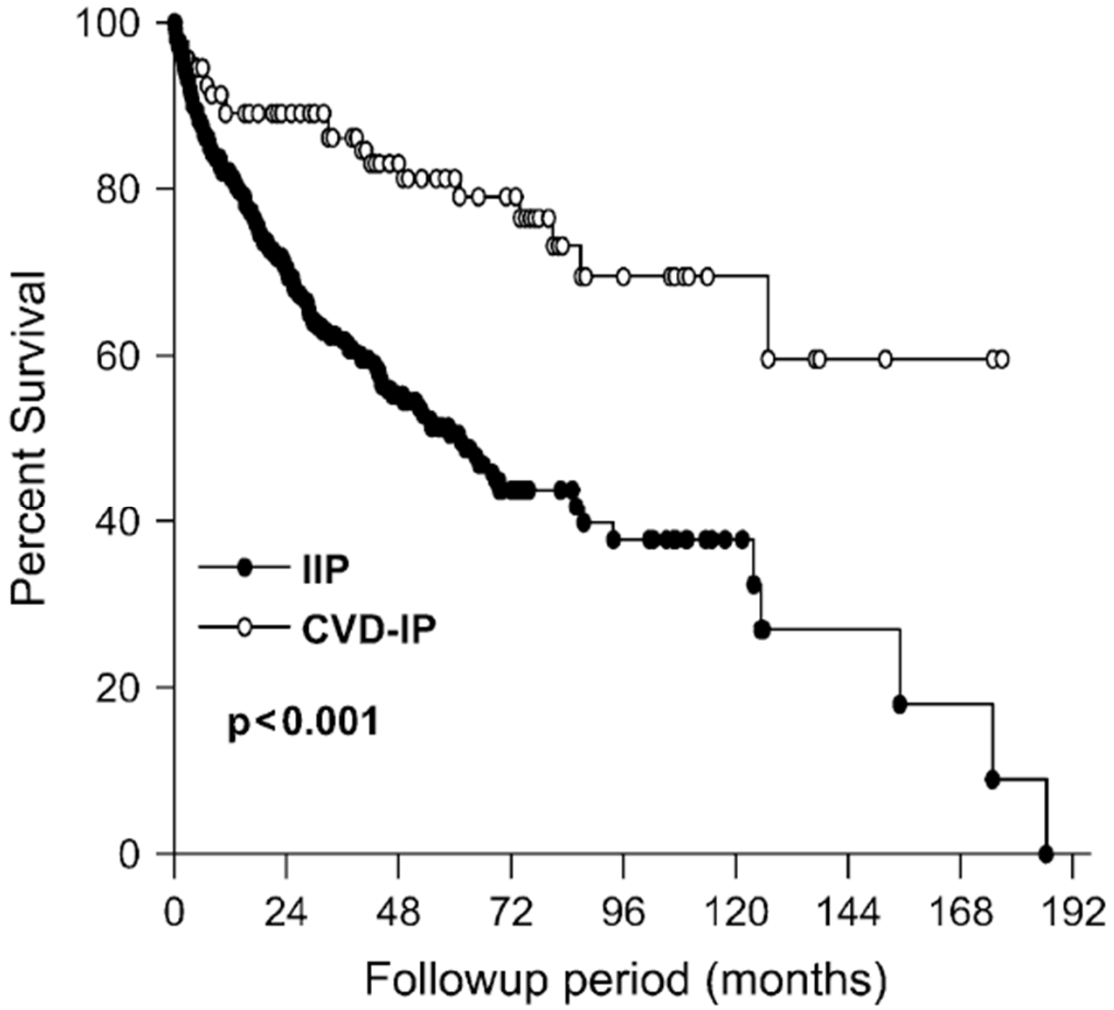
  (sauf PR)

- **Clinical features associated with CTD in a patient with ILD**
  - Gender : female
  - Younger age
  - Detection of Auto-Abs
  - HRCT : NSIP, OP

  (UIP is possible in CTD-ILD)

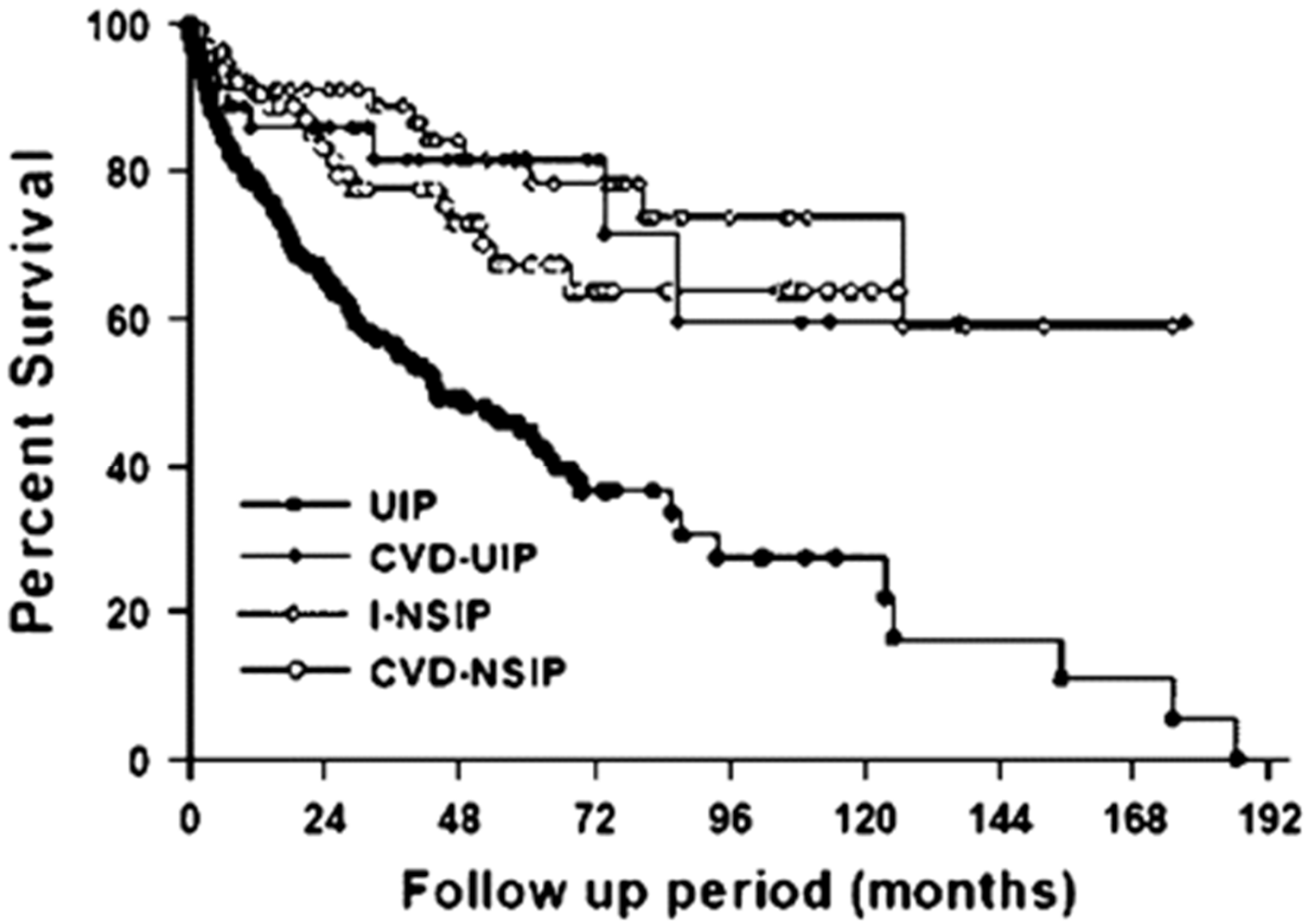
(Moua, Respir Res 2014)

CTD influences the prognosis



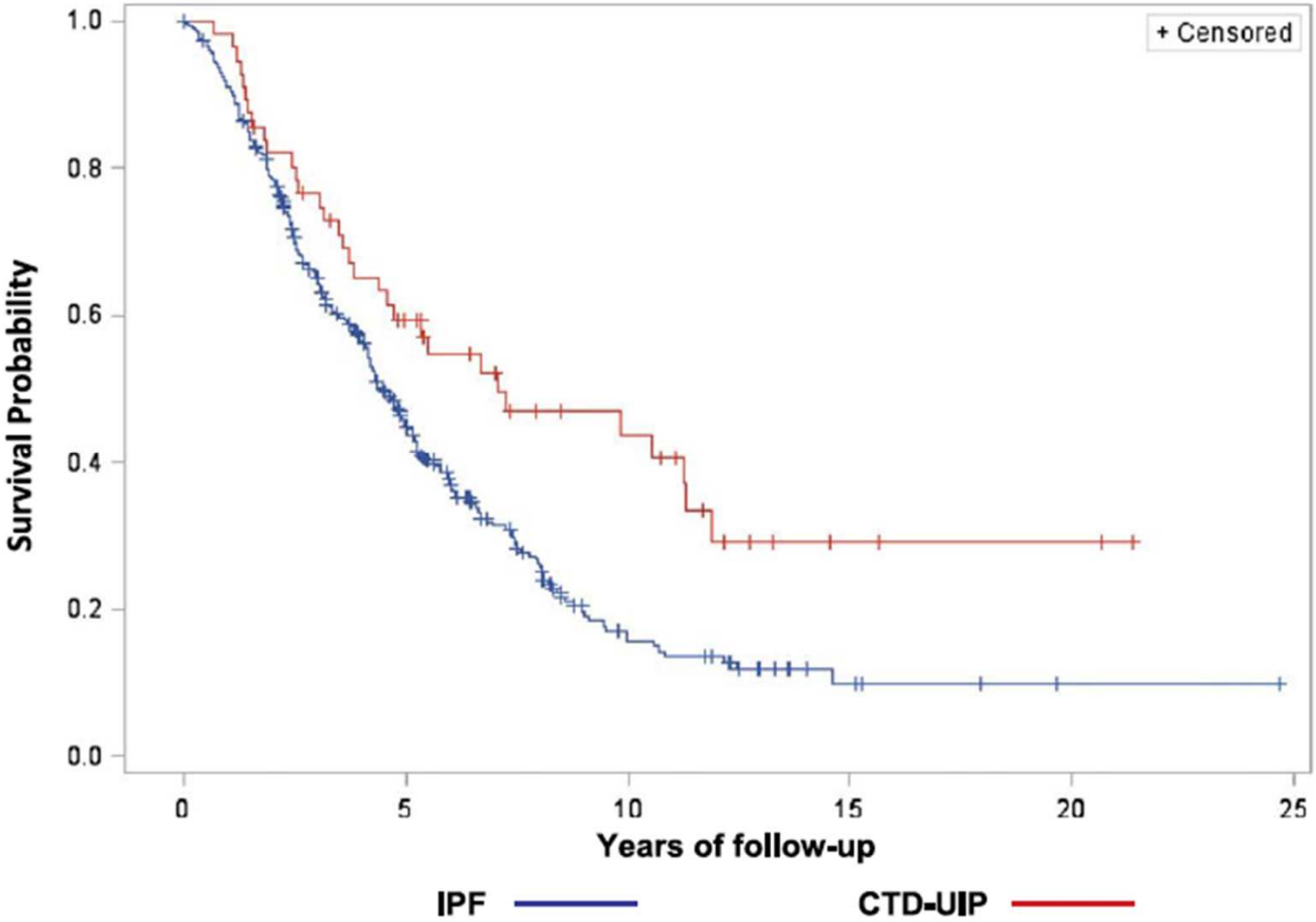
Park, AJRCCM 2007

Histology does not inform prognosis in CTD *(except RA)*



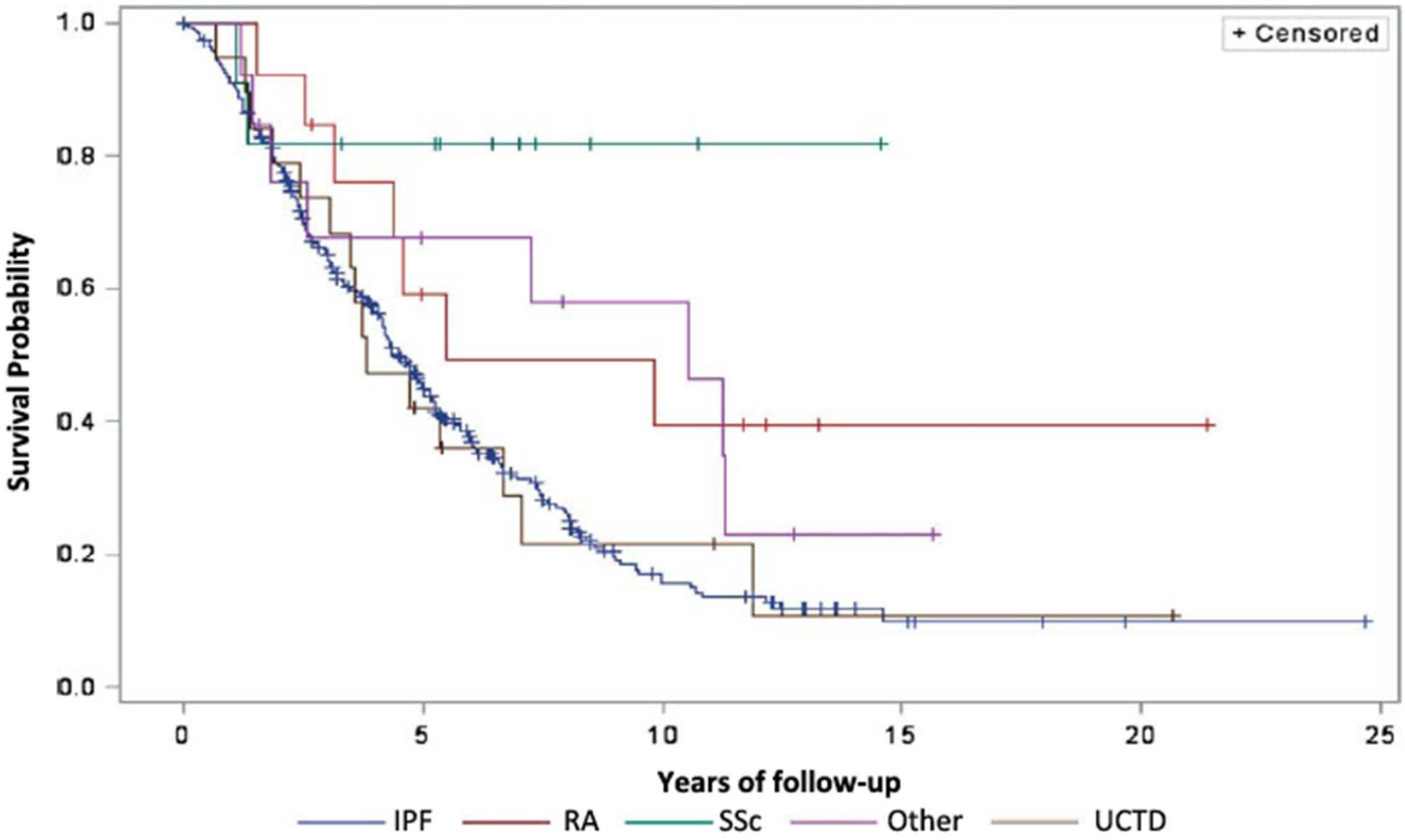
(Park, AJRCCM 2007)

CTD-UIP has a better prognosis than idiopathic UIP (IPF)



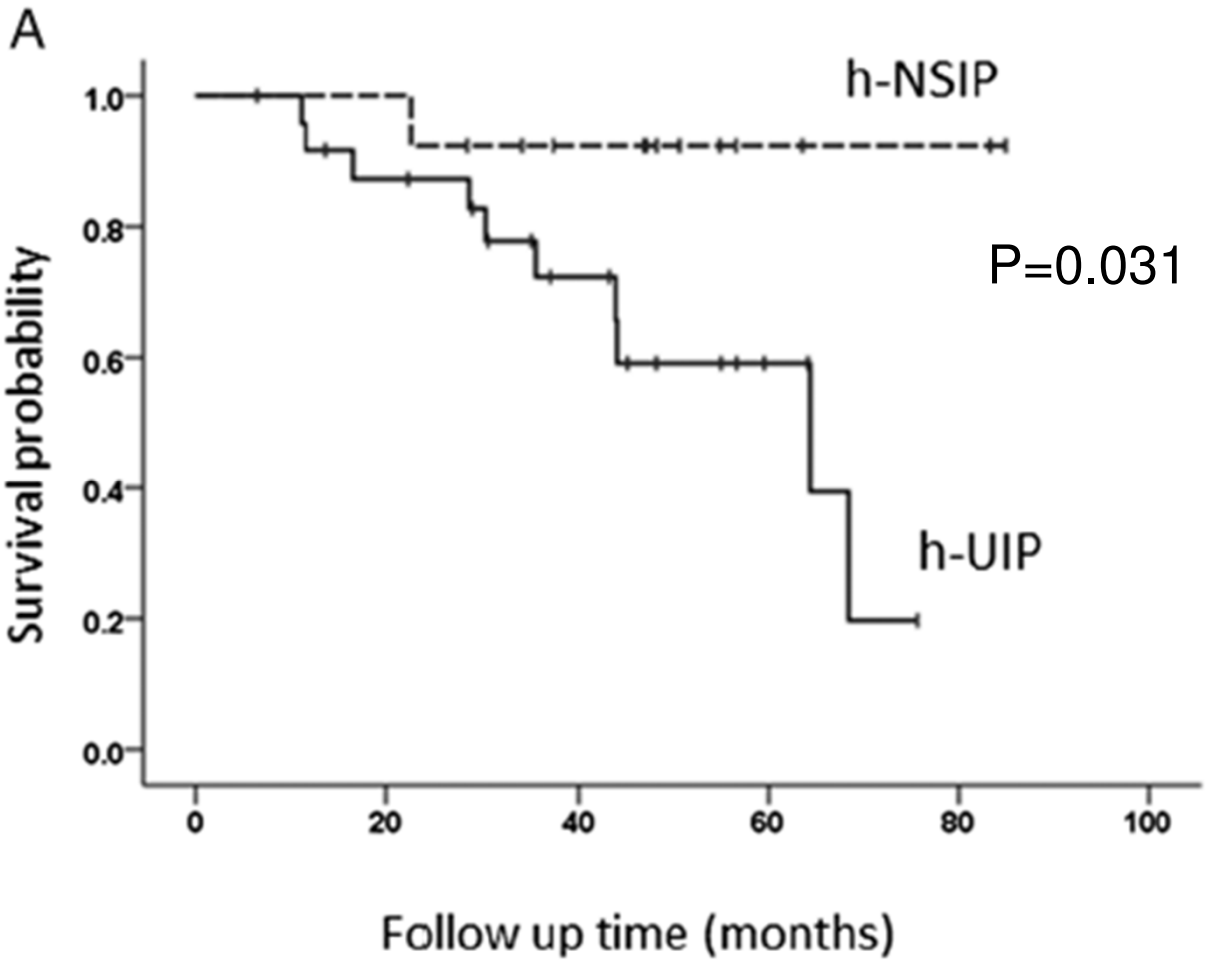
Strand, Chest 2014

CTD-UIP prognosis is influenced by the CTD



Strand, Chest 2014

Histology informs prognosis



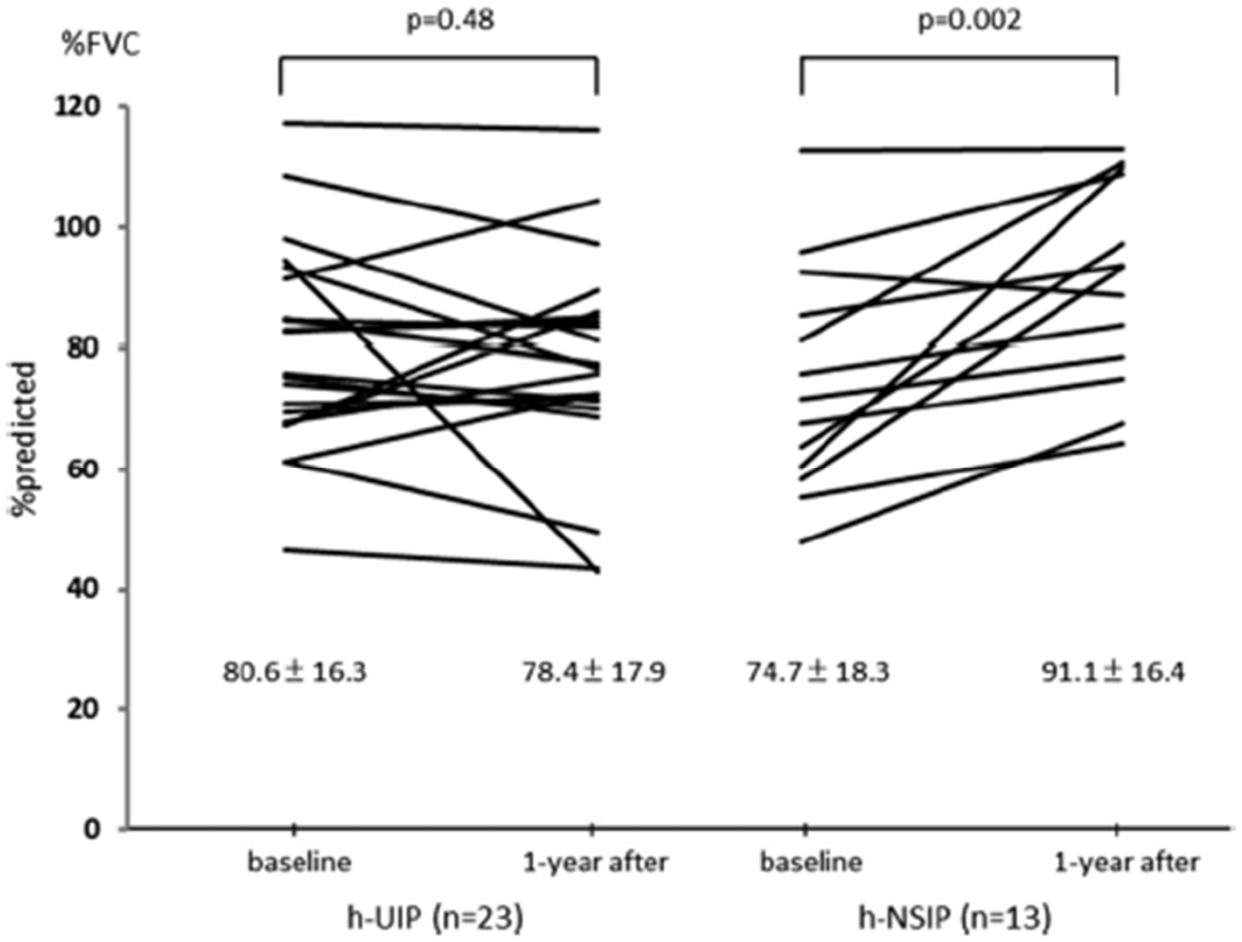
Lung dominant connective tissue disease

Omote, Chest 2015

Histology informs prognosis in terms of treatment response

Treatment

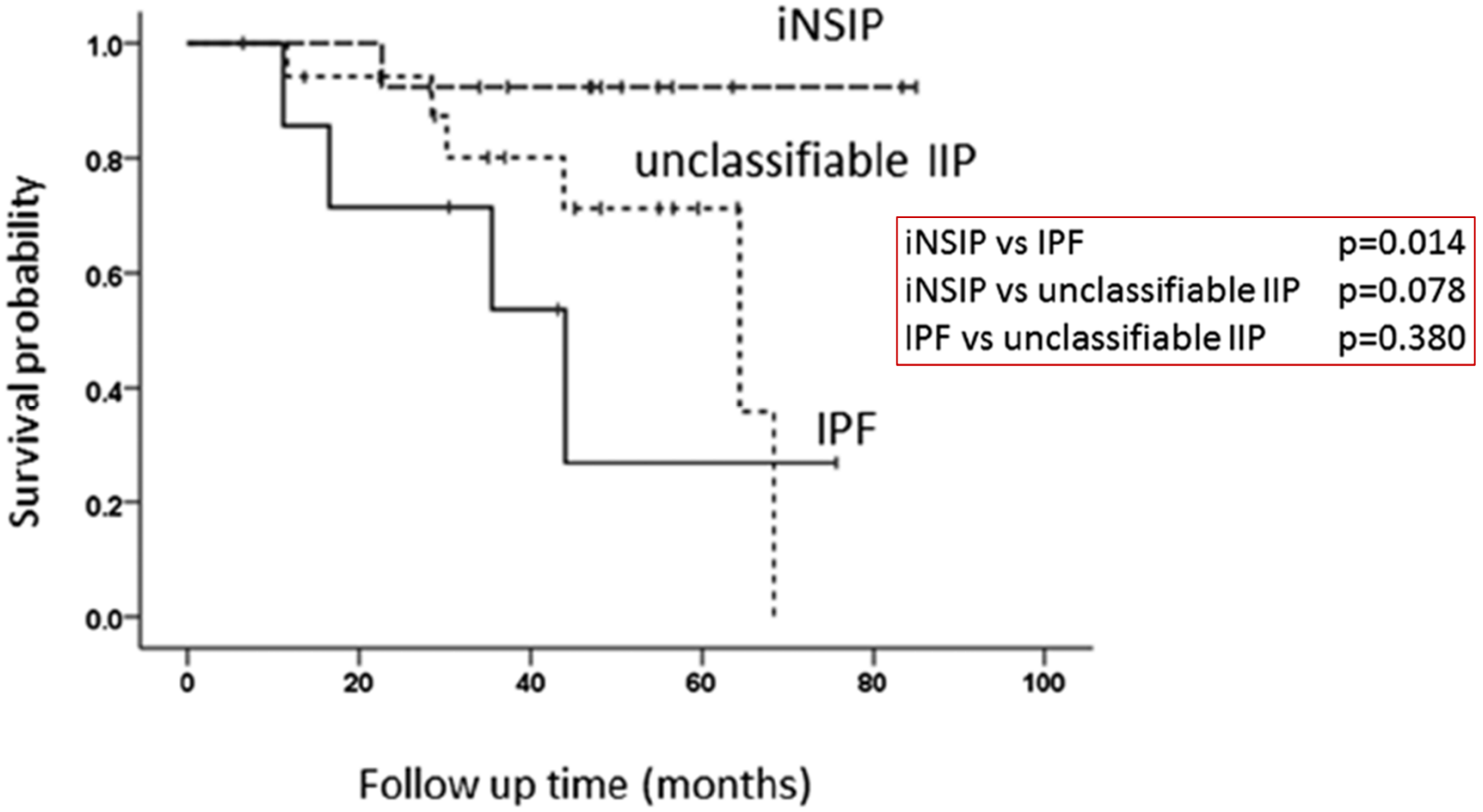
	h-UIP	h-NSIP
corticosteroids	52%	69%
ciclosporin	44%	62%
pirfenidone	20%	0%
No Tt	44%	31%



Lung dominant connective tissue disease

Omote, Chest 2015

Final diagnosis in MDD informs prognosis



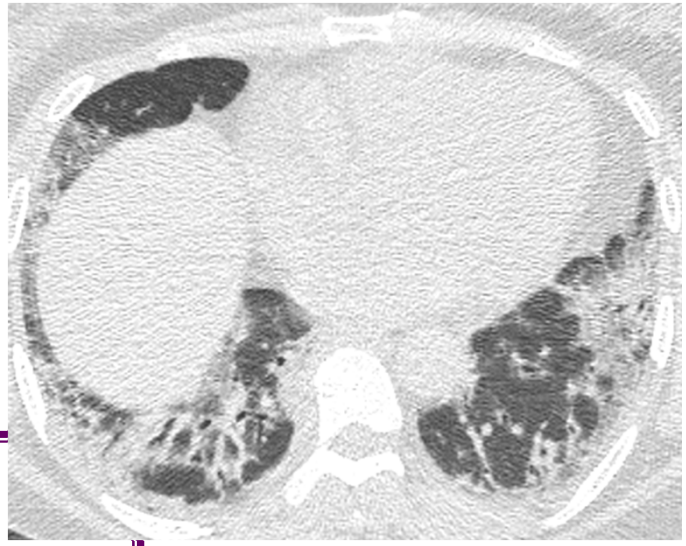
Lung dominant connective tissue disease

Omote, Chest 2015

Que faire des patietns sans connectivite définie?

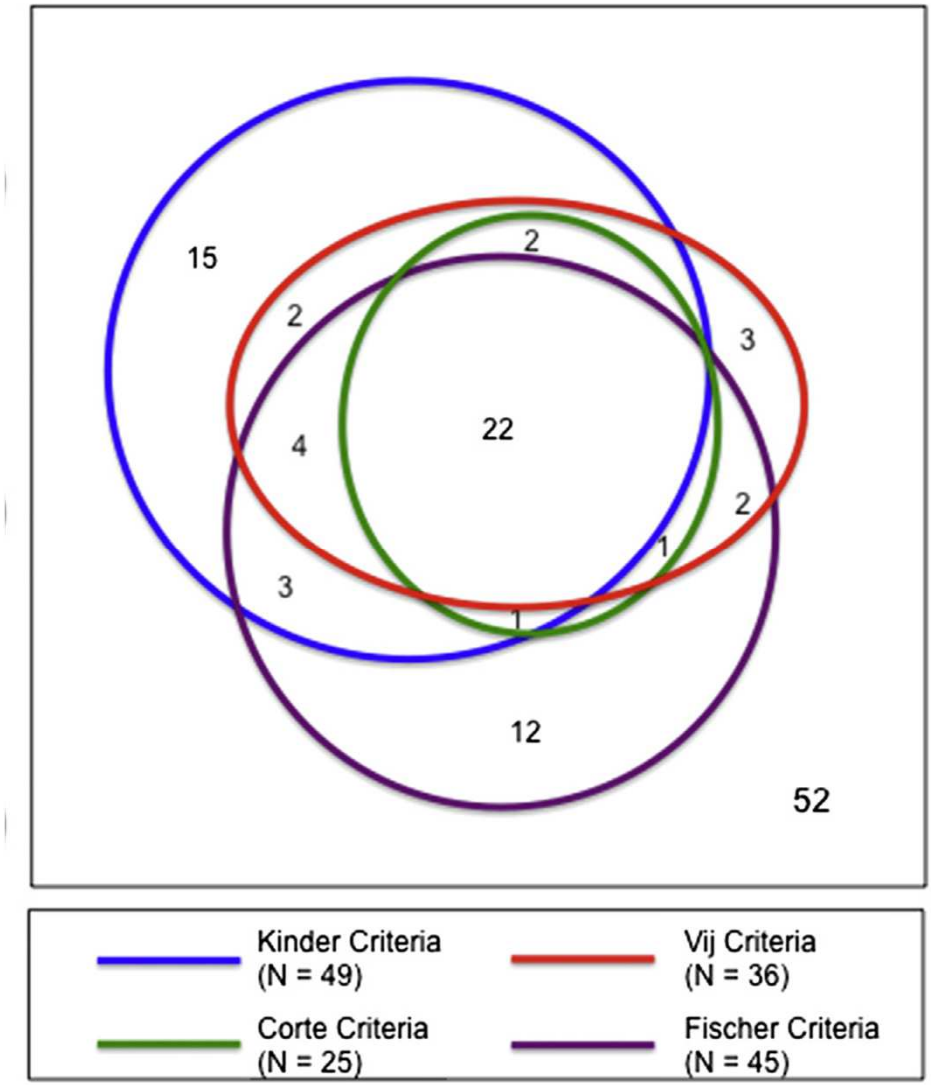
Ex de Discussion Multi-Disciplinaire:

- PID suggérant une PINS/PO
- Auto-anticorps
  - ANA 1/320,
  - anti-Sp100+
- Histologie : PINS fibrosante



- Idiopathic NSIP ?
- Forme fruste of CTD ?
- Lung-dominant CTD ?
- Undifferentiated CTD ?
- Auto-immune featured ILD ?
- Unclassifiable Lung Fibrosis ?

Undifferentiated CTD criteria : no consensus



(Corte, ERJ 2012)

Undifferentiated CTD criteria : no consensus
Diagnosis depends on criteria

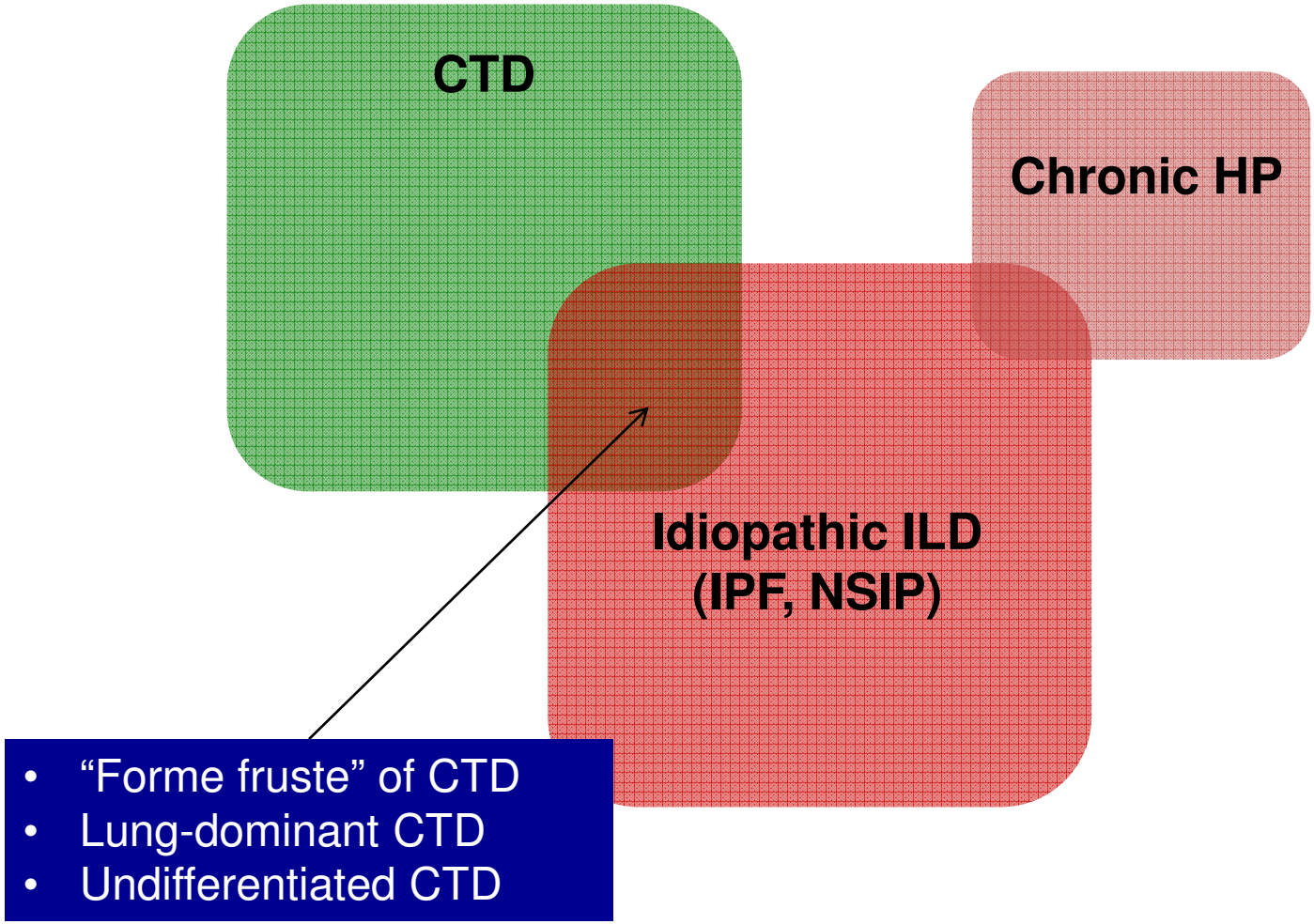
	NSIP (n=45)	IPF (n=56)
Strict *(Mosca, J Rheumatol 2002)*	21%	13%
Loose *(Kinder, AJRCCM 2007)*	71%	36%

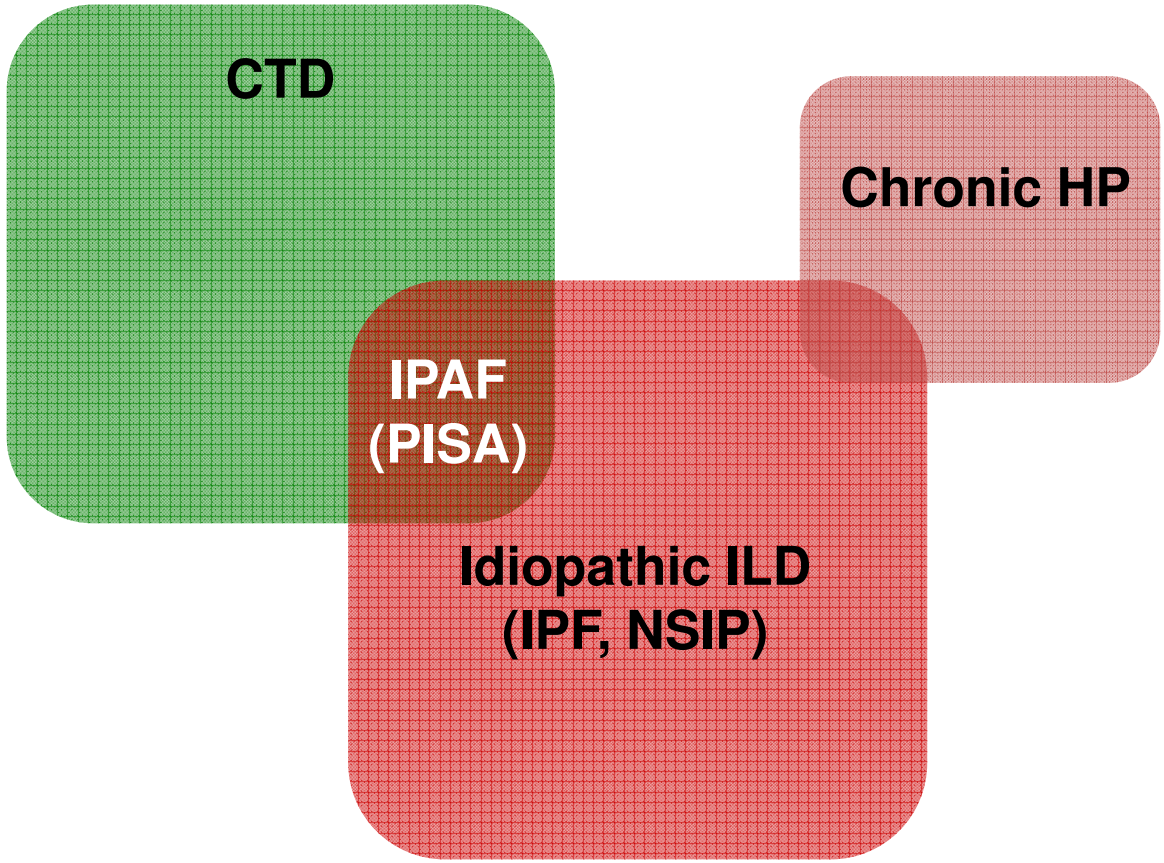
(Corte, ERJ 2012)

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

Aryeh Fischer[1,17,18], Katerina M. Antoniou[2], Kevin K. Brown[3], Jacques Cadranel[4], Tamera J. Corte[5,18], Roland M. du Bois[6], Joyce S. Lee[7,18], Kevin O. Leslie[8], David A. Lynch[9], Eric L. Matteson[10], Marta Mosca[11], Imre Noth[12], Luca Richeldi[13], Mary E. Strek[12,18], Jeffrey J. Swigris[3,18], Athol U. Wells[14], Sterling G. West[15], Harold R. Collard[7,18,19] and Vincent Cottin[16,18,19], on behalf of the "ERS/ATS Task Force on Undifferentiated Forms of CTD-ILD"

Fischer, Eur Respir J 2015

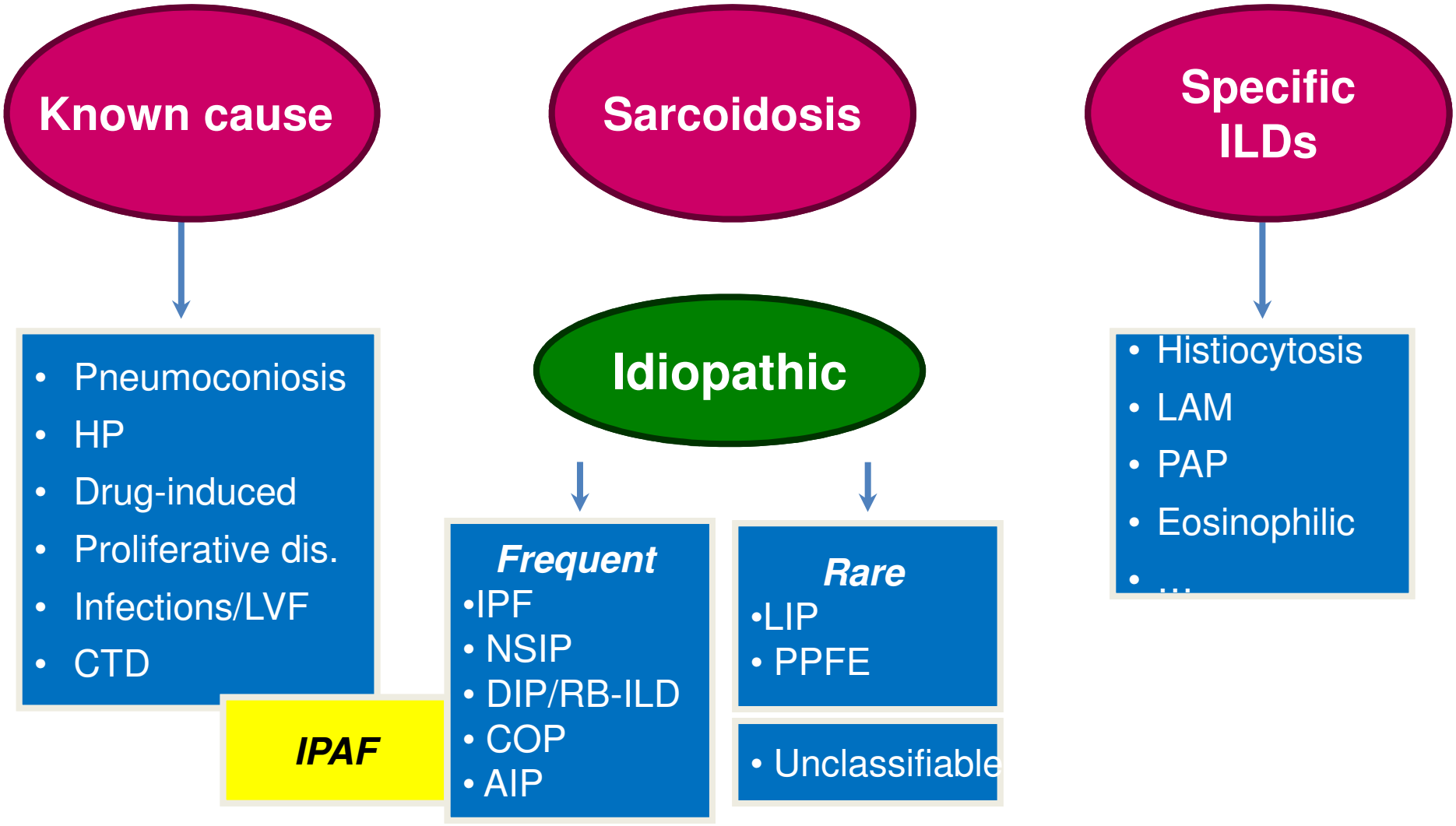

CTD
Chronic HP
Idiopathic ILD
(IPF, NSIP)
• “Forme fruste” of CTD
• Lung-dominant CTD
• Undifferentiated CTD



Interstitial Pneumonia with Auto-immune Features (IPAF)
Pneumopathie interstitielle avec signes auto-immuns (PISA)

Classification of ILDs

(Travis, AJRCCM 2013)



IPAF Criteria

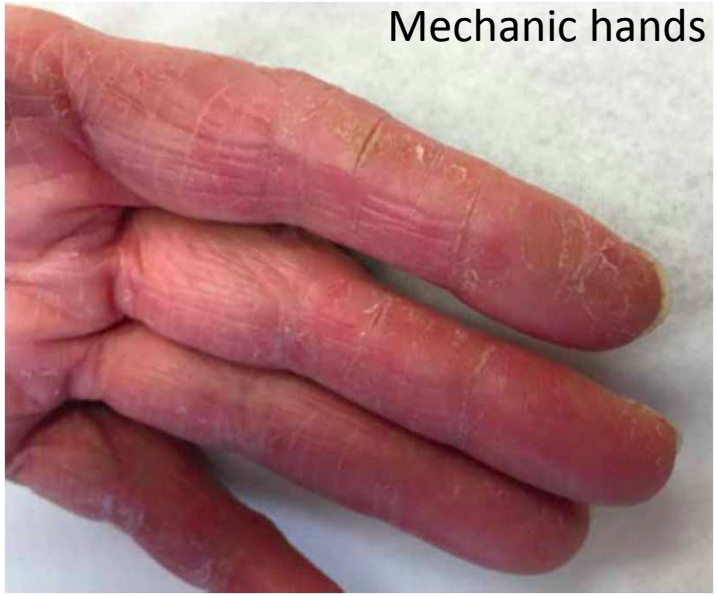
1. Presence of an interstitial pneumonia *(HRCT or Biopsy)*
2. Exclusion of alternative etiologies
3. Does not meet criteria of a definite CTD
4. At least one feature, from at least two of three domains
   - Clinical
   - Serological
   - Morphological

Fischer, Eur Respir J 2015

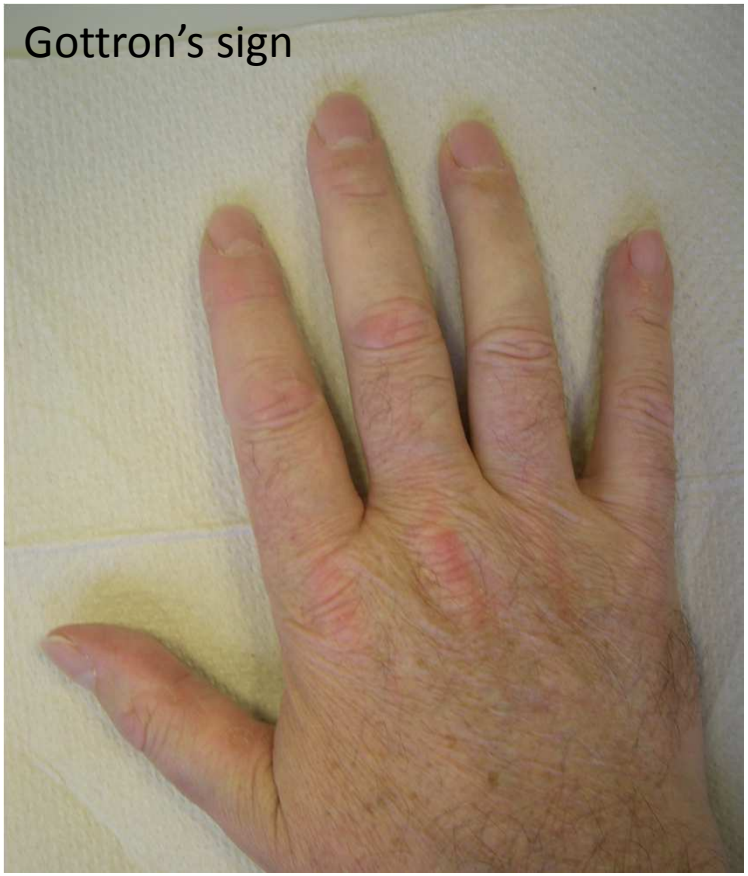
A. Clinical domain

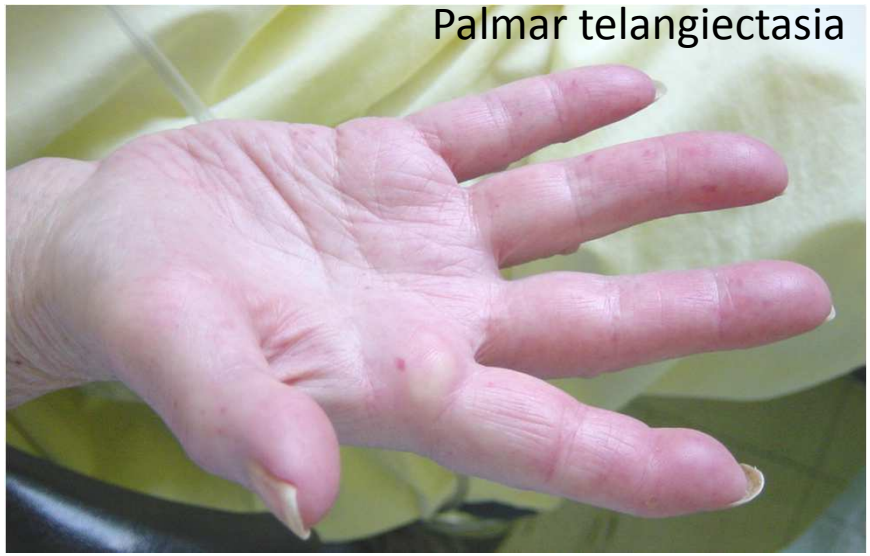
1. Distal digital fissuring (*i.e.* "mechanic hands")
2. Distal digital tip ulceration
3. Inflammatory arthritis *or* polyarticular morning joint stiffness ⩾60 min
4. Palmar telangiectasia
5. Raynaud's phenomenon
6. Unexplained digital oedema
7. Unexplained fixed rash on the digital extensor surfaces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

Fischer, Eur Respir J 2015



Fischer, ERJ 2015





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, OJ, KS, Zo, tRS)
11. Anti-PM-Scl
12. Anti-MDA-5

Fischer, Eur Respir J 2015

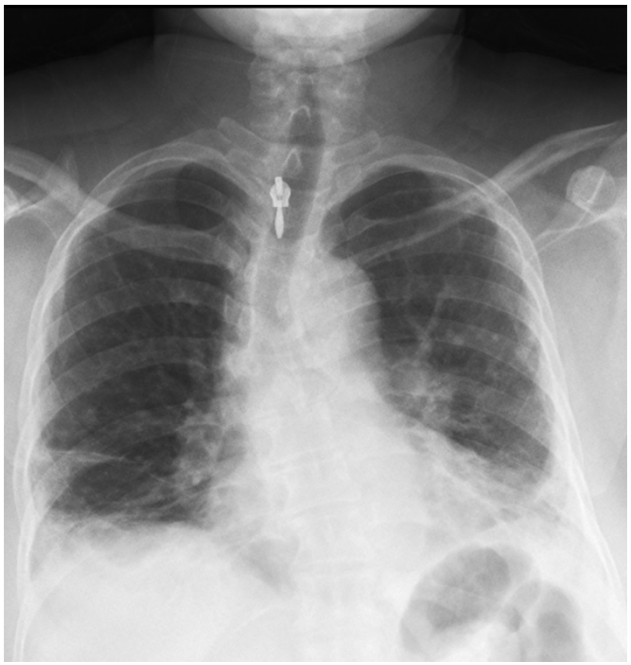
C. Morphologic domain

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
   b. Unexplained pericardial effusion or thickening
   c. Unexplained intrinsic airways disease[#] (by PFT, imaging or pathology)
   d. Unexplained pulmonary vasculopathy

Fischer, Eur Respir J 2015

MDD:

- ILD highly suggestive of NSIP/OP
- Auto-Abs but No definite CTD
- Histology : fibrotic NSIP



Final diagnosis : IPAF

Does it help prognosis and Treatment definition ?

Table 1. IPAF Cohort Baseline Demographic and Clinical Characteristics (n=144)	
Age, mean (±SD)	63.2 (11)
Female Gender, n (%)	75 (52.1)
Gastroesophageal reflux, n (%)	76 (52.8)
Ever Smoker, n (%)	79 (54.9)
Crackles, n (%)	125 (89.3)
Clubbing, n (%)	21 (18.9)
UIP by HRCT, n (%)	77 (54.6)
UIP by SLB, n (%)	61 (73.5)
FVC (% predicted)	61.9 (18.3)
DLCO (% predicted)	45.3 (20.6)

Oldham JM et al, Eur Respir J 2016

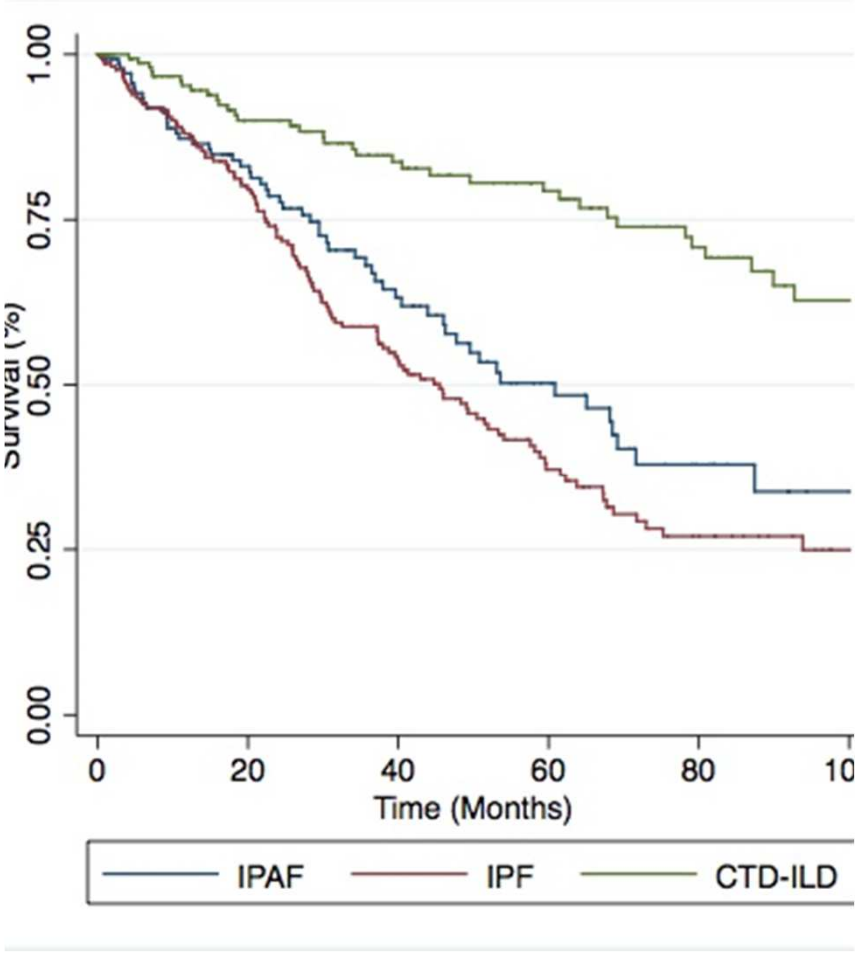
Initial diagnosis

TABLE 2 Interstitial pneumonia with autoimmune-features (IPAF) domains met by initial diagnosis

Domains met	IPAF cohort	Initial diagnosis			
		NSIP/COP	IPF	UCTD-ILD	Unclassifiable
Subjects	144	9	49	72	14
Clinical and serological	21 (14.6)	0 (0)	3 (6.1)	17 (23.6)	1 (7.1)
Clinical and morphological	12 (8.3)	2 (22.2)	0 (0)	6 (8.3)	4 (28.6)
Serological and morphological	73 (50.7)	7 (77.8)	43 (87.8)	16 (22.2)	7 (50)
All three domains	38 (26.4)	0 (0)	3 (6.1)	33 (45.8)	2 (14.3)

Oldham JM et al, Eur Respir J 2016

Survival by diagnosis



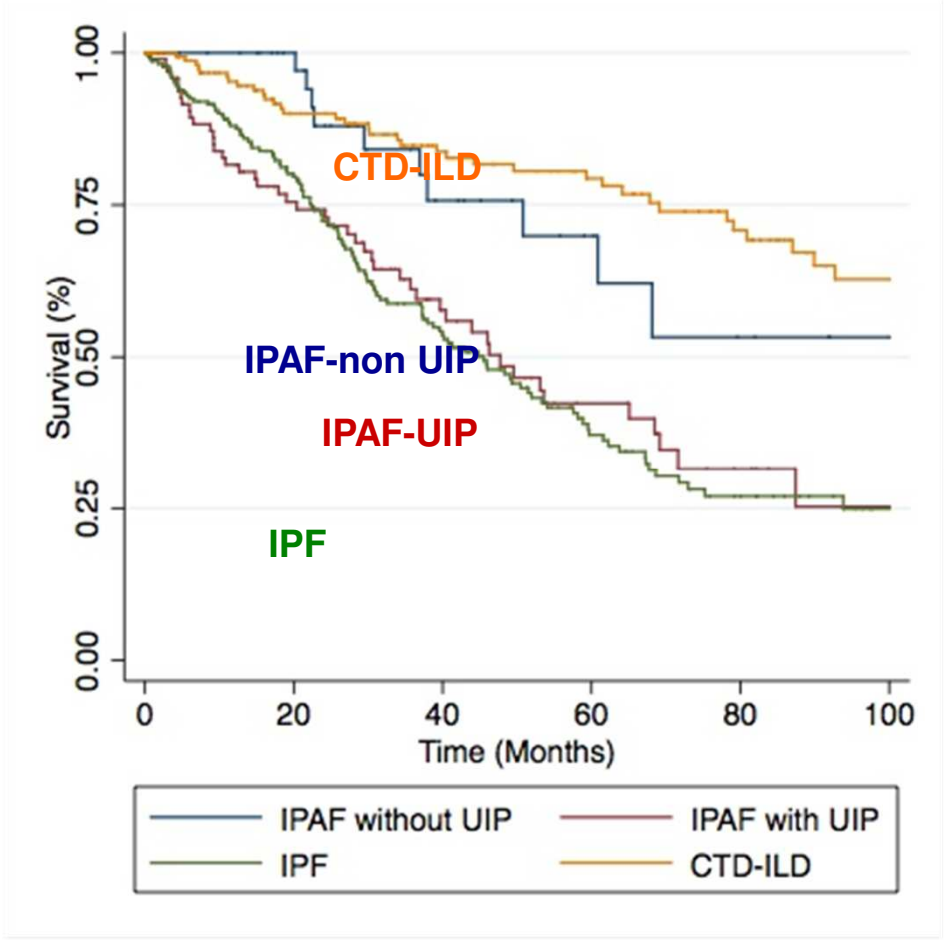
CTD-ILD

IPAF

IPF

Oldham JM et al, Eur Respir J 2016

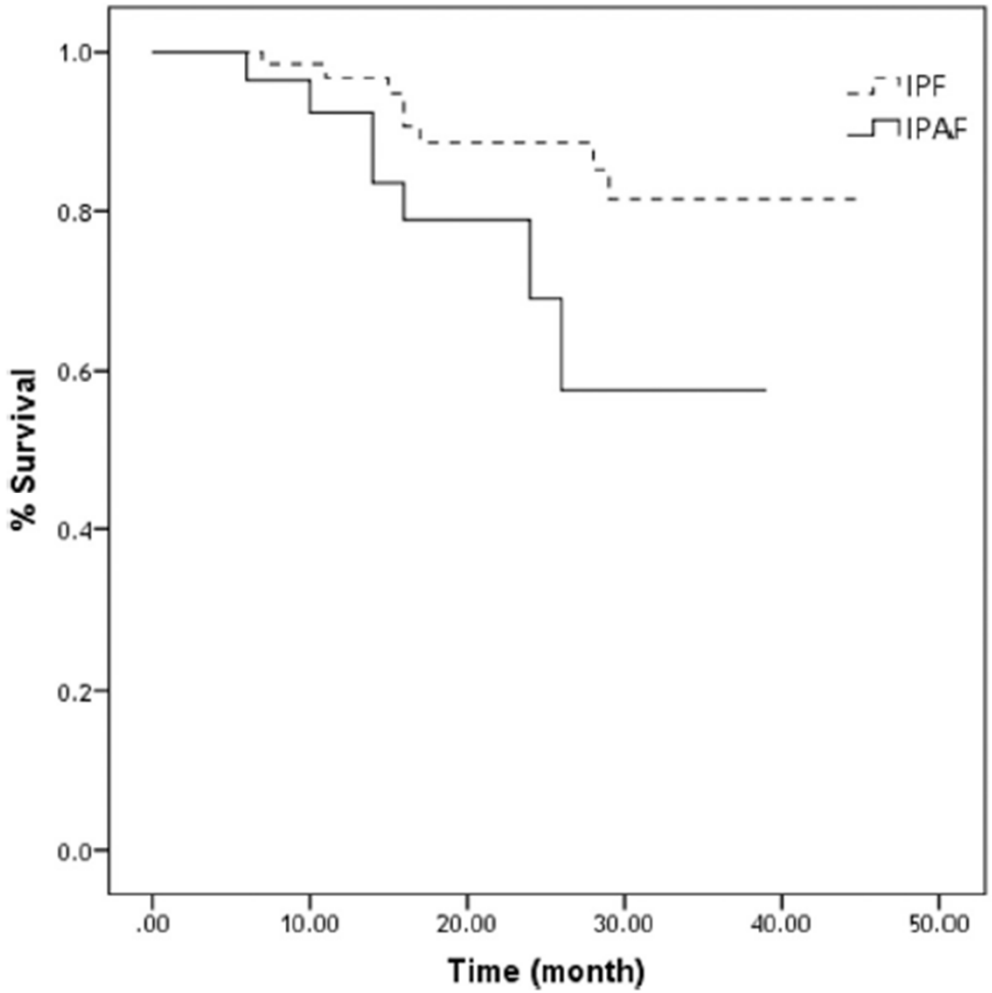
Survival by diagnosis



Oldham JM et al, Eur Respir J 2016

Survival by diagnosis

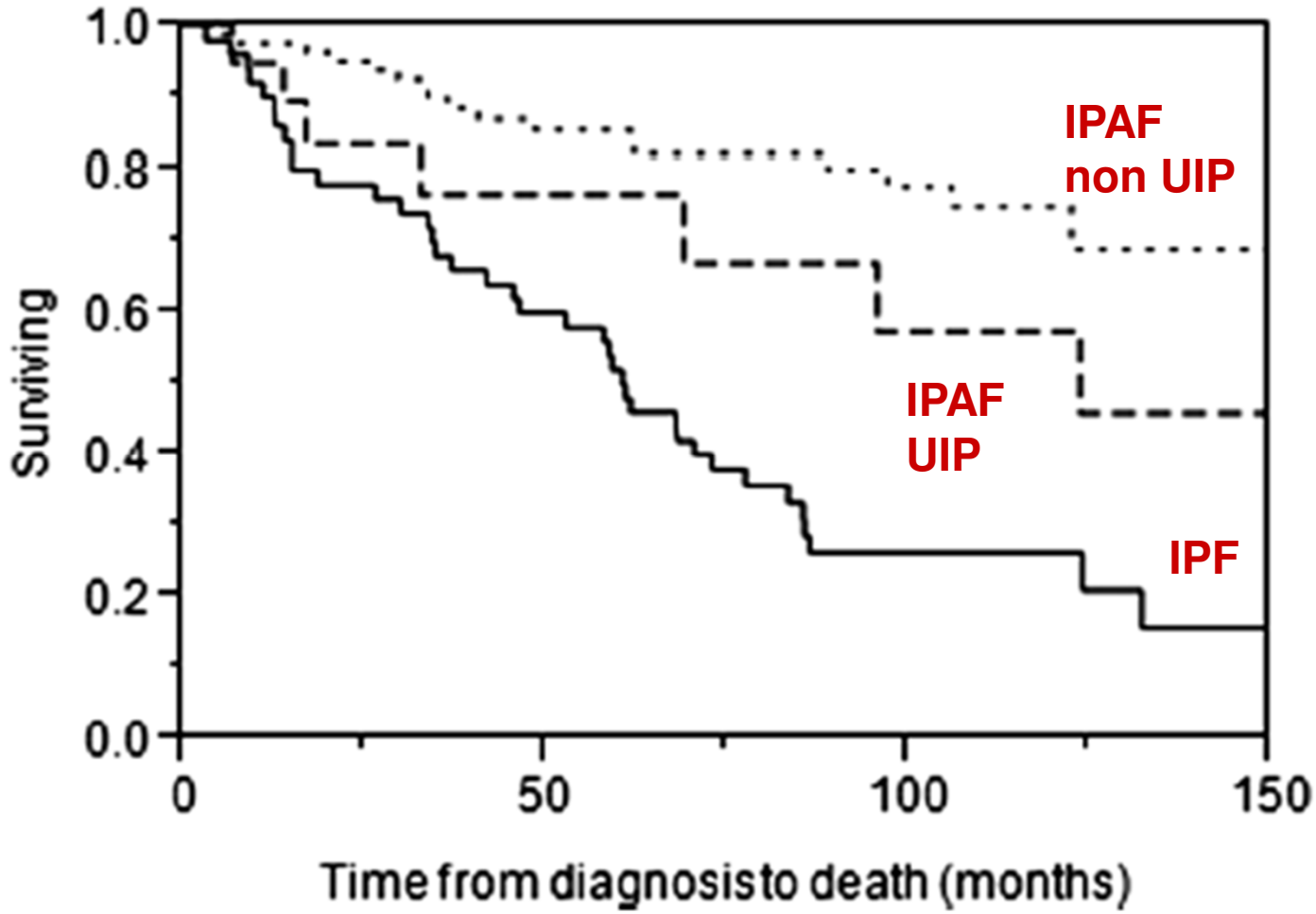
N=57



Ahmad, Respir Med 2019

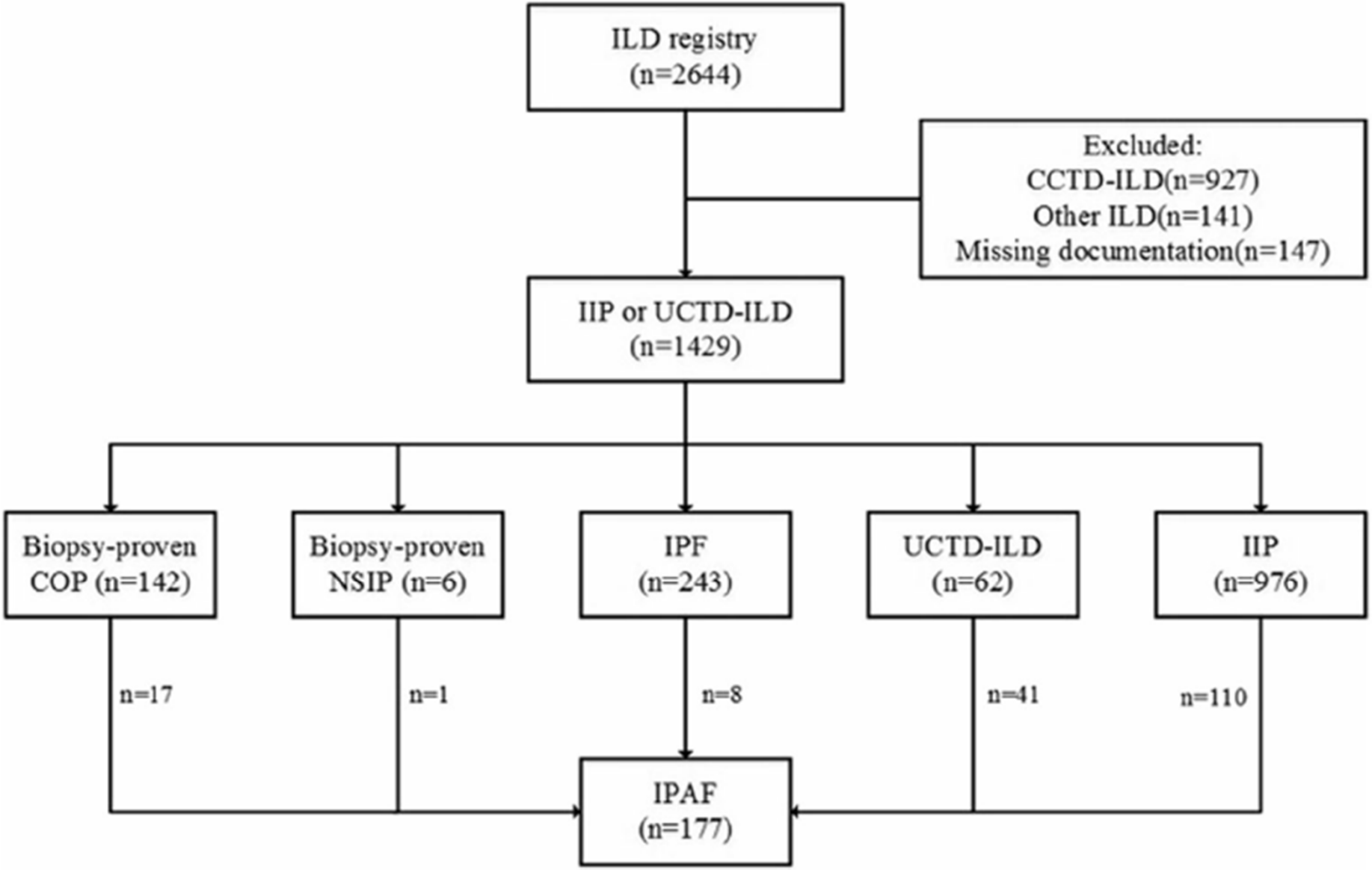
Survival by diagnosis

N=101



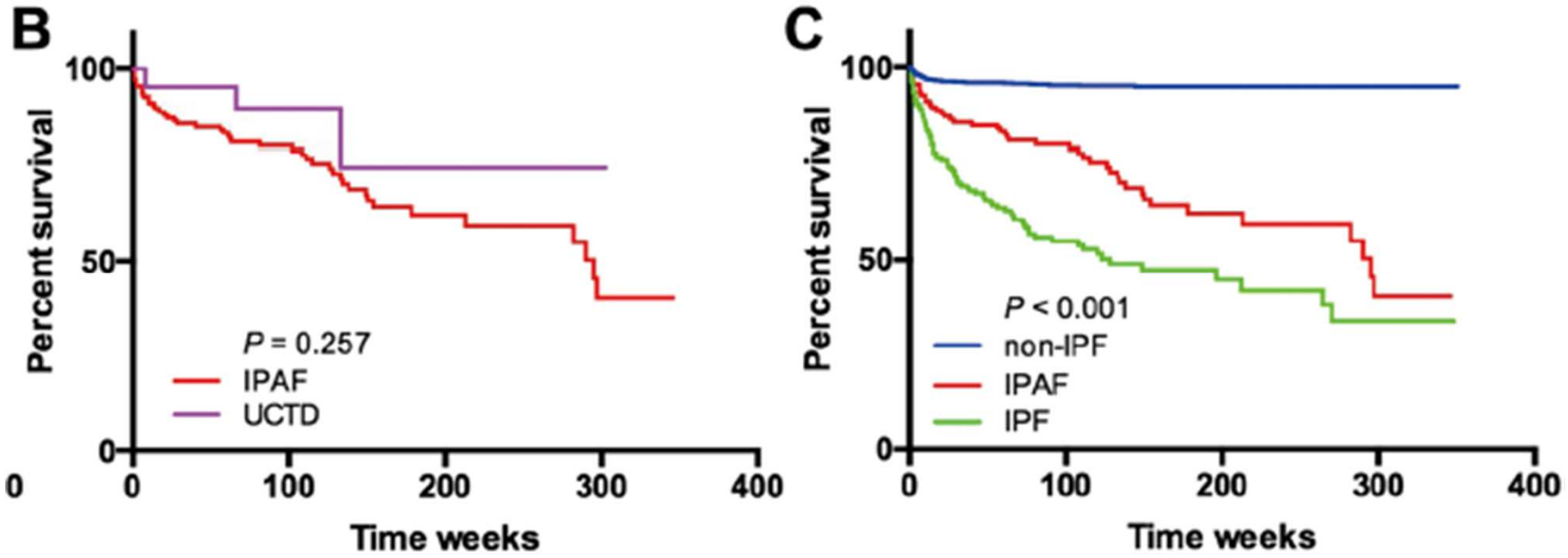
Kelly, Respirology 2018

Série chinoise



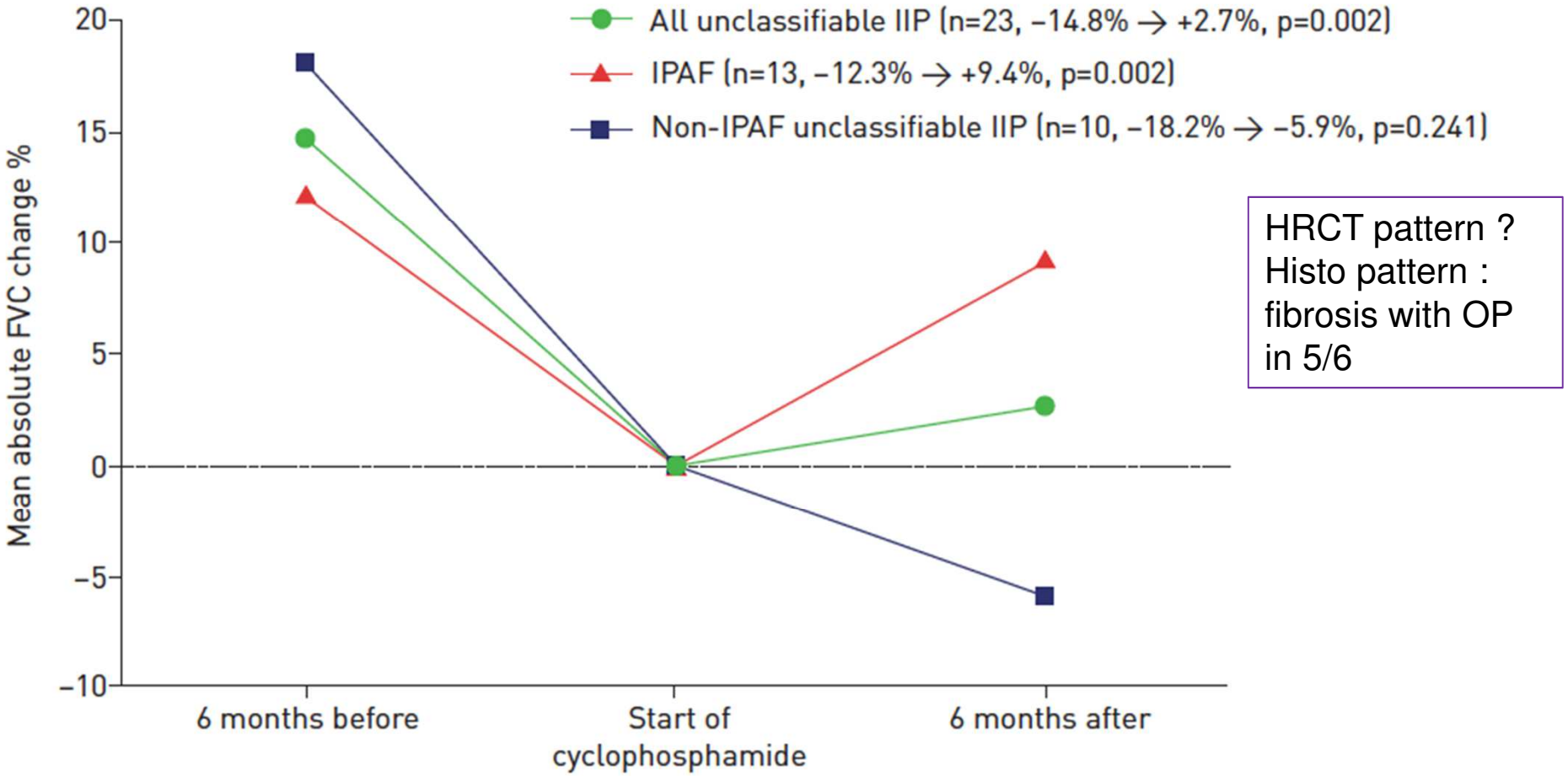
Dai, Clin Rheumatol 2018

Série chinoise



Dai, Clin Rheumatol 2018

Stratégie thérapeutique

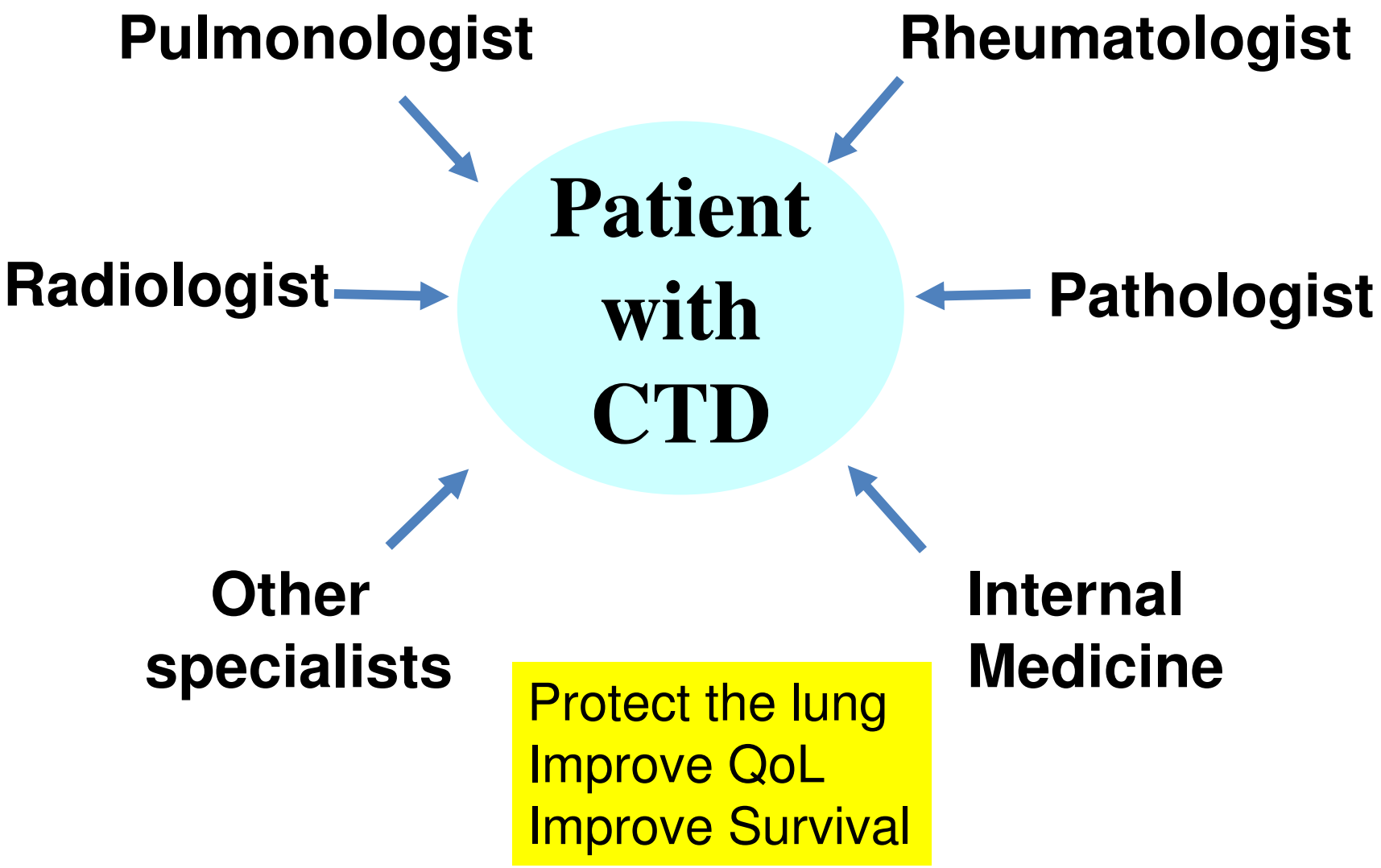


HRCT pattern ?
Histo pattern : fibrosis with OP in 5/6

Wiertz, Eur Respir J 2018

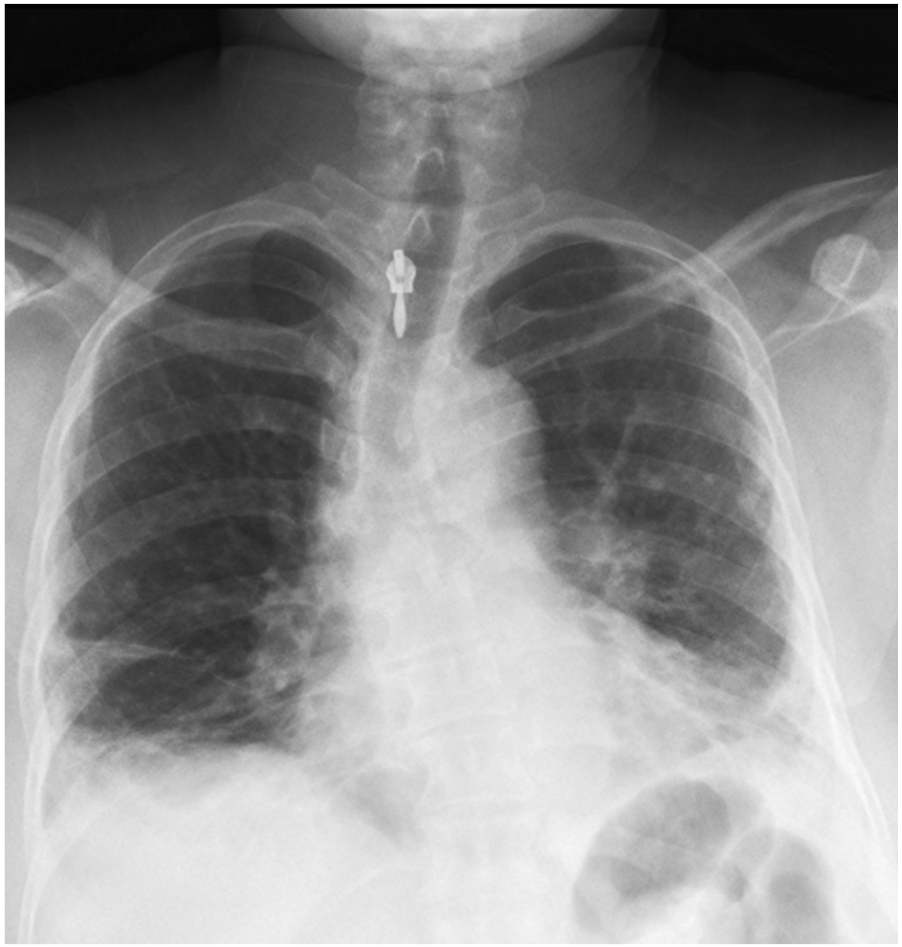
- The concept of IPAF is important
- Fits to the real life
- Treat according to the HRCT/Histo pattern ?
  - UIP→anti-fibrotics
  - Non UIP→ steroids and I°S

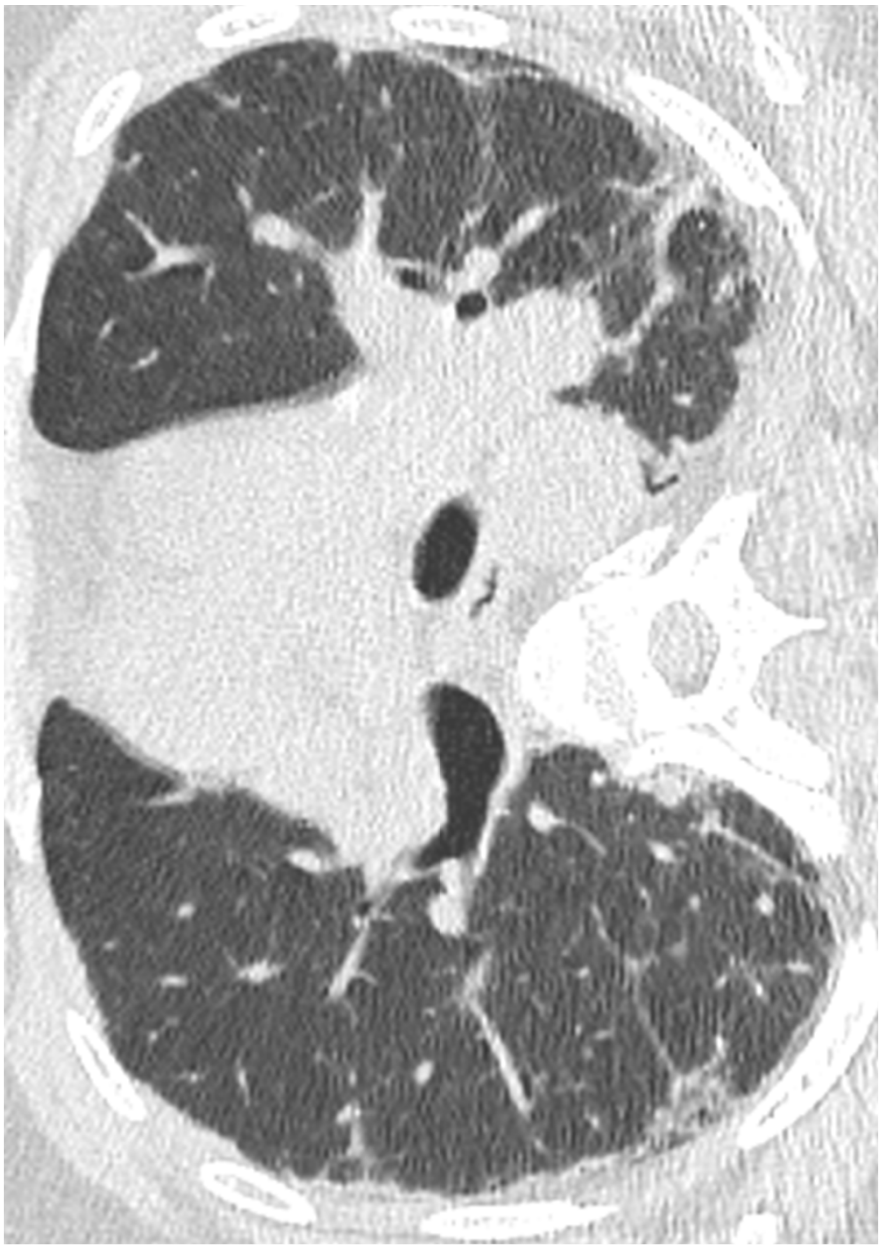
The Multidisciplinary approach

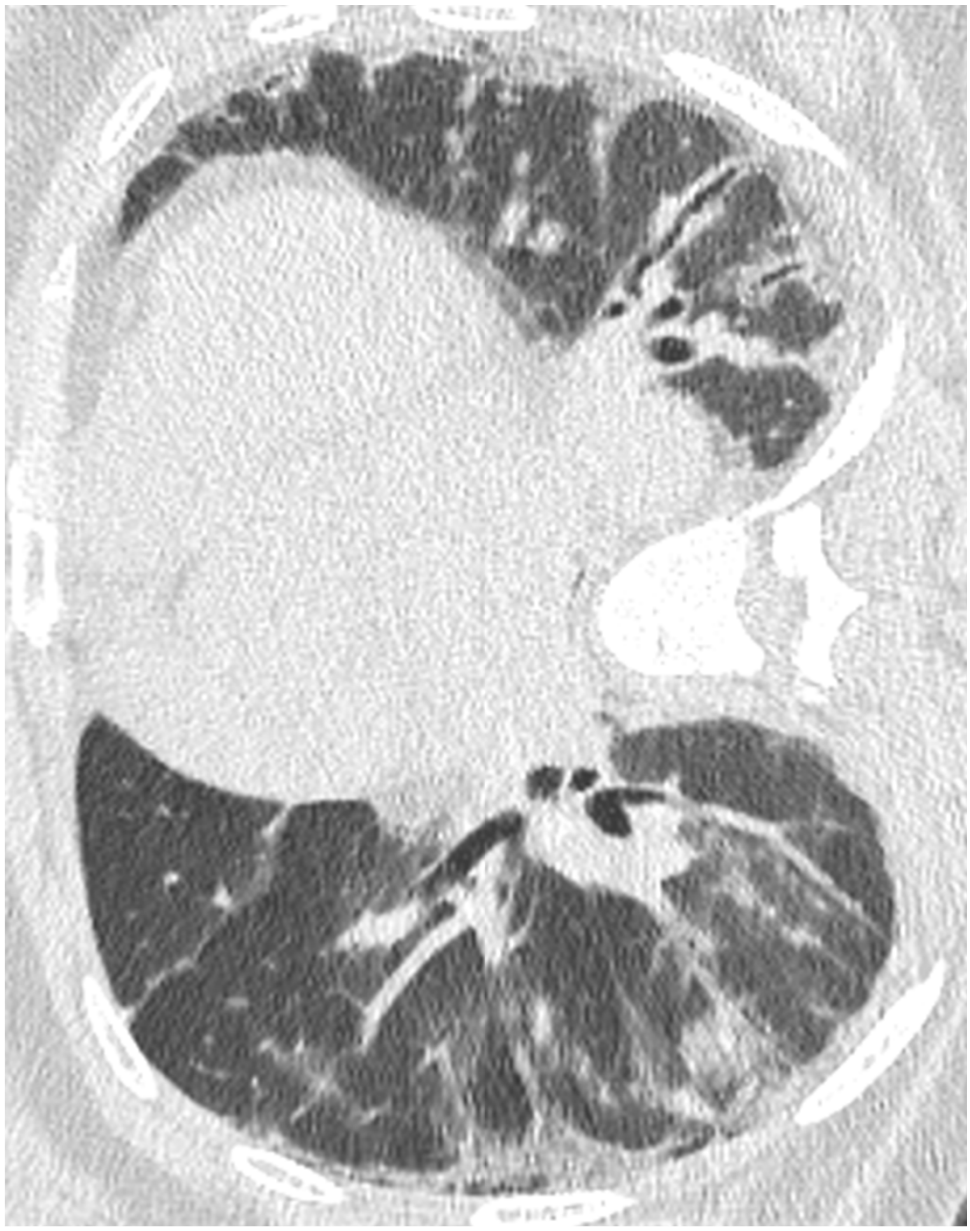


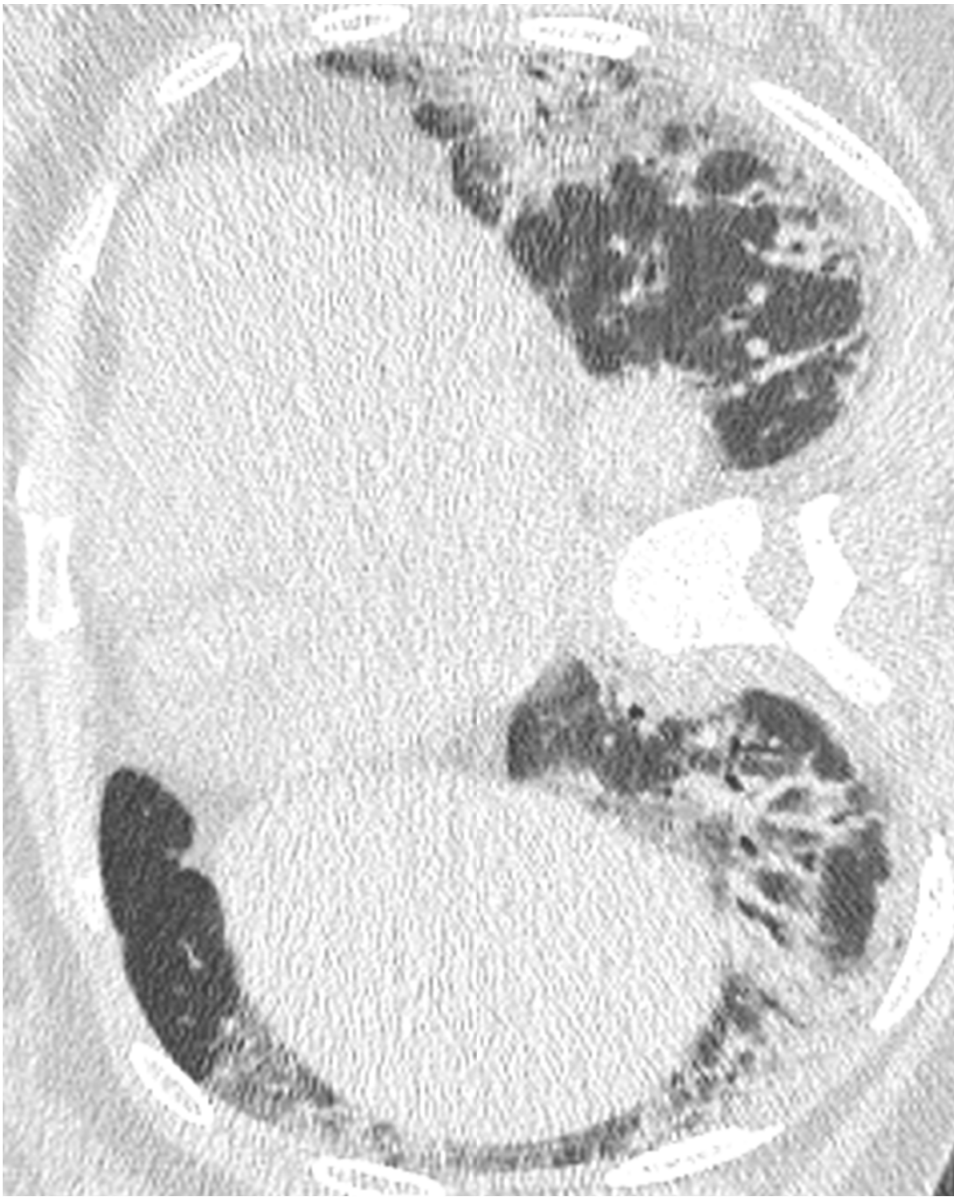
Mrs S. 55 yrs

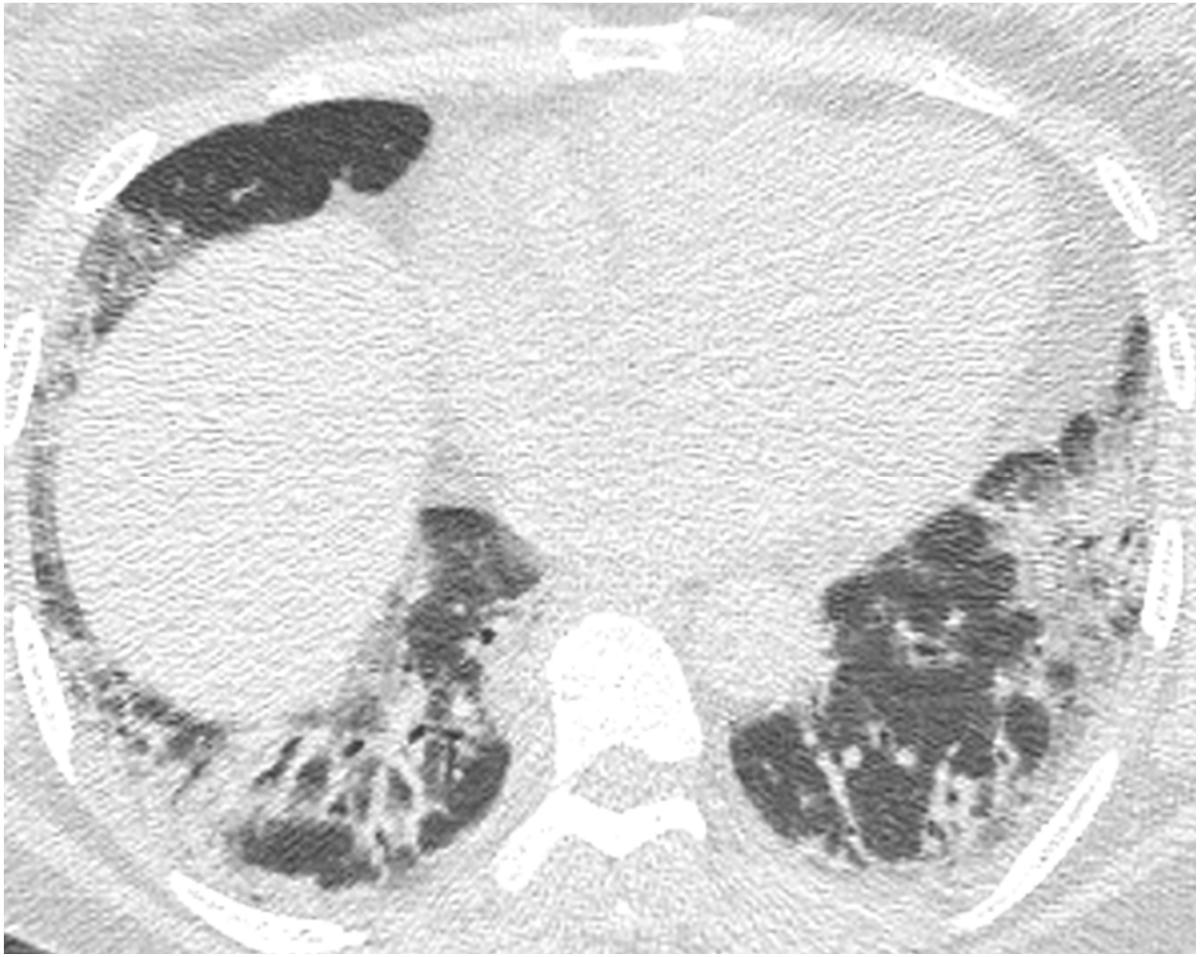
- Non smoker
- Shortness of breath since 2 yrs
- No extra-respiratory symptoms, no exposure
- Biological screen normal
- Minor salivary glands biopsy : Chisholm 1
- FVC 56%, DLCO 39%







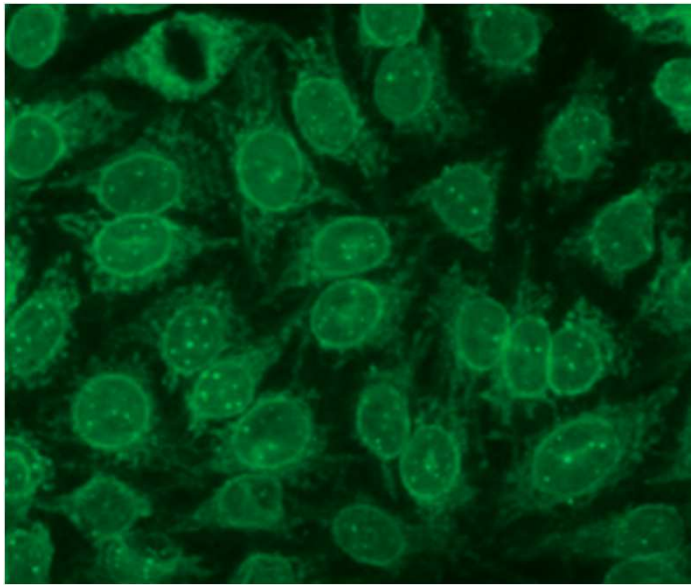




Probable NSIP with OP

Auto-immune screen :

- ANA 1/320, nuclear dots;
- anti-Sp100+



Nuclear dots (with membrane rim)

Rare pattern of fluorescence

- Primary Biliary Cirrhosis (particularly AMA negative)
- Other CTD (SLE, Sjögren, SSc)

Anti-Sp100 is the ELISA counterpart

(Granito, Aliment Pharmcol Therap 2006)

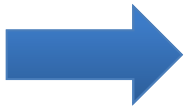
Mrs S. 55 yrs

Endoscopy

- BAL: Ly 18%; Neutro : 6%
- Bronchial biopsies <0
- Trans-bronchial biopsies : mild inflammation

Multi-Disciplinary Discussion:

- ILD highly suggestive of NSIP/OP
- Auto-Abs but No definite CTD

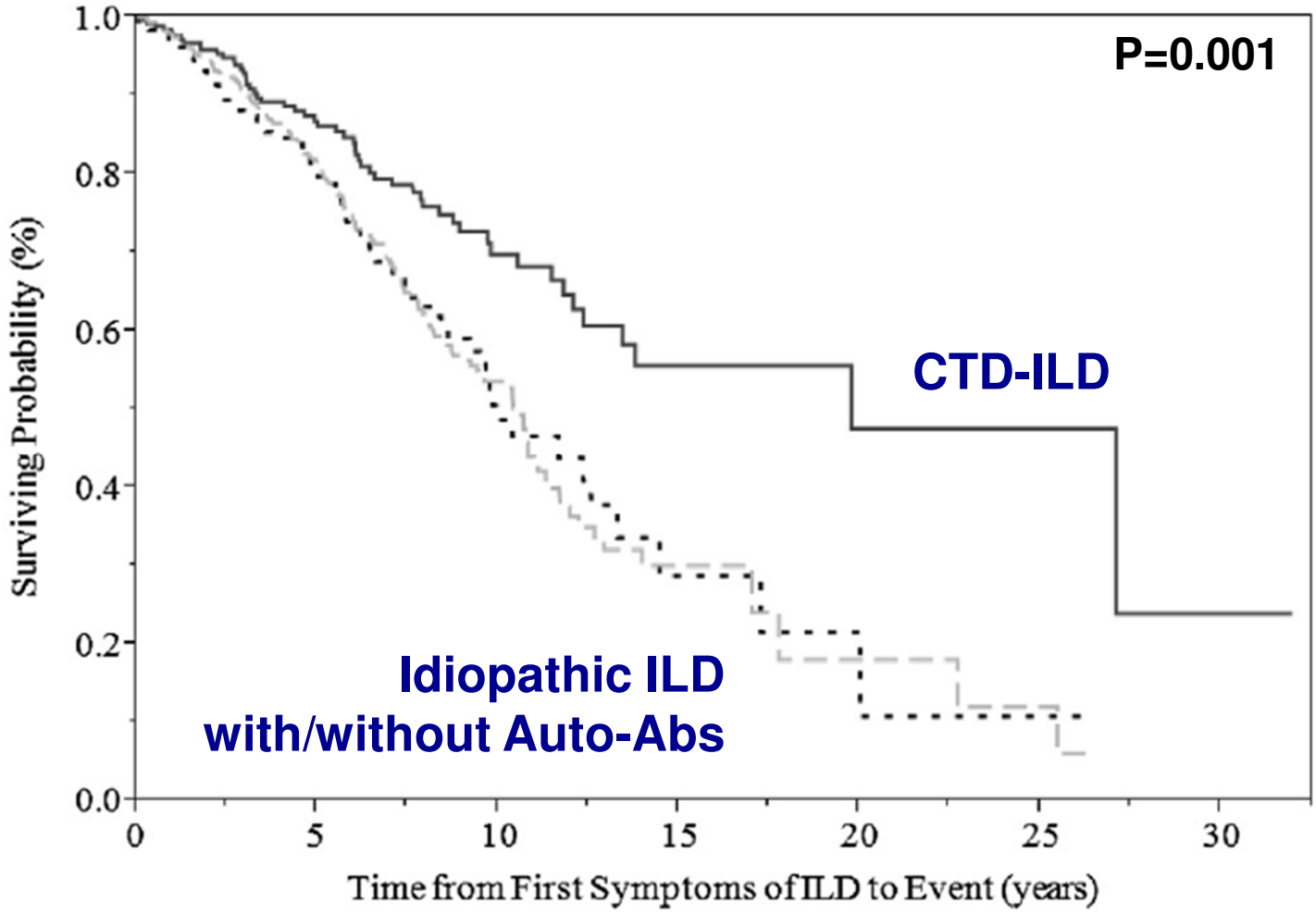


Biopsy or not ?

- An NSIP pattern on HRCT in an idiopathic context: 30% are UIP at histology
  - Travis, AJRCCM 2013

- Histology informs prognosis in the context of "Lung-dominant CTD"

Detection of auto-Abs does not influence the prognosis in an idiopathic context

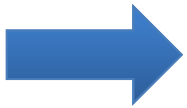


Auto-Abs tested : ANA, RF, anti-ENA

Brauer, Respir Med 2015

Multi-Disciplinary Discussion:

- ILD highly suggestive of NSIP/OP
- Auto-Abs but No definite CTD



Surgical lung biopsy: fibrotic NSIP with follicular bronchiolitis; no OP