IPAF should be considered as a Distinct Phenotype - Pro

울산대학교병원
제갈양진

We find it problematic …

- a 30-year-old woman with keratoconjuctivitis sicca and a positive anti-Ro antibody : **Sjögren syndrome**
- a 30-year-old woman with a positive anti-Ro antibody

+ biopsy proven NSIP with organizing pneumonia, lymphoid follicles with germinal centers, extensive pleuritis, and dense perivascular collagen

: **idiopathic ILD**

Fischer et al. CHEST 2010; 138(2):251–256

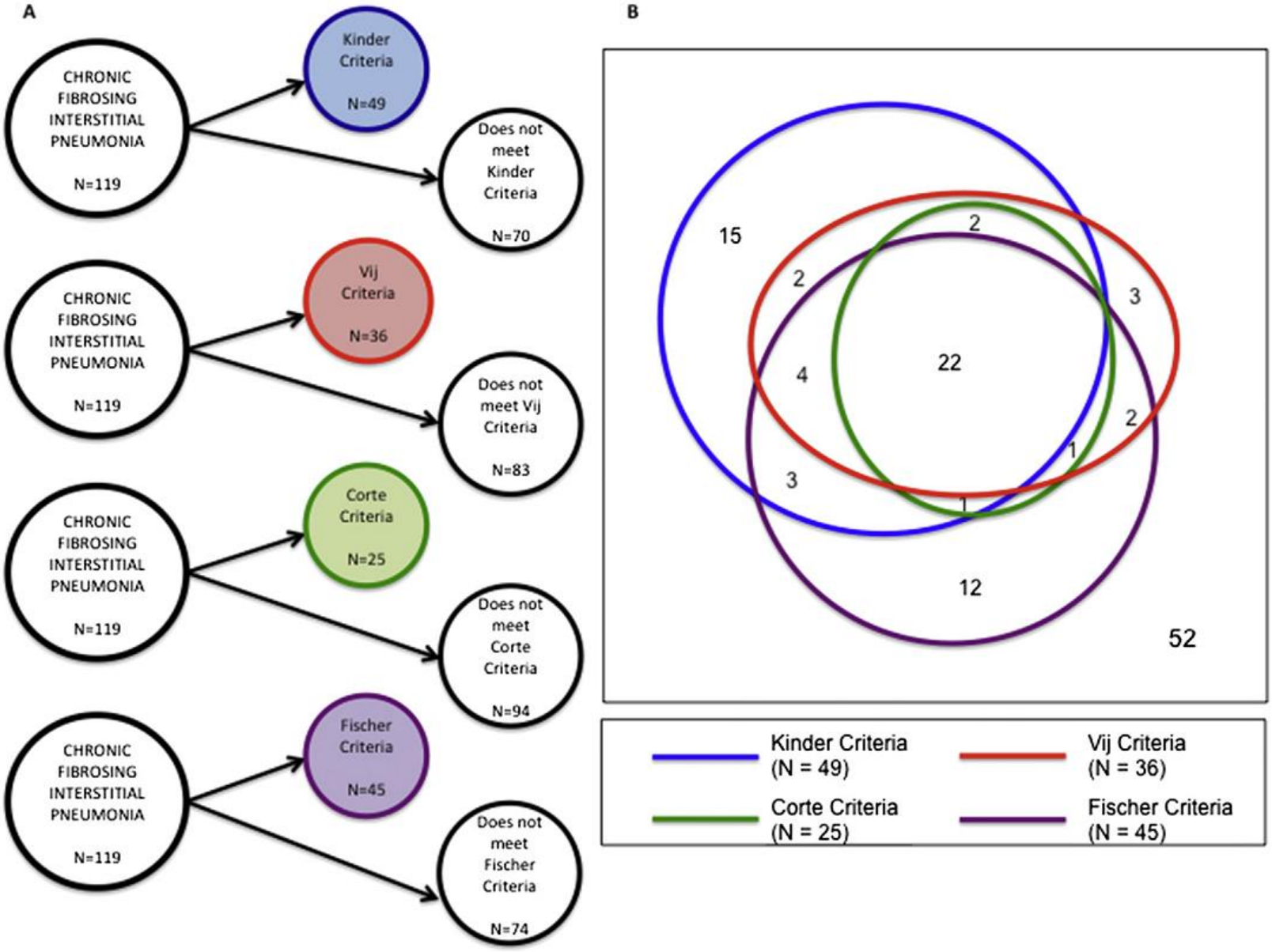
The problem is

- There was unanimous agreement that **some** patients diagnosed with an **IIP** have clinical, serologic or morphologic features that suggest the presence of a **systemic autoimmune process** but do **not meet** diagnostic criteria for a defined CTD.

A new term is needed

- Previously published terms describing this patient group, including broad and strict forms of **UCTD-ILD**, **lung-dominant CTD** and **autoimmune-featured ILD**, should be abandoned and replaced with consensus-derived nomenclature.

Fischer et al. CHEST 2010; 138(2):251–256


A
CHRONIC FIBROSING INTERSTITIAL PNEUMONIA N=119
Kinder Criteria N=49
Does not meet Kinder Criteria N=70
CHRONIC FIBROSING INTERSTITIAL PNEUMONIA N=119
Vij Criteria N=36
Does not meet Vij Criteria N=83
CHRONIC FIBROSING INTERSTITIAL PNEUMONIA N=119
Corte Criteria N=25
Does not meet Corte Criteria N=94
CHRONIC FIBROSING INTERSTITIAL PNEUMONIA N=119
Fischer Criteria N=45
Does not meet Fischer Criteria N=74
B
15
2
2
3
4
22
2
1
3
1
12
52
Kinder Criteria (N = 49)
Vij Criteria (N = 36)
Corte Criteria (N = 25)
Fischer Criteria (N = 45)

Survival by criteria

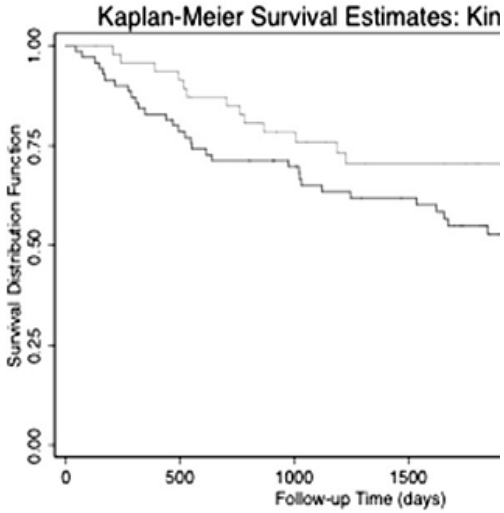
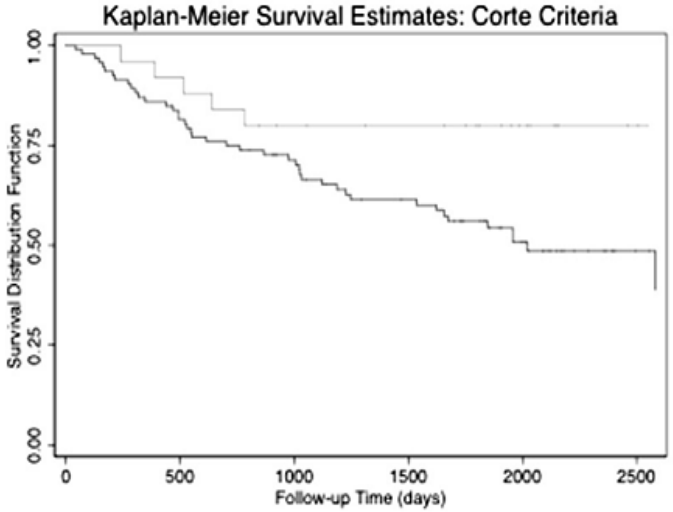
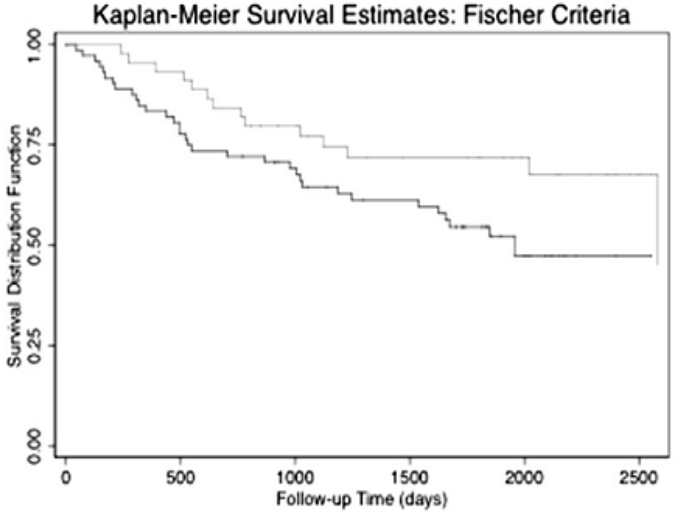


Table 3
Unadjusted and adjusted hazard ratios for mortality associated with each of the criteria.

	Hazard ratio (95% CI) p-value	
	Unadjusted	Adjusted for GAP score [12]
Kinder criteria	0.55 (0.30–1.03) 0.06	0.66 (0.35–1.26) 0.21
Vij criteria	0.45 (0.22–0.92) 0.03	0.50 (0.22–1.11) 0.09
Corte criteria	0.45 (0.19–1.06) 0.07	0.35 (0.13–0.97) 0.04
Fischer criteria	0.60 (0.33–1.10) 0.10	0.60 (0.31–1.18) 0.14





Assayag et al. Respiratory Medicine 109 (2015) 1326-1331

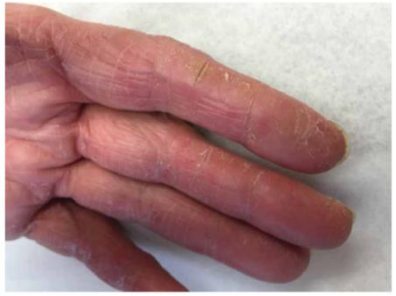
An official European Respiratory Society/ American Thoracic Society research statement: interstitial pneumonia with autoimmune features

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"

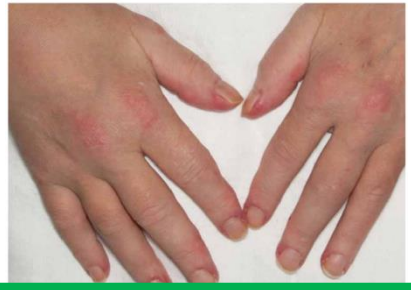
Classification criteria of interstitial pneumonia with autoimmune features

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. serological domain
    C. morphological domain

A. Clinical domain



1. Distal digital fissuring (i.e. “mechanic’s hands”)
2. Distal digital tip ulceration
3. Inflammatory arthritis or polyarticular morning 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)

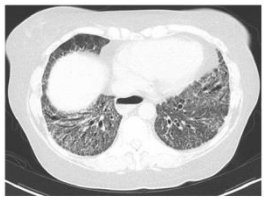
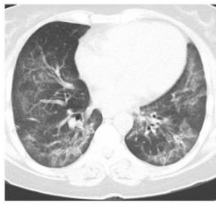
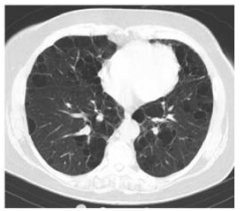


B. Serological domain

1. ANA ⩾1:320 titre, diffuse, speckled, homogeneous patterns or any titre for nuclear and centromere pattern
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, EJ, OJ, KS, Zo, tRS)
11. Anti-PM/Scl
12. Anti-MDA-5

C. Morphological domain

1. Suggestive radiology patterns by HRCT:
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP

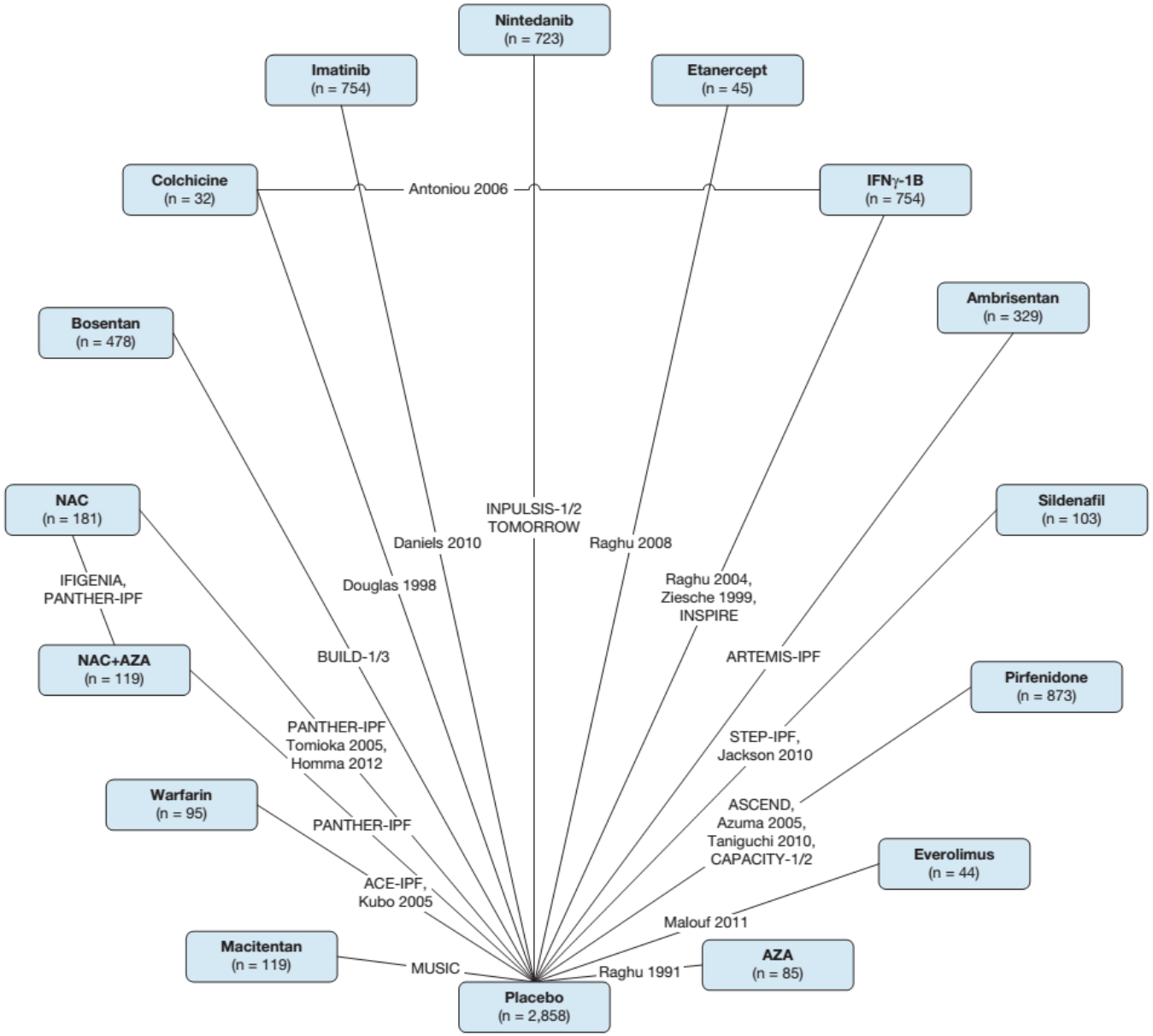




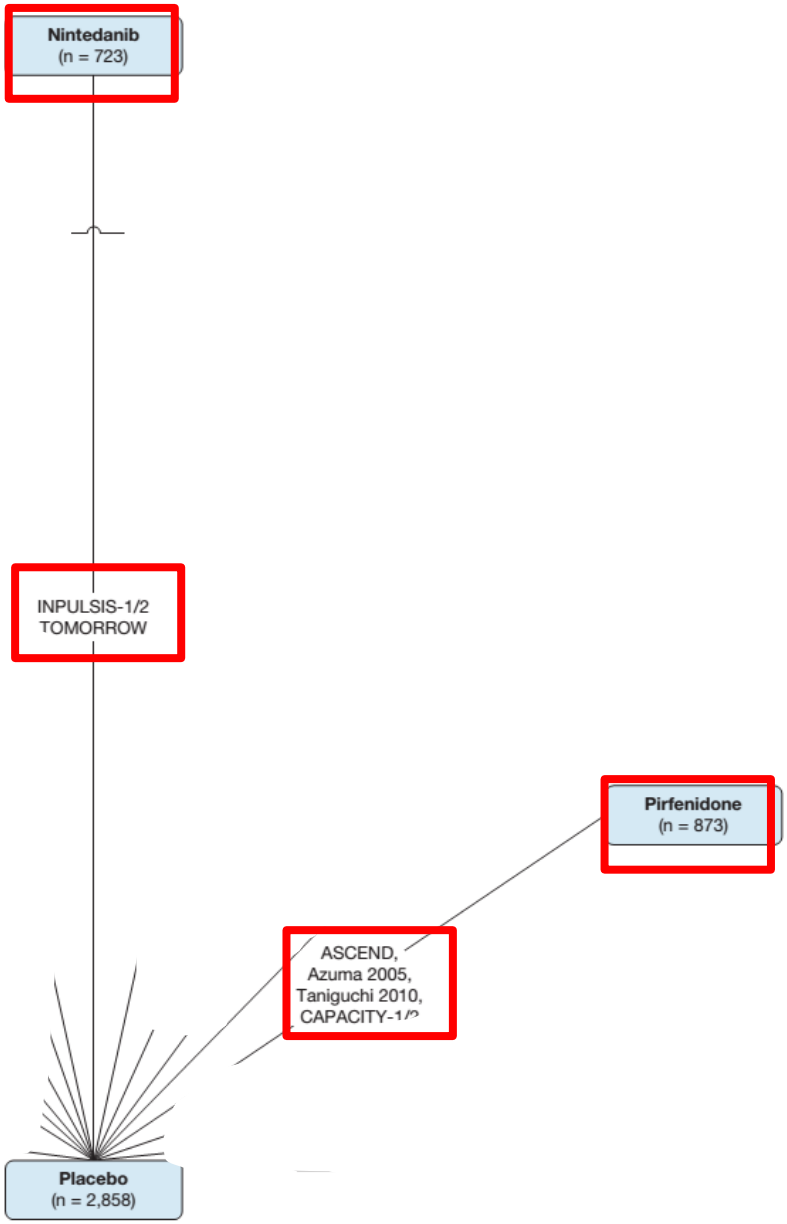
2. Histopathology patterns or features by surgical lung biopsy:
   a. NSIP
   b. OP
   c. NSIP with OP overlap
   d. LIP
   e. Interstitial lymphoid aggregates with germinal centres
   f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)
3. Multicompartment involvement (in addition 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

Frequency of autoimmune features

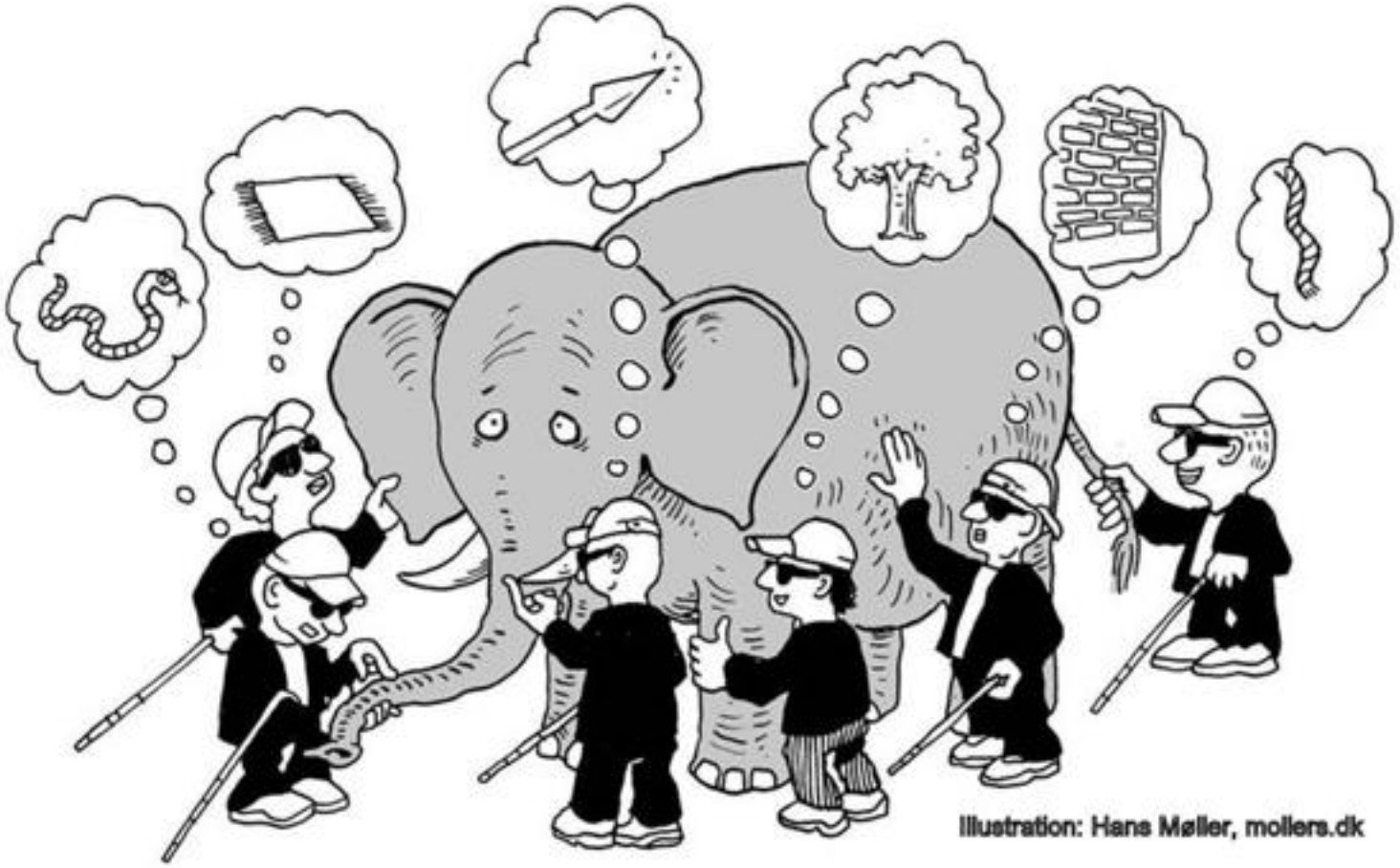
	N (%)
Clinical domain	27 (47.3)
Distal digital fissuring	2 (7.4)
Distal digital tip ulcerations	0 (0)
morning joint stiffness ≥ 60min	13 (48.1)
Raynaud's phenomenon	20 (74.1)
Serologic domain	53 (93)
ANA ≥20 titer, diffuse, speckled or homogeneous patterns, ANA nucleolar pattern (any titer), or ANA centromere pattern (any titer)	47 (82.4)
Rheumatoid factor ≥ 2x upper limit of normal	
Anti-CCP	5 (9.4)
Anti-dsDNA	3 (5.7)
Anti-Ro (SS-A)	5 (9.4)
Anti-La (SS-B)	1 (1.9)
Anti-ribonucleoprotein	0 (0)
Anti-Smith	0 (0)
Anti-topoisomerase (Scl-70)	3 (5.7)
Anti-tRNA synthetase	9 (17)
Anti-Pm-Scl	3 (5.7)
Anti-MDA-5	0 (0)
NSIP domain	
NSIP radiology patterns by HRCT (n = 54)	24 (42.1)
OP	2 (3.5)
NSIP with OP overlap	9 (15.8)
LIP	1 (1.8)
Histopathology patterns or features by surgical lung biopsy (n = 17)	
NSIP	5 (8.8)
OP	2 (3.5)
NSIP with OP overlap	1 (1.8)
LIP	1 (1.8)
Interstitial lymphoid aggregates with germinal centres	6 (10.5)
Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)	7 (12.3)
Multi-compartment involvement (in addition to interstitial pneumonia)	
Unexplained pleural effusion or thickening	1 (1.8)
Unexplained pericardial effusion or thickening	1 (1.8)
Unexplained intrinsic airways diseases (by PFT. imaging or pathology)	5 (8.8)
Unexplained pulmonary vasculopathy	10 (17.5)

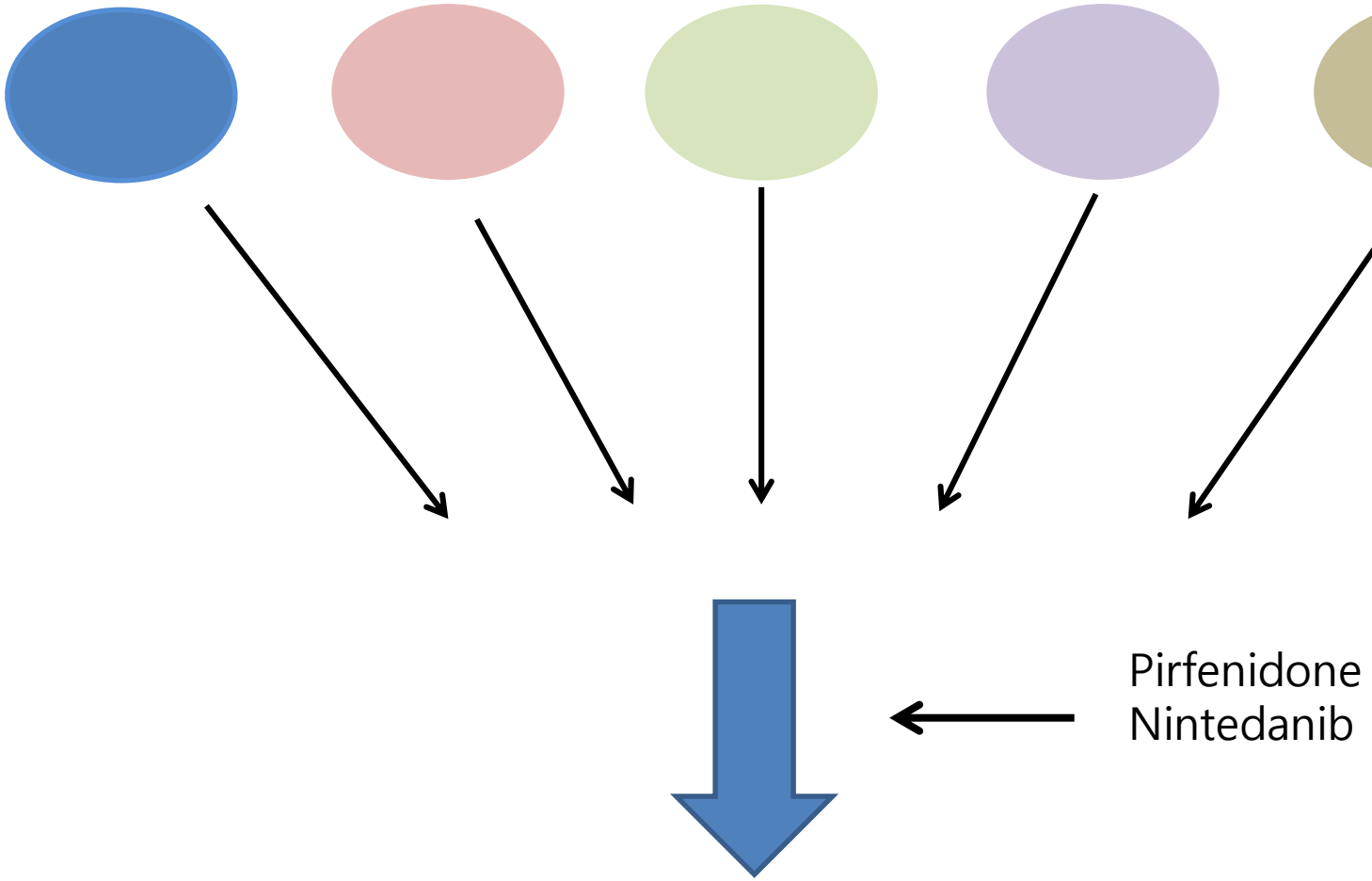
K. Ahmad et al. Respiratory Medicine 123 (2017) 56-62


Nintedanib
(n = 723)
Imatinib
(n = 754)
Etanercept
(n = 45)
Colchicine
(n = 32)
Antoniou 2006
IFNγ-1B
(n = 754)
Ambrisentan
(n = 329)
Bosentan
(n = 478)
NAC
(n = 181)
Sildenafil
(n = 103)
INPULSIS-1/2
TOMORROW
Daniels 2010
Raghu 2008
IFIGENIA,
PANTHER-IPF
Douglas 1998
Raghu 2004,
Ziesche 1999,
INSPIRE
NAC+AZA
(n = 119)
BUILD-1/3
ARTEMIS-IPF
Pirfenidone
(n = 873)
PANTHER-IPF
Tomioka 2005,
Homma 2012
STEP-IPF,
Jackson 2010
Warfarin
(n = 95)
PANTHER-IPF
ASCEND,
Azuma 2005,
Taniguchi 2010,
CAPACITY-1/2
Everolimus
(n = 44)
ACE-IPF,
Kubo 2005
Malouf 2011
Macitentan
(n = 119)
MUSIC
Raghu 1991
AZA
(n = 85)
Placebo
(n = 2,858)


Nintedanib
(n = 723)
INPULSIS-1/2
TOMORROW
Pirfenidone
(n = 873)
ASCEND,
Azuma 2005,
Taniguchi 2010,
CAPACITY-1/2
Placebo
(n = 2,858)

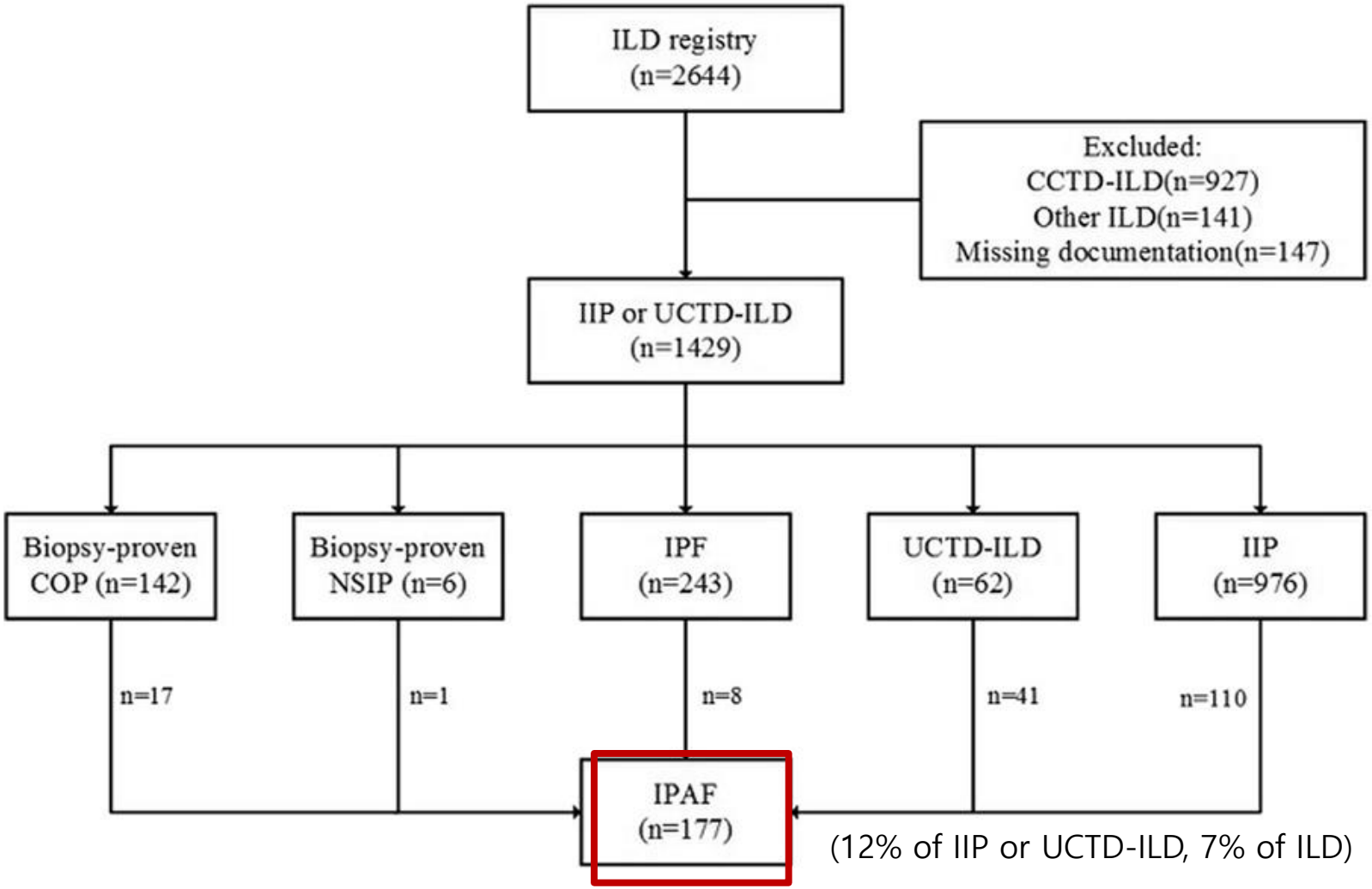
What is the truth?





Common pathway of fibrosis

Incidence of IPAF



(12% of IIP or UCTD-ILD, 7% of ILD)

Dai et al. Clinical Rheumatology (2018) 37:2125–2132

Differences Between IPAF and other ILDs

Table 3—*Symptoms Endorsed by Study Subjects*

Symptoms	AIF-ILD (n = 63)	IPF (n = 58)	CTD-ILD (n = 37)	*P* Value
Dry eyes/dry mouth	36 (57.1)	9 (15.5)	23 (62.2)	< .01[a]
GERD	28 (44.4)	10 (17.2)	19 (51.4)	< .01[a]
Leg/foot swelling	23 (36.5)	4 (6.9)	10 (27.0)	< .01[a]
Weight loss	23 (36.5)	6 (10.3)	7 (18.9)	< .01[a]
Joint pain/swelling	17 (27.0)	5 (8.6)	23 (62.2)	< .01[a]
Rash	6 (9.5)	3 (5.2)	10 (27.0)	< .01
Raynaud phenomenon	6 (9.5)	0 (0)	19 (51.4)	< .01[a]
Sensitivity to light	6 (9.5)	2 (3.4)	6 (16.2)	.10
Dysphagia	6 (9.5)	2 (3.4)	6 (16.2)	.10
Hand ulcers	1 (1.6)	0 (0)	5 (13.5)	< .01
Mouth ulcers	1 (1.6)	1 (1.7)	3 (8.1)	.24
Morning stiffness	1 (1.6)	0 (0)	5 (13.5)	< .01
Proximal muscle weakness	0 (0)	0 (0)	4 (10.8)	< .01

Data are presented as No. (%). Study subjects could endorse multiple symptoms. GERD = gastroesophageal reflux disease. See Table 2 for expansion of other abbreviations.

[a]Symptom was statistically significant when comparing subjects with AIF-ILD to subjects with IPF.

Vij et al.CHEST 2009; 136:23–30

Pathologic and Radiologic Differences Between Idiopathic and CTD-UIP

Table 8—*Comparison of Radiologic Scores Between IPF/UIP With Autoantibodies and Without Autoantibodies*

Category	IPF/UIP(Ab−) Patients	IPF/UIP(Ab+) Patients	CVD-UIP Patients	p Value*
GGO	1.73 ± 3.70†	5.17 ± 5.67‡	4.10 ± 5.26	0.004
HC	5.95 ± 6.79†	9.46 ± 10.85†	4.00 ± 6.77	0.021
Total extent	20.17 ± 10.62	28.60 ± 15.64†‡	18.74 ± 10.33	0.032
Emphysema	1.81 ± 3.64	1.29 ± 2.30	0.43 ± 0.76	NS
Reticulation	10.34 ± 6.76	11.93 ± 7.32	9.55 ± 4.89	NS
Consolidation	0.33 ± 1.20	0.75 ± 2.01	0.66 ± 1.59	NS

Data are presented as the mean ± SD, unless otherwise indicated. See Table 1 for abbreviation not used in the text.
*Kruskal-Wallis test.
†$p < 0.05$ (significant compared to CVD-UIP patients).
‡$p < 0.05$ (significant compared to IPF/UIP[Ab−]).

Table 7—*Comparison of Pathologic Scores Between IPF/UIP With Autoantibodies and Without Autoantibodies*

Category	CVD-UIP Patients	IPF/UIP(Ab+) Patients	IPF/UIP(Ab−) Patients	p Value*
Germinal centers	1.04 ± 1.07†	0.71 ± 0.92†	0.15 ± 0.28	< 0.001
Plasma cells	1.72 ± 0.68†	1.76 ± 0.81†	1.27 ± 0.62	0.003
Fibroblastic foci	1.56 ± 0.74†	1.89 ± 0.77	2.06 ± 0.84	0.009
Total inflammation	2.10 ± 0.69†	1.92 ± 0.67	1.65 ± 0.65	0.017
HC size	1.71 ± 1.09†	1.95 ± 1.03	2.31 ± 1.12	0.069
Intraalveolar macrophages	0.76 ± 0.54	0.82 ± 0.42	0.87 ± 0.47	NS
Pleural change	1.11 ± 0.31	1.05 ± 0.23	1.14 ± 0.35	NS
Organizing pneumonia	0.33 ± 0.53	0.47 ± 0.75	0.33 ± 0.53	NS

Data are presented as the mean ± SD, unless otherwise indicated. See Table 1 for abbreviation not used in the text.
*Kruskal-Wallis test.
†$p < 0.05$ (significant compared to IPF/UIP[Ab−] patients).

Song et al.CHEST 2009; 136:23–30

Differences Between IPAF and other ILDs

	IPF ($n = 235$)	IPAF ($n = 177$)	Non-IPF ($n = 996$)	P value
Age (years)	67.55 ± 8.64	60.23 ± 12.88	62.13 ± 13.14	< 0.001
Sex (male/female)	202/33	78/99	610/386	< 0.001
Ever smoker	141	34	333	< 0.001
Therapy	94	132	661	< 0.001
Corticosteroids	93	128	654	< 0.001
Immunosuppressant	13	44	59	< 0.001
Combined	12	40	52	0.001
Nonsurvivors	75	35	50	0.001
Mean survival time (weeks)	128.0	295.0	Not reach	< 0.001

IPF idiopathic pulmonary fibrosis, *IPAF* interstitial pneumonia with autoimmune features; combined, corticosteroids combined immunosuppressant

Dai et al. Clinical Rheumatology (2018) 37:2125–2132

Prognosis of IPAF - FVC

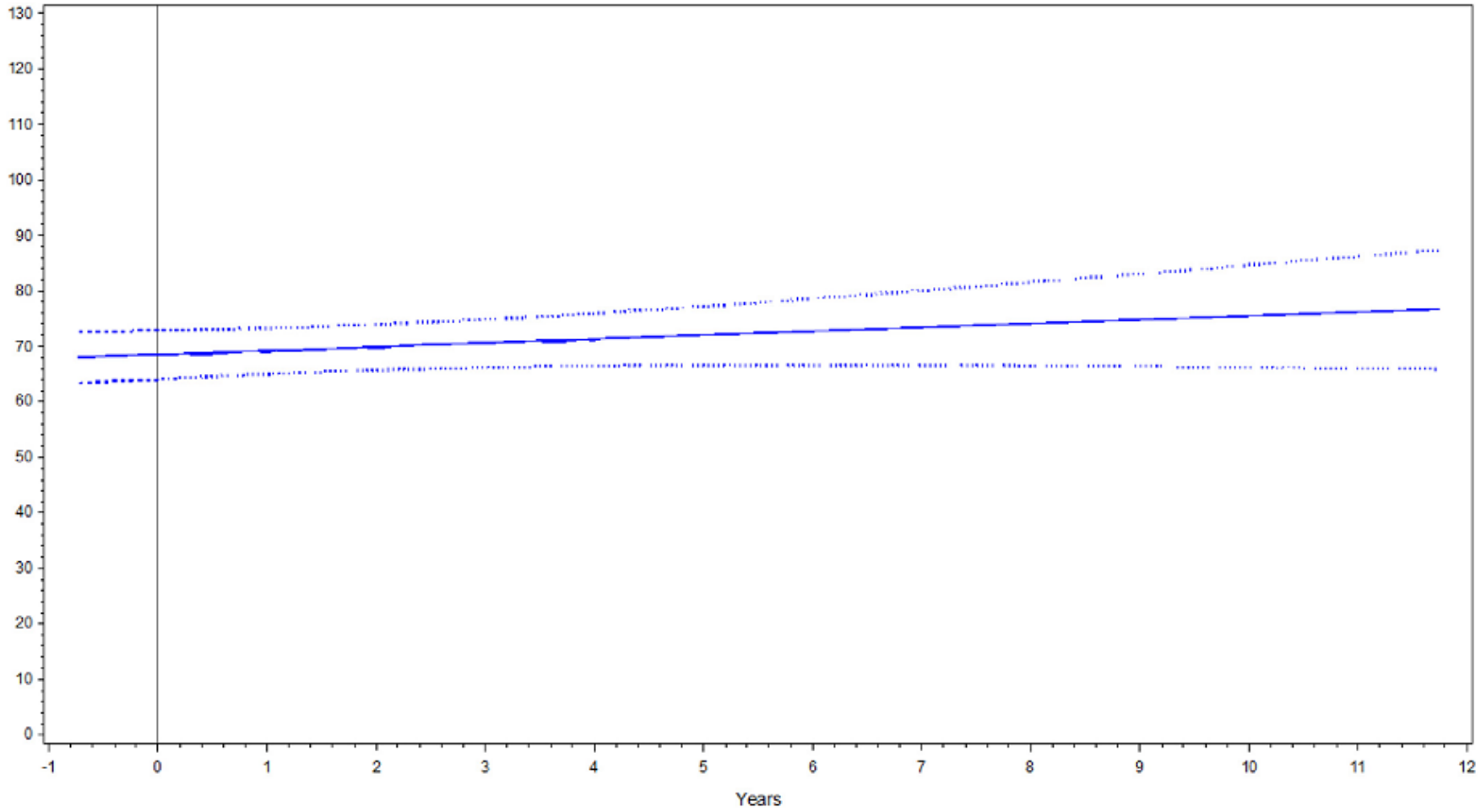
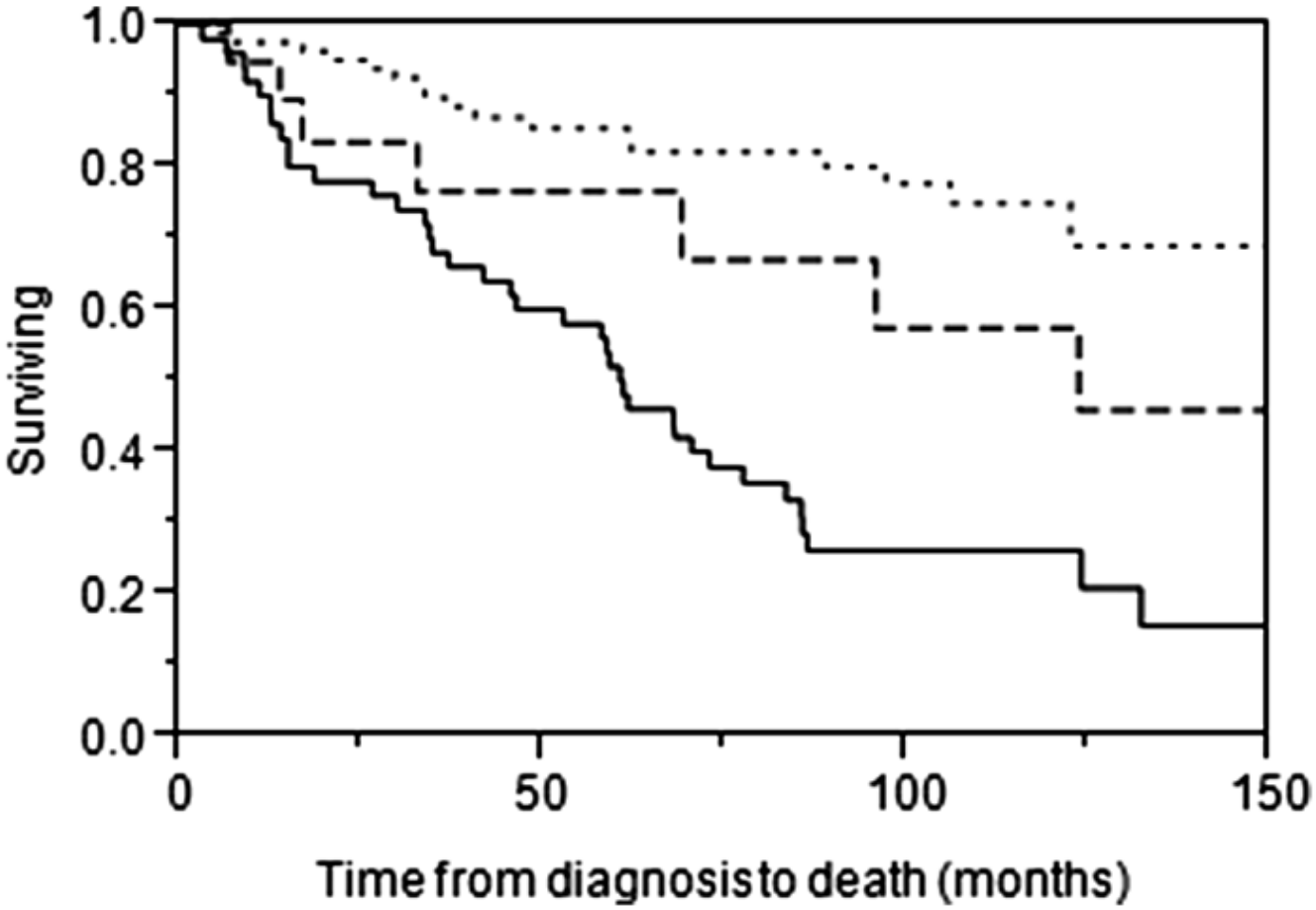


Fig. 1. Plot of mixed-effects model estimates for forced vital capacity in percent predicted (FVC%) over time for the entire cohort. (solid line = mean, dotted line = 95% confidence interval).

Chartrand et al. Respiratory Medicine 119 (2016) 150-154

Prognosis of IPAF – Survival (1)



P<0.0001

IPAF non-UIP

P=0.0418

IPAF UIP

P=0.08

IPF

Kelly et al. Respirology (2018) 23, 600–605

Prognosis of IPAF – Survival (2)

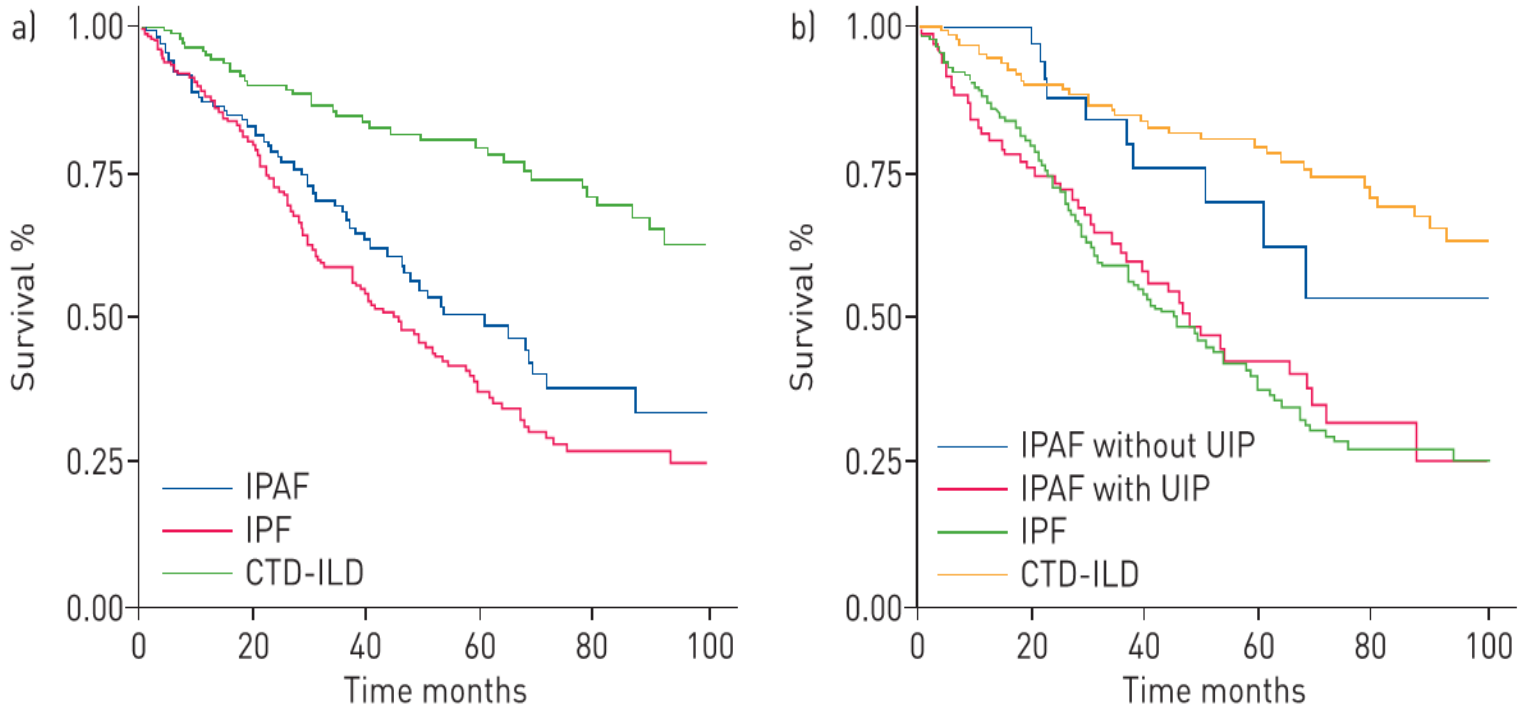
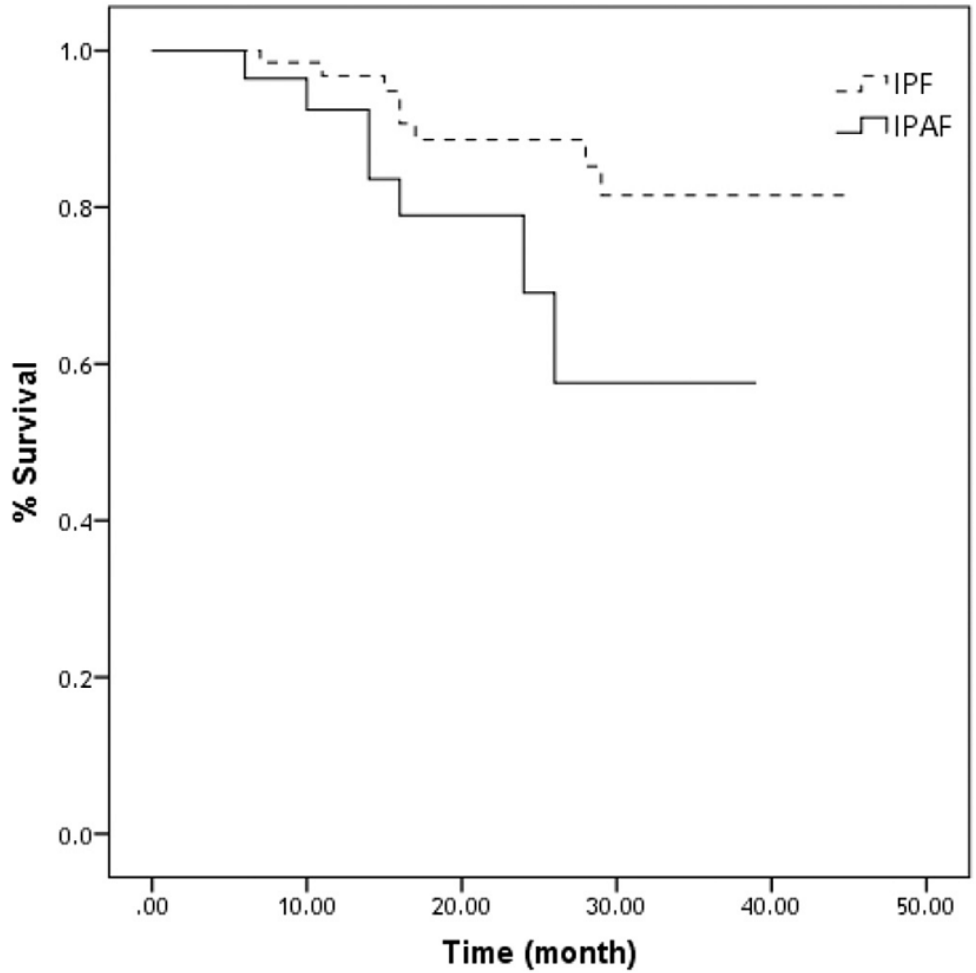


FIGURE 2 Kaplan–Meier survival curves of interstitial pneumonia with autoimmune features (IPAF), idiopathic pulmonary fibrosis (IPF) and connective tissue disease (CTD)-interstitial lung disease (ILD) cohorts. Overall a) IPAF cohort survival was significantly worse than the CTD-ILD cohort ($p<0.001$) and marginally better than the IPF cohort ($p=0.07$). After stratification of the IPAF cohort by the presence of a usual interstitial pneumonia pattern on high-resolution computed tomography and/or surgical lung biopsy b) IPAF patients without usual interstitial pneumonia (UIP) demonstrated survival similar to those with CTD-ILD ($p=0.45$), while those with UIP demonstrate survival similar to those with IPF ($p=0.51$).

Prognosis of IPAF – Survival (3)

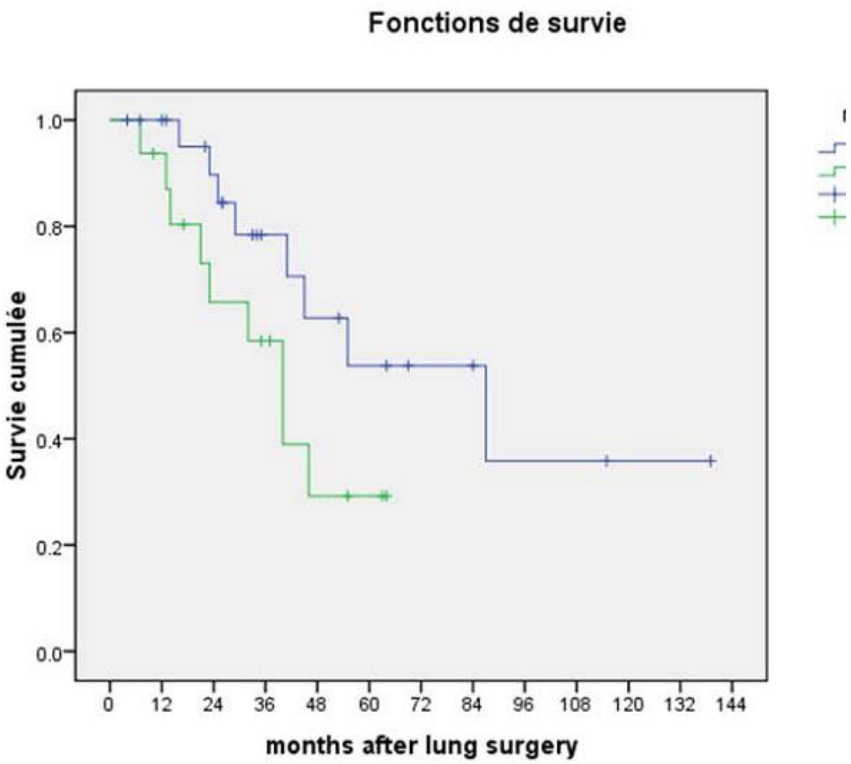


P=0.05

K. Ahmad et al. Respiratory Medicine 123 (2017) 56-62

	Oldham, et al. (24)	Chartrand, et al. (27)	Ahmad, et al. (29)	Ito, et al. (31)	Dai, et al. (32)	Yoshimura, et al. (34)	Kelly, et al. (35)
Patients	n = 144	n = 56	n = 57	n = 98	n = 177	n = 32	n = 101
Age, years (mean±SD)	63.2±11	54.6±10.3	64.4±14	67.5±9	67.6±8.6	63.4±12.6	56.9±14.2
Female	52.1	71.4	49.1	58.2	55.9	40.6	39
Ever-smoker	54.9	32.1	34	38.8	19.2	56.2	31
Clinical	49.3	62.5	47.3	NR	20.3	53.1	NR
Serologic	91.7	91.1	93	100*	92.1	71.9	NR
Morphologic	85.4	98.2	78.9	100†	95.5	96.9	NR
Clinical and serologic	14.6	2	NR	NR	NR	3.1	4
Clinical and morphologic	8.3	9	NR	NR	NR	28.1	14
Serologic and morphologic	50.7	37.5	NR	100	NR	46.9	26
All three domains	26.4	52	NR	NR	NR	21.9	56
UIP by HRCT	54.6	8.9	28	0	4.5	NR	NR
Underwent SLB, n (%)	83 (57.6)	36 (64.3)	16 (28.1)	17 (17.3)	0‡	22 (68.8)	51 (50.5)
UIP on SLB, n (%)	61 (73.5)	8 (22.2)	3 (18.8)	3 (17.6)	--	--	12 (23.5)
Treatment							
Corticosteroids	32.2	81.8	67.9	17.3	72.3	59.4	NR
Antifibrotic	NR	NR	5.4	2	NR	25	NR
Outcome							
Death	39.6	0	12.3	27.6	19.8	NR	28
Lung transplant	10.8	NR	NR	NR	NR	NR	NR

Does same survival mean same disease?



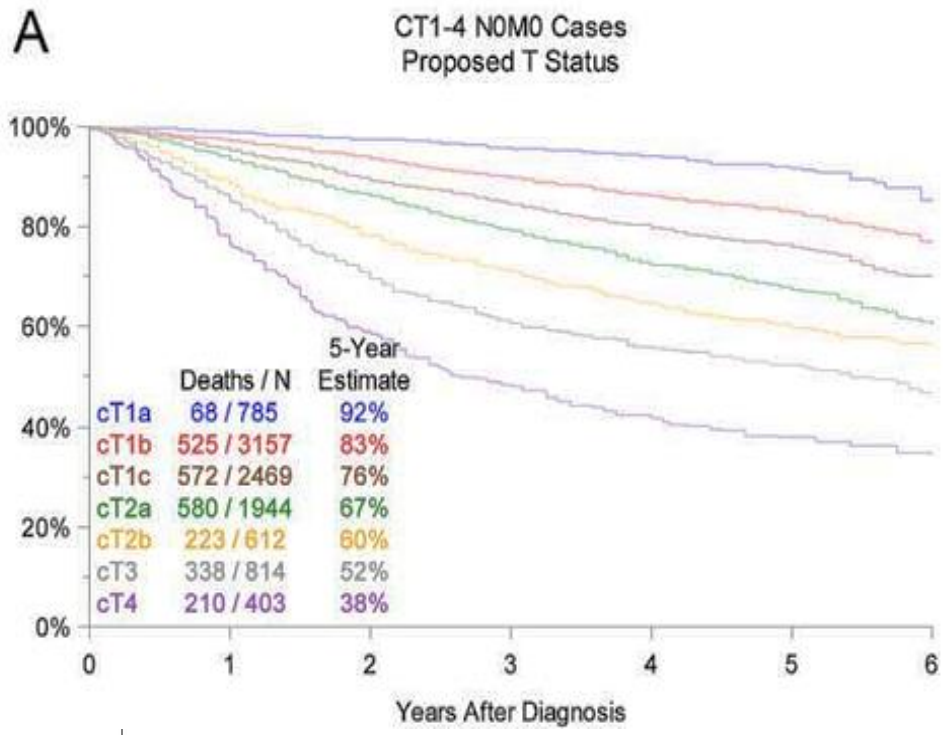
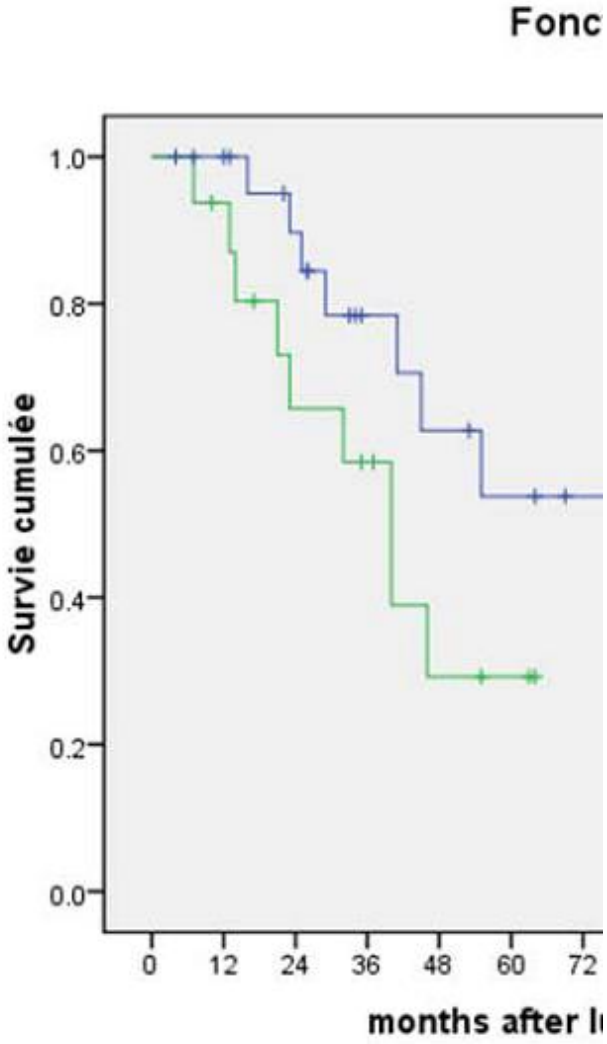
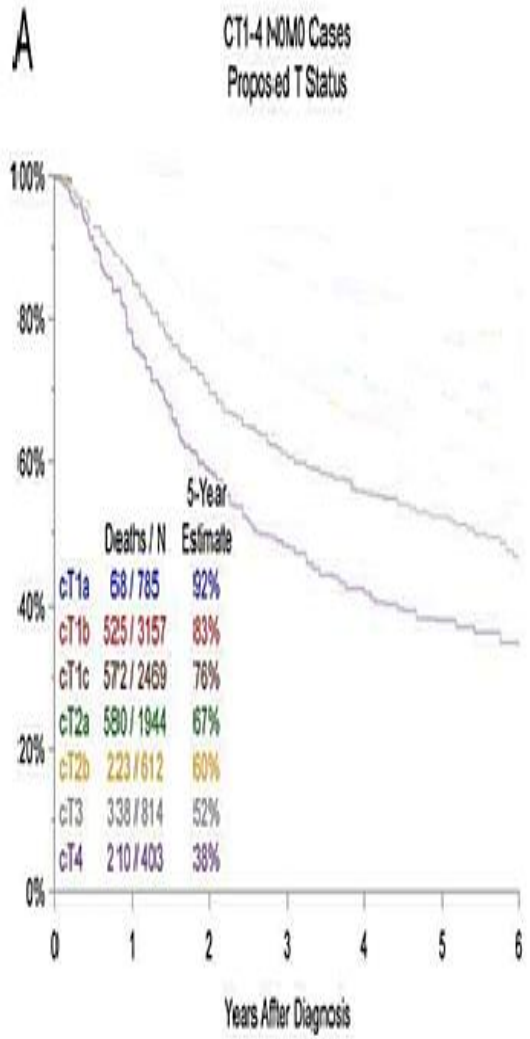


Figure 2 Kaplan-meier overall survival of colorectal cancer patients who underwent resection of lung metastases according to the presence or not of prior liver metastases.

Landes et al. BMC Surgery 2010, 10:17





Same diseases? Different diseases?

IPAF should be considered as a Distinct Phenotype

Because of

- Clinical, serologic, morphologic difference
- Possible differences in prognosis and treatment

IPAF sits between the IIPs and CTD-ILDs

프로크루스테스의 침대

감사합니다.