Doença Intersticial Fibrosante Progressiva

Conceito, epidemiologia e abordagem diagnóstica

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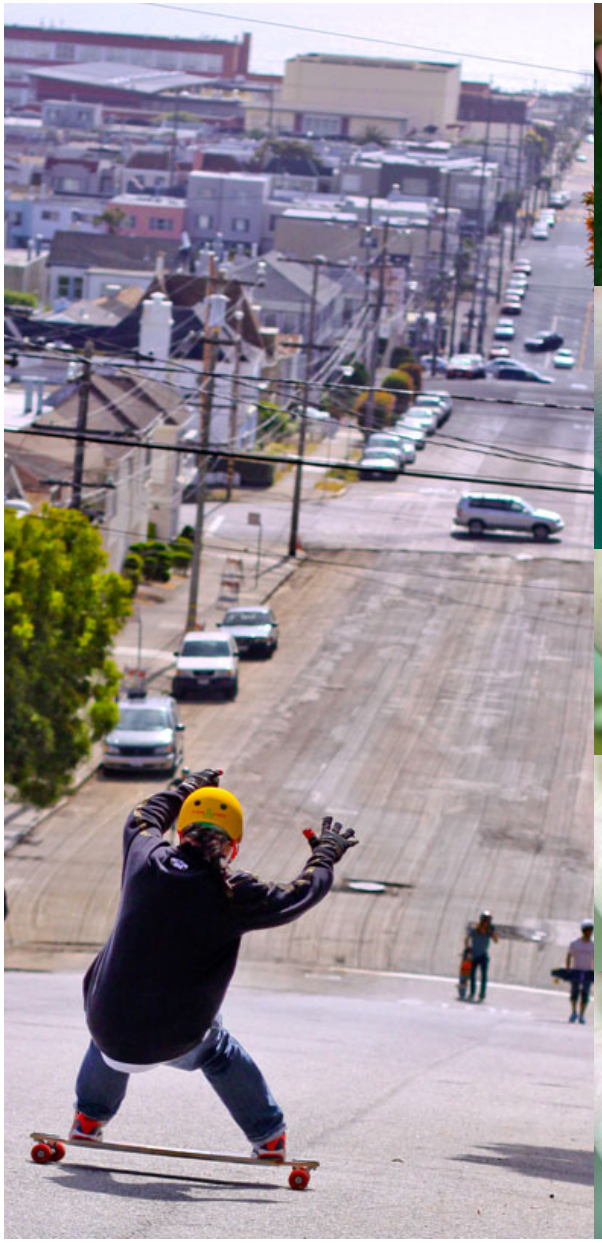
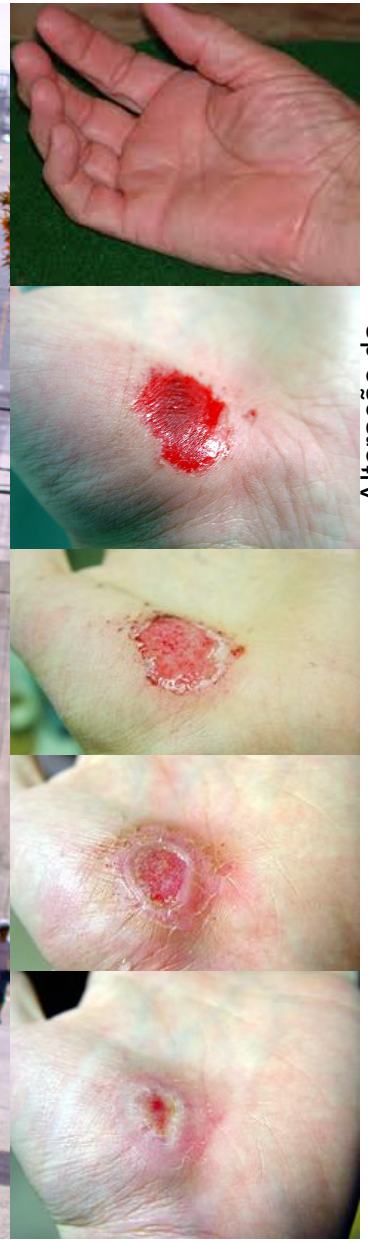
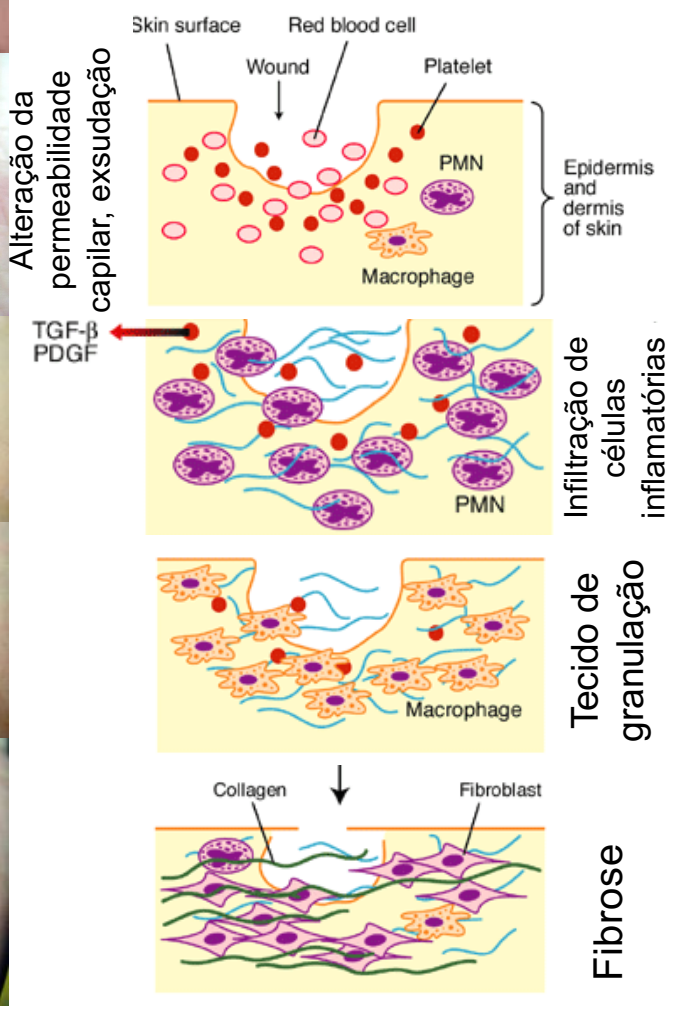
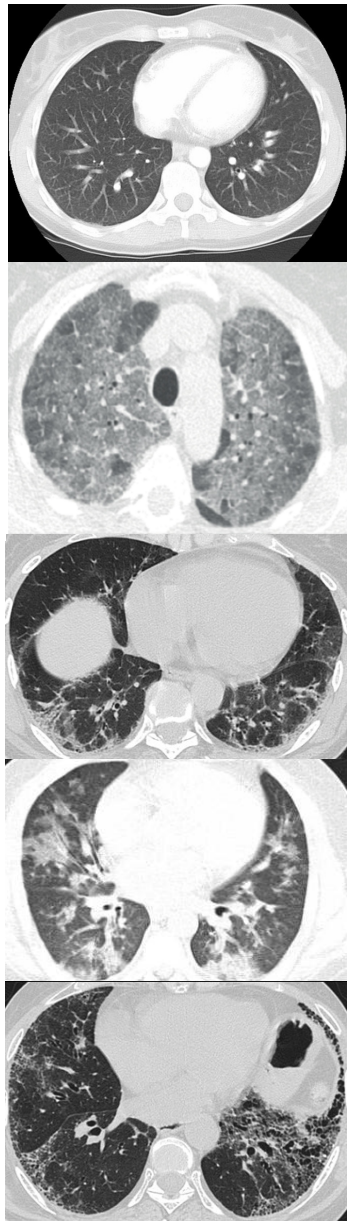


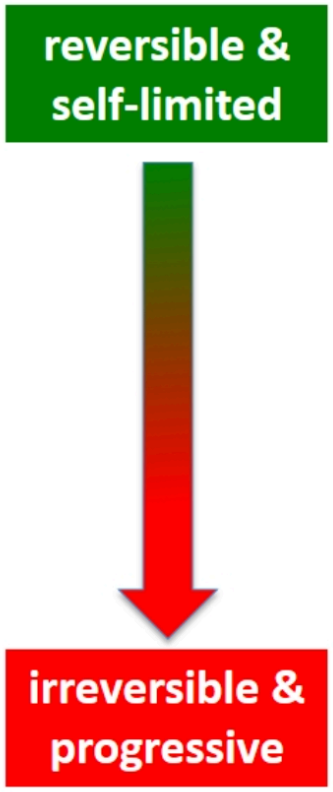



Alteração da permeabilidade capilar, exsudação
Skin surface
Red blood cell
Wound
Platelet
PMN
Epidermis and dermis of skin
Macrophage
TGF-β
PDGF
PMN
Infiltração de células inflamatórias
Macrophage
Tecido de granulação
Collagen
Fibroblast
Fibrose




AIP
NSIP
HP
OP
UIP

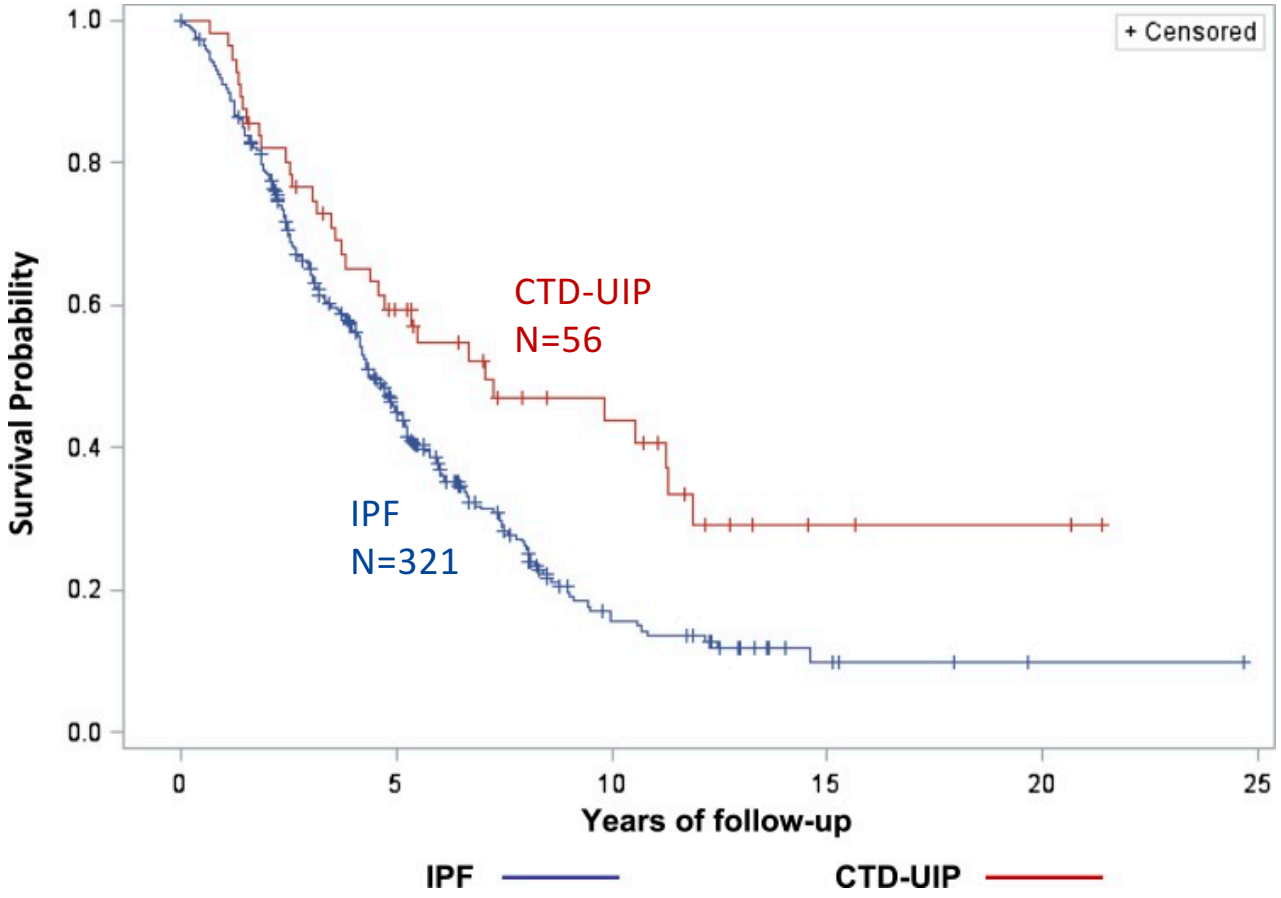
A classificação do comportamento da doença (2013)



CLINICAL BEHAVIOR	TREATMENT GOAL	MONITORING STRATEGY
Reversible and self-limited (e.g. RB-ILD)	**Remove possible cause**	Short-term (3-6 months) observation to confirm disease regression
Reversible with risk of progression (e.g. some NSIP, COP, DIP)	**Initially for a response and then rationalize longer term therapy**	Short-term observation to confirm response: long-term observation to ensure gains are preserved
Stable with residual disease (e.g. some NSIP)	**Maintain status**	Long-term observation to assess disease course
Progressive, irreversible with potential for stabilization (e.g. some NSIP)	**To stabilize**	Long-term (3-6 months) observation to assess disease course
Progressive, irreversible despite therapy (e.g. some NSIP, IPF)	**To slow progression**	Long-term observation to assess disease course and need for transplant or effective palliation

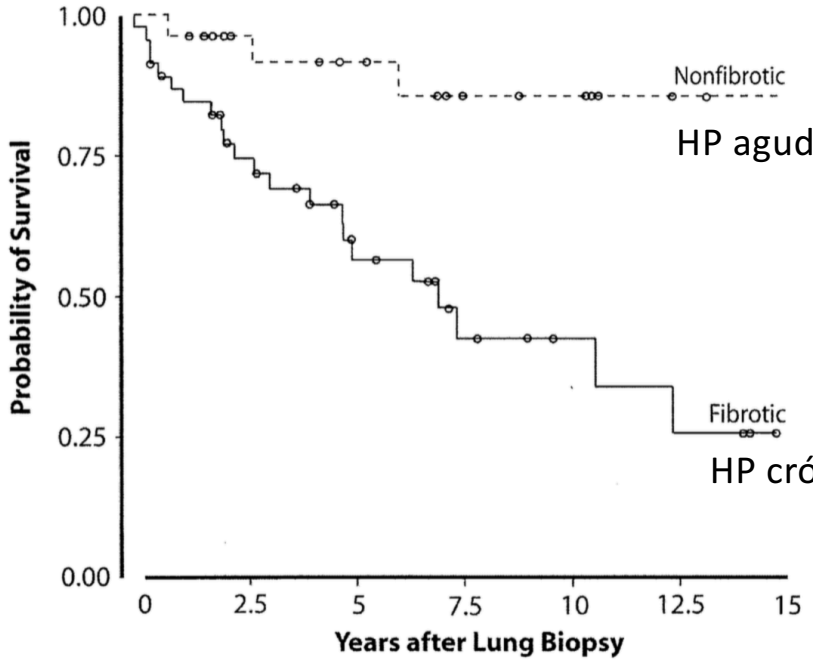
Travis WD et al; Am J Respir Crit Care Med 2013; 88: 733-748

O padrão patológico é um importante marcador de prognóstico



Strand et al. Chest 2014

...também a presença de fibrose na biopsia é um importante marcador de prognóstico



HP aguda/subaguda

HP crónica

Number at Risk				
Nonfibrotic Subjects	26	19	14	10
Fibrotic Subjects	46	28	18	5

Vourlekis JS et al. Am J Med. 2004

A alteração de função respiratória aos 6 meses é um preditor de sobrevida mais forte do que a patologia

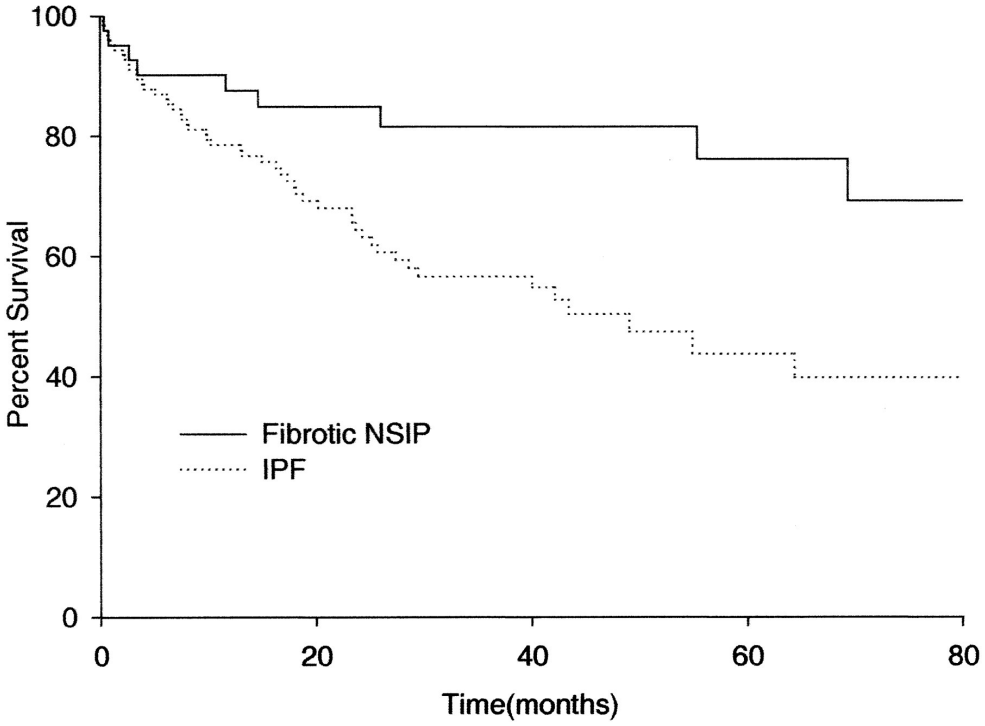


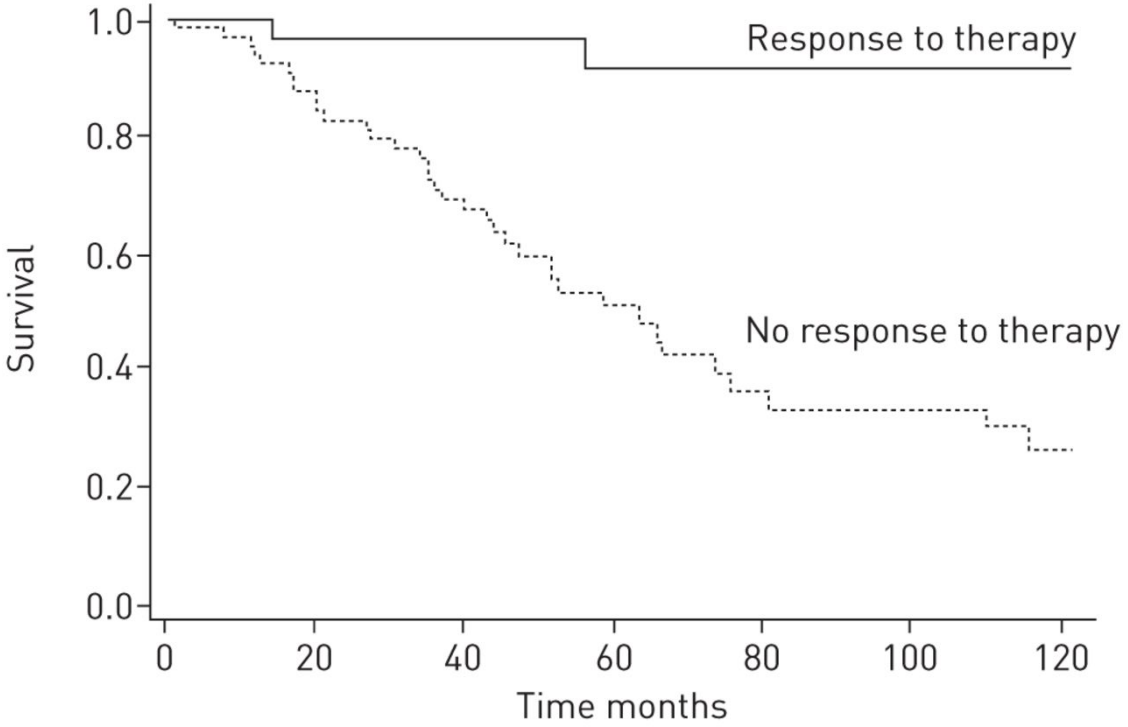
TABLE 7. RESULTS OF MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS OF PATIENTS WITH FIBROTIC NONSPECIFIC INTERSTITIAL PNEUMONIA AND IDIOPATHIC PULMONARY FIBROSIS AFTER 6 MONTHS OF FOLLOW-UP

	Hazard Ratio	95% CI	p Value
Age	1.027	0.992–1.064	0.134
Sex*	2.724	1.277–5.813	0.010
NSIP diagnosis	0.854	0.349–2.093	0.730
Initial FVC, % predicted†	0.987	0.964–1.010	0.262
Initial D_{LCO}, % predicted†	0.972	0.949–0.996	0.022
Six-month change in FVC†	0.925	0.893–0.958	< 0.001
Resting Pa_{O_2}	0.995	0.961–1.031	0.798

Jegal et al. Am J Respir Crit Care Med 2005

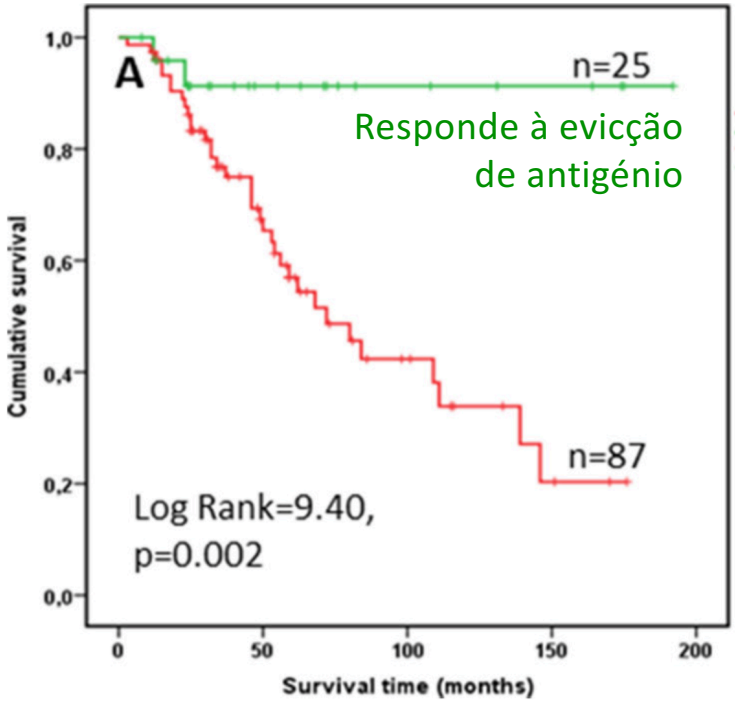
A ausência de resposta inicial à terapêutica de doenças com potencial de reversibilidade/estabilização, associa-se a um padrão clínico idêntico à IPF

NSIP (n=127)



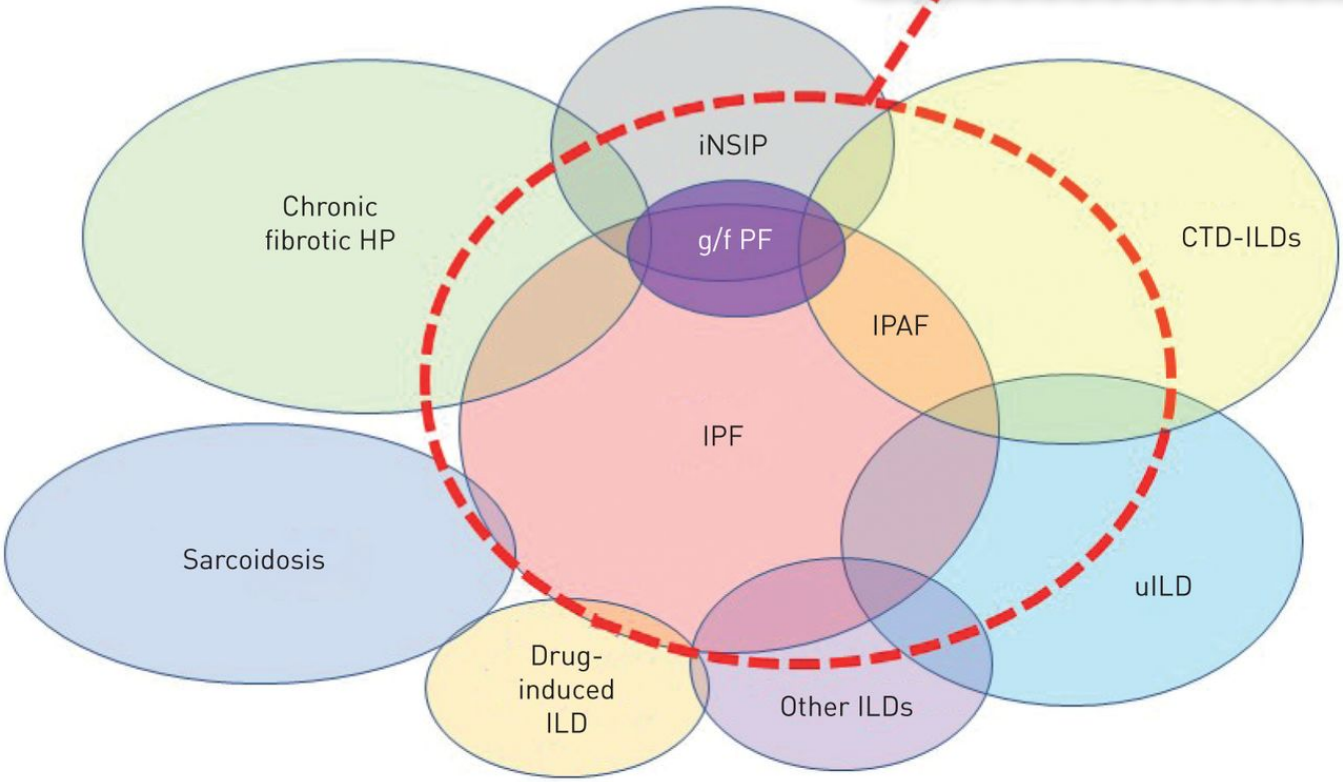
Nunes H, et al. Eur Resp J 2015

cPH (n=112)



Gimenez A, et al. Thorax 2017

"progressive fibrosing interstitial lung disease (PF-ILD)"[1]



(1) Flaherty KR, et al. BMJ Open Respir Res 2017; 4: e000212 | (Figura) Cottin V. Eur Respir Rev 2019;28:190109 | (Legendas) Olson AL, et al. Eur Respir Rev 2018; 27:180077

ORIGINAL ARTICLE
INTERSTITIAL LUNG DISEASES

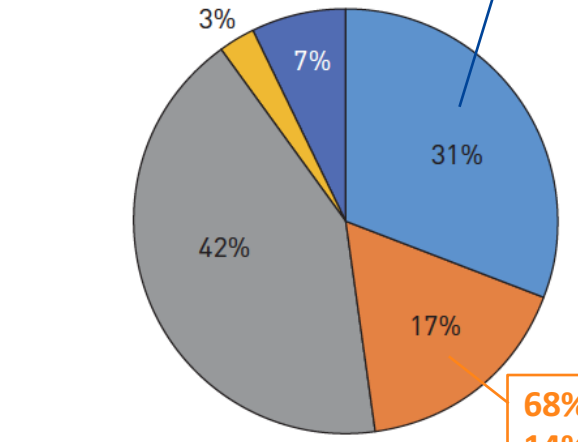
Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris

Boris Duchemann[1,2], Isabella Annesi-Maesano[3], Camille Jacobe de Naurois[4], Shreosi Sanyal[3], Pierre-Yves Brillet[2,5], Michel Brauner[5], Marianne Kambouchner[6], Sophie Huynh[7], Jean Marc Naccache[8], Raphael Borie[9], Jacques Piquet[10], Arsène Mekinian[11], Jerôme Virally[7], Yurdagul Uzunhan[1,2], Jacques Cadranel[8], Bruno Crestani[9], Olivier Fain[11], Francois Lhote[12], Robin Dhote[13], Nathalie Saidenberg-Kermanac'h[14], Paul-André Rosental[15], Dominique Valeyre[1,2] and Hilario Nunes[1,2]

TABLE 2 Crude prevalence and incidence of interstitial lung diseases (ILDs) in Seine-Saint-Denis (reviewed cases)

ILD cases	Population >15 years of age#				
	Subjects n	Prevalence per 100000	Subjects n	Incidence per 100000 per year	
All identified cases	1170	97.9	232	19.4	
Reviewed cases	848	71.0	219	18.3	
ILDs of known cause	260	21.8	77	6.5	
CTDs/vasculitis	145	12.1	39	3.3	17.1%
Pneumoconioses	42	3.5	9	0.8	5%
Drug-induced ILDs	31	2.6	14	1.2	
HP	28	2.3	11	0.9	3.3%
Radiation-induced pneumonitis	7	0.6	1	0.1	
Others¶	7	0.6	2	0.3§	
IIPs	145	12.14	52	4.4	
IPF	98	8.2	33	2.8	11.6%
NSIP	20	1.7	10	0.8	2.3%
Desquamative interstitial pneumonia	10	0.8	3	0.3	
Organising pneumonia	9	0.8	1	0.1	
Unclassified (despite SLB)	6	0.5	5	0.4	0.7%
RBILD	2	0.2	0	0.0	
LIP	0	0.0	0	0.0	
Sarcoidosis	361	30.2	58	4.9	42.6%
Particular ILDs	22	1.8	10	0.8	
LAM	9	0.8	4	0.3	
CIEP	5	0.4	1	0.1	
PLCH	4	0.3	2	0.2	
PAP	2	0.2	1	0.1	
Others+	2	0.2	2	0.1	
Undetermined diagnosis	60	5.0	22	1.8	7.1%
Differential diagnosis between IPF and NSIP	34	2.9	13	1.1	

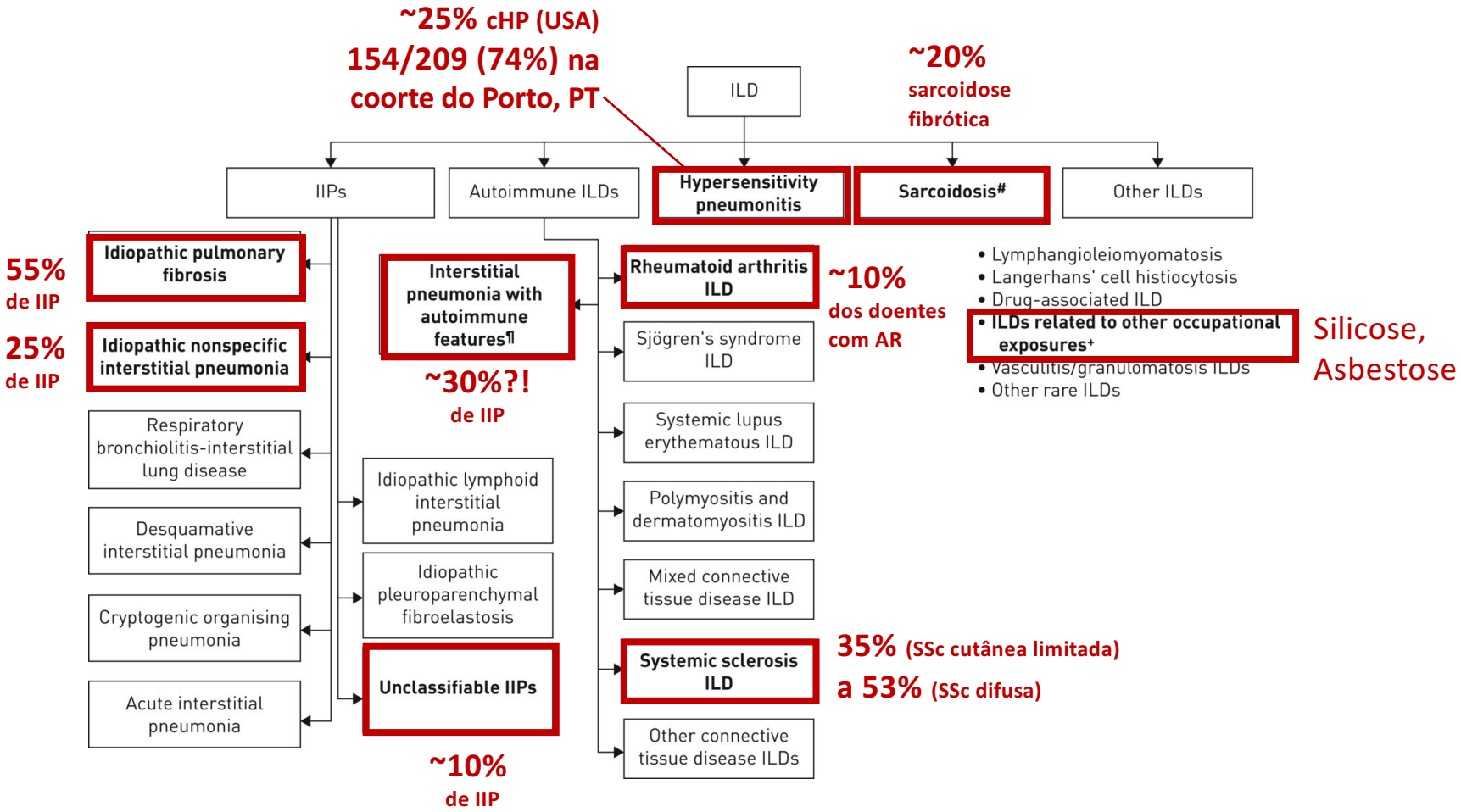
56% CTDs/vasculitis ILDs
16% Pneumoconioses
12% Drug-induced ILDs
11% HP
3% Radiation-induced pneumonitis



68% IPF
14% iNSIP
7% DIP
6% OP
4% uILD

Duchemann et al. Eur Respir J 2017; 50: 1602419 (Paris, Fr)

Doenças Pulmonares Difusas com maior probabilidade em apresentar fenótipo fibrosante progressivo



Cottin V et al. Eur Respir Rev 2018;27:180076 | Walker UA, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis 2007;66:754-63 | Oldham JM, et al. Characterization of patients with interstitial pneumonia with autoimmune features. Eur Respir J 2016;47:1767–1775 | Fernandez Perez ER, et al. Epidemiology of hypersensitivity pneumonitis among aninsured population in the United States: a claims-based cohort analysis. Ann Am Thorac Soc 2018; 15: 460–469| Santos V et al. Hypersensitivity pneumonitis: Main featurescharacterization in a Portuguese cohort. Pulmonology 2019

TABLE 2 Characteristics of unclassifiable interstitial lung disease patients

Country	Years	Unclassifiable n/total N (%)	With surgical biopsy %	Male %	Age years	FVC %	D_{LCO} %
Spain	1995–2004	73/500 (14.6)	26.2	47	66.7±13.6		
China	1999–2009	38/251 (15.1)	100				
Spain	2000–2001	26/511 (5.1)	22.7				
USA	2000–2011	132/1370 (9.6)	31	53	67.8±12.9	69.0±22.1	47.6±19.7
Denmark	2003–2009	62/431 (14)	34	45	59.3±14.5	73.7±22.8	55.8±21.4
Australia	2011–2013	23/232 (9.9)					

Data are presented as mean±SD, unless otherwise stated. Blank cells represent data that were not reported. FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide. Reproduced and modified from [39] with permission.

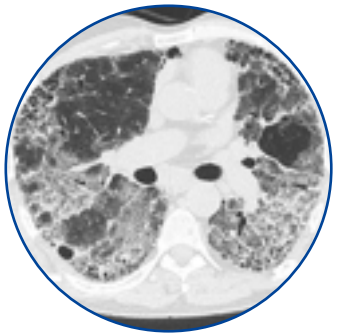
What's in a name? That which we call IPF, by any other name would act the same

AU Wells

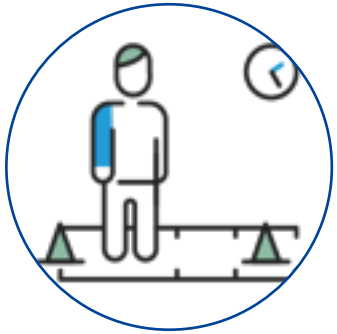
… meaning, how the term "progressive" should be defined?

Critérios propostos para definir PROGRESSÃO de doenças pulmonares difusas fibróticas

- Taxa declínio FVC (mL/ano)
- Variação absoluta ou relativa em FVC (mL ou %prev)
- Variação absoluta ou relativa em DLCO (%prev)



- Exacerbação aguda
- Hospitalização por causa respiratória
- Alteração da extensão ou textura das áreas fibróticas
- Alteração quantitativa do score de fibrose na TCAR



- Variação absoluta 6MWD
- Dessaturação (nadir) na 6MWT

- Início de oxigenoterapia de ambulatório em exercício
- Início de oxigenoterapia de ambulatório em repouso
- Alteração no débito de O2

- Agravamento dos sintomas
- Alteração da capacidade de exercício nas AVDs
- Questionários de gravidade da dispneia, tosse ou QoL

- Não validado e indisponível na prática clínica
- (PROFILE study, INMARK trial)

Collagen synthesis neoepitopes:
PRO-C3 (collagen type 3)
PRO-C6 (collagen type 6)

CRPM
C3M
CRP
KL-6
SP-D

ORIGINAL ARTICLE

Relative versus absolute change in forced vital capacity in idiopathic pulmonary fibrosis

Luca Richeldi,[1,2] Christopher J Ryerson,[3] Joyce S Lee,[2] Paul J Wolters,[2] Laura L Koth,[2] Brett Ley,[2] Brett M Elicker,[4] Kirk D Jones,[5] Talmadge E King Jr,[2] Jay H Ryu,[6] Harold R Collard[2]

Definition	Example of a 10% decline
Relative change of %-predicted FVC value	From 60% to 54% *
Absolute change in %-predicted FVC value	From 60% to 50%

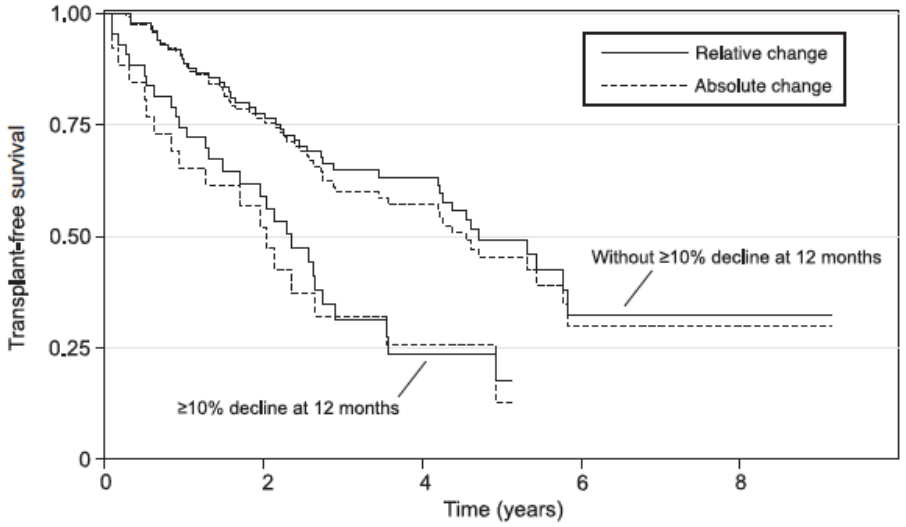
***Alteração relativa = $FVC_{baseline}$—$FVC_{12\ months}$/$FVC_{baseline}$,** using either FVC in litres or % predicted FVC

Table 2 Frequency of ≥5%, ≥10% and ≥15% decline in FVC at 12 months

Method of calculation	12-month FVC decline ≥5%	≥10%	≥15%
Whole cohort (n=142)			
Relative change	70 (49.3)	43 (30.3)	30 (21.1)
Absolute change	52 (36.6)	26 (18.3)	11 (7.7)
p Value for difference between methods	<0.001	<0.001	<0.001

Table 3 Relationship between decline in FVC at 12 months and transplant-free survival at 2 years

Method of calculation	12-month FVC decline of ≥5% OR (95% CI)	Adjusted OR* (95% CI)	12-month FVC decline of ≥10% OR (95% CI)	Adjusted OR* (95% CI)
Whole cohort (n=142)				
Relative change	2.09 (0.96 to 4.55)	2.76 (0.98 to 7.80)	2.47 (1.10 to 5.53)	3.39 (1.14 to 10.07)
Absolute change	2.04 (0.93 to 4.48)	5.21 (1.64 to 16.60)	3.10 (1.22 to 7.89)	4.52 (1.27 to 16.12)



Richeldi L, et al. Thorax (2012). doi:10.1136/thoraxjnl-2011-201184

Declínio FVC ≥10% associa-se a um aumento de cerca 2x a probabilidade de morte

TABLE 4. PROGNOSTIC EFFECT OF PREDICTOR WHEN IN COX MODEL ADJUSTED FOR INITIAL VALUE OF PREDICTOR IN UNIVARIATE ANALYSES OF DATA FOR PATIENTS WITH USUAL INTERSTITIAL PNEUMONIA

Predictor	n	Hazard Ratio	95% CI	p Value	LR p Value*
6-Month change					
FVC change, %	75				0.05
> 10% increase		0.89	(0.36, 2.24)	0.81	
10% decrease/10% increase		1.00	REF	REF	
> 10% decrease		2.06	(1.09, 3.89)	0.03	
TLC change, %	66				0.33
> 10% increase		1.51	(0.63, 3.65)	0.36	
10% decrease/10% increase		1.00	REF	REF	
> 10% decrease		1.68	(0.82, 3.44)	0.16	
D_{LCO} change, %	66				0.03
> 10% increase		2.49	(1.15, 5.39)	0.02	
10% decrease/10% increase		1.00	REF	REF	
> 10% decrease		0.95	(0.44, 2.05)	0.89	
CT-alv change, %	60				0.01
> 10% increase		2.88	(1.26, 6.57)	0.01	
10% decrease/10% increase		1.00	REF	REF	
> 10% decrease		0.81	(0.30, 2.21)	0.68	
CT-fib change, %	60				0.18
> 10% increase		1.09	(0.48, 2.47)	0.84	
10% decrease/10% increase		1.00	REF	REF	
> 10% decrease		0.46	(0.18, 1.16)	0.13	
12-Month change					
FVC change, %	59				0.15
> 10% increase		0.66	(0.15, 2.86)	0.58	
10% decrease/10% increase		1.00	REF	REF	
> 10% decrease		1.70	(0.76, 3.81)	0.20	
TLC change, %	31				0.29
> 10% increase		0.59	(0.09, 3.67)	0.57	
10% decrease/10% increase		1.00	REF	REF	
> 10% decrease		1.50	(0.31, 7.13)	0.61	
D_{LCO} change, %	35				0.82
> 10% increase		0.62	(0.09, 4.24)	0.63	
10% decrease/10% increase		1.00	REF	REF	
> 10% decrease		0.65	(0.18, 2.43)	0.53	

CT-alv = high-resolution computed tomography score for ground glass;

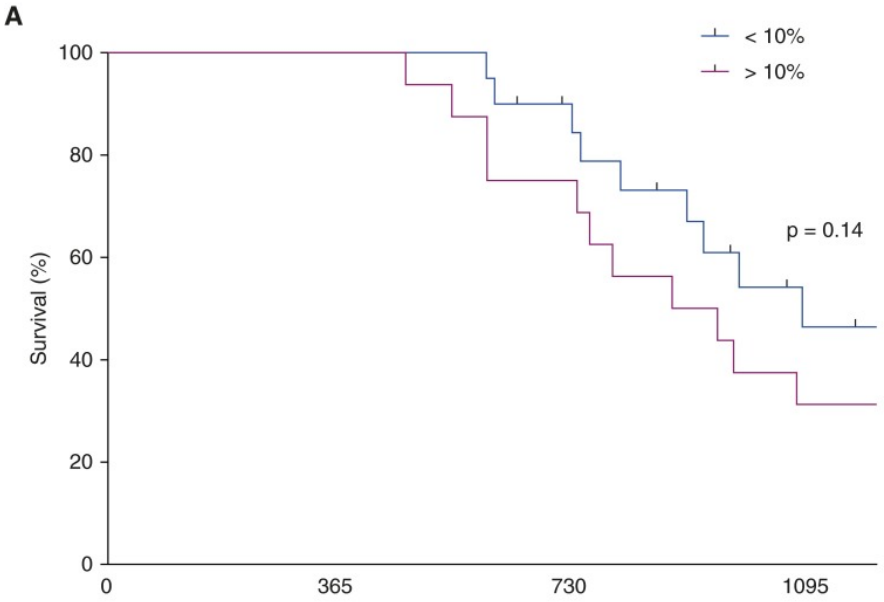
Flaherty KR, et al.Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. Am J Respir Crit Care Med 2003;168:543–8

Table 4—*Mortality According to Greatest Change in Physiologic Parameters During the Study Period in Patients Receiving Placebo

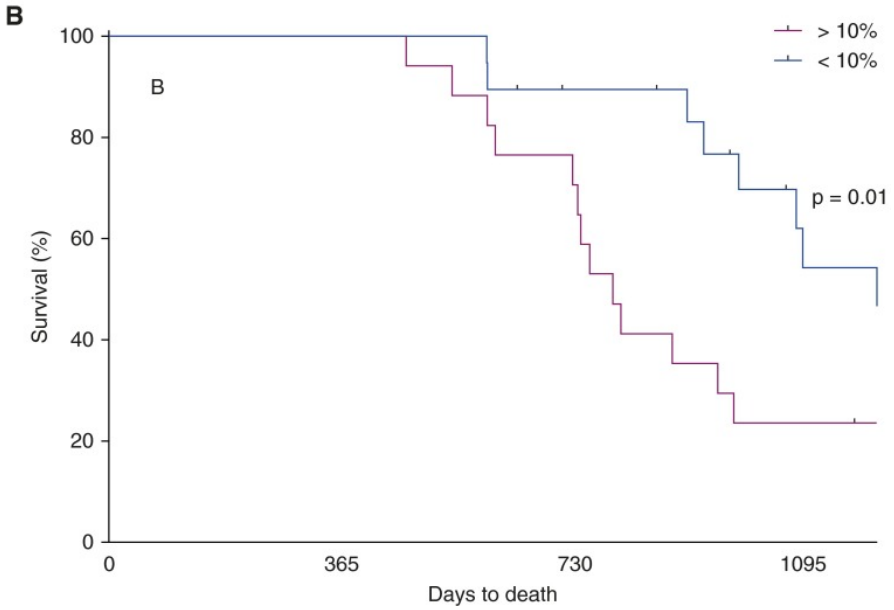
Variables	Total No. of Deaths/Total No. of Patients (%)	Relative Risk of Death
Change from baseline in $P(A\text{-}a)O_2$, mm Hg		
No change or improvement†	3/22 (14)	1.0
1–4 increase	4/38 (11)	0.8
5–9 increase	0/27 (0)	NA
10–14 increase	5/37 (14)	1.0
≥ 15 increase	13/39 (33)	2.4
Missing‡	3/5 (60)	4.3
Change from baseline in % predicted FVC, %		
No change or improvement†	3/24 (13)	1.0
1–4 decrease	1/41 (2)	0.2
5–9 decrease	6/49 (12)	0.9
≥ 10 decrease	15/49 (31)	2.4
Missing‡	3/5 (60)	4.6
Change from baseline in % predicted DLCO, %		
No change or improvement†	5/26 (19)	1.0
1–4 decrease	2/46 (4)	0.2
5–9 decrease	9/44 (20)	1.1
10–14 decrease	3/23 (13)	0.7
≥ 15 decrease	5/23 (22)	1.2
Missing‡	4/6 (67)	3.5

King et al. Analyses of Efficacy End Points in a Controlled Trial of Interferon-1b for Idiopathic Pulmonary Fibrosis. CHEST 2005; 127:171–177

Hospital-measured FVC



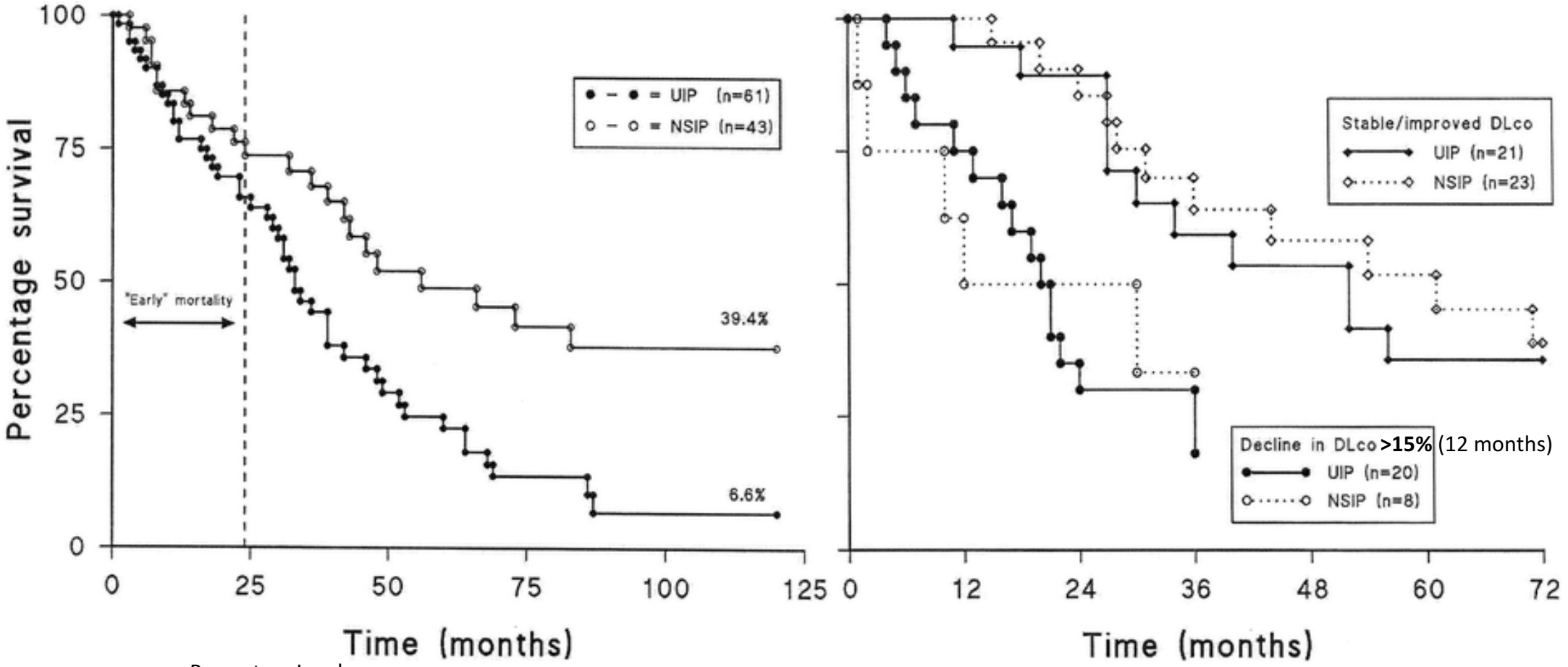
Home-based FVC



- Daily spirometry was recorded by 50 subjects for a median period of 279 days (range, 13–490 d)
- Home spirometry showed excellent correlation with hospital-obtained readings
- **The relationship between mortality and rate of change of FVC at 3 months suggests that daily FVC may be of value as a primary endpoint in short proof-of-concept IPF studies**

Russel et al. Daily Home Spirometry: An Effective Tool for Detecting Progression in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2016

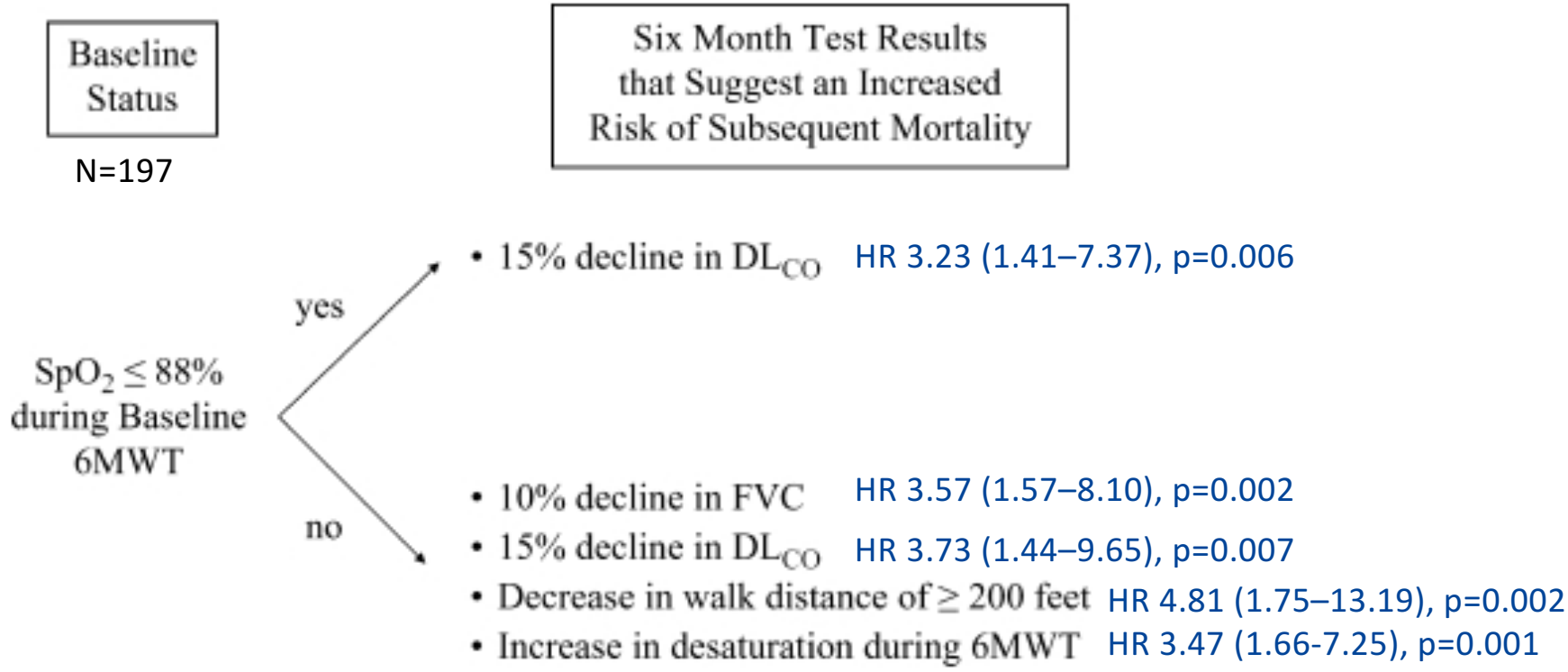
Declínio DLCO ≥15% também tem valor prognóstico, mas é menos reprodutível



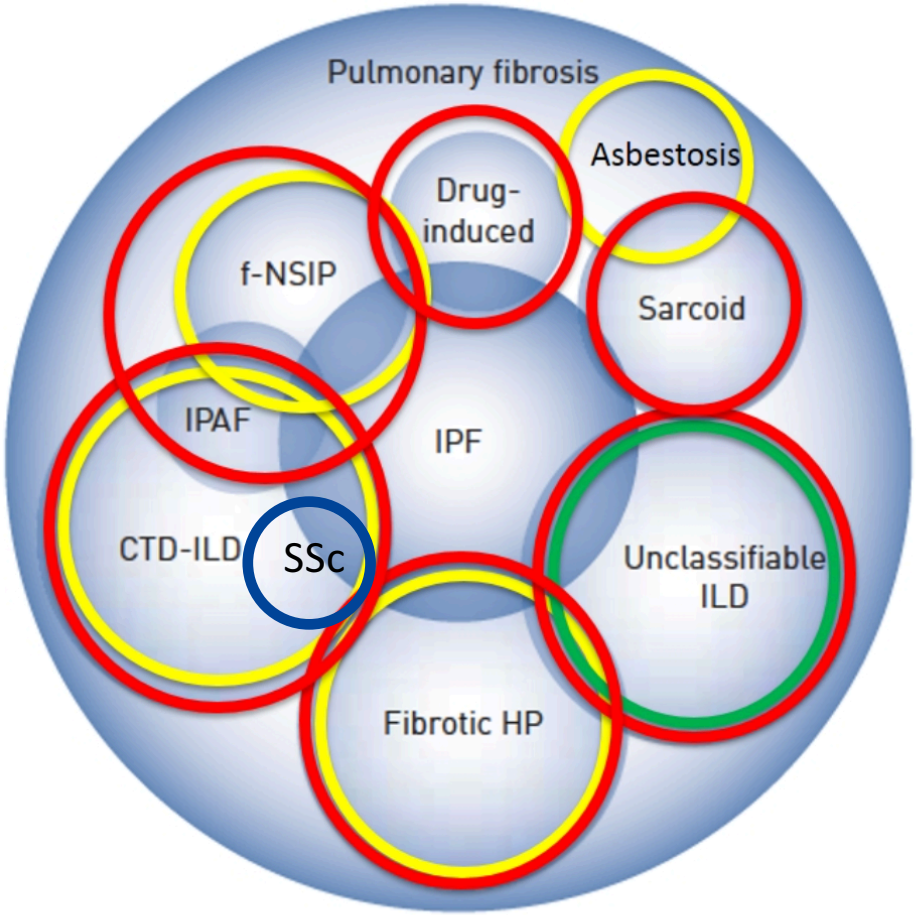
Brompton, Londres

Latsi PI, du Bois RM, Nicholson AG, et al. Fibrotic idiopathic interstitial pneumonia:the prognostic value of longitudinal functional trends. Am J Respir Crit Care Med 2003;168:531–7

O valor prognóstico da prova de marcha de 6 min



Flaherty KR, et al. Idiopathic pulmonary fibrosis: prognostic value of changes in physiology and six-minute-walk test. Am J Respir Crit Care Med 2006;174:803–9.



Wells AU. Eur Respir J 2018

Flaherty KR et al. N Engl J Med. 2019 (INBUILD)

Fibrose >10% do volume pulmonar em TCAR, FVC ≥45%, DLCO 30-80%

- Declínio relativo ≥10% de FVC (pred%) nos últimos 24 meses
- Declínio relativo 5-10% de FVC (pred%) + agravamento dos sintomas respiratórios nos últimos 24m
- Declínio relativo 5-10% de FVC (pred%) + aumento da extensão de fibrose na TCAR nos últimos 24m
- Agravamento dos sintomas respiratórios + aumento da extensão de fibrose na TCAR nos últimos 24m

Distler O et al. N Engl J Med. 2019 (SENSIS)

Fibrose >10% do volume pulmonar em TCAR, FVC ≥40%, DLCO 30-89%

Guenther A et al. Eur Respir J. 2019 (RELIEF)

FVC 40-90%, DLCO 30-90%, 6MWD ≥150 m

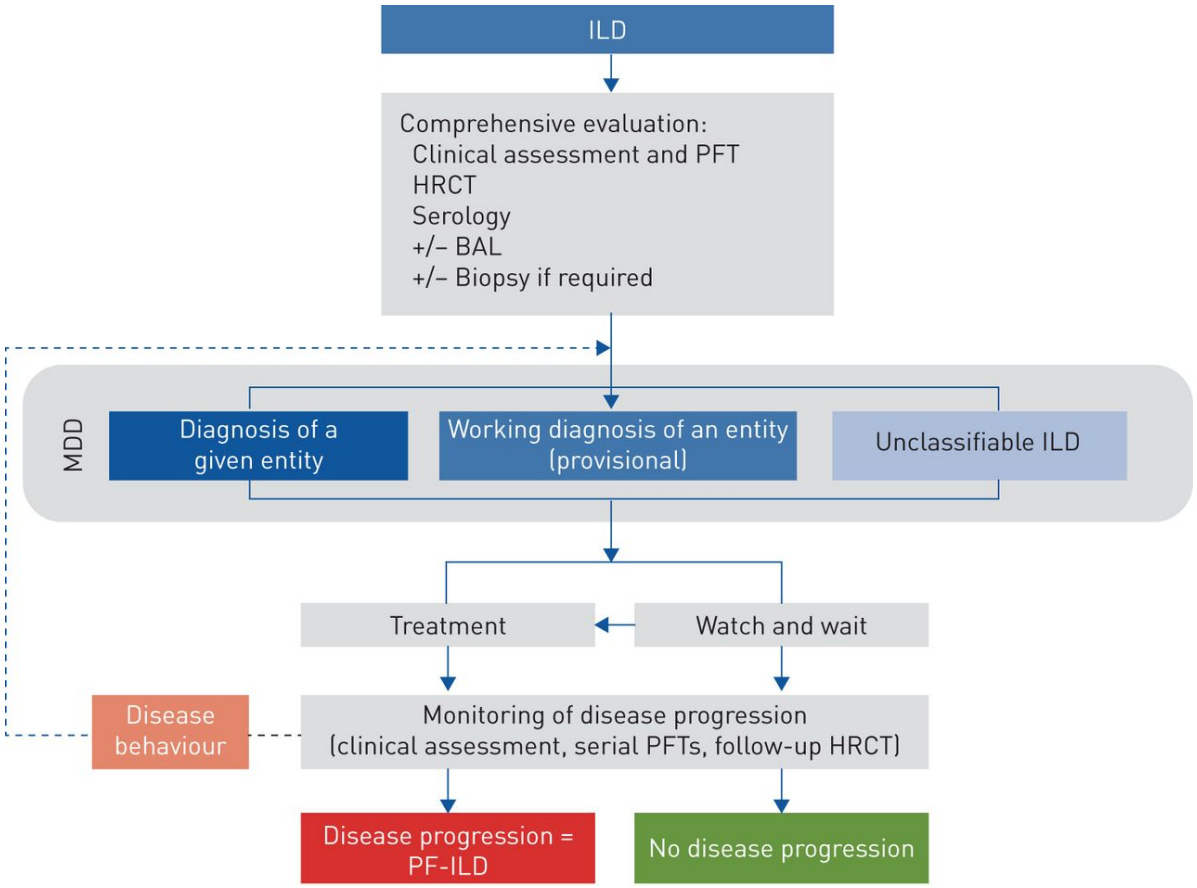
- Declínio absoluto FVC >5% por ano (através do cálculo do declive de pelo menos 3 valores de FVC nos últimos 6 meses), apesar de tratamento optimizado

Maher T et al. Lancet Respir Med. 2019 (uILD)

Fibrose >10% do volume pulmonar em TCAR, FVC ≥45%, DLCO ≥30%, 6MWD ≥150 m

- Declínio absoluto FVC >5% nos 6 meses prévios
- Agravamento sintomático significativo nos 6 meses prévios

Diagnosis of fibrosing interstitial lung diseases (ILDs) that may present a progressive phenotype



Vincent Cottin Eur Respir Rev 2019;28:190109

Doença Intersticial Fibrosante Progressiva

100% conhecido

100% desconhecido

50/50

Declínio da função respiratória
Agravamento da dispneia
Deterioração da qualidade de vida
Mortalidade precoce

Marcadores/preditores da progressão da doença

Mecanismos patogénicos comuns

Como se avalia a resposta ao tratamento

Fibrose auto-perpetuada

Papel da imunossupressão

Selecção dos doentes para tratamento anti-fibrótico

DPD	Anos, local	Incidência por 100.000/ano	Referência
IPF	2000–2012, UK	8.65	Maher, 2013
	2006–2012, USA	14.6	Esposito, 2015
	1997–2007, Taiwan	1.4	Lai, 2012

DPD	Local	Prevalência por 100.000 hab	Referência
IPF	Canadá	41.8	Hopkins, 2016
	EUA	58.7	Esposito, 2015
	Paris, França	8.2	Duchemann, 2017
iNSIP		1-9	Flaherty, 2006
uILD	Paris, França	0.5	Duchemann, 2017