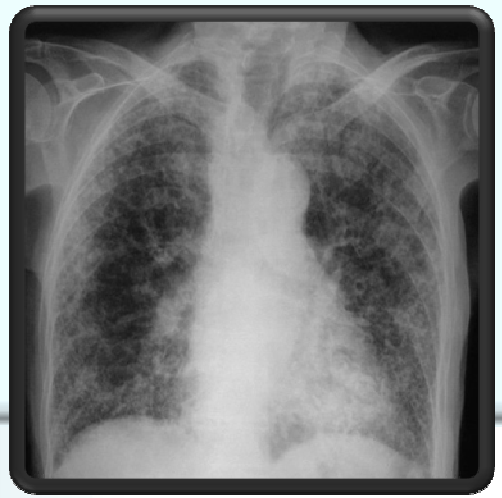
VII Reunión Nacional de Actualización en Enfermedades Autoinmunes Sistémicas para Residentes

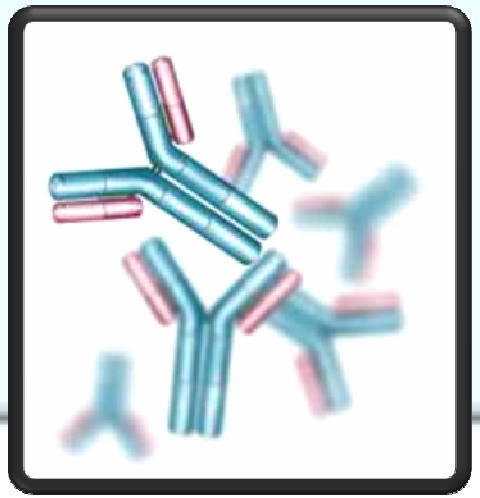
SEMI
LA VISIÓN GLOBAL DE LA PERSONA ENFERMA

GEAS

Vall d'Hebron Hospital

PERFIL INMUNOLÓGICO Y AFECCIÓN PULMONAR EN LA ESCLERODERMIA





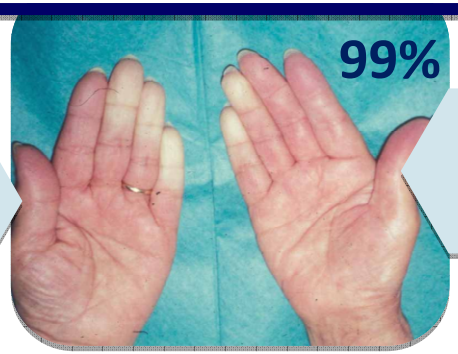
Alfredo Guillén del Castillo

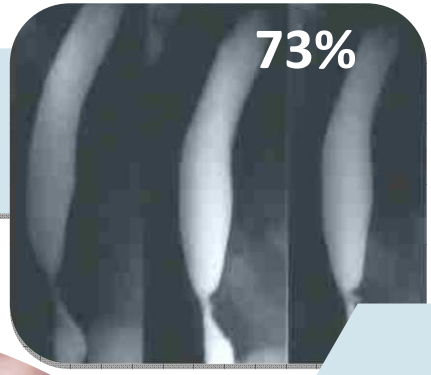
19 de Octubre de 2013- Zaragoza

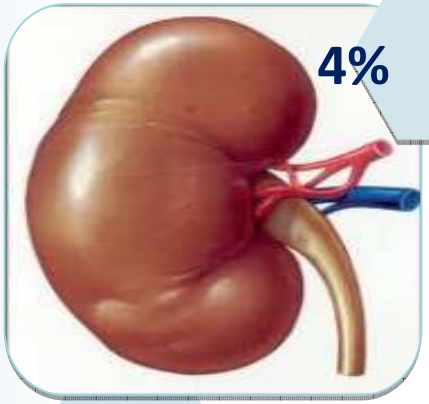
Unidad de Enfermedades Autoinmunes Sistémicas

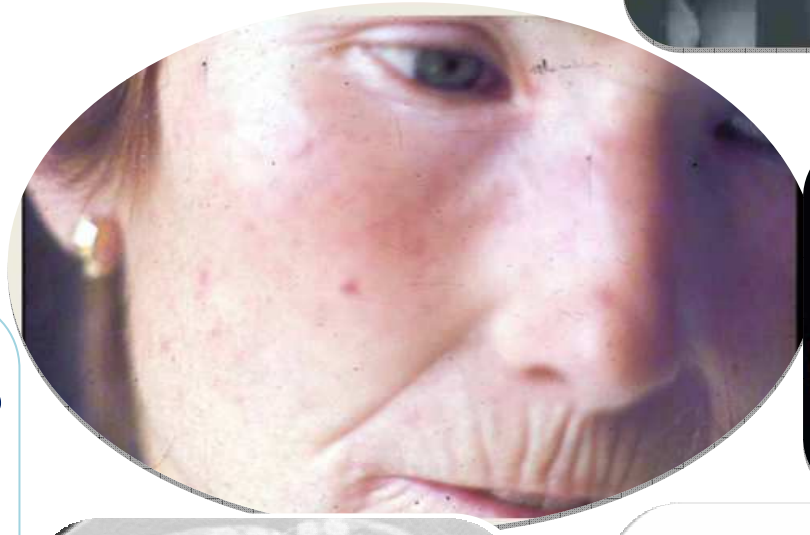
Hospital Vall d'Hebron, Barcelona

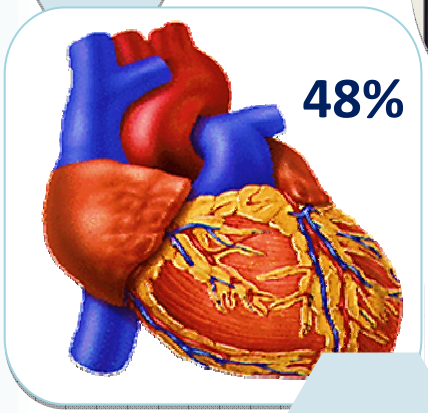
Esclerosis Sistémica (ES):

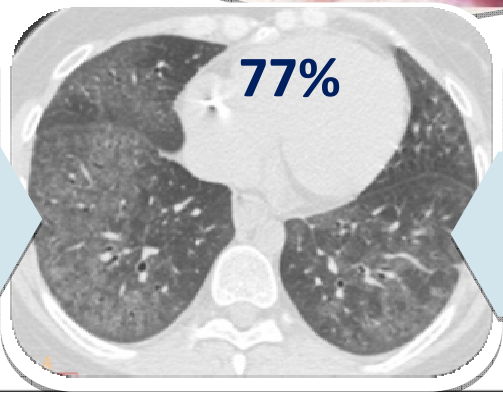


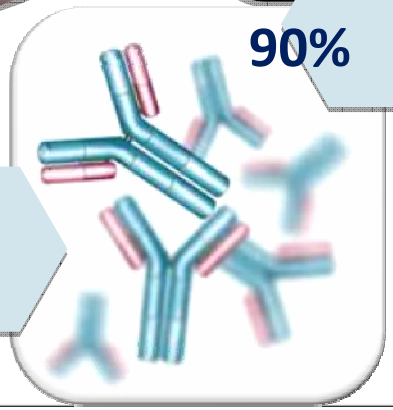




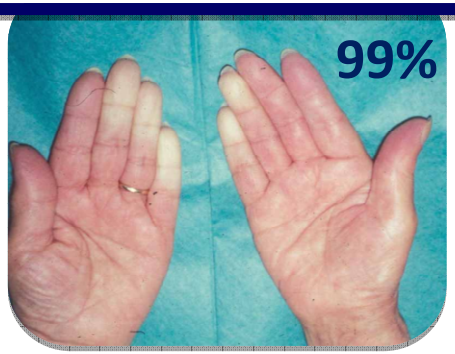


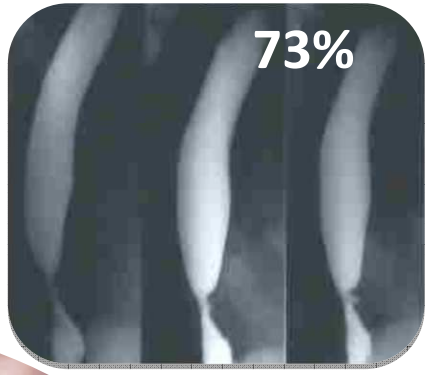


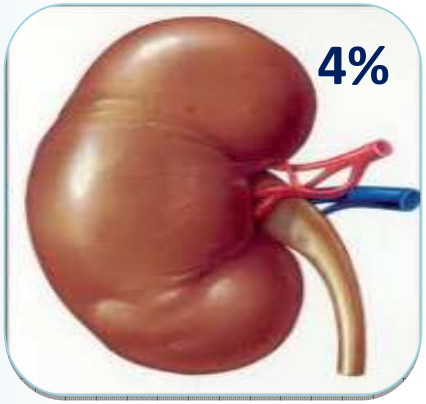


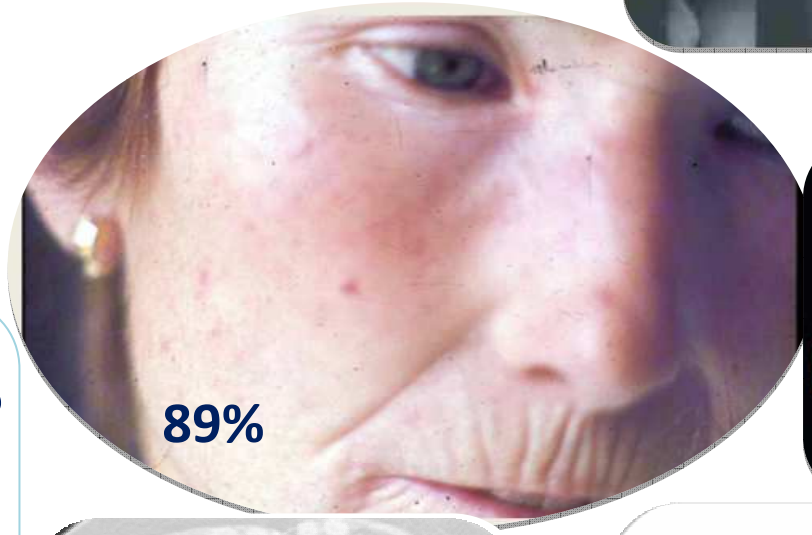


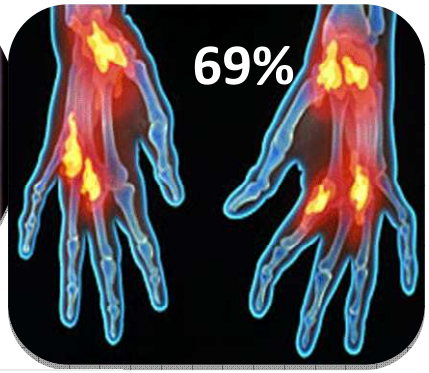
Esclerosis Sistémica (ES):

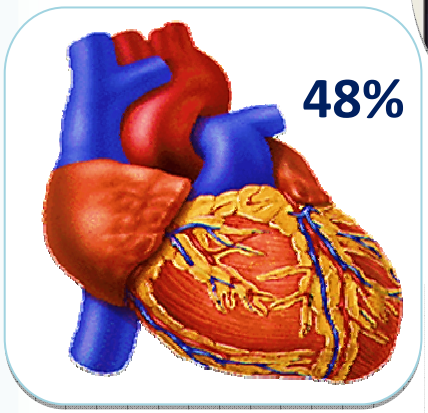


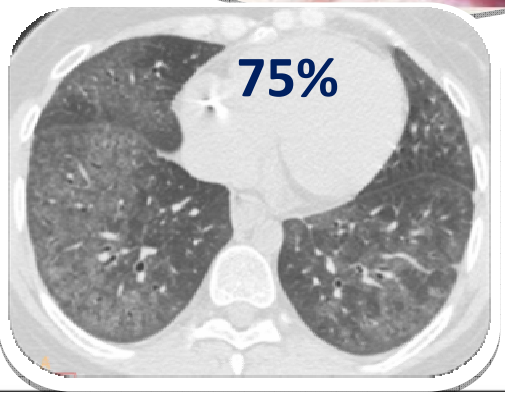


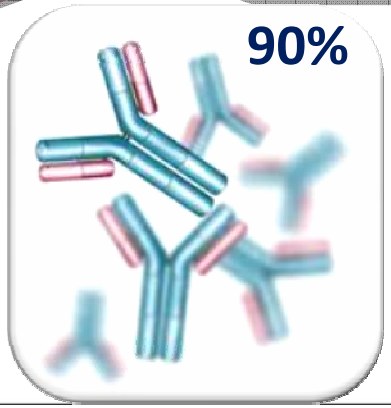












Registry of the Spanish Network for Systemic Sclerosis: Clinical Pattern According to Cutaneous Subsets and Immunological Status

Table 2 Cumulative Clinical Manifestations Among Patients with SSc Patients According to Their Cutaneous Subsets

	a lcSSc (%)	b dcSSc (%)	c ssSSc (%)	*P* Value a vs b	*P* Value a vs c	*P* Value b vs c
Osteomuscular	318 (56.6)	154 (63.4)	36 (52.2)	ns	ns	ns
Arthritis	81 (14.4)	66 (27.2)	9 (13)	<0.0001	ns	0.016
Myositis	25 (4.4)	34 (14)	2 (2.9)	<0.0001	ns	ns
Tendon friction rubs	14 (2.5)	28 (11.5)	1 (1.4)	<0.0001	ns	0.008
Acrosteolysis	46 (8.2)	37 (15.2)	1 (1.4)	0.0004	0.049	0.001
Digestive involvement	392 (69.8)	195 (80.2)	49 (71)	0.002	ns	ns
Esophagus	322 (57.3)	173 (71.2)	31 (44.9)	<0.0001	ns	<0.0001
Gastric	60 (10.7)	41 (16.9)	7 (10.1)	0.02	ns	ns
Malabsortion	9 (1.6)	13 (5.3)	1 (1.4)	0.004	ns	ns
PBC	24 (4.2)	0 (0)	7 (10)	<0.0001	ns	<0.0001
Lung involvement	315 (56)	197 (81.1)	49 (71)		<0.0001	0.02	ns
Dyspnea	169 (30.1)	136 (56)	28 (40.6)		<0.0001	ns	ns
ILD	221 (39.3)	170 (70)	27 (39.1)		<0.0001	ns	<0.0001
FVC ≤70%	70 (12.5)	87 (35.8)	15 (21.7)		<0.0001	ns	0.042
FVC (%) (mean ± SD)	90.7 ± 22.7	74.9 ± 22	83.1 ± 21.7		<0.0001	0.021	0.016
DLCO/VA (%) (mean ± SD)	76.5 ± 23.2	74.8 ± 22.5	70.1 ± 18.3		ns	ns	ns
Ground-glass pattern	62 (11)	77 (31.7)	9 (13)		<0.0001	ns	0.008
Reticular pattern	84 (14.9)	92 (37.9)	10 (14.5)		<0.0001	ns	<0.0001
PAH	91 (16.2)	53 (21.8)	17 (24.6)		ns	ns	ns
Isolated PAH#	30 (8.8)	10 (13.7)	3 (7.1)		ns	ns	ns
Ischemia	56 (10)	20 (8.2)	15 (21.7)	ns	0.007	0.004
Conduction alteration	67 (11.9)	25 (10.3)	10 (14.5)	ns	ns	ns
SRC	4 (0.7)	19 (7.8)	1 (1.4)	<0.0001	ns	ns
Sicca syndrome	211 (37.5)	80 (32.9)	10 (14.5)	ns	<0.0001	0.003
Capillaroscopy (n = 600)	383 (68.1)	131 (53.9)	54 (78.3)			
Slow pattern	231 (61.6)	50 (38.2)	37 (68.5)	<0.0001	<0.002	<0.0001
Active pattern	114 (30.4)	78 (59.5)	4 (7.4)	<0.0001	<0.002	<0.0001
Death	66 (11.7)	63 (25.9)	6 (8.7)	<0.0001	ns	0.002

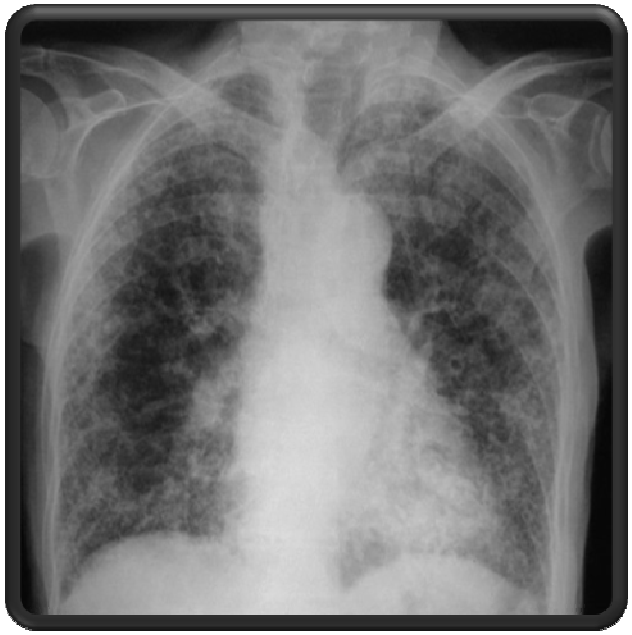
lcSSc, limited cutaneous systemic sclerosis; dcSSc, diffuse cutaneous systemic sclerosis; ssSSc, systemic sclerosis sine scleroderma; PBC, primary biliary cirrhosis; ILD, interstitial lung disease; FVC, forced vital capacity; DLCO/VA, diffusing capacity for carbon monoxide corrected by alveolar volume; PAH, pulmonary arterial hypertension; PAPs, systolic pulmonary arterial pressure, measured by echocardiography; PAPm, mean pulmonary arterial pressure, measured by right-sided heart catheterization; VTR, peak velocity of tricuspid regurgitation in meters/s; SCR, scleroderma renal crisis. #Results in patients without ILD.

Simeón-Aznar (GEAS), Semin Arthritis Rheum. 2012

Afección pulmonar en ES:

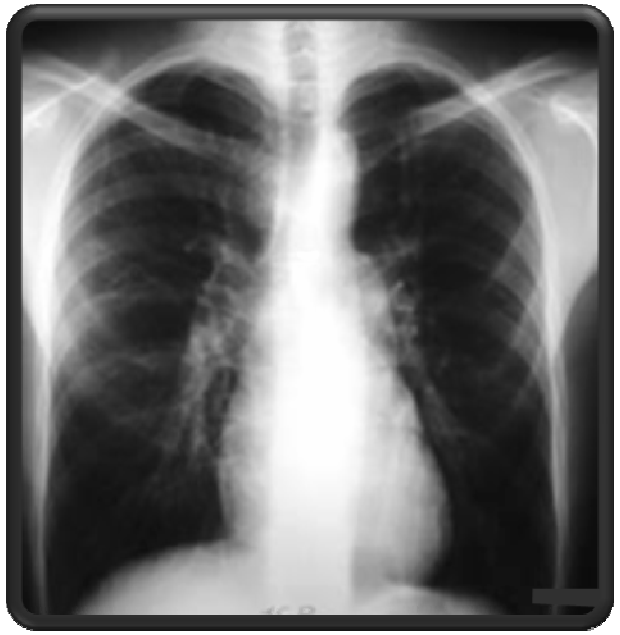
75%

EPI



56%

HP



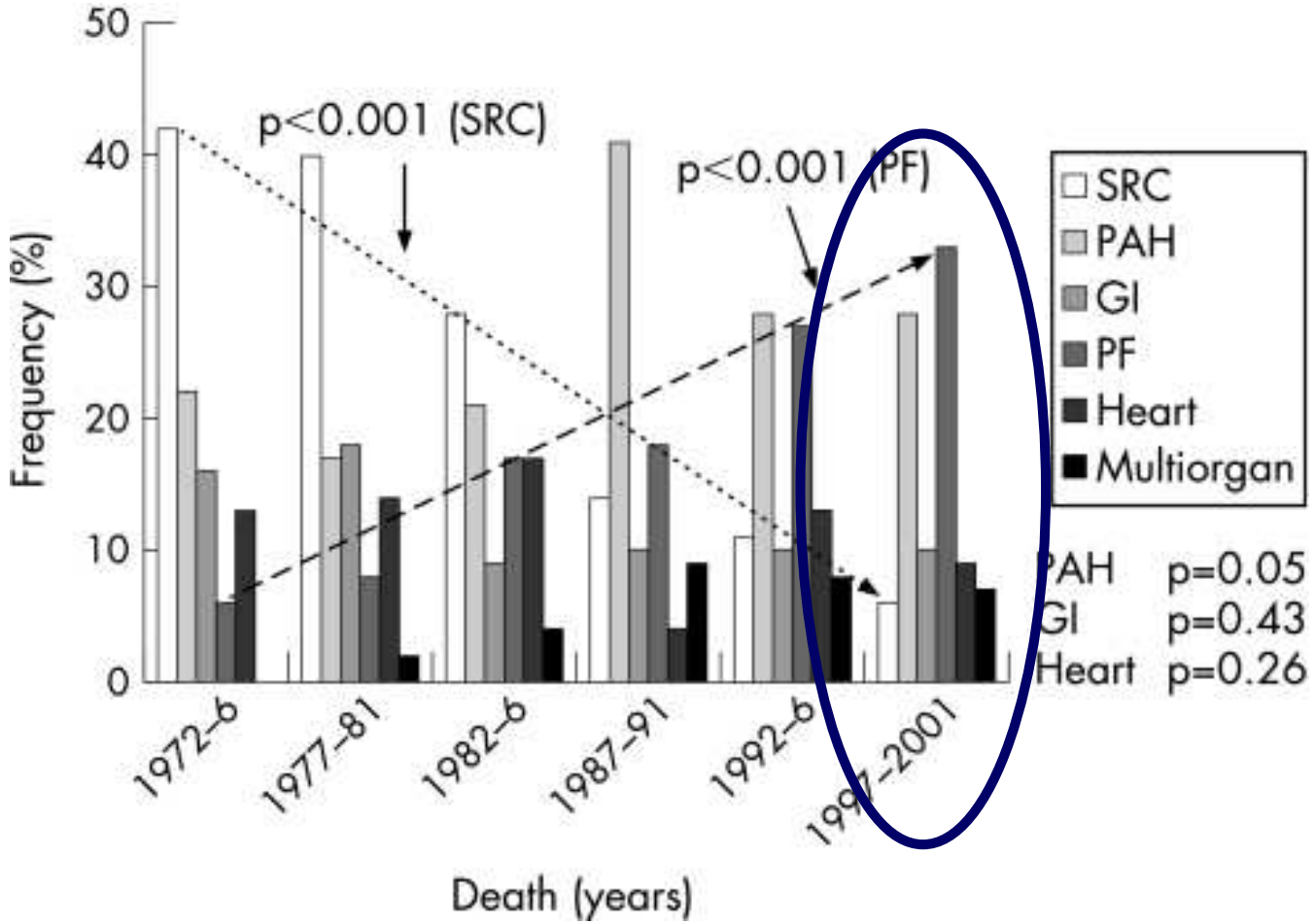
19%

Serie Hospital Universitario Vall d'Hebron

Changes in causes of death in systemic sclerosis, 1972–2002

Virginia D Steen, Thomas A Medsger

Ann Rheum Dis 2007



Características de los Autoanticuerpos en la ES:

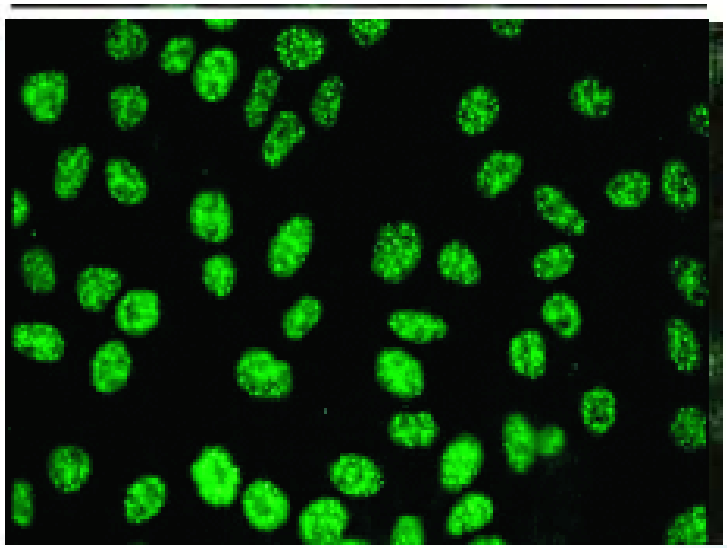
1. Los ANA están presentes en más del 90% de los enfermos con ES.
2. Los Ac tienen diferentes especificidades antigénicas, siendo altamente específicos.
3. Los diferentes Ac específicos son excluyentes.
4. Permanecen estables durante el curso de la enfermedad.
5. Existe asociación entre el tipo de Ac, las complicaciones orgánicas y la supervivencia.
6. Predictores del curso clínico tanto como el subtipo cutáneo.

Nihtyanova, Nature Rev Rheumatol. 2009
Hagmaguchi, Journal of Dermatology. 2010

Perfiles de IFI en la ES:

1. **Centromérico** (cromatina)
   - Anti-centrómero (ACA): CENP-A, -B, -C

2. **Homogéneo** (cromatina)
   - Anti-topo I (ATA, Scl-70): DNA topo I

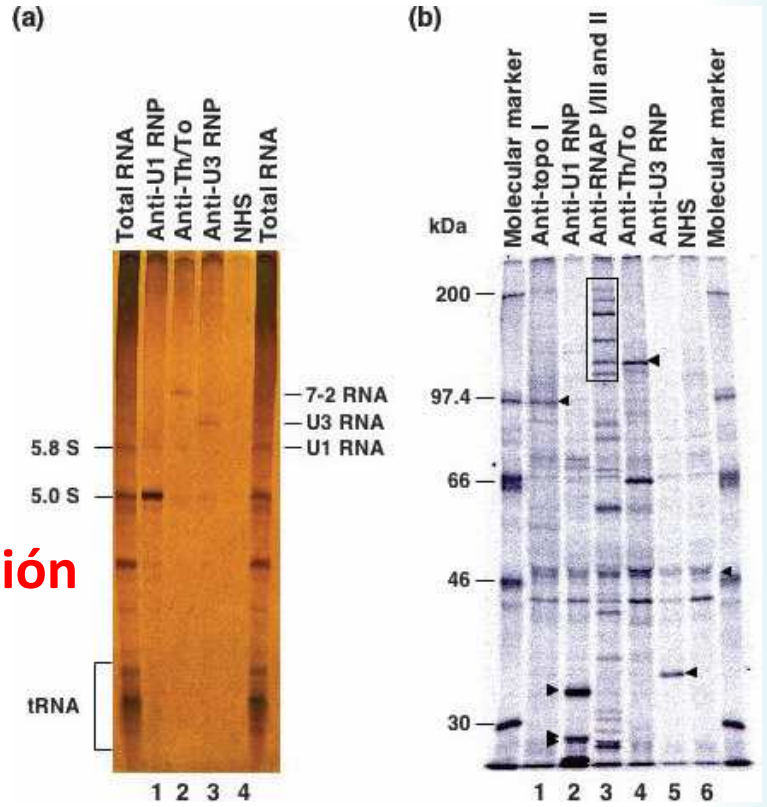


3. **Nucleolar** (nucleolo)
   - Anti-PM/Scl
   - Anti-Th/To
   - Anti-RNA pol III
   - Anti-U3RNP (fibrilarina)
   - Anti-NOR90

4. **Moteado** (nucleoplasma)
   - Anti-RNApol III
   - Anti-U1RNP
   - Anti-Ku

Confirmar especificidad Autoanticuerpos:

- **ELISA**
  - Anti-centrómero
  - Anti-topo I
  - Anti-RNA pol III
  - Anti-U1RNP
- **Inmunoprecipitación**
  - Anti-centrómero
  - Anti-topo I
  - Anti-RNA pol III
  - Anti-Th/To
  - Anti-U3RNP
  - Anti-NOR90
  - Anti-U1RNP
  - Anti-PM/Scl
  - Anti-Ku
- **Inmunoblot**
  - Anti-centrómero
  - Anti-topo I
  - Anti-U1RNP
  - Anti-PM/Scl
  - Anti-Ku
- **Doble inmunodifusión**
  - Anti-topo I
  - Anti-U1RNP
  - Anti-PM/Scl
  - Anti-Ku



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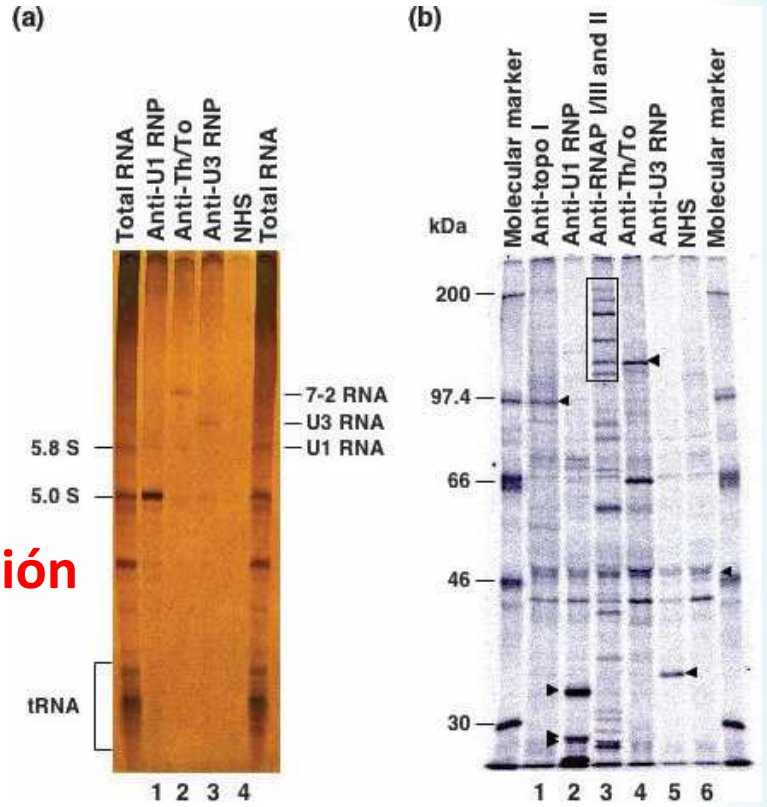


Auto-Ac como herramienta diagnóstica:

Criteria for the Classification of Early Systemic Sclerosis

LeRoy and Medsger, J Rheumatology. 2001

Table 1. Constellations of criteria for diagnosis.

lSSc:	RP (objective documentation)	
	plus any one:	SSc-type nailford capillary pattern
		or
		SSc selective autoantibodies
	or	
	RP (subjective only)	
	plus both:	SSc-type nailfold capillary pattern
		and
		SSc selective antibodies (see Table 2)
lcSSc:	criteria for lSSc	
	plus:	distal cutaneous changes
dcSSc:	criteria for lSSc	
	plus:	proximal cutaneous changes

→ **Anti-centrómero**
Anti-topo I
Anti-U3RNP
Anti-PM/Scl
Anti-RNA pol III

Auto-Ac como herramienta diagnóstica:

Criteria for the Classification of Early Systemic Sclerosis

LeRoy and Medsger, J Rheumatology. 2001

Table 2. Proposed criteria for limited forms of SSc (lSSc).

Limited SSc (lSSc):

Raynaud's phenomenon (RP), objectively documented by

1. Direct observation of any 2 of
   - A. pallor (well demarcated whitening of acral skin)
   - B. cyanosis (dusky blueness, which disappears on rewarming)
   - C. suffusion (well demarcated redness)

or 2. Direct measurement of response to cold by

- A. objective evidence of delayed recovery after cold challenge
- B. Nielsen test[8] or equivalent (see text)

plus 1. abnormal widefield nailfold capillaroscopy (consisting of dilation and/or avascular areas)[21]

or 2. SSc selective autoantibodies (anticentromere, antitopoisomerase I, anti-fibrillarin, anti-PM-Scl, anti-fibrillin or anti-RNA polymerase I or III in a titer of 1:100 or higher)[22]

If RP is subjective only, both SSc capillary pattern and SSc selective autoantibodies (in titer > 1:100) are required to define lSSc. lSSc can overlap with any other disease.

Limited cutaneous SSc (lcSSc):

In addition to the criteria for lSSc, lcSSc patients must demonstrate cutaneous involvement distal to the elbows, knees, and clavicles. Put the other way round, skin tautness of the fingers, hands, forearms, legs, feet, toes, neck, and face in the absence of skin tautness of the arms, chest, abdomen, back, or thighs (which defines diffuse cutaneous SSc), in addition to the criteria for lSSc, defines lcSSc. Also, lcSSc can overlap with any other disease (including type I diabetes mellitus), CREST (calcinosis, RP, esophageal involvement, sclerodactyly, and telangectasia) is a synonym for lcSSc.

→ **Anti-centrómero**
Anti-topo I
Anti-U3RNP
Anti-PM/Scl
Anti-RNA pol III

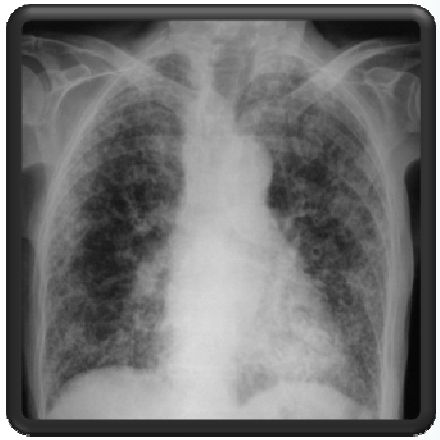
Enfermedad pulmonar intersticial (EPI):

PATOGÉNESIS:

Enfermedad pulmonar intersticial (EPI):

FRECUENCIA:

- **Aproximadamente el 60% de los enfermos con ES**
- **La ES es la enfermedad del tejido conectivo que con mayor frecuencia puede desarrollar una EPI.**
- **1-5% de los casos es la forma de inicio de la ES.**



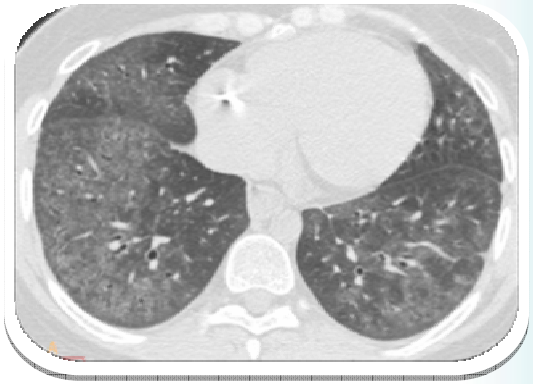
56%

	ILD
Systemic sclerosis	+++
Rheumatoid arthritis	++
Primary Sjögren's syndrome	++
Mixed CTD	++
Polymyositis/ dermatomyositis	+++
Systemic lupus erythematosus	+

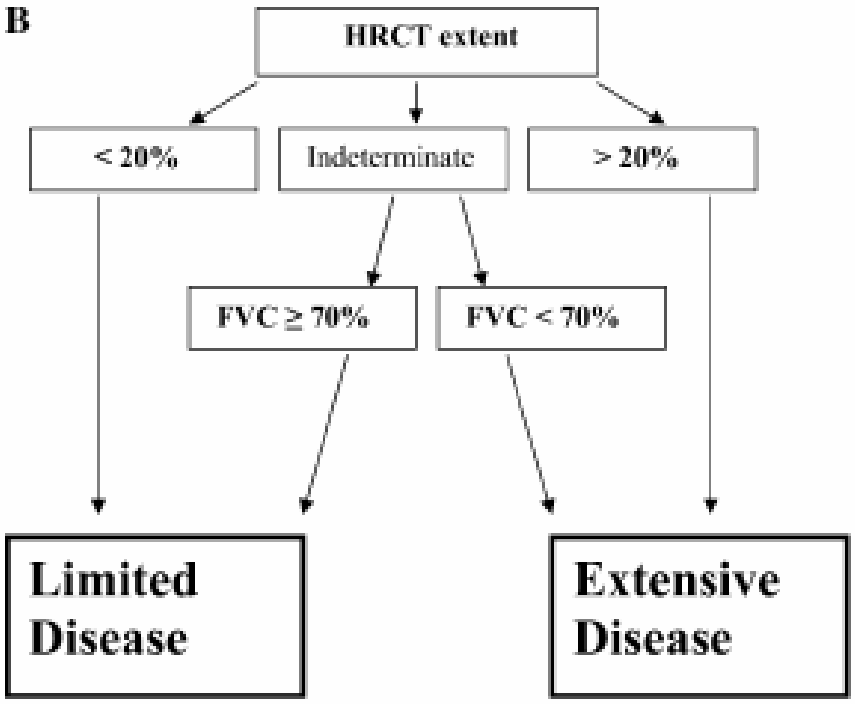
EPI – DIAGNÓSTICO:

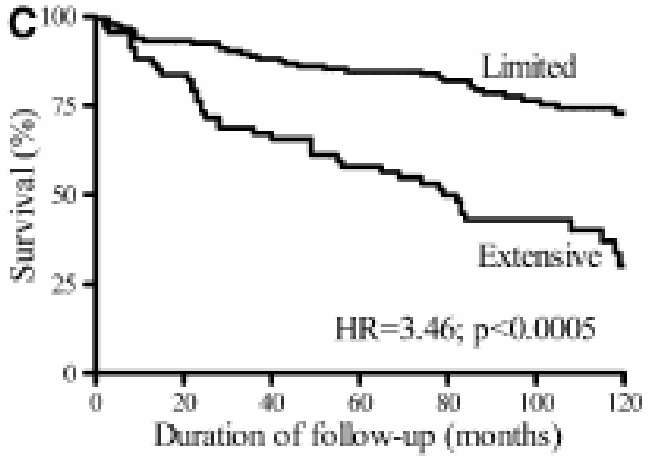
1) TACAR : diagnóstico y extensión de la EPI

2) Pruebas funcionales respiratorias completas: gravedad de la EPI y valor en el seguimiento.



NINE > NIU





Goh. Am J Respir Crit Care Med. 2008

EPI – DIAGNÓSTICO:

3) Lava[illegible]alveolar

Bronchoalveolar Lavage Cellular Profiles in Patients With Systemic Sclerosis–Associated Interstitial Lung Disease Are Not Predictive of Disease Progression

Nicole S. L. Goh,[1] Srihari Veeraraghavan,[2] Sujal R. Desai,[3] Derek Cramer,[1] David M. Hansell,[1] Christopher P. Denton,[4] Carol M. Black,[4] Roland M. du Bois,[1] and Athol U. Wells[1]

Persistence of Abnormal Bronchoalveolar Lavage Findings After Cyclophosphamide Treatment in Scleroderma Patients With Interstitial Lung Disease

Shikha Mittoo, Fredrick M. Wigley, Robert Wise, Huiqing Xiao, and Laura Hummers

EPI – DIAGNÓSTICO:

4) Biop[illegible]nar

Histopathologic Subsets of Fibrosing Alveolitis in Patients with Systemic Sclerosis and Their Relationship to Outcome

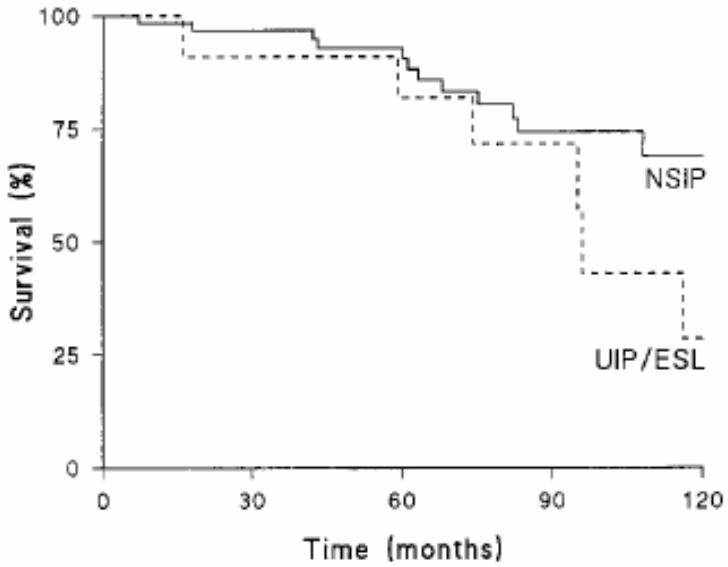
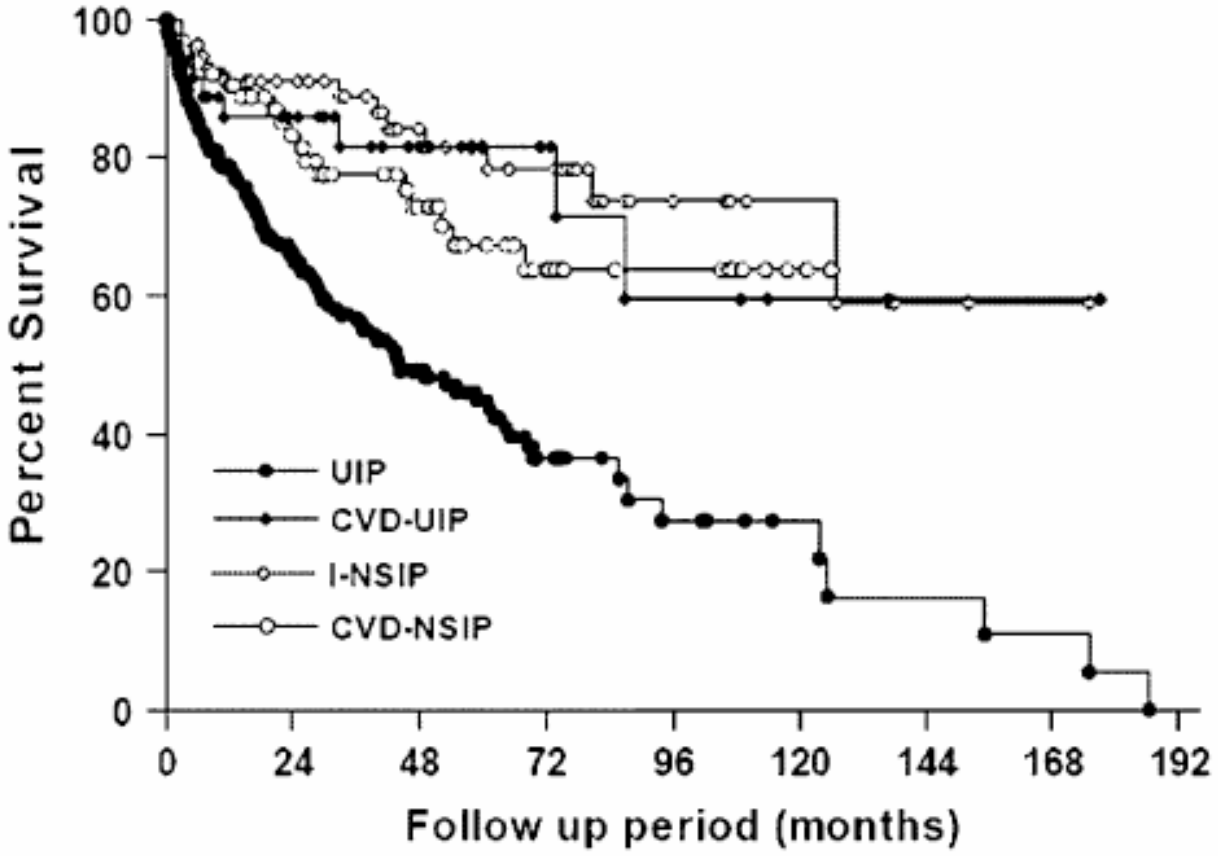


Figure 3. Survival compared between NSIP and UIP/ESL. No significant difference was disclosed.

Bouros, Am J Respir Crit Care Med. 2002

EPI – PRONÓSTICO:

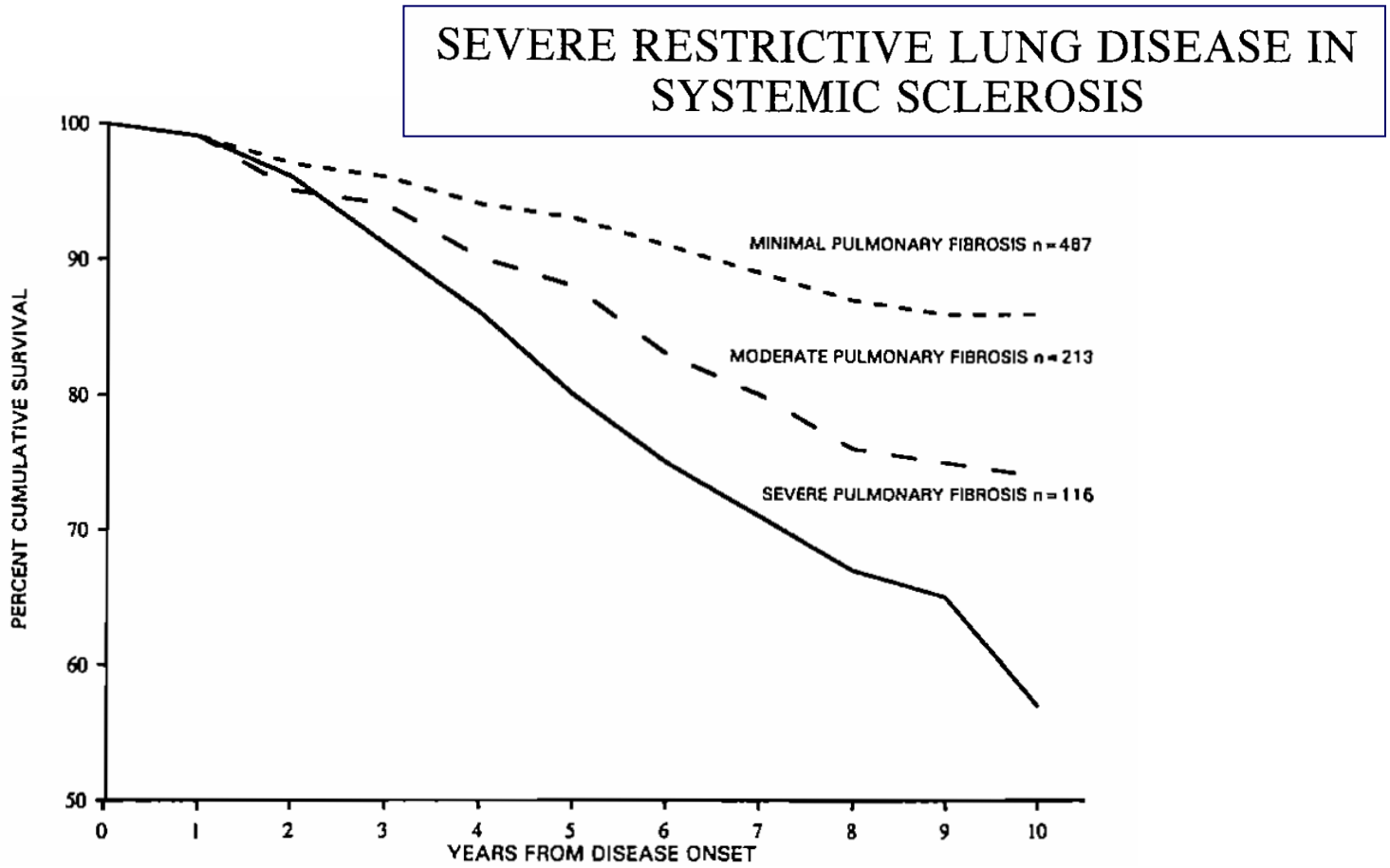
PRONÓSTICO DE LA EPI ASOCIADA A ENFERMEDAD TEJIDO CONECTIVO vs. IDIOPÁTICA:



Park, Am J Resp Crit Care Med. 2007

EPI – PRONÓSTICO:

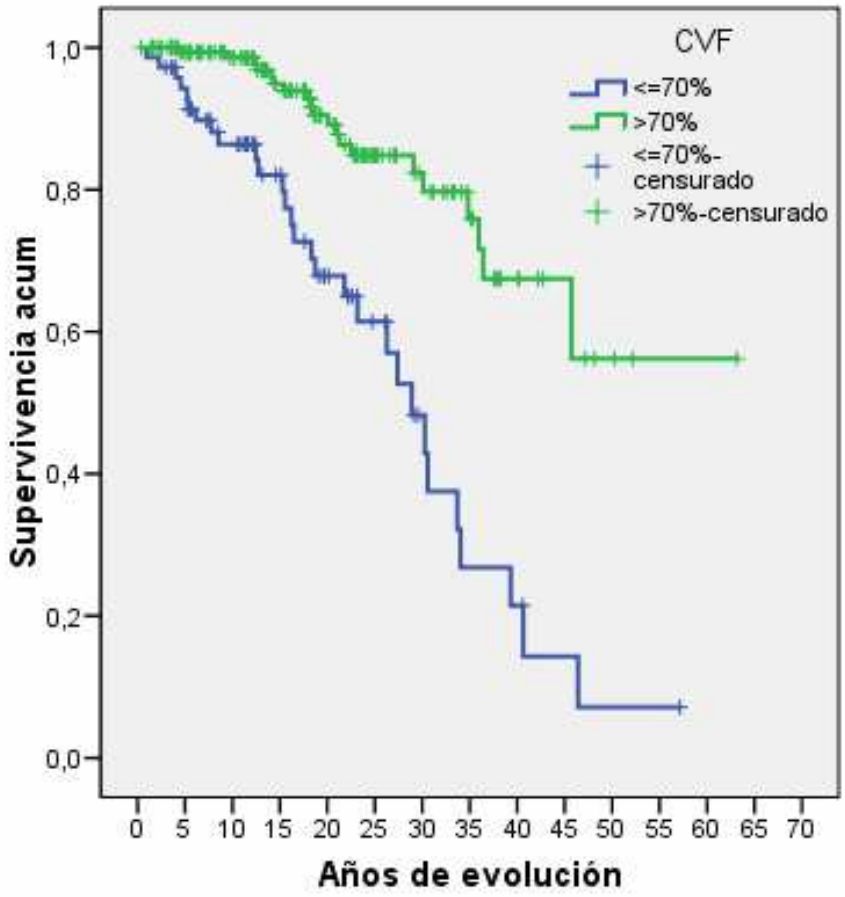
PRONÓSTICO DE LA EPI EN LA ESCLERODERMIA:



Steen, Arthritis Rheum. 1994.

EPI – PRONÓSTICO:

PRONÓSTICO DE LA EPI EN LA ESCLERODERMIA:



Factores pronósticos	RR	p
Esclerodermia difusa	2,730	0,001
Edad de comienzo	1,079	0,0001
Fibrosis pulmonar	2,463	0,003
HTAP	2,802	0,0001
Crisis renal	30,062	0,0001

Serie Hospital Universitario Vall d'Hebron

EPI – PERFIL INMUNOLÓGICO:

The association of antinuclear antibodies with organ involvement and survival in systemic sclerosis

TABLE 2. Distribution of disease subsets, and frequencies of organ involvement in 276 Swedish SSc patients, in relation to ANA pattern

	ANA pattern							
	Centromeric		Nucleolar		Homogeneous		Speckled	
	+ve $n=51$	−ve $n=225$	+ve $n=66$	−ve $n=210$	+ve $n=69$	−ve $n=207$	+ve $n=114$	−ve $n=162$
Max. ± S.D. skin score	9.6 ± 6.6***	15.0 ± 11.0	16.4 ± 11.3	13.3 ± 10.2	18.0 ± 12.3***	2.7 ± 9.1	13.1 ± 9.8	14.7 ± 10.9
Age at entry (yr)	48.8	49.8	50.8	49.2	51.0	49.1	47.6	51.0
Females (%)	86.3*	70.7	66.7	75.7	62.3*	77.3	77.2	71.0
lSSc (%)	94.1***	70.7	68.2	77.1	62.3**	79.2	77.2	73.5
Organ involvement (%)								
Organic vasculopathy	84.2*	65.8	66.2	69.7	68.4	68.9	70.0	67.9
Vasospasm	68.4	80.6	74.6	80.0	82.5	77.4	81.0	76.9
Pulmonary fibrosis	16.3**	40.3	51.6**	31.1	51.5**	30.9	35.4	36.3
VC <80%	18.4*	35.9	28.6	30.9	47.8**	27.8	36.3	30.2
DLCO <80%	90.9	79.3	80.4	81.8	86.0	80.0	84.8	79.0
Cst <60%	30.4	31.4	36.2	29.2	40.9	27.6	32.8	30.1
Isolated PHT	30.3	17.5	23.5	19.5	25.6	18.5	18.3	21.8
PHT associated with PF	9.1	21.9	26.5	16.8	30.8*	14.8	20.0	18.4

Hesselstrand. Rheumatology. 2003.

EPI – PERFIL INMUNOLÓGICO:

	Anti-topo I		Anti-U1 RNP		Anti-RNAP	
	+ve $n=26$	−ve $n=250$	+ve $n=59$	−ve $n=217$	+ve $n=60$	−ve $n=216$
Max. ± S.D. skin score	25.9 ± 12.6***	12.6 ± 9.50	11.8 ± 10.3	14.6 ± 10.5	14.7 ± 10.4	13.8 ± 10.5
Age at entry (yr)	48.8	49.7	45.1**	50.9	49.8	49.5
Females (%)	53.8*	75.6	74.6	73.3	75.0	73.1
lSSc (%)	42.3***	78.4	83.1	72.8	76.7	74.5
Organ involvement (%)						
Organic vasculopathy	77.3	67.9	73.5	67.6	55.8*	73.3
Vasospasm	81.8	78.3	89.8*	75.7	76.9	79.1
Pulmonary fibrosis	58.3*	33.7	31.0	37.3	41.4	34.4
VC <80%	64.0***	29.6	35.6	31.9	33.9	32.4
DLCO <80%	91.3	80.4	86.3	80.1	90.2	79.0
Cst <60%	41.2	30.1	30.6	31.5	39.4	29.1
Isolated PHT	17.6	20.8	19.4	20.7	25.0	18.9
PHT associated with PF	29.4	17.7	29.0	16.4	22.2	18.0

Hesselstrand. Rheumatology. 2003.

SSc-associated autoantibody	PF frequency
U11/U12 RNP	23/33 (70)
Centromere	59/436 (14)
Ku	6/14 (43)
PM-Scl	27/65 (42)
RNA polymerase III	63/343 (18)
Th/To	47/121 (39)
Topoisomerase I	204/425 (48)
U1 RNP	36/123 (29)
U3 RNP	16/84 (19)

Fertig. Arthritis Rheum. 2009

Table 2. Frequency of pulmonary fibrosis (PF) in systemic sclerosis (SSc) patients followed at the University of Pittsburgh from 1982–2004, according to the presence of different SSc-associated serum autoantibodies, compared with SSc patients in this study*

SSc-associated autoantibody	PF frequency	*P* vs. U11/U12
U11/U12 RNP	23/33 (70)	
Centromere	59/436 (14)	< 0.0001
Ku	6/14 (43)	NS
PM-Scl	27/65 (42)	< 0.009
RNA polymerase III	63/343 (18)	< 0.0001
Th/To	47/121 (39)	< 0.002
Topoisomerase I	204/425 (48)	< 0.02
U1 RNP	36/123 (29)	< 0.0001
U3 RNP	16/84 (19)	< 0.0001

* Values are number/total number of antibody-positive patients (percentage). Overlap patients are excluded; no patient had more than 1 SSc-associated autoantibody. NS = not significant.

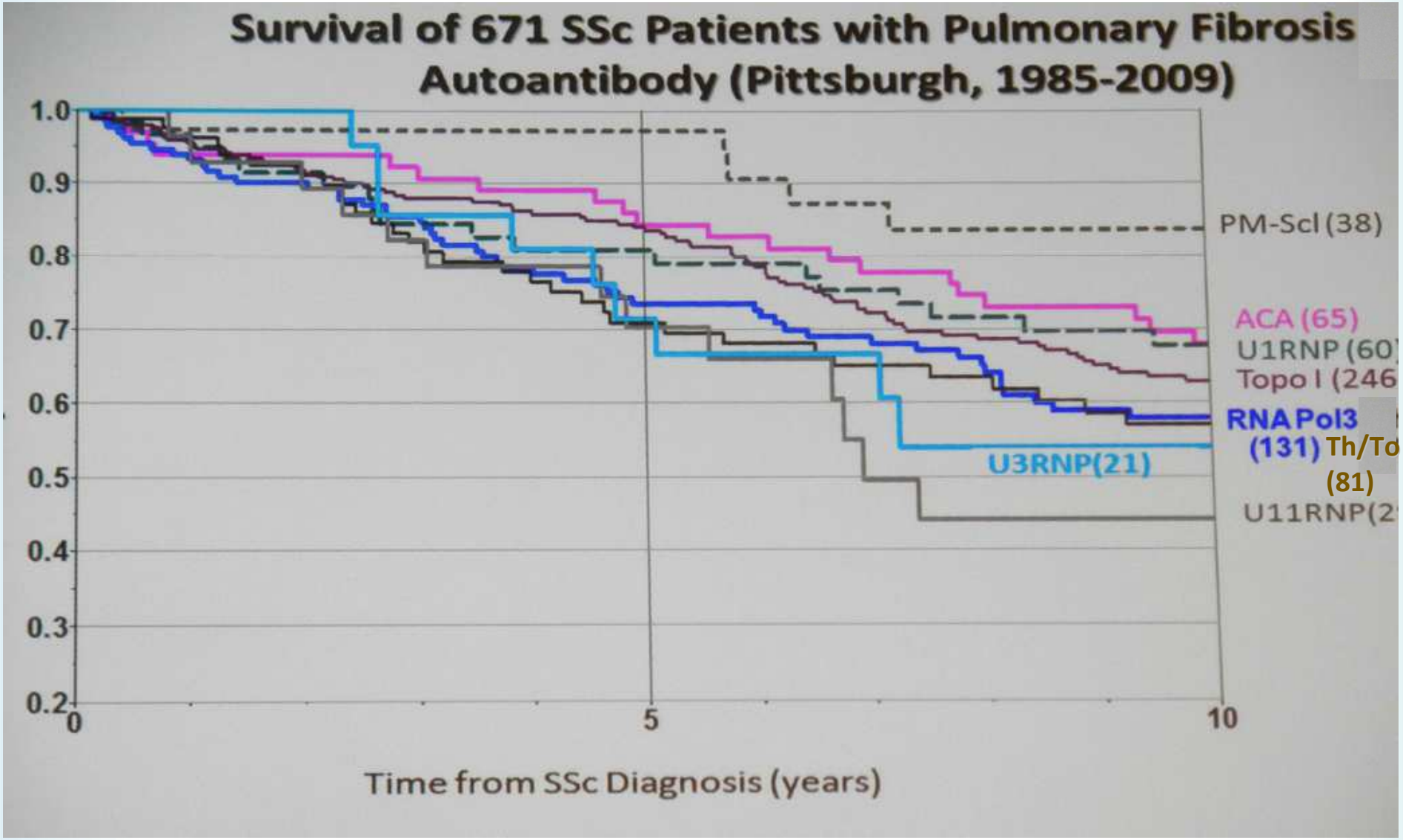
Fertig. Arthritis Rheum. 2009

Registry of the Spanish Network for Systemic Sclerosis: Clinical Pattern According to Cutaneous Subsets and Immunological Status

Table 4 Independent Predictors of Disease Manifestations in Patients with SSc

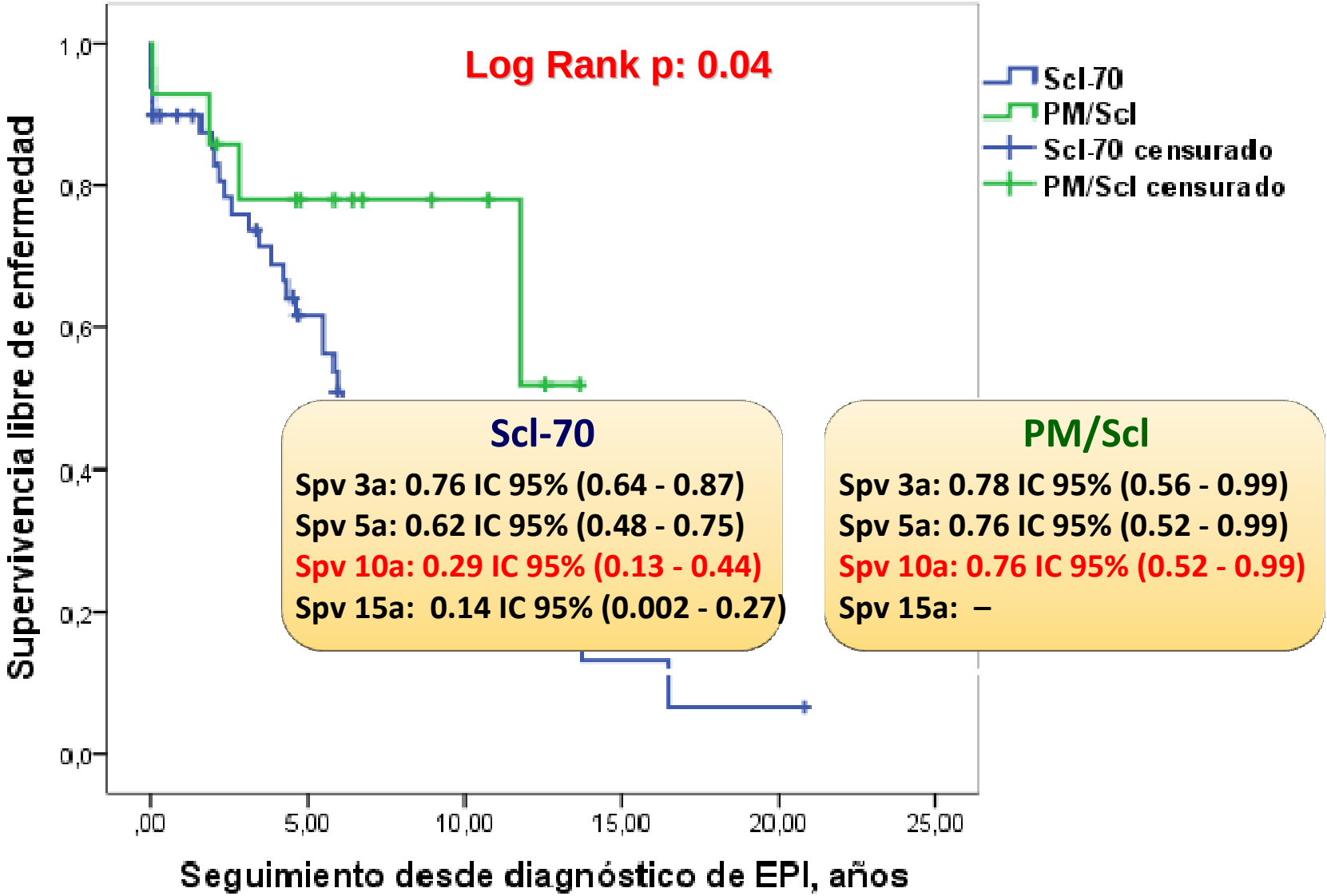
	1 OR (IC 95%)	2 OR (IC 95%)	3 OR (IC 95%)
Arthritis	dcSSc 2.555 (1.68; 3.88)	–	—
Myositis	ACA – 6.402 (2.39; 17.13)	dcSSc 3.006 (1.57; 5.74)	ATA I – 2.845 (1.36; 5.94)
Digital ulcers	dcSSc 4.380 (2.86; 6.72)	ATA I – 1.706 (1.07; 2.72)	
Raynaud's phenomenon	lcSSc 3.279 (1.70; 6.33)	—	—
Digestive involvement	dcSSc 2.185 (1.42; 3.37)	—	—
Esophagus	dcSSc 1.801 (1.19; 2.73)	ACA – 1.540 (1.07; 2.21)	–
Stomach	dcSSc 1.733 (1.09; 2.77)	—	—
Malabsorption	dcSSc 3.459 (1.30; 9.23)	—	—
Lung involvement	dcSSc 2.549 (1.61; 4.04)	ACA – 1.854 (1.28; 2.68)	—
ILD	ACA – 2.071 (1.43; 3.00)	dcSSc 2.024 (1.32; 3.10)	ATA I + 2.004 (1.23; 3.27)
FVC ≤70%	ACA – 1.861 (1.35; 2.58)	—	—
Ground-glass pattern	dcSSc 2.816 (1.64; 4.83)	ACA – 2.528 (1.39; 4.60)	
Reticular pattern	ACA – 2.672 (1.60; 4.47)	ATA I + 2.436 (1.53; 3.88)	dcSSc 1.748 (1.12; 2.74)
PAH	dcSSc 1.508 (1.01; 2.26)	—	—
Isolated PAH	—	—	—
Heart involvement	—	—	—
Pericarditis	ATA I + 3.500 (1.77; 6.93)	—	—
Myocardial ischemia	—	—	—
Conduction alteration	—	—	—
Kidney	dcSSc 4.219 (2.02; 8.81)	—	—
SRC	dcSSc 12.556 (3.59; 43.89)	—	—
Sicca Syndrome	ACA + 1.598 (1.16; 2.21)	—	—
Active capillaroscopic pattern	dcSSc 3.130 (2.00; 4.90)	—	—

Simeón-Aznar (GEAS), Semin Arthritis Rheum. 2012.


Survival of 671 SSc Patients with Pulmonary Fibrosis
Autoantibody (Pittsburgh, 1985-2009)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0
5
10
Time from SSc Diagnosis (years)
PM-Scl (38)
ACA (65)
U1RNP (60)
Topo I (246
RNA Pol3
(131)
Th/To
(81)
U3RNP(21)
U11RNP(2

Anti-Scl 70 vs anti-PM/Scl

Evento: exitus o descenso > 10% CVF



Scl-70

Spv 3a: 0.76 IC 95% (0.64 - 0.87)
Spv 5a: 0.62 IC 95% (0.48 - 0.75)
Spv 10a: 0.29 IC 95% (0.13 - 0.44)
Spv 15a: 0.14 IC 95% (0.002 - 0.27)

PM/Scl

Spv 3a: 0.78 IC 95% (0.56 - 0.99)
Spv 5a: 0.76 IC 95% (0.52 - 0.99)
Spv 10a: 0.76 IC 95% (0.52 - 0.99)
Spv 15a: –

EPI – PERFIL INMUNOLÓGICO:

- INCIDENCIA:

MAYOR INCIDENCIA	MENOR INCIDENCIA
• Anti-Topo I • IFI-nucleolar • Anti-Th/To • Anti-U11/U12 RNP • Anti-PM/Scl • Anti-Ku	• Anti-centrómero • Anti-RNA pol III • Anti-U3 RNP

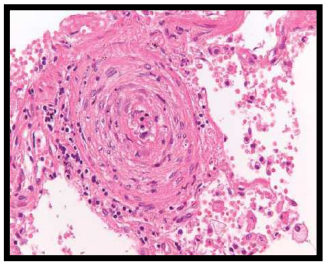
- GRAVEDAD:

MAYOR GRAVEDAD	MENOR GRAVEDAD
• Anti-Topo I • IFI-nucleolar • Anti-Th/To • Anti-U11/U12 RNP	• Anti-PM/Scl

Hesselstrand. Rheumatology. 2003
Fertig. Arthritis Rheum. 2009

Hipertensión arterial pulmonar (HAP):

PATOGÉNESIS:



Disfunción endotelial

↑ vasoconstrictores (tromboxano A2 y ET-1)

↓vasodiladatores (NO y prostaciclin sintetasa)

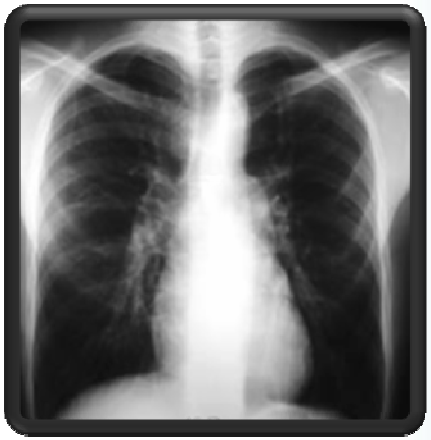
↑ tono vascular arterial

Remodelado pared vascular

↑ RVP

HTP

Hipertensión arterial pulmonar (HAP):



19%

FRECUENCIA:

- Aproximadamente el 20% de los enfermos con ES
- La ES es la enfermedad del tejido conectivo que con mayor frecuencia puede desarrollar una HAP.

Isolated CTD-PAH	
SSc	259 (76%)
MCTD	28 (8%)
SLE	28 (8%)
DM/PM	7 (2%)
RA	12 (3%)
UCTD	6 (2%)
Sjogren's	3 (1%)
Total	**343**

HAP – DIAGNÓSTICO:

1) Cateterismo derecho: PAPm ≥ 25mmHg

CLASIFICACIÓN DE *HIPERTENSIÓN PULMONAR*. DANA POINT. 2008

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic PAH
1.2. Heritable
1.2.1. BMPR2
1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3. Unknown
1.3. Drug- and toxin-induced
1.4. Associated with
1.4.1. Connective tissue diseases
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. Schistosomiasis
1.4.6. Chronic hemolytic anemia
1.5 Persistent pulmonary hypertension of the newborn

1′. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

2. Pulmonary hypertension owing to left heart disease
2.1. Systolic dysfunction
2.2. Diastolic dysfunction
2.3. Valvular disease

3. Pulmonary hypertension owing to lung diseases and/or hypoxia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental abnormalities

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1. Hematologic disorders: myeloproliferative disorders, splenectomy
5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Simonneau. J Am Coll Cardiol. 2009

HAP – DIAGNÓSTICO:

1) Cateterismo derecho: **PAPm ≥ 25mmHg**

CLASIFICACIÓN DE *HIPERTENSIÓN PULMONAR*. DANA POINT. 2008

1. Hipertensión arterial pulmonar (HAP)
1'. Enfermedad venooclusiva y /o hemangiomatosis capilar
2. HP debida cardiopatía izda
3. HP debida a enf. pulmonares o hipoxemia
4. HP tromboembólica crónica
5. HP por mec multifactoriales no aclarados

PCP <15mmHg

PCP >15mmHg

ES

Simonneau. J Am Coll Cardiol. 2009

HAP – DIAGNÓSTICO:

2) Ecocardiografía: PAPs ≥ 40mmHg

3) WT 6 minutos: seguimiento, dificultad técnica en ES

4) PFR anuales con DLCO

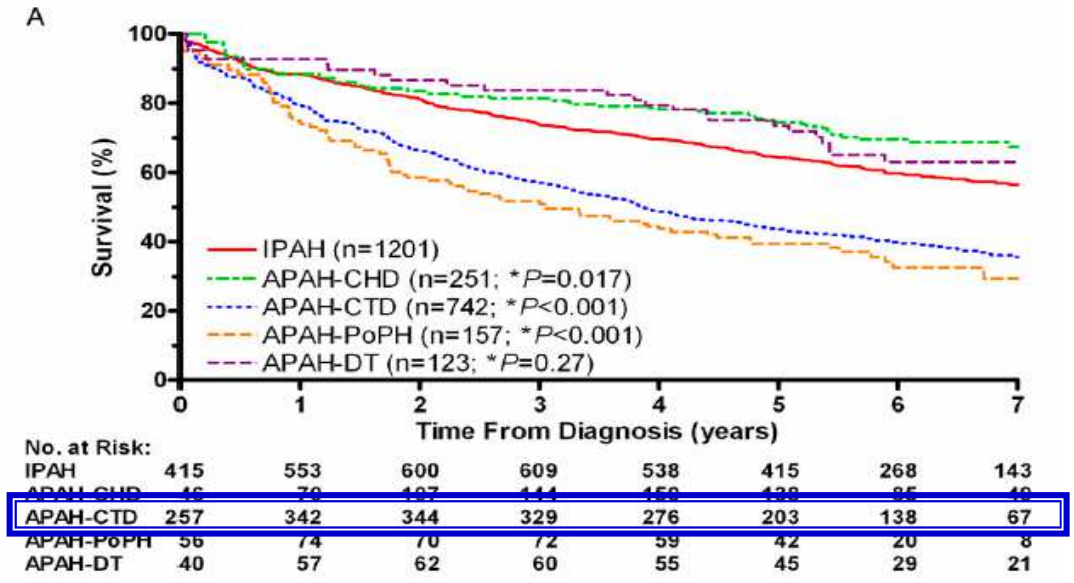
5) Clase funcional WHO

HAP– PRONÓSTICO:

PRONÓSTICO DE LA HAP ASOCIADA A ENFERMEDAD TEJIDO CONECTIVO vs. IDIOPÁTICA:

Table 2—*Survival Estimates of PAH Subgroups at Years 1, 3, 5, and 7*

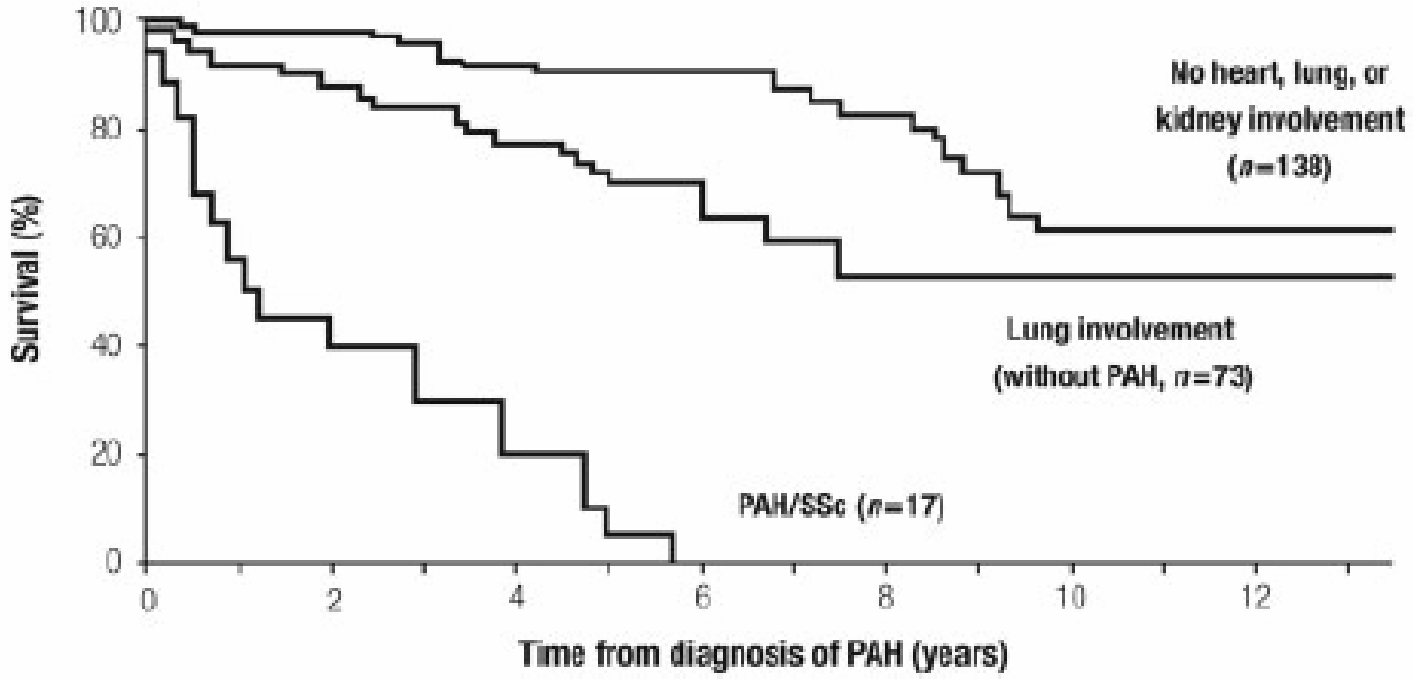
PAH Subgroup	No.	Years From Diagnosis 1	3	5	7
IPAH	1,201	88.4 ± 1.9	73.7 ± 2.0	64.3 ± 2.1	56.5 ± 2.2
APAH-CHD	251	88.3 ± 4.5	81.4 ± 4.8	74.4 ± 4.7	67.2 ± 4.8
APAH-CTD	742	79.5 ± 2.6	57.1 ± 2.6	43.7 ± 2.4	35.5 ± 2.5
APAH-PoPH	157	74.9 ± 5.8	51.6 ± 5.5	39.4 ± 4.9	29.3 ± 5.3
APAH-DT	123	92.7 ± 5.1	83.7 ± 5.7	73.5 ± 6.2	63.0 ± 6.6
APAH-HIV	48	93.3 ± 6.2	75.1 ± 8.8	63.8 ± 9.5	63.8 ± 9.5
APAH-other[a]	33	100.0	82.6 ± 8.8	64.4 ± 11.3	47.0 ± 12.8
FPAH	66	92.9 ± 6.6	72.2 ± 8.2	60.1 ± 8.1	50.5 ± 8.5



HAP– PRONÓSTICO:

PRONÓSTICO DE LA HAP EN LA ESCLERODERMIA:

Pulmonary Arterial Hypertension Is a Major Mortality Factor in Diffuse Systemic Sclerosis, Independent of Interstitial Lung Disease

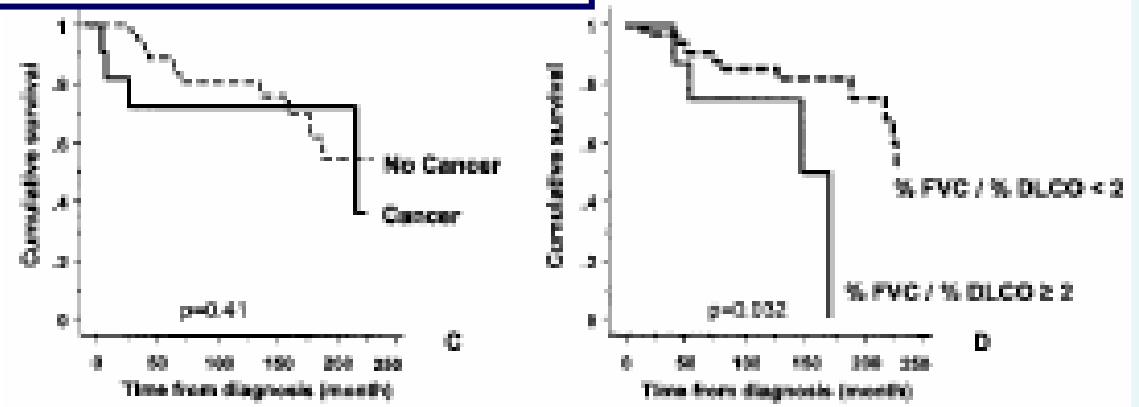


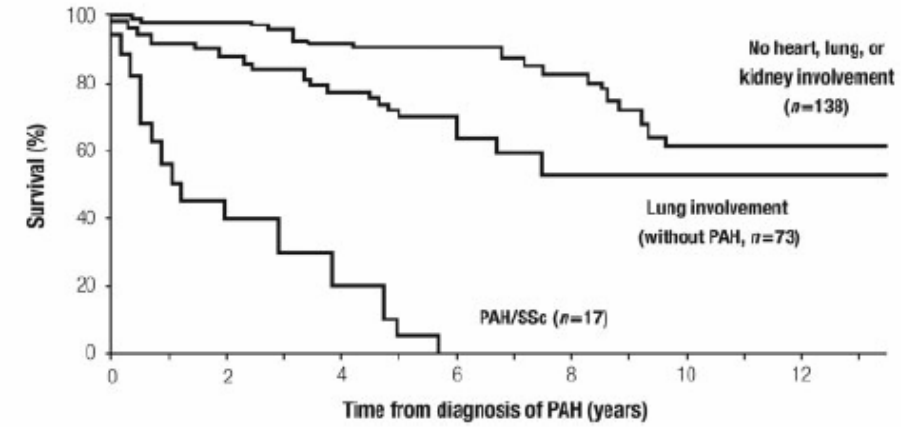
Trad. Arthritis Rheumatism. 2006

HAP– PRONÓSTICO:

PRONÓSTICO DE LA HAP EN LA ESCLERODERMIA:

Pulmonary Arterial Hypertension Is a Major Mortality Factor in Diffuse Systemic Sclerosis, Independent of Interstitial Lung Disease

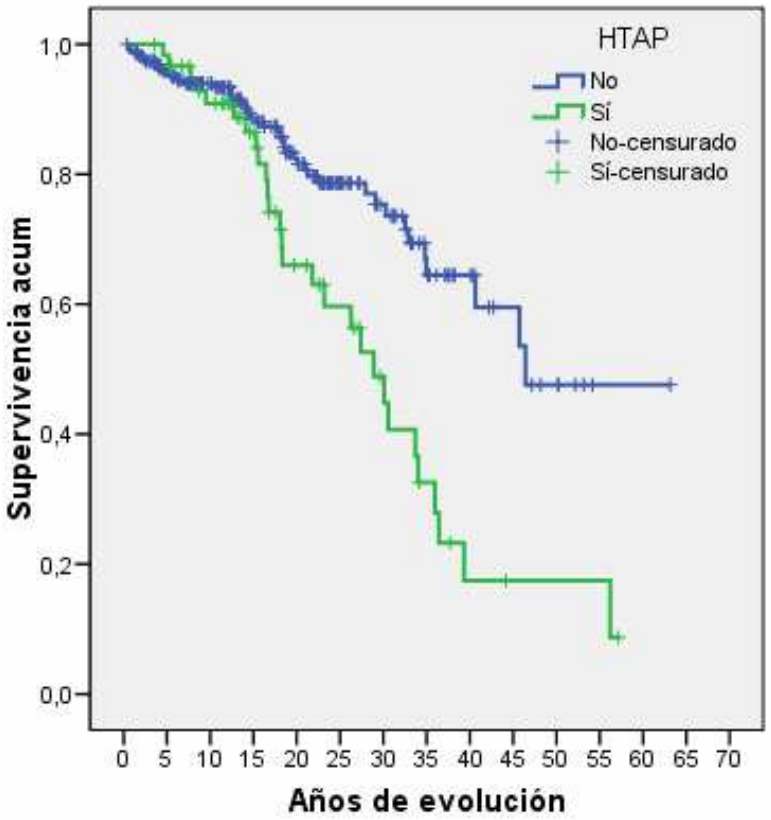




Trad. Arthritis Rheumatism. 2006

HAP– PRONÓSTICO:

PRONÓSTICO DE LA HAP EN LA ESCLERODERMIA:



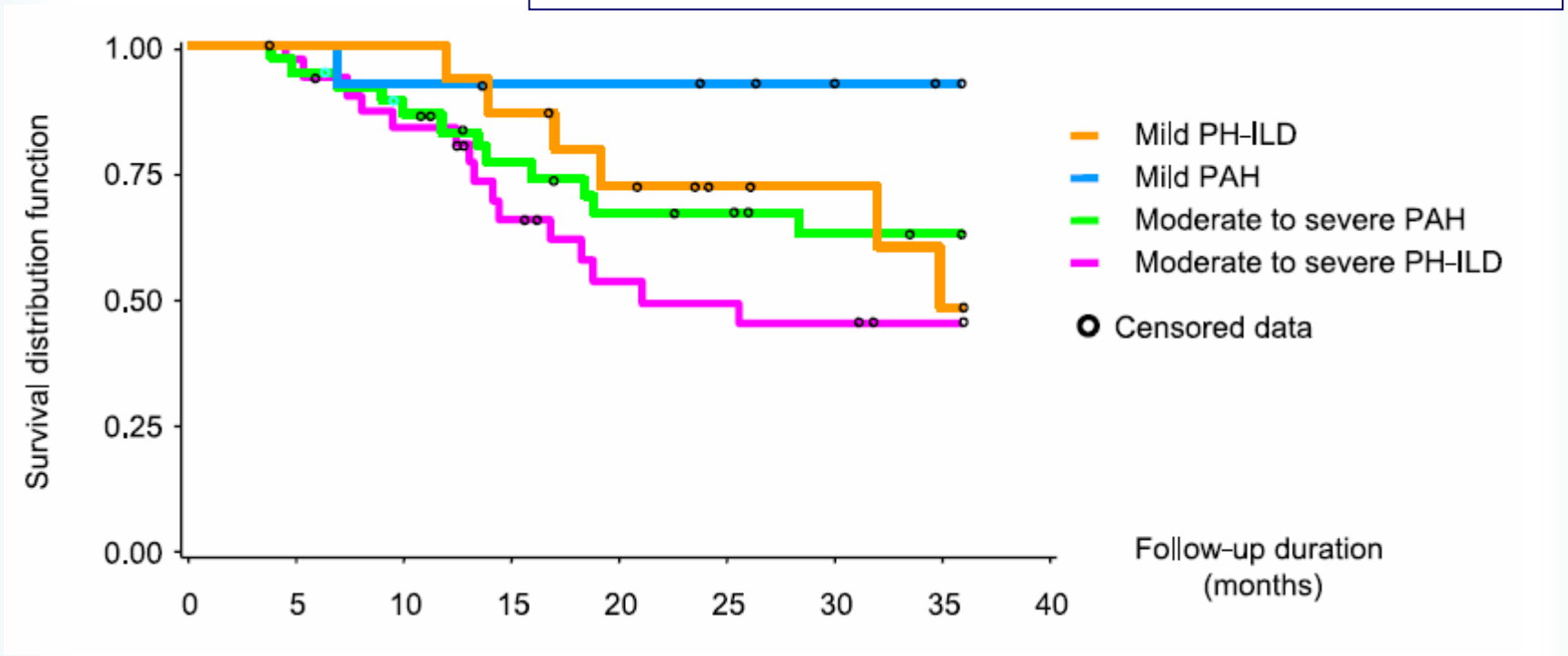
Factores pronósticos	RR	p
Esclerodermia difusa	2,730	0,001
Edad de comienzo	1,079	0,0001
Fibrosis pulmonar	2,463	0,003
HTAP	2,802	0,0001
Crisis renal	30,062	0,0001

Serie Hospital Universitario Vall d'Hebron

HAP– PRONÓSTICO:

PRONÓSTICO DE LA HAP-ILD EN LA ESCLERODERMIA:

Clinical Characteristics and Survival in Systemic Sclerosis-Related Pulmonary Hypertension Associated With Interstitial Lung Disease



Launay. Chest. 2011.

HAP– PERFIL INMUNOLÓGICO:

Autoantibodies in Systemic Sclerosis

Virginia D. Steen, MD

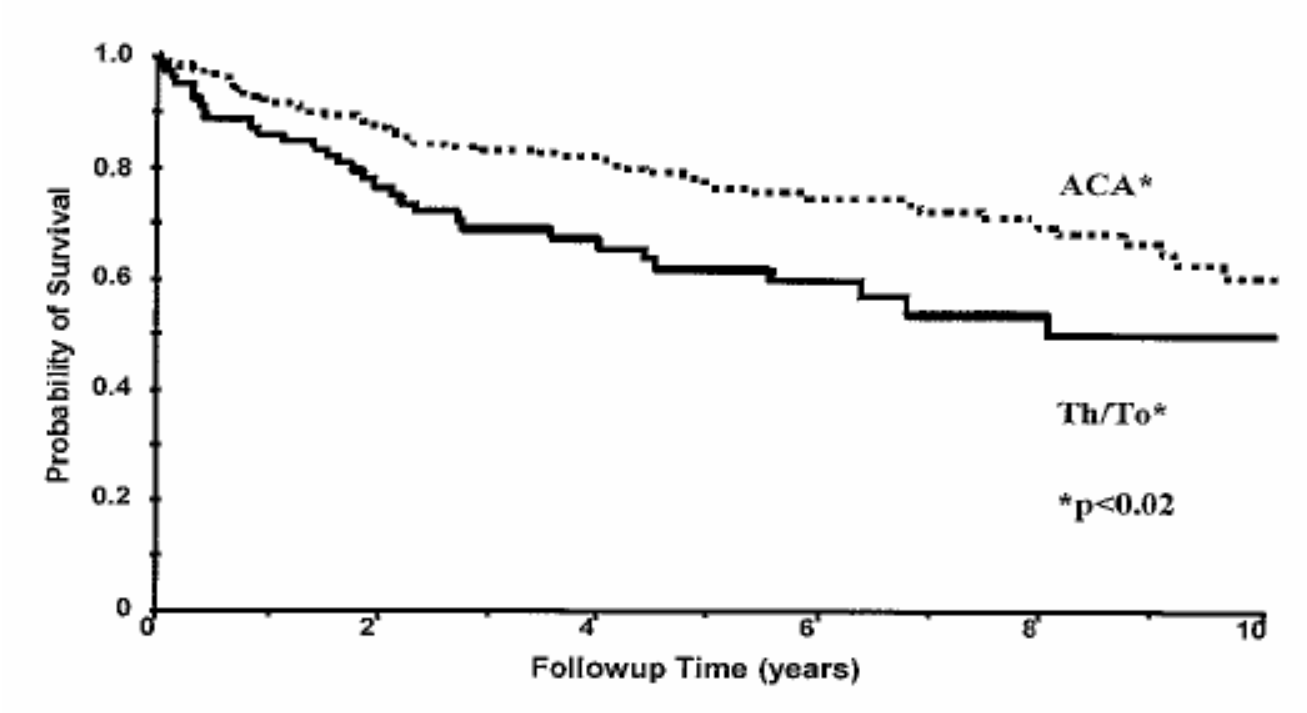
Table 3 Organ Involvement in Patients with Scleroderma-Specific Antibodies

Antibody	ACA	Th/To	PmScl	U1RNP	U3RNP	TOPO	Pol 3
Number of Patients	291	72	36	71	55	318	120
Any GI (%)	57	33	39	39	59	56	37
Severe GI (%)*	8	13	0	14	25	8	5
Number with PFTs	(184)	(49)	(22)	(40)	(37)	(235)	(74)
Any Lung (%)	45	62	58	53	67	73	49
Severe fibrosis (%)*	6	16	27	22	24	23	7
Lowest FVC* (% predicted)	87	79	74	75	68	67	81
Isolated PHT (%)	19*	32*	3	14	24*	2	6
Severe heart disease (%)*	4	7	6	11	18	16	7
Renal crisis (%)*	1	4	4	7	7	10	28

*$P < 0.01$ by ANOVA. Major differences in bold.

Semin Arthritis Rheum. Steen. 2005.

A Comparison Between Anti-Th/To– and Anticentromere Antibody–Positive Systemic Sclerosis Patients With Limited Cutaneous Involvement



Mitri. Arthritis Rheumatism. 2003

HAP– PERFIL INMUNOLÓGICO:

- **INCIDENCIA:**

MAYOR INCIDENCIA	MENOR INCIDENCIA
• Anti-centrómero • Anti- Th/To • Anti-U3 RNP	• Anti-PM/Scl

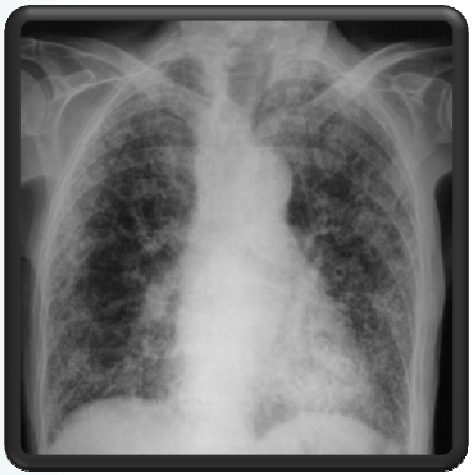
- **GRAVEDAD:**

MAYOR GRAVEDAD	MENOR GRAVEDAD
• IFI-nucleolar • Anti- Th/To	• Anti-centrómero

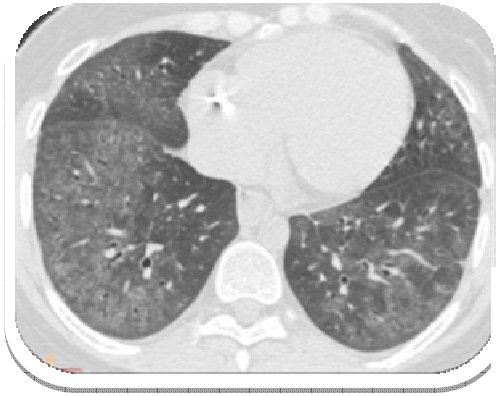
Hesselstrand. Rheumatology. 2003
Fertig. Arthritis Rheum. 2009

CASO CLÍNICO:

- **Mujer de 56 años, que acude a consultas de Neumología por disnea progresiva de 6 meses y crepitantes en la EF.**



TCAR



NINE

PFR

- **CVF: 65%**
- **FEV1%: 70%**
- **DLCO: 65%**

FIBROSIS PULMONAR IDIOPÁTICA???

CASO CLÍNICO:

Anamnesis:

- FR de 15 años de evolución
- Pirosis desde hace 4 años

ES *sine* – EPI – Scl-70+

ANAs y Anticuerpos ES específicos:

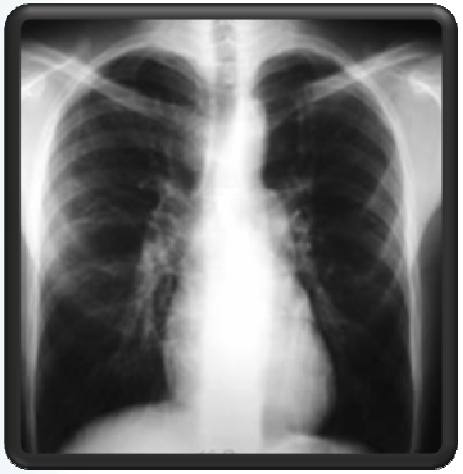
- Patrón IFI homogéneo/nucleolar
- anti-Scl-70 +

Anti-Th/To-positivity in a cohort of patients with idiopathic pulmonary fibrosis.
Fischer. J Rheumatol. 2006

8.8% de los pacientes tuvieron ANA con patrón nucleolar y de ellos la mitad se documentó Ac anti- Th/To +. Siendo diagnosticados de ES.

CASO CLÍNICO:

- **Mujer de 45 años, fumadora, que ingresa en servicio de Medicina Interna por disnea progresiva de 3 meses de evolución.**



Ecocardio

- FEVI: 63%
- TAPSE: 19mm
- IT ++
- PAPs: 61 mmHg

Cateterismo dcho:

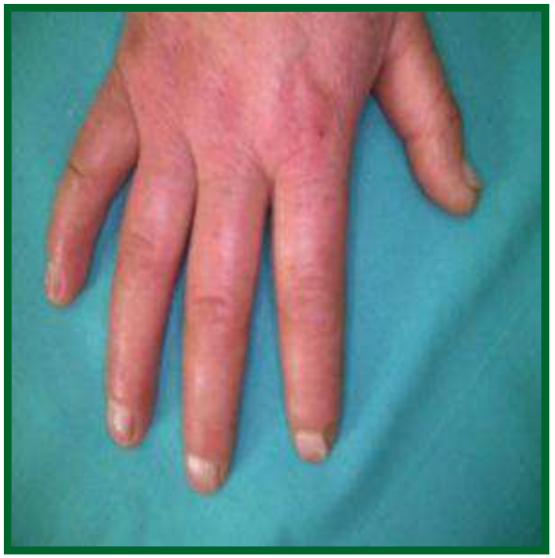
- PAPm: 34mmHg
- PCP: 9 mmHg

HIPERTENSIÓN ARTERIAL PULMONAR PRIMARIA???

CASO CLÍNICO:

Anamnesis:

- FR de 1.5 años de evolución
- 2 Úlceras digitales en los últimos 6 meses
- Discreta induración de dedos



ANAs y Anticuerpos ES específicos:

- Patrón IFI centromérico

ES limitada – HAP – ACA+

assessment unnecessary. Despite the strong clinical associations of antibodies, they are not 100% sensitive or specific for certain organ problems, therefore regular monitoring for all major organ complications needs to be done in all patients diagnosed with SSc, even if their antibody status confers relative protection from specific organ disease or overall good prognosis.

Nihtyanova, Nature Rev Rheumatol. 2009

CONCLUSIONES:

1. Los ANA están presentes en más del 90% de los enfermos con ES, siendo altamente específicos de ES.
2. Existe asociación entre el tipo de Ac, las complicaciones orgánicas y la supervivencia.
3. La EPI se diagnostica por TCAR y se valora por PFR.
4. La HAP se diagnostica por Cateterismo derecho
5. Hay que pensar siempre ante un paciente con FPI o HAP idiopáticas en la presencia de una enfermedad de tejido conectivo subyacente.

GRACIAS !!!