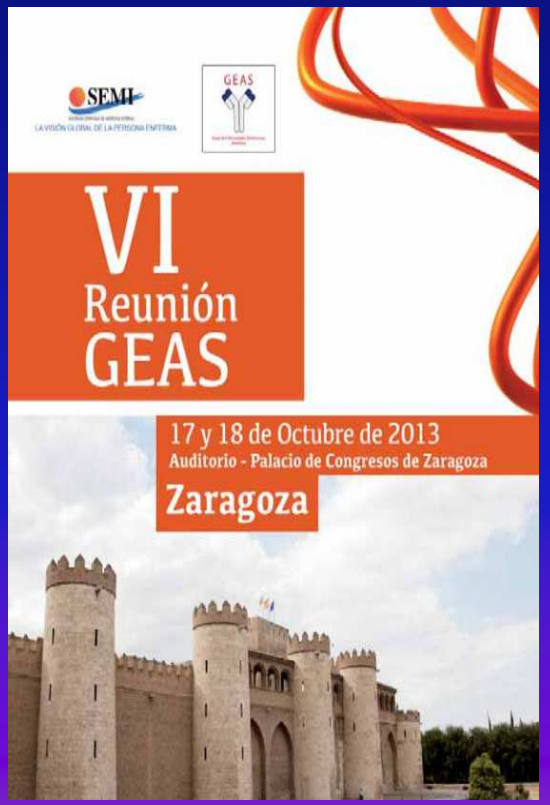
Universitat Autònoma de Barcelona

Nuevos conceptos en EAS 2013: TOP 5

ESCLERODERMIA

V. Fonollosa Pla - CP. Simeón Aznar
Unidad de Enfermedades Autoinmunes Sistémicas
Servicio de Medicina Interna



Arthritis & Rheumatism

An Official Journal of the American College of Rheumatology
www.arthritisrheum.org and wileyonlinelibrary.com

SPECIAL ARTICLE

2013 Classification Criteria for Systemic Sclerosis

An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative

Frank van den Hoogen,[1] Dinesh Khanna,[2] Jaap Fransen,[3] Sindhu R. Johnson,[4] Murray Baron,[5] Alan Tyndall,[6] Marco Matucci-Cerinic,[7] Raymond P. Naden,[8] Thomas A. Medsger Jr.,[9] Patricia E. Carreira,[10] Gabriela Riemekasten,[11] Philip J. Clements,[12] Christopher P. Denton,[13] Oliver Distler,[14] Yannick Allanore,[15] Daniel E. Furst,[12] Armando Gabrielli,[16] Maureen D. Mayes,[17] Jacob M. van Laar,[18] James R. Seibold,[19] Laszlo Czirjak,[20] Virginia D. Steen,[21] Murat Inanc,[22] Otylia Kowal-Bielecka,[23] Ulf Müller-Ladner,[24] Gabriele Valentini,[25] Douglas J. Veale,[26] Madelon C. Vonk,[3] Ulrich A. Walker,[6] Lorinda Chung,[27] David H. Collier,[28] Mary Ellen Csuka,[29] Barri J. Fessler,[30] Serena Guiducci,[7] Ariane Herrick,[31] Vivien M. Hsu,[32] Sergio Jimenez,[33] Bashar Kahaleh,[34] Peter A. Merkel,[35] Stanislav Sierakowski,[23] Richard M. Silver,[36] Robert W. Simms,[35] John Varga,[37] and Janet E. Pope[38]

2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative

Frank van den Hoogen, Dinesh Khanna, Jaap Fransen, et al.

Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581–90.

CRITERIO MAYOR

Esclerodermia proximal

CRITERIOS MENORES

Esclerodactilia

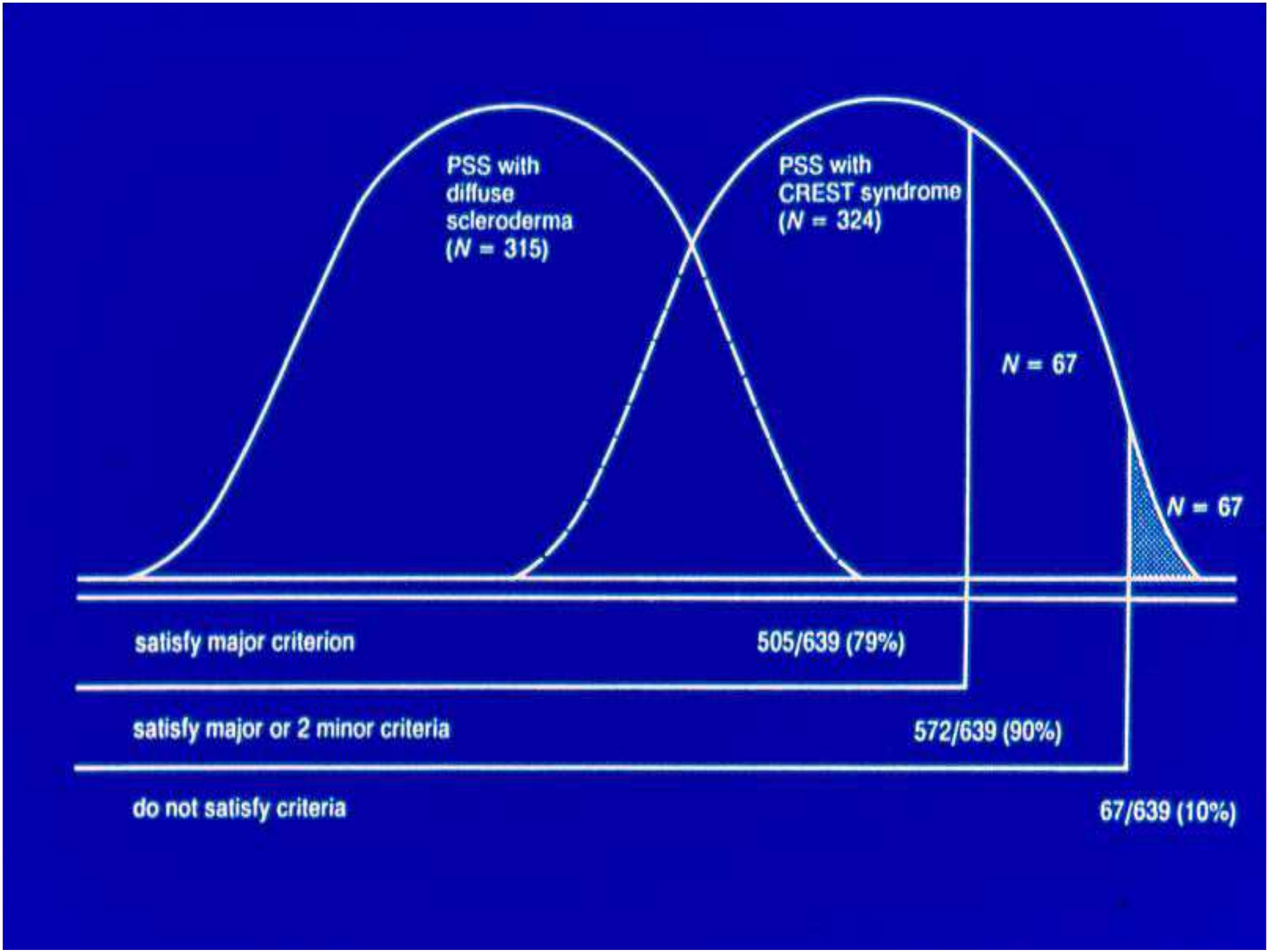
Cicatrices puntiformes en el pulpejo de los dedos

Fibrosis pulmonar bilateral

DIAGNÓSTICO

Criterio mayor

Dos o más de menores


PSS with diffuse scleroderma (N = 315)
PSS with CREST syndrome (N = 324)
N = 67
N = 67
satisfy major criterion
505/639 (79%)
satisfy major or 2 minor criteria
572/639 (90%)
do not satisfy criteria
67/639 (10%)

Classification Criteria for Systemic Sclerosis Subsets

SINDHU R. JOHNSON, BRIAN M. FELDMAN, and GILLIAN A. HAWKER

J Rheumatol 2007;34:1855–63

Table 1. Classification of systemic sclerosis subsets.

Study	Classification Scheme	Number of Citations
Barnett[36]	3 subsets: limited, moderate, extensive, based on skin involvement of the fingers only, limbs and face, and involvement of the trunk, respectively	66
Ferri[30]	4 subsets: sine scleroderma SSc: absence of cutaneous involvement with visceral involvement, NC changes and autoantibodies; limited cutaneous: skin involvement of fingers with or without involvement of neck, face, and axillae; intermediate cutaneous: skin involvement of upper and lower limbs, neck and face without truncal involvement, diffuse cutaneous: distal and truncal skin involvement	52
Giordano[28]	6 subsets: I: sclerodactyly only; II: sclerodactyly and skin involvement of neck, lower eyelid, or axillae; III: skin involvement of hands and forearms ± legs ± face; IV: group III and arm and/or thigh skin involvement; V: group III and thorax; VI: group III and/or IV and/or V plus the abdomen	121
	3 subsets: limited: skin involvement of fingers, face, neck, axillae; intermediate: skin involvement proximal to fingers; diffuse: truncal skin involvement	121
Goetz[22]	2 subsets: acrosclerosis and diffuse: based on skin thickening limited to extremities or includes trunk	227
Holzmann[53]	5 subsets (Types I–IV) based on presence/absence of RP, sclerosis, extracutaneous manifestations, ANA	10
LeRoy[25]	2 subsets: diffuse cutaneous SSc: onset of RP within 1 year; truncal and acral skin involvement; tendon friction rubs; early incidence of ILD, renal failure, diffuse GI disease, myocardial involvement; absence of ACA, abnormal ND; limited cutaneous SSc: RP for years, skin involvement limited to hands, face, feet, forearms or absent; late incidence of PAH, trigeminal neuralgia, calcinosis, telangiectasia; high incidence of ACA, abnormal NC	877
LeRoy and Medsger[41]	4 subsets: limited SSc (LSSc) consists of (1) objective RP plus any one of NC changes or SSc selective autoantibodies OR (2) subjective RP plus both NC changes and SSc selective autoantibodies; limited cutaneous SSc (lcSSc): criteria for LSSc plus distal cutaneous changes; diffuse cutaneous (dcSSc): criteria for lcSSc plus proximal cutaneous changes; diffuse fasciitis with eosinophilia: proximal cutaneous changes without criteria for lSSc or lcSSc	46
Maricq[6]	6 subsets: diffuse, intermediate, digital, scleroderma sine scleroderma, undifferentiated connective tissue disease with scleroderma, CREST syndrome	3
Masi[43]	3 subsets: digital: skin involvement of fingers or toes but not proximal extremity or trunk; proximal extremity: proximal extremities or face but not trunk; truncal: thorax or abdomen	42
Rodnan[2]	3 subsets: classical disease involving skin of the trunk, face and proximal extremities, and early involvement of esophagus, intestine, heart, lung and kidney; CREST syndrome; and overlap syndromes including sclerodermatomyositis and mixed connective tissue disease	79
Scussel-Lonzetti[39]	4 subsets: normal skin, limited: skin involvement restricted to fingers, with RP, calcinosis, esophageal involvement and telangiectasia; intermediate: skin involvement of arms proximal to metacarpophalangeal but not trunk; diffuse: skin involvement of the trunk	1
Tuffanelli and Winkelmann[35]	2 subsets: acrosclerosis: RP, acral skin involvement; diffuse SSc: no RP, skin involvement beginning centrally	42
Winterbauer[23]	CREST syndrome: calcinosis, RP, sclerodactyly, telangiectasia	176

RP: Raynaud's phenomenon; NC: nailfold capillary; ILD: interstitial lung diseases; GI: gastrointestinal; ACA: anticentromere antibodies; PAH: pulmonary arterial hypertension; LSSc: limited SSc.

Esclerodermia: Clasificación en subtipos, *según LeRoy*

TABLE 1. Some features of the LeRoy *et al.* 1988 [4] and LeRoy and Medsger [17] subsets of SSc

Diffuse cutaneous scleroderma (dcSSc)
- History of Raynaud's with onset within 1 yr
- Skin sclerosis extending proximal to the elbow; may involve truncal areas
- Tendon friction rubs may occur
- Early onset of pulmonary, renal and diffuse gastrointestinal involvement
- Rarely anticentromere antibodies but often antitopoisomerase 1 antibodies
- Nailfold capillary destruction

Limited cutaneous scleroderma (lcSSc)
- Skin involvement restricted to hands, face, forearms and feet
- Delayed but often severe onset of pulmonary arterial hypertension

Ectopic calcinosis, telangiectasias
- Anticentromere antibodies common but antitopoisomerase 1 very rare
- Dilated nailfold caps seen but no capillary destruction

Limited/unclassifiable/pre-SSc
- Raynaud's phenomenon objectively documented as well as *either* abnormal widefield nailfold capillaroscopy *or* SSc-selective autoantibodies (anticentromere antibodies, anti-topiisomerase 1, antifibrillin, anti-PM-Scl, anti-RNA polyisomerase I or III)
- Raynaud's phenomenon subjectively documented as well as abnormal widefield capillaroscopy *and* SSc selective autoantibodies

2 subsets: diffuse cutaneous SSc: onset of RP within 1 year; truncal and acral skin involvement; tendon friction rubs; early incidence of ILD, renal failure, diffuse GI disease, myocardial involvement; absence of ACA, abnormal ND; limited cutaneous SSc: RP for years, skin involvement limited to hands, face, feet, forearms or absent; late incidence of PAH, trigeminal neuralgia, calcinosis, telangiectasia; high incidence of ACA, abnormal NC

2013 Classification Criteria for Systemic Sclerosis

Table 1. The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc)*

Item	Sub-item(s)	Weight/score†
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	–	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	–	3
SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) *(maximum score is 3)*	Anticentromere	3
	Anti–topoisomerase I	
	Anti–RNA polymerase III	

* These criteria are applicable to any patient considered for inclusion in an SSc study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).

† The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥9 are classified as having definite SSc.

2013 Classification Criteria for Systemic Sclerosis

Table 2. Definitions of items/sub-items in the American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc)

Item	Definition
Skin thickening	Skin thickening or hardening not due to scarring after injury, trauma, etc.
Puffy fingers	Swollen digits—a diffuse, usually nonpitting increase in soft tissue mass of the digits extending beyond the normal confines of the joint capsule. Normal digits are tapered distally with the tissues following the contours of the digital bone and joint structures. Swelling of the digits obliterates these contours. Not due to other causes such as inflammatory dactylitis.
Fingertip ulcers or pitting scars	Ulcers or scars distal to or at the proximal interphalangeal joint not thought to be due to trauma. Digital pitting scars are depressed areas at digital tips as a result of ischemia, rather than trauma or exogenous causes.
Telangiectasia	Telangiectasiae are visible macular dilated superficial blood vessels, which collapse upon pressure and fill slowly when pressure is released. Telangiectasiae in a scleroderma-like pattern are round and well demarcated and found on hands, lips, inside of the mouth, and/or are large mat-like telangiectasiae. Distinguishable from rapidly filling spider angiomas with central arteriole and from dilated superficial vessels.
Abnormal nailfold capillary pattern consistent with systemic sclerosis	Enlarged capillaries and/or capillary loss with or without pericapillary hemorrhages at the nailfold. May also be seen on the cuticle.
Pulmonary arterial hypertension	Pulmonary arterial hypertension diagnosed by right-sided heart catheterization according to standard definitions.
Interstitial lung disease	Pulmonary fibrosis seen on high-resolution computed tomography or chest radiography, most pronounced in the basilar portions of the lungs, or occurrence of "Velcro" crackles on auscultation, not due to another cause such as congestive heart failure.
Raynaud's phenomenon	Self-reported or reported by a physician, with at least a 2-phase color change in finger(s) and often toe(s) consisting of pallor, cyanosis, and/or reactive hyperemia in response to cold exposure or emotion; usually one phase is pallor.
SSc-related autoantibodies	Anticentromere antibody or centromere pattern seen on antinuclear antibody testing, anti–topoisomerase I antibody (also known as anti–Scl-70 antibody), or anti–RNA polymerase III antibody. Positive according to local laboratory standards.

2013 Classification Criteria for Systemic Sclerosis

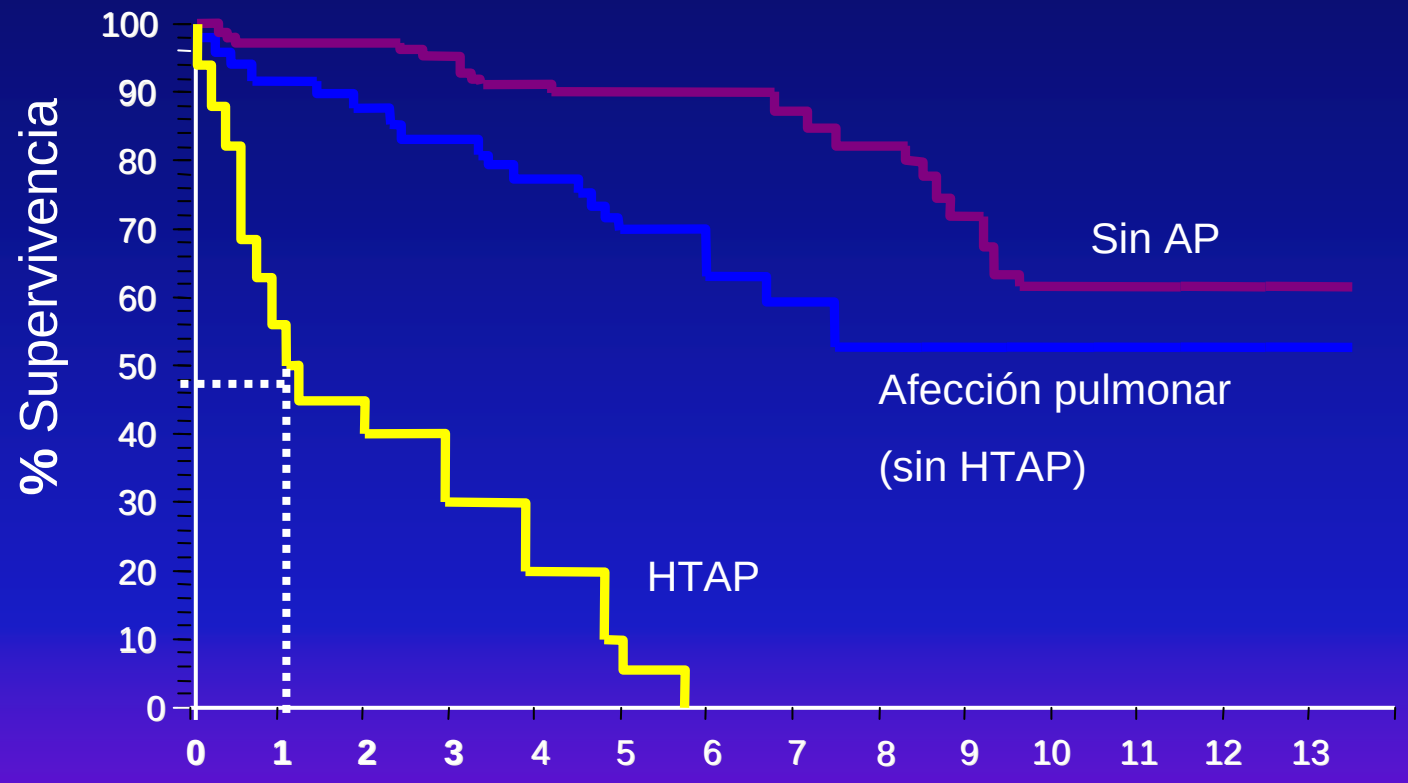
Table 4. Sensitivity and specificity of the 2013 SSc classification criteria and previous SSc classification criteria, overall and in early SSc*

	Derivation sample (n = 200)		Validation sample (n = 405)		Validation sample, disease duration ≤3 years (n = 100)	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
1980 ACR SSc criteria	0.80 (0.72–0.87)	0.77 (0.68–0.84)	0.75 (0.70–0.80)	0.72 (0.64–0.79)	0.75 (0.70–0.80)	0.72 (0.63–0.79)
2001 LeRoy/Medsger SSc criteria	0.76 (0.68–0.84)	0.69 (0.68–0.84)	0.75 (0.70–0.80)	0.78 (0.70–0.85)	0.80 (0.69–0.88)	0.76 (0.53–0.92)
2013 ACR/EULAR SSc criteria	0.95 (0.90–0.98)	0.93 (0.86–0.97)	0.91 (0.87–0.94)	0.92 (0.86–0.96)	0.91 (0.83–0.96)	0.90 (0.70–0.99)

Conclusions

The ACR/EULAR classification criteria for SSc perform better than 1980 ACR preliminary criteria in terms of both sensitivity and specificity. They are relatively simple to apply to individual subjects. These criteria may be endorsed as inclusion criteria for SSc studies. Validation in other populations is encouraged.

HTAP y supervivencia en la ESC

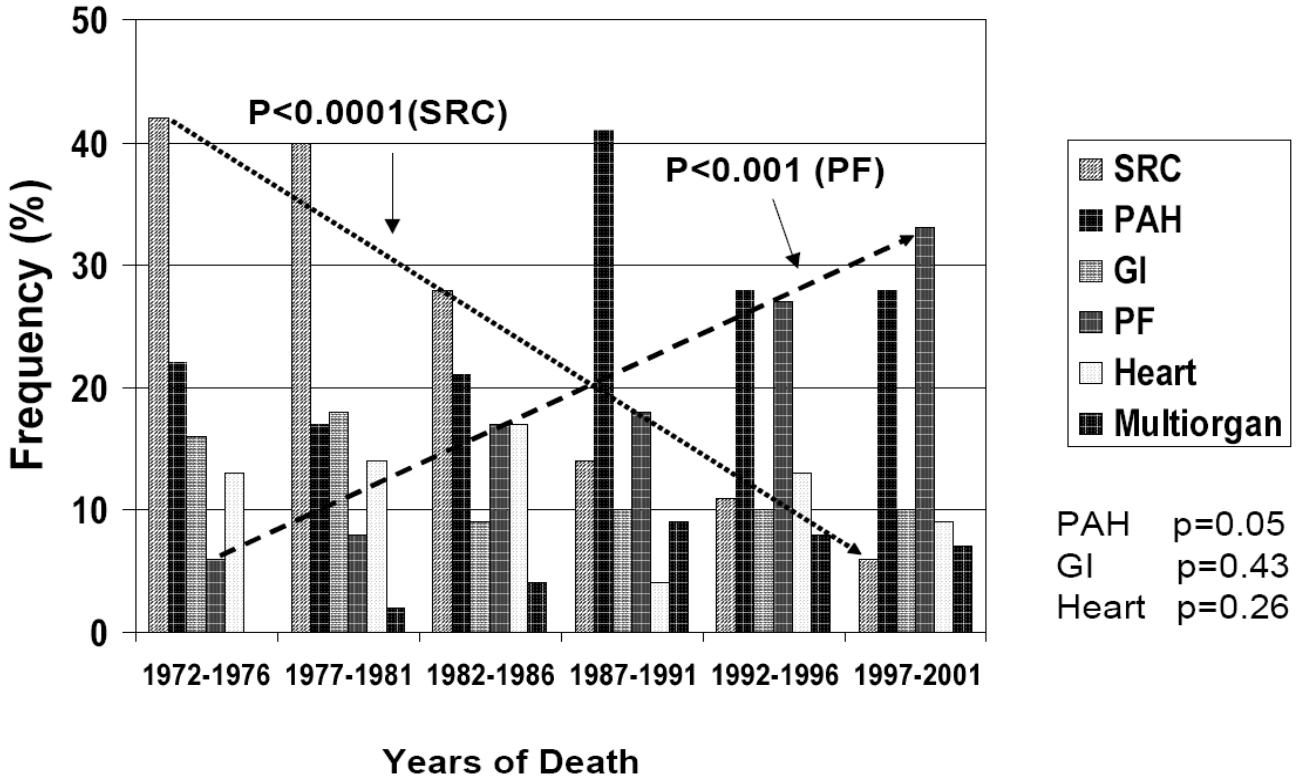


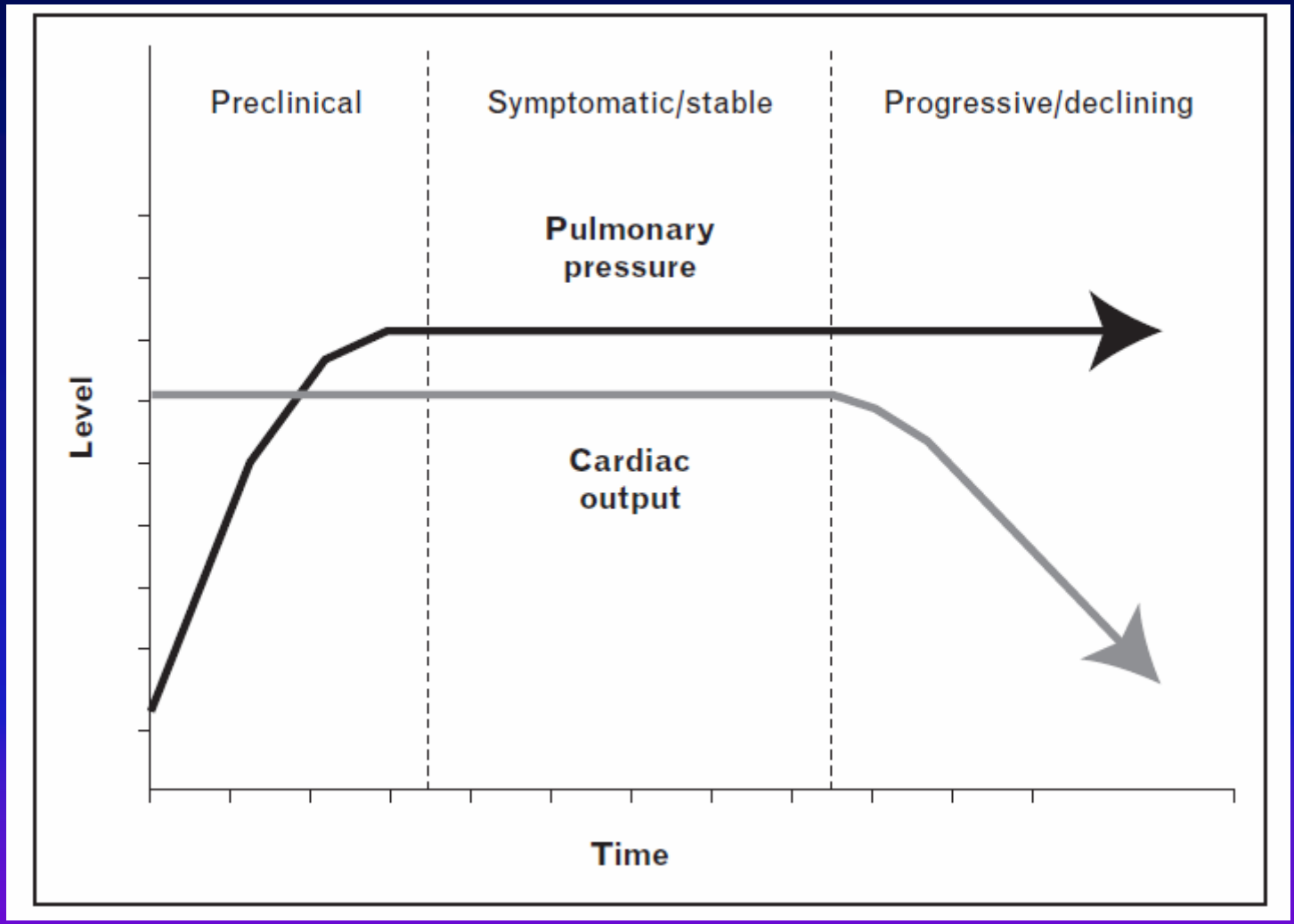
Koh ET, et al. *Brit J Rheumatol*. 1996;35:989.

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

Virginia D. Steen and Thomas A Medsger, Jr

Ann Rheum Dis, 2007




Preclinical
Symptomatic/stable
Progressive/declining
Pulmonary pressure
Cardiac output
Level
Time

Early Detection of Pulmonary Arterial Hypertension in Systemic Sclerosis

Hachulla E *Arthritis Rheum*. 2005

Ecografía cardíaca - VRT – Disnea:
Cateterismo
Prevalencia HTAP: 7,85%

Prediction of Pulmonary Hypertension Related to Systemic Sclerosis by an Index Based on Simple Clinical Observations

Meune C et al. *Arthriris & Rheum*. 2011

ÍNDICE DE "COCHIN"
Cochin RPS= 0,000117(edad) + 0,0207818(150 – CVF) + 0,04095(100-DI_{co}/VA)

Expert consensus for performing right heart catheterisation for suspected pulmonary arterial hypertension in systemic sclerosis: a Delphi consensus study with cluster analysis

Avouac J et al. *Ann Rheum Dis*. 2013

Insuficiencia cardíaca derecha
Cateterismo
Disnea:
EcoCar: PAPs > 45 mmHg
DLCO: < 50%
Cateterismo

High N-Terminal Pro–Brain Natriuretic Peptide Levels and Low Diffusing Capacity for Carbon Monoxide as Independent Predictors of the Occurrence of Precapillary Pulmonary Arterial Hypertension in Patients with Systemic Sclerosis

Allanore Y et al. Arthritis Rheum. 2008

Descenso de DL_{CO}/ Va
Aumento de NT-proBNP

Combination of Echocardiographic and Pulmonary Function Test Measures Improves Sensitivity for Diagnosis of Systemic Sclerosis-associated Pulmonary Arterial Hypertension: Analysis of 2 Cohorts

Glaude H et al. *J Rheumatol.* 2013

Table 5. Univariate logistic regression for association with pulmonary arterial hypertension (PAH).

	n	OR (95% CI)	p
Age	247	1.08 (1.05, 1.1)	< 0.001
Female	247	0.8 (0.4, 1.7)	0.58
SSc disease duration	244	1.06 (1.0, 1.1)	0.001
ACA	236	2.78 (1.5, 5.2)	0.001
ATA	235	0.41 (0.2, 0.9)	0.03
TTE (continuous)	241	1.17 (1.1, 1.2)	< 0.001
FVC%/DLCO% (continuous)	246	4.93 (2.8, 8.6)	< 0.001
eRVSP > 40 mm Hg	241	40.28 (17.7, 91.8)	< 0.001
FVC%/DLCO% ≥ 1.6	246	8.19 (4.2, 16.1)	< 0.001

ACA: anti-centromere antibody; ATA: anti-topoisomerase antibody; TTE: transthoracic echocardiogram in mm Hg; eRVSP: estimated right ventricular systolic pressure; FVC%/DLCO%: forced vital capacity/DLCO percent predicted ratio.

Table 6. Multivariate logistic regression for association with pulmonary arterial hypertension (PAH).

	OR (95% CI)	p
Age	1.04 (0.996, 1.09)	0.07
SSc disease duration	0.99 (0.93, 1.05)	0.78
ACA	1.54 (0.53, 4.42)	0.43
ATA	0.53 (0.16, 1.79)	0.31
eRVSP > 40 mm Hg	29.34 (11.26, 76.41)	< 0.001
FVC%/DLCO% ≥ 1.6	2.98 (1.16, 7.66)	0.02

ACA: anti-centromere antibody; ATA: anti-topoisomerase antibody; eRVSP: estimated right ventricular systolic pressure; FVC%/DLCO%: forced vital capacity/DLCO percent predicted ratio.

Conclusion. In 2 large SSc cohorts, screening with TTE and PFT captured a majority of patients with PAH. TTE and PFT complement each other for the diagnosis of PAH. (J Rheumatol First Release Aug 15 2013 2013; doi:10.3899/jrheum.130400)

Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study

Coghlan JG et al. *ARD*. 2013

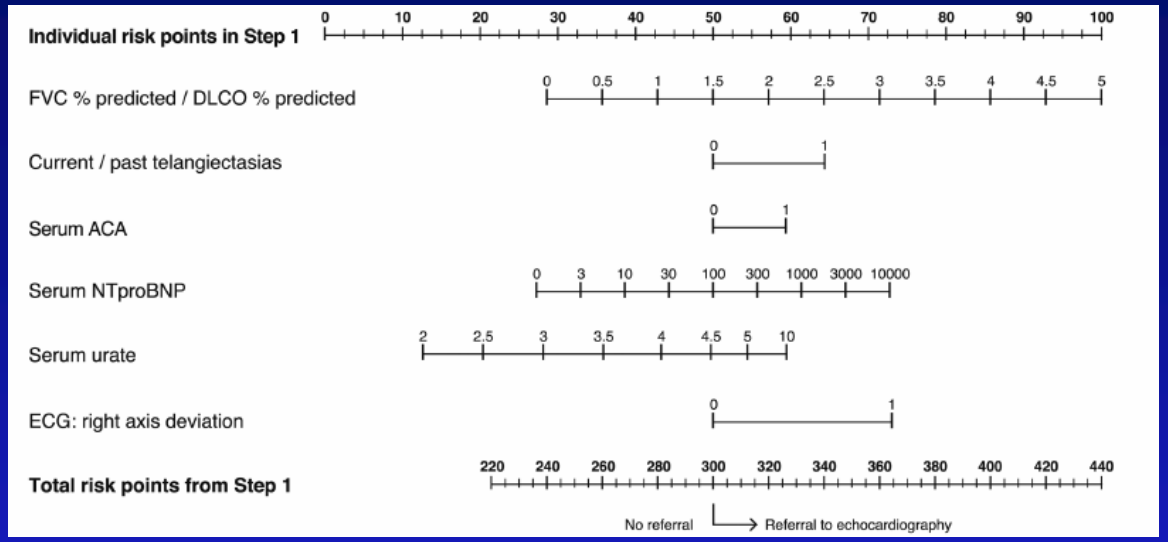
Step 1

Non-echocardiographic variables

- FVC % predicted / DLCO % predicted
- Current / past telangiectasias
- Serum ACA
- Serum NTproBNP
- Serum urate
- ECG: right axis deviation

Total risk points > 300?

(n=356)



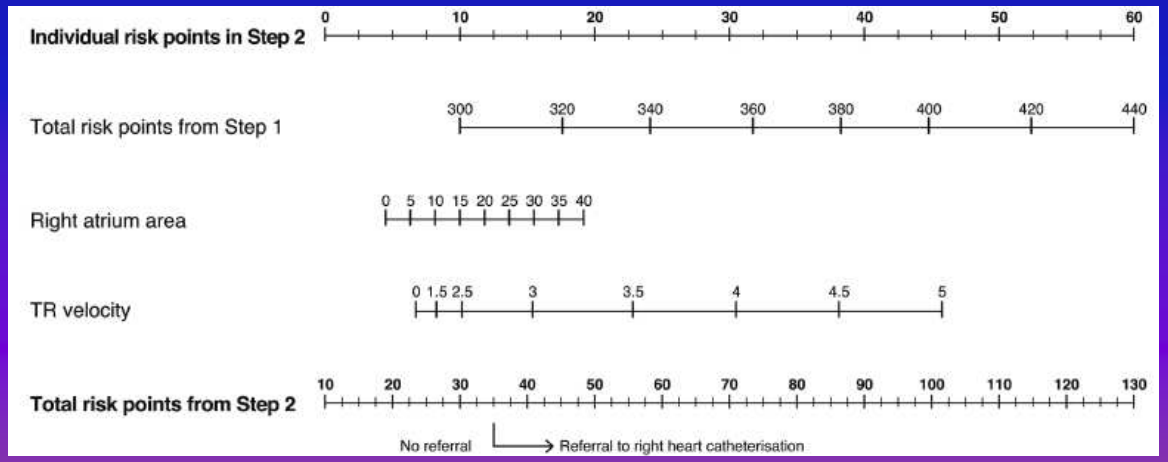
Step 2

Total risk points from Step 1 plus echocardiographic variables

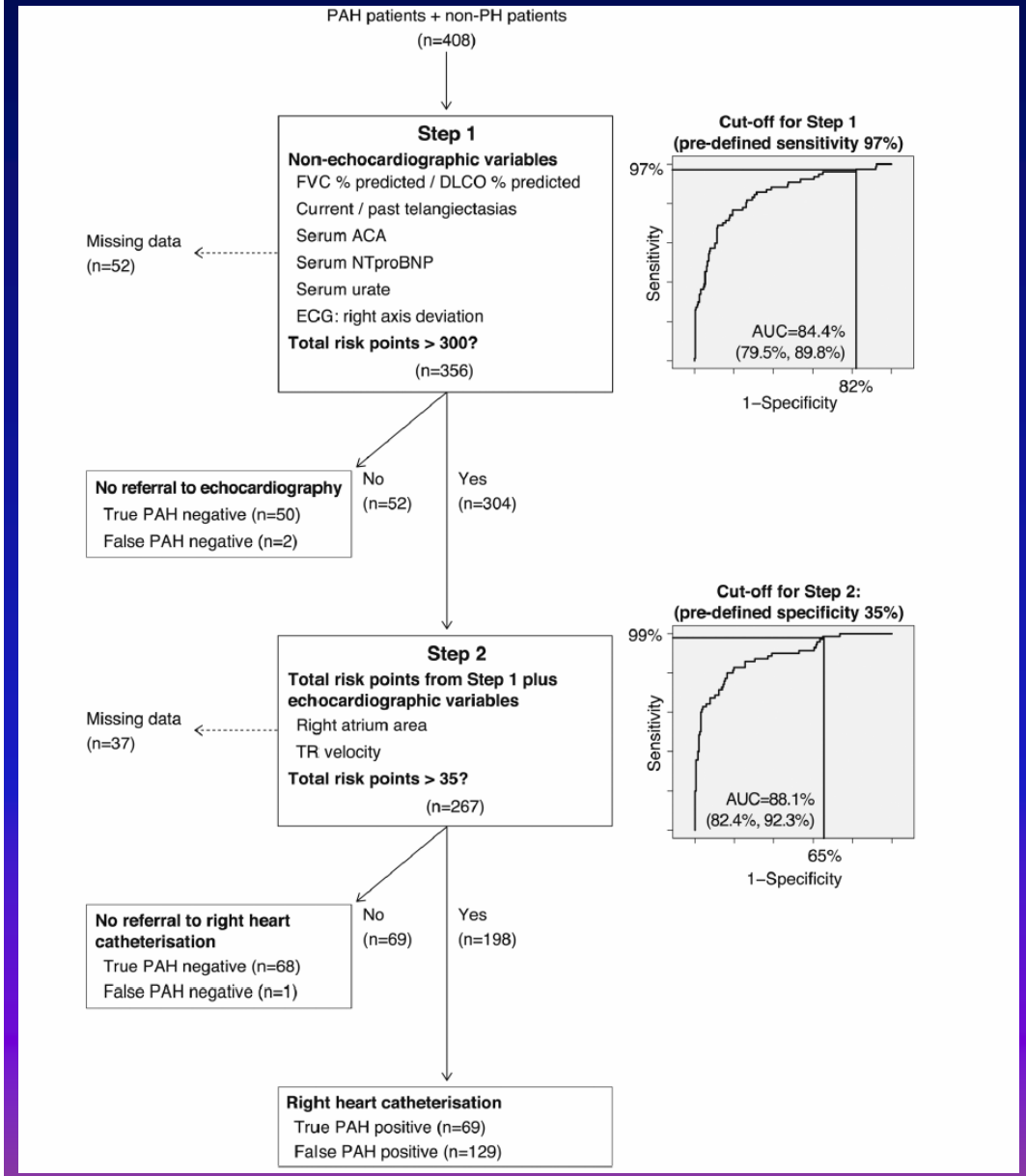
- Right atrium area
- TR velocity

Total risk points > 35?

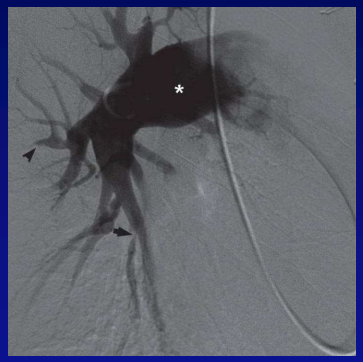
(n=267)



Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study

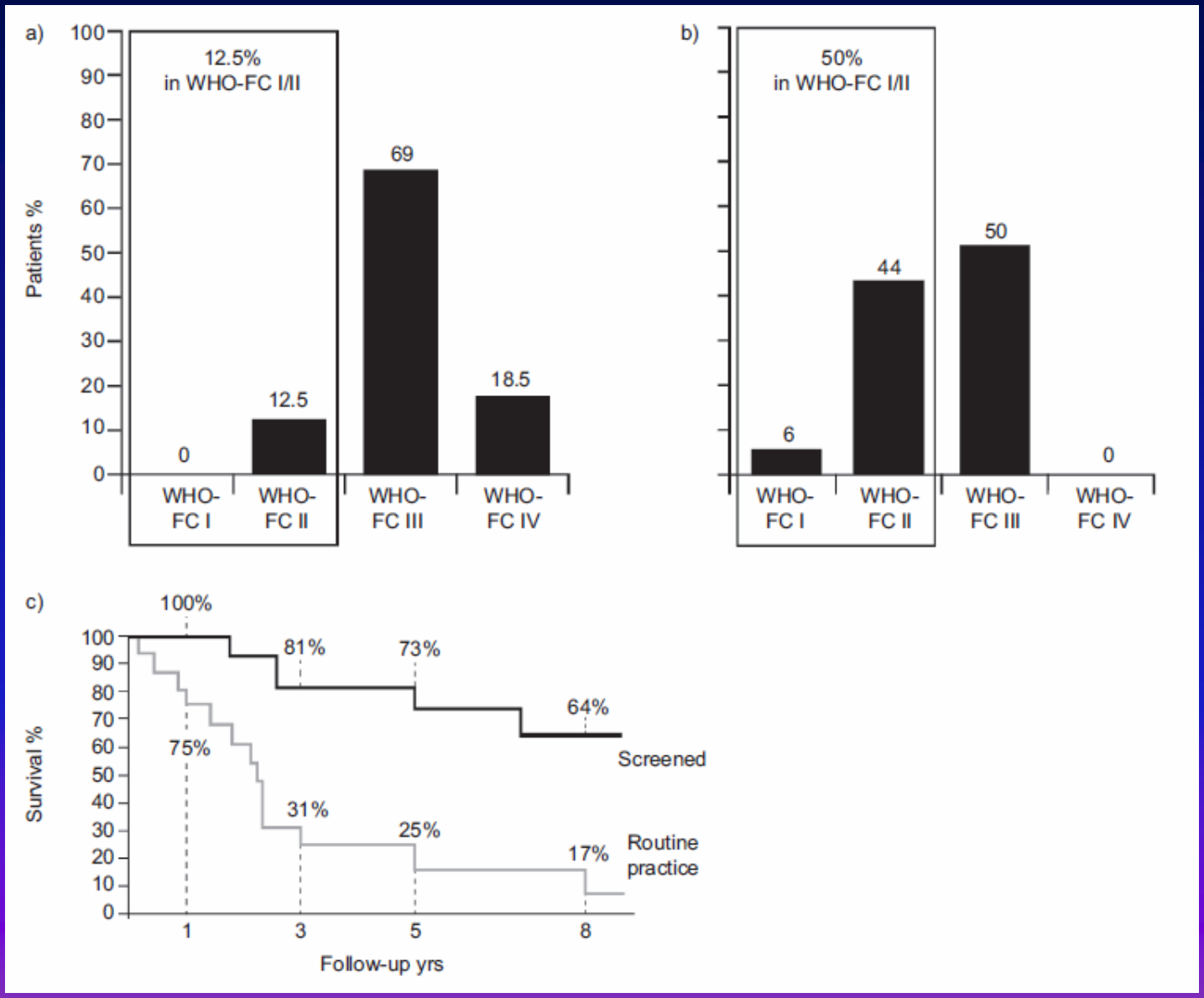


Coghlan JG et al. ARD. 2013



Riesgo elevado de HTAP:
- Evolución >3 años
- Dlco < 60&

HAP: 19%
HTAP no detectada: 4% (3)
Sensibilidad: 96%
Especificidad: 48%



Humbert M. et al. *Eu Respir Rev* 2012

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension

Tomás Pulido, M.D., Igor Adzerikho, M.D., Richard N. Channick, M.D., Marion Delcroix, M.D., Nazzareno Galiè, M.D., Hossein-Ardeschir Ghofrani, M.D., Pavel Jansa, M.D., Zhi-Cheng Jing, M.D., Franck-Olivier Le Brun, M.Sc., Sanjay Mehta, M.D., Camilla M. Mittelholzer, Ph.D., Loïc Perchenet, Ph.D., B.K.S. Sastry, M.D., Olivier Sitbon, M.D., Rogério Souza, M.D., Adam Torbicki, M.D., Xiaofeng Zeng, M.D., Lewis J. Rubin, M.D., and Gérald Simonneau, M.D., for the SERAPHIN Investigators*

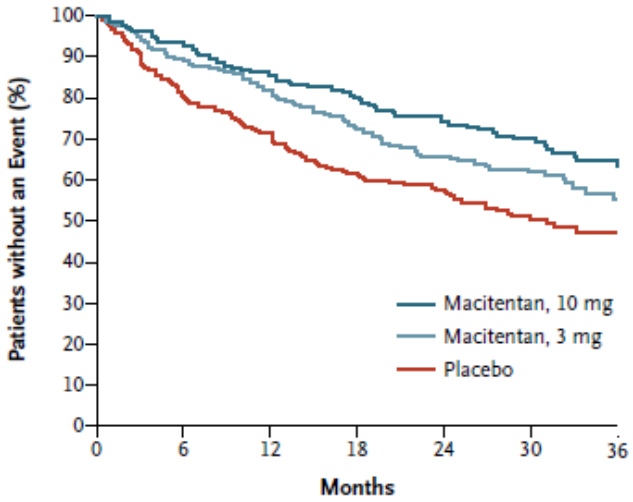
N Engl J Med 2013;369:809-18.
DOI: 10.1056/NEJMoa1213917

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=250)	Macitentan, 3 mg (N=250)	Macitentan, 10 mg (N=242)	All Patients (N=742)
Female sex — no. (%)	184 (73.9)	187 (75.4)	194 (80.2)	565 (76.5)
Age — yr	46.7±17.03	44.5±16.26	45.5±14.99	45.6±16.13
Race or ethnic group — no. (%)†				
White	131 (52.6)	137 (55.2)	135 (55.8)	403 (54.5)
Black	8 (3.2)	5 (2.0)	6 (2.5)	19 (2.6)
PAH classification — no. (%)				
Idiopathic	126 (51.0)	144 (58.3)	134 (55.6)	404 (55.0)
Heritable	3 (1.2)	8 (3.2)	2 (0.8)	13 (1.8)
Associated with connective-tissue disease	81 (32.8)	70 (28.3)	73 (30.3)	224 (30.5)
Associated with congenital shunts	26 (10.5)	15 (6.1)	21 (8.7)	62 (8.4)
Associated with HIV infection	3 (1.2)	1 (0.4)	6 (2.5)	10 (1.4)
Associated with drug use or toxin exposure	8 (3.2)	9 (3.6)	5 (2.1)	22 (3.0)
6-Min walk distance — m	352±110.6	364±95.5	363±93.2	360±100.2
Pulmonary-capillary wedge pressure — mm Hg	9.5±3.4	9.8±3.3	9.5±3.4	9.6±3.4
Cardiac index — liters/min/m² of body-surface area	2.44±0.80	2.36±0.79	2.36±0.78	2.39±0.79
Pulmonary vascular resistance — dyn·sec·cm^{-5}	996±784.3	1044±624.2	1040±672.5	1026±696.7
Receipt of background treatment for PAH — no. (%)				
No	95 (38.2)	85 (34.3)	88 (36.4)	268 (36.3)
Yes	154 (61.8)	163 (65.7)	154 (63.6)	471 (63.7)
Phosphodiesterase type 5 inhibitor	150 (60.2)	154 (62.1)	150 (62.0)	454 (61.4)
Oral or inhaled prostanoid	7 (2.8)	18 (7.3)	15 (6.2)	40 (5.4)
Anticoagulant therapy — no. (%)	119 (47.8)	134 (54.0)	125 (51.7)	378 (51.2)

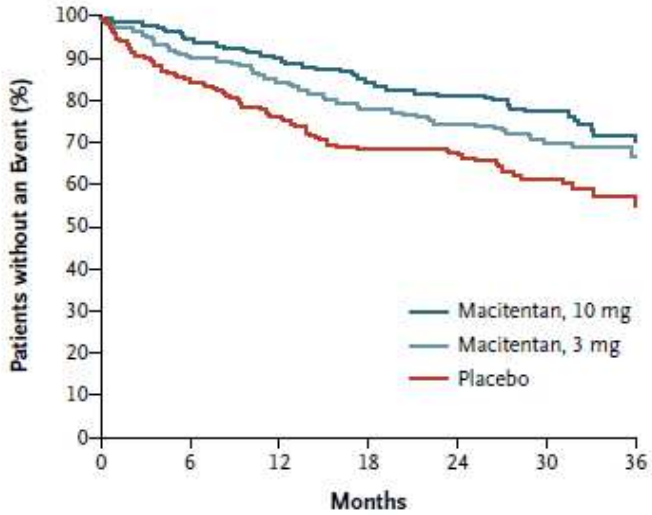
Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension

Pulido T et al. *N Engl J Med*. 2013



No. at Risk							
Placebo	250	188	160	135	122	64	23
Macitentan, 3 mg	250	213	188	166	147	80	32
Macitentan, 10 mg	242	208	187	171	155	91	41

Figure 1. Effect of Macitentan on the Composite Primary End Point of a First Event Related to Pulmonary Arterial Hypertension or Death from Any Cause.



No. at Risk							
Placebo	250	188	155	132	119	62	22
Macitentan, 3 mg	250	208	181	159	144	77	31
Macitentan, 10 mg	242	203	183	166	152	86	39

Figure 2. Effect of Macitentan on the Composite Secondary End Point of Death Due to Pulmonary Arterial Hypertension or Hospitalization for Pulmonary Arterial Hypertension as a First Event.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Riociguat for the Treatment of Pulmonary Arterial Hypertension

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Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Placebo (N=126)	Riociguat, Maximum 2.5 mg 3 Times Daily (N=254)	Riociguat, Maximum 1.5 mg 3 Times Daily (N=63)	Total (N=443)
Female sex — no. (%)	98 (78)	203 (80)	49 (78)	350 (79)
Race — no. (%)†				

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Characteristic	Placebo (N=126)	Riociguat, Maximum 2.5 mg 3 Times Daily (N=254)	Riociguat, Maximum 1.5 mg 3 Times Daily (N=63)	Total (N=443)
Pulmonary arterial hypertension classification — no. (%)				
Idiopathic	84 (67)	149 (59)	39 (62)	272 (61)
Familial	1 (1)	7 (3)	1 (2)	9 (2)
Associated with connective-tissue disease	25 (20)	71 (28)	15 (24)	111 (25)
Associated with congenital heart disease	12 (10)	15 (6)	8 (13)	35 (8)
Associated with portopulmonary hypertension	2 (2)	11 (4)	0	13 (3)
Associated with anorexigen or amphetamine use	2 (2)	1 (<1)	0	3 (1)
Receipt of additional treatment for pulmonary arterial hypertension — no. (%)				
No	66 (52)	123 (48)	32 (51)	221 (50)
Yes¶	60 (48)	131 (52)	31 (49)	222 (50)
Endothelin-receptor antagonist	54 (43)	113 (44)	27 (43)	194 (44)
Prostanoid	6 (5)	18 (7)	4 (6)	28 (6)
6-Min walk distance — m	368±75	361±68	363±67	363±69

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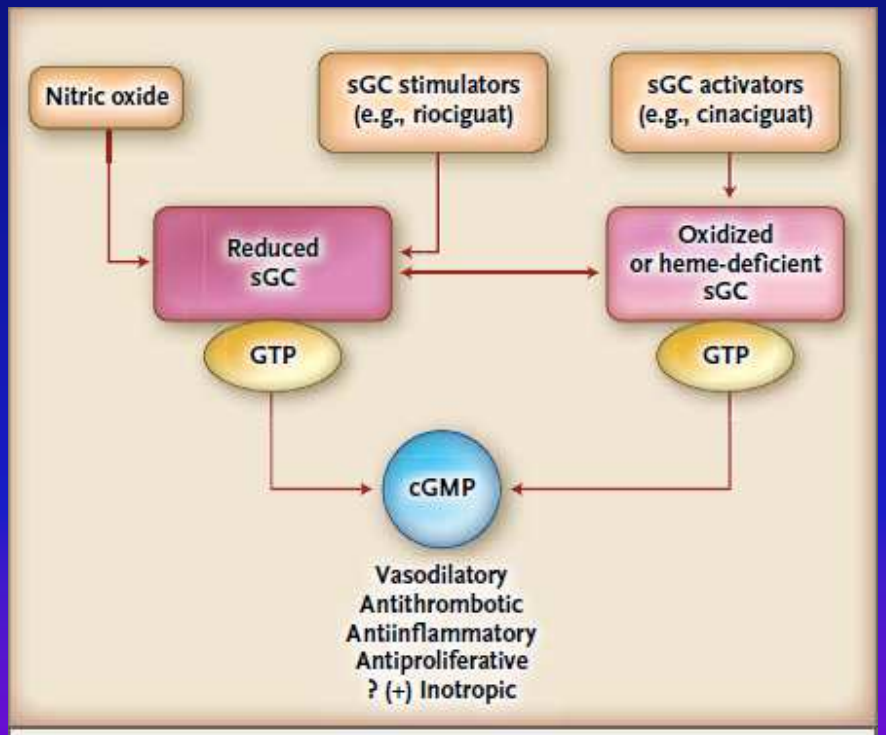

Figure 1. Activation of Soluble Guanylate Cyclase.

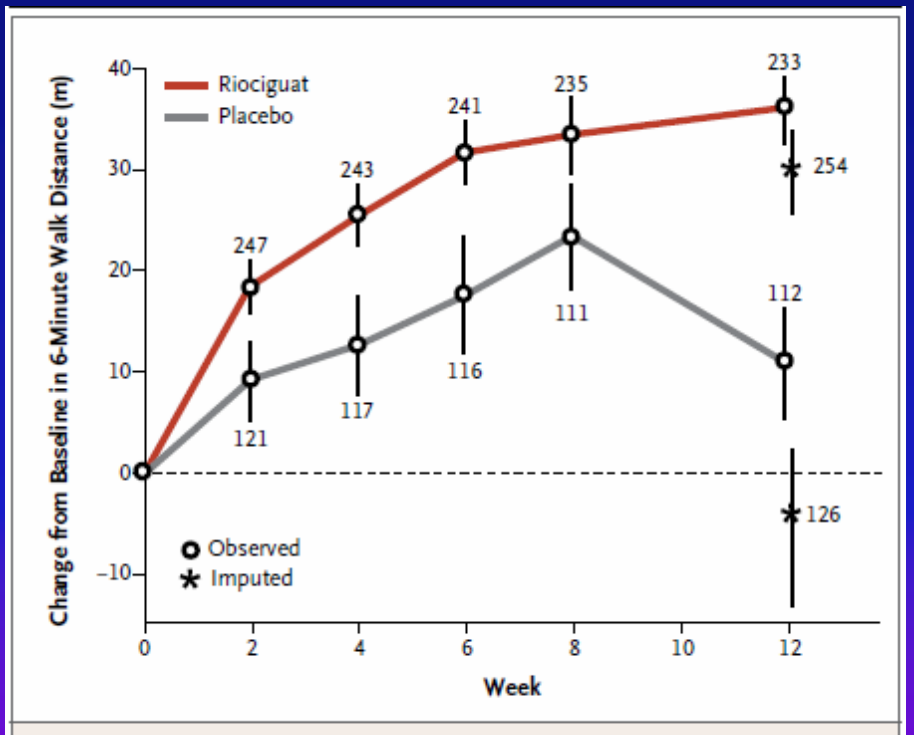

Figure 2. Mean Change from Baseline in the 6-Minute Walk Distance.

Archer SL. *N Engl J Med*. 2013

Differences in clinical presentation and outcome between early versus late onset systemic sclerosis: analysis of 1037 patients

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MEDICINE (Baltimore)

TABLE 2: Comparison of demographics characteristics and serologic profiles in patients grouped by age of SSc onset

	Group 1 ≤30 yr (n=195)	Group 2 31-59 yr (n=651)	Group 3 ≥60 yr (n=191)	p-value	p-value ≤30 vs 31-59	p-value ≤30 vs ≥60	p-value 31-59 vs ≥60
Sex (female, %)	178 (91.3)	561 (86.2)	168 (87.9)	0.164			
Age at disease onset (years)	22±5.8	45±8.1	67±5.9				
Time from onset-diagnosis, (years) (n=1022)	12±13	5.8±7.8	2.4±3.6	<0.001	<0.001	<0.001	<0.001
Follow-up, (mean±SD, years)	6.5±8.3	5.3±6.7	3.6±4.7	<0.001	0.073	0.007	<0.001
Deaths	19 (9.7)	97 (14.9%)	35 (18.3%)	0.053			
Type of scleroderma (n=1035)							
Limited cutaneous SSc	100 (51.3)	394 (60.5)	129 (67.5)	0.004	0.058	0.003	0.212
Diffuse cutaneous SSc	51 (26.2)	179 (27.5)	40 (20.9)	0.201			
Systemic sclerosis sine scleroderma	25 (13)	49 (7.5)	16 (8.4)	0.071			
Prescleroderma	19 (9.7)	28 (4.3)	5 (2.6)	0.002	0.007	0.004	1.000
First manifestation (n=939)							
Raynaud´s phenomenon	154 (88.0)	492 (84.0)	141 (78.0)	0.134			
Puffy hands	4 (2.3)	11 (1.9)	5 (2.9)	-			
Arthralgias	10 (5.7)	36 (6.1)	8 (4.5)	0.718			
Capillaroscopy							
Slow pattern (n=707)	75 (54.0)	254 (57.0)	59 (48.0)	0.217			
Active pattern (n=707)	44 (31.0)	140 (32.0)	46 (38.0)	0.407			
Immunologic features							
Antinuclear antibodies (n=1029)	174 (90.0)	570 (88.0)	162 (85.0)	0.327			
Scl-70 (n=910)	43 (25.0)	128 (22.0)	31 (20.0)	0.604			
Centromeric (n=913)	54 (33.0)	268 (46.0)	76 (47.0)	0.007	0.010	0.021	1.000
Pm-Scl (n=426)	5 (5.4)	13 (5.0)	2 (2.8)	-			
Rheumatoid factor (n=644)	35 (30.0)	83 (21.0)	35 (29.0)	0.045	0.122	1.000	0.191
Ro (n=892)	19 (11.0)	72 (13.0)	22 (13.0)	0.878			
La (n=885)	6 (3.7)	16 (2.8)	4 (2.5)	-			
RNP (n=870)	12 (7.6)	28 (5.1)	5 (3.1)	0.192			
IgG anticardiolipin (n=489)	10 (11)	23 (7.4)	8 (9.5)	0.560			
IgM anticardiolipin (n=489)	1 (1.1)	4 (1.3)	0 (0)	-			

TABLE 3: Comparison of cumulated clinical manifestations in patients grouped by age of onset of SSc

	Group 1 ≤30 yr (n=195)	Group 2 31-59 yr (n=651)	Group 3 ≥60 yr (n=191)	p-value	p-value ≤30 vs 31-59	p-value ≤30 vs ≥60	p-value 31-59 vs ≥60
Peripheral vascular manifestations							
Raynaud's phenomenon	186 (95.0)	605 (93.0)	176 (92.0)	0.390			
Digital ulcers (n=1036)	106 (54.0)	265 (41.0)	64 (34.0)	<0.001	0.002	<0.001	0.216
Telangiectasies (n=1036)	117 (60.0)	391 (60.0)	121 (63.0)	0.710			
Acrosteolysis (n=966)	19 (10.0)	53 (8.7)	13 (7.3)	0.538			
Osteomuscular							
Calcinosis (n=980)	39 (22.0)	125 (20.0)	29 (16.0)	0.257			
Arthritis (n=927)	26 (16.0)	114 (19.0)	33 (19.0)	0.564			
Myositis (n=928)	19 (11.0)	42 (7.2)	5 (2.9)	0.009	0.171	0.006	0.155
Tendon friction rubs (n=927)	7 (4.2)	27 (4.6)	12 (6.9)	0.432			
Digestive involvement							
Esophagus (n= 922)	118 (72.0)	393 (67.0)	97 (56.0)	0.004	0.608	0.005	0.022
Stomach (n=920)	22 (14.0)	82 (14.0)	25 (15.0)	0.974			
Malabsortion (n=769)	10 (7.9)	26 (5.3)	10 (6.5)	0.535			
Heart involvement							
Pericarditis (n=873)	7 (4.7)	28 (5.1)	11 (6.4)	0.749			
Ischemia (n=871)	16 (11.0)	62 (11.0)	16 (9.2)	0.763			
Conduction alteration (n=872)	13 (8.7)	69 (13.0)	36 (21.0)	0.004	0.674	0.005	0.016
Lung involvement							
ILD (n=983)	88 (50.0)	305 (49.0)	106 (57.0)	0.139			
Ground-glass pattern (n=506)	35 (35.0)	113 (36.0)	24 (26.0)	0.202			
Reticular pattern (n=887)	34 (22.0)	130 (23.0)	32 (19.0)	0.554			
PH by echocardiogram[1] (n=881)	18 (12.0)	106 (19.0)	43 (25.0)	0.010	0.165	0.007	0.185
PH by RSHC[2] (n=56)	6 (86.0)	34 (83.0)	7 (88.0)	0.940			
Isolated PAH (without ILD) (n=167)	2 (11.0)	8 (7.5)	6 (14.0)	-			
Renal involvement							
Scleroderma renal crisis (n=870)	5 (3.4)	19 (3.4)	5 (2.9)	-			
Other manifestations							
Peripheral neuropathy (n=155)	5 (15.0)	11 (11.0)	2 (8.3)	-			
Sicca syndrome (n=980)	51 (29.0)	210 (34.0)	67 (36.0)	0.343			

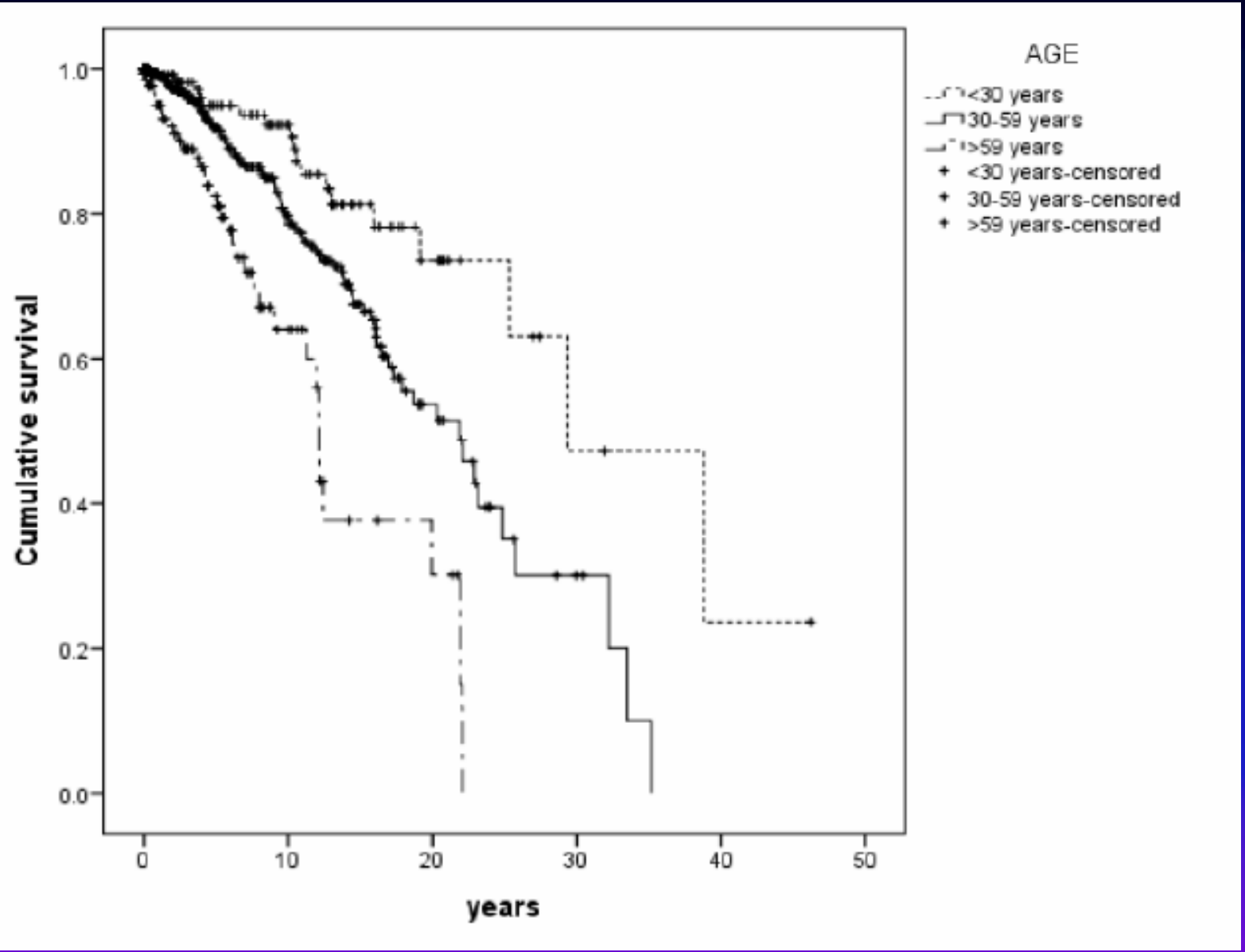

Fig 1: Kaplan-Meier estimate of the probability of death (since diagnosis) depending on age of disease onset

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GRUPO 1 (≤ 30)
Afección esofágica (+)
Miositis (+)
Anticentrómero (-)
HTP: 12%

GRUPO 3 (≥ 60)
Forma limitada (+)
Úlceras digitales (-)
Alts. sist. conducción (+)
HTP: 25%

Mortalidad estandarizada: 3.80

Rossell. Baix Maestrat