VI Reunión GEAS

17 y 18 de Octubre de 2013

Auditorio - Palacio de Congresos de Zaragoza

Zaragoza

Pre-esclerodermia o esclerodermia inicial

Dra. Carmen Pilar Simeón Aznar

Arthritis & Rheumatism

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SPECIAL ARTICLE

2013 Classification Criteria for Systemic Sclerosis

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

ARD

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.

Ann Rheum Dis 2013 72: 1747-1755
doi: 10.1136/annrheumdis-2013-204424

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.

ACR 1980

ACR 1980

ACR 1980

ACR 1980

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)

Proyecto RESCLE: Validación nuevos criterios ACR/EULAR

	Cohorte	SSc limitada	SSc sine
Nº pacientes	1145	698	102
Criterios ACR 1980	721 (63%)	435 (62.3%)	12 (11.8%)
Criterios ACR/EULAR 2013	991 (86.6%)	670 (96%)	41 (40.2%)

Criterios diagnósticos y de clasificación de SSc

Criterios de clasificación de SSc ARA del 1980 Limitaciones

1. Escasa sensibilidad en los casos de esclerodermia limitada o esclerodermia *sine* esclerodermia √

2. Exclusión de pacientes en estudios clínicos y ensayos terapéuticos √

3. Pacientes con síndromes esclerodermiformes pueden cumplir los criterios de ACR √

4. No se definen las características clínicas, inmunológicas ni el pronóstico ✕

5. Enfermos con esclerodermia inicial quedan excluidos

Skin disease: a cardinal feature of systemic sclerosis

Rheumatology 2009

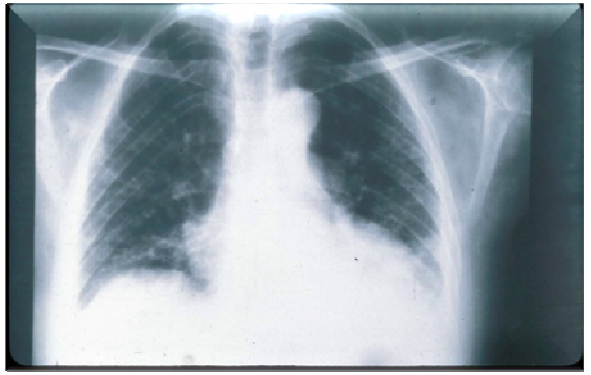
Table 1. Classification of systemic sclerosis subsets.

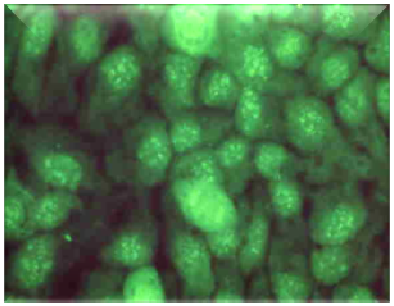
Study	Classification Scheme	Number of Citations
Barnett[36]	3 subsets: limited, moderate, extensive, based on skin involvement of the fingers only, limbs and face, and involvement of the trunk, respectively	66
Ferri[30]	4 subsets: sine scleroderma SSc: absence of cutaneous involvement with visceral involvement, 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
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
	cutaneous changes without criteria for lSSc or lcSSc	
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]	CRST syndrome: calcinosis, RP, sclerodactyly, telangiectasia	176

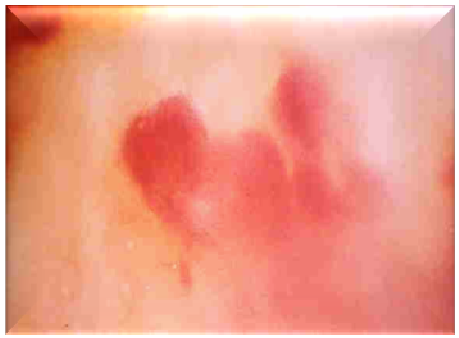
RP: Raynaud's phenomenon; NC: nailfold capillary; ILD: interstitial lung diseases; GI: gastrointestinal; ACA: anticentromere antibodies; PAH: pulmonary arterial hypertension; LSSc: limited SSc.

Esclerodermia *sine* esclerodermia

1) Fenómeno de Raynaud o equivalente
2) Anticuerpos antinucleares positivos
3) Afección visceral típica de SSc:
    - Hipomotilidad distal esofágica o intestinal
    - EPI o PAH
    - Afección cardíaca
    - CRE







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

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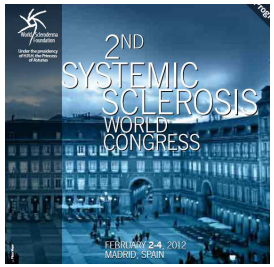


Recomendaciones para mejorar la investigación clínica en SSc
Prof Medsger 2nd SSc World Congress

1. Alternativas para evaluar el endurecimiento cutáneo.
2. Pacientes deben incluirse en los ensayos antes del pico máximo de endurecimiento cutáneo (12-15meses)
3. Considerar autoanticuerpos en el diseño del estudio para mejorar la estratificación
4. **Identificación temprana de los enfermos con SSc**

Criteria for the Classification of Early Systemic Sclerosis

E. CARWILE LeROY and THOMAS A. MEDSGER Jr

Limitada

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
Diffuse fasciitis with eosinophilia (DFE):		
		proximal cutaneous changes without criteria for lSSc or lcSSc

(J Rheumatol 2001;28:1573–6)

EDITORIAL

Systemic sclerosis

What does the clinician need to improve patient care in systemic sclerosis?

Madelon C Vonk, Frank H J van den Hoogen, Piet L C M van Riel, Gabriele Valentini

Ann Rheum Dis 2007;66;1129-1131

Validated clinimetric criteria, useful in the early phase of systemic sclerosis, are lacking

"Finally, following the suggestions of LeRoy and Medsger, data have been provided that support the diagnosis of SSc in an ***early "prescleroderma"*** *stage in cases where there is no skin thickening, referred to as* ***"limited" SSc.*** *Uniformly applicable diagnostic criteria of SSc require that these are developed in patients with* ***early SSc,*** *and not in patients with established disease."*

*Report of a Meeting of Physicians and Scientists, Royal Free Hospital School of Medicine, London**

Panel: **Classification of the systemic sclerosis subsets**

1. **"Pre-scleroderma"** Raynaud's phenomenon plus nailfold capillary changes; disease specific circulating anti-nuclear autoantibodies (anti-topoisomerase-I, anti-centromere [ACA], or nucleolar); and digital ischaemic changes.
2. **Diffuse cutaneous SSc (dcSSc)** Onset of skin changes (puffy or hidebound) within 1 year of onset of Raynaud's; (occasionally decades); skin involvement limited to hands, face, feet, and forearms (acral); a significant (10–15%) late incidence of pulmonary hypertension, with or without interstitial lung disease, skin calcification, telangiectasiae and gastrointestinal involvement; high prevalence of ACA (70–80%); dilated nailfold capillary loops, usually without capillary dropout.
4. **Scleroderma sine scleroderma** Raynaud's; no skin involvement; presentation with pulmonary fibrosis, scleroderma renal crisis, cardiac or gastrointestinal disease; antinuclear antibodies may be present (Scl70, ACA, nucleolar)

"Pre-scleroderma" Raynaud's phenomenon plus nailfold capillary changes; disease specific circulating anti-nuclear autoantibodies (anti-topoisomerase-I, anti-centromere [ACA], or nucleolar); and digital ischaemic changes.

Lancet 1996; **347:** 1453–58

REGISTRY OF THE SPANISH NETWORK FOR SYSTEMIC SCLEROSIS: CLINICAL PATTERN ACCORDING TO CUTANEOUS SUBSETS AND IMMUNOLOGICAL STATUS

Semin Arth Rheum 2011 Línea Esclerodermia (GEAS)

	LcSSc	*dcSSc*	*ssSSc*	*preSSc*	*overall*
Number patients n (%)	566 (61.8)	243 (26.5)	69 (7.5)	37 (4)	916
Ratio Female: Male	8:1	4.6:1[c]	8.8:1	17.5:1	7:1
Age at onset (yrs)	45:97±15.57	43.99±15.32	44.89±18.2	36±14[de]	45.02±15.23
Age at diagnosis (yrs)	53.36 ±14.41	46.76±15.51 [b*c]	53.22±15.98	41.7±14.3[df]	51.17±15.29
Time onset-diagosis (yrs)	7.37± 9.7	2.84± 5.96[b*c*]	8.31±10.49	5.69±6.40	6.16± 9.07
ACR criteria fulfilled	367 (65.3)[a*]	243 (100)[bc*]	10 (14.5)	0 (0)	620 (67.7)
First manifestation					
RP	434 (86.1)	149 (72.7)[bc]	60 (90.9)	35 (97.2)	678 (83.6)
Puffy hands	6 (1.2)	6 (2.9)	1 (1.5)	0 (0)	13 (1.6)
Arthralgia	31 (6.2)	16 (7.8)	2 (3)	1 (2.8)	50 (6.2)
Skin sclerosis	21 (4.2)	29 (14)[bc]	0 (0)	0 (0)	50 (6.2)
RP	533 (94.8)	215 (88.5)[b]	63 (91.3)	37 (100)	849 (92.7)
Digital Ulcers	219 (39)[a*]	155 (63.8)[b*c*]	10 (14.5)	10 (27)	394 (43.0)
Telangiectasias	355(63.2)	153(63)	40(58)	6 (16.2)	554 (60.5)
Calcinosis	111 (19.8)[a*]	57 (23.5)[c]	5 (7.2)	1 (2.7)	174 (19.0)
ANA positive	517 (92)	224 (92.2)	62 (89.9)	37 (100)	840 (91.7)
Scl70 positive	45 (9.4)	116 (52.7)[b*c*]	6 (9.5)	6 (18.8)	173 (18.9)
ACA positive	293 (58)[a]	17 (8.4)[b*c*]	27 (41.5)	19 (54.3)	356 (38.9)

Proyecto RESCLE: Validación nuevos criterios ACR/EULAR

	Pre SSc
Nº pacientes	71
Criterios ACR 1980	0 (0%)
Criterios ACR/EULAR 2013	11 (15.5%)

Diagnosis and Classification of Systemic Sclerosis

Eric Hachulla · David Launay

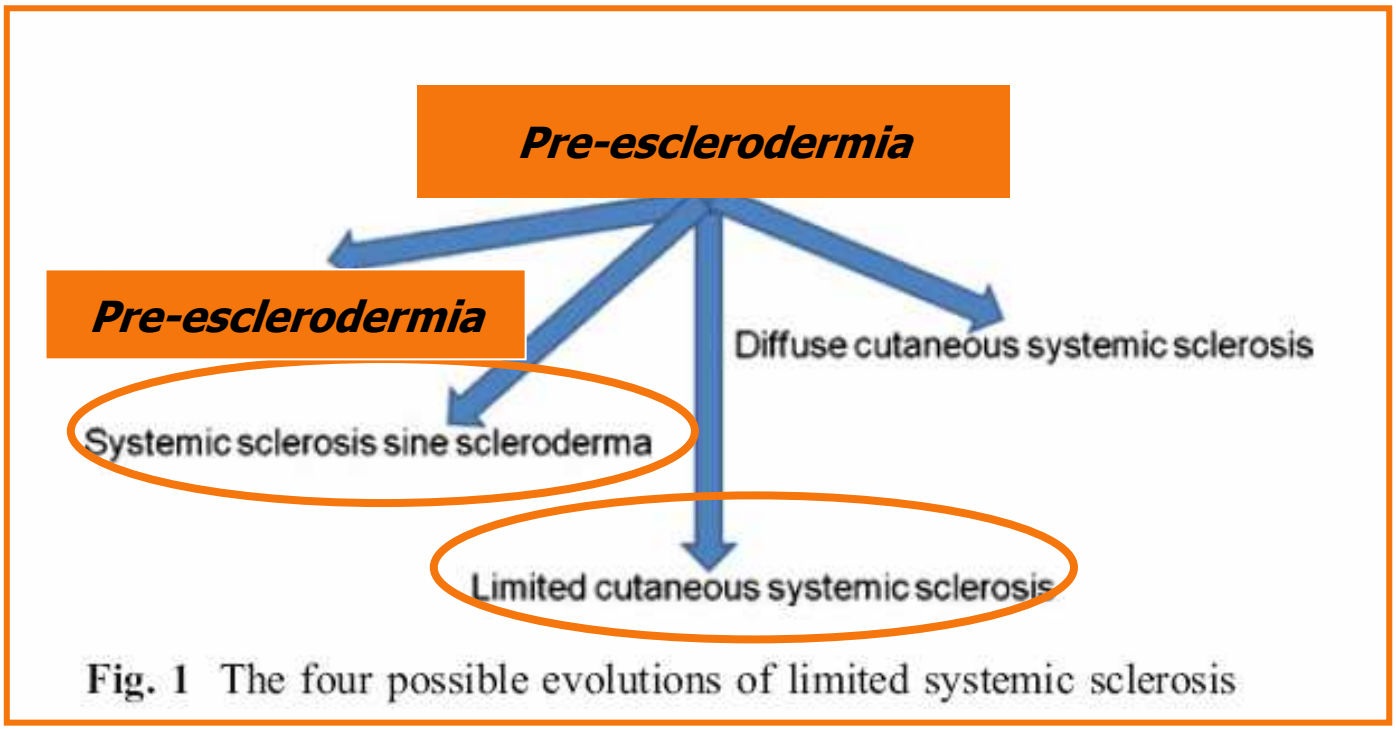


Fig. 1 The four possible evolutions of limited systemic sclerosis

Clinic Rev Allerg Immunol (2011) 40:78–83

Pre-esclerodermia

(Early SSc)

(FR + ANAs+ Alt capilaroscópicas)

Pre-esclerodermia: 40 pacientes

HVH cohorte: 414 pacientes. Seguimiento:1986-2012
Evaluación: manometría esofágica / ecocardiograma-Doppler/ PFR con DCO

Progresión: 12 (30%) media 9.7 años (3-17a)

lcSSc: 6 (50%)
ssSSc: 6 (50%)

Pre-esclerodermia: 28 pacientes media 6.6 años (1-27a):

11 DCO < 70%
7 Disfunción Diastólica VI
10 sin alteraciones

Early systemic sclerosis: assessment of clinical and pre-clinical organ involvement in patients with different disease features

TABLE 2 Prevalence of functional cardiac, lung and oesophageal alterations in 115 RP patients subdivided into three groups

	Early SSc	Probable SSc	UCTD	P1	P2	P3
E:A ratio <1[a]	1/19	1/51	1/45	0.5	0.5	0.9
FVC <80%	0	3/51	0	0.5	–	0.5
DL_{CO} <80%	7/19	26/51 (10 with effort dyspnoea)	10/45 (2 with effort dyspnoea)	0.4	0.2	0.006
DL_{CO} <70%	5/19	15/51 (6 with effort dyspnoea)	5/45 (2 with effort dyspnoea)	0.9	0.1	0.04
Basal LES pressure <15 mmHg	4/18	24/43 (21 with dysphagia/heartburn)	4/25 (4 with dysphagia/heartburn)	0.02	0.7	0.001
Plus distal oesophageal hypomotility	0/4	10/24	2/4	0.2	0.4	0.9

Considering the three abnormalities together, functional heart and/or lung and/or oesophageal abnormalities were detected in 8/19 (42%) early SSc patients.

Valentini et al Rheumatology 2010

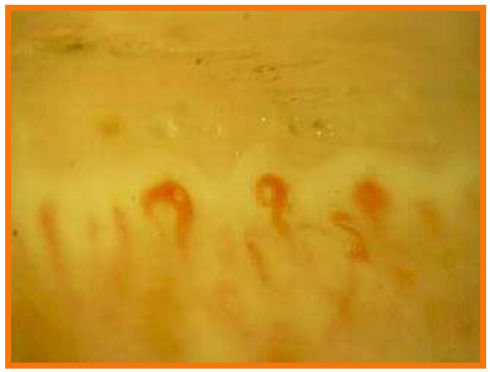
RHEUMATOLOGY

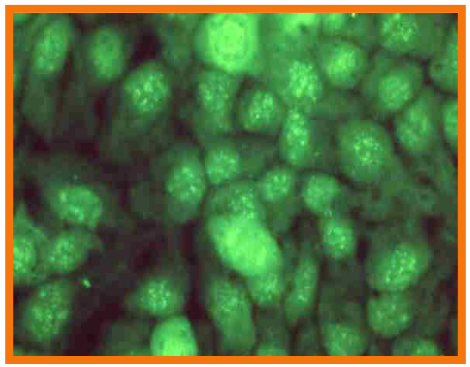
Editorial

doi:10.1093/rheumatology/keq374

Beyond Raynaud's phenomenon hides very early systemic sclerosis: the assessment of organ involvement is always mandatory

László Czirják[1] and Marco Matucci-Cerinic[2]





Rheumatology key messages

- Patients with early SSc should be investigated for pre-clinical internal organ involvement.

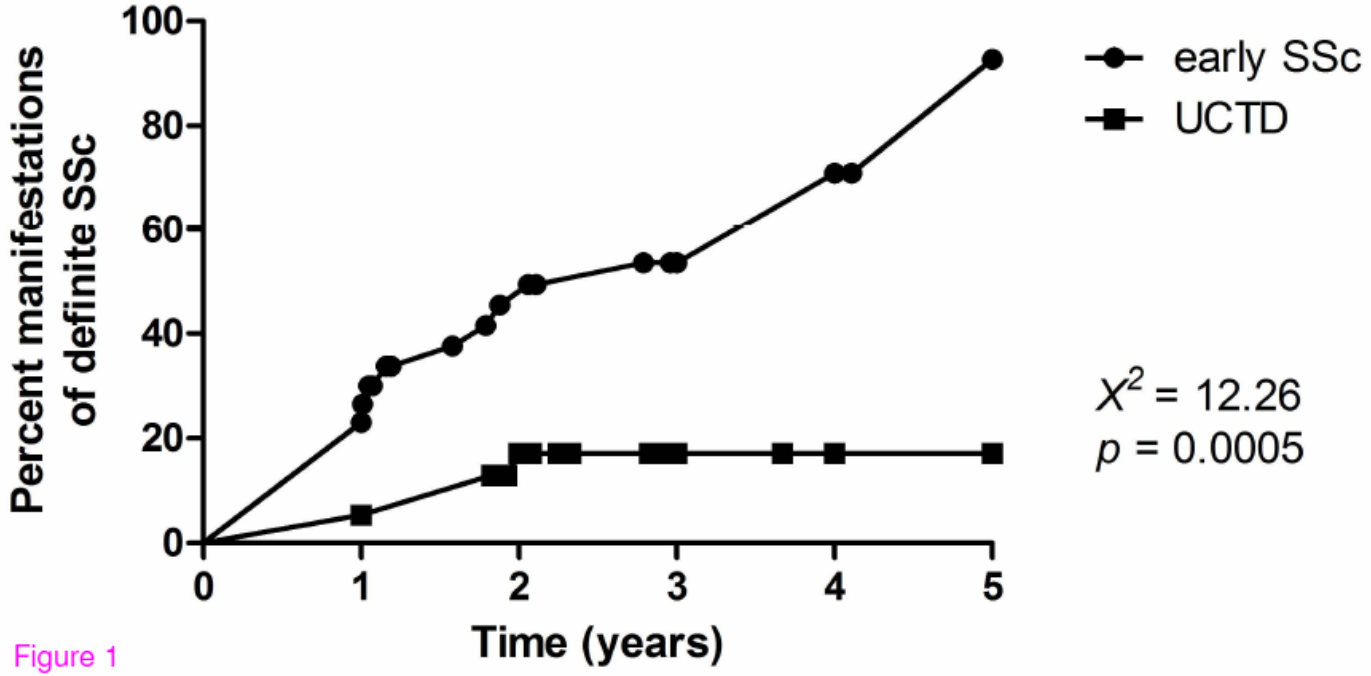


Figure 1

	Early SSc					UCTD		p†
	1° y	2° y	3° y	4° y	5° y	1° y	2° y*	
Definite SSc (%)	**9(23)**	**15(48)**	**17(63)**	**18(72)**	**23(92)**	**2(5.4)**	**5(17)**	**0.0005**

23 Definite SSc:
3 lcSSc
1 dcSSc
7 ssSSc
12¿subset?

Arthritis Research & Therapy 2012, **14**:R188 doi:10.1186/ar4019

Pre-esclerodermia
≠
SSc inicial

Pre-esclerodermia: 28 pacientes media 6.6 años (1-27a)

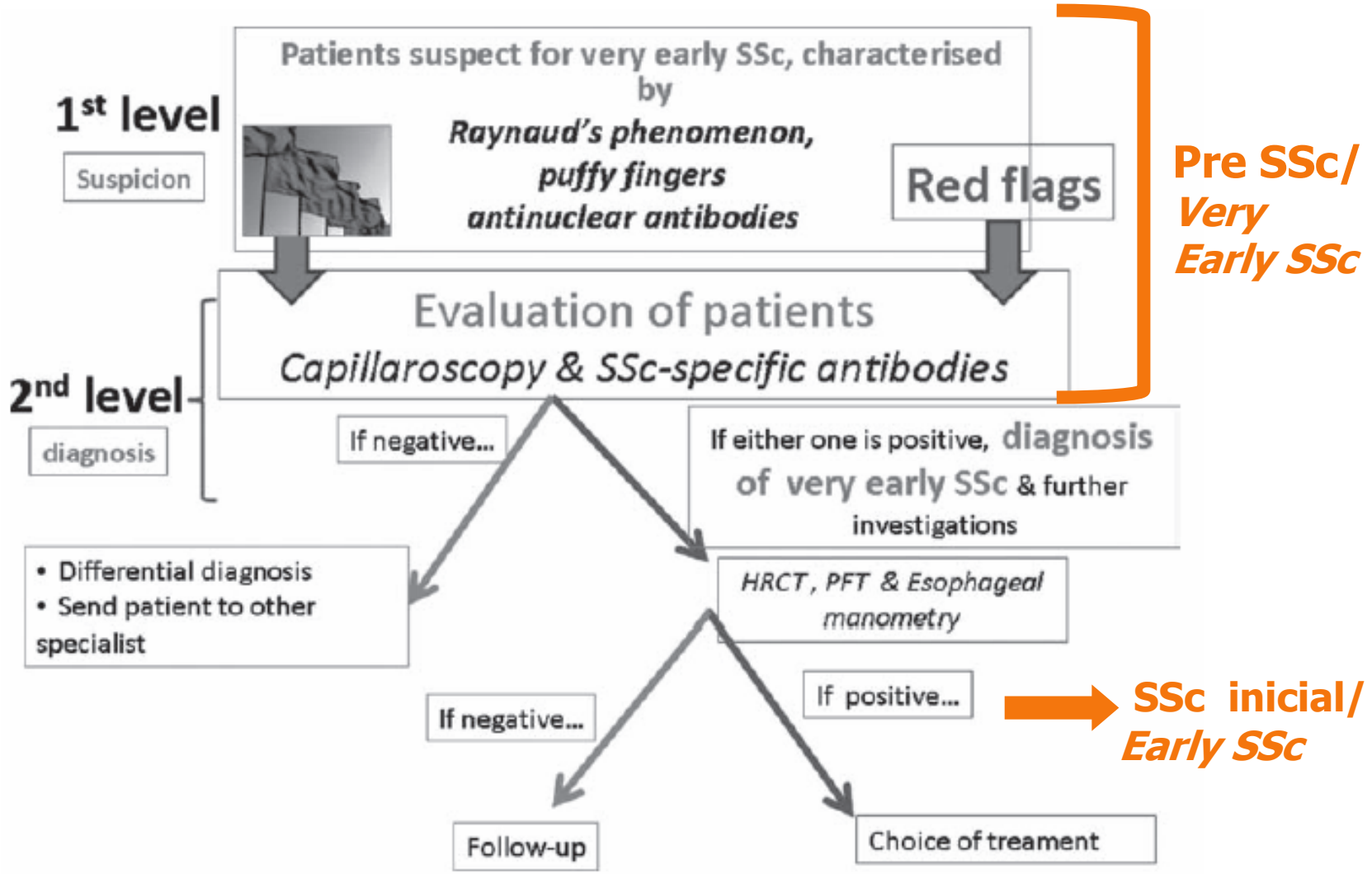
10 Sin alteraciones → **Pre- SSc**
Very Early SSc

11 DCO/VA < 70%
7 Disfunción Diastólica → **SSc inicial**
Early SSc

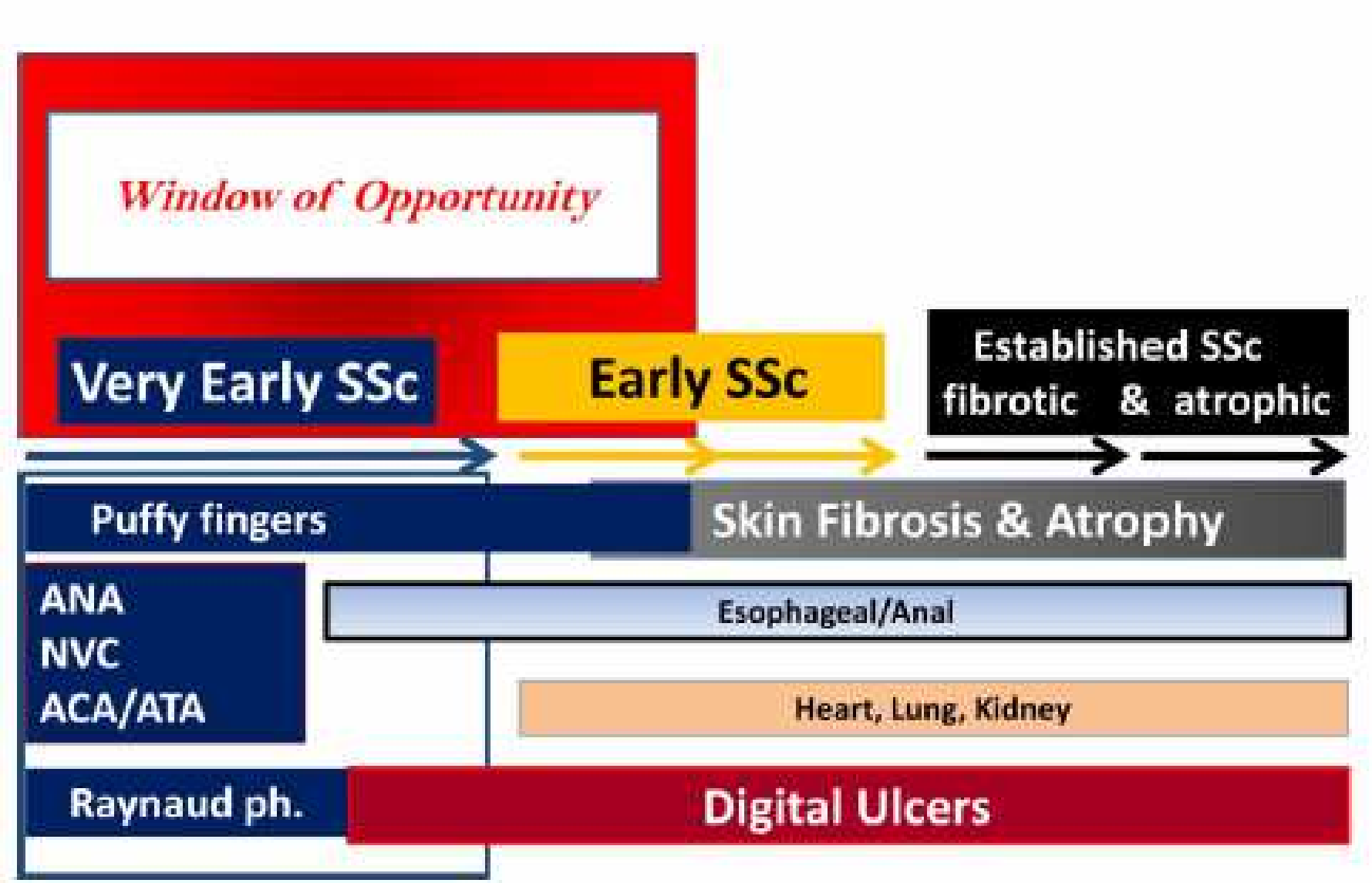
Los subtipos de esclerodermia "no cutáneos"

	Pre-SSc	SSc inicial	SSc sine
FR	Si	Si	Si
Alt capilares	Si	Si	Si
ANAs	Si	Si	Si
GI/EPI/HTAP/CRE Afec cardíaca	No	No	Si
EEI hipotenso	No	Si	----
DCO <70%	No	Si	----
DD	No	Si	----

Criterios preliminares para el diagnóstico precoz de SSc



Avouac et al ARD 2011



Matucci Cerinic ARD 2012

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Pre-esclerodermia y esclerodermia inicial

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Very early versus *early* disease: the evolving definition of the '*many faces*' of systemic sclerosis

Marco Matucci-Cerinic, Silvia Bellando-Randone, Gemma Lepri, Cosimo Bruni, Serena Guiducci

ARD 2012

Conclusiones

A los pacientes con **pre-esclerodermia** se les debe investigar la presencia de afección orgánica funcional al inicio del seguimiento y anualmente.

El cribaje ha de incluir: manometría esofágica, ecocardiografía-Doppler y pruebas funcionales respiratorias con DCO

Los pacientes con **pre-esclerodermia** que presentan alteraciones funcionales orgánicas (sin afección visceral establecida) se deben considerar **esclerodermia inicial**.

Los pacientes con **pre-esclerodermia** y con **esclerodermia inicial** pueden evolucionar a esclerodermia definida (subtipos limitada y sine)

El diagnóstico precoz de la enfermedad y de sus manifestaciones clínicas puede abrir nuevas perspectivas terapéuticas e influir en el pronóstico de los pacientes


El Pilar 2013