Influence of antibody profile in clinical features and prognosis in a cohort of Spanish patients with systemic sclerosis

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ABSTRACT

Objective. *To assess the clinical manifestations and prognosis of Spanish patients with systemic sclerosis (SSc) according to their immunological profile.*

Methods. *From the Spanish Scleroderma Study Group or RESCLE (Registro de ESCLErodermia as Spanish nomenclature) Registry we selected those patients in which anti-centromere (ACA), anti-topoisomerase I (ATA), and anti-RNA polymerase III (ARA) antibodies had been determined, and a single positivity for each SSc specific antibody was detected. Demographic, clinical, laboratory, and survival data were compared according to the serologic status of these antibodies.*

Results. *Overall, 209 SSc patients were included. In 128 (61%) patients ACA was the only positive antibody, 46 (22%) were only positive for ATA, and 35 (17%) for ARA. Of note, the three groups were mutually exclusive. In univariate analysis, patients with ACA presented more frequently limited cutaneous SSc (lcSSc) ($p<0.001$), whereas diffuse cutaneous SSc (dcSSc) was the most frequent subtype in patients with ATA (54%) and ARA (62%) (both $p<0.001$). Positive patients for ARA showed the highest prevalence of joint involvement ($p<0.001$) and those from ATA group had a higher prevalence of interstitial lung disease (ILD) ($p<0.001$). Scleroderma renal crisis was more frequent in the ARA group ($p<0.001$). In multivariate analysis, ACA were associated with female gender and were protective for dcSSc and ILD. ATA were found to be protective for lcSSc and they were independently associated with interstitial reticular pattern. ARA positivity was independently associated with dcSSc. We did not find differences in mortality between the three groups.*

Conclusion. *In Spanish SSc patients, the presence of SSc specific antibodies conferred a distinctive clinical profile.*

Introduction

Specific antibodies in autoimmune diseases constitute a helpful tool in diagnosis and identification of certain disease manifestations (1). Classically, clinical manifestations of systemic sclerosis (SSc) such as digital ulcers, pulmonary hypertension (PH), interstitial lung disease (ILD), and scleroderma renal crisis (SRC) have been associated with the extension of skin involvement, defining limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) (2). However, several authors suggest that these subtypes of the disease do not accurately correlate with internal organ complications (3, 4). Conversely, the presence of some specific antibodies would better define the clinical presentation, cumulative manifestations and prognosis of SSc patients (3, 5-7).

Circulating antinuclear antibodies (ANA) are almost a universal finding in SSc patients (4) and their absence should call into question for this diagnosis. Among them, anti-centromere (ACA), anti-topoisomerase I (ATA), and anti-RNA polymerase III (ARA) antibodies are the most SSc specific antibodies, found in over 50% of patients with the disease (8, 9). These antibodies are generally exclusive of each oth-

er and usually remain unchanged over time (8-10). Of interest, ACA, ATA and ARA have been recently included in the new American College of Rheumatology/EUropean League Against Rheumatism (ACR/EULAR) clinical classification criteria for SSc (11).

ACA are found in over 30% of SSc patients (4) being more frequent in Caucasians and women (3, 4). ACA are the antibodies most frequently found in lcSSc (3, 4, 6, 10, 12-16). Considering organ involvement, ACA have been related to a higher risk of developing PH (3, 14, 17) and calcinosis (4, 17) whereas they have been found to be protective for ILD (6, 14, 15, 18), and heart and renal involvement (19). ATA are the most frequent antibodies in dcSSc (2, 6, 8-10, 12-17, 20-22) and they have been linked to digital ulcers (3, 14, 17, 22), ILD (3, 6, 13, 14, 16, 17, 21-24), and to poor prognosis (25). Finally, ARA are frequently detected in dcSSc subtype (13, 14, 16, 17, 21) and they have been related with higher risk of developing SRC (13, 17, 26-28), gastric antral vascular ectasia (17, 29, 30), and recently a causal relation with cancer has been suggested (28, 31-34).

The aim of the present study was to compare the clinical manifestations and prognosis of SSc patients from the Spanish Scleroderma Study Group database or RESCLE (*Registro de ESCLErodermia* as Spanish nomenclature) Registry according to the presence of each one of the mutually exclusive single classificatory antibodies.

Table I. Demographic, clinical, and immunological characteristics of 209 patients with systemic sclerosis.

	n
Sex, male/female	28/181 (13/87)
Age at disease onset, mean ± SD (years)	44.2 ± 16.4
Age at disease diagnosis, mean ± SD (years) (n=178)	51.2 ± 16.0
Time disease onset-diagnosis, mean ± SD (years) (n=168)	7.1 ± 10.7
Time of follow-up since disease diagnosis, mean ± SD (years) (n=192)	9.3 ± 8.3
Time of follow-up since disease onset, mean ± SD (years) (n=178)	16.1 ± 12.5
Type of scleroderma (n=208)	
Limited cutaneous systemic sclerosis	111 (53)
Diffuse cutaneous systemic sclerosis	50 (24)
Sine scleroderma	31 (15)
Pre-scleroderma	11 (5)
First manifestation (n=204)	
Raynaud's phenomenon	173 (85)
Arthralgia	9 (4)
Puffy hands	7 (3)
Skin sclerosis	6 (3)
Cumulative clinical manifestations	
Peripheral vascular manifestations	
Raynaud's phenomenon (n=206)	202 (98)
Telangiectasias (n=209)	129 (62)
Digital ulcers (n=209)	89 (43)
Osteomuscular manifestations	
Calcinosis (n=206)	43 (21)
Arthritis (n=122)	22 (18)
Myositis (n=122)	17 (14)
Digestive tract involvement	
Oesophagus (n=134)	26 (19)
Lung Involvement	
Interstitial lung disease (n=207)	81 (39)
Pulmonary hypertension (n=174)	50 (29)
Heart involvement	
Ischaemia (n=70)	14 (20)
Conduction alterations	21 (10)
Pericarditis (n=69)	10 (14)
Renal involvement	
Scleroderma renal crisis (n=78)	8 (10)
Other manifestations	
Sicca syndrome (n=208)	65 (31)
Peripheral neuropathy (n=205)	26 (13)
Neoplasia (n=209)	24 (11)
Capillaroscopy pattern (n=172)	
Slow pattern	90 (52)
Active pattern	45 (26)
Death	23 (11)

*All data derived from 209 patients except when indicated. Values of categorical variables are the number and percentage and those for continuous variables are presented as mean ± standard deviation.

Methods

Patients

The RESCLE is the first Spanish nationwide cross-sectional registry created by the Spanish Society Internal Medicine in 2006 (6). Twenty centres with extensive experience in the management of patients with SSc are participating in the registry. We considered SSc diagnosis when patients fulfilled criteria of the modified classification proposed by LeRoy and Medsger (25) and/or the 2013 ACR/EULAR criteria for SSc (35). Demographic, clinical, immunological, and nailfold capillaroscopic data encompassing 260 variables were collected according to a standard protocol and then entered into a SPSS database. All participating centres obtained Ethics Committee approval and all participants provided written informed consent to participate in the study.

For the present study, we selected from the RESCLE those patients in which ACA, ATA, and ARA had been determined, and a single positivity for each SSc specific antibodies was detected. The three groups, ACA positive, ATA positive, and ARA positive were always mutually exclusive.

Laboratory features

Antinuclear antibodies were identified by indirect immunofluorescence assay using Hep-2 cell lines or by immunofluorescence using triple cryostat section (liver-stomach-kidney). The ACA and ATA were determined by ELISA kits. ARA were determined using ELISA, immunoblot kit or fluoroenzyme

Table II. Demographic characteristics, presenting manifestation, capillaroscopic patterns, and immunological features of patients with systemic sclerosis according their immunological profile.

	ACA group (n=128)	ATA group (n=46)	ARA group (n=35)	*p*-global	ACA *vs.* ATA	ACA *vs.* ARA	ATA *vs.* ARA
Type of scleroderma							
Limited cutaneous SSc	88 (69)	13 (28)	10 (29)	<0.001	<0.001	<0.001	NS
Diffuse cutaneous SSc	4 (3)	25 (54)	21 (62)	<0.001	<0.001	<0.001	NS
Sine scleroderma	27 (21)	2 (4)	2 (6)	0.006	0.010	0.044	NS
Pre-scleroderma	6 (5)	4 (9)	1 (3)	NS	-	-	-
Sex (female)	118 (92)	36 (78)	27 (77)	0.012	0.018	0.028	NS
Age at disease onset (yrs)(n=178)	45.3 ± 16.5	43.4 ± 16.2	41.4 ± 16.2	NS	-	-	-
Age at disease diagnosis (yrs)(n=178)	54.1 ± 15.5	47.5 ± 15.3	46.0 ± 16.9	0.008	0.049	0.032	NS
Time onset-diagnosis (yrs)(n=168)	9.4 ± 12.3	4.0 ± 6.5	3.6 ± 7.1	0.004	0.019	0.028	NS
Follow-up from disease onset (yrs)	18.3 ± 13.9	12.7 ± 9.4	13.4 ± 9.7	0.021	0.043	NS	NS
Follow-up from disease diagnosis (yrs)	9.2 ± 8.0	9.5 ± 9.5	9.5 ± 8.1	NS	-	-	-
Presenting manifestation (n=204)							
Raynaud's phenomenon	119 (94)	36 (80)	18 (55)	<0.001	0.013	<0.001	0.025
Puffy hands	0	3 (7)	4 (12)	0.001	0.017	0.020	NS
Arthralgia	1 (1)	2 (4)	6 (18)	<0.001	NS	<0.001	NS
Skin sclerosis	1 (1)	1 (2)	4 (12)	0.003	NS	0.007	NS
2013s ACR/EULAR criteria of SSc (n=188)	100 (90)	38 (88)	33 (97)	NS	-	-	-
Capillaroscopic patterns (n=172)							
Slow pattern	65 (58)	15 (43)	10 (42)	NS	-	-	-
Active pattern	24 (21)	12 (34)	9 (38)	NS	-	-	-
Immunological features							
Rheumatoid factor (n=170)	28 (27)	10 (26)	2 (7)	NS	-	-	-
Anti-Ro antibody (n=200)	18 (15)	5 (12)	3 (9)	NS	-	-	-
Anti-La antibody (n=199)	1 (1)	2 (5)	2 (6)	NS	-	-	-
Anti-Sm antibody (n=195)	0 (0)	1 (2)	0 (0)	NS	-	-	-
Anti-RNP antibody (n=196)	1 (1)	2 (5)	0 (0)	NS	-	-	-
Anti-M2 antibody (n=178)	17 (16)	1 (2)	3 (10)	NS	-	-	-
Anti-Ku antibody (n=129)	0 (0)	0 (0)	0 (0)	-	-	-	-
Lupus anticoagulant (n=141)	7 (8)	2 (6)	1 (5)	NS	-	-	-
IgG anticardiolipin antibody (n=153)	4 (4)	1 (3)	0 (0)	NS	-	-	-
IgM anticardiolipin antibody (n=153)	7 (7)	4 (11)	1 (5)	NS	-	-	-
Anti-thyroid antibody (n=110)	15 (21)	3 (16)	1 (6)	NS	-	-	-

All data derived from 209 patients except when indicated.
Values of categorical variables are expressed as number and percentage and those for continuous variables are presented as mean ± standard deviation.
ACA: anti-centromere antibody; ACR/EULAR: American College of Rheumatism/EUropean League Against Rheumatism; ARA: anti-RNA polymerase III antibody; ATA: anti-topoisomerase I antibody; NS: not significant; SSc: systemic sclerosis; yrs: years.

immunoassay kit. Manufacturer-specified cut-off points were used to define both antibodies as present or absent in each centre. Borderline results were considered as negative.

Statistical analysis

Results from continuous variables are presented as mean ± standard deviation (SD) and categorical data as percentages. A cross-sectional analysis of the antibodies was performed. For statistical evaluation a contingency table tests was used (Pearson Chi-Square test exact Fisher's test) to identify significant differences or associations among the groups for qualitative variables and ANOVA was used for the quantitative ones. The Bonferroni method was used for correction of multiple comparisons. Significance was considered whenever *p*-value was under 0.05. Significant differences on univariate comparisons were then retested by forward multivariate logistic regression with calculation of odds ratio (OR) estimates and 95% confidence interval (CI). Survival curves were calculated using the Kaplan-Meier method and log-rank ratio was used to identify differences. All statistical analysis was performed with SPSS 18.0 for Windows (SPSS, Chicago, IL, USA).

Results

The whole cohort comprised 209 patients. The main demographic characteristics and initial and cumulative clinical manifestations of the entire cohort are described in Table I. Considering the immunological profile, three mutually exclusive groups were defined: ACA group in 128 (61%) patients, ATA group in 46 (22%), and ARA group in 35 (17%) patients, respectively. Table II describes the demographic characteristics, initial presentation, and immunological features, Table III the prevalence of cumulative clinical characteristics, and Table IV the causes of death and survival rates of SSc patients according to the immunological profile.

Clinical associations according to the immunological profile

Patients with ACA presented more frequently the lcSSc subtype (69%) ($p<0.001$). Conversely, dcSSc was the most frequent subtype in patients with ATA (54%) and ARA (62%) (both

Table III. Cumulative clinical manifestations of patients with systemic sclerosis according their immunological profile.

	ACA group (n=128)	ATA group (n=46)	ARA group (n=35)	*P* global	ACA *vs.* ATA	ACA *vs.* ARA	ATA *vs.* ARA
Peripheral vascular manifestations							
Raynaud's phenomenon	123 (98)	46 (100)	33 (97)	NS	-	-	-
Digital ulcers	48 (38)	20 (43)	21 (60)	NS	-	-	-
Telangiectasias (n=209)	77 (60)	26 (57)	26 (74)	NS	-	-	-
Acro-osteolysis (n=122)	2 (3)	3 (9)	2 (8)	NS	-	-	-
Osteomuscular							
Calcinosis (n=206)	25 (20)	8 (18)	10 (29)	NS	-	-	-
Arthritis (n=122)	6 (9)	9 (26)	7 (29)	0.032	0.038	0.038	-
Myositis (n=122)	7 (11)	6 (18)	4 (17)	NS	-	-	-
Tendon friction rubs (n=122)	1 (2)	1 (3)	3 (13)	NS	-	-	-
Digestive involvement							
Oeesophagus (n=134)	17 (20)	3 (11)	6 (27)	NS	-	-	-
Stomach (n=174)	14 (13)	4 (10)	3 (10)	NS	-	-	
Malabsortion (n=206)	25 (20)	8 (18)	10 (29)	NS	-	-	-
Lung involvement							
ILD (n=207)	29 (23)	31 (67)	21 (60)	<0.001	<0.001	<0.001	NS
FVC (%) (n=195)	88.4 ± 21.2	73.4 ± 25.4	75.0 ± 16.6	<0.001	<0.001	0.006	NS
Severe ILD (FVC<70%) (n=195)	22 (18)	22 (51)	12 (36)	<0.001	<0.001	0.036	NS
DLCO/VA (%) (n=180)	73.2 ± 18.6	75.7 ± 16.8	72.0 ± 17.8	NS	-	-	-
Ground-glass pattern (n=145)	15 (20)	26 (67)	18 (56)	<0.001	<0.001	<0.001	NS
Reticular pattern (n=144)	10 (14)	21 (54)	11 (35)	<0.001	<0.001	0.016	NS
PH by echocardiogram (n=147)	27 (29)	6 (18)	3 (14)	NS	-	-	-
PH by RSHC (n=40)	20 (77)	5 (83)	5 (63)	NS	-	-	-
PAH (without ILD) (n=176)	13 (12)	1 (2)	1 (3)	NS	-	-	-
ILD and PH (n=147)	14 (15)	6 (18)	2 (10)	NS	-	-	-
Hearth involvement							
Pericarditis (n=69)	5 (13)	4 (22)	1 (8)	NS	-	-	-
Conduction alteration (n=209)	12 (9)	7 (15)	2 (6)	NS	-	-	-
Diastolic dysfunction (n=168)	53 (53)	21 (54)	15 (52)	NS	-	-	-
Ischaemia (n=70)	7 (18)	4 (22)	3 (23)	NS	-	-	-
Renal involvement							
Scleroderma renal crisis (n=78)	0	3 (17)	5 (33)	<0.001	0.021	0.001	NS
Other manifestations							
Peripheral neuropathy (n=205)	14 (11)	9 (20)	3 (9)	NS	-	-	-
Sicca syndrome (n=205)	47 (37)	13 (28)	5 (14)	0.033	NS	0.023	NS
Neoplasia (n=209)	13 (10)	3 (7)	8 (23)	NS	-	-	-
Synchronous with SSc onset (n=203)	0	0	1 (3)	NS	-	-	-
Synchronous with SSc diagnosis (n=207)	1 (1)	0	2 (6)	NS	-	-	-

All data derived from 209 patients except when indicated.Values of categorical variables are expressed in number and percentage and those for continuous variables are presented as mean ± standard deviation.
DLCO/VA: diffusing capacity of the lung for carbon monoxide divided by alveolar volume; FVC: forced vital capacity; ILD: interstitial lung disease; NS: not significant; PAH: pulmonary arterial hypertension; PH: pulmonary hypertension; RSHC: right-sided heart catheterisation; SSc: systemic sclerosis.

p<0.001). Interestingly, sine scleroderma subtype was more frequent in ACA group (*p*=0.006) (Table II). The time between disease onset and diagnosis was shorter in ATA (4.0±6.5 years) and ARA patients (3.6±7.1 years) than in ACA patients (9.4±12.3 years) (*p*=0.004). Follow-up from disease diagnosis was similar among the three groups.

Non-Raynaud's phenomenon features (puffy hands, arthralgia, and skin sclerosis) as presenting manifestation were more frequent in the ARA group (45%) compared with the ATA group (20%) (*p*=0.025), and the ACA group (6%) (*p*<0.001). Retrospective analysis showed that the percentages of patients who fulfilled the 2013 ACR/EULAR classification SSc criteria were similar in the three groups of patients. From the immunological point of view, the prevalence of other non-specific SSc antibodies was similar between the three groups (Table II).

Considering cumulative organ involvement, patients with ACA had less frequently arthritis (*p*=0.032), ILD (*p*<0.001), and severe ILD defined as forced vital capacity <70% (*p*<0.001). Conversely, positive patients for ATA had a higher prevalence of ILD (67%) (*p*<0.001) and severe ILD (51%) (*p*<0.001) whereas those from the ARA group showed the highest prevalence of joint involvement. Patients of the ARA group showed a trend to present more vascular involvement in form of digital ulcers (60%) (*p*=0.058). Although the prevalence of pulmonary arterial hypertension (without ILD) seemed to be higher in the ACA group (*p*=0.083), the prevalence of PH -assessed by echocardiography and/or right-sided heart catheterisation- was similar between the three groups. Of note, patients with ARA had higher prevalence of SRC (33%) versus 17%

Table IV. Death rate, causes of death, and survival rates of patients with SSc according their immunological profile.

	ACA group (n=128)	ATA group (n=46)	ARA group (n=35)	*p*
Death rate	11 (9)	7 (15)	5 (14)	NS
SSc-related causes of death	4 (36)	6 (86)	3 (60)	NS
ILD	0	2 (29)	2 (40)	NS
PH	3 (27)	1 (14)	0	NS
ILD and PH	1 (9)	1 (14)	1 (20)	NS
Scleroderma renal crisis	0	2 (29)	1 (20)	NS
Non-SSc related	7 (64)	1 (14)	2 (40)	NS
Neoplasia	1 (9)	0	1 (20)	NS
Ischaemic myocardiopathy	1 (9)	0	0	NS
Stroke	1 (9)	0	0	NS
Chronic renal failure	0	0	0	-
Chronic obstructive pulmonary disease	0	0	0	-
Sepsis	0	0	1 (20)	NS
Pulmonary embolism	0	0	0	-
Arrhythmia	0	0	0	-
Others	4 (36)	1 (4)	0	NS
Mean survival time since SSc onset (yrs)	51.3 ± 2.8	27.8 ± 2.7	31.2 ± 2.3	-
Survival since SSc onset				
At 5 years	0.960	1.000	1.000	NS
At 10 years	0.936	0.970	0.891	NS
At 20 years	0.923	0.637	0.891	NS
At 30 years	0.896	0.510	0.891	NS
Mean survival time since SSc diagnosis (yrs)	28.7 ± 1.2	30.6 ± 5.2	25.7 ± 2.2	-
Survival since SSc diagnosis				
At 5 years	0.945	1.000	0.969	NS
At 10 years	0.929	0.900	0.807	NS
At 20 years	0.851	0.585	0.807	NS
At 30 years	0.851	0.439	0.807	NS

Values of categorical variables are expressed in number and percentage and those for continuous variables are presented as mean ± standard deviation.
ILD: interstitial lung disease; NS: not significant; PH: pulmonary hypertension; SSc: systemic sclerosis; yrs: years.

in the ATA group (p=0.001) and 0% in the ACA group (p<0.001). In addition, they presented the highest prevalence of neoplasia (23%) compared with the ACA group (10%) and the ATA group (7%) although these differences did not reach statistical significance (p=0.055). Interestingly, synchronous malignancies with SSc (diagnosis made between 6 months before and 12 months after SSc onset or diagnosis) (32) were also more frequent in the ARA group (Table III).

In multivariate analysis, ACA were associated with female gender (OR 3.96, 95%CI 1.39–11.31; p=0.01), and were protective for dcSSc (OR 0.02, 95%CI 0.01-0.08; p<0.001), for arthralgia as first manifestation (OR 0.09, 95%CI 0.01–0.99; p=0.04), and ILD (OR 0.30, 95%CI 0.13–0.66; p<0.001). ATA were found to be protective for lcSSc (OR 0.22, 95%CI 0.09–0.52; p<0.001) and sine scleroderma subtypes (OR 0.09, 95%CI 0.01–0.76; p=0.027), respectively. Conversely, they were independently associated with interstitial reticular pattern by high-resolution computed tomography (OR 3.60, 95%CI 1.53–8.48; p<0.001). Finally, ARA positivity was independently associated with diffuse cutaneous involvement (OR 8.23, 95%CI 3.46-19-58; p<0.001), and arthralgia as presenting SSc manifestation (OR 10.22, 95%CI 1.93–54.06; p<0.001). Conversely, it was protective for sicca syndrome (OR 0.26, 95%CI 0.08–0.88; p=0.03).

Mortality according to the immunological profile

Twenty-three (11%) patients died during the follow-up in the overall cohort. We did not find differences in terms of death rate nor in causes of death (SSc or non-SSc related) according to the immunological profile (Table IV). The overall cohort survival rate from disease onset at 5, 10, 20, and 30 years were 97.6%, 93.8%, 87.1%, and 82.6%, respectively. Although patients with ATA had the lowest mean survival time from SSc onset (27.8±2.7 years), the Kaplan-Meier survival curves were not different for the three groups of patients (long-rank 0.116) (Fig. 1). No differences were found when SSc diagnosis instead of disease onset was considered (data not shown).

Discussion

In the present study we analysed the clinical manifestations and prognosis of a cohort of Spanish SSc patients according to their immunological profile. The main strength of the study was that SSc patients included had mutually exclusive single-SSc-specific antibodies. In the multivariate analysis, we identified distinctive clinical phenotypes considering immunological profiles. Conversely, prognosis in terms of survival curves was similar among the three groups of patients.

Patients positive for ACA were more frequently female (92%) and some clinical features such as diffuse cutaneous involvement and ILD were less common compared to patients positive for ATA and ARA, in accordance with previous data (3, 4, 6, 13-15, 18, 22, 36). Whereas age at disease onset was similar among three groups, the elapsed time to SSc diagnosis was longer in patients with ACA positivity. The low prevalence of non-Raynaud's phenomenon features as presenting manifestation and of lung involvement might explain this difference. In fact, the presence of ACA was protective for clinically significant ILD whereas ATA predicted its presence (36). The prevalence of PH, assessed by echocardiography and/or right-sided heart catheterisation, was similar among the three groups. The relationship between ACA positivity and development of PH has been confirmed in some studies (3, 14, 17), but not in others (13, 15, 21, 37, 38).

Significant clinical associations in positive ATA patients included higher prevalence of ILD by high-resolution

computed tomography and lesser prevalence of limited cutaneous and sine scleroderma subtypes in accordance with previous data (3, 6, 13, 14, 17, 20-22).

The prevalence of ARA in SSc patients ranges from 4-25%, higher in Northern than Southern countries in European series, suggesting differences in genetic background (39). As expected, most of the ARA patients had diffuse cutaneous subtype (13, 14, 16, 17, 21). One of the most dreadful complications of SSc was SRC, particularly in ARA patients (13, 17, 28, 40). However, although ARA positive patients showed a high prevalence of SRC, this was not significant in the multivariate analysis. The low prevalence of SRC (10%) in the overall series could explain the lack of significant differences with the other groups of patients. Globally, malignancies were more frequent (33%) in ARA-positive patients. Interestingly, the prevalence of synchronous neoplasia with both SSc onset and SSc diagnosis were also more frequent in ARA group. In the last years, a growing body of evidence associating ARA and malignancy has emerged (28, 31-34). Nowadays, a screening of cancer is advised in all ARA positive patients at SSc diagnosis, based on expert opinion. However, there is no formal recommendation on the screening tests and the length of the follow-up period (34).

Survival rate in the overall cohort ranged from 97.6% at 5 years to 82.6% at 30 years of follow-up with no differences neither in terms of death rate nor in causes of death according to the immunological profile. These results are very similar to previous data from a recent meta-analysis (41) and other European series (42-44).

As elegantly proposed by Steen (5), SSc could be considered as diverse distinct entities depending on their serology. In fact, some national (6, 13, 14, 22, 27) and international registries (3) of SSc patients have demonstrated that antibody status contributed to organ complications in more extent than the cutaneous subtype did. In front of the dynamic changes of skin involvement over time, the rarity of the specific SSc antibody disappearance (4) could be a useful marker to identify clinical phenotypes and prognosis of SSc patients.

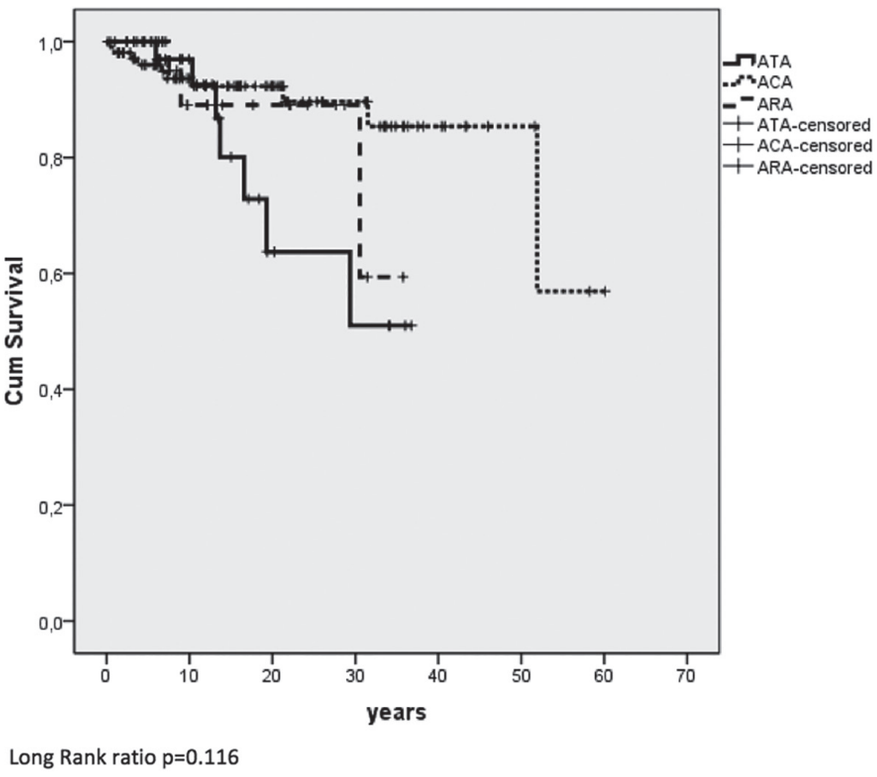

Fig. 1. Kaplan-Meier curves for patients with systemic sclerosis from disease onset according to immunological profile.

Long Rank ratio p=0.116
Patients at risk

Years	0-5	5-10	10-20	20-30	30-40
Overall series	165	128.5	83	44.5	21
ACA group	98.5	79	56	33.5	17
ATA group	38.5	29	16.5	5.5	2
ARA group	28	20.1	10.5	5.5	2

ACA: anti-centromere antibody; ARA: anti-RNA polymerase III antibody; ATA: anti-topoisomerase I antibody.

The main strengths of the present study include the large number of patients derived from the Spanish geographical location and the fact that three groups of patients were mutually exclusive from the immunological point of view. Moreover, the prevalence of other non-specific antibodies was similar among the three groups. Therefore, the distinctive clinical profiles identified were directly related to each specific SSc-antibody. The main limitation of our study is the low determination rate of some of these antibodies. Until recently, ARA could not be determined on a routine basis in some Spanish immunology laboratories. Moreover, the laboratory techniques to determine these antibodies were not the same in each participating centre, but borderline results were considered as negative. In the whole series, the number of right-sided heart catheterisation was too small to suggest a causal relationship between PH and the antibody profile. In addition, some clinical manifestations such as SCR and neoplasia were represented by a small number of patients giving difficult to achieve statistical significance.

In spite of these limitations, this is the first study performed in a large cohort of Spanish SSc patients that confirms

that the specific SSc antibody profile is associated with differences in clinical presentation and cumulative manifestations. Specific SSc autoantibodies are a useful tool to the physician providing additional and valuable information to the currently used classification according to the extent of skin involvement.

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