Serodiscordant patients with systemic sclerosis: when antibody does not correspond to skin involvement

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ABSTRACT

Objective. *Diffuse cutaneous systemic sclerosis (dcSSc) is associated with anti-topoisomerase (ATA) whereas limited cutaneous (lcSSc) and sine scleroderma (ssSSc) are mainly associated with anti-centromere antibody (ACA). Serodiscordant patients were defined as lcSSc subjects with ATA, dcSSc with ACA, and ssSSc with ATA. The aim of the present study was to compare the clinical manifestations and prognosis between serodiscordant patients and their counterparts (those with lcSSc with ACA, dcSSc with ATA and ssSSc with ACA, respectively).*

Methods. *From the Spanish Scleroderma Registry we selected those patients for whom skin involvement (dcSSc, lcSSc or ssSSc) was detailed at baseline and last visit and ACA and ATA had been determined. Demographic, clinical characteristics, and survival data were compared according to the antibody status.*

Results. *The whole cohort comprised 901 patients and six mutually exclusive groups were defined: lcSScACA in 511 (57%) patients, lcSScATA group in 87 (10%), dcSScATA group in 172 (19%), dcSScACA group in 21 (2%), ssSScACA group in 92 (10%), and ssSScATA group in 18 (2%) patients, respectively. Interstitial lung disease (ILD) and severe ILD were more frequent in patients with dcSScATA than in those with dcSScACA. Conversely, the prevalence of isolated pulmonary hypertension (without ILD) was higher in those with dcSScACA (15% vs. 2%; p=0.018). No differences were found regarding survival when comparing serodiscordant patients with the seroconcordants patients.*

Conclusion. *In our cohort, the prevalence of serodiscordant SSc patients was low. They differed from their counterparts in some clinical manifestations. The management of patients with SSc should be guided by both serology and cutaneous subtype.*

Introduction

Classically, patients with systemic sclerosis (SSc) have been divided into two main groups according to the extent of skin involvement, the diffuse cutaneous SSc (dcSSc) and the limited cutaneous SSc (lcSSc), respectively (1, 2). From an immunological point of view, the two most common antinuclear antibodies in SSc are anticentromere (ACA) and anti-topoisomerase I antibodies (ATA). They both can be found up to 50% of SSc patients (3). A close association between the cutaneous involvement and autoantibody status is known. In fact, ACA, the most common antibody in lcSSc – is present in 70–80% of them – whereas ATA is the most frequent in dcSSc, present in approximately 30% of patients (4). In an effort to better define disease subgroups, two studies showed that the classification according to autoantibodies was as strongly associated with the clinical manifestations as the categorisation into cutaneous subtypes (5, 6). In addition to lcSSc and dcSSc, a third subset of patients, SSc sine scleroderma (ssSSc), defined by the presence of Raynaud's phenomenon (RP), any typical scleroderma visceral involvement, and any SSc-associated autoantibodies but no cutaneous sclerosis has been considered (7). Given its similar prognosis, the majority of studies include

ssSSc patients in the lcSSc subtype. Some authors, however, have highlighted the existence of clinical differences between both types. In general, ACA is the most frequent autoantibody found in patients with ssSSc (6, 8).

In the majority of international and national registries of SSc patients (5, 9-11), a low number of serodiscordant subjects defined by dcSSc with ACA (dcSScACA), lcSSc with ATA (lcSScATA), and ssSSc with ATA (ssSScATA) have been described. In fact, around 30% of ATA patients present with lcSSc whereas 5% of ACA patients develop dcSSc (12). A recent multicentre study showed that 50% of ssSSc patients had ACA whereas only 17% presented with ATA (13). Little is known about the prognosis and clinical characteristics of this group of patients. In order to better define the clinical course and survival of these serodiscordant SSc patients, we described the clinical manifestations and prognosis of patients with dcSScACA, lcSScATA, and ssSScATA and compared them with those of dcSScATA, lcSScACA, and ssSScACA, respectively, from the Spanish Scleroderma Registry or RESCLE (Registro de ESCLErodermia as Spanish nomenclature) Registry. As a secondary objective we planned the rate of transition of skin subtype (from limited to diffuse and from sine to limited) and the characteristics of patients who transitioned during the evolution.

Patients and methods

The present study was a retrospective cohort study. Data were obtained from the Spanish Scleroderma Registry (RESCLE), a project created by the Autoimmune Diseases Working Group (GEAS) within the Spanish Society of Internal Medicine (SEMI) in 2006. The registry includes incident cases of SSc and patients with a previous diagnosis of SSc who fulfilled the 2013 ACR/EULAR criteria (14) and/or the modified criteria proposed by LeRoy and Medsger in 1988 (7) to avoid the possible missing of patients with ssSSc or lcSSc who would not fulfill the 2013 ACR criteria. Data were collected retrospectively until 2006 and prospectively onwards. Disease onset was defined as the date of the first self-reported symptom (RP in the majority of patients). Thirty hospitals nationwide are participating in the registry and all of them obtained local Ethics Committee approval. In addition, we also received ethics board approval from our institution (Hospital Clinic, Barcelona, Spain, ref. HCP 2011/6413).

Demographic, clinical, immunological and capillaroscopic data encompassing 260 variables were collected according to a standard protocol. Detailed definitions of the cutaneous subsets, clinical features, organ involvements, nailfold capillaroscopy patterns, and immunological features have been published elsewhere (6, 15-18). Since the modified Rodnan skin score (mRss) (19) is not included in the registry database, patients were classified as diffuse subtype if they ever had skin thickening proximal to elbow or knees (upper arms, thighs, chest, abdomen or back) prior to the baseline visit, even if it had regressed to a lcSSc distribution as previously described (20).

For the present study, we selected from the RESCLE those patients in which skin involvement (dcSSc, lcSSc or ssSSc) was detailed at the first and last visit and ACA and ATA had been determined, and a single positivity for each SSc specific antibodies was detected.

Immunological studies were performed in each participating centre. ANA was identified by indirect immunofluorescence assay using Hep-2 cell lines or by immunoflourescence using triple tissue cryostat section (liver-stomach-kidney). ACA and ATA were determined by ELISA kits. Manufacturer-specified cut-off points were used to define both antibodies as present or absent in each center. To avoid false positive results, borderline results were considered as negative.

Statistical analysis

Results from continuous variables are presented as median (interquartile range) and categorical data as percentages. For statistical evaluation a contingency table test was used (exact Fisher's test) to identify significant differences or associations among the groups for qualitative variables and t-test was used for the quantitative ones. The Bonferroni method was used for the correction of multiple comparisons. Significance was considered whenever *p*-value was under 0.05. 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 901 patients. The main demographic, initial and cumulative clinical manifestations of the entire cohort are described in Table S1 (Supplementary file). Of the total of 901 patients, 598 (66%) were classified as lcSSc, 193 (21%) were classified as dcSSc, and 110 (12%) were classified as ssSSc. Five hundred and eleven (85%) of the lcSSc were ACA positive and 87 (15%) were ATA positive. Within the dcSSc subtype, 172 patients (89%) were ATA positive and 21 (1%) were ACA positive. Ninety-two (84%) patients with ssSSc were ACA positive and 18 (16%) were ATA positive.

Demographic characteristics, initial presentation, and immunological features according to the type of cutaneous involvement and immunological profile

Demographic characteristics, initial presentation, immunological features, and capillaroscopic patterns of the six groups are listed in Table I. Of note, we did not find differences between dcSSc patients regardless their antibody status and the same fact occurred among patients with ssSSc. Time from onset of disease to diagnosis was shorter in lcSSc-ATA group (2.5 (0.7–7.2) years) compared with lcSScACA group (4.0 (1.1–12.4) years) (p=0.012). Compared with patients with lcSScATA, those with lcSScACA presented with higher percentage of RP (95% *vs*. 79%; p<0.001) and lower prevalence of puffy hands (3% *vs*. 9%; p=0.017) as presenting manifestations of SSc. Patients with ATA, were very similar regardless their skin involvement, except for a higher prevalence of active capillaroscopic pattern in those with dcSSc (51% *vs*. 33% and 21%, p<0.001). Similarly, the comparison between patients with ACA

Table I. Demographic characteristics, presenting manifestation, and capillaroscopic patterns of patients with systemic sclerosis according the skin involvement and immunological profile.

	dcSSc			lcSSc			ssSSc			
	ATA (n=172)	ACA (n=21)	*p*	ATA (n=87)	ACA (n=511)	*p*	ATA (n=18)	ACA (n=92)	*p*	*p* global
Sex (female)	148 (86)	20 (95)	NS	75 (86)	475 (93)	NS	15 (83)	87 (95)	NS	0.022
Age at disease onset (yrs) (836)	43.7 (33.5-55.7)	44.4 (39.8-48.3)	NS	46.7 (32.2-55.4)	45.3 (36.1-56.5)	NS	36.0 (22.8-55.4)	49.5 (36.1-57.0)	NS	NS
Age at disease diagnosis (yrs) (862)	47.6 (37.8-57.9)	48.4 (39.8-63.4)	NS	51.6 (38.9-60.9)	54.9 (44.2-65.4)	NS	44.7 (39.3-59.0)	55.7 (42.5-65.2)	NS	<0.001
Time onset-diagnosis (yrs) (812)	1.4 (0.3-4.4)	2.0 (0.1-9.2)	NS	2.5 (0.7-7.2)	4 (1.1-12.4)	0.012	4.1 (2.0-7.0)	5.2 (1.7-10.0)	NS	<0.001
Follow-up from disease onset (yrs) (836)	10.5 (5.4-18.8)	10.9 (6.3-16.4)	NS	12.7 (5.6-19.5)	15.7 (8.2-26.3)	NS	9.2 (5.3-20.0)	11.4 (5-0-18.1)	NS	<0.001
Follow-up from disease diagnosis (yrs) (862)	7.0 (3.6-15.5)	6.1 (4.0-10.1)	NS	7.3 (2.5-13.3)	8.2 (3.3-14.5)	NS	3.6 (1.9-10.9)	4.2 (1.4-9.8)	NS	0.003
Presenting manifestation (871)										
Raynaud's phenomenon	127 (78)	15 (83)	NS	69 (79)	461 (93)	<0.001	14 (82)	81 (91)	NS	<0.001
Puffy hands	9 (6)	1 (6)	NS	8 (9)	16 (3)	0.017	2 (12)	3 (3)	NS	NS
Arthralgia	4 (3)	0	NS	3 (3)	4 (1)	NS	0	0	NS	NS
Skin sclerosis	16 (10)	2 (11)	NS	3 (3)	9 (2)	NS	0	1 (1)	NS	<0.001
SSc criteria										
1980 ACR (898)	170 (99)	21 (100)	NS	63 (72)	311 (61)	NS	3 (17)	9 (10)	NS	<0.001
2013 ACR/EULAR (815)	172 (100)	21 (100)	NS	80 (98)	483 (98)	NS	2 (29)	28 (67)	NS	<0.001
Capillaroscopy patterns (720)										
Slow pattern	48 (41)	5 (29)	NS	33 (54)	257 (60)	NS	5 (36)	40 (51)	NS	0.001
Active pattern	60 (51)	10 (59)	NS	20 (33)	128 (30)	NS	3 (21)	13 (16)	NS	<0.001
Immunological features										
Rheumatoid factor (692)	29 (21)	4 (27)	NS	17 (25)	109 (28)	NS	1 (7)	17 (25)	NS	NS
Anti-Ro antibody (855)	22 (13)	3 (15)	NS	12 (15)	60 (12)	NS	4 (24)	13 (15)	NS	NS
Anti-La antibody (848)	8 (5)	1 (5)	NS	5 (6)	11 (2)	NS	0	8 (9)	NS	0.036
Anti-Sm antibody (827)	1 (1)	1 (5)	NS	0	5 (1)	NS	0	1 (1)	NS	NS
Anti-RNP antibody (840)	5 (3)	0	NS	5 (6)	14 (3)	NS	1 (6)	2 (2)	NS	NS
Lupus anticoagulant (368)	3 (4)	1 (9)	NS	3 (9)	18 (9)	NS	1 (10)	3 (7)	NS	NS
IgG anticardiolipin antibody (578)	2 (2)	1 (6)	NS	4 (8)	23 (7)	NS	0	1 (2)	NS	NS
IgM anticardiolipin antibody (578)	4 (4)	1 (6)	NS	6 (12)	20 (6)	NS	1 (8)	4 (8)	NS	NS
Anti-thyroid antibody (260)	10 (25)	3 (75)	NS	6 (27)	41 (25)	NS	3 (60)	6 (21)	NS	NS

All data derived from 901 patients, except when indicated.
Values of categorical variables are expressed as number and percentage and those for continuous variables are presented as median (interquartilic range).
ACA: anti-centromere antibody; ACR/EULAR: American College of Rheumatism/EUropean League Against Rheumatism; ATA: anti-topoisomerase I antibody; dcSSc: diffuse cutaneous SSc; lcSSc: limited cutaneous SSc; NS: not significant; ssSSc: sine scleroderma SSc; SSc: systemic sclerosis; yrs: years.

(dcSScACA, lcSScACA, and ssSScACA) only found differences in terms of distribution of capillaroscopic patterns (Table I). In fact, the great number of differences took place between patients with dcSScATA and those with lcSScACA and between patients with dcSScATA and those with ssSScACA (Table I).

Rates of overlapping with other autoantibodies were similar among the groups irrespective of their cutaneous subtype (dcSSc, lcSSc, and ssSSc) or immunological profile (ATA and ACA) (Table I).

Cumulative clinical manifestations according to the type of cutaneous involvement and immunological profile

Cumulative clinical manifestations in the six groups are listed in Table II. Interstitial lung disease (ILD) and severe ILD, defined as forced vital capacity (FVC) <70%, were more frequent in patients with dcSScATA than in those with dcSScACA (Table II). Conversely, the prevalence of isolated pulmonary hypertension (without ILD) was higher in those with dcSScACA than those with dcSScATA (15% *vs*. 2%; p=0.018). Some differences were found among patients with lcSScATA and those with lcSScACA. The former presented more frequently ILD (64% *vs*. 29%; p<0.001) and severe ILD (38% *vs*. 12%; p<0.001) whereas digital ulcers (42% *vs*. 29%; p<0.001) and telangiectasias (68% *vs*. 61%; p=0.016) were more frequent in the latter.

Considering patients with ssSSc, those with ATA had more frequently digital ulcers (28% *vs*. 10%; p<0.001) and severe ILD (40% *vs*. 9%; p=0.006). On the contrary, telangiectasia was more frequent in ssSSc-ACA+ patients (46% *vs*. 22%; p<0.001). Regarding pulmonary manifestations, FVC% predicted values were lower among the subtypes with ATA compared with those of ACA. Most of the differences were found among patients with dcSScATA and those with lcSScACA and between patients with dcSScATA and ssSScACA. Of note, we did not find differences between patients with lcSScATA and those with ssSScATA (Table II).

Mortality according to the type of cutaneous involvement and immunological profile

Overall, 165 (18%) patients died during the follow-up. We did not find differences in terms of death rate nor in the causes of death (SSc and non-SSc related) according to the immunological profile (dcSScATA *vs*. dcSScACA; lcSScATA *vs*. lcSScACA, and ssSScATA *vs*. ssSScACA) (Table III). In fact, the only difference that we found was a higher prevalence of pulmonary hypertension as SSc-related cause of death in dcSScACA *versus* dcSScATA (40% *vs*. 2%; p=0.001).

Of note, no differences were found considering the Kaplan-Meier survival curves from disease onset when we compared dcSScATA *versus* dcSScACA (log-rank p=0.431), lcSScATA *vs*. lcSScACA (log rank p=0.918), and ssSScATA and ssSScACA (log rank p=0.938), respectively (Fig. 1). No differences

Table II. Cumulative clinical manifestations of patients with SSc according to their cutaneous subtype and immunological profile.

	dcSSc			lcSSc			ssSSc			
	ATA (n=172)	ACA (n=21)	*p*	ATA (n=87)	ACA (n=511)	*p*	ATA (n=18)	ACA (n=92)	*p*	*p* global
Peripheral vascular manifestations										
Raynaud's phenomenon (898)	164 (95)	19 (90)	NS	83 (95)	502 (99)	NS	16 (89)	89 (98)	NS	0.009
Digital ulcers (900)	112 (65)	13 (62)	NS	25 (29)	212 (42)	<0.001	5 (28)	9 (10)	<0.001	<0.001
Telangiectasia (897)	112 (65)	16 (76)	NS	53 (61)	347 (68)	0.016	4 (22)	42 (46)	<0001	<0.001
Acro-osteolysis (627)	22 (15)	2 (11)	NS	5 (7)	26 (8)	NS	0	1 (2)	NS	0.053
Osteomuscular										
Calcinosis (897)	43 (25)	9 (43)	NS	16 (18)	131 (26)	NS	0	9 (10)	NS	<0.001
Arthritis (627)	45 (30)	3 (16)	NS	16 (24)	48 (14)	NS	1 (8)	2 (5)	NS	<0.001
Myositis (627)	29 (20)	1 (5)	NS	4 (6)	19 (6)	NS	1 (8)	3 (7)	NS	<0.001
Tendon friction rubs (627)	16 (11)	3 (16)	NS	2 (3)	8 (2)	NS	0	0	NS	<0.001
Digestive involvement										
Oesophagus (676)	132 (91)	15 (88)	NS	49 (82)	314 (85)	NS	12 (92)	65 (89)	NS	NS
Stomach (669)	33 (23)	2 (12)	NS	7 (12)	76 (21)	NS	2 (17)	11 (15)	NS	NS
Malabsortion (756)	13 (9)	2 (13)	NS	3 (4)	34 (8)	NS	1 (7)	4 (6)	NS	NS
Lung Involvement										
ILD (896)	144 (84)	12 (57)	0.007	56 (64)	146 (29)	<0.001	8 (44)	20 (22)	NS	<0.001
FVC (%) (805)	67.3 (53.6-85.0)	86.7 (76.0-103.0)	0.001	77.3 (62.0-94.0)	93.1 (81.0-105.0)	<0.001	79.0 (58.0-96.6)	93.0 (82.0-103.0)	NS	<0.001
Severe ILD (FVC<70%) (805)	85 (53)	3 (14)	<0.001	30 (38)	55 (12)	<0.001	6 (40)	8 (9)	0.006	<0.001
DLCO < 70% (%) (695)	105 (74)	10 (59)	NS	40 (58)	206 (54)	NS	8 (57)	37 (49)	NS	0.001
DLCO/VA (%) (703)	78.0 (60.0-85.8)	64.0 (58.0-94.0)	NS	79.0 (66.0-91.0)	74.9 (62.0-89.0)	NS	80.7 (51.0-89.9)	80.0 (67.5-91.0)	NS	NS
Ground-glass pattern (602)	97 (71)	6 (46)	NS	35 (54)	73 (23)	<0.001	5 (42)	10 (19)	NS	<0.001
Reticular pattern (651)	93 (60)	5 (33)	NS	38 (54)	53 (15)	<0.001	3 (23)	5 (9)	NS	<0.001
PH by echocardiogram (511)	28 (35)	4 (40)	NS	11 (24)	80 (25)	NS	2 (20)	9 (19)	NS	NS
PH by RSHC (122)	15 (63)	6 (100)	NS	4 (50)	55 (75)	NS	1 (50)	6 (67)	NS	NS
Isolated PH (w/o ILD) (781)	3 (2)	3 (15)	0.018	6 (7)	56 (13)	NS	0	7 (10)	NS	0.001
Hearth involvement										
Pericarditis (471)	22 (20)	2 (13)	NS	4 (8)	17 (6)	NS	0	2 (8)	NS	0.006
Conduction alteration	30 (17)	1 (5)	NS	15 (17)	57 (11)	NS	1 (6)	7 (8)	NS	<0.001
Diastolic dysfunction (570)	33 (38)	1 (9)	NS	19 (33)	133 (39)	NS	6 (46)	21 (35)	NS	NS
Renal involvement										
SCR (896)	12 (7)	2 (10)	NS	2 (2)	3 (1)	NS	0	0	-	NS
Neoplasia	16 (9)	0	NS	11 (13)	53 (10)	NS	4 (22)	8 (9)	NS	NS

All data derived from 901 patients, except when indicated.
Values of categorical variables are expressed as number and percentage and those for continuous variables are presented as median (interquartilic range).
ACA: anti-centromere antibody; ATA: anti-topoisomerase I antibody; dcSSc: diffuse cutaneous SSc; DLCO/VA: diffusing capacity of the lung for carbon monoxide divided by alveolar volume; FVC: forced vital capacity; ILD: interstitial lung disease; lcSSc: limited cutaneous SSc; NS: not significant; PH: pulmonary hypertension; RSHC: right-sided heart catheterization; SCR: scleroderma renal crisis; ssSSc: sine scleroderma SSc; SSc: systemic sclerosis; w/o: without; yrs: years.

were found when SSc diagnosis instead of disease onset was considered (Fig. 2).

Change of cutaneous subtype

A secondary objective was to describe the characteristics of patients who changed the cutaneous subtype (limited to diffuse and sine to limited) during the evolution. Overall, 11 out of 598 (2%) patients with lcSSc changed to dcSSc, 7 of them were ATA positive and 4 had ACA with a similar mean time to transition (9.6±10.6 years *vs*. 10.1±10.7 years, respectively). Of note, we did not find differences either in the demographic characteristics, presenting manifestations, capillaroscopic patterns, cumulative manifestations, death rates nor in the causes of death and survival curves among two groups. Sixteen out of 110 (14%) patients with ssSSc changed to lcSSc. The majority of them had ACA (n=14) whereas only 2 had ATA. The time to transition was longer in those with ACA but without significant difference (8.8±8.1 years *vs*. 4.5±0.0 years). Demographic, presenting and cumulative manifestations, capillaroscopic patterns, death rates and causes of death and survival curves were similar among these two groups.

Discussion

In the present study we analysed the clinical manifestations and prognosis of a cohort of Spanish SSc patients according to their cutaneous involvement and immunological profile focusing on the serodiscordant patients. The prevalence of these subsets of SSc patients in the present cohort was low, only 10% considering lcSScATA and 2% in case of dcSScACA and ssSScATA, respectively. Compared with dcSScATA, lcSScACA, and ssSScACA, serodiscordant SSc patients presented some differences in presenting and cumulative manifestations. Death rates, causes of death, and prognosis were similar in patients with the same cutaneous subtype regardless their immunological profile.

The prevalence of serodiscordant SSc patients varies between studies (Table IV) (5, 9-11, 21-30). In the majority of the studies (13, 31-33), the serological profile of patients with SSc was generally similar to those of lcSSc subjects showing high rates of ACA (ranging from 46% to 50%) whereas ATA rates were less frequent (from 7% to 17%). The different prevalence of serodiscordant patients in the present study may be explained by the different ethnic origin and genetic factors from SSc patients included in the different cohorts, but also by the methodological differences such as the inclusion criteria or the laboratory techniques employed in each of them.

In terms of demographic characteris-

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

	dcSSc			lcSSc			ssSSc			
	ATA (n=172)	ACA (n=21)	*p*	ATA (n=87)	ACA (n=511)	*p*	ATA (n=18)	ACA (n=92)	*p*	*p* global
Death rate	55 (32)	10 (48)	NS	10 (11)	77 (15)	NS	2 (11)	11 (12)	NS	<0.001
SSc-related causes of death (157)	31 (62)	8 (80)	NS	7 (70)	30 (41)	NS	0	6 (55)	NS	0.028
ILD (165)	8 (15)	2 (20)	NS	0	5 (6)	NS	0	0	-	NS
PH (165)	1 (2)	4 (40)	0.001	3 (30)	18 (23)	NS	0	2 (18)	NS	0.005
ILD and PH (165)	11 (20)	1 (10)	NS	1 (10)	2 (3)	NS	0	1 (9)	NS	0.045
Scleroderma renal crisis (165)	6 (11)	0	NS	1 (10)	0	NS	0	0	-	0.046
Non-SSc related causes of death (157)	19 (38)	2 (20)	NS	3 (30)	44 (59)	NS	2 (100)	5 (45)	NS	0.028
Neoplasia (165)	7 (13)	0	NS	1 (10)	6 (8)	NS	0	1 (9)	NS	NS
Ischaemic cardiopathy (165)	1 (2)	0	NS	0	3 (4)	NS	0	2 (18)	NS	NS
Stroke (165)	0	0	-	0	1 (1)	NS	0	0	-	NS
Chronic renal failure (165)	0	0	-	0	0	-	0	0	-	-
COPD (165)	0	0	-	0	1 (1)	NS	0	0	-	NS
Sepsis (165)	2 (4)	1 (10)	NS	0	4 (5)	NS	1 (50)	1 (9)	NS	NS
Pulmonary embolism (165)	0	0	-	0	1 (1)	NS	0	0	-	NS
Arrhythmia (165)	1 (2)	1 (10)	NS	0	0	-	0	0	-	NS
Mean survival time since SSc onset (yrs)	25.3±1.6	23.7±5.0	-	52.9±4.2	43.8±1.8	-	49.612.8	43.6±3.3	-	-
Survival since disease onset (836)										
At 5 years	0.947	0.854	NS	0.971	0.982	NS	0.933	0.954	NS	0.009
At 10 years	0.860	0.741	NS	0.955	0.964	NS	0.933	0.936	NS	<0.001
At 20 years	0.621	0.555	NS	0.814	0.900	NS	0.933	0.812	NS	<0.001
At 30 years	0.345	0.296	NS	0.705	0.785	NS	0.622	0.812	NS	<0.001
Mean survival time since SSc diagnosis (yrs)	22.1±2.2	16.1±3.6	-	26.8±1.8	33.6±2.2	-	16.5±1.3	18.7±1.5	-	-
Survival since disease diagnosis (862)										
At 5 years	0.887	0.782	NS	0.939	0.955	NS	1	0.899	NS	0.017
At 10 years	0.751	0.469	0.032	0.914	0.897	NS	1	0.814	NS	<0.001
At 20 years	0.534	0.352	NS	0.783	0.731	NS	0.800	0.597	NS	<0.001
At 30 years	0.186	0.352	NS	0.652	0.536	NS	0.800	0.597	NS	<0.001

All data derived from 901 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.
ACA: anti-centromere antibody; ATA: anti-topoisomerase I antibody; dcSSc: diffuse cutaneous SSc; ILD: interstitial lung disease; lcSSc: limited cutaneous SSc; NS: not significant; PH: pulmonary hypertension; ssSSc: sine scleroderma SSc; SSc: systemic sclerosis; yrs: years.

tics and presenting SSc manifestations, there were no differences in patients with dcSSc and ssSSc regardless their immunological profile. In patients with lcSSc, those with ATA presented high prevalence of RP and shorter time from SSc onset to diagnosis (2.5 *vs*. 4 years; p=0.012). In addition, the prevalence of initial active and slow capillaroscopic patterns were similar among the six groups of SSc patients.

Considering cumulative organ manifestations, the most important finding of the present study is the higher prevalence of ILD and severe ILD defined as FVC <70% in patients with ATA with lower mean of FVC% predicted despite they presented with the same cutaneous subtype. This finding is maintained in all groups of serodiscordant patients. Conversely, pulmonary hypertension was more frequent in those patients with ACA, although the difference was only statistically significant in the group of dcSSc. In the light of these results, antibody status seems to be more important in predicting pulmonary manifestations than skin status. These results are in accordance with previous observations from Canadian Scleroderma Research Group (10) and EUSTAR cohort (34) where the autoantibody profile seemed to associate stronger with demographics and visceral damage than the skin subgroup.

Table IV. Prevalence of serodiscordant patients with SSc.

Author (year) (ref)	n	dcSScACA	lcSScATA
Walker (2007) EUSTAR cohort (5)	2373	3.4%	20,7%
Srivastava (2015) CSRG (10)	511	16.5%	9.4%
Wuttge (2015) (21)	55	0	7.2%
Horimoto (2015) (22)	38	0	5.2%
Nihtyanova (2014) (23)	398	0.3%	10.0%
Mierau (2011) GNSSR (9)	686	1.7%	20.6%
Joven (2010) (24)	118	5.1%	13.5%
Ferri (2002) (25)	755	11.3%	25.3%
Scussel-Lonzetti (2002) (26)	96	1.0%	16.7%
Kranenburg (2016) (11)	-	-	58/460 (12.6%)
Patterson (2015) (27)	-	5/135 (3.7%)	-
Perera (2007) (28)	-	-	27/212 (12.7%)
Meyer (2007) (29)	-	6/75 (8%)	-
Allcock (2004) (30)	-	2/18 (11.1%)	11/61 (18%)
Present study	901	2%	10%

CSRG: Canadian Scleroderma Research Group; EUSTAR: EUropean Scleroderma Trials And Registry group; GNSSR: German Network for Systemic Scleroderma Registry.

One of the strengths of the present study is the inclusion of patients with ssSSc. Demographic characteristics and organ involvement at the moment of diagnosis did not relate with serological status. On the contrary, some cumulative manifestations were significantly associated with the presence of ATA such as

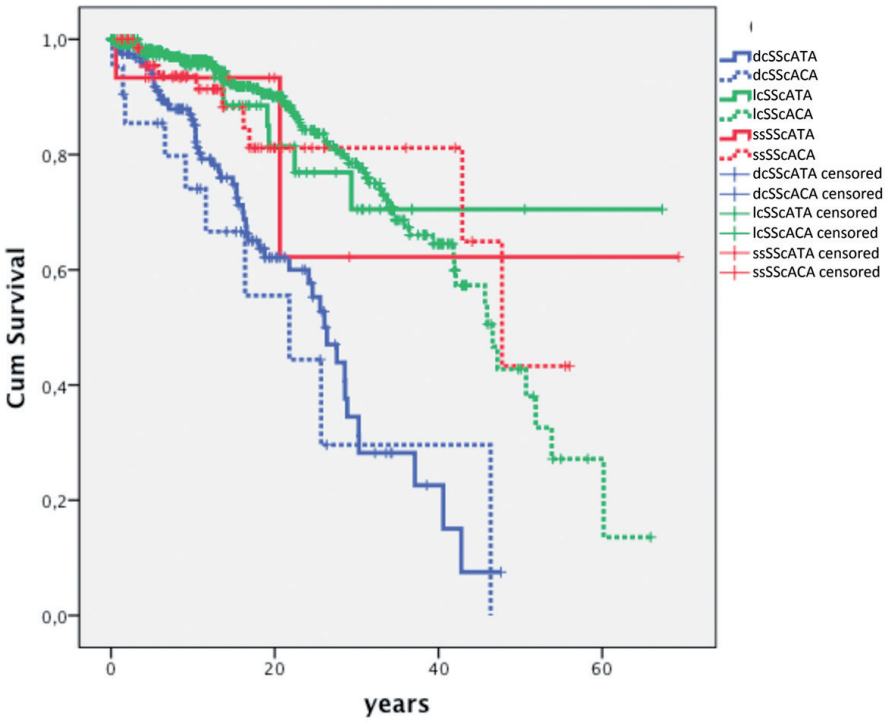

Fig. 1. Kaplan-Meier curves for patients with systemic sclerosis from disease onset according to cutaneous involvement and immunological profile.

Log-rank ratio *p*-value global (global) <0.001
Log-rank ratio *p*-value (dcSScATA *vs*. dcSScACA) = 0.431
Log-rank ratio *p*-value (lcSScATA *vs*. lcSScACA) = 0.918
Log-rank ratio *p*-value (ssSScATA *vs*. ssSScACA) = 0.938
Log-rank ratio *p*-value (dcSScATA *vs*. lcSScATA *vs*. ssSScATA) = 0.001
Log-rank ratio *p*-value (dcSScACA *vs*. lcSScACA *vs*. ssSScACA) <0.001

Patients at risk

	Years				
	0-5	5-10	10-20	20-30	30-40
Overall series	774	622	421	209	97
dcSScATA	153	117	74	28	9
dcSScACA	21	16	10	4	1
lcSScATA	76	59	39	17	7
lcSScACA	442	370	263	146	72
ssSScATA	14	10	5	3	1
ssSScACA	68	50	30	11	7

ACA: anti-centromere antibody; ATA: anti-topoisomerase I antibody; dcSSc: diffuse cutaneous SSc; lcSSc: limited cutaneous SSc; sine scleroderma SSc; SSc: systemic sclerosis.

digital ulcers and severe ILD whereas telangiectasia was more frequent in ssSScACA patients.

In terms of survival, no differences were found among serodiscordant patients and their respective counterparts. In other words, skin subtype would influence survival in more extent than the antibody status would. This in line with the classical studies in which diffuse subtype, usually associated with high prevalence and severity organ involvement and, therefore, burden of disease was related with higher mortality (26, 35). However, in a very recent study by Boonstra and colleagues (36), 22% (n=22/101) of ATA patients were classified as low-risk patients (*i.e*. those whose subgroup mortality was equal or lower than the cohort mortality rate), and 35% (54/153) of ACA patients were included in the high-risk group patients.

To the best of our knowledge, only few studies have specifically evaluated the organ involvement and survival of serodiscordant SSc patients. In one of them, Kranenburg *et al*. (11) compared the main characteristics of 58 patients with lcSScATA, 237 with lcSScATA negative, 78 with dcSScATA positive, and 87 patients with dcSScATA negative. Organ involvement at SSc diagnosis did not differ among the four subgroups. As cumulative manifestation, lcSScATA positive patients had a higher occurrence of ILD than those with lcSScATA negative. On the contrary, no differences were found in pulmonary hypertension, cardiac involvement or scleroderma renal crisis. Concerning survival, lcSScATA positive patients resembled those with lcSScATA negative. Of note, the authors did not describe in detail the antibody status of those patients ATA negative and they did not include patients with ssSSc. In another study, Srivastava *et al*. (10) compared the prevalence and clinical manifestations between serodiscordant patients (dcSScACA and lcSScATA) with their counterparts (dcSScATA and lcSScACA). Similarly to our results, pulmonary hypertension was more prevalent in lcSScACA patients than in those with lcSScATA (13.7% *vs*. 4.8%) and ILD was more frequent in lcSScATA patients than in those with lcSScACA (49.0% *vs*. 13.3%). In terms of survival, the authors did not find difference between patients with lcSScACA and those with lcSScATA (log-rank *p*=0.1290) whereas dcSScATA patients exhibited worse survival compared to those with dcSScACA (log-rank *p*=0.0313). However, these two studies (10, 11) and the previous from Perera *et al*. (28) differed from the current study in the objective. While we took into account the cutaneous subtype and then compared SSc patients according to their antibody status, they considered first the serological status (ATA or ACA) and then analysed the role of cutaneous subtype. This may explain some differences among them and the present study. In addition, previous studies did not include patients with ssSSc.

In the present study, the percentage of patients classified initially as lcSSc who transitioned to dcSSc was very low (2%) without differences in ATA or

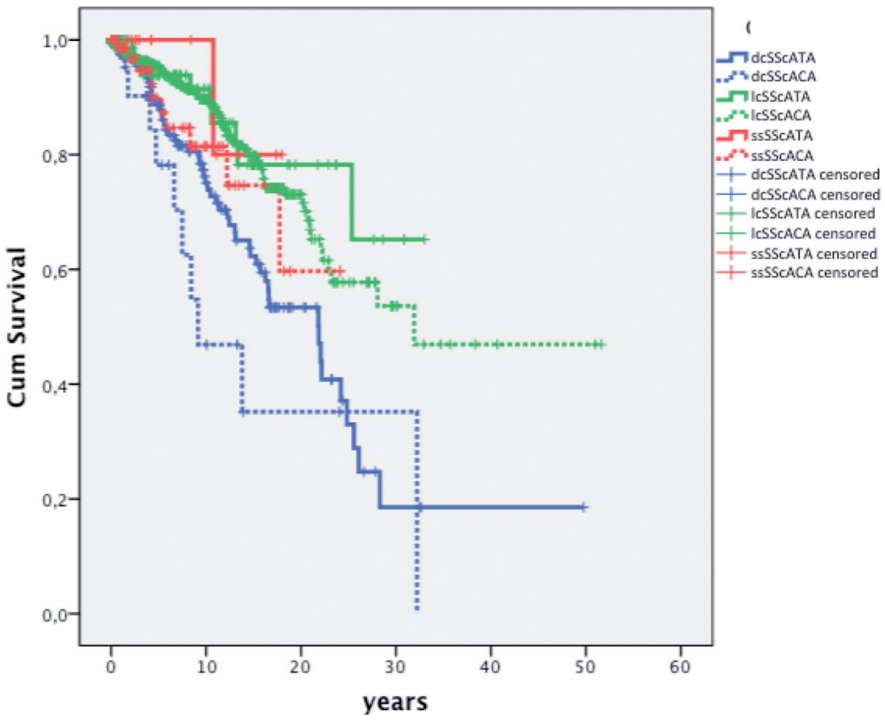

Fig. 2. Kaplan-Meier curves for patients with systemic sclerosis from disease diagnosis according to cutaneous involvement and immunological profile.

Log-rank ratio *p*-value global (global) <0.001
Log-rank ratio *p*-value (dcSScATA *vs*. dcSScACA) = 0.130
Log-rank ratio *p*-value (lcSScATA *vs*. lcSScACA) = 0.480
Log-rank ratio *p*-value (ssSScATA *vs*. ssSScACA) = 0.475
Log-rank ratio *p*-value (dcSScATA *vs*. lcSScATA *vs*. ssSScATA) = 0.006
Log-rank ratio *p*-value (dcSScACA *vs*. lcSScACA *vs*. ssSScACA) <0.001

Patients at risk

	Years				
	0-5	5-10	10-20	20-30	30-40
Overall series	724	459	239	61	12
dcSScATA	147	93	51	16	2
dcSScACA	19	12	5	2	1
lcSScATA	72	44	24	7	2
lcSScACA	415	276	145	35	7
ssSScATA	11	6	3	0	0
ssSScACA	60	28	11	1	0

ACA: anti-centromere antibody; ATA: anti-topoisomerase I antibody; dcSSc: diffuse cutaneous SSc; lcSSc: limited cutaneous SSc; sine scleroderma SSc; SSc: systemic sclerosis.

ACA distribution among them. Perera *et al*. (28) found that 7% of lcSSc patients transitioned to dcSSc subtype but they only analysed SSc patients with ATA. In the Canadian Scleroderma Research Group (10), 14% of lcSSc patients were classified as dcSSc during follow-up, 29.3% of them were ATA positive and 9.2% were ATA negative (p=0.001). Of note, in the present study, 14% of patients with ssSSc changed to lcSSc, and the majority of them had ACA. In a multicentre study, 30 out of 57 ssSSc patients were reclassified as lcSSc within 1.9 years (13). Unfortunately, information about their immunological status was not reported.

The main strengths of the present study include the fact that the six groups of patients were mutually exclusive from the cutaneous and immunological point of view. Of note, the prevalence of overlap with other non-specific autoantibodies were similar among the different groups of SSc patients regardless their cutaneous subtype and immunological profile. Therefore, the distinctive clinical profiles identified were directly related to each specific SSc-antibody. In addition, hospitals that participate in RESCLE have different levels and this ensures the inclusion of SSc patients with different degrees of organ involvement and severity. In this sense, the data provided by RESCLE represent a real picture of these subgroups of SSc patients. Furthermore, the present study is the first to compare the clinical profile and survival of ssSSc patients according to their immunological profile. The main limitation is the low number of serodiscordant patients despite the large originating cohort. This may prevent finding differences between groups and may be the cause of the differences found with previous studies. The present study does not have central laboratory and immunological studies were performed by each participating centre. To avoid false positive results, borderline results were considered as negative. Some clinical manifestations such as scleroderma renal crisis and neoplasia were underrepresented, giving difficult to achieve statistical significance. The effect of treatment on SSc patient survival has not been taken into account. We did not include in the analysis anti-RNA polymerase III antibody (ARA). However, the rate of SSc patients with ARA positive in the RESCLE is very low (15) precluding specific analysis. Another potentially important bias is the influence of duration of disease before SSc diagnosis on the analysis. In fact, the disease duration at the enrolment visit was relatively high but similar to other cohorts and, importantly, without differences between SSc subtypes. Moreover, Kaplan-Meier survival curves were similar regardless of whether the onset of disease or the diagnosis of disease was considered. In the end and as a National registry of patients, the quality on the acquisition data relies on the leading physician. However, death and well-defined SSc-specific organ involvements are robust endpoints, increasing the external validity of our findings.

In conclusion, this study showed that the prevalence of SSc serodiscord-

ant patients in RESCLE cohort is low and that antibody status may modulate some clinical manifestations of these subtypes of SSc patients. The management of patients with SSc should be guided by a combination of skin involvement and serology status. However, new biomarkers would be a helpful tool to explain the differences in these SSc subtypes (37). More studies on serodiscordant patients are warranted to confirm our results.

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Competing interests
M. Rubio-Rivas has received consulting fees or honoraria (less than $10,000 per year) from Actelion Pharmaceuticals; A. Guillén del Castillo has received personal fees from Boehringer Ingelheim and Actelion during the conduct of the study. The other co-authors have declared no competing interests.

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