Early- versus Late-Onset Systemic Sclerosis
Differences in Clinical Presentation and Outcome in 1037 Patients

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Abstract: Peak age at onset of systemic sclerosis (SSc) is between 20 and 50 years, although SSc is also described in both young and elderly patients. We conducted the present study to determine if age at disease onset modulates the clinical characteristics and outcome of SSc patients. The Spanish Scleroderma Study Group recruited 1037 patients with a mean follow-up of 5.2 ± 6.8 years. Based on the mean ± 1 standard deviation (SD) of age at disease onset (45 ± 15 yr) of the whole series, patients were classified into 3 groups: age ≤30 years (early onset), age between 31 and 59 years (standard onset), and age ≥60 years (late onset). We compared initial and cumulative manifestations, immunologic features, and death rates. The early-onset group included 195 patients; standard-onset group, 651; and late-onset, 191 patients. The early-onset group had a higher prevalence of esophageal involvement (72% in early-onset compared with 67% in standard-onset and 56% in late-onset; $p = 0.004$), and myositis (11%, 7.2%, and 2.9%, respectively; $p = 0.009$), but a lower prevalence of centromere antibodies (33%, 46%, and 47%, respectively; $p = 0.007$). In contrast, late-onset SSc was characterized by a lower prevalence of digital ulcers (54%, 41%, and 34%, respectively; $p < 0.001$) but higher rates of heart conduction system abnormalities (9%, 13%, and 21%, respectively; $p = 0.004$). Pulmonary hypertension was found in 25% of elderly patients and in 12% of the youngest patients ($p = 0.010$). After correction for the population effects of age and sex, standardized mortality ratio was shown to be higher in younger patients. The results of the present study confirm that age at disease onset is associated with differences in clinical presentation and outcome in SSc patients.

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*See Appendix for members of the RESCLE Registry.

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Abbreviations: ACA = anticentromere antibodies, ACR = American College of Rheumatology, ANA = antinuclear antibodies, CI = confidence interval, dcSSc = diffuse cutaneous systemic sclerosis, FVC = forced vital capacity, IIF = indirect immunofluorescence, ILD = interstitial lung disease, lcSSc = limited cutaneous systemic sclerosis, OR = odds ratio, PAP = pulmonary arterial pressure, PH = pulmonary hypertension, RESCLE = Registro de ESCLErodermia, RP = Raynaud phenomenon, RR = relative risk, RSHC = right-sided heart catheterization, SD = standard deviation, SMR = standardized mortality ratio, SSc = systemic sclerosis, ssSSc = systemic sclerosis sine scleroderma.

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease characterized by extensive fibrosis, vascular dysfunction, and the presence of several autoantibodies.[18,23] The disorder affects the skin and subcutaneous tissue in addition to internal organs, such as lungs, heart, gastrointestinal tract, and kidneys.[18,23] Worldwide, SSc is more common in women, with a ratio ranging from 3:1 to 14:1.[18] Peak age at onset is between ages 20 and 50 years, although SSc is also described in both young and elderly patients.[6,30,37]

Age at onset may modulate the clinical expression and associated prognosis in several autoimmune diseases.[2,21,22,35,43] Particularly for SSc, there is inconsistent information regarding the modifying role of age at onset in baseline and outcome features.[14,25,40,55,57] Some authors have proposed that older patients with SSc exhibit a different clinical presentation, disease course, and autoantibody repertory.[14,25,40,55,57] Controversies still exist regarding the associated mortality rates in relation to age at SSc onset, with some data pointing out that elderly onset is associated with poorer prognosis and decreased survival.[57]

Given the lack of uniform findings, and given that differences between older and younger patients would have implications for prognosis and treatment, we conducted the present study in a large, well-characterized cohort of 1037 patients with the objective of determining if age at onset alters the clinical characteristics and outcome of patients with SSc.

PATIENTS AND METHODS

Patients

The current analysis was performed on the frame of the Spanish Scleroderma Study Group (SSSG)[49] or RESCLE (Registro de ESCLErodermia as Spanish nomenclature) Registry. Briefly, the RESCLE Registry was created by the Spanish Society of Internal Medicine in 2006 with the aim of compiling a large cohort of patients with SSc.[49] With the participation of 14 centers with substantial experience in the management of this disorder,

1037 patients were recorded until July 2012. All participating centers obtained ethics committee approval.

To avoid excluding patients with a clear diagnosis of SSc who did not fulfill the American College of Rheumatology (ACR) preliminary classification criteria,[3] we also considered the diagnosis following a modification of the classification proposed by LeRoy and Medsger.[31] Demographic, clinical, immunologic, and capillaroscopic data encompassing 90 variables were collected according to a standard protocol and then entered into an SPSS database.

Based on the mean ± 1 standard deviation (SD) of the age at disease onset of the whole series (45 ± 15 yr), patients were classified into 3 groups: age ≤30 years (mean − 1 SD) (early-onset group), age between 31 and 59 years (standard-onset group), and age ≥60 years (mean + 1 SD) (late-onset group). This distribution was chosen to maximize age-related differences (early- vs. late-onset) in addition to having a control group for comparisons (standard onset, 31–59 yr).

Variable Definitions

We used the following definitions:

Disease onset: the date of the first self-reported symptom (Raynaud phenomenon [RP] in the majority of patients).

Disease diagnosis: the date when the patient fulfilled the ACR classification criteria[3,32] or the classification proposed by LeRoy and Medsger.[31]

Cutaneous subsets that included 4 groups of SSc according to the extent of skin sclerosis, following a modification of the classification proposed by LeRoy and Medsger[31]: pre-SSc was established by the presence of RP, puffy fingers, pathognomonic microvascular alteration detected by capillaroscopy, and/or disease-specific autoantibodies but no skin thickening or systemic vascular features/visceral fibrosis.[7] Limited cutaneous SSc (lcSSc) was considered when skin sclerosis was confined distally to the elbows and knees or the face. Diffuse cutaneous SSc (dcSSc) was considered when skin thickening extended proximally to the elbows and knees or included the trunk; and systemic sclerosis sine scleroderma (ssSSc) was defined by the presence of RP, typical vascular features, visceral fibrosis, and specific positive antinuclear antibodies (ANA) without skin sclerosis.[41]

Peripheral vascular manifestations: defined by the presence of RP with or without ischemic digital ulcers. Acro-osteolysis (bony resorption of the terminal digital tufts secondary to ischemia) and telangiectasias were also recorded under this category.

Gastrointestinal tract involvement: including any of the following diagnoses considered related to SSc: esophageal involvement, when hypomotility of the lower two-thirds of the esophagus and/or decreased peristalsis were confirmed by manometry or cine-radiographic study; gastric involvement, when gastric hypomotility was detected by radiographic or radionuclide study or when gastric antral vascular ectasia was identified by endoscopy; intestinal involvement, when an intestinal motility disturbance was confirmed by manometry or cine-radiographic study, when malabsorption syndrome was diagnosed by breath test, or when intestinal pseudo-obstruction was identified by simple radiology or computerized tomography scan. Diagnoses of primary biliary cirrhosis, autoimmune hepatitis, or nodular regenerative hyperplasia of the liver were encompassed under the term hepatic involvement.

Pulmonary involvement: defined by the presence of interstitial lung disease (ILD) or pulmonary hypertension (PH). The former was established if any of the following criteria were identified: a) restrictive pulmonary pattern with forced vital capacity (FVC) below 70% of expected value on pulmonary function tests, b) pulmonary interstitial pattern evidenced by chest radiograph or high-resolution computed tomography scan, or c) alveolitis confirmed by bronchoalveolar lavage (defined as neutrophilia of ≥3%, eosinophilia of ≥2%, or lymphocytosis ≥15%).[4,5] FVC level below 70% was selected because of its association with poorer prognosis in SSc patients.[47] PH was diagnosed when systolic pulmonary arterial pressure (PAP) was estimated to be >40 mm Hg by Doppler echocardiogram corresponding to maximum tricuspid regurgitant jet velocity of 3.0–3.5 m/s or when mean PAP was found to be equal or higher than 25 mm Hg at rest by right-sided heart catheterization (RSHC).[19]

Heart involvement: established by 1 or more of the following: pericarditis, ischemic cardiomyopathy with no known cause, reversible thallium perfusion defects after cold stimulation, any disturbance on color-Doppler echocardiography, electrocardiographic abnormalities with no other cause, left ventricular ejection fraction lower than 50%, or right ventricular ejection fraction lower than 40% on echocardiography or radionuclide ventriculography.

Muscle involvement: myopathy was established by the presence of proximal muscle weakness or myalgias and serum creatine kinase levels over the normal value in addition to characteristic results of electromyography (EMG) and nerve conduction studies. Calcinosis was defined as widespread soft-tissue calcification or in a localized area causing secondary muscle atrophy, joint contractures or skin ulceration.

Joint involvement: defined by the presence of arthralgia, tendon friction rubs, or arthritis (concomitant erosion and joint space narrowing).[8]

Scleroderma renal crisis: defined by the presence of a rapid deterioration of renal function (with concomitant normal urine sediment) within a period of less than 1 month in the absence of previous evidence of significant kidney disease or by the combination of abrupt onset or aggravation of moderate to severe arterial hypertension (>160/90 mm Hg) accompanied by manifestations of malignant hypertension (hypertensive grade III or IV retinopathy, pulmonary edema and/or hypertensive encephalopathy) and elevation of peripheral renin activity to at least twice the upper limit of normal.[53]

Sicca syndrome: defined when ocular and oral dryness was present with ocular signs or abnormal tests of salivary gland function or abnormalities in salivary gland biopsy.

Nailfold capillaroscopy: 2 main capillaroscopic patterns were distinguished[34]: a) active pattern characterized by predominant capillary loss, and b) slow pattern characterized by the presence of megacapillaries but no significant capillary loss.

Immunologic features: including ANA identified by indirect immunofluorescence (IIF) assay using Hep-2 cell lines or by IIF using triple tissue cryostat section (liver-stomach-kidney). Anticentromere antibodies (ACA), anti-PM-Scl, and antibodies to extractable nuclear antigens (SSA/Ro, SSB/La, Sm, RNP, and topoisomerase I [Scl-70]) were also determined.

Mortality: The standardized mortality ratio (SMR) was calculated. This is the measure used to assess the relative mortality of a disease in comparison with the general population. SMR was calculated according to the method described by Breslow and Day[10] with specific mortality data (1986–2010) obtained from the Spanish Statistics National Institute.

Statistical Analysis

This study is a nationwide, cross-sectional analysis of age groups. Results from continuous variables are presented as mean ± SD, and categorical data as percentages. Statistical evaluation was performed using a contingency table test (chi-square test) to identify significant differences or associations among the 3 age groups for qualitative variables. ANOVA and t-test was used for

quantitative variables. The Bonferroni method was used for correction of multiple comparisons. Values of $p < 0.05$ were considered significant. Survival curves were calculated using the Kaplan-Meier method, and the log rank ratio was used to identify differences. Multivariate Cox regression analysis was performed to identify independent variables related to diminished survival. Logistic regression was used to determine the risk of SSc major organ involvement (ILD, PH, scleroderma renal crisis, heart involvement, and digital ulcer) as a function of age at SSc onset. Adjustment was done for sex, cutaneous subtype of SSc, and presence of anti-Scl-70 or ACA.

For SMR calculation, indirect standardization was performed using year-specific population rates for Spain. Confidence intervals (CI) for the SMR were calculated using the assumption that the observed number of cases followed a Poisson distribution. All statistical analyses were performed with SPSS 18.0 for Windows (Chicago, IL).

RESULTS

General Characteristics

The whole cohort comprised 1037 patients (88% women) with a mean follow-up of 5.2 ± 6.8 years. Mean age at disease onset was 45 ± 15 years. LcSSc was the most prevalent subtype (n = 623, 60%), and RP was the most common initial disease manifestation (84%). Table 1 shows the demographic and main cumulative manifestations of the cohort. Table 2 presents the demographic, initial presentation, and immunologic features; Table 3 compares the prevalence of cumulative clinical characteristics of the SSc patients according to their age at onset.

Early-Onset SSc Group

Patients in the early-onset group were characterized by a longer interval (in years) from disease onset to diagnosis (12.0 ± 13.0 yr vs. 5.8 ± 7.8 in patients with standard onset and 2.4 ± 3.6 in those with late-onset SSc, $p < 0.001$) (see Table 2). Compared with elderly patients and considering cumulative organ damage, patients with early-onset SSc more frequently had myositis (11% vs. 7.2% vs. 2.9%, $p = 0.009$) and esophageal involvement (72% vs. 67% vs. 56%, $p = 0.004$) (see Table 3). Pre-scleroderma was more frequent in these patients (9.7% vs. 4.3% vs. 2.6%, $p = 0.002$). Regarding antibody profile, patients with early onset of SSc had lower prevalence of ACA than patients with standard onset and those with late onset of SSc (33% vs. 46% vs. 47%, respectively, $p = 0.007$).

Late-Onset SSc Group

Elderly patients had a higher prevalence of lcSSc (67.5% vs. 51% for early onset vs. 60.5% for standard onset, $p = 0.004$), a lower frequency of digital ulcers (34% vs. 54% vs. 41%, respectively, $p < 0.001$) and a higher prevalence of heart conduction system disorders (21% vs. 9% vs. 13%, respectively, $p = 0.004$) in addition to systemic hypertension (13% vs. 35% vs. 68%, $p < 0.001$) (see Tables 2 and 3). Patients with late-onset disease had an increased prevalence of PH (diagnosed by echocardiography) documented in 25%, compared to 12% in the youngest patients and 19% in the group of patients aged 31–59 years ($p = 0.010$). By this technique the mean systolic PAP was 41 ± 21 mm Hg for the elderly group vs. 31 ± 18 for the younger patients ($p = 0.006$). The prevalence of PH diagnosed by RSHC (performed in 56 patients: 7 in early onset, 41 for the group aged 31–59 yr, and 8 in the late-onset group) was not different between the 3 groups (see Table 3).

Age-Related Relationships

To analyze the independent effect of age on major organ involvement observed in the previous groups, multivariate analysis with logistic regression was performed. Relationships between age at diagnosis and ILD ($p < 0.001$; odds ratio [OR], 1.02; 95% CI, 1.01–1.03), PH ($p < 0.001$; OR, 1.02; 95% CI, 1.01–1.03), heart disease ($p < 0.001$; OR, 1.03; 95% CI, 1.02–1.04) and digital ulcer ($p < 0.001$; OR, 0.98; 95% CI, 0.97–0.99) were significant. The relationship between age at diagnosis and scleroderma renal crisis was not significant.

Differences among the 3 groups were not found in sex distribution, first clinical manifestation, nailfold capillaroscopy pattern,

TABLE 1. Demographic, Clinical, and Immunologic Characteristics of 1037 Patients With SSc*

Characteristic	No. (%)
Sex, male/female (%)	130/907 (22/88)
Age at disease onset, mean±SD (yr)	45±15
Age at diagnosis, mean±SD (yr) (n=1022)	51±15
Time of follow-up, mean ± SD (yr)	5.2±6.8
Death	151 (14.6)
SSc-related (n=151)	78 (51.7)
Type of scleroderma (n=1035)	
Limited cutaneous SSc	623 (60.2)
Diffuse cutaneous SSc	270 (26.1)
SSc sine scleroderma	90 (8.7)
Pre-SSc	52 (5.0)
First manifestation (n=939)	
Raynaud phenomenon	787 (83.8)
Arthralgia	54 (5.8)
Cumulative clinical manifestations	
Peripheral vascular manifestations	
Raynaud phenomenon (n=1037)	967 (93.2)
Telangiectasies (n=1036)	629 (60.7)
Digital ulcers (n=1036)	435 (41.9)
Osteomuscular manifestations	
Calcinosis (n=980)	193 (19.7)
Arthritis (n=927)	173 (18.7)
Myositis (n=928)	66 (7.1)
Digestive tract involvement	
Esophagus (n=922)	608 (65.9)
Lung involvement	
Interstitial lung disease (n=983)	499 (50.8)
Pulmonary arterial hypertension (n=881)	167 (18.9)
Heart involvement	
Conduction alteration (n=872)	118 (13.5)
Ischemia (n=871)	94 (10.8)
Pericarditis (n=873)	46 (5.3)
Renal involvement	
Scleroderma renal crisis (n=870)	29 (3.3)
Other manifestations	
Sicca syndrome (n=980)	328 (33.5)
Peripheral neuropathy (n=155)	18 (11.6)
Immunologic features	
Antinuclear antibodies (n=1029)	906 (88.0)
Anticentromere antibodies (n=913)	398 (43.6)
Anti-topoisomerase I (n=910)	202 (22.2)

*All data derived from 1037 patients except when indicated.

TABLE 2. Demographic Characteristics and Serologic Profiles, 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	P ≤30 vs. 31–59	P ≤30 vs. ≥60	P 31–59 vs. ≥60
Sex (female, %)	178 (91.3)	561 (86.2)	168 (87.9)	0.164			
Age at disease onset, mean±SD (yr)	22±5.8	45±8.1	67±5.9				
Time from onset to diagnosis, mean±SD (yr) (n=1022)	12±13	5.8±7.8	2.4±3.6	<0.001	<0.001	<0.001	<0.001
Follow-up, mean±SD (yr)	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			
SSc sine scleroderma	25 (13)	49 (7.5)	16 (8.4)	0.071			
Pre-SSc	19 (9.7)	28 (4.3)	5 (2.6)	0.002	0.007	0.004	1.000
First manifestation (n=939)							
Raynaud phenomenon	154 (88.0)	492 (84.0)	141 (78.0)	0.134			
Puffy hands	4 (2.3)	11 (1.9)	5 (2.9)	—			
Arthralgia	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)	—			

*All data derived from 1037 patients except when indicated; percentages in (%).

or cumulative clinical manifestations involving the kidney or peripheral nerves.

Mortality

During follow-up, 151 patients (14.6%) died. Cause of death was identified in 122 of the 151 patients and included pulmonary involvement in 61 (PH in 25, ILD in 19, and both in 17), cancer in 18, scleroderma renal crisis in 13, sepsis in 5, ischemic heart disease in 4, and other causes (stroke, chronic renal failure, chronic obstructive pulmonary disease, lethal arrhythmias, or pulmonary embolism) in 21. In 78 (63.9%) of these cases, the cause of death was considered directly related to SSc. On multivariate analysis, independent variables related to increased mortality were dcSSc ($p = 0.001$; relative risk [RR], 2.22; 95% CI, 1.39–3.58), age at diagnosis ($p = < 0.001$; RR, 1.05; 95% CI, 1.04–1.07), FVC < 70% ($p = 0.008$; RR, 1.79; 95% CI, 1.17–2.76), PH ($p = 0.003$; RR, 1.89; 95% CI, 1.24–2.86), and scleroderma renal crisis ($p = < 0.001$; RR, 6.16; 95% CI, 2.90–13.1). Differences between the early- and late-onset groups in relation to the specific causes of death were not found.

The overall cohort median survival time from diagnosis was 21.9 years, and the overall 5-year survival rate was 90.7%. The Kaplan–Meier survival curves were significantly different ($p < 0.0001$) for the 3 groups of patients (Figure 1), with a median survival time of 29.3 years in patients aged ≤30 years, 21.9 for those aged 31–59, and 12.2 years in the elderly patients. As there is some controversy regarding definitions of disease duration for patients with SSc, we performed sensitivity analyses using Kaplan-Meier curves to estimate if survival changes when a non-Raynaud symptom was used instead of RP. Results of this analysis did not indicate any difference (data not shown).

The SMR of the whole cohort calculated for a period of 24 years from 1986 to 2010 was 3.80 (95% CI, 3.18–4.43) compared with the background population. After correction for the population effects of age and sex, higher SMR values were found in younger patients aged ≤30 years (26.22; 95% CI, 14.43–38.01), followed by patients aged 31–59 years (13.32; 95% CI, 10.55–16.08). The lowest SMR was found in older patients ≥60 years (1.78; 95% CI, 1.17–2.39).

DISCUSSION

In this large cohort of Spanish patients, we confirmed that the age at disease onset influences the clinical manifestations, major organ involvement, and outcome of patients with SSc. Late-onset SSc was characterized by an elevated prevalence of lcSSc with high cardiopulmonary morbidity manifested as PH, heart

TABLE 3. Cumulative Clinical Manifestations in Patients 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	P ≤30 vs. 31–59	P ≤30 vs. ≥60	P 31–59 vs. ≥60
Peripheral vascular manifestations							
Raynaud 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			
Acro-osteolysis (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			
Malabsorption (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† (n=881)	18 (12.0)	106 (19.0)	43 (25.0)	0.010	0.165	0.007	0.185
PH by RSHC‡ (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			
Systemic hypertension (n=170)	5 (13.0)	36 (35.0)	19 (68.0)	<0.001	0.039	<0.001	0.002

Abbreviations: PAH = pulmonary arterial hypertension.

*All data derived from 1037 patients except when indicated; percentages in (%)

†Systolic pulmonary arterial pressure ≥40 mm Hg.

‡Mean pulmonary artery pressure ≥25 mm Hg.

disease, and systemic hypertension. This elderly group suffered less frequently from digital ulcers and had higher probability of being positive for ACA.

In previous studies, the cut-off for defining late-onset SSc ranged from 55 to 75 years. Taking into account this data, similar features in this subgroup of patients such as raised prevalence of cardiovascular and lung involvement have been previously reported.[25,33,40,55,57] In these previous studies, higher prevalence of PH, systemic arterial hypertension, abnormal diastolic function, and conduction system alterations were the most striking findings. Although the prevalence of PH in the current study was at the lower range (25%) of the spectrum (35%–45%) of previously reported data,[25,33,46] right heart catheterization was performed in only 56 patients in the present series. This precludes comparisons because many possible causes of elevated estimations in right ventricular systolic pressure already exist. Systemic arterial hypertension, diastolic dysfunction, and conduction abnormalities, all more prevalent in the late-onset group, can lead to left ventricular hypertrophy and thus to nonspecific elevation of pulmonary pressure.[25,44] We are aware that Doppler echocardiography may be misleading in the assessment of patients with suspected PH, as measurement of pulmonary artery systolic pressure by ultrasound can over- and underestimate true PAP.

Our data did not allow us to determine whether the higher frequency of conduction blocks in the late-onset group was due to SSc (cardiac fibrosis) or was related to the normal aging process. It is known that heart conduction system abnormalities and electrocardiographic changes increase with age,[17,42] and that among people aged >65 years the prevalence of electrocardiographic abnormalities is approximately 30%.[17,42] In addition, a possible bias related to differences in diagnostic workup can not be excluded, as older SSc-patients may be getting electrocardiograms more frequently than younger patients as part of their regular medical assessments.

The accompanying lower prevalence of digital ulcers and higher frequency of ACA found in the older patients are in

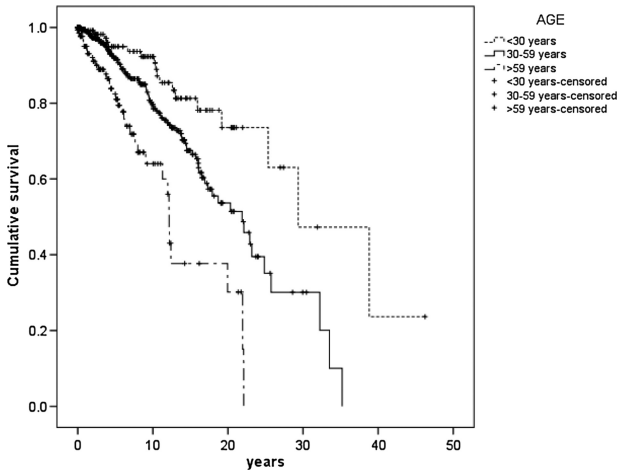

FIGURE 1. Kaplan-Meier estimate of the probability of death (since diagnosis) depending on age at disease onset.

accordance with results from other groups.[25,33,50,52,55] Why older patients had a lower prevalence of digital ulcer is unknown. We suggest that the SSc-cutaneous subset and the presence of specific autoantibodies are of relevance. Previous studies[13,50,52] have raised the possibility that specific autoantibodies are related to more severe peripheral vascular disease. The prevalence and the time elapsed for the development of digital ulcers were different in anti-Scl-70 and ACA-positive patients—that is, anti-Scl-70 was related to a higher prevalence of digital ulcers and the appearance of the first ulcer occurred a mean of 6 years earlier compared to ACA patients. In addition, the former patients were younger at the onset of first RP symptoms and had shorter time periods from the onset of RP to the first digital ulcer, probably reflecting more severe vascular disease.[13,50,52] Diffuse skin sclerosis has been associated as an independent risk factor for the development of digital ulcer.[50,52] Higher grade of sclerosis of the fingers and hands related to dcSSc probably impedes blood flow and wound healing and favors the formation of digital ulcers.[51] In the current study, the late-onset group was characterized by a higher prevalence of ACA and lcSSc, and, therefore, probably a milder peripheral vascular involvement. Other factors that probably play a role include the normal immune system senescence, aging-related changes of the skin's microcirculation, more cold avoidance among the elderly, and the fact that older patients are more likely to be on aspirin and calcium channel blockers for comorbidities.

In contrast to these referred similarities, we were unable to find an increased frequency of renal involvement and sicca syndrome in patients with late-onset SSc.[33,40] One explanation for these discrepancies may be the criteria that we used to define SSc-related manifestations. We considered only scleroderma renal crisis as renal manifestation of SSc, whereas in the study by Manno et al,[33] an elevation of creatinine levels beyond 1.3 mg/dL or >2+ protein in urine dipstick was considered to be kidney involvement in their SSc patients.

We note that patients with late onset were diagnosed faster that younger patients, an observation made also in other cohorts.[33,40] We speculate that the higher prevalence of extracutaneous involvement at disease onset and the earlier appearance of systemic manifestations (particularly lung and heart involvement) in the elderly allow early identification and diagnosis.[33,40] The more frequent medical assessments performed in older patients as part of the standard of care for common chronic disorders could also play a role. On the other hand, delayed diagnosis in younger patients may be secondary to the misclassification of RP as a primary condition, in particular when nailfold capillary microscopy and specific autoantibody tests are not available.[29] Finally, there could be a subgroup of young patients with pre-SSc or ssSSc with milder manifestations who are initially classified as having undifferentiated connective tissue disease (UCTD) but later develop features of definite SSc.[54]

We are aware that some of the differences that we and others[25,33,40,46,55,57] have found in older patients with SSc could be related to the normal aging process and concurrent related diseases. Aging is associated with several physiologic adaptations and an increased susceptibility to several diseases. Older age is related to large artery stiffening[9,39] that increases the risk for systemic hypertension and left ventricle hypertrophy.[20] Valve calcification and thickening[28] may predispose older patients to cardiac conduction problems.[28] Additionally, not only does systemic vascular resistance increase with age, but pulmonary vascular resistance is also increased, probably due to reduced compliance of the pulmonary vascular bed.[45,46]

In contrast to the similar clinical and immunologic features reported for late-onset presentation, early-onset SSc is less well characterized.[25,33,40,55] In previously reported cohorts,[25,33,40,55] patients were grouped based on an age limit higher or lower than 60–75 years, and therefore they lost the characteristics of the youngest patients. In the present study, we described for the first time that patients with early-onset disease (mean age, 25 ± 5.8 yr) presented more frequently with esophageal involvement and myositis. Previously, Manno et al[33] reported that gastrointestinal involvement was more common in patients aged younger than 65 years, and Weng et al[57] observed higher levels of creatine kinase in the group of patients aged 19–38 years; although this latter group did not have a higher prevalence of myopathy.

Our results from the group of early-onset SSc are in accordance with results from the European League Against Rheumatism Scleroderma Trial and Research (EUSTAR) database.[16] In that study of adult patients with disease onset between the ages of 20 and 40 years (mean age, 32 yr), lcSSc was found in 53% (51% in the current series), RP in the same frequency as our patients (95%), esophageal involvement in 65% (72% in our series), digital ulcers in 41% (54% in our series), pulmonary fibrosis in 36% (50% in our series), and pulmonary arterial hypertension in 14% (12% in our patients). ANA were present in 92.8% compared with 90% in the present series, topoisomerase-I antibodies were positive in 40.7% (25% in our series), and ACA in 27.8% (33% in our series). Features of this group of young patients with arthralgia, muscle involvement, dysphagia, and lower frequency of ACA resemble some of the main characteristics of juvenile SSc.[36,58] More studies are needed to clarify the clinical profile of the younger adult patients with SSc.

Although large geographic variations in SSc prevalence and incidence have been described,[12] there was no clear regional trend with regard to organ involvement.[56] The prevalence of both first and cumulative clinical manifestations of our population of Spanish patients with SSc is very similar to those described in other registries from the same geographic zone such as the EUSTAR database.[55]

Finally, we confirmed that mortality is increased in SSc patients compared with an age- and sex-matched population. The SMR of the whole RESCLE cohort was 3.80 (95% CI, 3.18–4.43). Notably, it was calculated for a period of 24 years (1986–2010), supporting comparability to other studies made within the same period for different populations. The SMR of our series was higher than that reported in Australia[24] (1.46) and Denmark[27] (2.9), but similar to the SMR of 3.9 from China,[38] 4.0 from the United Kingdom,[11] 4.2 from Spain,[47] and 4.7 from Canada.[1] Two recent

meta-analyses reported pooled SMRs of 3.53[15] and 1.5–7.2.[26] As expected, patients with late-onset SSc had the highest mortality rate. However, when we compared SMRs of patients with SSc with the general Spanish population in the same period, higher SMRs were found in patients aged ≤30 years (SMR 26.22; 95% CI, 14.43–38.01), followed by patients aged 30–59 years (SMR 13.32; 95% CI, 10.55–16.08). It is noteworthy that the lowest SMR was found in the elderly patients.

The overall 5-year survival rate reported in the present series (90%) was similar to that previously reported by other authors.[15,25,27,37,40] The cause of death was considered directly attributable to SSc in 64% of cases, most of these secondary to lung involvement. As previously reported,[47,48] we identified age at diagnosis, cutaneous subset, lung involvement, and scleroderma renal crisis as independent prognostic factors that influence survival.

Strengths of the present study include the large number of patients derived from the same geographic location as well as the multiple analyses and corrections made for exploring the effect of age on SSc manifestations. Limitations of the present study include missing information concerning time to development of each manifestation (systemic manifestations seemed to appear earlier in older patients according to previous series[25,33,40,55,57]) and treatment modalities. Also, the limited number of patients with RSHC precludes determining the real prevalence of pulmonary arterial hypertension. In addition, the absence of a control group of young and elderly matched populations without SSc is important because some of the differences observed could be due to the normal aging process. Finally, as in all registry studies, the accuracy of the clinical diagnosis as judged by the attending physician can not be verified.

In spite of these limitations, the present study suggests that age at onset is associated with differences in clinical presentation and outcome in patients with SSc. Knowledge of these different characteristics can help to improve the management of the disease.

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APPENDIX

RESCLE Registry

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