ORIGINAL ARTICLES

Clinical features and outcome of 1054 patients with Systemic Sclerosis: analysis of Reuma.pt/SSc registry

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ABSTRACT

Background: Systemic sclerosis (SSc) is a rare connective tissue disorder with heterogeneous manifestations and outcomes. Besides differences in disease characteristics among distinct ethnic groups and geographical regions, several questions regarding the impact of the disease and the effectiveness of treatments remain unanswered. To address these questions, the Rheumatic Diseases Portuguese Register (Reuma.pt) launched a specific protocol for the prospective follow-up of SSc patients.

Objectives: To describe the baseline characteristics, disease subsets, treatments used and survival of SSc patients registered in Reuma.pt/SSc.

Methods: Data from adult patients with SSc included in Reuma.pt up to November 2020 were analysed. Demographic features, SSc subsets, fulfilment of classification criteria, main clinical and immunological features, comorbidities, treatments used and survival data were described and compared between diffuse cutaneous (dc) and limited cutaneous (lc) disease subsets. Survival was calculated for patients included in Reuma.pt within the first two years of diagnosis.

Results: In total, 1054 patients were included, 87.5% female, with a mean age at diagnosis of 52.7 +/- 14.8 years. The most common subset was lcSSc (56.3%), followed by dcSSc (17.5%), preclinical SSc (13%), overlap syndrome (9.8%) and SSc sine scleroderma (3.3%). Raynaud's phenomenon (93.4%) and skin thickening (76.9%) were the most frequently observed clinical manifestations. Gastrointestinal (62.8% versus 47.8%), pulmonary (59.5% versus 23%) and cardiac (12.8% versus 6.9%) involvements were significantly more prevalent in dcSSc than lcSSc. Ninety per-cent of patients were Antinuclear antibody positive, 52.5% were Anti-centromere antibody positive and 21% anti-topoisomerase positive, with significant differences between lcSSc and dcSSc. One-third of patients were treated with immunomodulators, 53.6% with vasodilators, 23% with glucocorticoids and 2.3% with biologics.

During follow-up, 83 deaths (7.9%) were reported. The overall 1-, 2- and 5-year survivals were 98.0%, 96.8% and 92.6%, respectively, without significant differences between lcSSc and dcSSc.

Conclusion: Reuma.pt/SSc data highlights the importance of registries in improving knowledge about rare and complex diseases, such as SSc. Clinical features of Portuguese SSc patients are similar to those of other populations. In recently diagnosed patients, 5-year survival is over 92%. To the best of our knowledge, this is the first study showing that clinical features of Portuguese SSc are similar to those of other cohorts.

Keywords: Systemic sclerosis; Clinical features; Survival.

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Submitted: 14/05/2021
Accepted: 28/08/2021

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INTRODUCTION

Systemic sclerosis (SSc) is a rare connective tissue disease of unknown aetiology characterised by microvasculopathy, immune system disturbances and fibrosis of the skin and internal organs. The disease course varies from a relatively benign condition to a rapidly progressive disease, and has a broad spectrum of clinical and laboratory features. Considerable ethnic and geographical variation in clinical and laboratory manifestations, severity and mortality has been observed in previous studies[1-3], suggesting the possible involvement of genetic and environmental factors. Therefore, investigating SSc patients' distinctive manifestations and outcomes in different ethnic and geographical groups is relevant to better understand this rare disease and improve medical care.

The Rheumatic Diseases Portuguese Register (Reuma.pt) was created in June 2008 and prospectively follows patients with several rheumatic diseases. It is available as a web-based online system since 2012 (www.reuma.pt) and currently includes specific protocols for 14 rheumatic diseases. Reuma.pt gathers information on patients' clinical and immunological features, disease activity and function, health-related quality of life, comorbidities, implemented treatments and outcome. Follow-up visits are registered as per clinical practice, usually at 3-6 months' intervals. As of December 2020, 24 840 patients and 214 375 visits had been registered. In 2015, a specific protocol for SSc was launched (Reuma.pt/SSc). Its main goal was to clinically and immunologically characterise SSc patients, evaluate the impact of the disease and get long-term information on the safety and effectiveness of different treatment options.

This paper describes the Reuma.pt/SSc protocol, and SSc patients registered up to November 2020.

OBJECTIVES

The primary objective of this observational study was therefore to describe the clinical and immunological features of the Portuguese cohort of SSc patients. Additionally, we compared disease features between dcSSc and lcSSc patients and assessed survival rates for those patients included in the cohort within the first two years of diagnosis.

METHODS

Reuma.pt/SSc and Study Design

This is a multicenter prospective cohort study. All adult patients diagnosed with SSc by a rheumatologist and registered in Reuma.pt/SSc up to November 2020 were included in this study, regardless of follow-up time. Data was prospectively collected at each visit. Baseline information was complemented with data from medical records when necessary.

The Reuma.pt/SSc protocol displays a table of contents that includes General data, Today's visit and Evolution data (Figure 1) for each SSc patient. General data includes identification, demographic characteristics, SSc subtype, fulfilment of American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2013 classification criteria, clinical and immunological manifestations, date of disease onset and diagnosis, lifestyles and other associated medical conditions. In Today's visit, the physician can fill (i) disease assessment scores [digital ulcers, modified Rodnan skin score (mRSS), tender and swollen joints]; (ii) physician- and patient-reported outcomes (PRO) such as Health Assessment Questionnaire (HAQ); Medsger SSC severity scale; University of California Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0 (UCLA SCTC GIT 2.0), EuroQoL(EQ)-5D, Hospital Anxiety and Depression Scale (HADS), 36 Item Short Form Survey (SF36), Functional Assessment of Chronic Illness Therapy (FACIT) and Work Productivity and Activity Impairment (WPAI) questionnaire); (iii) exam results (laboratory tests, imaging findings, pulmonary function tests, echocardiogram and right heart catheterisation data, capillaroscopic patterns, among others); (iv) screenings data (vaccines and tuberculosis); and (v) medication and its adverse events. Besides, patients can access a dedicated online area to complete the PROs before each medical visit.

Variables Collected

Variables collected included demographic characteristics (sex, race, age at diagnosis, body mass index, education level); comorbidities (hypertension, dyslipidemia, cardiovascular diseases, diabetes mellitus); lifestyles (smoking and alcohol use); age at first symptoms; age at diagnosis; SSc subtype (lcSSc, dcSSc, preclinical SSc, SSc sin scleroderma, overlap syndrome); fulfillment of ACR/EULAR 2013 classification criteria; clinical features [Raynaud's phenomenon (RP), skin thickening, telangiectasias, digital ulcers, calcinosis, tendon friction rubs, arthralgia, arthritis, myositis and esophageal, gastric, intestinal, cardiac, pulmonary or renal involvement]; immunological features [antinuclear antibodies (ANA), anti-topoisomerase I (Scl70), anti-centromere (ACA), anti-RNA polymerase III, anti-Th/To, anti-U3 RNP,

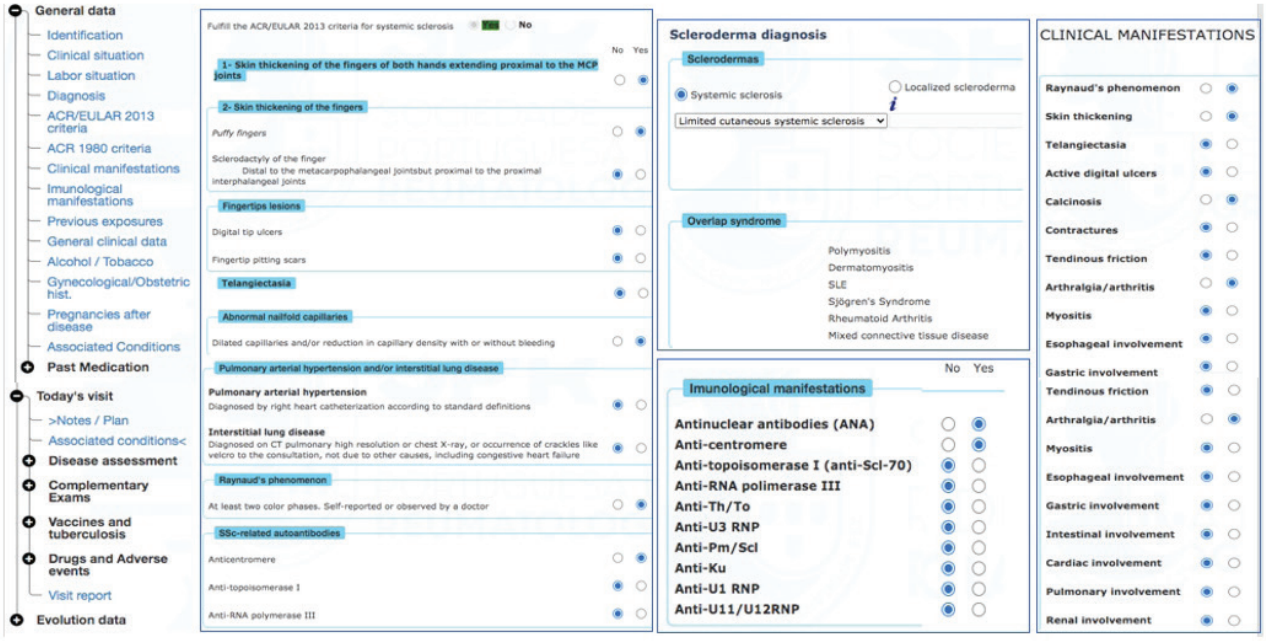

Figure 1. Brief sumary of the Reuma.pt/SSc. On the left side is the table of content (General data, Today's visit and Evolution data). On the middle and right side of the figure we have contents of information on General Data, specially ACR/EULAR 2013 criteria, scleroderma diagnosis (subtype), immunologic manifestation and clinical manifestation.

anti-Pm/Scl, anti-Ku, anti-U1 RNP, anti-U11/U12 RNP positivity]; medication (glucocorticoids, immunosuppressants/immunomodulators, biologic agents, vasodilators, medication for gastrointestinal symptoms); survival and follow-up time since diagnosis.

Statistical Analysis

Continuous variables with normal distributions were reported as means and standard deviations. If continuous variables had skewed distributions, the medians and interquartile ranges were reported. Categorical variables were presented as absolute frequencies and percentages.

Data referring to baseline clinical and immunological features, comorbidities and treatments used are presented both for the whole cohort and according to the clinical subtype. Comparison between lcSSc and dcSSc was made using the Chi-square test for categorical variables and Student's t-test or Man-Whitney test for continuous variables.

Only data from patients with SSc registered in Reuma.pt within the first two years of disease were used in the survival analysis (inception cohort). Survival was assessed using Kaplan-Meier survival analysis and the log-rank test for comparisons between lcSSc and dcSSc. Survival was calculated since diagnosis.

Statistical analysis was performed using SPSS software (IBM, version 23, Armonk, NY, USA). All calculations were made based on observed data. The threshold for statistical significance was a p-value inferior to 0.05.

Ethical Approval

The study was conducted according to the Declaration of Helsinki and was approved by the Coordinating and Scientific Board of Reuma.pt and by the Ethics Committee of Hospital Garcia de Orta. Reuma.pt was approved by the National Data Protection Authority (CNPD), and all patients provided written informed consent for data collection, analysis, and publication. The analyses were performed on an anonymous dataset.

RESULTS

In total, 1054 adult patients with SSc were registered in the Reuma.pt/SSc database. The most common SSc subset was lcSSc (56.3%), followed by dcSSc (17.5%), preclinical SSc (13%), overlap syndrome (9.8%) and SSc sine scleroderma (3.3%). Of the 1054 patients included, 716 (68%) fulfilled ACR/EULAR 2013 criteria. Overall, the whole cohort's characteristics are similar to those who fulfil ACR/EULAR 2013 criteria (supplementary Table I and II).

Table I. Demographic features and comorbidities

Demographic features	Total N=1054	Limited cutaneous SSc N= 576 (56.3%)	Diffuse cutaneous SSc N=180 (17.5%)	P value
Female - N (%) no=1054	922 (87.5)	525 (90.7)	136 (75.6)	<0.01
Caucasian – N (%) no=611	567 (92.8)	332 (96.2)	108 (89.3)	0.04
Education years – mean ± SD no=270	9 ± 3.9	7.7 ± 4	9.1 ± 3.6	0.03
Smokers/Former smoker - N (%) no=561	107 (25)	72 (23.2)	38 (34.9)	0.01
Alcohol consumers/Former consumer - N (%) no= 498	142 (25.3)	256 (74.2)	93 (92.8)	0.06
BMI – mean ± SD no=369	25 ± 5.2	25.3 ± 4.3	25.1 ± 6.6	0.89
Age at diagnosis – mean ± SD no=770	52.7 ± 14.8	54.5 ± 14	48.7 ± 15.4	<0.01
Years since 1st symptoms to diagnosis – median (IQR) no=734	1.6 (0.3-5)	2 (0.4-6)	1 (0.2-3.1)	0.01
Comorbidities				
Hypertension – N (%) no=431	117 (27.1)	76 (29.7)	67 (20.7)	0.1
Hyperlipidemia – N (%) no=431	71 (13.4)	72 (12.2)	24 (15.9)	0.08
Diabetes – N (%) no=431	26 (6)	18 (7)	6 (9)	0.38
CV disease – N (%) no= 431	35 (3.3)	22 (8.6)	9 (13.4)	0.17
Deaths – N (%) no=1054	83 (7.9)	36 (6.2)	28 (15.6)	<0.01

Total corresponds to all subtypes of SSc, including limited cutaneous SSc, diffuse cutaneous SSc, preclinic SSc, overlap syndrome and SSc sine scleroderma. N - number; no - Number of patients with available information; SD - Standard deviation; BMI - body mass index; IQR - Interquartile range; CV - cardiovascular. P value for comparison between lcSSc to dcSSc.

Demographic characteristics and comorbidities

Demographics and comorbidities of SSc patients are shown in Table I. The mean age at diagnosis was 52.7 ± 14.8 years and 87.5% were females (female/male ratio 7:1). Sex ratios were different in lcSSc (females/males ratio 10:1) and dcSSC (females/males ratio 3:1). dcSSc patients were younger at diagnosis, and the diagnosis was made earlier in the course of the disease (one year after the beginning of symptoms *vs* two years in lcSSc). Hypertension, hyperlipidemia and diabetes were the most prevalent comorbidities, without significant differences between dcSSc and lcSSc patients.

Clinical and immunological features

Clinical features of SSc patients are shown in Table II. RP (93.4%) and skin thickening (76.9%) were the most frequently observed manifestations, followed by gastrointestinal (48.2%) and pulmonary (28.5%) involvements. Cardiac (7.7%) and renal (1.9%) involvement were less frequently observed. dcSSc patients had higher frequencies of cutaneous manifestations, particularly puffy fingers (62.1% vs 47.3%, p<0.01), digital ulcers (51.5% vs 34.7%, p<0.01) and pitting scars (43.8% vs 30.6%, p<0.01) compared to lcSSc. Musculoskeletal, cardiac and gastrointestinal involvement were also more prevalent in dcSSc than lcSSc. Regarding pulmonary involvement, interstitial lung disease was more prevalent in dcSSc than in lcSSc (57.7% vs 22.7%, p<0.01). Few patients had pulmonary arterial hypertension confirmed by right heart catheterisation, but most of them had lcSSc.

Immunological features of SSc patients are presented in Table III. Ninety per cent of patients were ANA positive. ACA were significantly more common in lcSSc (67.1% vs 9.5%, p<0.01) and anti-topoisomerase I in dcSSc (60.1% vs 3.3%, p<0.01).

Treatments used

Immunomodulators and/or immunosuppressants were used in up to 40% of patients (Table IV). Almost a quarter of patients received low-dose glucocorticoids, and 2.3% received biologics (rituximab or tocilizumab). Patients with dcSSc were more likely to be treated with immunomodulators/immunossupressants (53.9% vs 36.8%, p<0.01), biologic agents (6.7% vs 0.7%, p<0.01) and low dose glucocorticoids (37.2% vs 18.1%, p<0.01) than lcSSc patients. In total, 53.6% of patients used vasodilators, and dcSSc patients were more frequently treated with prostacyclin analogues (18.9% vs 11.9%, p=0.01) and endothelin receptor antagonists (12.2% vs 6.6%, p=0.013). Proton pump inhibitors, ranitidine and prokinetics were used in up to 33.5% of all patients.

Table II. Cumulative clinical features

Clinical features	Whole cohort	Limited cutaneous SSc N= 576 (56.3%)	Diffuse cutaneous SSc N=180 (17.5%)	P value
Skin thickening proximal do MCF/MTF joints– N (%) no= 962	680 (76.9)	512 (88.9)	180 (100)	<0.01
Sclerodactyly – N (%) no= 855	547 (64)	369 (74.1)	114 (81.4)	0.045
Puffy fingers – N (%) no= 838	370 (44.2)	228 (47.3)	87 (62.1)	<0.01
Telangiectasias – N (%) no= 973	479 (49.2)	316 (58.3)	77 (48.1)	0.15
Digital ulcers –N (%) no=970	325(33.5)	186 (34.7)	94 (52.2)	<0.01
Pitting scars – N (%) no=846	248 (29.3)	148 (30.6)	64 (43.8)	<0.01
Calcinosis – N (%) no=946	132 (14)	78 (14.6)	31 (20.1)	0.07
Raynaud's Phenomenon – N (%) no=1010	943 (93.4)	539 (95.7)	157 (92.4)	0.06
Musculoskeletal involvement – N (%) no=972	346 (45.6)	247 (42.7)	99 (55)	<0.01
Contractures – N (%) no=922	76 (8.2)	29 (5.5)	36 (24.7)	<0.01
Tendon friction rubs – N (%) no=883	23 (2.6)	9 (1.8)	7 (5.2)	0.03
Inflammatory arthralgia/arthritis– N (%) no=966	392 (40.6)	212 (38.7)	72 (46.5)	0.05
Myositis – N (%) no=943	54 (5.7)	8 (1.5)	12 (7.8)	<0.01
Cardiac involvement – N (%) no=924	71 (7.7)	36 (6.9)	19 (12.8)	0.02
Renal involvement – N (%) no= 917	17 (1.9)	8 (1.5)	6 (4.1)	0.07
Gastrointestinal involvement - N (%) no=933	508 (48.2)	277 (47.8)	113 (62.8)	<0.01
Esophageal involvement – N (%) no=933	340 (36.4)	201 (38.1)	79 (51.3)	<0.01
Gastric involvement – N (%) no=916	114 (12.4)	63 (12.2)	30 (20.3)	0.01
Intestinal involvement– N (%) no=909	47 (5.2)	20 (3.9)	13 (9.6)	<0.01
Pulmonary involvement – N (%) no=915	261 (28.5)	119 (23)	88 (59.5)	<0.01
Pulmonar arterial hypertension – N (%) no= 871	14 (1.6)	12 (2.1)	2 (1.1)	0.23
Interstitial lung disease – N (%) no=765	218 (28.5)	100 (22.7)	75 (57.7)	<0.01

Total corresponds to all subtypes of SSc, including limited cutaneous SSc, diffuse cutaneous SSc, preclinic SSc, overlap syndrome and SSc sine scleroderma. Skin thickening does not include isolated sclerodactyly. Pulmonary arterial hypertension confirmed by right heart catheterization. N - number; no - Number of patients with available information. P value for comparisons between lcSSc and dcSSc.

Survival

During a median follow-up time of 12.4 years, 83 deaths (7.9%) were reported (Table I). For patients included in Reuma.pt within the two first years since diagnosis (N= 472), the overall 1-, 2- and 5-year survival rates were 98.0%, 96.8% and 92.6%, respectively, with no significant differences found between lcSSc and dcSSc patients (p=0.27) (Figure 2).

DISCUSSION

We present the clinical and immunological features and the survival rates of patients included in this large Portuguese SSc cohort. Reuma.pt/SSc database provides an opportunity to characterise SSc patients in detail, to evaluate the treatments used and patients' outcomes, contributing to improving the quality of clinical care. This is the first time an extensive and multicenter analysis of Reuma.pt/SSc is presented.

Only 68% of patients fulfilled the ACR/EULAR 2013 criteria for the classification of SSc[7]. This proportion is in line with other registries[6,8] and within what was anticipated, as the diagnosis is based on clinical judgement, and the registry includes a considerable number of patients with very early disease. However, the patient's clinical features are similar irrespective of the fulfilment of the classification criteria. As expected, lcSSc was the most prevalent subtype, but all SSc subsets are represented, including preclinical SSc.

Women outnumbered men by 7 to 1, and this ratio is similar to those observed in the EUSTAR and other cohorts[3,6]. The highest ratio of women/men was observed in lcSSc, which is also in agreement with other cohorts[6]. dcSSc occurs at a younger age, and the time from first symptoms to diagnosis was significantly shorter than in lcSSc. This finding probably reflects the faster progression of the skin thickening and the involvement of other organs, which occur

Table III. Immunologic characteristics

Immunological features	Whole cohort	Limited cutaneous SSc N= 576 (56.3%)	Diffuse cutaneous SSc N=180 (17.5%)	P value
Antinuclear antibodies - N (%) no=1040	934 (89.8)	522 (90.2)	154 (88.5)	0.57
Anti-centromere – N (%) no= 1027	540 (52.6)	383 (67.1)	16 (9.5)	<0.01
Anti-topoisomerase I – N (%) no=1020	214 (21)	12 (3.3)	104 (60.1)	<0.01
Anti-RNA polymerase III – N (%) no=710	25 (3.5)	12 (3.3)	7 (5.6)	0.38
Anti-Th/To – N (%) no=669	15 (2.2)	7 (2.1)	0	0.26
Anti-U3 RNP – N (%) no=694	17 (2.4)	6 (1.7)	8 (6.5)	0.02
Anti-Pm/Scl – N (%) no=715	34 (4.8)	15 (4.1)	4 (3.3)	0.898
Anti-Ku – N (%) no=690	13 (1.9)	7 (2)	0	0.287
Anti-U1 RNP – N (%) no=746	25 (3.4)	3 (0.8)	5 (3.8)	0.054
Anti-U11/U12 RNP – N (%) no=673	4 (0.6)	3 (0.9)	0	0.536
Tendon friction rubs – N (%) no=883	23 (2.6)	9 (1.8)	7 (5.2)	0.03
Inflammatory arthralgia/arthritis– N (%) no=966	392 (40.6)	212 (38.7)	72 (46.5)	0.05
Myositis – N (%) no=943	54 (5.7)	8 (1.5)	12 (7.8)	<0.01
Cardiac involvement – N (%) no=924	71 (7.7)	36 (6.9)	19 (12.8)	0.02
Renal involvement – N (%) no= 917	17 (1.9)	8 (1.5)	6 (4.1)	0.07
Gastrointestinal involvement - N (%) no=933	508 (48.2)	277 (47.8)	113 (62.8)	<0.01
Esophageal involvement – N (%) no=933	340 (36.4)	201 (38.1)	79 (51.3)	<0.01
Gastric involvement – N (%) no=916	114 (12.4)	63 (12.2)	30 (20.3)	0.01
Intestinal involvement– N (%) no=909	47 (5.2)	20 (3.9)	13 (9.6)	<0.01
Pulmonary involvement – N (%) no=915	261 (28.5)	119 (23)	88 (59.5)	<0.01
Pulmonar arterial hypertension – N (%) no= 871	14 (1.6)	12 (2.1)	2 (1.1)	0.23
Interstitial lung disease – N (%) no=765	218 (28.5)	100 (22.7)	75 (57.7)	<0.01

Total corresponds to all subtypes of SSc, including limited cutaneous SSc, diffuse cutaneous SSc, preclinic SSc, overlap syndrome and SSc sine scleroderma. N – number; no – Number of patients with available information. P value for comparisons between lcSSc and dcSSc.

Table IV. Treatment options in SSc patients

Medication	Whole cohort	Limited cutaneous SSc N= 576 (56.3%)	Diffuse cutaneous SSc N=180 (17.5%)	P value
Immunomodulators/ Immunossupressants – N (%)	420 (39.8)	213 (36.8)	97 (53.9)	<0.01
Biologic agents – N (%)	24 (2.3)	4 (0.7)	12 (6.7)	<0.01
Low dose glucocorticoids – N (%)	245 (23.2)	105 (18.1)	67 (37.2)	<0.01
Calcium channel blockers – N (%)	527 (50)	332 (57.3)	103 (57.2)	0.52
PDE-5 inhibitors – N (%)	35 (3.3)	26 (4.5)	4 (2.2)	0.12
Prostacyclin analogues – N (%)	131 (12.4)	69 (11.9)	34 (18.9)	0.01
Endothelin receptor antagonist – N (%)	64 (6.1)	38 (6.6)	22 (12.2)	0.013
Antifibrotic – N (%)	11 (1.1)	5 (0.9)	6 (3.3)	0.03
PPIs/Ranitidine/Prokinetics – N (%)	353 (33.5)	222 (38.3)	75 (41.7)	0.24

PDE-5 (phosdiasterase-5); PPIs (proton pump inhibitors); Immunomodulators include Methotrexate, Leflunomide, Hydroxychloroquine; Immunosuppressants include Azathioprine, Mycophenolate Mofetil and Cyclophosphamide; Antifibrotic included only Nintedanib. N - number; no - Number of patients with available information. P value for comparison between lcSSc to dcSSc.

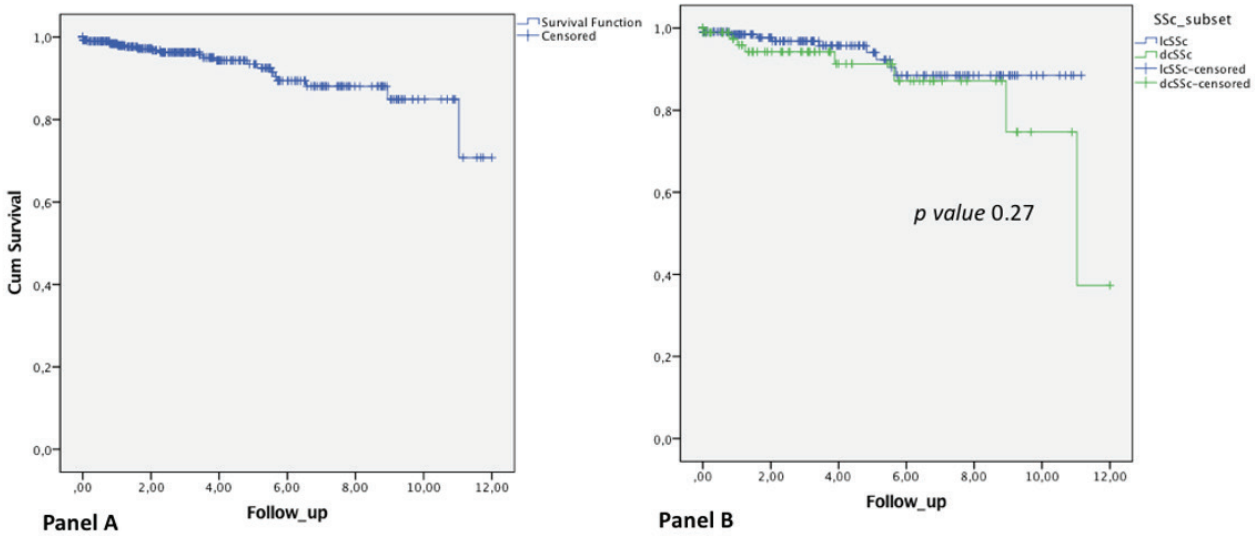

Figure 2. Survival from diagnosis of patients with SSc included in the cohort in the first 2 years of disease (N=472). Panel A includes all SSc patients and Panel B shows survival according to SSc subset (IcSSc and dcSSc). The X and Y axes represent follow-up time in years and the proportion of patients still on follow-up, respectively. Kaplan Meier with log rank test was used.

more frequently in dcSSc than in lcSSc patients[3,6]. The diagnosis delay in lcSSc may be due to patients trivialising their symptoms, especially when RP is the sole disease manifestation.

SSc patients have a remarkable disease heterogeneity in organ involvement. In our study, we found a lower prevalence of internal organs involvement compared to previously described cohorts. This may be explained by the higher proportion of preclinical SSc patients. However, we also found lower prevalence of internal organ involvement in dcSSc and lcSSc patients. This could possibly be explained by the shorter interval between the first symptoms and the diagnosis and access to more effective therapeutic options compared to older cohorts, but we cannot totally exclude registration bias and underreporting. Nevertheless, marked differences in clinical features were found between lcSSc and dcSSc, as previously reported in the literature[3-6]. Musculoskeletal, cardiac and gastrointestinal impairment was significantly more frequent in dcSSc than in lcSSc. This was also true for pulmonary involvement, especially for interstitial lung disease. Additionally, a clear predominance of ACA in lcSSc and anti-topoisomerase I in dcSSc was found, also in concordance with other cohorts[3,5,6].

There are no approved drugs that modify the SSc disease course, and treatment is aimed at symptom control and management of organ complications. Off-label use of immunomodulators and/or immunosuppressants is frequent in clinical practice, as is shown by Reuma.pt/SSc data. The antifibrotic nintedanib was recently approved for SSc-associated interstitial lung disease by the European Medicine Agency (EMA) and only recently received reimbursement. This may explain the low number of patients treated with this class of medications in our cohort.

The 5-year survival rate (92.6%) is similar to other inception cohorts recently reported in the literature[9-11]. Studies comparing recent and historical cohorts have suggested an improvement in survival rates over time[4,13,14], which may partly be explained by an earlier diagnosis. Moreover, the awareness about the disease's clinical manifestations and its possible complications, as well as better treatment options for specific organ-based involvement also play a role. The systematic screening for major organ complications is now routine in clinical practice, and this probably translates to an overall improvement in the early detection and management of these complications and longer survival. Additionally, some observational cohort studies analysing survival in SSc included prevalent cases, resulting in an underestimation of mortality due to survivor bias. To minimise this risk, we only used data from patients with recent-onset SSc in the survival analysis (inception cohort).

Although Reuma.pt/SSc is a robust nationwide sample of SSc patients, our study has several limitations. First, registration in the Reuma.pt database is voluntary and not a population-based cohort. As so, not all patients with SSc are registered, and possi-

ble registration bias exists. Also, underreporting and missing data is a real possibility, especially regarding more complex information. We tried to overcome these limitations by reinforcing the need to complete all the missing data in the participating centres before data extraction.

CONCLUSION

Reuma.pt/SSc registry is useful in the routine monitoring of patients and contributes to improving knowledge about this rare and complex disease. This is the first extensive analysis of a nationwide cohort of SSc, including such a large number of patients.

Clinical features of Portuguese SSc patients and the overall 5-year survival in recently diagnosed patients are similar to what has been described in other populations.

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Supplementary Table I. Demographic features and comorbidities in SSc patients that fulfil ACR/EULAR 2013 criteria

Demographic features	Whole cohort	Limited cutaneous SSc N= 576 (56.3%)	Diffuse cutaneous SSc N=180 (17.5%)	P value
Female - N (%) no=716	621 (86.7)	425 (90.6)	118 (76.1)	<0.01
Caucasian – N (%) no=469	428 (93)	284 (96.9)	96 (88.1)	0.01
Education years – median (IQR) N=209	9 (4-12)	6 (4-12)	9 (6-12)	0.02
Smokers/Former smoker - N (%) no=411	101 (24.6)	60 (23.2)	32 (32.7)	0.047
Alcohol consumers/Former consumer - no (%) N= 359	288 (57.3)	211 (44.9)	83 (53.5)	0.051
BMI – median (IQR) N=113	24.9 (21.7-27)	24.9 (22-26.8)	24.1 (21.6-27.3)	0.58
Age at diagnosis – mean ± SD no=636	52.4 ± 14.6	54.6 ± 13.9	47.9 ± 14.8	<0.01
Comorbidities				
Hypertension – N(%) no=336	86 (25.6)	63 (28.6)	13 (21.7)	0.17
Hyperlipidemia – N(%) no=336	40 (12)	3 (1.4)	0	0.47
Diabetes – N(%) no=336	21 (6.3)	17 (6.8)	5 (8.2)	0.44
CV disease – N(%) no= 336	28 (8.3)	18 (8.2)	8 (13.1)	0.17

PN - number; no - Number of patients with available information; SD - Standard deviation; BMI - body mass index; IQR - Interquartile range; CV - cardiovascular. P value comparing lcSSc to dcSSc.for comparison between lcSSc to dcSSc.

Supplementary Table II. Cumulative clinical and immunologic features in SSc that fulfil EULAR/ACR 2013 criteria

Clinical features	Whole cohort	Limited cutaneous SSc N= 576 (56.3%)	Diffuse cutaneous SSc N=180 (17.5%)	P value
Skin thickening proximal to MCF/MTF joints – N (%) no= 680	578 (85)	377 (84.7)	141 (95.3)	<0.01
Sclerodactyly – N (%) no= 671	537 (80)	363 (81.2)	114 (83.8)	0.289
Puffy fingers – N (%) no= 647	316 (48.8)	202 (47.4)	85 (62.5)	<0.01
Telangiectasias – N (%) no= 686	413 (60.6)	291 (64.7)	74 (51)	<0.01
Digital ulcer –N (%) no=686	282 (41.1)	172 (38)	76 (52.1)	<0.01
Pitting scars – N (%) no=658	237 (36)	143 (33.1)	64 (45.4)	<0.01
Calcinosis – N (%) no=667	111 (16.6)	68 (15.2)	27 (19.6)	0.143
Raynaud's Phenomenon – N (%) no=710	688 (96.9)	457 (98.1)	143 (93.5)	0.05
Musculoskeletal involvement – N (%) no=670	377 (56.3)	239 (51)	94 (60.3)	<0.01
Contractures – N (%) no=648	66 (10.2)	24 (5.5)	33 (10)	<0.01
Tendinous friction – N (%) no=615	19 (3.1)	8 (1.9)	7 (5.7)	0.034
Inflammatory arthralgia– N (%) no=684	291 (42.5)	175 (38.4)	68 (48.2)	0.02
Myositis – N (%) no=668	47 (7)	7 (1.6)	12 (8.6)	<0.01
Cardiac involvement – N (%) – no=652	61 (9.4)	32 (7.3)	17 (12.7)	0.043
Renal involvement – N (%) – no=645	15 (2.3)	8 (1.9)	5 (2.3)	0.173
Gastrointestinal involvement - N (%) no=660	397 (60.2)	272 (58.1)	104 (67.2)	0.02
Esophageal involvement – N (%) no=656	285 (43.4)	181 (41.2)	72 (43.8)	0.02
Gastric involvement – N (%) no=645	90 (14)	53 (12.4)	26 (19.4)	0.03
Intestinal involvement– N (%) no=638	39 (6.1)	19 (4.4)	13 (9.8)	0.02
Pulmonary involvement – N (%) no=645	224 (34.7)	110 (25.5)	82 (61.2)	<0.01
Pulmonar arterial hypertension – N (%) no= 663	14 (2.1)	10 (2.3)	1 (0.7)	0.2
Interstitial lung disease – N (%) no=589	200 (34)	96 (24.6)	73 (58.9)	<0.01
Immunological features				
Antinuclear antibodies - N (%) no=709	651 (91.8)	429 (92.3)	138 (90.8)	0.68
Anti-centromere – N (%) no= 699	364 (52.1)	310 (67.2)	15 (10.2)	<0.01
Anti-topoisomerase I – N (%) no=690	171 (24.8)	61 (13.5)	94 (62.3)	<0.01
Anti-RNA polymerase III – N (%) no=439	17 (3.9)	10 (3.5)	6 (5.8)	0.62

PN - number; no - Number of patients with available information; SD - Standard deviation; BMI - body mass index; IQR - Interquartile range; CV - cardiovascular. P value comparing lcSSc to dcSSc.for comparison between lcSSc to dcSSc.