
Systemic sclerosis Progression INvestiGation (SPRING)

Italian registry: demographic and clinico-serological features of scleroderma spectrum

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ABSTRACT

Objective. Systemic sclerosis (SSc) is a severe multiple-organ disease characterised by unpredictable clinical course, inadequate response to treatment, and poor prognosis. National SSc registries may provide large and representative patients cohorts required for descriptive and prognostic studies. Therefore, the Italian Society of Rheumatology promoted the registry SPRING (Systemic sclerosis Progression INvestiGation).

Methods. The SPRING is a multi-centre rheumatological cohort study encompassing the wide scleroderma spectrum, namely the primary Raynaud's phenomenon (pRP), suspected secondary RP, Very Early Diagnosis of Systemic Sclerosis (VEDOSS), and definite SSc. Here we describe the demographic and clinical characteristics of 2,028 Italian patients' population at the initial phase of enrollment, mainly focusing on the cohort of 1,538 patients with definite SSc.

Results. Definite SSc showed significantly higher prevalence of digital ulcers, capillaroscopic 'late' pattern, oesophageal and cardio-pulmonary involvement compared to VEDOSS, as expected on the basis of the followed classification criteria.

The in-depth analysis of definite SSc revealed that male gender, diffuse cutaneous subset, and anti-Sc170 seropositivity were significantly associated with increased prevalence of the most harmful disease manifestations.

Similarly, patients with very short RP duration (≤ 1 year) at SSc diagnosis showed a statistically increased prevalence of unfavorable clinico-serological features.

Conclusion. Nationwide registries with suitable patients' subsetting and follow-up studies since the prodromal phase of the disease may give us valuable insights on the SSc natural history and main prognostic factors.

Introduction

Systemic sclerosis (SSc) is a complex disease characterised by the involvement of the skin and internal organs, heavily affecting patient's quality of life and survival (1-5). The disease pathogenesis encompasses a number of causative genetic and/or environmental co-factors leading to a complex of immune-system, fibroblast, and vascular alterations responsible for diffuse collagen tissue deposition and microangiopathy (1, 2). A clinical heterogeneity of the disease is suggested by several studies frequently focusing on small patients' populations (6). For this reason, SSc registries have been developed worldwide to provide large and homogeneous patients' subgroups (7). In 2015, the Italian Society of Rheumatology (SIR) promoted the creation of the national SPRING (Systemic sclerosis Progression INvestiGation) registry, including both precursory clinical conditions and overt disease variants. The present multi-centre rheumatologi-

cal cohort study aimed to describe the clinico-serological characteristics of a large Italian SSc series recorded during the recruitment period of the SPRING, and represents the largest cohort of patients examined up to now on the Italian territory.

Patients and methods

Patients' recruitment and assessment

SPRING is a multicentre national no-profit cohort study, promoted by SIR in 2015 as part of SIR-Strategic Projects; therefore, all the Italian rheumatology centres were invited to participate. The study protocol was approved by the IRB in every participating centre (37 centres); all patients provided written informed consent to enter in the study with the explicit protection of their identity.

Study data were collected and managed using REDCap electronic data capture tools hosted at SIR REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies (8). Patients were consecutively screened and enrolled at each participating centre according to standardised study procedures.

All patients were hierarchically classified into 4 different cohorts: 1) primary RP (pRP); 2) suspected secondary RP (ssRP): RP with one or more clinico-serological features not fulfilling the classification criteria of SSc or other CTDs (3); 3) Very Early Diagnosis of Systemic Sclerosis (VEDOSS) according to previously proposed criteria (9, 10); 4) definite SSc according to ACR/EULAR 2013 classification criteria for systemic sclerosis (11). The main inclusion criteria were: 1) presence of Raynaud's phenomenon (RP) for the cohorts 1 and 2; 2) age > 18 years; 3) absence of a definite diagnosis of connective tissue disease (CTD) other than SSc for the cohorts 2 and 3.

At the time of patient's enrollment the following data were collected: demographic characteristics, disease history (including RP duration, date of diagnosis if appropriate) and clinical manifestations, life-styles (smoking, BMI), and comorbidities.

The evaluation of the collected varia-

bles followed previously described criteria (3, 5). In particular, the patient's age was calculated at the following conventional times: a) at the appearance of isolated RP; b) at the disease onset, considered to be the age at which the first non-Raynaud's sign(s) and/or symptom(s) compatible with the disease appeared, *i.e.* digital ischaemic lesions, puffy hands, sclerodactyly with or without proximal scleroderma, dyspnea, and/or dysphagia; c) at the SSc diagnosis at the referral centres. At the same time, patients were also classified based on the extent of skin sclerosis as limited cutaneous SSc (sclerosis of distal extremities, not above the elbows and knees, with or without sclerosis of neck and face), diffuse cutaneous SSc (sclerosis of both distal and proximal extremities, with or without truncal involvement), or *sine scleroderma* SSc (ssSSc) in the complete absence of cutaneous sclerosis. Besides, the following SSc-related symptoms and organ involvement were evaluated according to the criteria previously described (3, 5, 11, 12): modified Rodnan skin score (mRSS), digital ulcers, gangrene and/or osteomyelitis (13); arthritis (inflammatory changes observed in more than 2 joints); muscle weakness with/without elevated serum creatine kinase; oesophageal involvement (dysphagia and oesophageal radiographic dysmotility); pulmonary involvement (dyspnoea, ground glass and/or bibasilar fibrosis at HRCT and/or restrictive lung disease on pulmonary function tests, including decreased diffusion capacity for carbon monoxide (DLCO), cardiac involvement (at least 1 of the following features: pericarditis, severe arrhythmias and/or atrioventricular conduction abnormalities at EKG, left ventricle diastolic dysfunction and/or abnormal ejection fraction (< 50%) at Doppler echocardiography; pulmonary arterial hypertension (PAH) evaluated by means of systolic pulmonary arterial pressure (sPAP) at Doppler echocardiography and confirmed by right heart catheterization according to current diagnostic criteria (14); and scleroderma renal crisis (sudden onset of severe arterial hypertension together with acute renal failure).

Besides routine laboratory investigations, the following serological markers were detected by means of standard techniques (3, 5): anti-nuclear (ANA), anti-centromere (ACA), and anti-extractable nuclear antigen (anti-ENA) antibody specificities, including anti-Sc170.

At baseline and every yearly visit all the above features were collected, as well as previous/current treatments, including both vasoactive drugs (Ca-channel blockers, prostanoids, ERAs, PDE5- and/or ACE-inhibitors), and immunomodulants/immunosuppressors (corticosteroids, hydroxychloroquine, cyclophosphamide, methotrexate, azathioprine, and/or mycophenolate mofetil).

Statistical methods

Descriptive statistics were performed for demographic, clinical, laboratory, instrumental characteristics and for treatment, reporting results as percentages, mean with standard deviation (SD) or median and interquartile range (IQR).

Differences between groups are detected by Test T or non-parametric Wilcoxon Test for continuous variables while Chi-squared test or non-parametric Fisher exact test were performed to compare frequencies in different groups of categorical variables.

Analyses were performed using R-3.5.2 statistical software (Foundation for Statistical Computing, Vienna, Austria).

Results

Patients' population

Within October 2018, a series of 2,028 patients was enrolled and individuals distributed in the 4 cohorts according to the entry criteria; the demographic and clinico-serological features are summarised in Table I. The two cohorts of pRP and ssRP displayed demographic and clinical composition consistent with the above inclusion criteria. On the other hand, some significant differences observed between the two cohorts of SSc patients, namely the VEDOSS (242 pts) and definite SSc (1,538 pts cohorts) were in keeping with the followed classification criteria

Table I. Main demographic and clinico-serological features of 2028 SSc patients of the Italian registry SPRING.

	All	pRP	ssRP	VEDOSS	definite SSc	<i>p</i> ^o
Patients no.	2028	51	136	242	1538	
Demographic						
Sex Males no. (%)	210 (10.5%)	8 (16.3%)	19 (14.1%)	17 (7.1%)	161 (10.5%)	0.086
Age mean (DS)	58.0 (14.3)	54.2 (14.3)	54.1 (16.2)	53.3 (15.3)	59.2 (13.9)	<0.001
Dis dur yrs mean (DS)*	8.3 (7.5)	10.8 (8.0)	7.1 (6.9)	4.2 (4.9)	8.9 (7.7)	<0.001
Clinical						
Skin inv. no. (%) [^]	1474 (78.5%)	0 (0%)	27 (22.9%)	90 (38.5%)	1338 (90.2%)	<0.001
Puffy fingers no. (%)	815 (42.8%)	0 (0%)	10 (8.1%)	59 (25.4%)	740 (49.2%)	<0.001
Teleangectasias no. (%)	956 (50%)	0 (0%)	17 (13.7%)	27 (11.6%)	894 (59.3%)	<0.001
Calcinosis no. (%)	186 (9.8%)	0 (0%)	3 (2.4%)	5 (2.2%)	177 (11.8%)	<0.001
Digital ulcers (%)	352 (18.5%)	0 (0%)	7 (5.6%)	9 (3.9%)	332 (22%)	<0.001
Oesophageal inv. no. (%)	843 (44.1%)	0 (0%)	34 (27.6%)	68 (29.2%)	725 (48.1%)	<0.001
Sicca syndrome no. (%)	552 (29%)	0 (0%)	34 (27.4%)	64 (27.5%)	441 (29.4%)	0.774
Cardio-respiratory symptoms no. (%)	476 (25%)	0 (0%)	11 (8.9%)	22 (9.5%)	431 (28.7%)	<0.001
Lung inv (radiological)	566 (54.4%)	0 (0%)	8 (28.6%)	23 (21.1%)	523 (59.1%)	<0.001
Heart inv (EKG and/or ECHO)	423 (95.9%)	0 (0%)	15 (93.8%)	26 (83.9%)	366 (96.8%)	0.008
Capillaroscopy alterations** no. (%)	1521 (81%)	0 (0%)	42 (33.3%)	150 (64.1%)	1311 (89%)	<0.001
Serological						
ANA test - no (%)	1794 (93.2%)	0 (0%)	69 (53.1%)	233 (97.9%)	1454 (96.8%)	<0.001
anti- Scl70 - no (%)	561 (29.2%)	0 (0%)	4 (3.1%)	33 (13.9%)	513 (34.1%)	<0.001
ACA - n (%)	857 (42.3%)	0 (0%)	13 (9.6%)	126 (52.1%)	700 (45.5%)	<0.001

pRP: primary Raynaud's phenomenon; ssRP: suspected secondary RP; VEDOSS: very early diagnosis of systemic sclerosis; *disease duration from diagnosis; [^]limited or diffuse cutaneous involvement; heart involvement on the basis of EKG and/or Doppler echocardiography alterations.

ANA: anti-nuclear antibodies; anti-ENA: anti-extractable nuclear antigen antibodies.

**early, active and/or late patterns; ^ocomparison between the 4 cohorts.

(Table II); namely, patients with definite SSc were characterised by longer disease duration, higher mean age and mRSS. Moreover, the VEDOSS cohort showed a high prevalence of the ssSSc cutaneous subset, while several SSc manifestations were significantly more frequent in definite SSc cohort, *i.e.* puffy fingers, digital ulcers, teleangectasias, calcinosis, arthritis, tendon friction rubs, oesophageal dysmotility, and cardio-respiratory manifestations, including exercise dyspnea, interstitial lung involvement at HRCT, functional respiratory alterations, and left ventricular diastolic dysfunction at Doppler echocardiography (Table II). The presence of PAH, suspected on the basis of clinical symptoms and Doppler echocardiography, was diagnosed by right heart catheterization only in 26 patients with definite SSc. At capillaroscopic examination, VEDOSS patients showed a significantly increased prevalence of 'early' pattern, while definite SSc displayed a high percentage of either 'active' or 'late' patterns. The definite SSc was confirmed as more severe clinical condition as a whole, requiring more aggressive therapeutic approach

such as combined vasoactive and immunosuppressive treatments (Table II). Considering that definite SSc represented a wide cohort of patients with well-established disease (1,538 pts), in-depth statistical analysis of this cohort was carried out. In particular, male patients (161) showed a significantly lower mean age (56.1 ± 14.2 SD vs. 59.6 ± 13.8 SD years; $p = .002$) and shorter disease duration (7.6 ± 7.7 vs. 9 ± 7.7 years; $p = .003$) than females (1,377). Moreover, diffuse cutaneous subset, digital ulcers, anti-Scl70 antibodies, capillaroscopic late pattern (33.1 vs. 23.0%, $p = .036$), and severe lung fibrosis (honeycombing at HRCT) were significantly more prevalent in males (Fig. 1). These subjects underwent immunosuppressive treatments in a higher percentage of cases than females who, on the contrary, showed a higher prevalence of limited SSc and ssSSc, sicca syndrome (30.2 vs. 20.9%, $p = 0.019$), and serum ACA (Fig. 1).

According to cutaneous subset evaluation (Fig. 2), ssSSc had a shorter disease duration, (5.5 ± 5.7 SD years vs. diffuse 8.5 ± 7.4 SD and limited SSc 9.7 ± 7.9 SD; $p < 0.001$) while diffuse

cutaneous subset was associated with lower mean age at the time of diagnosis (46.1 ± 14.3 SD years vs. 51.9 ± 14.5 SD of limited and 53.5 ± 13.6 SD of ssSSc; $p < 0.001$) and higher percentage of the following clinical manifestations: esophageal involvement, digital ulcers, tendon friction rubs, arthritis, calcinosis, cardiac and/or pulmonary symptoms, severity of lung fibrosis (honeycombing at HRCT), renal crisis (2.5% vs. limited 0.7% and ssSSc 0%; $p = 0.018$), and capillaroscopic 'late' pattern (44.8% vs. limited 21.0% and ssSSc 8.3%; $p < 0.001$).

With regards the serological hallmarks, anti-Scl70 were significantly associated with diffuse SSc (68.7% vs. limited 27.2% and ssSSc 17.4%; $p < 0.001$), while ACA were more frequently detected in limited SSc and ssSSc (limited 52.1%, ssSSc 63.4%, diffuse 14.9%; $p < 0.001$). Finally, a higher percentage of individuals with diffuse cutaneous SSc underwent immunosuppression compared to the other two subsets (Fig. 3). On the other side, the presence of the two autoantibodies commonly found in scleroderma patients, *i.e.* ACA and anti-Scl70, was significantly asso-

Table II. Main clinico-epidemiological features of 1780 Italian SSc patients.

	Total	VEDOSS	definite SSc	p-value
Patients no.	1780	242	1538	//
Demographic				
Sex Males no. (%)	178 (10.1%)	17 (7.1%)	161 (10.5%)	0.125
Age mean (DS)	58.4 (14.2)	53.3 (15.3)	59.2 (13.9)	<0.001
Dis duration yrs mean (SD)*	8.3 (7.6)	4.2 (4.9)	8.9 (7.7)	<0.001
Clinical				
Limited SSc no. (%)	1149 (66.9%)	87 (37.2%)	1062 (71.6%)	<0.001
Diffuse SSc no. (%)	279 (16.2%)	0 (0%)	276 (18.6%)	<0.001
ssSSc no. (%)	289 (16.8%)	144 (61.5%)	145 (9.8%)	<0.001
mRSS - mean (SD)	5.2 (6.4)	0.4 (1.3)	5.9 (6.5)	<0.001
Puffy fingers no. (%)	799 (46.1%)	59 (25.4%)	740 (49.2%)	<0.001
Teleangectasias no. (%)	921 (53%)	27 (11.6%)	894 (59.3%)	<0.001
Calcinosis no. (%)	182 (10.5%)	5 (2.2%)	177 (11.8%)	<0.001
Digital ulcers no. (%)	341 (19.6%)	9 (3.9%)	332 (22%)	<0.001
Gangrena no. (%)	16 (0.9%)	0 (0%)	16 (1.1%)	0.151
Osteomyelitis no. (%)	11 (0.6%)	0 (0%)	11 (0.7%)	0.378
Oesophageal inv. no. (%)	793 (45.6%)	68 (29.2%)	725 (48.1%)	<0.001
Sicca syndrome no. (%)	505 (29.1%)	64 (27.5%)	441 (29.4%)	0.607
Renal crisis no. (%)	15 (0.9%)	1 (0.4%)	14 (0.9%)	0.708
Tendon friction rubs no. (%)	138 (8%)	1 (0.4%)	137 (9.1%)	<0.001
Arthritis no. (%)	228 (13.2%)	18 (7.8%)	210 (14.1%)	0.011
Cardio-respiratory symptoms no. (%)	453 (26.2%)	22 (9.5%)	431 (28.7%)	<0.001
Lung HRCT normal no. (%)	450 (45.2%)	86 (78.9%)	364 (41%)	<0.001
ILD at HRCT no. (%)	548 (55.0%)	23 (21.1%)	525 (59.2%)	<0.001
ground glass no. (%)	336 (33.7%)	12 (11%)	324 (36.5%)	<0.001
reticulation no. (%)	269 (27%)	12 (11%)	257 (29%)	<0.001
honeycomb - n (%)	80 (8%)	2 (1.8%)	78 (8.8%)	0.005
LV diastolic inv no. (%)	273 (19.9%)	16 (10%)	257 (21.2%)	0.001
FVC (%) mean (DS)	102.7 (22.5)	108.6 (18.4)	101.8 (23)	<0.001
DLco (%) mean (DS)	69.7 (20.2)	77.8 (17.1)	68.4 (20.4)	<0.001
Capillaroscopy				
Normal no. (%)	141 (8.3%)	68 (29.1%)	73 (5%)	<0.001
Early no. (%)	372 (21.8%)	91 (38.9%)	281 (19.1%)	<0.001
Active no. (%)	729 (42.7%)	54 (23.1%)	675 (45.8%)	<0.001
Late no. (%)	360 (21.1%)	5 (2.1%)	355 (24.1%)	<0.001
Laboratory findings				
ANA+ no. (%)	1687 (97%)	233 (97.9%)	1454 (96.8%)	0.478
anti-ENA no. (%)	1156 (70.3%)	135 (60%)	1021 (72%)	<0.001
anti-Sc170 no. (%)	546 (31.4%)	33 (13.9%)	513 (34.1%)	<0.001
ACA no. (%)	826 (46.4%)	126 (52.1%)	700 (45.5%)	0.056
Treatment				
Immunosuppressors no. (%)	426 (23.9%)	20 (8.3%)	406 (26.4%)	<0.001

VEDOSS: very early diagnosis of systemic sclerosis; *from diagnosis; mRSS: modified Rodnan skin score; HRCT: high-resolution computed tomography; ILD: interstitial lung diseases; LV: left ventricular; FVC: forced vital capacity; Dlco: diffusing capacity of the lungs for carbon monoxide; ANA: anti-nuclear antibodies; anti-ENA: anti-extractable nuclear antigen antibodies; *comparison between VEDOSS and definite SSc.

ciated with specific clinical features. In particular, anti-Sc170 seropositive individuals showed a significantly lower mean age (55.0±14.5 SD years vs. ACA+ 63.2±12.5 SD; $p<0.001$) and a higher percentage of male gender, diffuse cutaneous SSc, digital ulcers, tendon friction rubs, arthritis (18.8% vs. ACA+ 9.4%; $p<0.001$), ‘late’ capillaroscopic pattern (31.9% vs. ACA+ 19.3%; $p<0.001$), lung/heart manifestations, interstitial lung involvement at

HRCT. Moreover, a significant higher percentage of anti-Sc170 seropositive individuals underwent to immunosuppressive treatments (Fig. 3). Moreover, patients with definite SSc were subdivided in two groups according to the time interval between the anamnestic occurrence of RP and SSc diagnosis (≤ 1 year and > 1 year). Patients with very short RP duration at the time of SSc diagnosis (≤ 1 year) were significantly associated with diffuse cutane-

ous SSc, serum anti-Sc170, high rate of heart and/or lung involvement; these individuals more frequently required immunosuppressive treatment (Fig. 4).

Discussion

The present study described the main demographic and clinical characteristics of a large Italian scleroderma spectrum patients’ population recorded in the nationwide SPRING registry after the initial phase of enrollment, focusing mainly on the analysis of the sizeable cohort of patients with definite SSc. The comparison between VEDOSS and definite SSc showed some differences as expected on the basis of the followed classification criteria; definite SSc cohort was confirmed as more severe variant due to the presence of digital ulcers, interstitial lung fibrosis, and/or cardiac involvement.

Considering the cohort of definite SSc, some important clinical correlations were detected that frequently agreed with previous clinico-epidemiological studies (1-5, 15). In particular, the male gender *per se* was significantly associated with diffuse cutaneous subset, anti-Sc170, capillaroscopic ‘late’ pattern, and one or more severe SSc clinical manifestations like digital ulcers, and/or lung fibrosis. This confirms data from the literature that males are affected by more severe form of disease with respect to females and emphasizes the importance of an early treatment to tackle disease progression (16). Similarly, patients with diffuse cutaneous SSc showed an increased prevalence of digital ulcers, esophageal, cardiac/pulmonary involvement, renal crisis, serum anti-Sc170, and/or ‘late’ capillaroscopic pattern. Consequently, the combination of male gender, diffuse cutaneous scleroderma, and anti-Sc170 identified the worst SSc clinical subset. While females with limited skin involvement and ACA were medially characterised by less severe disease phenotypes (1-5, 15, 16-18). At the SSc diagnosis, the short duration of RP (≤ 1 year) was significantly correlated with some hallmarks of poor disease outcome like the presence of diffuse cutaneous involvement, anti-Sc170 autoantibodies, cardiac, and/or

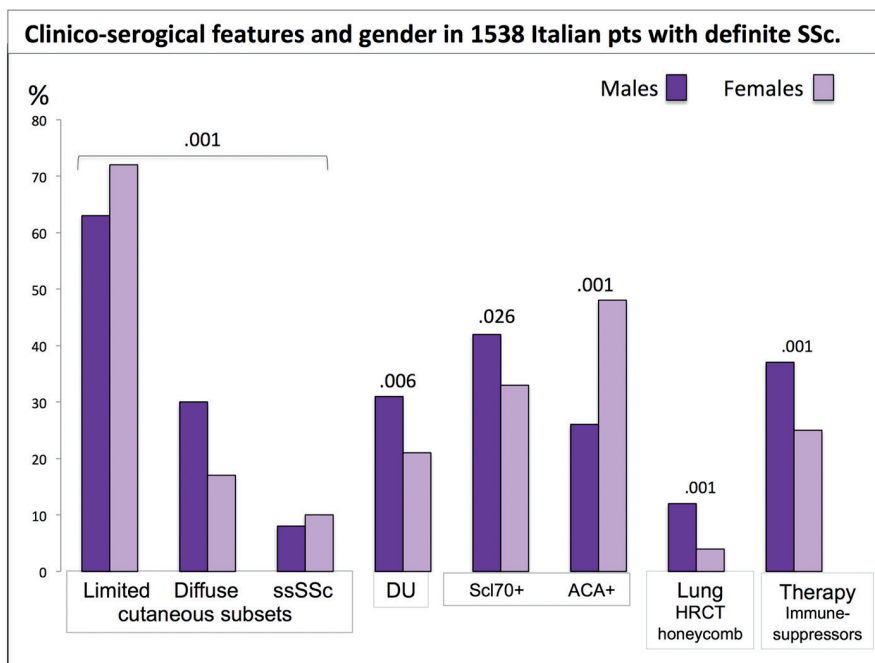


Fig. 1. Clinico-serological features and gender in 1538 Italian patients with definite SSc. The diffuse cutaneous subset, digital ulcers, anti-Scl70 antibodies, and severe lung fibrosis (honeycombing at HRCT) were significantly more prevalent in males (no. 161) compared to females (no. 1,368; see text).
ssSSc: sine scleroderma SSc; DU: digital ulcers; HRCT: high-resolution computed tomography.

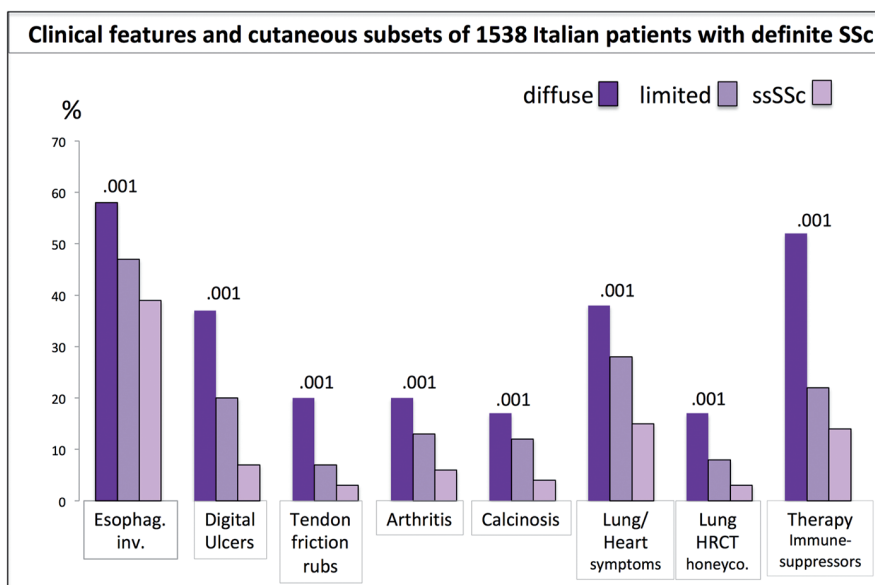


Fig. 2. Scleroderma clinical features and cutaneous subsets. Diffuse SSc was significantly associated with more severe SSc phenotype, characterised by increased prevalence of digital ulcers, tendon friction rubs, subcutaneous calcinosis, arthritis, and internal organ involvement (esophagus, heart, and lung), requiring more aggressive treatments (see text).
ssSSc: sine scleroderma SSc; HRCT: high-resolution computed tomography.

lung involvement. This peculiar relationship was previously described in smaller SSc patients' series (18). In the natural history of SSc, RP is found as the presenting symptom that may precede up to years the appearance of other

typical SSc manifestations, confirming the relevant role of vascular dysfunction in the multistep SSc pathogenetic process (1-5, 19, 20). The anamnestic finding of very short time interval between the appearance of RP and the

SSc diagnosis may identify patients with particularly severe disease variant. At SSc diagnosis, it may represent a suitable worse prognostic tool, which should alert the physician and foster a tight control.

It is well known that SSc is the expression of a complex etiopathogenetic process (1, 5, 20, 21) leading to heterogeneous clinical phenotypes, unpredictable clinical course, reduced life expectancy, and inadequate response to treatments. In this scenario, SSc registries may be very useful to identify key information concerning SSc progression and outcome. Several national and international SSc registries are currently conducted worldwide (7, 22-36). The strengths and limitations of SSc registry-based studies have been previously analysed (7). Apart from several strong points such as the recording of longitudinal data on large patients' populations with essential information on this rare condition, SSc registries show a number of limitations, specially their not uniform formulation. Possible dissimilarities in patients' selection criteria and/or treatment strategies make quite difficult to compare the observations of currently available registries (7). In addition, both genetic and environmental differences among patients' populations from different countries, and from particular sub-area in the same country, should be also considered. A careful registry construction along with a recruitment of sufficiently homogeneous and well-characterized SSc cohorts may overcome the above limitations. Moreover, 'big data' collection by SSc registries could provide valuable data for future epidemiological and clinico-pathogenetic studies, prognostic factor recognition, and real-life therapeutic protocol validation.

The identification of patients during the early phases of SSc is particularly relevant as regards its clinico-prognostic implications (9, 10, 37, 38). In a recent report by the Spanish Scleroderma Registry (RESCLE) study group, the authors underlined the usefulness of scleroderma subsetting into very early and early SSc (37). They observed that the evolution to definite SSc is more frequent in early than in very early SSc

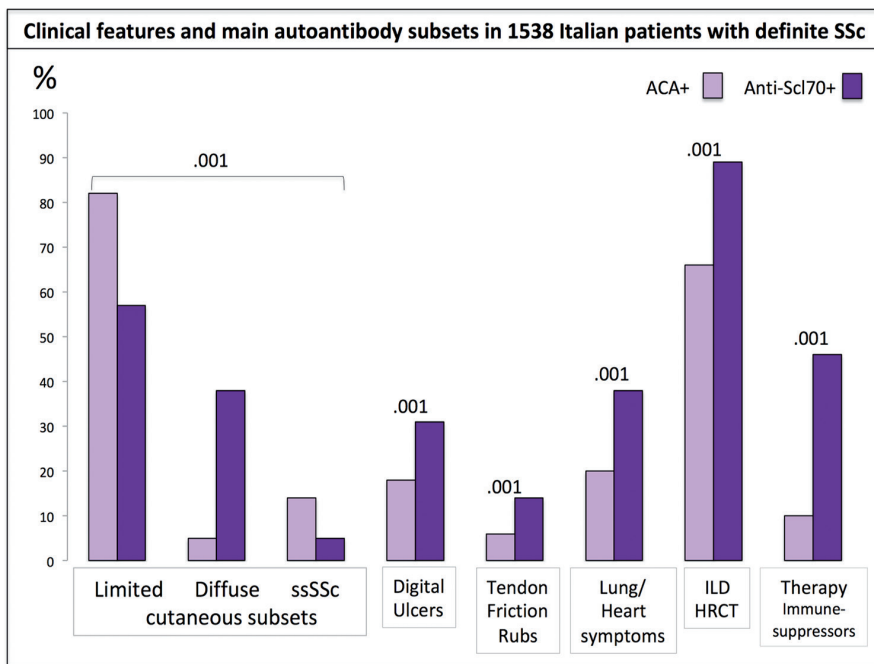


Fig. 3. Scleroderma clinical features and main autoantibody subsets. Compared to ACA-positive individuals, the presence of anti-Scl70 was more frequently associated with diffuse cutaneous SSc, digital ulcers, tendon friction rubs, and cardio-pulmonary symptoms, as well as with immunosuppressive treatments (see text). ssSSc: sine scleroderma SSc; ILD: interstitial lung disease; HRCT: high-resolution computed tomography.

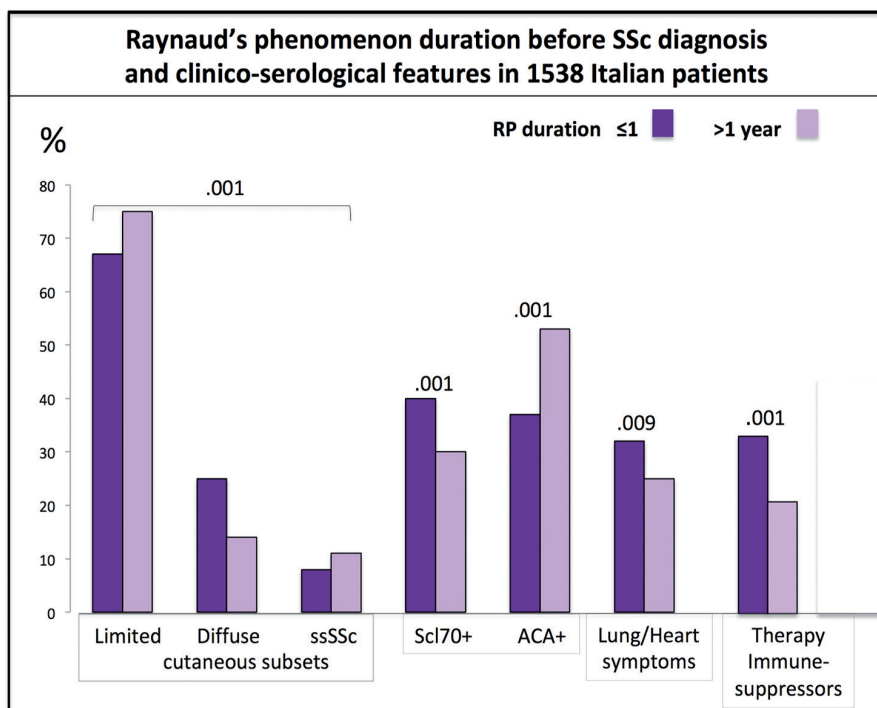


Fig. 4. Raynaud's phenomenon duration before SSc diagnosis and clinico-serological features in 1538 Italian patients. A shorter Raynaud's phenomenon (RP) duration before SSc diagnosis was correlated with worse prognostic disease manifestations, *i.e.*, diffuse cutaneous subset, anti-scl70 autoantibodies, and cardio-pulmonary involvement. Moreover, SSc patients with past history of RP lasting <1 year or appearing after the disease onset more frequently underwent immunosuppressive therapies (see text). RP: Raynaud's phenomenon; ssSSc: sine scleroderma SSc.

patients; moreover, the presence of gastrointestinal involvement represented a risk factor of disease progression. These findings suggested that a more detailed subsetting (37) and timely detection of early organ damage (38) in preclinical stages may help for the patients' clinical assessment and targeted management. In this respect, the frequent classification discrepancies should be clarified in the near future; while comparative analysis of different registry cohorts will allow us to definitely set up shared classification criteria of the patients, especially in the early phases of the disease. Therefore, the identification of possible predictive factors of SSc progression from RP to SSc may be achieved by long-term follow-up studies of the pivotal conditions that represent the entire clinical spectrum of the disease.

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