Autoimmunity Reviews 21 (2022) 103159

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

# Geographical heterogeneity of clinical and serological phenotypes of systemic sclerosis observed at tertiary referral centres. The experience of the Italian SIR-SPRING registry and review of the world literature

Clodoveo Ferri [a,*], Rossella De Angelis [b], Dilia Giuggioli [a], Gianluigi Bajocchi [c], Lorenzo Dagna [d], Giovanni Zanframundo [e], Rosario Foti [f], Fabio Cacciapaglia [g], Giovanna Cuomo [h], Alarico Ariani [i], Edoardo Rosato [j], Serena Guiducci [k], Francesco Girelli [l], Valeria Riccieri [m], Elisabetta Zanatta [n], Silvia Bosello [o], Ilaria Cavazzana [p], Francesca Ingegnoli [q], Maria De Santis [r], Giuseppe Murdaca [s], Giuseppina Abignano [t], Nicoletta Romeo [u], Alessandra Della Rossa [v], Maurizio Caminiti [w], Annamaria Iuliano [x], Giovanni Ciano [y], Lorenzo Beretta [z], Gianluca Bagnato [aa], Ennio Lubrano [ab], Ilenia De Andres [ac], Alessandro Giollo [ad], Marta Saracco [ae], Cecilia Agnes [af], Federica Lumetti [a], Amelia Spinella [a], Luca Magnani [c], Corrado Campochiaro [d], Giacomo De Luca [d], Veronica Codullo [e], Elisa Visalli [f], Francesco Masini [h], Antonietta Gigante [j], Silvia Bellando-Randone [k], Greta Pellegrino [m], Erika Pigatto [ag], Maria Grazia Lazzaroni [p], Franco Franceschini [p], Elena Generali [r], Gianna Mennillo [t], Simone Barsotti [v], Giuseppa Pagano Mariano [w], Francesca Calabrese [w], Federica Furini [ah], Licia Vultaggio [ah], Simone Parisi [ai], Clara Lisa Peroni [ai], Davide Rozza [aj], Anna Zanetti [aj], Greta Carrara [aj], Giampiero Landolfi [aj], Carlo Alberto Scirè [aj,ak], Gerolamo Bianchi [al], Enrico Fusaro [ai], Gian Domenico Sebastiani [x], Marcello Govoni [ah], Salvatore D'Angelo [t], Franco Cozzi [ag], Andrea Doria [n], Florenzo Iannone [g], Carlo Salvarani [c], Marco Matucci-Cerinic [d,k], On behalf of SPRING-SIR (Systemic Sclerosis PRogression INvestiGation group of the Italian Society of Rheumatology)

[a] *Rheumatology Unit, School of Medicine, University of Modena and Reggio Emilia, Modena, Italy*
[b] *Rheumatology Unit, Department of Clinical and Molecular Sciences, Polytechnic University of Marche, Ancona, Italy*
[c] *Rheumatology Unit, S. Maria Hospital-USL, IRCCS Institute, Reggio Emilia, Italy*
[d] *Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), IRCCS San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy*
[e] *Department of Rheumatology, Policlinico San Matteo, Pavia, Italy*
[f] *AOU Policlinico Vittorio Emanuele, Catania, Italy*
[g] *Rheumatology Unit, Department of Emergency Surgery and Organ Transplantations, University of Bari, Bari, Italy*
[h] *Luigi Vanvitelli University, Naples, Italy*
[i] *Department of Medicine, Internal Medicine and Rheumatology, Azienda Ospedaliero Universitaria di Parma, Parma, Italy*
[j] *Department of Translational and Precision Medicine, Sapienza University of Rome, Italy*
[k] *Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy*
[l] *Department of Medicine, Rheumatology Unit, Ospedale GB Morgagni - L Pierantoni, Forlì, Italy*
[m] *Department of Rheumatology, Sapienza University of Rome, Rome, Italy*
[n] *Department of Rheumatology, University of Padua, Padova, Italy*
[o] *Institute of Rheumatology and Affine Sciences, Division of Rheumatology, Catholic University of the Sacred Heart, Rome, Italy*
[p] *Department of Rheumatology, Spedali Civili di Brescia, Brescia, Italy*
[q] *Division of Clinical Rheumatology, ASST Pini, Dept. of Clinical Sciences & Community Health, Research Center for Adult and Pediatric Rheumatic Diseases, Research Center for Environmental Health, Università degli Studi di Milano, Milan, Italy*
[r] *Humanitas Clinical and Research Center IRCCS, Milan, Italy*
[s] *Martino Hospital-University of Genoa, Genoa, Italy*

* Corresponding author at: Rheumatology, Dpt of Internal Medicine, University of Modena and Reggio E., Azienda Ospedaliero-Universitaria, Via del Pozzo, 71 41100 Modena, Italy.
*E-mail address:* clferri@unimore.it (C. Ferri).

https://doi.org/10.1016/j.autrev.2022.103159
Received 13 July 2022; Accepted 24 July 2022
Available online 28 July 2022

[t] Rheumatology Institute of Lucania (IReL) and Rheumatology Department of Lucania, San Carlo Hospital, Potenza, Italy
[u] S. Croce e Carle Hospital, Cuneo, Italy
[v] Department of Rheumatology, University of Pisa, Pisa, Italy
[w] Departmental Rheumatology Unit, Grande Ospedale Metropolitano, Reggio Calabria, Italy
[x] Rheumatology Unit, San Camillo - Forlanini Hospital, Rome, Italy
[y] Local Health Department, Avellino, Italy
[z] Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico di Milano, Milan, Italy
[aa] Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy
[ab] Department of Rheumatology, University of Molise, Campobasso, Italy
[ac] Rheumatology Unit, Azienda Ospedaliera di Rilievo Nazionale ed Alta Specializzazione "Garibaldi", Catania, Italy
[ad] Rheumatology Section, Department of Medicine, University of Verona, Italy
[ae] Rheumatology Unit, Mauriziano-Umberto I Hospital, Turin, Italy
[af] San Lorenzo Hospital, Turin, Italy
[ag] Department of Medicine, Villa Salus Hospital, Venice, Italy
[ah] Rheumatology Unit, Department of Medical Sciences, University of Ferrara and Azienda Ospedaliera-Universitaria S. Anna di Ferrara, Ferrara, Italy
[ai] Rheumatology Unit, Città della Salute e della Scienza, Turin, Italy
[aj] Epidemiology Unit, Italian Society of Rheumatology, Milan, Italy
[ak] Rheumatology Unit, University of Ferrara-S. Anna Hospital, Ferrara, Italy
[al] Rheumatology Unit, Department of Musculoskeletal Sciences, Local Health Trust 3, La Colletta Hospital, Genoa, Italy

ARTICLE INFO

*Keywords:*
Systemic sclerosis
Scleroderma
Geographical areas
Macro-areas
Environmental
Referral

ABSTRACT

*Introduction:* Systemic sclerosis (SSc) is characterized by a complex etiopathogenesis encompassing both host genetic and environmental -infectious/toxic- factors responsible for altered fibrogenesis and diffuse micro-angiopathy. A wide spectrum of clinical phenotypes may be observed in patients' populations from different geographical areas. We investigated the prevalence of specific clinical and serological phenotypes in patients with definite SSc enrolled at tertiary referral centres in different Italian geographical macro-areas. The observed findings were compared with those reported in the world literature.
*Materials and methods:* The clinical features of 1538 patients (161 M, 10.5%; mean age 59.8 ± 26.9 yrs.; mean disease duration 8.9 ± 7.7 yrs) with definite SSc recruited in 38 tertiary referral centres of the SPRING (Systemic sclerosis Progression INvestiGation Group) registry promoted by Italian Society of Rheumatology (SIR) were obtained and clustered according to Italian geographical macroareas.
*Results:* Patients living in Southern Italy were characterized by more severe clinical and/or serological SSc phenotypes compared to those in Northern and Central Italy; namely, they show increased percentages of diffuse cutaneous SSc, digital ulcers, sicca syndrome, muscle involvement, arthritis, cardiopulmonary symptoms, interstitial lung involvement at HRCT, as well increased prevalence of serum anti-Scl70 autoantibodies. In the same SSc population immunusppressive drugs were frequently employed.
The review of the literature underlined the geographical heterogeneity of SSc phenotypes, even if the observed findings are scarcely comparable due to the variability of methodological approaches.
*Conclusion:* The phenotypical differences among SSc patients' subgroups from Italian macro-areas might be correlated to genetic/environmental co-factors, and possibly to a not equally distributed national network of information and healthcare facilities.

## 1. Introduction

Systemic sclerosis (SSc) involving the skin, the musculoskeletal system, and visceral organs,

may severely impair patient's quality of life and survival [1–5]. The etiopathogenesis of the SSc is complex and scarcely known and it may encompass both host genetic susceptibility and environmental toxic/infectious agents [6]. It is a rare disease characterized by different clinical phenotypes as suggested by previous studies [3–5,7]. Therefore, a number of registries and muulticenter cohort studies have been developed worldwide to provide large SSc series and homogeneous patients' subgroups to better investigate the possible role of genetic/environmental factors and disease variants in patients' populations from different geographical areas [7–10]. Recently, the Italian Society of Rheumatology (SIR) promoted the national SPRING (Systemic sclerosis Progression INvestiGation) registry, including the very early stages of SSc, to identify the predictive factors of disease progression and worse outcome [11,12]. Herein we focus on the clinical/serological phenotypes of difinite SSc patients recruited at tertiary referral centres of the main geographical macro-areas of Northern, Center, and Southern Italy. The observed findings were also compared with previous studies present in the world literature regarding the geographical/ethnic differences within patients' populations from different countries.

## 2. Patients and methods

The clinical data of 1538 patients with definite SSc (161 male and 1377 females; mean age 59.8 ± 26.9 yrs.; mean disease duration 8.9 ± 7.7 yrs) out of 2028 patients enrolled in the SPRING registry were studied. This register is a multicenter national no-profit cohort study, promoted by SIR [11] and currently includes 37 Italian rheumatology tertiary referral centres with proven expertise in the diagnosis and treatment of scleroderma. The study protocol was approved by the ethical Committes in each participating center, after the coordinating center's authorization (reference number OSS 15.010, AOU Careggi, Firenze); all patients provided written informed consent to enter in the study [11,12]. The SPRING database has been previously described [11,12] and briefly consists of patients with age > of 18 yrs. classified into 4 different cohorts: 1) primary Raynaud's phenomenon (pRP); 2) suspected secondary RP (ssRP); 3) very early diagnosis of systemic sclerosis (VEDOSS) [13] 4) definite SSc according to ACR/ EULAR 2013 classification criteria for SSc [14]. In the present study, we focused the attention on the group of patients with definite SSc.

At the patient's enrolment, the following data were collected: demographic characteristics, disease history (including RP duration, date of diagnosis if appropriate), clinical features, and comorbidities.

The evaluation of the collected variables followed previously described criteria [3,5,11]. In particular, the disease duration was calculated from the time of disease onset, i.e. the age at which the first

non-Raynaud's sign(s) and/or symptom(s) compatible with the disease appeared; namely, digital ischemic lesions, puffy hands, sclerodactyly with or without proximal scleroderma, dyspnea, and/or dysphagia. At the same time, patients were also classified as limited cutaneous SSc (lcSSc), diffuse cutaneous SSc (dcSSc), or *sine scleroderma* SSc (ssSSc). Besides, the following data were recorded [3,5,11,12]: modified Rodnan skin score (mRSS), digital ulcers, gangrene and/or osteomyelitis; arthritis (inflammatory changes observed in >2 joints); muscle weakness with/without elevated serum creatine kinase; oesophageal involvement (dysphagia and/or oesophageal radiographic dysmotility); pulmonary involvement (dyspnoea, ground glass and/or bibasilar fibrosis at high resolution computed tomography -HRCT- and/or restrictive lung disease on pulmonary function tests, including decreased diffusion capacity for carbon monoxide (DLCO)), cardiac involvement with at least 1 of the following features: pericarditis, severe arrhythmias and/or atrioventricular conduction abnormalities by electrocardiography, left ventricle diastolic dysfunction and/or abnormal ejection fraction (<50%) by Doppler echocardiography; pulmonary arterial hypertension (PAH) evaluated by means of systolic pulmonary arterial pressure (sPAP) at Doppler echocardiography and confirmed by right heart catheterization [14], and scleroderma renal crisis (sudden onset of severe arterial hypertension together with acute renal failure). Different autoantibodies were also determined; namely, anti-nuclear (ANA), anti-centromere (ACA), and anti-extractable nuclear antigen (anti-ENA) antibody specificities, including anti-Scl70 [3,5,11,12].

At baseline and every yearly visit, all the above features were collected along with the ongoing treatments, including both vasoactive, anti-inflammatory, and immunomodulant/immunosuppressor drugs [11].

### 2.1. Review of the literature

A search in PubMed, Embase, Scopus, Web of Science, Asian Science Citration Index (ASCI), IranMedex, Scientific Information, Database (SID), PaKMediNet, IndMed, and Index Medicus for the World Health Organization Eastern Mediterranean Region (IMEMR) regarding the geographical distribution of SSc phenotypes was done up to March 2022, using the key words scleroderma, systemic sclerosis, phenotypes, heterogeneity, geographical areas, referral. Single-center studies that otherwise assessed different patients' populations were included.

### 2.2. Statistical methods

Data were collected and handled using the tool Research Electronic Data Capture-REDCap, a web-based application to support data collection for research studies [11,12].

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).

## 3. Results

### 3.1. Characteristics of the population

Table 1 summarizes the clinico-epidemiological characteristics of the whole cohort of 1538 patients with definite SSc and of the three subgroups of Northern, Central, and Southern Italy. The number and distribution of the 37 referral centers and the size of the three patients' subgroups were in proportion to the general population resident in each macro-area (Fig. 1). Overall, demographic and clinico-serological features of definite SSc series were quite comparable with other large cohorts reported in the world literature [3,5,7–12].

**Table 1**
Clinical features of 1538 SSc patients resident in the three Italian geographical macroareas.

| | Total | Northern | Central | Southern | |
|---|---|---|---|---|---|
| Patients no. | 1538 | 814 | 194 | 445 | *p* |
| Demographic | | | | | |
| Sex Males no. (%) | 161 (10.5%) | 90 (11.1%) | 16 (8.3%) | 44 (10%) | 0.494 |
| Age mean (SD) | 59.8 (26.9) | 61.7 (34.5) | 60.8 (12.6) | 55.6 (13.5) | 0.001 |
| Age at SSc diagnosis (SD) | 51.5 (27.3) | 53.2 (34.7) | 50.9 (13.5) | 48.1 (14.5) | 0.001 |
| Disease duration yrs. mean (SD)° | 8.9 (7.7) | 9.2 (8.2) | 10.4 (7.6) | 7.9 (6.6) | 0.001 |
| Clinical | | | | | |
| Limited SSc no. (%) | 1062 (71.6%) | 590 (74.2%) | 131 (67.5%) | 282 (68%) | 0.005 |
| Diffuse SSc no. (%) | 276 (18.6%) | 142 (17.9%) | 32 (16.5%) | 86 (20.7%) | |
| sine SSc no. (%) | 145 (9.8%) | 63 (7.9%) | 31 (16%) | 47 (11.3%) | |
| Teleangectasias no. (%) | 894 (59.3%) | 534 (66.7%) | 115 (59.3%) | 189 (43.8%) | 0.001 |
| Calcinosis no. (%) | 177 (11.8%) | 94 (11.8%) | 24 (12.4%) | 46 (10.7%) | 0.782 |
| Digital ulcers no. (%) | 332 (22%) | 171 (21.4%) | 33 (17%) | 110 (25.5%) | 0.05 |
| Oesophageal involvement no. (%) | 725 (48.1%) | 354 (44.3%) | 110 (56.7%) | 224 (51.9%) | 0.002 |
| Sicca syndrome no. (%) | 441 (29.4%) | 215 (26.9%) | 52 (26.9%) | 145 (33.7%) | 0.035 |
| Renal crisis no. (%) | 14 (0.9%) | 10 (1.3%) | 3 (1.5%) | 1 (0.2%) | 0.107 |
| Musle involvement no. (%) | 236 (15.7%) | 112 (14.1%) | 23 (11.9%) | 87 (20.2%) | 0.006 |
| Arthritis no. (%) | 210 (14.1%) | 95 (11.9%) | 24 (12.4%) | 82 (19.4%) | 0.001 |
| Cardio-pulmonary involvement | | | | | |
| Symptoms no. (%)* | 431 (28.7%) | 194 (24.4%) | 53 (27.5%) | 162 (37.6%) | 0.001 |
| HRCT ILD no. (%)** | 1174 (59%) | 609 (58.8%) | 139 (50.9%) | 357 (63.9%) | 0.03 |
| FCV (%) mean (SD) | 101.8 (23) | 103.1 (22.7) | 102.8 (23.8) | 98.3 (23.4) | 0.006 |
| Laboratory findings | | | | | |
| ANA+ no. (%) | 1454 (96.8%) | 783 (98%) | 186 (95.9%) | 407 (94.9%) | 0.01 |
| anti-ENA no. (%) | 1021 (72%) | 556 (72.3%) | 120 (65.6%) | 308 (76.4%) | 0.023 |
| anti-Scl70 no. (%) | 513 (34.1%) | 260 (32.5%) | 53 (27.3%) | 173 (40.2%) | 0.002 |
| ACA no. (%) | 700 (45.5%) | 379 (46.6%) | 103 (53.1%) | 179 (40.2%) | 0.005 |
| Treatment | | | | | |
| Immunosuppressors no. (%) | 406 (26.4%) | 186 (22.9%) | 40 (20.6%) | 156 (35.1%) | 0.001 |
| Prostanoids no. (%) | 807 (52.5%) | 408 (50.1%) | 88 (45.4%) | 274 (61.6%) | 0.001 |
| Antiaggregants no. (%)°° | 650 (42.3%) | 314 (38.6%) | 88 (45.4%) | 223 (50.1%) | 0.001 |

### 3.2. Phenotipic comparison among Italian macro-areas

The comparative analysis among the three Italian macro-areas

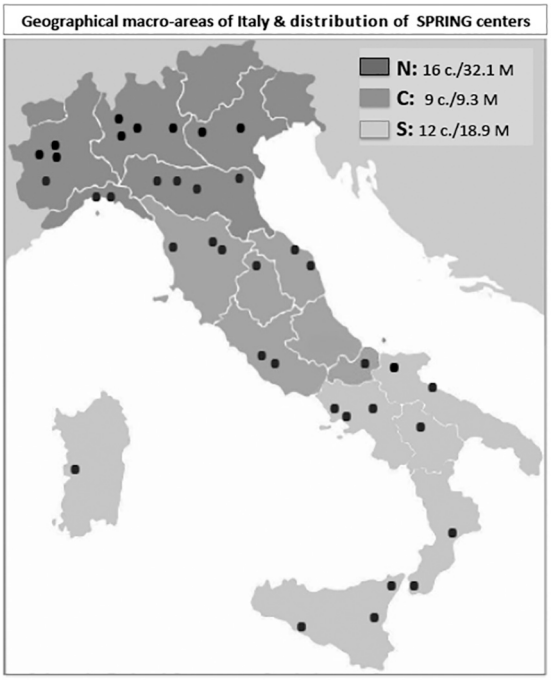


**Fig. 1.** Geographical macro-areas of Italy and distribution of centres participating to the SPRING registry. The three geographical macro-areas of Italy (N: Northern, C: Central, and S: Southern) showed a good relationship between the number of enrolled SSc patients (N: 814, C: 194, and S: 445), number/distribution of participating centres (N: 16 c., C: 9 c., and S: 12 c.) and resident general population (N: 32.1 Millions, C: 9.3 M, and S: 18.9 M).

revealed a number of statistically significant differences (Table 1). In particular, patients from Southern Italy showed a significantly lower mean age recorded either at patients' recruitment and at SSc diagnosis, as well a shorter disease duration compared that observed in Northern and Central Italian macro-areas (Table 1; Fig. 2). Moreover, in Southern Italy the following SSc features were more frequently observed: dcSSc subset, serum anti-Scl70 antibodies, digital ulcers, sicca syndrome, muscle involvement, arthritis, cardiopulmonary symptoms (often exertional dyspnoea), interstitial lung involvement at HRCT, and impaired forced vital capacity (Table 1). On the contrary, a lower percentage of ACA seropositivity was observed. Finally, immunosuppresants, prostanoids, and/or antiaggregants were more frequently employed in SSc patients from Southern Italy (Fig. 2).

The comparison between the two patients' subgroups from Northern and Central Italy showed only sporadic, often non significant differences as regards both clinical and serological SSc phenotypes (Table 1).

### 3.3. Review of the literature

Available studies present in the world literature can be subgrouped as i) epidemiological studies mainly focusing on the prevalence/incidence of the SSc in patients' populations from definite geographical areas [15], and ii) cohort studies analyzing patients' series recruited at tertiary referral centers. The latter focused on the differences in the clinico-serological phenotypes among SSc patients' populations from different countries, or among regional areas and/or ethnic groups of the same country [7,16–24]. In this context, our review of the literature revealed a number of interesting observations, often conflicting probably due to different methodological approaches [7,16–24].

These cohort studies are described in detail in the Table 2 [16–24]; they were invariably directed at identifying differences between geographical areas within the same country, with the exception of the EULAR Scleroderma Trials and Research (EUSTAR) report that included

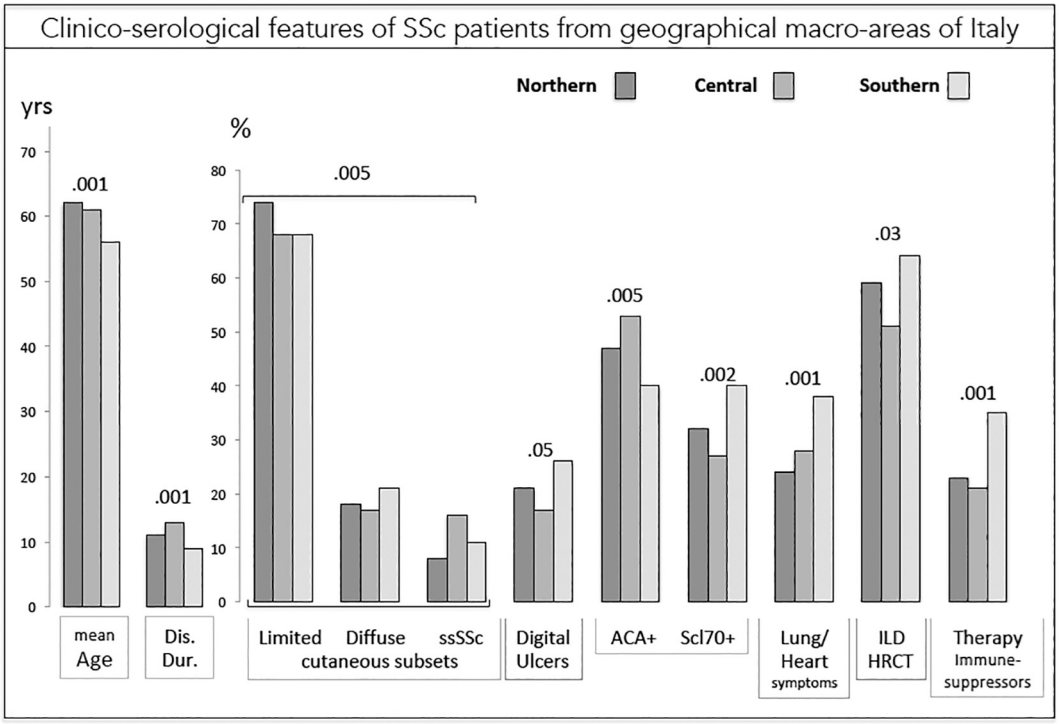


**Fig. 2.** Clinico-serological features of patients with definite SSc from the three geographical macro-areas of Italy. The comparison between SSc patients' subgroups recruited in different geographical macro-areas of Italy, i.e. Northern (pts no. 814), Central (pts no. 194), and Southern (pts no. 445) revealed that patients with definite SSc resident in Southern Italy were characterized by significantly lower mean age and disease duration, as well as higher prevalence of diffuse cutaneous SSc, digital ulcers, serum anti-Scl70, symptomatic heart and/or lung involvement, and interstitial lung involvement at HRCT. In the same subgroup, the percentage of patients undergoing immunosuppressive treatments was significantly higher compared to those from Central and Northern Italy (see text).

**Table 2**
Clinical and serological phenotypes in systemic sclerosis patients' populations referred to tertiary centers assessing macro-regional and ethnic differences.

| Author | Year (ref. No.) | Country | Geographical area | Enrolment | Criteria | No. of pts | Prevalent clinical/serological phenotypes | Comments |
|---|---|---|---|---|---|---|---|---|
| Mayes MD, et al | 2003 (16) | USA | Detroit tricounty metropolitan area (Michigan) | Multicenter, multi-ethnic study (academic, hospital, private rheumatologists, Scleroderma foundation) | 1980 ACR classification criteria | 706 | dcSSc was more frequent in blacks. ACA positivity less common in blacks | The parallel epidemiologic study found a higher SSc prevalence among blacks |
| Nietert PJ, et al | 2006 (17) | USA | South Carolina | Single-center multi-ethnic study | 1980 ACR classification criteria | 263 | dcSSc, DUs, anti-Scl70 and anti-RNP, anti-Ro more frequent in black patients | Differences remain even after adjusting for sex, education, disease classification and disease duration |
| Walker UA, et al | 2009 (7) | ^23 EUSTAR rheumatology centers | Europe | Multicenter database | 1980 ACR classification criteria | 3661 | "Pocket" distribution of ACA, anti-Scl70, lcSSc, dcSSc, even within regions of the same country | Large variability between observers to assess cutaneous subtype and antinuclear antibodies |
| Low AHL, et al | 2009 (18) | Canada | Toronto (Ontario) | Single-center multi-ethnic study | 1980 ACR classification criteria | 336 | Increased myositis and anti-Scl70, lower MS and GI manifestation in Chinese vs European descent | The largest heavily populated metropolitan area in Canada |
| Wang J, et al | 2013 (19) | China | Han Chinese from Shanghai, Hebei, Sichuan, Hunan regions | Multicenter study from hospital and outpatient clinics (rheumatology/dermatology) | 1980 ACR classification criteria | 419 | Higher dcSsc, anti-Scl70, anti-RNAP III and pulmonary fibrosis in Chinese vs Caucasian patients | Comparison between two homogeneous ethnic groups (Han population and US Caucasian registry) |
| Meyer A, et al. | 2016 (20) | France | Alsace, Lorraine, Seine-Saint-Denise | §Questionnaire | ICD-code 1980 ACR and LeRoy-Medsger criteria | 244 | No significant difference in the percentages of ACA, anti-Scl70 and skin subtypes | The parallel epidemiologic study found a higher SSc prevalence in Alsace |
| Souza EJR, et al | 2017 (21) | Brazil | Brazil (Northeast, Midwest, Southeast, and South). | §Multicenter registry | 2013 ACR/EULAR classification criteria | 141 | Higher risk of DUs in patients living in subtropical climate | The study focused only on DUs |
| Moon KW, et al | 2018 (22) | Korea | 11 University hospitals representing each geographical area | §Retrospective medical charts | 1980 ACR classification criteria | 751 | Residents in urban areas have higher dcSSc subtype | Residents of rural areas have a decreased survival |
| Moore DF, et al | 2019 (23) | USA | Washington DC, Georgetown University | Single-center retrospective, multiethnic study | 2013 ACR/EULAR classification criteria | 402 | African Americans more likely to have anti-U1-RNP and severe pulmonary disease | Self-reported race and ethnicity |
| Al-Sheikh H, et al | 2019 (24) | Canada | Toronto (Ontario) | Single-center multi-ethnic longitudinal cohort | 2013 ACR/EULAR classification criteria | 1005 | East Asian: less calcinosis and oesophageal involvement; Afro-Caribbeans: ILD and anti-U1-RNP; First Nations: dcSSc | Self-reported ethnicity/descent. The cohort reflects the immigration patterns in Toronto |
| Present study | 2022 | Italy | Northern, Central, Southern Italy | Multicenter database | 2013 ACR/EULAR classification criteria | 1538 | Patients from South Italy showed an increased percentage of severe clinico-serological SSc phenotypes (dcSSc, anti-Scl70+, internal organ involvement) | The increased prevalence of more severe phenotypes might be correlated to specific unknown genetic environmental co-factors, and/or to referral bias |

^ EUSTAR: Austria, Denmark, Belgium, Croatia, Czech Republic, France, Germany, Great Britain, Greece, Hungary, Italy, Malta, The Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland.

ACR: American College of Rheumatology; dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; DUs: digital ulcers; MS: musculoskeletal; GI: gastrointestinal; ILD: interstizial lung disease.

§ homogeneous population by ethnicity.

23 European countries [7].

The greatest differences in cutaneous subsets and autoantibody patterns seem to be predominantly correlated to ethnicity [16,17,19,24]. In particular, the dcSSc subset was more frequent in Afroamerican patients [16,17], as well in residents of large areas in China [19], or native peoples in Toronto [24]. An increased prevalence of serum anti-Scl70 antibodies was found in Afro americans [17], in China [19], and in Chinese descent from Toronto [18]. Afroamericans and Afrocaribbeans show a higher frequency of anti-U-RNP when compared with Caucasians living in the same geographical areas [23,24]. Interestingly, some clinical characteristics were found to be related to climate, such as digital ulcers [21], while others are dependent on living in urban or rural area such as dcSSc subset [22].

Finally, the observed differences in SSc phenotypes among patients' series from heterogeneous European geographic areas [7] are probably influenced by numerous, unknown genetic and/or environmental co-factors.

## 4. Discussion

### 4.1. Geographical heterogeneity of Italian SSc phenotypes

The present study revealed a geographical heterogeneity as regards the clinical and serological phenotypes among SSc patients' subgroups from the three Italian macro-areas. In particular, patients from Southern Italy were characterized by significantly higher prevalence of dcSSc subset, digital ulcers, musculoskeletal and internal organ damage, mainly lung fibrosis, as well by higher percentage of serum anti-Scl70 antibodies compared to patients from other two macro-areas. Taken together, these findings suggest that SSc patients referred to tertiary centers of Southern Italy show a worse clinico-serological phenotype compared to those of Northern and Central Italy. The same patients' population more frequently underwent immunosuppressive treatments during the clinical course of the disease.

### 4.2. Review of the world literature

The analysis of the world literature showed that a heterogeneous geographical distribution of disease phenotypes, in patients followed at tertiary referral centers, has been observed in cross-sectional studies on SSc populations from different countries and among different areas or ethnic groups within the same country. The largest study to date on 23 European countries investigated the SSc composition as regards clinical/serological subsets [7]. The study revealed several discrepancies among different countries as well as among different areas within the same country [7]. The cluster analysis failed to identify neither an East-West or North-South trend, postulated on the basis of some epidemiological studies [7,15], nor any geographical coordinate regarding the typical SSc features, such as the prevalence of a specific cutaneous subset and/or autoantibody (ACA, Scl-70), while a "pocket" distribution of SSc clinical/serological composition was evidenced. Of interest, the authors found that eastern European centers have taken care for SSc patients with frequent serious visceral organ manifestations (pulmonary arterial hypertension, cardiac involvement) than western centers, suggesting the presence of local referral bias [7].

Other studies [16–24], focusing on SSc symptom composition within a single country, were scarcely comparable in terms of recruitment modalities, number of enrolled patients and/or involved centers (mono−/multicenter), and settings (hospital or outpatients' clinics).

Overall, the most significant differences occurred in distinct ethnic groups living in the same geographic areas [16–19,23,24]. Two studies conducted in well-defined macro-areas of the United States confirmed the existence of a phenotype characterized by a higher frequency of anti-Scl70 and dcSSc in black patients [16,17], with increased prevalence of digital ulcers [17].

A single-center study in a densely populated area of Canada revealed that Chinese-descent patients showed less frequent joint and gastrointestinal manifestations, less severe vasculopathy, but increased prevalence of myositis and specific autoantibodies (anti-Ro and anti-U-RNP) [18]. On the contrary, data from a multicenter study on Han-Chinese ethnic group followed-up in rheumatology/dermatology centers, compared with a registry of US Caucasian patients, found that Chinese SSc patients are more frequently affected by dcSSc, with a higher prevalence of both anti-Scl-70 and anti-RNAP III autoantibodies (19). In addition, pulmonary fibrosis was present in nearly 80% of subjects, strongly associated with anti-Scl-70, which represents one of the worse disease phenotypes [19]. A retrospective study revealed a more severe pulmonary disease in African American patients and an unadjusted higher mortality when matched with non–African American subgroup [23]; moreover, the autoantibody profile differed between the 2 groups as African American were more likely to have anti-U1-RNP [23]. A single-center study carried out in Toronto, focusing on the immigration pattern, evidenced ethnic variations in SSc manifestations including internal organ involvement [24]. In particular, Est Asian patients revealed a low prevalence of both calcinosis and oesophageal involvement, while Afro-Caribbean more frequently had interstitial lung disease, and First Nations showed a dcSSc subset; finally, a low prevalence of anti-Scl-70 was recorded in Hispanic, and ACA in Afro-Caribbean patients [24].

Whit regard to local environmental and/or climate factors, a comparative analysis of SSc subgroups resident in three different geographical areas of France found no substantial differences in the prevalence of cutaneous subsets, ACA, and anti-Scl70, although a higher prevalence of the disease was found in Alsace [20]. Moreover, in a cross-sectional, multicenter study carried out in Brazil, a higher risk of digital ulcers in patients living in subtropical vs tropical climate was observed [21]. Moreover, a significant increase in dcSSc subset was found in residents of urban areas compared with patients from rural areas in Korea; the latter presented an unexpected increase in 5-year mortality [22].

### 4.3. Possible role of genetic/environmental factors

The geographical heterogeneity in SSc clinical/serological phenotypes reported in the observational cohort studies, including our study, is mirrored by epidemiological studies that evidenced a quite variable prevalence of SSc among different geographical areas [15,25,26]. This might be correlated to the complexity of the SSc etiopathogenesis that encompasses several putative agents; namely, the host genetic/epigenetic and/or environmental infectious/toxic co-factors [6,27,28]. The variable combination of the above factors may lead to specific SSc phenotypes, possibly through a multistep process that characterizes the natural history of the disease [6,28]; it can be particularly evident in patients' populations with specific genetic predisposition [29–31] and/or living in geographical areas characterized by endemic exposure to specific adverse environmental factors [6,25,27,32]. The latter condition is reported in some geographical areas characterized by high prevalence of occupational exposure to both silica and solvents, more often in male SSc patients [33]. Comparable conditions could very likely be present in Northern Italy, with high density of industries and climate conditions favoring the negative effects of pollution, as in the Po valley; an example of such combination has been observed in a restricted geographical area with high density of worksites with silica dust exposure, where resident SSc patients showed abnormal serum levels of silica nanoparticles that in turn were associated to severe scleroderma lung fibrosis [34].

### 4.4. Possible role of specialized referral center network

In-depth clinical/epidemiological studies, focusing on the entire clinical scleroderma spectrum, could identify these putative pathogenetic correlations. During the last decades, the phenotype composition

and outcomes of SSc patients' series recruited at tertiary referral centers showed an increasing percentage of milder disease variants, especially in countries with well-organized healthy system [5,11,12]. The overall improvement of SSc pathomorphosis might be explained, at least in part, to the improved physician/patient awareness of this harmful disease and to the diffusion of reliable diagnostic tools, mainly capillaroscopy and specific autoantibody detection, which may facilitate the early identification of milder disease variants [35]. Consequently, an increasing percentage of individuals with less severe SSc phenotypes, at early stage of disease, is increasingly addressed at tertiary referral centers.

In this scenario, the significant differences among SSc patients resident in the three Italian macro-areas observed in the present study are somewhat unexpected. Considering the quite homogeneous ethnic composition of the Italian population (https://eacea.ec.europa.eu/national-policies/eurydice/content/population-demographic-situation-languages-and-religions-39_it) and excluding some restricted areas with high population density and/or polluting industries, both climatic and environmental conditions in the Southern Italy are generally more healthful compared to the rest of the country, especially the macro-area of Northern Italy [36]. In particular, the southern regions have a milder annual average climate and a lower incidence of industrial pollution [37]. Thus, to explain the observed discrepancies in the SSc phenotypes, two possible non-mutually exclusive explanations could be tentatively hypothesized. From one side the presence among SSc patients of Southern Italy of environmental and/or genetic factors that might predispose to more severe SSc phenotypes, even if in the absence of objective supporting data; on the other hand, we can suppose that the high prevalence of worse disease phenotypes in the southern macro-area might reflect at least in part an inadequate network of either information for the patients/doctors and of referral specialized health facilities. Therefore, patients with more severe, often rapidly progressive SSc variants might be more likely to be referred to specialized tertiary centers than those with mild to moderate forms of the disease. This referral bias might explain the relatively higher number of worse phenotypes in SSc patients' population recruited in Southern Italy if compared to the other two Italian macro-areas. The first real-life nationwide study in Norwegian SSc patients supported the heterogeneity of the disease and evidenced referral-related differences in pulmonary hypertension rate across the considered area, thus preventing a sufficiently uniform SSc patients' assessment [38].

## 5. Conclusions

In this context, population-based cohort studies from well-defined areas are needed, also to understand the overall impact of the disease on national health organizations. An adequate information and health network is decisive for the early diagnosis and referral to specialized centers to precisely customize treatments for a rare, scarcely known diseases such as the SSc [39]. The present cohort study revealing some discrepancies among SSc patients' populations from different Italian macro-areas may stimulate thorough clinical investigations in order to better define the actual prevalence and distribution of SSc clinical phenotypes. Even more, the identification of definite SSc geographical clustering may be very valuable in understanding the actual role of genetic and/or environmental causative factors on this complex disease.

## Funding

This study was supported by the Italian Society of Rheumatology (SIR).

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Appendix

### A.1. SPRING group of the Italian Society of Rheumatology (SIR)

*Convenors*

Clodoveo Ferri, University of Modena & Reggio Emilia, Italy; clodoveo.ferri@unimore.it

Marco Matucci-Cerinic, University of Florence, Italy; marco.matuccicerinic@unifi.it

*Investigators (in alphabetical order)*

Abignano Giuseppina, AOR San Carlo di Potenza; g.abignano@hotmail.com

Agnes Cecilia, Ospedale San Lorenzo, Carmagnola (TO), ASL-TO5; ceciliaagnes909@gmail.com

Amato Giorgio, AOU Policlinico – Vittorio Emanuele, Catania; giorgioamato@hotmail.it

Ariani Alarico, AOU Parma; dott.alaricoariani@libero.it

Bagnato Gianluca, Università degli Studi di Messina; gianbagnato@gmail.com

Bajoicchi Gianluigi, Arcispedale *S. Maria* Nuova, Reggio Emilia; gianluigi.bajocchi@asmn.re.it

Barsotti Simone, AOU Santa Chiara, Pisa; simone.barsotti@outlook.com

Bellando-Randone Silvia, University of Florence; s.bellandorandone@gmail.com

Benenati Alessia, AOU 'Policlinico - Vittorio Emanuele, Catania; alessia.benenati@libero.it

Beretta Lorenzo, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano; lorberimm@hotmail.com

Bianchi Gerolamo, ASL3 Genova; gerolamo.bianchi@asl3.liguria.it

Bosello Silvia, Policlinico "A. Gemelli" –IRCCS – UOC di Reumatologia; Roma; silvia.bosello@libero.it

Cacciapaglia Fabio, UO Reumatologia – DETO, Università di Bari; fabio.cacciapaglia79@gmail.com

Calabrese Francesca, SSD Reumatologia, Reggio Calabria; francescacalabrese81@virgilio.it;

Caminiti Maurizio, Ospedale Bianchi-Melacrino-Morelli, SSD Reumatologia, Reggio Calabria; mauriziocaminiti@tin.it

Campochiaro Corrado, Ospedale S. Raffaele, Milano; corradocampochiaro@gmail.com

Carignola Renato, AOU San Luigi Gonzaga, Orbassano (TO); renatocarigno@gmail.com

Cavazzana Ilaria, Spedali Civili di Brescia; ilariacava@virgilio.it

Ciano Giovanni, Ospedale Ariano Irpino, ASL Avellino; giovanni.ciano55@gmail.com

Codullo Veronica, Policlinico San Matteo, Pavia; veronicacodullo@yahoo.it

Cozzi Franco, Villa Salus, Mestre; franco.cozzi@unipd.it

Cuomo Giovanna, Università degli Studi della Campania - Luigi Vanvitelli, Napoli; giovanna.cuomo@unicampania.it

D'Angelo Salvatore, AOR San Carlo di Potenza; saldangelo@katamail.com

Dagna Lorenzo, Ospedale S. Raffaele, Milano; dagna.lorenzo@hsr.it

Dall'Ara Francesca, UO Medicina Interna-Ambulatorio Reumatologia, Ospedale di Lodi; francesca.dallara@gmail.com

De Andres Ilenia, AO ARNAS Garibaldi, Catania; ilenia.deandres@gmail.com

De Angelis Rossella, Clinica Reumatologica, Università Politecnica delle Marche, Ancona; r.deangelis@staff.univpm.it

De Cata Angelo, Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG); a.decata@operapadrepio.it

De Luca Giacomo, Ospedale S. Raffaele, Milano; deluca.giacomo@hsr.it

De Santis Maria, Istituto Clinico Humanitas, Rozzano, Milano; maria.de_santis@humanitas.it

Della Rossa Alessandra, AOU Santa Chiara, Pisa; a.dellarossa69@

gmail.com

Doria Andrea, Università degli Studi di Padova; adoria@unipd.it

Doveri Marica, ASL3 Genova; marica.doveri@asl3.liguria.it

Foti Rosario, AOU Policlinico – Vittorio Emanuele, Catania; rosfoti5@gmail.com

Furini Federica, Department of Medical Sciences, University of Ferrara; fefe.furini@gmail.com

Fusaro Enrico, AOU Città della Salute e della Scienza di Torino; fusaro.reumatorino@gmail.com

Generali Elena, Istituto Clinico Humanitas, Rozzano, Milano; e.generali@gmail.com

Gigante Antonietta, Università degli Studi "La Sapienza", Roma; antonietta.gigante@uniroma1.it

Giollo Alessandro, AOUI Verona; alessandro.giollo@univr.it

Girelli Francesco, Ospedale GB Morgagni, Forlì; francesco.girelli@auslromagna.it

Giuggioli Dilia, University of Modena/Reggio Emilia; dilia.giuggioli@unimore.it

Govoni Marcello, AOU S. Anna, Ferrara; gvl@unife.it

Guiducci Serena, University of Florence; s.guiducci@hotmail.com

Iannone Florenzo, UO Reumatologia– DETO, Università di Bari; florenzo.iannone@uniba.it

Ingegnoli Francesca, Università degli Studi di Milano; francesca.ingegnoli@unimi.it

Iuliano Anna Maria, AO San Camillo Forlanini, Roma; annamariaiuliano@hotmail.it

Lazzaroni Maria Grazia, Spedali Civili and University of Brescia; mariagrazialazzaroni@gmail.com

Lubrano Ennio, Università del Molise, Campobasso; ennio.lubrano@unimol.it

Lumetti Federica, University of Modena & Reggio Emilia; fedelumetti@gmail.com

Magnani Luca, Arcispedale *S. Maria* Nuova, Reggio Emilia; luca.magnani@ausl.re.it

Masini Francesco, Università degli Studi della Campania "Luigi Vanvitelli"; masini.fr@gmail.com

Mennillo Gianna, AOR San Carlo di Potenza; giannaangelamennillo@virgilio.it

Murdaca Giuseppe Ospedale Policlinico S. Martino-Universita' di Genova; giuseppe.murdaca@unige.it

Pagano Mariano Giuseppa, Ospedale Bianchi-Melacrino-Morelli, Reggio Calabria; giusypaganomariano@libero.it

Parisi Simone, AOU Città della Salute e della Scienza, Torino; simone.parisi@hotmail.it

Pellegrino Greta, Sapienza, Università di Roma; greta.pellegrino01@gmail.com

Peroni Clara Lisa, AOU Città della Salute e della Scienza, Torino; claralisaperoni@gmail.com

Pigatto Erika, Università degli Studi di Padova; erika.pigatto@gmail.com

Riccieri Valeria, Sapienza Università di Roma; valeria.riccieri@uniroma1.it

Risa Anna Maria, Università Politecnica delle Marche, Ancona; annamaria.risa@hotmail.it

Romeo Nicoletta ASO S. Croce e Carle, Cuneo; romeo.n@ospedale.cuneo.it

Rosato Edoardo, Università degli Studi di Roma "La Sapienza" Policlinico Umberto I; edoardo.rosato@uniroma1.it

Sambataro Gianluca, Azienda Ospedaliera Cannizzaro, Catania.

Saracco Marta, AO Ordine Mauriziano, Torino; marta.saracco@gmail.com

Sebastiani Giandomenico, AO San Camillo Forlanini, Roma;gsebastiani@scamilloforlanini.rm.it

Spinella Amelia, University of Modena & Reggio Emilia; amelia.spinella@gmail.com

Talotta Rossella, L. Sacco Hospital, Milan; talotta1@virgilio.it

Visalli Elisa, AOU 'Policlinico – Vittorio Emanuele, Catania; elivisa21@gmail.com

Vultaggio Licia, AOU S. Anna, Ferrara, licia.vultaggio@unife.it

Zanatta Elisabetta, Università degli Studi di Padova; elisabetta.zanatta@yahoo.it

Zanframundo Giovanni, Policlinico San Matteo, Pavia; gio.zanframundo@gmail.com

### *A.2. Study Center of the Italian Society of Rheumatology (SIR)*

Carlo Scirè, Università degli Studi, Milano-Bicocca, Milan; c.scire@reumatologia.it

Greta Carrara, Epidemiology Unit, Italian Society for Rheumatology, Milan, Italy; g.carrara@reumatologia.it

Giampiero Landolfi, Epidemiology Unit, Italian Society for Rheumatology, Milan, Italy; g.landolfi@reumatologia.it

Davide Rozza, Epidemiology Unit, Italian Society for Rheumatology, Milan, Italy; d.rozza@reumatologia.it

Anna Zanetti, Epidemiology Unit, Italian Society for Rheumatology, Milan, Italy; a.zanetti@reumatologia.it

## References

[1] Steen VD. The many faces of scleroderma. Rheum Dis Clin N Am 2008;34:1–15. https://doi.org/10.1016/j.rdc.2007.12.001.

[2] Varga J, Trojanowska M, Kuwana M. Pathogenesis of systemic sclerosis: recent insights of molecular and cellular mechanisms and therapeutic opportunities. J Scleroderma Relat Disord 2017;2(3):137–52. https://doi.org/10.5301/jsrd.5000249.

[3] Ferri C, Valentini G, Cozzi F, Sebastiani M, Michelassi C, La Montagna G, et al. Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. Medicine (Baltimore) 2002;81:139–53. https://doi.org/10.1097/00005792-200203000-00004.

[4] Tyndall AJ, Bannert B, Vonk M, Airò P, Cozzi F, Carreira P, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis 2010;69:1809–15. https://doi.org/10.1136/ard.2009.114264.

[5] Ferri C, Sebastiani M, Lo Monaco A, Iudici M, Giuggioli D, Furini F, et al. Systemic sclerosis evolution of disease pathomorphosis and survival. Our experience on Italian patients' population and review of the literature. Autoimmun Rev 2014;13:1026–34. https://doi.org/10.1016/j.autrev.2014.08.029.

[6] Ferri C, Arcangeletti MC, Caselli E, Zakrewska K, Maccari C, Calderaro A, et al. Insights into the knowledge of complex diseases: environmental infectious/ toxic agents as potential etiopathogenetic factors of systemic sclerosis. J Autoimmun 2021;124:102727. https://doi.org/10.1016/j.jaut.2021.102727.

[7] Walker UA, Tyndall A, Czirjàk L, Denton CP, Farge-Bancel D, Kowal-Bielecka O, et al. Geographical variation of disease manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials and research (EUSTAR) group database. Ann Rheum Dis 2009;68:856–62. https://doi.org/10.1136/ard.2008.091348.

[8] Hunzelmann N, Genth E, Krieg T, et al. The registry of the German Network for systemic scleroderma: frequency of disease subsets and patterns of organ involvement. Rheumatology 2008;47:1185–92. https://doi.org/10.1093/rheumatology/ken179.

[9] Galluccio F, Walker UA, Nihtyanova S, Moinzadeh P, Hunzelmann N, Krieg T, et al. Registries in systemic sclerosis: a worldwide experience. Rheumatology (Oxford) 2011;50:60–8. https://doi.org/10.1093/rheumatology/keq355.

[10] Pokeerbux MR, Giovannelli J, Dauchet L, Mouthon L, Agard C, Lega JC, et al. Survival and prognosis factors in systemic sclerosis: data of a French multicenter cohort, systematic review, and meta-analysis of the literature. Arthritis Res Ther 2019;3(21):86. https://doi.org/10.1186/s13075-019-1867-1.

[11] Ferri C, Giuggioli D, Guiducci S, Lumetti F, Bajocchi G, Magnani L, et al. Systemic sclerosis progression INvestiGation (SPRING) Italian registry: demographic and clinico-serological features of the scleroderma spectrum. Clin Exp Rheumatol 2020;38 Suppl 125(3):40–7.

[12] De Angelis R, Giuggioli D, Bajocchi G, Dagna L, Zanframundo G, Foti R, et al. Sex-related differences in systemic sclerosis: a multicentre cross-sectional study from the National registry of the Italian Society for Rheumatology. J Rheumatol 2022;49:176–85. https://doi.org/10.3899/jrheum.210794.

[13] Avouac J, Fransen J, Walker UA, Riccieri V, Smith V, Muller C, et al. Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research Group. Ann Rheum Dis 2011;70:476–81. https://doi.org/10.1136/ard.2010.136929.

[14] van Den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. Classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum 2013;65:2737–47. https://doi.org/10.1002/art.38098.

[15] Bairkdar M, Rossides M, Westerlind H, Hesselstrand R, Arkema EV, Holmqvist M. Incidence and prevalence of systemic sclerosis globally: a comprehensive

systematic review and meta-analysis. Rheumatology 2021;60:3121–33. https://doi.org/10.1093/rheumatology/keab190.
[16] Mayes MD, Lacey JV, Beebe-Dimmer J, Gillespie BW, Cooper B, Laing TJ, et al. Prevalence, incidence, survival and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum 2003;48:2246–55. https://doi.org/10.1002/art.11073.
[17] Nietert PJ, Mitchell HC, Bolster MB, Shaftman SR, Tilley BC, Silver RM. Racial variation in clinical and immunological manifestations of systemic sclerosis. J Rheumatol 2006;33:263–8.
[18] Low AHR, Johnson SR, Lee P. Ethnic influence on disease manifestations and autoantibodies in Chinese-descent patients with systemic sclerosis. J Rheumatol 2009;36:787–93. https://doi.org/10.3899/jrheum.080915.
[19] Wang J, Assassi S, Guo G, Tu W, Wu W, Yang L, et al. Clinical and serological features of systemic sclerosis in a Chinese cohort. Clin Rheumatol 2013;32:617–21. https://doi.org/10.1007/s10067-012-2145-7.
[20] Meyer A, Chifflot H, Chatelus E, Kleinmann JF, Ronde-Ousteau C, Klein D, et al. Spatial heterogeneity of systemic sclerosis in France: high prevalence in the northeast region. Arthritis Rheum 2016;68:1731–7. https://doi.org/10.1002/art.39613.
[21] Souza EJR, Muller CS, Rezende RA, Guimarães I, Mariz HA, Dantas AT, et al. Geographic variation as a risk factor for digital ulcers in systemic sclerosis patients: a multicentre registryScandinavian. J Rheumatol 2017;46(4):288–95. https://doi.org/10.1080/03009742.2016.1233994.
[22] Moon KW, Lee SS, Lee YJ, Jun JB, Yoo SJ, Ju JH, et al. Clinical and laboratory characteristics, and mortality in Korean patients with systemic sclerosis: a nationwide multicentre retrospective cohort study. J Rheumatol 2018;45:1281–8. https://doi.org/10.3899/jrheum.171443.
[23] Moore DF, Kramer E, Eltaraboulsi R, Steen VD. Increased morbidity and mortality of scleroderma in African Americans compared to non-African Americans. Arthritis Care Res 2019;71:1154–63. https://doi.org/10.1002/acr.23861.
[24] Al-Sheikh H, Ahmad Z, Johnson SR. Ethnic variations in systemic sclerosis disease manifestations, internal organ involvement and mortality. J Rheumatol 2019;46:1103–8. https://doi.org/10.3899/jrheum.180042.
[25] Ranque B, Mouthon L. Geoepidemiology of systemic sclerosis. Autoimmun Rev 2010;9:A311–8. https://doi.org/10.1016/j.autrev.2009.11.003.
[26] Westerlind H, Bairkdar M, Gunnarson K, Svensson-Moshtaghi J, Sysojev AO, Hesselstrand R, et al. Incidence and prevalence of systemic sclerosis in Sweden, 2004–2015, a register-based study. Semin Arthritis Rheum 2022;53:151978. https://doi.org/10.1016/j.semarthrit.2022.151978.
[27] Muntyanu A, Ouchene L, Zhou S, Hudson M, Rezaeian M, LaChance A, et al. Geographical distribution of systemic sclerosis in Canada: an ecologic study based on the Canadian Scleroderma Research Group. J Am Acad Dermatol 2022. https://doi.org/10.1016/j.jaad.2021.12.055. S0190-9622(22)00031-7.
[28] Ota Y, Kuwana M. Updates on genetics in systemic sclerosis. Inflammation and Regeneration 2021;41:17. https://doi.org/10.1186/s41232-021-00167-6.
[29] Hinchcliff M, Huang CC, Wood TA, Matthew Mahoney J, Martyanov V, Bhattacharyya S, et al. Molecular signatures in skin associated with clinical improvement during mycophenolate treatment in systemic sclerosis. J Invest Dermatol 2013;133(8):1979–89. https://doi.org/10.1038/jid.2013.130.
[30] Gourh P, Safran SA, Alexander T, Boyden SE, Morgan ND, Shah AA, et al. HLA and autoantibodies define scleroderma subtypes and risk in African and European Americans and suggest a role for molecular mimicry. Proc Natl Acad Sci U S A 2020;117(1):552–6. https://doi.org/10.1073/pnas.1906593116.
[31] Ferri C, Bernini L, Cecchetti R, et al. Cutaneous and serologic subsets of systemic sclerosis. J Rheumatol 1991;18:1826–32.
[32] Kassamali B, Kassamali AA, Muntyanu A, Netchiporouk E, Vleugels RU, LaChance A. Geographic distribution and environmental triggers of systemic sclerosis cases from two large academic tertiary centers in Massachusetts. I Am Acad Dermatol 2022;86:925–7. https://doi.org/10.1016/j.jaad.2021.03.055.
[33] De Decker E, Vanthuyne M, Blockmans D, Houssiau F, Lenaerts J, Nemery Westhovens R, et al. High prevalence of occupational exposure to solvents or silica in male systemic sclerosis patients: a Belgian cohort analysis. Clin Rheumatol 2018;37:1977–82. https://doi.org/10.1007/s10067-018-4045-y.
[34] Ferri C, Artoni E, Sighinolfi GL, Luppi F, Zelent G, Colaci M, et al. High serum levels of silica nanoparticles in systemic sclerosis patients with occupational exposure: possible pathogenetic role in disease phenotypes. Semin Arthritis Rheum 2018;48:475–81. https://doi.org/10.1016/j.semarthrit.2018.06.009.
[35] Saketkoo LA, Frech T, Varju C, Domsic R, Farrell J, Gordon JK, et al. A comprehensive framework from navigating patients care in systemic sclerosis: a global response to the need for improving the practice of diagnostic and preventive strategies in systemic sclerosis. Best Pract Res Clin Rheumatol 2021;35:101707. https://doi.org/10.1016/j.berh.2021.101707.
[36] Istituto Nazionale di statistica. Rapporto sul Territorio. 2020. https://doi.org/10.1481/Istat.Rapportoterritorio.2020. Ambiente, economia e società. ISBN 978-88-458-2014-4.
[37] Istituto Superiore per la Protezione e la Ricerca Ambientale. Gli indicatori del clima in Italia nel. 2019. Anno XV. ISPRA, Stato dell'Ambiente 94/2020 ISBN978-88-448-0998-0.
[38] Fretheim H, Halse AK, Seip M, Bitter H, Wallenius M, Garen T, et al. Multidimensional tracking of phenotypes and organ involvement in a complete nationwide systemic sclerosis cohort. Rheumatology 2020;59:2920–9. https://doi.org/10.1093/rheumatology/keaa026.
[39] Lepri G, Hughes M, Bruni C, Matucci Cerinic M, Bellando-Randone S. Recent advances steer the future of systemic sclerosis toward precision medicine. Clin Rheumatol 2020;39:1–4. https://doi.org/10.1007/s10067-019-04834-5.