# Clinical risk assessment of organ manifestations in systemic sclerosis - a report from the EULAR Scleroderma Trials And Research (EUSTAR) group data base

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## Abstract

*Background:* Systemic sclerosis (SSc) is a multisystem autoimmune disease which is classified into a diffuse cutaneous (dcSSc) and a limited cutaneous (lcSSc) subset according to the skin involvement. In order to better understand the vascular, immunological and fibrotic processes of SSc and to guide its treatment the EULAR Scleroderma Trials And Research (EUSTAR) group was formed in June 2004.

*Aims and Methods:* EUSTAR collects prospectively the Minimal Essential Data Set (MEDS) on all sequential patients fulfilling the ACR diagnostic criteria in participating centres. We aimed to characterize demographic, clinical and laboratory characteristics of disease presentation in SSc and analysed EUSTAR baseline visits.

*Results:* In April 2006, a total of 3656 patients (1349 with dcSSc and 2101 with lcSSc) were enrolled in 102 centres and 30 countries. 1330 individuals had autoantibodies against Scl70 and 1106 against anticentromere antibodies. 87% of patients were female. On multivariate analysis, scleroderma subsets (dcSSc vs. lcSSc), antibody status and age at onset of Raynaud's phenomenon, but not gender were independently associated with the prevalence of organ manifestations. Autoantibody status in this analysis appeared more closely associated with clinical manifestations than were SSc subsets.

*Conclusion:* dcSSc and lcSSc subsets are associated with particular organ manifestations, but in this analysis the clinical distinction appeared superseded by an antibody based classification in predicting some scleroderma complications. The EUSTAR MEDS data base facilitates the analysis of clinical patterns in SSc and contributes to the standardised assessment and monitoring of SSc internationally.

## Introduction

Systemic Sclerosis (SSc) is a multisystem disease with prevalence rates around 5/ $10^5$ and an incidence of 1/ $10^5$. [1] Higher rates are seen in the US, Australia and Eastern Europe and lower in Northern Europe and Japan.[2-7] SSc may be rapidly fatal in its severe form, but may also have a prolonged course with patients being compromised only by distal vasospasm, sclerodactily and dysphagia. [8-11] Predicting outcome early in the course of the disease is critical in choosing the appropriate treatment, but is not yet sufficiently reliable in many patients. The diagnosis is generally established with high specificity according to the criteria of the American College of Rheumatology (ACR, formerly called American Rheumatism Association). [12] Early SSc can be further divided into diffuse cutaneous (dcSSc) and limited cutaneous (lcSSc, with a part of those patients previously called CREST syndrome). [13] Other forms are characterized by features of scleroderma combined with features of a second connective tissue disease. [14]

SSc subsets are also associated with the presence of autoantibodies: dcSSc has been associated with Scl70-autoantibodies (also called topoisomerase I autoantibodies), whereas anti-centromere autoantibodies (ACA) are typically detected in lcSSc. However autoantibody profiles do not completely predict disease presentation. A Japanese study for example showed that 31% of SSc patients with Scl70 antibodies had lcSSc.[15] Conversely 18% of patients with lcSSc were positive for Scl70 antibodies in a USA report.[16] Autoantibodies may even disappear during the course of the disease, which then predicted a more favourable outcome.[17]

Genetic factors also seem to have an influence on SSc, as the disease occurs more frequently within families than in the general population.[18] A relatively high concordance rate between monozygotic twins for antinuclear antibodies also supports the influence of a genetic factor on autoantibody production, although the low overall concordance between monozygotic twins demonstrates the importance of environmental factors.[19]

The low incidence of SSc and the clinical variability result in difficulties in understanding the pathogenesis and evolution of the disease, and in selecting appropriate patients for clinical trials.[20-22]

In order “to foster the awareness, understanding and research of scleroderma and its care and management throughout Europe” the EULAR Scleroderma Trials And Research (EUSTAR) group (www.eustar.org) was inaugurated and under the auspices of the EULAR Standing Committee on International Clinical Studies Including Therapeutic Trials (ESCISIT) has established a prospective multicentre scleroderma cohort.

In this paper, we report the cross-sectional prevalence of clinical and laboratory characteristics in SSc and present a multivariate analysis in order to gain insight into factors that are associated with particular organ manifestations and therefore possibly also with the disease process. By focussing on age at onset of Raynaud’s phenomenon, gender and autoantibodies, we also examined whether the dichotomy into limited and diffuse subsets is the best way to capture the disease and its organ manifestations and whether other variables may be more appropriate.

## Patients and Methods

*The EULAR Scleroderma Trials and Research (EUSTAR) database*

The EUSTAR database was inaugurated in June 2004 and documents a multinational, prospective and open scleroderma cohort. Participating centres seek ethics committee approval, followed by the entry of the Minimal Essential Data Set (MEDS) of all consecutive consenting patients most of whom fulfil the ACR classification criteria for SSc. [12] Scleroderma subsets are classified as "diffuse SSc" if skin thickening extends proximal to the elbows and knees or includes the trunk, and as "limited SSc", if confined to distal extremities and face, all within 2 years from onset of non-Raynaud's disease. [13] Patients who fulfil the ACR-criteria for scleroderma, but who had simultaneous overlap syndromes with typical features of one or more of other connective tissue diseases (mixed connective tissue disease, systemic lupus erythematosus, Sjögren's syndrome, dermatomyositis, polymyositis or rheumatoid arthritis) are classified as "other". Cases of localized scleroderma (morphea and linear disease) are not included. The MEDS dataset (Figure 1) was constructed in consensus by the EUSTAR members and covers demographic aspects, disease duration, organ involvement and laboratory data. Disease activity was calculated as a composite score from MEDS features according to the preliminary index for SSc as a whole, proposed by the European Scleroderma Study Group (EScSG) and detailed elsewhere. [23] Annual follow-up examinations are employed. The centres were coached several times on how to fill out the forms. Coaching sessions included ACR classification of SSc, definitions of the subgroups and the activity score. Standardised teaching sessions included the documentation of the modified Rodnan skin score at the bedside, following two "teach the teachers" sessions held in 2004 and 2005. Pseudonymised paper entry forms are faxed or mailed to the EUSTAR registry in Florence, Italy. Data monitoring includes suspect double entries, missing data and plausability checks. The definitions of the MEDS parameters and video coaching material are also available on the EUSTAR website (www.eustar.org).

*Data analysis*

SSc presentations were analysed crossectionally for differences in demographic and clinical features. For each patient, only the baseline data from the first visit was used. The dataset was analysed using the SPSS 13.0 (SPSS Corp.) statistical package. Group means and percentages within dichotomised groups were compared by t-tests.

Significant differences in disease presentation on univariate comparisons were then retested by forward multivariate logistic regression. The following variables were entered in the model: presence or absence of dcSSc, lcSSc, antinuclear antibodies (ANA), ACA, Scl70 autoantibodies and gender. Further variables included early vs. late onset of first Raynaud's phenomenon (dichotomized at the mean onset of Raynaud's phenomenon among all patients), and the time interval between the first Raynaud's phenomenon and first non-Raynaud's event (dichotomized at the mean interval among all patients). Variables with quantitatively minor explanatory power (contributing less than 0.01 to the overall Nagelkerkes-$R^2$) were removed from the model even if their effect to the model was statistically significant.

**Results**

As of April 2006, a total of 3656 patients has been enrolled from 102 participating centres in 24 European and 6 non-European countries. There were very little missing data (Table 1), apart from parameters relating to the onset of Raynaud's phenomenon, onset of first non-Raynaud's event and diffusing capacity of the lung for carbon monoxide (DLCO), as these three parameters were only included after the first year of data collection. 1,349 (36.9%) patients had dcSSc, 2,101 (57.5%) of patients had lcSSc and 206 (5.6%) had scleroderma in combination with another connective tissue disease (Table 1). Compared to patients with lcSSc, patients with dcSSC were on average 5.1 years younger. In all SSc subsets, there was a normal distribution of the age of the patients.

*Disease manifestations*

Patients with dcSSc and lcSSc had an identical mean age of onset (42.9 years) of Raynaud's phenomenon. However, the age at the onset of first non-Raynaud's manifestation differed between dcSSc and lcSSc, being 44.8 years (SD 14.2) on average in the former and 47.9 years (SD 13.4) in the latter subset (P<0.001). Consequently, there was a significantly longer lag period between the onset of Raynaud's phenomenon and the next non-Raynaud's clinical feature of disease in the lcSSc (average 4.8 years, SD 8.5), as opposed to the dcSSc (average 1.9 years, SD 5.4).148 patients (4.0%) fulfilled the ACR-criteria for scleroderma but had no Raynaud's phenomenon.

The mean skin score (modified Rodnan's skin score, mRSS) was higher (19.0, SD 10.0) in dcSSC than in lcSSc (8.1, SD 5.3) or in other scleroderma presentations (6.4, SD 6.6), as expected. Overlapping skin scores between dcSSc and lcSSc emphasise that the numerical number of the score is not just determined by distribution but also by the severity of skin involvement.

Disease activity was scored as "active" in 49.8% of dcSSc, 21.5% of lcSSc, and 28.2% of "other". Acute phase reactants were more frequently elevated in dcSSc (Table 1).

Musculoskeletal manifestations (joint contractures, tendon friction rubs, muscle weakness, muscle atrophy and creatine kinase (CK)-elevation) were almost twice as common in diffuse vs. limited systemic sclerosis. Joint contractures were observed most frequently. A substantial number of patients had muscle weakness and atrophy, but only a few had simultaneous CK-elevation.

Gastrointestinal involvement was most frequent in the oesophagus, but with the exception of a slightly more predominant gastric involvement in the dcSSC (26.6% in dcSSc vs. 22.8% in lcSSc) was observed in similar frequencies among the scleroderma subsets.

Pulmonary fibrosis was more frequent in dcSSc (53.4%) than in lcSSc (34.7%), whereas the frequency of PAH (diagnosed by echocardiography) was similar within the two subsets (in 22.3% of dcSSc patients and in 20.5% of lcSSc patients). Isolated PAH (PAH in the absence of lung fibrosis) was found in 26% of dcSSc with PAH and in 45% of lcSSc PAH patients.

Objective cardiac complications (conduction block, diastolic dysfunction and left ventricular ejection failure) were reported with a similar frequency among scleroderma subsets. Subjective manifestations (palpitations) were slightly more frequent in the dcSSc, compared to lcSSc (27.3% vs. 22.6%). Reduced left ventricular ejection fraction was combined with PAH in only 3.2% of patients with dcSSc. This prevalence was similar in patients with lcSSc (2.8%, P=0.52).

Renal complications (hypertensive renal crisis and proteinuria) were more frequent in the dcSSc subset.

*Differences in disease presentation according to gender*

Among all scleroderma patients, 87% were women; the female-to-male ratio was 6 : 1. Females were slightly older than males (mean age 55.5 years, SD 13.6 vs. 53.9 years, SD 13.3; P= 0.02). Females had an earlier onset of Raynaud's phenomenon than males (mean age 42.2 years SD 14.5 vs. 46.4 years, SD 14.3; P<0.001). Similarly, the onset of non-Raynaud's manifestations was observed at a slightly younger age in females than in males (46.4 years, SD 13.8 vs. 47.9 years, SD 13.8; P=0.04) among all scleroderma patients.

Within the dcSSc subset, 1094 patients were female and 254 patients were male (female : male ratio 4 : 1). Within the lcSSc subset, 1910 patients were female and 180 patients were male (female : male ratio 11 : 1.0). Males were more frequently affected by dcSSc than lcSSc (P<0.001). The mean age of patients did not differ between sexes when compared among individual SSc subsets (Table 2). Women compared to men however had an earlier onset of Raynaud's phenomenon in both SSc (by a mean of 4.3 years earlier) and lcSSC (by a mean of 4.6 years earlier). In absolute numbers, ACA were rarely

positive in men. Among the lcSSc subset, women had more frequently ACA and men more frequently Scl-70 autoantibodies (Table 2).

*Differences in disease presentation according to age at disease onset*

In order to analyse possible differences in organ manifestations according to the patient's age at disease onset (defined as first onset of Raynaud's phenomenon), we categorized patients according to their mean age at the onset of Raynaud's phenomenon into a group below, and one group above the mean. The former group of "early" onset of Raynaud's phenomenon had an average age of 42.8 years and the latter group of "late" onset of Raynaud's phenomenon had an average age of 60.9 years (Table 3). Although the groups exhibiting early and late onset of Raynaud's manifestation had no or only slight differences in their autoantibody profile within the individual systemic sclerosis subsets (Table 3), they differed in the prevalence of clinical manifestations. In both subsets, persons with an earlier onset of Raynaud's phenomenon had more often digital ulcers than those with a late onset. Patients with an early onset of in contrast had significantly less pulmonary fibrosis, pulmonary hypertension, diastolic dysfunction and arterial hypertension (Table 3).

*Differences in disease presentation according to autoantibodies*

Patients positive for ACA mostly (88.7%) had lcSSc (Table 4), whereas only 60% of those carrying Scl70 autoantibodies had dcSSc. In contrast, 36.1% of Scl70 positive patients were classified as lcSSc. Patients with ACA were slightly older, compared to those with anti-Scl70 autoantibodies. Although there was no significant difference in the mean age at onset of Raynaud's phenomenon within people carrying the two different autoantibodies (42.2 years in anti-Scl70 autoantibody positive individuals vs. 43.3 years in ACA positive patients), those harbouring ACA had a significantly longer lag period (mean 6.5 years, SD 10.0) until the onset of first non-Raynaud's manifestations, compared to those with anti-Scl70 autoantibodies (mean 2.4 years, SD 5.6).

Autoantibody associations with particular clinical complications are shown in Table 4. The presence of autoantibodies (Scl70 and ACA on the one hand), distinguished the frequency of clinical manifestations very similarly to the distinction of dcSSc and lcSSc subsets on the other hand. However there were some differences. Most notably, Scl70 positivity, unlike diffuse skin involvement was associated with significant differences in the prevalence of intestinal symptoms, myocardial conduction block, diastolic dysfunction, and renal hypertension. On the other hand, a positive history of gastric complications and hypertensive renal crisis was associated with skin involvement, but not autoantibody status.

*Multivariate analysis of disease determinants*

The multivariate analysis confirmed the results of most univariate comparisons (Table 5). The ranking of the variables according to the overall explanatory effect to the model shows, that for some disease manifestations, the contributory effect of antibody status exceeds that of the clinical dichotomy into lcSSc and dcSSc. For many other disease manifestations, antibody status also contributed as an independent variable. In accord with the univariate analysis, late onset of Raynaud's phenomenon was negatively associated with digital ulcers and positively with pulmonary fibrosis, PAH and renal hypertension. On multivariate analysis, gender was significantly associated only with a few disease manifestations such as CK-elevation with male gender. However gender was removed from all models because sex status did not have a quantitatively pronounced explanatory effect, as it contributed less than 0.01 to the overall Nagelkerkes $R^2$ in the model.

**Discussion**

In this large EUSTAR cohort of predominantly Caucasian scleroderma patients 57% of individuals were classified as lcSSc and 36.9% as dcSSc. Other investigators also found that limited disease occurred more frequently than diffuse disease among prevalent cases (65.1% vs. 34.9%). [7]

Female patients were six times more frequent than males in our cohort. This sex ratio is between the numbers reported in smaller cohorts for the UK [6] (female : male ratio 3 : 1) and Japan (female : male ratio 14 : 1), but more similar to those from Iceland (8 :1). [3,5] Differences may be explained in part by the proportion of the lcSSc within the cohorts, because our data suggest that the female : male ratio may be higher in lcSSc than in dcSSc. In the UK study however, the female . male ratio was lower in the lcSSc subset 3.2:1 than in the dcSSc subset (4.6 : 1). [6] In lcSSc, we found a higher prevalence of Scl70 autoantibodies and a lower prevalence of ACA among men with, compared to women, whereas in dcSSc there were no differences in autoantibodies between sexes. Other investigators also suggest that ACA are less common among men. [7]

In previous studies, the mean age at diagnosis was not different among sexes. [7] In our cohort, patients with dcSSc were slightly younger than patients with lcSSc when they experienced the first non-Raynaud's feature of their disease. Previous incidence calculations suggested that the difference in prevalence between diffuse and limited disease was not attributable to the survival advantage of patients with limited disease. [7]

Our analysis found no differences between the two SSc subsets with regard to the age at onset of Raynaud's phenomenon, but in patients with diffuse disease, the first non-Raynaud's manifestation developed sooner than in patients with limited disease. These findings fit well with the observation that ACA positivity was associated with longer duration Raynaud phenomenon before the diagnosis of SSc was made. [24] The onset of disease whether based on first Raynaud's phenomenon, or first non-Raynaud's event was earlier in women. Furthermore, an early onset of disease was associated with a reduced prevalence of the more severe complications of scleroderma such as lung fibrosis and PAH in our cohort. This is in accord with the observation that female gender positively affects survival [7] The gender specific differences of the disease features indicate a modifying influence of sex hormones or reproduction. They could also point to gender-specific environmental exposure.

In the multivariate analysis however, gender was not associated with disease manifestations. This suggests, that any effect of gender may be better explained by other variables, such as age of onset of Raynaud's phenomenon and/ or autoantibody status.

In both SSc subsets, individuals with an early onset of Raynaud's phenomenon had digital ulcers more frequently than those with a late onset, whereas an onset of Raynaud's phenomenon later in life was associated with a higher prevalence of more severe disease manifestations such as pulmonary fibrosis and PAH. The independent contribution of the time of onset of Raynaud's phenomenon to the prevalence of the above mentioned complications despite a similar prevalence of autoantibodies was confirmed in the multivariate analysis and is in accord with the finding of others that older age at diagnosis negatively affects survival. [7] It should be noted however hat, the time of onset of Raynaud's phenomenon does not discriminate between the two disease subsets. The first non-Raynaud's feature does follow the onset of Raynaud's phenomenon more rapidly in dcSSc than in lcSSc, the relatively small difference however may not be helpful in the assessment of an individual patient.

Scl70 autoantibodies are associated with the more severe diffuse form of SSc but 36.1% of patients were classified as lcSSc. Another study found that 31% of SSc patients with this autoantibody had limited disease. [15] Conversely 23.4% of patients with lcSSc in our cohort and 18% in other investigations were positive for anti-Scl70 [16] and serum levels of anti Scl70 autoantibody levels also appear to be correlated with disease activity in some studies. [25] Disappearance of anti-Scl70 autoantibodies has been noted in patients with a more favourable outcome. [17] The multivariate analysis demonstrates that autoantibody status contributes to 15 of the organ complications, whereas the clinical SSc subtype serves as an explanatory variable to 11 of the organ complications. This could imply that autoantibody status is more closely related to organ involvement than SSc subsets in the LeRoy classification.

Of note, the MEDS dataset does not capture the status of anti-RNA-polymerase antibodies which are associated with dcSSc and renal involvement [26]. The presence of anti-RNA-polymerase antibodies may explain the finding that hypertensive renal crisis was not more frequent in individuals carrying anti-Scl-70 autoantibodies (Table 4) but on the other hand was associated with the absence of Scl70 autoantibodies (Table 5) despite the link between renal complications and dcSSc (Table 1).

Our analysis nevertheless confirms the importance of dcSSc and lcSSc scleroderma subdivision in their association with particular organ manifestations. The age at onset of Raynaud's phenomenon may also contribute in the assessment of the likelihood of some organ complications. Clearly both clinical and laboratory parameters must be combined and evaluated longitudinally in the prognostication of SSc. Although only in its initial phase, the EUSTAR MEDS data base contributes to the critical assessment of the current diagnostic and prognostic dogma. The long-term prospective data on this large and still growing number of patients will continue to facilitate the analysis of clinical patterns in SSc and allow rapid evaluation of new diagnostic tests and therapeutic strategies. Large scale co-operation is a necessary and powerful tool in the study of a rare disease like SSc

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## Legends

**Figure 1** Items of the Minimal Essential Data Set (MEDS).

**Figure 2**. Age distribution of scleroderma subsets

**Table 1**. Prevalence of disease presentation among clinical scleroderma subsets. Abbreviations: ACA, anticentromere autoantibody; DLCO; Diffusion capacity of the Lung for Carbon Monoxide; LVEF, left ventricular ejection fraction; mRSS, modified Rodnan Skin Score; PAH, pulmonary artery hypertension assessed by echocardiography; RO, Onset of Raynaud's phenomenon; SD, standard deviation. * Disease duration was calculated on the basis of the onset of the first Non-Raynaud´s feature.

**Table 2.**Gender specific variations among SSc subsets.

**Table 3.** Prevalence of disease presentation according to the onset of Raynaud's phenomenon. Manifestations with statistically similar prevalence between early and late onset are not shown. For abbreviations refer to Table 1

**Table 4.** Prevalence of disease presentation according to autoantibody serology. For abbreviations refer to Table 1

**Table 5.** Independent predictors of disease presentation. The variables are calculated by multivariate logistic regression and ranked in columns 1, 2 and 3 according to the magnitude of their explanatory effect ("1" being the strongest predictor). Variables discarded from the model are not listed. Details are described in the Methods. Abbreviations: Late and early RO, age at onset of Raynaud's phenomenon above and below the mean age of all patients.

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| Table 1 | DcSSc | LcSSc | P Dc vs. LcSSC | Other | Missing data |
|---|---|---|---|---|---|
| ACR criteria fulfilled | 100% | 100% | NA | 100% | 0% |
| Number of patients | 1,349 (36.9%) | 2,101 (57.5%) | <0.001 | 206 (5.6%) | 0% |
| Female | 81.1% | 90.9% | <0.001 | 86.9% | 0.4% |
| Age (mean years ± SD) | 52.3 (± 13.7) | 57.4 (± 13.1) | <0.001 | 52.7 (± 13.9) | 0.4% |
| Age at RO (mean years ± SD) | 42.9 (± 14.7) | 42.9 (± 14.5) | 0.98 | 40.6 (± 14.3) | 11.2% |
| Age at first non-RO (mean years ± SD) | 44.8 (± 14.2) | 47.9 (± 13.4) | <0.001 | 43.8 (± 14.0) | 10.4% |
| Disease duration * (mean years ± SD) | 7.4 (± 6.9) | 9.6 (± 8.1) | <0.001 | 9.0 (± 7.5) | 10.7% |
| Time between RO and first non-RO (mean years ± SD) | 1.9 (± 5.4) | 4.8 (± 8.5) | <0.001 | 3.2 (± 7.3) | 12.2% |
| ANA positive | 92.1% | 91.3% | 0.19 | 89.3% | 0.8% |
| Scl70 positive | 60.8% | 23.4% | <0.001 | 26.1% | 3.4% |
| ACA positive | 6.0% | 46.7% | <0.001 | 21.4% | 4.4% |
| mRSS (mean ± SD) | 19.0 (± 10.0) | 8.1 (± 5.3) | <0.001 | 6.4 (± 6.6) | 3.0% |
| Active disease | 49.8% | 21.5% | <0.001 | 28.2% | 3.5% |
| Elevated acute phase reactants | 41.8% | 24.6% | <0.001 | 34.5% | 1.8% |
| Raynaud's phenomenon | 96.1% | 95.9% | 0.58 | 92.7% | 0.1% |
| Digital ulcers | 42.7% | 32.9% | <0.001 | 22.3% | 0.3% |
| Synovitis | 20.8% | 13.7% | <0.001 | 21.4% | 0.4% |
| Joint contractures (any joint) | 47.1% | 24.4% | <0.001 | 29.1% | 0.6% |
| Tendon friction rubs | 22.1% | 7.4% | <0.001 | 8.3% | 0.9% |
| Muscle weakness | 37.1% | 22.8% | <0.001 | 36.4% | 0.4% |
| Muscle atrophy | 21.1% | 10.8% | <0.001 | 20.9% | 1.1% |
| CK elevation | 11.3% | 4.4% | <0.001 | 12.1% | 2.8% |
| Oesophagus | 68.2% | 66.8% | 0.38 | 68.0% | 0.3% |
| Stomach | 26.6% | 22.8% | 0.04 | 21.8% | 0.7% |
| Intestine | 22.5% | 21.7% | 0.68 | 19.4% | 0.7% |
| Pulmonary fibrosis | 53.4% | 34.7% | <0.001 | 44.2% | 2.2% |
| Lung restrictive defect | 49.3% | 26.7% | <0.001 | 32.0% | 2.4% |
| % of predicted DLCO (mean ± SD) | 64.0 (± 20.7) | 71.8 (± 21.0) | <0.001 | 71.6 (± 19.5) | 62.5% |
| PAH | 22.3% | 20.5% | 0.32 | 18.9% | 2.5% |
| - PAH without fibrosis | 5.9% | 9.2% | <0.001 | 5.8% | 2.5% |
| - PAH with fibrosis | 15.8% | 11.0% | <0.001 | 12.6% | 3.9% |
| Dyspnoea | 44.9% | 34.0% | <0.001 | 37.4% | 0.2% |
| Palpitations | 27.3% | 22.6% | 0.003 | 31.6% | 0.5% |
| Conduction block | 12.7% | 10.4% | 0.12 | 9.7% | 1.9% |
| Diastolic dysfunction | 16.6% | 15.4% | 0.42 | 15.0% | 2.3% |
| LEVF | 7.2% | 5.0% | 0.59 | 2.4% | 3.2% |
| Hypertension | 19.3% | 18.6% | 0.46 | 15.5% | 0.3% |
| Hypertensive renal crisis | 4.2% | 1.1% | <0.001 | 1.9% | 0.4% |
| Proteinuria | 9.2% | 3.7% | <0.001 | 10.2% | 1.5% |

| **Table 2** | **DcSSc** | | **P** | **LcSSc** | | **P** |
|---|---|---|---|---|---|---|
| | **Male** | **Female** | **(♂ vs. ♀)** | **Male** | **Female** | **(♂ vs. ♀)** |
| Number of patients | 254 | 1094 | NA | 180 | 1910 | NA |
| Age (mean years ± SD) | 52.7 ± 12.6 | 52.3 ± 14.0 | 0.66 | 56.2 ± 13.2 | 57.5 ± 13.0 | 0.21 |
| Age at RO (mean years ± SD) | 46.4 ± 13.4 | 42.1 ± 14.9 | <0.001 | 47.1 ± 14.9 | 42.5 ± 14.4 | <0.001 |
| Age at first non-RO (mean years ± SD) | 47.6 ± 13.1 | 44.1 ± 14.3 | 0.001 | 49.0 ± 14.1 | 47.8 ± 13.3 | 0.26 |
| Disease duration (mean years ± SD) | 5.1 ± 5.0 | 7.9 ± 7.2 | <0.001 | 6.7 ± 5.7 | 9.8 ± 8.2 | <0.001 |
| Time between RO and first non-RO (mean years ± SD) | 1.4 ± 4.7 | 2.0 ± 5.6 | 0.10 | 2.0 ± 5.2 | 5.1 ± 8.7 | <0.001 |
| ANA positive | 93.7% | 93.0% | 0.71 | 92.7% | 91.8% | 0.67 |
| Scl-70 positive | 62.7% | 60.4% | 0.51 | 31.3% | 22.8% | 0.02 |
| ACA positive | 4.3% | 7.0% | 0.08 | 26.3% | 50.3% | <0.001 |

| **Table 3** | **DcSSc** | | **P (early vs. late)** | **LcSSc** | | **P (early vs. late)** |
|---|---|---|---|---|---|---|
| | **Early Raynaud** | **Late Raynaud** | | **Early Raynaud** | **Late Raynaud** | |
| Number of patients | 553 | 594 | NA | 914 | 1003 | NA |
| Age (mean years ± SD) | 42.8 ± 11.9 | 60.9 ± 8.5 | <0.001 | 49.9 ± 12.9 | 64.1 ± 8.6 | <0.001 |
| Female | 84.6% | 77.9% | 0.004 | 93.1% | 89.4% | 0.004 |
| ANA positive | 93.8% | 93.4% | 0.76 | 92.5% | 91.6% | 0.46 |
| Scl70 positive | 63.2% | 60.0% | 0.26 | 25.5% | 21.5% | 0.04 |
| ACA positive | 5.5% | 6.6% | 0.45 | 46.5% | 49.6% | 0.18 |
| mRSS (mean years ± SD) | 18.7 ± 9.4 | 19.5 ± 10.4 | 0.18 | 8.1 ± 5.2 | 8.0 ± 5.2 | 0.66 |
| Active disease | 43.8% | 52.7% | 0.005 | 18.1% | 21.9% | 0.05 |
| Elevated acute phase reactants | 37.3% | 44.3% | 0.02 | 21.8% | 26.3% | 0.03 |
| Digital ulcers | 50.8% | 35.2% | <0.001 | 38.8% | 27.9% | <0.001 |
| Muscle weakness | 32.7% | 39.2% | 0.02 | 21.0% | 22.5% | 0.43 |
| Pulmonary fibrosis | 47.4% | 59.4% | <0.001 | 31.8% | 37.2% | 0.02 |
| Lung restrictive defect | 47.9% | 50.3% | 0.26 | 24.1% | 29.2% | 0.009 |
| PAH | 17.7% | 26.3% | <0.001 | 16.8% | 23.4% | <0.001 |
| Dyspnoea | 37.8% | 52.2% | <0.001 | 31.3% | 37.0% | 0.008 |
| Palpitations | 23.5% | 30.3% | 0.006 | 20.6% | 23.6% | 0.07 |
| Conduction block | 11.4% | 13.5% | 0.18 | 9.0% | 12.2% | 0.01 |
| Diastolic dysfunction | 11.9% | 20.7% | <0.001 | 12.2% | 18.6% | <0.001 |
| Hypertension | 11.6% | 23.9% | <0.001 | 12.9% | 22.0% | <0.001 |

| **Table 4** | **ANA positive** | **Scl70 positive** | **ACA positive** | **P** (Scl70 vs. ACA) |
|---|---|---|---|---|
| Number of patients | 3346 | 1330 | 1106 | <0.001 |
| Presenting as dcSSC | 37.1% | 60.0% | 7.3% | <0.001 |
| Presenting as lcSSC | 57.4% | 36.1% | 88.7% | <0.001 |
| Presenting as "other" | 5.5% | 3.9% | 4.0% | 0.88 |
| Female | 87.3% | 83.7% | 94.4% | <0.001 |
| Age (mean years ± SD) | 55.1 ± 13.6 | 52.6 ± 13.7 | 59.6 ± 11.8 | <0.001 |
| Age at RO (mean years ± SD) | 42.7 ± 14.6 | 42.2 ± 14.4 | 43.4 ± 14.7 | 0.28 |
| Age at first non-RO (mean years ± SD) | 46.4 ± 13.8 | 44.5 ± 14.0 | 50.0 ± 12.6 | <0.001 |
| Time between RO and non-RO (mean years ± SD) | 3.7 ± 7.6 | 2.4 ± 5.6 | 6.5 ± 10.0 | <0.001 |
| mRSS (mean years ± SD) | 12.0 ± 9.1 | 15.1 ± 9.9 | 8.2 ± 5.9 | <0.001 |
| Active disease | 32.7% | 45.2% | 18.9% | <0.001 |
| Elevated acute phase reactants | 31.9% | 42.6% | 20.7% | <0.001 |
| Raynaud's phenomenon | 96.3% | 97.4% | 96.7% | 0.45 |
| Digital ulcers | 36.7% | 44.8% | 31.2% | <0.001 |
| Synovitis | 16.7% | 21.4% | 11.9% | <0.001 |
| Joint contractures (any joint) | 33.7% | 44.5% | 17.6% | <0.001 |
| Tendon friction rubs | 13.1% | 18.9% | 6.0% | <0.001 |
| Muscle weakness | 28.4% | 32.2% | 22.7% | <0.001 |
| Muscle atrophy | 14.6% | 16.1% | 9.5% | <0.001 |
| CK elevation | 7.6% | 8.7% | 2.9% | <0.001 |
| Oesophagus | 67.9% | 68.0% | 70.7% | 0.18 |
| Stomach | 24.5% | 24.1% | 26.9% | 0.11 |
| Intestine | 22.5% | 20.7% | 25.1% | 0.01 |
| Pulmonary fibrosis | 42.6% | 60.2% | 21.3% | <0.001 |
| Lung restrictive defect | 35.8% | 50.3% | 17.4% | <0.001 |
| % of predicted DLCO (mean ± SD) | 68.9 ± 21.6 | 65.1 ± 20.9 | 75.0 ± 20.9 | <0.001 |
| PAH | 21.1% | 23.2% | 22.0% | 0.36 |
| - PAH without fibrosis | 8.0% | 5.0% | 13.0% | <0.001 |
| - PAH with fibrosis | 12.7% | 17.2% | 8.0% | <0.001 |
| Dyspnoea | 38.6% | 44.5% | 29.4% | <0.001 |
| Palpitations | 24.8% | 27.2% | 23.2% | 0.01 |
| Conduction block | 11.2% | 13.6% | 9.1% | <0.001 |
| Diastolic dysfunction | 15.7% | 17.7% | 12.7% | 0.001 |
| Reduced LVEF | 5.7% | 5.9% | 5.2% | 0.29 |
| Hypertension | 18.5% | 14.4% | 20.0% | <0.001 |
| Hypertensive renal crisis | 2.3% | 2.0% | 1.3% | 0.15 |
| Proteinuria | 6.0% | 7.8% | 2.7% | <0.001 |

| **Table 5** | **1** | **2** | **3** |
|---|---|---|---|
| mRSS above mean | dcSSc | | |
| Active disease | dcSSc | ACA-negative | |
| Elevated acute phase reactants | Not lcSSc | Scl70-positive | |
| Digital ulcers | Scl70-positive | Early RO | |
| Synovitis | ACA-negative | | |
| Joint contractures (any joint) | DcSSc | ACA-negative | |
| Tendon friction rubs | DcSSc | ACA-negative | |
| Muscle weakness | Not lcSSc | | |
| Muscle atrophy | Not lcSSc | | |
| CK elevation | Not lcSSc | ACA-negative | |
| Oesophagus | None | | |
| Stomach | None | | |
| Intestine | None | | |
| Pulmonary fibrosis | Scl70-positive | ACA-negative | Late RO |
| Lung restrictive defect | dcSSc | Scl70-positive | ACA-negative |
| DLCO above mean | ACA-positive | | |
| PAH | Late RO | | |
| - PAH without fibrosis | ACA | | |
| - PAH with fibrosis | Scl70-positive | ACA-negative | |
| Dyspnoea | ACA-negative | Late RO | |
| Palpitations | None | | |
| Conduction block | None | | |
| Diastolic dysfunction | Late RO | | |
| LEVF | None | | |
| Hypertension | Scl70-negative | Late RO | |
| Hypertensive renal crisis | DcSSc | Scl70-negative | |
| Proteinuria | Not lcSSc | | |

# EUSTAR - MINIMAL ESSENTIAL DATA SET 1

Unique center N° .....

Unique patient N° .....

Date of birth (day/month/year) .....

Sex ..... male female

Onset of Raynaud ..... month year

Onset of first non - Raynaud feature of disease ..... month year

ACR Criteria fulfilled (yes / no) ..... yes no

Subset ..... diff. cut. SSc lim. cut. SSc other

| | yes | no | | yes | no |
|---|---|---|---|---|---|
| ANA positive ..... | | | Elevated acute phase reactants ..... | | |
| ACA positive ..... | | | Proteinuria (+ or more) ..... | | |
| Scl 70 positive ..... | | | Active disease * | | |

*Cross "yes" if activity score ≥ 3 according to attachment " EULAR Systemic Sclerosis Activity Score"

Date of filling out this form .....

*Complete only in case of death:* .....Date of death

| | yes | no | | yes | no | | yes | no |
|---|---|---|---|---|---|---|---|---|
| Death due to SSc | | | Death due to treatment | | | Death due to other | | |

# EUSTAR - MINIMAL ESSENTIAL DATA SET 2

Unique center N° ☐☐☐ Unique patient N° ☐☐☐☐ Date of birth ☐☐☐☐☐☐☐☐

WEIGHT (Kg – e.g. 68.4) ----------

SKIN Mod. Rodnan (max. 51)----------

| | | yes | no |
|---|---|---|---|
| VASCULAR | Raynauds ---------- | | |
| | Digital ulcers ---------- | | |
| JOINTS | Synovitis ---------- | | |
| | Joint contractures ---------- | | |
| TENDONS | Friction rubs ---------- | | |
| MUSCLES | C.K. elevation ---------- | | |
| | Weakness ---------- | | |
| | Atrophy ---------- | | |
| G.I.T. | Esophageal (dysphagia, reflux)---------- | | |
| | Stomach (early satiety, vomiting) ---------- | | |
| | Intestinal (diarrhea, bloating, constip.)---------- | | |
| RENAL | Hypertension ---------- | | |
| | Renal crisis ---------- | | |
| Cardio- | Dyspnoea (significant)---------- | | |
| Pulmonary | Palpitations ---------- | | |
| | Conduction blocks ---------- | | |
| | Diastolic function abnormal ---------- | | |
| | Reduced ventricular ejection fraction ---------- | | |
| | Fibrosis - plain X-ray ---------- | | |
| | Restrictive defect (lung function test) ---------- | | |
| | Pulmonary hypertension (ECHO)---------- | | |

DLCO (% predicted) ----------

COMMENTS

Fig. 2