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**Title:** Can patient-reported symptoms be used to measure disease activity in systemic sclerosis?

**Running Head:** SSc patient assessment of disease activity

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**Conflict of interest:**

Professor Murray Baron and A/Professor Mandana Nikpour are co-chairs of the Scleroderma Clinical Trials Consortium Activity Index Working Group.

**Abstract**

*Objective:*

To evaluate the association between patient-reported symptoms and changes in disease activity over time in systemic sclerosis (SSc).

*Methods:*

Using data from 1,636 patients enrolled in the Australian Scleroderma Cohort Study, we used generalised estimating equations to determine the relationship between patient-reported worsening of Raynaud phenomenon (RP), skin involvement and breathlessness in the month preceding each study visit and features of disease activity in the corresponding organ systems. The associations between the following parameters were analysed: patient-reported worsening RP and the presence of new-onset digital pitting and digital ulcers; patient-reported worsening skin involvement and increasing modified Rodnan skin score (mRSS), new areas of skin involvement and new-onset joint contractures; patient-reported worsening breathlessness and deteriorating respiratory functions tests (RFTs), indicated by 10% decrease in forced vital capacity (FVC) and 15% decrease in diffusing capacity of carbon monoxide (DLCO), new-onset interstitial lung disease (ILD) and new-onset pulmonary arterial hypertension (PAH).

*Results:*

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We found a significant association between patient-reported worsening RP and the presence of digital ulcers (OR 1.53; 95%CI:0.60-0.93); patient-reported worsening skin involvement and increasing mRSS (OR 2.10; 95%CI:1.54-2.86); and worsening patient breathlessness and deteriorating RFTs (FVC OR 2.12; 95%CI:1.70-2.65; DLCO OR 1.97; 95%CI:1.34-2.02), new-onset ILD (OR 1.91; 95%CI:1.40-2.61) and new-onset PAH (OR 5.08; 95%CI:3.59-7.19).

*Conclusion:*

These results demonstrate that patient-reported symptoms are associated with clinically meaningful changes in disease activity in SSc patients. This suggests that when objective measures of change in disease status are unavailable, patient-reported symptoms could be used to indicate a change in SSc-disease activity.

**Significance and Innovations:**

- Many organ systems involved in systemic sclerosis (SSc) lack validated biomarkers or objective measures of disease activity. Patient-reported symptoms could potentially be used to quantify disease activity in multi-system outcome measures. However, the relationship between patient-reported symptoms and objective features of SSc-disease activity is unknown.
- In this large cohort study, we found significant associations between patient-reported worsening of Raynaud phenomenon (RP), skin involvement and breathlessness, and clinical worsening in vascular, cutaneous and respiratory manifestations of disease, respectively.
- The results of this study indicate that patient-reported symptoms may be used to indicate SSc-disease activity when objective measures of disease are not available.

**Key words:**

Systemic sclerosis, patient-reported outcomes, symptoms, disease activity

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Quantifying disease activity in systemic sclerosis (SSc) remains challenging due to the complex aetiopathogenesis of the disease and a disease course that lacks clear clinical relapses and validated measures of various aspects of disease activity.(1) These factors and the episodic nature of certain disease manifestations mean evaluating disease status is often reliant upon patient-reported symptoms.(2)

To overcome the lack of objective measures of disease status in all organ systems, previously published multi-system outcome measures have included patient-reported assessments (see Table 1). The European Scleroderma Trials and Research Group (EUSTAR) disease activity indices have included patient-reported skin, vascular and cardiopulmonary symptoms(3,4). The provisional American College of Rheumatology (ACR) Composite Response Index for Clinical Trials in Early Diffuse Cutaneous SSc (ACR-CRISS) includes a patient global assessment of improvement following an intervention.(5) Patient-reported symptoms can evaluate disease status in organ systems where objective measures of disease activity are not available and can potentially be useful when assessing a patient for the first time when there are no previous assessments available.

The Scleroderma Clinical Trials Consortium (SCTC) is currently developing a new multi-system disease activity index for SSc.(1) Organ-specific disease activity will likely be measured by changes over time in either physical examination findings or investigation results. However, there are times when objective measures are not available, e.g. at a first clinical visit or when scheduled tests have been missed. To overcome this issue, the role of patient-reported symptoms in measuring disease activity has been considered.

Raynaud phenomenon (RP) is the most common vascular manifestation of SSc and is stereotypically episodic, meaning clinical assessment of this disease feature is dependent upon patient-reported outcomes.(2) Previous studies have demonstrated that patient assessment of the overall impact of RP on daily activities is associated with the presence of digital ulcers.(6,7) Yet, studies that have evaluated the nature of patients' RP have demonstrated a lack of association with RP pattern and clinical outcome, suggesting there may be limits to the use of patient-reported RP as a measure of disease activity.(8) Potentially limiting the utility of patient-assessed RP as a marker of disease activity is the

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marked response shift of RP symptoms associated with increasing SSc-disease duration. The longer a patient has lived with RP, the better they are able to manage their symptoms and therefore they generally report a less severe impact of RP symptoms.(2,8)

The modified Rodnan skin score (mRSS) is a commonly used primary end point in clinical trials. The mRSS has been shown to be correlated with patient-reported tight, hard, rigid or stiff skin, yet studies have reported variable associations between patient-reported skin symptoms and mRSS.(9) This may, in part, be explained by the fact that the mRSS measures skin thickness and the area of skin involved but it does not evaluate the physical symptoms and functional limitations of skin tightness as well as the emotional and social effects of SSc skin involvement. These are of importance to patients and have been found to be included by patients in their self-assessment of SSc skin disease.(10) This lack of specificity of patient-assessed skin involvement to the change in the extent of skin thickening and disease activity suggest that patient-reported skin symptoms may have a limited role in the assessment of SSc-disease activity.

Dyspnoea has been identified by both physicians and patients as an important domain to consider in the measurement of disease activity and treatment response in connective tissue disease-associated interstitial lung disease (ILD).(11) Patient-reported breathlessness is of prognostic significance in idiopathic pulmonary fibrosis(12) and an independent predictor of death from cardiac causes(13). Studies of pulmonary arterial hypertension (PAH) therapies have shown that breathlessness, measured by WHO functional class, improves or stabilises with therapy.(13) However, there is no consistent evidence that patient-reported dyspnoea correlates with change in physiological parameters of lung function in ILD, and no evidence as to the association between breathlessness and abnormal haemodynamics in PAH.(12,13) Measuring patient-reported breathlessness is an evaluation of a complex interplay of many processes. The influence of extra-pulmonary factors such as cardiac function, skeletal muscle conditioning and/or concurrent muscle disease, obesity, iron deficiency and anxiety all contribute to breathlessness and is particularly pertinent in a multi-system condition such as SSc.(13)

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The aim of this study was to assess whether there is a relationship between worsening symptoms reported by patients, specifically RP, skin involvement and shortness of breath, and objective measures of SSc-disease activity in the vascular, cutaneous and pulmonary systems. Our hypothesis was that patient-reported symptoms could act as a surrogate for objective changes in these organ systems and thus may be useful in a composite disease activity index when changes in objective data are missing.

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**Patient and Methods**

*Patients*

Patients included in this study were enrolled in the Australian Scleroderma Cohort Study (ASCS). The ASCS is a prospective multi-centre cohort study of risk and prognostic factors in SSc. Consecutive patients were recruited from Australian centres specialising in the care of SSc (St Vincent's Hospital, Melbourne and Monash Health, Victoria; Royal Adelaide Hospital and The Queen Elizabeth Hospital, South Australia; Fiona Stanley Hospital, Western Australia; Royal Prince Alfred Hospital, St George Hospital, Royal North Shore Hospital, Liverpool Hospital, John Hunter Hospital, New South Wales; Canberra Hospital, Australian Capital Territory; Sunshine Coast Rheumatology and Prince Charles Hospital, Queensland; Royal Hobart Hospital, Tasmania). Patient data were collected annually at a clinical review in an ambulatory care setting. Data collected included clinical history and examination, investigations including blood testing, transthoracic echocardiogram (TTE) and respiratory function tests (RFTs), and assessment of health-related quality of life. The ASCS is carried out in accordance with the *National Statement on Ethical Conduct in Research Involving Humans (May 2015)*. Human research ethics committees at each participating centre approved the study.

All adult patients, aged $\geq$ 18 years, recruited to the ASCS between January 2007 and October 2018, who fulfilled the 2013 ACR / European League Against Rheumatism (EULAR) Classification Criteria for SSc(14) and had data available to define a disease subtype as per LeRoy criteria(15) were included in this study. Written informed consent was obtained from all patients prior to the collection of data.

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*Data collection*

Demographic data, including age, sex and race, and disease-related data were collected prospectively according to a standardised protocol. Autoantibodies were defined as present if ever recorded during follow-up. Disease duration was defined from date of onset of the first non-Raynaud manifestation.

At each visit, patients were asked the following questions (answered yes/no) in regard to their symptoms of SSc: Has your RP been worse in the past month? Has your skin been worse in the past month? Have you been more breathless in the past month? The association between worsening patient-reported RP and the presence of digital ulcers on examination and new digital pitting was evaluated. Patient-reported worsening of skin disease was compared to worsening mRSS(16), new areas of skin involvement and new-onset joint contractures between study visits. The associations between patient-reported worsening breathlessness and deteriorating respiratory function tests (RFTs), new-onset PAH, new-onset ILD and new-onset left ventricular systolic dysfunction, were evaluated. These clinical features were selected as measures of disease activity as they corresponded to items nominated by the SCTC Activity Index Working Group via a Delphi exercise as appropriate measures of activity in each organ system. The SCTC Activity Index Working Group includes 37 rheumatologists and 1 dermatologist who have a special interest in the clinical management and research of SSc. The group was convened for the purpose of developing a multi-system disease activity index using a combination of consensus and data-driven methods. Potential items for inclusion in the activity index have been generated by the working group using the following steps: (1) Two-round survey and face-to-face meeting to define the construct of disease activity; (2) Two-round survey to identify the domains of SSc-disease activity to be included in the activity index; (3) A systematic review of existing measures of disease status in SSc(17) and a two-round survey and face-to-face meeting to identify potential items to measure disease activity within each domain of SSc-disease activity. Consensus for inclusion of a particular disease domain or measure of disease activity was reached when at least 70% agreement among respondents was achieved.

The mRSS(16) was calculated at annual study visit. Worsening skin disease was defined as an increase in mRSS of $>5$ points between study visits, as this cut off has been previously

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used to define a significant worsening of skin fibrosis(18), in keeping with the minimal clinically important difference in mRSS(19). New areas of skin involvement were considered present when a patient was recorded as having an increase in mRSS from 0 to a score of 1, 2 or 3 in a given skin assessment area between study visits. The presence of digital pitting, digital ulcers, and joint contractures was based on physician assessment at a study visit. New-onset digital pitting and new-onset joint contractures were considered present if no digital pitting or joint contracture was recorded on examination at the preceding study visit.

RFTs of interest were forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide corrected for haemoglobin (DLCO), recorded as percent predicted. Deteriorating RFTs were defined as a 10% decrease in FVC or 15% decrease in DLCO between visits, as these cut offs have been identified as poor prognostic markers and shown to identify patients at high risk of progression of ILD(20). ILD was defined by the presence of typical findings of pulmonary fibrosis on high resolution computed tomography (HRCT) of the chest. Patients were referred for an HRCT if ILD was suspected on the basis of abnormal RFTs or abnormal respiratory system examination. PAH was defined by a mean pulmonary artery pressure $\geq$ 25mmHg and pulmonary arterial wedge pressure $\leq$ 15mmHg on right heart catheterisation (RHC). Patients were referred for RHC if PAH was suspected on the basis of a systolic pulmonary artery pressure $\geq$ 40mmHg on TTE or DLCO <50% predicted, with preserved lung volumes (FVC >70%). Only patients with new-onset ILD or PAH were included in the analyses evaluating the association between breathlessness and ILD and PAH. Patients who had pre-existing ILD or PAH at enrolment to the ASCS were excluded from these analyses.

New-onset left ventricular systolic dysfunction was considered present if a patient had a left ventricular ejection fraction (LVEF) <50% on TTE for the first time, when previous TTE results had shown LVEF >50%.

*Statistical analysis*

Data are presented as number (percentage) for categorical variables and mean (±standard deviation) for continuous variables.

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The chi-square test was used to evaluate the association between patient-reported worsening of specific symptoms in the month preceding the study visit and features of disease activity assessed either by the clinician or clinical investigations in the corresponding organ system, recorded at the time of each annual study visit.

For variables found to be significantly associated by chi-square testing, generalised estimating equations (GEE) were used for further analysis of visits wherein all relevant data had been recorded to quantify these associations and to account for the expected correlation that arises when repeated measurements are taken from the same individual at multiple visits over time. A sub-group analysis was performed in patients who were recruited to ASCS within 2-years of disease onset.

All statistical analyses were performed using STATA 14.2 software (StataCorp, College Station, TX, USA).

**Results**

There were 1,636 patients enrolled in this study. Patients had a mean age of 57.37±12.56 years and a mean disease duration of 11.07±10.51 years at recruitment. Patients were followed for a mean 3.99±3.31 years with a mean 1.12 years between each study visit. Eighty-six percent of patients were female and 25.73% of patients had diffuse cutaneous SSc. Two hundred and seventy-six patients (16.86%) were recruited within 2-years of disease onset. The disease characteristics of the study population are detailed in Table 2.

Of the total 1,636 patients, 221 (13.51%) and 878 (53.67%) recorded a greater than 5-point increase in mRSS and a new area of skin involvement respectively throughout the study. Two hundred and eighty (17.11%) patients developed a new joint contracture during the study. In regard to development of vascular manifestations of SSc during the study, 433 (26.47%) patients developed new digital pitting and 530 (32.40%) had a digital ulcer present at the time of clinical review. Three hundred and sixteen (19.32%) patients experienced a decrease of $\geq$ 10% in FVC and 316 (19.32%) patients experienced a decrease of $\geq$ 15% of DLCO between study visits. Two hundred and fourteen (13.08%) patients were newly

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diagnosed with ILD during the study and 143 (8.74%) patients were newly diagnosed with PAH. Seventy-one (4.34%) patients had new onset left ventricular systolic dysfunction.

From a total of 7,067 study visits, data regarding patient-reported symptoms were available from 89.9% of study visits. Overall, 855 (52.26%) patients reported worsening RP, 659 (40.28%) patients reported worsening breathlessness and 604 (36.92%) patients reported worsening skin involvement in the month preceding clinical assessment at any time during the study.

*Chi-square testing*

Patient-reported worsening of RP was associated with digital ulcers on examination (chi square p=0.01) and new-onset digital pitting (p<0.01). Patient-reported worsening of skin involvement was associated with worsening mRSS (p<0.01) but was not associated with new areas of skin involvement (p=0.92) or new-onset joint contractures (p=0.80). Worsening patient-reported breathlessness was associated with a 10% decrease in FVC, 15% decrease in DLCO, new-onset ILD and new-onset PAH (p<0.01). Patient-reported breathlessness was not associated with new-onset LVEF<50% (p=0.60).

*Generalised estimating equation analysis*

The results of the GEE analysis are presented in Table 3. In summary, worsening RP was associated with the presence of digital ulcers (OR 1.53; 95%CI:1.34-1.74, p<0.01), symptoms of worsening skin involvement were associated with worsening mRSS (OR 2.10; 95%CI:1.54-2.86, p<0.01) and worsening breathlessness was associated with deteriorating RFTs (FVC: OR 2.12; 95%CI:1.70-2.65, p<0.01; DLCO: OR 1.97; 95%CI:1.34-2.02, p<0.01), new-onset ILD (OR 1.91; 95%CI:1.40-2.61, p<0.01) and new-onset PAH (OR 5.08; 95%CI:3.59-7.19, p<0.01).

In GEE analysis performed in patients who were recruited within 2-years of disease onset, worsening symptoms of RP were associated with the presence of digital ulcers (OR 1.56; 95%CI:1.13-2.16, p=0.01) and patient-reported worsening of skin involvement was associated with worsening mRSS (OR 3.79; 95%CI:2.15-6.70, p<0.01). Patient-reported worsening breathlessness remained significantly associated with worsening FVC (OR 1.88; 95%CI:1.06-3.31, p=0.03) but was not significantly associated with worsening DLCO (OR

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1.49; 95%CI:0.81-2.75, p=0.20). New-onset ILD (OR 3.18; 95%CI:1.84-5.50, p<0.01) and new-onset PAH (OR 5.50; 95%CI:2.54-11.89, p<0.01) were significantly associated with patient-reported worsening breathlessness.

**Discussion**

Our study has shown that there are a number of associations between patient-reported symptoms and clinically meaningful changes in disease activity. Patients who reported a worsening of RP in the preceding month were 53% more like to have digital ulcers present on examination, suggesting that patients' reporting of their RP symptoms can be a valuable item to assess vascular disease activity in SSc. This is consistent with the results of a clinical trial of oral iloprost for treatment of severe RP in which patient assessment of RP activity was found to be higher in patients with digital ulcers.(6) Importantly, in this cohort of patients who have long-standing disease, despite the response shift generally associated with RP in SSc, patient-reported worsening of RP symptoms could still distinguish active vascular disease to a degree comparable to patients with recent-onset SSc. Therefore, whilst the patient-reported severity of RP may diminish over time, this study indicates patients are still able to identify times when their RP is active throughout the course of their disease.

Patient-reported worsening skin involvement is associated with a 2-fold increased risk of worsening skin disease, measured by the mRSS. The strength of this association suggests that patient-reported worsening of skin disease in the preceding month is a good indicator of progressive skin involvement. The assessment of disease activity at the first clinical review, or when there has been a significant period of time between reviews, presents a challenge. A significant limitation of using the mRSS to assess skin disease is that if there is no prior assessment, the clinician is unable to ascertain whether a skin score represents disease activity or disease damage that is not potentially reversible with treatment. These findings suggest that ascertaining the patient's assessment of change in skin disease can distinguish between active progressive skin involvement and long-standing skin thickening and can be a useful adjunct to the mRSS in the clinical assessment of patients.

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Despite the multi-factorial nature of the patient experience of breathlessness, there remains a strong relationship between patient-reported worsening breathlessness and clinically meaningful change in RFTs and pulmonary dysfunction in SSc. These results demonstrate that worsening breathlessness is strongly predictive of the development of PAH and ILD and in the absence of adequate biomarkers and objective measures of disease status, breathlessness may be an appropriate surrogate measure of disease activity. This is particularly true for PAH where in both recent onset and long standing SSc, patients reporting increased breathlessness in the month preceding assessment are five times more likely to be diagnosed with PAH.

There are limitations to patient-reported assessments of disease activity. Patient-reported symptoms include an evaluation of a range of factors including physical symptoms, limitations to both physical and social function, as well as the psychological impact of SSc.(10,11) The relative importance of the various factors influencing a patient assessment of worsening symptoms is likely to vary significantly between patients and this cannot be easily quantified in clinical studies. Also, there is the potential for under-reporting the burden or change in disease status with increasing SSc duration as patients adapt to their disease and particular symptomatology.(8) Of note, this study did not demonstrate a significant response shift across any of the domains of SSc evaluated, particularly when evaluating patient-reported symptoms of RP and the development of DU. Only an increasing mRSS and new-onset ILD were more strongly associated with patient-reported worsening symptoms in those with recent-onset compared with prevalent SSc. This is consistent with the natural history of SSc whereby skin disease and development of ILD are more likely to occur early in the disease course.(21)

Relying upon patient-assessed symptoms as a measure of disease activity may introduce a lack of specificity to an outcome measure as patient-reported symptoms are a reporting of the overall burden of a particular aspect of the disease rather than a measure of the specific construct of disease activity. This is illustrated by the fact that in this study patient-reported worsening dyspnoea was associated with both ILD and PAH, implying patient symptomatology cannot differentiate between these two disease processes. Disease activity refers to aspects of disease that are reversible or can be halted with either time or

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treatment, whereas disease damage is irreversible end-organ dysfunction that occurs as a result of unchecked disease activity. Patient symptoms can be a manifestation of either disease activity or damage, and it is unlikely that patients will be able to differentiate symptoms that are due to activity versus those that are the result of damage.

Despite these limitations of patient-reported symptoms, our study has demonstrated that across the vascular, cutaneous and pulmonary domains of SSc-disease, worsening of patient assessed symptoms is associated with objectively assessed, clinically meaningful signs of disease activity. A simple, dichotomous assessment by the patient of worsening RP, skin involvement and breathlessness in the month preceding assessment can be a valuable indicator of a change in disease activity in the corresponding organ system and a useful addition to a multi-system SSc-disease activity index.

This is the largest study to date to evaluate the association between patient-reported symptoms and manifestations of SSc-disease activity, and the longitudinal nature of the data analysed is a strength of this investigation. However, there are limitations to this study as it is a retrospective analysis of observational data. Patients had variable lengths of follow-up and many patients in this study cohort had long-standing disease at recruitment. Significant accrual of organ involvement occurs early in the disease course in SSc and these changes may not have been captured in this study. Also, patient data are collected at once-yearly reviews. This is a long interval between study visits and even though SSc can be a slowly evolving disease, significant activity may occur between study visits that is not captured by the scheduled annual review.

Due to the nature in which data are collected at each study visit, both the patient and the physician may not be blinded to investigation results when answering questionnaires or performing the clinical examination. This may lead to a bias of over-emphasising worsening change in symptoms or clinical signs if a deterioration in investigation results has been noted prior to patient assessment.

A further limitation is that patient symptoms are only reported as a dichotomous outcome. Various questions with different wordings used as external anchors have been previously

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used to assess patient symptoms and disease states.(22) There is currently no uniform, standardised method for assessing patient symptoms in SSc. Studies may ask patients to evaluate their symptoms or overall condition using visual analogue scales, Likert scales or dichotomous questions. Patient symptoms are assessed as dichotomous outcomes in the ASCS, in keeping with the methodology used by Valentini *et al.* to assess change in patient symptoms in the original EUSTAR Activity Index.(3) The value of a dichotomous outcome is that it forces respondents to provide a clear answer without the option of a neutral response and it can provide clinically meaningful results in studies. However, using a dichotomous outcome in clinical studies comes at the cost of a potential loss of statistical power.(22) This was demonstrated in an evaluation of patient assessed clinical states in the faSScinate trial where only patient-assessed symptoms on a 7-point Likert scale could significantly distinguish between the treatment and placebo arms of the trial. When patients assessed their clinical state using a dichotomous outcome, there was only a trend towards statistical significance in distinguishing between treatment and placebo groups.(23) In the present study, with a large patient population, we did find statistically significant results through assessing patient symptoms as a dichotomous outcome. The size of the patient population is likely to have overcome the statistical limitation of the dichotomous reporting of patient-assessed outcomes. Using a similar method of assessing patient symptoms in studies with smaller patient populations, such as in clinical trials, may result in insufficient power to demonstrate a statistically significant result.

In conclusion, we have found that patient-reported symptoms are associated with objective features of SSc activity. When serial data of objective measures of disease activity over time are not available patient-reported changes in skin and RP may be substituted for objective indicators of worsening disease activity. Whilst worsening dyspnoea lacks specificity for a particular disease process, the strong association of worsening breathlessness and clinically meaningful deterioration of RFTs and the new diagnosis of lung parenchymal and pulmonary vascular disease suggests it too has a role in the subjective assessment of SSc-disease activity.

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*Table 1: Multi-system outcome measures of disease status in systemic sclerosis*

| **2001 EUSTAR AI** | **2017 EUSTAR AI** | **ACR-CRISS** |
|---|---|---|
| Total skin score >20 | mRSS >18 or<br>mRSS x 0.084 if <18 | Patients who develop new or worsening cardiopulmonary or renal involvement not improved |
| Scleredema | Digital ulcers | mRSS |
| Patient-reported worsening skin symptoms* | Patient-reported worsening skin symptoms* | FVC (% predicted) |
| Digital necrosis | Tendon friction rub | HAQ DI |
| Patient-reported worsening vascular symptoms* | DLCO <70% predicted | PtGA of improvement |
| Arthritis | CRP >10mg/L | PhyGA of improvement |
| DLCO <80% predicted | | |
| Patient-reported worsening cardiopulmonary symptoms* | | |
| ESR >30mm/hr | | |
| Hypocomplementaemia | | |

*worsening in month preceding assessment

*Abbreviations: ACR-CRISS:* American College of Rheumatology Composite Response Index for Trials in Early Diffuse Cutaneous Systemic Sclerosis; AI: activity index; CRP: C-reactive protein; DLCO: diffusing capacity of the lung for carbon monoxide; ESR: erythrocyte sedimentation rate; EUSTAR: European Scleroderma Trials and Research Group; FVC: forced vital capacity; HAQ DI: Health Assessment Questionnaire Disability Index; mRSS: modified Rodnan skin score; PhyGA: physician global assessment; PtGA: patient global assessment

*Table 2: Study population characteristics*

| **Characteristic** |
|---|

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| | |
|---|---|
| Total patients | 1,636 |
| Female, *n (%)* | 1,409 (86.12) |
| Age at recruitment, mean (S.D.), years | 57.38 (12.56) |
| Disease duration[a] at recruitment, mean (S.D.), years | 11.07 (10.52) |
| Follow-up, mean (S.D.), years | 3.99 (3.31) |
| Race, *n (%)* | |
| - Caucasian | 1,447 (88.45) |
| - Asian | 70 (4.28) |
| - Aboriginal or Torres Strait Islander | 17 (1.04) |
| - Hispanic | 11 (0.67) |
| - Other | 19 (1.16) |
| SSc subtype, *n (%)* | |
| - lcSSc | 1,215 (74.27%) |
| - dcSSc | 421 (25.73%) |
| Serology, *n (%)* | |
| - ANA centromere pattern | 763 (48.41) |
| - Scl-70 positive | 242 (15.59) |
| - RNA polymerase III positive | 145 (13.80)[b] |
| Clinical manifestations[c] | |
| - Raynaud phenomenon | 1,554 (95.81) |
| - Digital ulcers | 882 (54.44) |
| - Interstitial lung disease | 427 (26.10) |
| - Cardiac involvement | 124 (7.58) |
| - Pulmonary arterial hypertension | 181 (11.06) |
| - Scleroderma renal crisis | 45 (2.75) |
| - Gastrointestinal involvement | 1,404 (85.82) |

[a] Disease duration defined by time since onset of first non-Raynaud disease manifestation

[b] RNA polymerase III antibody % calculated from 1,051 patients who have had testing. This test is not available at all Australian Scleroderma Cohort Study sites.

[c] Clinical manifestations defined as present if ever recorded during follow-up. Interstitial lung disease was defined by the presence of characteristic findings on high-resolution CT scan of the chest; Cardiac involvement was defined by positive endomyocardial biopsy or cardiac magnetic resonance imaging for systemic sclerosis cardiac involvement or arrhythmia, conduction defect or ventricular systolic or diastolic dysfunction

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attributable to systemic sclerosis as assessed by the treating physician; Pulmonary arterial hypertension was defined by mean pulmonary artery pressure of ≥ 25mmHg and pulmonary arterial wedge pressure of ≤ 15mmHg on right heart catheterisation; Scleroderma renal crisis was defined by presence of at least two of new-onset hypertension, microangiopathic anaemia or rising serum creatinine; Gastrointestinal involvement included the presence of any of the following: gastro-oesophageal reflux, oesophageal stricture, gastric antral vascular ectasia, bowel dysmotility or faecal incontinence.

*Abbreviations:* ANA: anti-nuclear antibody; dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; Scl-70: anti-scleroderma-70 antibodies; S.D.: standard deviation; SSc: systemic sclerosis

*Table 3: Association between patient-reported symptoms and manifestations of systemic sclerosis*

| | Odds ratio (95% CI) | p value |
|---|---|---|
| *Patient-reported Raynaud phenomenon* | | |
| New-onset digital pitting | 0.75 (0.60-0.93) | 0.01 |
| Digital ulcers | 1.53 (1.34-1.74) | <0.01 |
| *Patient-reported skin worsening* | | |
| Worsening mRSS | 2.10 (1.54-2.86) | <0.01 |
| *Patient-reported breathlessness* | | |
| 10% decrease in FVC | 2.12 (1.70-2.65) | <0.01 |
| 15% decrease in DLCO | 1.65 (1.34-2.02) | <0.01 |
| New-onset ILD | 1.91 (1.40-2.61) | <0.01 |
| New-onset PAH | 5.08 (3.59-7.19) | <0.01 |

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*Abbreviations:* CI: confidence interval; DLCO: diffuse capacity of the lung for carbon monoxide; FVC: forced vital capacity; ILD: interstitial lung disease; mRSS: modified Rodnan skin score; PAH: pulmonary arterial hypertension

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