Development and Validation of the Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI): a novel instrument to quantify organ damage in systemic sclerosis

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ABSTRACT

Objective

We sought to develop the first damage index (DI) in systemic sclerosis (SSc).

Methods

The conceptual definition of ‘damage’ in SSc was determined through consensus by a working group of the Scleroderma Clinical Trials Consortium (SCTC). Systematic literature review and consultation with patient partners and non-rheumatologist experts produced a list of potential items for inclusion in the DI. These steps were used to reduce the items: (1) Expert members of the SCTC (n=331) were invited to rate the appropriateness of each item for inclusion, using a web-based survey. Items with >60% consensus were retained; (2) Using a prospectively acquired Australian cohort data set of 1,568 patients, the univariable relationships between the remaining items and the end points of mortality and morbidity (physical component summary score of the Short Form 36) were analysed, and items with p value < 0.10 were retained; (3) using multivariable regression analysis, coefficients were used to determine a weighted score for each item. The DI was externally validated in a Canadian cohort.

Results

Ninety-three (28.1%) complete survey responses were analysed; 58 of 83 items were retained. The univariable relationships with death and/or morbidity endpoints were statistically significant for 22 items, with one additional item forced into the multivariable model by experts due to clinical importance, to create a 23-item weighted SCTC Damage Index (SCTC-DI). The SCTC-DI was predictive of morbidity and mortality in the external cohort.

Conclusions

Through the combined use of consensus and data driven methods, a 23-item SCTC-DI was developed and retrospectively validated.

Key words: systemic sclerosis, organ damage, outcome measure

INTRODUCTION

Systemic sclerosis (SSc; ‘scleroderma’) is a multi-organ disease wherein the pathogenic processes of inflammation, vasculopathy and fibrosis lead to multiple disease manifestations.[1] Unlike other rheumatological diseases that have a relapsing-remitting course, the course of SSc is often one of progressive damage to multiple organs including the skin, joints, heart, lungs, gastrointestinal (GI) tract and kidneys. Using a preliminary *ad hoc* set of criteria to define ‘organ damage’ in SSc, we found that irreversible organ damage accrues very early in the disease course, with 40% of patients having damage in one or more organ systems within 2 years of disease onset.[2]

Despite the fundamental importance of organ damage in SSc, there has been no clinical tool to identify and quantify damage in SSc, with current tools assessing disease severity, activity or combined treatment responses.[3] The lack of an existing tool, together with the observation of damage accrual early in the disease course of SSc, led to an initiative to develop the multi-organ Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI). Potential applications of this instrument include use as an outcome measure in interventional drug trials and in observational studies, and as a selection tool to enrich clinical trials for patients at risk of developing organ damage who are most likely to benefit from therapy.

The development of the SCTC-DI was an international collaboration using a combined approach of consensus and data driven methods applied to data from the prospective Australian Scleroderma Cohort Study (ASCS). External validation of the SCTC-DI was performed in the prospective Canadian Scleroderma Research Group (CSRG) registry.

METHODS

Investigators

The Scleroderma Clinical Trials Consortium Damage Index Working Group

The Scleroderma Clinical Trials Consortium (SCTC) is an international consortium representing researchers and clinicians who have particular interest and expertise in care and research of SSc. The goal of the SCTC is to conduct, sponsor or facilitate clinical research in SSc, in particular projects aimed at improving and developing outcome measures for clinical trials and observational studies.

In 2013, under the auspices of the SCTC, a working group comprised of 22 international experts in SSc, representing Australasia, the Americas and Europe was assembled to develop a disease Damage Index (DI) in SSc. The working group was led by a steering committee comprised of 6 members (MN, MB, MH, WS, SP, NF) overseeing the day-to-day development of the DI.

Non-rheumatology expert advisors

A panel of 7 non-rheumatologist experts with an interest in SSc was assembled to give recommendations regarding what constitutes significant damage in each organ system. This panel comprised two cardiologists, two respiratory physicians, two gastroenterologists and one nephrologist. Input from this panel was sought for: i) item generation for a survey of SSc experts; and ii) ensuring face and content validity of the final instrument.

Patient partners

Three experienced SSc patient partners (from Australia, Canada and the UK) provided insight from the patients' perspective. Input from these patient partners was sought at several stages in the process of instrument development: (i) conceptual definition of organ damage; (ii) item generation for a survey of SSc experts; (iii) ensuring face and content validity of the final instrument.

Development of the SCTC-DI

Conceptual definition of organ damage

The working group members participated in a two-round survey to achieve consensus regarding the *conceptual* definition of organ damage in SSc. In the second round, responses from the first round were provided, with the survey focusing on resolution of contentious areas. The definition was then presented to each working group member to ensure further comments and feedback were exhausted. All working group members had to approve the final definition.

Item generation

A systematic review of existing measures of disease status in SSc was performed to generate items for potential inclusion in the DI.[3] The working group members, expert

advisors and patient partners, made further revisions to item definitions and provided further items for inclusion in a survey.

Item reduction using consensus survey

Three hundred and thirty one expert members of the SCTC, European Scleroderma Trials and Research Group (EUSTAR), Canadian Scleroderma Research Group (CSRG) and the Australian Scleroderma Interest Group (ASIG) were invited by email to take part in an online survey (REDCap, Vanderbilt University, Nashville Tennessee; survey included as a supplementary file) to rate the appropriateness (on a scale of 1 to 7 with 1 = very inappropriate, 2 = inappropriate, 3 = somewhat inappropriate, 4 = neither inappropriate or appropriate, 5 = somewhat appropriate, 6 = appropriate, 7 = very appropriate) in terms of both importance and feasibility of recording in a day-to-day setting, of including each item in a SSc DI. The survey items were categorised according to organ systems and for each organ system, a link was provided within the survey to a repository of 64 articles from the systematic literature review.[4-67] An *a priori* cut-off of 60% votes for 'appropriate' (score of 5 or above) was used to reduce the items. Where applicable, responders were also asked to select an option regarding a time period for which the item needed to be present in order to constitute damage (present ever, 6 months, 12 months or 2 years).

Statistical analysis to achieve further item reduction and item weighting

Data from 1,568 patients in the Australian Scleroderma Cohort Study (ASCS) fulfilling the EULAR/ACR criteria for SSc[4] were used to retrospectively assess the univariable relationship of each damage item with the end-point of mortality using time-dependent Cox hazards regression models. ASCS is an ongoing longitudinal study of patients with SSc recruited from 9 sites in Australia since 2007, in whom standardised clinical (including the health-related quality of life (HRQoL) questionnaire Short Form 36 (SF-36))[68] and laboratory data are collected at each annual visit and recorded in a customised database.

As there is no specific measure of morbidity in SSc *per se*, the Physical Component Summary (PCS) score of the SF-36 questionnaire was used as a surrogate for morbidity. SF-36 data were available for 1,877 visits and panel logistic regression was used to determine the univariable relationship between each damage item and the SF-36 PCS

(dichotomised for analysis based on median value in the cohort) measured at each visit for each patient. This method allows for the expected correlation between repeated measures over time within an individual. As not all items in the ASCS were defined exactly according to the definitions used in the DI, the closest possible equivalent of each item was used in item reduction and weighting. Items not demonstrating a univariable relationship ($p < 0.10$) with the mortality or morbidity endpoints were removed. In addition, items that were highly clinically collinear with other items or lacked feasibility were removed as per steering committee consensus.

In order to create a weighted score, the multivariable coefficients were then calculated for the remaining items against each of the mortality and morbidity end points. The following rules were used to combine the correlation coefficients from each of the mortality and morbidity analyses in order to create a weighted score for each item: (1) if both coefficients were positive, an average was taken; (2) if one coefficient was negative and one positive, we took the positive only; (3) if both coefficients were negative, indicating protection from damage, the item was discarded. For scoring items, the following methods were utilized: (1) all the coefficients were divided by the smallest coefficient and multiplied by 0.25. The multiplier of 0.25 was chosen to ensure that if the smallest coefficient was very small (< 0.10), the scores did not become too large; (2) the result was rounded to the nearest integer.

Validation

The performance of the SCTC-DI in the derivation cohort (internal validation) was determined using receiver operating characteristic (ROC) curves. Kaplan Meier survival estimates against mortality and morbidity endpoints with patients divided into risk groups based on their SCTC-DI scores were generated. Risk groups were determined by looking for clear demarcation of the cumulative frequency percentage of total scores within the derivation cohort. Both of these analyses were used to demonstrate criterion validity. Frequency of damage items in a subset of patients with early disease at each year of follow up was determined to demonstrate construct validity and responsiveness to change over time.

External validation was conducted using the CSRG patient registry. The CSRG is an ongoing longitudinal study of patients with SSc fulfilling the EULAR/ACR criteria[4]

recruited from 14 sites in Canada and one site in Mexico since 2004, using a standardized data collection protocol that is comparable to that of ASCS. Once again, ROC analyses were performed. Kaplan Meier survival estimates were performed using the SCTC-DI risk scores generated in the derivation cohort. Damage accrual was assessed using the mean SCTC-DI score at each year of follow up in each organ domain and in the overall cohort.

Ethics approval and patient consent

Ethics approval for the survey of international experts was obtained from the Human Research Ethics Committee of St. Vincent's Hospital Melbourne. Ethics approval for the ASCS was obtained from the Human Research Ethics Committees of each of the participating centres, led by St. Vincent's Hospital Melbourne. Ethics approval for the CSRG registry was obtained from the Human Research Ethics Committees of each of the participating centres, led by the Jewish General Hospital, Montreal. All patients provided written informed consent at enrolment into the ASCS and CSRG registry.

RESULTS

Development of the SCTC-DI

Conceptual definition of organ damage

A total of 20 (of 22) responses from the working group members was received (for a summary of results see Supplementary File 1, Tables 1 and 2). The resulting definition of *damage* in SSc was as follows: 'Damage in SSc is the permanent and irreversible loss of anatomical structure or physiological function, caused by SSc and not secondary to its treatment or comorbidities. Damage should be differentiated from disease activity, which is potentially reversible, and disease severity which encompasses both activity and damage. The damage index will not include patient reported outcomes. The damage index should be reflective of morbidity and/or mortality. The duration that each abnormality must be present before constituting damage may depend on the particular item.'

It must be noted that damage items caused by treatment of SSc were originally included in the definition, but later removed (see below).

Item generation

A total of 83 items for potential inclusion in the damage index were generated through the systemic review of the literature [3] and consultation with expert advisors and patient partners (all items included in the survey can be seen in Supplementary File 2). The variables come from six different organ system groupings, as follows: musculoskeletal and skin, vascular, gastrointestinal, respiratory, cardiovascular and renal.

Item reduction using consensus survey

A total of 93 of 331 (28.1%) international SSc experts provided complete responses. Of the 83 items presented, 58 items had greater than 60% consensus with 36 items removed (Supplementary File 1, Table 3). Of these 58 items, 9 items (bony erosions seen on radiographic imaging, acro-osteolysis on radiographic imaging, sicca signs confirmed on objective testing, surgical limb amputation, insertion of permanent pacemaker or implantable cardioverter defibrillator, histologically proven Barrett's esophagus, rectal prolapse, lung malignancy with SSc interstitial lung disease (ILD), left ventricular failure on clinical assessment and confirmed on transthoracic echocardiography (TTE)) were not collected in the ASCS database and could not be analysed. Overall, the working group was comfortable with the removal of these items given the inclusion of similar alternatives, and in most cases, more clinically appropriate items.

Removal of 'damage due to treatment' items

A preliminary conceptual definition of damage included 'damage caused by the treatment of SSc'. Inclusion of these items was deemed unnecessary as most drug treatment clinical trials would be collecting extensive data on drug related adverse outcomes. Furthermore, ascertaining attribution of damage to treatment was deemed unreliable.

Removal of six-minute walk distance

The six-minute walk distance (6MWD) is only used in some countries as a means of monitoring cardiopulmonary disease in SSc, and in Australia, it is a requirement for access to drugs that treat right heart catheterisation-proven pulmonary arterial hypertension. Because of the lack of widespread use in clinical practice and

accessibility, the working group members and patient partners decided to remove this item.

Inclusion of renal items

The items in the renal domain, such as ‘scleroderma renal crisis’ and ‘need for renal replacement therapy’ (dialysis), occur rarely in SSc, and therefore their relationship with mortality did not reach statistical significance in our derivation dataset. Two of the 3 renal items (scleroderma renal crisis (SRC) and SRC requiring renal replacement therapy) did however have a significant univariable relationship with morbidity. Given its clinical importance, the working group decided to also include the third renal item (SRC and persistent renal impairment) despite the lack of a statistically significant relationship with either morbidity or mortality in the derivation data set.

Items removed due to clinical collinearity

The following 12 items were removed as their definition was very similar to that of other item(s) retained in the DI that were either more strongly associated with the mortality and morbidity endpoints, or were more feasible to record reliably in a clinical care setting: joint contracture in any large and/or small joint; joint contracture of the fingers with finger to palm distance > 1cm; calcinosis on physical examination; proximal muscle atrophy; digital pitting scar; modified Rodnan skin score (mRSS) > 20, left ventricular systolic dysfunction on TTE alone, right ventricular dilation and/or enlargement on TTE, right ventricular failure on clinical assessment AND confirmed on TTE, ILD of any extent on imaging, symptoms of gastroparesis, and malabsorption syndrome (Supplementary File 1, Tables 4 and 5). Persistent erectile dysfunction was also removed given its lack of applicability to all patients.

Items removed due to insufficient observations

The following 3 items were removed as they had insufficient observations to allow for meaningful statistical analysis: SRC with proteinuria, need for intravenous hyperalimentation and need for enteral feeding. Please refer to Figure 1, which summarises the item generation and reduction steps.

Table 1. SCTC-DI final items – coefficient calculations and weighted score

	Item	Mortality coeff	Morbidity coeff	Combined coeff	Weighted Score
	Musculoskeletal and Skin				
1	Joint contracture defined as any degree of contracture with the inability to reduce the joint to the anatomically neutral position in any small joint of the fingers	-0.35	0.49	0.49	2
2	Joint contracture defined as any degree of contracture with the inability to reduce the joint to the anatomically neutral position in the large joints, specifically elbows and knees	-0.35	0.49	0.49	2
3	Sicca symptoms defined as presence of patient reported dry eyes and/or dry mouth requiring treatment on a daily basis e.g. lubricant eye drops, punctual plugs, saliva replacement etc.	-0.10	0.75	0.75	3
4	Proximal muscle weakness on clinical examination defined as shoulder abduction and/or hip or knee flexion less than 5/5 power (not due to contracture or pain)	0.60	0.92	0.76	3
5	Calcinosis complicated by infection or requiring surgery	-0.21	1.08	1.08	4
	Vascular				
6	Digital ulceration defined as loss of epithelialization, of any degree, of the epidermis, the dermis and/or the subcutaneous tissue, distal to or at the proximal interphalangeal joint of the hands or feet not thought to be due to trauma, and refractory to therapy	0.79	0.37	0.58	2
7	Digital amputation (surgical or auto-amputation)	0.96	1.09	1.03	3
	Gastrointestinal				
8	Esophageal dysmotility defined as distal dysphagia refractory to treatment with differential diagnoses (e.g. esophageal stricture or malignancy) excluded by endoscopy	-0.21	0.12	0.12	1
9	Pseudo-obstruction with symptoms such as vomiting or constipation, with dilatation of the small and/or large bowel on imaging	0.93	-0.82	0.93	3
10	Low body mass index (BMI) of < 18.5 kg/m ² OR weight loss of > 10% in the last 12 months	0.68	0.74	0.71	2
11	Gastric antral vascular ectasia confirmed on endoscopy	0.67	0.32	0.50	2
12	Esophageal stricture confirmed on testing such as endoscopy or barium swallow	0.15	0.20	0.18	1
13	Symptoms of gastro-esophageal reflux disease (heart burn) refractory to treatment and confirmed on endoscopy	0.03	0.71	0.37	1
	Respiratory				
14	Moderate to severe interstitial lung disease with > 20% extent on HRCT of the chest	0.19	0.97	0.58	2
15	Moderate to severe interstitial lung disease with > 20% extent on HRCT of the chest and forced vital capacity <70% on lung function tests	1.11	2.47	1.79	6
16	Dependence on home oxygen	0.88	1.99	1.44	5
	Cardiovascular				
17	Pulmonary arterial hypertension (defined as mean pulmonary arterial pressure $\geq$ 25mmHg at rest and pulmonary arterial wedge pressure $\leq$ 15mmHg on right heart catheterization)	0.75	0.59	0.67	2
18	Moderate to severe right ventricular dysfunction noted on echocardiography report based on assessment of any measure of RV function by experienced cardiologist	1.81	2.49	2.15	7
19	Myocardial disease attributable to SSc based on a constellation of clinical features AND supportive investigations e.g. syncope secondary to conduction abnormality, arrhythmia requiring defibrillator, heart block requiring permanent pacemaker or ablation, systolic or diastolic dysfunction on TTE etc.	0.85	0.77	0.81	3
20	Presence of moderate to large pericardial effusion equivalent to greater than 1 cm on transthoracic echocardiogram	0.45	0.09	0.27	1
	Renal				
21	History of scleroderma renal crisis (SRC), either hypertensive or normotensive, as defined by the International Scleroderma Renal Crisis Study Investigators [46]	0.46	1.54	1.00	3
22	History of SRC or other SSc related kidney disease and persistent renal impairment with estimated glomerular filtration rate < 45mL/min/1.73 m ²	0.66	1.76	1.21	4
23	SRC with stage 5 renal impairment defined as need for renal replacement therapy	1.08	2.16	1.62	5

Coeff = coefficient; HRCT = high resolution computed tomography; RV = right ventricular; TTE = transthoracic echocardiogram.

Statistical analysis to achieve further item reduction and item weighting

The univariable relationship with mortality and morbidity (dichotomised using the cohort median SF-36 PCS = 37.2) was significant ($p < 0.10$) in 17 and 22 items, respectively (Supplementary File 1, Tables 4 and 5). These items were then weighted and scored using multivariable regression (Table 1). Four items were removed at this stage as they did not reach statistical significance in both the mortality and morbidity analyses (late-stage nailfold capillaroscopic changes, moderate to severe left ventricular diastolic dysfunction on TTE, any conduction defect on ECG or Holter monitor, and fecal incontinence).

Scleroderma Clinical Trials Consortium Damage Index

The 23-item multi-organ weighted Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI) is presented in Table 2. The scores are additive with a maximum possible total score of 55. In the final product, items addressing the same issue, for example SRC, are grouped together and scores are added if further clinical markers of severity are present. Members of the working group reviewed the final SCTC-DI for face and content validity and potential feasibility of application of each item.

Table 2: Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI)

Item	Score
Musculoskeletal and Skin	
Joint contracture defined as any degree of contracture with the inability to reduce the joint to the anatomically neutral position in any small joint of the fingers*^	2
Joint contracture defined as any degree of contracture with the inability to reduce the joint to the anatomically neutral position in the large joints, specifically elbows and knees*^	2
Sicca symptoms defined as presence of dry eyes and/or dry mouth requiring treatment on a daily basis e.g. lubricant eye drops, punctal plugs, saliva replacement etc.*	3
Proximal muscle weakness on clinical examination defined as shoulder abduction and/or hip or knee flexion less than 5/5 power (not due to contracture or pain)*	3
Calcinosis complicated by infection or requiring surgery	4
Vascular	
Digital ulceration defined as loss of epithelialization, of any degree, of the epidermis, the dermis and/or the subcutaneous tissue, distal to or at the proximal interphalangeal joint of the hands or feet not thought to be due to trauma and refractory to therapy*	2
- add 1 if digital amputation required (surgical or auto-amputation)	1
Gastrointestinal	
Esophageal dysmotility defined as distal dysphagia refractory to treatment, with differential diagnoses (e.g. esophageal stricture or malignancy) excluded by endoscopy	1
Esophageal stricture confirmed on testing such as endoscopy or barium swallow	1
Symptoms of gastro-esophageal reflux disease (heart burn) refractory to treatment (e.g. proton pump inhibitors) and confirmed on endoscopy*	1
Gastric antral vascular ectasia confirmed on endoscopy	2
Pseudo-obstruction with symptoms such as vomiting or constipation, with dilatation of the small and/or large bowel on imaging	3
Low body mass index (BMI) of < 18.5 kg/m ² OR weight loss of > 10% in the last 12 months	2
Respiratory	
Moderate to severe interstitial lung disease > 20% extent on HRCT of the chest	2
- Add 4 points if forced vital capacity <70% on lung function tests (not due to respiratory muscle weakness)*	4
Dependence on home oxygen	5
Cardiovascular	
Pulmonary arterial hypertension (defined as mean pulmonary arterial pressure $\geq$ 25mmHg at rest and pulmonary arterial wedge pressure $\leq$ 15mmHg on right heart catheterization)	2
- add 5 if moderate to severe right ventricular dysfunction noted on echocardiography report based on assessment of any measure of RV function by experienced cardiologist	5
Myocardial disease attributable to SSc based on a constellation of clinical features AND supportive investigations e.g. syncope secondary to conduction abnormality, arrhythmia requiring defibrillator, heartblock requiring permanent pacemaker or ablation, systolic or diastolic dysfunction on TTE etc.	3
Presence of moderate to large pericardial effusion equivalent to greater than 1 cm on transthoracic echocardiogram*	1
Renal	
History of scleroderma renal crisis (SRC), either hypertensive or normotensive, as defined by the International Scleroderma Renal Crisis Study Investigators [46]	3
- add 1 if history of SRC or other SSc related kidney disease and persistent renal impairment with estimated glomerular filtration rate < 45mL/min/1.73 m ²	1
- add 2 if SRC with stage 5 renal impairment and need for renal replacement therapy	2
TOTAL SCORE	55

Note – attribution to SSc required for all items.

HRCT = high resolution computed tomography, RV = right ventricular, TTE = transthoracic echocardiogram.

*item must be present for a minimum of 6 months

^see figure below for 'anatomically neutral' position

Validation of the SCTC-DI

Characteristics of the ASCS and CSRG cohorts

The characteristics of the ASCS (derivation data set) and CSRG (validation data set) cohorts and the frequency of items together with percentage missing within each cohort are presented in Supplementary File 1, Tables 6, 7, 8 and 9.

Performance of the SCTC-DI in the derivation and external cohorts

The mean (SD), median, minimum and maximum DI scores within the ASCS derivation data set were 6.65 (4.8), 6, 0 and 33, respectively. Within the external cohort of CSRG patients, the mean (SD), median, minimum and maximum DI score were 6.9 (4.7), 6, 0, 33, respectively.

ROC analysis revealed a good discriminatory capability of the SCTC-DI with ROC area under the curve of 0.77 (95% CI 0.73-0.82) and 0.73 (95% CI 0.69-0.77) for mortality in the ASCS and CSRG cohorts, respectively (Figures 2(a) and 2(b)). For morbidity (SF-36 PCS), ROC area under the curve was 0.69 (95% CI 0.65-0.72) and 0.72 (95% CI 0.69-0.74) in the ASCS and CSRG cohorts, respectively (Figures 2(c) and 2(d)).

Damage accrual over time within the derivation cohort was demonstrated in a subset of patients recruited within 2 years of disease onset, where the percentage of items present at each year of follow up shows a steady increase (Figure 3(a)). Steady accrual of the mean DI score was also demonstrated in the CSRG cohort at each year of follow up (Figure 3(b)). When total scores were categorised into risk groups (low damage score <5, moderate damage score 6-12, high damage score ≥ 13), Kaplan Meier survival estimates showed a statistically significant graded relationship of damage score and time to death or first reduction (i.e. worsening) of SF-36 PCS below the median score of 37.2 (log rank $p < 0.001$) in the derivation cohort. Similar results were seen when the SCTC-DI was assessed in the CSRG validation cohort (Figures 4(a) and 4(b)).

DISCUSSION

Through use of consensus methods with data-driven item reduction and weighting, an international working group of the SCTC has produced the first instrument developed

specifically for the purpose of quantifying organ damage in SSc. The 23-item SCTC-DI has been designed to capture damage that is reflective of both morbidity and mortality in each of the 6 major organ systems affected. Although it was considered that separate damage indices each reflective of mortality or morbidity be created, the working group felt that the creative approach of combining the two analyses as a single index would be more practical in the research and clinical care setting. Relative to other damage indices such as the Vasculitis Damage Index (VDI)[69] and the Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index in Systemic Lupus Erythematosus (SLE) (SLICC/ACR DI),[70] with 65 and 39 items respectively, the SCTC-DI of 23 items is shorter and would be easy to use in clinical trials. While the total possible damage score is 55, the maximum score in the derivation data set was 33, indicating that the SCTC-DI is not limited by a ceiling effect and that damage scores exceeding 33 are likely incompatible with life. In the derivation data set, the SCTC-DI demonstrated good discriminatory capability for mortality risk and also morbidity.

The international collaborative approach of the working group, the survey of a large number of SSc experts outside of the working group, contributions of experts in non-rheumatology specialities and patient partners, together with robust statistical methods used to reduce, weight and score the items make the development of the SCTC-DI rigorous and unique. While the SCTC survey response rate was 28%, we received 93 complete survey responses from international experts to work with. The development of the SCTC-DI also benefited from a recent mortality study that we undertook using both ASIG and CSRG data where we traced losses to follow-up and confirmed all deaths.[2]

Existing multi-organ outcome measures in SSc include the European Scleroderma Study Group (EScSG) activity index and the Combined Response Index in Systemic Sclerosis (CRISS).[71-73] As the name suggests, the EScSG activity index measures disease activity, which inherently implies that it measures potentially reversible components of SSc and is not cumulative in nature. The CRISS on the other hand, is a set of outcome measures used to measure the effect of treatments in SSc. Whilst both are valuable clinical trial tools, they do not capture the concept of cumulative, irreversible organ damage which invariably occurs in the natural history of SSc.

Experience with both the VDI and the SLICC/ACR DI as endpoints in clinical trials also demonstrates the potential applications of a damage index in SSc.

The value of the patient perspective in the development of disease indices has become increasingly recognised.[74] Although the conceptual definition of damage in SSc stipulated that patient reported outcomes not be included in the damage index, the patient perspective was still taken into account through inclusion of patient partners who were consulted at all steps of instrument development. Furthermore, the use of the HRQoL measure SF-36 as an endpoint for weighting the scores allowed for a patient-reported outcome to be included in instrument development.

Our conceptual definition of ‘damage’ in SSc has inherent limitations. However, this could be said of all complex multi-organ connective tissue diseases where assignment of direct attribution to the disease and irreversibility is based on physician judgement. Some items in the DI are required to be present for a minimum of 6 months to ensure they are ‘irreversible’. The future availability of truly disease modifying drugs may mean that some items in the DI may indeed be made reversible. In such a situation, an updated revision of the DI will be needed. The use of an existing prospectively acquired clinical database for statistical analyses meant that a handful of items were not present or did not have a definition identical to that presented in the survey of experts. However, where this was the case, a surrogate definition, which was as close as possible to the original item, was used. Despite this limitation, both internal and external validity were demonstrated against the endpoints of mortality and morbidity, as was responsiveness to change over time. To complete validation of the SCTC-DI, future studies need to evaluate reliability/reproducibility and feasibility of application of the SCTC-DI.

The use of retrospective data in a prevalent cohort underscores the need for further validation of the SCTC-DI in a prospective data set where all items in the damage index, together with those that did not make the final index but were deemed appropriate by experts surveyed, are collected. In addition, the early mortality[75] and early accrual of damage in SSc has provided a rationale for the creation of an international inception cohort (International Systemic Sclerosis Inception Cohort; INSYNC) of patients with SSc in order to prospectively validate disease outcome measures, including the SCTC-DI.

KEY MESSAGES

What is already known about this subject?

- Organ damage is part of the natural history of SSc
- Organ damage occurs early in the disease course of SSc
- Based on a systematic review of the literature, no tool currently exists to measure organ damage in SSc

What does this study add?

- The first ever composite disease damage index in SSc has been developed
- The methodology used to develop the index is somewhat unique, with the combination of both consensus methods and statistical analysis of patient data

How might this impact on clinical practice or future developments?

- The damage index can potentially be used in observational studies and clinical trials as an endpoint, and for the enrichment of clinical trials

COMPETING INTERESTS

None

AUTHOR CONTRIBUTIONS

NF: study design, data collection, data analysis, interpretation of results, preparation of manuscript; MH (biostatistician): data analysis, interpretation of results, preparation of manuscript; WS: study design, data collection, interpretation of results, preparation of manuscript; MH: study design, data collection, data analysis, interpretation of results, preparation of manuscript; MW (biostatistician): data analysis, interpretation of results, preparation of manuscript; TT: study design, data collection, interpretation of results, preparation of manuscript; JLB: study design, data analysis, interpretation of results, preparation of manuscript; SM: study design, data analysis, interpretation of results, preparation of manuscript; CR: data collection, interpretation of results, preparation of manuscript; VS: study design, data analysis, interpretation of results, preparation of manuscript; DP: study design, interpretation of results, preparation of manuscript; SP: study design, data collection, interpretation of results, preparation of manuscript; MB: study design, data collection, data analysis, interpretation of results, preparation of

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ETHICAL APPROVAL INFORMATION

Ethics approval for the survey of international experts was obtained from the Human Research Ethics Committee of St. Vincent's Hospital Melbourne. Ethics approval for the ASCS was obtained from the Human Research Ethics Committees of each of the participating centres, led by St. Vincent's Hospital Melbourne. Ethics approval for the CSRG registry was obtained from the Human Research Ethics Committees of each of the participating centres, led by the Jewish General Hospital, Montreal. All patients provided written informed consent at enrolment into the ASCS and CSRG registry.

DATA SHARING STATEMENT

All data that can be made available have been included in supplementary files.

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Figure 1. SCTC-DI - item generation and reduction steps

Legend: *SF 36 PCS = Short Form 36 Physical Component Score

Figures 2(a) - 2(d). ROC curves for mortality (2a and 2b) and morbidity (2c and 2d) in the ASCS (derivation) and CSRG (validation) cohorts

Figure 3(a) and 3(b). Accrual of organ damage in an incident subset of cohort

Legend: Graphs demonstrating the accrual of damage within the incident population of the ASCS (3a) and CSRG (3b) cohorts, recruited within 2 years of SSc diagnosis. In addition to overall damage accrual, accrual of damage is also separated into organ systems.

*Disease duration from first non-Raynaud disease manifestation

Figures 4(a) and 4(b). Survival according to organ damage score

Legend: When the ASCS cohort is divided into risk groups based on cumulative damage score, Kaplan Meier survival estimates demonstrate a significant reduction in survival as the cumulative damage score increases. Diseaseonset is defined according to the onset of the first non-Raynaud manifestation.

Table 1. SCTC-DI final items – coefficient calculations and weighted score

	Item	Mortality coefficient	Morbidity coefficient	Combined coefficient	Weighted Score
	Musculoskeletal and Skin				
1	Joint contracture defined as any degree of contracture with the inability to reduce the joint to the anatomically neutral position in any small joint of the fingers	-0.35	0.49	0.49	2
2	Joint contracture defined as any degree of contracture with the inability to reduce the joint to the anatomically neutral position in the large joints, specifically elbows and knees	-0.35	0.49	0.49	2
3	Sicca symptoms defined as presence of patient reported dry eyes and/or dry mouth requiring treatment on a daily basis e.g. lubricant eye drops, punctal plugs, saliva replacement etc.	-0.10	0.75	0.75	3
4	Proximal muscle weakness on clinical examination defined as shoulder abduction and/or hip or knee flexion less than 5/5 power (not due to contracture or pain)	0.60	0.92	0.76	3
5	Calcinosis complicated by infection or requiring surgery	-0.21	1.08	1.08	4
	Vascular				
6	Digital ulceration defined as loss of epithelialization of any degree of the epidermis, the dermis and/or the subcutaneous tissue, distal to or at the proximal interphalangeal joint of the hands or feet not thought to be due to trauma and refractory to therapy	0.79	0.37	0.58	2
7	Digital amputation (surgical or auto-amputation)	0.96	1.09	1.03	3
	Gastrointestinal				
8	Esophageal dysmotility defined as distal dysphagia refractory to treatment with differential diagnoses (e.g. esophageal stricture or malignancy) excluded by endoscopy	-0.21	0.12	0.12	1
9	Pseudo-obstruction with symptoms such as vomiting or constipation, with dilatation of the small and/or large bowel on imaging	0.93	-0.82	0.93	3
10	Low body mass index (BMI) of < 18.5 kg/m ² OR weight loss of > 10% in the last 12 months	0.68	0.74	0.71	2
11	Gastric antral vascular ectasia confirmed on endoscopy	0.67	0.32	0.50	2
12	Esophageal stricture confirmed on testing such as endoscopy or barium swallow	0.15	0.20	0.18	1
13	Symptoms of gastro-esophageal reflux disease (heart burn) refractory to treatment and confirmed on endoscopy	0.03	0.71	0.37	1
	Respiratory				
14	Moderate to severe interstitial lung disease with > 20% extent on HRCT of the chest	0.19	0.97	0.58	2
15	Moderate to severe interstitial lung disease with > 20% extent on HRCT of the chest and forced vital capacity <70% on lung function tests	1.11	2.47	1.79	6
16	Dependence on home oxygen	0.88	1.99	1.44	5
	Cardiovascular				
17	Pulmonary arterial hypertension (defined as mean pulmonary arterial pressure $\geq$ 25mmHg at rest and pulmonary arterial wedge pressure $\leq$ 15mmHg on right heart catheterization)	0.75	0.59	0.67	2
18	Moderate to severe right ventricular dysfunction noted on echocardiography report based on assessment of any measure of RV function by experienced cardiologist	1.81	2.49	2.15	7
19	Myocardial disease attributable to SSc based on a constellation of clinical features AND supportive investigations e.g. syncope secondary to conduction abnormality, arrhythmia requiring defibrillator, heartblock requiring permanent pacemaker or ablation, systolic or diastolic dysfunction on TTE etc.	0.85	0.77	0.81	3
20	Presence of moderate to large pericardial effusion equivalent to greater than 1 cm on transthoracic echocardiogram	0.45	0.09	0.27	1
	Renal				
21	History of scleroderma renal crisis (SRC), either hypertensive or normotensive, as defined by the International Scleroderma Renal Crisis Study Investigators	0.46	1.54	1.00	3
22	History of SRC or other SSc related kidney disease and persistent renal impairment with estimated glomerular filtration rate < 45mL/min/1.73 m ²	0.66	1.76	1.21	4
23	SRC with stage 5 renal impairment defined as need for renal replacement therapy	1.08	2.16	1.62	5

HRCT = high resolution computed tomography; RV = right ventricular; TTE = transthoracic echocardiogram.

Table 2: Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI)

Item	Score
Musculoskeletal and Skin	
Joint contracture defined as any degree of contracture with the inability to reduce the joint to the anatomically neutral position in any small joint of the fingers*^	2
Joint contracture defined as any degree of contracture with the inability to reduce the joint to the anatomically neutral position in the large joints, specifically elbows and knees*^	2
Sicca symptoms defined as presence of dry eyes and/or dry mouth requiring treatment on a daily basis e.g. lubricant eye drops, punctal plugs, saliva replacement etc.*	3
Proximal muscle weakness on clinical examination defined as shoulder abduction and/or hip or knee flexion less than 5/5 power (not due to contracture or pain)*	3
Calcinosis complicated by infection or requiring surgery	4
Vascular	
Digital ulceration defined as loss of epithelialization of any degree of the epidermis, the dermis and/or the subcutaneous tissue, distal to or at the proximal interphalangeal joint of the hands or feet not thought to be due to trauma and refractory to therapy*	2
- add 1 if digital amputation required (surgical or auto-amputation)	1
Gastrointestinal	
Esophageal dysmotility defined as distal dysphagia refractory to treatment with differential diagnoses (e.g. esophageal stricture or malignancy) excluded by endoscopy	1
Esophageal stricture confirmed on testing such as endoscopy or barium swallow	1
Symptoms of gastro-esophageal reflux disease (heart burn) refractory to treatment (e.g. proton pump inhibitors) and confirmed on endoscopy*	1
Gastric antral vascular ectasia confirmed on endoscopy	2
Pseudo-obstruction with symptoms such as vomiting or constipation, with dilatation of the small and/or large bowel on imaging	3
Low body mass index (BMI) of < 18.5 kg/m ² OR weight loss of > 10% in the last 12 months	2
Respiratory	
Moderate to severe interstitial lung disease with > 20% extent on HRCT of the chest	2
- Add 4 points if forced vital capacity <70% on lung function tests (not due to respiratory muscle weakness)*	4
Dependence on home oxygen	5
Cardiovascular	
Pulmonary arterial hypertension (defined as mean pulmonary arterial pressure $\geq$ 25mmHg at rest and pulmonary arterial wedge pressure $\leq$ 15mmHg on right heart catheterization)	2
- add 5 if moderate to severe right ventricular dysfunction noted on echocardiography report based on assessment of any measure of RV function by experienced cardiologist	5
Myocardial disease attributable to SSc based on a constellation of clinical features AND supportive investigations e.g. syncope secondary to conduction abnormality, arrhythmia requiring defibrillator, heartblock requiring permanent pacemaker or ablation, systolic or diastolic dysfunction on TTE etc.	3
Presence of moderate to large pericardial effusion equivalent to greater than 1 cm on transthoracic echocardiogram*	1
Renal	
History of scleroderma renal crisis (SRC), either hypertensive or normotensive, as defined by the International Scleroderma Renal Crisis Study Investigators	3
- add 1 if history of SRC or other SSc related kidney disease and persistent renal impairment with estimated glomerular filtration rate < 45mL/min/1.73 m ²	1
- add 2 if SRC with stage 5 renal impairment and need for renal replacement therapy	2
TOTAL SCORE	55

Note – attribution to SSc required for all items.

HRCT = high resolution computed tomography, RV = right ventricular, TTE = transthoracic echocardiogram.

*item must be present for a minimum of 6 months

^see figure below for 'anatomically neutral' position

Figure 1. SCTC-DI - item generation and reduction steps

*SF 36 PCS = Short Form 36 Physical Component Score

Figures 2(a) - 2(d). ROC curves for mortality (2a and 2b) and morbidity (2c and 2d) in the ASCS (derivation) and CSRG (validation) cohorts

(a) ASCS cohort – mortality

(b) CSRG cohort - mortality

(c) ASCS cohort - morbidity

(d) CSRG cohort - morbidity

Figure 3(a) and 3(b). Accrual of organ damage in an incident subset of cohort

Legend: Graphs demonstrating the accrual of damage within the incident population of the ASCS (3a) and CSRG (3b) cohorts, recruited within 2 years of SSc diagnosis. In addition to overall damage accrual, accrual of damage is also separated into organ systems.

(a) ASCS cohort

(b) CSRG cohort

*Disease duration from first non-Raynaud disease manifestation

Figures 4(a) and 4(b). Survival according to organ damage score

Legend: When the ASCS cohort is divided into risk groups based on cumulative damage score, Kaplan Meier survival estimates demonstrate a significant reduction in survival as the cumulative damage score increases. Diseaseonset is defined according to the onset of the first non-Raynaud manifestation.

4(a) ASCS cohort

4(b) CSRG Cohort

SUPPLEMENTARY FILE 1.**Table 1. Summary of round 1 working group survey to define the concept of damage in SSc**

Concept of Damage in Systemic Sclerosis – Summary of Round 1 results			
Concept of organ damage	Yes	No	Comments
Permanent & irreversible	17	1	
Loss of anatomical structure or physiological function	18	2	
Predicts morbidity	17	1	
Predicts mortality	12	4	
Differentiates from activity & severity	15	0	
Patient reported outcomes (PRO's)			
Exclude	15	5	
Etiology of organ damage			
Due to disease	20	0	
Due to treatment	11	8	<ul style="list-style-type: none"> • Damage due to therapy is a contributor to overall damage • Ideal to distinguish damage from therapy although this may be difficult
Due to co-morbidities	7	12	<ul style="list-style-type: none"> • Attribution can be difficult, therefore should be included • Need to differentiate damage due to SSc from comorbidities
Regardless of etiology	8	7	<ul style="list-style-type: none"> • In SLICC Damage Index for SLE and in Myositis Damage Index, damage was defined regardless of etiology as it can be very difficult to determine the cause of damage • Should be limited to items that we can attribute to SSc even if this means we miss part of the patient experience

How long should the item be present before calling it damage?			
≥ 6 months	12	5	<ul style="list-style-type: none"> • 6 months is appropriate for RCT's
≥ 12 months	5	12	<ul style="list-style-type: none"> • Too long for RCT
Variable depending on organ	12	3	<ul style="list-style-type: none"> • Too complicated I suspect • This makes damage index hard to deal with

Table 2. Summary of round 2 working group survey to define the concept of damage in SSc

Concept of Damage in Systemic Sclerosis – Summary of Round 2 results			
Etiology of organ damage	Yes	No	Summary of Comments
Due to treatment	15	5	<ul style="list-style-type: none"> • Damage due to therapy is a contributor to overall damage
Due to co-morbidities	6	14	<ul style="list-style-type: none"> • Need to differentiate damage due to SSc from comorbidities • Attribution can be difficult but we should try to distinguish, because patients with comorbidities will score higher in the damage index and it will not be a reflection of their SSc
Regardless of etiology	9	11	<ul style="list-style-type: none"> • The damage index should inform us about the natural history of SSc progression and damage should be due to the disease process itself
Duration of organ damage			
>6 months	14	6	<ul style="list-style-type: none"> • Has face/content validity, easy to implement and likely most useful time frame for randomized controlled trials
>12 months	5	14	<ul style="list-style-type: none"> • Depends on the item • This is congruent with REGISTRY DESIGN
Variable depending on organ	12	8	<ul style="list-style-type: none"> • Although this is TRUE in practice, it may make the index impractical for use in trials
Having specific damage durations would make the index impractical with recruiting to trials	9	11	<ul style="list-style-type: none"> • It definitely needs to be described for each or any of the organs targeted in a trial. This may be useful in cohort enrichment and damage sub-group analyses

Table 3. SSc expert survey responses (items shaded in grey had >60% consensus)

Items	Group Scores	
	1 to 4	5 to 7
Joint contracture in any large and/or small joint	23(20.35)	90(79.64)
Joint contracture in any small joint of the fingers	18(16.22)	93(83.78)
Joint contracture in any large joints	33(29.73)	78(70.26)
Joint contracture of the fingers with finger to palm distance > 1cm	27(24.55)	81(73.64)
Bony erosions seen on radiographic imaging	36(33.64)	66(61.67)
Acro-osteolysis on radiographic imaging	6(5.6)	100(93.46)
Calcinosis on physical examination or radiograph	40(38.47)	64(61.54)
Calcinosis associated with symptoms	42(40.39)	62(59.61)
Calcinosis complicated by infection or requiring surgery	38(36.54)	66(63.46)
Proximal muscle weakness on clinical examination	37(35.92)	66(64.07)
Proximal muscle atrophy on clinical examination	39(38.24)	63(61.76)
Myositis on clinical presentation with positive investigation findings	46(45.09)	56(54.9)
Any degree of scleroderma skin involvement	49(50)	49(50)
Modified Rodnan Skin Score (MRSS) > 20	36(37.12)	60(61.85)
Histological changes typical of scleroderma biopsy	76(78.35)	20(20.62)
Skin hyper or hypopigmentation	51(52.58)	46(47.42)
Sicca symptoms (dry eyes or dry mouth)	56(58.34)	40(41.67)
Sicca signs confirmed on objective testing	37(38.54)	59(61.46)
Sicca symptoms and signs confirmed on testing	22(22.9)1	74(77.09)
Digital pitting scar	23(23.96)	73(76.04)
Digital ulceration distal to PIP in hands or feet	31(32.29)	65(67.71)
Ulceration in any location other than the digits	49(51.04)	46(47.92)
Digital amputation	2(2.08)	94(97.92)
Surgical limb amputation	18(18.75)	77(80.21)
<u>Men only: Persistent erectile dysfunction</u>	22(22.92)	70(72.92)
Late stage nailfold capillaroscopic changes	21(21.87)	75(78.13)
Raynaud phenomenon requiring vasodilator therapy	54(56.25)	42(43.75)
Pulmonary arterial hypertension confirmed on RHC	8(8.42)	86(90.53)
Right ventricular failure on clinical assessment alone	43(45.26)	49(51.58)
Right ventricular failure on clinical assessment AND confirmed on TTE	12(12.64)	81(85.27)
Moderate to severe right ventricular dysfunction on TTE	16(16.85)	78(82.1)
Right ventricular dysfunction on TTE (TAPSE < 16mm and/or RV end-systolic area < 10mm)	21(22.1)	55(57.89)
Right ventricular dilation and/or enlargement on TTE	26(27.37)	65(68.42)
Moderate to severe tricuspid regurgitation on TTE	50(52.63)	39(41.05)
Enlarged right atrium (defined as > 18cm ²) on TTE	34(35.79)	52(54.73)
Presence of pericardial effusion greater than 1 cm on TTE	47(49.47)	47(49.47)
Left ventricular failure on clinical assessment	56(59.58)	36(38.3)
Left ventricular failure on clinical assessment and confirmed on TTE (LVEF < 50%)	24(25.53)	69(73.41)
Left ventricular systolic dysfunction on TTE alone	31(32.97)	61(64.9)
Moderate to severe left ventricular diastolic dysfunction on TTE	20(21.27)	67(71.27)
Scleroderma myocardial disease based on clinical features and supported by MRI and/or endomyocardial	16(17.02)	78(82.98)

biopsy		
Any conduction defect detected on ECG or Holter monitor	20(21.27)	70(74.47)
Any arrhythmia irrespective of type	34(36.17)	55(58.51)
Supraventricular arrhythmias only	54(57.45)	36(38.31)
Ventricular arrhythmias only	38(40.43)	51(54.25)
Insertion of PPM or implantable cardioverter defibrillator	13(13.83)	76(80.86)
Reduced 6 minute walk distance < 250 meters	31(32.97)	61(64.9)
ILD based on clinical assessment only	68(73.12)	25(26.88)
ILD of any extent on CXR or HRCT chest	34(36.56)	59(63.44)
ILD > 20% extent on HRCT chest	9(9.69)	84(90.31)
ILD with FVC < 70% predicted	12(12.92)	80(86.02)
ILD with DLCO < 60% predicted	15(16.13)	78(83.86)
Dependence on home oxygen	12(12.9)	81(87.09)
Symptoms of GERD requiring PPI therapy	47(50.54)	46(49.46)
Symptoms of GERD confirmed on endoscopy	31(33.34)	62(66.67)
Suspected esophageal dysmotility on symptoms alone	46(49.45)	47(50.53)
Esophageal dysmotility on symptoms and confirmed on testing	12(12.91)	81(87.1)
Esophageal stricture on endoscopy or barium swallow	12(12.91)	81(87.1)
Esophageal ulcer on endoscopy or barium swallow	48(51.62)	45(48.38)
Histologically proven Barrett's esophagus	25(26.88)	68(73.11)
Symptoms of gastroparesis confirmed on gastric emptying test	11(11.84)	81(87.09)
GAVE confirmed on endoscopy	14(15.06)	77(82.8)
Malabsorption syndrome responsive to cyclical antibiotics and/or probiotics	12(12.91)	81(87.09)
BMI < 18.5 kg/m ² OR weight loss of > 10% in the last 12 months	22(23.66)	71(76.35)
Need for intravenous hyperalimentation	8(8.61)	85(91.4)
Need for enteral feeding	12(12.9)	81(87.09)
Pseudo-obstruction confirmed on imaging	10(10.75)	83(89.24)
Chronic constipation	44(47.31)	49(52.69)
Rectal prolapse	32(34.41)	58(62.36)
Fecal incontinence	7(7.53)	83(89.25)
History of SRC	18(19.36)	75(80.64)
SRC with stage 5 renal impairment and need for renal replacement therapy	6(6.46)	86(92.48)
History of SRC and persistent renal impairment (eGFR < 45)	5(5.38)	87(93.55)
History of SRC with proteinuria (PCR > 25 mg/mmol)	26(27.96)	62(66.67)
Malignancy in patients who have received immunosuppressive therapy	48(51.63)	43(46.23)
Lung malignancy with SSc ILD	33(35.48)	58(62.36)
Bladder cancer with cyclophosphamide exposure	22(23.66)	71(76.35)
Osteoporosis on BMD with corticosteroids exposure	30(32.26)	62(66.66)
Osteoporosis with minimal trauma fracture with corticosteroid exposure	28(30.11)	64(68.82)
Osteopenia with corticosteroid exposure	61(65.59)	31(33.33)
Premature gonadal failure	19(20.65)	71(77.18)
Bone marrow hypoplasia	42(45.65)	48(52.18)
Cyclophosphamide induced cystitis	30(32.61)	60(65.22)

TTE = transthoracic echocardiogram, TAPSE = tricuspid annular plane systolic excursion, LVEF = left ventricular ejection fraction, MRI = magnetic resonance imaging, ECG = electrocardiography, ILD = interstitial lung disease, CXR = chest x-ray, HRCT = high resolution computed tomography, FVC = forced vital capacity, DLCO = diffusing capacity of the lung for carbon monoxide, GERD = gastroesophageal reflux disease, GAVE = gastric antral vascular ectasia, BMI = body mass index, SRC = scleroderma renal crisis, eGFR = estimated glomerular filtration rate, PCR = protein to creatinine ratio, BMD = bone mineral density.

Table 4. Univariable time dependent Cox hazard regression model for mortality

	Item	HR	p value	95% CI
1	Joint contracture in any large and/or small joint**	1.57	0.031	1.04 – 2.36
2	Joint contracture in any small joint of the fingers [#]	1.57	0.031	1.04 – 2.36
3	Joint contracture in any large joints [#]	1.57	0.031	1.04 – 2.36
4	Joint contracture of the fingers with finger to palm distance > 1cm**	0.14	0.169	0.01 – 2.28
5	Bony erosions seen on radiographic imaging [^]	-	-	-
6	Acro-osteolysis on radiographic imaging [^]	-	-	-
7	Calcinosis on physical examination or radiograph**	1.39	0.105	0.93 – 2.07
8	Calcinosis complicated by infection or requiring surgery	1.18	0.971	0.54 – 2.58
9	Proximal muscle weakness on clinical examination	2.24	<0.001	1.50 – 3.35
10	Proximal muscle atrophy on clinical examination**	3.01	<0.001	2.05 – 4.42
11	Modified Rodnan Skin Score (MRSS) $\geq$ 20**	2.36	<0.001	1.51 – 3.68
12	Sicca signs confirmed on objective testing [^]	-	-	-
13	Sicca symptoms and signs confirmed on testing [#]	1.16	0.593	0.68 – 1.99
14	Digital pitting scar **	1.22	0.344	0.81 – 1.85
15	Digital ulceration distal to PIPs in hands or feet	2.12	0.001	1.38 – 3.25
16	Digital amputation	2.61	0.001	1.51 – 4.52
17	Surgical limb amputation [^]	-	-	-
18	<u>Men only</u> : Persistent erectile dysfunction**	1.02	0.956	0.45 – 2.35
19	Late stage nailfold capillaroscopic changes	0.25	0.173	0.04 – 1.82
20	Pulmonary arterial hypertension confirmed on RHC	4.22	< 0.001	2.86 – 6.23
21	Right ventricular failure on clinical assessment AND confirmed on TTE	13.51	<0.001	7.37 – 24.77
22	Moderate to severe right ventricular dysfunction on TTE	6.74	<0.001	4.50 – 10.10
23	Right ventricular dilation and/or enlargement on TTE**	5.62	0.019	1.33 – 23.82
24	Left ventricular failure on clinical assessment and confirmed on TTE (LVEF < 50%) [^]	-	-	-
25	Left ventricular systolic dysfunction on TTE alone**	2.18	0.028	1.09 – 4.35
26	Moderate to severe left ventricular diastolic dysfunction on TTE	1.17	0.845	0.25 – 5.47
27	Scleroderma myocardial disease on clinical features and supported by MRI and/or endomyocardial biopsy [#]	2.18	0.028	1.09 – 4.35
28	Any conduction defect detected on ECG or Holter monitor	1.54	0.402	0.56 – 4.24
29	Insertion of PPM or implantable cardioverter defibrillator [^]	-	-	-
30	Reduced 6 minute walk distance < 250 meters**	7.17	<0.001	4.70 – 10.93
31	ILD of any extent on CXR or HRCT chest**	2.25	<0.001	1.53 – 3.31

32	ILD > 20% extent on HRCT chest	3.34	<0.001	2.16 – 5.17
33	ILD with FVC < 70% predicted	6.56	<0.001	3.50 – 12.30
34	ILD with DLCO < 60% predicted	9.01	<0.001	3.83 – 21.16
35	Dependence on home oxygen	9.54	<0.001	5.92 – 15.38
36	Symptoms of GERD confirmed on endoscopy	1.31	0.189	0.87 – 1.97
37	Esophageal dysmotility on symptoms and confirmed on testing	0.94	0.841	0.51 – 1.72
38	Esophageal stricture on endoscopy or barium swallow	2.04	0.002	1.30 – 3.20
39	Histologically proven Barrett's esophagus [^]	-	-	-
40	Symptoms of gastroparesis confirmed on gastric emptying test ^{**}	1.33	0.420	0.66 – 2.67
41	GAVE confirmed on endoscopy	1.98	0.019	1.12 – 3.50
42	Malabsorption syndrome responsive to cyclical antibiotics and/or probiotics ^{**}	1.35	0.416	0.65 – 2.80
43	BMI < 18.5 kg/m ² OR weight loss of > 10% in the last 12 months	2.29	<0.001	1.50 – 3.49
44	Need for intravenous hyperalimentation [*]	-	-	-
45	Need for enteral feeding [*]	-	-	-
46	Pseudo-obstruction confirmed on imaging	2.61	0.007	1.30 – 5.2
47	Rectal Prolapse [^]	-	-	-
48	Fecal incontinence	0.94	0.792	0.61 – 1.45
49	History of SRC	1.28	0.628	0.47 – 3.51
50	SRC with stage 5 renal impairment and need for renal replacement therapy	1.58	0.531	0.38 – 6.57
51	History of SRC and persistent renal impairment (eGFR < 45)	1.62	0.503	0.40 – 6.63
52	History of SRC with proteinuria (PCR > 25 mg/mmol) [*]	-	-	-
53	Lung malignancy with SSc ILD [^]	-	-	-
54	Bladder cancer with cyclophosphamide exposure ^{**^}	-	-	-
55	Osteoporosis on BMD with corticosteroids exposure ^{**^}	-	-	-
56	Osteoporosis with minimal trauma fracture with corticosteroid exposure ^{**^}	-	-	-
57	Premature gonadal failure ^{**^}	-	-	-
58	Cyclophosphamide induced cystitis ^{**^}	-	-	-

*Insufficient observations

**Removed by working group due to issues of clinical collinearity or feasibility

[^]Item not collected in ASCS database

Surrogate item used (for the item 'joint contractures in small joints only', the database variable of 'finger to palm distance >2cm' was used as a surrogate measure of joint contractures of the fingers; for the item 'joint contracture in large joints only' the surrogate of 'ever had a joint contracture' was used; for the item 'Sicca symptoms and signs confirmed on testing' the surrogate of 'sicca symptoms only' was used; for the item 'Scleroderma myocardial disease on clinical features and supported by MRI and/or endomyocardial biopsy' the surrogate of 'left ventricular ejection fraction <50%' was used)

Items shaded in grey retained and analysed in multivariable analysis

PIP = proximal interphalangeal, RHC = right heart catheterization, TTE = transthoracic echocardiogram, TAPSE = tricuspid annular plane systolic excursion, LVEF = left ventricular ejection fraction, MRI = magnetic resonance imaging, ECG = electrocardiography, ILD = interstitial lung disease, CXR = chest x-ray, HRCT = high resolution computed tomography, FVC = forced vital capacity, DLCO = diffusing capacity of the lung for carbon monoxide, GERD = gastroesophageal reflux disease, GAVE = gastric antral vascular ectasia, BMI = body mass index, SRC = scleroderma renal crisis, eGFR = estimated glomerular filtration rate, PCR = protein to creatinine ratio, BMD = bone mineral density.

Table 5. Univariable panel logistic regression for morbidity (dichotomised using the median PCS of SF 36 in derivation cohort)

	Item	OR	p value	95% CI
1	Joint contracture in any large and/or small joint**	3.44	<0.001	2.19 – 5.43
2	Joint contracture in any small joint of the fingers^	3.44	<0.001	2.19 – 5.43
3	Joint contracture in any large joints^	3.44	<0.001	2.19 – 5.43
4	Joint contracture of the fingers with finger to palm distance > 1cm**			
5	Bony erosions seen on radiographic imaging^	-	-	-
6	Acro-osteolysis on radiographic imaging^	-	-	-
7	Calcinosis on physical examination or radiograph**	2.16	0.003	1.30 – 3.58
8	Calcinosis complicated by infection or requiring surgery	8.20	0.003	2.03 – 33.14
9	Proximal muscle weakness on clinical examination	4.28	<0.001	2.42 – 7.56
10	Proximal muscle atrophy on clinical examination**	6.49	<0.001	3.55 – 11.87
11	Modified Rodnan Skin Score (MRSS) $\geq$ 20**	5.13	<0.001	2.84 – 9.26
12	Sicca signs confirmed on objective testing^	-	-	-
13	Sicca symptoms and signs confirmed on testing#	2.75	<0.001	1.72 – 4.39
14	Digital pitting scar **	1.53	0.045	1.01 – 2.33
15	Digital ulceration distal to PIPs in hands or feet	3.07	<0.001	1.91 – 4.93
16	Digital amputation	4.53	<0.001	2.06 – 9.98
17	Surgical limb amputation^	-	-	-
18	<u>Men only</u> : Persistent erectile dysfunction**	4.54	0.002	1.71 – 12.10
19	Late stage nailfold capillaroscopic changes	0.98	0.982	0.24 – 4.04
20	Pulmonary arterial hypertension confirmed on RHC	5.41	<0.001	2.90 – 10.11
21	Right ventricular failure on clinical assessment AND confirmed on TTE**	112.11	<0.001	19.47 – 645.51
22	Moderate to severe right ventricular dysfunction on TTE	7.58	<0.001	3.20 – 17.98
23	Right ventricular dilation and/or enlargement on TTE**	5.89	0.402	0.09 – 370.96
24	Left ventricular failure on clinical assessment and confirmed on TTE (LVEF < 50%)^	-	-	-
25	Left ventricular systolic dysfunction on TTE alone**	3.28	0.039	1.06 – 10.14
26	Moderate to severe left ventricular diastolic dysfunction on TTE	2.31	0.196	0.65 – 8.23
27	Scleroderma myocardial disease on clinical features and supported by MRI and/or endomyocardial biopsy#	3.28	0.039	1.06 – 10.14
28	Any conduction defect detected on ECG or Holter monitor	1.71	0.386	0.51 – 5.76
29	Insertion of PPM or implantable cardioverter defibrillator^	-	-	-
30	Reduced 6 minute walk distance < 250 meters**	58.04	<0.001	14.89 – 226.26
31	ILD of any extent on CXR or HRCT chest**	3.26	<0.001	1.79 – 5.93
32	ILD > 20% extent on HRCT chest	4.67	0.002	1.78 – 12.21

33	ILD with FVC < 70% predicted	36.46	<0.001	6.57 – 202.27
34	ILD with DLCO < 60% predicted	19.78	<0.001	5.91 – 66.18
35	Dependence on home oxygen	66.36	<0.001	10.43 – 422.25
36	Symptoms of GORD confirmed on endoscopy	3.16	<0.001	1.96 – 5.08
37	Esophageal dysmotility on symptoms and confirmed on testing	2.29	0.040	1.04 – 5.03
38	Esophageal stricture on endoscopy or barium swallow	2.56	0.001	1.69 – 7.50
39	Histologically proven Barrett's esophagus [^]	-	-	-
40	Symptoms of gastroparesis confirmed on gastric emptying test**	6.55	<0.001	2.31 – 18.54
41	GAVE confirmed on endoscopy	2.74	0.047	1.01 – 7.40
42	Malabsorption syndrome responsive to cyclical antibiotics and/or probiotics	1.94	0.230	0.66 – 5.74
43	BMI < 18.5 kg/m ² OR weight loss of > 10% in the last 12 months	3.27	<0.001	1.79 – 5.98
44	Need for intravenous hyperalimentation*	-	-	-
45	Need for enteral feeding*	-	-	-
46	Pseudo-obstruction confirmed on imaging	1.10	0.892	0.28 – 4.26
47	Chronic constipation **	1.78	0.008	1.17 – 2.73
	Rectal Prolapse [^]	-	-	-
48	Fecal incontinence	1.57	0.066	0.97 – 2.54
49	History of SRC	6.95	0.009	1.64 – 29.50
50	SRC with stage 5 renal impairment and need for renal replacement therapy	13.82	0.050	1.00 – 191.43
51	History of SRC and persistent renal impairment (eGFR < 45)	8.66	0.113	0.60 – 125.13
52	History of SRC with proteinuria (PCR > 25 mg/mmol)*	-	-	-
53	Lung malignancy with SSc ILD [^]	-	-	-
54	Bladder cancer with cyclophosphamide exposure**	-	-	-
55	Osteoporosis on BMD with corticosteroids exposure**	-	-	-
56	Osteoporosis with minimal trauma fracture with corticosteroid exposure**	-	-	-
57	Premature gonadal failure**	-	-	-
58	Cyclophosphamide induced cystitis**	-	-	-

*Insufficient observations

**Removed by working group due to issues of clinical collinearity or feasibility

[^]Item not collected in ASCS database

Surrogate item used (for the item 'joint contractures in small joints only', the database variable of 'finger to palm distance >2cm' was used as a surrogate measure of joint contractures of the fingers; for the item 'joint contracture in large joints only' the surrogate of 'ever had a joint contracture' was used; for the item 'Sicca symptoms and signs confirmed on testing' the surrogate of 'sicca symptoms only' was used; for the item 'Scleroderma myocardial disease on clinical features and supported by MRI and/or endomyocardial biopsy' the surrogate of 'left ventricular ejection fraction <50%' was used)

Items shaded in grey retained and analysed in multivariable analysis

PIP = proximal interphalangeal, RHC = right heart catheterization, TTE = transthoracic echocardiogram, TAPSE = tricuspid annular plane systolic excursion, LVEF = left ventricular ejection fraction, MRI = magnetic resonance imaging, ECG = electrocardiography, ILD = interstitial lung disease, CXR = chest x-ray, HRCT = high resolution computed tomography, FVC = forced vital capacity, DLCO = diffusing capacity of the lung for carbon monoxide, GERD = gastroesophageal reflux disease, GAVE = gastric antral vascular ectasia, BMI = body mass index, SRC = scleroderma renal crisis, eGFR = estimated glomerular filtration rate, PCR = protein to creatinine ratio, BMD = bone mineral density.

Table 6. Characteristics of the ASCS and CSRG data sets

	Number (%) or mean (SD)	
	ASCS	CSRG
Patient total	1568	1624
Female (%)	1359 (86.7)	1403 (86.4)
Disease subtype		
- diffuse	384(24.5)	596 (36.7)
- limited	1034 (65.9)	953 (58.7)
Age at disease onset* (yrs)	44 ± 15.3	45.9 ± 13.7
Disease duration at recruitment (yrs)	13.1 ± 12.7	9.6 ± 9.3
Patient recruited with 2 years of diagnosis	229 (14.6)	319 (19.6)
Patients recruited within 4 years of diagnosis	408 (26.0)	590 (36.3)
Follow up since recruitment (yrs)	4.8 ± 2.4	3.9 ± 3.2
No. of deaths	177 (11.3)	264 (16.3)

* Disease onset defined as date of onset of the first non-Raynaud manifestation

Table 7. Frequency of items and number of visits with data available for analysis in the ASCS dataset

	Item	Frequency (%) n=1568 patients	Missing (%)
1	Joint contracture in any large and/or small joint	536 (34.2)	79 (5.0)
2	Joint contracture in any small joint of the fingers#	827 (52.7)	329 (21.0)
3	Joint contracture in any large joints#	536 (34.2)	79 (5.0)
4	Joint contracture of the fingers with finger to palm distance > 1cm	827 (52.7)	329 (21.0)
5	Bony erosions seen on radiographic imaging^	-	-
6	Acro-osteolysis on radiographic imaging^	-	-
7	Calcinosis on physical examination or radiograph	538 (34.3)	0 (0)
8	Calcinosis complicated by infection or requiring surgery	46 (3.0)	0 (0)
9	Proximal muscle weakness on clinical examination	72 (4.6)	106 (6.8)
10	Proximal muscle atrophy on clinical examination	268 (17.1)	98 (6.3)
11	Modified Rodnan Skin Score (MRSS) $\geq$ 20	381 (24.3)	110 (7.0)
12	Sicca signs confirmed on objective testing^	-	-
13	Sicca symptoms and signs confirmed on testing	806 (51.4)	74 (4.7)
14	Digital pitting scar	821 (52.4)	70 (4.5)
15	Digital ulceration distal to PIPs in hands or feet	440 (28.1)	65 (4.2)
16	Digital amputation	149 (9.5)	68 (4.3)
17	Surgical limb amputation^	-	-
18	<u>Men only</u> : Persistent erectile dysfunction	57 (3.6)	0 (0%)
19	Late stage nailfold capillaroscopic changes^	-	-
20	Pulmonary arterial hypertension confirmed on RHC	249 (15.9)	0 (0)
21	Right ventricular failure on clinical assessment AND confirmed on TTE	51 (3.4)	49 (3.1)
22	Moderate to severe right ventricular dysfunction on TTE	264 (16.8)	116 (7.4)
23	Right ventricular dilation and/or enlargement on TTE	317 (20.2)	115 (7.9)
24	Left ventricular failure on clinical assessment and confirmed on TTE (LVEF < 50%)^	-	-
25	Left ventricular systolic dysfunction on TTE alone	57 (3.6)	0 (0)
26	Moderate to severe left ventricular diastolic dysfunction on TTE	117 (7.5)	0 (0)
27	Scleroderma myocardial disease on clinical features and supported by MRI and/or endomyocardial biopsy	107 (6.8)	0 (0)
28	Any conduction defect detected on ECG or Holter monitor	77 (4.9)	0 (0)
29	Insertion of PPM or implantable cardioverter defibrillator^	-	-
30	Reduced 6 minute walk distance < 250 meters	109 (7.0)	1320 (84.2)*
31	ILD of any extent on CXR or HRCT chest	335 (21.4)	0 (0)
32	ILD > 20% extent on HRCT chest	141 (9.0)	0 (0)
33	ILD with FVC < 70% predicted	60 (3.8)	83 (2.3)
34	ILD with DLCO < 60% predicted	90 (5.7)	22 (6.6)
35	Dependence on home oxygen	59 (3.8)	0 (0)
36	Symptoms of GORD confirmed on endoscopy	747 (47.6)	0 (0)
37	Esophageal dysmotility on symptoms and confirmed on testing	143 (9.1)	0 (0)
38	Esophageal stricture on endoscopy or barium swallow	171 (10.9)	0 (0)
39	Histologically proven Barrett's esophagus^	-	-

40	Symptoms of gastroparesis confirmed on gastric emptying test	79 (5.0)	0 (0)
41	GAVE confirmed on endoscopy	115 (7.3)	0 (0)
42	Malabsorption syndrome responsive to cyclical antibiotics and/or probiotics	76 (4.9)	0 (0)
43	BMI < 18.5 kg/m ² OR weight loss of > 10% in the last 12 months	801 (51.1)	137 (8.7)
44	Need for intravenous hyperalimentation	4 (0.2)	0 (0)
45	Need for enteral feeding	3 (0.2)	0 (0)
46	Pseudo-obstruction confirmed on imaging	45 (2.9)	0 (0)
47	Chronic constipation	673 (42.9)	66 (4.2)
48	Fecal incontinence	374 (23.9)	65 (4.2)
49	History of SRC	39 (2.5)	0 (0)
50	SRC with stage 5 renal impairment and need for renal replacement therapy	7 (0.5)	0 (0)
51	History of SRC and persistent renal impairment (eGFR < 30)	4 (0.3)	35 (2.2)
52	History of SRC with proteinuria (PCR > 25 mg/mmol)	11 (0.7)	28 (1.8)
53	Lung malignancy with SSc ILD [^]	-	-
54	Bladder cancer with cyclophosphamide exposure [^]	-	-
55	Osteoporosis on BMD with corticosteroids exposure [^]	-	-
56	Osteoporosis with minimal trauma fracture with corticosteroid exposure [^]	-	-
57	Premature gonadal failure [^]	-	-
58	Cyclophosphamide induced cystitis [^]	-	-

[^]Item not collected in ASCS database

Surrogate item used

*In the ASCS cohort, 6MWT is performed only in those with PAH

PIP = proximal interphalangeal, RHC = right heart catheterization, TTE = transthoracic echocardiogram, TAPSE = tricuspid annular plane systolic excursion, LVEF = left ventricular ejection fraction, MRI = magnetic resonance imaging, ECG = electrocardiography, ILD = interstitial lung disease, CXR = chest x-ray, HRCT = high resolution computed tomography, FVC = forced vital capacity, DLCO = diffusing capacity of the lung for carbon monoxide, GERD = gastroesophageal reflux disease, GAVE = gastric antral vascular ectasia, BMI = body mass index, SRC = scleroderma renal crisis, eGFR = estimated glomerular filtration rate, PCR = protein to creatinine ratio, BMD = bone mineral density.

Table 8. Frequency of items and number of visits with data available for analysis in the CSRG dataset

	Item	Frequency (%) n=1624 patients	Missing (%)
1	Joint contracture in any large and/or small joint	305 (18.8)	0 (0)
2	Joint contracture in any small joint of the fingers#	584 (36.0)	0 (0)
3	Joint contracture in any large joints#	305 (18.8)	0 (0)
4	Joint contracture of the fingers with finger to palm distance > 1cm	525 (36.7)	194 (11.9)
5	Bony erosions seen on radiographic imaging^	-	-
6	Acro-osteolysis on radiographic imaging^	-	-
7	Calcinosis on physical examination or radiograph	675 (41.6)	0 (0)
8	Calcinosis complicated by infection or requiring surgery	-	-
9	Proximal muscle weakness on clinical examination	236 (14.5)	1 (0.1)
10	Proximal muscle atrophy on clinical examination	-	-
11	Modified Rodnan Skin Score (MRSS) $\geq$ 20	349 (21.7%)	17 (1.0)
12	Sicca signs confirmed on objective testing^	-	-
13	Sicca symptoms and signs confirmed on testing	785 (48.3)	0 (0)
14	Digital pitting scar	970 (60.0)	8 (0.5)
15	Digital ulceration distal to PIPs in hands or feet	264 (16.3)	1 (0.1)
16	Digital amputation	134 (8.3)	2 (0.1)
17	Surgical limb amputation^	-	-
18	<u>Men only</u> : Persistent erectile dysfunction	9 (0.6)	17 (1.0)
19	Late stage nailfold capillaroscopic changes^	-	-
20	Pulmonary arterial hypertension confirmed on RHC	125 (7.7)	0 (0)
21	Right ventricular failure on clinical assessment AND confirmed on TTE	-	-
22	Moderate to severe right ventricular dysfunction on TTE	-	-
23	Right ventricular dilation and/or enlargement on TTE	-	-
24	Left ventricular failure on clinical assessment and confirmed on TTE (LVEF < 50%)^	81 (5.0)	0 (0)
25	Left ventricular systolic dysfunction on TTE alone	-	-
26	Moderate to severe left ventricular diastolic dysfunction on TTE	-	-
27	Scleroderma myocardial disease on clinical features and supported by MRI and/or endomyocardial biopsy	-	-
28	Any conduction defect detected on ECG or Holter monitor	545 (38.7)	216 (13.3)
29	Insertion of PPM or implantable cardioverter defibrillator^	-	-
30	Reduced 6 minute walk distance < 250 meters	44 (12.0)	1257 (77.4)*
31	ILD of any extent on CXR or HRCT chest	695 (42.8)	0 (0)
32	ILD > 20% extent on HRCT chest	365 (22.5)	0 (0)
33	ILD with FVC < 70% predicted	268 (16.5)	0 (0)
34	ILD with DLCO < 60% predicted	418 (25.7)	0 (0)
35	Dependence on home oxygen	117 (7.2)	0 (0)
36	Symptoms of GORD confirmed on endoscopy	-	-
37	Esophageal dysmotility on symptoms and confirmed on testing	1160 (71.4)	0 (0)

38	Esophageal stricture on endoscopy or barium swallow	218 (13.4)	6 (0.4)
39	Histologically proven Barrett's esophagus [^]	-	-
40	Symptoms of gastroparesis confirmed on gastric emptying test	-	-
41	GAVE confirmed on endoscopy	-	-
42	Malabsorption syndrome responsive to cyclical antibiotics and/or probiotics	324 (20.0)	6 (0.4)
43	BMI < 18.5 kg/m ² OR weight loss of > 10% in the last 12 months	361 (22.2)	0 (0)
44	Need for intravenous hyperalimentation	92 (5.7)	3 (0.2)
45	Need for enteral feeding	58 (3.9)	135
46	Pseudo-obstruction confirmed on imaging	146 (9.0)	3 (0.2)
47	Chronic constipation	600 (40.3%)	136
48	Fecal incontinence	465 (31.3%)	136
49	History of SRC	77 (4.8)	6 (0.4)
50	SRC with stage 5 renal impairment and need for renal replacement therapy	33 (2.0)	6 (0.4)
51	History of SRC and persistent renal impairment (eGFR < 30)	34 (2.1)	6 (0.4)
52	History of SRC with proteinuria (PCR > 25 mg/mmol)	44 (2.7)	6 (0.4)
53	Lung malignancy with SSc ILD [^]	-	-
54	Bladder cancer with cyclophosphamide exposure [^]	-	-
55	Osteoporosis on BMD with corticosteroids exposure [^]	-	-
56	Osteoporosis with minimal trauma fracture with corticosteroid exposure [^]	-	-
57	Premature gonadal failure [^]	-	-
58	Cyclophosphamide induced cystitis [^]	-	-

[^]Item not collected in ASCS database

Surrogate item used

*In the CSRG cohort, 6MWT is performed only in those with PAH

PIP = proximal interphalangeal, RHC = right heart catheterization, TTE = transthoracic echocardiogram, TAPSE = tricuspid annular plane systolic excursion, LVEF = left ventricular ejection fraction, MRI = magnetic resonance imaging, ECG = electrocardiography, ILD = interstitial lung disease, CXR = chest x-ray, HRCT = high resolution computed tomography, FVC = forced vital capacity, DLCO = diffusing capacity of the lung for carbon monoxide, GERD = gastroesophageal reflux disease, GAVE = gastric antral vascular ectasia, BMI = body mass index, SRC = scleroderma renal crisis, eGFR = estimated glomerular filtration rate, PCR = protein to creatinine ratio, BMD = bone mineral density.

Table 9. Frequency of final SCTC-DI items in CSRG patient registry

		Frequency (%)
	Musculoskeletal/Skin	
1	Joint contracture defined as any degree of contracture with the inability to reduce the joint to the anatomically neutral position in any small joint of the fingers	584 (36.0)
2	Joint contracture defined as any degree of contracture with the inability to reduce the joint to the anatomically neutral position in the large joints, specifically elbows and knees	305 (18.8)
3	Sicca symptoms defined as presence of patient reported dry eyes and/or dry mouth requiring treatment on a daily basis e.g. Lubricant eye drops, punctual plugs, saliva replacement etc.	785 (48.3)
4	Proximal muscle weakness on clinical examination defined as shoulder abduction and/or hip or knee flexion less than 5/5 power (not due to contracture or pain)	236 (14.5)
5	Calcinosis complicated by infection or requiring surgery	
	Vascular	
6	Digital ulceration defined as loss of epithelialization of any degree of the epidermis, the dermis and/or the subcutaneous tissue, distal to or at the proximal interphalangeal joint of the hands or feet not thought to be due to trauma and refractory to therapy	264 (16.3)
7	Digital amputation (surgical or autoamputation)	134 (8.3)
	Gastrointestinal	
8	Esophageal dysmotility defined as distal dysphagia refractory to treatment with differential diagnoses (eg. esophageal stricture or malignancy) excluded by endoscopy	1160 (71.4)
9	Pseudo-obstruction with symptoms such as vomiting or constipation, with dilatation of the small and/or large bowel on imaging	146 (9.0)
10	Need for intravenous hyperalimentation	92 (5.7)
11	Low body mass index (BMI) of < 18.5 kg/m ² OR weight loss of > 10% in the last 12 months	361 (22.2)
12	Gastric antral vascular ectasia confirmed on endoscopy	
13	Esophageal stricture confirmed on testing such as endoscopy or barium swallow	218 (13.4)
14	Symptoms of gastro-esophageal reflux disease (heart burn) refractory to treatment and confirmed on endoscopy	1029 (63.4)
	Respiratory	
15	Moderate to severe interstitial lung disease with > 20% extent on HRCT of the chest	365 (22.5)
16	Moderate to severe interstitial lung disease with > 20% extent on HRCT of the chest and forced vital capacity <70% on lung function tests	39 (7.1)
17	Dependence on home oxygen	117 (7.2)
	Cardiovascular	
18	Pulmonary arterial hypertension (defined as mean pulmonary arterial pressure > 25mmHg at rest and pulmonary arterial wedge pressure < 15mmHg on right heart catheterization)	125 (7.7)
19	Moderate to severe right ventricular dysfunction noted on echocardiography report based on assessment of any measure of RV function by experienced cardiologist	
20	Myocardial disease attributable to SSc based on a constellation of clinical features AND supportive investigations eg. syncope secondary to conduction abnormality, arrhythmia requiring defibrillator, heartblock requiring permanent pacemaker or ablation, systolic or diastolic dysfunction on TTE etc.	81 (5.0)
21	Presence of moderate to large pericardial effusion equivalent to greater than 1 cm on transthoracic echocardiogram	45 (2.8)
	Renal	
22	History of scleroderma renal crisis (SRC), either hypertensive or normotensive, as defined by the International Scleroderma Renal Crisis Study Investigators	77 (4.7)
23	History of SRC or other SSc related kidney disease and persistent renal impairment with estimated glomerular filtration rate < 45mL/min/1.73 m ²	34 (2.1)
24	SRC with stage 5 renal impairment defined as need for renal replacement therapy	33 (2.0)