**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** | * 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** | * Attribution can be difficult, therefore should be included * Need to differentiate damage due to SSc from comorbidities |
| **Regardless of etiology** | **8** | **7** | * 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** | * 6 months is appropriate for RCT’s |
| **> 12 months** | **5** | **12** | * Too long for RCT |
| **Variable depending on organ** | **12** | **3** | * 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** | * Damage due to therapy is a contributor to overall damage |
| Due to co-morbidities | **6** | **14** | * 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** | * 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** | * Has face/content validity, easy to implement and likely most useful time frame for randomized controlled trials |
| >12 months | **5** | **14** | * Depends on the item * This is congruent with REGISTRY DESIGN |
| Variable depending on organ | **12** | **8** | * 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** | * 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) |
| Men only: Persistent erectile dysfunction | 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 > 18cm2) 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 biopsy | 16(17.02) | 78(82.98) |
| 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/m2 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) > 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 | Men only: 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/m2 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 catherterization, 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) > 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 | Men only: 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/m2 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 catherterization, 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 * limited | 384(24.5)  1034 (65.9) | 596 (36.7)  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) > 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 | Men only: 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/m2 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 catherterization, 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) > 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 | Men only: 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/m2 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 catherterization, 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/m2 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 m2 | 34 (2.1) |
| 24 | SRC with stage 5 renal impairment defined as need for renal replacement therapy | 33 (2.0) |