# Progressive skin fibrosis is associated with a decline in lung function and worse survival in patients with diffuse cutaneous systemic sclerosis in the European Scleroderma Trials and Research (EUSTAR) cohort

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# ABSTRACT

**Objectives** To determine whether progressive skin fibrosis is associated with visceral organ progression and mortality during follow-up in patients with diffuse cutaneous systemic sclerosis (dcSSc).

**Methods** We evaluated patients from the EUSTAR database with dcSSc, baseline modified Rodnan skin score (mRSS) ≥7, valid mRSS at 12±3 months after baseline and ≥1 annual follow-up visit. Progressive skin fibrosis was defined as an increase in mRSS >5 and ≥25% from baseline to 12±3 months. Outcomes were pulmonary, cardiovascular and renal progression, and all-cause death. Associations between skin progression and outcomes were evaluated by Kaplan–Meier survival analysis and multivariable Cox regression.

**Results** Of 1021 included patients, 78 (7.6%) had progressive skin fibrosis (skin progressors). Median follow-up was 3.4 years. Survival analyses indicated that skin progressors had a significantly higher probability of forced vital capacity (FVC) decline ≥10% (53.6% versus 34.4%; p<0.001) and all-cause death (15.4% versus 7.3%; p=0.003) than non-progressors. These significant associations were also found in subgroup analyses of patients with either low baseline mRSS (≤22/51) or short disease duration (≤15 months). In multivariable analyses, skin progression within 1 year was independently associated with FVC decline ≥10% (hazard ratio [HR]: 1.79, 95% CI: 1.20–2.65) and all-cause death (HR: 2.58, 95% CI: 1.31–5.09).

**Conclusions** Progressive skin fibrosis within 1 year is associated with decline in lung function and worse survival in dcSSc during follow-up. These results confirm mRSS as a surrogate marker in dcSSc, which will be helpful for cohort enrichment in future trials and risk stratification in clinical practice.

# INTRODUCTION

Systemic sclerosis (SSc) is a highly heterogeneous connective tissue disease with major morbidity and mortality caused by the development of visceral organ complications. These include interstitial lung fibrosis, pulmonary arterial hypertension, scleroderma renal crisis (SRC), and cardiac and gastrointestinal involvement.[1] A major challenge for physicians is to identify patients at high risk of future complications before irreversible visceral involvement occurs. With several new disease-modifying agents in late-stage development,[2] improved identification of at-risk patients will become even more important to inform early treatment intervention. In addition, it will provide important information for cohort enrichment in future clinical trials.[3]

Skin fibrosis is a hallmark of SSc. The modified Rodnan skin score (mRSS) rates skin thickness from 0 (normal) to 3 (severe) at 17 body surface areas in a standardised manner.[4] The mRSS is feasible, reliable and sensitive to change, and is now commonly used in routine practice and clinical trials.[5-7]

Using the European Scleroderma Trials and Research (EUSTAR) database, we previously identified short disease duration (≤15 months) and low baseline mRSS (≤22/51) as independent predictors of progressive skin fibrosis (defined as >5 units and ≥25% increment in mRSS at 1-year follow-up) in patients with diffuse cutaneous SSc (dcSSc).[8 9] While this evidence-based strategy of including dcSSc patients with low baseline mRSS can improve cohort enrichment for progressive skin fibrosis in clinical trials,[10] it might lead to recruitment of patients with overall milder disease. Previous studies have suggested that mRSS may be a potential surrogate marker for disease severity and mortality, but these data were derived from old studies (Pittsburgh) and/or selected patients from clinical trials (D-penicillamine).[11 12] Therefore, new data are required to clarify whether worsening skin fibrosis is an appropriate surrogate marker for new onset or deterioration of visceral organ disease and overall survival in dcSSc.

In a previous single-centre retrospective study of patients with early dcSSc, patients with high baseline mRSS and no subsequent skin improvement within 2 years had significantly higher mortality than those with skin improvement irrespective of baseline mRSS, while the results for internal organ-based endpoints were contradictory.[13] The study thus suggested the prognostic value of the evolution of skin fibrosis, in addition to absolute skin scores, in predicting disease outcome for dcSSc patients.

We herein hypothesised that progression of skin fibrosis within 1 year might be associated with progression of visceral organ disease and mortality in dcSSc during follow-up. The aim of the current study was to test this hypothesis in the large, systematic, longitudinal, real-life EUSTAR registry.

# METHODS

More details on methods can be found in the online supplement.

## Patients and study design

For this observational study, data from patients' visits from 1 January 2009 to 31 August 2017 were exported from the EUSTAR database. The structure of the EUSTAR database and minimum essential dataset have been described previously.[14 15]

Inclusion criteria for the study were: classification of SSc (1980 American College of Rheumatology criteria[16]); diffuse cutaneous involvement as described by LeRoy *et al*;[17] at least 1 available annual follow-up visit; mRSS ≥7 (the minimal value for subclassification as dcSSc) at the first available visit (baseline); and valid mRSS data at 12±3 months after baseline.

## Definition of 'progressor' patients

Patients with progression of skin fibrosis (skin progressors) were defined as those with an increase in mRSS >5 units and by ≥25% from baseline to 12±3 months. This mRSS threshold is considered as the minimally clinical important difference.[18] The 1-year period to define skin progression was chosen as it is considered sufficient to capture significant changes in mRSS, and is thus frequently used in clinical trials in skin fibrosis.[19]

## Follow-up and outcome measures

Follow-up was defined as the time between the first available visit (baseline) and the last available annual follow-up for each patient. All outcome events were accounted during this period. Outcome measures reflecting visceral organ progression were defined by consensus of an expert group (YA, MM-C, JEP, CD, DK and OD) using the nominal group technique. Organ progression was defined as occurrence of one of the following events during follow-up: (1) relative decrease in forced vital capacity (FVC) ≥10% from baseline; (2) reduction of left ventricular ejection fraction (LVEF) to <45%, or relative decrease of LVEF >10% for patients with baseline LVEF <45%, assessed by echocardiography; (3) new-onset pulmonary hypertension (PH) as globally judged on echocardiography by the treating physician; (4) new-onset SRC; (5) all-cause death.[25,35,36,45] Overall disease progression was defined

as the presence of any of the above outcomes. In addition, an exploratory analysis in which lung progression was defined as a relative decrease from baseline to follow-up in FVC ≥10%, or 5–9% combined with diffusing capacity for carbon monoxide (DLCO) ≥15% (instead of definition 1), was performed based on recently proposed criteria.[20]

## Statistical analysis

Baseline characteristics were described as mean (standard deviation [SD]) for continuous variables and number (frequency) for categorical variables. Baseline variables were compared between skin progressors and non-progressors by univariate analysis followed by Bonferroni correction. Chi-squared tests or Fisher's exact tests were used for categorical variables, and independent sample *t* tests were used for continuous variables.

Kaplan–Meier curves and log-rank tests were performed to compare outcomes between skin progressors and non-progressors for up to 8 years of follow-up. Only the first event was considered. Patients with PH or SRC at baseline were excluded from analyses of PH and SRC outcomes, as these patients could not show any new event of these types. Kaplan–Meier analyses were also conducted in subgroups stratifying patients by either baseline mRSS (≤22/51 versus >22/51 units) or disease duration (≤15 versus >15 months). Multivariable Cox regression analyses were performed to examine independent associations between skin progression and both FVC decline ≥10% and all-cause death. Confounding variables for multivariable cox regression models were selected using the nominal group technique. Spearman rho analyses were conducted to measure the correlation between variables before multivariable regression. Multiple imputation with 10 imputed datasets was used before regression analysis to handle missing values.

Significance was defined as p<0.05. Statistical analyses were performed by the biostatistician (NG) using R programming language (version 3.3.3), packages 'survival' and 'mice'.[21-23]

# RESULTS

## Baseline characteristics

In total, 1021 patients were included for analysis, of whom 78 (7.6%) had progression of skin fibrosis at 1-year follow-up. Demographic and clinical characteristics are summarised in table 1. Mean age was 52.0 years, mean disease duration was 7.7 years and mean±SD mRSS was 16.9±7.7 at baseline. Median follow-up was 3.4 years. By using Bonferroni correction, the modified critical p value (α) was

determined as 0.0013. Skin progressors had a significantly shorter disease duration at baseline than non-progressors, confirming previous results.[8] [9] All other baseline characteristics were comparable between groups (table 1).

**Table 1** Baseline demographic and clinical characteristics of skin progressors and non-progressors

| Characteristics | Missing cases, n (%) | Whole cohort (n=1021) | Progressors (n=78) | Non-progressors (n=943) | p-value |
|---|---|---|---|---|---|
| *Demographic* | | | | | |
| Age, years (mean±SD) | 0 (0) | 52.0±13.7 | 51.7±12.9 | 52.0±13.7 | 0.869 |
| Male sex | 0 (0) | 248 (24.3) | 30 (38.5) | 218 (23.1) | 0.004 |
| Disease duration* | | | | | |
|     Years (mean±SD) | 78 (7.6) | 7.7±7.5 | 5.3±6.2 | 7.9±7.5 | 0.006 |
|     ≤15 months | 78 (7.6) | 126 (13.4) | 19 (27.9) | 107 (12.2) | <0.001 |
|     ≤36 months | 78 (7.6) | 298 (31.6) | 36 (52.9) | 262 (29.9) | <0.001 |
| *Vascular* | | | | | |
| Raynaud's phenomenon | 2 (0.2) | 997 (97.8) | 74 (94.9) | 923 (98.1) | 0.141 |
| Digital ulcers | 11 (1.1) | 384 (38.0) | 30 (38.5) | 354 (38.0) | 1.000 |
| Active digital ulcers | 25 (2.4) | 199 (20.0) | 16 (21.1) | 183 (19.9) | 0.925 |
| *Skin* | | | | | |
| mRSS, unit (mean±SD) | 0 (0) | 16.9±7.7 | 14.8±6.2 | 17.1±7.7 | 0.010 |
| mRSS ≤22/51 | 0 (0) | 819 (80.2) | 67 (85.9) | 752 (79.7) | 0.245 |
| *Musculoskeletal* | | | | | |
| Tendon friction rubs | 11 (1.1) | 156 (15.4) | 10 (13.0) | 146 (15.6) | 0.648 |
| Joint synovitis | 6 (0.6) | 180 (17.7) | 16 (20.5) | 164 (17.5) | 0.607 |
| Joint contractures | 7 (0.7) | 505 (49.8) | 42 (53.8) | 463 (49.5) | 0.532 |
| Muscle weakness | 6 (0.6) | 255 (25.1) | 17 (22.1) | 238 (25.4) | 0.614 |
| *Gastrointestinal* | | | | | |
| Oesophageal symptoms | 1 (0.1) | 687 (67.4) | 51 (65.4) | 636 (67.5) | 0.795 |
| Stomach symptoms | 2 (0.2) | 300 (29.4) | 27 (34.6) | 273 (29.0) | 0.361 |
| Intestinal symptoms | 3 (0.3) | 281 (27.6) | 21 (26.9) | 260 (27.7) | 0.994 |
| *Cardiopulmonary* | | | | | |
| Dyspnoea (NYHA) | 84 (8.2) | | | | 0.186 |
|     Stage 1 | | 520 (55.5) | 34 (51.5) | 486 (55.8) | |
|     Stage 2 | | 315 (33.6) | 28 (42.4) | 287 (33.0) | |
|     Stage 3/4 | | 102 (10.9) | 4 (6.1) | 98 (11.2) | |
| Diastolic dysfunction | 150 (14.7) | 195 (22.4) | 12 (18.5) | 183 (22.7) | 0.526 |
| Pericardial effusion | 215 (21.1) | 59 (7.3) | 7 (12.1) | 52 (7.0) | 0.238 |
| Conduction blocks | 124 (12.1) | 123 (13.7) | 6 (8.8) | 117 (14.1) | 0.300 |

| Characteristics | Missing cases, n (%) | Whole cohort (n=1021) | Progressors (n=78) | Non-progressors (n=943) | p-value |
|---|---|---|---|---|---|
| LVEF <45% | 266 (26.1) | 16 (2.1) | 2 (3.4) | 14 (2.0) | 0.797 |
| Pulmonary hypertension by echocardiography† | 138 (13.5) | 120 (13.6) | 11 (16.7) | 109 (13.3) | 0.568 |
| Lung fibrosis on CT scan | 351 (34.4) | 403 (60.1) | 33 (60.0) | 370 (60.2) | 1.000 |
| FVC, % predicted (mean±SD) | 168 (16.5) | 87.0±20.7 | 86.6±17.5 | 87.0±20.9 | 0.879 |
| FVC <70% predicted | 168 (16.5) | 182 (21.3) | 13 (21.7) | 169 (21.3) | 1.000 |
| $FEV_1$, % predicted (mean±SD) | 272 (26.6) | 85.7±18.4 | 87.2±16.5 | 85.6±18.6 | 0.547 |
| TLC, % predicted, (mean±SD) | 427 (41.8) | 86.6±20.6 | 86.5±15.3 | 86.6±20.9 | 0.991 |
| DLCO, % predicted (mean±SD) | 179 (17.5) | 65.6±19.3 | 65.6±17.2 | 65.6±19.4 | 0.995 |
| DLCO <70% predicted | 179 (17.5) | 479 (56.9) | 33 (57.9) | 446 (56.8) | 0.984 |
| *Kidney* | | | | | |
| Renal crisis history | 4 (0.4) | 30 (2.9) | 2 (2.6) | 28 (3.0) | 1.000 |
| *Laboratory parameters* | | | | | |
| ANA positive | 16 (1.6) | 961 (95.6) | 75 (96.2) | 886 (95.6) | 1.000 |
| ACA positive | 64 (6.3) | 88 (9.2) | 6 (8.2) | 82 (9.3) | 0.929 |
| Anti-Scl-70 positive | 42 (4.1) | 616 (62.9) | 49 (66.2) | 567 (62.7) | 0.628 |
| Anti-U1RNP positive | 237 (23.2) | 35 (4.5) | 1 (1.6) | 34 (4.7) | 0.514 |
| Anti-RNA polymerase III positive | 453 (44.4) | 58 (10.2) | 5 (9.8) | 53 (10.3) | 1.000 |
| Creatinine kinase elevation | 75 (7.3) | 100 (10.6) | 8 (10.8) | 92 (10.6) | 1.000 |
| Proteinuria | 78 (7.6) | 64 (6.8) | 5 (6.9) | 59 (6.8) | 1.000 |
| Hypocomplementaemia | 192 (18.8) | 58 (7.0) | 3 (4.8) | 55 (7.2) | 0.613 |
| ESR >25 mm/h | 117 (11.5) | 371 (41.0) | 24 (35.3) | 347 (41.5) | 0.382 |
| CRP elevation | 63 (6.2) | 294 (30.7) | 31 (41.9) | 263 (29.8) | 0.041 |
| Active disease (VAI>3)‡ | 154 (15.1) | 340 (39.2) | 20 (30.8) | 320 (39.9) | 0.187 |
| Immunosuppressive therapy§ | 66 (6.5) | 667 (69.8) | 54 (73.0) | 613 (69.6) | 0.632 |

Definitions of items and organ manifestation are according to EUSTAR.[14]

Data are presented as number (%) unless otherwise stated.

p-values of univariate comparisons of baseline characteristics between skin progressors and non-progressors are shown (Chi-squared tests or Fisher's exact tests used for categorical variables and independent sample *t* tests used for continuous variables, as appropriate).

*Disease duration was calculated as the difference between the date of the baseline visit and the date of the first non-Raynaud's symptom of the disease as reported by the patient.

†Pulmonary hypertension was globally judged on echocardiography by the treating physician.

‡Active disease was defined as a score >3 by calculating European Scleroderma Study Group disease activity indices for systemic sclerosis proposed by Valentini *et al.*[24]

§Immunosuppressive therapy was defined as treatment with corticosteroids (prednisone dose ≥2.5 mg/day or other dosage forms in equal dose) or any immunosuppressant.

ACA, anti-centromere antibody; ANA, antinuclear antibody; anti-Scl-70, anti-topoisomerase 1 antibody; CRP, C-reactive protein; CT, computed tomography; DLCO, diffusing capacity for carbon monoxide; ESR, erythrocyte

sedimentation rate; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; mRSS, modified Rodnan skin score; NYHA, New York Heart Association; TLC, total lung capacity; VAI, Valentini activity index.

## Associations between skin progression and visceral organ progression

Lung progression

In total, 282 of 788 patients (35.8%) met the FVC definition of lung progression (relative decrease in FVC ≥10%) during a median follow-up of 3.7 years (interquartile range [IQR]: 1.8–6.2 years). In the overall cohort, 403 of 670 patients (60.1%) had lung fibrosis on CT scan at baseline. The mean±SD FVC at baseline was 86.9±20.5%, with 164 patients (20.8%) having a baseline FVC <70%. There were 30 (53.6%) and 252 (34.4%) events in the skin progressor and non-progressor groups, respectively. The probability of FVC decline was significantly higher for skin progressors than non-progressors (log-rank test p<0.001; figure 1A). In the subgroups of patients with low baseline mRSS and short disease duration, which reflect evidence-based recruitment parameters for recent clinical trials in skin fibrosis,[8] skin progressors also had a significantly higher probability of FVC decline than non-progressors (baseline mRSS ≤22/51 units: 27/47 [57.4%] versus 202/596 [33.9%], p<0.001; disease duration ≤15 months: 7/12 [58.3%] versus 26/89 [29.2%], p=0.019, respectively) (figures 2A and C). There was no significant difference in the probability of FVC decline in the subgroups of patients with baseline mRSS >22/51 units and disease duration >15 months (figures 2B and D).

Overall, 320 of 781 patients (41.0%) met the FVC-DLCO composite definition of lung progression (relative decrease in FVC ≥10%, or 5–9% combined with DLCO ≥15%) during a median follow-up of 3.9 years (IQR: 1.9–6.2 years). There were 31 (56.4%) and 289 (39.8%) events in the skin progressor and non-progressor groups, respectively. Again the probability of FVC-DLCO decline was significantly higher for skin progressors than non-progressors (log-rank test p=0.004; figure 1B). In the subgroup of patients with low baseline mRSS, skin progressors also had a significantly higher probability of FVC-DLCO decline than non-progressors (27/47 [57.5%] versus 237/590 [40.2%]; p=0.002). In patients with short disease duration, skin progressors had a trend towards higher probability of FVC-DLCO decline than non-progressors (7/11 [63.6%] versus 29/89 [32.6%]; p=0.050). In the subgroups of patients with baseline mRSS >22/51 units and disease duration >15 months, no significant difference was seen in the probability of FVC-DLCO decline between groups (online supplementary figure S1).

Systolic heart dysfunction and SRC

Despite the large patient cohort, a low number of systolic heart dysfunction and SRC events occurred, limiting interpretation of the data.

During a median follow-up of 3.2 years (IQR: 1.3–5.5 years), 15 of 662 patients (2.3%) cumulatively had an LVEF reduction. There were 3 (6.3%) and 12 (2.0%) events in the skin progressor and non-progressor groups, respectively. The probability of LVEF reduction was significantly higher for skin progressors than non-progressors (log-rank test p=0.038; online supplementary figure S2A). However, there was no significant difference in the probability of LVEF reduction between patients with and without skin progression in any subgroup when stratified by either baseline mRSS or disease duration.

During a median follow-up of 3.1 years (IQR: 1.6–5.6 years), 21 of 985 patients (2.1%) cumulatively had a new SRC. There were 0 (0.0%) and 21 (2.3%) events in the skin progressor and non-progressor groups, respectively, and no significant difference in the probability of a new SRC between groups (log-rank test p=0.196; online supplementary figure S2B). When stratified by either baseline mRSS or disease duration, no significant difference in the probability of a new SRC was observed between patients with and without skin progression in any subgroup.

PH

During a median follow-up of 3.8 years (IQR: 1.9–5.8 years), 109 of 693 patients (15.7%) developed new PH. There were 5 (10.4%) and 104 (16.1%) events in the skin progressor and non-progressor groups, respectively, with no significant difference in probability of new PH between groups (log-rank test p=0.316; online supplementary figure S2C). When stratified by either baseline mRSS or disease duration, the only significant difference in probability of new PH between groups occurred in patients with disease duration >15 months, in whom skin progressors had a significantly lower probability of new PH compared with non-progressors (0/28 [0.0%] versus 89/528 [16.9%], respectively; p=0.026).

All-cause death

During a median follow-up of 3.4 years (IQR: 1.8–5.9 years), 81 of 1021 patients (7.9%) died. There were 12 (15.4%) and 69 (7.3%) deaths in the skin progressor and non-progressor groups, respectively. The probability of all-cause death was significantly higher for skin progressors than non-progressors (log-rank test p=0.003; figure 1C). In the subgroups of patients with low baseline mRSS

and short disease duration, skin progressors also had a significantly higher probability of all-cause death than non-progressors (baseline mRSS ≤22/51 units: 9/67 [13.4%] versus 54/752 [7.2%], p=0.017; disease duration ≤15 months: 4/19 [21.1%] versus 3/107 [2.8%], p=0.009, respectively) (figures 3A and C). In the subgroups of patients with baseline mRSS >22/51 units and disease duration >15 months, there was no significant difference in probability of all-cause death between groups (figures 3B and D).

Overall disease progression

During a median follow-up of 4.6 years (IQR: 2.2–6.6 years), 389 of 685 patients (56.8%) cumulatively had overall disease progression as defined above. There were 37 (74.0%) and 352 (55.4%) events in the skin progressor and non-progressor groups, respectively. The probability of overall disease progression was significantly higher for patients with skin progression than those without (log-rank test p=0.012; figure 1D). In the subgroups of patients with low baseline mRSS and short disease duration, skin progressors also had a significantly higher probability of overall disease progression than non-progressors (baseline mRSS ≤22/51 units: 33/45 [73.3%] versus 283/521 [54.3%], p=0.010; disease duration ≤15 months: 10/11 [90.9%] versus 31/71 [43.7%], p<0.001, respectively) (figures 4A and C). In the subgroups of patients with baseline mRSS >22/51 units and disease duration >15 months, no significant difference was observed in the probability of overall disease progression between groups (figures 4B and D).

Independent associations between skin progression and FVC decline and all-cause death

In the final multivariable Cox regression models, skin progression was independently associated with FVC decline ≥10% (hazard ratio [HR]: 1.79; 95% confidence interval [CI]: 1.20–2.65; p=0.004) and all-cause death (HR: 2.58; 95% CI: 1.31–5.09; p=0.006). History of SRC, LVEF <45%, FVC <70%, DLCO <70% and age at baseline were also independently associated with all-cause death (table 2). Skin progression had a trend-towards association with overall disease progression (HR: 1.40; 95% CI: 0.98–1.99; p=0.063) (online supplementary table S1).

**Table 2** Independent factors associated with FVC decline ≥10% and all-cause death as determined by multivariable Cox regression

| Baseline characteristics | HR (95% CI) |
|---|---|
| *FVC decline ≥10%* | |
| **Skin progression** | 1.79 (1.20–2.65) |
| Age | 1.00 (0.99–1.01) |
| Male sex | 0.89 (0.67–1.19) |
| mRSS | 1.01 (0.99–1.03) |
| Disease duration | 1.00 (0.99–1.00) |
| Lung fibrosis on CT scan | 1.25 (0.90–1.72) |
| Pulmonary hypertension by echocardiography | 1.31 (0.93–1.85) |
| Dyspnoea NYHA stage ≥2 | 1.23 (0.94–1.62) |
| Joint synovitis | 1.10 (0.81–1.49) |
| FVC <70% predicted | 0.89 (0.64–1.24) |
| DLCO <70% predicted | 1.28 (0.97–1.69) |
| Anti-Scl-70 positive | 0.99 (0.75–1.29) |
| ACA positive | 1.07 (0.69–1.66) |
| CRP elevation | 1.22 (0.92–1.60) |
| *All-cause death* | |
| **Skin progression** | 2.58 (1.31–5.09) |
| **Age** | 1.05 (1.03–1.07) |
| Male sex | 1.56 (0.95–2.57) |
| Lung fibrosis on CT scan | 1.68 (0.84–3.36) |
| Pulmonary hypertension by echocardiography | 0.84 (0.47–1.50) |
| **Renal crisis history** | 3.15 (1.18–8.43) |
| Digital ulcers | 1.58 (0.99–2.53) |
| Proteinuria | 1.50 (0.74–3.04) |
| **LVEF <45%** | 3.51 (1.22–10.12) |
| **FVC <70% predicted** | 2.60 (1.49–4.55) |
| **DLCO <70% predicted** | 2.00 (1.04–3.84) |

Factors highlighted in bold are significantly associated with the outcome.

Skin progression is defined as an increase in mRSS >5 and ≥25% from baseline to 12±3 months later.

ACA, anti-centromere antibody; anti-Scl-70, anti-topoisomerase 1 antibody; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; HR, hazard ratio; LVEF, left ventricular ejection fraction; mRSS, modified Rodnan skin score; NYHA, New York Heart Association.

# DISCUSSION

We investigated the association between skin progression and subsequent visceral organ progression in the large, prospective, multicentre, real-life EUSTAR cohort. Our findings indicate that patients with dcSSc and skin progression within 1 year have a higher probability of lung progression and worse survival during follow-up. These findings suggest that such patients should be monitored very carefully in clinical practice. The results also support the concept that inclusion of patients with lower mRSS or shorter disease duration can enrich clinical trials for progressive skin fibrosis, and this enrichment leads to study populations with more severe disease at higher risk of organ progression and overall death. Notably, this increased risk of more severe disease occurs at >1 year's follow-up and will thus not be detectable in a classical 1-year randomised controlled trial. Our findings emphasise that mRSS progression within 1 year is an appropriate surrogate marker for more severe disease during follow-up.

This study also provides evidence for cohort enrichment in clinical studies aiming primarily at lung fibrosis. Several parameters, including dcSSc, anti-topoisomerase 1-positive status and decreased baseline FVC have been identified in multiple studies as predictors of lung progression in SSc.[25-32] However, few studies have focused specifically on patients with dcSSc. In the current EUSTAR analysis, skin progression was associated with subsequent decline of lung function in dcSSc patients, even after adjustment for potentially confounding predictors. We examined two definitions of lung progression based on pulmonary function tests. The conventional definition (relative decrease in FVC ≥10%), based on expert group consensus, has been widely used as an endpoint in previous clinical studies, while the exploratory FVC-DLCO composite definition has recently been shown to predict mortality in patients with SSc-related interstitial lung disease.[33] Analyses with both definitions produced similar results, strengthening our findings.

We also found that skin progression within 1 year was independently associated with higher all-cause mortality. Previously, several prognostic studies have tried to predict mortality in SSc patients. The most common baseline characteristics independently associated with worse survival reported in different cohorts include older age, male sex, dcSSc, lung fibrosis, PH, systolic heart dysfunction, restrictive lung function defect, defective diffusing capacity of the lung, proteinuria, history of SRC and digital ulcers, all of which have been confirmed in studies derived from the EUSTAR database.[34-44] We included these potentially significant and clinically relevant predictors in our

multivariable Cox regression analysis, and found that skin progression, along with several other factors, was still an independent prognostic factor for all-cause death.

In our cohort, average disease duration at baseline was >7 years, indicating that most cases were not early disease. In subgroup analyses, we confirmed that disease course is worse in dcSSc patients with early disease, although there were also patients with later-stage disease who showed organ progression. This underlines the heterogeneity of the disease course and clinicians should therefore pay attention to all patients with progression of skin fibrosis, even those with longer disease duration. Our findings are supported by the results of a study that focused on early dcSSc using a different definition of skin progression.[45]

One limitation of our analysis is the problem of missing values and loss to follow-up, which was inevitable in such a huge multicentre registry database. This partly explains the low number of patients during long-term follow-up. However, we tried to overcome this by multiple imputation before regression analysis and for most variables there were relatively few missing values. Second, we were unable to determine specific causes of death at all participating centres, and therefore only all-cause mortality, regardless of attribution to SSc, could be assessed. However, all-cause mortality is considered a more robust measure of disease outcome than SSc-associated mortality, as cause of death is often difficult to assign. Third, there was a relatively high proportion of new PH cases during follow-up in our cohort. This was the result of basing the definition on assessment of PH on echocardiography by the treating physician rather than on right heart catheterisation, which is required for formal diagnosis of PH. Unfortunately, right heart catheterisation data are not reliably available in the EUSTAR database, and echocardiography was the best available approximation of PH for the present analysis. Finally, as a result of the observational design, we did not evaluate the effect of treatment on outcomes. However, treatment of SSc, especially with immunosuppressive therapy, is always individualised and organ specific, and it is therefore difficult to accurately exclude the influence of treatment in an unselected heterogeneous cohort. In addition, there is a meaningful treatment-by-indication error in observational studies, making interpretation of results difficult. In our cohort, the proportions of patients receiving immunosuppressive treatment between groups at baseline were equal.

In conclusion, progressive skin fibrosis is associated with decline in lung function and worse survival in dcSSc during follow-up. The evidence-based findings obtained from the large prospective

EUSTAR cohort allow optimisation of cohort enrichment in future clinical trials aimed at skin and lung fibrosis, and also help clinicians to identify patients at risk of lung progression in clinical practice.

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**Ethics approval** All contributing EUSTAR centres have obtained approval from their respective local ethics committee for including patients' data in the EUSTAR database and written informed consent was obtained in those centres, where required by the ethics committee.

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## FIGURE LEGENDS

**Figure 1** Kaplan–Meier survival plots for (A) time to FVC decline ≥10%, (B) time to FVC-DCLO composite endpoint, (C) time to all-cause death and (D) time to overall disease progression during follow-up depending on the presence or absence of skin progression within 1 year. DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity.

**Figure 2** Kaplan–Meier survival plots for FVC decline ≥10% during follow-up depending on the presence or absence of skin progression within 1 year in subgroups of patients with (A) baseline mRSS ≤22/51 units, (B) baseline mRSS >22/51 units, (C) disease duration ≤15 months and (D) disease duration >15 months. FVC, forced vital capacity; mRSS, modified Rodnan skin score.

**Figure 3** Kaplan–Meier survival plots for all-cause death during follow-up depending on the presence or absence of skin progression within 1 year in subgroups of patients with (A) baseline mRSS ≤22/51 units, (B) baseline mRSS >22/51 units, (C) disease duration ≤15 months and (D) disease duration >15 months. mRSS, modified Rodnan skin score.

**Figure 4** Kaplan–Meier survival plots for overall disease progression during follow-up depending on the presence or absence of skin progression within 1 year in subgroups of patients with (A) baseline mRSS ≤22/51 units, (B) baseline mRSS >22/51 units, (C) disease duration ≤15 months and (D) disease duration >15 months. mRSS, modified Rodnan skin score.

**Supplementary Figure S1** Kaplan–Meier survival plots for FVC-DLCO composite endpoint during follow-up depending on the presence or absence of skin progression within 1 year in subgroups of patients with (A) baseline mRSS ≤22/51 units, (B) baseline mRSS >22/51 units, (C) disease duration ≤15 months and (D) disease duration >15 months. DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; mRSS, modified Rodnan skin score.

**Supplementary Figure S2** Kaplan–Meier survival plots for (A) time to LVEF reduction, (B) time to new renal crisis and (C) time to new pulmonary hypertension during follow-up depending on the presence or absence of skin progression within 1 year. LVEF, left ventricular ejection fraction.

Figure 1

Figure 2

Figure 3

Figure 4