Arthritis Research & Therapy

RESEARCH

Open Access

Does regression of skin thickening predict improvement of internal organ involvement and survival in patients with diffuse cutaneous systemic sclerosis? A EUSTAR analysis

Anja Wyss[1], Suzana Jordan[1], Nicole Graf[2], Patricia E. Carreira[3], Jörg Distler[4,5], Marco Matucci Cerinic[6], Elise Siegert[7], Jörg Henes[8], Elisabetta Zanatta[9], Valeria Riccieri[10], Marie-Elise Truchetet[11], Fahrettin Oksel[12], Mengtao Li[13], Eugene J. Kucharz[14], Kilian Eyerich[15], Francesco Del Galdo[16], Madelon C. Vonk[17], Anna-Maria Hoffman Vold[18], Armando Gabrielli[5,19], Oliver Distler[1*] and EUSTAR collaborators

Abstract

Objective Patients with diffuse cutaneous systemic sclerosis (dcSSc) frequently show spontaneous improvement of skin fibrosis. Our aim was to examine whether an improvement in skin fibrosis predicts lower likelihood of visceral organ progression and better survival.

Methods Patients from the European Scleroderma Trials and Research (EUSTAR) cohort with dcSSc, baseline modified Rodnan skin score (mRSS) ≥7, and valid mRSS at 12±3 months follow up were included. Regression/progression of skin fibrosis was defined as a decrease/increase in mRSS >5 points and≥25% from baseline to follow up. The outcomes included progression of lung, renal, cardiac and gastrointestinal manifestations using consensus derived definitions and all-cause death. Regressive, stable and progressive patients were compared by univariate, Kaplan-Meier survival curve and Cox regression analysis.

Results Of 1257 included patients, 883 (70.2%) were stable, 282 (22.4%) regressive, and 92 (7.3%) progressive. Regressive patients, adjusted for baseline mRSS, baseline immunosuppression, baseline FVC, and disease duration, showed a significantly lower probability of FVC decline ≥10% than progressive patients (p=0.00003), lower probability of all-cause mortality during follow up (p=0.035) compared to progressive patients. .Improvement of skin fibrosis was not associated with progression of other organ manifestations.

Conclusion We found that regression of skin fibrosis is associated with a lower probability of lung progression and better survival at follow up. The link between the disease course of skin and lung fibrosis in SSc can help to better stratify patients in clinical practice and enrich for ILD progressive patients in clinical trials.

Key messages

• Diffuse SSc patients with improvement of skin fibrosis had a lower probability of lung function progression and all-cause mortality than skin progressive patients.

*Correspondence:
Oliver Distler
oliver.distler@usz.ch
Full list of author information is available at the end of the article

• This allows better risk stratification of SSc patients in clinical practice.

• It could help to improve the design of clinical trials in SSc and better enrichment of ILD progressive patients.

Keywords Scleroderma and related disorders, Skin, Observation studies, Rare diseases, Respiratory

Introduction

Systemic sclerosis (SSc) is a rare autoimmune disease with complex visceral organ involvement leading to substantial morbidity and mortality. As such, interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), scleroderma renal crisis (SRC), and cardiac or gastrointestinal involvement can occur [1]. The identification of patients at high risk for further complications is challenging for physicians.

Skin fibrosis is a hallmark feature of SSc. The modified Rodnan skin score (mRSS) is a semi-quantitative method for the assessment of skin fibrosis. It meets the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) criteria as a validated outcome measure and a surrogate for more severe internal organ involvement and mortality in early diffuse SSc. The mRSS has been playing an important role in clinical trials and it has been the most frequently used primary endpoint [2–5]. It evaluates skin thickness on a scale from 0 (normal) to 3 (severe) at 17 different and standardized body surface areas [6]. Importantly, the mRSS is also the key component of the new revised American College of Rheumatology Composite Response Index in Systemic Sclerosis (revised ACR-CRISS), which is a strong candidate measure as a primary endpoint clinical trials [7, 8]. Consequently, changes of the mRSS strongly influence the CRISS [9].

In our previous prospective, multicentre, real-life cohort study, we have discovered that in patients with diffuse cutaneous SSc (dcSSc) skin worsening within one year is associated with decline in lung function and worse survival during follow-up. Thus, progression of mRSS could be used as a surrogate marker to predict later ILD progression and mortality [10].

However, patients with diffuse SSc are reaching their peak skin score very early in the disease course and later spontaneous regression of mRSS is seen in clinical practice even more often than skin progression. Discovering associations between regression of mRSS and consecutive changes in visceral organ function would therefore be practically relevant. It could further improve clinical management and inform cohort enrichment for clinical trials [11, 12].

Therefore, the aim of our study was to explore associations between regression of mRSS and later visceral organ involvement in dcSSc using the large, longitudinal, real-life EUSTAR registry.

Methods

Patients and study design

This was a post-hoc analysis of prospectively collected data from the European Scleroderma Trials and Research (EUSTAR) registry (a project number CP93). Patients' visits from 1 January 2009 (because online database with extended data started in 2009) to 7 July 2019 were analyzed. The structure of the EUSTAR database and minimum essential data set have been described [13, 14].

Patients from the EUSTAR registry with dcSSc, baseline mRSS $\geq$ 7, valid mRSS assessment at 12 ± 3 months after baseline and additional $\geq$ 1 annual follow-up visits were recruited [15–17].

Regression of skin fibrosis was defined as decrease in mRSS > 5 and $\geq$ 25%, and progression of skin fibrosis as increase in mRSS > 5 and $\geq$ 25% from baseline to 12 ± 3 months follow up. These thresholds are based on the minimally clinical important difference for mRSS as defined previously [12, 18]. Patients were classified as stable skin fibrosis when neither a decrease nor an increase in mRSS > 5 score and $\geq$ 25% from baseline to 12 ± 3 months was observed. The 12 months follow up for the definition of progression or improvement of skin fibrosis was chosen, because it is the standard follow up in clinical practice and is the preferred duration of randomized controlled clinical trials.

Follow-up and outcome measures

The baseline visit was defined as the first available visit in the database. The first follow-up was defined as the visit with a time interval of 12 ± 3 months after the baseline visit. The duration of follow-up was calculated as the time between the baseline visit and the last annual visit with available data for the respective outcome.

The outcomes defining visceral organ progression were previously developed by consensus of an expert group using the nominal group technique [19]. Organ progression was defined as occurrence of one of the following events during follow-up:

1) ILD progression defined as decrease in forced vital capacity (FVC) $\geq$ 10% from baseline or decrease of FVC $\geq$ 5–9% combined with diffusing capacity for carbon monoxide (DLCO) $\geq$ 15%;
2) Cardiac progression defined as reduction of left ventricular ejection fraction (LVEF) to < 45% or relative decrease of LVEF > 10% or new onset of any of the

following: conduction disturbance or diastolic function abnormalities assessed by echocardiography;
3) Intestinal progression defined as new onset of any of the following: malabsorption syndrome, paralytic ileus, weight loss > 10%, oesophageal symptoms (dysphagia, reflux), stomach symptoms (early satiety, vomiting), intestinal symptoms (diarrhoea, bloating, constipation);
4) New onset of scleroderma renal crisis (SRC);
5) All-cause death.

For the intestinal involvement (3), the analysis was performed with and without stomach symptoms (early satiety, vomiting) and intestinal symptoms (diarrhoea, bloating, constipation), because malabsorption syndrome, paralytic ileus and weight loss > 10% as severe manifestations needed to be weighted stronger, and we investigated whether this separate analysis was leading to different results.

Regarding events with multiple components, an event was defined as present if there was worsening for at least one of the components stated above. Censoring was present if there was no worsening for any of the components. Consequently, an event was missing if at least one of the components was missing at every follow-up visit and worsening was not present for any of the components. Patients with missing information for event could not be used for the survival analyses.

We compared the occurrence of the above-mentioned outcomes during follow up between regressive, stable and progressive dcSSc patients at the first 12 ± 3 months' observation period.

Statistical analysis

Continuous data are expressed as mean ± SD and categorical data as frequency and percentage (%). Baseline variables were compared between skin regressive, stable and progressive patients by univariate analysis and with Bonferroni correction for multiple comparisons. Chi-squared tests or Fisher's exact tests were used for categorical variables, and Kruskal-Wallis test for continuous variables. *P*-values < 0.05 were considered statistically significant.

As measure for median follow-up, the reverse Kaplan-Meier (KM) estimate was calculated [20]. Survival analysis was censored at 7 years, because of low number of patients under observation after 7 years. Associations between skin changes in the first 12 ± 3 months and occurrence of long-term organ outcomes were evaluated by Kaplan–Meier survival analysis and KM estimates with 95% confidence intervals based on a log-log transformation were calculated. Only the first event was considered. Log-rank tests were executed for comparison of stable, progressive and regressive patients. In case of $p < 0.05$ in the log rank- test, pairwise comparisons with Bonferroni-Holm correction were performed.

For ILD progression, intestinal progression, and all-cause death, a Cox regression model was performed. Log-linearity and proportional hazards assumptions were checked with spline fits and Schoenfeld residuals.

For the analysis of new onset of renal crisis, conduction blocks, and diastolic function abnormalities, patients with these conditions present at baseline were excluded from the KM analysis, as they could not show any event by definition.

The statistical analyses were accomplished by the biostatistician Nicole Graf using R programming language (V.3.3.3), packages "prodlim", "survival", "survminer", "ggplot2" and "tableone".

Results

Baseline characteristics

Out of 17,212 patients from the EUSTAR database and from 103 EUSTAR collaborative partners at time of data extraction, 1257 met the requirement criteria. Of these, 282 (22.4%) were regressive, 883 (70.2%) stable and 92 (7.3%) were progressive for skin fibrosis at 1-year follow-up. Table 1 shows a summary of the clinical and demographic characteristics of the SSc patients.

The mean ± SD age of the 1257 patients at baseline was 51.9 ± 13.8 years, mean disease duration 7.6 years, the median follow-up was 4.2 years (95% CI: 1.96–7.09) and mean ± SD mRSS 16.9 ± 7.8. In most baseline characteristics, the three groups were comparable. After Bonferroni correction, significant differences were found between the groups regarding sex and baseline mRSS. In addition, disease duration at baseline was significantly shorter for skin progressors compared to the others, which confirms previous findings [7, 22, 23].

Associations between skin regression and visceral organ progression

Interstitial lung disease

In total, 320/981 (32.76patients fulfilled the definition of lung progression (= event) during follow up (relative decrease in FVC ≥ 10% or decrease of FVC ≥ 5–9% combined with relative decrease of DLCO ≥ 15%). There were 31/64 (48.4%) events in skin progressive patients, 231/695 (33.2%) in skin stable patients and 58/222 (26.1%) in skin regressive patients.

The probability of FVC decline was differing between the study groups of progressive, stable, and regressive patients (log-rank test $p < 0.001$; Fig. 1). Pairwise comparisons with Bonferroni-Holm correction were as follows: progressors vs. stable ($p = 0.0021$), progressors vs. regressors ($p = 0.0003$), regressors vs. stable ($p = 0.129$). When controlled for baseline mRSS, baseline

Table 1 Baseline clinical and demographic characteristics of SSc patients

Characteristics	Missing cases, *n* (%)	Whole cohort (*n* = 1257)	Regressive SSc (*n* = 282)	Stable SSc (*n* = 883)	Progressive SSc (*n* = 92)
Demographics					
Age mean (SD)	0 (0)	51.9 ± 13.8	50.2 (14.0)	52.5 (13.7)	51.2 (13.6)
Male sex*	0 (0)	300 (23.9)	67 (23.8)	196 (22.2)	37 (40.2)
Disease duration*years mean (SD)	109 (8.7)	7.6 ± 7.5	6.6 (6.8)	8.2 (7.7)	4.8 (5.6)
ACR/EULAR criteria fulfilled (%)	207 (16.5)	565 (53.8)	125 (53.2)	400 (54.4)	40 (50)
Vascular					
Raynaud's Phenomenon	4 (0.3)	1222 (97.5)	272 (97.5)	864 (98)	86 (93.5)
Digital ulcers	24 (1.9)	449 (36.4)	82 (29.6)	334 (38.6)	33 (36.3)
Active digital ulcers	39 (3.1)	251 (20.6)	48 (17.5)	185 (21.6)	18 (20.2)
Pitting scars	796 (63.3)	255 (55.3)	73 (62.4)	163 (53.1)	19 (51.4)
Skin					
Telangiectasia	787 (62.6)	246 (52.3)	67 (55.8)	164 (52.7)	15 (38.5)
mRSS mean (SD)*	0 (0)	16.9 (7.8)	20.6 (7.6)	15.8 (7.6)	15.5 (6.2)
Abnormal NVC	608 (48.4)	611 (94.1)	121 (92.4)	446 (94.7)	44 (93.6)
Musculoskeletal					
Tendon friction rubs	14 (1.1)	182 (14.6)	40 (14.4)	131 (15)	11 (12.1)
Joint synovitis	10 (0.8)	212 (17)	45 (16.1)	146 (16.7)	21 (22.8)
Joint contractures	10 (0.8)	587 (47.1)	139 (49.8)	399 (45.5)	49 (53.5)
Muscle weakness	9 (0.7)	296 (23.7)	80 (28.6)	196 (22.3)	20 (22)
Gastrointestinal					
Oesophageal symptoms	2 (0.2)	836 (66.6)	192 (68.6)	587 (66.5)	57 (62)
Stomach symptoms	3 (0.2)	353 (28.1)	92 (32.9)	234 (26.5)	27 (29.3)
Intestinal symptoms	4 (0.3)	319 (25.5)	80 (28.6)	216 (24.5)	23 (25)
Cardiopulmonary					
Dyspnoea (NYHA)	94 (7.5)				
Stage 1		642 (55.2)	148 (55.6)	454 (55.4)	40 (51.9)
Stage 2		400 (34.4)	86 (32.3)	281 (34.3)	33 (42.9)
Stage 3/4		121 (10.4)	32 (12)	85 (10.4)	4 (5.2)
Diastolic dysfunction	190 (15.1)	226 (21.2)	42 (19.2)	170 (22.1)	14 (17.9)
Pericardial effusion	263 (21)	71 (7.1)	17 (7.9)	46 (6.5)	8 (11.3)
Conduction blocks	158 (12.6)	152 (13.8)	45 (18.8)	97 (12.5)	10 (12)
LVEF < 45%	334 (26.6)	923 (73.4)	194 (68.7)	658 (74.5)	71 (77.1)
Pulmonary hypertension on echocardiography	171 (13.6)	156 (14.4)	27 (11.9)	115 (14.8)	14 (17.1)
Lung fibrosis on HRCT	417 (33.2)	480 (57.1)	109 (58.3)	334 (56.9)	37 (56.1)
FVC, % mean (SD)	190 (15.1)	87 (21)	85.5 (21.2)	87.4 (21.3)	87.8 (17.5)
FVC ≥ 70%	190 (15.1)	847 (79.4)	183 (76.9)	606 (79.9)	58 (81.7)
FEV, % predicted mean (SD)	315 (25.1)	86 (18.9)	85.1 (19.2)	86.1 (19)	88.3 (16.2)
TLC, % predicted mean SD	519 (41.3)	86.5 (20.5)	86.3 (19.2)	86.6 (21.3)	88.3 (16.2)
DLCO, % mean (SD)	214 (17)	65.5 (19.6)	64.1 (19.6)	65.8 (19.8)	67.1 (17.4)
DLCO ≥ 70%	214 (17)	444 (42.6)	93 (40.6)	322 (43.2)	29 (42.6)
Kidney					
Renal crisis	4 (0.3)	35 (2.8)	11 (3.9)	22 (2.5)	2 (2.2)
Laboratory parameters					
ANA positive	28 (2.2)	1178 (95.9)	253 (92.7)	837 (96.9)	88 (95.7)
ACA positive	95 (7.6)	125 (10.8)	23 (8.8)	97 (11.9)	5 (5.9)
Anti-Scl-70 positive	62 (4.9)	714 (59.7)	137 (51.3)	522 (62.0)	55 (64.0)
Anti RNA-polymerase III positive	553 (44)	76 (10.8)	22 (14.3)	46 (9.3)	8 (14.8)
Creatinine kinase elevation	99 (7.9)	125 (10.8)	35 (13.7)	81 (9.9)	9 (10.6)
Proteinuria	101 (8)	81 (7)	24 (9.6)	52 (6.3)	5 (5.9)

Table 1 (continued)

Characteristics	Missing cases, *n* (%)	Whole cohort (*n* = 1257)	Regressive SSc (*n* = 282)	Stable SSc (*n* = 883)	Progressive SSc (*n* = 92)
Hypocomplementaemia	259 (20.6)	74 (7.4)	17 (8.4)	53 (7.3)	4 (5.6)
ESR > 25 mm/h	140 (11.1)	441 (39.5)	90 (36.1)	321 (40.8)	30 (36.6)
CRP elevation	80 (6.4)	360 (30.6)	89 (34.2)	234 (28.1)	37 (43.5)
Active disease (VAI > 3)	47 (3.7)	427 (35.3)	110 (40.4)	288 (33.8)	29 (33.7)
Immunosuppressive therapy	121 (9.6)	620 (54.6)	163 (62.9)	407 (51.2)	50 (61.0)

Clinical parameters were defined according to the EUSTAR [14]. All variables are presented either as mean ± standard deviation (SD), by normal distribution, or as median and 25th-75th percentile (Q1-Q3) if non-Gaussian distribution; categorical variables are shown as frequencies/available cases and valid percentages. Data are presented as number (n)/total valid cases (N) (%). Esophageal symptoms were defined as dysphagia or reflux, stomach symptoms were defined as early satiety or vomiting, intestinal symptoms were defined as diarrhoea, bloating or constipation. Active disease was defined as a score > 3 by calculating the European Scleroderma Study Group disease activity index for systemic sclerosis proposed by Valentini [21]*- significant difference after Bonferroni-Holm correction between the three groups.

Immunosuppressive therapy was defined as treatment with corticosteroids (prednisone dose ≥ 10 mg/day or other dosage forms in equal dose) or any dose of immunosuppressant (cyclophosphamide, methotrexate, azathioprine, mycophenolate, D-penicillamine, rituximab, imatinib mesylate, or TNF-alpha-antagonist).

Abbreviations: ACA anti-centromere antibodies, *ANA* anti-nuclear antibodies, *anti-Scl-70* anti-topoisomerase antibodies, *Anti-RNA-pol III* anti RNA polymerase III antibodies, *CRP* C-reactive protein, *CK* creatine kinase, *disease duration* time from the first non-Raynaud phenomenon, *DLCO* diffusing capacity for carbon monoxide, *ESR* erythrocyte sedimentation rate, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity % predicted, *HRCT* high resolution computed tomography, *ILD* interstitial lung disease, *LVEF* left ventricular ejection fraction, *mRSS* modified Rodnan skin score, *NVC* nailfold capillaroscopy, *NYHA* New York Heart, *TLC* total lung capacity, *VAI* Valentini activity index.

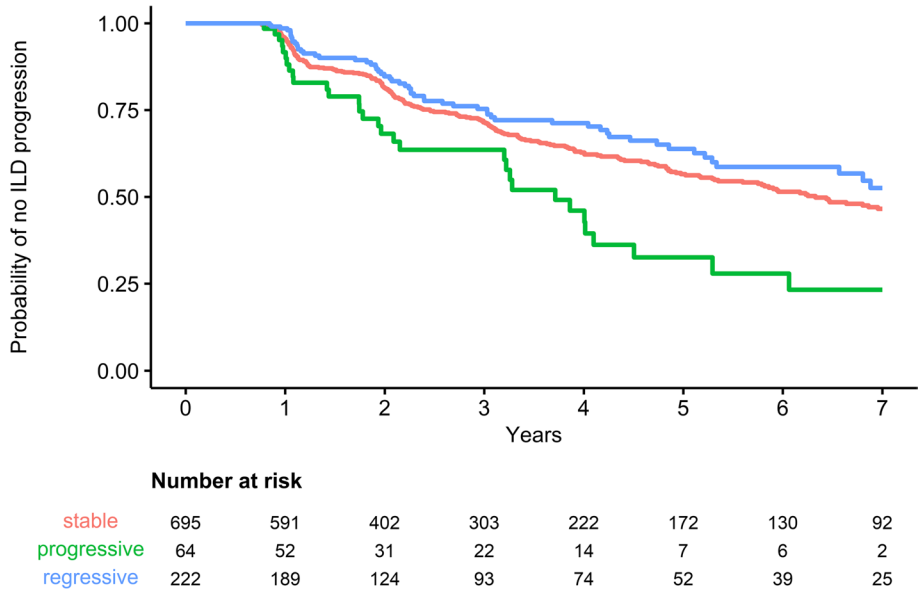

Fig. 1 Probability of lung function progression depending on previous change of skin fibrosis

immunosuppression, baseline FVC, and disease duration, Cox regression analysis indicated a significantly lower probability of later FVC decline ≥ 10% in the regressive group than in progressive patients ($p = 0.00003$).

While the analysis above has been performed for all patients without considering presence of ILD, we repeated the analysis for patients with ILD on HRCT. Four hundred three out of 981 (40.1%) patients with data on lung progression had ILD on HRCT. In skin progressive patients, there were 12/31 (38.7%) events, while in skin stable patients, there were 86/280 (30.7%) events, and in skin regressive patients, there were 34/92 (37.0%) events. Controlling for baseline mRSS, baseline immunosuppression, baseline FVC, and disease duration, skin regressive patients tended to be less likely to face ILD progression compared to progressive patients ($p = 0.085$).

Cardiac progression

In the overall group 308/838 (36.8%) patients experienced a cardiac progression during the follow-up, with

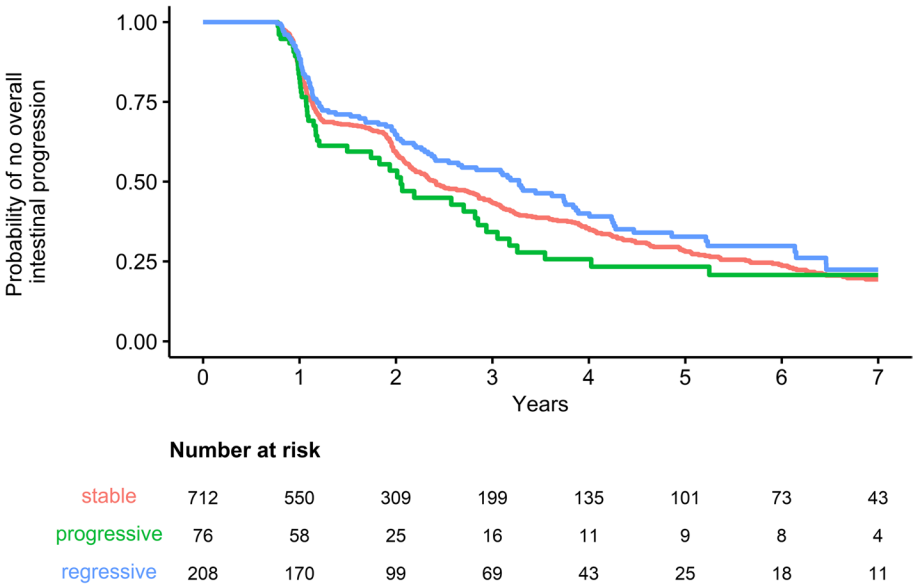

Fig. 2 Probability of intestinal progression depending on previous change of skin fibrosis

19/845 (2.2%) having LVEF progression, 156/862 (18.1%) showing new conduction blocks and 189/769 (24.6%) new diastolic function abnormalities. There were 27/61 (44.3%), 227/604 (37.6%) and 54/173 (31.2%) patients with cardiac progression in the group of skin progressive, skin stable und skin regressive patients, respectively. No significant difference in the probability of cardiac progression between skin regressive patients and either stable or progressive patients was found (Supplementary Figure S1).

Intestinal progression

During the follow-up, overall 570/996 (57.2%) patients had intestinal progression, 46/76 (60.5%) of the skin progressors, 415/712 (58.3%) of the skin stable patients and 109/208 (52.4%) of the skin regressors, without significant differences between the groups ($p=0.1$) (Fig. 2).

Using a more stringent definition of intestinal progression with new onset of malabsorption, weight loss > 10%, and paralytic ileus, 213/785 (27.1%) in the overall group, 20/57 (35.1%) in the progressive group, 148/549 (27.0%) in the stable group and 45/179 (25.1%) in the regressive group had intestinal progression. Although the Kaplan-Meier curve pointed to a slightly more favourable course of disease for regressive patients compared to progressive patients, the log-rank test was not significant ($p=0.3$) (Fig. 3). Controlling for baseline mRSS, baseline immunosuppression, and disease duration, did not change this result ($p=0.216$ for regressive vs. progressive patients).

New onset of scleroderma renal crisis (SRC)

Even though a large cohort was recruited, only a few patients developed new onset SRC during the follow-up. In total 19/1215 (1.6%) had a new onset of SRC and 1/89 (1.1%), 14/856 (1.6%) and 4/270 (1.5%) in the progressive, stable and in the regressive skin group, respectively. Between these groups, there was no significant difference in the probability of a new SRC (Supplementary Figure S2).

All-cause death

During follow-up, 98/1257 (7.8%) of all patients died, with 13/92 (14.1%) progressive, 69/883 (7.8%) stable and 16/282 (5.7%) skin regressive patients. The log-rank test was not significant with $p=0.06$ (Fig. 4). When adjusted for baseline mRSS, baseline immunosuppression, and disease duration, the probability of all-cause death during follow up was significantly lower in patients with regression of skin fibrosis compared to skin progressive patients ($p=0.035$).

Discussion

Our study analysed the associations between regression of skin fibrosis and the following occurrence of progressive visceral organ diseases in patients with dcSSc. We were able to show that skin regressive patients have a lower probability of lung progression, better survival. Thus, regression of patients over a 12 months period can be used as surrogate to predict long term outcome. This allows individual stratification of patients into lower risk groups and may support decision making to initiate or

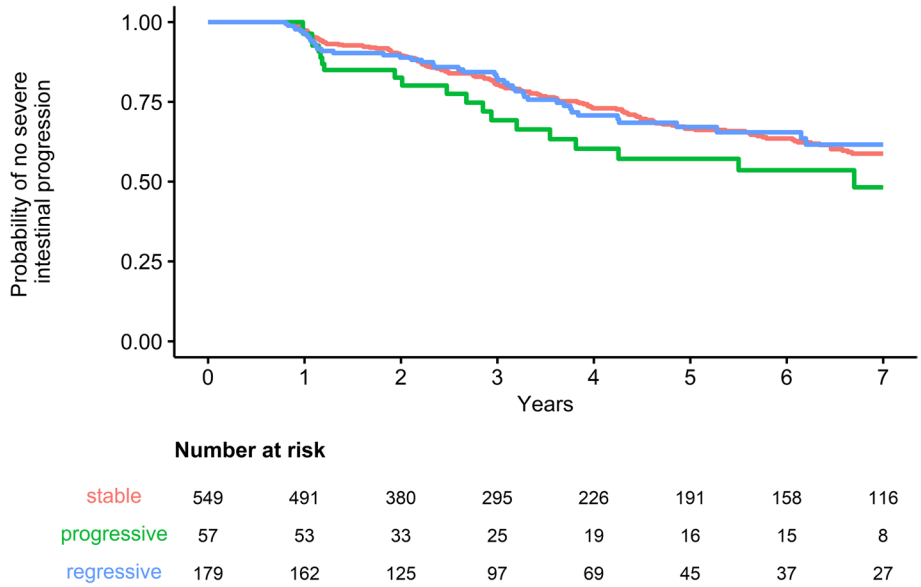

Fig. 3 Probability of severe intestinal progression depending on previous change of skin fibrosis

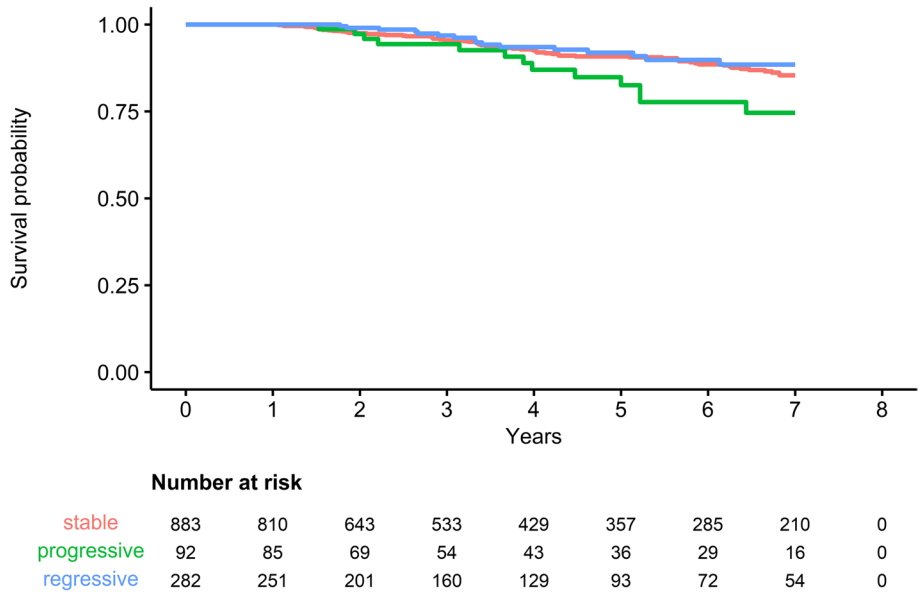

Fig. 4 Probability of all-cause death depending on previous change of skin fibrosis

continue with therapies. It also helps to identify inclusion and exclusion criteria for clinical trials, in which enrichment for patients with progressive organ involvement during the trial is often required. For example, patients with regression of skin fibrosis in the year before inclusion in a clinical trial targeting SSc-ILD should be avoided based on our data, as a lower number of progressive ILD is expected during the study.

This goes along with a study from the Pittsburgh database with 278 subjects, which concluded that improvement in skin thickening occurs in up to two-thirds of patients who are surviving the first few years of diffuse

scleroderma and is associated with improved survival [24].

In addition, our study could confirm the findings of Wu et al., where patients with progressive skin involvement had a significantly higher probability of FVC decline and all-cause death. Furthermore, we observed that patients with progressive skin involvement and ILD at baseline had a higher probability of experiencing FVC decline, compared to non-progressive patients.

The associations of progressors with a worse outcome were seen versus all other patients (non-progressors), whereas the association of regressive patients with better survival in our present study could only be seen versus progressive patients. Together, these data indicate that the disease course of skin fibrosis and ILD is linked together in SSc, and that disease progression or regression in skin fibrosis can be used to for risk assessment of patients [10].

It is noteworthy that there was a time lag between the occurrence of skin progression or regression and ILD progression. In both studies, skin progression or regression was associated with later, but not parallel ILD progression/lack of ILD progression, and the association was continuous over time with stronger effects over longer follow up.

Our study has strengths and limitations. Data for this study were derived from a very large, multicentre, real-life cohort reflecting clinical practice in SSc expert centres. The large number of patients and events allows detecting differences, which are not possible to be analysed in smaller cohorts. Follow up of the patients in the study was long and reached 7 years in a reasonable number of patients. Definitions of organ progression were defined by expert consensus and have been used successfully in other studies. Limitations include missing values and loss to follow-up as typically seen in registry studies. We lack data on co-existing lung diseases, which could possibly influence our lung outcomes. Moreover, since it was an observational study, we could not assess the impact of possible treatments on outcomes. The SSc treatment is often individualised and organ specific, particularly when immunosuppressive therapy is used. As a result, effectively excluding the impact of treatment in an unselected heterogeneous cohort is challenging in observational studies with a significant treatment-by-indication error. However, in our population, there were similar proportions of patients undergoing immunosuppressive treatments in each group. Finally, it was not possible to identify the exact cause of death for all affected patients. As a result, we could only evaluate all-cause mortality, without the association to SSc. Nevertheless, all-cause mortality is seen as a more robust indicator of disease outcome than only SSc-related mortality.

Conclusion

Our study demonstrated that regression of skin fibrosis is associated with a lower probability of lung progression and better survival at follow up. These observations support the link between the disease course of skin and lung fibrosis in SSc and can help to risk stratify patients. It might be helpful to support decision making to initiate or continue with therapies and might be informative for clinical trial design in the enrichment of ILD progressive patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13075-024-03418-2.

Supplementary Material 1.

Supplementary Material 2.

Acknowledgements

We thank to all below mentioned EUSTAR Collaborators for participating to the EUSTAR Database with the patients' data.

***EUSTAR Collaborators**

Centre Nr	Principal Investigator	Affiliation
2	Ulrich Walker	Basel (Switzerland)
4	Florenzo Iannone	Bari (Italy)
7	Radim Becvar	Prague (Czech Republic)
11	Maurizio Cutolo	Genova (Italy)
13	Giovana Cuomo	Naples (Italy)
16	Simona Rednic	Cluj-Napoca (Romania)
17	Yannick Allanore	Paris (France)
19	C. Montecucco	Pavia (Italy)
24	Srdan Novak	Rijeka (Croatia)
25	László Czirják	Pecs (Hungary)
28	Michele Iudici	Geneva (Switzerland)
32	Katja Perdan-Pirkmajer	Ljublijana (Slovenia)
33	Bernard Coleiro	Balzan (Malta)
35	Dominique Farge Bancel	Paris (France)
38	Paolo Airò	Brescia (Italy)
40	Roger Hesselstrand	Lund (Sweden)
41	Mislav Radic	Split (Croatia)
42	Alexandra Balbir-Gurman	Haifa (Israel)
44	Nicolas Hunzelmann	Köln (Germany)
49	Raffaele Pellerito	Torino (Italy)
50	Alessandro Giollo	Verona (Italy)
52	Christopher Denton	London (United Kingdom)
55	Nemanja Damjanov	Belgrade (Serbia)
57	Vera Ortiz-Santamaria	Granollers, Barcelona (Spain)
58	Stefan Heitmann	Stuttgart (Germany)

Centre Nr	Principal Investigator	Affiliation
60	Matthias Seidel	Bonn (Germany)
68	Maria João Salvador	Coimbra (Portugal)
73	Bojana Stamenkovic	Niska Banja (Serbia)
74	Carlo Francesco Selmi	Rozzano, Milano (Italy)
77	Mohammed Tikly	Johannesburg (South Africa)
78	Lidia P. Ananieva	Moscow (Russia)
81	Ulf Müller-Ladner	Bad Nauheim (Germany)
86	Merete Engelhart	Hellerup (Denmark)
93	Eric Hachulla	Lille (France)
96	Ruxandra Maria Ionescu	Bucharest (Romania)
100	Ana Maria Gheorghiu	Bucharest (Romania)
102	Cord Sunderkötter	Münster (Germany)
110	Francesca Ingegnoli	Milano (Italy)
112	Luc Mouthon	Paris (France)
113	Vanessa Smith	Gent (Belgium
115	Francesco Paolo Cantatore	Foggia (Italy)
116	Susanne Ullman	Copenhagen (Denmark)
118	Maria Rosa Pozzi	Monza (Italy)
120	Piotr Wiland	Wroclaw (Poland)
123	Juan Jose Alegre-Sancho	Valencia (Spain)
124	Brigitte Krummel-Lorenz	Frankfurt (Germany)
125	Kristine Herrmann	Dresden (Germany)
126	Ellen De Langhe	Leuven (Belgium)
128	Branimir Anic	Zagreb (Croatia)
130	Maria Üprus	Tallin (Estonia)
133	Sule Yavuz	Altunizade-Istanbul (Turkey)
135	Carolina de Souza Müller	Curitiba (Brasil)
137	Svetlana Agachi	Chisinau (Republic of Moldova)
138	Thierry Zenone	Valence (France)
141	Simon Stebbings	Dunedin (New Zealand)
142	Alessandra Vacca	Monserrato (CA (Italy)
147	Lisa Stamp	Christchurch (New Zealand)
148	Kamal Solanki	Hamilton (New Zealand)
149	Douglas Veale	Dublin (Ireland)
152	Esthela Loyo	Santiago (Dominican Republic)
160	Cristina-Mihaela Tanaseanu	Bucharest (Romania)
161	Rosario Foti	Catania (Italy)
162	Codrina Ancuta	Iasi (Romania)
164	Britta Maurer	Bern (Switzerland)
169	Paloma García de la Peña Lefebvre	Madrid (Spain)
172	Jean Sibilia	Strasbourg (France)
173	Ira Litinsky	Tel-Aviv (Israel)
175	Francesco Del Galdo	Leeds (United Kingdom)
176	Goda Seskute	Vilnius (Lithuania)
177	Lesley Ann Saketkoo	New Orleans (USA)
178	Eduardo Kerzberg	Buenos Aires (Argentina)
182	Massimiliano Limonta	Bergamo (Italy)
185	François Spertini	Lausanne (Switzerland)
189	Thierry Martin	Strasbourg (France)
191	Lorinda S Chung	Stanford (USA)
192	Tim Schmeiser	Wuppertal-Elberfeld (Germany)
193	Dominik Majewski	Poznan (Poland)
198	Vera Bernardino	Lisboa (Portugal)
199	Gabriela Riemekasten	Lübeck (Germany)
202	Elena Rezus	Lasi (Romania)
205	Piercarlo Sarzi Puttini	Milano (Italy)
209	Ina Kötter	Hamburg (Germany)
213	Petros Sfikakis	Athens (Greece)
215	Daniel Furst	Los Angeles (USA)
216	Ana-Maria Ramazan	Constanta City (Romania)
217	Jeska de Vries-Bouwstra	Leiden (The Netherlands)
220	Lorenzo Dagna	Milano (Italy)

Authors' contributions
Anja Wyss and Suzana Jordan prepared the data for analysis, the Table 1 and wrote the manuscript together with Oliver Distler. Nicole Graf analyzed the data, prepared the figures and statistical outputs. Anja Wyss, Suzana Jordan, Nicole Graf, Patricia E. Carreira, Jörg Distler, Marco Matucci Cerinic, Elise Siegert, Jörg Henes, Elisabetta Zanatta, Valeria Riccieri, Marie-Elise Truchetet, Fahrettin Oksel, Mengtao Li1, Eugene J. Kucharz, Kilian Eyerich, Francesco Del Galdo, Madelon C. Vonk, Anna-Maria Hoffman Vold, Armando Gabrielli, Oliver Distler contributed patients, reviewed data, read and reviewed the final version of the manuscript.

Funding
This project was funded from the internal money of the Department for Rheumatology, University Hospital Zurich, University of Zurich, Switzerland.

Data availability
Data are owned by EUSTAR and could be available upon request.

Declarations

Ethics approval and consent to participate
This project is approved by ethical approval of the Cantonal Ethics Commission Zurich (KEK-ZH) for observational studies (BASEC-Nr 2018–02165) and by ethical approval for collection of data (BASEC KEK-Nr.-2016-01515). Besides, the project was approved by the EUSTAR Steering Committee (CP93).

Consent for publication
All authors gave their consent for the publishing of the article.

Competing interests
None: AG, SJ; NG, PEC; JHD; MMC, ES, JH; VR, FO, ML,EJK, KE, FDG, MV; AMHV, AG;EZ: speaking and lecture fees, consulting/advisory: Janssen, GSK, Boehringer Ingelheim. MET has/had consultancy relationship with and/or has received research funding from and/or has served as a speaker for the following companies in the area of potential treatments for systemic sclerosis and its complications in the last three calendar years: Abbvie, Boehringer Ingelheim, Janssen, UCB, Lilly, Pfizer and Novartis.OD has/had consultancy relationship with and/or has received research funding from and/or has served as a speaker for the following companies in the area of potential treatments for systemic sclerosis and its complications in the last three calendar

years: 4P-Pharma, Abbvie, Acceleron, Alcimed, Altavant, Amgen, AnaMar, Argenx, Arxx, AstraZeneca, Blade, Bayer, Boehringer Ingelheim, Corbus, CSL Behring, Galderma, Galapagos, Glenmark, Gossamer, Horizon, Janssen, Kymera, Lupin, Medscape, Merck, Miltenyi Biotec, Mitsubishi Tanabe, Novartis, Orion, Prometheus, Redxpharma, Roivant, Topadur and UCB. Patent issued "mir-29 for the treatment of systemic sclerosis" (US8247389, EP2331143). Co-founder of CITUS AG.

Author details
[1]Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland. [2]Graf Biostatistics, Winterthur, Switzerland. [3]Servicio de Reumatología, Hospital, 12 de Octubre Avda. De Córdoba, S/N, Madrid, Spain. [4]Department of Rheumatology, Medical Faculty of Heinrich, University Hospital Düsseldorf, Heine University, Düsseldorf, Germany. [5]Hiller Research Unit, University Hospital Düsseldorf, Medical Faculty of Heinrich-Heine University, Düsseldorf, Germany. [6]Department of Medicine, Section of Rheumatology, Florence, Italy. [7]Department of Rheumatology, Charité University Hospital, Berlin, Germany. [8]Center for Interdisciplinary Rheumatology, Immunology and Autoimmune diseases (INDIRA), University Hospital Tübingen, Tübingen, Germany. [9]Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Padova, Padova, Italy. [10]Dipartimento di Medicina Interna e Specialità Mediche, "Sapienza" Università di Roma, Rome, Italy. [11]Rheumatology Department, Bordeaux University Hospital, Centre national de référence des maladies auto-immunes et systémiques rares Est/Sud-Ouest (RESO), Bordeaux F-33000, France. [12]Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology Bornova, Ege University, Izmir, Turkey. [13]Department of Rheumatology, Peking Union Medical College Hospital (West Campus), Chinese Academy of Medical Sciences, Beijing, China. [14]Department of Internal Medicine and Rheumatology, Medical University of Silesia Katowice, Katowice, Poland. [15]Department of Dermatology, University of Freiburg, Freiburg, Germany. [16]Scleroderma Programme, NIHR BRC and Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK. [17]Department of Rheumatic Diseases, Radboud University Medical Center, Nijmegen, Netherlands. [18]Department of Rheumatology, University Hospital Oslo, Oslo, Norway. [19]Fondazione di Medicina Molecolare e Terapia Cellulare Università Politecnica delle Marche, Ancona, Italy.

Received: 4 March 2024 Accepted: 16 October 2024
Published online: 31 October 2024

References

1. Khanna D, Denton CP. Evidence-based management of rapidly progressing systemic sclerosis. Best Pract Res Clin Rheumatol. 2010;24(3):387–400.
2. Khanna D, Merkel PA. Outcome measures in systemic sclerosis: an update on instruments and current research. Curr Rheumatol Rep. 2007;9(2):151–7.
3. Merkel PA, Clements PJ, Reveille JD, et al. Current status of outcome measure development for clinical trials in systemic sclerosis. Report from OMERACT 6. J Rheumatol. 2003;30(7):1630–47.
4. Clements PJ, Hurwitz EL, Wong WK, et al. Skin thickness score as a predictor and correlate of outcome in systemic sclerosis: high-dose versus low-dose penicillamine trial. Arthritis Rheum. 2000;43(11):2445–54.
5. Steen VD, Medsger TA. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum. 2000;43(11):2437–44.
6. Khanna D, Furst DE, Clements PJ, et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. J Scleroderma Relat Disord. 2017;2(1):11–8.
7. Khanna D, Distler O, Avouac J, et al. Measures of response in clinical trials of systemic sclerosis: the combined response index for systemic sclerosis (CRISS) and outcome measures in pulmonary arterial hypertension related to systemic sclerosis (EPOSS). J Rheumatol. 2009;36(10):2356–61.
8. Khanna D, Huang S, Lin CJF, Spino C. New composite endpoint in early diffuse cutaneous systemic sclerosis: revisiting the provisional American College of Rheumatology Composite Response Index in systemic sclerosis. Ann Rheum Dis. 2021;80(5):641–50.
9. Khanna D, Berrocal VJ, Giannini EH, et al. The American College of Rheumatology provisional composite response Index for clinical trials in early diffuse cutaneous systemic sclerosis. Arthritis Rheumatol. 2016;68(2):299–311.
10. Wu W, Jordan S, Graf N, et al. 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. Ann Rheum Dis. 2019;78(5):648–56.
11. Dobrota R, Maurer B, Graf N, et al. Prediction of improvement in skin fibrosis in diffuse cutaneous systemic sclerosis: a EUSTAR analysis. Ann Rheum Dis. 2016;75(10):1743–8.
12. Maurer B, Graf N, Michel BA, et al. Prediction of worsening of skin fibrosis in patients with diffuse cutaneous systemic sclerosis using the EUSTAR database. Ann Rheum Dis. 2015;74(6):1124–31.
13. Walker UA, Tyndall A, Czirják L, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis. 2007;66(6):754–63.
14. Meier FM, Frommer KW, Dinser R, et al. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis. 2012;71(8):1355–60.
15. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum. 1980;23(5):581–90.
16. LeRoy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol. 1988;15(2):202–5.
17. Wu W, Jordan S, Becker MO, et al. Prediction of progression of interstitial lung disease in patients with systemic sclerosis: the SPAR model. Ann Rheum Dis. 2018;77(9):1326–32.
18. Kumánovics G, Péntek M, Bae S, et al. Assessment of skin involvement in systemic sclerosis. Rheumatology (Oxford). 2017;56(suppl5):v53-66.
19. McMillan SS, King M, Tully MP. How to use the nominal group and Delphi techniques. Int J Clin Pharm. 2016;38(3):655–62.
20. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials. 1996;17(4):343–6.
21. Fasano S, Riccardi A, Messiniti V, et al. Revised European scleroderma trials and Research Group Activity Index is the best predictor of short-term severity accrual. Ann Rheum Dis. 2019;78(12):1681–5.
22. Clements P, Lachenbruch P, Siebold J, et al. Inter and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. J Rheumatol. 1995;22(7):1281–5.
23. Furst DE, Clements PJ, Steen VD, et al. The modified Rodnan skin score is an accurate reflection of skin biopsy thickness in systemic sclerosis. J Rheumatol. 1998;25(1):84–8.
24. Steen VD, Medsger TA Jr. Improvement in skin thickening in systemic sclerosis associated with improved survival. Arthritis Rheum. 2001;44(12):2828–35.

Publisher's note