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Late Skin Fibrosis in Systemic Sclerosis: A Study from the EUSTAR Cohort

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Abstract

Objectives

The early trajectory of skin fibrosis provides insights into the disease course of systemic sclerosis (SSc) including mortality; however, little is known about late skin fibrosis. The aims of our study were to ascertain the prevalence and characteristics of late skin fibrosis in SSc.

Methods

We developed and tested three conceptual scenarios of late (>5 years after 1st non-RP feature) skin fibrosis including new worsening of skin disease, and failure to improve after worsening within 5-year window. We defined skin worsening as change in modified Rodnan skin score (mRSS) ≥ 5 units or ≥ 25%. Using strict inclusion criteria including complete mRSS, we identified 1,043 (out of 19,115) patients within the EUSTAR database for our analysis. We further restricted analysis within 887 (out of 1,043) patients who had lcSSc or dcSSc at baseline.

Results

One-fifth of patients among the whole cohort (n=208/1043, 19.9%) experienced mRSS worsening, including in patients with lcSSc or dcSSc at baseline (n=193/887, 21.8%). This was largely due to new skin worsening after the 5-year window or failure to improve with worsening within 5-year window. Patients with lower baseline mRSS and lcSSc were more likely to develop late skin fibrosis. Anti-Scl-70 was associated with progression from baseline lcSSc to dcSSc, and anticentromere was protective.

Conclusions

Late skin fibrosis is not uncommon in SSc. We have identified different patterns relevant to clinical practice and trial design. Late skin fibrosis is a neglected manifestation of SSc and warrants further investigation including to determine clinical outcomes and optimal therapeutic strategy.

Key words: Systemic sclerosis; Scleroderma; Skin; Fibrosis; Late disease; Clinical trial design; Cohort enrichment

Key messages

- Late skin fibrosis affects approximately 20% of SSc patients >5 years after onset of disease.
- Late skin fibrosis is usually due to new worsening or failure of skin to improve.
- Approximately two-thirds with new worsening or failure of skin to improve were anti-Scl-70 antibody positive.

Introduction

Skin fibrosis (i.e., scleroderma) is a cardinal feature of systemic sclerosis (SSc) and a surrogate of future disease severity and mortality (1–3). Traditionally, SSc is divided into two major subsets: diffuse and limited cutaneous SSc (dcSSc and lcSSc), based upon the distribution of skin fibrosis (4). In the diffuse subset of the disease, skin fibrosis can include the distal and proximal limbs such as the trunk and abdomen (4). Although there is significant patient heterogeneity, the skin stereotypically in the diffuse subset passes through three phases, which can overlap. Initially, there is an oedematous phase which typically lasts 6 to 12 months primarily in dcSSc, and patients with lcSSc may have a prolonged oedematous phase. Second, is a fibrotic (or indurative) phase which can last several years. Then finally an atrophic phase which persists for the rest of the patient's life (5).

Skin fibrosis in SSc is associated with significant disability including impaired hand function and major flexion contractures, as well predisposing to cutaneous ulceration, in particular, overlying the small joints of the hands (6,7). In general, skin thickening tends to increase in patients with early dcSSc and then decrease in late dcSSc (5). In patients with lcSSc, there is little change over time apart from those who are anti-Scl-70 antibody positive who have the greatest variability in evolution into the diffuse subset of the disease (5). The trajectory of skin disease is also influenced by autoantibody status. For example, patients with anti-RNA-polymerase-III progress much more rapidly (and have a higher peak) than patients with anti-Scl-70 antibody (5).

The modified Rodnan skin score (mRSS) is a semiquantitative score which is performed at 17 body sites to evaluate skin thickness from 0 (normal) to 3 (severe) and has been extensively used as the primary and secondary outcome measure in SSc clinical trials (5). The minimal clinically important difference at 12 months of the mRSS has been estimated (from two large randomised clinical trials) to be 3-4 units (20-27% from baseline) for *all* SSc patients, and 5 units (24% from baseline) specifically for dcSSc (8).

The early trajectories of skin disease in SSc are associated with distinct patterns of disease, including development of major internal organ-based complications and mortality (9–13). To date, clinical trials have focussed on patients with *early* (≤ 5 years) disease (from first non-Raynaud's symptom) and dcSSc. Furthermore, there is significant interest in understanding the

natural history of skin disease in SSc including to facilitate clinical trials including enrichment criteria for progressive skin fibrosis in early dcSSc (e.g., based upon baseline mRSS and disease duration) (14).

Unlike early disease, to date, little is known about the trajectory of skin fibrosis in patients with late SSc. This is of importance because there has been major improvement in treating the organ-based complications of the disease (e.g., pulmonary fibrosis/hypertension and renal crisis) including through regular screening and early pharmacological intervention (15-17). Therefore, due to improved outcomes there is an ever increasing unmet need to understand late skin disease in long-term survivors of the disease.

Against this background, the aims of our study were to 1) ascertain the prevalence, and 2) describe the characteristics, of patients with late skin disease (defined as new skin worsening or non-improvement later in the disease) in SSc.

Methods

Data collection

We conducted an analysis of patients enrolled in the prospective European Scleroderma Trials and Research group (EUSTAR) database who fulfilled the 2013 American College of Rheumatology/ European League Against Rheumatism SSc classification criteria. The structure of the EUSTAR database has been previously described elsewhere, including the collected data set and definitions of the clinical variables (18–22). Data/assessments are done based on standard of care therapy. Disease duration was defined from the time of the first non-RP manifestation.

We calculated the patient's total mRSS where all the 17 mRSS body site data were available. Diffuse disease was defined as any fibrosis in chest, abdomen, upper arms, and upper legs (4). For inclusion, from the date of their first non-RP feature, participants required at least 2 visits within 5-year window: one was assigned as baseline, and all others were assigned as follow-up within 5 years. Patients were required to have at least 1 visit after 5-year window. The structure of visits included in our analysis is depicted in Figure 1. Baseline was defined as the first visit after onset of non-RP feature and within 5-year window. Follow-up time was calculated from baseline visit to last available visit. We included all mRSS after onset of patient's first non-RP feature.

Definition of late skin fibrosis

We defined three conceptual scenarios of late skin fibrosis in SSc as illustrated in Figure 2:

A. Worsening and then improvement (mRSS decreased >3 units) during the first 5 years, and then worsened again after 5 years.
B. Worsening for the first time after 5 years.
C. Worsening in the first 5 years and stayed high after 5 years (i.e., failure to improve with worsening within 5-year window).

Definition of mRSS worsening

Based upon the known minimal clinically important difference (MCID) we defined worsening of mRSS as mRSS ≥5 units or ≥ 25% (8).

Patient and public involvement

EUSTAR is part of the World Scleroderma Foundation, which has patient representatives from the Federation of European Scleroderma Associations in its governing board.

Ethics

All the patients included in our current analysis agreed to participate in the EUSTAR cohort by signing informed consent forms which were approved by the relevant local ethics committees.

Statistical analysis

We tabulated demographics and baseline characteristics for mRSS not worsened/worsened among the overall 887 patients who were with dcSSc or lcSSc at baseline. For numerical variables, mean and standard deviation were reported; T-test was performed if the variable followed a normal distribution, and Wilcoxon rank sum test was performed if the variable did not follow a normal distribution. For categorical variables, count and percentage were reported; Chi-square test or Fisher exact test was performed. Skin worsening and dcSSc progression are different events. Skin worsening is defined as an increase in mRSS score (5 units or 25%) in our analysis, while dcSSc progression is skin involvement in body areas: chest, abdomen, upper arms, and upper legs. Therefore, time to skin worsening and time to dcSSc progression are not necessarily correlated.

We explored the relationship between progression from lcSSc to dcSSc and autoantibodies: anticentromere, anti-Scl-70, and anti-RNA-polymerase III. We compared the proportion of progressed in autoantibody positive vs. negative among overall baseline limited, mRSS worsened, and mRSS not worsened, for each of the scenarios. Chi-square test of Fisher exact test was performed.

Results

Patient identification

We identified 19,115 patients within the EUSTAR database, of which 16,051 patients had the date of their first non-RP feature available (Figure 3). We then included patients (n=11,074) with >/=1 complete mRSS (i.e., none of the 17 body areas were missing), and 2,359 patients had >/=2 complete mRSS within 5 years of non-RP onset (Figure 3). Subsequently, 1,043 patients had >/=2 complete mRSS within 5 years of non-RP onset, and >/= 1 complete mRSS after 5 years (Figure 3). We further restricted analysis within 887 patients who had limited or diffuse SSc at baseline after excluding those with no skin involvement (n=156).

Late skin fibrosis in SSc

Late skin disease was observed in ~20% of SSc patients among the whole cohort (n=208/1043, 19.9%) over a mean (SD) of 6.6 (3.1) years, including those with either lcSSc or dcSSc at baseline (n=193/887, 21.8%) over a mean (SD) of 6.6 (3.1) years. Among lcSSc and dcSSc patients (n=887), Scenarios B (105, 11.8%) and C (82, 9.2%) were most common and scenario A was rare (6, 0.7%).

Time to skin worsening and time to peak mRSS from onset of RP are provided as **Supplementary Data S1**, available at *Rheumatology* online. The mean (SD) time to skin worsening (n=1043) for Scenario A was 1.9 (0.9) years, for Scenario B was 7.4 (2.2) years, and for Scenario C was 3.4 (1.0) years. Mean (SD) time to peak mRSS (n=1043) was 3.9 (2.8) years and in those with lcSSc/dcSSc (n=887) was 3.8 (2.8) years. To highlight, the former is follow-up time among 1043 patients (including dcSSc, lcSSc, and mRSS=0), whereas the latter is follow-up time among 887 patients (only including dcSSc and lcSSc).

Due to the relative rarity of scenario A, we elected to focus on scenarios B and C for our current analysis, as these are more relevant for clinical practice. Patient and disease-related baseline

characteristics for Scenarios B and C of mRSS worsening are presented in Tables 1 and 2, respectively.

New worsening of skin after 5 years (Scenario B)

Patients with new worsening (Table 1) had lower baseline mRSS (8.2 vs. 12.1 units, P=<0.0001), longer disease duration (28.8 vs. 25.0 months, P=0.0080), and were more likely to have lcSSc vs. dcSSc (P=0.067). There was no evidence with Scenario B that autoantibody status was associated with mRSS worsening (Table 2). The mean (SD) of follow-up for patients with worsening was 7.5 (3.5) vs. 6.5 (3.0) years for those who did not worsen.

Subset analysis in lcSSc at baseline

In those who were lcSSc at baseline associations of worsening after 5 years were lower mRSS (5.1 vs. 6.6 units, P=0.0087) and longer disease duration (28.3 vs. 24.9 months, P=0.0626). Approximately one-third (23/70) of patients progressed from baseline lcSSc to dcSSc among worsened (Table 3) over a mean of 3.8 (2.3) years.

Subset analysis in dcSSc at baseline

In those who were dcSSc at baseline associations of worsening after 5 years were lower mRSS (14.3 vs. 19.5 units, P=0.0005) and longer disease duration (29.7 vs. 25.1 units, P=0.0514).

Failure of skin improvement after 5 years (Scenario C)

Patients with failure of improvement (Table 2) had lower baseline mRSS (7.0 vs. 12.0 units, P=<0.0001), shorter disease duration at baseline (21.6 vs 25.8 months, P=0.0103), and were more likely to have lcSSc vs. dcSSc (P=0.0020). There was a trend that patients with failure of improvement in mRSS were more likely to be anti-Scl-70 (55.7% vs. 45.0%, P=0.0704) positive, and no patients were anti-RNA-polymerase III positive (0.0% vs. 7.5%, P=0.0608). The mean (SD) of follow-up for patients with worsening was 6.5 (2.8) vs. 6.6 (3.1) for those who did not worsen.

Subset analysis in lcSSc at baseline

In those who were lcSSc at baseline associations of non-improvement after 5 years were lower mRSS (4.9 vs. 6.6 units, P=0.0014) and shorter disease duration (20.8 vs. 25.9 months, P=0.0099). Over half (37/61) progressed from baseline lcSSc to dcSSc among non-improvement (Table 3) over a mean of 2.6 (2.5) years.

Subset analysis in dcSSc at baseline

In those who were dcSSc at baseline associations of non-improvement after 5 years were lower mRSS (13.0 vs. 19.0 units, P=0.0001) but not shorter disease duration (24.1 vs. 25.6 months, P=0.6060).

Impact of autoantibodies on progression from baseline limited to diffuse cutaneous SSc

We examined the impact of autoantibody status on progression from baseline lcSSc to dcSSc (Table 3) for skin new worsening (Scenario B) and failure to improve (Scenario C). Among 518 patients classified as lcSSc at baseline, 135 (26.1%) progressed to dcSSc during mean 2.7 (2.3) years of follow-up. Approximately two-thirds (68.2%) of those who progressed in scenario B (68.2%) were anti-Scl-70 antibody positive, and none were anti-RNA-polymerase III antibody positive. Similarly, two-thirds (65.2%) of those who progressed in scenario C were anti-Scl-70 antibody positive, and only one patient (4.5%) was anti-RNA-III polymerase antibody positive. The mean mRSS was 8.3 (3.6) at baseline to 12.8 (6.1) in Scenario B (n=23) and was 6.0 (3.9) at baseline to 15.5 (6.8) in Scenario C (n=37), when they converted from lcSSc to dcSSc subset.

Discussion

The main finding of our study is that late skin fibrosis is not an uncommon phenomenon, occurring in ~20% of patients with SSc in our current analysis of the international EUSTAR cohort. To our knowledge, ours is the first study to comprehensively examine late skin disease in SSc and provides novel insights into this neglected clinical manifestation. We have tested three conceptual scenarios of late skin fibrosis SSc which are relevant to clinical practice and trial design. The two most common (both ~10%) patterns of late skin fibrosis were of new skin disease progression (scenario B) after 5 years from disease onset, or failure of early skin fibrosis within 5 years to improve thereafter (Scenario C).

The natural history of skin progression in dcSSc is that the peak is typically reached by 18 to 24 months and is dependent on the autoantibody profile (e.g., anticentromere compared to anti-Scl-70 and anti-RNA-polymerase III antibodies) (4,23). Furthermore, longer disease duration is generally associated with improvement in skin disease (24–26). Based on these findings, previous trials have focussed on earlier disease duration of <5 years as an inclusion criterion and many clinicians slowly withdraw immunomodulatory treatment in those with longer

disease duration, with a notion that skin will improve as part of the natural history. However, in clinical practice, late progression of skin disease (either worsening or non-improvement) in individual patients with SSc is recognised by clinicians but has not been studied to date.

To date, late skin disease in SSc has been little studied. In a recent study which included 492 SSc patients from the Leiden Combined Care In SSc Cohort, the authors concluded that among anticentromere antibody positive patients, skin progression does occur and is typically observed in longstanding disease (23). Of note, in patients who presented with lcSSc, one-fifth (17%) progressed to dcSSc, and this most frequently occurred within the first 5 years of their non-RP symptom (23). This is comparable to our study in which one quarter (26.1%) of patients progressed from lcSSc to dcSSc over a mean period of 2.7 years.

Our data provides a number of novel and practical insights. We should wait to classify someone as definitively as lcSSc until substantial time has passed from onset of SSc symptoms, as some patients take longer to progress to dcSSc, especially those with lower baseline mRSS and lcSSc with anti-Scl-70 antibodies, and anticentromere was protective. The optimal duration should be defined in additional future research. Patients with anti-Scl-70 antibody may have persistent thickening of skin and do not resolve over the first 5 years. Anti-RNA-polymerase-III antibody is associated with significantly less likelihood of worsening of disease after 5 years. In clinical practice, these considerations may define optimal duration of immunosuppressive therapy (e.g., longer therapy for patients with anti-Scl-70 positivity). For clinical trials, we may have an opportunity to expand the patient population for those with non-improvement or new worsening of skin fibrosis after 5 years as these patients are excluded currently in the trials

A key strength of our study is that we utilised the large, prospective EUSTAR database with standardised, longitudinally collected data. However, due to our strict inclusion criteria based on complete mRSS data and specified time points for our analyses, we only included a relatively small number (n=887 with baseline dcSSc or lcSSc) of patients that could have introduced unintentional potential for bias. Of course, there are a number of important considerations related to research undertaken using registry data including the potential for incomplete data and selection bias (27). It is also important to highlight that we a definition of the MCID for of progression of skin disease for dcSSc that is developed from clinical studies, in which the same investigator is examining the patient longitudinally. This is not a given in the EUSTAR registry and therefore could identify patients without a true difference. Another

limitation of our study is that, due to the limited final sample size, some observations were found to be of various predetermined threshold levels for statistical significance, but of questionable potential clinical importance. Furthermore, we could have potentially overestimated the prevalence of dcSSc (e.g., those with the diffuse subset were more likely to have to received follow-up visits). The impact of autoantibody specificity should also be confirmed. Another limitation is that we did not exclude any patients that could have potentially satisfied inclusion in >1 conceptual model. Unlike patients with early dcSSc, tendon friction rubs were not overrepresented in patients with late skin fibrosis Another limitation of our current study is that we were also unable to accurately determine the impact of treatment intervention and overall late disease progression, including internal organ-based complications, which could be especially relevant to Scenario A. In particular, it still needs to be shown that patients with late compared to early dcSSc are also associated with more severe internal organ involvement at follow-up and worse outcomes. Future research should also explore whether the autoantibody profile changes in SSc patients with late skin fibrosis.

In conclusion, late skin fibrosis is not uncommon in patients with SSc. We have identified different patterns which are relevant to clinical practice and trial design. Future research is required to understand the trajectory and impact of late skin fibrosis in SSc, including to investigate the optimal therapeutic strategy.

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EUSTAR Collaborators

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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		Not Worsened (n=782)	Worsened (n=105)	P-value
Age (mean, SD)		49.2 (13.6)	46.8 (13.9)	0.0822
Sex (female, %)		598 (76.5%)	83 (79.0%)	0.5571
Disease duration (months, mean [SD])		25.0 (13.8)	28.8 (14.4)	0.0080
Smoking (%)	*Current*	46 (5.9%)	2 (1.9%)	
	Ever	65 (8.3%)	1 (1.0%)	0.0045
	Never	671 (85.8%)	102 (97.1%)	
Disease subset (%)	*Diffuse*	334 (42.7%)	35 (33.3%)	0.0672
	Limited	448 (57.3%)	70 (66.7%)	
mRSS (mean, SD)		12.1 (9.0)	8.2 (6.3)	<0.0001
Antibodies (%)	*ANA*	735/768 (95.7%)	100/102 (98.0%)	0.4178
	Anti-Scl-70	336/744 (45.2%)	53/101 (52.5%)	0.1664
	Anticentromere	188/736 (25.5%)	24/96 (25.0%)	0.9085
	Anti-RNA-Pol-3	32/488 (7.1%)	2/52 (3.8%)	0.5614
	Anti-PM-Scl	23/474 (4.9%)	1/57 (1.8%)	0.4981
	Anti-U1-RNP	18/590 (3.1%)	3/71 (4.2%)	0.4850
Pulmonary hypertension (%)		57/679 (8.4%)	8/93 (8.6%)	0.9461
Abnormal diastolic function (%)		123/694 (17.7%)	14/98 (14.3%)	0.3997
Conduction blocks (%)		73/695 (10.5%)	5/96 (5.2%)	0.1028
Tendon friction rubs (%)		84 (11%)	9 (8.7%)	0.4764
Joint synovitis (%)		124/777 (16.0%)	17 (16.2%)	0.9515
Digital ulcers (%)	*Current*	40/280 (14.3%)	2/18 (11.1%)	1.0000
	Never	173/280 (61.8%)	12/18 (66.7%)	
	Previously	67/280 (23.9%)	4/18 (22.2%)	
Digital pitting scars (%)	*Current*	112/269 (41.6%)	9/17 (52.9%)	0.5903
	Never	129/269 (48.0%)	6/17 (35.3%)	
	Previously	129/269 (48.0%)	2/17 (11.8%)	

Capillaroscopy scleroderma pattern	*Active* *Early* *Late*	160/331 (48.3%) 98/331 (29.6%) 73/331 (22.1%)	18/43 (41.9%) 11/43 (25.6%) 14/43 (32.6%)	0.3085

Table 1. Patient and disease-related baseline characteristics of new skin worsening for the first time after 5 years (Scenario B).

		Not Worsened (n=805)	**Worsened (n=82)**	**P-value**
Age (mean, SD)		49.1 (13.7)	47.3 (13.3)	0.2458
Sex (female, %)		187 (23.2%)	19 (23.2%)	0.9904
Disease duration (months, mean [SD])		25.8 (14.0)	21.6 (12.5)	0.0103
Smoking (%)	*Current* *Ever* *Never*	42 (5.2%) 64 (8.0%) 699 (86.8%)	6 (7.3%) 2 (2.4%) 74 (90.2%)	0.1538
Disease subset (%)	*Diffuse* *Limited*	348 (43.2%) 457 (56.8%)	21 (25.6%) 61 (74.4%)	0.0020
mRSS (mean, SD)		12.1 (8.9)	7.0 (5.6)	<0.0001
Antibodies (%)	*ANA* *Anti-Scl-70* *Anticentromere* *Anti-RNA-Pol-3* *Anti-PM-Scl* *Anti-U1-RNP*	755/789 (95.7%) 345/766 (45.0%) 188/758 (24.8%) 34/456 (7.5%) 23/489 (4.7%) 19/597 (3.2%)	80/81 (98.8%) 44/79 (55.7%) 24/74 (32.4%) 0/44 (0.0%) 1/42 (2.4%) 2/64 (3.1%)	0.2423 0.0704 0.1505 0.0608 0.7113 1.0000
Pulmonary hypertension (%)		179/800 (22.4%)	11/81 (13.6%)	0.1469
Abnormal diastolic function (%)		131 (18.2%); n=718	6 (8.1%); n=74	0.0282
Conduction blocks (%)		70/717 (9.8%)	8/74 (10.8%)	0.7734
Joint synovitis (%)		122/800 (15.3%)	19/82 (23.2%)	0.0623
Tendon friction rubs (%)		85 (10.8%)	8 (9.8%)	0.7765
Digital ulcers (%)	*Current* *Never* *Previously*	37/268 (13.8%) 167/268 (62.3%) 64/268 (23.9%)	5/30 (16.7%) 18/30 (60.0%) 7/30 (23.3%)	0.9124
Digital pitting scars (%)	*Current* *Never* *Previously*	116/259 (44.8%) 120/259 (46.3%) 23/259 (8.9%)	5/27 (18.5%) 15/27 (55.6%) 7/27 (25.9%)	0.0037

Capillaroscopy scleroderma pattern	*Active*	154/334 (46.1%)	24/40 (60.0%)	0.1557
	Early	98/334 (29.3%)	11/40 (27.5%)	
	Late	82/334 (24.6%)	5/40 (12.5%)	

Table 2. Patient and disease-related baseline characteristics of skin worsening in the first 5 years and failed to improve after 5-year window.

		Skin worsening after 5 years (Scenario B) (n=70)			**Skin worsening within 5 years and failed to improve after 5-year window (Scenario C) (n=61)**		
		Progressed to dcSSc (n=23)	***Not progressed to dcSSc (n=47)***	***P-value***	***Progressed to dcSSc (n=37)***	***Not progressed to dcSSc (n=24)***	***P-value***
Anticentromere	***+ve***	2/22 (9.1%)	19/42 (45.2%)	0.0034	6/34 (17.6%)	14/21 (66.7%)	0.0002
	-ve	20/22 (90.9%)	23/42 (54.8%)		28/34 (82.4%)	7/21 (33.3%)	
Anti-Scl-70	***+ve***	15/23 (65.2%)	14/44 (31.8%)	0.0088	22/36 (61.1%)	8/23 (34.8%)	0.0485
	-ve	8/23 (34.8%)	30/44 (68.2%)		14/36 (38.9%)	15/23 (65.2%)	
Anti-RNA-Polymerase-III	***+ve***	0/12 (0.0%)	1/22 (4.5%)	1.0000	0/6 (0.0%)	0/14 (0.0%)	--
	-ve	12/12 (100%)	21/22 (95.5%)		6/6 (100%)	14/14 (100%)	

Table 3. Impact of autoantibody status on progression from baseline limited to diffuse cutaneous SSc (dcSSc).

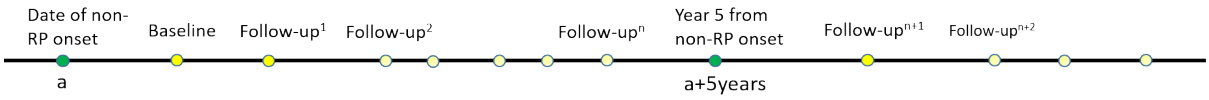

Figure 1. Visit structure and timeline.

Follow-up^{1}~Follow-up^{n+2}: follow-up visit sequence, there must be baseline and at least one follow-up visit within 5-year window, and at least one follow-up visit after 5-year window.

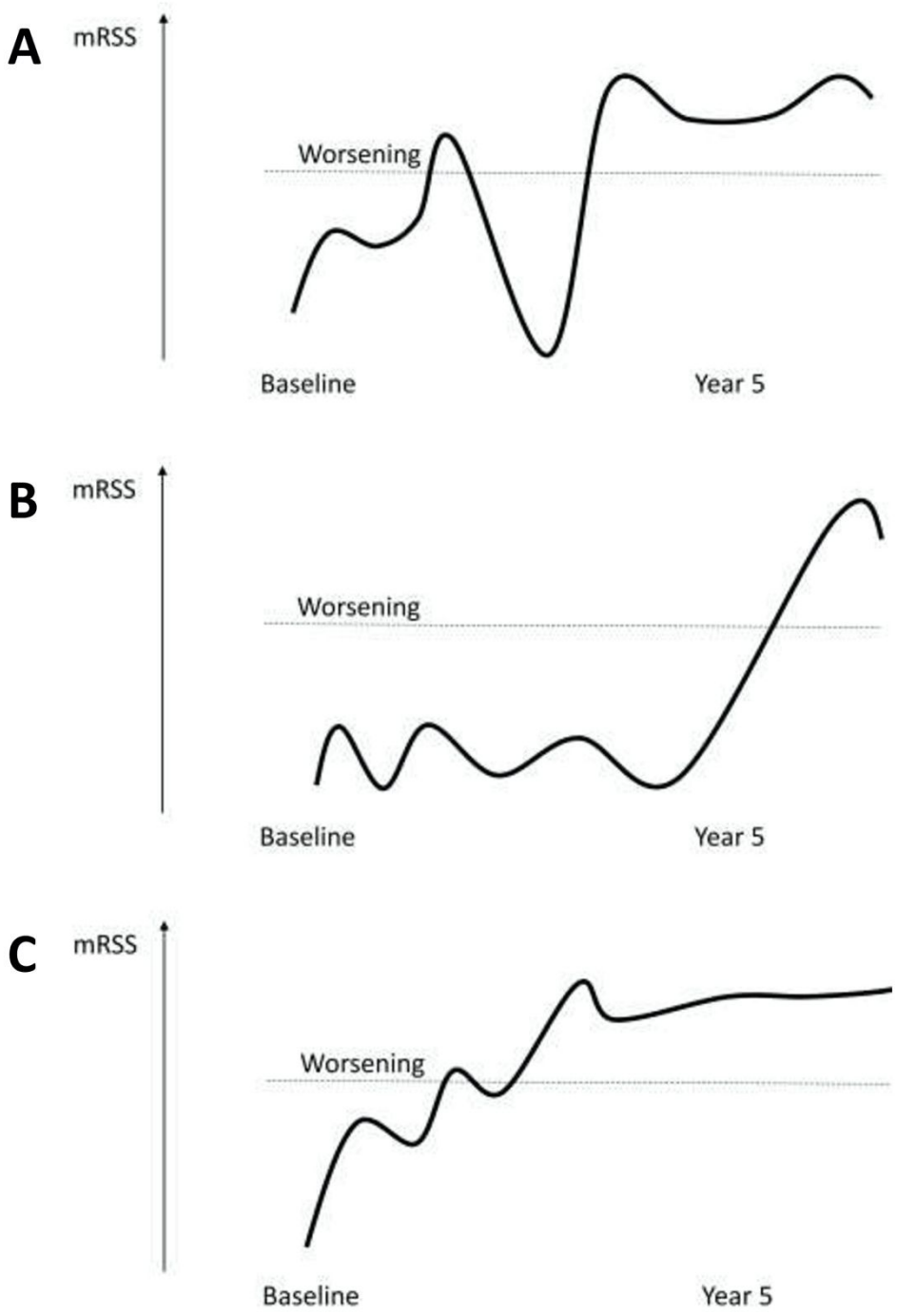

Figure 2. Conceptual scenarios of late skin fibrosis in SSc.

A: worsening and then improvement (mRSS decreased >3 units) during the first 5 years, and then worsened again after 5 years. B: worsening for the first time after 5 years. C: worsening in the first 5 years and stayed high after 5 years (i.e., failure to improve).

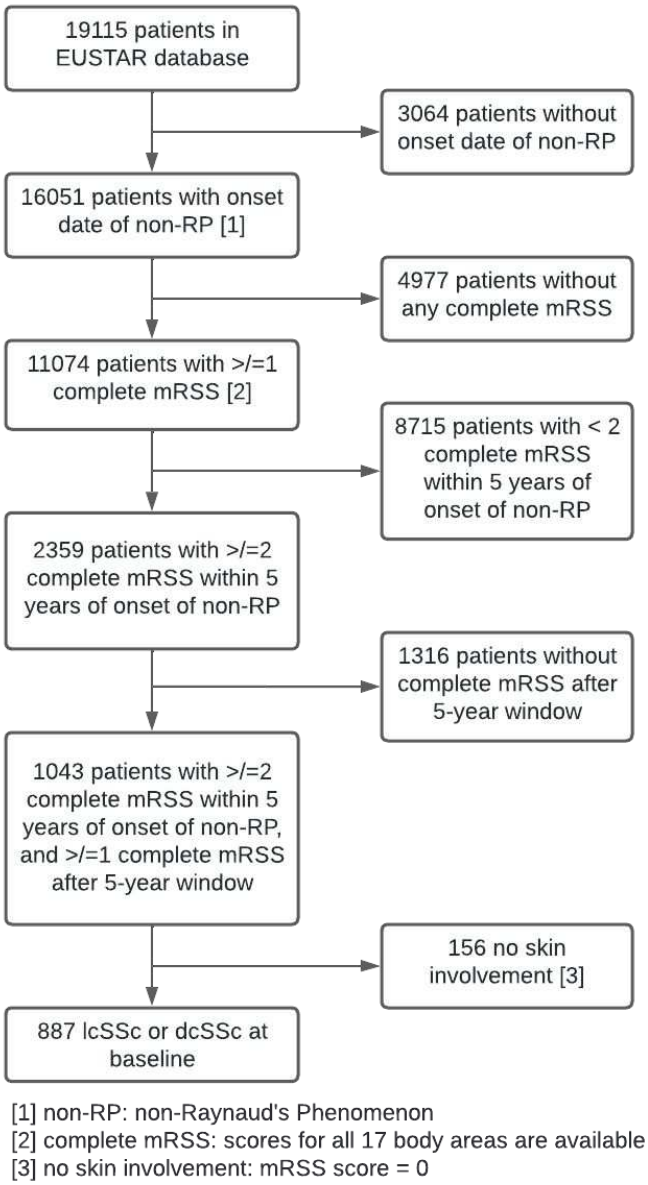

Figure 3. Flow diagram detailing the patient selection procedure.