Long-term organ damage accrual and late mortality in systemic sclerosis

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Abstract

Objective

Progressive organ damage accrual in patients with systemic sclerosis (SSc) can be measured using the Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI). We aimed to evaluate the long-term evolution of organ damage accrual in SSc patients with at least 10 years of follow-up, identifying clinical and laboratory features associated with moderate and severe damage, and the association of SCTC-DI with "late mortality" (death >10 years after diagnosis).

Methods

In this single-centre retrospective study, patients with SSc were included when fulfilling the following characteristics: 1) a baseline visit corresponding to the time of diagnosis; 2) a minimum of 10 years of follow-up after diagnosis; 3) available follow-up visits at predefined timepoints.

Results

In 253 patients included in the study, SCTC-DI progressively increased from the baseline to 10 years after diagnosis, with 34% of patients showing moderate or severe damage at this time point. During the follow-up, the SCTC-DI score was higher, and had a higher annual rise, in dcSSc patients than in lcSSc and in ACA-negative patients than in ACA+. Multivariable analyses identified dcSSc, lack of ACA, and the SCTC-DI scores at previous timepoints as independent variables associated with moderate or severe damage.

In patients with "late mortality", as compared to surviving patients, the SCTC-DI score was demonstrated to be significantly higher at the baseline and at every timepoint, with a higher annual rise.

Conclusion

Factors associated with damage accrual in SSc patients with long-term follow-up were identified. Higher SCTC-DI and higher SCTC-DI annual rise were associated with late mortality in SSc.

Key words

systemic sclerosis, damage index, late mortality

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Introduction

Systemic sclerosis (SSc) is a multiorgan systemic autoimmune disease associated with a significant burden of morbidity and mortality (1-10), and characterised by immune dysregulation with vasculopathy, leading to an excess in collagen and other extracellular matrix proteins deposition, finally resulting in multiorgan damage due to fibrotic and vascular changes in the skin and visceral organs (1, 2). The first tool created to measure this multiorgan damage, the Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI) was developed and validated in 2019 (11). This index was proven to be predictive of morbidity and mortality in a retrospective evaluation of two cohorts of SSc patients with prospectively collected data (11).

Recently, the analysis of incident SSc cohorts during the first 4 years of follow-up after diagnosis allowed the identification of features associated with different SCTC-DI trajectories. The probability of having the worst damage trajectory was shown to be increased by diffuse cutaneous SSc (dcSSc), tendon friction rubs, elevated baseline C-reactive protein levels, older age and male sex, while anti-centromere antibodies (ACA) and Caucasian ethnicity decreased it (12). Moreover, patients with the faster damage accrual had higher SCTC-DI scores at baseline (12).

Since the damage trajectories of patients with dcSSc were very different from those with limited cutaneous SSc (lcSSc), further analyses led to the development of a simplified model including only cutaneous subset, baseline SCTC-DI and sex, which was shown to predict "early" damage trajectory within the first 4 years after diagnosis (13).

On the other hand, limited information is currently available regarding late damage accrual in SSc. Considering that survival at 10 years after SSc diagnosis is estimated between 62.5 and 89.4% (5-9), this information would be relevant for a large proportion of SSc patients. Therefore, we aimed at: 1) the evaluation of the long-term evolution of organ damage in our historical SSc cohort, focusing on patients with at least 10 years of follow-up; 2) the identification of clinical and laboratory features associated with moderate and severe organ damage at different time points during the disease course; 3) the association of SCTC-DI scores with late mortality (*i.e.* death occurring more than 10 years after disease diagnosis).

Patients and methods

This was a retrospective single-centre study considering SSc patients prospectively followed in an Italian Rheumatology Unit with long-term experience in SSc patient management. Clinical, laboratory and demographic data were retrieved from clinical charts and collected in an *ad-hoc* database.

Inclusion criteria and selection of patients

All adult patients (≥18 years) with SSc fulfilling the 1980 ARA and/or 2013 ACR/EULAR classification criteria (14, 15), attending our Unit between 1989 and 2019, with at least one follow-up visit, or data regarding death available, were considered for the present study. Patients without any information after a follow-up visit were considered as lost to follow-up and censored at the time of the last available visit. Disease duration was calculated since first non-Raynaud symptom onset.

Since the main purpose of our study was to evaluate long-term damage accrual in SSc patients, we selected from the total cohort of SSc patients only those with: 1) a baseline visit corresponding to the time of diagnosis; 2) a minimum of 10-years follow-up after diagnosis; 3) available follow-up visits at predefined timepoints (below specified) (Fig. 1).

Organ damage

Organ damage was retrospectively evaluated with data reported in clinical charts through the calculation of SCTC-DI, as previously described (11), at different timepoints: at baseline (T0), and at 1 (T1), 5 (T5) and 10 (T10) years after diagnosis. Three different levels of damage were defined, according to the SCTC-DI score (11): mild (0-4), moderate (5-12) and severe (>12).

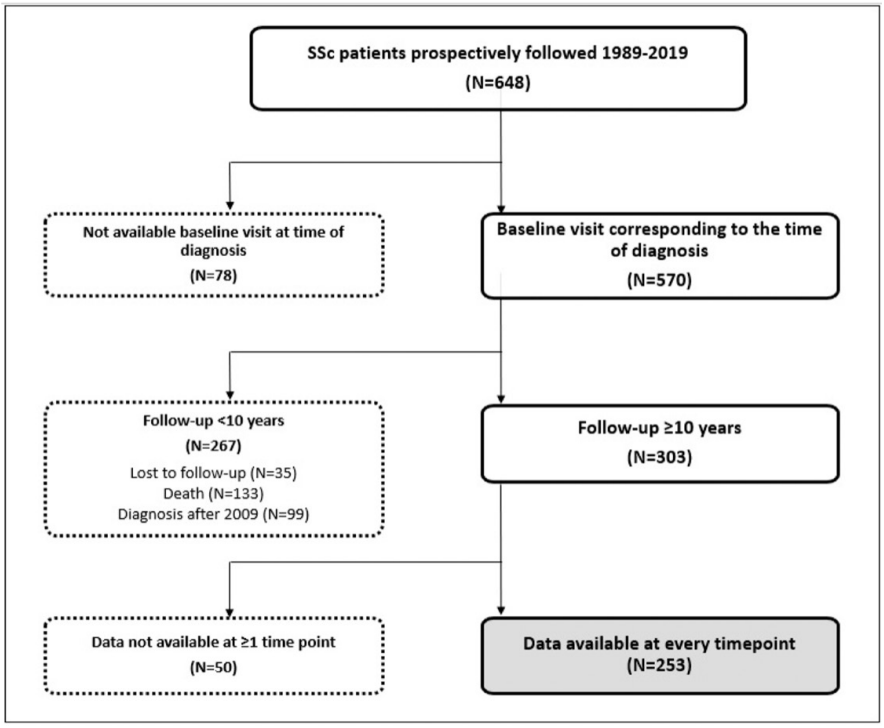

Fig. 1. Selection of SSc patients with: 1) a baseline visit corresponding to the time of diagnosis; 2) at least 10 years of follow-up after SSc diagnosis; 3) available follow-up visits at predefined timepoints (T0, T1, T5, T10).

Comorbidities

The age-adjusted Charlson Comorbidity index (CCI, a single index accounting for both age and medical comorbidity) (16) was calculated at T0 and T10.

Mortality

Mortality was ascertained according to follow-up visit information and data on hospital or administrative records. As in previous studies (6), the main cause of death was classified as SSc-related (further divided into 6 categories: interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), gastro-intestinal (GI), cardiac, or renal involvement, and others), or non-SSc-related (distinguished into 4 categories: neoplasia, cardiovascular, infection, others).

Death occurring more than 10 years after SSc diagnosis was defined as 'late mortality'.

Statistical analysis

Continuous variables are presented as median and interquartile range (IQR) and were compared using non-parametric tests (Mann-Whitney, Kruskal-Wallis, or Wilcoxon, as appropriated). Categorical variables are presented as number/percentages and were compared using contingency tables; *p*-value was calculated with Chi-Square or Fisher exact test. Correlations were evaluated by Spearman test. For the multivariable analysis, logistic regression models with *a priori* selection of variables were used.

Ethical statement

Ethics approval was obtained from the local ethics committee, and patients included in the database gave their written informed consent. The study was conducted in accordance with Helsinki Declaration principles.

Results

Overall, 648 patients with SSc were prospectively followed in our centre in the time interval indicated (1989-2019). Their clinical and demographic data are reported in Supplementary Table S1. Among them, 90% were women and 19% had dcSSc. ACA positivity was detected in 52%, while anti-Topoisomerase 1 (Topo1) in 22%, anti-RNA Polymerase 3 in 5% and other antibodies in 21%. Median follow-up for the entire cohort was 10.2 years (5.0–16.8). Male patients more frequently showed dcSSc and anti-Topo1 positivity, with higher frequency of smokers and higher mortality rate, and with lower age at death as compared with females (Suppl. Table S2).

After a median time of 6.9 years (2.9-12.8), 111 patients (17%) were lost at follow-up, and 240 out of 537 patients with available information (45%) died at a median age of 76.5 years (67.9-82.4): 99 (41%) died for SSc complications and 95 (40%) for causes not related to SSc, while in 46 (19%) the cause of death could not be determined. Among 99 patients who died because of SSc, the causes were: PAH (35%), ILD (30%), cardiac involvement (13%), GI involvement (11%) and renal (9%). SSc non-related deaths were: neoplasia (42%), cardio-vascular diseases (19%), infections (6%) and other mixed causes (20%). In 12 cases (13%) death was not related to SSc, but not otherwise specified. In 50% of patients with diagnosis after 2001, death was related to SSc, as compared with 34% before 2001 (p=0.0175).

Analysis of long-term damage accrual

Among 648 SSc patients evaluated in our centre, 253 who had a baseline visit corresponding to the time of diagnosis, at least 10 years of follow-up after SSc diagnosis, and available follow-up visits at predefined timepoints were included in this study focused on long-term damage accrual (Fig. 1). As compared with the remaining 395 patients not included in the analysis (Suppl. Table S1), they were more frequently female, younger at diagnosis, with a milder disease phenotype, less frequently treated with glucocorticoids, and with less comorbidities.

During the follow-up, the damage index in included patients progressively increased from T0 (baseline, corresponding to the time of SSc diagnosis) to T10 (10 years after diagnosis) (p<0.0001; Kruskal-Wallis test; Fig. 2a). Moreover, the proportion of patients with SCTC-DI ≥5, indicating moderate or severe damage, progressively increased from 9% at baseline to 34% at 10 years (Fig. 2b).

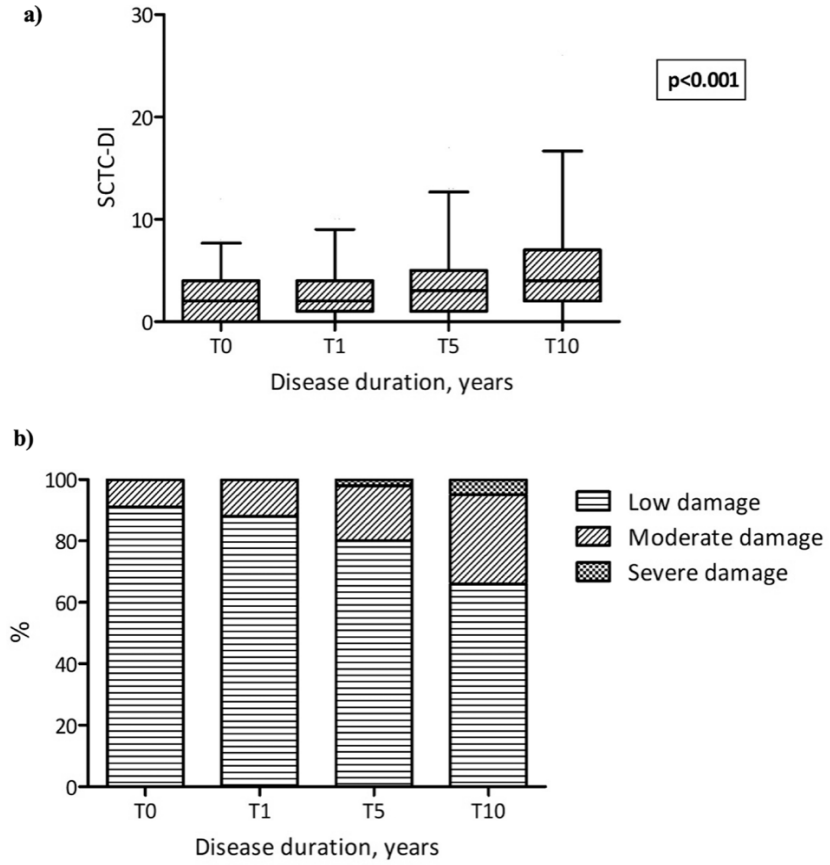

Fig. 2. a) SCTC-DI at every timepoint (T0, T1, T5, T10): SCTC-DI T0= 2 (0-4); SCTC-DI T1= 2 (1-4); SCTC-DI T5= 3 (1-5); SCTC-DI T10= 4 (2-7). **b)** Proportions of patients with low (SCTC-DI <5), moderate (5≤ SCTC-DI <13) and severe (SCTC-DI ≥13) damage at every timepoint (T0, T1, T5, T10). Low damage: T0: 91%, T1: 88%, T5: 80%, T0: 66%; moderate damage: T0: 9%, T1: 12%, T5: 18%, T10: 29%; severe damage: T0: 0%, T1: 0%, T5: 2%, T10: 5%.
Continuous variables are presented as median (IQR) and compared with Kruskal-Wallis test; categorical variables are presented %. *p*-value <0.05 was considered statistically significant.
DI: damage index; SCTC: Scleroderma Clinical Trial Consortium.

The age-adjusted CCI also progressively increased from T0 to T10 (p<0.001). A weak positive correlation between CCI and SCTC-DI was observed at T0 (Rs:0.185, 95% CI [0.059.0.305], p=0.003) while no significant correlation was observed at T10 (Rs:0.064, 95% CI [-0.063–0.190], p=0.308).

Evaluation of damage across different subgroups

At the baseline, no differences in SCTC-DI scores were observed among different subgroups, separated according to sex (males *vs*. females), auto-antibodies (ACA+ *vs*. ACA-), and cutaneous subset (dcSSc *vs*. lcSSc) (Fig. 3). During the follow-up, SCTC-DI score was higher in dcSSc than in lcSSc patients at every time point evaluated (1, 5, and 10 years after diagnosis) (Fig. 3a). *Vice versa,* SCTC-DI score was lower in SSc patients with ACA+ as compared with those ACA-negative at the same timepoints (Fig. 3b). Although SCTC-DI score was numerically higher in SSc male patients than in females, the differences were not statistically significant (Fig. 3c).

As shown in Table Ia, between T0 and T5, the SCTC-DI annual rise was higher in dcSSc patients (0.7/year (0.4–1.2)) than in lcSSc (0.0/year (0.0–0.4); p<0.001), and in ACA-negative patients (0.4/year (0.0–0.6)) than in ACA+ (0.0/year (0.0–0.4); p<0.001), while no significant differences were observed in males *versus* females. On the other hand, no difference of the SCTC-DI annual rise among subgroups was observed in the time interval between T5 and T10.

Indeed, in patients with dcSSc the SCTC-DI score annual rise observed in the time interval from T5 to T10 (0.2/year (0.0-0.8)) was lower than that observed in the first 5 years after diagnosis (0.7/year (0.4–1.2); p=0.013). A similar trend of a slower damage accrual after the first 5 years was observed in male patients (p=0.059; Table Ib).

When we divided SSc patients enrolled in our study into two groups, according their diagnosis date (before or after 2001), we did not observe any difference between the two groups as far as SCTC-DI at baseline or at the other timepoints are concerned (data available on request from the authors).

Analysis of factors associated with moderate and severe damage

To evaluate factors potentially associated with moderate or severe organ damage (defined as SCTC-DI score ≥5) at 5 and 10 years after diagnosis, we performed multivariable analyses using logistic regression models with *a priori* selected variables. As shown in Table II moderate or severe organ damage at 5 years after SSc diagnosis was recorded in 51 patients (*vs*. 202 with mild damage), and was found to be positively associated with dcSSc, lack of ACA and with SCTC-DI scores at baseline (T0) and one year after the diagnosis (T1)**.** At 10 years after SSc diagnosis, 86 patients showed moderate or severe damage (*vs*. 167 with mild damage) and this was associated with dcSSc and with the SCTC-DI scores at T5 (5 years after the diagnosis) (Table II, Model 1). Anti-topoisomerase 1 or lack of both ACA and anti-topoisomerase 1 antibodies were not significantly associated with SCTC-DI in multivariate analysis (data available on request from the authors).

An alternative model considering the variations of SCTC-DI over time (instead of SCTC-DI at specific timepoints, T0 and T5) demonstrated a positive association of Delta T0-T5 and Delta T5-T10 with moderate or severe damage at 10 years (p<0.0001 for both), together with dcSSc (p=0.027) and a negative association with ACA positivity (p=0.034) (Table II, Model 2). In the same alternative model, moderate or severe damage at 5 years was positively associated with Delta T0-

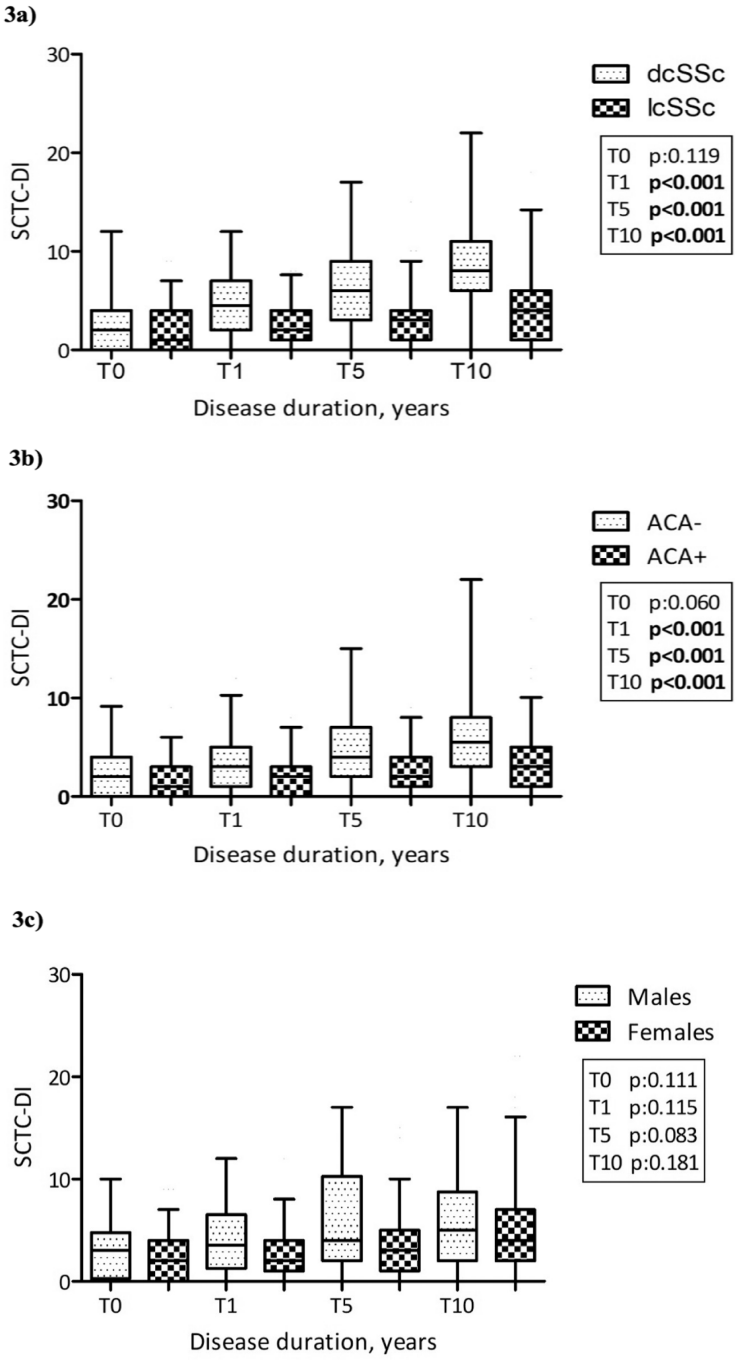

Fig. 3. Comparison of SCTC-DI at every timepoint (T0, T1, T5, T10): **a)** dcSSc *vs*. lc SSc; **b)** ACA-negative *vs*. ACA+; **c)** males *vs*. females.
Continuous variables are presented as median (IQR) and compared with Mann-Whitney test.
p-value <0.05 was considered statistically significant.
ACA: anti-centromere; dc: diffuse cutaneous; DI: Damage Index; lc: limited cutaneous; SCTC: Scleroderma Clinical Trial Consortium; SSc: systemic sclerosis.

T5 ($p<0.0001$), and age-adjusted CCI at T0, but not with dcSSc, and negatively associated with ACA positivity ($p=0.021$) (Table II, Model 2).

Association of damage with late mortality

In the present study death occurring more than 10 years after SSc diagnosis was defined as 'late mortality'. Among 253 patients with at least 10 years of follow-up included in this study, we identified 90 cases (36%) with late mortality. Median age, disease duration, and follow-up duration at death in these patients were 76.8 (71.1-81.9) years, 19.9 (15.5-25.2) years, and 16.0 (12.4-19.9) years, respectively. Causes of late mortality were SSc-related in 30/90 cases (33%) (15 ILD, 6 PAH, 4 GI involvement; 5 others), non-SSc-related in 44/90 (18 cancers, 4 infections, 6 cardio-vascular events, 10 others), and could not be determined in 16/90. As compared with patients who died in the first 10 years after SSc diagnosis, patients with late mortality, in general died less frequently due for SSc-related causes (p:0.013), and particularly SSc-PAH (p:0.034); of note, however, they died more frequently because of SSc-ILD (p:0.003) (Supplementary Table S3).

SCTC-DI score was significantly higher at the baseline (T0) and at every timepoint (T1, T5, T10) in patients with late mortality, as compared with 163 patients surviving at December 31, 2019 (Fig. 4). Moreover, in patients with late mortality, the SCTC-DI annual rise was higher than in surviving patients between T1-T5 (p:0.046) and T5-T10 (p:0.006), as well as between T0-T10 (p:0.003; Table Ic). Finally, SCTC-DI score was lower at the baseline (T0) and at every timepoint (T1, T5) in patients with late mortality, as compared with patients who died in the first 10 years after SSc diagnosis (Supplementary Table S3).

Discussion

Our analysis of a cohort of SSc patients with long-term follow-up confirms and extends the results of previous studies evaluating disease-associated early damage accrual in the first 4 years after diagnosis, that identified dcSSc and male sex as factors associated with worse damage index trajectories (12, 13). Moreover, it was reported that patients with higher damage scores within the first 2 years of disease were also the ones with the highest rate of damage accrual in the following years, indicating that a high SCTC-DI score may represent a predictor of further damage accrual (12). The previous observation of mild plateauing of damage trajectories at 4 years led to the suggestion that disease stabilisation after the first years is generally associated with slower damage progression (12).

Indeed, in our SSc cohort of 253 patients

Table I. Evaluation of SCTC-DI annual rise in 253 SSc patients.
a) SCTC-DI annual rise: comparisons among different subgroups of SSc patients according to sex, auto-antibody status and cutaneous subsets.
b) SCTC-DI annual rise: comparisons between [T5-T0] and [T10-T5] within the same subgroups of SSc patients.
c) SCTC-DI annual rise: comparisons between patients with late mortality *vs*. survivors.

a.	Total SSc n=253	Males n=16	Females n=237	*p*-value	ACA- n=114	ACA+ n=139	p-value	dcSSc n=28	lcSSc n=215	*p*-value
SCTC-DI annual rise [T5-T0]	0.2/year (0.0-0.6)	0.4/year (0.0-0.7)	0.2/year (0.0-0.6)	*0.203*	0.4/year (0.0-0.6)	0.0/year (0.0-0.4)	***<0.001***	0.7/year (0.4-1.2)	0.0/year (0.0-0.4)	***<0.001***
SCTC-DI annual rise [T10-T5]	0.0/year (0.0-0.4)	0.0/year (0.0-0.1)	0.0/year (0.0-0.4)	*0.137*	0.0/year (0.0-0.6)	0.0/year (0.0-0.4)	*0.145*	0.2/year (0.0-0.8)	0.0/year (0.0-0.4)	*0.112*
SCTC-DI annual rise [T10-T0]	0.4/year (0.0-0.8)	0.4/year (0.2-0.9)	0.4/year (0.0-0.8)	*0.541*	0.6/year (0.0-1.0)	0.2/year (0.0-0.6)	***<0.001***	1.1/year (0.6-1.6)	0.2/year (0.0-0.6)	***<0.001***

b.	SCTC-DI annual rise **[T5-T0]**	SCTC-DI annual rise **[T10-T5]**	SCTC-DI annual rise **[T10-T0]**	*p*-value
Total SSc (n= 253)	0.2/year (0.0-0.6)	0.0/year (0.0-0.4)	0.4/year (0.0-0.8)	*0.396*
Males (n= 16)	0.4/year (0.0-0.7)	0.0/year (0.0-0.1)	0.4/year (0.2-0.9)	*0.059*
Females (n= 237)	0.2/year (0.0-0.6)	0.0/year (0.0-0.4)	0.4/year (0.0-0.8)	*0.725*
ACA- (n= 114)	0.4/year (0.0-0.6)	0.0/year (0.0-0.6)	0.6/year (0.0-1.0)	*0.146*
ACA+ (n= 139)	0.0/year (0.0-0.4)	0.0/year (0.0-0.4)	0.2/year (0.0-0.6)	*0.769*
dcSSc (n= 28)	0.7/year (0.4-1.2)	0.2/year (0.0-0.8)	1.1/year (0.6-1.6)	***0.013***
lcSSc (n= 215)	0.0/year (0.0-0.4)	0.0/year (0.0-0.4)	0.2/year (0.0-0.6)	*0.795*

c.	Patients with late mortality n=90	Survivors n=163	*p*-value
SCTC-DI annual rise [T1-T0]	0.0/year (0.0-0.4)	0.0/year (0.0-0.2)	*0.726*
SCTC-DI annual rise [T5-T1]	0.0/year (0.0-0.6)	0.0/year (0.0-0.2)	***0.046***
SCTC-DI annual rise [T10-T5]	0.4/year (0.0-0.6)	0.0/year (0.0-0.2)	***0.006***
SCTC-DI annual rise [T10-T0]	0.6/year (0.0-1.0)	0.2/year (0.0-0.6)	***0.003***

Continuous variables are presented as median (IQR) and compared with Mann-Whitney test; *p*-value <0.05 was considered statistically significant.
ACA: anti-centromere; dc: diffuse cutaneous; DI: damage index; lc: limited cutaneous; SSc: systemic sclerosis.

with long-term follow-up, we observed a continuous progression of damage accrual, with 34% of surviving patients showing moderate or severe damage at 10 years after SSc diagnosis. It should be emphasised that this cohort was selected on the basis of survival at 10 years, thus representing a group of patients with favourable outcome, which is further confirmed by the significant lower prevalence of negative prognostic factors at the baseline (male sex, dcSSc) as compared with the entire cohort of 648 SSc patient. However, it is noteworthy that in dcSSc patients the rate of damage accrual observed in the first 5 years after SSc diagnosis did decrease in the following time interval between 5 and 10 years, confirming the hypothesis of a lower rate of late damage accrual only for this subset.

The observation of early damage accrual in dcSSc can be explained with the higher frequency of some serious end-organ complications, such as scleroderma renal crisis, within the very first years after diagnosis in this subset (12, 17, 18). It was also suggested that the first 4 years after diagnosis represent the interval with the highest accrual of damage related to ILD, that shows stability or even a "burn out" in the following period (12, 19). However, SSc-ILD shows a heterogeneous and often variable course (20), and in long-term survivors the expected plateau in the progression disappears with stratification into prognostic subgroups to account for survival bias (21).

On the other hand, the long-term observation of lcSSc patients highlighted the necessity of a careful follow-up for this subset, as they can experience the persistence of disease manifestations, even if skin disease is mostly stable (22). Specifically, damage accrual might be related to peripheral vasculopathy complicated by digital ulcers or calcinosis, but also to late ILD progression (22). Noteworthy, in the large international multicentre EUSTAR registry about a quarter of patients with lcSSc had anti-Topo1 antibodies positivity and carried a risk of developing ILD similar to

Table II. Multivariable analyses. Logistic regression models with *a priori* selection of variables to evaluate factors potentially associated with moderate/severe organ damage at 5 and 10 years after diagnosis.

Characteristics	5-year follow-up			10-year follow-up		
	p-value	OR	95% CI	*p*-value	OR	95% CI
Model 1						
dcSSc	*0.009*	4.55	1.46-14.1	*0.013*	4.31	1.36-13.70
Anti-centromere+	*0.024*	0.32	0.12-0.86	*0.216*	0.61	0.28-1.34
Male sex	*0.284*	0.40	0.07-2.15	*0.376*	0.46	0.08-2.57
Age-adjusted-CCI (T0)	*0.361*	1.15	0.85-1.55	*0.866*	1.02	0.83-1.25
SCTC-DI (T0)	*0.015*	1.34	1.06-1.70	*0.081*	1.18	0.98-1.43
SCTC-DI (T1)	*<0.0001*	1.65	1.30-2.07	*NA*	NA	NA
SCTC-DI (T5)	*NA*	NA	NA	*<0.0001*	1.67	1.38-2.01
Model 2						
dcSSc	*0.260*	1.88	0.63-5.66	*0.027*	4.68	1.19-18.38
Anti-centromere+	*0.213*	0.34	0.13-0.85	*0.034*	0.39	0.16-0.93
Male sex	*0.506*	0.57	0.11-3.04	*0.834*	0.84	0.16-4.36
Age-adjusted-CCI (T0-T5)	*0.050*	1.35	1.00-1.81	*0.179*	1.25	0.90-1.72
Delta SCTC-DI (T0-T5)	*<0.0001*	1.90	1.51-2.38	*<0.0001*	1.68	1.35-2.08
Delta SCTC-DI (T5-T10)	-	-	-	*<0.0001*	2.92	2.13-4.02

CCI: Charlson Comorbidity Index; CI: confidence interval; dc: diffuse cutaneous; DI: Damage Index; OR: odds ratio; SCTC: Scleroderma Clinical Trial Consortium; SSc: systemic sclerosis.

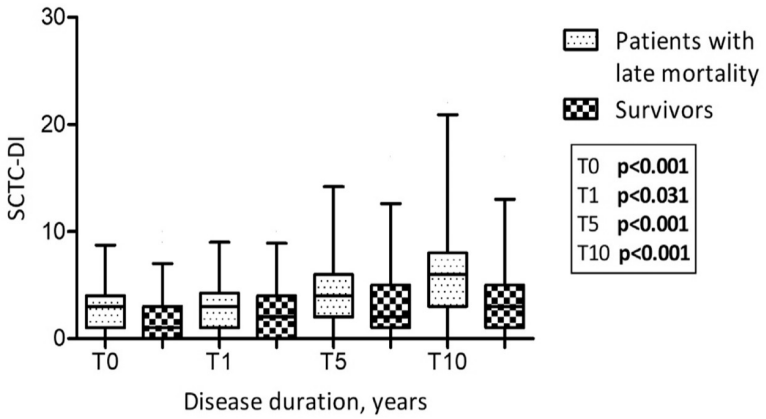

Fig. 4. Comparison of SCTC-DI at every timepoint (T0, T1, T5, T10): patients with late mortality *vs.* survivors.
Continuous variables are presented as median (IQR) and compared with Mann-Whitney test.
p-value <0.05 was considered statistically significant.
DI: Damage Index; SCTC: Scleroderma Clinical Trial Consortium.

anti-Topo1+ patients with dcSSc, and 4.5-fold higher than those with lcSSc and ACA+ (23). These results could strengthen the observations from the present and other previous studies, indicating ACA, and not lcSSc, as an independent predictor of lower damage accrual at least in the first 5 years after diagnosis (12). The protective role of ACA positivity was no longer confirmed when organ damage was evaluated at 10 years, thus suggesting the possibility of late accrual for some of these patients. It could be indeed speculated that the occurrence of PAH, which usually represents a long-term disease complication associated with ACA positivity (24), could explain this observation.

Additionally, we also confirmed that high SCTC-DI scores are associated with development of significant damage in subsequent timepoints, indicating that patients with more damage continue to accrue further damage at a faster rate in the following years. Moreover, both SCTC-DI at T0 and T5, and the variations of damage score over time (represented by Delta T0-T5 and T5-T10) were associated with moderate and severe damage at 10 years in alternative statistical models evaluating damage. Therefore, the present study not only extends the usefulness of the application of SCTC-DI to SSc patients with a long-term follow up, but also highlights some implications relevant to clinical practice. Importantly, the SCTC-DI both at the baseline and its variations over time were proven to have an association with development of significant damage at 10 years of follow-up and with late mortality, thus suggesting the utility of regularly monitoring this score at the time of diagnosis and during the whole follow-up.

Our study suffers from several limitations: the inclusion criteria carry inherent survival bias with the exclusion of patients who died before 10 years of follow-up. Moreover, damage accrual might have been influenced by disease activity, but unfortunately, reliable data on SSc activity indexes were not available in our cohort, so that we could not evaluate the interrelationship between disease activity and damage in our patients**.** Even if considering a large SSc single-centre cohort, the study was not adequately powered for the analysis of small subgroups of patients, including those with male sex, rare autoantibodies and non-Caucasian ethnicities. In particular, 99% of our cohort was of Caucasian ethnicity, that was previously demonstrated as a protective factor for damage accrual (12), indicating that our results cannot be extended to non-Cau-

casian SSc subgroups. Finally, given the specific design of the study, only patients who received SSc diagnosis before 2009 were included, so that the potential role of new therapeutic approaches (including antifibrotic drugs, biologics, improved strategies for PAH treatment, etc) could not be ascertained (25).

In conclusion, in this single-centre cohort of SSc patients prospectively followed for at least 10 years after diagnosis, we observed a continuous damage accrual and confirmed previously identified factors associated with higher damage scores, such as dcSSc and ACA-negativity. Moreover, we were able to detect a variable impact of these factors over time, observing that in dcSSc patients damage accrual is faster in the first 5 years after diagnosis and then decreases, whereas in lcSSc patients is quite stable, with ACA positivity no longer representing a protective factor at 10 years after SSc diagnosis. Finally, SCTC-DI measure and monitoring predicted both further damage accrual within time and late mortality in SSc patients, indicating that potential utility of this index in clinical practice.

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