

Original article

Older age onset of systemic sclerosis – accelerated disease progression in all disease subsets

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Abstract

Objectives. Systemic sclerosis is a heterogeneous, multisystem disease. It can occur at any age, but most patients develop the disease between the age of 40 to 50 years. There is controversial evidence on whether/how the age at disease onset affects their clinical phenotype. We here investigate the relationship between age at disease onset and symptoms in a large cohort of SSc patients (lcSSc, dcSSc and SSc-overlap syndromes).

Methods. Clinical data of the registry of the German Network for Systemic Scleroderma including 3281 patients were evaluated and subdivided into three age groups at disease onset (<40 years, 40–60 years, >60 years).

Results. Among all SSc patients, 24.5% developed their first non-Raynaud phenomenon symptoms at the age <40 years, and 22.5% were older than 60 years of age. In particular, older patients at onset developed the lcSSc subset significantly more often. Furthermore, they had pulmonary hypertension more often, but digital ulcerations less often. Remarkably, the course of the disease was more rapidly progressing in the older cohort (>60 years), except for gastrointestinal and musculoskeletal involvement. No significant difference was found for the use of corticosteroids. However, significantly, fewer patients older than 60 years received immunosuppressive treatment.

Conclusion. In this large registry, ~25% of patients developed SSc at an age above 60 years with an increased frequency of lcSSc. In this age group, an onset of internal organ involvement was significantly accelerated across all three subsets. These findings suggest that, in the elderly cohort, more frequent follow-up examinations are required for an earlier detection of organ complications.

Key words: scleroderma, systemic sclerosis, older age, age at disease onset, SSc, German Network for Systemic Scleroderma

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Rheumatology key messages

- Relationship between age at disease onset and symptoms in lcSSc, dcSSc and SSc-overlaps patients.
- Older age at disease onset is clearly an additional risk factor for disease progression.
- Older age at disease onset should lead to more frequent investigations for organ manifestations.

Introduction

Systemic sclerosis (SSc) is a complex and heterogeneous multisystem disease, which affects the skin together with many internal organs, such as the cardiopulmonary system, the gastrointestinal tract, the musculoskeletal system and the kidney [1]. The disease is characterized by endothelial cell damage, altered regulation of the immune system, and an extensive deposition of collagen and other extracellular matrix proteins leading to fibrosis [1]. Importantly, SSc is a heterogeneous disease and different SSc subsets are associated with distinct expression of organ manifestations/clinical features and a divergent progression of the disease. This has also been shown for patients with SSc overlap syndromes who, despite their limited skin involvement, develop a completely different course of disease, distinct from lcSSc and dcSSc patients [2].

The majority of SSc patients develop initial clinical symptoms between the age of 40 to 50 years [3, 4]. However, there is a very broad range of disease onset and also much younger and older patients can develop SSc [3, 5]. Furthermore, various authors have observed that elderly patients express different clinical features, which is reflected by characteristic autoantibodies [3, 5–11]. There is, however, still a controversial discussion; several studies indicate that older patients have a more severe course of the disease including different organ involvement and a worse prognosis. Recently, a more progressive disease with a poor prognosis and a higher mortality rate compared with younger SSc patients was reported [5]. In particular, although elderly patients (>60 years) have a lower prevalence of digital ulcers, they developed cardiac involvement more frequently [5, 9, 12] with an increased mortality [6–11, 13, 14]. Furthermore, Nihtyanova and colleagues reported that a greater age at disease onset predicts a higher risk for both lung fibrosis and pulmonary hypertension (PH) [15]. This is supported by an analysis of a SSc cohort by the Johns Hopkins University. It has been demonstrated that patients older than 65 years have not only a greater risk for PH, but for renal, cardiac and musculoskeletal involvement [3]. Apart from the organ involvement, it is controversial whether older patients more frequently belong to a certain SSc subset with a rather limited [6, 7] or diffuse skin involvement [16–18]. On the other hand, the Spanish Scleroderma Study Group have shown in their SSc cohort of 1037 patients that younger patients (age ≤30 years) had a higher prevalence of oesophageal and musculoskeletal involvement, but a lower

prevalence of anti-centromer antibodies (ACA). Furthermore, the mortality ratio was higher in younger patients [10, 14].

To further evaluate the controversial situation regarding the relationship between the age at disease onset, disease course and clinical characteristics, we here present data from an independent, very large cohort of patients with different SSc subsets, which have been carefully analysed with many consecutive visits over 15 years.

Methods

The patient registry of the German Network for Systemic Scleroderma (DNSS) was founded in 2003 and >4500 patient cases have been recorded as of now. The Network involves >40 clinical centers with different subspecialties including rheumatologists, dermatologists, pulmonologists and nephrologists. The Ethics Committee of the coordinating center, i.e. the Department of Dermatology at the University Hospital Cologne, approved the patient information and consent form of the DNSS registry (approval number, 04–037), which was used by all participating centers to receive the approval of their local ethics committees prior to registering patients. To participate in the study, written informed consent was obtained from all patients.

The four-page disease- and organ-specific questionnaire collects clinical data to determine the current disease status with information on gender, date of birth, onset of organ manifestations as well as current symptoms together with characteristic laboratory findings including antinuclear antibodies and therapies as recently described [2, 19].

Definition for organ manifestations and clinical signs

RP was defined by repetitive spasms of small digital arterioles/arteries at fingers and/or toes. The first non-RP onset has been defined as the time/age when first skin changes or first organ manifestation (first non-RP symptom) has occurred. For skin manifestation, we used the modified Rodnan Skin Score (mRSS).

PH was defined by an increase of the mean pulmonary arterial pressure (PAPm) of ≥25 mmHg in rest, evaluated by right heart catheterization. Additionally, an estimated right ventricular systolic pressure (RVSP) >35/40 mmHg as determined by echocardiography was used to define likely PH. Lung fibrosis was defined by bilateral fibrosis, confirmed by both X-ray and high-resolution CT scan of the chest together with restrictive pulmonary

changes seen in the pulmonary function test [forced vital capacity (FVC) <80%]. Gastrointestinal involvement included gastrointestinal motility disturbance, dysphagia, nausea, malabsorption, oesophageal stenosis, gastro-oesophageal reflux or intestinal pseudo-obstruction. Heart involvement was defined as one of the following: dyspnea (NYHA), syncope, palpitations, pericarditis, conduction disturbance or diastolic dysfunction on the echocardiogram. Kidney involvement was defined as the presence of renal insufficiency secondary to acute renal crisis (creatinine clearance age-related <80 mL/min). The diagnosis of proteinuria was fulfilled in cases of albuminuria ≥ 30 mg/24 h or ≥ 20 mg/l as well as proteinuria ≥ 300 mg/24 h or ≥ 200 mg/l. Skeletal muscle involvement was present in case of proximal muscle weakness or atrophy recorded on clinical evaluation and raised serum muscle enzyme levels [creatin kinase (CK) >3 times higher than the upper limit of the reference range]. The diffusing capacity for carbon monoxide (DLCO/SB) was defined as diffusing capacity or transfer factor of the lung for carbon monoxide with a range of 20–95%; the standard value is >75%. Digital ulcers were defined as loss of dermis and epidermis of at least 2 mm of tissue at the fingertips.

Definition of included SSc subsets

The registry encompasses five different subsets of SSc including early undifferentiated forms (early and very early SSc), SSc sine scleroderma, diffuse cutaneous SSc (dcSSc), limited cutaneous SSc (lcSSc) and SSc overlap syndromes. Patients included fulfilled the ACR/EULAR 2013 classification criteria [20]. The SSc subset (lcSSc, dcSSc) was based on the classification criteria established by LeRoy *et al.* [18, 21]. Follow-up visits were performed at least once per year.

In the present analysis, we focused on patients with lcSSc, dcSSc and SSc overlap syndromes. Furthermore, we excluded patients with missing information on date of disease onset and patients with time since disease onset >20 years at registration. Using this selection, data of 3281 patients registered between 2003 and 2018 with 8079 follow-up visits were reviewed for this analysis.

Patients suffering from lcSSc were defined by skin sclerosis of the extremities distal to the knee and elbow joints and facial skin. The RP usually appeared many years prior to skin involvement and patients were mostly positive for ACA, which is in line with previously published data [18, 19]. Patients with dcSSc had a progressive course of disease with an early onset of RP (usually within 1 year prior to the onset of first skin thickening). These patients are defined by rapid skin involvement of the trunk, face, proximal and distal extremities and they most frequently are anti-topoisomerase (ATA) antibody positive [2, 18]. SSc overlap syndromes showed clinical features of SSc, according to the ACR criteria, or main SSc-associated symptoms, simultaneously with those typical for other rheumatic diseases [2, 22]. These patients, although showing a limited expression of skin

sclerosis, are considered as a separate SSc subset, distinct from lcSSc and dcSSc patients [2].

Age at disease onset – three main subgroups

In addition to the assignment to the three main SSc subsets, we assigned the patients to three age groups according to the disease onset [<40 years (early disease onset), 40–60 years (standard disease onset), and >60 years (late disease onset)]. The disease onset was defined as the age of the onset of the first non-RP symptom.

Statistics

An association of specific age groups with other clinical data was descriptively evaluated comparing patients younger than 40 years, between 40 and 60 years and older than 60 years. To compare demographic and serological parameters, we used data of the initial visit. To compare organ manifestations, clinical symptoms and medication, we used follow-up data on all visits (i.e. organ manifestation at last follow-up visit, and clinical symptoms/medication use ever/never documented at any visit). For group comparisons, we used Pearson's χ^2 test (qualitative data) and Kruskal–Wallis test (quantitative data). To compare the disease progression within the three age subgroups, the onset of different organ involvements is illustrated within the course of the disease. For this purpose, the proportion-free of organ involvement was estimated using Kaplan–Meier method and compared using log rank tests. Results are presented as Kaplan–Meier curves and as rates with corresponding 95% confidence intervals at time points 5 and 10 years after SSc onset (time of first non-RP manifestation, starting-point used for Kaplan–Meier analysis). All reported *P*-values are two-sided and *P*-values of <0.05 were considered statistically significant. As the analyses were regarded as explorative, we did not adjust for multiple testing. Calculations and figures were carried out using SPSS (23.0.0.3 64-Bit, IBM Corp., Armonk, NY, USA) and Excel (Microsoft Corp., Redmond, WA, USA) as well as R (version 3.4.0, R Foundation for Statistical Computing, Vienna, Austria).

Results

Overall patient characteristics

To compare demographic and serological parameters, we used data of the initial visit. For determining organ manifestations, clinical symptoms and medication data from all follow-up visits were analysed. Among all 3281 SSc patients, 54.2% (1777/3281) suffered from lcSSc, 34.8% (1142/3281) from dcSSc, and 11.0% (362/3281) from SSc overlap syndromes. The gender analysis revealed 79.7% (2568/3281) female patients, and 20.3% (655/3281) male patients. The mean age of SSc onset of the entire SSc cohort was 49.1 ± 14.0 years. Overall, 24.5% of patients developed first non-RP symptoms at the age of <40 years, 53.0% between the age of 40–

TABLE 1 Patient characteristics – demographic and serological parameters according to three age groups

Variable	Total n	<40 yrs % (n)	40–60 yrs % (n)	>60 yrs % (n)	P-value	
Analysis set	Total	3281	24.5% (804)	53.0% (1738)	22.5% (739)	—
Number of visits	Mean (s.d.)	3.4 (2.9)	3.5 (2.9)	3.5 (3.0)	3.1 (2.7)	0.003
Age at disease onset (yrs)	Valid n	3273	801	1734	738	0.001
	Mean (s.d.)	49.1 (14.0)	30.5 (7.0)	50.0 (5.8)	67.4 (5.2)	
Disease duration at first visit (yrs)	Valid n	3248	799	1720	729	0.001
	Mean (s.d.)	5.7 (5.1)	7.4 (6.0)	5.8 (5.0)	3.7 (3.5)	
Gender	Male	655	19.8% (156)	22.1% (378)	16.6% (121)	0.008
	Female	2568	80.2% (633)	77.9% (1329)	83.4% (606)	
Diagnosis	lcSSc	1777	43.4% (349)	54.5% (948)	65.0% (480)	0.001
	dcSSc	1142	41.8% (336)	35.4% (616)	25.7% (190)	
	Overlap S.	362	14.8% (119)	10.0% (174)	9.3% (69)	
ANA positive, first visit	no	268	8.8% (67)	8.6% (141)	8.5% (60)	0.986
	yes	2837	91.2% (698)	91.4% (1494)	91.5% (645)	
Scl 70 positive, first visit	no	1951	59.5% (434)	66.0% (1032)	72.8% (485)	0.001
	yes	1008	40.5% (296)	34.0% (531)	27.2% (181)	
ACA positive, first visit	no	1897	74.0% (534)	63.4% (987)	55.9% (376)	0.001
	yes	1055	26.0% (188)	36.6% (570)	44.1% (297)	
RNA polymerase (RNAP) positive, first visit	no	2906	98.8% (724)	97.7% (1540)	97.9% (642)	0.228
	yes	59	1.2% (9)	2.3% (36)	2.1% (14)	
modified Rodnan Skin Score (mRSS)	Valid n	2959	721	1565	673	0.023
	Mean (s.d.)	10.2 (8.8)	10.5 (8.7)	10.4 (9.0)	9.4 (8.4)	
Diffusing capacity for carbon monoxide/single breath (DLCOc/SB)	Valid n	1986	497	1046	443	0.010
	Mean (s.d.)	69.1 (21.1)	70.1 (19.2)	69.7 (21.7)	66.8 (21.39)	
Forced vital capacity (FVC)	Valid n	459	103	230	126	0.350
	Mean (s.d.)	88.1 (20.4)	88.4 (20.1)	89.0 (20.4)	86.4 (20.6)	
FEV1	Valid n	509	119	252	138	0.933
	Mean (s.d.)	86.0 (18.3)	86.3 (18.1)	86.0 (18.1)	85.7 (18.8)	

60 years, and 22.5% were older than 60 years of age (Table 1). The mean age at disease onset in the early disease onset cohort (<40 years) was 30.5 ± 7.0 years, in the standard disease onset cohort (40–60 years) 50.0 ± 5.8 years, and in the late disease onset cohort (>60 years) 67.4 ± 5.2 years. The mean follow-up time was 4.9 (3.5) years and 2200 (67.1%) patients had at least 2 registered visits.

Age-related clinical manifestations within the entire SSc cohort and within each SSc subset

SSc patients with a late disease onset (>60 years) developed the lcSSc subtype significantly more often (65.0%) compared with dcSSc (25.7%), and 9.3% of SSc overlap syndromes ($P < 0.001$). Significantly more elderly patients (>60 years) were female compared with the younger cohort ($P = 0.008$) (Table 1). The antibody distribution matched also to the distribution of the subsets; here, SSc patients with a late disease onset were significantly less often positive for Scl-70, but significantly more often positive for ACA antibodies ($P < 0.001$). Accordingly, these patients had a significantly lower mRSS (9.4 (8.4), $P = 0.023$), but all three main SSc subsets developed first skin changes significantly earlier compared with patients with an early disease onset (<40 years). Patients with the diffuse form and SSc overlap syndromes developed first skin changes after a

mean duration of 3.1 (3.5) years whereas lcSSc patients showed first skin fibrosis after 4.0 (3.5) years ($P < 0.001$).

Furthermore, compared with the early disease onset cohort, the elderly cohort suffered overall significantly more often from PH (19.2%, $P < 0.001$), heart involvement (14.8%, $P = 0.030$) as well as significantly less often from oesophageal (48.3%, $P = 0.01$), and musculoskeletal involvement (31.3%, $P = 0.005$) (Table 2). Of these, the elderly lcSSc (17.6%) and dcSSc patients (24.9%) developed significantly more often PH ($P < 0.001$), but only the elderly dcSSc patients more frequently lung fibrosis (73.5%, $P < 0.001$) and heart involvement (23.8%, $P = 0.005$) compared with the younger cohort. In contrast, elderly SSc patients developed musculoskeletal involvement less often compared with the younger cohort, which was significant for SSc overlap patients (37.3%; $P = 0.011$) (Tables 2 and 3).

Furthermore, patients with a late disease onset compared with patients with an early disease onset had digital ulcers significantly less often ($P < 0.001$) and significantly more often arterial hypertension ($P < 0.001$), which consists for all SSc subsets. Elderly patients diagnosed with lcSSc and dcSSc suffered more frequently from dyspnea ($P < 0.001$), and only lcSSc patients from proteinuria ($P = 0.006$) (Table 3).

No significant difference was found for the use of corticosteroids within the three age groups. However, fewer patients older than 60 years at disease onset underwent

TABLE 2 Patient characteristics – organ manifestations and clinical symptoms according to three age groups

Variable	Total n	<40 years % (n)	40–60 years % (n)	>60 years % (n)	P-value
Analysis set	Total 3281	24.5% (804)	53.0% (1738)	22.5% (739)	—
Organ manifestation					
Pulmonary hypertension	no 2825	92.5% (731)	88.2% (1505)	80.8% (589)	0.001
	yes 401	7.5% (59)	11.8% (202)	19.2% (140)	
Lung fibrosis	no 2021	62.5% (495)	64.1% (1094)	59.3% (432)	0.081
	yes 1208	37.5% (297)	35.9% (614)	40.7% (297)	
Oesophagus involvement	no 1517	44.4% (352)	46.2% (788)	51.7% (377)	0.010
	yes 1711	55.6% (441)	53.8% (918)	48.3% (352)	
Heart involvement	no 2833	89.5% (709)	88.1% (1503)	85.2% (621)	0.030
	yes 394	10.5% (83)	11.9% (203)	14.8% (108)	
Musculoskeletal involvement	no 1970	61.1% (466)	62.6% (1019)	68.7% (485)	0.005
	yes 1127	38.9% (297)	37.4% (609)	31.3% (221)	
Clinical symptoms					
Raynaud phenomenon	no 141	3.7% (29)	4.2% (72)	5.5% (40)	0.206
	yes 3095	96.3% (765)	95.8% (1637)	94.5% (693)	
Digital ulcers	no 1784	44.6% (354)	56.0% (956)	65.7% (474)	0.001
	yes 1437	55.4% (439)	44.0% (751)	34.3% (247)	
Flexion contractures	no 1815	57.2% (443)	56.6% (941)	60.4% (431)	0.204
	yes 1337	42.8% (332)	43.4% (723)	39.6% (282)	
Tendon friction rubs	no 2714	84.7% (664)	84.3% (1425)	87.2% (625)	0.181
	yes 478	15.3% (120)	15.7% (266)	12.8% (92)	
Dysphagia	no 999	33.3% (264)	28.3% (484)	34.7% (251)	0.002
	yes 2227	66.7% (529)	71.7% (1225)	65.3% (473)	
Reflux	no 573	39.9% (147)	39.1% (286)	47.6% (140)	0.038
	yes 820	60.1% (221)	60.9% (445)	52.4% (154)	
Dyspnea	no 1502	54.2% (427)	45.2% (770)	42.3% (305)	0.001
	yes 1710	45.8% (361)	54.8% (933)	57.7% (416)	
Hypertension	no 1978	80.3% (629)	60.3% (1024)	45.3% (325)	0.001
	yes 1221	19.7% (154)	39.7% (675)	54.7% (392)	
Proteinuria	no 2519	83.3% (644)	81.1% (1343)	76.8% (532)	0.006
	yes 604	16.7% (129)	18.9% (314)	23.2% (161)	
Creatine kinase (CK) elevation (>3 times)	no 2627	85.5% (654)	83.9% (1368)	86.9% (605)	0.151
	yes 465	14.5% (111)	16.1% (263)	13.1% (91)	

immunosuppressive treatment (35.1%; 244/696; $P = 0.017$) compared with patients younger than 40 years (42.0%, 319/759). Only the elderly dcSSc cohort had been treated significantly more often with corticosteroids ($P = 0.026$) compared with younger patients with dcSSc. Otherwise, no significant difference for corticosteroids and other disease-modifying agents within other SSc subsets was present (Table 3).

Age-related disease progression within the three SSc subtypes (follow-up time >10 years)

Across all three subsets, patients with a late disease onset had a significantly higher and earlier incidence of an organ manifestation, e.g. PH, lung fibrosis or heart involvement ($P < 0.001$; Fig. 1), except the musculoskeletal system and the gastrointestinal involvement (Fig. 1A–D). The proportion of patients free of organ manifestation after 10 years was lower in the late onset cohort (>60 years) compared with the early onset cohort (<40 years) for PH (61.8% vs 90.5%), lung fibrosis (47.8% vs 56.7%) and heart involvement (67.6% vs 84.3%) (Table 4).

This trend was also evident for each SSc subset (dcSSc, lcSSc and SSc overlap syndromes); patients diagnosed with late onset dcSSc showed the most pronounced organ manifestation, followed by the SSc overlap syndromes and the lcSSc patients. In contrast, the proportion-free rate of gastrointestinal (GI) involvement rate was almost the same for all SSc subsets (74.5% for dcSSc, 74.4% for lcSSc and 70.6% for SSc overlaps). Deviating from all other organ manifestations, musculoskeletal involvement occurred significantly earlier and more frequently in SSc overlap patients (proportion-free of organ involvement, 51.8% for dcSSc; 60.9% for lcSSc; and 34.2% for SSc overlap syndromes). Nevertheless, no significant difference for musculoskeletal involvement between early and late disease onset could be demonstrated (Fig. 1A–D).

Discussion

This study revealed that approximately one quarter of patients developed SSc after the age of 60 years with a significantly higher proportion of women in the late

TABLE 3 Patient characteristics for lcSSc, dcSSc and SSc overlap syndromes according to three age groups

Variable		<40 years % (n)	40–60 years % (n)	>60 years % (n)	P-value
Pulmonary hypertension	lcSSc	6.5% (22/349)	10.0% (93/948)	17.6% (83/480)	<0.001
	dcSSc	8.7% (29/336)	15.3% (93/616)	24.9% (47/190)	<0.001
	SSc-O	6.7% (8/119)	9.2% (16/174)	14.5% (10/69)	0.212
Lung fibrosis	lcSSc	23.5% (80/349)	22.2% (206/948)	27.6% (130/480)	0.078
	dcSSc	55.3% (184/336)	57.1% (346/616)	73.5% (139/190)	<0.001
	SSc-O	27.7% (33/119)	35.8% (62/174)	40.6% (28/69)	0.159
Oesophagus involvement	lcSSc	51.3% (175/349)	53.7% (498/948)	48.2% (227/480)	0.151
	dcSSc	63.1% (210/336)	55.9% (338/616)	52.4% (99/190)	0.031
	SSc-O	47.1% (56/119)	47.4% (82/174)	37.7% (26/69)	0.355
Heart involvement	lcSSc	7.9% (27/349)	7.6% (70/948)	10.8% (51/480)	0.106
	dcSSc	12.6% (42/336)	17.3% (105/616)	23.8% (45/190)	0.005
	SSc-O	11.8% (14/119)	16.2% (28/174)	17.4% (12/69)	0.477
Musculoskeletal involvement	lcSSc	28.1% (92/349)	31.5% (277/948)	27.9% (127/480)	0.303
	dcSSc	42.1% (134/336)	42.5% (245/616)	37.5% (69/190)	0.468
	SSc-O	60.2% (71/119)	50.6% (87/174)	37.3% (25/69)	0.011
Digital ulcers	lcSSc	48.6% (168/349)	39.0% (363/948)	34.5% (162/480)	<0.001
	dcSSc	64.8% (214/336)	54.1% (328/616)	34.8% (64/190)	<0.001
	SSc-O	48.7% (57/119)	35.1% (60/174)	30.9% (21/69)	0.022
Dysphagia	lcSSc	62.9% (217/349)	71.2% (663/948)	64.9% (305/480)	0.005
	dcSSc	71.3% (236/336)	73.6% (447/616)	68.1% (126/190)	0.319
	SSc-O	65.0% (76/119)	67.3% (115/174)	60.9% (42/69)	0.641
Dyspnea	lcSSc	39.2% (134/349)	48.3% (449/948)	51.9% (243/480)	0.001
	dcSSc	52.3% (172/336)	63.5% (383/616)	70.4% (131/190)	<0.001
	SSc-O	47.0% (55/119)	59.1% (101/174)	62.7% (42/69)	0.058
Arterial hypertension	lcSSc	18.8% (64/349)	39.7% (369/948)	55.1% (256/480)	<0.001
	dcSSc	20.2% (66/336)	38.0% (229/616)	52.5% (96/190)	<0.001
	SSc-O	20.5% (24/119)	45.8% (77/174)	58.0% (40/69)	<0.001
Proteinuria	lcSSc	11.6% (39/349)	15.4% (139/948)	21.4% (97/480)	<0.001
	dcSSc	23.0% (74/336)	23.6% (138/616)	30.3% (53/190)	0.149
	SSc-O	13.9% (16/119)	22.0% (37/174)	16.9% (11/69)	0.212
Glucocorticoids	lcSSc	32.1% (109/349)	35.6% (326/948)	36.8% (170/480)	0.359
	dcSSc	51.1% (168/336)	59.9% (357/616)	59.6% (109/190)	0.026
	SSc-O	73.5% (86/119)	66.5% (113/174)	59.4% (41/69)	0.132
Immuno-suppressants	lcSSc	44.0% (149/349)	41.2% (377/948)	39.0% (181/480)	0.372
	dcSSc	65.9% (216/336)	66.3% (395/616)	67.2% (123/190)	0.952
	SSc-O	79.5% (93/119)	75.9% (129/174)	66.7% (46/69)	0.142

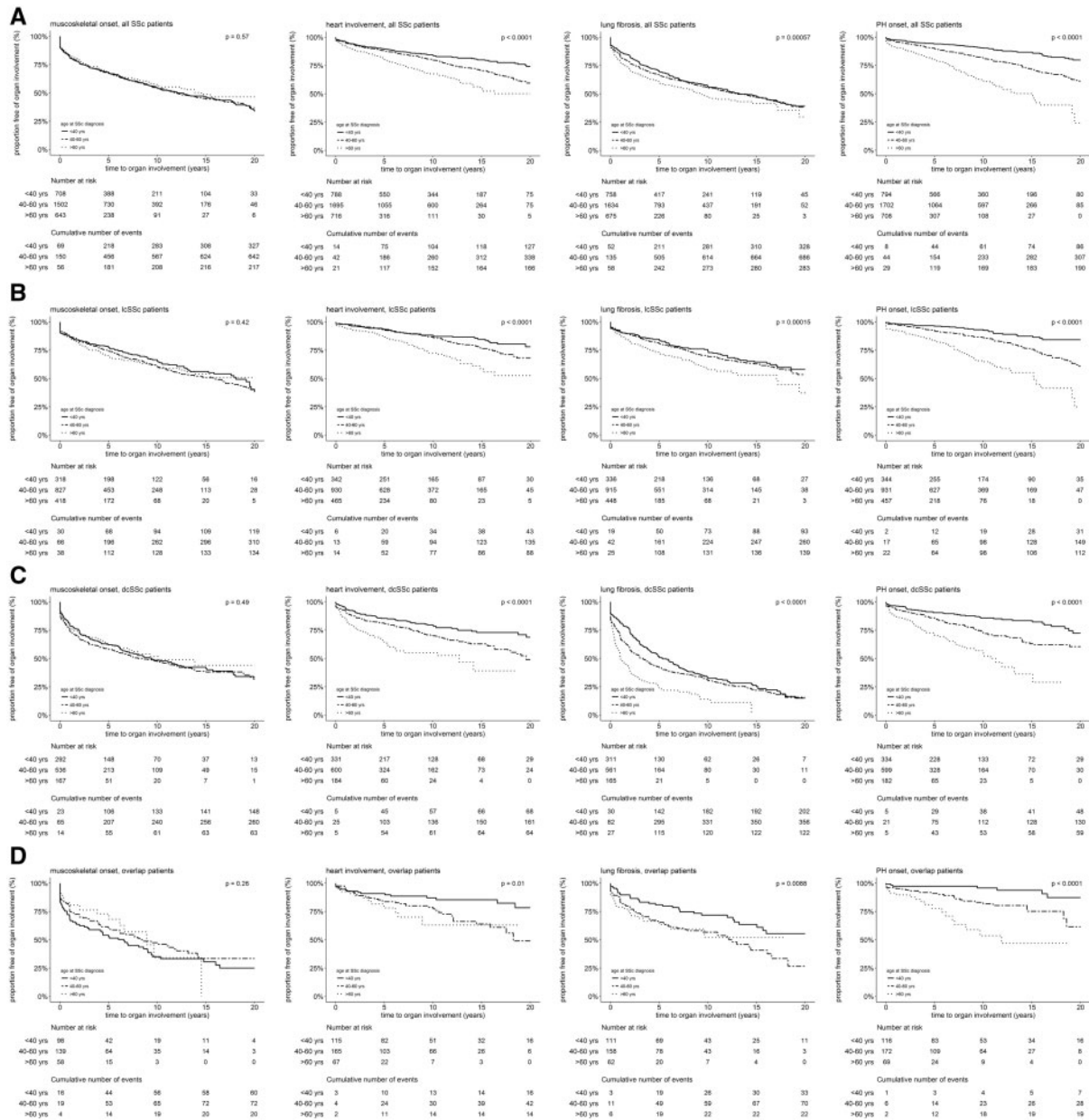
disease onset cohort. The main finding of the present study is a shift in the distribution of subsets. This was also reflected by the antibody distribution, with significantly more ACA and less ATA within the elderly cohort. Moreover, SSc overlap syndromes show a significantly different age distribution within the late-onset cohort.

The second main finding is that, independent of the subsets, older patients, although having a significantly lower modified Rodnan Skin Score, developed significantly earlier first skin changes as well as specific organ manifestations, compared with patients with the early disease onset. This is in line with recent observations that the disease progression was significantly faster in lcSSc patients with late disease onset compared with the early-onset cohort [6, 7]. Nevertheless, diffuse cutaneous SSc patients showed the most rapidly progressing subtype independent from disease onset groups compared with the other two subsets.

In terms of organ manifestation, our data suggest that PH and heart involvement occurred significantly

more often within the late-onset cohort, which is in line with other reports [3, 15]. However, a more detailed analysis of the development of clinical symptoms and organ manifestations within the different subsets showed that late-onset lcSSc and dcSSc patients developed significantly more often PH, while only late-onset dcSSc patients suffered more frequently from lung fibrosis and heart involvement. In addition, the analysis of all follow-up data over >15 years, using Kaplan–Meier analyses confirmed the results that late onset scleroderma patients in all subsets had a significantly higher and especially earlier incidence of organ manifestation, e.g. PH, lung fibrosis and heart involvement with the exception of the musculoskeletal system and the gastrointestinal involvement. It is interesting to note that SSc overlap patients characterized by more intense musculoskeletal involvement compared with the other two subsets developed those complications more often in the early disease onset cohort. This supports the notion that these patients represent a specific

Fig. 1 (A–D) Kaplan–Meier curves showing the time to onset of organ manifestations



Kaplan–Meier curves showing the time to onset of organ manifestations (PH, lung fibrosis, heart, musculoskeletal and gastrointestinal involvement) in three age subgroups at disease onset (<40 years, 40–60 years and >60 years) for all SSc patients and according to the SSc subset (lcSSc, dcSSc and SSc overlap syndromes). *P*-values correspond to log rank tests. Number at risk and cumulative number of events are given at starting point (SSc diagnosis) and every 5 years of follow-up.

subset with a different disease course as suggested earlier [2].

Basically, our findings are in line with previous publications but also extend these observations. The EULAR Scleroderma Trials and Research Group (EUSTAR) published their data recently regarding the association between age subgroups and clinical characteristics; they also showed that patients with a late

disease onset suffered more frequently from the limited subtype, with ACA positivity and PH/cardiac involvement [23].

However, it has not been reported so far that we determined no difference for the use of corticosteroids within the three age groups and significantly fewer patients older than 60 years at disease onset who underwent disease-modifying/immunosuppressive treatment.

TABLE 4 Proportion free of organ involvement subdivided for different SSc subsets according to three age groups

Age at SSc diagnosis	Time point (years)	PH		Lung fibrosis		Gastrointestinal involvement		Heart involvement		Musculoskeletal involvement		
		Proportion free of organ involv. (%)	95% CI	Proportion free of organ involv. (%)	95% CI	Proportion free of organ involv. (%)	95% CI	Proportion free of organ involv. (%)	95% CI	Proportion free of organ involv. (%)	95% CI	
all	5	94	92.2 95.7	70	66.6 73.5	87.7	85.3 90.1	89.8	87.6 92	67.7	64.2 71.3	
	10	90.5	88.2 92.8	56.7	52.9 60.8	79.9	76.8 83.2	84.3	81.5 87.2	54.5	50.5 58.7	
	40-60	5	89.7	88.2 91.3	66.5	64.1 69	87.3	85.6 89	87.7	86.1 89.4	67.4	64.9 69.9
		10	81.4	79.1 83.7	55.6	52.9 58.4	78.7	76.4 81.1	80	77.7 82.3	55.2	52.4 58.2
	>60	5	80.1	76.8 83.4	59.9	56 64.1	84.9	81.9 87.9	80.2	77 83.6	68.1	64.2 72.2
		10	61.8	56.8 67.3	47.8	42.9 53.2	74.1	69.6 78.8	67.6	62.9 72.7	57.1	52.2 62.6
lcSSc	5	96.2	94.2 98.4	84.3	80.3 88.4	91.3	88.3 94.5	93.7	91 96.4	77.5	72.9 82.4	
	10	93.1	90.1 96.2	74.4	69.4 79.8	84.3	80 88.8	87.8	83.9 91.8	66	60.5 72	
	40-60	5	92.1	90.3 94	80.9	78.2 83.6	88.6	86.5 90.8	92.7	90.9 94.5	74.3	71.3 77.5
		10	86.1	83.5 88.8	69.8	66.4 73.3	80.4	77.5 83.5	86.2	83.6 89	61.6	57.8 65.5
	>60	5	83.9	80.2 87.7	72.5	68.1 77.2	84	80.4 87.9	86.6	83.2 90.2	69.9	65.3 74.9
		10	65.7	59.7 72.3	59.3	53.4 66	74.4	69.1 80	72.5	66.8 78.8	60.9	55.2 67.2
dcSSc	5	90.5	87.2 93.9	51.2	45.7 57.4	83	78.9 87.4	85.4	81.5 89.5	62.1	56.7 68.2	
	10	85.9	81.6 90.3	33.1	27.7 39.6	74	68.8 79.6	79.6	74.9 84.7	48.4	42.4 55.3	
	40-60	5	85.5	82.4 88.6	42.1	37.9 46.8	85.3	82.3 88.4	81	77.7 84.4	58.6	54.4 63.2
		10	72.9	68.4 77.7	31	26.7 35.9	74.6	70.4 79.2	70.4	66.1 75.1	47.8	43.1 53
	>60	5	70.5	63.1 78.7	22.9	16.6 31.5	82.9	76.8 89.5	63.5	55.8 72.2	62.1	54.3 71
		10	54.6	44.8 66.6	13.9	7.9 24.6	74.5	66.4 83.7	55	46.6 65.1	51.8	42.3 63.3
overlap	5	97.3	94.4 100	81	73.5 89.1	89.9	84.4 95.8	90.8	85.5 96.4	52.7	43.4 64.1	
	10	95.7	91.6 100	71.8	63 81.9	83.6	76.4 91.5	87.1	80.6 94	35.1	25.8 47.7	
	40-60	5	90.9	86.5 95.6	66.3	58.9 74.5	86.9	81.5 92.6	83.6	77.8 89.9	59.6	51.7 68.8
		10	81.7	74.9 89.1	56.7	48.7 66.1	82.6	76.2 89.6	77.7	70.7 85.3	46.1	37.5 56.6
	>60	5	77.7	66.8 90.5	66.6	55.2 80.4	97.2	92 100	78.1	66.8 91.4	72.8	61.2 86.7
		10	53.6	38 75.7	52.1	36.4 74.5	70.6	52.4 94.9	63.1	46.7 85.1	34.2	15.6 75.2

Although it has also been observed in other studies, it remains unclear why our patients had significantly fewer digital ulcers at late disease onset [3, 24, 25], but demonstrated a more severe course of the disease with more extensive PH [3, 23]. This observation may be explained by the increased use of vasodilators due to arterial hypertension and/or PH in older patients. It should also be mentioned that in a retrospective study it was shown that digital amputation was associated with older age, long history of RP, long disease duration and presence of anticentromere antibody. This could probably be explained by the coexistence of other micro/macrovascular disease processes [26]. Our observation that vasculopathic organ manifestations, except digital ulcers, were more common in the late onset cohort, and inflammatory symptoms more frequent in the early onset cohort support this conclusion. This is also in agreement with the relatively rare use of immunosuppressive drugs in patients with later disease onset; however, the fact that elderly patients are more vulnerable to risks of immunosuppressive therapies, especially to infections and malignancies, and that physicians might be more reluctant to prescribe immunosuppressive drugs in the elderly might also contribute to this observation. Our data support the suggestion of several other studies to use the older age at disease onset as an independent prognostic factor, together with the diffuse subset, lung involvement, PH and renal crisis [10, 26, 27] for a poor prognosis.

This study contributes further important and unique findings due to the well-defined patient cohort of 3281 patients and >8000 follow-up visits. The presentation of the course of the disease on the basis of Kaplan–Meier curves nicely presents the variation in disease expression and progression in all three different SSc subsets. In contrast to other studies, our data clearly show differences between the individual SSc subsets, the lcSSc, dcSSc and SSc overlap syndromes together with a new contribution of therapeutic approaches in different age groups.

The following limitations of our study need to be discussed. It should be noted, that, as in many other studies, the data within this register are pre-collected and definitions have been established when the register was established in 2003. Specific data that turned out to be interesting during the analysis could not be collected retrospectively. Missing data were fortunately only <10% for all main variables, except for some variables (e.g. FVC, FEV1) that have been added after revision of the questionnaire in 2014. A further general limitation in the interpretation of register-based studies is that only data of included patients are considered, leaving an unclear number of unrecorded patients. However, assuming a prevalence of SSc of 100–200 patients per million, our data are based on 25–50% of all patients in Germany indicating a high reliability of the findings.

In summary, our findings may have an important impact for recommendations on the number of follow-up visits and additional diagnostics in SSc patients. Not

only the specific SSc subset [2], but also the patients with an older age at disease onset represent subgroups at risk and should be examined more frequently regarding potential organ manifestations. Importantly, an older age at disease onset is an additional risk factor for disease progression in addition to well-known risk factors such as SSc subsets, specific antibodies and specific organ manifestations.

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