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Elderly-onset systemic sclerosis defines a distinct clinical subset: analysis from the SPRING registry of the Italian Society for Rheumatology

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ABSTRACT

Objective: Elderly-onset systemic sclerosis (SSc) is relatively uncommon, and its clinical phenotype and prognostic implications remain poorly characterized, with conflicting evidence regarding disease course and outcomes.

Methods: Within the Italian SPRING (Systemic Sclerosis PRogression INvestiGation) registry, we compared demographic and clinical characteristics of patients with elderly-onset SSc (≥70 years at the time of the first non-Raynaud's manifestation) to those with younger onset. Cross-sectional analyses, multivariable logistic regression, and unsupervised cluster analysis were conducted to identify features associated with elderly-onset SSc. Longitudinal analysis was performed to assess mortality risk within SSc patients and compared to the general Italian population.

Results: Elderly-onset accounted for 8.5 % (160/1893) SSc cases in SPRING. These patients exhibited fewer peripheral vascular complications (digital ulcers: 13 % vs. 23 %; p = 0.016), higher prevalence of anticentromere antibodies (60 % vs. 39 %; p = 0.007), a lower prevalence and likelihood of diffuse skin subset (OR 0.40; 95 % CI 0.19–0.83) but an increased risk of pulmonary arterial hypertension confirmed on right-heart catheterization (OR 14.1; 95 % CI 3.68–54.5) at multivariate analysis. As expected, patients with elderly onset SSc had an increased risk of death compared to younger-onset individuals. Compared with the age-, sex-, and calendar year-matched general Italian population, patients with SSc showed a fivefold increased mortality, with a trend toward a higher risk in young-onset (SMR 6.3; 95 %CI 4.1–9.1) compared with elderly-onset (SMR 4.5; 95 %CI 2.4–7.7) cases.

Conclusions: Elderly-onset identifies a distinct clinical subset of SSc, mainly characterized by mild cutaneous and peripheral vascular involvement, but showing a greater burden of pulmonary vascular disease and increased mortality compared to the age-matched general population.

1. Introduction

With the steady increase in average life expectancy, the proportion of elderly patients affected by rheumatic diseases is rising [1]. This demographic shift has prompted growing interest in elderly-onset forms of these conditions. However, definitions of "elderly-onset" vary across studies, particularly with regard to the age cut-off used to define this subgroup [2–4]. In several autoimmune diseases, late-onset is associated with distinct clinical presentations—for instance, a polymyalgia-like phenotype in rheumatoid arthritis and spondyloarthritis—or a different pattern of organ involvement in systemic lupus erythematosus [2,3,5].

Elderly-onset systemic sclerosis (SSc) remains relatively understudied. Existing data are largely derived from single-center cohorts or case series [6–8], and the few available multicenter studies report heterogeneous findings regarding clinical phenotype, disease severity, and prognosis [4,9]. Additionally, the lack of consensus on age thresholds across studies further hampers comparability of results.

The SPRING (Systemic Sclerosis PRogression INvestiGation) registry, established in 2014 by the Italian Society for Rheumatology (SIR), is one of the largest national multicenter datasets dedicated to SSc [10]. The aim of the present study was to characterize patients with elderly-onset SSc within the SPRING cohort, defined as those with the onset of the first non-Raynaud's phenomenon manifestation at ≥70 years of age. While no universal age threshold exists to define elderly people, the adopted cut-off—approximately ten years below the average life expectancy in Italy during the study period—has been proposed as a more appropriate entry point into the geriatric population, compared to the yet outdated 65-year threshold [11].

[1] These authors share first co-authorship.

2. Methods

2.1. Study design, data source, and setting

SPRING was a retrospective, multicenter, nationwide cohort study involving 38 tertiary centers of referral for SSc. Data were collected using the REDCap (Research Electronic Data Capture) platform. Clear definitions for all variables were established and shared *a priori* to minimize heterogeneity across participating centers, and periodic quality checks were performed by the coordinating team [10]. The study was approved by the ethics committee of the Azienda Ospedaliera Universitaria Careggi (Florence), reference number OSS 15.010. All participants provided informed consent prior to enrollment. Data extracted covers information entered as late as July 15, 2022.

2.2. Study population and recorded variables

Patients from the SPRING registry were eligible for inclusion in this study if they were aged ≥18 years at enrollment, fulfilled the 2013 classification criteria for SSc [12], and had clearly documented both the date of SSc onset (i.e., the time of appraisal of the first non-Raynaud manifestation) and the date of enrollment in the registry. Disease duration was calculated from SSc onset, defined as above, to the date of the first visit recorded in the SPRING registry (i.e., enrollment).

The data collected included demographic [13] and clinical characteristics at the time of enrollment in the registry, as follows: skin subsets (diffuse cutaneous—dcSSc, limited cutaneous—lcSSc and sine scleroderma—ssSSc) [14], esophageal symptoms (dysphagia, reflux), intestinal symptoms (diarrhea, abdominal bloating, constipation, malabsorption), *sicca* syndrome (dry eyes/mouth), scleroderma renal crisis (SRC—sudden onset of severe arterial hypertension with acute renal failure), skin signs (puffy fingers, calcinosis, telangiectasia), peripheral vascular signs (digital pitting scars—DPS, digital ulcers—DUs, gangrene) and joint/muscular involvement (tenosynovitis and/or arthritis defined as inflammatory changes observed in more than two joints; joint contractures; tendon friction rubs—TFR; myopathy defined as muscle weakness, atrophy, pain and tenderness in the proximal muscles). Laboratory parameters included autoantibody profiles, i.e. antinuclear antibodies (ANA), anti-extractable nuclear antigens encompassing SSc-related antibodies (anticentromere—ACA, anti-topoisomerase I—TOPO1, and anti-RNA polymerase III—POLR3), and routine biochemistry as earlier described [15]. Modified Rodnan skin score (mRSS), nailfold capillaroscopy patterns, pulmonary function tests (including predicted forced vital capacity—FVC%, and diffusion capacity for carbon monoxide—DLCO%), presence of ILD at high-resolution chest computed tomography (HRCT), and non-invasive cardiac assessments [electrocardiography (ECG) to detect conduction blocks and arrhythmias; echocardiography to assess systolic pulmonary artery pressure (sPAP, mmHg) left ventricular ejection fraction (LVEF %), and diastolic dysfunction] were also collected [10,14,15]. Pulmonary arterial hypertension (PAH) was defined as present if confirmed by right heart catheterization and classified as WHO group 1, in accordance with established diagnostic criteria valid at the time of data collection [16]. PAH was considered absent if (a) there was no suspicion according to validated non-invasive screening methods routinely adopted in clinical practice (i.e., low probability of pulmonary hypertension according to the DETECT algorithm) [17], or (b) in patients in whom right heart catheterization excluded PAH. Reported comorbidities included ischemic heart disease, stroke, arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, cancer history, osteoporosis, and thyroiditis.

Treatment data included prior and current use of systemic glucocorticoids, immunosuppressants (cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil, rituximab, tocilizumab), vasoactive/vasodilating agents (endothelin receptor antagonists—bosentan, macitentan; phosphodiesterase-5 inhibitors—sildenafil, tadalafil; intravenous iloprost; calcium channel blockers), and antiplatelet agents.

Within the SPRING registry, follow-up visits were scheduled annually (±2 months) after baseline, with a maximum follow-up duration of five years. Dates of death or loss to follow-up were also recorded until the date of data extraction, i.e.: July 15, 2022. Finally, to compare SSc-related mortality to that of the general Italian population, age-, sex-, and calendar year-specific mortality rates were obtained from the public repository of the Italian National Institute of Statistics (ISTAT; https://demo.istat.it/app/?i=TVM, accessed on September 17, 2025).

2.3. Exposure

The main exposure of interest was elderly-onset systemic sclerosis (SSc), defined as the onset of the first non-Raynaud's symptom at age ≥70 years. Sensitivity analyses were also performed considering as exposures: (a) enrollment in the SPRING registry at age ≥70 years, irrespective of age at disease onset; and (b) elderly-onset SSc, as defined above, restricted to patients aged ≥70 years at enrollment.

2.4. Outcomes

In the cross-sectional analysis we compared baseline patients' characteristics at enrollment in patients with disease onset ≥70 years and those with disease onset <70 years.

In the survival analysis, the main outcome was all-cause mortality. Covariates were ascertained before or on the enrollment in the SPRING registry. Patients were followed up from the enrollment in the SPRING registry to the latest date among death, last study date, loss to follow-up, and 60 months of follow-up.

In addition, SSc-related mortality was estimated by comparing the observed number of deaths in SPRING with the expected number in the age-, sex-, and calendar year-matched general Italian population.

2.5. Statistical analysis

Continuous variables are reported as means with standard deviations or medians with interquartile ranges (IQR), depending on their distribution according to the Shapiro-Wilk test. Categorical variables are summarized as frequencies and percentages. Analyses were conducted on individuals with complete data for each variable, as reflected in the denominators provided in the tables.

Comparisons between groups were performed using the χ^2 test or Fisher's exact test for categorical variables, and the *t*-test or Mann-Whitney *U* test for continuous variables, as appropriate. Correction for multiple testing was applied using the Benjamini-Hochberg procedure.

Multivariable logistic regression models were used to evaluate the association between elderly-onset disease and relevant clinical outcomes. Covariates were selected *a priori* based on demographic factors (age, sex, disease duration), clinical relevance (as informed by previous literature and expert opinion), and evidence of association ($p < 0.1$) in univariable analyses, along with evidence of association ($p < 0.1$) on univariable analysis. The list of covariates included in each model is provided in Supplementary Table 1.

Poisson mortality rates were calculated and compared using Poisson's test. Survival analyses were performed for all patients with at least one follow-up visit recorded in the registry after baseline. Mortality was compared between patients with elderly-onset SSc vs. onset <70 years. A sensitivity analysis was also performed considering three groups: (i) elderly-onset SSc, (ii) onset <70 years but enrollment ≥70 years, and (iii) onset and enrollment <70 years. Independent predictors of mortality during follow-up were identified using multivariable Cox proportional hazards models; the proportional hazards assumption was assessed using Schoenfeld residuals.

To compare SSc-related mortality with that of the general Italian population, standardized mortality ratios (SMRs) were calculated as the ratio of observed deaths in the SSc cohort to the expected number of

deaths based on age-, sex-, and calendar year-specific mortality rates from ISTAT. 95 % confidence intervals were derived assuming a Poisson distribution. SMRs were computed within subgroups defined by sex and age at onset (≥70 vs. <70 years). To formally compare SMRs between groups, Poisson regression models with the log of expected deaths included as an offset were fitted, providing relative risk estimates and confidence intervals.

Cluster analysis was performed to identify distinct clinical phenotypes within the SPRING cohort, based on a set of clinical and serological variables, encompassing gastrointestinal involvement, skin subset, DUs, telangiectasias, arthritis, calcinosis, TFR, myopathy, conduction block, arrhythmia, diastolic dysfunction, ILD, PAH, ACA and anti-TOPO1. The Gower distance metric was calculated using the daisy function, and Partitioning Around Medoids (PAM) clustering was applied to the Gower distance matrix. The optimal number of clusters (k) was determined by maximizing the average silhouette width, and k = 3 clusters were selected for subsequent analyses. To visualize the cluster structure, dimensionality reduction was performed using t-distributed Stochastic Neighbor Embedding (t-SNE) on the Gower distance matrix. Cluster characteristics were summarized by calculating the proportion of each variable within clusters. To facilitate comparison across variables and clusters, the data matrix was standardized (z-score normalization by variable). A heatmap was generated to visually display the relative prominence of clinical features in each cluster; comparisons of feature distribution among clusters were performed using the chi-square test, adopting the Benjamini-Hochberg correction.

Statistical significance was defined as a two-sided p-value <0.05. All analyses were conducted using RStudio (2024.12.0 + 467).

3. Results

3.1. Patients' characteristics

A total of 1893 SSc patients met the inclusion criteria. Demographics, comorbidities, and clinical features are summarized in Tables 1 and 2. The cohort was predominantly female (89 %), with a median age at disease onset of 50 years (IQR 39–60) and a median disease duration of 8 years (IQR 4–15). In detail, dcSSc was observed in 20 % of patients, DUs in 22 %, calcinosis in 12 %, arthritis in 11 %, ILD in 35 %, PAH in 2.2 %, and gastrointestinal involvement in 57 %. ACA were positive in 41 % of patients, anti-TOPO1 in 35 %, and anti-POLR3 autoantibodies in 1.9 %. Moreover, 32 % of patients received immunosuppressive therapy at some point, and 73 % had been exposed to at least one vasoactive/vasodilating drug.

3.2. Comparison of patients according to age at disease onset: elderly-onset SSc vs. onset <70 years

Elderly-onset disease was observed in 160 out of 1893 patients (8.5 %) and was associated with a shorter disease duration [4 years (IQR 1–7) vs. 9 years (IQR 4–15); p = 0.001]. The onset of Raynaud's phenomenon occurred at a significantly older age in patients with elderly-onset SSc compared with their younger counterparts [72 years (IQR 69–75) vs. 44 years (IQR 33–54), p = 0.007]. However, no differences were observed in the interval from Raynaud's phenomenon to SSc onset or from disease onset to diagnosis between the two groups (Table 1, p-values *a*). Regarding comorbidities, patients with elderly-onset SSc had a higher prevalence of systemic arterial hypertension but not of other cardiovascular diseases (ischemic heart disease, stroke). Diabetes mellitus, hyperlipidemia, osteoporosis, and chronic kidney disease were also more frequent in the elderly-onset group (Table 1, p-values *a*). Geographically, elderly-onset SSc was more frequently observed in Northern Italy (107/942, 11 %) compared to both Central (20/387, 5.2 %; p < 0.001) and Southern regions (33/531, 5.9 %; p < 0.001), whereas no significant difference was detected between Central and Southern Italy (p > 0.99).

Clinical characteristics are reported in Table 2, p-values *a*. Compared to younger-onset, the cutaneous phenotype was more frequently limited (lcSSc; 77 % vs. 67 %; p = 0.043), while dcSSc was significantly less common (6.5 % vs. 21 %; p = 0.007). The severity of skin involvement in the dcSSc subset, assessed with the mRSS, had numerically lower values in elderly patients [10 (IQR 8–15) vs. 14 (IQR 10–20); p = 0.284], despite not reaching significance. Peripheral vascular complications, encompassing DPS (25 % vs. 49 %; p = 0.007) and DUs (13 % vs. 23 %; p = 0.016), were less common in elderly-onset SSc. Conversely, PAH was more frequent in this group (7.5 % vs. 1.8 %; p = 0.007), consistent with

Table 1
Demographic features and comorbidities of patients with SSc in the SPRING-SIR registry. Data are reported for the overall cohort and in patient subgroups according to age at SSc onset or age at enrollment in the registry. Pairwise comparisons are reported according to (a) the age at SSc onset (onset ≥70 vs. onset <70) (p-value *a*), and (b) the age at the entry in the SPRING cohort (age at enrollment ≥70 vs. age <70) (p-value *b*).

	Whole cohort (N = 1893)	SSc onset ≥70 (N = 160)	SSc onset <70 (N = 1733)	Adj. p (a)	Enrollment ≥70 (N = 463)	Enrollment <70 (N = 1430)	Adj. p (b)
Demographic features							
Female sex	1677/1889 (89)	149/160 (93)	1528/1729 (88)	0.149	422/461 (92)	1255/1428 (88)	0.080
Disease duration, yrs	8 (4–15) [1891]	4 (1–7) [160]	9 (4–15) [1731]	0.001*	10 (4–16) [463]	8 (3–14) [1428]	0.001*
Age at RP onset, yrs	45 (34–56) [1885]	72 (69–75) [158]	44 (33–54) [1727]	0.007*	62 (50–69) [459]	41 (31–51) [1426]	0.012*
Age at SSc onset, yrs	50 (39–60)	74 (72–76) [160]	48 (38–57) [1733]	0.012*	66 (59–72) [463]	45 (36–54) [1430]	0.012*
Age at SSc diagnosis, yrs	51 (40–62) [1889]	75 (72–77) [160]	49 (40–59) [1729]	0.012*	67 (60–73) [462]	46 (37–55) [1427]	0.012*
RP onset to SSc onset, yrs	1 (0–4) [1885]	1 (0–5) [158]	1 (0–4) [1727]	0.411	1 (0–6) [459]	1 (0–4) [1426]	0.080
Smoke	559/1683 (33)	32/141 (23)	527/1542 (34)	0.029*	98/408 (24)	461/1275 (36)	0.006*
Comorbidities							
Ischemic heart disease	55/1893 (2.9)	6/160 (3.8)	50/1733 (2.9)	0.848	27/463 (5.8)	28/1430 (2.0)	0.006*
Stroke	17/1893 (0.9)	4/160 (2.5)	13/1733 (0.8)	0.112	7/463 (1.5)	10/1430 (0.7)	0.264
Arterial hypertension	447/1893 (24)	91/160 (57)	356/1733 (21)	0.007*	204/463 (44)	243/1430 (17)	0.006*
Dyslipidemia	208/1893 (11)	29/160 (18)	179/1733 (10)	0.016*	82/463 (18)	126/1430 (8.8)	0.006*
Diabetes mellitus	60/1893 (3.2)	13/160 (26)	47/1733 (2.7)	0.007*	24/463 (5.2)	36/1430 (2.5)	0.012*
Chronic pulmonary disease	84/1893 (4.4)	13/160 (26)	71/1733 (4.1)	0.065	32/463 (6.9)	52/1430 (3.6)	0.010*
Chronic kidney disease	47/1893 (2.5)	10/160 (6.3)	37/1733 (2.1)	0.007*	24/463 (5.2)	23/1430 (1.6)	0.006*
Moderate/severe liver disease	24/1893 (1.3)	5/160 (3.1)	19/1733 (1.1)	0.107	15/463 (3.2)	9/1430 (0.6)	0.006*
Cancer	135/1893 (7.1)	19/160 (12)	116/1733 (6.7)	0.060	56/463 (12)	79/1430 (5.5)	0.006*
Osteoporosis	248/1893 (13)	41/160 (26)	207/1733 (12)	0.007*	120/463 (26)	128/1430 (9.0)	0.006*
Thyroiditis	108/1893 (5.7)	5/160 (3.1)	103/1733 (5.9)	0.292	10/463 (2.2)	98/1430 (6.9)	0.006*

Legend – RP: Raynaud's phenomenon; SSc: systemic sclerosis.

Table 2
Clinical-laboratory features of patients with SSc in the SPRING-SIR registry. Data are reported for the overall cohort and in patient subgroups according to age at SSc onset or age at enrollment in the registry. Pairwise comparisons are reported according to (a) the age at SSc onset (onset ≥70 vs. onset <70) (p-value *a*), and (b) the age at the entry in the SPRING cohort (age at enrollment ≥70 vs. age <70).

	Whole cohort (N = 1893)	SSc onset ≥70 (N = 160)	SSc onset <70 (N = 1733)	Adj. p (a)	Enrollment ≥70 (N = 463)	Enrollment <70 (N = 1430)	Adj. p (b)
Clinical features							
dcSSc	365/1846 (20)	10/154 (6.5)	355/1692 (21)	0.007*	54/452 (12)	311/1394 (22)	0.006*
lcSSc	1256/1846 (68)	119/154 (77)	1137/1692 (67)	0.043*	351/452 (78)	905/1394 (65)	0.006*
ssSSc	225/1846 (12)	25/154 (16)	200/1692 (12)	0.220	47/452 (10)	178/1394 (13)	0.299
mRSS	4 (2–9)	2 (0–4) [136]	4 (2–9) [1596]	0.012*	4 (2–6) [419]	4 (2–10) [1313]	0.018*
DPS	878/1865 (47)	40/158 (25)	838/1707 (49)	0.007*	191/456 (42)	687/1409 (49)	0.032*
DUs	411/1871 (22)	20/158 (13)	391/1713 (23)	0.016*	84/457 (18)	327/1414 (23)	0.080
Telangiectasis	1133/1873 (61)	94/159 (59)	1039/1711 (61)	0.799	305/456 (67)	828/1414 (59)	0.007*
Calcinosis	219/1864 (12)	11/157 (7.0)	208/1707 (12)	0.121	64/455 (14)	155/1409 (11)	0.155
Arthritis	209/1856 (11)	19/157 (12)	190/1699 (11)	0.798	43/455 (9.5)	166/1401 (12)	0.276
Joint contractures	243/1623 (13)	8/158 (5.1)	235/1708 (14)	0.011*	50/456 (11)	193/1410 (14)	0.240
TFR	156/1866 (8.4)	7/158 (4.4)	149/1708 (8.7)	0.149	33/456 (7.2)	123/1410 (8.7)	0.475
Myopathy	297/1862 (16)	16/158 (10)	281/1704 (17)	0.094	77/455 (17)	220/1407 (16)	0.632
GI involvement	1058/1869 (57)	75/158 (48)	983/1711 (58)	0.060	251/457 (55)	803/1412 (57)	0.570
Sicca	542/1867 (29)	51/157 (33)	491/1710 (29)	0.499	158/454 (35)	384/1413 (27)	0.007*
SRC	22/1866 (1.2)	2/157 (1.3)	20/1708 (1.2)	0.804	4/456 (0.9)	18/1410 (1.3)	0.705
ILD	659/1893 (35)	46/160 (29)	613/1733 (35)	0.192	155/463 (34)	504/1430 (35)	0.611
PAH	31/1409 (2.2)	8/106 (7.5)	23/1303 (1.8)	0.007*	17/306 (5.6)	14/1103 (1.3)	0.006*
Autoantibodies							
ACA	769/1893 (41)	96/160 (60)	673/1733 (39)	0.007*	253/463 (55)	516/1430 (36)	0.006*
TOPO1	644/1849 (35)	27/159 (17)	617/1690 (37)	0.007*	107/453 (24)	537/1396 (39)	0.006*
POLR3	28/1481 (1.9)	4/132 (3.0)	24/1349 (1.8)	0.486	9/360 (2.5)	19/1121 (1.7)	0.515
Instrumental							
Conduction block	130/1108 (12)	17/103 (17)	113/1005 (11)	0.224	51/266 (19)	79/842 (9.4)	0.006*
Arrhythmia	50/1109 (4.5)	6/102 (6.8)	44/1007 (4.4)	0.668	18/266 (6.8)	32/843 (3.8)	0.096
sPAP, mmHg	25 (20–31) [1552]	30 (25–39) [131]	25 (20–30) [1421]	0.012*	30 (25–39) [379]	25 (20–30) [1173]	0.012*
LVEF (%)	60 (60–65) [1484]	60 (55–65) [127]	60 (60–65) [1357]	0.073	60 (55–65) [363]	60 (60–65) [1121]	0.012*
Diastolic dysfunction	346/1513 (23)	44/115 (38)	302/1398 (22)	0.007*	134/361 (37)	212/1152 (18)	0.012*
DLCO (%)	69 (55–81) [1344]	67 (52–80) [99]	69 (55–82) [1245]	0.658	65 (52–78) [303]	69 (56–83) [1041]	0.007*
FVC (%)	102 (87–116) [1412]	108 (89–128) [116]	102 (87–115) [1296]	0.012*	106 (88–125) [333]	101 (87–114) [1079]	0.012*
Capillaroscopy							
Early SSc pattern	364/1677 (22)	35/136 (26)	329/1541 (21)	0.466	75/392 (19)	289/1285 (23)	0.299
Active SSc pattern	789/1677 (47)	70/136 (52)	719/1541 (47)	0.499	162/392 (41)	627/1285 (49)	0.032*
Late SSc pattern	434/1677 (26)	18/136 (13)	416/1541 (27)	0.007*	131/392 (33)	303/1285 (24)	0.006*

Legend – ACA: anticentromere antibodies; dcSSc: diffuse cutaneous SSc; DPS: digital pitting scars; DUs: digital ulcers; GI: gastrointestinal; ILD: interstitial lung disease; lcSSc: limited cutaneous SSc; LVEF: left ventricle ejection fraction; mRSS: modified Rodnan skin score; PAH: pulmonary arterial hypertension; POLR3: RNA polymerase III; sPAP: pulmonary artery systolic pressure; SRC: scleroderma renal crisis; SSc: systemic sclerosis; ssSSc: SSc sine scleroderma; TOPO1: Topoisomerase 1; TFR: tendon friction rubs.

higher sPAP values on echocardiography [30 mmHg (IQR 25–39) vs. 25 mmHg (IQR 20–30); p = 0.012]. Diastolic dysfunction was also more prevalent (38 % vs. 22 %; p = 0.007) in elderly-onset, whereas no differences were observed in the prevalence of gastrointestinal involvement, scleroderma renal crisis, arthritis, myopathy, ILD, or TFR. Overall, a lower disease burden characterized elderly-onset SSc, except for a higher prevalence of PAH, as illustrated in the radar chart in Fig. 1A. Regarding serum autoantibodies, elderly-onset patients had a higher prevalence of ACA (60 % vs. 39 %; p = 0.007) and a lower prevalence of anti-TOPO1 (17 % vs. 37 %; p = 0.007). Nailfold capillaroscopy revealed a lower frequency of the *late* scleroderma pattern in elderly-onset SSc (13 % vs. 27 %; p = 0.007).

Patients with elderly-onset SSc were less likely to receive immunosuppressants, particularly cyclophosphamide and methotrexate, compared to patients with onset <70 years. Vasoactive therapies, including endothelin receptor antagonists, iloprost, and calcium-channel blockers, were also less frequently administered in this group, whereas no differences were observed for phosphodiesterase-5 inhibitors and antiplatelet agents (Supplementary Table 2).

3.3. Comparison of patients according to the age at enrollment in SPRING (≥70 vs. <70 years)

At the time of enrollment, 463 patients (25 %) were aged ≥70 years. Compared to younger patients, they had a higher prevalence of cardiometabolic, respiratory, and oncological comorbidities (Table 1, p-values *b*). The clinical phenotype of older enrolled patients was milder (Fig. 1B), encompassing more frequent lcSSc (78 % vs. 65 %; p = 0.006), *sicca* syndrome and telangiectasias, but less DPS. PAH was also more represented in this group, along with instrumental cardiac abnormalities (conduction blocks, arrhythmias, diastolic dysfunction) (Table 2, p-values *b*). A higher prevalence of ACA and lower of anti-TOPO1 were reported in older enrolled patients (Table 2, p-values *b*), in whom the proportion of subjects receiving immunosuppressants, iloprost, and calcium-channel blockers was also significantly lower (Supplementary Table 2).

3.4. Sub-analysis on patients aged ≥70 years at enrolment according to age at SSc onset

Table 3 summarizes the characteristics of patients aged ≥70 at enrolment in the SPRING registry, stratified according to their age at disease onset (elderly-onset vs. onset <70). Patients with elderly-onset represented 35 % (160/463) of the considered subgroup and were significantly older at registry entry [78 years (IQR 76–81) vs. 73 years (IQR 71–77); p < 0.001]. The interval from Raynaud's phenomenon to SSc onset was comparable between the two groups, and comorbidities were similarly distributed.

In elderly-onset disease, the cutaneous phenotype was milder with a higher frequency of sine scleroderma (16 % vs. 7.4 %; p = 0.046) and a

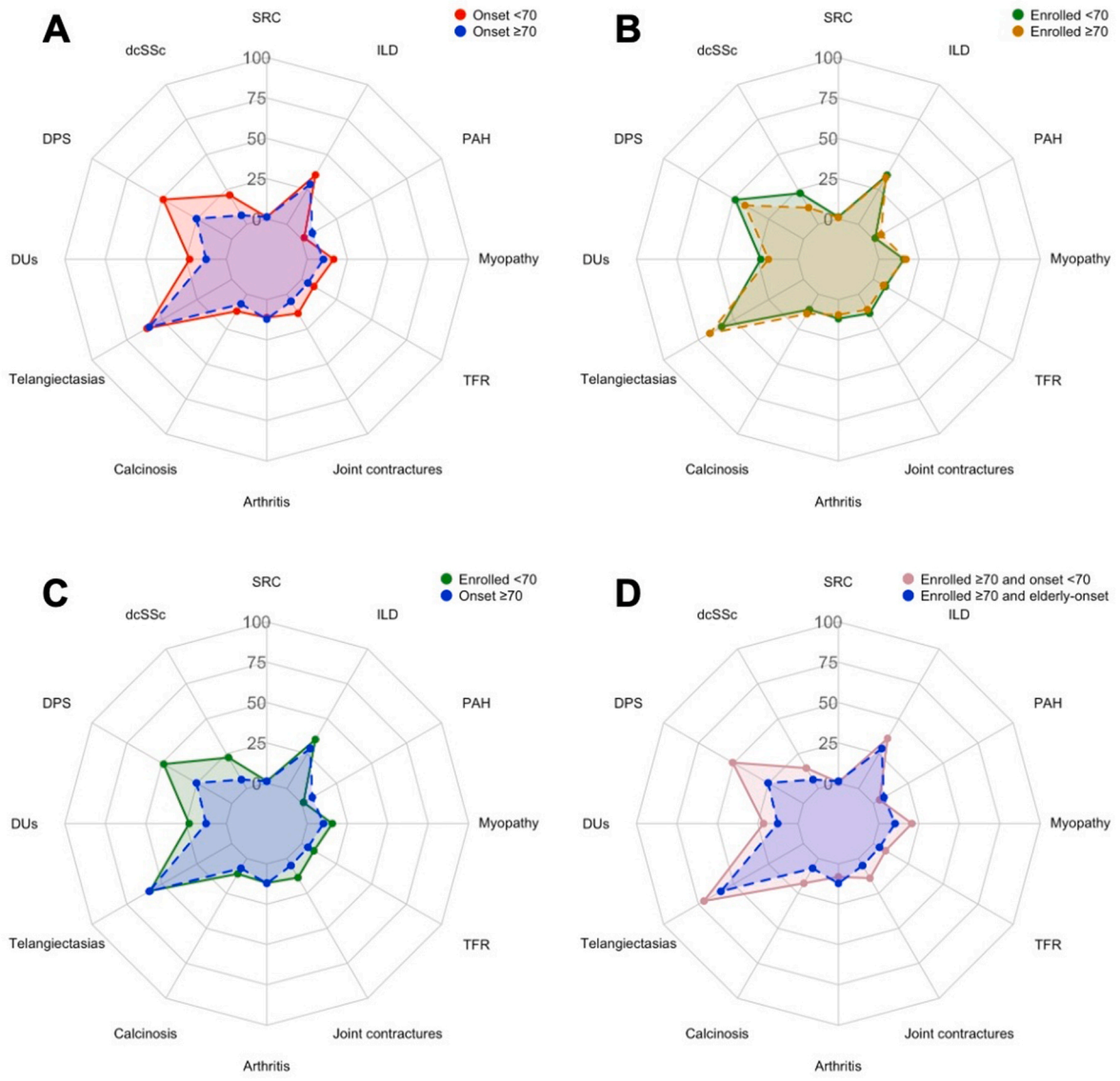

Fig. 1. Radar charts showing the burden of complications in SSc patients enrolled in SPRING. The area enclosed in each polygon represents the overall SSc burden in the considered subgroup. **Panel A** stratifies all SPRING patients according to the age at SSc onset ≥70 years (blue) vs. <70 years (red): patients with elderly-onset SSc have a lower disease burden but higher prevalence of PAH. **Panel B** stratifies patients according to the age at enrollment in the registry ≥70 years (orange) vs. <70 years (green). **Panel C** compares patients with SSc onset ≥70 years (blue) and those enrolled in the registry at <70 years (green). **Panel D** represents the sub-analysis including only patients aged ≥70 at the time of enrollment in SPRING: within this subgroup, patients with elderly-onset (blue) had less peripheral vascular complications compared with those with onset of SSc <70 years (pink). *Legend – dcSSc: diffuse cutaneous SSc; DPS: digital pitting scars; DUs: digital ulcers; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; SRC: scleroderma renal crisis; TFR: tendon friction rubs.* (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

trend toward less dcSSc. DPS (25 % vs. 51 %; $p < 0.001$), calcinosis (7.0 % vs. 18 %; $p = 0.034$), joint contractures (5.1 % vs. 14 %; $p = 0.046$), and myopathy (10 % vs. 21 %; $p = 0.051$) were rarer with elderly-onset disease (Fig. 1D). PAH was observed in 7.5 % patients with elderly-onset disease versus 4.5 % of the counterpart. Nailfold capillaroscopy revealed a higher frequency of the *active* (52 % vs. 36 %; $p = 0.045$) and a lower frequency of the *late*scleroderma pattern (13 % vs. 44 %; $p < 0.001$) in patients with elderly-onset SSc compared with those with disease onset <70 years.

As regards therapies, no differences were observed, except for iloprost, which was less frequently required for patients with elderly-onset SSc compared to the counterpart (37 % vs. 59 %; $p = 0.001$).

3.5. Elderly-onset is associated with lcSSc and PAH

Considering the whole cohort, on multivariable logistic regression, elderly-onset (vs. onset <70 years) was negatively associated with dcSSc (OR 0.4; 95 % CI 0.2–0.8; $p = 0.015$) and positively associated with PAH. Due to the low number of PAH events (N = 31), multiple models were fitted, each including a maximum of three covariates with clinical meaning or statistical relevance on univariable analysis (*not shown*). Specifically, we tested elderly-onset SSc and disease duration in combination with telangiectasias, calcinosis, ILD, DLCO (% predicted), conduction block on ECG, or diastolic dysfunction on echocardiography. Elderly-onset disease remained an independent predictor of PAH across all models; among the other covariates, only calcinosis, DLCO, and ILD retained significance in multivariable analysis (Fig. 2A). Elderly-onset showed no independent association with DUs, calcinosis, TFR, joint

Table 3
Subgroup analysis of patients aged ≥70 at the time of enrollment in the SPRING registry: comparison according to the age at SSc onset (elderly-onset SSc vs. onset <70 years).

Variabile	All patients ≥70 at enrollment (463)	Enrollment ≥70, elderly-onset (160)	Enrollment ≥70, onset <70 (303)	Adj. p
Demographic features				
Age at enrollment, yrs	75 (72–78)	78 (76–81)	73 (71–77)	<0.001*
Female sex	422/461 (92)	149/160 (93)	273/301 (91)	0.753
RP to SSc onset, yrs	1 (0–6) [459]	1 (0–5) [158]	1 (0–7) [301]	1.000
Smoke	98/408 (24)	32/141 (23)	66/267 (25)	0.933
Comorbidities				
Ischemic heart disease	27/463 (5.8)	5/160 (3.1)	22/303 (7.3)	0.290
Stroke	7/463 (1.5)	4/160 (2.5)	3/303 (1.0)	0.482
Arterial hypertension	204/463 (44)	91/160 (57)	113/303 (37)	0.001*
Dyslipidemia	82/463 (18)	29/160 (18)	53/303 (18)	1.000
Diabetes mellitus	24/463 (5.2)	13/160 (8.1)	11/303 (3.6)	0.197
Chronic pulmonary disease	32/463 (6.9)	13/160 (8.1)	19/303 (6.3)	0.842
Chronic kidney disease	24/463 (5.2)	10/160 (6.2)	14/303 (4.6)	0.846
Clinical features				
dcSSc	54/452 (12)	10/154 (6.5)	44/298 (15)	0.084
lcSSc	351/452 (78)	119/154 (77)	232/298 (78)	1.000
ssSSc	47/452 (10)	25/154 (16)	22/298 (7.4)	0.046*
mRSS	4 (2–6) [419]	2 (0–4) [136]	4 (2–8) [283]	<0.001*
DPS	191/456 (42)	40/158 (25)	151/298 (51)	<0.001*
DUs	84/457 (18)	20/158 (13)	64/299 (21)	0.110
Telangiectasis	305/456 (67)	94/159 (59)	211/297 (71)	0.078
Calcinosis	64/455 (14)	11/157 (7.0)	53/298 (18)	0.034*
Arthritis	43/455 (9.5)	19/157 (12)	24/298 (8.1)	0.463
Joint contractures	50/456 (11)	8/158 (5.1)	42/298 (14)	0.046*
TFR	33/456 (7.2)	7/158 (4.4)	26/298 (8.7)	0.320
Myopathy	77/455 (17)	16/158 (10)	61/297 (21)	0.051
GI involvement	252/457 (55)	75/158 (48)	177/299 (59)	0.095
Sicca	158/454 (35)	51/157 (33)	107/297 (36)	0.786
SRC	4/456 (0.9)	2/158 (1.3)	2/298 (0.7)	0.852
ILD	155/463 (34)	46/160 (29)	109/303 (36)	0.328
PAH	17/306 (5.6)	8/106 (7.5)	9/200 (4.5)	0.708
Laboratory				
ACA	253/463 (55)	96/160 (60)	157/303 (52)	0.290
TOPO1	107/453 (24)	27/159 (17)	80/294 (27)	0.095
POLR3	9/360 (2.5)	4/132 (3.0)	5/228 (2.2)	0.933
Instrumental evaluation				
Conduction block	51/266 (19)	17/103 (17)	34/163 (21)	0.753
Arrhythmia	18/266 (6.8)	6/102 (5.9)	12/164 (7.3)	1.000
sPAP, mmHg	30 (25–39) [379]	30 (25–39) [131]	30 (25–38) [248]	0.290
LVEF (%)	60 (55–65) [363]	60 (55–65) [127]	60 (57–64) [236]	1.000
Diastolic dysfunction	134/361 (37)	44/115 (38)	90/246 (37)	1.000
DLCO (%)	65 (52–78) [303]	67 (53–80) [99]	65 (51–78) [204]	0.614
FVC (%)	106 (88–125) [333]	108 (89–128) [116]	105 (87–122) [217]	0.304
Capillaroscopy				
Early	75/392 (19)	35/136 (26)	40/256 (16)	0.095
Active	162/392 (41)	70/136 (52)	92/256 (36)	0.045*
Late	131/392 (33)	18/136 (13)	113/256 (44)	<0.001*

Legend – ACA: anticentromere antibodies; dcSSc: diffuse cutaneous SSc; DPS: digital pitting scars; DUs: digital ulcers; GI: gastrointestinal; ILD: interstitial lung disease; lcSSc: limited cutaneous SSc; LVEF: left ventricle ejection fraction; mRSS: modified Rodnan skin score; PAH: pulmonary arterial hypertension; POLR3: RNA polymerase III; RP: Raynaud's phenomenon; sPAP: pulmonary artery systolic pressure; SRC: scleroderma renal crisis; ssSSc: SSc sine scleroderma; TFR: tendon friction rubs; TOPO1: Topoisomerase 1.

contractures, gastrointestinal involvement, and ILD, after adjusting for covariates (*data not shown*).

When considering only patients aged ≥70 years at the time of enrollment in SPRING, multivariable logistic regression revealed elderly-onset to be negatively associated with DPS (OR 0.4; 95 % CI 0.3–0.8; p = 0.003) (Fig. 2B). No independent associations were observed for other outcomes, including the cutaneous phenotype, DUs, calcinosis, TFR, joint contractures, gastrointestinal involvement, and ILD (*data not shown*), while the sample size (N = 18) prevented fitting a reliable multivariable model for PAH.

3.6. Cluster analysis to characterize the phenotype of elderly-onset SSc

Unsupervised clustering of 1893 SSc patients identified three groups based on clinical and serological features, as detailed in the Methods (Supplementary Fig. 1 and Supplementary Table 3). Briefly, Cluster 1 ("*ILD-dominant*") was characterized by ILD and accompanying features of severe disease, including dcSSc, TFR, myopathy, and the highest prevalence of anti-TOPO1 autoantibodies. Cluster 2 ("*ACA-limited*") was defined by ACA positivity and a predominant lcSSc phenotype. Cluster 3 ("*diffuse-low burden*") shared a similar prevalence of dcSSc with Cluster 1 but lacked evidence of ILD and had an overall lower burden of disease complications. The prevalence of PAH was similar across the three clusters. When stratifying patients by age at disease onset, the majority of elderly-onset cases (61 %) belonged to Cluster 2, while 15 % and 24 % were assigned to Clusters 1 and 3, respectively (p < 0.0001).

3.7. Mortality in patients with elderly-onset SSc

Among patients with available follow-up data, 13 deaths occurred over 184 person-years in the elderly-onset group (n = 79; mortality rate 71 per 1000 person-years, 95 % CI 38–121), while 37 deaths were observed over 2581 person-years in patients with SSc onset <70 years (n = 972; mortality rate 14 per 1000 person-years, 95 % CI 10–20). Hence, mortality was significantly higher in the elderly-onset group (log-rank p < 0.0001; Kaplan-Meier curves in Fig. 3A). Among deceased patients, right heart catheterization-confirmed PAH was present in 1/6 (18 %) of those with elderly-onset and in 2/20 (10 %) of their younger counterparts (Fisher's exact test, p > 0.99).

More in detail, in the subgroup of patients who developed SSc before the age of 70 but were enrolled in SPRING at ≥70 years, 13 deaths occurred over 409 person-years (n = 175; mortality rate 32 per 1000 person-years, 95 % CI 17–54). By contrast, among patients enrolled before the age of 70, 24 deaths over 2172 person-years were recorded (n = 797; mortality rate 11 per 1000 person-years, 95 % CI 7.1–16). The three-group comparison (elderly-onset vs. onset <70 with enrollment ≥70 vs. enrollment <70) was statistically significant (log-rank p < 0.0001; Kaplan-Meier curves in Fig. 3B). Specifically, patients with elderly-onset SSc showed a significantly higher mortality rate compared with both patients aged ≥70 years with onset <70 (p = 0.037) and patients aged <70 (p < 0.0001). In addition, among patients with disease onset before 70 years, mortality was higher in patients aged ≥70 years than in their younger counterparts (p = 0.002).

On multivariable Cox proportional hazards analysis, adjusted for age at enrollment in SPRING, diffuse cutaneous subset, sex, and PAH, elderly-onset SSc did not independently predict mortality (Supplementary Table 4). The proportional hazards assumption was satisfied for the global model (p = 0.39) and model discrimination was good (concordance = 0.75).

When compared with the age-, sex-, and calendar year-matched general Italian population, females with elderly-onset SSc showed an SMR of 4.5 (95 % CI 2.4–7.7; 13 observed vs. 3 expected deaths), while those with SSc onset before the age of 70 had an SMR of 6.3 (95 % CI

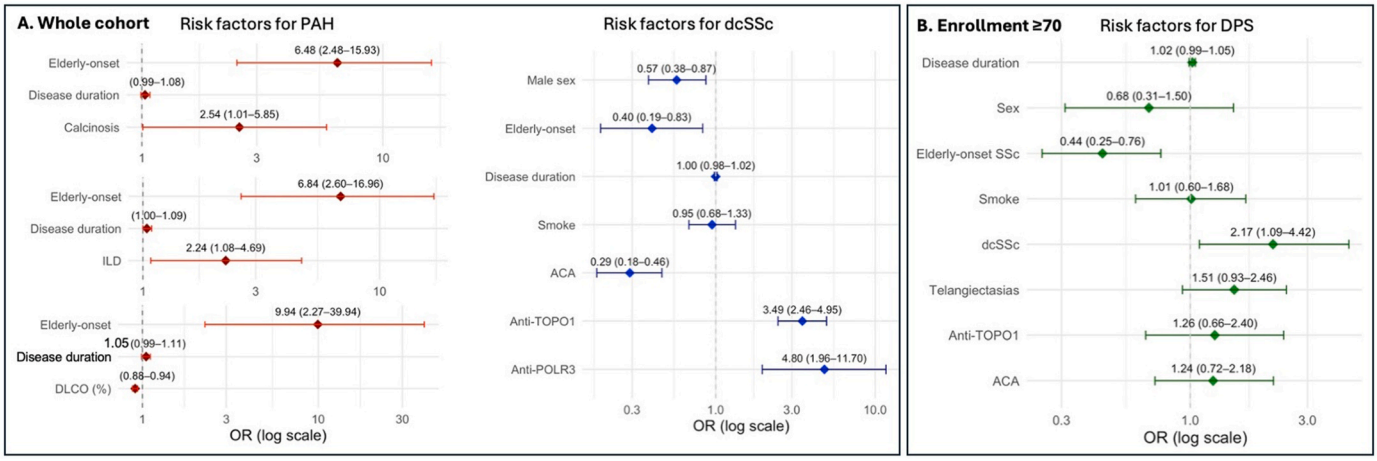

Fig. 2. Multivariable logistic regression analysis. In the SPRING cohort, elderly-onset SSc was independently associated with a lower likelihood of dcSSc and a higher likelihood of PAH (**Panel A**). Among patients aged ≥70 at registry enrollment (**Panel B**), elderly-onset was associated with a lower likelihood of DPS but still a higher likelihood of PAH.

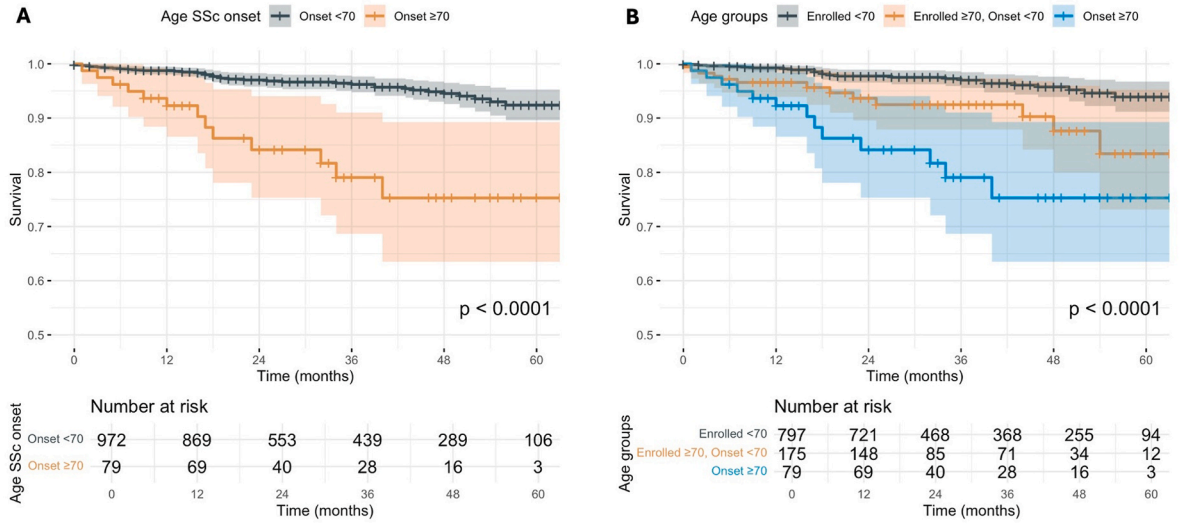

Fig. 3. Kaplan-Meier survival curves of patients with SSc enrolled in the SPRING registry with available follow-up data. Stratification by age at SSc onset (≥70 vs. <70 years) shows a significantly higher mortality in the elderly-onset group compared to the younger SSc counterpart (**Panel A**). The comparison by both age at SSc onset and age at enrollment (elderly-onset SSc; onset <70 years and enrollment ≥70 years; onset and enrollment <70 years), highlights a statistically significant difference in overall survival among the three groups (**Panel B**). Log-rank *p*-values are reported within the panels.

4.1–9.1; 27 observed vs. 4 expected deaths). Direct comparison of SMR between the two groups yielded a relative risk of death of 1.4 (95 % CI 0.7–2.8) for younger-onset versus elderly-onset females, but this difference was not statistically significant (p = 0.32). Among males, no deaths were observed in the elderly-onset group, resulting in unstable estimates and precluding a reliable SMR calculation.

4. Discussion

The geriatric dimension of autoimmune diseases is increasingly being recognized, yet data on elderly-onset SSc remain limited [1–3]. In this large multicenter Italian cohort, 8.5 % of SSc patients had disease onset at or after 70 years, representing 35 % of patients aged ≥70 at enrollment in the registry. These proportions are consistent with prior reports from smaller studies, although often using lower age thresholds to define late-onset SSc [18]. It is likely that our estimates are conservative, as the milder phenotype of elderly-onset SSc may have reduced the likelihood of referral to tertiary centers compared with younger patients [13]. This interpretation is reinforced by the observed geographic heterogeneity, the prevalence of elderly-onset SSc being highest in centers from Northern Italy, in contrast to the previously described North-to-South increasing gradient of disease severity [13]. Moreover, although—as expected—metabolic comorbidities were more frequent in patients aged ≥70 years in our registry, fewer major cardiovascular events, chronic pulmonary, and liver diseases were reported in the elderly-onset subgroup, highlighting that the milder phenotype of this subset is also reflected by a lower overall comorbidity burden [19].

Overall and in line with previous evidence [4,6,18,20], patients with elderly-onset SSc exhibited shorter disease duration, which could have influenced the overall phenotype, and older age at the onset of Raynaud's phenomenon compared with their younger counterparts, likely reflecting a genuine late-onset disease. However, they showed a similar interval between Raynaud's phenomenon and the first non-Raynaud's manifestation. Considering the inverse relationship between the Raynaud-to-SSc interval and disease severity, our findings suggest a comparable degree of disease severity between the two subsets, despite phenotypic differences. Elderly-onset SSc was also associated with a milder cutaneous phenotype, consistent with previous studies [4,7,9,20,

21] despite some geographic heterogeneity [6,8]. Likewise, ACA were more frequent and anti-TOPO1 less common among older patients in our cohort, according to earlier reports [4,7,18,20]. Unsupervised cluster analysis confirmed these associations in the SPRING cohort.

In our study, a "paradoxical" vascular phenotype emerged in elderly-onset SSc, as confirmed throughout multiple comparisons. In detail, while showing a lower prevalence of peripheral vascular complications such as DUs and DPS [4,7,9,18,21], as well as less frequent *late*-scleroderma pattern on nailfold capillaroscopy, subjects with elderly-onset SSc exhibited a higher burden of pulmonary vascular involvement. Such trend persisted even when analyzing the subgroup of patients aged ≥70 years at registry entry, although statistical significance was not reached for all variables. These observations are consistent with evidence from the SPRING registry, showing a higher frequency of PAH among women with post-menopausal SSc onset compared to those with pre-menopausal onset [22]. Preliminary evidence from mouse models points to enhanced pro-fibrotic pulmonary vascular remodeling associated with aging [23]. Whether this mechanism could at least partially account for the phenotypic differences in vasculopathy observed between patients with elderly- and young-onset SSc warrants further investigation.

Previous papers reported a higher prevalence of pulmonary hypertension in late-onset SSc, but mostly lacked confirmation via right heart catheterization [4,6,7,9,18,20,21], and features of left heart dysfunction and ILD were often described in association with pulmonary vascular findings [4,20], raising concern about post-capillary and chronic respiratory-related contributions. Although left heart dysfunction may have contributed to some degree of PAH exacerbation, strict criteria were applied to define pulmonary vascular involvement in this study. Indeed, PAH was overall infrequent in our cohort, being reported in 2.2 % of patients and possibly reflecting selection bias, as right heart catheterization was not systematically performed in all subjects. In line with routine practice [21], patients with catheterization-confirmed diagnosis were classified as PAH, whereas those with normal findings or not referred to invasive testing were considered negative. This strategy may have underestimated PAH prevalence, particularly among high-risk patients who did not undergo catheterization [17,24]. Nevertheless, the adopted criteria helped to minimize the risk of misclassifying other forms of pulmonary hypertension—such as group II/post-capillary disease—as PAH. Also, elderly-onset remained independently associated with PAH in multivariable analysis after adjusting for echocardiographic signs of left heart disease.

Over the past decades, a progressive change in SSc pathomorphosis has been noted, with an increasing prevalence of milder phenotypes, likely related to earlier diagnosis and more timely initiation of treatment [25]. Nevertheless, SSc remains associated with increased mortality compared with the general population [26]. This was previously described across cutaneous subsets, autoantibody profiles, and major organ complications [27]. Our study confirms that the SMR is markedly increased—about fivefold—in SSc patients compared with the general population, a finding that is consistent across the two age groups analyzed. However, a relatively higher mortality risk compared to that of the general population was observed in patients with disease onset <70 years compared with elderly-onset, possibly correlating with the overall milder phenotype observed in the latter group. These observations are also consistent with recent reports describing a more severe disease phenotype in juvenile SSc, i.e., at the opposite extreme of the age spectrum [28].

When considering only SSc patients, a fivefold higher mortality was observed in elderly-onset SSc compared with the younger counterpart, in line with previous reports adopting different age cut-offs [4,6,9,29]. Nevertheless, the multivariable Cox model did not confirm an independent association, likely suggesting that comorbidities and older age *per se* may contribute to the worse prognosis in elderly-onset SSc [4,7,9]. We also found a similar prevalence of PAH among deceased patients across age groups, suggesting that further studies are needed to clarify the impact of cardio-pulmonary disease on prognosis when stratifying patients according to age at SSc onset. Of note, patients with elderly-onset disease in our cohort less frequently received immuno-suppressants and vasoactive drugs, possibly reflecting their observed milder clinical phenotype. Such treatment differences might have anyway contributed to the higher frequency of PAH observed in elderly-onset SSc [30,31].

While SPRING represents one of the largest multicentric SSc cohorts with robust data collection and follow-up, some limitations must be acknowledged. The retrospective design of the study introduced the risk of selection bias, as enrolled patients were mainly from tertiary referral centers and could reflect more severe disease cases [13]. The lack of systematic testing for selected laboratory and instrumental features (e.g., rare autoantibodies, advanced cardiac imaging) limited our ability to fully assess emerging risk factors and phenotypes that could be associated with a worst prognosis (e.g., primary heart involvement) [32] in older age. Similarly, the role and impact of recently approved treatments [33] could not be appropriately assessed. Polypharmacy and prescription appropriateness are major concerns in the elderly population [34]. Although these issues could not be addressed due to the structure of the registry, studying their impact on the prognosis of patients with elderly-onset SSc would be highly relevant. Finally, follow-up duration was not uniform and may have been influenced by age-related factors or natural attrition.

In conclusion, elderly-onset SSc is a clinically relevant subset of patients showing a distinctive phenotype, characterized by predominance of ACA positivity, mild cutaneous involvement, fewer peripheral vascular complications, but is associated with PAH. Despite their apparently milder phenotype, these patients experience unfavorable outcomes, potentially exacerbated by comorbidities or ageing *per se*. Indeed, when mortality is compared with that of the general population, the relative excess risk appears lower in elderly-onset SSc patients than in the younger-onset counterpart. Our findings underscore the need for age-tailored assessment, vigilant cardiovascular monitoring, and potentially different management strategies specifically for elderly-onset SSc.

CRediT authorship contribution statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2025.103501.

Data availability

Supporting data are available as Supplementary materials

References

[1] W. van Lankveld, M. Franssen, A. Stenger, Gerontorheumatology: the challenge to meet health-care demands for the elderly with musculoskeletal conditions, Rheumatology 44 (4) (2005 Apr) 419–422.
[2] O. Zimba, C. Baimukhamedov, B.F. Kocyigit, Late-onset rheumatoid arthritis: clinical features, diagnostic challenges, and treatment approaches, Rheumatol. Int. 45 (6) (2025 June 9) 152.
[3] M. Piga, K. Tselios, L. Viveiros, E. Chessa, A. Neves, M.B. Urowitz, et al., Clinical patterns of disease: from early systemic lupus erythematosus to late-onset disease, Best Pract. Res. Clin. Rheumatol. 37 (4) (2023 Dec) 101938.
[4] T. Hügle, P. Schuetz, T. Daikeler, A. Tyndall, M. Matucci-Cerinic, U.A. Walker, et al., Late-onset systemic sclerosis–a systematic survey of the EULAR scleroderma trials and research group database, Rheumatology 50 (1) (2011 Jan) 161–165.
[5] K. Abacar, G. De Marco, J. Weddell, K. Meridor, T. Macleod, A. Scarsbrook, et al., Late-onset spondylarthritis presenting as glucocorticoid-resistant polymyalgia rheumatica: a hitherto underappreciated entity where TNF or IL-17 blockade may have a therapeutic role, Arthritis Rheumatol. (2025 July 22).
[6] L. Czirják, Z. Nagy, G. Szegedi, Systemic sclerosis in the elderly, Clin. Rheumatol. 11 (4) (1992 Dec) 483–485.
[7] P. Moinzadeh, K. Kuhr, E. Siegert, U. Mueller-Ladner, G. Riemekasten, C. Günther, et al., Older age onset of systemic sclerosis - accelerated disease progression in all disease subsets, Rheumatology 59 (11) (2020 Nov 1) 3380–3389.
[8] R. Apipattarakul, C. Foocharoen, S. Netwijitpan, A. Mahakkanukrauh, S. Suwannaroj, P. Limpawattana, et al., Clinical characteristics and mortality rate of Thai elderly-onset systemic sclerosis, Clin. Exp. Rheumatol. 36 (4) (2018) 76–81.
[9] M.A. Alba, C. Velasco, C.P. Simeón, V. Fonollosa, L. Trapiella, M.V. Egurbide, et al., Early- versus late-onset systemic sclerosis: differences in clinical presentation and outcome in 1037 patients, Medicine (Baltim.) 93 (2) (2014) 73–81.
[10] C. Ferri, D. Giuggioli, S. Guiducci, F. Lumetti, G. Bajocchi, L. Magnani, et al., Systemic sclerosis progression INvestiGation (SPRING) Italian registry: demographic and clinico-serological features of the scleroderma spectrum, Clin. Exp. Rheumatol. 38 (3) (2020) 40–47.
[11] J.M. Jacobs, Y. Maaravi, A. Cohen, M. Bursztyn, E. Ein-Mor, J. Stessman, Changing profile of health and function from age 70 to 85 years, Gerontology 58 (4) (2012) 313–321.
[12] F. van den Hoogen, D. Khanna, J. Fransen, S.R. Johnson, M. Baron, A. Tyndall, et al., Classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative, Ann. Rheum. Dis. 72 (11) (2013) 1747–1755.
[13] C. Ferri, R. De Angelis, D. Giuggioli, G. Bajocchi, L. Dagna, G. Zanframundo, et al., Geographical heterogeneity of clinical and serological phenotypes of systemic sclerosis observed at tertiary referral centres. The experience of the Italian SIR-SPRING registry and review of the world literature, Autoimmun. Rev. 21 (10) (2022 Oct) 103159.
[14] R. De Angelis, C. Ferri, D. Giuggioli, G. Bajocchi, L. Dagna, S. Bellando-Randone, et al., Systemic sclerosis sine scleroderma: clinical and serological features and relationship with other cutaneous subsets in a large series of patients from the national registry "SPRING" of the Italian Society for Rheumatology, RMD Open 9 (1) (2023 Mar) e002890.
[15] R. De Angelis, D. Giuggioli, G. Bajocchi, L. Dagna, G. Zanframundo, R. Foti, et al., Sex-related differences in systemic sclerosis: a multicenter cross-sectional study from the national registry of the Italian society for rheumatology, J. Rheumatol. 49 (2) (2022 Feb) 176–185.
[16] M. Humbert, G. Kovacs, M.M. Hoeper, R. Badagliacca, R.M.F. Berger, M. Brida, et al., ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension, Eur. Heart J. 43 (38) (2022) 3618–3731.

[17] J.G. Coghlan, C.P. Denton, E. Grünig, D. Bonderman, O. Distler, D. Khanna, et al., Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study, Ann. Rheum. Dis. 73 (7) (2014 July) 1340–1349.
[18] R.L. Manno, F.M. Wigley, A.C. Gelber, L.K. Hummers, Late-age onset systemic sclerosis, J. Rheumatol. 38 (7) (2011 July) 1317–1325.
[19] M. Orlandi, S. Bellando-Randone, R. De Angelis, C. Ferri, D. Giuggioli, F. Cacciapaglia, et al., Towards a comprehensive approach to the management and prognosis of systemic sclerosis's patients: the role of comorbidities in the SPRING-SIR registry, Eur. J. Intern. Med. 130 (2024 Dec) 130–136.
[20] E. Wielosz, K. Wiąk-Walerowicz, E. Łyś, A. Lipska, M. Dryglewska, M. Majdan, Late-age onset systemic sclerosis-clinical and serological characteristics, Clin. Rheumatol. 43 (8) (2024 Aug) 2565–2572.
[21] C. Pérez-Bocanegra, R. Solans-Laqué, C.P. Simeón-Aznar, M. Campillo, V. Fonollosa-Pla, M. Vilardell-Tarrés, Age-related survival and clinical features in systemic sclerosis patients older or younger than 65 at diagnosis, Rheumatology 49 (6) (2010 June) 1112–1117.
[22] M. Orlandi, D. Giuggioli, C. Ferri, R. De Angelis, V. Riccieri, F. Cacciapaglia, et al., Menopause in systemic sclerosis: the impact on clinical presentation in a multicenter cross-sectional analysis from the National Registry of the Italian Society for Rheumatology (SPRING-SIR), Ther Adv Musculoskelet Dis 17 (2025) 1759720X251354898.
[23] M. Truchi, M. Gautier-Isola, G. Savary, C. Scribe, A. Lingampally, H. Cadis, et al., Aging affects reprogramming of pulmonary capillary endothelial cells after lung injury in male mice, Nat. Commun. 16 (1) (2025 Aug 6) 7234.
[24] A. Guillén-Del Castillo, E.L. Callejas-Moraga, G. García, J.F. Rodríguez-Palomares, A. Román, C. Berastegui, et al., High sensitivity and negative predictive value of the DETECT algorithm for an early diagnosis of pulmonary arterial hypertension in systemic sclerosis: application in a single center, Arthritis Res. Ther. 19 (1) (2017 June 14) 135.
[25] C. Ferri, M. Sebastiani, A. Lo Monaco, M. Iudici, D. Giuggioli, F. Furini, et al., Systemic sclerosis evolution of disease pathomorphosis and survival. Our experience on Italian patients' population and review of the literature, Autoimmun. Rev. 13 (10) (2014 Oct) 1026–1034.
[26] C. Ferri, G. Valentini, F. Cozzi, M. Sebastiani, C. Michelassi, G. La Montagna, et al., Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients, Medicine (Baltim.) 81 (2) (2002 Mar) 139–153.
[27] C. Ferri, L. Bernini, R. Cecchetti, A. Latorraca, G. Marotta, G. Pasero, et al., Cutaneous and serologic subsets of systemic sclerosis, J. Rheumatol. 18 (12) (1991 Dec) 1826–1832.
[28] U. Kaneko, T. Miyamae, Y. Hamaguchi, M. Shimizu, I. Ueda-Hayakawa, H. Ishikawa, et al., Clinical and epidemiological features of juvenile-onset systemic sclerosis from a nationwide survey in Japan, J. Rheumatol. 15 (2025) [cited 2025 Sept 19]; Available from: https://www.jrheum.org/content/early/2025/09/10/jrheum.2025-0175.
[29] C.T. Derk, C.M. Artlett, S.A. Jimenez, Morbidity and mortality of patients diagnosed with systemic sclerosis after the age of 75: a nested case-control study, Clin. Rheumatol. 25 (6) (2006 Nov) 831–834.
[30] C. Bruni, L. Tofani, H. Fretheim, Y. Weber, E. Hachulla, P. Carreira, et al., Op0238 immunosuppression with targeted dmards reduces morbidity and mortality in pre-capillary pulmonary hypertension associated with systemic sclerosis: a eustar analysis, Ann. Rheum. Dis. 82 (Suppl 1) (2023 June 1) 157–159.
[31] F. Cacciapaglia, R. De Angelis, C. Ferri, G. Bajocchi, S. Bellando-Randone, C. Bruni, et al., Pulmonary arterial hypertension incidence in patients with systemic sclerosis treated with bosentan for digital ulcers: evidence from the SPRING-SIR registry, J. Rheumatol. 52 (4) (2025 Apr 1) 375–382.
[32] A.H. Györfi, T. Filla, A. Polzin, K. Tascilar, M. Buch, M. Tröbs, et al., Evaluation of systemic sclerosis primary heart involvement and chronic heart failure in the European Scleroderma trials and research cohort, J. Am. Heart Assoc. 14 (5) (2025 Mar 4) e036730.
[33] F. Del Galdo, A. Lescoat, P.G. Conaghan, E. Bertoldo, J. Čolić, T. Santiago, et al., EULAR recommendations for the treatment of systemic sclerosis: 2023 update, Ann. Rheum. Dis. 84 (1) (2025 Jan) 29–40.
[34] M. Delara, L. Murray, B. Jafari, A. Bahji, Z. Goodarzi, J. Kirkham, et al., Prevalence and factors associated with polypharmacy: a systematic review and meta-analysis, BMC Geriatr. 22 (1) (2022 July 19) 601.