Late-age Onset Systemic Sclerosis

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ABSTRACT. ***Objective.*** Although patients who develop systemic sclerosis (SSc) later in life (≥ 65 yrs) may express the entire clinical spectrum of disease, we hypothesize that patients with late-age onset SSc incur a different risk for specific organ manifestations of disease compared to those with early-age onset SSc.

Methods. In total, 2300 patients with SSc were evaluated between 1990 and 2009 and reviewed from a university-based scleroderma center cohort. Demographic profile, SSc subtype, autoantibody status, Medsger severity scores, pulmonary function tests, echocardiography, and right heart catheterization measures were compared between late-age onset vs younger-age onset patients with SSc.

Results. Overall, 2084 patients (91%) developed SSc prior to age 65, while 216 (9%) were ≥ 65 years. Late-age onset patients had a significantly higher proportion of anticentromere antibodies (42% vs 27%; p = 0.001) compared to early-age onset patients. Risk of pulmonary hypertension (OR 1.76, 95% CI 1.00, 3.12), muscle weakness (OR 1.85, 95% CI 1.30, 1.64), renal impairment (OR 2.83, 95% CI 1.98, 4.04), and cardiac disease (OR 2.69, 95% CI 1.92, 3.78) was greater among those with late-age onset SSc; although risk of digital ischemia (OR 0.64, 95% CI 0.47, 0.86) was reduced. The cumulative incidence of pulmonary hypertension at 5 years was greater among those with late-age onset SSc (9%) compared to those with early-age onset SSc (2.7%; log-rank, p < 0.001).

Conclusion. These findings suggest that older patients with SSc are at greater risk for pulmonary hypertension, renal impairment, cardiac disease, and muscle weakness. Awareness of the distinct risk for specific organ manifestations in SSc, in particular pulmonary hypertension, should guide the care of patients with SSc whose disease begins after age 65. (J Rheumatol First Release June 17 2011; doi:10.3899/jrheum.100956)

Key Indexing Terms:
SCLERODERMA ELDERLY AGING

Systemic sclerosis (SSc) is an uncommon multisystem autoimmune disease characterized by immune abnormalities, fibrosis of the skin and internal organs, and an obliterative vasculopathy. It is a heterogeneous disease ranging from mild limited cutaneous features to widespread skin thickening. Internal organ involvement can be minimal, with mild gastroesophageal reflux, subtle skin changes, and Raynaud's phenomenon (RP) as the sole manifestations. Alternatively, it can be a fulminant and catastrophic multisystem disease with interstitial lung disease, severe digital ischemia, gastrointestinal (GI) malfunction, myopathy, renal failure, and/or fatal pulmonary hypertension[1].

While SSc affects adults across the life spectrum, with peak age of onset between 40 and 50 years, incident cases continue to occur into late adult life[2]. Indeed, several US epidemiologic studies underscore incident SSc in the sixth, seventh, and eighth decades of life[3,4,5,6]. In one such study, the peak incidence of SSc at diagnosis among white women occurred in the age group of 65–74 years[3].

Phenotypic variation by age has been established for younger patients with SSc (i.e., juvenile-onset SSc), who have been shown to have an increased prevalence of overlap syndrome with myositis, SSc-specific antibodies (anti-PM-Scl, anti-U1RNP), and improved survival compared with adult-onset SSc[7]. Surprisingly, whether the SSc disease phenotype varies with older age of SSc onset is unclear. This lack of clarity stems in part from inconsistent previous descriptions of SSc features in the elderly. While early case descriptions suggested that late-age onset SSc represented a milder form of disease, with limited morbidity and minimal skin and internal organ involvement[8,9,10], subsequent larger case series demonstrated the severity and breadth of organ involvement in late-age onset SSc[11,12,13]. Further, whether the limited versus the diffuse cutaneous subset of disease predominates in the elderly is a matter of debate. For example, both a Hungarian and an American cohort demonstrated that the majority of patients with late-age onset SSc had diffuse disease[12,13]. Other descriptions of SSc in the elderly favor subtle and minimal skin thickening more consistent with the limited subtype[8,9]. It is also unclear whether the cardinal organ systems affected by SSc (e.g., skin, cardiac, pulmonary, musculoskeletal, gastrointestinal, renal) are more or less frequently involved in

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the older SSc population. In this regard, a report from our center demonstrated a 2-fold increase in the risk of pulmonary hypertension among patients with SSc onset after age 60 years[14].

Although patients who develop SSc later in life (≥ 65 yrs of age) can express the entire clinical spectrum of the disease, we hypothesize that those with late-age onset SSc will have a greater risk for specific organ manifestations compared to those with early-age onset SSc.

MATERIALS AND METHODS

Patients and measurements. Our investigation surveyed a large, well characterized cohort of patients with SSc to determine the clinical features of late-age onset SSc. The collection of clinical, serologic, and diagnostic data was approved for this study by the Johns Hopkins Office of Human Subjects Research and Institutional Review Board. Clinical and laboratory data are collected at the first visit to the Johns Hopkins Scleroderma Center (JHSC) and then prospectively ascertained in an ongoing longitudinal database among those with followup visits to the center. Each patient satisfied 1 of these criteria: (1) American College of Rheumatology (ACR) criteria for SSc[15]; (2) 3 or more of the 5 features of the CREST syndrome (calcinosis, RP, esophageal dysmotility, sclerodactyly, telangiectasias)[16,17]; or (3) the combination of definite RP, abnormal nailfold capillaries, and a SSc-specific autoantibody[18]. A total of 2481 patients with SSc were enrolled in the database from 1990 until 2009, among which 2300 had a recorded date of SSc onset and comprehensive assessments, and therefore were included in the analyses.

We defined SSc onset according to age at first non-RP symptom. Patients were categorized as having late-age onset SSc if this occurred at age 65 years or older. Demographic data including sex, race, diabetes, smoking status (described as current or former vs never), and SSc subtype (based on classification criteria established by LeRoy, *et al*[16,18]), were recorded on initial presentation to the JHSC and updated if new information became available. Patients with skin thickening proximal to the elbows or knees (at any time during their illness) were categorized as having the diffuse cutaneous scleroderma subtype; all other patients were categorized as having limited cutaneous disease (lcSSc). Serologic status was recorded on initial presentation to the JHSC and updated if new information became available. Clinical data regarding patients' SSc included all available pulmonary function testing, echocardiography, Medsger severity scores (MSS)[19,20], and modified Rodnan skin scores. For patients with return visits to JHSC, these data were updated every 6 months or as it became available. Functional status was evaluated using the Health Assessment Questionnaire Disability Index (HAQ-DI) and the Scleroderma Health Assessment Questionnaire (SHAQ) on the first visit to the JHSC and on followup if applicable. Measurement of lung volumes [forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), total lung capacity (TLC)] and diffusing capacity (DLCO) by pulmonary function testing were standardized[21,22] and reported as percentage predicted.

Given that disease features may vary with time, and in keeping with our hypothesis that patients with late-age onset SSc have a greater risk for organ impairment compared to patients with early-age onset SSc, we characterized the involvement of each major organ system by its most abnormal value. We abstracted the maximum recorded HAQ-DI, SHAQ, MSS, and Rodnan skin scores to define organ impairment any time during initial or followup visits to the JHSC. Similarly, an individual's minimum value for each lung function measure and ejection fraction was used to define peak pulmonary and cardiac disease, respectively.

Definitions for organ involvement. Pulmonary hypertension was defined by right heart catheterization with a resting mean pulmonary artery pressure ≥ 25 mm Hg in the setting of a pulmonary capillary wedge pressure < 15 mm Hg. We also examined the outcome of pulmonary hypertension defined by echocardiographic evidence of elevated pulmonary vascular pressures [right ventricular systolic pressure (RVSP) ≥ 40 mm Hg] or right heart cardiac catheterization measures.

Restrictive lung disease (RLD) was defined as FVC < 70% in an individual with a nonobstructive pattern (FEV1/FVC ≥ 70%) on pulmonary function testing.

Cardiac disease was defined as cardiac MSS ≥ 1, which includes clinically significant conduction or structural cardiac abnormalities or overt heart failure.

Digital ischemia was defined by peripheral vascular/RP MSS ≥ 2, which includes digital pitting, ulcers, or gangrene, and indicates tissue damage.

Severe GI involvement was defined as GI MSS ≥ 2, which includes any GI involvement beyond gastroesophageal reflux requiring routine treatment.

Renal involvement was defined as renal MSS ≥ 1, which is based exclusively on renal indices, and includes a creatinine ≥ 1.3 mg/dl or ≥ 2+ protein on urine dipstick.

Muscle weakness was defined by muscle MSS ≥ 1, which equates to motor strength < 5/5 in upper or lower extremity proximal muscle groups.

Statistical analysis. Continuous, normally distributed variables were summarized as mean value ± SD. Discrete variables were summarized as proportions. The MSS is an ordinal measurement; hence central tendency was reported as a median with nonparametric testing (Wilcoxon signed-rank test) to determine equality of the distributions. To account for missing data, denominators in proportions included only individuals with data available for that particular variable. Differences between means and proportions were examined using Student t test for continuous and chi-squared test for discrete, dichotomous variables.

Logistic regression was used to calculate OR and determine the risk of SSc organ involvement as a function of age at SSc onset. Age was modeled as a dichotomous variable (cutoff ≥ 65 yrs) to specifically evaluate the effect of late-age onset compared to early-age onset SSc. Age was also modeled as a continuous variable in 10-year periods to determine the effect of age across the entire life spectrum. Multivariate logistic regression was performed for each outcome, adjusting as appropriate for race, sex, SSc subtype, smoking status, disease duration, and FVC (continuous variable).

We undertook stratified analyses based on potential effect modifiers. Specifically, obstructive lung disease (FEV1/FVC < 70%) is common in the older population[23,24,25] and could be an effect modifier when evaluating for the effect of age on risk of RLD. In addition, diabetes may be a potential effect modifier of digital ulcer severity, and we therefore stratified on this variable as well.

Kaplan-Meier cumulative incidence plots were generated to evaluate time to development of pulmonary hypertension among all cohort participants with 2 or more visits to the Scleroderma Center[26]. Pulmonary hypertension was selected as the outcome for this analysis because previous literature has described its association with age of SSc onset[14,27,28,29]. Kaplan-Meier cumulative incidence curves using both definitions of pulmonary hypertension were generated. These analyses were conducted with the origin defined as SSc onset (first non-RP SSc symptom) and the patients stratified by age at SSc onset. Pulmonary hypertension is a prominent vascular manifestation of SSc, and analyses were repeated using "onset of RP" as the origin and then stratified by age of RP onset. Log-rank testing was used to compare the incidence rates in each analysis between those with SSc onset before and those after age 65 years[30]. Statistical analyses were performed using Stata IC 10.0. All reported p values are 2-sided with $\alpha = 0.05$.

RESULTS

Overall characteristics of the population. Among the study population of 2300 patients with SSc, 1909 (83%) were women and 403 (18%) were African American. In addition,

1900 (83%) met ACR criteria for SSc, 384 (16%) satisfied 3 or more of the 5 features of the CREST syndrome, and 16 (1%) met criteria by the combination of definite RP, abnormal nailfold capillaries, and an SSc-specific autoantibody. The mean age at SSc onset among the entire cohort was 45.5 years (Figure 1). In the cohort, 2084 (91%) had disease onset before age 65 and 216 (9%) at 65 years or older. Of those with late-age onset SSc, 105 (49%) had onset between 65 and 70 years, 68 (31%) between 70 and 75 years, 36 (17%) between 75 and 80 years, and 7 (3%) at > 80 years. For the overall cohort, the mean age at RP onset was 42 ± 15 years and mean age at first non-RP symptom was 46 ± 14.3 years; 1449 (63%) had the lcSSc subtype.

Overall, 1521 patients (66%) had > 1 recorded visit to the JHSC; however, the median number of followup visits was significantly higher among the younger compared to the older patients with SSc (Table 1). The mean duration of followup at the JHSC was also significantly greater for those with early compared to late-age onset SSc (5 ± 4 yrs vs 4 ± 3 yrs; $p < 0.001$). On average, patients with late-age onset SSc were diagnosed by a physician faster than those with early SSc onset (0.5 ± 2.4 yrs vs 2 ± 5 yrs; $p < 0.001$), and similarly had a shorter disease duration at initial presentation to the JHSC (2 ± 3 yrs vs 6 ± 8 yrs; $p < 0.001$).

Patient demographics, SSc duration, and serology are summarized in Table 1 by age at SSc onset. Individuals with late-age onset SSc had a mean age at RP onset of 65 ± 13 years, mean age at first non-RP symptom of 71 ± 5 years, and 147 (68%) had lcSSc. Among individuals with SSc onset after age 75 (n = 43), 34 (79%) had lcSSc. Late-age onset patients had more anticentromere antibodies [50 of 119 (42%) vs 348 of 1288 (27%); $p = 0.001$] but fewer anti-U1RNP antibodies [3 of 99 (3%) vs 102 of 1084 (9%); $p = 0.033$] than those with early-age onset disease.

Prevalence of organ involvement. Patients with late-age onset SSc had the same median maximum MSS as their younger counterparts in the domains of renal, cardiac, GI, and muscle, reflecting the highly skewed distribution of these measures. However, by nonparametric testing, the MSS distributions between older and younger patients were significantly different ($p < 0.05$). Older patients with SSc had a lower median MSS in the RP domain compared to patients with early-age onset SSc (1 vs 2; $p < 0.001$). SSc organ involvement by dichotomized MSS is summarized in Table 2. In addition, there was no significant difference in the prevalence of renal crisis between the older and younger-age onset patients with SSc [11 of 216 (5%) vs 63 of 2084 (3%); $p = 0.101$].

The mean maximum HAQ-DI was higher for older patients versus younger ones, but this difference was not statistically significant (mean maximum score 1.23 ± 0.8 vs 1.11 ± 0.8; $p = 0.055$). The mean maximum HAQ-DI increased with age at SSc onset: 65–69 years (1.13 ± 0.82), 70–74 years (1.28 ± 0.78), 75–79 years (1.34 ± 0.80), and ≥ 80 years (1.68 ± 0.66).

SSc lung involvement, as assessed by pulmonary func-

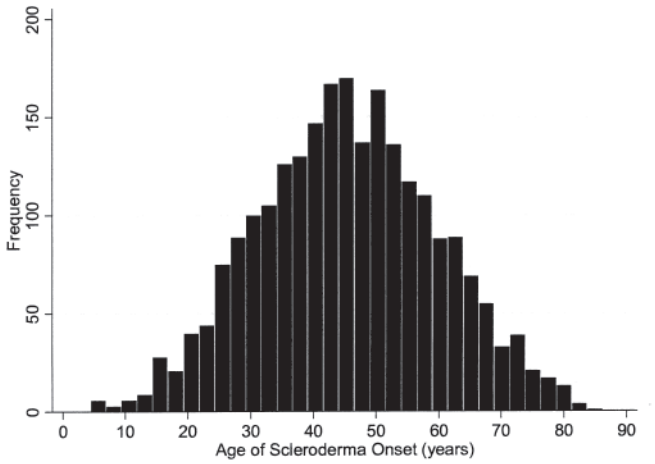

Figure 1. Age of onset of systemic sclerosis (SSc; scleroderma) as defined by age at first non-Raynaud's phenomenon SSc symptom among 2300 patients evaluated at the Johns Hopkins Scleroderma Center 1990-2009.

Table 1. Demographics, disease duration, and serologic profile among 2300 patients with SSc evaluated 1990–2009.

Characteristic	Age at Onset < 65 Yrs, n = 2084	Age at Onset ≥ 65 Yrs, n = 216	p
Women, n (%)	1725 (83)	184 (85)	0.369
African American, n (%)	379 (18)	24 (11)	0.040
Limited subtype disease, n (%)	1302 (62)	147 (68)	0.108
Smoking status, current or former[§]	992 (48)	105 (50)	0.601
Median no. visits to JHSC, range	3 (1, 28)	2 (1, 19)	< 0.001
Mean followup from first visit to JHSC among patients with > 1 visit[§§] (yrs, ± SD)	5 ± 4	4 ± 3	< 0.001
SSc duration, mean ± SD			
Disease duration (yrs) at time of first visit to JHSC	6 ± 8	2 ± 3	< 0.001
Duration (yrs) of RP at time of first visit to JHSC[†]	9 ± 10	8 ± 13	0.4113
Age of RP onset, yrs[†]	40 ± 13	65 ± 13	< 0.001
Age at first non-RP symptoms, yrs	43 ± 12	71 ± 5	< 0.001
Years from RP onset to first non-RP SSc symptom[†]	3 ± 8	6 ± 13	< 0.001
Years from first non-RP SSc symptom to diagnosis of SSc by physician[††]	2 ± 5	0.5 ± 2.4	< 0.001
Serology, n/total analyzed (%)			
ANA	1259/1306 (96)	120/124 (97)	0.831
Antitopoisomerase I	277/1175 (23)	18/107 (17)	0.112
Anticentromere	348/1288 (27)	50/119 (42)	0.001
Anti-U1RNP	102/1084 (9)	3/99 (3)	0.033

[§] Data analyzed from 2272 individuals with data recorded regarding smoking status. [§§] Data analyzed from 1521 individuals with > 1 visit to JHSC. [†] Data analyzed from 2227 individuals with a reported date of onset for RP. [††] Data analyzed from 2291 individuals with a reported date of diagnosis by a physician. SSc: systemic sclerosis (scleroderma); JHSC: Johns Hopkins Scleroderma Center; RP: Raynaud's phenomenon; ANA: antinuclear antibody.

tion testing (Table 3), demonstrated a greater proportion of late-age onset patients with an obstructive pattern (FEV1/FVC < 70%) compared to early-age onset patients [56 of 179 (31%) vs 363 of 1808 (20%); p = 0.001]. Among those with a nonobstructive pattern, FVC (76% ± 22% vs 69% ± 21%; p = 0.001) and TLC (85% ± 26% vs 78% ± 21%; p = 0.001) were significantly higher in the older compared to younger patients. In contrast, percentage predicted DLCO was similar between the 2 groups (65% ± 29% vs 62% ± 26%; p = 0.176).

By echocardiography (Table 3) there was no difference in minimum ejection fraction (55% ± 10% vs 56% ± 9%; p = 0.133) between the 2 groups. However, the older patients did have a higher mean maximum RVSP compared to younger patients (49 ± 20 mm Hg vs 44 ± 21 mm Hg; p = 0.007). Thirty-five (16%) individuals with late-age onset SSc and 260 (12%) with earlier SSc onset underwent right heart catheterization. The proportion of patients with pulmonary hypertension by right heart catheterization was nearly equal among younger vs older-age onset patients [19 of 216 (9%) vs 151 of 2084 (7%); p = 0.413]. Using the broader definition of pulmonary hypertension consisting of both right heart catheterization measures and elevated RVSP by echocardiography, there was a significantly higher proportion of patients with pulmonary hypertension among older compared to younger patients [97 of 216 (45%) vs 627 of 2084 (30%); p < 0.001].

Multivariate analysis of organ risk. Table 4 summarizes the risk of organ involvement by age of SSc onset. The relationship between late-age onset (≥ 65 yrs) SSc and pulmonary hypertension defined by cardiac catheterization was of borderline significance (p = 0.05) after adjustment for race, sex, SSc subtype, FVC, and disease duration (OR 1.76, 95% CI 1.00, 3.12). Further, when age was modeled as a continuous variable, there was a 9% increase in the unadjusted odds of having pulmonary hypertension (OR 1.09, 95% CI 0.98, 1.22) as measured by right heart catheterization for each 10-year increase in age of SSc onset. This relationship was strengthened and became statistically significant after adjustment for race, sex, SSc subtype, FVC, and disease duration (OR 1.34, 95% CI 1.17, 1.54). The relationship between late-age onset SSc and odds of pulmonary hypertension was also strengthened when the definition of pulmonary hypertension was broadened to include both right heart catheterization and elevated RVSP by echocardiography; this association was maintained when age was modeled as a continuous (OR 1.66, 95% CI 1.52, 1.81) or dichotomous variable (OR 3.28, 95% CI 2.34, 4.60), demonstrating > 3 times the risk of developing pulmonary hypertension among those with late-age onset SSc compared to early-age onset SSc in the adjusted analysis.

Among those with nonobstructive pulmonary function tests (n = 1568, FEV1/FVC ≥ 70%), age at SSc onset did not significantly increase the risk of RLD (FVC ≤ 70%; Table 4) when modeled as a continuous (OR 1.01, 95% CI 0.93, 1.09) or dichotomized variable (OR 0.80, 95% CI 0.54, 1.19). The adjusted risk of cardiac disease, as assessed by

Table 2. Organ involvement and functional measures among 2300 patients with SSc evaluated 1990–2009.

	Frequency of Dichotomized Medsger Severity Scores (%)				
	Age of Onset < 65 Yrs		Age of Onset ≥ 65 Yrs		
	No	Yes	No	Yes	p
Cardiac disease*	1386 (77)	425 (23)	113 (63)	67 (37)	< 0.001
Digital ischemia§	893 (43)	1180 (57)	133 (62)	80 (38)	< 0.001
GI involvement†	206 (19)	857 (81)	31 (34)	59 (66)	0.001
Renal involvement**	1536 (84)	302 (16)	127 (69)	57 (31)	< 0.001
Muscle weakness††	1384 (77)	418 (23)	118 (68)	56 (32)	0.008
	Maximum SSc HAQ score, mean ± SD (n)				
	Age of Onset < 65 Yrs		Age of Onset ≥ 65 Yrs		
General disease	1.58 ± 2.70 (1478)		1.50 ± 0.91 (138)		0.742
Intestine	0.95 ± 0.97 (1475)		0.79 ± 0.90 (136)		0.059
Breathing	1.00 ± 0.98 (1482)		1.07 ± 1.01 (135)		0.435
RP	1.28 ± 1.04 (1461)		0.94 ± 0.92 (131)		< 0.001
Digital ulcers	0.97 ± 1.22 (1463)		0.66 ± 0.97 (129)		0.005
	Maximum general HAQ Disability Index, mean ± SD (n)				
Score	1.11 ± 0.8 (1847)		1.23 ± 0.8 (185)		0.055

* Cardiac MSS ≥ 1, which includes clinically significant conduction or structural cardiac abnormalities or overt heart failure. §RP MSS ≥ 2, which includes digital pitting, ulcers, or gangrene, and indicates tissue damage. † GI MSS ≥ 2, which includes any GI involvement beyond gastroesophageal reflux requiring routine treatment. ** Renal MSS ≥ 1, which includes creatinine ≥ 1.3 mg/dl or ≥ 2+ protein on urine dipstick. †† Muscle MSS ≥ 1, which equates to motor strength < 5/5 in upper or lower extremity proximal muscle groups. SSc: systemic sclerosis; MSS: Medsger severity scores; GI: gastrointestinal; HAQ: Health Assessment Questionnaire; RP: Raynaud's phenomenon.

Table 3. Cardiopulmonary diagnostic testing among 2300 patients with SSc evaluated 1990–2009. Data are mean ± SD unless otherwise specified.

Pulmonary Function Tests	Age of Onset < 65 Yrs	Age of Onset ≥ 65 Yrs	p
No obstruction: FEV1/FVC ≥ 70%	1445/1808 (80%)	123/179 (69%)	0.001
FEV1/FVC	0.79 ± 0.06	0.79 ± 0.06	0.109
Minimum percent predicted FVC	69 ± 21	76 ± 22	0.001
Minimum percent predicted TLC	78 ± 21	85 ± 26	0.001
Minimum percent predicted DLCO	62 ± 26	65 ± 29	0.176
Obstruction: FEV1/FVC < 70%	363/1808 (20%)	56/179 (31%)	0.001
FEV1/FVC	0.62 ± 0.12	0.61 ± 0.09	0.654
Minimum percent predicted FVC	70 ± 21	74 ± 17	0.129
Minimum percent predicted TLC	83 ± 21	93 ± 26	0.002
Minimum percent predicted DLCO	58 ± 23	54 ± 25	0.211
Echocardiography			
Minimum ejection fraction, n = 1736	56 ± 9	55 ± 10	0.133
Maximum RVSP, mm Hg, n = 1428	44 ± 21	49 ± 20	0.007
Right heart catheterization			
PA pressure ≥ 25 mm Hg and PCWP ≤ 15 mm Hg	151 (7%)*	19 (9%)*	0.413
PA pressure ≥ 25 mm Hg and PCWP > 15 mm Hg	35 (2%)*	6 (3%)*	0.248

* 260 right heart catheterizations were completed among patients with younger SSc onset (< 65 yrs); and 35 right heart catheterizations were completed among patients with late-age SSc onset (≥ 65 yrs). The percentages represent number of catheterizations meeting criteria out of the total number of younger SSc onset patients (n = 2084) or late-age SSc onset patients (n = 216). SSc: systemic sclerosis; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; TLC: total lung capacity; DLCO: diffusing capacity; RVSP: right ventricular systolic pressure; PA: pulmonary artery; PCWP: pulmonary capillary wedge pressure.

MSS, was significantly greater among those with late-age onset SSc (OR 2.69, 95% CI 1.92, 3.78).

Muscle weakness was associated with age (OR 1.09, 95% CI 1.01, 1.17), particularly among those with SSc onset after age 65 (OR 1.57, 95% CI 1.12, 2.20). After adjustment for race, sex, SSc subtype, and disease duration, those with SSc onset after age 65 had an 85% increase in the odds of weakness compared to those with early-age onset SSc (OR 1.85, 95% CI 1.30, 2.64).

Patients with late-age onset SSc had a 36% reduction in risk for digital ischemia (OR 0.64, 95% CI 0.47, 0.86) compared to those with early-age onset disease after adjustment for race, sex, SSc subtype, disease duration, and smoking status. This finding was congruent with less impairment on the digital ulcer domain of the SHAQ (Table 2). Among patients with diabetes (n = 95), there was no increase in risk of digital ischemia among those with late-age onset compared to early-age onset SSc (OR 2.99, 95% CI 0.58, 15.39). Risk of severe GI involvement yielded conflicting results and did not reach statistical significance (Table 4). Patients with late-age onset SSc had an increased risk of renal impairment (OR 2.83, 95% CI 1.98, 4.04).

Cumulative incidence of pulmonary hypertension. Figure 2 shows time to development of pulmonary hypertension by right heart catheterization from the onset of SSc. Regardless of whether the origin is defined as time of first non-RP SSc symptom (Figure 2A), or as the onset of RP (Figure 2B), individuals with late-age onset disease develop pulmonary hypertension at a greater rate than those with early-age onset disease ($p < 0.001$). The cumulative incidence of pulmonary hypertension at 5 years from SSc onset was 9% (95% CI 4%, 17%) among the older compared to 2% (95% CI 2%, 3%) among the younger patients (log-rank $p < 0.001$).

Figure 3 shows the time to development of pulmonary hypertension as measured by right heart catheterization or RVSP ≥ 40 mm Hg by echocardiography. Similar to the findings for Figure 2, regardless of whether the origin is defined as time of first non-RP SSc symptom (Figure 3A), or as the onset of RP (Figure 3B), patients with late-age onset SSc have a higher cumulative incidence of pulmonary hypertension (log-rank $p < 0.001$).

DISCUSSION

While the full spectrum of SSc is seen among those with late-age onset SSc, our study suggests that these patients are at greater risk for pulmonary hypertension, cardiac disease, muscle weakness, and renal impairment compared to those with early-age onset disease. However, older patients surprisingly have less severe RP, with reduced risk for digital ischemic ulcers, compared to those with earlier SSc onset. In addition, older patients have a higher prevalence of anticentromere antibodies but not the limited cutaneous subtype, compared to their younger counterparts. The prevalence of anti-U1RNP antibodies was significantly less among patients with late-age onset SSc. These data confirm that late-age onset SSc (age ≥ 65 yrs) occurs frequently, representing almost 10% of this large university-based cohort. Our study in fact demonstrated that the new onset of SSc

Table 4. Risk of organ involvement in SSc. Age of SSc onset are modeled as both dichotomous and continuous variables in logistic regression.

Outcome	Age at Onset† Modeled As Dichotomous Variable OR (95% CI)	Age at Onset† Modeled As Continuous Variable†† OR (95% CI)
Pulmonary hypertension (right heart catheterization), n = 2300		
Unadjusted	1.23 (0.75, 2.03)	1.09 (0.98, 1.22)
Adjusted*	1.76 (1.00, 3.12)	1.34 (1.17, 1.54)
Pulmonary hypertension (echocardiogram or right heart catheterization), n = 2300		
Unadjusted	1.89 (1.42, 2.52)	1.25 (1.17, 1.33)
Adjusted*	3.28 (2.34, 4.60)	1.66 (1.52, 1.81)
Restrictive lung disease (FVC < 70%): among nonobstructed, n = 1568		
Unadjusted	0.69 (0.47, 1.00)	0.95 (0.88, 1.02)
Adjusted**	0.80 (0.54, 1.19)	1.01 (0.93, 1.09)
Cardiac disease, n = 1991		
Unadjusted	1.93 (1.40, 2.66)	1.30 (1.21, 1.40)
Adjusted**	2.69 (1.92, 3.78)	1.60 (1.46, 1.75)
Muscle weakness, n = 1976		
Unadjusted	1.57 (1.12, 2.20)	1.09 (1.01, 1.17)
Adjusted§	1.85 (1.30, 1.64)	1.14 (1.05, 1.23)
Digital ischemia, n = 2286		
Unadjusted	0.45 (0.34, 0.61)	0.75 (0.71, 0.80)
Adjusted**	0.64 (0.47, 0.86)	0.82 (0.76, 0.87)
Severe gastrointestinal involvement, n = 1153		
Unadjusted	0.46 (0.29, 0.72)	0.92 (0.83, 1.02)
Adjusted§	0.80 (0.49, 1.30)	1.11 (0.99, 1.25)
Renal impairment, n = 2022		
Unadjusted	2.28 (1.63, 3.19)	1.27 (1.17, 1.38)
Adjusted§	2.83 (1.98, 4.04)	1.41 (1.28, 1.55)

† SSc onset defined as age of first non-Raynaud's phenomenon SSc symptom. †† Age at onset per 10 years. * Adjusted for race, sex, subtype, disease duration and FVC. ** Adjusted for race, sex, subtype, disease duration, and smoking status. § Adjusted for race, sex, subtype, and disease duration. SSc: systemic sclerosis; FVC: forced vital capacity

occurs even in the very old, with 43 individuals over the age of 75 years, including 7 octogenarians, in our cohort.

We confirmed that pulmonary hypertension is a significant health concern among older patients with SSc. Using the "gold standard" for pulmonary hypertension measurement, cardiac catheterization, individuals with SSc onset after age 65 years had almost twice the risk of developing pulmonary hypertension compared to their younger counterparts. Our study, therefore, is similar to the findings of other investigators regarding the strong association between age at SSc onset and pulmonary hypertension[14,29,31]. However, our study is unique in that we examined this relationship by cardiac catheterization, which allowed for a more precise measurement of right-side pressures, particularly in an older population, where there may be considerable left-side heart disease[27]. This may explain some of the increase in risk when an echocardiographic definition was included, because diastolic dysfunction is prevalent among the older population[32].

According to pulmonary function testing, patients with late-age onset SSc had more obstructive lung disease (FEV1/FVC < 70%). We speculate that this is predominantly an effect of age, an established risk factor for chronic obstructive pulmonary disease[25]. Among nonobstructed patients, there was a suggestion of less RLD risk (as measured by FVC among older patients with SSc), which may be expected in a group of patients with higher rates of anticentromere positivity. The influence of age-related changes in the lungs on SSc is not known.

Late-age onset SSc was surprisingly protective against digital ischemia in our cohort. This was consistent from the patient perspective (RP severity and digital ulcer severity domains of SHAQ), provider assessment (MSS), and in multivariate logistic regression. Early age at RP onset has previously been described as a risk factor for digital ulcers in SSc[33,34]. Walker, *et al* examined a cohort of 3064 patients with SSc and categorized them into early or late-age onset SSc by age at RP onset in relation to the cohort mean (42.9 yrs)[33]. With this categorization, they found that individuals with early-age onset RP had more digital ulcers. One can speculate that RP in an older host with SSc may be influenced by a number of factors, such as the effect of an aging immune system, aging-related changes of the skin's microcirculation response to cold[35,36], generalized decreases in vascular compliance[37], and differences in cold exposure between younger and older individuals (i.e., more cold

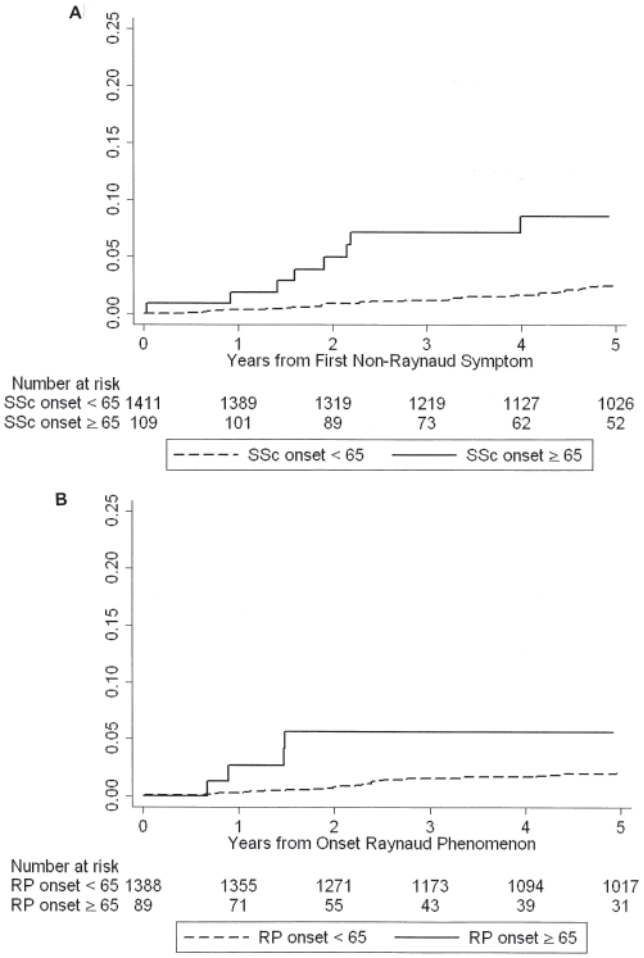

Figure 2. Cumulative incidence of pulmonary hypertension, defined by right heart catheterization, by age of onset of systemic sclerosis (SSc) among patients with 2 or more visits to the Johns Hopkins Scleroderma Center. P < 0.001. A. Origin defined as time of first non-Raynaud's phenomenon (RP) SSc symptom. B. Origin defined as time of onset of RP.

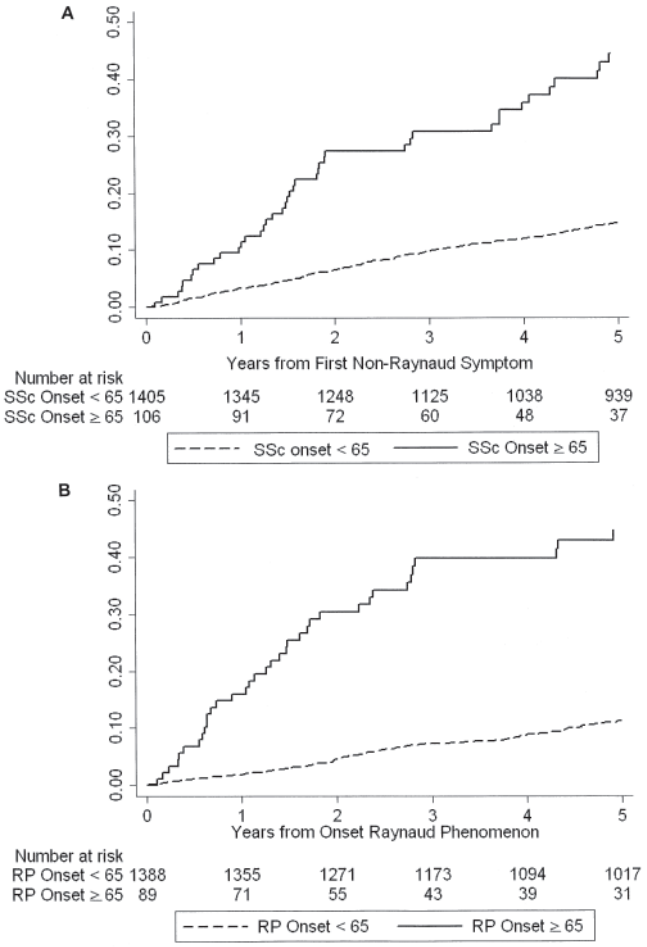

Figure 3. Cumulative incidence of pulmonary hypertension, defined by right heart catheterization or echocardiogram, by age of onset of systemic sclerosis (SSc) among patients with 2 or more visits to the Johns Hopkins Scleroderma Center. P < 0.001. A. Origin defined as time of first non-Raynaud's phenomenon (RP) SSc symptom. B. Origin defined as time of onset of RP.

avoidance among the elderly). The reasons for these differences in digital ischemia between those with earlier versus later onset of SSc are unknown and warrant further study with longer prospective followup among older patients, to determine whether this SSc feature develops over time.

The risk for SSc organ involvement, as assessed by MSS, was greater for those with late-age onset SSc in renal and cardiac domains. We speculate that these findings may be due to age-related changes and comorbid conditions. Particularly for these 2 domains, the MSS is not specific for SSc-related disease. When examining other measures of kidney and cardiac disease, we found no difference in the prevalence of renal crisis or ejection fraction (measured by echocardiography) based on age at SSc onset. The risk of severe GI involvement as assessed by MSS yielded conflicting results, and objective testing was not available for comparison. The effect of age on these SSc-specific domains has not been previously described.

Finally, in our cohort we identified significant functional limitations among individuals with late-age onset SSc. Individuals with late-age onset disease were more disabled overall as measured by HAQ-DI scores compared to their younger counterparts. They also had more muscle weakness. These findings persisted in multiple logistic regression, with a 57%–85% increase in the odds of muscle weakness among those with SSc onset after age 65 years. To our knowledge, the association we describe between muscle weakness and age at SSc onset has not been described in other epidemiologic SSc cohorts. The reason for this difference in strength is unclear. Muscle mass and strength have been demonstrated to decline with age[38]. Loss of muscle density and weakness in the general older population have been associated with increased risk of hospitalization[39], and muscle weakness has been associated with pathologic states of aging such as frailty[40]. HAQ-DI scores also increase with age in the general population[41]. This is most notable after

age 75 years, when the mean HAQ-DI increases sharply from 0.34 ± 0.64 (women age 70–74 yrs) to 0.77 ± 0.72 (women age 75–79 years), with even greater increases after age 80 years (1.49 ± 1.08)[41]. It is notable that older patients with SSc, in addition to having higher HAQ-DI scores compared to their younger counterparts, also have higher mean HAQ-DI scores compared to age-matched non-SSc counterparts[41].

Although we demonstrated that age was associated with functional decline, as measured by HAQ-DI score, the effect of age-related changes in muscle superimposed on SSc is not known. Objective muscle data (electromyography, creatine kinase, biopsy) in this cohort was limited to a very small number of patients overall, particularly among those with late-age onset SSc, and therefore was not included in our analyses. We are not able to conclude whether differences in strength are due to structural muscle changes (myopathy, myositis, atrophy) or simply to differences in rates of testing.

The reasons for the differences between those with earlier versus later onset of SSc are unknown and need further study. These changes, which are part of normal aging, may lead to a physiology that is exaggerated in the setting of SSc. The strengths of our study include the large cohort size with a large proportion of elderly, and comprehensive clinical assessments. We used 2 definitions for pulmonary hypertension, which support the validity of our findings.

There are limitations in our study. We did not have a control group of elderly age-matched individuals without SSc with whom to make comparisons on non-SSc measures. There may be data acquisition bias in that older individuals may be less likely to be referred for invasive procedures (i.e., cardiac catheterizations, muscle biopsies). Next, about 35% of the cohort had a single visit, among whom the older patients with SSc were disproportionately represented. In this group, significant future events and organ involvement may be missed. Hence, these data may underrepresent the organ severity and involvement in this group. Finally, although the MSS can be a useful standardized tool by which to measure SSc organ involvement broadly, it lacks specificity in certain domains (renal and cardiac domains not specific to SSc) and may be differentially abnormal based on age-related factors. However, our use of additional objective data, such as echocardiography, pulmonary function tests, and right heart catheterization values, provided additional corroborative data on which to draw meaningful conclusions.

We have demonstrated that the full spectrum of SSc features can occur in a large cohort of elderly patients with SSc, and that patients with late onset are at increased risk for specific organ involvement, particularly pulmonary hypertension. Differences in disease characteristics between late-age onset and early-age onset patients with SSc should be considered when caring for older patients with SSc and may allow for more focused care of the multimorbid elderly.

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