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Calcinosis is associated with digital ulcers and osteoporosis in patients with systemic sclerosis: A Scleroderma Clinical Trials Consortium study

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Abstract

Objectives—We sought to identify the clinical factors associated with calcinosis in an international multicenter collaborative effort with the Scleroderma Clinical Trials Consortium (SCTC).

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Methods—This is a retrospective cohort study of 5218 patients with systemic sclerosis (SSc). Logistic regression was used to obtain odds ratios (OR) relating calcinosis to various clinical features in multivariate analyses.

Results—A total of 1290 patients (24.7%) had calcinosis. In univariate analyses, patients with calcinosis were older than patients without calcinosis, more likely to be female, and had longer disease duration from the first non-Raynaud phenomenon symptom. Patients with calcinosis were more likely to have digital ulcers, telangiectasias, acro-osteolysis, cardiac disease, pulmonary hypertension, gastrointestinal involvement, arthritis, and osteoporosis, but less likely to have muscle disease. Anti-Scl-70, RNA-polymerase-III, and U1-RNP autoantibodies were significantly less common in patients with calcinosis, while anticentromere (ACA), anti-PM/Scl, and anticardiolipin antibodies were more frequent. In multivariate analysis, the strongest associations with calcinosis were digital ulcers (OR = 3.9; 95% CI: 2.7–5.5; $p < 0.0001$) and osteoporosis (OR = 4.2; 95% CI: 2.3–7.9; $p < 0.0001$).

Conclusion—One quarter of patients with SSc have calcinosis at some time during their illness. Our data confirm a strong association of calcinosis with digital ulcers, and support a novel association with osteoporosis.

Keywords

Systemic sclerosis; Calcinosis; Digital ulcers; Osteoporosis

Introduction

Calcinosis is a rare disorder characterized by deposition of calcium in skin and subcutaneous tissues [1]. It is associated with connective tissue diseases including systemic sclerosis (SSc) and dermatomyositis (DM). Two general mechanisms of calcification in soft tissues have been described: (1) metastatic calcification, where the deposition of calcium occurs in normal cutaneous or subcutaneous tissue in the presence of elevated levels of serum calcium and/or phosphate, and (2) dystrophic calcification–the most common presentation of calcinosis occurring in association with SSc–where the deposition of calcified material happens in diseased tissues, and associated with normal serum calcium and phosphate levels [2]. Calcinosis is often painful and may be associated with recurrent episodes of local inflammation or infection, leading to considerable functional impairment [3].

Calcinosis in patients with SSc is a late manifestation, most often occurring more than 7.5 years after the diagnosis [1]. It typically involves the hands and feet, particularly the fingers [4]. Calcinosis in SSc has been associated with male gender [5], digital ulcers [5–7], digital tip pitting scars [6], acro-osteolysis [8], late nailfold videocapillaroscopy pattern [7], anticentromere antibody (ACA) [9], and anti-PM/Scl antibody [10]. These findings are primarily derived from small single-center studies, and the effects of confounding variables were not taken into account.

We previously found an overall frequency of calcinosis of 22% in a multicenter international cohort of 7056 SSc patients (data unpublished). Given that calcinosis is a frequent, debilitating complication of SSc with no effective therapies, we sought to identify clinical

associations of calcinosis that may shed light on the underlying pathogenesis, and provide novel therapeutic targets.

Methods

Study design

This is a retrospective multicenter cohort study of 5218 patients with SSc from 9 cohorts within the United States (Stanford University, University of Pittsburgh, Northwestern University, and Rutgers-RWJMS), Australia, Canada, United Kingdom, Italy, and Mexico. We collected information on demographics, clinical findings, internal organ involvement, co-morbid diseases (osteoporosis, renal disease), and serum autoantibodies. We defined diffuse cutaneous SSc as skin thickness proximal to elbows and knees or truncal involvement, and limited cutaneous SSc as skin thickness distal to elbows and knees without truncal involvement at any time during the disease course, following the classification proposed by LeRoy and Medsger [11]. We defined organ system involvement as described previously [12]; chronic renal disease as a creatinine > 2 mg/dl, osteoporosis as a T-score ≤ − 2.5 SD on bone densitometry, or a clinical history of osteoporosis requiring medical treatment; digital ulcers as denuded areas with a defined border, loss of epithelialization and loss of epidermis and dermis on the volar aspect distal to the proximal interphalangeal joints, and acro-osteolysis as the resorption of the distal phalangeal tufts on physical examination and/or radiography. Calcinosis was defined as ever having evidence of subcutaneous calcium deposition on physical examination and/or radiography, or a clear history of calcium extruding from the skin as described by the patient. This study was designed in accordance with the general ethical principles outlined in the Declaration of Helsinki.

Study population

We included all patients diagnosed with SSc, mixed connective tissue disease, and other overlap connective tissue diseases who fulfilled 2013 revised ACR/EULAR criteria for SSc [13].

Statistical analysis

To characterize patients with and without calcinosis, we used student's *t*-test for continuous variables and chi-square or Fisher's exact test for categorical variables, as appropriate. p Values from univariate analysis were adjusted using the Bonferroni correction for multiple comparisons. We then developed stratified and non-stratified logistic multivariate regression models to obtain odds ratios (OR) for the association between calcinosis and significant risk factors, and to control for potential confounders [including chronic renal disease, body mass index (BMI), and steroid use for the association between calcinosis and osteoporosis]. Multicollinearity and interactions among the candidate predictors were assessed. We used stepwise elimination to determine the final regression model, retaining those factors with a p value < 0.05 in univariate analysis. Statistical tests of the regression estimates were based on the chi-squared approximation for the likelihood ratio statistic and 95% confidence intervals were based on Wald's test. Statistical significance was defined as $p \leq 0.05$. All statistical analyses were performed using SAS statistical software, version 9.3 (SAS Institute Inc, Cary, NC).

Results

Patient characteristics and calcinosis

Of 5218 patients with SSc, 4428 (84.9%) were female, and racial distribution was 81.7% Caucasian, 6.1% Hispanic, 2.6% Asian, and 0.9% African-American. Overall, 61.4% had limited cutaneous SSc, and 38.4% had diffuse cutaneous SSc. Mean age at last visit was 57.4 ± 13.3 years, and mean disease duration from first non-Raynaud phenomenon (RP) symptom was 9.4 ± 9.7 years.

A total of 1290 patients (24.7%) had calcinosis. Patients with calcinosis were older than patients without calcinosis, more likely to be female, and had longer disease duration from first non-RP symptom, but there was no difference in cutaneous subtype. Patients with calcinosis were significantly more likely to have digital ulcers (65.5% vs. 34.4%, $p < 0.0001$), telangiectasias, and acro-osteolysis, but less likely to have puffy fingers. Regarding internal organ involvement, patients with calcinosis more often had SSc-associated cardiac disease, pulmonary hypertension, gastrointestinal involvement, and arthritis, but less frequently had muscle disease. Osteoporosis was much more common in patients who had calcinosis (22.8% vs. 2.8%, $p < 0.0001$; Table 1).

Autoantibodies and calcinosis

Anti-Scl-70, RNA-polymerase-III, and U1-RNP autoantibodies were significantly less common in patients with calcinosis, while ACA, and anti-PM/Scl were more frequent. In the small subgroup of patients who had anticardiolipin antibodies tested, these were also more frequently found in patients with calcinosis. There were no statistically significant differences in antinuclear antibodies (ANA), lupus anticoagulant, and anti-beta-2-glycoprotein antibody frequency between patients with and without calcinosis (Table 2).

Factors associated with calcinosis in univariate and multivariate analysis

In univariate analysis, the strongest associations with calcinosis were digital ulcers (OR = 3.6, 95% CI: 3.1–4.1), and osteoporosis (OR = 10.2, 95% CI: 6.9–15). In multivariate analysis, digital ulcers and osteoporosis remained the strongest significant associations with calcinosis (OR = 3.9, 95% CI: 2.7–5.5 and OR = 4.2, 95% CI: 2.3–7.9, respectively; Table 3). Telangiectasias and ACA also remained highly significant ($p < 0.0001$). After controlling for steroid use and BMI in the model, the association with osteoporosis persisted in stratified analyses in non-obese patients (OR = 6.5; 95% CI: 1.8–23.8; $p = 0.004$).

Discussion

Calcinosis is a common manifestation in patients with SSc, and has a substantial impact on quality of life. Our large database was able to confirm with high statistical certainty prior studies showing an association between calcinosis and digital ulcers, as well as other ischemic manifestations of SSc, including digital tip pitting scars, loss of digital pulp, nailfold capillary changes, and acro-osteolysis. One study of 103 patients with SSc found that a history of digital ulcers was a significant independent predictor for radiographic progression of calcinosis (HR = 3.16, 95% CI: 1.22–9.43) [5]. Koutaissoff et al. [6] reported

that SSc patients with terminal tuft calcinosis on hand radiographs were more likely to have digital ulcerations (28% vs. 11%, $p = 0.03$), digital pitting scars (64% vs. 38%, $p = 0.03$), and a history of digital gangrene (75% vs. 45%, $p = 0.008$). A retrospective study of 101 SSc patients concluded that those with moderate or severe acro-osteolysis (assessed by hand radiographs) were more likely to have severe calcinosis (33% vs. 13%), although this did not reach statistical significance after adjustment for potential confounders [8]. More recently, a cross-sectional study that included 155 SSc patients from a single center showed that a history of and/or active digital ulcers was independently associated with calcinosis (OR = 3.39, 95% CI: 1.32–8.69) [14]. Similarly, in a cross-sectional study of 126 patients with DM, our group found that patients with calcinosis were significantly more likely to have fingertip ulcers than patients without calcinosis (50.0% vs. 9.3%, $p < 0.001$) [15]. In the same line, vasodilator therapy has been tried for the management of calcinosis in patients with systemic sclerosis. Several case reports have shown positive results with diltiazem, the calcium channel blocker most frequently used for the medical treatment of calcinosis. More powerful vasodilatory therapies such as phosphodiesterase 5 inhibitors and prostacyclins need to be further evaluated, but preliminary observations in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) registry have found improvement in calcinosis lesions with subcutaneous treprostinil in SSc patients being treated for PAH [16]. These findings support a potential role for vasculopathy in the pathogenesis of calcinosis.

We also found a significant association between osteoporosis and calcinosis, particularly in non-obese patients. There is a well-known association between osteoporosis and vascular calcification [17]. Although poorly understood, proposed mechanisms have included inflammation [18], osteoblast-like behavior of vascular cells [19], involvement of pathways including osteoprotegerin, an inhibitor of bone resorption and calcification, and RANKL, a key factor of osteoclast maturation [20], and circulating cells with osteogenic/calcifying potential [18]. Although there are no data supporting the association of osteoporosis and extravascular calcifications, it is plausible that there might be shared mechanisms. Multiple mouse models with deletions of bone-related genes display vascular and ectopic calcification, including targeted deletions of osteoprotegerin and fetuin-A, another inhibitor of calcification, in knockout mice [19]. A systematic review [21] identified calcinosis as a candidate risk factor for low bone mineral density (BMD) in SSc patients; however, the data were conflicting with two small studies (37 and 25 SSc patients, respectively) reporting lower total bone mineral content in patients with calcinosis ($p < 0.05$) [22,23], while another (43 SSc females) noted no effect of calcinosis on BMD [24]. One study that included 60 SSc patients showed that circulating levels of osteoprotegerin, but not RANKL, were higher in those with calcinosis. The authors suggested that this probably represented an inadequate compensatory response of osteoprotegerin as an inhibitor of calcification [25]. Two case reports showed successful use of bisphosphonates for the treatment of calcinosis in SSc patients suggesting that impaired bone metabolism may play a role in the pathogenesis of calcinosis [26,27]. Notably, we found that SSc patients with calcinosis had a lower rate of steroid usage than those without calcinosis, yet have a higher frequency of osteoporosis. This is consistent with the previously mentioned systematic review by Omair et al. [21] who concluded that the use of steroids did not have a significant effect on BMD in SSc patients.

Of note, areas of calcinosis overlying the field of the lumbar spine, or the proximal femur might artifactually increase BMD, but these are not common locations for calcinosis [4], and if any effect, would lead to underdiagnosis of osteoporosis. Finally, a recent article by Park et al. found that acro-osteolysis in patients with SSc was correlated with increased osteoclastogenesis and higher VEGF levels [27]. Subjects with acro-osteolysis were more likely to have calcinosis than subjects without acro-osteolysis, leading us to speculate that a similar hypoxia-induced process might also underlie calcinosis and lead to an increased risk for osteoporosis. Further research is needed to confirm the association between calcinosis and osteoporosis, and to determine its implication in the development of targeted therapies.

Although historically calcinosis has been thought to be more common in patients with lcSSc, we did not find a difference in the distribution of calcinosis in the cutaneous subtypes, and this was also the case in a recent study aimed to determine whether calcinosis and acro-osteolysis were related to specific nailfold video-capillaroscopy features in SSc [14]. The present study confirmed the association between calcinosis and ACA and anti-PM/Scl autoantibodies. A previous study of 95 patients with lcSSc found that 60% of those who were ACA positive had calcinosis in any location compared with 26% of those who were ACA negative [9]. The positive association between calcinosis and anti-PM/Scl antibody was also described by D' Aoust et al. [10] in a study of 763 SSc patients, where 58% of patients with positive anti-PM/Scl antibodies had calcinosis vs. 30% in patients without these antibodies. However, muscle disease was less frequent in our calcinosis group. The discrepancy between the higher frequency of anti-PM/Scl and lower frequency of muscle disease in the calcinosis group may partially be explained by the fact that muscle involvement in our study included the spectrum of non-inflammatory myopathy as well as myositis. In the subgroup of patients who had anticardiolipin antibodies assessed, we found they were more frequent in the calcinosis group. This variable was not included in the multivariate model given that results were only available in 18% of patients. The association between anticardiolipin antibodies and calcinosis suggests the possibility that these antibodies might play a role in the development of vascular injury in SSc with subsequent development of calcinosis [28].

A noteworthy strength of our study is that it is the largest to examine specific clinical associations with calcinosis including multiple centers throughout the world. However, we recognize some limitations. Our study is retrospective in design, thus missing data were unavoidable. Since not all patients had radiographs available, we cannot exclude the possibility of subclinical calcinosis. Likewise, densitometry for the assessment of osteoporosis was not performed systematically on all patients. Another limitation is that patients with overlap disease were included in this study, and we do not know how many of these patients had dermatomyositis overlap, which certainly might affect the prevalence of calcinosis. However, given that we did not find an association between muscle disease and calcinosis, the number of patients with classical DM (as opposed to amyopathic) overlap was likely small. Finally, we did not have information on the localization or severity of calcifications in this study, but we are currently performing a prospective cohort study that will provide more details regarding the distribution and quantity of calcinosis using the novel radiographic scoring system [29]. Nonetheless, our data support a strong association

of calcinosis with digital ulcers as well as osteoporosis, which may shed light on the pathogenesis of calcinosis and guide the development of future therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix A. Supplementary material

Supplementary data are available in the online version of this article at http://dx.doi.org/10.1016/j.semarthrit.2016.05.008

Abbreviations

SSc	systemic sclerosis
DM	dermatomyositis
ACA	anticentromere antibody
OR	Odds ratios
RP	Raynaud phenomenon
ANA	antinuclear antibodies
BMI	body mass index
BMD	bone mineral density

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Table 1

Demographic characteristics and clinical features in SSc patients with and without calcinosis

	Sample size *n* (%)	Without calcinosis *n* (%)	With calcinosis *n* (%)	*p* Value
Total	5218 (100)	3928/5218 (75.3)	1290/5218 (24.7)	–
Age at last visit (mean years ± SD)	4929 (94.5)	56.8 ± 13.4	59.4 ± 12.8	< 0.0001
Female	5218 (100)	3279/3928 (83.5)	1149/1290 (89.1)	< 0.0001
Race	5022 (96.2)			0.7584
Caucasian		3220/3787 (85)	1047/1235 (84.8)	
Asian		108/3787 (2.9)	30/1235 (2.4)	
African-American		33/3787 (0.9)	12/1235 (1)	
Hispanic		232/3787 (6.1)	86/1235 (7)	
Other or unknown		194/3787 (5.1)	60/1235 (4.9)	
Smoking	5057 (96.9)			0.4136
Never		2023/3811 (53.1)	678/1246 (54.4)	
Ever		1788/3811 (46.9)	568/1246 (45.6)	
SSc Subtype	5211 (99.9)			0.6200
Diffuse		1511/3922 (38.5)	495/1289 (38.4)	
Limited		2411/3922 (61.5)	794/1289 (61.6)	
mRSS at first visit (mean ± SD)	4978 (95.4)	10.0 ± 10.5	10.7 ± 9.8	0.0635
mRSS ≥ 11 at first visit	4978 (95.4)	1275/3745 (34.1)	454/1233 (36.8)	0.0758
Maximum mRSS (mean ± SD)	3838 (73.6)	12.3 ± 11.9	13.6 ± 11.4	0.0071
Disease duration from RP symptom (mean years ± SD)	4915 (94.2)	10.4 ± 11.7	17.1 ± 13.8	< 0.0001
Disease duration from first non-RP symptom (mean years ± SD)	5052 (96.8)	8.3 ± 9.2	12.9 ± 10.4	< 0.0001
BMI	3473 (66.6)	26.0 ± 6.6	25.4 ± 24.9	0.006
Obese	3473 (66.6)	557/2561 (21.8)	163/912 (17.9)	0.0131
Steroid use ever	3509 (67.2)	1292/2565 (50.4)	392/938 (41.8)	< 0.0001
Chronic renal disease	3736 (71.6)	88/2963 (3.0)	20/773 (3.8)	0.2665
Raynaud phenomenon	5199 (99.6)	3773/3912 (96.5)	1271/1287 (98.8)	< 0.0001
Digital ulcers	4992 (95.7)	1293/3764 (34.4)	804/1228 (65.5)	< 0.0001
Digital pitting scars	5182 (99.3)	1477/3898 (37.9)	835/1284 (65)	< 0.0001
Loss of digital pulp	3452 (66.1)	735/2365 (31.1)	619/1087 (57)	< 0.0001
Nailfold capillary changes[a]	3826 (73.3)	1365/3051 (44.7)	534/775 (68.9)	< 0.0001
Puffy fingers	4922 (94.3)	2531/3726 (67.9)	770/1196 (64.4)	0.0232
Sclerodactyly	5204 (99.7)	3420/3917 (87.3)	1181/1287 (91.8)	< 0.0001
Acro-osteolysis	1156 (22.1)	82/871 (9.4)	76/285 (26.7)	< 0.0001
Telangiectasias	4888 (93.7)	2392/3701 (64.6)	1048/1187 (88.3)	< 0.0001
Tendon friction rub	4869 (93.3)	627/3676 (17.1)	219/1193 (18.4)	0.3030
Osteoporosis	2127 (40.8)	51/1816 (2.8)	71/311 (22.8)	< 0.0001
SRC	5176 (99.2)	188/3891 (4.8)	60/1285 (4.7)	0.8132
Cardiac disease	4907 (94)	463/3709 (12.5)	217/1198 (18.1)	< 0.0001
Pericardial involvement	1986 (38)	73/1292 (5.7)	72/694 (10.4)	< 0.0001

	Sample size *n* (%)	Without calcinosis *n* (%)	With calcinosis *n* (%)	*p* Value
Myocardial involvement	1986 (38)	48/1292 (3.7)	60/694 (8.7)	< 0.0001
Conduction abnormalities	2076 (40)	188/1486 (12.7)	79/590 (13.4)	0.6503
PAH	4990 (95.8)	517/3757 (13.8)	202/1233 (16.4)	0.0229
Pulmonary fibrosis	3860 (74)	1081/3070 (35.2)	283/790 (35.8)	0.7486
GI disease	5179 (99.3)	2477/3920 (63.2)	938/1259 (74.5)	< 0.0001
GERD symptoms	3343	1663/2299 (73.3)	837/1044 (80.2)	< 0.0001
Esophageal dysmotility	3316	753/2277 (33.1)	397/1039 (38.2)	0.0039
Esophageal stricture	3423	148/2360 (6.3)	165/1063 (15.5)	< 0.0001
Use of antibiotics for SIBO	3440	111/2372 (4.7)	112/1068 (10.5)	< 0.0001
Malabsorption	2098	89/1518 (5.9)	58/580 (10)	0.0009
GAVE	1997	69/1320 (5.2)	45/677 (6.7)	0.1955
Muscle disease[b]	4580 (87.8)	410/3325 (12.3)	111/1255 (8.8)	0.0009
Arthritis[c]	4606 (88.3)	936/3504 (26.7)	329/1102 (29.9)	0.0415
Use of vasodilators ever[d]	5218 (100)	2079/3928 (52.93)	825/1290 (63.95)	< 0.0001
Use of biphosphonates ever	2395 (45.9)	69/1987 (3.47)	48/408 (11.76)	< 0.0001

Abbreviations: mRSS = modified Rodnan skin score, RP = Raynaud phenomenon, BMI = body mass index, SRC = Scleroderma renal crisis, PAH = pulmonary artery hypertension, GI = gastrointestinal, GERD = gastroesophageal reflux, SIBO = small intestine bacterial overgrowth, GAVE = gastric antral vascular ectasia.

[a]Nailfold capillary changes included pericapillary hemorrhages, dilated loops, and drop-outs.

[b]Muscle disease was defined as proximal muscle weakness on physical examination and any of the following: muscle biopsy showing myositis, electromyogram showing a myopathic pattern, or elevated serum enzymes reflecting muscle disease.

[c]Arthritis was defined as radiologic evidence of erosive arthritis or clinical synovitis, defined by tender and swollen joints.

[d]Vasodilators included calcium channel blockers, endothelin-1 receptor antogonists, phosphodiesterase inhibitors, and prostanoids.

Table 2

Autoantibodies in SSc patients with and without calcinosis

	Sample size *n* (%)	Without calcinosis *n* (%)	With calcinosis *n* (%)	*p* Value
Positive ANA	4689 (89.9)	3316/3494 (94.9)	1123/1195 (94)	0.2164
Positive Scl-70	4578 (87.7)	698/3409 (20.5)	166/1169 (14.2)	< 0.0001
Positive ACA	3370 (64.6)	717/2651 (27.1)	277/719 (38.5)	< 0.0001
Positive anti-PM/Scl	1825 (35)	87/1365 (6.4)	49/460 (10.7)	0.0025
Positive RNA-polymerase-III	2414 (46.3)	481/1772 (27.1)	143/642 (22.3)	0.0157
Positive U1-RNP	4286 (82.1)	238/3174 (7.5)	47/1112 (4.2)	0.0002
Positive Lupus anticoagulant	1637 (31.4)	44/1118 (3.9)	28/519 (5.4)	0.1803
Positive anti-beta-2-glycoprotein	588 (11.3)	105/401 (26.2)	46/187 (24.6)	0.6819
Positive anticardiolipin	949 (18.2)	200/653 (30.6)	125/296 (42.2)	0.0005

Abbreviations: ANA = antinuclear, ACA = anticentromere, RNP = ribonucleoprotein.

Table 3

Univariate and multivariate analyses

	Univariate analysis			Multivariate analysis**		
	OR	**95% CI**	***p* Value**	**OR**	**95% CI**	***p* Value**
Age at last visit	1.02	1.01–1.02	< 0.0001 *			
Disease duration	1.05	1.04–1.05	< 0.0001 *	–	–	–
Female	1.6	1.3–2	< 0.0001 *	3.1	1.5–6.2	0.0016
Obese	0.8	0.6–0.9	0.0133			
Steroids use ever	0.7	0.6–0.8	< 0.0001 *			
mRSS > 11	1.1	0.98–1.3	0.0759	–	–	–
Puffy fingers	0.8	0.7–0.9	0.0232			
Sclerodactyly	1.6	1.3–2.0	< 0.0001 *			
Raynaud phenomenon	2.9	1.7–4.9	< 0.0001 *			
Digital ulcers	3.6	3.2–4.2	< 0.0001 *	3.9	2.7–5.5	< 0.0001
Digital pitting scars	3.0	2.7–3.5	< 0.0001 *			
Loss of digital pulp	2.9	2.5–3.4	< 0.0001 *			
Nailfold capillary changes	2.7	2.3–3.2	< 0.0001 *			
Acro-osteolysis	3.5	2.5–4.9	< 0.0001 *			
Telangiectasias	4.1	3.4–4.9	< 0.0001 *	3.6	2.2–5.8	< 0.0001
Osteoporosis	10.2	6.9–15	< 0.0001 *	4.2	2.3–7.9	< 0.0001
Cardiac disease	1.6	1.3–1.9	< 0.0001 *	1.8	1.1–2.9	0.0181
PAH	1.2	1.0–1.5	0.0231			
GI disease	1.7	1.5–2	< 0.0001 *	1.7	1.1–2.6	0.0128
Muscle disease	0.7	0.6–0.9	0.001 *	–	–	–
Arthritis	1.2	1.0–1.4	0.0416			
Scl-70	0.6	0.5–0.8	< 0.0001 *			
Anticentromere	1.7	1.4–2	< 0.0001 *	2.2	1.5–3.2	< 0.0001
Anti-PM/Scl	1.8	1.2–2.5	0.0028			

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	Univariate analysis			Multivariate analysis**		
	OR	95% CI	*p* Value	OR	95% CI	*p* Value
RNA-polymerase-III	0.8	0.6–0.9	0.0159			
U1-RNP	0.5	0.4–0.8	0.0002 *			
Anticardiolipin	1.7	1.2–2.2	0.0005 *			
Vasodilators use	1.6	1.4–1.8	< 0.0001 *			

Abbreviations: mRSS = modified Rodnan skin score, PAH = pulmonary artery hypertension, GI = gastrointestinal, ACA = anticentromere, RNP = ribonucleoprotein.

* Adjusted $p < 0.05$.

** Multivariate model included: disease duration from first non-RP symptoms, gender, mRSS, digital ulcers, telangiectasias, osteoporosis, cardiac disease, GI disease, muscle disease, and anticentromere antibody. Age at last visit was correlated with disease duration. Although not significant in univariate analysis, we retained mRSS in the model given its clinical relevance. RP, digital pitting scars, loss of digital pulp, nailfold capillary changes, acro-osteolyisis, vasodilators use, and PAH were excluded given correlation with digital ulcers. Scl-70, PM-1, RNA-polymerase.

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