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Vascular Complications in Systemic Sclerosis: A Prospective Cohort Study

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Abstract

Objective: Two major complications in scleroderma patients that cause substantial morbidity and mortality are ischemic digital lesions (DL) and pulmonary hypertension (PH). The clinician's ability to predict which patients will develop these complications is imperfect.

Methods: We conducted a prospective observational cohort study of 300 patients with scleroderma who were followed for at least a five-year period. At baseline, patients lacked evidence of PH and were without a current DL. At each six-month visit the patient was examined for signs/symptoms of PH and/or a DL. The primary outcomes were (1) PH defined as a mean pulmonary artery pressure ≥ 25 mmHg by right heart catheterization and (2) 1 DL defined as new onset of severe vascular compromise.

Results: 30 patients (10%) developed PH (11 Group I/PAH, 4 Group II, 15 Group III) and 69 developed DL. The average time from enrollment until diagnosis of PH was 3.2 ± 2 years. In multivariable analyses, patients who developed PH were more likely to have diffuse disease (HR 3.2, $p=0.004$), a FVC/DLCO ratio >1.6 (HR 1.7, $p=0.008$) and elevated RVSP (HR=1.07, $p=0.007$). Patients who developed PAH were more likely to have a FVC/DLCO ratio >1.6 (HR=5.8, $p=0.014$) and patients who developed Group III PH were less likely to have an elevated FVC (HR=0.92, $p=0.001$). Patients were more likely to develop a DL if they had a history of prior DL (HR=7.0, $p<0.001$), or were men (HR=2.3, $p=0.007$).

Conclusion: In a prevalent cohort of scleroderma patients, individuals who develop PH or DL have simple to measure clinical features that can predict these complications years before they occur.

Keywords

scleroderma; pulmonary hypertension; cohort studies; wounds and injuries

INTRODUCTION

Two major complications in scleroderma patients that cause substantial morbidity and mortality are ischemic digital lesions (DL) and pulmonary hypertension (PH)[1–6]. PH has an estimated prevalence of 8–15%, and is responsible for a significant percentage of mortality in patients with scleroderma[2–3]. Ischemic DLs affect approximately half of patients[7–9] and are associated with significant morbidity; up to 15–20% of patients with recurrent digital ischemic ulcers develop irreversible tissue loss with gangrene or amputation of one or more digits[4,8–10].

In the past few decades there have been great strides in developing novel and efficacious treatments for PH and ischemic DL[11–15]. Unfortunately, the recognition of both conditions often occurs only after advanced vascular injury causes severe clinical outcomes. Furthermore, there is little information to identify which patients will go on to develop these complications. Early detection and measures to predict those at risk would provide the opportunity to initiate more aggressive treatment early in the disease course that may prevent progression of vascular damage. Defining clinical biomarkers that predict who is at risk to develop PH or DL is most important because there is a substantial pre-clinical period that provides an opportunity to intervene.

At our center we have followed a cohort of 300 patients prospectively over 5 years, throughout which time both clinical data and serum have been collected at regular intervals as outlined by a pre-designed protocol. Our goal was to identify clinical features that are predictive of PH and ischemic DL. We aim to validate prior work[18–25] and determine if novel, more practical routine clinical measures can aid in prediction.

MATERIALS AND METHODS

We conducted a prospective cohort study of 300 prevalent SSc patients enrolled between March 1st,2006 and March 31st,2008. The Johns Hopkins University Institutional Review Board approved of this study (NA_00001412).

Subjects

Patients were recruited from the Johns Hopkins Scleroderma Center. Patients were recruited during routine outpatient follow-up and new patient visits based on whether they met the appropriate inclusion/exclusion criteria. All patients gave informed consent. Inclusion criteria included:

- i. Meeting the American College of Rheumatology criteria for scleroderma[26], having at least 3 of 5 features of CREST (Calcinosis, Raynaud, Esophageal dysmotility, Sclerodactyly, Telangiectasia) syndrome. We retrospectively analyzed the cohort to determine who met 2013 ACR criteria[27]
- ii. Age>18
- iii. Ability to make visits every 6 months for at least 5 years

- iv. The absence of evidence of PH, which was defined by an estimated right ventricular pressure (RVSP) of <40 mmHg by transthoracic echocardiography (ECHO) or if RVSP ≥ 40 mmHg there was no other evidence of PH defined by unexplained dyspnea, decline in absolute value of DLCO > 15% of predicted, or elevated NT-pro BNP > 2 times the upper limit of normal

Exclusion criteria included:

- i. A history of PH diagnosed by right heart catheterization or those undergoing therapy for PH
- ii. Active scleroderma renal crisis
- iii. Current active DL including a digital ischemic ulcer, gangrene or ischemic event threatening loss of digit or limb
- iv. A history of other clinically active non-scleroderma related vascular disease such as unstable angina, uncontrolled hypertension or recent cerebrovascular accident

Data Collection

Initial Visit: The following data were collected into the Scleroderma Center Database: Medsger organ-specific scleroderma severity scores [28], modified Rodnan skin score, ECHO, 6 minute-walk-test (6MWT), and autoantibody status.

Follow-up Visits: At each visit the patient was examined for signs and symptoms of development of PH and DL, and history of interval DL were determined at visits and by chart review. Every year patients underwent pulmonary function testing and an ECHO as part of routine clinical care or more frequently at the discretion of the treating physician. FVC and DLCO were standardized for age and sex and reported as the percentage of the predicted value [29,30]. Our center's algorithm for screening PH includes obtaining routine yearly pulmonary function testing and ECHO. Patients were referred for right heart catheterization (RHC) at the discretion of the treating rheumatologist. Our center's protocol for RHC is based on the following guidelines: A decline in DLCO out of proportion to decline in FVC or TLC, echocardiogram with estimated RVSP ≥ 40 mmHg OR increase in RVSP > 10 mmHg from prior study, echocardiogram evidence of right ventricular abnormalities (enlargement, dilatation), dyspnea on exertion not explained by other causes, or clinical signs suggestive of PH (lower extremity edema, increased jugular venous pressure).

NT-proBNP levels were obtained using serum samples on the MesoScale Discovery platform (Rockville, MD). 85% of patients had a sample available for NT-proBNP testing upon cohort entry. Values of NT-proBNP were log-transformed given right-skewed distributions. For autoantibody data, the Euroline Systemic sclerosis profile (IgG) was assayed (EUROIMMUN, Lübeck, Germany). The panel consisted of Scl-70, CENP A, CENP B, RP11 (recombinant subunit POLR3K of human RNA polymerase III), RP155 (recombinant subunit POLR3A of human RNA polymerase), Fibrillarin (U3RNP), NOR90, Th/To, PM-Scl100, PM-Scl75, Ku, PDGF receptor, and Ro-52. Patients were considered positive for anti-centromere, RNA polymerase III, or PM-Scl antibodies if they were positive

for either of the respective subunits on the Euroline profile (i.e. anti-centromere positive if positive for either CENP-A or CENP-B). Sensitivity analyses were performed using different cut-off values for a positive result (low positive 11 units; moderate-strong positive 26 units).

Outcomes

The primary outcomes were (1) any form of PH defined as a mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg obtained by RHC [31–32] and (2) digital ischemic lesions (DL) defined as new onset of severe vascular compromise of fingers as evidenced by development of ischemic digital ulcerations (a lesion on the distal fingertip with loss of surface epithelium), gangrene (the presence of demarcated ischemic territory on a digit which is dark, cool, and painful; the area is clearly demarcated from viable flesh) or digital loss from a scleroderma related vascular event. Secondary outcomes included PH subsets defined by the 2009 Dana Point classification criteria: Group I (mPAP ≥ 25 mmHg, pulmonary capillary wedge pressure < 15 mmHg, and PVR > 3 Woods units without significant restrictive lung function suggesting interstitial lung disease (ILD) as defined by a forced vital capacity (FVC) $\geq 65\%$ predicted, and mild, if any, ILD by high resolution computerized tomography (HRCT) according to the reading radiologist); Group II (mPAP ≥ 25 mmHg and a pulmonary capillary wedge pressure ≥ 15 mmHg); and Group III (mPAP ≥ 25 mmHg and a pulmonary capillary wedge pressure < 15 mmHg but also had a significant restrictive lung function secondary to ILD with an FVC $< 65\%$ predicted and/or a thoracic HRCT scan that showed moderate to severe ILD with or without honeycombing).

Statistical Analysis

Statistical analysis was performed using Stata software Version 14 (College Station, TX). Statistical significance was defined as a two-sided p-value < 0.05 . The Student t-test was used to assess for differences between continuous variables. For variables that did not follow a normal distribution, the non-parametric test Wilcoxon (Mann-Whitney) was used to compare differences in variables between groups. For NT-proBNP, a log transformation was performed given the right-skewed nature of the distribution. For binary and categorical variables, Fisher's exact test was used.

Time-to-event analysis was performed using Cox-Proportional Hazards modeling incorporating the baseline values of covariates of clinical relevance. Patients were censored upon withdraw from study or censored administratively on the date 12/31/2016 at which point the data set was closed.

One specific covariate, RVSP, had a number of missing data points due to the inability to measure RVSP because of lack of tricuspid regurgitation. An estimated RVSP was obtained from the initial echocardiogram upon study entry in 192 individuals. Of the remaining 108 patients with missing RVSP, we performed simple imputation on 101 data entries (7 patients were excluded due to evidence suggestive of PH as defined by right ventricular/atrial dilatation on echocardiogram). This process was performed by regressing the observed RVSP on the covariates of interest for those who had RVSP data, and using the predicted

RVSP values as the imputed RVSP values. The resulting imputed RVSP (iRVSP) was subsequently used in all analyses.

RESULTS

Participants

Patient characteristics for the overall cohort (N=300) can be found in Table 1. 93% of the cohort met 1980 ACR classification criteria. Upon applying the 2013 ACR criteria retrospectively, 93% of our cohort satisfied criteria, the remainder meet criteria for CREST. The majority of the patients were middle-aged Caucasian females, with 13% patients being male and 14% identifying as African American. 58% of the patients had limited cutaneous scleroderma. Autoantibody data were available for 246 patients (82%). Frequencies of antibodies can be found in Table 2; 27% were centromere positive, 22% RNA polymerase III positive, and 22% topoisomerase positive (Scl-70). U1RNP antibody data (not included on Euroimmune) were also available based on clinical blood testing. Of 274 patients with RNP data, 7.3% (n=20) were positive for U1RNP antibodies, three of which developed PH (Fischer exact $p=0.42$). Patients on average had a diagnosis of scleroderma 10 ± 8.4 years from 1st non-RP symptom at study entry. A total of 30 patients (10%) developed PH throughout the study, and 69 (23%) developed a DL. The average time from enrollment into the cohort until the development of outcome was 3.2 ± 2 years for PH and 3.5 ± 2.4 years for DL. During the first 5 years of study, 45 patients died (15%) and 41 were lost to follow-up (14%). Those lost to follow-up contributed an average of 580 ± 343 days (0–1401).

There were 62 patients who underwent at least one right heart cardiac catheterization. Of this group, 26 (42%) were diagnosed with PH based on their first RHC. The four remaining patients who went on to develop PH were diagnosed on subsequent RHCs. The mean PA pressure for all patients who underwent an initial RHC was 27.3 ± 11 mmHg (range 9–58). The mean PA pressure for all patients who developed PH was 36.4 ± 10 (range 25–58). Patients with PAH had a mean PA pressure of 35 ± 11 mmHg and mean PVR of 7.2 ± 5.3 ; patients with Group III PH had a mean PA pressure of 37 ± 12 mmHg and PVR of 7.2 ± 5.3 .

Tables 3 and 4 show demographic data and baseline values for clinical tests by each of the individual outcomes: pulmonary hypertension (PH) and digital lesions (DL). Table 3 shows that baseline RVSP, FVC, FEV1, DLCO, and skin subtype are significantly different comparing patients who eventually developed PH compared to those who did not develop PH. iRVSP was higher (36 vs 32, $p=0.002$), FVC, FEV1, and DLCO were lower (66 vs 82, 66 vs 81, and 62 vs 81, respectively, all $p<0.001$), and more patients had diffuse subtype (67% vs 38%, $p=0.003$). The baseline 6MWT was significantly lower in patients who developed PH compared to those who did not (550 vs 599 feet, $p=0.029$); however, upon excluding 51 patients in our cohort who had musculoskeletal disease (myositis, synovitis, tendon friction rubs), this significance was lost. Table 4 shows the comparison of groups by DL status from cohort entry. DLCO at baseline, age at RP onset, and age at diagnosis were all statistically significantly lower in those who developed DLs over time. There were significantly more men who developed DL than women (22% vs 11%, $p=0.026$). There was no difference observed in the prevalence of DL in PH (29%) compared to non-PH groups

(22%), Fisher exact $p=0.38$. Similar results were also observed when examining DL prevalence amongst patients with and without PAH ($p=0.26$)

Baseline median NT-proBNP levels did not differ significantly between patients who developed PH compared to those who did not (941 pg/mL vs 391 pg/mL $p=0.23$). As no significant difference was observed in univariable analyses for developing PH, NT-proBNP was not carried into the multivariable analyses

For the secondary outcomes, 11 patients developed PAH, 4 developed Group II PH and 15 developed Group III PH. Eleven of the 30 patients (36%) who developed PH were RNA polymerase positive (4 with PAH, 2 with Group II, and 5 with Group III). In the overall cohort, 12 patients had SRC (7 prior to enrollment, five during study). Of these 12 patients, only two developed PH, and both were PAH. Of the 11 RNA pol patients who developed PH, only one experienced scleroderma renal crisis.. Patients with Group III PH and RNA pol positive had lower but not statistically significant FVC compared to patients who were RNA pol negative (50.7% vs 60.5%).

Time-to-Event Analyses

In univariable analyses, incident PH was associated with diffuse disease (HR=3.25, $p=0.002$), lower baseline DLCO (HR=0.95, $p<0.001$), lower baseline FVC (HR=0.95, $p<0.001$) and FVC/DLCO>1.6 (HR=2.9, $p=0.022$), and higher baseline RVSP (HR=1.1, $p=0.001$). All covariates with significant associations were carried into the multivariable analyses. Upon performing multivariable analyses, age at enrollment, sex, race, and skin subtype were kept in all models. For the outcome of PH, diffuse disease (HR 3.2, $p=0.004$), FVC/DLCO>1.6 (HR 1.7, $p=0.008$) and iRVSP HR 1.07, $p=0.007$) were significantly associated.

For PAH, in univariable analysis DLCO was significantly associated with a HR of 0.96 $p=0.016$, and FVC/DLCO>1.6 with a HR of 4.8, $p=0.027$. In multivariable analyses, only age of enrollment (HR 1.07, $p=0.026$) and FVC/DLCO>1.6 (HR 5.8, $p=0.014$) were significant.

For Group III PH, in univariable analysis diffuse disease (HR of 3.3, $p=0.029$), FVC (HR 0.92, $p<0.0001$), DLCO (HR 0.95, $p<0.0001$), and iRVSP (HR 1.09, $p=0.004$) were significant. In multivariable analyses, only FVC was significant (HR 0.92, $p=0.001$).

For DL, significant associations in univariate analysis include a prior history of digital ulcerations (HR 8.5, $p<0.0001$), male sex, (HR 2.03, $p=0.015$), centromere antibodies (HR 1.7, $p=0.038$), and DLCO (HR 0.98, $p<0.0001$). In multivariable regression, only male sex HR 2.33 ($p=0.007$) and history of DU (HR 7.4, $p<0.0001$) were significant.

DISCUSSION

Our study demonstrates that pulmonary function parameters and the echocardiogram estimate of RVSP are altered years before patients are diagnosed with PH. Significant differences were observed in patients who went on to develop PH versus those who did not in average baseline RVSP, DLCO, FEV₁, and FVC. These differences were observed on

average over 2 years before PH was diagnosed. In determining which parameters are most predictive of PH, skin subtype, the FVC/DLCO ratio, and RVSP were most important.

Our study confirms findings by others that focused on the specific outcome PAH; we show that RVSP and FVC/DLCO ratio >1.6 are predictive of the development of all PH [17]. While modeling PH as a composite outcome did not demonstrate that low DLCO was predictive of developing PH as has been demonstrated by others [11,16–17]; sub-analysis of PAH revealed lower DLCO as a significant predictor (HR=0.97, $p=0.016$).

Notably, one-third of the patients who developed PH during this prospective cohort study were positive for high-titer RNA polymerase III antibodies. With the exception of two patients, all of them had either PAH or Group III PH; furthermore, those who developed Group III had more severe interstitial lung disease based on PFT measurements. There has been conflicting data regarding the risk that RNA polymerase III antibodies confer to cardiopulmonary risk in scleroderma patients. Historically, the presence of RNA polymerase III has been associated with a lower risk of both PH as well as lung fibrosis ($<10\%$) [33]. Similarly, in a French cohort, RNA pol III was found to be protective of PAH and pulmonary fibrosis, defined as TLC $<80\%$ (although neither achieved statistical significance) [34]. In contrast, an Australian cohort reported higher numbers; 20% of RNA pol patients had ILD, and 10% developed PAH [35]. A Japanese study from 2015 reported higher prevalence of ILD than previously reported (78.6%) and PAH (7.1%) [36]. A recent observational Norwegian cohort study reported severe ILD in 18% of RNA pol III patients and PH in 12%. Hazard ratios were 1.7 for pulmonary fibrosis $>20\%$ by HRCT ($p=0.223$) and 4.4 for fibrosis progression $<20\%$ to $>20\%$ ($p=0.018$) [37]. Taken together, it appears that over the last few decades an increasing number of studies are reporting a higher prevalence of cardiopulmonary disease in RNA pol III patients – both PH and ILD [33–37]. Based on this trend and our study, we would advise continued screening of RNA pol III positive patients with long-standing disease for PH and ILD.

It is worth noting that while NT-proBNP was perhaps clinically significant comparing PH and non-PH groups, it was not statistically significant in our study. There are several possibilities for this including the duration of time from cohort entry to the development of PH. Allanore et al first reported the predictive value of NT-proBNP in a prospective cohort study, but his follow-up time from entry to detection of PH was shorter, an average of 18 months compared to ours of 32 months [38]. Similar to our results, Chung et al noted a lack of difference at baseline NT-proBNP levels in the PHAROS cohort [39]. The discordance of these studies may be attributable to occult cardiovascular disease (diastolic dysfunction) or renal disease, responsible for the production and clearance of NT-pro-BNP, respectively. Alternatively, differing results may be due to patient factors such as intermittent compliance with calcium channel blocker therapy, known to dramatically affect the levels of NT-pro-BNP [40].

We observed that the baseline distance walked at 6MWT is lower in patients who subsequently develop PH by ~ 50 feet ($p=0.029$). This is in alignment with the PHAROS cohort [39], who demonstrated patients with PH have lower 6MWT distances than those at-risk for PH. However, upon excluding 51 patients in our cohort who had musculoskeletal

disease (myositis, synovitis, tendon friction rubs), this significance was lost, perhaps consistent with the opinion of those who doubt the utility of the 6MWT to assess PH because of non-pulmonary factors impacting the measurement [41].

In our cohort, the occurrence of DL was predicted by a prior history of DL and male sex. The magnitude of the prediction of prior DU for future DL is supported by prior work [20]. However, the risk factor of sex is controversial – while it has been noted in a German cohort [42], a Canadian study did not find the same results [43]. The biologic rationale that males are at increased risk for digital ulcers, even upon adjusting for smoking, is unclear. Potential explanations include confounding by other vascular risk factors such as hypertension or diabetes. Alternatively, hormonal or genetic differences relating to the Y chromosome may play a role, which are often cited as grounds for the increased cardiovascular disease risk in males [44–45].

Our 10% incidence of PH over 5 years is lower compared to other studies recently published [46], which have reported a 25% prevalence of PH. Of note, the authors of the study performed RHCs at baseline and again at three years per protocol independent of patient signs and symptoms. In addition, our cohort was not enriched for patients at high-risk for PH (e.g. DLCO <60% on cohort entry). These key methodologic differences likely explain the different incidence rates.

The strengths of the study are the large cohort size and duration of follow-up with only 14% dropout. In addition, our study is prospective benefited from *a priori* exposure and outcome definitions. The prospective nature allowed for accurate assessment of clinical findings and standardized entry of test results. Also, our cohort represented a random sampling of prevalent scleroderma patients without the focus on high-risk patients for developing PH/PAH as has been done in the PHAROS cohort [17]. Our study has a number of limitations. Our center does not use a strict protocol for referring patients for right heart catheterization; rather, this is done based on the physicians' clinical judgment based on agreed-upon guidelines but may have changed over time as practice patterns evolved. This may have resulted in a misclassification of PH. However, the single-center nature of the study likely decreases variability in clinical-decision making. Notably, our cohort was not an inception cohort but a prevalence cohort; the average disease duration for patients upon entry was 10±8 years. This was intentional to maximize the number of PH cases diagnosed over the cohort period. A prevalent cohort also offers the ability to understand risk factors in patients with established disease - patients relocate, change providers, or seek second opinions years after diagnosis; therefore, understanding the risk factors of this patient population is both valuable and pragmatic. However, as a result of this design we may have missed patients who developed PH early in their disease course, which may have different predictors of PH.

We describe a large cohort of patients prospectively followed for the development of relevant vascular outcomes, namely PH and DL. Our study shows that simple to measure clinical features can be assessed in scleroderma patients to predict who is at risk for PH or DL.

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Table 1.

Baseline Characteristics of Cohort at Study Entry. Scleroderma = systemic sclerosis, RP = Raynaud's Phenomenon, ACR = American College of Rheumatology 1980 or 2013 Criteria, CREST = 3 out of 5 of the following criteria: calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias, PH = pulmonary hypertension, PAH = pulmonary arterial hypertension.

Demographics	N=300 (%)
Sex	40 (13) Male
Race	238 (79) Caucasian
	43 (14) African American
	19 (7) Other
Disease Characteristics	
Classification of SSc	280 (93) ACR, 20 CREST (7)
Type	175 (58) Limited
	124 (41) Diffuse
Age at diagnosis	44.7 ± 12
Age at entry into cohort	52.2 ± 11.8
Time from RP to cohort entry (yr)	12.3 ± 10.9
Time from non-RP sx to cohort entry	10 ± 8.4
Treatment At Cohort Entry	
Vasoactive medications	
calcium-channel blockers	143 (47)
phosphodiesterase inhibitors	5 (1.6)
prostacyclin	1 (0.3)
Disease-modifying agents	
corticosteroids	55 (18)
mycophenolate	37 (12)
methotrexate	30 (10)
cyclophosphamide	6 (2)
intravenous immunoglobulin	2 (0.67)
Outcome	
Digital Lesions	69 (23)
Pulmonary Hypertension (All)	30 (10)
Class I PH (PAH)	11 (4)
Class II PH	4 (1)
Class III PH	15 (5)

Table 2.

Prevalence Euroline Autoantibody data for available patients using high positive cut-off values (>25 units).

Autoantibody	N=246 (%)
Centromere (either/or)	67 (27)
Centromere A	62 (25)
Centromere B	67 (27)
Ro52	61 (25)
PDGF	0
Ku	3 (1)
PM-Scl (either/or)	23 (9)
PM75	20 (8)
PM100	7 (3)
ThTo	8 (3)
Nor90	4 (2)
Fib	13 (5)
RNA pol (either/or)	55 (22)
RP155	52 (21)
RP11	49 (19)
Scl-70	52 (22)

Table 3.

Baseline Characteristics of Cohort by Pulmonary Hypertension (PH) Status. RP=Raynaud's phenomenon, DLCO = diffusing capacity of the lungs for carbon monoxide, FEV1 = forced expiratory volume, FVC = forced vital capacity, iRVSP = right ventricular systolic pressure with imputation; Scl-70 antibodies (topoisomerase), CENP=centromere A or B antibodies.

	PH	No PH	P-value
Demographics	N=30	N=270	
Sex	80% Female	87% Female	0.258
Race	63% Caucasian	81% Caucasian	0.109
	30% African Americans	12% African Americans	
	7% Other	7% Other	
Disease Characteristics			
Type	33% Limited	62% Limited	0.003
Age at diagnosis	45±13	44±12	0.405
Age of first non-RP sx (yr)	44±13	41.8±12	0.199
Age of RP (yr)	42±14	39±14	0.185
Age at enrollment in cohort (yr)	54±12	52±12	0.192
Scl-70 positive	6 (20%)	81 (30%)	0.238
CENP positive	4 (13%)	26 (28%)	0.085
RNA polymerase III positive	11 (40%)	57 (23%)	0.033
Studies			
Baseline 6 Minute Walk distance (ft)	550±110	599±160	0.029
Baseline DLCO	60±21	81±22	<0.0001
Baseline FEV1	66±17	81±16	<0.0001
Baseline FVC	66±17	82±17	<0.0001
Baseline NT-proBNP, median (pg/mL)	941±1400	390±2859	0.9031
Baseline RVSP	36±6.5	32±5.8	0.0016
Demographics	N=30	N=270	
Sex	80% Female	87% Female	0.258
Race	63% Caucasian	81% Caucasian	0.109
	30% African Americans	12% African Americans	
	7% Other	7% Other	
Disease Characteristics			
Type	33% Limited	62% Limited	0.003
Age at diagnosis	45±13	44±12	0.405
Age of first non-RP sx (yr)	44±13	41.8±12	0.199
Age of RP (yr)	42±14	39±14	0.185
Age at enrollment in cohort (yr)	54±12	52±12	0.192

	PH	No PH	P-value
Demographics	N=30	N=270	
Scl-70 positive	6 (20%)	81 (30%)	0.238
CENP positive	4 (13%)	26 (28%)	0.085
RNA polymerase III positive	11 (40%)	57 (23%)	0.033
Studies			
Baseline 6 Minute Walk distance (ft)	550±110	599±160	0.029*
Baseline DLCO	60±21	81±22	<0.0001
Baseline FEV1	66±17	81±16	<0.0001
Baseline FVC	66±17	82±17	<0.0001
Baseline NT-proBNP, median (pg/mL)	941±1400	390±2859	0.9031
Baseline RVSP	36±6.5	32±5.8	0.0016

* Upon controlling for musculoskeletal symptoms (myositis, synovitis, tendon friction rubs, statistical significance was lost, p>0.05.

Table 4.

Baseline Characteristics of Cohort by Digital Lesion (DL) Status. RP=Raynaud's phenomenon, DLCO = diffusing capacity of the lungs for carbon monoxide, FEV1 = forced expiratory volume, FVC = forced vital capacity, iRVSP = right ventricular systolic pressure with imputation; Scl-70 antibodies (topoisomerase), CENP=centromere A or B antibodies

	DU since cohort entry	No DU	P-value
Demographics	N=69	N=231	
Sex	78% Female	89% Female	0.026
Race	79% Caucasian	79% Caucasian	0.937
	16% African American	14% African American	
	5% Other	7% Other	
Disease Characteristics			
Type	65% Limited	56% Limited	0.340
Age at diagnosis	41.5±12.9	45.1±11.9	0.042
Age at first non-RP sx (yr)	39.5±13.5	43.1±11.9	0.051
Age of RP onset (yr)	36.8±13.8	40.6±13.5	0.048
Age at enrollment in cohort (yr)	50.6±11.3	52±12	0.196
History of digital ulcers	56 (81%)	44 (19%)	<0.001
Scl-70 positive	22 (32%)	65 (29%)	0.589
CENP positive	25 (36%)	54 (24%)	0.037
RNA polymerase III positive	11 (17%)	57 (26%)	0.110
Studies			
Baseline 6 Minute Walk distance (ft)	587±147	595±159	0.684
Baseline DLCO	71.8±19	81.2±22.7	<0.001
Baseline FEV1	79.5±17.6	79.9±16.7	0.871
Baseline FVC	79.2±17	80.5±17.2	0.596
Baseline RVSP	33.2±5.6	32.5±6.1	0.412

Table 5.

Univariable and Multivariable Cox Proportional Hazard Models for the Development of DL.

Univariable				*Multivariable			
Covariate	HR	P value	95% CI	Covariate	HR	P value	95% CI
History of DU	8.50	<0.0001	4.6–15.6	History of DU	7.00	<0.0001	3.7–13.3
High-titer Centromere Ab	1.70	0.038	1.03–2.78	High-titer Centromere Ab	1.40	0.197	0.84–2.4
Male sex	2.04	0.016	1.15–3.62	Male sex	2.33	0.007	1.26–4.34
Baseline DLCO	0.98	<0.0001	0.96–0.99	Baseline DLCO	0.99	0.277	0.97–1.00
History of Smoking (ever)	1.50	0.296	0.69–3.3	History of Smoking (ever)	N/A	N/A	N/A

* Adjusted for age at enrollment, sex, race, skin type, baseline DLCO, high-titer centromere antibodies, and history of DU

Table 6.

Univariable and Multivariable Cox Proportional Hazard Models for the Development of PH.

Univariable				*Multivariable			
Covariate	HR	P value	95% CI	Covariate	HR	P value	95% CI
Baseline iRVSP	1.08	0.001	1.03–1.13	Baseline iRVSP	1.08	0.007	1.02–1.13
FVC/DLCO > 1.6	2.90	0.022	1.16–7.06	FVC/DLCO > 1.6	3.56	0.008	1.40–9.06
Diffuse subtype	3.25	0.002	1.52–6.95	Diffuse subtype	3.20	0.004	1.45–7.07
Baseline DLCO	0.95	<0.001	0.93–0.97	Baseline DLCO	N/A	N/A	N/A
Baseline FVC	0.95	<0.001	0.93–0.96	Baseline FVC	N/A	N/A	N/A

* Adjusted for age at enrollment, sex, race, skin type, iRVSP, and FVC/DLCO