Risk Factors for Mortality and Cardiopulmonary Hospitalization in Systemic Sclerosis Patients At Risk for Pulmonary Hypertension, in the PHAROS Registry

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ABSTRACT. ***Objective.*** We sought to identify predictors of mortality and cardiopulmonary hospitalizations in patients at risk for pulmonary hypertension (PH) and enrolled in PHAROS, a prospective cohort study to investigate the natural history of PH in systemic sclerosis (SSc).

Methods. The at-risk population for PH was defined by the following entry criteria: echocardiogram systolic pulmonary arterial pressure > 40 mmHg, or DLCO < 55% predicted or ratio of % forced vital capacity/%DLCO > 1.6, measured by pulmonary function testing. Baseline clinical measures were evaluated as predictors of hospitalization and death between 2005 and 2014. Cox proportional hazards models were censored at date of PH onset or latest study visit and adjusted for age, sex, race, and disease duration.

Results. Of the 236 at-risk subjects who were followed for a median of 4 years (range 0.4–8.5 yrs), 35 developed PH after entering PHAROS (reclassified as PH group). In the at-risk group, higher mortality was strongly associated with male sex, low %DLCO, exercise oxygen desaturation, anemia, abnormal dyspnea scores, and baseline pericardial effusion. Risks for cardiopulmonary hospitalization were associated with increased dyspnea and pericardial effusions, although PH patients with DLCO < 50% had the highest risk of cardiopulmonary hospitalizations.

Conclusion. Risk factors for poor outcome in patients with SSc who are at risk for PH were similar to others with SSc-PH and SSc-pulmonary arterial hypertension, including male sex, DLCO < 50%, exercise oxygen desaturation, and pericardial effusions. This group should undergo right heart catheterization and receive appropriate intervention if PH is confirmed. (J Rheumatol First Release October 1 2018; doi:10.3899/jrheum.180018)

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Systemic sclerosis (SSc) is a rare, often fatal, multisystem disease characterized by fibrosis and excessive collagen deposition within the skin and internal organs, chronic inflammation, immune dysregulation, and microvascular endothelial dysfunction[1,2]. Pulmonary involvement leads to the most serious complications in SSc, including pulmonary arterial hypertension (SSc-PAH), which has a prevalence of 8–12%, and SSc–associated interstitial lung disease (SSc-ILD or pulmonary fibrosis), which can be found in up to 90% of the diffuse cutaneous SSc population by high-resolution computed tomography (HRCT) scan of the chest[3,4]. SSc-ILD and PAH combined are the leading causes of death[1,2] in SSc. The clinical course of SSc- ILD is variable and median survival is 5–8 years, while overall survival of those with SSc-PAH is reported to be 50% at 3 years[5] in some studies. New treatments for PAH have significantly improved outcomes from this previously uniformly fatal complication, but compared to idiopathic PAH, SSc patients with PAH have worse outcomes[5,6]. Nevertheless, approved drugs have greatly improved survival of SSc-PAH, approaching those of idiopathic PAH[7,8,9]. Mortality increases dramatically in those with both pulmonary fibrosis and pulmonary hypertension (PH). The pathogenesis of PH associated with ILD is complex. Advanced pulmonary fibrosis associated with chronic hypoxia is thought to drive the fibrotic vasculopathy process, while isolated SSc-PAH is histologically similar to idiopathic PAH[10,11]. Predictors of poor outcomes for both SSc-ILD and SSc-PAH are poorly understood, although several factors have been suggested: older age, male sex, abnormal hemodynamics, exercise desaturation during the 6-minute walk test (6-MWT), and abnormal pulmonary function tests[5,10,11]. Longterm outcomes among those at risk for PH have not been adequately studied. Our unique population is one of the largest prospective studies of patients with SSc at risk for PH followed over an extended period. In our present investigation, we sought to identify risk factors for overall mortality and cardiopulmonary hospitalizations in those at risk for PH who enrolled in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (or PHAROS) registry between 2005 and 2014.

MATERIALS AND METHODS

Study population. The PHAROS registry is a prospective cohort study established in 2005 with the overarching objective to determine the natural course of a group of patients with predetermined risk factors for developing PH and PAH, as well as the natural history of definite SSc-PAH and SSc-PH. Approval was obtained from the lead participating center at Georgetown University School of Medicine's Institutional Review Board (IRB, approval #2004-227). Twenty medical centers in the United States participated in PHAROS and each participating center's local IRB approved the study protocol. Eligible subjects were identified by the principal investigator at each site and all subjects provided written informed consent. Eligible adult patients with a clinical diagnosis of SSc based on the 1980 and 1988 American College of Rheumatology criteria for definite SSc[12,13] were enrolled between 2005 and 2014. For this analysis, SSc subjects were considered at risk for PH based on any one of the following criteria for study entry: abnormal pulmonary function testing (PFT) defined as (1) DLCO < 55% predicted, or (2) forced vital capacity (FVC) %predicted/DLCO %predicted ratio > 1.6, or (3) estimated systolic pulmonary arterial pressure (sPAP) > 40 mmHg, obtained by Doppler echocardiography (Echo/Doppler). ILD was confirmed by thoracic HRCT scan according to local radiologist interpretation, including ground glass opacities (thought to represent early ILD) and honeycombing (thought to represent more advanced ILD)[14]. A total of 558 patients were enrolled in the PHAROS registry, and 260 subjects met the at-risk criteria for PH. We excluded 24 patients because of insufficient data, of whom 8 had only 1 visit and 16 had incomplete data for key variables including demographic data, yielding an analytic sample of 236.

Study visits. Clinical data collected at baseline for inclusion in PHAROS included baseline demographics: age at diagnosis of SSc and PH, clinical history, SSc subtype (limited or diffuse cutaneous), disease duration, medication, and smoking history. Subjects completed questionnaires including the Scleroderma Health Assessment Questionnaire[15], the University of California at San Diego Dyspnea Index (UCSD-DI)[16] and the 36-item Medical Outcomes Study Short Form-36[17] that were administered by study personnel every 6 months. Clinical information such as the New York Heart Association/World Health Organization functional classification, dyspnea symptoms, SSc physical examination, and PH features were recorded. Each participating center performed baseline laboratory testing including SSc-specific autoantibodies as per standard of care. Autoantibody profiles consisted of anticentromere, antitopoisomerase, an isolated anti-nucleolar pattern on antinuclear antibody (ANA without other SSc-specific antibodies), anti-U1-RNP, anti-RNA polymerase III, a positive ANA without the previous antibodies, or a negative ANA. HRCT and right heart catheter-

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ization (RHC) were performed when clinically indicated as determined by the clinician investigator. As part of the standard of care, baseline studies including PFT, Echo/Doppler, and 6-MWT using forehead probes for oxygen saturation were repeated and recorded yearly along with the medical history, hospitalizations, medication information, and outcome events. The change in PFT over time was calculated for those who had 2 or more PFT tests during their participation in PHAROS. Changes in FVC and DLCO were calculated as the last PFT minus first PFT, divided by elapsed time between them. The collection of data from the study visits ended in September 2014.

The PH group. The at-risk patients who were clinically suspected of having PH underwent RHC to confirm the diagnosis and were grouped according to the current acceptable 2013 classification by Simonneau, *et al*[18]. RHC was performed at the discretion of the local physician(s) without standardized algorithm for RHC. However, the local principal investigator followed each patient for clinical deterioration, including serial PFT, Echo/Doppler, 6-MWT, and dyspnea symptoms as part of the PHAROS protocol and would consider RHC if worsening of these variables became apparent. Subjects received an average of 3–4 PFT and Echo/Doppler studies over the course of the study period. Those who met criteria for PH or PAH by RHC conducted during followup were reassigned to the "PH group" using a time-dependent variable, to identify predictors of outcomes separately in those at risk for PH and for those after they were diagnosed with PH. Subjects who had normal RHC or never had RHC during followup remained in the at-risk group. In exploratory analyses, we grouped a subset of patients with "borderline" PH at baseline, defined as having a mean baseline pulmonary arterial pressure (mPAP) of 21–24 mmHg at rest, and examined them over the duration of followup without regard to PH status. Patients already diagnosed with incident PH before entering PHAROS were excluded from our analysis.

Endpoints. Primary outcomes of interest were all-cause mortality, defined as death from any cause, and the date of death was confirmed by the local physician, thus allowing inclusion in our all-cause mortality analysis. The secondary outcome was cardiopulmonary hospitalization, which was confirmed by the local physician, and defined as any hospitalization due to PH, including worsening dyspnea, congestive heart failure, and/or hypoxia.

Statistical analysis. Differences in patient clinical and demographic characteristics by PH status during followup were examined using Pearson chi-square or Fisher's exact tests for categorical variables, and Student t tests or Mann-Whitney U tests for continuous variables. We constructed Cox proportional hazards models to assess predictors of outcomes while adjusting for race, sex, and disease duration (from onset of Raynaud phenomenon). Exploratory analyses were performed to examine whether "borderline PH" was a predictor of all-cause mortality among those who underwent RHC at baseline. We also examined PH status as a predictor of mortality using models in which PH status was allowed to vary over time[19], thereby comparing the mortality rate (deaths per time at risk) prior to PH onset versus after PH onset. Further models were constructed independently for each predictor of interest. We evaluated relative rates for all-cause mortality separately for prior to and after PH onset by including an interaction term between the predictor of interest and time-dependent PH status. This enabled us to examine separately the predictors of mortality among those at risk and those who had been diagnosed with PH. Using the counting process method with age as the time scale, individuals defined as at risk were considered at risk for death starting at study enrollment through date of death and were censored at date of latest study visit or onset of PH. In this fashion, we derived estimates for hazards of death associated with each predictor prior to PH onset. Likewise, risk of death between PH diagnosis and death or latest study visit, and predictors of death among those with PH were similarly examined, with predictors measured at time of (or within 6 mos prior to) diagnosis. Because only 1 cardiopulmonary hospitalization event occurred after PH diagnosis, time at risk for this outcome was restricted to the period at risk for PH. Exploratory tests for significant heterogeneity in ability for covariates to predict mortality were computed from interaction terms between time-dependent PH status and each variable of interest. All analyses were restricted to participants with complete data for the variable of interest. Analyses were performed using SAS 9.3 (SAS Institute Inc.), and all probabilities were 2-sided at a level of significance of 5%.

RESULTS

There were 236 at-risk patients at baseline. Over the course of followup, 35 subjects developed PH as confirmed by RHC (21 had World Pulmonary Hypertension Symposium group 1 PAH, 10 had pulmonary venous hypertension or group 2, and 4 had PH due to ILD, or group 3)[15]. Thus, 201 patients remained in the at-risk group for the duration of followup, including 36 subjects who had borderline PH and 28 others with normal RHC.

Table 1 shows the distribution of baseline clinical and sociodemographic characteristics by PH status. Whites and females were more predominant in both the PH and non-PH or at-risk groups, although the at-risk group had 17% African Americans and nearly 23% of the PH cohort were African Americans. There were no significant differences in changes over time of %FVC or %DLCO between the 2 groups. The baseline mean sPAP obtained by Echo/Doppler was significantly higher in the group that developed PH ($p = 0.0049$). Baseline 6-MWT showed that those at-risk patients who evolved to PH walked significantly less distance than the patients who did not evolve to PH ($p = 0.035$). Oxygen saturation at rest was similar in both groups, but significant exercise oxygen desaturation occurred more commonly in the PH group ($p = 0.01$), and more patients with PH had exercise O_2 saturation below 90% compared to those who did not develop PH ($p = 0.033$). There were no other significant differences between the 2 groups at baseline.

Patients were followed for a median of 4 years (range 0.4–8.5 yrs). There were 32 documented deaths overall. Of those who did not develop PH, 25 (11%) died. Of those deaths, 36% were due to cardiopulmonary-related reasons and 64% were unrelated to SSc, including infection and malignancy. In contrast, there were 7 deaths in the group that developed PH (20%), of which 75% were cardiopulmonary-related and 25% were due to other causes, including infection. The overall rate of survival in the non-PH group was as follows: 3-year, 91%; 5-year, 87%; and 8-year, 76%. In the PH group from time of PH diagnosis: 3-year, 83%; 5-year, 71%; and 8-year, 71%. As shown in Supplementary Table 1 (available with the online version of this article), after controlling for age, sex, duration since first Raynaud symptoms, and race, patients with borderline PH (mPAP 21–24 mmHg) at baseline (n = 35) and who were identified to be at high risk to develop PH[20] had a significantly higher risk of death compared to those who did not have an RHC at baseline [adjusted HR (aHR): 2.99, 95% CI 1.30–6.88].

Table 2 depicts predictors of overall mortality in the at-risk group that did not develop PH. In models adjusted for age, sex, race, and disease duration, the following predictors were significantly associated with increased risk of mortality: male

Table 1. Distribution of demographic and baseline clinical characteristics among the at-risk patient population stratified by those who did not develop PH (at risk) and those who did develop PH.

Baseline Characteristics	N (total) = 236, n (%)	"At risk" for PH, n = 201	Developed PH, n = 35	p*
Age, yrs, mean (SD)		56.2 (11.2)	59.1 (8.6)	0.1939
Sex, female, n (%)	207 (88)	177 (88.1)	30 (85.7)	0.6965
Race, n (%)				0.45935
White	170 (72)	148 (73.6)	22 (62.9)	
Hispanic	14 (6)	11 (5.5)	3 (8.6)	
Black	43 (18)	35 (17.4)	8 (22.9)	
Other	9 (4)	7 (3.5)	2 (5.7)	
Disease type	154 (65)	132 (65.7)	22 (62.9)	0.44329
Unclassified	7 (3)	7 (3.5)	0	
Duration from first non-Raynaud symptom, yrs, n (%)	229 (97)	10.2 (11.0)	10.9 (8.5)	0.3977
Autoantibodies, n (%)				0.12886
Negative	18	14 (7.5)	4 (11.8)	
Anticentromere	54	45 (24.1)	9 (26.5)	
Topoisomerase	39	37 (19.8)	2 (5.9)	
U1-RNP	12	12 (6.4)	0 (0.0)	
Isolated nucleolar	37	27 (14.4)	10 (29.4)	
Mixed or other	55	46 (24.6)	9 (26.5)	
RNA polymerase III	1	1 (0.5)	0 (0.0)	
PFT, mean (SD)				
%FVC	225	83.7 (18.1)	79.9 (14.7)	0.2734
%DLCO	221	50.6 (18.2)	47.2 (17.7)	0.3073
Echo/Doppler				
Systolic PAP, mmHg	216	38.6 (9.9)	42.7 (9.5)	0.0049
Ejection fraction (%)	212	61.7 (6.3)	59.8 (5.8)	0.3534
Pericardial effusion present	183	17 (11.0)	4 (13.8)	0.7499
Six-minute walk test, mean (SD)				
Distance, m	154	421.8 (122.2)	352.1 (155.9)	0.0358
% O_2 saturation at rest	155	97.7 (2.4)	98.1 (1.4)	0.9457
% O_2 saturation during exercise	152	93.7 (5.8)	89.5 (8.7)	0.0100
Decline in O_2 saturation below 90% during exercise	127	23 (18.1)	9 (37.5)	0.033

* P values for Wilcoxon rank-sum test for continuous variables and for Pearson chi-square test or Fisher's exact test (where appropriate) for categorical variables. PH: pulmonary hypertension; PFT: pulmonary function test; FVC: forced vital capacity; Echo/Doppler: Doppler echocardiography; PAP: pulmonary arterial pressure.

sex (aHR = 4.72, 95% CI 1.79–12.45), low PFT readings (low %DLCO, aHR per 15% decrease: 2.07, 95% CI 1.43–3.01), low oxygen desaturation during 6-MWT (aHR per 15% decrease: 5.39, 95% CI 1.66–17.5), pericardial effusion (aHR = 5.32, 95% CI 1.85–16), and anemia (hemoglobin < 11.2 g/dl vs ≥ 11.2 g/dl: aHR = 3.76, 95% CI 1.33–10.63). In this group, those who desaturated (below 90%) during their 6-MWT had nearly 10-times higher risk of death than those who did not (aHR 9.53, 95% CI 2.58–35.20). In the group that developed PH (Supplementary Table 2, available with the online version of this article), no statistical significance could be identified with any of these clinical characteristics.

To further examine factors related to a higher mortality risk among males compared to females, we examined the distributions of clinical characteristics between males and females at baseline (Supplementary Table 3, available with the online version of this article). Males tended to have more diffuse SSc (though not statistically significantly), shorter disease duration from Raynaud onset (mean 7.7 yrs, compared to 12.4 years in females, p = 0.0192), and lower exercise-induced oxygen desaturation during their 6-MWT (p = 0.0044). No other meaningful differences were observed.

Hospitalizations during the followup period were as follows: in the group who did not develop PH, 8% were hospitalized owing to cardiopulmonary complications (9 events), 33% owing to other SSc complications (including multisystem organ failure), and 59% owing to non-SSc–related causes. There was 1 hospitalization event in the PH group due to cardiopulmonary disease. Table 3 examines the predictors of cardiopulmonary hospitalizations (first event during followup period) in the at-risk group that did not develop PH. We observed that a 6% decrease in FVC per year was associated with a 55% increase in risk for cardiopulmonary hospitalizations (aHR: 1.55, 95% CI 1.01–2.38). No other characteristic was associated with cardiopulmonary hospitalizations.

Table 2. HR of overall mortality across demographic and clinical characteristics among the at-risk patients.

Characteristics^	n (%)	HR (95% CI)*	p
Sex			
Female	207 (88)	1 (ref)	
Male	29 (12)	4.72 (1.79–12.45)	0.0017
Race			
Other	66 (28)	1 (ref)	
White	170 (72)	1.18 (0.41–3.40)	0.7603
UCSD-DI score			
No difficulty	109 (48)	1 (ref)	
Difficulty	116 (52)	2.32 (0.90–5.99)	0.0808
SHAQ score			
Normal (< 1)	138 (61)	1 (ref)	
Abnormal (1–3)	88 (39)	1.50 (0.58–3.87)	0.3995
Pulmonary function test**			
% FVC predicted	224	1.34 (1.03–1.75)	0.0276
% DLCO predicted	216	2.07 (1.43–3.01)	0.0001
6-MWT, m**	154	1.07 (1.01–1.13)	0.0292
Exercise O_2 desaturation (%)	152	5.39 (1.66–17.5)	0.005
Decline in O_2 saturation below 90% during exercise***			
No	119 (79)	1 (ref)	
Yes	32 (21)	9.53 (2.58–35.20)	0.0007
HRCT			
Normal HRCT	43 (26)	1 (ref)	
Fibrosis, ground glass, honeycombing on HRCT	121 (74)	2.74 (0.76–9.91)	0.1251
Echo/Doppler**			
Ejection fraction (%)	212	0.87 (0.54–1.40)	0.5661
Pericardial effusion			
Without effusion	163 (89)	1 (ref)	
With effusion	21 (11)	5.32 (1.78–15.84)	0.0027
Mean PAP, mmHg	61	0.58 (0.21–1.60)	0.292
Right heart catheterization**			
Pulmonary capillary wedge pressure, mmHg	61	1.12 (0.71–1.78)	0.6199
Cardiac output, l/min	59	1.17 (0.85–1.60)	0.3392
Pulmonary vascular resistance, dynes-sec/cm^5	58	0.48 (0.28–0.83)	0.0084
Hemoglobin, g/dl			
≥ 11.2	188 (85)	1 (ref)	
< 11.2	33 (15)	3.76 (1.33–10.63)	0.0126
Disease type			
Limited	154 (67)	1 (ref)	
Diffuse	75 (33)	1.64 (0.62–4.34)	0.3223

^ Characteristics were defined at baseline or within 6 mos prior to PH diagnosis. * HR were derived from separate models for each predictor while adjusting for age, sex, race (white vs nonwhite), and duration since first Raynaud symptoms; with an interaction term between time-dependent PH status and the predictor of interest. ** For continuous variables, HR correspond to a decrease in the predictor variable of the specified number of units: % FVC predicted (15%), % DLCO predicted (15%), 6-MWT (15 m), exercise oxygen saturation (15%), ejection fraction (6%), mean PAP (4 mmHg), pulmonary capillary wedge pressure (2 mmHg), cardiac output (0.5 l/min), pulmonary vascular resistance (40 dynes-sec/cm^5). *** Defined as participants with O_2 saturation below 90% during exercise and above 90% at rest; excludes those with missing 6-MWT and 1 participant with O_2 saturation below 90% at rest. 6-MWT: six-minute walk test; UCSD-DI: University of California at San Diego Dyspnea Index; SHAQ: Scleroderma Health Assessment Questionnaire; FVC: forced vital capacity; HRCT: high-resolution computed tomography; PAP: pulmonary arterial pressure; PH: pulmonary hypertension.

DISCUSSION

Survival. Our study is the largest prospective study, to our knowledge, of a unique group of patients with SSc at risk for PH and followed for a prolonged period. We previously reported that 35 at-risk patients developed PH as documented by RHC during followup[21] and that a low DLCO, high FVC/DLCO ratio, exercise-induced hypoxia, and entry echo estimated sPAP > 40 mmHg were strongly associated with future PH. In our at-risk cohort who did not develop PH, we found that male sex, low %DLCO, exercise oxygen desaturation, and pericardial effusion were each strongly associated with high mortality, thus expanding our previous findings.

Our unique at-risk population was selected based on abnormal entry PFT and/or Echo/Doppler results, composed

Table 3. HR of cardiopulmonary hospitalizations across demographic and clinical characteristics among the at-risk patients.

Characteristics^	N	HR (95% CI)*	p
Sex			
Male	29 (12)	1 (ref)	
Female	207 (88)	0.80 (0.08–7.74)	0.844
Race			
Other	66 (28)	1 (ref)	
White	170 (72)	0.67 (0.14–3.31)	0.6248
UCSD-DI score			
No difficulty	109 (48)	1 (ref)	
Difficulty	116 (52)	2.29 (0.55–9.47)	0.2537
SHAQ score			
Normal (< 1)	138 (61)	1 (ref)	
Abnormal (1–3)	88 (39)	3.62 (0.86–15.32)	0.0802
Pulmonary function test**			
% FVC predicted	224	1.30 (0.86–1.94)	0.2237
% DLCO predicted	216	2.14 (1.14–4.02)	0.1372
FVC change (% change per year)	127	1.55 (1.01–2.38)	0.039
DLCO change (% change per year)	116	1.24 (0.62–2.48)	0.6775
6-MWT distance, m**	154	1.08 (0.98–1.18)	0.0806
Exercise oxygen desaturation (%)***	152	1.23 (0.13–11.5)	0.5101
Decline in O_2 saturation below 90% during exercise***			
No	119 (79)	1 (ref)	
Yes	32 (21)	1.20 (0.10–14.54)	0.2565
HRCT			
Normal HRCT	43 (26)	1 (ref)	
Fibrosis, ground glass, honeycombing on HRCT	121 (74)	0.41 (0.09–1.92)	0.2565
Echo/Doppler**			
Ejection fraction (%)	212	1.21 (0.63–2.32)	0.8566
Pericardial effusion			
Without effusion	163 (89)	1 (ref)	
With effusion	21 (11)	3.19 (0.46–22.03)	0.2397
Hemoglobin, g/dl			
≥ 11.2	188 (85)	1 (ref)	
< 11.2	33 (15)	0.85 (0.09–7.71)	0.8847
Disease type			
Limited	154 (67)	1 (ref)	
Diffuse	75 (33)	0.88 (0.16–4.78)	0.883

^ Defined at baseline or within 6 months prior to PH diagnosis. * HR were derived from separate models for each predictor while adjusting for age, sex, race (white vs nonwhite), and duration since first Raynaud symptoms; with an interaction term between time-dependent PH status and the predictor of interest. ** For continuous variables, HR correspond to a decrease in the predictor variable of the specified number of units: % FVC predicted (15%), % DLCO predicted (15%), 6-MWT (15 m), exercise oxygen saturation (15%), FVC change (6% decrease per year), DLCO change (6% decrease per year), ejection fraction (6% change). *** Defined as participants with O_2 saturation below 90% during exercise and above 90% at rest; excludes those with missing 6-minute walk test and 1 participant with O_2 saturation below 90% at rest. 6-MWT: 6-minute walk test; UCSD-DI: University of California at San Diego Dyspnea Index; SHAQ: Scleroderma Health Assessment Questionnaire; FVC: forced vital capacity; HRCT: high-resolution computed tomography; PH: pulmonary hypertension.

of nearly two-thirds with limited cutaneous SSc; more than half had abnormal chest HRCT due to ILD. The overall survival did not vary significantly between those who developed PH after entering PHAROS and the at-risk group by any of the characteristics tested. However, our at-risk cohort appeared to have a worse overall survival rate (3-year, 91%; 5-year, 87%, and 8-year, 76%) compared to other similar SSc populations without PH. A Canadian cohort[22] reported overall 5-year survival rate of 90% and 10-year survival of 82%, and a larger Australian cohort[23] reported a better 10-year survival of 91% in their limited SSc population. A combined Australian, Canadian, and Spanish cohort of patients with SSc (more than half had limited SSc) experienced better overall survival of 96.7% at 5 years and 94.6% at 8 years[24,25]. This suggests that our population at risk for PH was "sicker," as represented by their abnormal entry criteria. Our study did not collect information on other organ complications such scleroderma renal crisis[23], which could have lowered survival in our population. African Americans have been reported to have more severe SSc

disease manifestations and higher mortality from PAH[26,27]. Our cohort was composed of 20% African Americans (17% who did not develop PH and nearly 23% in the PH group), higher than other similar SSc-PH registries. However, because of the low number of events in this group, we were inadequately powered to evaluate outcomes. In exploratory analyses, we found that the mortality risk in patients with borderline PH at baseline was similarly increased because of cardiopulmonary complications. Thus, we recommend close followup for clinical deterioration (including worsening symptoms, PFT, Echo/Doppler, and 6-MWT) and consideration for early RHC in any subject at risk for PH, especially those already diagnosed with borderline PH, because earlier intervention may lead to better outcomes.

Predictors of poor outcome. Our predictors of poor outcome were similar to those of other cohorts with SSc-PH or SSc-PAH, including significantly higher rates of mortality in males, low %DLCO or exercise oxygen desaturation, anemia (hemoglobin < 11.2 g/dl), higher UCSD-DI scores, and pericardial effusion. Our findings corroborate several others[5,25,28] that say SSc males had higher risk of mortality, for various reasons, including the fact that these patients often present with more advanced SSc complications. We found that males in our cohort indeed had more diffuse SSc, shorter disease duration from Raynaud onset, and lower exercise-induced oxygen desaturation during their 6-MWT. Despite our relatively small male cohort size, the high mortality risk among males compared to females remained quite robust in multivariable analyses.

In our at-risk cohort that did not develop PH, abnormal PFT served as a much better predictor of mortality compared to the extent or severity of lung disease seen on HRCT; in particular, low % predicted DLCO (< 50%) served as a more robust predictor of mortality than did low % predicted FVC. Although abnormal baseline PFT did not predict risk for cardiopulmonary hospitalization, a drop in % predicted FVC over time served as a modest predictor for cardiopulmonary hospitalization, likely due to worsening pulmonary disease. Our findings contrast with Mathai, *et al*[10], who reported ILD as a strong predictor of poor outcome, even after adjusting for PH severity. Launay, *et al*[11] found similar poor outcomes in their SSc patients with PH and ILD compared to SSc-PAH, and predictors of poor survival in their population included the presence of pericardial effusion and low % predicted DLCO.

Other predictors, including worse functional class with high dyspnea scores (e.g., UCSD-DI > 2) and presence of pericardial effusion, were independently associated with elevated risk of death. Although the presence of pericardial effusions at baseline were similar in both the PH and at-risk groups, 42% of the PH patients had pericardial effusion some time during the course of followup in comparison to 20% in the at-risk population. The etiology of pericardial effusions is not well understood, possibly immune-mediated and/or a reflection of more severe cardiac disease[29,30] in our population. Interestingly, pericardial effusions in the incident PH cohort (PH diagnosed before enrollment in PHAROS) did not predict poor outcome[31]. Our data suggest that this group deserves further study to improve our understanding of the cause and consequences of these effusions.

We recognize several limitations to our study. First, our sample size of patients who evolved to PH was small, which limited statistical power to find significant associations. Second, there were missing data at baseline, although every effort was made to collect the comprehensive data. Third, RHC procedures were not standardized across evaluating physicians and not all patients had RHC or chest HRCT at the time of study enrollment to be sure that PH or ILD were not present. Another limitation is that we did not include an important biomarker for PH, the N-terminal pro-brain natriuretic peptide, because there were insufficient data in the at-risk group for analysis; this biomarker may serve as a useful predictor for PH as well as a prognostic indicator. Lastly, we did not ascertain the vital status of censored patients who dropped out of the study, which might have contributed to selection bias. This may have been present if the HR of death in this group were higher than those who remained in the study. Despite these limitations, we nevertheless observed several robust predictors for mortality in our large multicentered cohort of a unique group of patients at risk for PH.

Risk factors for worse outcome in those patients with SSc at risk for PH were similar to others with confirmed SSc-PH and SSc-PAH. Male sex, %DLCO < 50%, exercise oxygen desaturation, and the presence of pericardial effusions in those at risk for PH were independently associated with higher mortality. Patients with these risk factors should undergo RHC and receive appropriate intervention if PH is confirmed.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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