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Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS): Baseline Characteristics and Description of Study Population

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Abstract

Objective—Pulmonary arterial hypertension (PAH) increases mortality in systemic sclerosis (SSc). The multicenter PHAROS (Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma) registry prospectively follows SSc subjects at high-risk for, or with incident pulmonary hypertension (PH). Herein, we describe registry design and baseline characteristics of subjects enrolled during the first 18 months since study inception.

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Methods—High-risk subjects are enrolled and classified as Pre-PAH if they have 1) carbon monoxide diffusing capacity (DLCO) < 55% predicted, 2) % predicted forced vital capacity/DLCO ratio ≥ 1.6 , or 3) an estimated right ventricular systolic pressure > 35 mm Hg on echocardiography. Subjects with right heart catheterization confirmed incident PH (mean pulmonary artery pressure ≥ 25 mm Hg within previous 6 months) are subclassified into PAH, pulmonary venous hypertension secondary to left-sided heart disease (PVH), and PH due to interstitial lung disease (PH-ILD). Baseline and biannual demographic, clinical, and laboratory data as well as patient-reported health questionnaires are collected.

Results—There are 237 subjects enrolled in PHAROS. The majority are Caucasian (73%) and women (87%). There are 166 Pre-PAH and 71 Definite PH subjects (49 PAH, 7 PVH, and 15 PH-ILD).

Conclusion—PHAROS is the largest U.S. and Canadian cohort of SSc subjects at high-risk for or with incident PAH. PAH-specific therapies are approved for 49/71 subjects with RHC-confirmed-PAH. Analyses of PHAROS registry data will permit identification of risk factors for the development of PAH amongst SSc patients at high-risk for PAH and enhance our understanding of the course of SSc-PAH.

Key indexing terms

Systemic sclerosis; Pulmonary hypertension; Registry; Pulmonary arterial hypertension

INTRODUCTION

Systemic sclerosis (scleroderma, SSc) is a multisystem connective tissue disease characterized by immune disturbance, abnormal vasculature, organ fibrosis and dysfunction. Pulmonary complications of SSc, including interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH), are well established as the leading cause of SSc-related deaths(1). The prevalence of right heart catheterization (RHC) confirmed PAH in SSc is estimated to be between 7.5 and 12%(2, 3). Prior to the availability of PAH-specific therapies, the five-year survival rate was 10% for SSc with PAH compared to 80% in SSc without PAH(4).

As more effective PAH-specific therapies have become available, it is increasingly important to accurately predict which SSc patients are most likely to develop SSc-PAH. The vascular changes in SSc likely occur throughout the disease course and identifying those with the earliest clinical signs of pulmonary vascular disease should lead to an earlier diagnosis of PAH. Earlier detection should promote earlier initiation of PAH-specific therapies to improve cardiac hemodynamics, pulmonary function, quality of life measures, and possibly survival.

The most recent clinical classification of pulmonary hypertension (PH) separates patients into five specific groups(5, 6). Patients with SSc are at risk for the development of PH Groups 1–3 (Table 1). This includes the primary pulmonary arterial vasculopathy of pulmonary arterial hypertension (PAH, Group 1), pulmonary venous hypertension associated with left-sided heart disease, (PVH, Group 2) or pulmonary hypertension secondary to chronic lung disease such as ILD (PH, Group 3). It is important to highlight that these classification distinctions require a RHC and that PAH-specific therapies are approved only for patients with Group 1 disease.

The Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) study was established in 2006 to prospectively follow SSc subjects at high-risk for developing or with incident SSc-associated PAH (SSc-PAH) within 6 months of RHC-

based diagnosis. The goals of PHAROS are to: 1) determine the rate of evolution to PAH in a high-risk SSc population, 2) identify which risk factors are most predictive for development of SSc-PAH, 3) characterize the types and features of PH that occur in SSc, and 4) determine the effectiveness of PAH-specific therapies. Studies utilizing PHAROS registry data will enable the development of rational treatment strategies for SSc-PAH. In this study, we describe the design of the PHAROS registry and report baseline characteristics including the PH classification of PHAROS registry subjects for the first 18 months since study inception.

PATIENTS AND METHODS

PHAROS is a Health Insurance Portability and Accountability Act (HIPAA)-compliant, multicenter study conducted at 18 US and Canadian sites. Each participating center's Institutional Review Board approved the study protocol. Although funded via commercial support, the sponsoring companies had no role in study design, data analysis or manuscript preparation. The PHAROS registry includes two subgroups of subjects: 1. those at increased risk for developing SSc-PAH who are classified as "Pre-PAH", and 2. those with incident PH enrolled within 6 months of RHC-confirmed diagnosis according to the Dana Point criteria for PH (mean pulmonary artery pressure/mPAP $\geq$ 25 mm Hg at rest)(5). We defined a classification listing of "Pre-PAH" based on the presence of any one of these three criteria on study entry:

1. Diffusing capacity for carbon monoxide (DLCO) $<$ 55% predicted without severe ILD (as defined by forced vital capacity (FVC) $<$ 65% predicted and/or a thoracic high resolution computed tomography (HRCT) scan that showed moderate to severe ILD according to the local radiologist)(7) or
2. FVC %predicted / DLCO %predicted ratio $\geq$ 1.6 or
3. Estimated right ventricular systolic pressure (RVSP) $>$ 35 mmHg on Doppler echocardiography.

Inclusion criteria were age $>$ 18 years, and fulfillment of American College of Rheumatology criteria for SSc(8) or the LeRoy definitions of limited cutaneous or diffuse cutaneous SSc(9). Patients with PH were excluded if they were receiving PAH-specific treatment at the time of the initial RHC, had a left ventricular ejection fraction $<$ 50% on echocardiography or signs or symptoms of systolic heart failure at the baseline clinical examination. An additional exclusion criterion included PH attributed to other diseases included in the current PH classification system (e.g. congenital systemic-to-pulmonary shunt, HIV infection, cardiopulmonary disease attributed to drugs and toxins, sarcoidosis, histiocytosis X, lymphangioleiomyomatosis, etc.)(5).

The investigator entering data for each subject confirmed the PH group according to the 2009 Dana Point classification PH criteria prior to this analysis(5).

Group 1: Pulmonary arterial hypertension (PAH): on RHC a mean pulmonary artery pressure (mPAP) $\geq$ 25 mm Hg at rest with a pulmonary capillary wedge pressure (PCWP) $\leq$ 15 mm Hg without significant ILD as defined by a FVC $\geq$ 65% predicted, and mild, if any, ILD by HRCT according to the local radiologist(7).

Group 2: Pulmonary venous hypertension (PVH): an RHC mPAP $\geq$ 25 mm Hg at rest with a PCWP $>$ 15 mm Hg.

Group 3: Pulmonary hypertension secondary to chronic lung disease (PVH): these patients had mPAP $\geq$ 25 mm Hg with a PCWP $\leq$ 15 mm Hg but also had significant ILD with an FVC $<$ 65% predicted and/or a thoracic HRCT scan that showed moderate

to severe ILD with or without honeycombing. Fibrosis was graded as normal (no fibrosis), mild, moderate or severe fibrosis by the local radiologist interpreting the study(7).

Other information collected included baseline demographics: age at diagnosis of SSc and PH, clinical history, SSc subtype, disease duration, medication, and smoking history. Subjects completed questionnaires including the Scleroderma HAQ(10), the University of California at San Diego Dyspnea Index(11), and the SF-36(12) that were administered by study personnel either in person, by phone, or by mailing or faxing forms to participating subjects every 6 months. Physical examination of SSc and PH features were recorded. Each participating center performed baseline laboratory testing including autoantibody profiles, brain natriuretic peptide (BNP) or N-terminal pro-BNP. Autoantibody profiles consisted of anticentromere, anti-topoisomerase, an isolated anti-nucleolar pattern on ANA (without other SSc specific antibodies), anti-U1-RNP, anti-RNA polymerase III, other or none. A subject without an SSc-specific antibody who had multiple ANA patterns was characterized as “other”.

High-resolution thoracic CT scans, RHC, pulmonary function tests (PFTs), Doppler echocardiography, and 6-minute walk tests (6MWD) were performed as clinically indicated as determined by the clinician investigator. As part of the standard of care, baseline studies were repeated and recorded yearly along with the medical history, hospitalizations, medication information and outcome events. Outcome events were defined as the development of PH as defined above, hospitalization for PH, or the need for PAH-specific therapy. PAH-specific therapy was initiated at the discretion of the treating clinicians.

All data were collected using paper case report forms and manually entered into a central computerized database by site-specific research coordinators. Vital status was reported for study subjects by each participating site prior to analyses.

Continuous variables were summarized by mean $\pm$ standard deviation and compared using t-tests (or non-parametric equivalent when appropriate). Categorical variables were compared using the chi-squared statistic (or Fisher's exact test when appropriate). For all analyses, a two-sided p-value < 0.05 was considered statistically significant. For analyses comparing the three PH groups, subjects in groups 2 and 3 were collapsed into one group due to the small number of subjects in these groups. SAS version 9.2 (Cary, NC) was used for all statistical analyses.

RESULTS

Two hundred thirty-seven subjects met echo or PFT PHAROS criteria and were enrolled in the registry. Of these, 87 underwent RHC at the discretion of the clinical investigator. Seventy-one had Definite PH based on the Dana Point criteria. Sixteen had a normal mPAP and were classified as Pre-PAH.

Pre-PAH cohort

There were 166 subjects who were classified as Pre-PAH at entry. Table 2 summarizes the clinical features of these patients. There were no significant differences in demographics or autoantibodies between the Pre-PAH and Definite PH subjects. The mean age at enrollment into PHAROS was 57 years (range 35 to 79), 87% female, 75% Caucasian, 16% African American, 6% Hispanic and 2% Asian. The mean time from first non-Raynaud's symptom to study entry was 9 years while the mean time from the appearance of Raynaud's phenomenon to study entry was 13 years. Fifty-three percent had SSc-specific autoantibodies (67/127), of these 42% (28/67) had anticentromere antibodies, 32% (23/67)

had anti-topoisomerase antibodies, and 25% (17/67) had an isolated nucleolar antibody pattern without other specificity. The remainder either had a mixed ANA, negative ANA or no autoantibody information available. Pre-PAH patients with different SSc-specific autoantibodies had similar pulmonary physiologic features based on PFTs (Table 3). The mean New York Heart Association (NYHA) classification for those with Pre-PAH was 1.3 (SD 1.0) although 39 were not classified due to lack of dyspnea. Figure 2 depicts the entry criteria of the Pre-PAH cohort.

At baseline, 16 subjects (10%) of the Pre-PAH group had symptoms, an elevated RVSP (mean $\pm$ SD 38 $\pm$ 10, range 19–62), or PFT abnormalities that led individual investigators to do a RHC that revealed a normal mPAP. Four of these had an estimated RVSP on echocardiogram > 40 mm Hg, the mean $\pm$ SD DLCO% predicted in this group was markedly reduced (38% $\pm$ 16) and the mean PCWP was 8 mm Hg. Ten RHC-negative subjects had undergone a thoracic HRCT that revealed no (n=5), mild (n=3), moderate (n=1), or severe (n=1) fibrosis.

Definite PH cohort

There were 71 subjects who were entered as “Definite PH” as confirmed by RHC. These subjects were classified according to 2009 Dana Point criteria for PH: 49 (69%) met criteria for Group 1 PAH with a resting mPAP ≥ 25 mm Hg and a PCWP ≤ 15 mm Hg; 7 (10%) had a mPAP ≥ 25 mm Hg and a PCWP > 15 mm Hg fulfilling Group 2 PH criteria (PVH); 15 (21%) patients had mPAP ≥ 25 mm Hg and significant ILD (as defined above) and were classified as Group 3 (PH-ILD). Table 4 describes the demographics of this cohort by PH group.

Cardiopulmonary features are presented in Table 4. The mPAP on RHC was remarkably similar in all three groups: 36, 35, and 34 mm Hg respectively. The mean RVSP on echocardiogram was also similar in the three groups: 57, 45, 52 mm Hg respectively. As expected, the PFT parameters revealed no significant restriction in Group 1 (mean FVC 86%) whereas both the PVH and PH-ILD patients had significant reductions in FVC (62% and 56%, $p < 0.0001$). The DLCO was significantly lower in Groups 2 and 3 compared to 1 ($p = 0.04$), while the FVC/DLCO ratio was higher, though not significantly ($p = 0.29$). Group 1 subjects had a trend of more dyspnea, shorter 6-MWD, and higher NYHA functional class compared to Group 2 and 3 subjects combined (not statistically significant).

Group 1 PAH subjects were most likely to have a positive anticentromere antibody; 45% Group 1, 25% Group 2, 10% Group 3, $p = 0.053$. Although an isolated anti-nucleolar antibody is not a common antibody in SSc (1), it was prevalent in relatively high numbers in all three PH groups; 40% with PAH, 40% with PVH and 30% with PH-ILD ($p = 0.75$). Twenty-one subjects were receiving endothelin I receptor antagonists and 24 subjects were receiving phosphodiesterase inhibitors.

DISCUSSION

In this study, we describe the PHAROS registry study design as well as the baseline characteristics and initial clinical insights using data collected during the first 18 months since study inception. Pulmonary hypertension is a leading cause of death in SSc and identifying the factors that predict the development of PAH amongst SSc patients at high-risk for PAH as well as the response to various PAH-specific therapies are some of the goals of the PHAROS registry.

PH is defined as a resting mPAP ≥ 25 mm Hg on resting RHC. Several disease entities can cause elevations in pulmonary artery pressures in SSc, but the most common causes are

intrinsic pulmonary arterial vasculopathy (Group 1, PAH), left-sided heart disease (Group 2, PVH) and ILD (Group 3, PH-ILD) (Table 1). We found that one-third (22/71) of subjects thought to be at high-risk for PAH according to our three criteria were found to have PVH or PH-ILD. Thus, it is imperative that clinicians treating patients with SSc realize that a right heart catheterization is necessary to accurately establish the diagnosis of PAH. Further, PAH-specific therapies are only approved for patients with Group 1 disease (PAH). The use of PAH-specific therapies in SSc patients with PVH and PH-ILD has not been studied and should only be done with great caution because increased vasodilatation in the pulmonary vasculature of these patients may increase ventilation-perfusion mismatch and worsen symptoms.

There were significant differences between subjects with Pre-PAH and Definite RHC-confirmed incident PH. Patients with RHC-confirmed incident PH had higher mean estimated RVSP on echocardiogram, mean pulmonary vascular resistance (PVR), and BORG Dyspnea Index scores, and lower NYHA functional class. Six-Minute Walk Testing did not significantly vary between those with Pre- and Definite PH which may be due to insufficient power to detect significant differences secondary to small numbers of subjects.

Of the 127/166 Pre-PAH subjects for whom autoantibody data were available, the majority had positive SSc-specific antibodies (anticentromere, anti-topoisomerase and nucleolar ANA). It has been recently shown that dcSSc patients with a U3 RNP, a specific nucleolar antibody, have an increased prevalence of PAH(13). We found a high prevalence of anti-nucleolar antibodies especially among African American subjects with PAH. This is particularly important to highlight because many commercial laboratories are no longer performing the immunofluorescent ANA testing, and thus the ANA pattern is not reported. We emphasize that ANA pattern determination is very useful in the clinical care of SSc patients, and all providers involved in the care of patients with SSc should ensure that ANA patterns are part of the autoantibody assessments for these patients.

Amongst patients with Definite PH, the majority 69% (49) had PAH (Group 1 disease). These subjects tended to be Caucasian with lcSSc without a positive anti-topoisomerase antibody compared to subjects with PVH and PH-ILD. As expected, we found a significantly lower FVC and DLCO in those with PVH and PH-ILD compared to those with PAH. The DLCO was very low in all groups. Only 14% of those with PH had a DLCO that was > 55% predicted. Interestingly, the mean DLCO was lowest in Groups 2 and 3 showing that a low DLCO itself does not necessarily predict PAH compared to PVH and PH-ILD. However, the mean FVC% predicted was significantly lower in the non-PAH groups, and importantly the mean FVC%/DLCO% ratio was highest in those with PAH. Eighty-two percent of those with PAH, 70% with PVH and only 25% with PH-ILD had a FVC/DLCO ratio >1.6. Thus, the high ratio may be a useful parameter to use as part of the determination of whether an SSc-PH patient has PAH compared to other causes of PH.

The mPAP in the three Definite PH groups was lower compared to other clinical trials that have included SSc subjects, and we believe this likely reflects ascertainment bias. PHAROS investigators are rheumatologists with dedicated scleroderma programs who are specifically trying to identify high-risk and incident cases of PAH. We are hopeful that the longitudinal study of the PHAROS cohort will show whether the earlier detection of SSc-PAH will prompt earlier initiation of PAH-specific therapies and lead to improved survival.

Currently available PAH-specific medications target one of three pathophysiological pathways(14). The dual endothelin receptor antagonist bosentan appears to improve exercise tolerance and hemodynamics in SSc-PAH in the short-term although it is unclear whether treatment with bosentan imparts long-term functional and survival benefits(15–19). The

prostacyclin analogues epoprostenol and treprostinil appear to improve exercise tolerance and hemodynamics in SSc-PAH(20–22). And, sildenafil and tadalafil, phosphodiesterase type-5 inhibitors that improve the production of nitric oxide, may be useful drugs in SSc-PAH as well(23, 24).

Prior to the availability of the newer PAH-specific therapies few patients with SSc-PAH lived longer than 5 years from the time of diagnosis of PAH(25). With the arrival of new treatments, survival may be improving although patients with SSc-PAH continue to fare worse than patients with idiopathic PAH. Additionally, SSc patients with PH-ILD have a worse prognosis than the SSc-PAH patients with a 3-year survival 39% compared with 64% ($p < 0.01$)(26). There are several reasons why SSc-PAH patients may have increased mortality rates compared with other forms of PAH including concomitant ILD, pulmonary veno-occlusive disease(27), myocardial disease (28) and diastolic dysfunction or a combination of these(26, 29). A unique phenotype consisting of both ILD and PAH that imparts an increased burden on a straining right ventricle may account for worse disease. Chang and colleagues reported 18% of 618 SSc patients had evidence for combined PAH and PH-ILD(30). Overbeek and colleagues found evidence of small vessel intimal fibrosis in both arterioles (8/8) and venules (7/8) in 8 SSc-PAH subjects examined, but in only 3/11 subjects with idiopathic PAH(27). Additionally, left ventricular diastolic dysfunction is common in SSc and causes PVH and increased pulmonary arterial pressures. Consequently, PH in SSc is likely multifactorial and the interaction of several disease entities may contribute to decreased survival. We anticipate that the PHAROS registry will allow for the exploration of outcomes of subjects in the Pre- and Definite PH groups and determine which factors influence survival.

Because the PH in an individual SSc patient may be multi-factorial and include varying degrees of PAH, PVH and PH-ILD, longitudinal analyses of PHAROS registry data collected from patients with multifactorial PH will be important to determine whether the institution of PAH-specific therapies is beneficial or harmful.

The PHAROS registry was designed to capture data on SSc subjects thought to be at increased risk for PAH as defined by three inclusion criteria or with newly established PH identified by RHC. There are a number of limitations to the conclusions that can be drawn from this study population. First, we have no means of assessing what percentage of patients with SSc are seen at PHAROS participating centers, and what percentage of eligible SSc patients seen at each center are actually enrolled in PHAROS. Second, as mentioned, there were no standardized protocols for laboratory, echocardiographic, PFT or RHC testing. All tests and clinical assessments were performed at the discretion of the individual clinician investigator according to practices at each participating center, thus there is the potential for bias due to unequal duration in follow-up. However, one of the strengths of the PHAROS registry is that it provides for the longitudinal collection of a large amount of data on a large, multicenter group of SSc subjects by rheumatologists specializing in SSc rather than based in PH centers.

We assert that subjects in PHAROS, both Pre-PAH and those newly diagnosed with Definite PH, are going to be an important population to follow over time. Monitoring the time course between Pre-PAH and Definite PH in SSc will assist in the design of future prevention trials that can assess the ability of therapies to positively impact on the natural history of the disease. Determining risk factors for SSc-PAH will enhance the development of practical screening programs to monitor patients at highest risk most closely and avoid unnecessary invasive testing for low-risk patients. Ultimately, we hope that data from the PHAROS registry will also lead to better care for patients and contribute to interventions that reduce SSc-PAH-associated morbidity and mortality.

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Figure 1.

Flow-chart of PHAROS patients. Of the 237 PHAROS patients enrolled since study inception, 166 are classified as pre-pulmonary artery hypertension (Pre-PAH) and 71 have right-heart catheterization (RHC) confirmed incident pulmonary hypertension (PH). Sixteen patients underwent RHC for suspected PH and mean pulmonary artery pressure was normal (<25 mm Hg). Of the 71 patients with Definite PH, 49, 7 and 15 had Groups 1–3 PH respectively(32). Diastolic dysfunction=DD and interstitial lung disease=ILD.

Figure 2.
Pie charts depicting the breakdown of patients meeting PHAROS eligibility criteria.

Table 1

Types of Pulmonary Hypertension (PH) Affecting Patients with Systemic Sclerosis

Group	Pulmonary Hypertension	Abbreviation
I	Pulmonary Arterial Hypertension Associated with Connective Tissue Diseases	PAH
II	Pulmonary Venous Hypertension Associated with Left Heart Disease (e.g. Diastolic Dysfunction)	PVH
III	Pulmonary Hypertension Associated with Respiratory Disease (e.g. pulmonary fibrosis)	PH-ILD

Adapted from the Dana Point 2009 PH Criteria(5).

Table 2

Demographic, clinical and laboratory features of patients with Pre-PAH and Definite PH

Parameter	Pre-PAH (N=166)	Definite PH (N=71)
Demographic/Clinical		
Female, N (%)	138 (87)	55 (87)
Ethnicity, N (%)		
Caucasian	116 (75)	42 (67)
African-American	25 (16)	14 (22)
Hispanic	9 (6)	2 (3)
Asian	3 (2)	4 (6)
Age at SSc diagnosis (y), mean (SD)	46 (13)	45 (14)
Age at PHAROS enrollment (y), mean (SD) (range 35–79)	57 (11)	57 (10)
Time from first non-Raynaud's until study entry (y), mean (SD)	9 (8)	9 (7)
Time from first Raynaud's until study entry (y), mean (SD)	13 (10)	13 (10)
Limited SSc, N (%)	58 (63)	20 (57)
Autoantibodies, N (%)	N=127	N=50
Anticentromere	28 (22)	19 (38)
Anti-topoisomerase	23 (17)	8 (16)
Isolated nucleolar ANA	17 (13)	19 (38)
BNP (pg/ml), mean (SD)	35 (15)	94 (70)
Entry criteria		
DLCO < 55% predicted	91 (55)	58 (79)
FVC/DLCO > 1.6	88 (53)	51 (70)
Estimated RVSP on echo > 35mm Hg	50 (30)	47 (64)
Cardiopulmonary		
Echo RVSP (mmHg), mean (SD) *	38 (10)	57 (17)
Right Heart Catheterization (normal ranges(31)), mean (SD)	N=16	
mPAP (<25 mm Hg) *	20 (4)	35 (11)
PVR (20–120 dyn•s/cm ⁵) *	180 (94)	366 (230)
CO (4–8 L/min)	5.4 (1.3)	5.3 (1.5)
PCWP(6–12 mm Hg)	8.2 (3.3)	11.8 (4.1)
BORG Dyspnea Index, mean (SD) *	1.9 (1.8)	3.2 (2.3)
6MWD (m), mean (SD)	393 (134)	337 (135)
NYHA functional class, N (%) *		
Unclassified (no dyspnea)	36 (23)	5 (7)
1	51 (33)	10 (15)
2	42 (27)	29 (44)
3	25 (16)	17 (25)
4	1 (1)	6 (9)

* Denotes a statistically significant difference ($P<0.05$). Autoantibody percentages calculated using the number of patients with an autoantibody present as the denominator ($n=112$ for Pre-PAH, and $n=50$ for Definite PH). BNP=brain natriuretic peptide, FVC=% predicted forced vital capacity, DLCO=% predicted diffusing lung capacity for carbon monoxide, RVSP= estimated right ventricular pressure on 2-dimensional Doppler echocardiography. Right-heart catheterization (RHC) parameters with normal values listed: mPAP=mean systolic pulmonary artery pressure, PVR=pulmonary vascular resistance, CO=cardiac output, PCWP=pulmonary capillary wedge pressure. Functional class parameters: NYHA=New York Heart Association, 6MWD=6-minute walk distance. The Pre-PAH cohort includes 16 patients who underwent a RHC that revealed a normal mPAP.

Table 3

Scleroderma specific antibodies and pulmonary function and echocardiography parameters in patients with Pre-PAH.

Mean (SD)	ACA (n=28)	Scl-70 (n=23)	Nucleolar (n=17)
FVC (% predicted)	95 (16)	79 (15)	79 (16)
DLCO (% predicted)	56 (22)	46 (16)	51 (22)
FVC/DLCO	1.78 (0.46)	1.85 (0.52)	1.74 (0.60)
RVSP (mm Hg)	37 (7)	41 (10)	39 (9)

Autoantibody data was available for 127/166 Pre-PAH patients. Pre-PAH patients were divided according to the three most commonly present autoantibodies to determine the association between scleroderma specific antibodies and clinical PAH markers. The other 59/166 patients did not have detectable autoantibodies or had an anti-U1-RNP, anti-RNA polymerase III, other or no autoantibody information available. A patient without an SSc-specific antibody who had multiple ANA patterns was characterized as “other”. There were no statistically significant differences between groups. ACA=anticentromere, Scl-70=anti-topoisomerase antibodies.

Table 4

Demographic, clinical and laboratory features of patients with Definite PH

	PH group		
	1-PAH (N=49)	2-PVH (N=7)	3-PH/ILD (N=15)
Female n (%)	40 (91)	5 (83)	12 (80)
Age at SSc diagnosis (y), mean (SD)	44 (18)	40 (21)	44 (10)
Age at PHAROS enrollment (y), mean (SD)	59 (12)	54 (13)	54 (8)
Race n (% Caucasian)*	31 (76)	1 (20)	8 (57)
Limited SSc n (%)*	33 (72)	3 (50)	5 (36)
Time from first non-Raynaud's, Mean, y (SD)	10 (6)	10 (7)	9 (7)
Time from first Raynaud's, Mean, y (SD)	13 (9)	15 (12)	11 (9)
RHC, mean (SD)			
• mPAP (< 25 mmHg)	36 (12)	35 (8)	34 (9)
• PCWP (5–15 mmHg)*	11 (3)	20 (4)	11 (4)
• CO (3–4 L/min)	5.2 (1.5)	6.6 (0.6)	5.4 (1.1)
• PVR (150-250 dyn•s/cm ⁵)	400 (240)	297 (255)	287 (115)
Autoantibodies, n (%)			
• ACA	15 (45)	1 (25)	1 (10)
• Scl-70*	1 (3)	0	6 (50)
• Nucleolar	12 (40)	2 (40)	3 (30)
PFT, mean % predicted (SD)			
• FVC*	86 (28)	62 (26)	56 (12)
• DLCO*	43 (18)	34 (7)	30 (10)
• FVC/DLCO	2.30 (1.1)	2.06 (0.6)	2.08 (0.6)
Echo			
• RVSP (mmHg), mean (SD)	57 (21)	45 (15)	52 (16)
6MWD (m), mean (SD)	337 (133)	420 (116)	292 (132)
NYHA functional class, N (%) Unclassified (no dyspnea)	2 (4)	2 (33)	1 (8)
1	9 (19)	1 (17)	0
2	20 (42)	2 (33)	7 (54)
3	13 (27)	1 (17)	3 (23)
4	4 (8)	0	2 (15)

* Denotes a statistically significant difference ($P < 0.05$). SSc disease duration=time from onset of first non-Raynaud's symptom to the date of first visit. FVC=% predicted forced vital capacity, DLCO=% predicted diffusing lung capacity for carbon monoxide, RVSP= estimated right ventricular pressure on 2-dimensional Doppler echocardiography. Right-heart catheterization parameters (n=16) with normal values listed: mPAP=mean pulmonary artery pressure, PVR=pulmonary vascular resistance, CO=cardiac output, PCWP=pulmonary capillary wedge pressure. Functional class parameters: NYHA=New York Heart Association, 6MWD=6-minute walk distance.