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Prevalence, Treatment, and Outcomes of Coexistent Pulmonary Hypertension and Interstitial Lung Disease in Systemic Sclerosis

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Objective. Systemic sclerosis (SSc) is associated with interstitial lung disease (ILD) and pulmonary hypertension (PH). This study was undertaken to determine the prevalence, characteristics, treatment, and outcomes of PH in a cohort of patients with SSc-associated ILD.

Methods. Patients with SSc-associated ILD on high-resolution computed tomography (HRCT) were included in a prospective observational cohort. Patients were screened for PH based on a standardized screening algorithm and underwent right-sided heart catheterization (RHC) if indicated. PH classification was based on hemodynamic findings and the extent of ILD on HRCT. Summary statistics and survival using the Kaplan-Meier method were calculated.

Results. Of the 93 patients with SSc-associated ILD included in the study, 76% were women and 65.6% had diffuse cutaneous SSc. The mean age was 54.9 years, and the mean SSc disease duration was 8 years. Twenty-nine patients (31.2%) had RHC-proven PH; of those 29 patients, 24.1% had PAH, 55.2% had World Health Organization (WHO) Group III PH, 34.5% had WHO Group III PH with pulmonary vascular resistance >3.0 Wood units, 48.3% had a PH diagnosis within 7 years of SSc onset, 82.8% received therapy for ILD, and 82.8% received therapy for PAH. The survival rate 3 years after SSc-associated ILD diagnosis for all patients was 97%. The survival rate 3 years after PH diagnosis for those with SSc-associated ILD and PH was 91%.

Conclusion. In a large cohort of patients with SSc-associated ILD, a significant proportion of patients had coexisting PH, which often occurs early after SSc diagnosis. Most patients were treated with ILD and PAH therapies, and survival was good. Patients with SSc-associated ILD should be evaluated for coexisting PH.

INTRODUCTION

Systemic sclerosis (SSc) can be a devastating multiorgan system autoimmune disease. It can affect the skin, peripheral vasculature, muscles, joints, tendons, kidneys, gastrointestinal tract, lungs, and heart through fibrosis, vascular damage, and immune dysregulation. Interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are the leading causes of mortality in SSc (1,2).

Up to 90% of patients with SSc have ILD on high-resolution computed tomography (HRCT), and ~40% of patients with SSc have clinically significant ILD (3,4). Pulmonary hypertension (PH) is also common in SSc, and patients with SSc can have various types of PH. Three common types of PH in patients with SSc include World Health Organization (WHO) Group I PH (PAH), WHO Group II PH (PH due to left-sided heart disease), and WHO Group III PH (PH due to ILD). However, in observational cohorts of SSc, which

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are enriched for patients at risk of or with early PH, the majority of patients are diagnosed as having PAH and a smaller proportion are classified as having WHO Group II PH or WHO Group III PH (5,6). For example, in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) study, ~69% of the patients with PH were classified as having PAH, 10% of the patients were classified as having WHO Group II PH, and 21% of the patients were classified as having WHO Group III PH (5). In the DETECT study, which recruited patients at high risk of PH, ~60% of the patients with PH were classified as having PAH, 21% were classified as having WHO Group II PH, and 19% were classified as having WHO Group III PH (6).

Although previous studies have analyzed patients with concomitant SSc-associated ILD and PH, to our knowledge there is a lack of in-depth review of the clinical characteristics and management of PH in patients with established SSc-associated ILD. This is an essential clinical question, since worsening dyspnea in a patient with underlying ILD may represent progressive ILD, new-onset PH, or a combination of both. In addition, many ongoing clinical trials are specifically recruiting patients with SSc-associated ILD, particularly for the evaluation of new and existing pharmacologic therapies for the treatment of ILD. Hence, it is imperative to recognize the prevalence of PH with concomitant ILD in SSc and its impact on the clinical course, outcome measures, such as dyspnea and quality of life, and survival. This need prompted us to investigate the prevalence of PH in a well-characterized cohort of patients with SSc-associated ILD, and to explore the clinical characteristics, pharmacologic therapies, and outcomes of patients with PH in that cohort.

PATIENTS AND METHODS

Study design and patients. Patients evaluated in this study were participants in a prospective observational cohort study of SSc-associated ILD (Figure 1). Patients were recruited from the University of Michigan Scleroderma and Connective Tissue Disease (CTD)–ILD clinics starting January 8, 2014, and data were extracted on October 1, 2016. Patients who were at least 18 years of age, met the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc (7), had ILD on HRCT, and could provide informed consent were included in the study, which was approved by the University of Michigan Institutional Review Board. All reported experiments performed by the authors have been previously published and complied with all applicable ethical standards (including the Declaration of Helsinki and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

All patients in this study had a baseline HRCT confirming the presence of ILD, defined as the presence of bilateral, subpleural, lower lobe predominant distribution of either 1) reticular and/or ground-glass opacity with or without traction bronchiectasis or 2) honeycombing with the absence of a pattern that is predominantly nodular, cystic, peribronchovascular/central or upper lung predominant, mosaic attenuation, or consolidation. Pulmonary function tests (PFTs) were performed at baseline for each patient. Patients with a forced expiratory volume in 1 second/forced vital capacity (FVC) ratio of <0.7 were excluded to rule out patients with concomitant obstructive pulmonary disease. Demographic characteristics and additional clinical variables were obtained for each patient.

All patients in the University of Michigan Scleroderma and CTD-ILD clinics undergo screening for PH based on the 2013 recommendations for screening and detection of CTD-associated PAH by Khanna et al, which also include the DETECT algorithm (8). Although the DETECT algorithm has been validated in patients with a disease duration of >3 years and diffusing capacity for carbon monoxide (DL_{CO}) <60%, we use it for all SSc patients with uncorrected DL_{CO} ≤80% (6). We performed a chart review for all patients in this SSc-associated ILD cohort to determine which patients fulfilled criteria indicating possible PH based on the 2013 recommendations and had undergone right-sided heart catheterization (RHC) during their SSc disease course. Within this SSc-associated ILD cohort, the 2013 recommendations were prospectively applied to 81 patients during routine clinical care (Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40862/abstract) and retrospectively applied to 12 patients who had undergone RHC prior to 2013 (Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40862/abstract) (8).

A total of 53 patients in the cohort had undergone RHC. Patients who had PH on RHC, which was defined as a mean pulmonary artery pressure (PAP) of ≥25 mm Hg, are referred to herein as patients with "SSc-associated ILD and PH," and patients who did not meet the 2013 recommendations or had a mean PAP of <25 mm Hg on RHC are referred to herein as patients with "SSc-associated ILD without PH." For those with SSc-associated ILD and PH, the HRCT scan was reviewed by a chest radiologist (DV) to determine ILD severity. ILD severity was based on Goh's criteria, in which <20% extent of ILD on HRCT was considered minimal and >20% extent of ILD on HRCT was considered moderate-to-severe (9,10). The HRCT scans chosen for review were the scans obtained closest to the time of diagnosis of RHC. (One patient's HRCT images were not available for review, so a CT angiogram was reviewed, and another patient did not have any images available at our institution for review, so ILD type and severity were based on an external radiologist's initial report.)

Classification of PH. Patients classified as having WHO Group I PH/PAH had a mean PAP of ≥25 mm Hg, pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg, and <20% extent of ILD on HRCT (10–12). Patients classified as having WHO Group

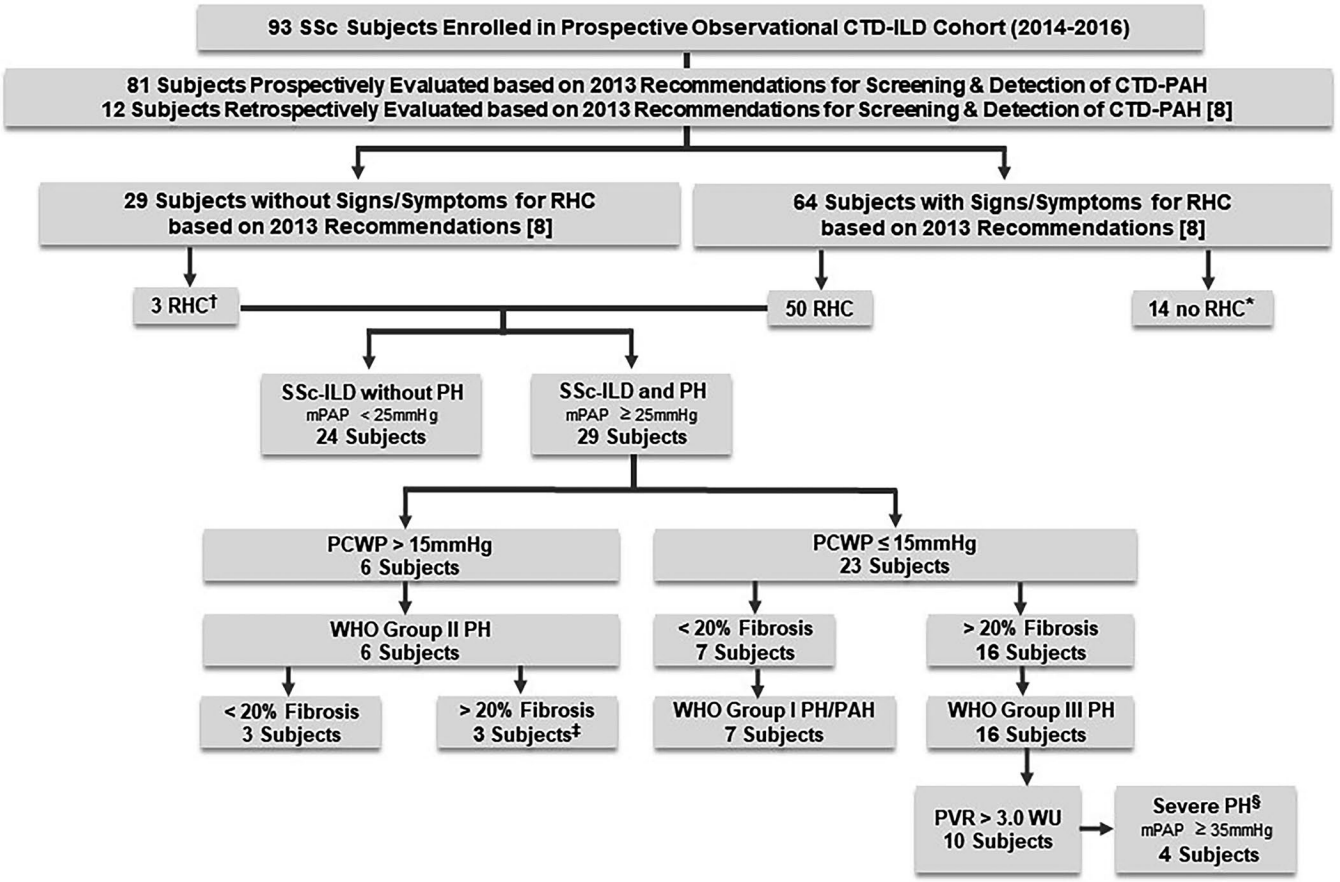

Figure 1. Study design and characterization of pulmonary hypertension (PH) in a cohort of patients with systemic sclerosis (SSc)–associated interstitial lung disease (ILD). * Of the 14 patients who did not undergo right-sided heart catheterization (RHC), 7 were referred to cardiology but did not undergo RHC since there was a low likelihood of PH based on evidence, 2 refused RHC, 1 was lost to follow-up, 2 had negative findings on RHC after data analysis, 1 had normailization of transthoracic echocardiography (TTE) findings, and 1 had stable lower diffusing capacity for carbon monoxide (DL_{CO}), normal N-terminal pro–brain natriuretic peptide levels, and no pulmonary arterial hypertension (PAH) findings on TTE. † Of the 3 patients without signs/symptoms for RHC who underwent RHC, 2 underwent RHC due to severe symptoms and had negative RHC findings, and 1 underwent RHC due to a decline in DL_{CO} and had World Health Organization (WHO) Group III PH; the data needed to calculate DETECT scores were not available for any of these patients. ‡ Of the 3 patients with WHO Group II PH with >20% extent of ILD, 1 also had combined postcapillary and precapillary PH according to the guidelines by Vachiery et al (16) (pulmonary capillary wedge pressure [PCWP] >15 mm Hg and diastolic pulmonary artery pressure [PAP] – PCWP ≥7 mm Hg) and had features of chronic thromboembolic disease based on pulmonary artery angiography. § Patients with severe PH had SSc-associated ILD with PH due to ILD with a mean PAP (mPAP) of ≥35 mm Hg on RHC according to the criteria by Seeger et al (13). CTD = connective tissue disease; PVR = pulmonary vascular resistance; WU = Wood units.

II PH had a mean PAP of ≥25 mm Hg and PCWP >15 mm Hg. Patients classified as having WHO Group III PH had a mean PAP of ≥25 mm Hg, PCWP ≤15 mm Hg, and >20% extent of ILD on HRCT (10–12). Of the patients with WHO Group III PH, those with a mean PAP of ≥35 mm Hg were further classified as having severe PH based on the recommendations of Seeger et al (13) (Figure 1).

Statistical analysis. Descriptive statistics for the overall SSc-associated ILD cohort, patients with SSc-associated ILD without PH, and patients with SSc-associated ILD and PH were calculated for demographic and clinical characteristics using the mean ± SD for continuous variables and percentage for categorical variables. The differences between the group without PH and the group with PH were compared using Student's *t*-test for continuous variables and the chi-square test for categorical variables.

The Kaplan-Meier method was used to evaluate time until patient death in the overall SSc-associated ILD cohort and in the subset of those with SSc-associated ILD and PH, or censored at October 1, 2016. The log rank test was used to determine if there was a statistically significant difference in survival time in patients with SSc-associated ILD and PH versus those with SSc-associated ILD without PH. Cox proportional hazards regression was used to determine if race (non-Hispanic white versus non-white) and age predicted survival in both subsets.

To evaluate whether there was a significant trend over time in FVC and DL_{CO} for the PFT findings obtained in the prospective observational cohort, a linear mixed-effects model

Table 1. Baseline characteristics of the patients with SSc-associated ILD*

	All patients (n = 93)	Patients with SSc-associated ILD without PH (n = 64)	Patients with SSc-associated ILD and PH (n = 29)	*P*
Age at initial non-RP sign/symptom, years	46.9 ± 13.3	45.2 ± 13.2	50.9 ± 12.8	0.054
Age at ILD diagnosis, years	51.6 ± 12.2	49.7 ± 11.8	55.8 ± 12.1	0.02
Age at study enrollment, years	54.9 ± 11.5	52.9 ± 11.4	59.3 ± 10.6	0.01
Sex, no. (%) women	71 (76.3)	47 (73.4)	24 (82.8)	0.33
Race, no. (%)				0.02
White	79 (84.9)	57 (89.1)	22 (75.9)	
African American	8 (8.6)	2 (3.1)	6 (20.7)	
Asian/Asian American	3 (3.2)	3 (4.7)	0	
Native American/Alaska Native	1 (1.1)	0	1 (3.4)	
Other	2 (2.2)	2 (3.1)	0	
Ethnicity, no. (%)				0.51
Hispanic	9 (9.7)	7 (10.9)	2 (6.9)	
Non-Hispanic	82 (88.2)	55 (85.9)	27 (93.1)	
Other	2 (2.2)	2 (3.1)	0	
SSc subtype, no. (%)				0.34
dcSSc	61 (65.6)	44 (68.8)	17 (58.6)	
lcSSc	32 (34.4)	20 (31.3)	12 (41.4)	
Disease duration				
Time from initial non-RP sign/symptom to study enrollment, years	7.9 ± 7.2	7.7 ± 7.6	8.5 ± 6.1	0.65
Time from initial non-RP sign/symptom to ILD diagnosis, years	4.7 ± 6.4	4.6 ± 6.9	4.9 ± 5.4	0.80
Time from ILD diagnosis to study enrollment, years	3.2 ± 3.6	3.2 ± 3.2	3.5 ± 4.3	0.65
ILD duration, years	4.7 ± 3.6	4.6 ± 3.2	4.8 ± 4.3	0.74
MRSS (at enrollment) (n = 89)	9.4 ± 9.5	9.9 ± 9.8	8.4 ± 8.9	0.51
Autoantibodies, no. (%)				
ANA positivity (n = 86)	79 (91.9)	57 (95)	22 (84.6)	0.19
ANA pattern (n = 76)				0.10
Nucleolar	11 (14.5)	9 (16.4)	2 (9.5)	
Centromere	6 (7.9)	2 (3.6)	4 (19)	
Other†	59 (77.6)	44 (80)	15 (71.4)	
Scl-70 positivity (n = 85)	24 (28.2)	20 (33.3)	4 (16)	0.12
RNA polymerase III positivity (n = 51)	11 (21.6)	9 (25.7)	2 (12.5)	0.47
PM/Scl positivity (n = 35)	2 (5.7)	1 (4.2)	1 (9.1)	0.54
ILD (on HRCT), no. (%)				0.13
Nonspecific interstitial pneumonia	84 (90.3)	60 (93.8)	24 (82.8)	
Usual interstitial pneumonia	9 (9.7)	4 (6.3)	5 (17.2)	
PFTs (obtained closest to the ILD diagnosis date)				
FVC, % predicted (n = 93)	76.2 ± 15.7	77.2 ± 14.3	73.9 ± 18.5	0.35
TLC, % predicted (n = 66)	83 ± 16.3	85.0 ± 14.8	78.7 ± 18.8	0.14
D_{LCO}, % predicted (n = 85)	58.3 ± 20.3	63.4 ± 20.1	46.8 ± 15.6	<0.001
FVC, % predicted/D_{LCO}, % predicted (n = 85)	1.5 ± 0.8	1.3 ± 0.5	1.9 ± 1.2	0.007

(Continued)

Table 1. (*Cont'd*)

	All patients (n = 93)	Patients with SSc-associated ILD without PH (n = 64)	Patients with SSc-associated ILD and PH (n = 29)	*P*
TTE‡				
RV function, no. (%) (n = 92)				<0.001
Normal	84 (91.3)	62 (98.4)	22 (75.9)	
Abnormal	8 (8.7)	1 (1.6)	7 (24.1)	
RV enlargement, no. (%)				0.02
No	80 (86.0)	59 (92.2)	21 (72.4)	
Yes	13 (14.0)	5 (7.8)	8 (27.6)	
RVSP, mm Hg (n = 63)§	37.8 ± 19.6	30.9 ± 8.2	49 ± 26.7	<0.001

* Except where indicated otherwise, values are the mean ± SD. SSc = systemic sclerosis; ILD = interstitial lung disease; PH = pulmonary hypertension; RP = Raynaud's phenomenon; dcSSc = diffuse cutaneous SSc; lcSSc = limited cutaneous SSc; MRSS = modified Rodnan skin thickness score; HRCT = high-resolution computed tomography; PFTs = pulmonary function tests; FVC = forced vital capacity; TLC = total lung capacity; DLco = diffusing capacity for carbon monoxide; RV = right ventricular; RVSP = right ventricular systolic pressure.
† Antinuclear antibody (ANA) positivity indicated by any immunofluorescence pattern other than nucleolar or centromere.
‡ Transthoracic echocardiography (TTE) data were captured after enrollment in the cohort.
§ No tricuspid regurgitation jet was observed in 30 patients.

with a fixed effect for time (continuous, in months) and a random effect for the patient was used to predict change from baseline for both FVC and DLco. All analyses were performed using SAS software version 9.4. *P* values less than 0.05 were considered significant.

RESULTS

Baseline characteristics of the total cohort. A total of 93 patients with SSc-associated ILD were evaluated in this study. The mean ± SD time from ILD diagnosis to study enrollment was 3.2 ± 3.6 years. Most patients were white (84.9%), female (76.3%), non-Hispanic (88.2%), and had diffuse cutaneous SSc (dcSSc) (65.6%). The mean ± SD overall SSc disease duration from initial non-Raynaud's phenomenon (RP) sign/symptom for the entire cohort was 7.9 ± 7.2 years, and the mean ± SD time to diagnosis of ILD after initial non-RP sign/symptom was 4.7 ± 6.4 years. The mean ± SD modified Rodnan skin thickness score was 9.4 ± 9.5. The most common ILD pattern on HRCT was nonspecific interstitial pneumonia (NSIP; 90.3%). PFTs at ILD diagnosis revealed an FVC % predicted of 76.2 ± 15.7, total lung capacity (TLC) % predicted of 83.0 ± 16.3 (n = 66), DLco % predicted of 58.3 ± 20.3 (n = 85) (4 patients had DLco assessment attempted without success, 2 patients were ill, and 2 patients did not have DLco ordered with PFTs at the time of ILD diagnosis), and a ratio of FVC % predicted to DLco % predicted of 1.5 ± 0.8 (n = 85) (Table 1).

The mean ± SD study duration for patients within this SSc-associated ILD cohort was 16.6 ± 4.3 months. At the time of data analysis, 12 patients were considered lost to follow-up since they had not followed up in clinic for >12 months, 2 patients had withdrawn consent, and 3 patients had died. There was a significant trend over time for both FVC and DLco after ILD diagnosis in all 93 patients with SSc-associated ILD in this cohort. Each year after ILD diagnosis, FVC was reduced by a mean ± SEM of 1.23 ± 0.14% and DLco was reduced by a mean ± SEM of 1.22 ± 0.18%. However, there was no significant change in FVC or DLco from study enrollment for any of the 93 patients in the cohort.

Prevalence of SSc-associated ILD and PH and baseline characteristics of the patients. Twenty-nine patients (31.2%) in this SSc-associated ILD cohort had RHC-proven PH, referred to herein as the subgroup with "SSc-associated ILD and PH." The mean ± SD time from initial non-RP signs/symptoms to PH diagnosis was 7.0 ± 5.5 years, and 75.9% of the patients with PH (22 of 29) had PH diagnosed prior to enrollment in the ILD cohort. Thirty-one percent of the patients with SSc-associated ILD and PH (9 of 29) were diagnosed as having PH prior to the development of the 2013 recommendations for screening and detection of CTD-associated PAH, 65.5% of the patients with SSc-associated ILD and PH (19 of 29) were at risk for PH according to the 2013 recommendations, and 1 patient with SSc-associated ILD and PH did not have signs/symptoms indicating a need for RHC based on the 2013 recommendations but underwent RHC due to progressive symptoms and declining DLco.

The remaining 64 patients with SSc-associated ILD are referred to herein as patients with "SSc-associated ILD without PH." Twenty-four patients had negative findings on RHC. The remaining 40 patients did not have signs/symptoms to proceed for an evaluation for RHC based on the 2013 PAH screening rec-

ommendations by Khanna et al (n = 26), were believed by a PH expert to have a low likelihood of PH based on available evidence (n = 7), had a pending RHC at the time of data analysis (n = 2), refused RHC (n = 2), were lost to cardiology follow-up (n = 1), had normalization of previously abnormal transthoracic echocardiography (TTE) findings (n = 1), or had stability of lower DLCO in the setting of normal N-terminal pro–brain natriuretic peptide levels and normal TTE findings (n = 1) (Figure 1). When compared to patients with SSc-associated ILD without PH, patients with SSc-associated ILD and PH were older at ILD diagnosis (mean age 55.8 years versus 49.7 years; $P = 0.02$), were more likely to be African American (20.7% versus 3.1%, $P = 0.02$), had lower DLCO % predicted (46.8% versus 63.4%; $P < 0.001$) and had a higher ratio of FVC % predicted to DLCO % predicted (1.9 versus 1.3; $P = 0.007$) at ILD diagnosis (Table 1).

Analysis of the time to diagnosis of PH after the initial non-RP sign/symptom showed that 37.9%, 44.8%, and 48.3% of the patients had a diagnosis of PH within 3, 5, and 7 years, respectively. We also performed analyses to evaluate baseline characteristics, cardiopulmonary characteristics, treatments, and outcomes for those with PH diagnosed <7 years (n = 14) compared to ≥7 years (n = 15) after the initial non-RP sign/symptom, which was based on the inclusion of patients with a disease duration of <7 years from initial non-RP sign/symptom in recent SSc-associated ILD clinical trials (14,15). There were no significant differences between patients with early diagnosis of PH (<7 years from initial non-RP symptom) and patients with late diagnosis of PH (≥7 years from initial non-RP symptom) except age at initial non-RP sign/symptom (mean ± SD 57.2 ± 12.6 versus 45 ± 10.2 years; $P = 0.008$), Scl-70 positivity (0 versus 4 [33.3%]; $P = 0.04$) (n = 25); ILD pattern on HRCT (14 NSIP [100%] versus 10 NSIP [66.7%] and 5 usual interstitial pneumonia [33.3%]; $P = 0.04$), and cardiac output measured by thermodilution (mean ± SD 5.9 ± 1.8 versus 4.8 ± 1.1; $P = 0.047$) (data not shown).

Cardiopulmonary characteristics of the patients with SSc-associated ILD and PH. All CT scans assessed for ILD severity were obtained a median of 2.2 months (interquartile range 0.3–6.3 months) after the diagnosis of PH based on diagnostic RHC. Seven patients with SSc-associated ILD and PH (24.1%) were classified as having PAH. Six patients (20.7%) were classified as having WHO Group II PH; 3 of those patients had <20% extent of ILD on HRCT, and 3 patients had >20% extent of ILD on HRCT. One of the patients with WHO Group II PH with >20% extent of ILD on HRCT also had features of combined postcapillary and precapillary PH based on PCWP >15 mm Hg and diastolic PAP – PCWP ≥7 mm Hg according to the classification by Vachiery et al (16). That patient also had features of chronic thromboembolic disease based on pulmonary artery angiogram (16). Sixteen patients (55.2%) were classified as having WHO Group III PH. Ten patients (34.5%) with WHO Group III PH had pulmonary vascular resistance (PVR) >3.0 Wood units, and 4 of those patients (13.8%) were classified as having severe PH based on a mean PAP of ≥35 mm Hg (13) (Figure 1). Cardiopulmonary characteristics are summarized for patients with SSc-associated ILD and PH in Table 2.

We also applied a previously published definition of clinically significant ILD, which classifies patients as having clinically significant ILD if they have >30% disease extent on HRCT, or 10–30% disease extent on HRCT and an FVC of <70% (17,18). Of the 29 patients with PH in the present study, 15 (51.7%) had clinically significant ILD.

Treatment and outcomes of SSc-associated ILD and PH. Twenty-four patients (82.8%) with SSc-associated ILD and PH underwent ILD treatment during their SSc-associated ILD disease course. Eleven patients were treated only with mycophenolate mofetil monotherapy, 6 patients received mycophenolate mofetil after treatment with cyclophosphamide, 2 patients participated in clinical trials and transitioned to mycophenolate mofetil, and other patients received mycophenolate mofetil and pirfenidone (1 patient), cyclophosphamide followed by rituximab (1 patient), rituximab followed by mycophenolate mofetil and tocilizumab (1 patient), rituximab only (1 patient), and autologous hematopoietic stem cell transplantation (1 patient) (Table 3).

During their SSc-associated PH disease course, 24 patients with SSc-associated ILD and PH (82.8%) were treated with PAH-specific therapies. Nine patients (31%) were treated with dual PAH-targeted therapy, 1 of whom was treated with inhaled prostacyclins and 1 of whom was treated with intravenous (IV) prostacyclins. Four patients (13.8%) were treated with triple PAH-targeted therapy, 2 of whom were treated with inhaled prostacyclins and 2 of whom were treated with IV prostacyclins. Five patients (17.2%) with SSc-associated ILD and PH, 3 of whom were characterized as having WHO Group II and 2 of whom were characterized as having WHO Group III, were not prescribed PAH-specific therapies. The majority (79.2%) of the patients treated with PAH-specific therapies were started on phosphodiesterase 5 (PDE5) inhibitors alone, and the majority (45.8%) of the patients treated with PAH-specific therapies during their SSc-associated PH disease course were treated with single-agent therapy only (Table 3).

Of the 24 patients who were treated with PAH-specific therapies, 7 patients had PAH, 10 patients had WHO Group III PH with PVR >3.0 Wood units, 1 patient had WHO Group II PH with >20% extent of ILD on HRCT and PVR >3.0 Wood units, and 1 patient had combined postcapillary and precapillary PH. The remaining 5 patients had WHO Group II or Group III PH with PVR <3.0 and were treated with PAH therapy due to unexplained decline in DLCO, worsening symptoms, and/or severe WHO functional class. Twenty patients (69%) were receiving ILD therapies and PAH-specific therapies simultaneously. Adverse events due to PAH-specific therapies were

Table 2. Cardiopulmonary characteristics of the patients with SSc-associated ILD and PH (n = 29)*

WHO PH group, no. (%)	
Group 1	7 (24.1)
Group 2	6 (20.7)
Group 3	16 (55.2)
ILD involvement on HRCT, no. (%)	
>20%	19 (65.5)
<20%	10 (34.5)
PFTs (at PH diagnosis)	
FVC, % predicted	70.3 ± 18.1
TLC, % predicted	84.7 ± 16.5
DLco, % predicted	43.1 ± 15.8
FVC, % predicted/DLco, % predicted	2 ± 1.5
TTE (at PH diagnosis)	
RVSP, mm Hg (n = 27)†	44.9 ± 21.6
RAP, mm Hg (n = 27)†	7.9 ± 3.2
RA dilation, no. (%)	13 (44.8)
RV dilation, no. (%)	11 (37.9)
Abnormal RV function, no. (%) (n = 28)	6 (21.4)
RHC	
Mean PAP, mm Hg	33.4 ± 7.2
Mean PCWP, mm Hg	13.2 ± 3.2
Mean RAP, mm Hg	9.9 ± 3.3
Cardiac output (by the Fick method)	5.3 ± 1.5
Cardiac output (by thermodilution)	5.3 ± 1.5
PVR (Wood units)	4.3 ± 3.3
Mean PAP on RHC, no. (%)	
25–35 mm Hg	20 (69)
35–45 mm Hg	8 (27.6)
>45 mm Hg	1 (3.4)
PVR on RHC, no. (%)	
0–6 Wood units	21 (72.4)
6–12 Wood units	7 (24.1)
>12 Wood units	1 (3.4)

* Except where indicated otherwise, values are the mean ± SD. WHO = World Health Organization; RAP = right atrial pressure; RA = right atrial; RHC = right-sided heart catheterization; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance (see Table 1 for other definitions).
† No tricuspid regurgitation jet was observed in 2 patients.

known side effects of the PAH-specific therapies, and no case of worsening ventilation/perfusion mismatch was observed based on chart review.

At PH diagnosis and at the time of data analysis, most patients had a WHO functional class of II or III. Five patients with SSc-associated ILD and PH, who were receiving ILD therapies and PAH-specific therapies, improved by at least 1 WHO functional class from PH diagnosis to the time of data analysis. One patient with WHO Group III PH, with hemodynamic

Table 3. Treatment of and outcomes in patients with SSc-associated ILD and PH (n = 29)*

History of treatment with PAH-targeted therapies	24 (82.8)
Initial treatment with PAH-targeted therapies	
None	5 (17.2)
PDE5 inhibitor	19 (65.5)
PDE5 inhibitor and ERA	4 (13.8)
IV prostacyclin	1 (3.4)
Most recent PAH-targeted therapy regimen	
None	6 (20.7)
PDE5 inhibitor	13 (44.8)
ERA	1 (3.4)
PDE5 inhibitor and ERA	3 (10.3)
PDE5 inhibitor and inhaled prostacyclin	1 (3.4)
ERA and IV prostacyclin	1 (3.4)
PDE5 inhibitor, ERA, and inhaled prostacyclin	2 (6.9)
PDE5 inhibitor, ERA, and IV prostacyclin	1 (3.4)
PDE5 inhibitor, ERA, and clinical trial	1 (3.4)
Use of single-agent PAH-targeted therapy	11 (37.9)
Use of dual-agent PAH-targeted therapy	9 (31)
Use of triple-agent PAH-targeted therapy	4 (13.8)
Requirement of prostacyclin during PH therapy	6 (20.7)
History of ILD treatment	24 (82.8)
History of ILD treatment with mycophenolate mofetil	21 (72.4)
History of ILD treatment with IV pulse cyclophosphamide	8 (27.6)
Most recent ILD treatment	
None	9 (31)
Mycophenolate mofetil	15 (51.7)
Rituximab	2 (6.9)
Tocilizumab and mycophenolate mofetil	1 (3.4)
Pirfenidone and mycophenolate mofetil	1 (3.4)
Cyclophosphamide	1 (3.4)
History of supplemental oxygen use	9 (31)
History of transplantation†	1 (3.4)
Alive or deceased	
Alive	27 (93.1)
Deceased	2 (6.9)
WHO functional class (prior to PH diagnosis)	
Class I	0 (0)
Class II	12 (41.4)
Class III	16 (55.2)
Class IV	1 (3.4)
WHO functional class (most recent)	
Class I	4 (13.8)
Class II	8 (27.6)
Class III	17 (58.6)
Class IV	0 (0)

* Values are the number (%). PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase 5; ERA = endothelin receptor antagonist; IV = intravenous; WHO = World Health Organization (see Table 1 for other definitions).
† Autologous hematopoietic stem cell transplantation (HSCT).

features of PAH with PVR >3.0, who had a PDE5 inhibitor and endothelin receptor antagonist (ERA) added to prior long-term mycophenolate mofetil therapy, improved by 2 functional classes from functional class III to functional class I. Sixteen patients with SSc-associated ILD and PH receiving PAH-specific therapies, 4 of whom were never treated with ILD therapy, had a stable WHO functional class during their disease course (Figure 2).

Nine patients with SSc-associated ILD and PH (31%) received supplemental oxygen during their PH disease course. No patients with SSc-associated ILD and PH underwent heart or lung transplantation during their ILD and/or PH disease course; however, 1 patient had undergone autologous hematopoietic stem cell transplantation 1 year after ILD diagnosis. Two patients with SSc-associated ILD and PH (6.9%) died during the study. One patient whose cause of death was PH had WHO Group III PH and had been treated with cyclophosphamide followed by mycophenolate mofetil and was not treated with PAH-specific therapy. The other patient had PAH, was treated with an ERA and IV prostacyclin, and died of a respiratory infection.

Survival analysis. Overall, 3 patients in the entire SSc-associated ILD cohort died (1 of respiratory infection, 1 of PH, and 1 of an unknown cause due to the patient being lost to follow-up). The survival rate 3 years after diagnosis of SSc-associated ILD for all patients in the cohort was 97% (survival standard error 0.03). Survival analysis for those with SSc-associated ILD and PH indicated that after diagnosis of PH 2 patients died (1 of respiratory infection and the other of PH), resulting in a survival rate at 3 years after PH diagnosis of 91% (survival standard error 0.06); one of the patients with SSc-associated ILD and PH who died had clinically meaningful ILD. For the entire SSc-associated ILD cohort and those with SSc-associated ILD and PH, Cox proportional hazards regression of time to death was conducted with adjustment for current age and race (non-Hispanic white versus non-white) to account for differences between the cohorts; however, neither of those variables were significant in either survival model.

DISCUSSION

In this study, we examined the prevalence and explored the clinical characteristics, pharmacologic therapies, and outcomes in SSc-associated ILD. Our results demonstrate that a large proportion of patients with SSc-associated ILD (31.2%) have coexisting PH, and 37.9% and 48.3% of PH diagnoses occurred within 3 years and 7 years, respectively, of the onset of SSc. Most patients with SSc-associated ILD and PH had WHO Group III PH based on >20% extent of ILD on HRCT (55.2%), and the majority (10 of 16 [63%]) of those patients with WHO Group III PH had hemodynamic features of PAH with PVR >3.0 Wood units. The group with

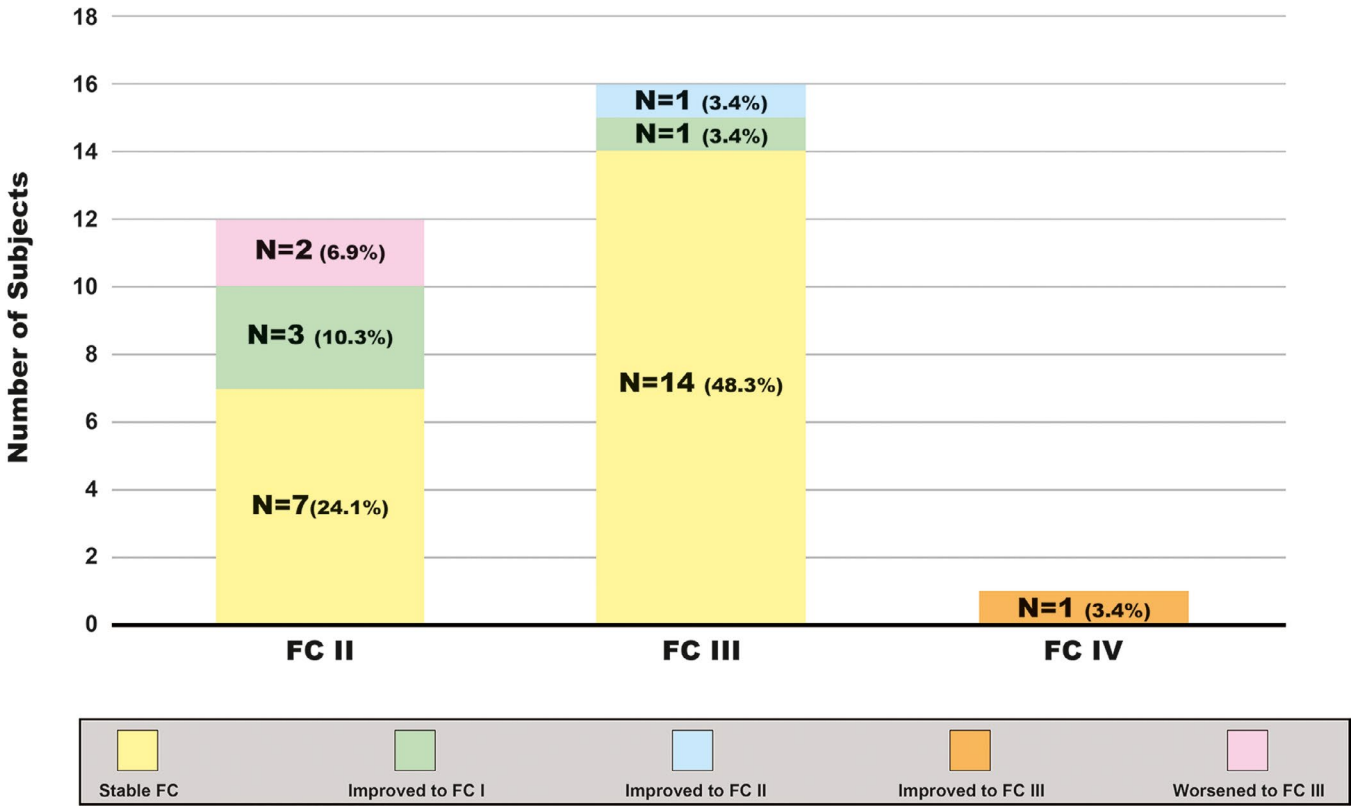

Figure 2. World Health Organization functional class (FC) prior to diagnosis of pulmonary hypertension (PH) in patients with systemic sclerosis–associated interstitial lung disease and PH and change in functional class at the time of data analysis.

SSc-associated ILD and PH also included a significant proportion of African Americans, consistent with prior studies of SSc that have shown that African Americans have a higher incidence of PH, and a recent multicenter African American cohort in which a similar proportion of patients (18%) had RHC-proven PH (19–21). The majority of patients who had SSc-associated ILD and PH had received immunosuppressive therapy for their ILD (82.8%), and 82.8% received PAH-specific therapy. The survival rate for those with SSc-associated ILD and PH 3 years after PH diagnosis was 91%, irrespective of ILD- and/or PAH-specific therapies.

Compared to prior studies that evaluated SSc patients with ILD and PH, our study is unique in that it focused on a cohort of patients with SSc-associated ILD and assessed the prevalence and the clinical course of PH in a prospective fashion, which indicated that the coexistence of PH with SSc-associated ILD is not uncommon. Thus, patients with SSc-associated ILD may not have cardiopulmonary symptoms solely due to ILD, and may in fact have PH contributing to their abnormal cardiopulmonary symptoms and physiology. Most studies report PH prevalence only for PAH in patients without significant lung fibrosis, so direct comparison of our results with other study populations is difficult. Also, the high prevalence of PH in our SSc-associated ILD cohort may reflect some referral bias, since our institution is well known for its PH expertise and our adherence to the 2013 recommendations for screening and detection of CTD-associated PAH in our population (8). Our review of the literature identified 7 original studies of RHC-proven SSc-associated PH with and without ILD. Of those, 4 studies evaluated SSc-associated PH related to ILD (SSc-associated PH-ILD) (17,18,22,23), 2 studies evaluated coexisting ILD in SSc patients who were initially evaluated for RHC-proven PAH (24,25), and an additional study by Trad et al (26) evaluated a cohort of patients with dcSSc, 17% of whom had ILD and PAH, although some of those patients had only TTE-proven PAH. Thus, future studies need to focus on assessing the prevalence of coexisting PH and ILD in a systematic fashion.

Although the development of PAH is largely thought to be a late complication in SSc, our study indicates that a large proportion of patients with SSc-associated ILD and PH have a diagnosis of PH within 5 years of SSc onset (27). Similar results were reported in a study by Mathai et al (23), which demonstrated a median SSc disease duration of 4 years for all patients with PH, 3 years for patients with SSc-associated PH-ILD, and 4.5 years for those with SSc-associated PAH (23). Also, in a retrospective multicenter study by Hachulla et al, the mean ± SD SSc disease duration at PAH diagnosis was 6.3 ± 6.6 years, 55.1% of the patients were classified as having early-onset PAH based on a PAH diagnosis occurring within 5 years of an initial non-RP symptom, and >50% of the population studied had evidence of pulmonary fibrosis on CT as well (28). One possible explanation for the earlier diagnosis of PH may be the recognition and incorporation of screening algorithms for PH in SSc (6,8,12). This evidence of early development of PH in SSc patients sheds light on a potential problem that may exist in the current design of SSc-associated ILD clinical trials, which typically recruit patients within 5–7 years of the initial SSc non-RP sign/symptom and do not require a diagnostic RHC to rule out PH as a cause of cardiopulmonary signs and symptoms.

Clinical trials evaluating PAH therapies typically exclude patients with clinically significant ILD and/or PH due to SSc-related PH-ILD; however, according to our experience and previous studies by Launay et al (22) and Mathai et al (23), patients with clinically significant ILD and PH receive both ILD-specific and PAH-specific therapies. The 5th World Symposium on Pulmonary Hypertension (12) has endorsed management of WHO Group III PH by expert centers. Their recommendations acknowledge the lack of evidence for the use of PAH-specific therapies for patients with WHO Group III PH, citing the potential for worsening gas exchange in ILD patients due to ventilation/perfusion mismatch. Despite this, our cohort and other cohorts highlight the use of PAH-specific therapies in these patients. However, we acknowledge that differentiating WHO Group I PH from WHO Group III PH in this population remains a challenge, and should not be based upon arbitrary cutoffs involving FVC and HRCT findings (13).

Patients with SSc-associated ILD and PH may also have a combination of WHO Group I PH and WHO Group III PH, which have different disease mechanisms. PAH is a vasculopathy characterized by vascular remodeling with inflammation, fibrosis, and thrombosis, whereas WHO Group III PH is due to vascular destruction from lung fibrosis, vasoconstriction due to chronic hypoxia, and/or a vasculopathy similar to that seen in PAH but "disproportionate" to what is seen in PH due to chronic lung disease (13,29). "Out of proportion" PH in some forms of chronic lung diseases has recently been defined by Seeger et al (13) as severe PH due to chronic lung disease with hemodynamic findings of a mean PAP of ≥35 mm Hg or a mean PAP of ≥25 mm Hg and a low cardiac index (<2.0 liters/minute/m^2). As evidenced in our cohort, a large proportion of patients with >20% extent of ILD on HRCT actually have features of both PAH and WHO Group III PH, and individuals within this group were treated with both PAH-specific therapies and immunosuppression for ILD on a case-by-case basis. The majority of patients in our study tolerated PAH-specific therapy regardless of simultaneous or prior ILD treatment and had stability in WHO functional class and/or 6-minute walk test.

Survival for patients with coexisting PH in the setting of SSc-associated ILD has varied across cohorts, but despite the existence of various PAH therapies, survival overall remains poor for both SSc-associated PAH and SSc-associated PH-ILD, but tends to be worse if PH is due to ILD. However, our 91% survival rate 3 years after PH diagnosis is higher than survival rates reported in studies by Launay et al (22), Le Pavec et al (17), Mathai et al (23), Michelfelder et al (25), and Volkmann et al (18). Based on the average mean PAP and PVR on RHC and use of prostacyclins, patients in our SSc-associated ILD and PH cohort appear to have less severe PH than those in the previously mentioned studies, which is likely due to our aggressive PH screening, creating lead

time bias and improved survival rates. Our survival rates may also be overestimated due to our small cohort size and infrequent events. We also evaluated our population of patients for clinically significant ILD (>30% disease extent on HRCT, or 10–30% disease extent on HRCT and an FVC <70%), and found that 51.7% of the patients with PH (15 of 29) had clinically significant ILD. In comparison, the cohorts in the studies by Le Pavec et al (17) and Volkmann et al (18) included SSc patients with PH and clinically significant ILD with a total of 70 patients with a 3-year survival estimate of 21% and 71 patients with a 3-year survival estimate of 50%, respectively (17,18). The 3-year survival rate of 91% in our SSc-associated ILD and PH cohort, with >50% of patients with clinically significant ILD, is likely related to inclusion of HRCT and implementation of the 2013 recommendations in all patients seen at the University of Michigan and milder PH based on hemodynamic findings and the use of prostacyclins in our cohort (8).

Our cohort study also highlights an ongoing dilemma in the classification of SSc-associated PH, as there is lack of a standard definition of what constitutes a significant degree of ILD based on pulmonary physiology and/or radiographic severity to classify patients as having WHO Group I PH/PAH or WHO Group III PH. Recent data from a single-center cohort highlight the lack of specificity of FVC % predicted for the assessment of the presence and severity of ILD in SSc (30). Additional differences in the definition of clinically significant ILD are evident when evaluating 2 recent large clinical trials of PAH-targeted therapies. In the PAH trial evaluating combination therapy with ambrisentan and tadalafil and the PAH trial evaluating the use of selexipag, patients with moderate-to-severe restrictive lung disease defined as a TLC of <60–70% were excluded (31,32). In the cohort evaluated in the present study, moderate-to-severe ILD causing WHO Group III PH was defined using Goh's criteria (10), with all patients with features of WHO Group III PH having >20% extent of ILD on HRCT. Fischer et al (24), Volkmann et al (18), and Le Pavec et al (17) defined SSc-associated PH-ILD similar to or based on Goh's criteria. Volkman et al and Le Pavec et al specifically defined significant ILD as an extent of fibrosis of >30% of lung involvement on HRCT, or an extent of fibrosis of 10–30% and an FVC of <70%. Launay et al (22) and Mathai et al (23) based their SSc-associated PH-ILD diagnosis on PFTs and HRCT findings. A consensus is urgently needed for the definition of significant ILD to determine whether a patient has SSc-associated PAH or SSc-associated PH-ILD.

Our study has many strengths. First, we studied a well-characterized prospective SSc-associated ILD cohort recruited at a single center. Second, all patients underwent screening for PH based on the 2013 recommendations by Khanna et al, and those who met the criteria underwent RHC (8). However, this study is not without limitations. Our results may be skewed since patients were recruited at a tertiary care center with highly specialized scleroderma, ILD, and PAH clinics. Like other cohorts, the management of PH and ILD was not standardized, which may have impacted the outcomes. Last, although we instituted a standardized algorithm for PH screening, we may have missed some patients with mild PH.

Patients with SSc-associated ILD can also develop PH early on in their SSc disease course. These patients with ILD and PH often have dcSSc and often have features of WHO Group III PH due to their ILD but also have hemodynamic features of PAH, which may warrant the use of both immunosuppressive therapies and PAH-specific therapies. The presence of PH early on in patients with SSc-associated ILD is a key factor we must recognize when designing clinical trials for SSc-associated ILD, since PH may be confounding patient-reported outcomes and cardiopulmonary physiology in these patients, which may affect the outcome of clinical trials. Future prospective studies in SSc-associated ILD should confirm our findings and also explore the impact of the new hemodynamic definition of PH, which was recently proposed at the 6th World Symposium on Pulmonary Hypertension (33,34).

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Khanna had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Young, Visovatti, Flaherty, McLaughlin, Khanna.

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ADDITIONAL DISCLOSURES

Author Khanna is an employee of CiviBioPharma.

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