Natural History of Mild–Moderate Pulmonary Hypertension and the Risk Factors for Severe Pulmonary Hypertension in Scleroderma

BETTY CHANG, LIONEL SCHACHNA, BARBARA WHITE, FREDRICK M. WIGLEY, and ROBERT A. WISE

ABSTRACT. ***Objective.*** To determine risk factors for developing pulmonary hypertension (PH) in patients with scleroderma (SSc, systemic sclerosis).

Methods. We used a cohort of 1136 SSc patients using severe PH as the primary outcome in a natural history study.

Results. Among 361 individuals with no initial echocardiographic PH, 92 (26.0%) developed mild–moderate PH and 48 (13.6%) severe PH. Patients developing severe PH had lower initial DLCO (48.8% of predicted) than those who did not develop PH (56.8% of predicted). Patients with mild–moderate PH had a 17% probability of progressing to severe PH, and 15.6% probability of regressing to no PH. Individuals with limited disease, mild–moderate PH, and age ≥ 47 years at diagnosis had a 27.3% probability of developing severe PH, compared to 8.5% in individuals with diffuse disease, no evidence of PH, and age < 47 years at diagnosis. Longitudinal regression models estimated that individuals with limited disease, mild–moderate PH, and DLCO < 50% predicted had an age-adjusted odds ratio of 8.6 of developing severe PH within 2 years compared to individuals without these risk factors.

Conclusion. Development of severe PH is uncommon in certain subgroups of SSc patients. Risk factors for progression of PH include older age, limited skin disease, and elevated pulmonary artery pressures at the time of initial evaluation. (J Rheumatol 2006;33:269–74)

Key Indexing Terms:
SCLERODERMA PULMONARY HYPERTENSION DLCO RISK FACTORS

Pulmonary hypertension (PH) is a frequent cause of morbidity and mortality in patients with systemic sclerosis (SSc, scleroderma). Only when the disease has progressed into a severe stage with right heart failure is the bedside diagnosis obvious. Ten to thirty percent of patients with SSc have echocardiographic evidence of PH, often without signs or symptoms of cardiopulmonary disease[1,2]. Once PH is associated with signs of right heart failure, the prognosis is poor with or without therapy[3,4]. Recent investigations have shown that echocardiography can detect elevated right ventricular and pulmonary circulation pressures before there is clinical evidence of PH[5,6]. As a result, more SSc centers are performing routine screening echocardiograms on asymptomatic patients[7]. Drugs are now available for the treatment of severe, symptomatic PH with hemodynamic, functional, and quality of life benefits[8,9]. Currently, only individuals who have New York Heart Association (NYHA) Class III and IV functional classification of symptoms or limitation, associated with PH, are considered candidates for these drugs. Early intervention with these therapies may be of benefit in patients with mild to moderate PH, who are at high risk for disease progression. The natural history of mild–moderate PH is not known and risk factors for the development of severe PH are incompletely understood; therefore, it is unclear which SSc patients would be candidates for trials of early intervention. Given the cost, the potential side effects, and the relative rarity of PH as a complication of SSc, defining the higher risk population of patients with SSc is important to determine who might benefit from early therapy. The goal of our retrospective analysis was to determine the risk factors for developing severe PH and to define the risk of developing severe PH among SSc patients with mild–moderate PH. To answer these questions, we analyzed longitudinal data from a well characterized cohort of patients with SSc.

From the Division of Pulmonary and Critical Care Medicine, University of New Mexico, Albuquerque, New Mexico; Division of Rheumatology and Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland, USA; Austin and Repatriation Medical Center, Victoria, Australia; Amgen, California, USA.

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B. Chang, MDCM, PhD, Assistant Professor, Pulmonary and Critical Care Medicine Division, Department of Medicine, University of New Mexico; L. Schachna, MD, PhD, Assistant Professor, Austin and Repatriation Medical Center, Victoria, Australia; B. White, MD, PhD, Amgen; F. Wigley, MD, Professor; R. Wise, MD, Professor, Johns Hopkins University.

Address reprint requests to Dr. B. Chang, Pulmonary and Critical Care Medicine Division, Department of Medicine, University of New Mexico, 2211 Lomas Blvd., NE, ACC-5, Albuquerque, NM 87131-5271.
E-mail: betchang@salud.unm.edu

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MATERIALS AND METHODS

Patient selection. All SSc patients seen at least once at the Johns Hopkins Scleroderma Center between January 1, 1990, and August 31, 2001, were eligible. A never-smoker smoked less than a pack in their lives, and a former smoker was abstinent for at least 6 months. Limited cutaneous scleroderma was defined as skin tightening distal to elbows and knees with or without facial involvement. Diffuse cutaneous scleroderma was defined as tightening proximal to the elbows and knees. Once classified as diffuse, the subtype remained diffuse for all further longitudinal analyses even if the extent of skin involvement regressed. Autoantibodies, pulmonary function tests (PFT), and echocardiograms were performed as routine screening tests or at the discretion of the clinician for evaluation of symptoms. An antinuclear or anticentromere antibody > 1:160 was considered positive. Other autoantibodies were reported as either positive or negative.

Echocardiograms. Right ventricular systolic pressure (RVSP) estimated by Doppler echocardiography as an estimate of pulmonary artery pressure (PAP) was used to classify PH. RVSP ≤ 35 mm Hg was considered normal, 36–55 mm Hg mild–moderate, and ≥ 56 mm Hg, severe PH. We included in the analyses all technically adequate echocardiograms except for those performed more than 1 year prior to the diagnosis of scleroderma. All echocardiograms with normal right heart chamber size and a normal interventricular septum but which could not assess PH for lack of tricuspid jet were presumed to have no PH. Echocardiograms were done at various clinical sites and reports were reviewed by the investigators using a standard protocol.

Pulmonary function tests. The results of spirometry, helium lung volumes, and carbon monoxide diffusing capacity (DLCO) were standardized using normal prediction equations[10-12]. We used the result of the patient's initial PFT performed closest to the date of first visit in analyses.

Statistical analysis. The date of scleroderma diagnosis was considered time zero. We compared clinical and demographic characteristics of patients with multiple echocardiograms to those with single studies to determine if there was a testing bias. Among patients without PH on initial echocardiography, we compared demographic and disease characteristics of those who did not develop PH to those who developed mild–moderate and severe PH.

Statistical significance testing used the Student's t test for continuous variables, the z test for binomial variables, and chi-square test for categorical variables. Statistical significance was inferred for a p value ≤ 0.05. Because not all testing was performed on the same day and not all patients were seen at a similar time interval, we used longitudinal logistic regression with the development of severe PH as a binomial outcome with time as an independent variable[13]. Transitional longitudinal logistic regression techniques were used to determine the probability of developing severe PH if the patient had documented mild–moderate PH on a prior echocardiogram. DLCO as a predictor of severe PH was explored using the DLCO as a continuous variable, in deciles and quartiles. Gender, race, body mass index, age at diagnosis, lung volume by initial PFT, and time interval from initial DLCO measurement to diagnosis of severe PH by echocardiogram were explored for their independent effect and interaction with the DLCO on development of severe PH. All variables that were not statistically significant were removed from the logistic model to obtain the most parsimonious model predicting severe PH. Analyses were performed using Stata 6.0 (Stata Corp., College Station, TX, USA).

RESULTS

Between January 1, 1990, and August 31, 2001, the Scleroderma Center evaluated 1136 patients with scleroderma. Of these, 820 (72.1%) underwent echocardiography suitable for the evaluation of PH, and 457 (40.2%) underwent serial echocardiography [mean of 3.0 echocardiograms (range 2–9), and a mean 3.2 yrs between first and last echocardiogram] (Figure 1). There were no differences in sex, race, or age between those with no, one, or multiple echocardiograms (Table 1). Patients who underwent multiple echocardiograms were more likely to be smokers and to meet American College of Rheumatology (ACR) criteria for scleroderma, but no disease subtype (limited or diffuse) predominated. Initial PFT of those with multiple echocardiograms were statistically more impaired than the tests of those with no echocardiograms.

Among patients with serial echocardiography, 361 individuals did not have initial evidence of PH. Subsequently, 92 (25.5%) developed mild–moderate PH and 49 (13.6%) developed severe PH (Table 2, Figure 1). The remaining 220 individuals (60.9%) continued to show no evidence of PH on serial echocardiography. Of the patients with mild–moderate PH initially, 17.7% progressed to severe PH by serial echocardiograms, and 15.6% regressed to having no evidence of PH. Of the severe PH, 25.0% regressed to mild–moderate PH by serial echocardiograms and 3% regressed to having no evidence of PH. NYHA functional classification was not assessed at time of echocardiography, as not all patients had clinic visits near or at the time of the echocardiogram.

In bivariate analysis, patients who were more likely to develop severe PH were men ($p = 0.02$), those meeting ACR criteria for scleroderma at presentation ($p = 0.04$), and those older at disease onset and diagnosis ($p = 0.04$ for Raynaud's phenomenon onset, $p = 0.01$ for first non-Raynaud's symptom, and $p < 0.01$ for physician diagnosis of scleroderma). Race, smoking status, disease subtype (limited vs diffuse), and Raynaud's phenomenon did not predict the development of severe PH. Patients who developed severe PH had more impaired initial PFT (except residual volume), and patients who developed mild–moderate PH had more impaired initial DLCO than those who did not (Table 2). For those progressing from no PH to severe PH, the time from initial PFT to echocardiogram diagnosing severe PH was longer, despite a correlation of the initial DLCO and the development of severe PH. Thromboembolic disease as a cause of PH was not evaluated.

In multivariate analysis, the overall probability of severe PH rose to 27.3% if the patient had limited disease and was greater than median age (46.9 yrs) at the time of diagnosis. Age at diagnosis was a statistically significant covariate when treated as either a continuous or a categorical variable. Therapeutic modalities were examined (calcium channel blockers, prostaglandin, Bosentan), but given that some of the current modalities for treating PH were developed during the study period, and that the number of patients taking specific pharmacotherapies was small, no meaningful analyses could be made.

The risk of developing severe PH over time increased dramatically when the initial DLCO was < 50% of predicted (Figure 2). For all patients, an initial DLCO < 50% of predicted was a statistically significant predictor of developing severe PH risk for up to 5 years after that abnormal

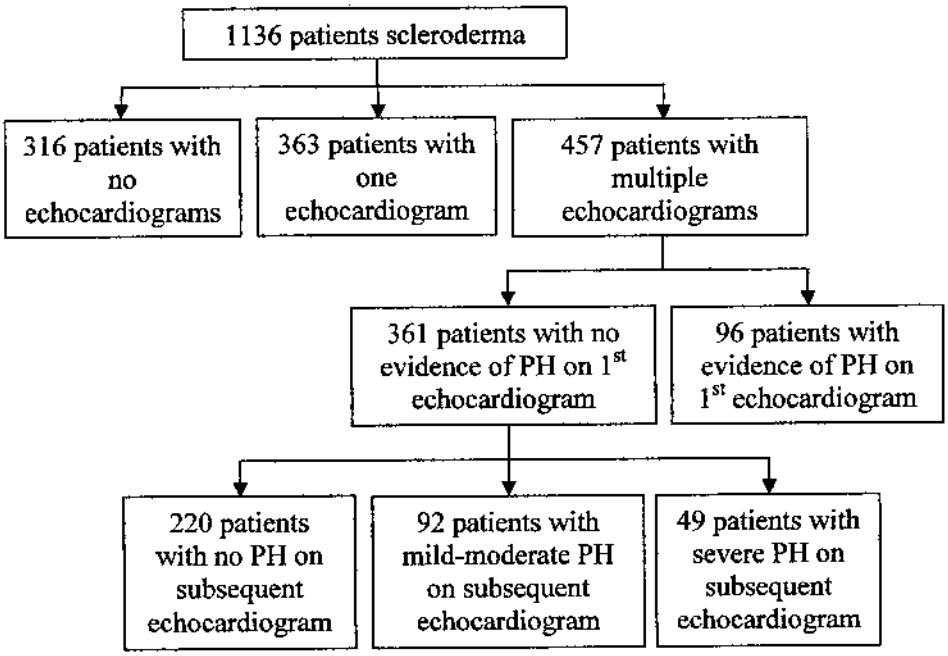

Figure 1. Classification of patients with and without echocardiograms including serial echocardiograms.

Table 1. Demographics and disease characteristics of individuals who had an echocardiogram performed compared to individuals who did not have an echocardiogram.

	No Echocardiogram, n = 316	One Echocardiogram, n = 363	More Than One Echocardiogram, n = 457
Female, %	81.3	84.4	82.9
Race, %			
Caucasian (n = 848)	70.5	78.5	74.6
African American (n = 217)	20.3	16.0	20.6
Other (n = 71)	9.2	5.5	4.8
Age, yrs			
At diagnosis	46.8 ± 14.6	47.1 ± 13.7	47.0 ± 13.7
At Raynaud's onset	40.2 ± 15.6	42.3 ± 14.7	42.0 ± 14.3
At first non-Raynaud's symptom onset	44.1 ± 15.5	43.8 ± 13.9	44.6 ± 14.1
Met ACR criteria, %	69.0	68.2	76.1*
Limited skin subtype, %	67.4	64.1	57.8
Smoking status at first visit, %			
Never smoker (n = 300)	44.0	51.0	48.5
Former smoker (n = 359)	33.3	31.8	37.2
Current smoker (n = 452)	22.7	17.3	14.4*
Serology positivity, %			
Antinuclear antibody	81.1	87.8*	87.1*
Anticentromere antibody	22.7	25.2	17.7
Antitopoisomerase antibody	12.2	12.9	13.2
Initial pulmonary function tests (% of predicted ± SD)			
FEV_1	82.2 ± 20.9	81.1 ± 19.6	76.1 ± 19.1*
FVC	83.5 ± 21.7	83.1 ± 19.8	77.0 ± 19.9*
TLC	87.6 ± 19.6	87.0 ± 17.5	81.2 ± 18.9*
VC	83.5 ± 21.5	82.6 ± 20.4	77.8 ± 20.1*
RV	99.6 ± 47.0	97.4 ± 32.0	90.2 ± 29.5*
DLCO	60.0 ± 19.3	56.6 ± 18.7	52.3 ± 18.7*

* $p \leq 0.05$ compared to the group with no echocardiogram. FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; TLC: total lung capacity; VC: vital capacity; RV: residual volume; DLCO: diffusing capacity carbon monoxide.

Table 2. Comparison of the 361 patients with no evidence of pulmonary hypertension (PH) initially who developed PH over time compared to those who did not.

Demographic or Disease Characteristic	No PH, n = 220	Mild–Moderate PH, n = 92	Severe PH, n = 49
Female, %	85.0	81.1	71.4*
Race, %			
Caucasian	75.0	71.1	83.7
African American	19.6	28.9	16.3
Other	5.4	0	0
Age, yrs			
At diagnosis	44.0 ± 12.7	48.8 ± 14.4*	51.0 ± 13.8*
At Raynaud's onset	39.6 ± 13.5	43.9 ± 14.1*	44.5 ± 15.1*
At first non-Raynaud's symptom onset	42.0 ± 12.8	47.0 ± 14.7*	47.8 ± 14.5*
Smoking status, %			
Never smoker	49.8	51.7	42.9
Former smoker	34.7	40.5	38.8
Current smoker	15.5	7.9	18.4
At first visit, %			
Met ACR criteria	75.9	78.9	89.8*
Limited subtype	54.5	50.0	65.3
Raynaud's phenomenon severity, %			
No Raynaud's	5.1	5.6	0
Raynaud's only	52.8	44.9	44.7
Digital pits/ulcers	38.8	47.2	53.2
Digital gangrene	3.3	2.3	2.1
Missing fingers/toes, %	6.5	5.7	6.5
Serology positivity, %			
Antinuclear antibody	86.9	93.4*	81.4
Anticentromere antibody	16.8	19.7	20.9
Antitopoisomerase antibody	14.1	15.8	9.3
Initial pulmonary function testing (% of predicted ± SD)			
Time to echo (days)	177 ± 679	146 ± 1277	480 ± 1292
FEV_1	78.8 ± 19.1	75.8 ± 18.7	71.3 ± 18.0*
FVC	80.3 ± 20.1	75.8 ± 19.3	71.5 ± 18.1*
TLC	83.7 ± 18.7	81.1 ± 18.5	75.1 ± 18.1*
VC	80.8 ± 19.6	77.0 ± 19.3	71.4 ± 19.0*
RV	92.1 ± 29.3	89.4 ± 29.4	85.7 ± 29.6
DLCO	56.8 ± 16.3	52.1 ± 18.2*	48.8 ± 25.0*

* $p \leq 0.05$ compared to patients who do not develop PH. For definitions see Table 1.

DLCO measurement was observed (Wald statistic for model, 74.0). Other pulmonary function measures failed to predict the development of severe PH within our study period. A person with limited disease, mild–moderate PH, and an initial DLCO < 50% of predicted had an age-adjusted odds ratio of 8.55 for developing severe PH within 2 years compared to someone with diffuse disease, mild–moderate PH, and an initial DLCO ≥ 50% of predicted. As in the bivariate analysis, race and body mass index were not statistically significant covariates in multivariate analysis. Sex, PFT (measure of interstitial lung disease severity), the time interval from DLCO measurement, and diagnostic echocardiogram did not improve the logistic model predicting development of severe PH, and were not found to be confounders, and therefore were not included. We attempted similar modeling using the absence of severe PH predicting for the development of severe PH, and no to mild PH predicting for the development of moderate–severe PH; however, the models failed to converge.

DISCUSSION

The main finding of this study was that 13.6% of scleroderma patients without PH on initial echocardiography subsequently developed severe PH, while 17.7% of individuals with mild–moderate PH on initial echocardiography progressed to severe PH over a mean follow up of 3.2 years. The highest proportion developing severe PH was 27.3%; this occurred in individuals with limited disease, older than median age (47 yrs) at diagnosis, and having mild–moderate PH. This longitudinal analysis confirms that older-onset patients are at greater risk for developing PH, but we could not determine if duration of limited disease prior to diagnosis played a role[14,15]. Further, a DLCO < 50% of predicted was predictive for developing severe PH within the next 5 years in those initially without evidence of PH. The predictive utility of a low DLCO declines after 5 years, which likely reflects a reduction in statistical precision after 5 years given that our mean followup time was 3.2 years. However, it is possible that this initial risk effect may be related to the

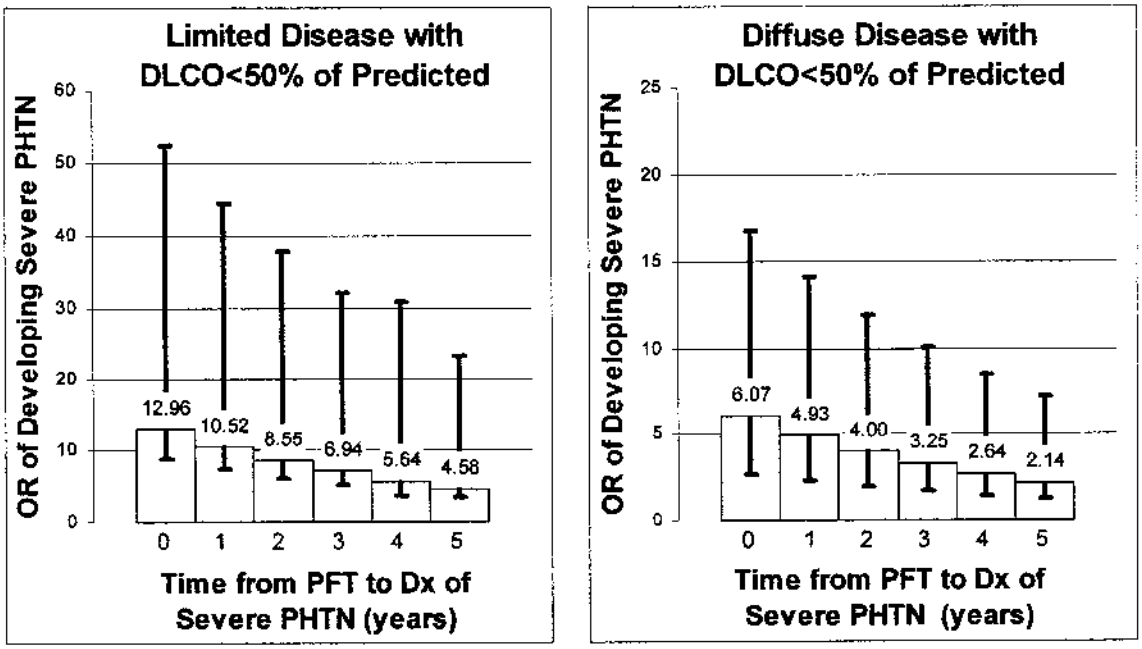

Figure 2. Odds ratios (OR) of developing severe PH for patients with a DLCO < 50% of predicted showing time from initial PFT to time of severe PH diagnosis, controlling for age of diagnosis (Wald statistic for model, 74.0). The reference group for this regression analysis had diffuse disease and DLCO ≥ 50% predicted, controlling for age of diagnosis of scleroderma. The 95% confidence intervals are demarcated by error bars and the value of the OR just above the end of the bar (note the 2 graphs are not to the same OR scale).

Table 3. The probability (p) of developing severe PH dependent upon disease subtype and median age for those with mild or moderate PH in a previous echocardiogram, determined by longitudinal logistic regression.

p (overall severe PH)	p (severe PH by disease subtype)		p (severe PH by disease subtype and median age of diagnosis)	
17.7%	Diffuse	11.3%	≤ 46.9—Diffuse	8.5%
			> 46.9—Diffuse	14.2%
	Limited	22.8%	≤ 46.9—Limited	17.5%
			> 46.9—Limited	27.3%

development of pulmonary fibrosis during the first 20 years after diagnosis[16]. The failure of lung volumes to predict for PH may reflect independent processes leading to distinct disease complications, although severe interstitial lung disease may lead to development of PH.

Our study is consistent with the findings of MacGregor, *et al* that the cumulative prevalence of PH was 13%[17]. Our results are also consistent with Steen's finding that 75% of individuals with PH had a DLCO < 55% of predicted[16]. The decreased DLCO may also be an early marker of pulmonary vascular obliteration prior to elevations in pulmonary artery pressures. Although DLCO may be decreased secondary to interstitial lung disease, adjusting for lung volumes in multivariate analysis did not decrease the DLCO association. This suggests that patients with low initial DLCO may benefit from earlier assessment for PH. The association of limited disease and PH has been reported previously[18] and is confirmed by our study. We also found an association of increased age at diagnosis with severe PH. Previous studies found a strong cross-sectional association between decreased DLCO, increased age, diffuse disease, and PH and increased risk of death, but did not quantify these risk factors longitudinally for development of severe PH[19-22]. Knowledge of the risk of progression or regression of PH is essential for making informed decisions about patient care including prognosis and treatment of patients, and may influence clinical study designs. It is also critical in counselling patients who have mild–moderate PH on screening tests about the likelihood of a serious disease complication, severe PH, in the future.

One limitation of the study is the use of a referral center cohort, which may be biased toward more severe cases of SSc. There is also a bias introduced by the fact that patients with worse pulmonary function testing were more likely to have echocardiograms performed; thus, we are more likely to uncover cases of lung disease. Therefore, it is evident that our study group reflected a biased sample of scleroderma patients. Although this would limit our ability to generalize

our conclusions to the entire SSc population, our demographics are still similar to those of other published scleroderma populations. Another limitation is the use of echocardiography to detect PH rather than right heart catheterization. Echocardiography is noninvasive, less expensive, and more readily available at medical centers; it has also been shown to have excellent sensitivity (90%) and good specificity (75%) compared to right heart catheterization[4-6]. The accuracy of echocardiography increases as the PAP increases[23] and therefore we used severe PH as our endpoint to improve the accuracy of the echocardiographic classification. Correlating NYHA functional classification would have been interesting at the time of echocardiogram, as many therapeutic decisions are based on functional classification, not PAP estimates; however, this information was not available for all patients. We also were not able to evaluate the effects of therapy on the natural history of PH in scleroderma because there were too few patients taking specific therapies for meaningful analysis within the context of the other findings. Therefore, the time to PH progression may be altered by the efficacy of therapeutic modalities utilized by individual patients and PH severity under- or overestimated. The major strength of our study is the size of the overall cohort and the relative number of patients who initially had no PH and developed severe PH during followup.

Once clinical symptoms occur, patients with scleroderma associated PH have a median survival as low as 12 months[4,21]. If new therapies could delay or prevent progression to this devastating complication, a major advance in this disease will have been achieved. Our study identifies those at high risk to develop severe PH, namely, patients older at diagnosis, with limited disease, and with an initial DLCO < 50% of predicted. Moreover, our study identifies that 17.7% of those diagnosed with mild–moderate PH will develop severe PH and 15.6% will regress to having no PH, providing additional insight into the natural history of progression of PH. This will enable clinicians to counsel patients regarding prognosis. With these risk factors, these patients may require close followup for progression to severe PH, and possibly more aggressive therapies to prevent progression as therapies become available.

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