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Improved Transplant-Free Survival in Patients With Systemic Sclerosis–Associated Pulmonary Hypertension and Interstitial Lung Disease

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Objective. **Survival in patients with systemic sclerosis (SSc)–associated pulmonary hypertension (PH) and interstitial lung disease (ILD) is poor. Evidence supporting the efficacy of aggressive pulmonary arterial hypertension (PAH)–targeted therapy in this population is limited. The aim of this study was to investigate transplant-free survival in patients with isolated SSc-related PAH or SSc-related PH-ILD who were treated with aggressive PAH-targeted therapy.**

Methods. **SSc patients with right-sided heart catheterization (RHC)–diagnosed precapillary PH (mean pulmonary artery pressure ≥25 mm Hg, pulmonary capillary wedge pressure ≤15 mm Hg, and pulmonary vascular resistance ≥240 dynes × second/cm^5) were included. Patients were classified as having ILD based on review of high-resolution computed tomography (CT) chest imaging and spirometry. The Kaplan-Meier method was applied and Cox proportional hazards models were constructed to analyze survival and identify predictive variables.**

Results. **Of 99 patients with SSc-related precapillary PH, 28% had SSc-related PAH and 72% had SSc-related PH-ILD. The 1- and 2-year survival estimates were, respectively, 72% and 59% in the SSc-related PH-ILD group versus 82% and 66% in the SSc-related PAH group ($P = 0.5$). Within 6 months of the diagnostic RHC, 24% of all patients were started on prostanoid therapy; an additional 24% were started on prostanoid therapy after 6 months. In the multivariate model, male sex (hazard ratio [HR] 0.7, $P = 0.01$) and prostanoid therapy initiation within 6 months of the RHC (HR 1.4, $P = 0.01$) were the only factors significantly associated with transplant-free survival, after accounting for the presence of ILD and severity of PH.**

Conclusion. **In this study, survival of patients with SSc-related PH-ILD was modestly improved relative to historical series. While these findings may not be generalizable, improved survival may be due partly to aggressive PAH-targeted therapy.**

Pulmonary arterial hypertension (PAH) is a leading cause of death in patients with systemic sclerosis (SSc). Although survival in patients with SSc-related PAH may appear improved in the current era of PAH-targeted therapy, this may be confounded by early screening and diagnosis (1), lead time bias (2), and predominant use of cohorts of patients with prevalent disease (3).

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Compared with isolated SSc-related PAH, SSc patients with both pulmonary hypertension (PH) and interstitial lung disease (ILD) have an increased risk of death (4–6). Despite use of PAH-targeted therapy, SSc-related PH-ILD has a 3-year survival rate of 21% (6). However, aggressive PAH-targeted therapy, defined as either combination therapy or the use of parenteral prostanoid, is underutilized in patients with SSc-related PAH and SSc-related PH-ILD as compared with patients with idiopathic PAH (7). At our center, the threshold to introduce aggressive PAH-targeted therapy for SSc-related PAH is perhaps lower than that in usual practice (8) and is not influenced by the extent of concurrent ILD. The purpose of the present study was to assess survival rates and prognostic variables in patients with SSc-related PAH and SSc-related PH-ILD, and to determine whether aggressive PAH-targeted therapy improves survival, particularly in patients with SSc-related PH-ILD.

PATIENTS AND METHODS

Patient population. This was a retrospective cohort study of patients with SSc-related PAH and SSc-related PH-ILD, who were all treated with PAH-targeted therapy. The Institutional Review Board at the University of California, Los Angeles (UCLA) approved this study (no. 12-000738).

Eligibility criteria. Criteria for study eligibility were as follows: 1) ≥18 years of age, 2) diagnosed as having SSc (9), 3) referred to the UCLA PH clinic between January 1, 2000 and January 1, 2012, and 4) diagnosed as having precapillary PH (defined as a mean pulmonary arterial pressure [PAP] ≥25 mm Hg, pulmonary capillary wedge pressure [PCWP] ≤15 mm Hg, and pulmonary vascular resistance [PVR] ≥240 dynes × seconds/cm^5, in the absence of other causes of PH) (10).

Baseline assessments. The date of the diagnostic right-sided heart catheterization (RHC) served as the baseline date, and all assessments were independently extracted in duplicate from electronic medical records. The extent of missing data was minimized by rigorous chart extraction, including extracting records from other institutions/clinics. Duration of SSc was based on the difference between the dates of the diagnostic RHC and SSc onset (defined as the date a rheumatologist diagnosed the patient as having SSc). Relevant laboratory data were extracted if tests were performed within 6 months of the diagnostic RHC.

Selected comorbidities were recorded, including type 1 and type 2 diabetes requiring insulin, systemic hypertension, coronary artery disease (defined as prior documented myocardial infarction, typical angina, coronary revascularization, or coronary artery stenosis of ≥50% on angiography), and renal insufficiency as determined by the Modification of Diet in Renal Disease (MDRD) estimated glomerular filtration rate (GFR).

Data on supplemental oxygen use, pulmonary function test results, and 6-minute walk distance were extracted if collected within 6 months of the diagnostic RHC. Oxygen saturation data related to the 6-minute walk test were not extracted due to a lack of systematic assessment and/or use of temporal pulse oximetry.

Primary predictors. *Interstitial lung disease.* The diagnosis of ILD was primarily based on review of high-resolution computed tomography (CT) imaging of the chest obtained within 6 months of the diagnostic RHC. Patients were classified as having significant ILD if the total disease extent was >30%; when high-resolution CT yielded indeterminate results (i.e., disease extent was 10–30%), a forced vital capacity (FVC) of <70% of the predicted value was used to classify patients as having ILD (11). This valid ILD staging system has had prognostic significance in prior survival analyses of patients with SSc ILD (6). A pulmonologist (Rajan Saggar) reviewed the high-resolution CT images under blinded conditions to determine disease presence/extent. Patients were classified as not having significant ILD if the extent of the disease was <10% on high-resolution CT or if the FVC was ≥70%. High-resolution CT images were unavailable for 11 patients; in all of those patients, results of radiology reports confirmed the presence of diffuse ILD (i.e., >30%). As such, these 11 patients were classified as having ILD.

Aggressive PAH-targeted therapy. Data on PAH-targeted therapy were extracted by reviewing the medication portion of every progress note for all patients until the censor date. Aggressive PAH-targeted therapy was defined a priori as the use of a prostanoid (oral, inhaled, or parenteral), and prostanoid initiation within 6 months of the diagnostic RHC (12). This 6-month threshold was selected based on the following: 1) the clinical experience of the authors, 2) the time cutoff reported in a study on the long-term survival experience of patients with SSc-related PAH in the setting of PH-targeted therapy with epoprostenol (12), and 3) the recognition that oral therapies are often considered first-line PH-targeted therapy in the population of patients with SSc-related PH-ILD (6) and that parenteral therapies often require a reasonable amount of time for insurance authorization and actual initiation.

Prostanoids were administered via the following routes: parenteral (n = 33 patients), inhaled (n = 7 patients), and oral (n = 4 patients). Treprostinil was used in all patients who received parenteral prostanoids. For patients with SSc-related PH-ILD receiving prostanoids, 25 (74%) were receiving parenteral prostanoid, while 5 (15%) were receiving inhaled prostanoid, and 4 (12%) were receiving oral prostanoid. The median maximum dosage achieved in the parenteral prostanoid cohort was 54 ng/kg/minute (interquartile range [IQR] 42.0–82.3).

Outcome measures. The primary outcome measure was transplant-free survival. Dates of death and lung transplantation were recorded until the censor date of June 1, 2012. Mortality data were obtained from the electronic medical record, National Death Index, Social Security Death Index, as well as via online obituaries. If a patient was lost to followup, the date of last contact at UCLA was entered as the censor date.

Secondary outcome measures included 1) time to initiation of prostanoid therapy from the diagnostic RHC, 2) differences in baseline hemodynamics and pulmonary function test results between patients who received early (≤6 months

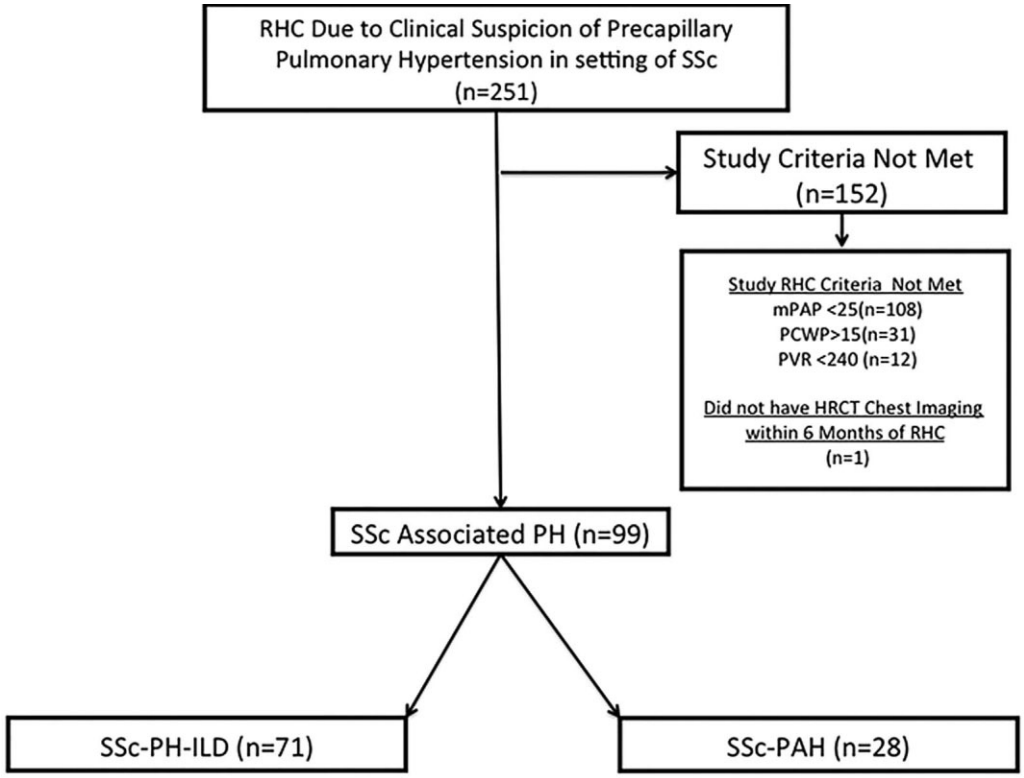


Figure 1. Flow chart of the selection of systemic sclerosis (SSc) patients for study inclusion. RHC = right-sided heart catheterization; mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; HRCT = high-resolution computed tomography; PH = pulmonary hypertension; ILD = interstitial lung disease; PAH = pulmonary arterial hypertension.

from the RHC) versus late (>6 months from the RHC) versus no prostanoid use, and 3) maximum dosage of parenteral prostanoid administered.

Statistical analysis. Analyses were performed using JMP 10.0 for Macintosh. Continuous parametric data were expressed as the mean ± SD, and continuous nonparametric data were expressed as the median and IQR. Between-group comparisons were conducted using independent *t*-tests for continuous parametric data, Wilcoxon's rank sum test for continuous nonparametric data, and chi-square tests and Fisher's exact tests for proportions. The Kaplan-Meier method was used for the survival analysis, and the log rank test was used to compare groups. Multivariate Cox proportional hazards modeling was performed to determine the variables associated with transplant-free survival.

RESULTS

Patient characteristics. Among the 251 patients with SSc who underwent RHC during the study period, 99 met RHC criteria for either SSc-related PAH (n = 28) or SSc-related PH-ILD (n = 71) (Figure 1). Of these 99 patients, the majority (71%) underwent their diagnostic RHC at UCLA. For the remaining patients, the median time from the outside RHC to the initial PH clinic consultation at UCLA was 3.5 months (IQR 1.4–18.5 months).

Baseline demographic characteristics and comorbidities were similar among patients with SSc-related PAH and those with SSc-related PH-ILD, with the exception of sex and estimated GFR (Table 1). The majority of patients in both groups had limited cutaneous SSc, with a median disease duration of 7 years. The presence of diabetes mellitus requiring insulin was rare (7% in both groups), as was status as a current smoker (3 patients with SSc-related PAH and 1 patient with SSc-related PH-ILD). More patients in the SSc-related PH-ILD group as compared with the SSc-related PAH group were receiving low-dose prednisone (48% versus 21%, respectively; $P = 0.02$) and immunosuppressive agents other than prednisone (39% versus 21%, respectively; $P = 0.07$).

Hemodynamics and pulmonary function. Baseline systemic and pulmonary hemodynamics, 6-minute walk distance, and need for supplemental oxygen were

Table 1. Baseline characteristics of the study population*

	SSc-related PAH (n = 28)	SSc-related PH-ILD (n = 71)
Age, mean ± SD years	59.7 ± 12.8	54.5 ± 12.1
Sex, female	26 (92.9)†	50 (70.4)
Ethnicity‡		
White	18 (64.3)	37 (52.1)
African American	3 (10.7)	9 (12.7)
Hispanic	5 (17.9)	16 (22.5)
Asian	1 (3.6)	9 (12.7)
Other	1 (3.6)	0
SSc type§		
Limited cutaneous	20 (71.4)	50 (70.4)
Diffuse cutaneous	8 (28.6)	21 (29.6)
SSc duration, median (IQR) years	7.0 (2.8–13.9)	7.3 (2.7–13.2)
Coronary artery disease	4 (14.3)	4 (5.6)
Systemic hypertension	9 (32.1)	16 (22.5)
Hgb, mean ± SD mg/dl¶	12.3 ± 1.6	12.5 ± 1.9
MDRD estimated GFR, median (IQR) ml/minute/1.73 m^2	58.3 (53.1–77.4)#	76.4 (59.1–105.0)

* Except where indicated otherwise, values are the number (%). IQR = interquartile range; Hgb = hemoglobin; MDRD = Modification of Diet in Renal Disease; GFR = glomerular filtration rate.
† $P = 0.02$ versus systemic sclerosis (SSc)–related pulmonary hypertension (PH) complicated by interstitial lung disease (ILD).
‡ Due to low numbers in subgroups, chi-square test was not performed.
§ Information on SSc type was missing for 1 patient in the SSc-related PH-ILD group; for analysis, the patient was classified as having limited cutaneous SSc.
¶ Data available on 26 patients with SSc-related pulmonary arterial hypertension (PAH) and 68 patients with SSc-related PH-ILD.
# $P = 0.01$ versus SSc-related PH-ILD.

similar among patients with SSc-related PAH and patients with SSc-related PH-ILD (Table 2). Forty-nine percent of all SSc patients had severe precapillary PH, defined as a mean PAP ≥40 mm Hg (54% of patients with SSc-related PAH and 48% of patients with SSc-related PH-ILD). Patients with SSc-related PH-ILD had significantly lower FVC (% predicted) and diffusing capacity for carbon monoxide (DLco) (% predicted) as compared with SSc-related PAH patients; however, the mean FVC/DLco was identical in both groups.

PAH-targeted therapies. Data on PAH-specific therapy were available for 91 patients (92% of the patient cohort) (Table 3). None of the patients were receiving aggressive PAH-targeted therapy (i.e., combination therapy or prostanoid) during the initial PH consultation at the UCLA clinic. For the majority of patients, initial PAH therapy included a phosphodiesterase 5 (PDE-5) inhibitor (43%) or an endothelin receptor antagonist (45%). Over 50% of the entire cohort was treated with at least 2 PH-specific therapies during the study period. Twenty-four percent of patients (1 patient with SSc-related PAH [4% of the group] and 21 patients with SSc-related PH-ILD [32% of the group]) started on prostanoid ≤6 months after the RHC (early prostanoid initiation), while an additional 24% (9 patients with SSc-related PAH [36% of the group] and 13 with SSc-related PH-ILD [20% of the group]) started on prostanoid >6 months after the diagnostic RHC (late prostanoid initiation). The median time from RHC to initiation of a prostanoid was 0.5 months (IQR 0–2.9 months) for early prostanoid initiators and 26.4 months (IQR 10.9–40.4 months) for late prostanoid initiators.

Early versus late prostanoid initiation. *Pulmonary hemodynamics.* The mean PAP was significantly lower among patients who never received prostanoid therapy versus patients who were started on prostanoid therapy early or late, with a mean ± SD of 38.1 ± 9.0 in those who never received prostanoid, 45.0 ± 10.2 in those who received the drug ≤6 months after the RHC, and 44.1 ± 11.7 in those who received prostanoid >6 months after the RHC ($P = 0.03$). The same was true for the PVR index, with a median of 768.1 (IQR 511.3–1,124.9) in those who never received prostanoid therapy, 1,184.8 (IQR 643.5–1,584.4) in those who received the drug early, and 1,032.1 (IQR 619.7–1,404.1) in those who received the drug late ($P = 0.03$). There was no difference in the mean PAP or median PVR index between patients who started on a prostanoid early versus late.

Pulmonary function. Patients who were started on treatment with a prostanoid early had a trend toward a lower mean FVC (% predicted) (mean ± SD 56.3 ± 20.0) as compared with patients who were started on prostanoid therapy late (71.0 ± 13.8) and patients who never received prostanoid therapy (62.2 ± 23.3) ($P = 0.09$). There was no difference in mean DLco (% predicted) between the 3 groups.

Transplant-free survival. Followup time was similar between the 2 groups, with a mean ± SD of 30.9 ± 29.7 months and a median of 19.8 months (IQR 6.3–50) among patients with SSc-related PAH and a mean ± SD of 26.8 ± 24.3 months and a median of 18.6 months (IQR 8.1–37.7) among patients with SSc-related PH-ILD. Only 3 patients were lost to followup (1 patient with SSc-related PAH and 2 patients with SSc-related PH-ILD). During the study, 41 patients (41%) died (15 patients [54%] in the SSc-related PAH group and 26 patients [37%] in the SSc-related PH-ILD group), and 14 patients (14%) underwent lung transplantation (all 14 had SSc-related PH-ILD). The 1-, 2-, and 3-year survival estimates were, respectively, 82%, 66%, and 60% among patients with SSc-related PAH and 72%, 59%, and 50%

Table 2. Baseline hemodynamic and pulmonary function features of the study population*

	SSc-related PAH (n = 28)	SSc-related PH-ILD (n = 71)
Hemodynamics		
SBP, mm Hg	124.3 ± 23.8	120.8 ± 21.3
DBP, mm Hg	71.6 ± 13.6	69.7 ± 11.8
Heart rate, bpm	87.7 ± 12.3	87.0 ± 16.0
Mean PAP, mm Hg	43.4 ± 12.5	39.7 ± 9.4
PAWP, mm Hg	9.9 ± 3.3	9.6 ± 3.5
PVR index, median (IQR) dynes × seconds/cm^5	1,064.2 (551.7–1,300)	832.0 (600–1,280)
RAP, mm Hg	9.8 ± 6.8	7.4 ± 4.8
Cardiac output	4.6 ± 1.3	4.6 ± 1.2
Cardiac index	2.8 ± 0.7 (n = 21)	2.8 ± 0.7 (n = 57)
Use of supplemental oxygen, no. (%)	14 (53.8) (n = 26)	27 (39.1) (n = 69)
6-minute walk distance, median (IQR) meters	279 (132.5–414) (n = 18)	275 (121.5–346.5) (n = 48)
FVC, % predicted	82.7 ± 15.2 (n = 21)†	56.0 ± 18.2 (n = 59)
$DLCO_{adj}$ for Hgb, % predicted	50.6 ± 13.6 (n = 18)‡	34.4 ± 13.4 (n = 56)
FVC/DLCO ratio	1.8 ± 0.5 (n = 18)	1.8 ± 0.7 (n = 55)

* Except where indicated otherwise, values are the mean ± SD. SBP = systolic blood pressure; DBP = diastolic blood pressure; bpm = beats per minute; PAP = pulmonary artery pressure; PAWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; FVC = forced vital capacity; $DLCO_{adj}$ = diffusing capacity for carbon monoxide adjusted (see Table 1 for other definitions).
† $P < 0.0001$ versus SSc-related PH-ILD.
‡ $P = 0.0001$ versus SSc-related PH-ILD.

among patients with SSc-related PH-ILD (Figure 2). There were no differences in transplant-free survival between patients with SSc-related PAH and those with SSc-related PH-ILD (log rank $P = 0.5$).

To minimize the possibility of lead time bias, we performed a second survival analysis that excluded 13 patients who had their first pulmonary consultation at UCLA >3 months after their diagnostic RHC was performed at a center other than UCLA. The results of this survival analysis did not differ from those of the overall analysis: there was no difference in survival between the remaining SSc-related PAH patients (n = 22) and SSc-related PH-ILD patients (n = 64) (log rank $P = 0.9$). The 1-, 2-, 3- year survival estimates were, respectively, 76%, 63%, and 55% among patients with SSc-related PAH and 70%, 60%, 49% among patients with SSc-related PH-ILD. In addition, to address the issue of a possible immortality bias, we explored whether patients who were referred to UCLA after their outside diagnostic RHC (n = 29 patients) disproportionately received early prostanoid therapy. We found that only 3 of these patients received early prostanoid therapy (12 received late prostanoid therapy, 12 received no prostanoid therapy, and 2 patients had missing medication data).

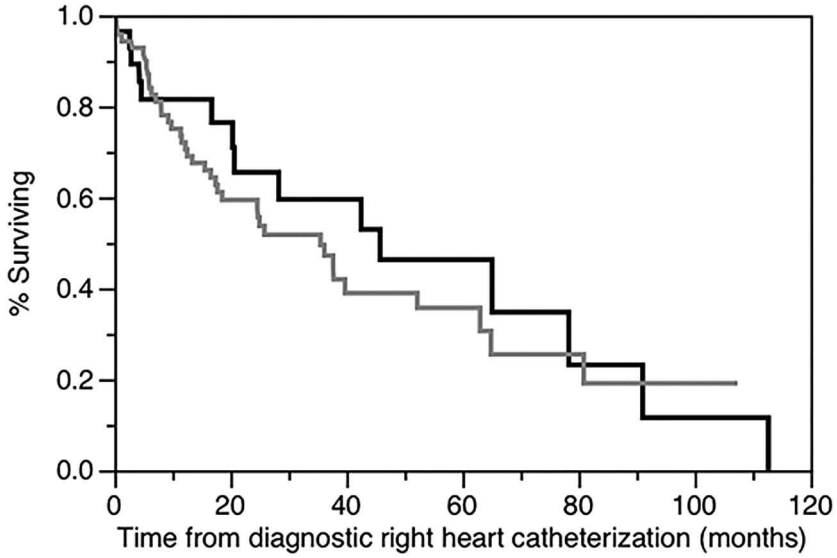
Table 3. Initial PH medication taken during the study*

	SSc-related PAH (n = 25)	SSc-related PH-ILD (n = 66)
Phosphodiesterase 5 inhibitor	13 (52.0)	26 (39.4)
Endothelin receptor antagonist	11 (44.0)	30 (45.5)
Prostanoid	0	7 (10.6)
Phosphodiesterase 5 inhibitor and endothelin receptor antagonist	1 (4.0)	2 (3.0)
Phosphodiesterase 5 inhibitor and prostanoid	0	1 (1.5)

* Values are the number (%). See Table 1 for definitions.

Factors associated with transplant-free survival. To avoid overfitting (i.e., including too many variables in the model for the number of outcome events), the following initial covariates were entered into the model: ILD (i.e., extent of ILD based on the scoring system described by Goh et al [11]; categorical variable), PVR index (in dynes × seconds/cm^5/m^2; continuous variable), prostanoid use (early use [i.e., within 6 months of RHC], late use [i.e., 6 months after RHC], or no prostanoid use; categorical variable). The first 2 variables were included in the model given their independent association with survival in SSc (5). In this initial model, only early prostanoid use was significantly associated with improved survival (hazard ratio [HR] 1.3, $P = 0.006$).

The following covariates, which in prior studies were associated with survival in patients with SSc-related ILD, were added to the model sequentially and retained if significantly associated with the outcome: age (years), sex, African American, SSc type (diffuse cutaneous or limited cutaneous), SSc duration (years), hemoglobin level (gm/dl), MDRD estimated GFR, supplemental oxygen at diagnosis, use of prednisone or other immu-



Number at risk

	0	1 year	2 years	3 years
SSc-PAH	28	20	13	10
SSc-PH-ILD	71	68	45	32

Figure 2. Kaplan-Meier survival curves demonstrating no difference in survival between patients with systemic sclerosis (SSc)–related pulmonary arterial hypertension (PAH) alone (black line) and patients with SSc-related pulmonary hypertension (PH) complicated by interstitial lung disease (ILD) (gray line) ($P = 0.5$ by log rank test).

nosuppressive agent (yes or no). Among these additional covariates, only sex was significantly associated with the outcome and included in the final model with the initial covariates (Table 4). After accounting for sex, PVR index data, and ILD status, early prostanoid use remained significantly associated with improved survival (HR 1.4, $P < 0.01$).

Table 4. Multivariate model of factors associated with transplant-free survival in patients with SSc-related PH*

Variable	Hazard ratio	Standard error	*P*
ILD (referent: no significant ILD)	0.9	0.2	0.6
Prostanoid initiation (referent: no prostanoid therapy)			0.01
≤6 months after RHC	1.4	0.2	
>6 months after RHC	0.5	0.3	
Sex (referent: women)	0.7	0.2	0.01
PVR index	1.0	0.0003	0.04

* RHC = right heart catheterization; PVR = pulmonary vascular resistance (see Table 1 for other definitions).

DISCUSSION

We evaluated transplant-free survival rates and associated prognostic factors among patients with SSc-related PAH and SSc-related PH-ILD, in the setting of rigorous phenotyping for degree of ILD and precapillary PH, as well as aggressive PAH-targeted therapy, where nearly half of all patients received prostanoid therapy. The results reported herein demonstrate similar survival rates among patients with SSc-related PH-ILD and SSc-related PAH. Of the baseline variables, aggressive PAH-targeted therapy (i.e., prostanoid initiation within 6 months of the diagnostic RHC) was a predictor of improved transplant-free survival, while the presence of ILD was not a significant factor.

Compared with patients with SSc-related PAH, patients with SSc-related PH-ILD historically have inferior survival rates, with an estimated 3-year survival rate of 21–35% in prior series (4,6,13). Despite the fact that heterogeneous methodology was used to define ILD in some of these prior studies, the present cohort of patients with SSc-related PH-ILD had a 3-year survival

rate of 50%. While multiple factors may explain this relatively improved survival rate, our cohort has similar hemodynamic and pulmonary function profiles compared with the aforementioned cohorts (4,6).

One possible explanation for improved survival is our aggressive use of PAH-targeted therapy, specifically the early use of prostanoid therapy. In general, prostanoid therapy is underutilized in PAH (14), particularly in the population of patients with SSc-related PAH (7). Nevertheless, parenteral prostanoid is considered optimal therapy for patients with advanced/progressive PAH who are at higher risk of death (15), and it may confer a survival advantage when compared with oral PAH-targeted therapies (16).

Prostanoid is likely further restricted as a treatment for SSc-related PH-ILD due to the possibility of ventilation/perfusion mismatch–induced hypoxemia (17). This concern is reflected in reduced prostanoid use (between 9% and 17%) in prior SSc-related PH-ILD cohorts (5,6,18). In contrast, approximately half of the present SSc-related PH-ILD cohort received prostanoid therapy during the study period. Despite the gas exchange concerns, SSc-related PH-ILD may in fact be the ideal phenotype for prostanoid therapy given the often severely advanced and progressive pulmonary vascular disease evident at diagnosis (including World Health Organization [WHO] functional class III or IV symptomatology [6], baseline oxygen requirements greater than those required in SSc-related PAH [5], and increasing oxygen requirements over time [6]).

In addition, when a parenteral prostanoid is administered, suboptimal dosing (<40 ng/kg/minute for infusions of treprostinil) may affect its efficacy and has been independently associated with poor survival in patients with WHO Group I PAH (19), and may also contribute to the modest outcomes observed in prior SSc-related PAH cohorts that used epoprostenol (12,20). In our study, 75% of patients received a maximum dose above 40 ng/kg/minute, which was the favorable prognostic threshold reported by Benza and colleagues (19). Cautious use of prostanoids may have a therapeutic role in the setting of pulmonary venoocclusive disease (PVOD)–like lesions (21), which appear to be a distinguishing feature of the pulmonary vasculopathology of SSc-related PAH (22) and may be increased in the setting of superimposed ILD (23). While patients in the present study were not specifically assessed for pathologic evidence of PVOD, we did not observe clinical worsening clearly related to initiation of PAH-targeted therapy that may have suggested underlying PVOD.

However, given that this was a retrospective study, there may be unexamined or unidentified factors that favorably affect survival (i.e., greater family support, superior insight into their condition, or determination to overcome their disease), which differed between patients who received early prostanoid therapy compared with the reference group of patients who received no prostanoid therapy. However, the baseline hemodynamic and pulmonary function parameters were significantly worse in patients who received early prostanoid therapy compared with the reference group; thus, it is possible that the patients who received early prostanoid therapy had a potential survival disadvantage at baseline. Nevertheless, the implication that early prostanoid use is independently associated with improved survival in SSc-related PH is hypothesis-generating only and requires confirmation in a prospective, randomized controlled trial.

The multivariate model also indicated that late prostanoid use portends a survival disadvantage. Given that patients who received late prostanoid therapy had worse baseline hemodynamics compared with patients who never received prostanoid therapy, this survival disadvantage is unlikely to be a result of late prostanoid administration and more realistically, a reflection of the advanced illness in this subset of patients receiving prostanoid late in the course of the disease. This interpretation is consistent with the results of a recent study, which demonstrated that delayed and urgent prostanoid initiation was associated with increased mortality in patients with PAH (24). Overall, the present findings suggest that there may be a finite, early window of opportunity to possibly improve survival rates in patients with SSc-related PAH and SSc-related PH-ILD using prostanoid therapy.

In addition to early prostanoid use, male sex was independently associated with survival in the multivariate model. Although prior studies have shown that male sex 1) is a predictor of poor survival in SSc (without lung involvement) (25) and SSc-related PAH (13,26), 2) is a predictor of the development of severe ILD (without associated PH) (27), and 3) may be overrepresented in SSc-related PH-ILD (versus SSc-related PAH) (18), our study is the first to suggest that male sex is an independent predictor of poor survival in the setting of well-characterized SSc-related PH-ILD. In addition, the PVR index has been previously reported by Mathai and coworkers (5) as a predictor of mortality in SSc-related PH-ILD; however, the hazard ratio (1.05) was similar to that in our study (1.00). Other factors previously reported as being independently associated with survival in

SSc-related PH-ILD were either not associated with survival in our study (i.e., MDRD estimated GFR [6]) or were not assessed due to significant missing data (i.e., pericardial effusion [13], diffusing capacity [13], and worsening oxygenation [6]).

Interestingly, the present study demonstrated that significant ILD was not an independent risk factor for death or need for transplant in patients with SSc-related PH, in contrast to prior studies, which employed the same methodology to define significant ILD (11,28). In addition, there was no difference in transplant-free survival in patients with or without ILD. While most of the ILD patients had established ILD of >2 years' duration, these results suggest that early prostanoid therapy may be effective in patients with SSc-related PH-ILD.

The present study has several strengths. First, 2 study physicians (Rajeev Saggar and Rajan Saggar) performed the majority of the RHCs, thereby improving reliability. Second, a single investigator (Rajan Saggar) used a validated measure of ILD (11,28) to diagnose ILD under blinded conditions. Third, patient followup was a mean of >2 years. Finally, the size of our SSc-related PH-ILD cohort was comparable with those in a prior series by Le Pavec and colleagues (n = 70) (6) and a prior series by Condliffe and colleagues (n = 56) (4). The high percentage of ILD patients in the present SSc-related PH cohort is likely a reflection of the relatively large number of lung transplants performed at our institution in patients with SSc-related ILD and the high referral rate.

Our study has important limitations. The analysis was limited to the data available and is subject to both measurement and reporting bias. Moreover, inferences cannot be made regarding causality.

Given the retrospective nature of this study, systematic bias is possible, and patients who received early prostanoid therapy may have had improved survival for reasons other than early prostanoid therapy. Furthermore, the 3-year survival estimate should be interpreted with caution given that the median followup time per patient was <3 years. Type II errors may occur in any inference test, particularly in retrospective studies. However, our finding of a P value of <0.01 for the aggressive use of prostanoid in the multivariate model is somewhat reassuring.

There is likely some selection bias. For example, patients with SSc-related PH-ILD may have appeared more ill at the time RHC was performed, prompting the initiation of more aggressive PAH-targeted therapy. The observation that patients who received early prostanoid therapy were more likely to have ILD supports this possibility. In addition, background PAH-targeted therapy (i.e., type and onset of PDE-5 inhibitor or endothelin receptor antagonist use) was not included as a covariate in the multivariate model given variability in the use and administration of these agents. Similarly, the impact of type of prostanoid administered (i.e., parenteral versus oral versus inhaled) on survival was also not explored in the present analysis due to the small numbers of patients receiving oral and inhaled prostanoid.

While survival in our cohort appears improved as compared with historical series, this is a single-center study and results may not be generalizable to other populations. Finally, to adequately address the question as to whether early aggressive PAH-targeted therapy improves survival in SSc-related PH-ILD, one would need a control population of SSc-related PH-ILD patients who were not receiving PAH therapy; this population does not exist at our institution.

In conclusion, survival in patients with SSc-related PH-ILD is historically poor and this may in part be due to the fact that these patients are understudied in clinical trials and likely undertreated for PH. Our experience suggests modestly improved survival rates in these patients compared with patients in prior series. While multiple factors may affect survival in patients with SSc-related PH-ILD, early use of prostanoid therapy was associated with improved survival in our cohort. Future randomized controlled trials are needed to investigate outcomes associated with early use of prostanoid therapy in this vulnerable patient population.

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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. Rajan Saggar 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.

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