Title

Transplant-Free Survival in Patients with Systemic Sclerosis-Associated Pulmonary Hypertension and Interstitial Lung Disease

Author

Volkmann, Elizabeth

Publication Date

2014

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Transplant-Free Survival in Patients with Systemic Sclerosis-Associated Pulmonary Hypertension and Interstitial Lung Disease

A thesis submitted in partial satisfaction

of the requirements for the degree Master of Science

in Clinical Research

by

Elizabeth R. Volkmann, M.D.

2014

ABSTRACT OF THESIS

Transplant-Free Survival in Patients with Systemic Sclerosis-Associated Pulmonary Hypertension and Interstitial Lung Disease

by

Elizabeth R. Volkmann, M.D.

Master of Science in Clinical Research

University of California, Los Angeles, 2014

Professor Robert M. Elashoff, Chair

Background: Survival in patients with systemic sclerosis (SSc) associated pulmonary hypertension (PH) and interstitial lung disease (ILD) [SSc-PH-ILD] is poor. This study investigates transplant-free survival in patients with isolated SSc pulmonary arterial hypertension (SSc-PAH) and SSc-PH-ILD treated with aggressive PAH-targeted therapy.

Methods: Kaplan-Meier and Cox proportional hazards models were constructed to analyze survival and identify predictive variables.

Results: The 1- and 2-year survival estimates were 72% and 59% versus 82% and 66% for the SSc-PH-ILD and SSc-PAH groups, respectively (p=0.5). In the Cox model, male gender (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: Survival of patients with SSc-PH-ILD has improved relative to historical series and may in part be due to aggressive PAH-targeted therapy.

The thesis of Elizabeth R. Volkmann is approved.

Ning Li

Rajan Saggar

Van Savage

Donald P. Tashkin

Robert M. Elashoff, Committee Chair

University of California, Los Angeles

2014

DEDICATION PAGE

For Bijan

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

ACKNOWLEDGEMENTS

Chapter 1 is a version of *Improved Transplant-Free Survival in Patients with Systemic Sclerosis-Associated Pulmonary Hypertension and Interstitial Lung Disease* (Volkmann ER, Saggar R, Khanna D, Torres B, Flora A, Yoder L, Clements PJ, Elashoff RM, Ross DJ, Agrawal H, Borazan N, Furst DE, Saggar R. Arthritis Rheum July 2014 [doi: 10.1002/art.38623]). Below is a description of the co-author contributions.

Rajeev Saggar: Project conception, measurement of right heart catheterization parameters, manuscript preparation and revision

Dinesh Khanna: Manuscript preparation and revision

Bryant Torres: Project conception, chart extraction

Lynne Yoder: Project conception, chart extraction

Philip J. Clements: Project conception, manuscript preparation

Robert M. Elashoff: Statistical analysis

David J. Ross: Manuscript preparation

Harsh Agrawal: Project conception, chart extraction

Nabeel Borazan: Chart extraction

Daniel E. Furst: Project conception, manuscript preparation

Rajan Saggar: Principal investigator

The Specialty Training and Advanced Research (STAR) Program at the David Geffen School of Medicine at UCLA provided funding for this work.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a leading cause of death in systemic sclerosis (SSc). Although survival in SSc-PAH patients 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 analysis of predominantly prevalent cohorts (3).

Compared with isolated SSc-PAH, SSc patients with combined pulmonary hypertension and interstitial lung disease (SSc-PH-ILD) have a 5-fold increased risk of death (4, 5, 6). Patients with combined SSc-PH-ILD are generally excluded from clinical trials evaluating PH-targeted therapy, and as such, there is minimal data available on the efficacy of these agents in this patient population. In a retrospective study of 70 patients with SSc-PH-ILD treated with PH-targeted therapies, Le Pavec and colleagues (6) found no difference in survival compared with historical series of patients who were not treated with PH-targeted therapy (1-, 2-, and 3-year survival estimates were 71%, 39%, and 21%, respectively)

In this study, the majority of patients received initial monotherapy with either an endothelial receptor antagonist (ERA) (66%), or a phosphodiesterase type 5 (PDE-5) inhibitor (29%), and only 6% received a prostanoid (6). However, few patients in this study (6) received aggressive PAH-targeted therapy, defined as either combination therapy or the use of parenteral prostanoid (7).

At our center, the threshold to introduce aggressive PAH-targeted therapy for SSc-PAH is perhaps lower than 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-PAH and SSc-PH-ILD, and to determine whether aggressive PAH-targeted therapy improves survival, particularly in SSc-PH-ILD patients.

PATIENTS AND METHODS

Patient population

This is a retrospective cohort study of patients with SSc-PAH and SSc-PH-ILD, who were all treated with PAH-targeted therapy. The Institutional Review Board at UCLA approved this study (IRB #12-000738).

Eligibility criteria

Eligible participants fulfilled the following criteria: (*i*) ≥18 years of age; (*ii*) SSc (9); (*iii*) referral to the UCLA PH clinic between January 1, 2000 and January 1, 2012; and (*iv*) precapillary PH, defined as a mean pulmonary arterial pressure (mPAP) ≥25 mm Hg, pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg, and pulmonary vascular resistance (PVR) ≥240 dynesxseconds/cm^5, in the absence of other causes of PH (10).

Baseline assessments

The date of the diagnostic RHC served as the baseline date, and all assessments were doubly and independently extracted from electronic medical records. Extent of missing data was minimized by rigorous chart extraction, including records from outside 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 with SSc). Relevant laboratory studies were extracted if collected within six months of the diagnostic RHC.

Selected co-morbidities were recorded, including type I/II diabetes requiring insulin, systemic hypertension, and coronary artery disease (defined as prior documented myocardial infarction, typical angina, coronary revascularization, or coronary artery stenosis by angiography

≥50%), and renal insufficiency as determined by the Modification of diet in renal disease (MDRD) estimated glomerular filtration rate (eGFR).

Supplemental oxygen use, pulmonary function test (PFT) results, and six-minute walk distance (6MWD) were extracted if available within 6 months of the diagnostic RHC. Oxygen saturation data related to 6MW testing was 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 (HRCT) 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 HRCT findings were indeterminant (i.e. disease extent 10-30%), a forced vital capacity (FVC) <70% predicted value qualified as ILD (11). This valid ILD staging system has been used in prior survival analyses of patients with SSc-PH-ILD with prognostic significance (6). A pulmonologist (RS) blindly reviewed HRCT imaging to determine disease presence/extent. Patients were classified as without significant ILD with either HRCT extent of disease <10%, or FVC ≥70% in the setting of indeterminate HRCT extent of disease. HRCT images were unavailable for review for 11 patients; all of these patients had radiology reports confirming the presence of diffuse ILD (i.e. >30%). As such, these 11 patients were classified as having ILD.

Aggressive PAH-targeted therapy

PAH-targeted therapy data was 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: (*i*) the use of a prostanoid (oral, inhaled or parenteral), and (*ii*) prostanoid initiation within six months of the diagnostic RHC (12). This six month threshold was selected based on the following: (i) the clinical experience of the authors; (ii) the time 'cutoffs' reported in the long-term survival experience of SSc-PAH patients in the setting of PH-targeted therapy with epoprostenol (12); and (iii) the appreciation that oral therapies are often considered first-line PH-targeted therapy in the SSc-PH-ILD population (6) and that parenteral therapies often require a reasonable amount of time for insurance authorization and actual initiation.

The types of prostanoids used for the entire cohort were as follows: parenteral (n=33 patients), inhaled (n=7 patients), and oral (n=4 patients). Treprostinil was used in all patients who received parenteral prostanoid. For SSc-PH-ILD patients initiated on a prostanoid, 25 (74%) used parenteral prostanoid, while 5 (15%) used inhaled and 4 (12%) used oral prostanoid. The median maximum dosage achieved in the parenteral prostanoid cohort was 54 ng/kg/min (IR 42.0-82.3).

Outcome measures

The primary outcome was transplant free survival. Dates of death and lung transplantation (LT) were collected up until the censor date of June 1, 2012. Mortality data was obtained from the EMR, National Death Index, Social Security Death Index, as well as online obituaries. If a patient was lost to follow up, the date of last contact at UCLA was entered as the censor date.

A secondary aim was determine factors associated with transplant free survival. Additional exploratory analyses included: (*i*) time to initiation of prostanoid therapy from the diagnostic RHC; (*ii*) differences in baseline hemodynamics and PFT results between patients who received early (≤6 months from the RHC) versus late (>6 months from the RHC) versus no prostanoid use; and (*iii*) maximum dosage of parenteral prostanoid used.

Statistical analysis

Analyses were performed using JMP 10.0 for Macintosh. Mean and standard deviation (SD) were used to describe continuous parametric data, whereas the median and interquartile ranges (IR) were used to describe continuous nonparametric data. Between-group comparisons were conducted using independent t-tests for continuous parametric data, Wilcoxon-Rank-Sum tests for continuous non-parametric data, and chi-square tests and Fishers 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 a RHC during the study period, 99 met RHC criteria for either SSc-PAH (n=28) or SSc-PH-ILD (n=71) (Figure 1). Of these 99 patients, the majority of patients underwent their diagnostic RHC at UCLA (71%). For the remaining patients, the median time from the outside RHC to initial PH clinic consultation at UCLA was 3.5 months (IR 1.4-18.5).

Baseline demographics and co-morbidities were similar between patients with SSc-PAH and SSc-PH-ILD with the exception of gender and eGFR (Table 1). The majority of patients in both groups had limited SSc with a median SSc disease duration of 7 years. The presence of diabetes mellitus requiring insulin use was rare (7% in both groups), as was current smoker status (3 SSc-PAH and 1 SSc-PH-ILD). More patients in the SSc-PH-ILD group were receiving low-dose prednisone (48% vs. 21% in SSc-PAH, p=0.02), and immunosuppression other than prednisone (39% vs. 21% in SSc-PAH, p=0.07).

Hemodynamics and pulmonary function

Baseline systemic and pulmonary hemodynamics, 6MWD, and need for supplemental oxygen were similar between the SSc-PAH and SSc-PH-ILD groups (Table 2). Forty-nine percent of all SSc patients had severe precapillary PH, defined as an mPAP ≥40mmHg (SSc-PAH [54%] and SSc-PH-ILD [48%]). Patients with SSc-PH-ILD had significantly lower FVC (% predicted) and DL_{CO} (% predicted) compared with SSc-PAH patients; however, the mean FVC/DL_{CO} was identical in both groups.

PAH-targeted therapies

PAH-specific therapy data were available for 91 (92%) of the patient cohort (Table 3). At the initial UCLA PH clinic consultation, no patients were receiving aggressive PAH-targeted therapy (i.e. combination therapy or prostanoid). For the majority of patients, the initial PAH therapy was a PDE-5 inhibitor (43%), or an ERA (45%). Over 50% of the entire cohort was treated with at least two PH-specific therapies during the study period. Twenty-four percent of patients (1 [4%] SSc-PAH and 21 [32%] SSc-PH-ILD) started a prostanoid ≤6 months of the RHC (early prostanoid initiation), while an additional 24% (9 [36%] SSc-PAH and 13 [20%] SSc-PH-ILD) started a prostanoid >6 months after the diagnostic RHC (late prostanoid initiation). The median time from RHC to initiation of a prostanoid was 0.5 months (IR 0-2.9) for early prostanoid initiators and 26.4 months (IR 10.9-40.4) for late prostanoid initiators.

Early versus late prostanoid initiation

Pulmonary Hemodynamics

The mean mPAP and median PVR index were significantly lower for patients who never initiated a prostanoid (38.1 [SD 9.0]; 768.1 [IR 511.3-1124.9])), compared with patients who initiated a prostanoid early (45.0 [SD 10.2]; 1184.8 [IR 643.5-1584.4]) and late (44.1 [SD 11.7]; 1032.1 [IR 619.7-1404.1]); p=0.03. There was no difference in the mean mPAP and median PVR index between patients who initiated on a prostanoid early versus late.

Pulmonary Function

Patients initiated on a prostanoid early had a trend towards lower a mean FVC (% predicted) (56.3 [SD 20.0]), compared with patients initiated on a prostanoid late (71.0 [SD

13.8]) and patients who never initiated a prostanoid (62.2 [SD 23.3]), p=0.09. There was no difference in mean DLCO (% predicted) between the three different groups.

Transplant-free survival

Mean and median follow up time (months) were similar for patients with SSc-PAH (30.9 [SD 29.7] and 19.8 [IR 6.3-50]) and SSc-PH-ILD (26.8 [SD 24.3] and 18.6 [IR 8.1-37.7]). Only three patients were lost to follow up (1 PAH; 2 PH-ILD). During the follow up period, 41 patients (41%) died (SSc-PAH: n=15 [54%] and SSc-PH-ILD: n=26 [37%]), and 14 (14%) patients underwent lung transplantation (all SSc-PH-ILD). The 1-, 2-, and 3-year survival estimates were 82%, 66%, 60%, and 72%, 59%, 50% for the SSc-PAH and SSc-PH-ILD, respectively (Figure 2). There were no differences in transplant-free survival between patients with SSc-PAH and SSc-PH-ILD (log rank p-value 0.5).

To minimize the possibility of lead time bias, we performed a second survival analysis excluding patients who had their first pulmonary consultation at UCLA greater than 3 months after their diagnostic RHC performed outside of UCLA (n=13 patients). The results of this survival analysis were unchanged: There was no difference in survival between the remaining SSc-PAH (n=22) and SSc-PH-ILD (n=64) patients (log rank p-value = 0.9). The 1-, 2-, 3- year survival estimates were 76%, 63%, 55%, and 70%, 60%, 49%, for the SSc-PAH and SSc-PH-ILD groups, respectively. 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 and found that only three of these patients received early prostanoid therapy (12 received late prostanoid therapy; 12 received no prostanoid therapy; 2 patients had missing medication data).

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 (categorical variable based on extent of ILD using the Goh scoring system (11)), PVR index (in dynesxsec/cm^5/m^2; continuous variable), prostanoid use (categorical variable; analyzed as either (*i*) early use (i.e. within 6 months of RHC), (*ii*) late use (i.e. after 6 months of RHC), or (*iii*) no prostanoid use. The first two 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 (HR 1.3; p=0.006).

The following covariates, which in prior studies were associated with survival in SSc-ILD, were sequentially added to the model and retained if significantly associated with the outcome: age (years), gender (categorical), African American (categorical), SSc type (diffuse or limited), SSc duration (years), hemoglobin level (g/dL), MDRD eGFR, supplemental oxygen at diagnosis (categorical), use of prednisone or other immunosuppression (categorical). Among these additional covariates, only gender was significantly associated with the outcome and included in the final model with the initial covariates (Table 4). After accounting for gender, PVR index, and ILD status, early prostanoid use remained significantly associated with improved survival (HR 1.4, $p<0.01$).

DISCUSSION

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

Compared with SSc-PAH patients, SSc-PH-ILD patients historically have inferior survival rates with prior series estimating a 3-year survival rate of 21% to 35% (4, 6, 13). Despite the fact that some of these prior studies used heterogeneous methodology for defining ILD, the present cohort of SSc-PH-ILD patients 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 SSc-PAH population (7). Nevertheless, parenteral prostanoid is considered optimal therapy for advanced/progressive PAH at higher risk of death (15), and may confer a survival advantage when compared with oral PAH-targeted therapies (16).

Prostanoid therapy is likely further restricted in SSc-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%) (5, 6, 18) in prior SSc-PH-ILD cohorts. In contrast, approximately half of the present SSc-PH-ILD cohort received prostanoid therapy during the study period. Despite the gas exchange concerns, SSc-PH-ILD may in fact be the ideal phenotype for prostanoid therapy given the often severely advanced and progressive pulmonary vascular disease phenotype at diagnosis, including, (*i*) WHO functional class III or IV symptomatology (6), (*ii*) baseline oxygen requirements above those of SSc-PAH (5), and (*iii*) increasing oxygen requirements over time (6).

In addition, when a parenteral prostanoid is employed, suboptimal dosing (<40ng/kg/min for infusional treprostinil) may affect its efficacy and has been independently associated with poor survival in WHO Group I PAH (19), and may also contribute to the modest outcomes observed in prior SSc-PAH cohorts that used epoprostenol (12, 20). In our study, 75% of patients achieved a maximum dose above 40ng/kg/min, which was the favorable prognostic threshold reported by Benza and colleagues (19). Lastly, cautious use of prostanoids may have a therapeutic role in the setting of pulmonary veno-occlusive disease (PVOD)-like lesions (21), which appear to distinguish the pulmonary vasculopathology of SSc-PAH (22) and may be increased in the setting of superimposed ILD (23). While the present study did not specifically assess for pathologic evidence of PVOD, we did not observe a scenario of 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 to 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 to 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-PH is hypothesis-generating only and requires confirmation with a prospective, randomized controlled trial.

The multivariate model also suggested 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 late prostanoid subset. This interpretation is consistent with that of a recent study, which found 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 the survival in SSc-PAH and SSc-PH-ILD patients, using prostanoid therapy.

In addition to early prostanoid use, male gender was also independently associated with survival in the multivariate model. Although prior studies have determined that male gender (i) predicts poor survival in SSc (without lung involvement) (25) and SSc-PAH (26) (27), (ii) predicts the development of severe ILD (without associated PH) (28), and (iii) may be over-represented in SSc-PH-ILD (vs. SSc-PAH) (18), our study is the first to suggest male gender is an independent predictor of poor survival in the setting of a well-characterized SSc-PH-ILD cohort. In addition, PVR index has been previously reported by Mathai and coworkers (5) as a predictor of mortality for SSc-PH-ILD; however, the hazard ratio (1.05) was similar to our study (1.00). Other factors previously reported as independently associated with survival in SSc-PH-

ILD were either not appreciated in our study (i.e. MDRD eGFR (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 found that significant ILD was not an independent risk factor for death/transplant in patients with SSc-PH, in contrast to prior studies, which employed the same methodology to define significant ILD (11, 29). In addition, there was no difference in transplant-free survival in patients with and 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-PH-ILD.

The present study has several strengths. First, two study physicians (RS, RS) performed the majority of RHCs, thereby improving reliability. Second, a single blinded investigator (RS) used a validated measure of ILD (11, 29) to diagnose ILD. Third, our mean patient follow up was >2 years. Lastly, the size of our SSc-PH-ILD cohort was comparable to prior series by Le Pavec and colleagues (n=70) (6) and Condliffe and colleagues (n=56) (4). The high percentage of ILD patients in the present SSc-PH cohort likely reflects the fact that our institution performs a relatively large number of lung transplants for SSc-ILD and has a high referral rate for SSc-ILD patients.

Our study has important limitations. The analysis is 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 follow up time per patient was less than 3 years. Type 2 errors may occur in any inference test, particularly in retrospective studies. However, our finding of a $p<0.01$ for the aggressive prostanoid use variable in the multivariate model is somewhat reassuring.

There is likely some selection bias. For example, SSc-PH-ILD patients may have appeared more ill at the time of their RHC, 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 ERA use) was not included as a covariate in the multivariate model given the variability in the use and administration of these agents. Similarly, the impact of type of prostanoid used (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 our survival appears improved from historical series, this is a single-center study and the results may not be generalizable to other populations. Finally, to adequately assess the question as to whether early aggressive PAH-targeted therapy improves survival in SSc-PH-ILD, one would need a control population of SSc-PH-ILD patients who were not receiving PAH therapy; this population does not exist at our institution.

In conclusion, survival in patients with SSc-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 in these patients compared with prior series. While multiple factors may affect survival in patients with SSc-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.

Table 1. Baseline characteristics of study population*

	SSc-PAH (n=28)	SSc-PH-ILD (n=71)	p-value
Age (years)	mean 59.7 (SD 12.8)	mean 54.5 (SD 12.1)	0.07
Female	26 (92.9%)	50 (70.4%)	0.02
Ethnicity†			
White	18 (64.3%)	37 (52.1%)	
African	3 (10.7%)	9 (12.7%)	
American			
Hispanic	5 (17.9%)	16 (22.5%)	
Asian	1 (3.6%)	9 (12.7%)	
Other	1 (3.6%)	0	
SSc Type			0.9
Limited	20 (71.4%)	50 (70.4%)‡	
Diffuse	8 (28.6%)	21 (29.6%)	
SSc Duration (years)	Median 7.0 (IR 2.8-13.9)	Median 7.3 (IR 2.7-13.2)	0.9
Coronary Artery Disease	4 (14.3%)	4 (5.6%)	0.2
Systemic Hypertension	9 (32.1%)	16 (22.5%)	0.3
Hemoglobin (mg/dL) §	Mean 12.3 (SD 1.6)	Mean 12.5 (SD 1.9)	0.5
Estimated GFR (MDRD) (mL/min/1.73 m^2)	Median 58.3 (IR 53.1-77.4)	Median 76.4 (IR 59.1-105.0)	0.01

***** Values are n (%), except where otherwise noted.

† Chi-square test not performed due to low cell counts.

‡ One patient in the ILD group was sine and labeled as limited SSc.

§ Hemoglobin measurements were obtained for 26/28 SSc-PAH and 68/71 SSc-PH-ILD.

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

	SSc-PAH (n=28)	SSc-PH-ILD (n=71)	p-value
Hemodynamics			
SBP (mmHg)	124.3 (23.8)	120.8 (21.3)	0.5
DBP (mm Hg)	71.6 (13.6)	69.7 (11.8)	0.5
Heart rate (bpm)	87.7 (12.3)	87.0 (16.0)	0.8
mPAP (mm Hg)	43.4 (12.5)	39.7 (9.4)	0.2
PAWP (mm Hg)	9.9 (3.3)	9.6 (3.5)	0.7
PVR index (dyne $s/cm^5/m^2$)	Median 1064.2 (IR 551.7- 1300)	Median 832.0 (IR 600- 1280)	0.4
RAP (mm Hg)	9.8 (6.8)	7.4 (4.8)	0.1
Cardiac output	4.6 (1.3)	4.6 (1.2)	0.9
Cardiac index	2.8 (0.7), (N=21)	2.8 (0.7), (N=57)	0.8
Oxygen use, N (%)	14 (53.8), (N=26)	27 (39.1), (N=69)	0.3
Six minute walk distance (meters)	Median 279 (IR 132.5-414), (N=18)	Median 275 (IR121.5-346.5), (N=48)	0.3
FVC (% predicted)	82.7 (15.2), (N=21)	56.0 (18.2), (N=59)	<0.0001
DL_{CO}-Hgb (% predicted)	50.6 (13.6), (N=18)	34.4 (13.4), (N=56)	0.0001
FVC/DL_{CO} Ratio	1.8 (0.5), (N=18)	1.8 (0.7), (N=55)	0.6

***** Values are mean (standard deviation), except where otherwise noted.

Definitions: systolic blood pressure (SBP); diastolic blood pressure (DBP), mean pulmonary artery pressure (mPAP); pulmonary capillary wedge pressure (PAWP); pulmonary vascular resistance (PVR); right atrial pressure (RAP); forced vital capacity (FVC); diffusing capacity for carbon monoxide (D_LCO); hemoglobin (Hgb).

Table 3. Initial pulmonary hypertension medication used during study*

	SSc-PAH (n=25)	SSc-PH-ILD (n=66)
Initial PH medication		
(A) Phosphodiesterase-5 inhibitor	13 (52.0%)	26 (39.4%)
(B) Endothelin receptor antagonist	11 (44.0%)	30 (45.5%)
(C) Prostanoid	0	7 (10.6%)
(D) Combination of A, B	1 (4.0%)	2 (3.0%)
(E) Combination of A, C	0	1 (1.5%)

*Values are n (%)

Table 4. Multivariate model of factors associated with transplant-free survival in patients with systemic sclerosis-related pulmonary hypertension.

Variable	Hazard ratio	Standard error	P-value
Interstitial lung disease	0.9	0.2	0.6
(Reference group: No significant ILD)			
Prostanoid initiation			0.01
(Reference group: No prostanoid)			
Prostanoid ≤6 months	1.4	0.2	
Prostanoid >6 months	0.5	0.3	
Gender	0.7	0.2	0.01
(Reference group: Female)			
Pulmonary vascular resistance index (dyne s/cm^5/m^2)	1.0	0.0003	0.04

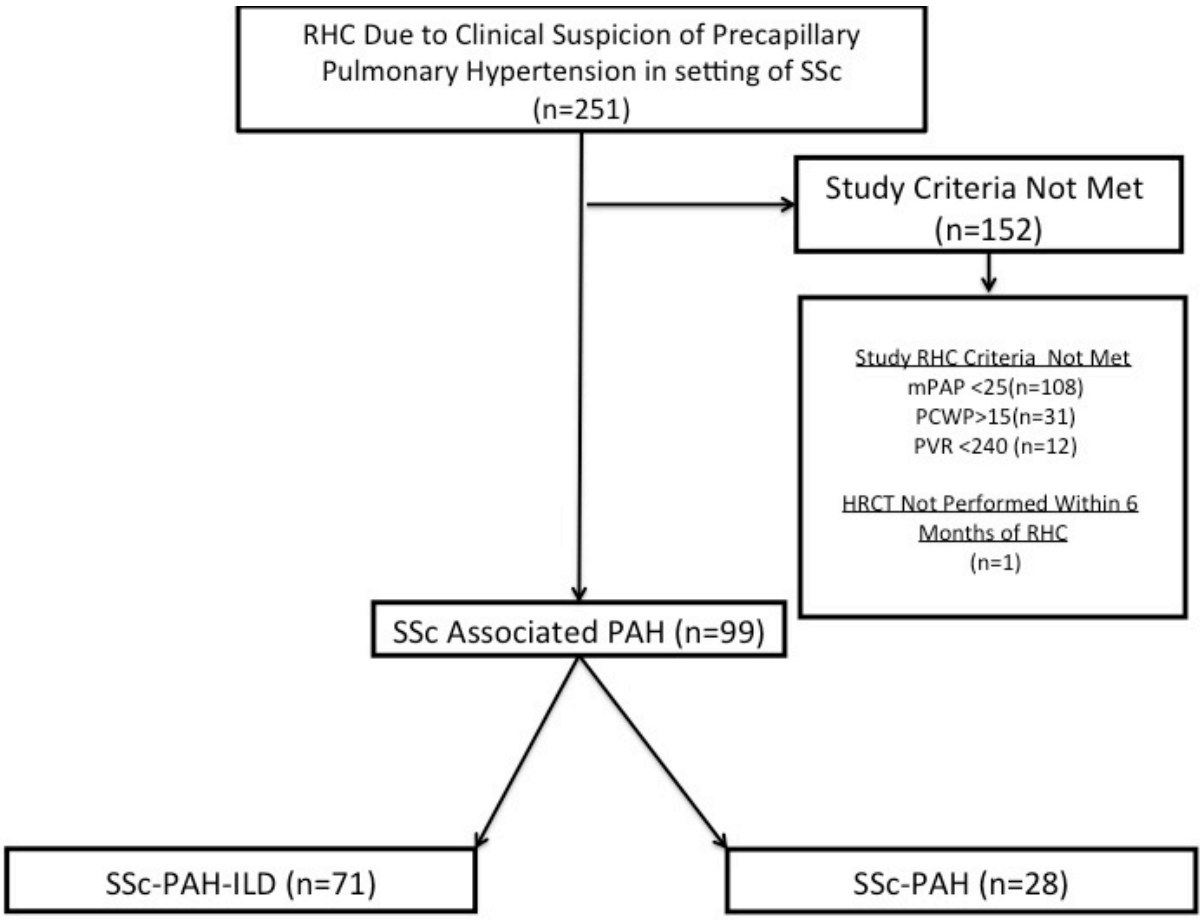

Figure 1. Flow chart of selection of patients for study inclusion.

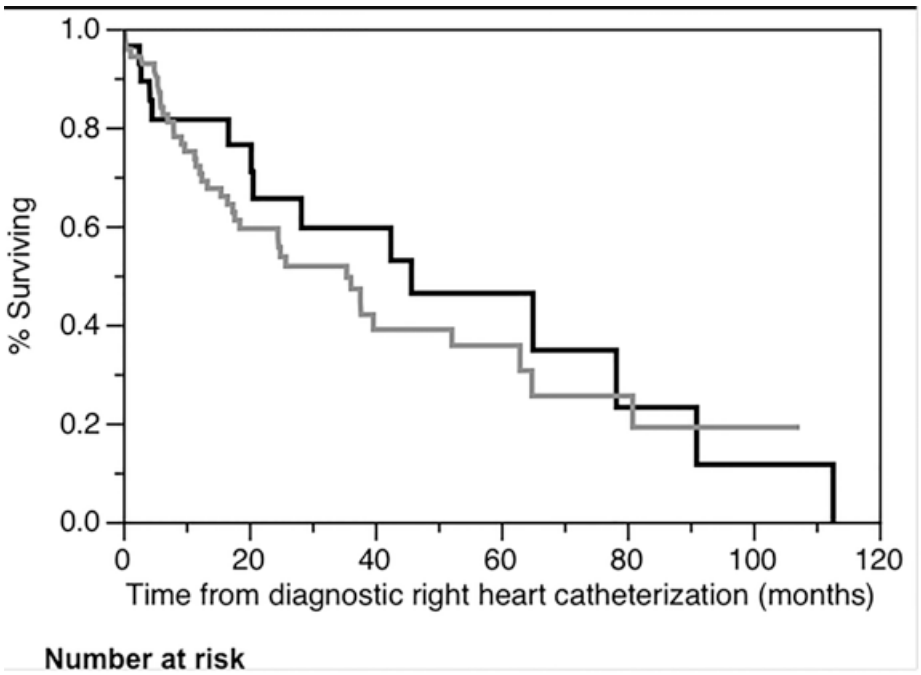

Figure 2. Kaplan Meier survival curves demonstrating no difference in survival between SSc patients with SSc-PAH alone (black line) and SSc-PH- ILD (gray line) (Log rank test p-value = 0.5).

APPENDIX A. DESIGN AND STATISTICAL ANALYSIS

Approach to Study Design

The primary aims of this exploratory analysis were to examine survival and predictors of survival in an understudied patient population of SSc patients with both PH and ILD. We selected a retrospective cohort study design to address these aims. This design yields information about multiple predictors, and yields stronger evidence for causality compared with a case-control or cross-sectional study, given its longitudinal nature. In addition, compared with a prospective design, our approach is more feasible from an economic standpoint. However, in a retrospective cohort study, the existing data may be incomplete and the predictor variables may be measured inconsistently. For instance, some providers measured oxygen saturation from the finger during six-minute walk tests, which is problematic in patients with SSc who have severe Raynaud's phenomenon, while others measure oxygen saturation from the forehead, which is more reliable measurement in this particular cohort. Our analysis is therefore limited to the data available and is subject to both measurement and reporting bias. Moreover, patients were treated with PAH-specific therapy based on practice standards and therapy availability at the discretion of the treating physician. Adjuvant therapy, such as anticoagulants, diuretics and supplemental oxygen, were also used. Variability in the use of both PAH-specific therapy and adjuvant therapy may influence survival.

Patient Selection

All patients with SSc-related precapillary PH diagnosed by right heart catheterization (RHC) from January 1, 2000, to January 1, 2011, at UCLA were enrolled. Eligible participants included patients greater than or equal to 18 years of age, with a diagnosis of SSc based on the

LeRoy and Medsger classification criteria (9). The gold standard for diagnosing precapillary PH is right heart catheterization (RHC). Precapillary PH is defined based on the RHC findings of a mean pulmonary artery pressure (mPAP) greater than or equal to 25 mm Hg. Isolated PAH is defined as a mPAP greater than or equal to 25 mm Hg, pulmonary capillary wedge pressure (PCWP) less than or equal to 15 mm Hg, and pulmonary vascular resistance (PVR) greater than or equal to 240 dynes x seconds/cm^5, in the absence of other known causes of PH (6). However, selecting patients with only RHC-proven PH may exclude patients who have precapillary PH who never received a RHC. This subgroup is relatively rare at UCLA as the threshold to perform a RHC on an SSc patient with unexplained dyspnea is relatively low. However, because RHCs may be performed less frequently in the community, our results may not be generalizable to non-academic medical settings.

Primary predictors

The primary predictors for this study were extensive ILD and PAH medication aggressiveness. The former predictor was based on the Goh criteria (11). While several methods exist for measuring extent of ILD, the Goh criteria takes into account both radiographic findings (e.g. HRCT visual assessment of fibrosis) and spirometry (e.g. FVC % predicted). Moreover, this ILD staging system has been validated and is predictive of mortality (6). An alternative approach for measuring extent of ILD would be to use a quantitative measure of radiographic fibrosis, such as a computer-assisted diagnosis (CAD) score for fibrosis (30, 31). This alternative method uses sophisticated computer software to compute the percentage of CT pixels representing fibrosis in the whole lung and in zone of maximal involvement. While the quantitative approach may be a more sensitive and reproducible measure of fibrosis than visual assessment, the

computer software is not widely available at this time. A single, blinded reviewer examined all of the HRCT scans thereby improving the internal consistency of these findings.

The other primary predictor in this study was PAH medication aggressiveness. While no universally-accepted definition of PAH medication aggressiveness exists, many would argue that aggressiveness relates to the use of prostanoid. We decided *a priori* to distinguish between early prostanoid initiation (≤6 months from the RHC), versus late prostanoid initiation (>6 months from the RHC), versus no prostanoid initiation. The rationale for this six-month threshold is described in Chapter 1. Alternatively, we could have dichotomized the variable into prostanoid initiated ever versus prostanoid never initiated. While this approach may have simplified the interpretation of the Cox proportional hazards model findings, we wanted to distinguish between patients who were started on a prostanoid at an early disease stage when their disease course may be potentially modifiable and patients who were started on a prostanoid at a late stage as a "last resort" intervention. The retrospective nature of this study precludes us from making any inferences regarding causality with regard to early prostanoid therapy and survival; however, the findings are hypothesis-generating for future randomized controlled trials in SSc-PH patients.

Outcome measures

Transplant-free survival served as the primary outcome for this study. We considered lung transplantation as synonymous with death because patients undergoing transplantation would not survive without transplantation. Moreover, few centers in the world perform lung transplantation for patients with SSc; thus, for the majority of patients with end-stage lung disease related to SSc-IL, transplantation is not an option. This approach contrasts with diseases, such as end-stage renal disease where patients can live without transplantation if they go on

dialysis. In these patients, renal transplantation can be entered as time-depended covariate in a survival analysis. However, by convention and with reason, transplant-free survival is used in SSc-ILD survival studies.

We considered assessing other secondary outcomes related to SSc-ILD, such as the Health Assessment Questionnaire (HAQ) disability index, which has been found to predict morbidity and mortality in SSc patients (32), or the six-minute walk test distance. However, we discovered that the HAQ was inconsistently measured among the patient providers and the six-minute walk test was performed using different protocols in various patient care settings. To avoid introducing systematic bias, we eliminated these variables as secondary outcomes. In a prospective study, we could assess these variables at regular intervals using a standard protocol.

Statistical analysis

JMP (10.0) was used to generate all descriptive statistics, tables, figures, as well as the Cox proportional hazards model, and Kaplan-Meier curve (based on mortality). All statistical tests were two-tailed and the accepted level of significance was set at an alpha level of 0.05. We did not logarithmically transform any of the variables because we did not want to make any assumptions about symmetry.

Since this was retrospective cohort study, the baseline characteristics of the two study groups (i.e. SSc-PAH versus SSc-PH-ILD) were compared using independent t-tests for continuous parametric data, Wilcoxon-Rank-Sum tests for continuous non-parametric data, and chi-square tests and Fishers exact tests for proportions. As these comparisons were considered exploratory analyses, we did not explicitly correct for the false positive error rate (i.e. Bonferroni correction).

For the survival analysis, the Kaplan-Meier estimate was employed to compute survival over time. By taking into account varying observation times for study patients, this approach computes probabilities of occurrence of death at a certain point of time and multiplies these successive probabilities by an earlier computed probability to obtain the final estimate. The survival probability at any particular time is calculated by the formula given below:

$$S_t = \frac{\text{Number of subjects living at the start} - \text{Number of subjects who have died}}{\text{Number of subjects living at the start}}$$

In generating the Kaplan-Meier survival curve, we made the following assumptions: (i) patients who were censored have the same survival prospects as those who continued to be followed; (ii) survival probabilities are the same for study patients recruited early and late in the study; and (iii) the event happened at the time specified.

We subsequently compared the two survival curves (i.e. SSc-PAH versus SSc-PH-ILD) by testing the null hypothesis that there is no difference in survival between the two patient groups. The log-rank test was used to test this hypothesis. This test calculates the expected number of events in each group (E_1 and E_2), while O_1 and O_2 are the number of observed events in each group, respectively (Please see formula below).

$$\textbf{Log-rank test statistic} = \frac{(O_1 - E_1)2}{E_1} + \frac{(O_2 - E_2)2}{E_2}$$

Because the log-rank test cannot test the effect of the other independent variables, we used a Cox proportional hazards model to identify the variables associated with transplant free survival. Both the log-rank test and Cox proportional hazard test assume that the hazard ratio is

constant over time. The Cox proportional hazards model also assumes that the relationship between log cumulative hazard and a covariate is linear.

To avoid overfitting given the low event rate, we initially selected 3 variables for inclusion in the Cox proportional hazards model. The first two variables (i.e. Presence of extensive ILD and severity of PH as measured by the PVR index) were selected because numerous prior studies demonstrated their independent effect on mortality. The third variable (i.e. PH medication aggressiveness as defined as the early use of prostanoid) was selected because we wanted to assess the effect of this variable on mortality. The group receiving no prostanoid was selected as the reference group because this group had the largest sample size.

In our initial model, the early use of prostanoid was the only variable significantly associated with improved survival (HR 1.3, p=0.006). Subsequently, we sequentially added other independent variables to the model and retained them if the variable was statistically significant. The only variable retained was gender. In the final model, female gender and early prostanoid use were both independently associated with improved survival. Although the PVR index variable was statistically significant (p=0.04), this is likely because the standard error was so small for this variable since the hazard ratio was 1.001.

We recognize that sequentially adding variables to the model can lead to biased estimates. To assess the adequacy of the Cox model in the presence of censoring, Martingale residuals were computed, but as expected no important differences occurred. The advantage of using the martingale residuals is that departures from the expected values can be evaluated at every observed survival time for the overall fit of the Cox model. However, we acknowledge that the power of residuals to detect modest differences requires a large sample size.

REFERENCES

1. Humbert M, Yaici A, de Groote P, Montani D, Sitbon O, Launay D, et al. Screening for pulmonary arterial hypertension in patients with systemic sclerosis: clinical characteristics at diagnosis and long-term survival. Arthritis Rheum 2011;63:3522-30.

2. Hassoun PM, Shafiq M. Tackling the challenges of systemic sclerosis-associated pulmonary hypertension: one step forward. Arthritis Rheum 2013;65:2240-2.

3. O'Callaghan DS, Humbert M. A critical analysis of survival in pulmonary arterial hypertension. Eur Respir Rev 2012;21:218-22.

4. Condliffe R, Kiely DG, Peacock AJ, Corris PA, Gibbs JS, Vrapi F, et al. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. Am J Respir Crit Care Med 2009;179:151-7.

5. Mathai SC, Hummers LK, Champion HC, Wigley FM, Zaiman A, Hassoun PM, et al. Survival in pulmonary hypertension associated with the scleroderma spectrum of diseases: impact of interstitial lung disease. Arthritis Rheum 2009;60:569-77.

6. Le Pavec J, Girgis RE, Lechtzin N, Mathai SC, Launay D, Hummers LK, et al. Systemic sclerosis-related pulmonary hypertension associated with interstitial lung disease: impact of pulmonary arterial hypertension therapies. Arthritis Rheum 2011;63:2456-64.

7. Chung L, Liu J, Parsons L, Hassoun PM, McGoon M, Badesch DB, et al. Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: identifying systemic sclerosis as a unique phenotype. Chest 2010;138:1383-94.

8. Sadushi-Kolici R, Skoro-Sajer N, Zimmer D, Bonderman D, Schemper M, Klepetko W, et al. Long-term treatment, tolerability, and survival with sub-cutaneous treprostinil for severe pulmonary hypertension. J Heart Lung Transplant 2012;31:735-43.

9. LeRoy EC, Medsger TA, Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol 2001;28:1573-6.

10. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54:S43-54.

11. Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med 2008;177:1248-54.

12. Badesch DB, McGoon MD, Barst RJ, Tapson VF, Rubin LJ, Wigley FM, et al. Longterm survival among patients with scleroderma-associated pulmonary arterial hypertension treated with intravenous epoprostenol. J Rheumatol 2009;36:2244-9.

13. Lefevre G, Dauchet L, Hachulla E, Montani D, Sobanski V, Lambert M, et al. Survival and prognostic factors in systemic sclerosis-associated pulmonary hypertension: a systematic review and meta-analysis. Arthritis Rheum 2013;65:2412-23.

14. Farber HW, Miller DP, Meltzer LA, McGoon MD. Treatment of patients with pulmonary arterial hypertension at the time of death or deterioration to functional class IV: Insights from the REVEAL Registry. J Heart Lung Transplant 2013;32:1114-22.

15. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest

Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol 2009;53:1573-619.

16. Delcroix M, Spaas K, Quarck R. Long-term outcome in pulmonary arterial hypertension: a plea for earlier parenteral prostacyclin therapy. Eur Respir Rev 2009;18:253-9.

17. Ghofrani HA, Wiedemann R, Rose F, Schermuly RT, Olschewski H, Weissmann N, et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. Lancet 2002;360:895-900.

18. Launay D, Humbert M, Berezne A, Cottin V, Allanore Y, Couderc LJ, et al. Clinical characteristics and survival in systemic sclerosis-related pulmonary hypertension associated with interstitial lung disease. Chest 2011;140:1016-24.

19. Benza RL, Gomberg-Maitland M, Naeije R, Arneson CP, Lang IM. Prognostic factors associated with increased survival in patients with pulmonary arterial hypertension treated with subcutaneous treprostinil in randomized, placebo-controlled trials. J Heart Lung Transplant 2011;30:982-9.

20. Badesch DB, Tapson VF, McGoon MD, Brundage BH, Rubin LJ, Wigley FM, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. Ann Intern Med 2000;132:425-34.

21. Montani D, Jais X, Price LC, Achouh L, Degano B, Mercier O, et al. Cautious epoprostenol therapy is a safe bridge to lung transplantation in pulmonary veno-occlusive disease. Eur Respir J 2009;34:1348-56.

22. Dorfmuller P, Humbert M, Perros F, Sanchez O, Simonneau G, Muller KM, et al. Fibrous remodeling of the pulmonary venous system in pulmonary arterial hypertension associated with connective tissue diseases. Hum Pathol 2007;38:893-902.

23. Colombat M, Mal H, Groussard O, Capron F, Thabut G, Jebrak G, et al. Pulmonary vascular lesions in end-stage idiopathic pulmonary fibrosis: Histopathologic study on lung explant specimens and correlations with pulmonary hemodynamics. Hum Pathol 2007;38:60-5.

24. Badagliacca R, Pezzuto B, Poscia R, Mancone M, Papa S, Marcon S, et al. Prognostic factors in severe pulmonary hypertension patients who need parenteral prostanoid therapy: the impact of late referral. J Heart Lung Transplant 2012;31:364-72.

25. Fransen J, Popa-Diaconu D, Hesselstrand R, Carreira P, Valentini G, Beretta L, et al. Clinical prediction of 5-year survival in systemic sclerosis: validation of a simple prognostic model in EUSTAR centres. Annals of the rheumatic diseases 2011;70:1788-92.

26. Lefevre G, Dauchet L, Hachulla E, Montani D, Sobanski V, Lambert M, et al. Survival and prognostic factors in systemic sclerosis-associated pulmonary hypertension: a systematic review and meta-analysis. Arthritis Rheum 2013;65:2412-23.

27. Launay D, Sitbon O, Hachulla E, Mouthon L, Gressin V, Rottat L, et al. Survival in systemic sclerosis-associated pulmonary arterial hypertension in the modern management era. Annals of the rheumatic diseases 2012 [Epub 2012/11/28].

28. Steen VD, Conte C, Owens GR, Medsger TA, Jr. Severe restrictive lung disease in systemic sclerosis. Arthritis Rheum 1994;37:1283-9.

29. Moore OA, Goh N, Corte T, Rouse H, Hennessy O, Thakkar V, et al. Extent of disease on high-resolution computed tomography lung is a predictor of decline and mortality in systemic sclerosis-related interstitial lung disease. Rheumatology 2013;52:155-60.

30. Kim HJ, Tashkin DP, Clements PJ, Li G, Brown MS, Elashoff R, et al. A computer-aided diagnosis system for quantitative scoring of extent of lung fibrosis in scleroderma patients. Clin Exp Rheumatol 2010;5:S26-35.

31. Kim HJ, Li G, Gjertson D, et al. Classification of parenchymal abnormality in scleroderma lung using a novel approach to denoise images collected via a multicenter study. Acad Radiol 2008;1004-16.

32. Sultan N, Pope JE, Clements PJ, Scleroderma Trials Study Group. The health assessment questionnaire (HAQ) is strongly predictive of good outcome in early diffuse scleroderma: results from an analysis of two randomized controlled trials in early diffuse scleroderma. Rheumatology 2004;43:472-8.