CHEST

Unique Predictors of Mortality in Patients With Pulmonary Arterial Hypertension Associated With Systemic Sclerosis in the REVEAL Registry

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BACKGROUND: Patients with pulmonary arterial hypertension (PAH) associated with systemic sclerosis (SSc-APAH) experience higher mortality rates than patients with idiopathic disease and those with other connective tissue diseases (CTD-APAH). We sought to identify unique predictors of mortality associated with SSc-APAH in the CTD-APAH population.

METHODS: The Registry to Evaluate Early and Long-Term PAH Management (REVEAL Registry) is a multicenter, prospective US-based registry of patients with previously and newly diagnosed (enrollment within 90 days of diagnostic right-sided heart catheterization) PAH. Cox regression models evaluated all previously identified candidate predictors of mortality in the overall REVEAL Registry population to identify significant predictors of mortality in the SSc-APAH (n = 500) vs non-SSc-CTD-APAH (n = 304) populations.

RESULTS: Three-year survival rates in the previously diagnosed and newly diagnosed SSc-APAH group were 61.4% ± 2.7% and 51.2% ± 4.0%, respectively, compared with 80.9% ± 2.7% and 76.4% ± 4.6%, respectively, in the non-SSc-CTD-APAH group ($P < .001$). In multivariate analyses, men aged > 60 years, systolic BP (SBP) ≤ 110 mm Hg, 6-min walk distance (6MWD) < 165 m, mean right atrial pressure (mRAP) > 20 mm Hg within 1 year, and pulmonary vascular resistance (PVR) > 32 Wood units remained unique predictors of mortality in the SSc-APAH group; 6MWD ≥ 440 m was protective in the non-SSc-CTD-APAH group, but not the SSc-APAH group.

CONCLUSIONS: Patients with SSc-APAH have higher mortality rates than patients with non-SSc-CTD-APAH. Identifying patients with SSc-APAH who are at a particularly high risk of death, including elderly men and patients with low baseline SBP or 6MWD, or markedly elevated mRAP or PVR, will enable physicians to identify patients who may benefit from closer monitoring and more aggressive treatment.

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ABBREVIATIONS: 6MWD = 6-min walk distance; BNP = brain natriuretic peptide; CTD = connective tissue disease; CTD-APAH = pulmonary arterial hypertension associated with connective tissue disease; D_{LCO} = diffusion capacity of the lung for carbon monoxide; FC = functional class; HR = hazard ratio; ILD = interstitial lung disease; IPAH = idiopathic pulmonary arterial hypertension; mRAP = mean right atrial pressure; non-SSc-CTD = connective tissue disease other than systemic sclerosis; NT-pro-BNP = N-terminal-pro-brain natriuretic peptide; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; REVEAL Registry = Registry to Evaluate Early and Long-Term PAH Management; RHC = right-sided heart catheterization; SBP = systolic BP; SSc = systemic sclerosis; SSc-APAH = pulmonary arterial hypertension associated with systemic sclerosis; WHO = World Health Organization; WU = Wood units

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Pulmonary arterial hypertension (PAH) is a rare complication in patients with connective tissue diseases (CTDs), and it is associated with high mortality rates, particularly in patients with systemic sclerosis (SSc).[1] Studies have shown that patients with CTD-associated PAH (CTD-APAH) experience poorer survival compared with patients with idiopathic PAH (IPAH).[2-4] In addition, despite similar baseline hemodynamics, patients with PAH associated with SSc (SSc-APAH) have the poorest survival rates when compared with other CTD-APAH subgroups, including patients with systemic lupus erythematosus, mixed CTD, and rheumatoid arthritis, in both incident and prevalent populations.[3,5]

Risk score calculators have been developed for patients with PAH as a whole, incorporating variables predictive of high mortality, including World Health Organization (WHO) group 1 subgroup, age, sex, New York Heart Association (NYHA) functional class (FC), vital signs, 6-min walk distance (6MWD), brain natriuretic peptide (BNP) level, presence of pericardial effusion, diffusion capacity of the lung for carbon monoxide (DLCO), and baseline hemodynamic variables such as mean right atrial pressure (mRAP), pulmonary vascular resistance (PVR), and cardiac output.[6,7] A study focusing on the CTD-APAH population found that higher mRAP, lower 6MWD, higher FC, and the presence of a pericardial effusion were predictive of death.[8] In contrast, studies including patients with SSc-APAH alone have identified male sex, lower DLCO, older age, and FC IV status as independent predictors of death.[9,10] No studies have evaluated a large cohort of patients with CTD-APAH to identify unique predictors of mortality in patients with SSc-APAH. We sought to use the large Registry to Evaluate Early and Long-Term PAH Management (REVEAL Registry) cohort of patients with CTD-APAH to identify unique predictors of mortality in the patients with SSc-APAH compared with patients with CTD other than SSc (non-SSc-CTD)-APAH that may account for the mortality differences between these groups.

Materials and Methods

REVEAL Registry

The REVEAL Registry is a longitudinal registry involving 54 pulmonary hypertension centers in the United States (e-Appendix 1). Each participating center obtained institutional review board approval prior to patient enrollment. The design and objectives of the REVEAL Registry are described elsewhere.[11] All patients provided informed consent prior to enrollment, and "enrollment" was defined as the date consent was given. "Diagnosis" was defined as the date of diagnostic right-sided heart catheterization (RHC) occurring at or before the date of enrollment. Patients with new diagnoses were defined as those whose diagnostic RHC occurred within 90 days of enrollment. All consecutive patients who, in the opinion of the enrolling investigator, had a clinical diagnosis of PAH WHO group 1[12] and met the following inclusion criteria were eligible for enrollment: (1) mean pulmonary artery pressure of >25 mm Hg at rest or 30 mm Hg with exercise, (2) mean pulmonary capillary wedge pressure or left ventricular end diastolic pressure of ≤ 18 mm Hg, (3) PVR of ≥ 240 dynes/s/cm^5 (divide by 80 for Wood units [WU]), and (4) ≥ 3 months of age.

Data Collection

The data in the REVEAL Registry was collected prospectively, but the analyses for this study were performed retrospectively. Data collection methods have been described previously.[3] Patients were enrolled from March 2006 through December 2009. Demographics, clinical characteristics, and outcomes were assessed at enrollment and quarterly thereafter. The database of 3,515 patients was locked on February 4, 2013, for the current analyses. We developed an algorithm (Fig 1) to exclude patients with exercise-induced PAH, in accordance with the Dana Point Classification Criteria,[12] and those with pulmonary capillary wedge pressure >15 mm Hg, who have been shown to differ in many respects from those meeting the traditional hemodynamic definition of PAH,[13] and included only patients with CTD-APAH. We also excluded those with evidence of significant interstitial lung disease (ILD), defined as those with evidence of "severe" fibrosis on high-resolution CT scan of the chest or "moderate" fibrosis if pulmonary function testing revealed a total lung capacity of $<60\%$ predicted.[14] We divided the patients with CTD-APAH into those with SSc-APAH (SSc group) and those with non-SSc-CTD-APAH (non-SSc group).

Statistical Analysis

Baseline characteristics at the time of enrollment were compared between the SSc and non-SSc groups, using the Student *t* or Wilcoxon test to compare continuous variables and the χ^2 or Fisher exact test to compare categorical variables. Because BNP levels were highly skewed, the variables were log transformed for comparison as continuous variables. Cumulative probabilities of survival at 3 years were calculated using the Kaplan-Meier estimator for both the previously and newly diagnosed populations, and differences between the SSc and non-SSc groups were compared using the log-rank test. Follow-up time was calculated from the date of enrollment. Cox regression models identified significant predictors of mortality in the SSc and non-SSc

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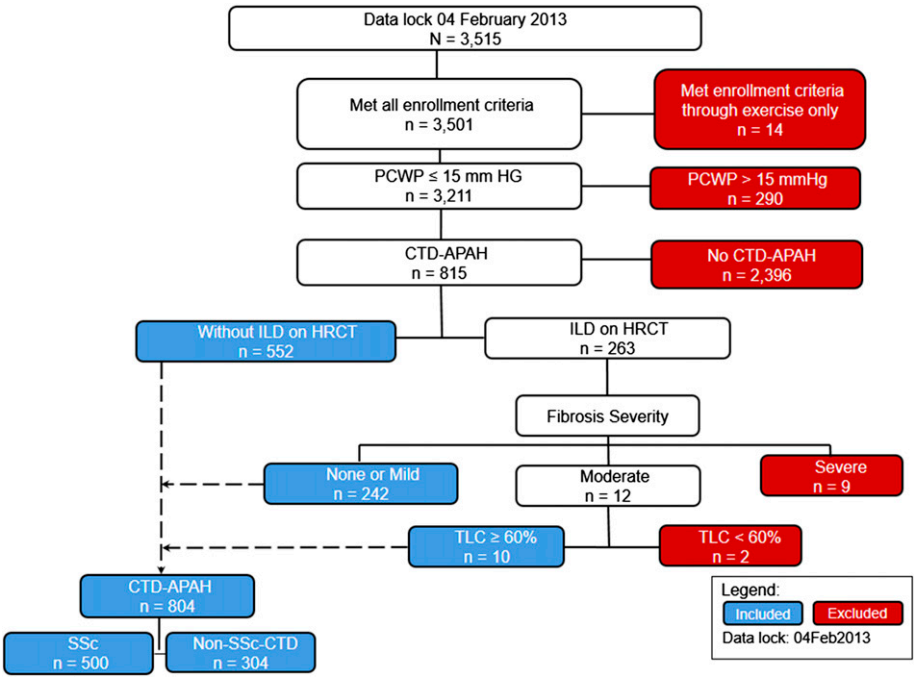

Figure 1 – *STROBE diagram of the Registry to Evaluate Early and Long-Term PAH Management (REVEAL) Registry patients used in this analysis. We included only patients with CTD-APAH who met the strict criteria of World Health Organization group 1 pulmonary arterial hypertension. CTD-APAH = pulmonary arterial hypertension associated with connective tissue disease; HRCT = high-resolution CT scan of the chest; ILD = interstitial lung disease; non-SSc-CTD = connective tissue disease other than systemic sclerosis; PCWP = pulmonary capillary wedge pressure; SSc = systemic sclerosis; TLC = total lung capacity.*

populations. All variables identified previously as candidate predictors of mortality in the overall REVEAL Registry population were evaluated in univariate and multivariate models. Stepwise selection was used to determine the final model, retaining only variables with $P < .05$. SAS, version 9.1 (SAS Institute Inc) statistical software was used for all analyses.

Results

Baseline Characteristics in Patients With CTD-APAH

Of 3,515 patients enrolled in the REVEAL Registry, 815 were identified as having CTD-APAH (Fig 1). Of these, 804 (500 SSc and 304 non-SSc) who did not have significant ILD were selected for these analyses. The majority of patients in the non-SSc group had systemic lupus erythematosus-APAH or mixed CTD-APAH (Table 1). Patients with SSc were older and had a shorter time between diagnostic RHC and enrollment into the database than did the patients with non-SSc-CTD-APAH (Table 2). Patients with SSc-APAH had more severe disease overall, with a higher NYHA FC, shorter 6MWD, higher Borg dyspnea index, lower D_{LCO}, and higher BNP level. Patients with SSc-APAH were also more likely to have renal insufficiency and pericardial effusions than patients with non-SSc-CTD-APAH. Although there was a strong trend toward higher mRAP in the SSc group, there were no significant differences in hemodynamics or PAH-specific therapies at the time of enrollment in the SSc vs non-SSc groups.

Poorer Survival in SSc-APAH Compared With Non-SSc-CTD-APAH

Three-year survival in the SSc group was worse than in the non-SSc group in both the previously and newly

TABLE 1] Types of CTD-APAH

Type of CTD	No. (%)
All SSc-APAH	500 (62.2)
SSc, limited	299 (37.2)
SSc, diffuse	99 (12.3)
SSc, unknown subtype	102 (12.7)
All non-SSc-CTD-APAH	304 (37.8)
Systemic lupus erythematosus	127 (15.8)
Mixed CTD	71 (8.8)
Rheumatoid arthritis	42 (5.2)
Sjogren syndrome	15 (1.9)
Dermatomyositis/polymyositis	8 (1.0)
Undifferentiated CTD	12 (1.5)
Overlap syndrome	15 (1.9)
Other	4 (0.5)
Unknown	10 (1.2)

APAH = associated with pulmonary arterial hypertension; CTD = connective tissue disease; non-SSc-CTD = connective tissue disease other than systemic sclerosis; SSc = systemic sclerosis.

TABLE 2] Characteristics, Hemodynamics, and Cardiac and Pulmonary Function at Enrollment

Characteristic	SSc-APAH (n = 500)	Non-SSc-CTD-APAH (n = 304)	*P* Value
Age at baseline,[a] y			
No.	500	304	…
Mean ± SD	61.65 ± 11.25	49.88 ± 14.38	< .001
Male sex, No. (%)	63 (12.6)	28 (9.2)	.14
Time from diagnostic RHC to enrollment, mo			
No.	500	304	…
Mean ± SD	19.33 ± 23.11	26.72 ± 35.66	< .001
Newly diagnosed, No. (%)	166 (33.2)	88 (28.9)	0.21
NYHA FC, No. (%)			< .0001
I	15 (3.4)	25 (9.2)	
II	121 (27.8)	105 (38.7)	
III	256 (58.9)	127 (46.9)	
IV	43 (9.9)	14 (5.2)	
6MWD, m			
No.	380	248	…
Mean ± SD	294.01 ± 114.6	360.21 ± 122.2	< .001
Heart rate, bpm			
No.	471	287	…
Mean ± SD	84.29 ± 14.94	83.64 ± 14.41	.55
Systolic BP, mm Hg			
No.	477	287	…
Mean ± SD	118.71 ± 18.97	119.28 ± 19.56	.69
Borg dyspnea index			
No.	327	220	…
Mean ± SD	3.67 ± 2.07	3.15 ± 2.28	.005
Renal insufficiency, No. (%)	41 (8.4)	9 (3.0)	.0024
mRAP, mm Hg			
No.	449	276	…
Mean ± SD	9.04 ± 5.77	8.21 ± 5.06	.052
mPAP at rest, mm Hg			
No.	500	304	…
Mean ± SD	44.59 ± 11.43	45.48 ± 10.67	.27
PCWP at rest, mm Hg			
No.	500	304	…
Mean ± SD	9.11 ± 3.48	8.85 ± 3.48	.29
Cardiac output,[b] L/min			
No.	499	303	…
Mean ± SD	4.42 ± 1.45	4.28 ± 1.35	.20
Cardiac index, L/min/m^2			
No.	391	237	…
Mean ± SD	2.50 ± 0.81	2.40 ± 0.75	.11

(Continued)

TABLE 2] *(continued)*

Characteristic	SSc-APAH (n = 500)	Non-SSc-CTD-APAH (n = 304)	*P* Value
PVR,[c] Wood units			
No.	499	303	…
Mean ± SD	9.31 ± 5.24	9.79 ± 5.34	.21
PVR index,[c] Wood units × m^2			
No.	391	237	…
Mean ± SD	16.37 ± 9.05	17.36 ± 9.46	.19
FEV_1,[d] % predicted			
No.	350	179	…
Mean ± SD	71.93 ± 18.43	73.90 ± 19.20	.25
FVC,[d] % predicted			
No.	352	181	…
Mean ± SD	74.08 ± 19.22	76.93 ± 20.12	.11
FEV_1/FVC ratio[e]			
No.	374	200	.068
Mean ± SD	0.76 ± 0.09	0.77 ± 0.10	…
DLCO,[d] % predicted			
No.	344	186	…
Mean ± SD	40.83 ± 16.27	50.36 ± 1 9.00	< .001
Pericardial effusion, No. (%)			
None	222 (57.1)	159 (68.2)	.0090
Mild	121 (31.1)	62 (26.6)	…
Moderate	36 (9.3)	12 (5.2)	…
Moderate-severe	5 (1.3)	0 (0.0)	…
Severe	5 (1.3)	0 (0.0)	…
BNP, pg/mL			
No.	223	154	…
Mean ± SD	562.38 ± 929.9	313.49 ± 685.4	.005
N-terminal BNP, pg/mL			
No.	65	26	…
Mean ± SD	3192.37 ± 4687	932.73 ± 1345	.018
PAH medications at enrollment, No. (%)			
Prostacyclin	154 (31.8)	96 (32.8)	.77
ERA	217 (44.7)	120 (41.0)	.30
PDE-5 inhibitor	223 (46.0)	137 (46.8)	.83
CCB for PAH	42 (8.7)	27 (9.2)	.79
PAH medications, No. (%)			
0	90 (18.6)	49 (16.7)	.47
1	231 (47.6)	149 (50.9)	…

(Continued)

TABLE 2] *(continued)*

Characteristic	SSc-APAH (n = 500)	Non-SSc-CTD-APAH (n = 304)	*P* Value
2	129 (26.6)	81 (27.6)	...
3	35 (7.2)	14 (4.8)	...
On combination PAH medications, No. (%)	164 (33.8)	95 (32.4)	.69

P value calculation uses χ^2 test for categorical data or Fisher exact test for categorical data with small cell counts (≤ 5%), and Student *t* test for continuous data. 6MWD = 6-min walk distance; BNP = brain natriuretic peptide; bpm = beats per min; CCB = calcium channel blocker; DLco = diffusion capacity of the lung for carbon monoxide; ERA = endothelin receptor agonist; FC = functional class; FCO = Fick cardiac output; mPAP = mean pulmonary arterial pressure; mRAP = mean right atrial pressure; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PDE-5 = phosphodiesterase type-5; PVR = pulmonary vascular resistance; RHC = right-sided heart catheterization. See Table 1 legend for expansion of other abbreviations.

[a]Age = (date of informed consent − date of birth)/365.25.

[b]Cardiac output = FCO, or, if FCO is missing, then cardiac output = thermodilution cardiac output.

[c]PVR (Wood units) = (mean pulmonary arterial pressure at rest − PCWP at rest)/cardiac output, where cardiac output = FCO, or, if FCO is missing, then cardiac output = thermodilution cardiac output.

[d]Predicted value based on Hankinson et al[14] computation.

[e]FEV_1/FVC ratio is missing if FVC is zero.

diagnosed populations (61.4% ± 2.7% vs 80.9% ± 2.7% and 51.2% ± 4.0% vs 76.4% ± 4.6%, respectively; $P < .001$) (Fig 2).

Unique Predictors of Mortality in SSc-APAH

Figure 3 shows the univariate analyses of previously identified predictors of mortality from the overall REVEAL Registry cohort in the SSc and non-SSc groups. The following variables were predictive of mortality in both groups: age > 60 years, NYHA FC III or IV status, 6MWD < 165 m, and BNP > 180 pg/mL. 6MWD ≥ 440 m was protective in both groups. Unique predictors of mortality in the SSc group, but not the non-SSc group, included male sex, systolic BP (SBP) ≤ 110 mm Hg, pericardial effusion, DLCO ≤ 32% predicted, mRAP > 20 mm Hg within 1 year, PVR > 32 WU, and newly diagnosed status. BNP levels < 50 pg/mL were protective in patients with SSc (hazard ratio [HR] = 0.34; 95% CI, 0.16-0.72; $P = .005$) but not in the non-SSc group (HR = 0.68; 95% CI, 0.36-1.29; $P = .24$). Figure 3 also shows the univariate analyses of additional variables that are relevant to the CTD-APAH population. A higher glomerular filtration rate was protective in both groups. Mild to moderate ILD was the only feature that increased mortality in patients with non-SSc-CTD-APAH but not in patients with SSc-APAH (HR = 2.19; 95% CI, 1.14-4.23; $P = .02$ vs HR = 0.84; 95% CI, 0.55-1.30; $P = .44$). When compared with IPAH, mRAP > 20 mm Hg within 1 year, PVR > 32 WU, and newly diagnosed status remained unique predictors of death in the SSc-APAH group.

In multivariate analyses, the following variables remained predictive of mortality in both the SSc and non-SSc groups: NYHA FC III or IV status and BNP > 180 pg/mL (Table 3). Unique predictors of mortality in the SSc group included men > 60 years, SBP ≤ 110 mm Hg, 6MWD < 165 m, mRAP > 20 mm Hg within 1 year, and PVR > 32 WU. 6MWD ≥ 440 m was protective in the non-SSc group, but not in the SSc group, whereas BNP < 50 pg/mL was protective in the SSc group, but not in the non-SSc group.

Discussion

Our study provides further evidence that patients with SSc-APAH experience higher mortality rates than do patients with other CTD-APAH in both incident and prevalent populations. Our results validate the usefulness of the risk score calculator in patients with CTD-APAH, including in patients with SSc-APAH. We identified several baseline risk factors that were significantly associated with mortality in the SSc-APAH population in comparison with the non-SSc-CTD-APAH population, including being an elderly man, having a low SBP, having poor exercise capacity, and having severe hemodynamic indices including elevated mRAP and PVR. Identifying patients with SSc-APAH with high mortality risk based on the presence of these unique predictors of mortality will enable physicians to monitor these patients more closely and escalate therapy when indicated.

Three-year survival in the newly diagnosed SSc-APAH population was 51%, which is similar to survival rates found in other cohorts assessed in the modern treatment era.[1,5,9,15,16] Other studies have found better survival rates (75%-81%) in patients with SSc-APAH; these rates are similar to the survival rate of 77% that we and others observed in patients with non-SSc-CTD-APAH.[3,5,10,17,18] This survival discrepancy could be related to early

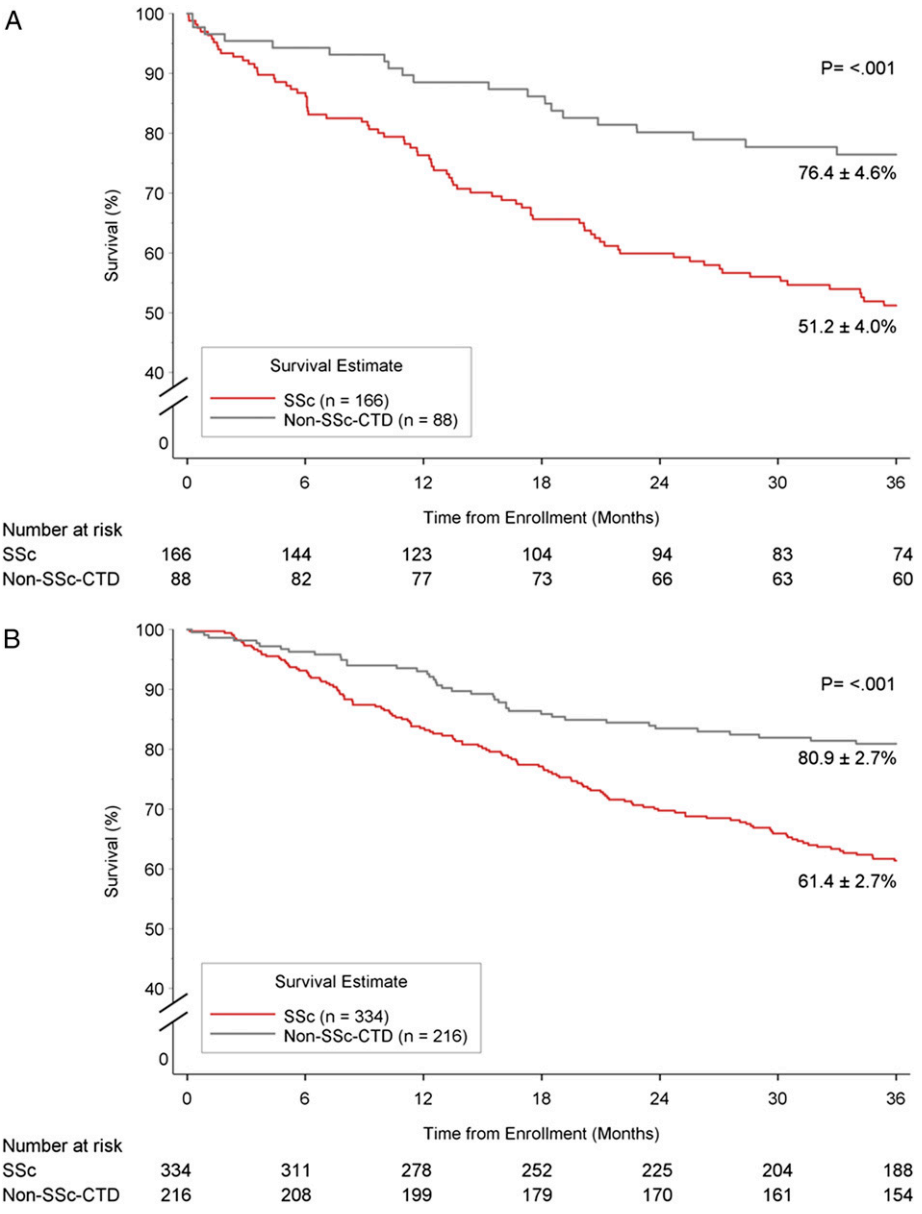

Figure 2 – *Three-year survival curves in patients with SSc and non-SSc-CTD-APAH. A, Three-year survival from enrollment in the newly diagnosed SSc group was 51.2% ± 4.0% compared with 76.4% ± 4.6% in the non-SSc-CTD group (P < .001). B, Three-year survival from enrollment in the previously diagnosed SSc group was 61.4% ± 2.7% compared with 80.9% ± 2.7% in the non-SSc-CTD group (P < .001). See Figure 1 legend for expansion of abbreviations.*

detection algorithms that have been implemented in these SSc-APAH cohorts, with the goal to initiate PAH-specific therapy when the disease is less severe. Survival in patients with non-SSc-CTD-APAH appears to be more similar to those with IPAH than to those with SSc-APAH, despite similar baseline hemodynamics and PAH-specific therapies.[3] Whether initiating aggressive PAH treatment in patients with SSc-APAH with a particular high mortality risk may improve outcomes remains an important question to be answered.

Overall, predictors identified in the multivariate model in SSc-APAH were very similar to the core predictors for PAH as a whole, including all subtypes.[6] Our results concur with those of other studies on patients with SSc-APAH in that male sex, older age, and FC III and IV status were significant predictors of death.[5,9,10,15] Our results confirmed those of a single-center study that identified high PVR as a strong predictor of mortality.[19] Unlike these other studies, we did not find that low D_{LCO} or glomerular filtration rate were predictive of mortality in the SSc-APAH group in multivariate analyses, although they were significant in univariate analyses. Lefèvre et al[15] identified additional poor prognostic factors in patients with SSc with pulmonary hypertension in a meta-analysis including patients with WHO groups II and III pulmonary hypertension: pericardial

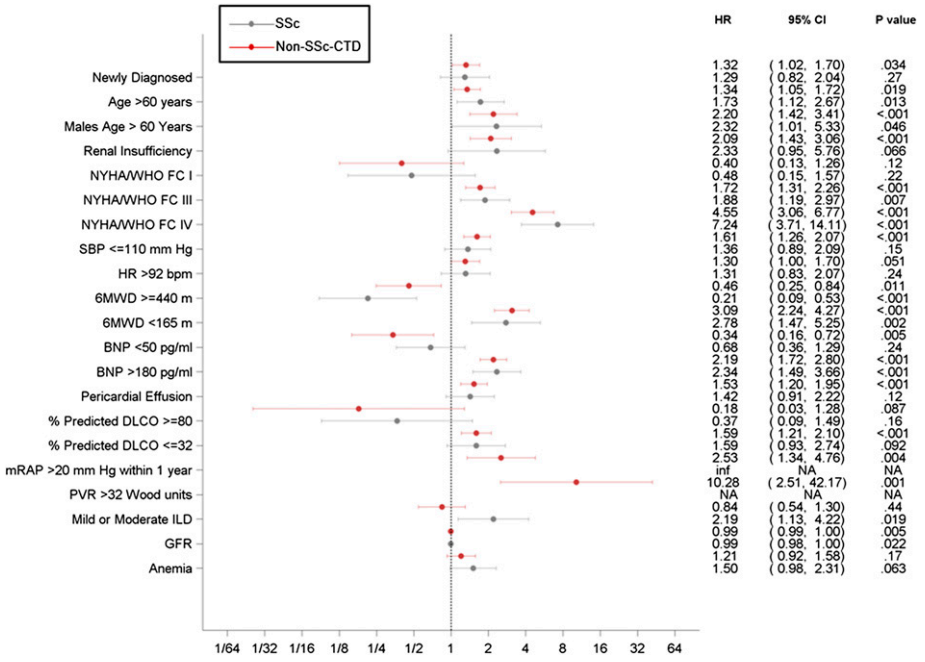

Figure 3 – *Predictors of mortality for patients with SSc-APAH and non-SSc-CTD-APAH using univariate Cox regression analyses. Unique predictors of mortality in the SSc group, but not the non-SSc group, included male sex, SBP ≤ 110 mm Hg, pericardial effusion, DLCO ≤ 32% predicted, mRAP > 20 mm Hg within 1 y, PVR > 32 WU, and newly diagnosed status. BNP levels < 50 pg/mL were protective in patients with SSc, but not in the non-SSc group. Higher GFR was protective in both groups. Mild to moderate ILD was the only feature that increased mortality in the non-SSc group but not in patients with SSc. 6MWD = 6-min walk distance; BNP = brain natriuretic peptide; DLCO = diffusion capacity of the lung for carbon monoxide; FC = functional class; GFR = glomerular filtration rate; HR = hazard ratio; mRAP = mean right atrial pressure; NYHA = New York Heart Association; PVR = pulmonary vascular resistance; SBP = systolic BP; WHO = World Health Organization; WU = Wood units. See Figure 1 legend for expansion of other abbreviations.*

effusion, low 6MWD, high mean pulmonary arterial pressure, poor cardiac index, and elevated mRAP were poor prognostic factors. Although pericardial effusion lost its significance in our multivariate analysis of patients with SSc-APAH, poor exercise capacity and elevated mRAP remained significant predictors of death. Interestingly, 6MWD < 165 m was predictive of death only in the SSc group, whereas 6MWD ≥ 440 m was protective only in the non-SSc-CTD-APAH group in multivariate analyses. A potential explanation for these discrepancies is that patients with SSc can suffer from the presence of contractures and tendon friction rubs that can significantly limit mobility (particularly those with diffuse skin disease) in addition to other factors that limit exercise capacity (such as anemia and joint or muscle inflammation) in patients with other CTDs.[20,21] However, including all variables in the multivariate model without stepwise selection, 6MWD < 165 m was a significant predictor of death in the non-SSc group (HR = 2.03; 95% CI, 1.01-4.12; $P = .05$), and 6MWD ≥ 440 m showed a trend toward a protective effect in the SSc group (HR = 0.62; 95% CI, 0.33-1.15; $P = .13$). In addition, when we evaluated the effect of 6MWD on mortality risk in the various cutaneous subgroups of SSc, an increase in distance of 100 m was significantly protective in all three groups ($P < .001$): diffuse HR = 0.53 (95% CI, 0.38-0.75); limited 0.59 (95% CI, 0.51-0.68); unclassified 0.54 (95% CI, 0.40-0.71).

In our study, BNP > 180 pg/mL increased the risk of death in both the SSc and non-SSc-APAH groups by more than twofold, as has also been shown in patients with IPAH.[22] We and others have shown that patients with SSc-APAH have markedly elevated BNP and N-terminal-pro-BNP (NT-pro-BNP) levels compared with patients with IPAH and patients with non-SSc-CTD-APAH.[3,23] Williams et al[24] found in a UK SSc-APAH cohort that for every order of magnitude increase in baseline NT-pro-BNP level there was a fourfold increased risk of death ($P = .002$). In addition, several studies have found that NT-pro-BNP is useful in the screening and early detection of PAH in patients with SSc, and this biomarker has been integrated into novel screening algorithms.[25-27] To our knowledge, our study is the first to show that BNP is an independent predictor of mortality in patients with CTD-APAH and SSc-APAH, in particular. Unfortunately NT-pro-BNP levels were not available in 89% of our CTD-APAH cohort, and, therefore, they could not be included in the regression models.

TABLE 3] Multivariate Model of Predictors of Mortality

Risk Score Characteristic	HR	95% CI	*P* Value
SSc-APAH			
Men aged > 60 y	2.222	1.421-3.474	< .001
NYHA FC III	1.326	1.002-1.756	.049
NYHA FC IV	2.938	1.921-4.492	< .001
Systolic BP ≥ 110 mm Hg	1.334	1.034-1.723	.027
6MWD < 165 m	2.252	1.614-3.142	< .001
BNP < 50 pg/mL	0.450	0.209-0.966	.040
BNP > 180 pg/mL	2.082	1.617-2.682	< .001
mRAP > 20 mm Hg within 1 y	1.910	1.003-3.637	.049
PVR > 32 Wood units	14.567	3.464-61.262	< .001
Non-SSc-CTD-APAH			
NYHA FC III	1.679	1.067-2.641	.025
NYHA FC IV	5.427	2.588-11.383	< .001
6MWD ≥ 440 m	0.293	0.118-0.732	.009
BNP > 180 pg/mL	2.466	1.589-3.826	< .001

HR = hazard ratio. See Table 1 and 2 legends for expansion of other abbreviations.

To our knowledge, this is the first study to identify low baseline SBP ≤ 110 mm Hg as an independent predictor of death in patients with SSc-APAH. Other studies have shown that low SBP, both at peak exercise and upon admission to the hospital for right-sided heart failure, is an independent risk factor for death in PAH.[28,29] A potential pathophysiologic explanation for this finding is that the presence of high right ventricular pressure results in a more pronounced effect of low SBP on coronary perfusion. Thus, low SBP can lead to greater right ventricular dysfunction caused by ischemia. In addition, low SBP may be a sign of low cardiac output, reduced stroke volume, and neurohormonal activation.[29] Unless complicated by renal disease, patients with SSc have relatively low baseline BP,[30] and the mean SBP was 119 ± 19 mm Hg in the patients with SSc-APAH in our study. Given that BP can be monitored easily, identification of low baseline SBP as a risk factor in SSc-APAH is an important finding.

We did not find that mild to moderate ILD was predictive of death in patients with SSc-APAH. Although a significant predictor in the non-SSc-APAH group in univariate analysis, it was no longer significant in multivariate analysis. We attempted to exclude patients with substantial ILD as defined previously but did not have precise measurements regarding the degree of fibrosis on imaging.

Our study does have some limitations. The SSc-APAH and non-SSc-CTD-APAH cohorts are smaller than the overall cohort. Thus, differences in significant multivariable predictors may be caused by loss of power as opposed to true differences in predictors for different subtypes. In addition, the model does not include therapies. The majority of REVEAL Registry patients, particularly patients who had previous diagnoses, were receiving phosphodiesterase-5 inhibitors, endothelin receptor antagonists, prostacyclins, or a combination. Therefore, the model does not provide insights into prognosis for untreated patients. Although 86% of the patients with CTD-APAH were enrolled at sites that routinely involve a rheumatologist in the diagnosis and care of these patients, misclassification of some patients may have occurred. Finally, the analysis only assessed variables available in the REVEAL Registry database. There may be additional factors particular to patients with CTD-APAH, such as autoantibody status, that could impact the results.

Conclusions

In conclusion, patients with SSc-APAH have higher mortality rates than patients with non-SSc-CTD-APAH. Our results validate the usefulness of the PAH risk score in patients with SSc-APAH. We have identified unique predictors of mortality in patients with SSc-APAH, including being an older man, having a low baseline SBP, having poor exercise capacity, and having an elevated mRAP and PVR; these can be used to identify high-risk patients who may benefit from closer monitoring and more aggressive treatment.

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