DOI: 10.1002/pul2.12118

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

Prevalence of aortic stenosis and TAVR outcomes in patients with systemic sclerosis-associated pulmonary hypertension

Kirsten Alman[1] | **Corey J. Sadd**[1] | **Amish Ravel**[2] | **Farhan Raza**[2] | **Amy Chybowski**[3] | **James R. Runo**[3]

[1]Department of Medicine, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, Wisconsin, USA

[2]Division of Cardiology, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, Wisconsin, USA

[3]Division of Pulmonary and Critical Care Medicine, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, Wisconsin, USA

Correspondence
Corey J. Sadd, Department of Medicine, School of Medicine and Public Health, University of Wisconsin-Madison, 600 Highland Ave, Madison, WI 53792, USA.
Email: csadd@uwhealth.org

Funding information
None

Abstract

There is little known about performing transcatheter aortic valve replacement (TAVR) in patients with group 1 pulmonary arterial hypertension (PAH) on advanced pulmonary vasodilator therapy. Retrospective cohort study among 90 patients with systemic sclerosis-associated pulmonary arterial hypertension and systemic sclerosis-associated pulmonary hypertension (SSc-PAH/PH) evaluated at a tertiary PH center. The SSc-PAH/PH cohort was stratified by the presence or absence of aortic stenosis (AS) to identify differences in baseline characteristics, hemodynamics, and long-term outcomes. Of the 90 SSc-PAH/PH patients, 13 patients were diagnosed with AS at PH diagnosis and another 6 patients developed AS during the study period. The period prevalence of AS was 21.1% (19/90, 95% confidence interval: 13.2%–30.1%) of which 94.7% was mild (18/19) at diagnosis with mean age at AS diagnosis of 66.3 + 2.2 years. Among AS patients, 31.6% (6/19) progressed to severe AS, five of which underwent TAVR (median age: 70 years) while on advanced PAH therapy. One of the five TAVR patients developed worsening pulmonary hypertension post-TAVR. The 5-year survival rate for all AS patients from diagnosis date was 37.2%. There was a high prevalence of AS in this cohort of SSc-PAH/PH patients, with mean age of onset younger than patients with nonbicuspid aortic valve stenosis. This is the largest series of SSc-PAH/PH patients on advanced pulmonary vasodilator therapy who underwent TAVR with acceptable early outcomes.

KEYWORDS
autoimmune disease, pulmonary vascular disease, valvular disease

Abbreviations: AS, aortic stenosis; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHC, right heart catheterization; RV, right ventricle; SSc, systemic sclerosis; SSc-PAH, systemic sclerosis-associated pulmonary arterial hypertension; TAVR, transcatheter aortic valve replacement; TTE, transthoracic echocardiography.

Joint First Authorship: Kirsten Alman and Corey J. Sadd contributed equally to this study.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is present in an estimated 9% of patients with systemic sclerosis (SSc) and is the leading cause of death.[1,2] It has been previously observed that patients with connective tissue disease are at increased risk for developing aortic valve disease.[3] However, aortic stenosis (AS) is not a commonly reported manifestation of SSc and there are only case reports of SSc patients receiving aortic valve replacement.[4] Interestingly, in one report of a patient with SSc who underwent aortic valve replacement for severe AS, examination of the aortic valve demonstrated acellular fibrosis with little calcification.[4] Among patients with systemic sclerosis-associated pulmonary arterial hypertension (SSc-PAH), the presence of co-existing aortic valve disease may predict a particularly poor prognosis.[5] Patients with pulmonary hypertension (PH) and co-existing aortic valve stenosis are challenging to manage as they are high risk for poor outcomes with surgical aortic valve replacement[6] and pulmonary vasodilator therapy can be contra-indicated. Transcatheter aortic valve replacement (TAVR) offers a less invasive option for patients with SSc-PAH/PH, but little is understood about peri and post procedural outcomes. Herein, we report the prevalence of aortic valve stenosis and TAVR-associated hemodynamic, imaging and clinical event outcomes among a cohort of SSc-PAH/PH patients evaluated in a tertiary care PH clinic.

METHODS

After obtaining local institutional review board approval, we performed a single center retrospective cohort study of adult patients with right heart catheterization (RHC) confirmed SSc-PAH/PH who were evaluated in the Pulmonary Hypertension Clinic between January 01, 2005 and August 15, 2020. All patients underwent diagnostic (RHC) and a comprehensive workup to exclude other etiologies of PH. Baseline characteristics, transthoracic echocardiography (TTE) results, pulmonary function tests and RHC hemodynamics were collected within 6 months of RHC confirmed PH diagnosis. The degree of left ventricular diastolic function was determined by extraction from TTE reports from the University of Wisconsin echo lab which adheres to the American society of echocardiography guidelines for reporting of diastolic dysfunction. This includes parameters such as medial E/E′, lateral E/E′, E/A ratio, and left atrial volume index.

SSC-PAH/PH patients were identified through an institutional PH registry. The retrospective data was then obtained by using the electronic medical record to collect prespecified data elements. Patients were categorized into an AS-Present cohort and AS-Absent cohort based on presence or absence of AS during the study period confirmed by a cardiologist on TTE. If patients demonstrated evidence of mild, moderate, or severe AS at PH diagnosis or developed AS during the study period, they were grouped into the AS-Present cohort. Patients who only demonstrated evidence of aortic sclerosis (defined by leaflet thickening without leaflet restriction) or normal valve morphology during the entire study period were grouped into the AS-Absent cohort. The point prevalence of aortic valve disease at PH diagnosis was determined by presence of aortic valve disease on TTE within 1 year of PH diagnosis date. The period prevalence of aortic valve disease was defined by evidence of aortic valve disease on TTE between RHC diagnosis date and censor date. Aortic valve stenosis data at peak severity was collected before TAVR, study end date, or death.

Statistical analysis

Continuous variables are presented as mean with standard error if normally distributed or median with interquartile range (IQR) for not normally distributed data. All data were assessed for normality with the Shapiro–Wilks test. Categorical variables are presented as absolute numbers and percentages. Tests for differences between groups were performed using the Fisher exact test for categorical data or by the unpaired Student's *t*-test with Welch's correction (normally distributed data) or Mann–Whitney *U*-test (not normally distributed data) for continuous variables. Kaplan–Meier curves were created for survival from PH diagnosis date in both cohorts, from AS diagnosis date in the AS-Present cohort. Two-sided tests were used and $p < 0.05$ was considered statistically significant for all included analyses. Statistical analysis was performed with GraphPad Prism 8.0 and 9.0.

RESULTS

Patient demographic and echocardiography characteristics

During the study period, a total of 90 patients with RHC confirmed SSc-PAH/PH were evaluated in the Pulmonary Hypertension Clinic. Baseline characteristics for the cohort at PH diagnosis are listed in Table 1. The mean age of the cohort at PH diagnosis was 64.2 ± 1.1 years. The cohort was predominantly female, 62/90 (68.9%),

TABLE 1 Baseline characteristics, medical comorbidities, and systemic sclerosis manifestations at pulmonary arterial hypertension diagnosis

	All, $n = 90$ (%)	AS-Present, $n = 19$ (%)	AS-Absent, $n = 71$ (%)	p Value
Age (years)	64.2 ± 1.1	66.3 ± 2.2	63.7 ± 1.3	0.33
Gender (female)	62 (68.9)	10 (52.6)	52 (73.2)	0.10
BMI (kg/m^2)	26.6 ± 0.6	27.1 ± 1.2	26.5 ± 0.7	0.69
Diabetes mellitus	14 (15.6)	0 (0)	14 (19.7)	0.04[a]
Hypertension	50 (55.6)	13 (68.4)	37 (52.1)	0.29
Coronary artery disease	20 (22.2)	6 (31.6)	14 (19.7)	0.35
Dyslipidemia	41 (45.6)	10 (52.6)	31 (43.7)	0.61
Chronic obstructive pulmonary disease	11 (12.2)	4 (21.0)	7 (9.9)	0.24
Smoker (>10 pack years)	41 (45.6)	11 (57.9)	30 (42.3)	0.30
Chronic kidney disease	18 (20.0)	5 (26.3)	13 (18.3)	0.52
Scleroderma type				
Limited cutaneous	72 (80.0)	17 (89.5)	55 (77.5)	0.34
Diffuse cutaneous	12 (13.3)	1 (5.3)	11 (15.5)	0.45
Overlap syndrome	4 (4.4)	0 (0.0)	4 (5.6)	0.58
Sine	2 (2.2)	1 (5.3)	1 (1.4)	0.38
Scleroderma manifestations				
Telangiectasias	82 (91.1)	18 (94.7)	64 (90.1)	0.99
Raynaud's phenomenon	88 (97.8)	18 (94.7)	70 (98.6)	0.38
Sclerodactyly	76 (84.4)	17 (89.5)	59 (83.1)	0.73
Calcinosis cutis	29 (32.2)	7 (36.8)	22 (30.1)	0.78
GERD	71 (78.9)	13 (68.4)	58 (81.7)	0.22
Antibody profile				
Anti-centromere	36 (40.0)	9 (47.4)	27 (30.0)	0.60
SCl-70	11 (12.2)	1 (5.3)	10 (14.1)	0.45
SSB or SSA	10 (11.1)	1 (5.3)	9 (12.7)	0.68
Rheumatoid factor	9 (10.0)	1 (5.3)	8 (11.3)	0.68
RNA polymerase II	1 (1.1)	0 (0)	1 (1.4)	0.99
Anti-U1-RNP	3 (3.3)	0 (0)	3 (4.2)	0.99
Interstitial lung disease	36 (40.0)	7 (36.8)	29 (40.8)	0.80

Note: Variance = standard error.

Abbreviations: AS, aortic stenosis; BMI, body mass index; GERD, gastroesophageal reflux disease.

[a]Statistically significant at $p < 0.05$, the unpaired t-test with Welch's correction was used for continuous variables and the Fischer-exact test was used for categorical variables.

and 80% of patients carried a diagnosis of limited sclerosis. Three SSc patients were excluded from our analysis because their pulmonary hypertension was predominantly secondary to heart failure with reduced ejection fraction or severe heart failure with preserved ejection fraction. Two SSc patients were excluded due to severe interstitial lung disease and one patient was excluded due to questionable SSc diagnosis.

TTE analysis for the cohort at PH diagnosis are listed in Table 2. Echocardiography determined left ventricular diastolic dysfunction was present in 62/90 (68.9%) patients and a pericardial effusion was present in 22/90

TABLE 2 Transthoracic echocardiogram data at pulmonary arterial hypertension diagnosis

	All, $n = 90$ (%)	AS-Present, $n = 19$ (%)	AS-Absent, $n = 71$ (%)	p Value
Aortic valve disease				
Normal leaflets	35 (38.9)	2 (10.5)	33 (46.5)	n/a
Aortic sclerosis	42 (46.7)	4 (21.1)	38 (53.5)	
Aortic stenosis	13 (14.4)	13 (68.4)	0 (0)	
Mitral valve disease				
Normal leaflets	45 (50.0)	6 (31.6)	39 (54.9)	0.10[a]
Thickened leaflets	41 (45.6)	11 (57.9)	30 (42.3)	
Mitral stenosis	4 (4.4)	2 (10.5)	2 (2.8)	
Right ventricular size				
Normal size	21 (23.3)	4 (21.1)	17 (23.9)	0.30[a]
Mildly enlarged	23 (25.6)	5 (26.3)	18 (25.4)	
Moderately enlarged	20 (22.2)	7 (36.8)	13 (18.3)	
Severely enlarged	26 (28.9)	3 (15.8)	23 (32.4)	
Right ventricular function				
Normal function	31 (34.4)	6 (31.6)	25 (35.2)	0.31[a]
Mildly reduced	16 (17.8)	4 (21.1)	12 (16.9)	
Moderately reduced	22 (24.4)	7 (36.8)	15 (21.1)	
Severely reduced	21 (23.3)	2 (10.5)	19 (26.8)	
Mitral regurgitation	24 (26.7)	8 (42.1)	16 (22.5)	0.14[b]
Pericardial effusion	22 (24.4)	6 (31.6)	16 (22.5)	0.55[b]
RVSP ($n = 88$)	68.3 ± 2.1	72.3 ± 3.4	67.2 ± 2.5	0.24[b]

Note: Variance = standard error.

Abbreviations: AS, aortic stenosis; RVSP, right ventricular systolic pressure.

[a]Fischer-exact test.

[b]Unpaired *t*-test with Welch's correction.

*Statistically significant at $p < 0.05$.

(24.4%) patients. No patients had bicuspid, unicuspid aortic valve deformities, or rheumatic aortic valve stenosis.

Over a median follow-up of 3.3 years (IQR: 1.3–5.9) from PH diagnosis to censor date or development of aortic valve stenosis, 6/77 (7.8%) patients not already diagnosed with AS at PH diagnosis developed AS, representing an incidence rate of six cases over 295.7 person years (20.3 cases per 1000 person years). For the six incident AS cases, median time from PH diagnosis to echocardiographic evidence of AS was 2.3 years (IQR: 1.5–3.9). The period prevalence of AS in this SSc-PAH/PH cohort was 19/90 (21.1%, 95% confidence interval [CI]: 13.2–30.1) patients. At the time of AS diagnosis, 1 patient had moderate AS and the other 18 patients had mild AS. Of the 19 AS-Present patients, 4/19 (21.1%) patients were diagnosed between the age of 50 and 59, 7/19 (36.8%) patients were diagnosed between the age of 60 and 69, and 8/19 (42.1%) patients between the ages of 71 and 80. The mean age of AS diagnosis was 66.9 ± 1.95 years. None of the patients included underwent surgical aortic valve replacement.

Clinical evaluation and echocardiography comparisons

Baseline characteristics at PH diagnosis for the SSc-PAH/PH cohort divided by the presence or absence of AS during the study period are listed in Table 1. There was a higher proportion of females in the AS-Absent cohort relative to the AS-Present cohort, 72.3% versus 52.6%,

respectively. The mean age of onset of SSc symptoms (characterized by Raynaud's syndrome, dyspnea, or gastroesophageal symptoms) in the AS-Present cohort compared to the AS-Absent cohort was 53.8 years ± 2.4 versus 52.2 years ± 1.8, $p = 0.61$, respectively. The median time from SSc onset to PH diagnosis in the AS-Present and AS-Absent cohort was 10 years (IQR: 8–19) versus 10 years (IQR: 3–17), $p = 0.40$, respectively. SSc type, clinical manifestations, antibody profile, and presence of interstitial lung disease are listed in Table 1.

TTE data for the AS-Present and AS-Absent cohort are reported in Table 2. RHC hemodynamic data is listed in Table 3. At the time of PH diagnosis, AS was not severe or contributing to abnormal RHC hemodynamics, and PH was deemed group 1 precapillary PAH in 77/90 SSc patients. There were seven patients in the AS-Present cohort and seven patients in the AS-Absent cohort with a pulmonary capillary wedge pressure greater than 15 mmHg who were diagnosed with combined group 1 and group 2 pulmonary hypertension. At the time of diagnosis there was no patient with severe AS requiring treatment. There was a significant difference in the mean pulmonary artery diastolic pressure between the AS-Present cohort relative to the AS-Absent cohort, 29.1 ± 1.3 mmHg versus 25.6 ± 1.1 mmHg, $p = 0.048$, respectively. In the AS-Present cohort, 8/19 (42.1%) patients achieved stability with nonparenteral pulmonary vasodilator therapy compared to 46/70 (65.7%) patients in the AS-Absent cohort, $p = 0.07$.

In the AS-Present cohort, 16/19 (84.2%) patients presented in NYHA class 3 or 4; while in the AS-Absent cohort, 47/71 (66.2%) patients presented in NYHA class 3 or 4 at PH diagnosis, $p = 0.17$. Between the AS-Present and AS-Absent cohorts, there was no significant difference in the forced expiratory volume in the first second: 68% ($n = 17$, IQR: 57.5–85.5) versus 72% ($n = 68$, IQR: 57.25–83.0), $p = 0.65$; forced vital capacity: 72.4 ± 3.8% ($n = 17$) versus 72.4 + 2.3% ($n = 68$), $p = 0.99$; diffusion capacity for carbon monoxide: 39% ($n = 17$, IQR: 28.0–47.5) versus 37% ($n = 65$, IQR: 27.5–50.0); or 6 min walk distance: 647 feet ($n = 19$, IQR: 330–960) versus 812 feet ($n = 65$, IQR: 469–1123) ($p = 0.25$).

Aortic valve stenosis progression

Aortic valve stenosis data at peak severity is reported in Table 4. Over the study period, 3/19 (15.8%) patients progressed to moderate aortic valve stenosis and 6/19 (31.6%) progressed to severe aortic valve stenosis meeting criteria for aortic valve replacement. The median age at peak severity among the six patients with severe aortic valve stenosis was 70 years (IQR: 66–76). For the six patients with severe AS, median peak velocity was 396 cm/s (IQR: 373–416), median mean gradient was 36.5 mmHg (IQR: 56.5–69.3), median peak gradient was 64.5 mmHg (35.6–42.0), and median aortic valve area was 0.85 cm^2 (IQR: 0.60–0.95).

See Figure 1 for management of SSc-PAH/PH patients on pulmonary vasodilator therapy during TAVR. Of the six severe AS patients, five patients underwent TAVR and one patient died while undergoing TAVR evaluation. Four (4/5) of the TAVR patients were women and the median age of TAVR was 70 years (IQR: 65.0–74.5). Peri-operative TAVR data is listed in Table 5. At time of TAVR, patient 1 and patient 2 had

TABLE 3 Right heart catheterization hemodynamic data at pulmonary arterial hypertension diagnosis

	All ($n = 90$)	AS-Present ($n = 19$)	AS-Absent ($n = 71$)	p Value
PASP (mmHg)	67.1 ± 2.1	72 ± 3.4	65.7 ± 2.5	0.14[a]
PADP (mmHg)	26.3 ± 0.9	29.1 ± 1.3	25.6 ± 1.1	0.048[a,*]
MPAP (mmHg)	42.1 ± 1.2	45.3 ± 1.8	41.3 ± 1.4	0.09[a]
RAP (mmHg)	9 (7–11.3)	10 (7–11)	9 (7–13)	0.49[b]
PCWP (mmHg)	12 (9–15)	13 (9–16)	11 (8–14)	0.19[b]
Cardiac Output (L/min)	4.1 (3.3–5.4)	4.4 (3.7–5.5)	4 (3.2–5.4)	0.18[b]
Cardiac Index (L/min/m^2)	2.3 (1.8–2.9)	2.4 (2–2.9)	2.3 (1.8–2.9)	0.51[b]
PVR (dynes/s/cm^{-5})	512 (356–841)	528 (368–789)	504 (344–856)	0.97[b]

Note: Variance = standard error or IQR.

Abbreviations: AS, aortic stenosis; MPAP, mean pulmonary artery pressure; PADP, pulmonary artery diastolic pressure; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

[a]Unpaired *t*-test with Welch's correction.

[b]Mann–Whitney *U*-test.

*Statistically significant at $p < 0.05$.

TABLE 4 Aortic valve stenosis data at peak severity

	AS-Present, $n = 19$ (%)
Age (years)	70 (66–76)
Aortic valve severity	
Mild	10 (52.6)
Moderate	3 (15.8)
Severe	6 (31.6)
TAVR	5 (26.3)
Peak velocity (m/s)	255 (208–373)
Peak gradient (mmHg)	26 (17–57)
Mean gradient (mmHg)	15 (11–36)
Aortic valve area (VTI) (cm^2)	1.20 (0.90–1.94)
Indexed orifice area	0.53 (0.40–0.84)
RV systolic function	
Normal	8 (42.1)
Mildly reduced	7 (36.8)
Moderately reduced	1 (5.3)
Severely reduced	3 (15.8)
RVSP (mmHg, $n = 16$)	62.7 ± 5.4
RV size	
Normal	4 (21.1)
Mildly enlarged	6 (31.6)
Moderately enlarged	5 (26.3)
Severely enlarged	4 (21.0)
LV diastolic dysfunction	15 (78.9)

Note: Variance = standard error or IQR.

Abbreviations: AS, aortic stenosis; LV, left ventricle; RV, right ventricle; RVSP, right ventricular systolic pressure; TAVR, transcatheter aortic valve replacement.

mildly reduced RV function and normal RV size. Both patient 1 and patient 2 had no complications in the peri-operative TAVR period. Patient 3 had severe mitral stenosis, mildly enlarged RV size, and normal RV function. This patient underwent TAVR complicated by atrioventricular block before valve deployment and required a permanent pacemaker. Patient 4 had normal RV function, normal RV size, and required a balloon aortic valvuloplasty before TAVR. Patient 5 had severely reduced RV function and severely reduced RV size. Two months before TAVR, patient 5 had increasing left sided filling pressures secondary to AS so their epoprostenol was gradually weaned and discontinued. Patient 5 developed worsening pulmonary hypertension shortly after the TAVR and required re-initiation of epoprostenol with successful stabilization of pulmonary hypertension. After TAVR, all five patients remained on the same pulmonary vasodilator therapy regimen until the end of the investigation period or death. None experienced paravalvular prosthetic leak. Patient 1 and patient 2 underwent TAVR within 3 months of study end date and were still alive at the end of the investigation period. The remaining three patients died during the investigational period, with a median survival time of 711 days post-TAVR.

Figure 2 illustrates survival in the AS-Present and AS-Absent cohort from PH diagnosis; 1-year survival was 89.5% versus 80.1%, 3-year survival was 62.4% versus 69.5%, and 5-year survival was 42.1% versus 54.7%, respectively, log rank $p = 0.58$, hazard ratio (HR): 1.19, CI: 0.6–2.3. In the AS-Present cohort from AS diagnosis date, 1-year survival was 78.9%, 3-year survival was 57.9%, and 5-year survival was 37.2%.

DISCUSSION

We have reported the first detailed clinical, imaging and hemodynamic evaluation of patients with aortic valve stenosis and SSc-PAH/PH. We observed a high period prevalence of AS of 19/90 (21.1%) patients in a cohort of 90 patients with RHC confirmed SSc-PAH/PH, in which more than half of the AS patients were diagnosed under the age of 70 years. Of the AS patients, 6/19 (31.6%) patients progressed to severe AS warranting aortic valve replacement. Five of these patients successfully underwent TAVR at a median age of 70 years, four of which were on combination oral and parenteral pulmonary vasodilator therapy at the time of the procedure with only one patient developing worsened PH post-TAVR. The 5-year survival from AS diagnosis date was only 37.2%. The prevalence of diastolic dysfunction in this cohort is consistent with prior studies which have demonstrated an increased frequency of left ventricular diastolic dysfunction among patients with SSc and is associated with increased SSc disease duration.[7] As to why SSC-PAH/PH patients in our study seemed to have a high prevalence of AS relative to the general population requires further investigation. This may be related to the dysregulated autoimmunity and pro-inflammatory state in SSc-PAH, influenced by a combination of inflammatory cytokines, autoantibodies, and endothelial cell dysfunction.[8]

There has also been investigation into the role anti-endothelial cell antibodies play in the development of SSc-PAH.[9–11] Further studies are needed to understand the pathogenesis of AS in SSC-PAH/PH patients. Investigating novel PAH biomarkers like endothelin-1, vascular endothelial growth factor, and microRNA-206

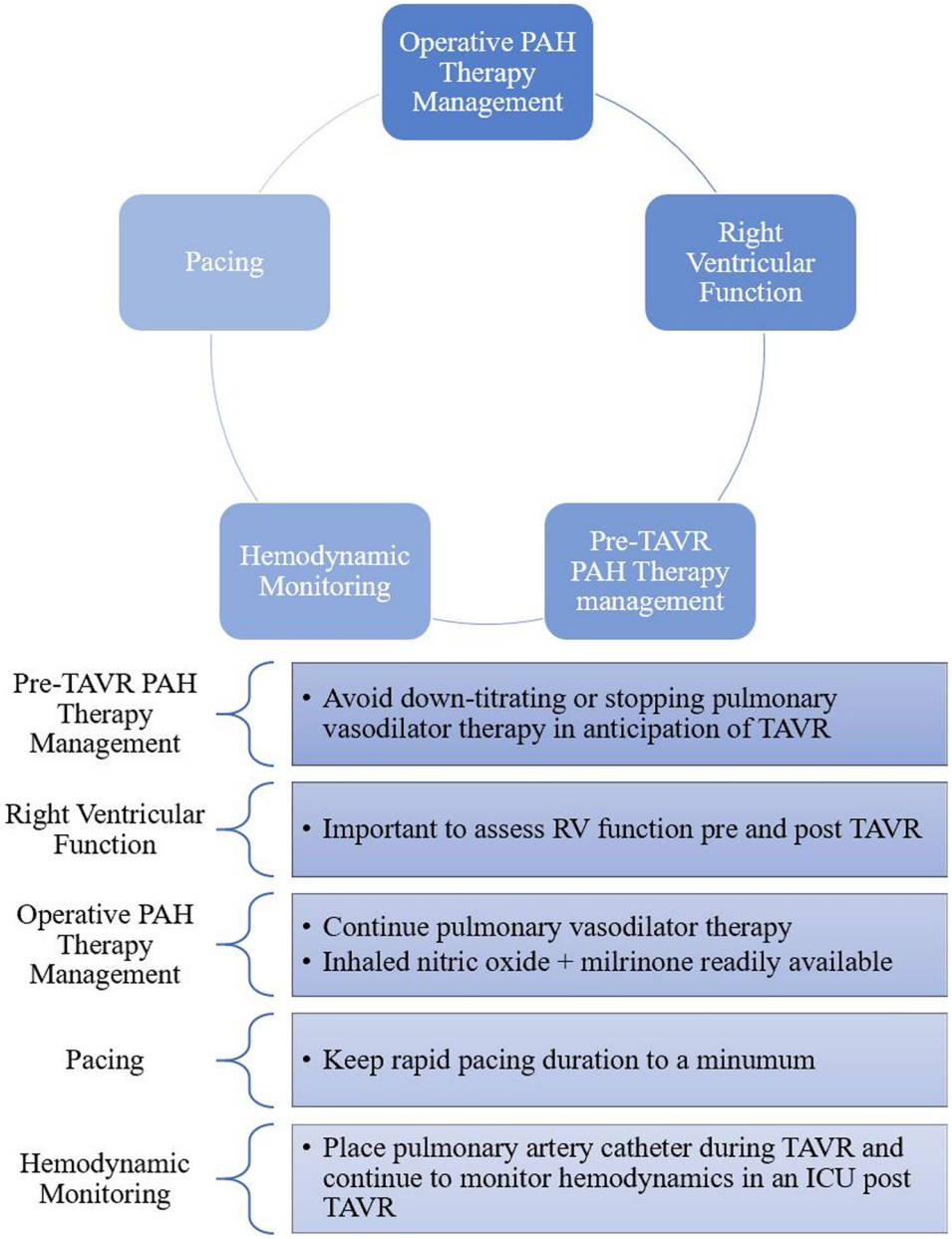

FIGURE 1 Management of patients with pulmonary arterial hypertension (PAH) on advanced pulmonary vasodilator therapy during transcatheter aortic valve replacement (TAVR). The core management principles of patients with PAH on advanced pulmonary vasodilator therapy receiving TAVR at our center.

may help identify SSc patients at risk of accelerated valvular heart disease.[12]

The AS patients also presented with a trend toward higher mean pulmonary artery pressure, lower 6-min walk distance, higher proportion of NYHA class 3 or 4, and a higher proportion of patients requiring parenteral pulmonary vasodilator therapy, relative to the cohort of patients without AS. This is despite only one patient having more than mild AS at PH diagnosis and six patients not showing evidence of AS at PH diagnosis. Whether there is an association between more aggressive SSc-associated pulmonary vascular injury and the development of AS as part of a more robust inflammatory response affecting the pulmonary vasculature and valvular endothelium will require further investigation.

AS is a disease with increasing prevalence in Western societies. In the United States and Europe, the prevalence of degenerative calcific aortic valve stenosis is approximately 12.4% with severe AS comprising 3.4% in those 75 years and older[13] and 5% in those under age 65. In a more recent study of an Icelandic cohort, findings were similar with a prevalence of 4.3% in those aged 70 years

TABLE 5 Peri-operative TAVR data including PAH therapy at time of TAVR, PCWP via RHC 1 month before TAVR, and TAVR access site/valve type/peri-operative complications

Patient	Age (years)	Gender	PAH therapy	Access site	PCWP (mmHg)	Valve type	Complications
1	62	F	Inhaled Treprostinil + Ambrisentan + Sildenafil	Right transfemoral	13	26 mm S3 Sapien	None
2	70	F	Sildenafil + Epoprostenol	Right transfemoral	15	23 mm S3 Sapien Ultra	None
3	68	F	Sildenafil + Treprostinil (IV)	Left transfemoral	24	29 mm Evolut R Corevalve	AV block requiring dual chamber pacemaker
4	77	F	Bosentan	Transapical	22	26 mm Sapien Edwards	None
5	72	M	Sildenafil	Right transfemoral	27	26 mm Sapien XT	Worsened PAH

Abbreviations: AV, Atrioventricular; F, female; IV, intravenous; M, Male; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; RHC, right heart catheterization; TAVR, transcatheter aortic valve replacement.

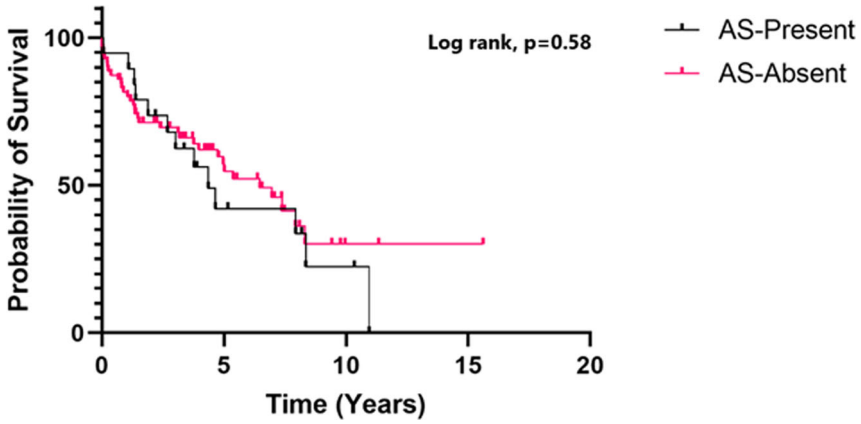

FIGURE 2 Survival from pulmonary arterial hypertension (PAH) diagnosis in the aortic stenosis (AS)-Present cohort ($n = 19$) and AS-Absent cohort ($n = 71$). In the AS-Present and AS-Absent cohort from PAH diagnosis, 1-year survival was 89.5% versus 80.1%, 3-year survival was 62.4% versus 69.5%, and 5-year survival was 42.1% versus 54.7%, respectively, log rank $p = 0.58$, HR: 1.19, CI: 0.6–2.3. The median survival from PAH diagnosis in the AS-Present cohort and AS-Absent cohort was 4.4 and 6.5 years, respectively. Tick mark represents censor date of lost to follow-up or study end date.

and older and an incidence of new AS of 5 per 1000 per year with 60 years being the initial mean age of participants.[14] In our study cohort, however, greater than 50% of patients diagnosed with AS were under the age of 70. Additionally, 21.1% (4/19) of AS patients were diagnosed before age 60. This is in stark contrast to previous meta-analysis studies of the general population which have reported AS to be relatively uncommon in those under age 65 years. Interestingly, none of the patients in our cohort had a bicuspid aortic valve or rheumatic AS to explain this discrepancy in age as compared to previous studies. These findings suggest that the prevalence of AS in SSc may be a complication of the disease process and greater than previously thought.

Previous studies have described only case reports of severe aortic valve stenosis requiring aortic valve replacement in patients with SSc, with only three case reports in the last decade.[15] In 2019, contrary to prior literature, Butt et al.[16] demonstrated an increased risk of AS in patients with scleroderma as compared to matched controls in addition to numerous other cardiac manifestations. This retrospective cohort study utilizing the Danish healthcare registers reported an incidence rate of AS to be 0.29 per 100 person years as compared to 0.10 in their matched controls with HR (2.99; 95% CI: 2.25–3.97) among patients with scleroderma. Although, this study did not detail whether the scleroderma patients with AS also had a high prevalence of SSc-PAH.

In the general population, the mean and median age of TAVR are approximately 83 and 84 years, respectively.[17] Within our cohort, however, the median age at peak severity of AS and TAVR was notably younger at 70 years. However, it is important to note that surgical aortic valve replacement is preferred in younger patients without significant comorbidities, while TAVR is a preferred approach for patients who are older and have significant comorbidities, which makes them less favorable surgical candidates.[18]

Historically, pulmonary hypertension has been associated with increased mortality after surgical aortic valve replacement or TAVR and severe PAH patients were excluded from the PARTNER 3 trial.[19] In the context of significant pulmonary artery pressure elevation, the clinical benefits of TAVR may be called into question. One study by Lindman et al.[20] showed that in patients with symptomatic AS, increased pulmonary pressures were associated with higher mortality as well as higher rates of hospitalization and stroke. They additionally showed that hemodynamic indices were not a helpful tool in risk stratification of patients considering TAVR. However, Alushi et al.[21] demonstrated that post-TAVR patients had similar all-cause mortality across varying levels of baseline pulmonary artery systolic pressure elevation. Within our cohort, five patients underwent successful TAVR on pulmonary vasodilator therapy with a median survival time of 711 days post-TAVR among those patients greater than 3 months post-TAVR at study end date. This suggests that, in selected SSC-PAH/PH patients, TAVR can be performed safely even in those with severe disease who are optimized with pulmonary vasodilator therapy.

Periprocedural management of PH patients undergoing TAVR offers unique challenges, particularly with how to manage pulmonary vasodilator therapy, intraoperative airway/sedation, and periprocedural monitoring. In our experience, we learned to avoid down-titrating or stopping pulmonary vasodilator therapy in anticipation of TAVR. We determined it was helpful to place an invasive pulmonary artery catheter in all of these patients pre-TAVR and left in place post-TAVR for at least 48 h. During the TAVR, we attempted to keep rapid pacing duration to a minimum. In all cases, inhaled nitric oxide and milrinone was prepped and available, but was not routinely used. Immediately following valve deployment and during the hospital stay, we made a concerted effort to repeatedly evaluate right ventricular function using echocardiography. Unlike other routine TAVR cases, all of these patients were monitored for at least 48 h in an intensive care unit capable of managing an invasive pulmonary artery catheter and pulmonary vasodilator therapy.

LIMITATIONS

There are several limitations of our study. The retrospective design led to incomplete data in several patients including NYHA class at PH diagnosis. The echocardiograms were interpreted and reported by several cardiologists, rather than a Core lab, which could lead to interobserver variability. However, all TTE data was reviewed by a board-certified cardiologist to minimize the degree of interobserver variability. There were 14 patients in the SSC-PAH/PH cohort with a pulmonary capillary wedge pressure greater than 15 mmHg. These patients were diagnosed with combined group 1 and group 2 pulmonary hypertension. The group 2 pulmonary hypertension was secondary to a component of diastolic heart failure. These patients were still thought to have predominantly group 1 PAH physiology. PH patients on pulmonary vasodilator therapy typically have frequent echocardiograms, which could lead to enhanced detection of aortic valve pathology compared to non-PH patients. Additionally, some patients did not receive their first echocardiogram until PH diagnosis, which could lead to a higher mean age at AS diagnosis in this cohort. We need prospective studies in SSc focusing on valvular heart disease. It may be that there is a relationship between PH and the progression of valvular heart disease, but without balanced data collection in contemporary cohorts this remains unknown. Furthermore, larger studies of patients with SSc and AS undergoing TAVR are needed to determine outcome in these patients.

CONCLUSIONS

In conclusion, aortic valve stenosis was highly prevalent in our cohort of patients with scleroderma-associated PAH, with an age onset of severe stenosis that is younger than patients with nonbicuspid aortic valve stenosis. We have reported the largest series of patients with SSc-PAH/PH on advanced pulmonary vasodilator therapy who underwent TAVR with acceptable periprocedural and early outcomes.

AUTHOR CONTRIBUTIONS

Kirsten Alman, Corey J. Sadd, and James R. Runo contributed to study design, data collection, and writing of the manuscript. Amish Ravel, Farhan Raza, and Amy Chybowski contributed to study design and manuscript revisions.

ACKNOWLEDGMENT

Funding is not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

The permission for this study was got from local institutional review board.

ORCID

Corey J. Sadd http://orcid.org/0000-0001-9578-3527

REFERENCES

1. Avouac J, Airò P, Meune C, Beretta L, Dieude P, Caramaschi P, Tiev K, Cappelli S, Diot E, Vacca A, Cracowski JL, Sibilia J, Kahan A, Matucci-Cerinic M, Allanore Y. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. J Rheumatol. 2010;37(11):2290–8.
2. Kolstad KD, Li S, Steen V, Chung L, PHAROS Investigators. Long-term outcomes in systemic sclerosis-associated pulmonary arterial hypertension from the pulmonary hypertension assessment and recognition of outcomes in scleroderma registry (PHAROS). Chest. 2018;154(4):862–71.
3. Grimaldi A, Figini F, Maisano F, Montorfano M, Chieffo A, Latib A, Pappalardo F, Spagnolo P, Cioni M, Vermi AC, Ferrarello S, Piraino D, Cammalleri V, Ammirati E, Sacco FM, Arendar I, Collu E, La Canna G, Alfieri O, Colombo A. Clinical outcome and quality of life in octogenarians following transcatheter aortic valve implantation (TAVI) for symptomatic aortic stenosis. Int J Cardiol. 2013;168(1):281–6.
4. Ferrari G, Pratali S, Pucci A, Bortolotti U. Aortic valve replacement in systemic sclerosis. J Cardiovasc Med (Hagerstown). 2015;16(Suppl 1):S60–1.
5. Perera A, Fertig N, Lucas M. Clinical subsets, skin thickness progression rate, and serum antibody levels in systemic sclerosis patients with anti-topoisomerase I antibody. Arthritis Rheum. 2007;56(8):2740–6.
6. Holmes DR Jr, Mack MJ, Kaul S, Agnihotri A, Alexander KP, Bailey SR, Calhoon JH, Carabello BA, Desai MY, Edwards FH, Francis GS, Gardner TJ, Kappetein AP, Linderbaum JA, Mukherjee C, Mukherjee D, Otto CM, Ruiz CE, Sacco RL, Smith D, Thomas JD. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement. J Am Coll Cardiology. 2012;59(13):1200–54.
7. Hinchcliff M, Desai CS, Varga J, Shah SJ. Prevalence, prognosis, and factors associated with left ventricular diastolic dysfunction in systemic sclerosis. Clin Exp Rheumatol. 2012;30(2, Suppl 71):S30–7.
8. Kherbeck N, Tamby MC, Bussone G, Dib H, Perros F, Humbert M, Mouthon L. The role of inflammation and autoimmunity in the pathophysiology of pulmonary arterial hypertension. Clinic Rev Allerg Immunol. 2013;44:31–8.
9. Negi VS, Tripathy NK, Misra R, Nityanand S. Antiendothelial cell antibodies in scleroderma correlate with severe digital ischemia and pulmonary arterial hypertension. J Rheumatol. 1998;25(3):462–6.
10. Chizzolini C, Raschi E, Rezzonico R, Testoni C, Mallone R, Gabrielli A, Facchini A, Del Papa N, Borghi MO, Dayer JM, Meroni PL. Autoantibodies to fibroblasts induce a proadhesive and proinflammatory fibroblast phenotype in patients with systemic sclerosis. Arthritis Rheum. 2002;46(6):1602–13.
11. Pignone A, Scaletti C, Matucci-Cerinic M, Vázquez-Abad D, Meroni PL, Del Papa N, Falcini F, Generini S, Rothfield N, Cagnoni M. Anti-endothelial cell antibodies in systemic sclerosis: significant association with vascular involvement and alveolo-capillary impairment. Clin Exp Rheumatol. 1998;16(5):527–32.
12. Todd N, Lai YC. Current understanding of circulating biomarkers in pulmonary hypertension due to left heart disease. Front Med (Lausanne). 2020;7:570016. https://doi.org/10.3389/fmed.2020.570016
13. Osnabrugge RL, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, Bogers AJ, Piazza N, Kappetein AP. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol. 2013;62:1002–12.
14. Danielsen R, Aspelund T, Harris TB, Gudnason V. The prevalence of aortic stenosis in the elderly in Iceland and predictions for the coming decades: the AGES–Reykjavík study. Int J Cardiol. 2014;176:916–22.
15. Grygiel-Górniak B, Oduah MT, Olagunju A, Klokner M. Disorders of the aorta and aortic valve in connective tissue diseases. Curr Cardiol Rep. 2020;22:70.
16. Butt SA, Jeppesen JL, Torp-Pedersen C, Sam F, Gislason GH, Jacobsen S, Andersson C. Cardiovascular manifestations of systemic sclerosis: a Danish Nationwide Cohort Study. J Am Heart Assoc. 2019;8(17):e013405.
17. Coffey S, Cox B, Williams MJ. The prevalence, incidence, progression, and risks of aortic valve sclerosis: a systematic review and meta-analysis. J Am Coll Cardiol. 2014;63(25, pt A):2852–61.
18. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S, PARTNER Trial I. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363:1597–607.
19. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, Leipsic J, Hahn RT, Blanke P, Williams MR, McCabe JM, Brown DL, Babaliaros V, Goldman S, Szeto WY, Genereux P, Pershad A, Pocock SJ, Alu MC, Webb JG, Smith CR, PARTNER 3 Investigators. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019;380(18):1695–705.
20. Lindman BR, Zajarias A, Maniar HS, Miller DC, Suri RM, Arnold SV, Webb J, Svensson LG, Kodali S, Xu K, Ayele GM, Lin F, Wong SC, Babaliaros V, Thourani VH, Douglas PS, Lim S, Leon MB, Mack MJ. Risk stratification in patients with

pulmonary hypertension undergoing transcatheter aortic valve replacement. Heart. 2015;101(20):1656–64.
21. Alushi B, Beckhoff F, Leistner D, Franz M, Reinthaler M, Stähli BE, Morguet A, Figulla HR, Doenst T, Maisano F, Falk V, Landmesser U, Lauten A. Pulmonary hypertension in patients with severe aortic stenosis: prognostic impact after transcatheter aortic valve replacement: pulmonary hypertension in patients undergoing TAVR. JACC Cardiovasc Imaging. 2019;12(4):591–601.

How to cite this article: Alman K, Sadd CJ, Ravel A, Raza F, Chybowski A, Runo JR. Prevalence of aortic stenosis and TAVR outcomes in patients with systemic sclerosis-associated pulmonary hypertension. Pulm Circ. 2022;12;e12118. https://doi.org/10.1002/pul2.12118