Increased Risk of Valvular Heart Disease in Systemic Sclerosis: An Underrecognized Cardiac Complication

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Abstract

Objective: Cardiac involvement is a poor prognostic marker in systemic sclerosis (SSc). While diastolic dysfunction, myocardial fibrosis, and arrhythmias are traditionally considered features of primary cardiac involvement in SSc, the incidence of valvular heart disease (VHD) is not well reported. Our objective was to examine the prevalence of VHD at time of SSc diagnosis and incidence of VHD during follow up compared to non-SSc subjects.

Methods: Medical records of patients with suspicion of SSc were reviewed to identify incident cases. SSc subjects were matched 1:2 by age- and sex to non-SSc subjects.

Results: The study included 78 incident SSc cases and 156 non-SSc comparators [56 years (± 15.7), 91% female]. A nearly 4-fold increase in the prevalence of moderate/severe VHD prior to SSc diagnosis compared to non-SSc subjects (6% vs. 0%; P=0.004) was identified. During follow up, 18 SSc and 12 non-SSc patients developed moderate/severe VHD. The cumulative incidence of VHD at 10 years after SSc incidence/index was 17.9% (95% CI: 10.7-29.9%) in patients with SSc compared with 2.3% (95% CI: 0.7-6.3%) in non-SSc subjects (HR: 4.23; 95% CI: 2.03-8.83). Coronary heart disease was the only significant risk factor for VHD.

Conclusion: SSc patients have a 4-fold increase in the prevalence of moderate/severe VHD at diagnosis compared to non-SSc patients. They also have a 4-fold increased risk of developing moderate/severe VHD after diagnosis of SSc. Aortic stenosis and mitral regurgitation have a much higher prevalence in SSc patients, besides secondary tricuspid regurgitation. Underlying mechanisms for this association require further elucidation.

Significance and Innovations

- First population-based study to investigate prevalence of valvular heart disease (VHD) in systemic sclerosis (SSc)
- VHD is 4 times more prevalent in patients with compared to those without SSc
- Aortic stenosis and mitral regurgitation have a much higher prevalence in SSc patients, besides secondary tricuspid regurgitation

- Assessment for VHD may be considered in SSc patients at diagnosis and follow up

Introduction

Systemic sclerosis (SSc) is a complex, heterogeneous autoimmune connective tissue disease characterized by microvascular injury, extracellular matrix deposition and widespread fibrosis of numerous tissues and organs, particularly lungs and heart.(1-3) Cardiac involvement in SSc is common with reported prevalence in the range of 15-35%.(4-7) Cardiac involvement is likely underestimated and underrecognized until late in the disease course since most manifestations remain subclinical and occult in nature. Subclinical cardiac involvement has been reported in about 70% of patients depending on degree of suspicion and screening tools utilized. (4-7) Involvement of the heart is a strong predictor of mortality in SSc and is associated with a poor prognosis with up to 70% mortality reported at 5 years. (4, 5) Therefore, early detection and monitoring of cardiac conditions are important aspects in the management in this patient population. All anatomic domains of the heart can be affected by the fibrotic and vascular processes of SSc.(5) In addition, cardiac involvement can occur secondary to interstitial lung disease, pulmonary arterial hypertension, scleroderma renal crisis or by medications used to treat SSc. (4-6) Most studies have looked at pericarditis, myocarditis, heart failure, diastolic dysfunction, arrhythmias and conduction disturbances. (4-7) However, little is known about the occurrence of valvular heart (VHD) in SSc. Therefore, the purpose of our study was to investigate the prevalence of VHD at time of SSc diagnosis and the incidence of VHD during follow up compared to non-SSc subjects in a population-based cohort.

Materials and Methods

The Mayo Clinic and Olmsted Medical Center Institutional Review Boards approved this study (IRB 17-005603). In this retrospective study, we reviewed all adults (≥18 years of age) with a diagnosis or suspicion of SSc among residents of Olmsted County, Minnesota from January 1, 1980 to December 31, 2016 to identify incident cases of SSc. The diagnosis of SSc was established based on physician diagnosis, and fulfillment of 2013 criteria for SSc was ascertained.(8) Clinical data was gathered by using the Rochester Epidemiology Project (REP), a medical record system linking together all the medical records of Olmsted County residents from multiple healthcare providers and institutions (9). Patients with other rheumatologic diseases were excluded from the study. A comparison cohort was randomly selected from the same population of Olmsted County residents for comparison. The SSc and comparator patients were matched 1:2 by age (+/- 3 years) and sex. Index/incidence date was based on date of physician diagnosis of SSc and/or date of appearance of any additional non-Raynaud symptoms.

Data about clinical characteristics and cardiovascular risk factors, including smoking status, obesity, hypertension, dyslipidemia, diabetes mellitus, use of aspirin, known coronary heart disease, peripheral artery disease, abdominal aneurysm, atrial fibrillation and heart failure, were manually extracted from the medical record and based on physician diagnosis. Anti-hypertensive medications alone were not counted as a diagnosis of hypertension in patients with SSc due to the increased prevalence of vasodilator use in this population of patients. Renal involvement was defined as scleroderma renal crisis, while gastrointestinal involvement was defined gastrointestinal dysmotility or pseudo-obstruction or gastric antral vascular ectasia or small intestinal bacterial overgrowth. Interstitial lung disease diagnosis was based on computed tomography. Pulmonary arterial hypertension diagnosis was based on right heart catheterization or echocardiogram criteria. Definitive pulmonary arterial hypertension diagnosis was based on right heart catheterization as the gold standard for diagnosis with mean pulmonary artery

pressure >20 mm Hg, pulmonary vascular resistance ≥3 Wood Units and pulmonary arterial wedge pressure ≤ 15 mm Hg. Probable pulmonary arterial hypertension diagnosis was based on echocardiogram for patients who didn't have right heart catheterization; criteria including both right ventricular systolic pressure >45 mm Hg and tricuspid regurgitant velocity >3.4 m/sec. Echocardiogram and right heart catheterization reports from January 1, 1980 to December 31, 2018 were manually reviewed to determine the occurrence of any VHD including aortic, mitral, pulmonary or tricuspid valve stenosis and/or regurgitation as defined by the 2014 American College of cardiology (ACC) / American Heart Association (AHA) guidelines.(10)

Descriptive statistics (percentages, mean, etc.) were used to summarize patient characteristics for each cohort. Baseline comparisons between cohorts were performed using Chi-square and rank sum tests. The analyses of VHD were performed using all patients and in the subset of patients who received echocardiograms. The prevalence of prior VHD overall and by type was compared between cohorts using Fisher's exact tests. Cumulative incidence of VHD adjusting for the competing risk of death was estimated (11). These methods are similar to the Kaplan-Meier method with censoring of patients who are still alive at last follow-up. However, patients who died before experiencing VHD were appropriately accounted for to avoid overestimation of the rate of occurrence of VHD, which can occur if such subjects are simply censored at death. Cox models were used to examine potential associations between baseline factors of interest and the development of VHD. Time-dependent covariates were used to model renal and gastrointestinal involvement, which developed during follow-up. For all comparisons, a p-value of less than 0.05 was considered statistically significant. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The study included a total of 78 incident SSc cases and 156 non-SSc subjects [mean age 56 (SD 15.7), 91% female for both cohorts]. Table 1 summarizes baseline clinical characteristics of the cases and comparators. At index date, patients with SSc had lower prevalence of diabetes (3% vs. 12%; P=0.015) and obesity (21% vs. 39%; P=0.008) than comparators. The prevalence of pulmonary hypertension was 8% in SSc vs. 1% in non-SSc controls (P=0.003). There was no difference in the prevalence of hypertension, hyperlipidemia, or coronary artery disease. Among this cohort of patients, 33 patients with SSc and 31 non-SSc subjects had at least 1 echocardiogram performed before incidence/index date. The prevalence of any VHD at that time was 19/78 (24%) in patients with SSc vs. 8/156 in non-SSc patients (5%) (P<0.001). Among the subset of patients who had an echocardiogram, the prevalence of any VHD at that time was 19/33 (58%) in patients with SSc vs. 8/31 in non-SSc patients (25%) (P=0.12). Of these patients, 5 SSc had moderate/severe VHD (2 moderate/severe mitral regurgitation (MR), 3 moderate/severe tricuspid regurgitation (TR), and 1 moderate/severe pulmonary regurgitation) vs. none in the non-SSc group. There was a higher prevalence of moderate/severe VHD prior to SSc diagnosis compared to non-SSc subjects (6% vs. 0%; P=0.004). Similarly, among those with echocardiograms, there was a higher prevalence of moderate/severe VHD prior to SSc diagnosis compared to non-SSc subjects (15% vs. 0%; P=0.05).

During a median of 10.5 years of follow-up in patients with SSc and 13.0 years of follow-up in non-SSc comparators, 65 patients with SSc and 53 non-SSc subjects had at least 1 echocardiogram performed. Among those without any VHD at SSc incidence/index date, VHD developed during follow-up in 32 patients with SSc and 33 comparators. The 10 year cumulative incidence of any VHD during follow up was higher among patients with SSc (36.8%; 95% confidence interval [CI}: 26.1-51.7%) compared to non-SSc subjects (13.2%; 95% CI: 8.5-20.7%; p<0.001). Similarly, among patients who received echocardiograms, the 10 year cumulative incidence of any VHD during follow up was higher among patients with SSc (37.1%;

95% confidence interval [CI}: 23.5-58.7%) compared to non-SSc subjects (17.5%; 95% CI: 7.3-42.0%; P=0.009).Of those without moderate/severe VHD at SSc incidence/index date, 18 SSc and 12 non-SSc patients developed moderate/severe VHD (4 aortic stenosis (AS), 3 MR and 14 TR in SSc; 5 AS, 1 mitral stenosis, 5 MR, and 6 TR in non-SSc). The 10 year cumulative incidence of moderate/severe VHD during follow up was higher among patients with SSc (17.9%; 95% CI: 10.7-29.9%) compared to non-SSc subjects (2.3%; 95% CI: 0.7-6.3%; p<0.001; Figure 1). This corresponds to a 4-fold difference (hazard ratio [HR]: 4.23; 95% CI: 2.053 – 8.83). Similarly, among those with echocardiograms, the 10 year cumulative incidence of moderate/severe VHD was higher among patients with SSc (13.5%; 95% CI: 5.4-33.4%) compared to non-SSc subjects (4.2%; 95% CI: 0.6-28.4%), but this difference did not reach statistical significance due to limited sample size (P=0.22).The cumulative incidence for moderate/severe VHD of each type is reported in Table 2.

The prevalence of pulmonary hypertension (PHT) as cause for moderate/severe TR was 6 PHT (4 probable and 2 definite) in SSc patients and 1 probable PHT in non-SSc. Secondary TR due to pacemaker-leads was not present in our cohort. Supraventricular tachycardia (atrial fibrillation or flutter) adding to TR severity was identified in 7 (9%) SSc and 9 (6%) non-SSc patients. Preexisting coronary artery disease was found to be the only risk factor associated with developing VHD over time in SSc with 5 fold increased risk (Table 3). No other traditional CV risk factor such as diabetes, hypertension, smoking status or dyslipidemia was predictive. Antiphospholipid antibody test results were available in 27/78 SSc cases - none tested positive for lupus anti-coagulant; 1 SSc patient tested positive for anti-cardiolipin and beta-2 glycoprotein, and another one tested positive for anti-cardiolipin antibody alone. Only one patient with positive anti-phospholipid antibodies developed moderate/severe valve disease, but none had antiphospholipid syndrome (APS).

Discussion

To our knowledge, this is the first population-based study to recognize the elevated risk of VHD in SSc, showing up to a 4-fold increased risk of moderate to severe VHD in patients with known SSc. These findings are not limited to secondary tricuspid valve regurgitation in patients with PHT, but include dysfunction of the aortic valve and the mitral valve, leading to stenosis and regurgitation respectively. Aortic stenosis in particular has a higher than expected prevalence and warrants further detailed study.

Valvular heart disease in SSc has not yet been thoroughly investigated. Most data originate from pathology studies describing endocarditis-like changes on the mitral, tricuspid or aortic valve on autopsy cases.(12) Aortic regurgitation and mitral valve (MV) prolapse secondary to nodular valve thickening of the aortic and mitral valve have been previously described, but to our knowledge, no systematic study of valvular disease in a population based incident cohort has been reported.(13-15) The most common valvular involvement in SSc is TR which is mostly, but not solely secondary related to pulmonary hypertension.

In our cohort, 6/14 (43%) had secondary TR related to PHT. Secondary TR due to pacemaker-leads at index/ incident date was not present in any SSc or non-SSc comparators. Supraventricular tachycardia (atrial fibrillation or flutter) adding to TR severity in patients with SSc was identified in 7 (9%) and 9 (6%) in non-SSc patients at incidence/ index date. Nevertheless, the majority had primary tricuspid valve changes leading to moderate/severe TR. Interestingly, patients with SSc seem to develop VHD prematurely. The VHD that was seen in our study occurred in a much younger population than in the general non-SSc population.(16) Chronic inflammation is known to be associated with accelerated atherosclerosis and has also been associated with myocarditis and cardiomyopathies.(17) Inflammation may have a role in valvular heart disease development and progression, especially AS, as seen in patients with RA and psoriasis.(18, 19). In SSc, microvascular dysfunction may potentially lead to earlier fibrotic changes in the cardiac valves. Nevertheless, there is no study that has specifically evaluated

systematically the pathologic changes in VHD in autoimmune rheumatologic disorders. In the general population, there appear to be sex-based differences in mechanisms leading to VHD. In females, valvular fibrosis is more prominent than valvular calcification in severe aortic stenosis.(20, 21) So hypothetically in SSc, which has a female predominance, a higher prevalence of valvular pathology may be secondary to the autoimmunity which hastens fibrotic tissue changes. In addition, the increased prevalence of VHD before SSc diagnosis suggests that subclinical disease activity may alter cardiac structures such as heart valves even before cutaneous or other organ manifestations become apparent. Valvular pathology has been more extensively described in systemic lupus erythematosus (SLE). Typical valvular lesions in SLE have been described as nodules or non-bacterial thrombotic endocarditis (ranging from small lesions to large verrucous masses), often related to APS.(22) There were no patients with APS in our SSc cohort. Other CIDs such as psoriasis show an increased risk of developing AS, not explained by traditional cardiovascular (CV) risk factors. (18) Case studies have described endocarditis-like changes in patients with SSc, but there are no prior studies on the prevalence of VHD in this population of patients.(23, 24)

The primary strengths of our study include the use of the Rochester Epidemiology Project, a population-based cohort, using a comprehensive record-linkage system able to capture information on the health care of all residents of Olmsted County regardless of age, sex, ethnicity, socio-economic status, insurance status or setting of health-care delivery. By using this population-based comprehensive record-linkage system, we were able to follow SSc cases across the full spectrum of disease for decades, from symptoms through final diagnosis, without relying only on administrative data, unlike referral cohorts. By manually reviewing every medical record, we were able to confirm diagnosis and minimize the eventuality of disease misdiagnosis, which is a major concern in studies which are based on administrative claims data.

The development of VHD takes multiple years, therefore following patients for an extended time is crucial to detect changes in valve function. Finally, the population is relatively stable, so the duration of medical record information available to investigators was substantial.

The limitations include the retrospective design of our study and limited numbers of observed, incident SSc patients. Due to the design, clinical and echocardiography information was not collected prospectively. Patients without an echocardiogram were rated as not having VHD. This might be valid for moderate and severe VHD, but is prone to underestimation of mild valvular disease. Surveillance bias might contribute significantly in SSc studies, due to the frequent and much closer monitoring of these patients for PHT. SSc patients undergo more frequent clinical, echocardiographic examinations and laboratory testing.

SSc is a disease with a high female predominance. Sex differences in CV risk factors and VHD have been evaluated in other studies.(25-27) Nevertheless, sex difference in VHD in SSc patients is unknown and difficult to elucidate.

This study was conducted in Olmsted County, MN, USA where the predominant population is white. Some ethnic and racial groups are under-represented in our population. Therefore, the generalizability of this study to other ethnic cohorts might vary, and our results must be looked at on a case-by-case basis when generalizing to more diverse populations.(28)

In conclusion, although VHD has not been considered to be a major primary cardiac manifestation of SSc, our current study revealed a higher than anticipated prevalence and incidence of valvular involvement in these patients compared to age and sex matched comparators without SSc. Patients with SSc have a 4-fold increased prevalence of moderate/severe VHD at diagnosis compared to non-SSc patients. They also have a 4-fold increased risk of developing moderate/severe valvular dysfunction after diagnosis of SSc compared to Non-SSc subjects. Aortic and mitral valve disease is of key interest and cannot be explained by ILD or PHT which are often associated with secondary pulmonary or tricuspid

valve pathology in these patients. Underlying mechanisms for this association require further study. SSc-associated cardiac disease is linked with major increase in morbidity and mortality, therefore screening with appropriate diagnostic tools is essential for early detection. The optimal evaluation and management of cardiac involvement in patients with SSc requires an integrated multidisciplinary approach involving rheumatologists, pulmonologists and cardiologists.

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Table 1. Baseline Clinical Characteristics

Characteristic	SSc (n=78)	Non-SSc (n=156)	P value
Age at diagnosis, years	56.0 (±15.6)	56.1 (±15.7)	0.97
Female sex	71 (91%)	142 (91%)	1.0
Ethnicity			0.24
Caucasian	68 (87%)	147 (94%)	
African American	2 (3%)	3 (2%)	
Hispanic	1 (1%)	2 (1%)	
Asian	5 (6%)	3 (2%)	
Other/unknown	2 (3%)	1 (1%)	
Follow up, years	10.5 (4.0, 17.5)	13.0 (6.7, 20.0)	—
BMI, kg/m^2	26.5 (±5.9)	29.4 (±7.6)	0.004
Obesity (BMI≥30 kg/m^2)	15 (21%)	61 (39%)	0.008
Smoking status			0.54
Current	12 (16%)	30 (20%)	
Former	24 (31%)	38 (25%)	
Fulfill 2013 ACR/EULAR classification criteria at baseline	71 (91%)	--	--
Prior diabetes	2 (3%)	19 (12%)	0.015
Prior hypertension	30 (38%)	57 (37%)	0.77
Prior hyperlipidemia	27 (35%)	55 (35%)	0.92
Prior coronary artery disease	11 (14%)	17 (11%)	0.48
Prior pulmonary hypertension	6 (8%)	1 (1%)	0.003
Prior interstitial lung disease	7 (9%)	—	—

Skin involvement, no. (%)		
Limited cutaneous	65 (83)	—
Diffuse cutaneous	11 (14)	—
Sine scleroderma	2 (3)	—
SSc-specific antibodies, n/N (%)	38/75 (51)	—
Scl-70+	7/35 (20)	—
Centromere +	29/35 (83)	—
RNA Pol III+	2/35 (6)	—

Values in the table are mean (±SD) or median (25th percentile, 75th percentile) for continuous characteristics and N (%) for discrete characteristics; Abbreviation: BMI=Body Mass Index

Table 2. Cumulative incidence rate of valve disease in 78 patients with SSc compared with 156 subjects without SSc

Outcome*	Number of events after incidence/ index in SSc / non-SSc	Cumulative incidence at 10 years for SSc patients (95% CI)**	Cumulative incidence at 10 years for non-SSc subjects (95% CI)**	Hazard ratio (95% confidence interval)***
Any valve disease	32 / 33	36.8 (26.1, 51.7)	13.2 (8.5, 20.7)	3.40 (2.08, 5.57)
Moderate/severe valve disease	18 / 12	17.9 (10.7, 29.9)	2.3 (0.7, 7.0)	4.23 (2.03, 8.83)
Moderate/severe aortic stenosis	4 / 5	1.4 (0.2, 9.8)	0.0†	2.45 (0.64, 9.45)
Moderate/severe mitral regurgitation	3 / 5	2.6 (0.7, 10.3)	0.8 (0.1, 5.9)	1.82 (0.39, 8.42)
Moderate/severe tricuspid regurgitation	14 / 6	16.0 (9.3, 27.6)	1.4 (0.4, 5.7)	5.73 (2.19, 14.94)

* There were no cases of moderate/severe aortic regurgitation, mitral stenosis, tricuspid stenosis, pulmonary stenosis or pulmonary regurgitation in either cohort; **Cumulative incidence is adjusted for the competing risk of death; ***adjusted for age, sex and calendar year of SSc/index date; †All events in this group occurred more than 10 years after index date

Table 3. Risk factors for VHD during follow up in 73 SSc patients without prior moderate/severe valve disease at SSc diagnosis

Characteristic	Value*	Hazard ratio[a] (95% CI)
Age, years	55.3 (±15.5)	1.36** (0.98, 1.91)
Sex, male	6 (8%)	0.76 (0.10, 5.76)
Calendar year of diagnosis	2001 (±9)	1.04 (0.97, 1.11)
Coronary artery disease at SSc diagnosis	8 (11%)	5.66 (1.83, 17.51)
Diabetes	1 (2%)	—
Hypertension	16 (25%)	1.28 (0.46, 3.52)
Hyperlipidemia	17 (27%)	1.11 (0.41, 3.05)
Ever smoker	28 (44%)	1.76 (0.69, 4.46)
Current smoker	10 (16%)	1.09 (0.24, 4.86)
Body mass index, kg/m^2	26.0 (±5.9)	0.99 (0.90, 1.08)
Obesity (BMI≥30 kg/m^2)	11 (19%)	1.25 (0.39, 3.96)
Telangiectasia	35 (48%)	0.82 (0.30, 2.21)
Digital ulcers	14/29 (48%)	0.39 (0.08, 1.93)
Pulmonary artery hypertension	2 (3%)	3.41 (0.42, 28.04)
Interstitial lung disease	6 (8%)	0.56 (0.06, 5.11)
Raynaud's	70 (96%)	0.31 (0.04, 2.47)
Diffuse skin disease vs limited/sine	11 (15%)	1.50 (0.42, 5.39)
Calcinosis	15 (21%)	1.37 (0.50, 3.74)
GI involvement †	39	1.86 (0.69, 5.02)
Renal involvement †	6	1.07 (0.14, 8.10)
Anti-centromere +	26/35 (74%)	0.66 (0.16, 2.64)
Anti-Scl-70 +	7/35 (20%)	0.90 (0.18, 4.42)

*value is n (%) or mean (±standard deviation)

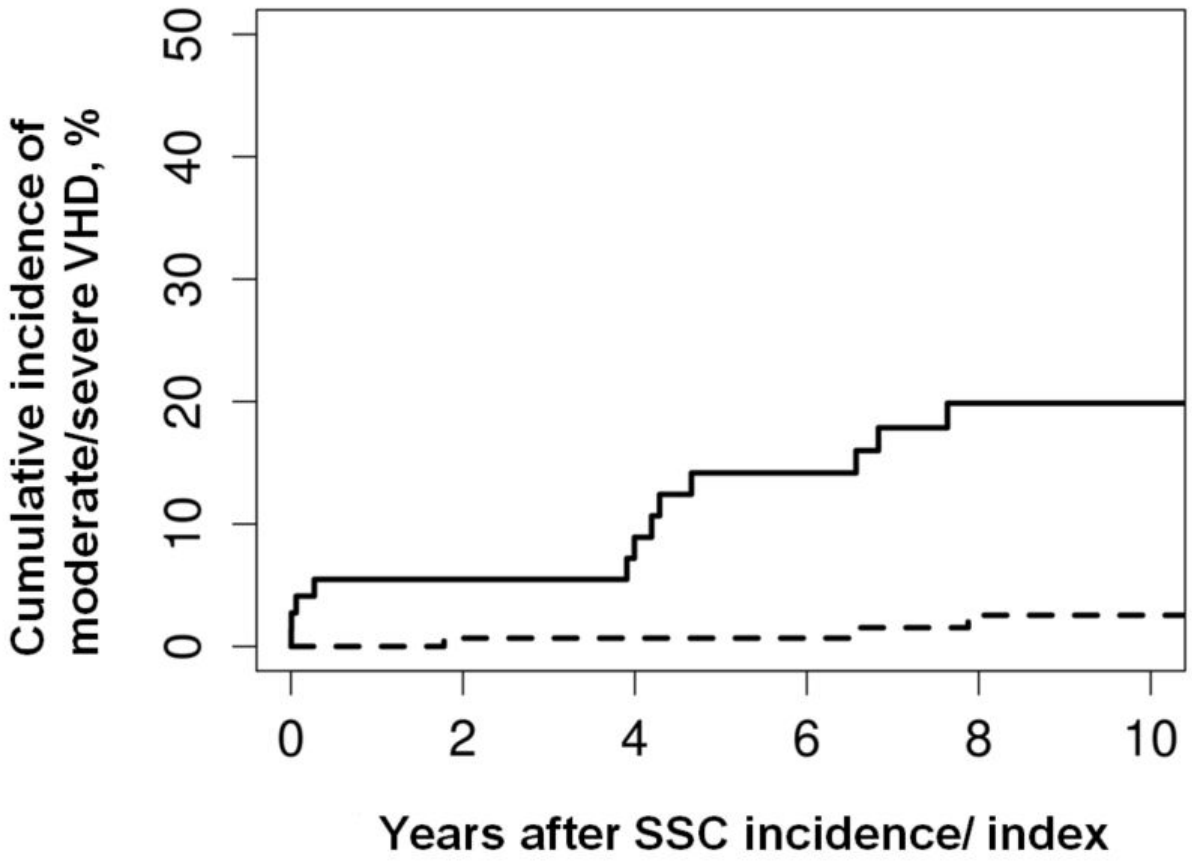
**per 10 years

[a]Age-adjusted univariable models

[†]time-dependent variable

Figures

Figure 1. Cumulative incidence of moderate/severe valve disease in SSc patients vs. non-SSc comparators



Cumulative incidence of moderate/severe valve disease in SSc patients (solid line) vs age and sex matched non-SSc comparators (dashed line)