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Increased Prevalence of Moderate to Severe Mitral and Aortic Valve Dysfunction in Systemic Sclerosis: A Case-control Study

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ABSTRACT. ***Objective***. To investigate the prevalence, severity, and associated clinical factors of mitral and aortic valvular involvement in patients with systemic sclerosis (SSc).

Methods. Our case-control study included 172 patients with SSc and 172 non-SSc adults without known cardiac disease matched by age, sex, and prevalence of cardiovascular (CV) risk factors. The screening of mitral and aortic valvular involvement was performed by transthoracic Doppler echocardiogram. The prevalence of aortic stenosis (AS) was also compared with that reported in a population-based study performed in our community during the same period.

Results. Patients with SSc showed an almost 5-fold increased prevalence of moderate to severe mitroaortic valve dysfunction compared to non-SSc controls (OR 4.60, 95% CI 1.51–13.98; P = 0.003). The most common lesion was mitral regurgitation (MR), which was observed in 5.2% of patients, followed by AS in 3.5%, and aortic regurgitation (AR) in 1.7%. Analyzing the different types of valvular lesion separately, we observed a significantly higher frequency of MR compared to controls (OR 4.69, 95% CI 1.12–22.04; P = 0.032), as well as a higher frequency of AS in the 65–75 (OR 7.51, 95% CI 1.22–46.23, P = 0.01) and 76–85 age groups (OR 3.53, 95% CI 1.03–12.22, P = 0.043) when compared to the general population in our community.

Conclusion. We found an increased prevalence of moderate to severe MR and AS in SSc compared to age-matched non-SSc controls with similar CV comorbidities. While results from this study do not allow for establishing a direct causal relationship, they strongly support the contribution of SSc-specific factors in the development of these complications.

Key Indexing Terms: aortic valve, mitral valve, systemic sclerosis, valvular heart disease

Systemic sclerosis (SSc) is a heterogeneous, chronic, multisystem disease characterized by widespread microvascular injury and progressive fibrosis of the skin and internal organs[1].

The heart is one of the major organs frequently affected by SSc, although its involvement often goes unrecognized until late in the disease. All aspects of the heart can be affected, including the myocardium, pericardium, and conduction system[2,3,4,5]. Clinically evident cardiac involvement is associated with poor prognosis, involving a 2.8-fold increased risk of death[6] and being the third leading cause of death in SSc, after interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH)[7].

Valvular heart disease (VHD) has not gained much attention, and until fairly recently it was considered rare in SSc, with the exception of functional tricuspid regurgitation associated with PAH. However, a previous Danish nationwide cohort study[8] reported a 3-fold increased relative risk of aortic stenosis (AS), a 4-fold increased relative risk of aortic regurgitation (AR), and an almost 5-fold increased relative risk of mitral regurgitation (MR) in patients with SSc when compared to the general population. This increased prevalence might be explained by an increased screening echocardiography, or it could be due to SSc-specific factors that may contribute to its development.

In order to confirm if mitral and aortic valvular involvement should be regarded as a specific SSc-related cardiac complication, we conducted a case-control study to examine its frequency, severity, and associated clinical factors (beyond conventional variables, such as age and cardiovascular [CV] comorbidities) in a large cohort of patients with SSc.

MATERIALS AND METHODS

Our sample included 172 adult patients with SSc attending the rheumatology department at a referral tertiary care hospital, as well as 172 non-SSc adults from the general population as controls.

SSc was diagnosed according to the American College of Rheumatology (ACR) criteria (1980 ACR criteria initially and later, the 2013 ACR/European League Against Rheumatism criteria)[9] or to the 2001 LeRoy and Medsger classification[10]. All our patients with SSc were registered in a specific database and were followed in a protocolized manner with annual or biannual transthoracic Doppler echocardiogram (TTDE) as part of

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our routine center follow-up protocol to detect the development of PAH as early as possible. TTDE studies were performed in accordance with a standardized protocol by cardiologists specializing in echocardiography and following the American and European Society of Echocardiography recommendations[11,12,13].

Inpatient and outpatient charts were comprehensively reviewed to obtain demographic characteristics (sex, ethnicity, and age at the time of the echocardiogram; disease duration), clinical manifestations of SSc, autoantibody profile, CV disease (CVD) risk factors (i.e., smoking status, obesity, hypertension, dyslipidemia, and diabetes mellitus), disease course data, and the frequency of mitral and aortic valve disease (MAVD) at the last TTDE examination. The endpoint of patient follow-up was the date of the last clinic visit. A retrospective analysis of prospectively collected data was performed.

Valvular lesions were defined as sclerosis, regurgitation, or stenosis on the mitral or aortic valves. Similar to previous studies, valve sclerosis was defined as the presence of thickening and/or calcification[14]. The former was considered in the presence of a mitral valve > 3 mm thickness or an aortic valve > 2 mm thickness. Calcification was defined in the presence of an acoustic shadow. Regurgitation was classified as mild, moderate, or severe, according to the standard variables of the regurgitant jet in Doppler mode[15]. AS was considered when the antegrade peak velocity across an abnormal valve was at least 2 m/s[16,17]. Severe AS was defined as a maximum aortic transvalvular velocity ≥ 4 m/s, typically with an aortic valve area ≤ 1 cm[16,17].

For comparison, we recruited 172 non-SSc adults without known cardiac disease, matched to patients by age, sex, and prevalence of CV risk factors who had undergone a TTDE with the same standardized echo protocol. Some of these controls were selected from a registry of health checkups for executive employees, although we also included patients for whom TTDE was prescribed in order to investigate palpitations, chest pain, or heart bruits, or in cases of stroke with uncertain etiology.

In addition to comparisons with controls, in the specific case of AS, we also compared the prevalence of this complication in SSc patients with that reported in a population-based study performed in our community during the same period[18]. The methodological, general characteristics, and main results of this study have already been published[18]. Briefly, it was a population-based cross-sectional study involving a random sample of 1068 people ≥ 65 years (which can be considered representative of the population aged ≥ 65 yrs in Barcelona) specifically designed to determine the prevalence of aortic valve sclerosis and stenosis in the elderly general population in our community.

Statistical analysis. Results are expressed as mean ± SD or as the median (IQR) as appropriate for continuous data, whereas categorical variables are presented as the number of cases and percentages.

Prevalence rates of valve involvement were calculated for mitral and aortic valves and compared between patients with SSc and controls (and with the prevalence in the general population of our community in the case of AS). Since the prevalence of AS in the general population increases with age, the comparative study was performed on both the total population and on different age groups.

Comparisons of numerical variables were obtained using a *t* test or a Mann-Whitney U test, according to normality adjustments, and of categorical variables by using a chi-square or Fisher exact test as necessary.

Variables reaching statistical significance in the unadjusted analysis were entered in a multivariate model (Cox proportional hazards regression) to examine associations between the occurrence of MAVD and SSc characteristics, as well as CVD risk factors, adjusting for age and sex.

Survival analysis, using the Kaplan-Meier method, was conducted to assess whether the development of moderate to severe MAVD was associated with lower survival in patients with SSc. Subsequent comparisons between survival curves were made by using a log-rank test. Statistical significance was defined as $P < 0.05$.

The present report has been approved by our institution (Clinical Research Ethics Committee of Bellvitge University Hospital–IDIBELL; approval number: PR312/20). Informed consent was obtained from the patients, and their clinical records and information were anonymized prior to analysis. The confidential information of the patients was protected according to national normative regulations. This study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference for Harmonization. The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are included in our paper.

RESULTS

Patient characteristics. Demographics, SSc characteristics (including autoantibody profile), and baseline CV risk factors of the entire study population are reported in Table 1. Since

Table 1. Main characteristics of patients with SSc and non-SSc controls.

	Patients with SSc, n = 172	Controls, n = 172	*P*
Sex			NS
Female	146 (85)	146 (85)	
Male	26 (15)	26 (15)	
Age at last cardiac ultrasound, yrs, mean ± SD	59 ± 15	59 ± 13	NS
Ethnic groups			NS
White	151 (88)	151 (88)	
Hispanic	16 (9)	21 (12)	
Arab	5 (3)		
SSc cutaneous subset			
Limited	118 (69)		
Diffuse	36 (21)		
SSc sine scleroderma	3 (2)		
Very early SSc	15 (8)		
Median time from diagnosis, yrs (IQR)	6.5 (3–11)		
Clinical manifestations			
Raynaud phenomenon	170 (99)		
Prior digital ulcers	52 (30)		
Calcinosis	37 (21.5)		
Arthritis	47 (27)		
Myositis	14 (8)		
Gastroesophageal disease	119 (69)		
Intestinal involvement[a]	14 (8)		
Interstitial lung disease	82 (48)		
Primary PAH[b]	18 (10.5)		
Primary renal involvement	14 (8)		
Autoantibody profile			
ANA	169 (98)		
Anticentromere	56 (32.5)		
Anti–Scl-70	59 (34)		
Anti–RNA polymerase III	28 (16)		
Ever smoker	70 (41)	65 (38)	NS
BMI, kg/m^2 (mean ± SD)	24 (9 ± 16.7)	27 (3 ± 12)	NS
Arterial hypertension	63 (37)	75 (44)	NS
Diabetes mellitus	19 (11)	28 (16)	NS
Hyperlipidemia	69 (40)	72 (42)	NS
Chronic kidney disease	16 (9)	20 (12)	NS
Coronary artery disease	17 (10)	21 (12)	NS

Values are presented as n (%) unless otherwise stated. [a] Including chronic intestinal pseudo-obstruction and/or fecal incontinence. [b] PAH confirmed by right heart catheterization. ANA: antinuclear antibodies; NS: not significant; PAH: pulmonary arterial hypertension; SSc: systemic sclerosis.

patients were intentionally frequency matched, there were no significant differences between age, sex, or CVD comorbidities between groups.

Patients with SSc were predominantly female (85%), with a mean ± SD age of 59 ± 15 years at the start of our study investigation. The median time from the diagnosis of SSc to our investigation was 6.5 years (IQR 3–11). Limited SSc was the most common type of SSc (69%). Fifty-two percent (n = 91) of the patients had at least 1 CV risk factor. None of our patients had a history of acute rheumatic fever/rheumatic heart disease.

Valvular disease. The prevalence of the different types of mitroaortic valve lesions are shown in Table 2. For the purpose of our study, when we analyzed valve dysfunction, only cases of moderate to severe degree were considered, since a mild degree is often a benign incidental finding, especially in the elderly[19].

Overall, the frequency of valvular sclerosis did not differ significantly between patients and controls (16.3% vs 11.6%, P = 0.213). By contrast, the prevalence of moderate-to-severe MAVD was significantly higher in patients with SSc than in controls, being detected in nearly 10% (17/172) of cases compared to 2.3% (4/172) of controls (OR 4.60, 95% CI 1.51–13.98; P = 0.003; Table 2). Antiphospholipid antibodies were positive only in 1 (6%) of these patients (data not shown).

The most common moderate to severe valvular dysfunction in SSc was MR, which was observed in 5.2% (n = 9) of patients, followed by AS in 3.5% (n = 6), and AR in 1.7% (n = 3). One patient had combined AS and regurgitation. No cases with significant mitral stenosis (MS) were observed. Of interest, the dysfunction was severe in all SSc patients with AS, whereas all but 1 case with MR or AR were moderate in severity (Table 2). None of the cases with AS were associated with a congenitally abnormal valve (uni- or bicuspid).

Prevalence of the different types of valvular dysfunction in patients with SSc and controls. The prevalence of MR was significantly higher in patients with SSc than in controls, regardless of the degree of regurgitation (57.5% vs 15.1%; OR 7.6, 95% CI 4.54–12.74; P = 0.00001) or even when examining only moderate to severe cases (5.2% vs 1.16%; OR 4.69, 95% CI 1.12–22.04; P = 0.032; Table 2).

Regarding aortic valve involvement, SSc cases were also found to have significantly higher frequencies of AR compared to controls (14.5% vs 3.4%; OR 4.70, 95% CI 1.87–11.78; P = 0.0003), although the difference was not statistically significant when we considered only moderate to severe cases (1.8% vs 0.6% in controls; OR 3.03, 95% CI 0.31–29.47; P = 0.314; Table 2).

Table 2. Prevalence of mitral and aortic valve disease at echocardiogram in patients with SSc and controls.

Valve Disease Type and Severity	SSc Patients, n (%) [95% CI]	Controls, n (%) [95% CI]	P (OR, 95% CI)
Moderate to severe valvular sclerosis	28 (16.3)	20 (11.6)	0.213
Any moderate to severe mitroaortic valve dysfunction[a]	17 (9.8)	4 (2.3)	0.003 (4.60, 95% CI 1.51–13.98)
Mitral regurgitation			
Any degree	99 (57.5)	26 (15.1)	0.00001 (7.6, 4.54–12.74]
Trace/mild	90 (52.3)	24 (13.9)	
Moderate	9 (5.2)	2 (1.16)	
Severe	0	0	
Moderate + severe	9 (5.2) [0.02–0.09]	2 (1.16) [0.003–0.04]	0.032 (4.69, 1.12–22.04)
Mitral stenosis			
Any degree	1 (0.6)	0	
Trace/mild	1 (0.6)	0	
Moderate	0	0	
Severe	0	0	
Moderate + severe	0	0	NS
Aortic regurgitation			
Any degree	25 (14.5)	6 (3.4)	0.0003 (4.70, 1.87–11.78)
Trace/mild	22 (12.8)	5 (2.9)	
Moderate	2 (1.2)	1 (0.6)	
Severe	1 (0.6)	0	
Moderate + severe	3 (1.7) [0.006–0.05]	1 (0.6) [0.001–0.03]	0.314 (3.03, 0.31–29.47)
Aortic stenosis			
Any degree	14 (8.1)	5 (2.9)	0.033 (2.95, 1.08–8.07)
Trace/mild	8 (4.7)	4 (2.3)	
Moderate	0	1 (0.6)	
Severe	6 (3.5)	0	
Moderate + severe	6 (3.5) [0.01–0.07]	1 (0.6) [0.001–0.03]	0.05 (6.18, 0.96–39.39)

Results are presented as n (%) unless otherwise stated. [a] One patient had combined aortic stenosis and regurgitation. SSc: systemic sclerosis.

Similarly, AS was significantly higher in patients wih SSc (8.1%) than in controls (2.9%; OR 2.95, 95% CI 1.08–8.07, P = 0.033), although when we compared only moderate to severe cases, the differences did not clearly achieve statistical significance (3.5% vs 0.6%; OR 6.18, 95% CI 0.96–39.39, P = 0.05; Table 2). Since the prevalence of AS increases with age, to clarify whether or not the risk becomes greater, the prevalence of this complication in patients with SSc was compared with that reported in different age groups in a population-based study performed in our community during the same period[18] (Table 3). The results of this comparison further confirmed an increased risk of AS in patients with SSc compared to controls in age groups 65–75 years (4.44% vs 0.61%; OR 7.51, 95% CI 1.22–46.23, P = 0.01) and 76–85 years (13.64% vs 4.28%; OR 3.53, 95% CI 1.03–12.22, P = 0.043).

Factors associated with the development of moderate to severe mitroaortic valve dysfunction. Comparisons between patients with and without moderate-to-severe MAVD are shown in Table 4. Patients with this complication were significantly older (P = 0.001), and more frequently presented the diffuse cutaneous form (P = 0.047) and ILD (P = 0.023). In age- and sex-adjusted hazard models, only age remained a significant risk factor (OR 1.07, 95% CI 1.02–1.13; P = 0.002). The OR values were quite similar when we analyzed mitral (OR 1.06, 95% CI 1.003–1.12; P = 0.03) or aortic (OR 1.08, 95% CI 1.009–1.16; P = 0.02; data not shown) valve dysfunction separately. No other significant risk factors were found.

Mortality. The total period of follow-up for SSc patients with MAVD was 158 patient-years. After a median follow-up of 7 years (IQR 1.8–15), 4 of the 17 patients (23.5%) died. The cause of death was terminal heart failure in only 2 cases. Nevertheless, the development of this complication was not associated with a significant survival rate reduction (87.7% vs 76.5%, P = 0.277).

Of the 6 patients with severe AS, 2 underwent surgery for aortic valve replacement, while a transcatheter aortic valve implantation (TAVI) was performed in 2 others with very good clinical results. Finally, 2 died due to acute cardiogenic pulmonary edema.

DISCUSSION

With the exception of functional tricuspid regurgitation associated with PAH, VHD is considered rare in SSc, although it has not been well studied since it derives, in the majority, from studies focused on myocardial involvement.

In our present study, we sought to investigate the prevalence of mitral and aortic valve involvement in this condition, focusing on moderate to severe cases since the development of a mild degree of valvular dysfunction is often a benign incidental finding in the general population, especially in the elderly[20].

Our study shows that patients with SSc have an almost 5-fold increased prevalence of moderate to severe MAVD compared to non-SSc patients (OR 4.60). The most common lesion was MR, followed by AS and AR. The development of MS seems to be rare in this condition. Analyzing the different types of valvular lesion separately, we observed a significantly higher frequency of MR compared to controls (OR 4.69), as well as higher frequencies of moderate-to-severe AS in groups aged 65–75 years (OR 7.51) and 76–85 years (OR 3.53) when compared to the general population in our community.

Our results agree with the data provided by other population-based studies that have also analyzed the prevalence and/or incidence of any degree of MAVD in patients with SSc[8,19,21–28]. The main results of these studies are summarized in Table 5; three studies have not yet been published[25,26,27]. The great heterogeneity between the studies (discrepancies in study design; lack of control groups in some cases; selection biases, including only patients without clinical manifestations of heart failure; and great variability regarding disease duration) make their results difficult to compare. However, although the prevalence rate of MAVD in SSc varies widely, in all cases in which it was compared to a control group, the rate was statistically higher in patients with SSc, with a 2- to 6-fold increase in prevalence compared to non-SSc subjects[8,19,21–27]. MR was also by far the most common VHD found, followed by AS or AR[8,19,21–28]. Most cases of AS presented with severe disease, whereas MR and AR cases were usually mild or moderate in severity. Similar to our results, the presence of MS was uncommon in all studies (Table 5).

In line with this, 2 studies found significantly higher incidence rates of any degree of MR (with a 2- to almost 5-fold increase), AR (4-fold increase), and AS (3- to 4-fold increase) in patients with SSc when compared to controls[8,27]. Considering only moderate to severe cases, patients with SSc have a 3-fold increased risk of MAVD compared to non-SSc subjects[26], with severe AS having the highest incidence rate of all[25].

The fact that patients with SSc who are older tend to have a higher prevalence of mitroaortic valve involvement than non-SSc patients in a similar age range and with similar CVD comorbidities proves that age is not the only risk factor, and that there

Table 3. Comparative study of the prevalence of AS between patients with SSc and the elderly general population (≥ 65 years).

Age Group, yrs	SSc Patients			General Population[a]			P (OR, 95% CI)
	Patients, n	AS, Severe, n	Prevalence, % (95% CI)	Patients, n	Cases With Any Degree of AS	Prevalence, % (95% CI)	
65–75	45	2	4.44 (0.01–0.14)	488	3	0.61 (0.002–0.01)	0.01 (7.51, 1.22–46.23)
76–85	22	3	13.64 (0.04–0.33]	444	19	4.28 (0.02–0.06)	0.043 (3.53, 1.03–12.22)
> 85	1	0					
Total	109	6	5.50 (0.02–0.11)	1068	32	2.99 (0.02–0.04)	0.158 (1.88, 0.77–6.61)

[a] Age and sex standardized prevalence from Ferreira-González, *et al*[18]. AS: aortic stenosis; SSc: systemic sclerosis.

Table 4. Variables associated with the development of moderate to severe MAVD in patients with SSc.

	Patients with Moderate to Severe MAVD, n = 17	Patients Without MAVD, n = 155	Univariate Analysis *P*	Multivariate Analyses OR (95% CI)	*P*
Sex			0.684	0.86 (0.17–4.25)	0.856
Female	15	131			
Male	2	24			
Age at last cardiac ultrasound, yrs, mean ± SD	70 ± 11	58 ± 14.5	0.001	1.07 (1.02–1.13)	0.002
Ethnic groups	White: 16 (94) / Hispanic: 1 (6)	White: 135 (87) / Hispanic: 15 (10) /Arab 5 (3)	0.647		
SSc cutaneous subset					
Limited	5 (29.5)	113 (73)	0.047	1.28 (0.309–5.32)	0.731
Diffuse	12 (70.5)	24 (15.5)			
SSc sine scleroderma		3 (1.5)			
Very early SSc		15 (10)			
Time from diagnosis, yrs, median ± SD	9.29 ± 10.1	7.4 ± 6.6	0.292		
Clinical manifestations					
Raynaud phenomenon	17 (100)	153 (99)	0.551		
Prior digital ulcers	6 (35)	46 (30)	0.087		
Calcinosis	6 (35)	31 (20)	0.457		
Arthritis	6 (35)	41 (26.5)	0.727		
Myositis	1 (6)	13 (8)	0.492		
Gastroesophageal disease	8 (47)	111 (72)	0.807		
Intestinal involvement[a]	1 (6)	13 (8)	0.492		
Interstitial lung disease	9 (53)	73 (47)	0.023	1.15 (0.47–2.78)	0.753
Primary PAH[b]	3 (18)	15 (10)	0.188		
Primary renal involvement	2 (12)	12 (7.5)	0.208		
Autoantibody profile					
ANA	17 (100)	152 (98)	0.500		
Anti-centromere	4 (23.5)	52 (33.5)	0.393		
Anti–Scl-70	6 (35)	53 (34)	0.324		
Anti –RNA polymerase III	5 (29)	23 (15)	0.221		
Ever smoker	7 (42)	63 (41)	0.159		
BMI, kg/m^2, mean ± SD	25.48 ± 8.87	25 ± 7.16	0.967		
Arterial hypertension	7 (41)	56 (36)	0.670		
Diabetes mellitus	2 (12)	17 (11)	0.649		
Hyperlipidemia	6 (35)	63 (41)	0.175		
Chronic kidney disease	2 (12)	14 (9)	0.355		
Coronary artery disease	3 (18)	14 (9)	0.308		

Results are presented as n (%) unless otherwise stated. [a] Including chronic intestinal pseudo-obstruction and/or fecal incontinence. [b] PAH confirmed by right heart catheterization. ANA: antinuclear antibodies; MAVD: mitral and aortic valve disease; PAH: pulmonary artery hypertension; SSc: systemic sclerosis

must be SSc-specific factors that contribute to the increase in prevalence. Underlying mechanisms have not been clearly elucidated, but increased fibrosis of the mitroaortic curtain could play a role. Histological examination of explanted valves from a patient with SSc and severe AS showed fibrous thickening of the cusps, characterized by diffuse deposits of dense, acellular collagen with calcified nodules within the areas of fibrosis[29]. These findings are quite different from those observed in "pure" degenerative AS, characterized by diffuse calcifications with variously combined osseous metaplasia, neoangiogenesis, and/or inflammatory infiltrates that together replace the normal structure of the valve cusps[30,31].

Stronger calcification in the valve sites exposed to higher hemodynamic stress, particularly when it is excessive considering the patient's age, has also been described in cases of SSc lacking a history of hypertension[32]. In SSc, it is well known that calcium deposition occurs at those skin and musculoskeletal system sites exposed to higher mechanical stress[33]. Further, 1 study not yet published has demonstrated that the prevalence of AS is higher in SSc-PAH compared to other forms of PAH, and that this association appears to be independent of age, sex, and/or CV risk factors[34]. Indirectly, these results support the hypothesis that the underlying inflammatory burden present in SSc-PAH and not in other forms of PAH could be a factor in the development of AS in this condition. In fact, low-grade chronic inflammation of the myocardium has been shown to result in fibrosis, which in turn leads to diastolic and/or systolic dysfunction in SSc[4,5].

Since MAVD may cause cardiac remodeling and hemodynamic changes, additional studies examining its effect on CV outcomes in SSc and appropriate management strategies in this population are warranted. In this sense, TAVI appears to be a safe

Table 5A. Main results of studies that analyzed the prevalence of mitral and aortic valve disease in SSc.

First Author, Country, Year	SSc Patients, n	Mitral Regurgitation	Mitral Stenosis	Aortic Regurgitation	Aortic Stenosis
Candell-Riera, *et al*[19], Spain, 1996	Patients with limited SSc: 63; healthy controls: 26	Total: 49% $P < 0.0001$, compared with healthy controls (8%) OR adjusted for age: 6.1 (95% CI 1.6–23)	NA	NA	NA
de Groote, *et al*[21], France, 2007	570 patients (diffuse: 150, limited: 420) without severe pulmonary function abnormalities, severe cardiac disease, and known PAH	Degree II: 38 (6.7%) Degree: III–IV: 2 (0.4%) Total (any degree): 40 (7.01%) Only moderate to severe: 2 (0.4%)	0 (0%)	Degree II: 14 (2.5%) Degree III–IV: 0 (0%) Total (any degree): 14 (2.5%) Only moderate to severe: 0	Aortic stenosis < 1 cm^2 was noted in 19 (3.3%) patients
Meune, *et al*[22], France, 2008	Patients without pulmonary arterial hypertension or clinical manifestations of heart failure: 100 (diffuse: 42, limited: 58); number of healthy controls: 26	Degree I: 45% Degree II: 3% Total (any degree): 48 (48%) Only moderate: 3 (3%) P not significant compared with healthy controls (30.7%)	Total: 2 (2%)	Degree I: 15% Degree II: 3% Total (any degree): 18 (18%) Only moderate: 3 (3%) $P = 0.023$, compared with healthy controls (0%)	Total: 3 %
Muresan, *et al*[23], Romania, 2016	110 (diffuse: 47, limited: 63)	12 (10.9%)	2 (0.2%)	4 (3.6%)	4 (3.6%)
Fernández Codina, *et al*[28], Spain, 2017	173 patients (diffuse: 37, limited: 116, sine scleroderma: 20)	Any degree: 116 (67%)	NA	Any degree: 52 (30%)	NA
Nordin, *et al*[24], Sweden, 2017	110 patients (diffuse: 22, limited: 78); healthy controls: 105	Any degree: 2 (1.8%) $P = 0.03$ compared with controls	NA	Any degree: 1 (0.9%) $P = 0.06$ compared with controls	NA
Butt, *et al*[8], Denmark, 2019	SSc patients: 2278; controls: 13.890	OR adjusted for age and sex: 2.03 (95% CI 1.07–3.87)	OR adjusted for age and sex: 3.33 (95% CI: 0.56–19.95)	OR adjusted for age and sex: 3.17 (95% CI 1.78–5.63)	OR adjusted for age and sex: 2.18 (95% CI 1.18–4.02)
Elnagar, *et al*[25], USA, 2019	506	Total: 121 (24%) Mild: 99 (19.5%) Moderate: 18 (3.5%) Severe: 4 (0.8%)	Total: 1 (0.2%) Moderate: 1 (0.2%)	Total: 39 (7.7%) Mild: 36 (7%) Moderate: 3 (1%) Severe: 0%	Total: 6 (1.2%) Mild: 3 (1%) Moderate: 1 (0.2%) Severe: 2 (0.4%)
Kurmann, *et al*[26], USA, 2018	SSc patients: 79; controls: 158	Prevalence of moderate/severe valvular heart disease (unspecified type of lesion): SSc: 11%		Controls: 3%	$P = 0.011$

NA: not analyzed; ND: not done; PAH: pulmonary arterial hypertension.

Table 5B. Main results of studies that analyzed the incidence of mitral and aortic valve disease in SSc.

	Incidence		
	SSc Cases, Incidence Rate per 100 PY (95% CI)	Controls, Incidence Rate per 100 PY (95% CI)	Analysis of Differences, *P* or HR
Butt, *et al*[8], Denmark, 1995–2015			
SSc patients, n = 2278			
Controls, n = 13,890			
Mitral regurgitation (any degree)	0.18 (0.14–0.24)	0.04 (0.03–0.05)	HR 4.60; 95% CI 3.12–6.79
Mitral stenosis (any degree)	0.02 (0.01–0.05)	NA (≤ 3 incident cases)	NS
Aortic regurgitation (any degree)	0.16 (0.12–0.22)	0.04 (0.03–0.05)	HR 3.78; 95% CI 2.55–5.58
Aortic stenosis (any degree)	0.29 (0.23–0.36)	0.10 (0.08–0.12)	HR 2.99; 95% CI 2.025–3.97
Alvarado, *et al*[27], Argentina, 2000–2017			
SSc patients, n = 127			
Controls, n = 497			
Moderate to severe mitral regurgitation	1.9 (1.3 –2.7)	0.9 (0.7-1.2)	*P* = 0.01
Moderate to severe mitral stenosis	0.2 (0.08–0.7)	0.06 (0.02-0.17)	*P* = 0.06
Moderate to severe aortic regurgitation	1.4 (0.1–2.1)	1.1 (0.8 – 1.4)	*P* = 0.16
Moderate to severe aortic stenosis	1.1 (0.7–1.8)	0.3 (0.2-0.5)	*P* < 0.001
Elnagar, et al[25], USA, 2000–2018			
SSc patients, n = 506			
Controls, n = 0			
Mild mitral regurgitation	6.36 (5.24–7.59)	ND	
Moderate mitral regurgitation	1.46 (1.03–1.95)	ND	
Severe mitral regurgitation	0.04 (0.00–0.13)	ND	
Mild mitral stenosis	0.21 (0.08–0.42)	ND	
Moderate mitral stenosis	0.07 (0.01–0.20)	ND	
Severe mitral stenosis	0.04 (0.00–0.13)	ND	
Mild aortic regurgitation	1.80 (1.3–2.36)	ND	
Moderate aortic regurgitation	0.29 (0.12–0.52)	ND	
Severe aortic regurgitation	0.00	ND	
Mild aortic stenosis	1.25 (0.87–1.70)	ND	
Moderate aortic stenosis	0.65 (0.38 – 0.98)	ND	
Severe aortic stenosis	0.28 (0.12 – 0.51)	ND	
Kurmann, *et al*[26], USA, 1980–2016	The cumulative incidence of moderate/severe valvular heart disease (unspecified type of lesion) in patients:		
SSc patients, n = 79	SSc (after diagnosis): 23.6% (95% CI 14.5–38.4)	Controls: 7.4% (95% CI 4.0–13.5)	HR 2.86; 95% CI 1.38–5.91; *P* = 0.004
Controls, n = 158			

NA: not analyzed; ND: not done; NS: not significant; PAH: pulmonary arterial hypertension; PY: person-years.

and effective procedure in patients with SSc whose AS is inoperable due to specific comorbidities (thoracic skin involvement, severe ILD, or PAH)[35].

When interpreting the results of our study, one needs to consider the potential limitations derived from its observational nature, the retrospective review, and the small sample size.

In summary, we found an increased prevalence of moderate to severe MR and AS in patients with SSc compared to age-matched non-SSc controls with similar CV comorbidities. While results from this study do not allow a direct causal relationship to be established, they strongly support the idea that SSc-specific factors may contribute to this increased prevalence. This is in line with previous studies that have also shown that mitral and aortic valve involvement is more frequent than initially believed, raising the possibility that they might represent yet another primary cardiac complication of SSc[8,19,21–28]. This should be kept in mind in the differential diagnosis of patients with SSc who presented symptoms of heart failure or angina.

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