# Sex-specific difference in cardiac function in patients with systemic sclerosis: association with cardiovascular outcomes

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Abstract: BACKGROUND Cardiovascular involvement is one of the leading causes of mortality in systemic sclerosis (SSc) and is reported to be higher in men as compared with women. However, the cause of this difference is largely unknown. The objective of this study was to assess sex differences in echocardiographic characteristics, including left ventricular global longitudinal strain (LV GLS), as a potential explanation of sex differences in outcomes. METHODS A total of 746 patients with SSc from four centres, including 628 (84%, 54±13 years) women and 118 (16%, 55±15 years) men, were evaluated with standard and advanced echocardiographic examinations. The independent association of the echocardiographic parameters with the combined endpoint of cardiovascular events-hospitalisation/death was evaluated. RESULTS Men and women with SSc showed significant differences in disease characteristics and cardiac function. After adjusting for the most important clinical characteristics, while LV ejection fraction and diastolic function were not significantly different anymore, men still presented with more impaired LV GLS as compared with women (-19% (IQR -20% to -17%) vs -21% (IQR: -22% to -19%), p<0.001). After a median follow-up of 48 months (IQR: 26-80), the combined endpoint occurred in 182 patients. Men with SSc experienced higher cumulative rates of cardiovascular events-hospitalisation/mortality ($\chi^2$=8.648; Log-rank=0.003), and sex differences were maintained after adjusting for clinical confounders, but neutralised when matching the groups for LV GLS. CONCLUSION In patients with SSc, male sex is associated with worse cardiovascular outcomes even after adjusting for important clinical characteristics. LV GLS was more impaired in men as compared with women and potentially explains the sex difference in cardiovascular outcomes.

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ORIGINAL RESEARCH

# Sex-specific difference in cardiac function in patients with systemic sclerosis: association with cardiovascular outcomes

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## ABSTRACT

**Background** Cardiovascular involvement is one of the leading causes of mortality in systemic sclerosis (SSc) and is reported to be higher in men as compared with women. However, the cause of this difference is largely unknown. The objective of this study was to assess sex differences in echocardiographic characteristics, including left ventricular global longitudinal strain (LV GLS), as a potential explanation of sex differences in outcomes.

**Methods** A total of 746 patients with SSc from four centres, including 628 (84%, 54±13 years) women and 118 (16%, 55±15 years) men, were evaluated with standard and advanced echocardiographic examinations. The independent association of the echocardiographic parameters with the combined endpoint of cardiovascular events-hospitalisation/death was evaluated.

**Results** Men and women with SSc showed significant differences in disease characteristics and cardiac function. After adjusting for the most important clinical characteristics, while LV ejection fraction and diastolic function were not significantly different anymore, men still presented with more impaired LV GLS as compared with women (−19% (IQR −20% to −17%) vs −21% (IQR: −22% to −19%), p<0.001). After a median follow-up of 48 months (IQR: 26–80), the combined endpoint occurred in 182 patients. Men with SSc experienced higher cumulative rates of cardiovascular events-hospitalisation/mortality ($\chi^2$=8.648; Log-rank=0.003), and sex differences were maintained after adjusting for clinical confounders, but neutralised when matching the groups for LV GLS.

**Conclusion** In patients with SSc, male sex is associated with worse cardiovascular outcomes even after adjusting for important clinical characteristics. LV GLS was more impaired in men as compared with women and potentially explains the sex difference in cardiovascular outcomes.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cardiovascular involvement is highly prevalent in patients with systemic sclerosis (SSc) and is associated with poor prognosis. Sex has been also associated with the prognosis in patients with SSc, with men being at higher risk of death and cardiovascular complications.

## WHAT THIS STUDY ADDS

⇒ Men and women with SSc showed differences in terms of disease characteristics and cardiac function. Left ventricular global longitudinal strain (LV GLS) was more impaired in men as compared with women. After adjusting for clinical characteristics, while LV ejection fraction and diastolic function were not significantly different, men still presented with more impaired LV GLS as compared with women. Men with SSc experienced higher cumulative rates of cardiovascular outcomes. Sex difference in outcomes was maintained after adjusting for clinical characteristics, but neutralised when matching the groups for LV GLS.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In patients with SSc, early assessment of subtle myocardial changes and cardiac involvement by LV GLS may improve risk stratification and define the need for further diagnostic assessment, closer follow-up and eventually specific treatment in both men and women; in fact, the lack of interaction between sex and LV GLS suggested an equally high prognostic role of LV GLS for both sexes among patients with SSc. However, taking into account sex-specific clinical and echocardiographic parameters may help to better define factors associated with outcomes.

## INTRODUCTION

Systemic sclerosis (SSc) is a chronic auto-immune disease characterised by progressive fibrosis, microvascular changes and multiorgan involvement. According to previously published data, 7%–40% of patients with SSc have cardiovascular involvement,[1–4] which also showed an association with poor

prognosis.[5] Sex has also been associated with adverse events in patients with SSc, men being at higher risk of death and cardiovascular complications.[1 6]

Echocardiography is the first-line imaging technique to identify left ventricular (LV) systolic or diastolic dysfunction in these patients; however, diagnosis of cardiac involvement remains challenging, especially at an early stage, as conventional echocardiographic measures lack sensitivity to detect subtle myocardial dysfunction. Previous studies have demonstrated that 2D speckle tracking strain echocardiography (STE) is a reliable and sensitive tool for detecting subtle LV dysfunction in various cardiovascular diseases,[7 8] and LV global longitudinal strain (LV GLS) has been introduced in the most recent recommendations for chamber quantification.[9] In patients with SSc, LV GLS has shown an association with lower functional capacity, occurrence of arrhythmias[7] and all-cause mortality and cardiovascular events.[10] However, sex differences in standard and novel echocardiographic measures have never been explored in these patients as well as the impact of these differences on prognosis and cardiovascular risk profile.

The aim of this study was therefore to identify potential differences in clinical and echocardiographic parameters, including LV GLS, between men and women in a large, well-characterised multicentre cohort of patients with SSc and to test their potential association with all-cause mortality and cardiovascular events.

## METHODS
### Patient population
Consecutive patients with SSc referred for a specifically designed multidisciplinary healthcare programme at the Department of Rheumatology of the Leiden University Medical Centre (The Netherlands), University Hospital of Zurich (Switzerland), Oslo University Hospital (Norway) and the University of Medicine and Pharmacy 'Carol Davila', Bucharest (Romania) were included.[11 12] Patients were diagnosed according to the classification criteria American College of Rheumatology (ACR) 2013.[13] A baseline echocardiogram, defined as the first one available, was selected and corresponding visit at the abovementioned departments was defined as a baseline visit. Only patients with a minimum of 1 year follow-up were included in this analysis. Furthermore, to avoid the potential confounding effect on the assessment of cardiac function, patients with previous myocardial infarction or severe valvular heart disease were excluded. Written informed consent was obtained at the time of inclusion in the multidisciplinary healthcare programmes. Additional informed consent was acquired when patients were contacted by telephone to evaluate the occurrence of the pre-specified endpoints.

### Baseline clinical variables
Disease-related characteristics at baseline included SSc subtype according to LeRoy et al,[14] modified Rodnan Skin Score (mRSS), presence of digital ulcers, arthritis, proximal muscle weakness, myositis, calcinosis and pitting scars.[15] General medical history, medications and cardiovascular risk factors were also noted. Laboratory testing was performed systematically and included creatine phosphokinase (CK), erythrocyte sedimentation rate, renal function (estimated glomerular filtration rate (eGFR)) and N-terminal pro-brain natriuretic peptide (NT-proBNP). Spirometry was performed in all patients according to the American Thoracic Society and the European Respiratory Society guidelines,[16 17] and included the percentage of predicted values for forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1) and single breath diffusing capacity of carbon monoxide (DLCO-SB). The presence of lung involvement was assessed using thoracic high-resolution CT (HRCT) and defined by abnormal findings including interstitial fibrosis in patients with available HRCT images.[18 19] To assess the percentage of predicted peak oxygen consumption (VO$_2$max), cardiopulmonary exercise testing was performed using an electrically ramped cycle ergometer according to the guidelines.[20] Finally, (24-hour) Holter ECG was performed. The presence of a bundle branch block, ventricular arrhythmias including premature ventricular contraction >100/day and sustained ventricular tachycardias, and supraventricular arrhythmias including atrial fibrillation, atrial flutter and premature atrial contraction when >7% were recorded and considered abnormal.[21]

### Conventional transthoracic echocardiography
Transthoracic echocardiography was performed in the left lateral decubitus position, using a commercially available system (Vivid 7 and E9; General Electric-Vingmed, Horten, Norway) and a 3.5-MHz or 5MS transducer. Standard M-mode and 2D, colour, pulsed wave and continuous wave Doppler images were acquired and digitally stored in cine-loop format. Off-line analysis was performed using EchoPAC (version 112.0.1; GE Medical Systems, Horten, Norway). LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LV ejection fraction (LVEF) and LV dimensions, including end-diastolic diameter, interventricular septum thickness and posterior wall thickness were measured according to current guidelines.[9] LV diastolic function was assessed according to current recommendations based on a multiparametric approach and included: peak early (E) and late (A) diastolic velocities measured on pulsed wave Doppler recordings of the trans-mitral flow,[22] Left Atrial Volume Index measured before mitral valve opening on the apical four-chamber and two-chamber views according to the biplane Simpson's method and indexed to the patient's body surface area. Additionally, e′ with tissue Doppler imaging at the lateral and septal sides of the mitral annulus in the four-chamber view was measured and averaged; E-wave/e′ ratio was then calculated.[22] Systolic pulmonary arterial pressure was estimated by the right ventricular systolic pressure which was calculated by
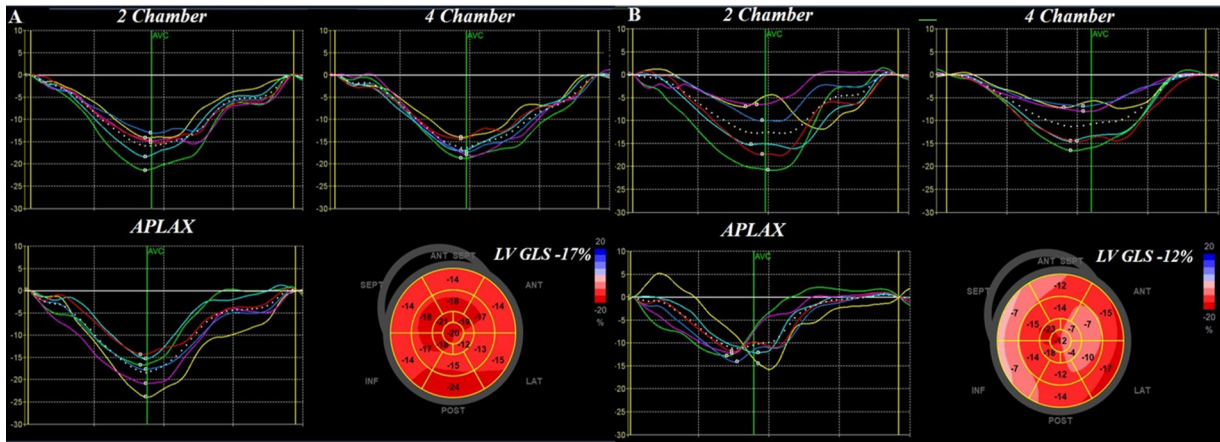
**Figure 1** Example of assessment of LV GLS by speckle tracking strain echocardiography in a woman with SSc (panel A) versus a man with SSc (panel B). Color-coded Bull's eye plots and the curves for longitudinal strain (panel A, LV GLS=−17%, panel B, LV GLS=−12%) are displayed; the strain curves are showed per segment and averaged among the segments (dotted line for the three-chamber, four-chamber and two-chamber apical views). LV GLS, left ventricular global longitudinal strain; SSc, systemic sclerosis.

adding the peak tricuspid regurgitation gradient to the right atrial pressure which was estimated by the inferior vena cava diameter and degree of respiratory collapse.[23] Right ventricular function was evaluated by measuring the tricuspid annular plane systolic excursion.[24] The presence of pericardial effusion was also recorded.

## Two-dimensional STE

LV GLS was measured as previously described by using the four-chamber, two-chamber and three-chamber views to obtain measurements of all LV segments.[10 25 26] LV GLS was automatically calculated as the average peak systolic strain of 17 LV segments (figure 1). Negative values are used to express LV GLS since this represents the shortening of the myocardial wall, a more negative value represents better myocardial deformation.

## Follow-up and endpoint

The endpoint of this study was defined as all-cause mortality or hospitalisations for cardiovascular reasons which included pacemaker/cardioverter defibrillator implantations, heart failure, myocardial infarction, arrhythmias, angina pectoris, percutaneous coronary interventions, stroke and peripheral ischaemic disease. Endpoint data were obtained by reviewing the electronic information system and retrieval of survival status through the municipal civil registries (according to availability). If the last available follow-up data were dated more than 1 year ago or incomplete, patients and their general practitioners were contacted by telephone for more recent information (in selected centres).

## Statistical analysis

Data analysis was performed using SPSS software V.23.0 (IBM, Armonk, New York, USA). Continuous variables are presented as mean±SD or as median with IQRs according to presence of normal distribution. Categorical data are presented as frequencies and percentages. Continuous variables were compared using one-way analysis of variance (ANOVA), applying the Bonferroni's post-hoc analysis, or the Kruskal-Wallis one-way ANOVA. Categorical variables were compared with the $\chi^2$ test. Propensity matching score was used to match men and women groups based on age, disease duration (since Raynaud), subtype of SSc (diffuse cutaneous SSc (dcSSc)), presence of interstitial lung fibrosis, DLCO-SB and NT-proBNP, and in a second step also adding LV GLS (these variables were chosen as significantly different among men and women, and also based on clinical relevance). The matching tolerance was set at 0.05. Cumulative event rates for all-cause mortality or cardiovascular hospitalisation were estimated with the Kaplan-Meier curves and compared with log-rank tests. P values <0.05 were considered significant. The association between LV GLS and cardiovascular outcomes, as well as interaction between LV GLS and sex was evaluated with Cox regression analyses. To assess the incremental value of LV GLS, we compared $\chi^2$ of different multivariate cox-regression models which included the variables selected for the propensity score matching and other variables which were significantly different between men and women.

## RESULTS
### Baseline clinical characteristics

A total of 746 patients with SSc from four different centres were included, of which 628 (84%, 55±14 years) were women and 118 (16%, 54±13 years) were men. Baseline clinical characteristics are shown in table 1. Men and women patients with SSc showed several differences in terms of disease characteristics: greater mRSS, higher prevalence of dcSSc than limited cutaneous SSc (lcSSc), myositis and interstitial lung disease (ILD), higher CK and higher eGFR were observed in men as compared with women (table 1). In addition, disease duration was significantly longer in women as compared with men and

**Table 1** Baseline clinical characteristics in the overall population and divided by men and women

| Baseline clinical characteristics | Total (n=746) | Men (n=118) | Women (n=628) | P value |
|---|---|---|---|---|
| Age (years), mean±SD | 55±14 | 54±13 | 55±14 | 0.351 |
| Body surface area (m$^2$), mean±SD | 1.77±0.19 | 1.95±0.19 | 1.73±0.17 | **<0.001** |
| Diffuse cutaneous SSc, n (%) | 192 (30) | 52 (48) | 140 (26) | **<0.001** |
| Time since Raynaud (years), median (IQR)-till first echo | 10 (4–19) | 7 (3–14) | 10 (4–19) | **0.006** |
| Time since non-Raynaud (years), median (IQR)-till first echo | 5 (2–10) | 4 (1–9) | 5 (2–11) | 0.059 |
| Disease characteristics, n (%) | | | | |
| mRSS >15 | 94 (16) | 26 (26) | 68 (13) | **0.002** |
| Digital ulcers | 226 (32) | 39 (35) | 187 (32) | 0.267 |
| Pitting scars | 227 (38) | 45 (45) | 182 (36) | 0.060 |
| Proximal muscle weakness | 39 (9) | 8 (12) | 31 (9) | 0.240 |
| Myositis | 12 (3) | 7 (13) | 5 (2) | **<0.001** |
| Calcinosis | 166 (28) | 18 (19) | 148 (29) | 0.097 |
| Lung fibrosis | 332 (49) | 67 (63) | 265 (46) | **0.002** |
| Medical history and cardiovascular risk factors, n (%) | | | | |
| Hypertension | 151 (21) | 24 (21) | 127 (21) | 0.537 |
| Diabetes | 16 (4) | 4 (6) | 12 (3) | 0.234 |
| (History of) smoking | 346 (50) | 76 (65) | 270 (47) | **<0.001** |
| Coronary artery disease | 67 (9) | 14 (12) | 53 (9) | 0.172 |
| Prior/current pericarditis | 55 (7) | 9 (8) | 46 (7) | 0.513 |
| Holter ECG abnormalities (prior or current arrhythmias) | 125 (31) | 25 (40) | 100 (29) | 0.052 |
| History of renal crisis | 15 (4) | 4 (6) | 11 (3) | 0.188 |
| Laboratory tests | | | | |
| Creatine phosphokinase (U/L), median (IQR) | 84 (61–122) | 115 (79–200) | 79 (58–111) | **<0.001** |
| eGFR (mL/min/1.73 m$^2$), mean±SD | 89±27 | 103±31 | 87±26 | **<0.001** |
| NT-proBNP (ng/L), median (IQR) | 60 (19–143) | 37 (11–98) | 62 (22–150) | **0.005** |
| ANA/ANF (n=397) | 380 (96) | 55 (89) | 325 (97) | **0.009** |
| Pulmonary function tests, mean±SD | | | | |
| FVC % of predicted | 96±22 | 86±20 | 98±22 | **<0.001** |
| FEV1 % of predicted | 90±20 | 82±20 | 91±20 | **<0.001** |
| DLCO-SB % of predicted | 66±21 | 60±22 | 67±20 | **0.001** |
| VO2max % of predicted, n=284 | 87±24 | 72±23 | 90±23 | **<0.001** |
| Mean heart rate, beats per minute | 79±10 | 80±11 | 79±10 | 0.242 |
| Cardiovascular medication, n (%) | | | | |
| ACEi/ARB | 268 (37) | 56 (48) | 212 (35) | **0.004** |
| Beta-blocker | 126 (18) | 21 (18) | 105 (17) | 0.480 |
| Ca$^{2+}$ channel blocker | 431 (60) | 77 (66) | 354 (59) | 0.077 |
| Diuretics | 184 (26) | 30 (26) | 154 (26) | 0.520 |
| Immunosuppressive medication, n (%) | | | | |
| Corticosteroids | 63 (15) | 16 (25) | 47 (14) | **0.020** |
| Cyclophosphamide | 10 (2) | 1 (1) | 9 (3) | 0.511 |
| Methotrexate, n=414 | 54 (13) | 7 (11) | 47 (14) | 0.627 |
| Azathioprine, n=414 | 21 (5) | 6 (9) | 15 (4) | 0.097 |

p value <0.05 is considered significant.
ACEi, ACE inhibitor; ANA, antinuclear antibodies; ANF, antinuclear factor; ARB, angiotensin II receptor antagonist; DLCO-SB, diffusing capacity for carbon monoxide single breath; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; mRSS, modified Rodnan skin score; NT-proBNP, N-terminal pro-brain natriuretic peptide; SSc, systemic sclerosis; VO2max, maximal oxygen uptake.

**Table 2** Baseline echocardiographic characteristics

| | Total (n=746) | Men (n=118) | Women (n=628) | P value |
|---|---|---|---|---|
| LVEDV (mL), median (IQR) | 85 (69–101) | 104 (89–118) | 82 (57–96) | **<0.001** |
| LVEDV/BSA (mL/m$^2$) | 48 (40–56) | 54 (44–62) | 47 (40–55) | **<0.001** |
| LVESV (m), median (IQR) | 32 (25–41) | 41 (34–50) | 31 (25–39) | **<0.001** |
| LVESV/BSA (mL/m$^2$) | 19 (15–23) | 21(17–25) | 18 (14–22) | **<0.001** |
| LVEF %, mean±SD | 60±7 | 59±8 | 60±7 | **0.035** |
| IVST (mm), mean±SD | 9±2 | 10±2 | 9±2 | **<0.001** |
| LVEDd (mm), mean±SD | 48±5 | 51±5 | 47±5 | **<0.001** |
| PWT (mm), mean±SD | 8±2 | 10±2 | 9±2 | **<0.001** |
| LAVI (mL), median (IQR) | 31 (25–38) | 32 (25–38) | 30 (25–37) | 0.502 |
| E/A ratio, median (IQR) | 1 (0.9–1.3) | 1 (0.9–1.00) | 1 (0.9–1.00) | 0.852 |
| e′ (cm/s), mean±SD | 9±3 | 9±3 | 9±3 | 0.912 |
| E/e′ ratio, median (IQR) | 9 (7–11) | 8 (6–11) | 9 (7–11) | 0.865 |
| sPAP (mm Hg), mean±SD | 32±17 | 32±14 | 32±17 | 0.988 |
| sPAP >35 mm Hg, n (%) | 97 (23) | 16(29) | 81(22) | 0.219 |
| TAPSE (mm), mean±SD | 23±4 | 23±4 | 22±4 | 0.163 |
| Pericardial effusion, n (%) | 55 (7) | 11 (9) | 44 (7) | 0.379 |
| LV GLS %, median (IQR)* | −20 (−22 to −18) | −19 (−20 to −17) | −21 (−22 to −19) | **0.001** |

p value <0.05 is considered significant.
BSA, body surface area; IVST, interventricular septum thickness; LAVI, Left Atrial Volume Index; LVEDd, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LV GLS, left ventricular global longitudinal strain; PWT, posterior wall thickness; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

positivity for antinuclear antibodies/antinuclear factor was higher in women (table 1).

Women and men were comparable in terms of cardiovascular disease risk factors, although smoking was more prominent in men. Pulmonary functional tests (FVC, FEV, DLCO-SB, VO$_2$max) were more impaired in men and NT-proBNP was higher in women. ACE/angiotensin II receptor antagonists and corticosteroids were more frequently prescribed in men (table 1).

### Baseline echocardiographic characteristics

The baseline echocardiographic characteristics of the overall population are presented in table 2. When comparing standard echocardiographic measures between men and women patients with SSc (particularly LV systolic function), we observed that men were characterised by larger LV indexed volumes (LVEDV: 54 (44–62 mL/m$^2$) vs 47 (40–55 mL/m$^2$), p<0.001; LVESV: 21 (17–25 mL/m$^2$) vs 18 (14–22 mL/m$^2$), p<0.001) and lower LVEF (men SSc 59±8% vs women SSc 60±7%, p=0.035). By the STE analysis, LV GLS was more preserved in women (−21% (IQR: −22% to −19%) as compared with men (−19% (IQR −20% to −17%), p<0.001); in turn, there were no significant differences between men and women in terms of LV diastolic function parameters (table 2).

Considering the significant difference between men and women for important clinical characteristics, a propensity matching score was applied to explore whether the sex differences in the echocardiographic parameters were maintained also after adjusting for these confounders. The matching was performed according to age, disease duration since Raynaud, presence of dcSSc, interstitial lung fibrosis, DLCO-SB and NT-proBNP; after matching (n=140 patients), LV GLS still showed a significant difference between men and women, whereas LV volumes and LVEF did not (table 3).

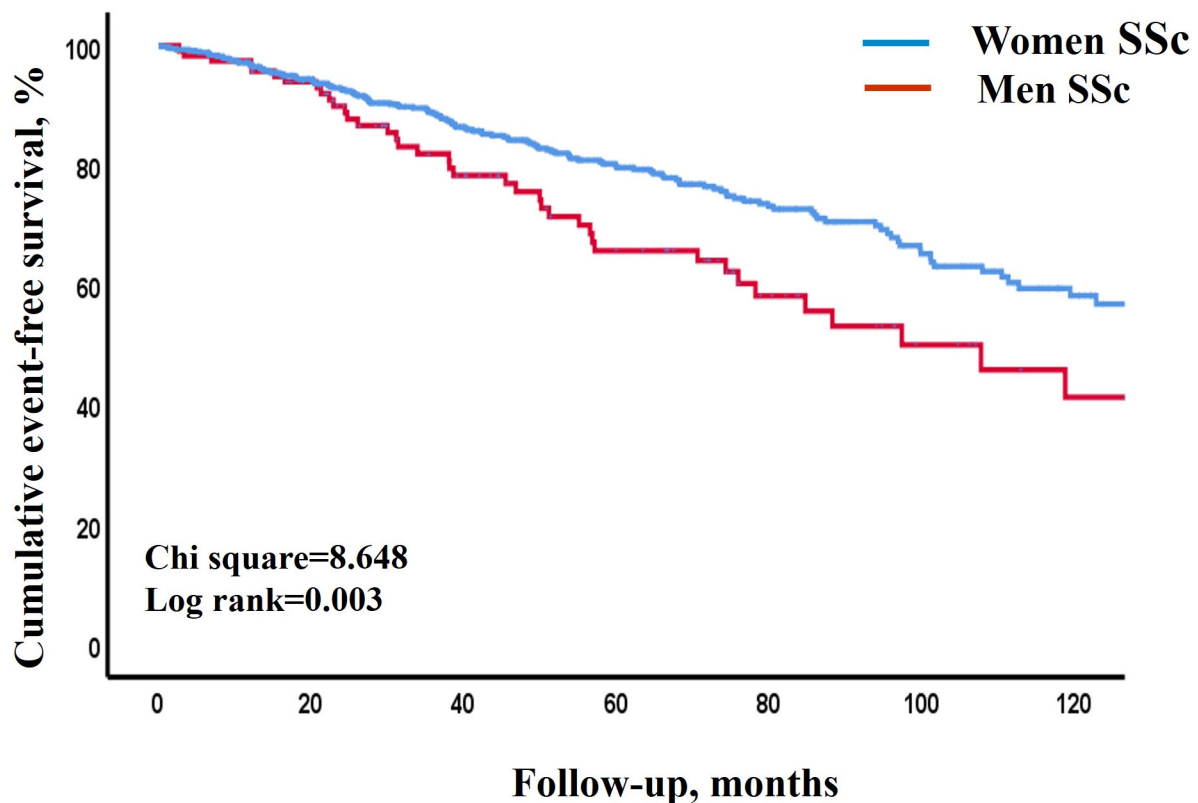### Sex differences in outcomes in patients with SSc

After a median follow-up of 48 months (IQR: 26–80), the combined endpoint occurred in 182 (24.4%) patients. Kaplan-Meier survival curves showed that men experienced higher cumulative rates of cardiovascular events-hospitalisation/death as compared with women ($\chi^2$ 8.648; Log rank 0.003, figure 2). When using propensity score matching to match men and women according to the abovementioned clinical characteristics (age, disease duration since Raynaud, type of SSc, lung fibrosis, DLCO-SB and NT-proBNP, n=140 patients), men still experienced higher cumulative rates of cardiovascular events/death as compared with women ($\chi^2$ 7.211; Log rank 0.007, figure 3A). Sex difference in outcome was neutralised when matching the groups according to the LV GLS on top of the abovementioned clinical characteristics (n=112 patients, $\chi^2$ 0.474; Log rank 0.491, figure 3B).

**Table 3** Echocardiographic findings in men and women patients with SSc after propensity score matching (based on age, disease duration since onset of Raynaud, SSc type, interstitial lung fibrosis, DLCO-SB, NT-proBNP)

| Baseline echocardiographic characteristics | Propensity matched patients | | | |
|---|---|---|---|---|
| | Total (n=140) | Men (n=70) | Women (n=70) | P value |
| LVEDV/BSA (mL/m$^2$) | 49 (41–57) | 53 (42–60) | 46 (40–55) | 0.059 |
| LVESV/BSA (mL/m$^2$) | 18 (15–23) | 19 (17–24) | 18 (14–23) | 0.059 |
| LVEF %, mean±SD | 60±7 | 60±8 | 61±6 | 0.226 |
| LAVI (mL), median (IQR) | 27 (22–34) | 26 (20–33) | 27 (23–35) | 0.583 |
| E/A ratio, median (IQR) | 1 (0.9–1.3) | 1 (0.9–1.3) | 1 (0.9–1.2) | 0.812 |
| E/e′ ratio, median (IQR) | 8 (6–10) | 7 (5–8) | 9 (6–10) | 0.132 |
| sPAP (mm Hg), mean±SD | 34±17 | 33±15 | 35±20 | 0.656 |
| TAPSE (mm), mean±SD | 23±4 | 24±4 | 22±3 | 0.059 |
| LV GLS %, median (IQR) | −20 (−21 to −18) | −19 (−20 to −18) | −20 (−22 to −18) | **0.003** |

p value <0.05 is considered significant.
BSA, body surface area; DLCO-SB, diffusing capacity for carbon monoxide single breath; LAVI, Left Atrial Volume Index; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LV GLS, left ventricular global longitudinal strain; NT-proBNP, N-terminal pro-brain natriuretic peptide; sPAP, systolic pulmonary artery pressure; SSc, systemic sclerosis; TAPSE, tricuspid annular plane systolic excursion.



**Figure 2** Survival function (for cardiovascular hospitalisation/death) in women and men patients with systemic sclerosis (SSc).
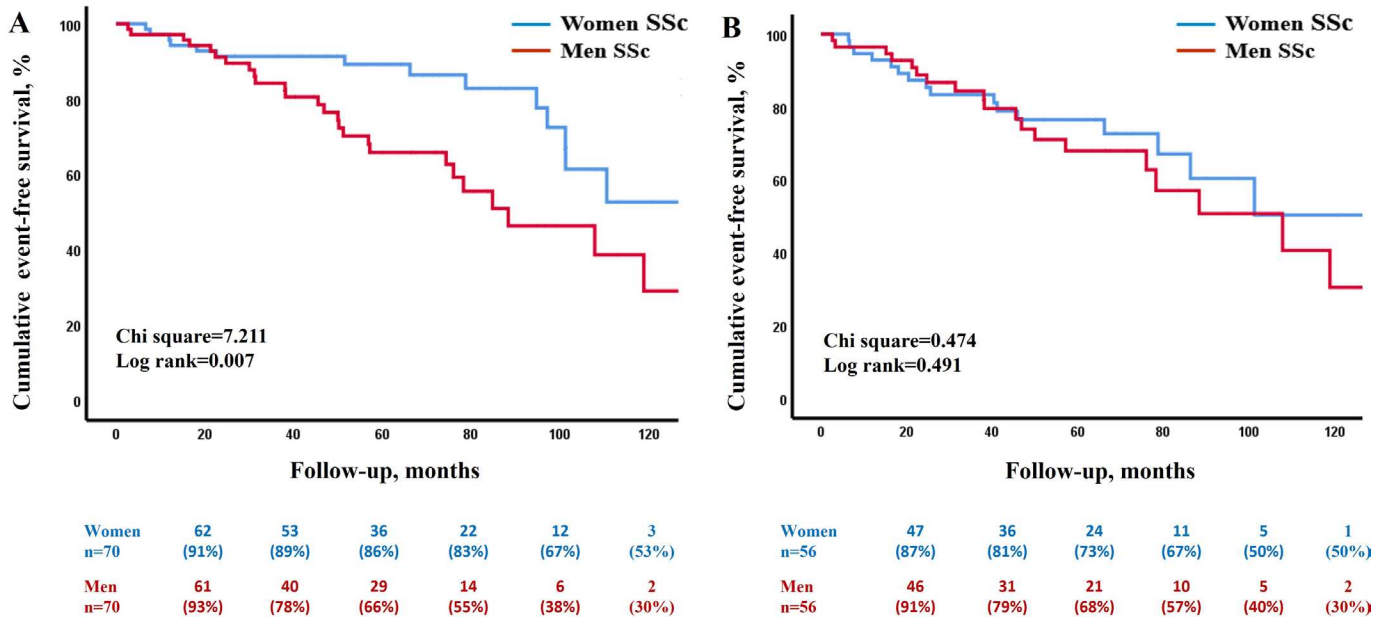
**Figure 3** Survival function in women and men patients with SSc in panel A after adjusting for age, disease duration (since Raynaud), type of SSc, lung fibrosis, DLCO-SB and NT-proBNP, in panel B after adjusting for age, disease duration (since Raynaud), type of SSc, lung fibrosis, DLCO-SB, NT-proBNP and LV GLS. DLCO-SB, diffusing capacity for carbon monoxide single breath; LV GLS, left ventricular global longitudinal strain; NT-proBNP, N-terminal pro-brain natriuretic peptide; SSc, systemic sclerosis.

In addition, LV GLS showed an association with outcomes in the overall group (HR: 1.163; 95% CI: 1.103 to 1.226, p<0.001) and no interaction between sex and LV GLS was detected (HR: 0.936; 95% CI: 0.811 to 1.082, p=0.373), indicating an equally high prognostic role of LV GLS for both sex in the SSc population. We also performed an additional Cox regression analysis in the overall populations including the variables of the propensity score matching and sex. When adding LV GLS to a multivariable model including all these variables (basal model), it significantly increased the predictivity of the model; in turn, adding any of the other variables which were different between men and women (but still not included in the propensity matching analysis) did not increase the predictivity of the model significantly, confirming the importance of GLS to predict prognosis and possibly its role in the higher cardiovascular risk of men (online supplemental figures 1a–e).

## DISCUSSION

The main findings of the present study, which included a large cohort of patients with SSc from multiple centres, can be summarised as follows: (1) after matching for the various clinical and SSc-related characteristics, men with SSc presented with more impaired LV GLS as compared with women, but no differences in LVEF or diastolic function parameters were observed and (2) LV GLS was significantly associated with cardiovascular outcome both in men and women but the sex difference in outcome was no longer observed when matching the groups according to LV GLS on top of the clinical characteristics.

## Differences in LV function between men and women with SSc

In patients with SSc, cardiovascular system involvement is observed both in men and women, but previous studies have shown that LV dysfunction (as defined by an impaired LVEF) is more prevalent in men. Similarly in our study, men showed lower LVEF and, as shown for the first time, also more impaired LV GLS as compared with women. However, it has not been demonstrated so far whether this sex difference in cardiac involvement remains significant after adjusting for important characteristics which have been shown to be associated with LV dysfunction, such as age, disease duration and type of disease, digital ulcers, muscle and lung involvement.[5] Like in other cohorts, also in our study men patients with SSc had more severe disease with more frequent dcSSc, SSc-associated ILD and more impaired DLCO. In general, higher burden of organ fibrosis formation may explain the higher prevalence of LV dysfunction in men.[27–29] Also the dcSSc subtype has been previously associated with cardiovascular involvement.[30 31] In the study by Ferri et al,[2] patients with dcSSc presented more frequently with cardiac involvement at the time of diagnosis as compared with patients with lcSSc. An increased risk of cardiac disease in dcSSc was also reported in the German Network for Systemic Scleroderma cohort.[30] Sex differences in LV dysfunction should be therefore corrected for these important factors, and in our study a more impaired LV GLS (but not LVEF) was confirmed in men as compared with women even after adjusting for the presence of dcSSc and ILD, both reflecting more severe fibrotic disease.

In our cohort, no significant sex differences were observed in digital ulcers or proximal muscle weakness; furthermore, NT-proBNP levels were higher in women as compared with men. In the study by Lau et al, which extensively explored sex differences in circulating biomarkers among different cardiovascular diseases, NT-proBNP showed typically higher values in women.[32] This might explain the observation in our patient cohort (higher NT-proBNP level in women) as well, although LVEF values were still relatively preserved. However, also after correction for NT-proBNP values, the difference in LV GLS between men and women remained significant.

### Clinical and echocardiographic associates of cardiovascular outcomes in men and women with SSc

Cardiovascular events are one of the major causes of mortality in patients with SSc.[1 33] Although several studies have shown that male sex is associated with worse cardiovascular outcome/mortality in general in SSc,[5 6] it has never been shown whether this difference was related with the prevalence of LV dysfunction, particularly when assessed with advanced echocardiographic measures such as LV GLS. In SSc, LV GLS has emerged as an important marker of subtle myocardial involvement (due to myocardial fibrosis related to microangiopathy and microvascular injury, myocardial stunning due to repeated focal ischemia caused by abnormal vasoreactivity or peri-myocarditis) and dysfunction, even when LVEF is preserved.[5 34] In the study by van Wijngaarden et al, LV GLS showed to be independently associated with cardiovascular outcomes in a large cohort of patient with SSc together with NT-proBNP and DLCO.[10]

In the current study, including a large cohort of patients from multiple centres, we confirmed that men were characterised by a higher incidence of cardiovascular events/mortality and LV GLS was associated with the outcome both in men and women. Interestingly, sex differences in outcomes were maintained also after correcting for important clinical characteristics but were neutralised after matching for LV GLS, suggesting therefore an important role of LV GLS in the higher incidence of cardiovascular events/mortality in men. GLS might be the underlying problem by which the survival difference between men and women is caused. Additional studies aiming at demonstrating the underlying pathophysiology of LV GLS impairment in SSc are therefore highly warranted as well as characterisation of sex differences and potentially changes over time.

### CLINICAL IMPLICATIONS

In patients with SSc, the presence of impaired LVEF and cardiovascular symptoms is of important prognostic value but identifies an advanced stage of the cardiac involvement, whereas risk stratification should help to identify patients at higher risk prior to developing advanced disease for which earlier treatment can still potentially change the natural course and prognosis of the disease.

Early assessment of subtle myocardial changes and cardiac involvement by LV GLS may improve risk stratification and define the need for further diagnostic assessment (eg, cardiac MRI, right heart catheterisation, Holter ECG monitoring), closer follow-up and eventually specific treatment in both men and women; in fact, lack of interaction between sex and LV GLS suggested an equally high prognostic role of LV GLS for both sexes among patients with SSc. However, considering sex-specific clinical and echocardiographic parameters may help to better define factors associated with outcomes of the disease and therefore risk-stratifying and managing these patients. In particular, normal values of LV GLS in men patients with SSc may reassure the treating physician of the absence of cardiac involvement in this group considered at high risk for cardiovascular complications.

### LIMITATIONS

The limitations of this study include: (1) specific analyses for myocardial ischemia were not systematically performed; however, most of the patients underwent cardiopulmonary exercise testing without showing signs of myocardial ischemia making therefore its presence unlikely; (2) treatment strategies were not taken into account during follow-up and potential association with cardiac function could not be evaluated; however, considering the absence of homogeneous recommendations, therapeutic changes were also not included in previously published prognostic models; (3) the relatively small number of men patients with SSc still gives some statistical power limitation but propensity score matching was used for group comparison; (4) echocardiograms were not read in a core lab but were directly entered in the database in each centre that, nevertheless, has great experience in analysing standard and advanced echocardiography and (5) significant differences between men and women for important clinical characteristics were observed, and not all of those variables were included in the propensity score matching; however, we have also built different models to further test the incremental prognostic value of LV GLS on top of those variables observed as different between men and women.

### CONCLUSIONS

In SSc, male sex is associated with worse cardiovascular outcomes even after adjusting for important clinical characteristics. LV GLS was more impaired in men patients with SSc, as compared with women and this may potentially explain the sex differences in cardiovascular events. Using LV GLS for early assessment of myocardial involvement for both sexes may improve risk stratification and surveillance in patients with SSc. Further research that aims at elucidating the cause of LV GLS impairment in SSc is highly recommended, as this might lead to improved and targeted treatment strategies.

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