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Original article

Clinical assessment of cardiac impairment favored by two-dimensional speckle tracking echocardiology in patients with systemic sclerosis

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Abstract

Background. Cardiac involvement is a major cause of death in SSc, while early detection remains a challenge.
Objectives. The purpose of this study was to investigate the prevalence and clinical implications of cardiac impairment in SSc.
Methods. Ninety-five consecutive SSc patients [55.6 (13.8) years old, 5.3 (8.1) years from diagnosis] were included in the study. Patients with heart diseases onset prior to SSc were excluded. All patients underwent two-dimensional speckle-tracking echocardiology (2D-STE) with measuring left and right ventricular global longitudinal strain (GLS/RGLS). Clinical manifestation, laboratory evaluation (CRP, cTnI, antibodies, etc.) and ECG were collected at the same time. Comparisons between the SSc subgroups (lcSSc and dcSSc) were performed using Student's *t*-test, Mann–Whitney U or Fisher's exact test. Binary logistic regression was applied to determine the independent effects of variables in cardiac impairment.
Results. Early left and right ventricular impairment measured by GLS and RGLS were detected in 22.1% and 24.2% of the SSc patients, respectively. In comparison, only 2.1% showed reduced left ventricular ejection fraction (LVEF). Impaired GLS was mainly observed in the basal and medial segments of anterior, lateral and posterior left ventricle walls, and more profound in dcSSc. Elevated CRP (OR 3.561 95% CI: 1.071, 11.839, $P < 0.05$) was associated with reduced GLS/RGLS. The adoption of GLS/RGLS enhanced the efficacy of routine screening for cardiac impairment that 52.6% of patients showed potential cardiac impairment.
Conclusions. Cardiac impairment is a common manifestation in SSc. Increasing awareness of early cardiac impairment is warranted with elevated CRP and dcSSc.

Key words: systemic sclerosis, early cardiac impairment assessment, two-dimensional speckle-tracking echocardiology

CLINICAL SCIENCE

Rheumatology key messages

- Two-dimensional speckle-tracking echocardiology (2D-STE) is a novel tool to detect early cardiac impairment.
- Over 50% of SSc patients showed potential cardiac involvement by combining 2D-STE and traditional modalities.
- Increasing awareness of early SSc cardiac impairment is warranted in a new era with 2D-STE.

Introduction

Cardiac damage and related complication is a leading cause of death among SSc patients [1, 2]. The SSc cardiac involvement has various manifestations as myocardial damage, arrhythmia, pericardial and valvular disease [3, 4]. The diagnosis of myocardial impairment is usually conducted in the late stage, and thus associated with a poor prognosis of the disease [5, 6]. Novel

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practical and sensitive methods are required for the early diagnosis of myocardial impairment and risk stratification in SSc.

Recent advantages in echocardiography that are equipped with 2D speckle-tracking echocardiology (2D-STE), in particular, have improved the sensitivity and reproducibility of cardiac function assessment compared with traditional techniques [7]. Global longitudinal strain (GLS) measured by 2D-STE provides an objective measurement for early and subtle left ventricular systolic impairment before the occurrence of profound cardiac insufficiency [left ventricular ejection fraction (LVEF) $\leq$50%] [8]. In SSc patients, reduced GLS and right ventricular GLS (RGLS) were observed compared with healthy controls [9–13], and GLS impairment has been linked to rhythm disturbances, pulmonary arterial hypertension (PAH), interstitial cardiac fibrosis and elevated CRP [11, 13–15]. Moreover, in prospective studies conducted by Spethmann *et al.* and van Wijngaarden *et al.*, a nearly 2% decrease of GLS was observed while LVEF remained unaltered after 2 years of follow-up in SSc patients [8, 16], which indicate a deterioration of cardiac function despite LVEF was preserved.

The advantages of 2D-STE as high sensitivity, standardized, non-invasive, cost- and time-effective, and ease of cooperation make it an ideal tool in detecting early SSc cardiac dysfunction, although it still faces technical challenges as image quality, arrhythmia and pulmonary fibrosis, which require an interpretation by an experienced cardiologist or sonographer [7]. In addition, 2D-STE cannot analyse myocardial fibrosis compared with cardiac magnetic resonance (CMR) that has exclusive advantages in detecting myocardial fibrosis and inflammation [17]. However, CMR has its pitfalls compared with 2D-STE due to the contraindications such as low estimated glomerular filtration rate (eGFR), allergy to contrast, metal implantations, etc [18]. Moreover, the high cost and time-consuming nature of CMR makes the usage of CMR as a screening methodology still limited in comparison to 2D-STE.

In the present study, we aimed to investigate the prevalence and clinical implications of cardiac impairment with comparisons between different SSc subgroups by 2D-STE and evaluate the contribution of 2D-STE in routine screening for early cardiac impairment in SSc patients.

Material and method

Patients

Ninety-five consecutive patients enrolled in this study were from the inpatient and outpatient ward of the Department of Rheumatology and Immunology, Peking University People's Hospital (PKUPH) between March 2019 and January 2020. All patients fulfilled the 1980 ACR criteria or the 2013 ACR/EULAR classification criteria for SSc [19, 20], and the exclusion criteria in our study are patients with heart diseases prior to the onset of SSc, which includes congenital heart diseases, coronary heart disease, arrhythmia, pulmonary hypertension, heart failure and valvular disease that debuted before the onset of SSc. Demographic characteristics and clinical manifestations were obtained at the time of enrolment. Written informed consents from all participants were collected according to the Declaration of Helsinki and with the approval of the Ethics Committee of Peking University People's Hospital.

Among all the 95 SSc patients, 89.5% were females. The average age was 55.6 (13.8) years old with a disease duration of 5.3 (8.1) years, and the age at disease onset was 45.7 (15.1) years old. Patients were categorized into 45 diffuse cutaneous SSc (dcSSc) and 50 limited cutaneous SSc (lcSSc) referring to LeRoy's criteria [21].

Regarding the organ involvement, cardiac symptoms and signs (after excluding other causes as pulmonary or renal involvement) were defined as a fulfillment of at least one of the following symptoms including breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, palpitations, dizziness, blackouts, chest pain, fatigue and peripheral oedema etc [22], and at least one of the following signs including pulmonary congestion with rales/crackles, leg oedema, elevated jugular venous pressure, irregular pulse/heart sounds, etc [22]. Congestive heart failure (CHF) was diagnosed according to the Framingham criteria [23]. Interstitial lung disease (ILD) was defined by high-resolution computed tomography (HRCT) showing $>$20% extent on the HRCT of the chest [4]. Pulmonary hypertension (PH) was considered when the estimated pulmonary artery systolic pressure (PASP) was $\geq$30 mmHg, as determined by echocardiography [24]. Chronic kidney disease (CKD) was defined by the estimated glomerular filtration rate (eGFR) $\leq$60 ml/min $\times$1.73 m^2 for $>$3 months [25]. Gastroesophageal reflux disease (GERD) was considered by clinical assessment of symptoms such as heartburn and regurgitation, with or without gastroscopy [26].

Treatments regarding glucocorticoids, immunosuppressive agents, NSAIDs, peripheral vasodilators and other treatments were collected. BMI, ECG and laboratory data were also collected. Blood sample testing was performed for traditional cardiac markers including cardiac troponin I (cTnI), B type natriuretic peptide (BNP) or N-terminal of the prohormone BNP (NT-proBNP); inflammatory markers including hypersensitive C-reactive protein (CRP); immunity parameters including complement C3/C4, anti–topoisomerase I (Scl-70), anti-CENP A/B, anti Ro52 antibodies and eGFR was calculated based on serum creatinine value with age adjustment. All tests were performed in the laboratory of PKUPH.

Traditional echocardiography and 2D-STE analyses

All images were collected by transthoracic echocardiography GE E9, equipped with a transthoracic probe M5Sc. In the traditional echocardiography, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD) and LVEF were measured using M-mode echocardiography to assess the systolic function of the left ventricle. The flow velocity of each

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valve was measured by spectrum Doppler. Evaluation of left ventricular diastolic function was based on: (i) the ratio E/A; and (ii) the ratio E/e'. In the evaluation of the systolic function of the right ventricular, tricuspid annular plane systolic excursion (TAPSE), which was the displacement of the tricuspid annulus from diastole to systole, was measured at the tricuspid annulus of the right ventricular free wall using M-mode echocardiography. In addition, the endocardium of the right ventricular free wall was traced at the apical 4-chamber view, and the right ventricular end-diastolic area (RVAd) and right ventricular end-systolic area (RVAs) were measured. The right ventricular fractional area of change (FAC) was calculated as (RVAd-RVAs)/RVAd to evaluate the global systolic function of the right ventricle.

In addition, two-dimensional speckle tracking was applied to evaluate the left ventricular strain and right ventricular strain. Based on high frame rate two-dimensional gray-scale ultrasound imaging, pattern-matching technology was used to recognize the motion of speckles in the myocardium and track speckles on a frame-to-frame basis within the cardiac cycle. The images of apical 2-chamber view (including anterior wall and inferior wall), apical 2-chamber view (including posteroseptal wall and lateral wall) and apical 3-chamber view (including anteroseptal wall and posterior wall) were collected. Each wall was divided into three different levels, including basal segment, middle segment and apical segment, and the strain curves and values of the 17 segments were obtained. GLS was calculated as the average peak strain of the 17 segments. In addition, RGLS was obtained by tracing the right ventricular free wall and septum. An absolute value of GLS/RGLS $\leq$18% was considered as GLS/RGLS impairment.

Statistical analysis

Variables were categorized as categorical or continuous. Categorical variables (gender, dcSSc, the presence of RP and other clinical manifestations) were analysed using Fisher's exact test. For continuous data (age, BMI, GLS, and other parameters measured by echocardiology), Gaussian distribution was tested using the normality test, thereafter median and interquartile range or mean value (S.D.) were calculated. Comparisons were performed using the Student's *t*-test or Mann–Whitney *U* test, when appropriate. Binary logistic regression with odds ratios (ORs) was applied to determine the independent effects of all the variables in the impairment of GLS/RGLS. A $P < 0.05$ was considered statistically significant. All calculations were performed using SPSS 23.0.

Results

GLS/RGLS favoured the detection of early cardiac function impairment in SSc

By applying the traditional echocardiogram, 2.1% (2/95) and 4.2% (4/95) of the patients showed left and right ventricular deformation based on the enlargement of the two ventricles, respectively (Table 1). Regarding cardiac function, the majority of the patients had preserved LVEF [71.4% (68.4%–75.5%)] whereas two patients showed left ventricle systolic dysfunction by reduced LVEF ($\leq$50%). Meanwhile, the prevalence of left ventricular diastolic dysfunction was higher than systolic dysfunction, as 36.8% (35/95) with reduced E/A and 27.4% (26/95) with elevated E/e', respectively (Table 1). On the other hand, right ventricular systolic dysfunction shown by decreased FAC (11.6%) and TAPSE (15.8%) was more common than LVEF impairment. Notably, the occurrence of FAC impairment was significantly higher in the dcSSc than the lcSSc group (20.0% *vs* 4.0%, $P < 0.05$) shown in Table 1.

In comparison, 2D-STE analyses showed an impaired early left ventricular systolic function indicated by reduced GLS (absolute value $\leq$18%) in 22.1% (21/95) of the patients (Table 1). Similarly, a larger number of patients displayed an impaired early right ventricular systolic function indicated by RGLS (24.2%, 23/95) shown in Table 1. No significant difference was found in total GLS and RGLS impairment between the subgroups. Of note, 56.5% (13/23) of the patients with reduced GLS/RGLS did not show any type of cardiac impairment.

Anterior and lateral wall in left ventricle were more vulnerable for early cardiac function impairment

To further characterize the location and extent of GLS impairment in SSc, we analysed each of the 17 segments of the left ventricle with a comparison between lcSSc and dcSSc patients. As shown in Fig. 1, the longitudinal strain showed a gradual impairment in a basal>medial>apical pattern (Fig. 1A and B). Among the basal segments, the anterior-septal wall, anterior wall and lateral wall of the left ventricle were the most vulnerable segments indicated by reduced longitudinal strains (absolute value ≤ -18%). Likewise, longitudinal strains in the anterior wall and lateral wall in medial segments were also impaired. In comparison, the longitudinal strains in the apical segments were preserved (Fig. 1B). On the other hand, ECG results did not match ST-T abnormality to corresponding regions for longitudinal strain impairment.

Despite that the total GLS between lcSSc and dcSSc was comparable as shown above, longitudinal strains impairment in the posterior, lateral and anterior walls was more profound in dcSSc patients (Fig. 1C). In particular, the longitudinal strain in the posterior wall of the medial segment was significantly lower in dcSSc compared with lcSSc (Supplementary Fig. S1, available at *Rheumatology* online).

Elevated CRP was associated with early cardiac function impairment

To further investigate the clinical implications of GLS/RGLS (patients who fulfilled either GLS or RGLS impairment) in SSc, univariate and multivariate analyses were performed

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Table 1 Characterization of echocardiogram with 2D-STE in SSc patients

	Total ($n = 95$)	lcSSc ($n = 50$)	dcSSc ($n = 45$)
Left ventricle (LV)			
LV enlargement, *n* (%)	2/95(2.1)	1/50(2.0)	1/45(2.2)
LVEF (%)	71.4(68.4–75.5)	72.3(69.8–75.7)	71.0(66.8–74.9)
LVEF $\leq$ 50%, *n* (%)	2/95(2.1)	0/50(0.0)	2/45(4.4)
LV GLS (%)	−21.4(18.4–23.5)	−21.6(18.1–24.5)	−21.4(18.8–23.3)
LV GLS$\geq$−18%, *n* (%)	21/95(22.1)	12/50(24.0)	9/45(20.0)
E/A	0.89(0.71–1.10)	0.85(0.70–1.02)	0.95(0.77–1.10)
E/A $\leq$ 0.8, *n* (%)	35/95(36.8)	22/50(44.0)	13/45(28.9)
E/e'	11.7(9.2–14.8)	12.0(9.9–15.7)	10.6(8.9–14.4)
E/e'$\geq$14, *n* (%)	26/95(27.4)	14/50(28.0)	12/45(26.7)
Right ventricle (RV)			
RV enlargement, *n* (%)	4/95(4.2)	2/50(4.0)	2/45(4.4)
FAC	0.44(0.39–0.51)	0.46(0.41–0.52)	0.43(0.38–0.50)
FAC $\leq$ 0.35, *n* (%)	11/95(11.6)	2/50(4.0)	9/45(20.0)*
TAPSE	2.0(1.8–2.2)	2.0(1.9–2.3)	2.0(1.8–2.2)
TAPSE $\leq$ 1.7, *n* (%)	15/95(15.8)	5/50(10.0)	10/45(22.2)
RGLS (%)	−21.9(18.0–25.2)	−22.2(16.4–24.8)	−21.8(19.4–25.4)
RGLS$\geq$−18%, *n* (%)	23/95(24.2)	15/50(30.0)	8/45(17.8)

*dcSSc: diffuse cutaneous SSc; FAC: fractional area change; GLS: global longitudinal strain; lcSSc: limited cutaneous SSc; LVEF: left ventricular ejection fraction; RGLS: right ventricular global longitudinal strain; TAPSE: tricuspid annular plane systolic excursion. dcSSc *vs* lcSSc $P < 0.05$.

on the demographic and clinical characteristics of the SSc patients shown in Table 2. No significant difference was found in terms of gender or age between patients with normal and reduced GLS/RGLS. Univariate analysis on the cardiac features indicated cardiac symptoms and signs were more prevalent in patients with impaired GLS/RGLS (28.1%) than in patients with normal GLS/RGLS (11.1%, $P < 0.05$). Likewise, the prevalence of CHF was also higher in patients with impaired GLS/RGLS (12,5%) (0.0%, $P < 0.05$). In comparison, no difference was found in terms of tachyarrhythmia and conduction block disorders, ST-T abnormality, pericardial effusion, valvulopathy and coronary artery disease, neither the occurrence of other systemic nor organ damage as shown in Table 2.

Regarding the lab parameters, elevated cTnI and CRP were found in patients with reduced GLS/RGLS by univariate analysis (25.0% *vs* 4.0%, $P < 0.01$ and 35.5% *vs* 13.1%, $P < 0.05$) while no difference in BNP level or the antibody profile (Table 2). In addition, administration of cardiovascular medicine as angiotensin-converting enzyme inhibitor and angiotensin receptor blockers (ACEI/ARB), β-Blockers, calcium channel blockers (CCB), and NSAIDs or immune-suppressing drugs including corticosteroids, cyclophosphamide (CTX), AZA, MMF, ciclosporin A (CSA) did not differ between patients with and without impaired GLS/RGLS (Table 2).

Nonetheless, further multivariate analysis showed only elevated CRP remained significant as an independent risk factor for GLS/RGLS impairment (OR 3.561 95% CI: 1.071, 11.839, $P < 0.05$) (Table 3). This finding remained significant even with excluding the two patients who had reduced EF (OR 4.543 95% CI: 0.086, 0.902, $P < 0.05$) (Supplementary Table S1, available at *Rheumatology* online). In addition, elevated CRP remained as an independent risk factor for GLS impairment; however, not RGLS impairment (Supplementary Table S2, available at *Rheumatology* online).

GLS/RGLS enhanced the screening efficacy for cardiac function impairment

Given the high sensitivity of GLS/RGLS, we evaluated their efficacy in screening cardiac function impairment in combination with traditional parameters (Fig. 2). Among the 95 SSc patients, 4.2% presented symptoms and signs of cardiac dysfunction (Fig. 2, (1)). By adopting BNP/NT-pro-BNP, the traditional serum marker for cardiac dysfunction, the percentage of cardiac dysfunction was increased to 30.5% (Fig. 2, (2)). Further traditional echocardiology assessment (LVEF, TAPSE and FAC, etc.) favoured the percentage to 38.9% (Fig. 2, (3)). When applying 2D-STE analyses, GLS and RGLS evaluation heightened the percentage to 52.6% on the top of previous traditional indices (Fig. 2, (4)).

Discussion

In the present study, cardiac function impairment was assessed using 2D-STE. Reduced GLS and RGLS were found in nearly one-fifth of the SSc patients that were much more common than the prevalence of cardiac dysfunction indicated by traditional parameters (LVEF and FAC). Impaired longitudinal strains were mainly observed in the basal and medial segments of anterior,

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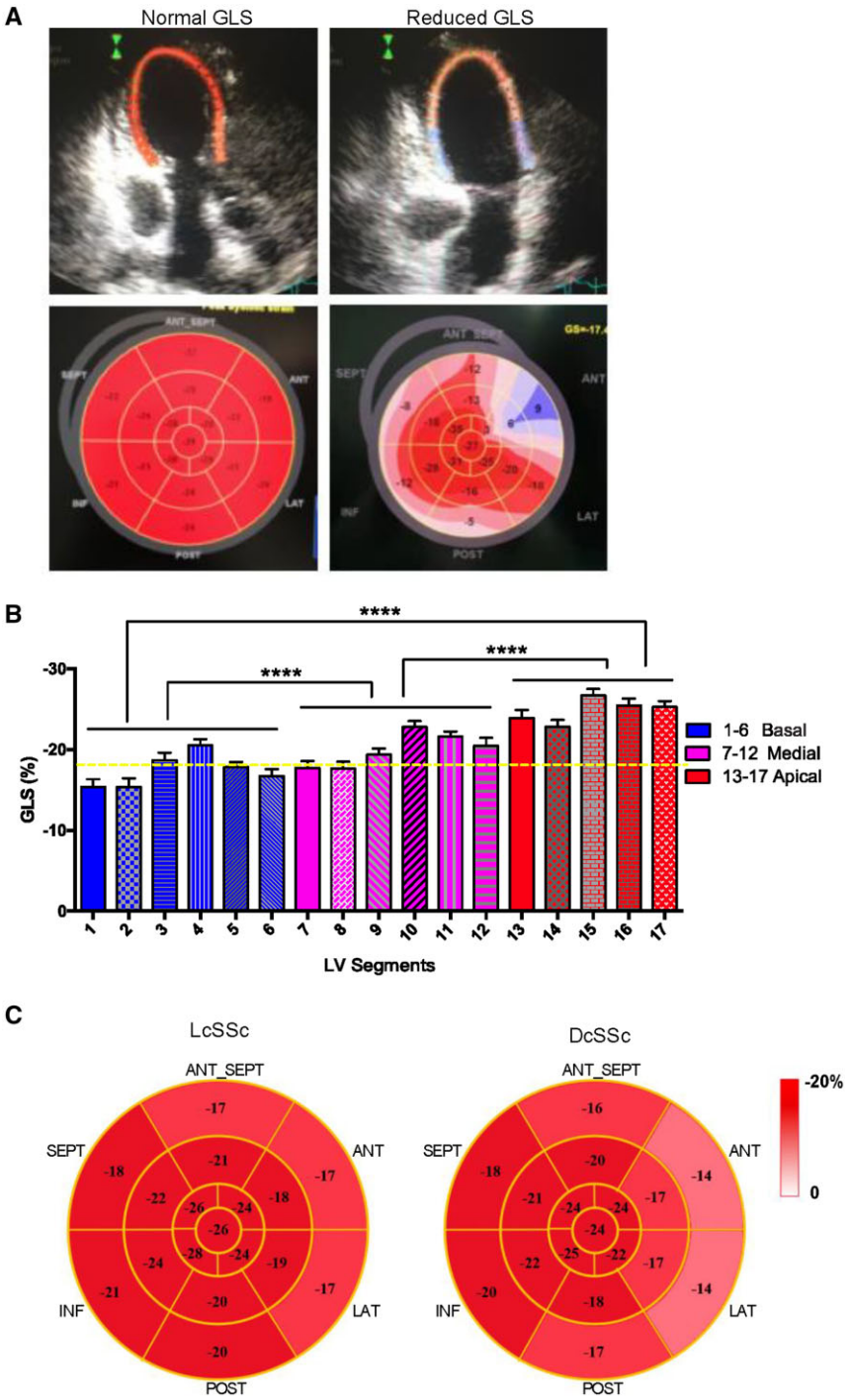
Fig. 1 Illustration and analysis of regional longitudinal strain in SSc patients



(**A**) Long-axis view of left ventricle by 2D-STE and bull's eye diagram of SSc patients with normal (left) or reduced GLS (right). (**B**) The analysis of the mean longitudinal strain in each segment of the left ventricle. Mean longitudinal strain between basal (1–6 segment), medial (7–12 segment) and apical (13–17 segment) segments were compared using one-way ANOVA. ****$P < 0.0001$. The 17 segments consist of 1 basal anterior, 2 basal lateral, 3 basal posterior, 4 basal inferior, 5 basal septal, 6 basal anteroseptal, 7 mid anterior, 8 mid lateral, 9 mid posterior, 10 mid inferior, 11 mid septal, 12 mid anteroseptal, 13 apical anterior, 14 apical lateral, 15 apical inferior, 16 apical septal, 17 apical. (**C**) Bull's eye diagram for the mean longitudinal strain in each segment of lcSSc and dcSSc patients. dcSSc: diffuse cutaneous SSc; GLS: global longitudinal strain; lcSSc: limited cutaneous SSc.

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TABLE 2 Demographic and clinical characteristics of the SSc patients depending on GLS or RGLS impairment

	Total ($n = 95$)	Nor-GLS/RGLS ($n = 63$)	Re-GLS/RGLS ($n = 32$)
Demographic characteristics			
Female, *n* (%)	85/95(89.5)	57/63(90.5)	28/32(87.5)
Age at onset, mean (S.D.) years	45.7(15.1)	44.5(13.7)	48.2(17.5)
Disease duration, median years	6.0(3.0–14.0)	7.0(3.0–13.0)	5.0(3.0–14.8)
Clinical characteristics			
Cardiac symptom/signs, *n* (%)	16/95(16.8)	7/63(11.1)	9/32(28.1)*
Congestive heart failure, *n* (%)	4/95(4.2)	0/63(0.0)	4/32(12.5)*
Tachyarrhythmia, *n* (%)	8/95(8.4)	4/63(6.3)	4/32(12.5)
Conduction block, *n* (%)	9/95(9.5)	4/63(6.3)	5/32(15.6)
ST-T abnormality	6/95(6.3)	2/63(3.2)	4/32(12.5)
Pericardial effusion, *n* (%)	12/95(12.6)	8/63(12.7)	4/32(12.5)
Valvulopathy, *n* (%)	1/95(1.1)	1/63(1.6)	0/32(0.0)
Coronary artery disease, *n* (%)	2/95(2.1)	1/63(1.6)	1/32(3.1)
PH, *n* (%)	34/95(35.8)	23/63(36.5)	11/32(34.4)
dsSSc, *n* (%)	45/95(47.4)	34/63(54.0)	11/32(34.4)
RP, *n* (%)	82/95(86.3)	53/63(84.1)	29/32(90.6)
Digital ulcers, *n* (%)	21/95(22.1)	15/63(23.8)	6/32(18.8)
Joint involvement, *n* (%)	43/95(45.3)	25/63(39.7)	18/32(56.3)
ILD, *n* (%)	64/95(67.4)	42/63(66.7)	22/32(68.8)
CKD, *n* (%)	8/95(8.4)	3/63(4.8)	5/32(15.6)
GERD, *n* (%)	49/95(51.6)	32/63(50.8)	17/32(53.1)
Arterial hypertension, *n* (%)	26/95(27.4)	16/63(25.4)	10/32(31.3)
BMI (kg/m2)	22.1(4.2)	21.7(3.7)	23.1(5.6)
Lab parameters, *n* (%)			
Elevated cTNI	9/78(11.5)	2/50(4.0)	7/28(25.0)**
Elevated BNP/NT-pro-BNP	29/79(36.7)	15/50(30.0)	14/29(48.3)
Elevated CRP	19/92(20.7)	8/61(13.1)	11/31(35.5)*
Reduced C3/C4	11/94(11.7)	6/62(9.7)	5/32(15.6)
Scl-70	30/95(31.6)	21/63(33.3)	9/32(28.1)
CENP A/B	27/95(28.4)	18/63(28.6)	9/32(28.1)
Treatment, *n* (%)			
ACEI/ARB, *n* (%)	12/95(12.6)	7/63(11.1)	5/32(15.6)
CCB, *n* (%)	15/95(15.8)	8/63(12.7)	7/32(21.9)
β-Blocker, *n* (%)	7/95(7.4)	5/63(7.9)	2/32(6.3)
NSAIDS, *n* (%)	15/95(15.8)	10/63(15.9)	5/32(15.6)
Glucocorticoids, *n* (%)	70/95(73.7)	47/63(74.6)	23/32(71.9)
CTX, *n* (%)	44/95(46.3)	27/63(42.9)	17/32(53.1)
AZA, *n* (%)	11/95(11.6)	7/63(11.1)	4/32(12.5)
MTX, *n* (%)	13/95(13.7)	6/63(9.5)	7/32(21.9)
MMF, *n* (%)	33/95(34.7)	20/63(31.7)	13/32(40.6)

ACEI/ARB: angiotensin converting enzyme inhibitors/angiotensin receptor blocker; BNP: B type natriuretic peptide; CCB: calcium channel blockers; CHF: congestive heart failure; CKD: chronic kidney disease; CRP: C-reaction protein; cTNI: cardiac troponin I; CTX: cyclophosphamide; dcSSc: diffuse cutaneous SSc; GERD: gastroesophageal reflux disease; ILD: interstetial lung disease; lcSSc: limited cutaneous SSc; Nor-: normal; PH: pulmonary hypertension; Re-: reduced. *$P < 0.05$, **$P < 0.01$, based on Fisher's exact test.

lateral and posterior walls in left ventricles, and were more profound in dcSSc than lcSSc patients. Elevated CRP is an independent risk factor for subclinical myocardial dysfunction. Notably, we for the first time showed a high prevalence of cardiac impairment in SSc patients (52.6%) by using a clinical assessment model that analysed different parameters mimicking the scenario in clinical practice as shown in Fig. 2. Nearly one-quarter of these patients with a cardiac impairment only presented a subclinical cardiac impairment that can be only detected by 2D-STE, which indicates the adoption of GLS and RGLS to a large extent enhanced the efficacy of routine screening for cardiac involvement.

The study evaluated the prevalence of SSc cardiac impairment at all stages without specific selection, which means both patients with advanced cardiac

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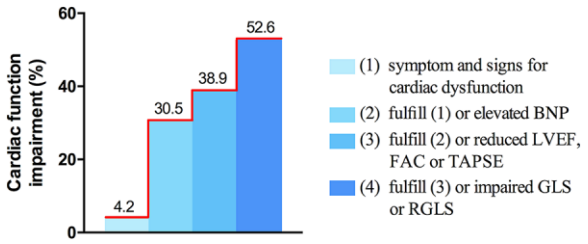
Table 3 Multivariate analysis for GLS/RGLS impairment

	β	S.E.	*P*	OR(95% CI)
Cardiac symptom/signs	0.042	0.718	0.954	1.043 (0.255, 4.262)
Congestive heart failure	21.069	18285.558	0.999	—
Elevated cTnI	1.512	0.943	0.109	4.534 (0.714, 28.776)
Elevated CRP	1.270	0.613	0.038	3.561 (1.071, 11.839)

CRP: C-reaction protein; cTNI: cardiac troponin I; GLS: global longitudinal strain; OR: odds ratio; RGLS: right ventricular global longitudinal strain. Analysis was based on binary logistic regression.

Fig. 2 Screening for cardiac involvement in SSc patients



The cumulative percentage of patients with cardiac function impairment is shown. Patients showing symptoms and signs for cardiac dysfunction, elevated BNP, traditional echocardiography abnormalities and reduced GLS/RGLS were calculated in turn. BNP: B-type natriuretic peptide; FAC: fractional area of change; GLS: global longitudinal strain; LVEF: left ventricular ejection fraction; RGLS: right ventricular GLS; TAPSE: tricuspid annular plane systolic excursion.

impairment (LVEF/FAC reduction) and patients with early cardiac impairment (GLS/RGLS reduction) after their onset of SSc were included and analysed. A profound discrepancy was found regarding the prevalence of advanced cardiac impairment (2.1%) and early cardiac impairment (22.1%) in our cohort. These findings supported 2D-STE as a sensitive and potent tool for early diagnosis and risk stratification on cardiac damage, and early heart damage might have emerged a long time before the clinical manifestations. Consistently, recent biopsy and imaging studies have also shown that cardiac involvement in SSc patients has been considerably underestimated before clinical symptoms and signs are observed and linked with poor prognosis [2, 14, 27–29]. Moreover, several prospective studies showed a nearly 2% GLS impairment after a 2-year follow-up while LVEF remained unaltered in SSc patients [8, 16, 30], indicating that a subtle deterioration of cardiac function despite LVEF was preserved.

In line with the findings from previous 2D-STE studies in SSc patients [9, 10, 28], basal segments in the left ventricle have been shown as the most vulnerable parts in terms of longitudinal strain impairment compared with apical and medial segments. In addition, our results further suggested anterior and lateral walls in the left ventricle as a 'dangerous area' for longitudinal strain impairment. On the other hand, the underlying mechanism and clinical relevance of regional cardiac function impairment are still elusive, although several hypotheses including ischaemia-reperfusion abnormalities, myocardial inflammation and fibrosis have been suggested. Indeed, ECG analysis in the present study did not support any link between regional myocardial ischaemia and longitudinal strain impairment. Moreover, a recent study by Stronati *et al.* provided valuable information to understand the pathophysiology of SSc-related cardiomyopathy. By showing GLS impairment was most dominant in the endocardium layer, Stronati *et al.* suggest that microvascular dysfunction plays a vital role in heart involvement in SSc patients [30]. Taken together, we assume that microvasculitis might be one of the major underlying mechanisms for cardiac dysfunction. However, the contribution of myocardial ischaemia and fibrosis to regional cardiac function impairment needs to be further validated by coronary angiography and cardiac magnetic resonance.

The regional longitudinal strain analysis in our study showed a more profound early cardiac impairment in dcSSc patients in comparison to lcSSc patients, which is in line with the recognized increased frequency of internal organ involvement in dcSSc. In addition, previous studies conducted by Rodriguez-Reyna *et al*. [31] showed that myocardial fibrosis was more dominant in dcSSc patients although with a different distribution pattern [9, 10]. The clinical relevance of dcSSc in early cardiac function impairment needs to be validated in systemic longitudinal studies.

Despite that elevated CRP has been previously shown in SSc patients with impaired GLS [13], the present study for the first time proposed elevated CRP as an independent risk factor for subclinical myocardial dysfunction. Of note, increased CRP has been found in early disease and reflects SSc disease activity according to the European Scleroderma Trials and Research Group (EUSTAR) activity index [24]. In addition, IL-6, the upstream cytokine of CRP in the inflammatory cascade, has been shown as increased in SSc patients and significantly correlates with diastolic dysfunction in the left ventricle [32]. Thus, these results suggest CRP and IL-6 would serve as blood biomarkers in the development of cardiac disease in SSc patients. However, elevated CRP and IL-6 to a large extent may be attributed to a systemic inflammatory response, yet cardiac-specific

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involvement. The role of IL-6 and its upstream cytokine IL-1β in SSc cardiomyopathy needs to be further investigated in large-scale clinical cohorts and experimental models. Thus, the value of blood biomarkers needs to be complemented with sensitive echocardiography assessment as 2D-STE.

Furthermore, our study design enabled an assessment in SSc-related cardiac impairment that mirrored the investigation in clinical practice to the greatest extent. Adopting GLS and RGLS significantly improved the efficacy of cardiac involvement screening shown in our study. In total, 52.6% of the patients displayed potential cardiac impairment after adding GLS and RGLS to the traditional screening modalities. These results further proposed GLS and RGLS as sensitive and efficient tools in monitoring cardiac impairment, showing potential as important novel items in routine screening. Notably, in the current clinical practice, the screening of SSc cardiac involvement is, however, to a large extent depending on the traditional diagnostic modalities including cardiac manifestations, serum biomarkers, ECG and conventional echocardiography as recommended by the UK Systemic Sclerosis Study group [22]. On the other hand, despite the generation of consensus such as the Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI) has provided a useful tool for organ damage and risk stratification for SSc patients [4], its advantage in routine screening of cardiac impairment in SSc may be also limited. The cardiac evaluation according to SCTC-DI mainly favours an assessment of advanced cardiac damage rather than early cardiac impairment. Nonetheless, SCTC-DI has laid particular emphasis on right heart assessment so that right heart dysfunction has been highlighted as an independent item according to SCTC-DI whereas left heart dysfunction has only been described under the item SSc myocardial disease [4]. Thus, due to the high prevalence of early cardiac impairment and potent efficacy of 2D-STE, additional parameters such as GLS and RGLS may serve as promising parameters for a comprehensive assessment of SSc cardiac involvement in combination with SCTC-DI. In addition, other advantages including cost and time effectiveness and ease of operation highlight 2D-STE as an ideal tool in early SSc cardiac assessment.

Limitations

There are several limitations in the present study. First, this is single-center cross-sectional research with a relatively small sample size, and imaging follow-up was not studied. Future work requires, therefore, larger multicentre prospective studies to ascertain whether early cardiac impairment would be used to monitor disease development and affect treatment decisions. Second, the present study mainly focussed on the longitudinal strain, the most used parameter by 2D-STE, whereas circumferential and radial strains have not been assessed. Moreover, longitudinal strain in separate myocardial layers was not measured in this study. Thus, a more comprehensive evaluation is required in future studies. Third, despite the advantage of 2D-STE in the assessment of early cardiac dysfunction, it still faces technical challenges as we discussed previously. Last but not least, 2D-STE cannot analyse myocardial fibrosis compared with CMR as the golden stardard [17]. The combination of these technologies could provide more information to understand the pathophysiology of SSc-related cardiomyopathy.

Conclusions

In conclusion, cardiac impairment is a common manifestation in SSc while early cardiac impairment may be easily neglected with traditional methodologies. Global longitudinal strain measured by 2D-STE is a sensitive and practical method for early cardiac damage assessment, which should be considered as a first-line screening and risk stratification tool in SSc patients.

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Data availability statement

Data are available upon reasonable request.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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