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Cardiac involvement assessment in systemic sclerosis using speckle tracking echocardiography: a systematic review and meta-analysis

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ABSTRACT

Objectives Cardiac involvement in patients with systemic sclerosis (SSc) is associated with poor prognosis. Early detection of myocardial impairment is essential for treatment. The present study aimed to systematically review the value of detecting subclinical myocardial impairment in SSc patients using myocardial strain obtained from speckle tracking echocardiography (STE).

Design A systematic review and meta-analysis.

Data sources The PubMed, Embase and Cochrane library databases were searched in the period from the earliest available indexing date to 30 September 2022.

Eligibility criteria for selecting studies Studies evaluating myocardial function in SSc patients comparison with healthy controls based on myocardial strain data obtained from STE were included.

Data extraction and synthesis Ventricle and atrium data on myocardial strain were extracted to assessing the mean difference (MD).

Results A total of 31 studies were included in the analysis. Left ventricular global longitudinal strain (MD: −2.31, 95% CI −2.85 to −1.76), left ventricular global circumferential strain (MD: −2.93, 95% CI −4.02 to −1.84) and left ventricular global radial strain (MD: −3.80, 95% CI −5.83 to −1.77) was significantly lower in SSc patients than in healthy controls. Right ventricular global wall strain (MD: −2.75, 95% CI −3.25 to −2.25) was also decreased in SSc patients. STE revealed significant differences in several atrial parameters including left atrial reservoir strain (MD: −6.72, 95% CI −10.09 to −3.34) and left atrial conduit strain (MD: −3.26, 95% CI −6.50 to −0.03), as well as right atrial reservoir strain (MD: −7.37, 95% CI −11.20 to −3.53) and right atrial conduit strain (MD: −5.44, 95% CI −9.15 to −1.73). There were no differences in left atrial contractile strain (MD: −1.51, 95% CI −5.34 to 2.33).

Conclusion SSc patients have a lower strain than healthy controls for the majority of STE parameters, indicating the presence of an impaired myocardium involving both the ventricle and atrium.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study provided comprehensive evidence for cardiac involvement in systemic sclerosis using speckle tracking echocardiography.
⇒ We included studies in which analysis was performed on the entire heart, including ventricles and atria.
⇒ The heterogeneity was analysed using meta-regression.
⇒ Publication bias was present in some parameter analyses in the included studies.
⇒ The use of different equipment to perform speckle tracking echocardiography in the included studies potentially increases heterogeneity.

INTRODUCTION

Systemic sclerosis (SSc), also known as scleroderma, is an immune-mediated rheumatic disease, characterised by fibrosis of the skin and internal organs.[1] SSc is uncommon, but patients with SSc have a high risk of morbidity and mortality. Improved understanding of the condition of patients with SSc could lead to better disease management through accurate staging of the disease and comprehensive assessment of the patient.[2] Cardiac involvement, pathologically manifested as myocardial fibrosis, is a negative prognostic factor when it is clinically evident in SSc patients.[3] Mortality rate is as high as 70% in SSc patients with cardiac involvement, of which 28% is related to cardiac complications.[4] However, cardiac involvement is often asymptomatic, especially in its early stage. Thus, early identification of subclinical cardiac involvement is a major challenge.

Myocardial deformation is considered to be an early indicator of cardiac fibrosis that occurs before myocardial function is significantly impaired. Speckle tracking echocardiography (STE), a recently emerged quantitative ultrasound technique, can be used to estimate myocardial deformation using strain with good feasibility, reproducibility and diagnostic accuracy. Myocardial strain appears to be an optimal quantitative index in several clinical settings,[5] which can especially be used for identification of

myocardial fibrosis, including hypertrophic cardiomyopathy[6] and dilated cardiomyopathy.[7]

In the setting of rheumatic disease, STE can provide additional value in the different clinical stages.[8] Changes in myocardial strain reflect myocardial impairment involving both the left and right ventricles in patients with systemic lupus erythematosus.[9] STE is also increasingly used to detect myocardial impairment in patients with SSc based on myocardial strain.[10] However, results from studies are controversial, especially for the entire heart including ventricles and atria.[11 12] The purpose of the present study was to conduct a meta-analysis to characterise cardiac involvement in patients with SSc compared with healthy controls using STE.

METHODS

Screening of publications

A detailed search for studies on STE examination in SSc patients was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.[13] Using the electronic databases of PubMed, Embase and the Cochrane library, publications on STE examination in SSc patients were searched from the earliest available date of indexing up to 30 September 2022. A search strategy was used based on combined the terms: (1) "Speckle tracking" or "Strain" or "STE" and (2) "Echocardiography" or "Echocardiogram" and (3) "Systemic Sclerosis" or "Systemic Scleroderma" (see online supplemental file 1 for detailed search strategy). The present study performed a systematic review and meta-analysis.

Data extraction and quality assessment

Literature extraction was carried out after the search was completed. Studies comparing myocardial strain parameters in SSc patients and healthy controls were included. Duplicate records and studies that did not provide original data and information of interest, such as case reports, conference papers, review articles, letters, basic research studies and non-relevant studies, were excluded. Non-English language articles were also excluded. Two researchers independently reviewed the abstracts of the selected articles using the previous inclusion and exclusion criteria. Disagreements between researchers were resolved via a consensus reached with the help of a third researcher.

Full-text articles containing key parameters were eligible for the final inclusion in the analysis. The key parameters were as follows: values (means with SD or transformed) for left ventricular (LV) global longitudinal strain (LVGLS), LV global circumferential strain (LVGCS) or LV global radial strain (LVGRS) and LV ejection faction (LVEF), right ventricular global or free wall longitudinal strain (RVFLS), systolic pulmonary artery pressure (sPAP), left atrial (LA) and right atrial (RA) global peak longitudinal strain in systolic period (LA, RAεR: reservoir strain, or LA, $RA\varepsilon_{pos\ peak}$: global/total strain), peak longitudinal strain in early diastole period (LA, RAεCD: conduit strain, or sec LA, $RA\varepsilon_{pos\ peak}$: positive strain) and peak longitudinal strain in late diastole period (LA, RAεCT: contractile strain, orLA, $RA\varepsilon_{neg\ peak}$: negative strain). Data on demographic variables and major clinical variables were also extracted from each study.

Quality of the included studies was assessed using the Newcastle-Ottawa quality assessment scale (NOS) in three broad categories. The scores were displayed on a nine-point scale as poor quality (0–2 points), medium quality (3–5 points) and high quality (6–9 points).[14] Studies of poor quality would be excluded from the analysis.

Risk of bias assessment and sensitivity analyses

Publication bias was assessed by the Egger's test for included analyses. The random-effect method was used to consider the variability among the included studies. The trim-and-fill method was used to assess the impact of bias. Sensitivity analyses were performed by excluding studies one after another to estimate the stability of the pooled results.

Statistical analysis and meta-regression analysis

Differences in myocardial strain parameters between SSc patients and healthy controls were expressed as mean difference (MD) with pertinent 95% CIs. The pooled effect was tested using Z scores. Heterogeneity among studies was assessed using χ^2 Cochran's Q test to measure the inconsistency. The I^2 statistic was used to describe the proportion of total variation in studies due to heterogeneity. I^2 statistic <25% indicates low heterogeneity and >50% indicates a high heterogeneity. We hypothesised that inconsistencies among included studies may be affected by demographic variables including number of subjects, gender, mean age and body mass index (BMI), as well as clinical data including duration of disease, diffused type ratio, skin score and Scl-70 positivity rate. To assess the possible effect of these factors on differences across studies, meta-regression analyses were performed using LVGLS, LVGCS, LVGRS, right ventricular global wall strain (RVGLS) or RVFLS as dependent variables (y) and the demographic and clinical covariates as independent variables (x). Statistical analyses were performed using STATA V.15.1 (StataCorp LP). P<0.05 was considered statistically significant.

Patient and public involvement statement

Neither patients nor the public were involved in the design and planning of the study.

RESULTS

Literature search and study selection

A total of 296 records were identified in the electronic databases using the search strategy. The duplicate records (66) were excluded. Additionally, articles that did not provide useful data were excluded, including conference abstracts (119), reviews (19), basic research studies (1), case reports,

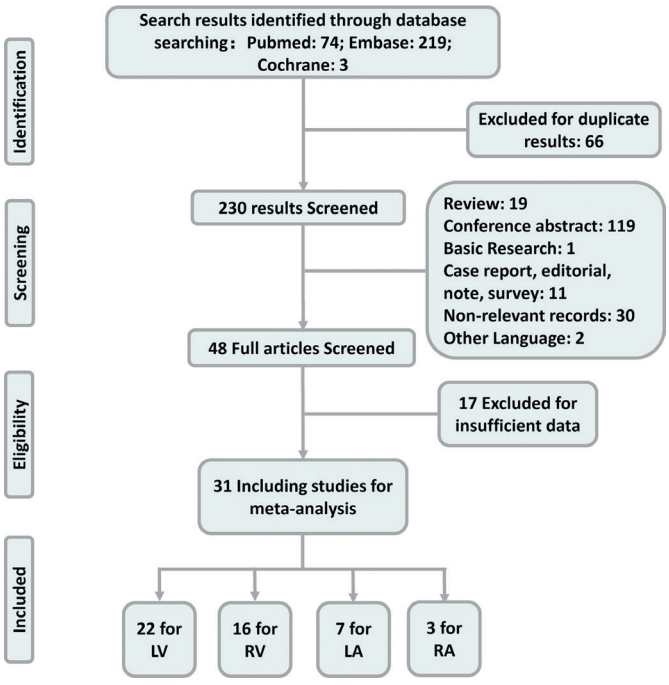

Figure 1 Publication screening flow chart. LA, left atrial; RA, right atrial; LV, left ventricle; RV, right ventricle.

editorials, notes and surveys (11), non-relevant records (30), as well as studies not written in English language (2). The remaining 48 studies were further evaluated based on full-text articles, of which 17 articles were excluded due to insufficient data. Finally, the remaining 31 studies were included in the meta-analysis to calculate pooled MDs. Of these, 22 were used for LV analysis, 16 for RV analysis, 7 for LA analysis and 3 for RA analysis. The study selection procedure is shown in figure 1.

Study characteristics

In total, 31 studies with 1985 SSc patients and 1212 healthy controls were included. These studies were published between 2011 and 2022. All included studies had a case-control design, and in the majority of studies, the controls were matched based on age and sex. The average age of the patient group and control group was 51.1 and 50.2 years, respectively. The characteristics of the studies and the participants are summarised in table 1.

Publication bias and sensitivity analyses

Publication bias was non-significant for LVGLS (P for Egger's test=0.119), LVGCS (P for Egger's test=0.819) and LVEF (P for Egger's test=0.744). There was also no publication bias for RVGLS (P for Egger's test=0.286), RVFLS (P for Egger's test=0.835) and sPAP (P for Egger's test=0.430). Furthermore, publication bias was not significant for LAεCD (P for Egger's test=0.827), LAεCT (P for Egger's test=0.695) and RAεR (P for Egger's test=0.732). There was publication bias for LVGRS (P for Egger's test=0.021) and LAεR (P for Egger's test=0.042). The trim-and-fill method was then used to obtain the corrected pooled values for LVGRS and LAεR. Publication bias test was not applicable for RAεCD because too few studies were included. Sensitivity analysis was performed to explore the stability of the results. None of the studies had a significant effect on pooled strain, which supports the robustness of the results.

Quality assessment

All of the included studies were of high quality based on NOS, with 17 studies receiving 7 points and 14 studies receiving 6 points. No study was excluded for analysis. The scores for each study are presented in table 1.

Comparison of myocardial strain between SSC patients and healthy controls based on LV strain assessed by STE

In total, 22 studies were included in the analysis of LV strain. Of these, all studies reported data on LVGLS in 1368 SSc patients and 865 healthy controls, 10 studies reported data on LVGCS in 595 SSc patients and 405 healthy controls and 7 studies reported data on LVGRS in 376 SSc patients and 229 healthy controls. In addition, there were 22 studies reporting LVEF in 1368 SSc patients and 865 healthy controls. LVGLS (MD: −2.31, 95% CI −2.85 to −1.76, p=0.000; I^2=85.1%;-figure 2A), LVGCS (MD: −2.93, 95% CI −4.02, to −1.84, p=0.000; I^2=74.4%; figure 2B) and LVGRS (MD: −3.80, 95% CI −5.83 to −1.77, p=0.000; I^2=28.8%; figure 2C) were significantly lower in SSc patients than in healthy controls. LVEF was also significantly lower in SSc patients than in healthy controls (MD: −1.70, 95% CI −2.56 to −0.84, p=0.000; I^2=83.7%) but within the normal range (see online supplemental file 1).

RV strain assessed by STE

In total, 16 studies were included in the analysis of RV strain. Of these, 13 studies reported data on RVGLS in 729 SSc patients and 494 healthy controls, and five data on RVFLS in 308 SSc patients and 187 healthy controls. In addition, 12 studies reported on sPAP in 802 SSc patients and 471 healthy controls. RVGLS (MD: −2.75, 95% CI −3.25 to −2.25, p=0.000; I^2=17.1%; figure 3A) and RVFLS (MD: −3.67, 95% CI −5.49 to −1.86, p=0.000; I^2=76.3%; figure 3B) was significantly lower in SSc patients than in healthy controls. In addition, sPAP was significantly higher in SSc patients than in healthy controls (MD: 9.19, 95% CI 6.82 to 11.57, p=0.000; I^2=88.8%), which cannot be defined as pulmonary hypertension (see online supplemental figure S2).

LA strain assessed by STE

In total, seven studies were included in the analysis of LA strain. Of these, all studies reported data on LAεR in 356 SSc patients and 242 healthy controls, four studies reported data on LAεCD in 211 SSc patients and 131 healthy controls and three studies reported data on LAεCT in 158 SSc patients and 105 healthy controls. LAεR (MD: −6.72, 95% CI −10.09 to −3.34, p=0.000; I^2=89.4%; figure 4A) and LAεCD (MD: −3.26, 95% CI −6.50 to −0.03, p=0.048; I^2=89.8%; figure 4B) was significantly lower in SSc patients than in healthy controls, while LAεCT was not (MD: −1.51, 95% CI −5.34 to 2.33, p=0.441; figure 4C).

Table 1 Study characteristics

Authors	Country	Year	Total sample size (N)	Female (%)	Patient age (years)	Control age (years)	BMI (kg/m^2)	Duration of disease (years)	Diffused type ratio (%)	Skin score	Scl-70+ rate (%)	Platform	Cardiac chamber	Measured index	NOS
Yiu *et al*[23]	Netherlands	2011	141	75.9	54±12	54±10	NR	5.1±2.3	51.0	5.6±6.1	NR	Vivid 7, GE; EchoPAC	LV	LVGLS, LVGCS, LVGRS	6
Spethmann *et al*[22]	Germany	2012	44	84.1	57.1±13.3	57.4±14.0	25.1±6.0	NR	50.0	9.9±1.3	40.9	Vivid 7, GE; EchoPAC	LV	LVGLS, LVGCS, LVGRS	7
Tigen *et al*[27]	Turkey	2014	79	87.3	49.1±11.5	42.8±11.7	25.6±3.6	7.4±5.8	43.4	15.1±7.2	NR	Vivid 7, GE; EchoPAC	LA, LV	LAεR, LAεCD, LVGLS, LVGCS, LVGRS	6
Agoston *et al*[28]	Hungary	2014	84	95.2	50±14	49±13	NR	NR	16.7	NR	31.0	Vivid 7, GE; EchoPAC	LA	LAεR, LAεCD, LAεCT	6
Cadeddu *et al*[20]	Italy	2015	65	80.0	60.4±10.3	60.8±10.8	NR	6.3±5.75	31.1	NR	0.3	Artida, Toshiba; NR	LV	LVGLS	7
Durmus *et al*[21]	Istanbul	2015	80	61.3	48.5±11.4	45.9±7.6	25.8±3.9	8.0±6.3	50.0	NR	32.4	Vivid 7, GE; EchoPAC	RA, LV, RV	RAεR, RAεCD, LVGLS, LVGCS, LVGRS, RVGLS	6
Pigatto *et al*[26]	Italy	2015	88	NR	56±13	NR	24	13.6±9.4	37.8	NR	37.8	Vivid E9, GE; EchoPAC	RV	RVGLS, RVFLS	6
Yiu *et al*[33]	Netherlands	2016	138	74.6	54±14	51±12	NR	6.2±7.4	51.0	5.7±5.9	NR	Vivid 7, GE; EchoPAC	RV	RVFLS	7
Ataş *et al*[29]	Turkey	2016	79	92.4	49.5±11.6	48.5±10.8	26.1±3.9	6.3±4.7	31.7	14.8±6.2	29.3	IE33, Philips; Qlab	LA	LAεR	7
D'Andrea *et al*[34]	Italy	2016	145	74.5	52.4±15.2	50.6±12.4	NR	12.1±10.3	61.1	NR	NR	Vivid E9, GE; EchoPAC	RV	RVGLS	7
Mukherjee *et al*[35]	USA	2016	178	87.6	54.3±12.6	53.5±14	NR	13.5±11.3	39.9	NR	27.9	IE33, Phillips; Qlab	RV	RVGLS	7
Zlatanovic *et al*[36]	Serbia	2017	71	93.0	56±11	54±9	25.1±4.2	6±3.8	46.3	16±7	41.5	Vivid 7, GE; EchoPAC	LV, RV	LVGLS, LVGCS, LVGRS, RVGLS	6
Dedeoglu *et al*[37]	Turkey	2017	40	100.0	15.38±2.74	14.33±3.48	NR	2.65±2.6	NR	14.8±11.9	NR	IE33, Phillips; Qlab	LV, RV	LVGLS, LVGCS, RVFLS	6
Tadic *et al*[30]	Serbia	2017	77	96.1	53±10	52±8	25.0±3.7	6±4	43.2	16±6	45.5	Vivid 7, GE; EchoPAC	LA	LAεR, LAεCD, LAεCT	6
Hromádka *et al*[38]	Czech Republic	2017	53	73.6	56.6±12.2	53.7±13.1	27.2±5.0	10±9.8	87.9	17.4±4.4	NR	Vivid 7, GE; EchoPAC	LV	LVGLS	7
Tadic *et al*[39]	Serbia	2017	87	92.0	54±10	53±8	24.8±3.8	6±4	42.9	15±6	44.9	Vivid 7, GE; EchoPAC	LV	LVGLS, LVGCS, LVGRS	6

Continued

Table 1 Continued

Authors	Country	Year	Total sample size (N)	Female (%)	Patient age (years)	Control age (years)	BMI (kg/m^2)	Duration of disease (years)	Diffused type ratio (%)	Skin score	Scl-70+ rate (%)	Platform	Cardiac chamber	Measured index	NOS
Mincu *et al*[40]	Romania	2018	103	68.0	36±10	34±10	23.5±3.8	5.2±5.0	NR	NR	NR	Vivid 9, GE; EchoPAC	LV, RV, LA	LVGLS, LVGCS, LVGRS RVGLS LAεR	7
Saito *et al*[41]	Australia	2018	206	78.6	63(57–71)	63(57–71)	26.9±3.8	NR	NR	NR	NR	Vivid 7, Vivid 9 or Vivid I, GE; EchoPAC	LV	LVGLS, LVGCS	7
Tadic *et al*[42]	Serbia	2018	80	93.8	55±10	53±8	25.0±4.1	5.5±3.6	46.7	17±8	42.2	Vivid 7, GE; EchoPAC	RV	RVGLS, RVFLS	6
Porpáczy *et al*[31]	Hungary	2018	102	88.2	53±10	57.1±11	NR	7.2±6.3	54.2	NR	NR	Epiq 7, Philips; Qlab	LA, LV	LAεR, LAεCD, LAεCT, LVGLS	7
Nógrádi *et al*[32]	Hungary	2018	95	86.3	57±12	54±7	NR	7.2±5.8	54.3	NR	NR	Epiq7, Philips; Qlab	RA	RAεR, RAεCD, RAεCT	7
Guerra *et al*[43]	Italy	2018	104	88.5	54.6±16.1	53.9±16.6	23.3±4.7	NR	34.6	NR	51.9	Vivid 7 Pro, GE; EchoPAC	LV, RV	LVGLS, RVGLS	7
Zairi *et al*[24]	Tunisia	2019	50	98.0	53.64±3.456	60.8±8.72	25.1±5.6	NR	92.0	NR	NR	Vivid 9, GE; EchoPAC	LV, RV	LVGLS, RVGLS	7
Şahin *et al*[44]	Turkey	2019	67	NR	48.2±12.4	47.5±9.4	NR	8.8±8.2	25.5	11.1±5.5	0.4	C256, Siemens; IE33, Philips; Qlab	LV, RV	LVGLS, RVGLS	6
Tountas *et al*[45]	Greece	2019	149	86.6	53.3±13.7	53.5±12	NR	7±2	41.0	NR	70.5	Vivid 7pro, GE; EchoPAC	LV, RV	LVGLS, LVGCS, RVFLS	7
Tennøe *et al*[46]	Norway	2019	257	NR	NR	NR	24±4	1.7±5.4	NR	6±7.4	NR	Vivid 7 or Vivid E9, GE; EchoPAC	LV	LVGLS	6
Karadag *et al*[25]	Turkey	2020	83	92.6	52.1±12.4	49.4±8.4	27.4±4.8	8.5±5.9	70.2	NR	NR	Vivid 7, GE; EchoPAC	LV, RV	LVGLS, RVGLS	7
Hajsadeghi *et al*[47]	Iran	2020	60	71.7	45.9±11.73	43.76±12.93	23.1±3.7	NR	NR	NR	NR	IE33, Phillips; Qlab	LV	LVGLS	6
Mercurio *et al*[48]	USA	2021	218	86.7	54.3±12.6	53.9±15.4	26.0±5.8	16.0±11.2	39.9	NR	NR	IE33, Philips; Qlab	LV	LVGLS	7
Demirci *et al*[49]	Turkey	2021	100	89.0	50.5±11.3	46.5±10.2	27.3±4.4	5.2±5.1	38.2	NR	NR	Epiq 7, Philips; Qlab	LV, RV	LVGLS, RVGLS	6
Sharifkazemi *et al*[50]	Iran	2022	74	67.6	46.97±1.15	44.43±11.93	24.7±3.6	9.62±6.02	NR	NR	NR	SC2000, Siemens; NR	LV, RV, LA, RA	LVGLS, RVGLS LAεR RAεR,	7

BMI, body mass index; FLS, free wall longitudinal strain; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LA, left atrium; LV, left ventricle; NOS, Newcastle-Ottawa quality assessment scale; NR, no report; RA, right atrium; RV, right ventricle; εCD, conduit strain; εCT, contractile strain; εR, reservoir strain.

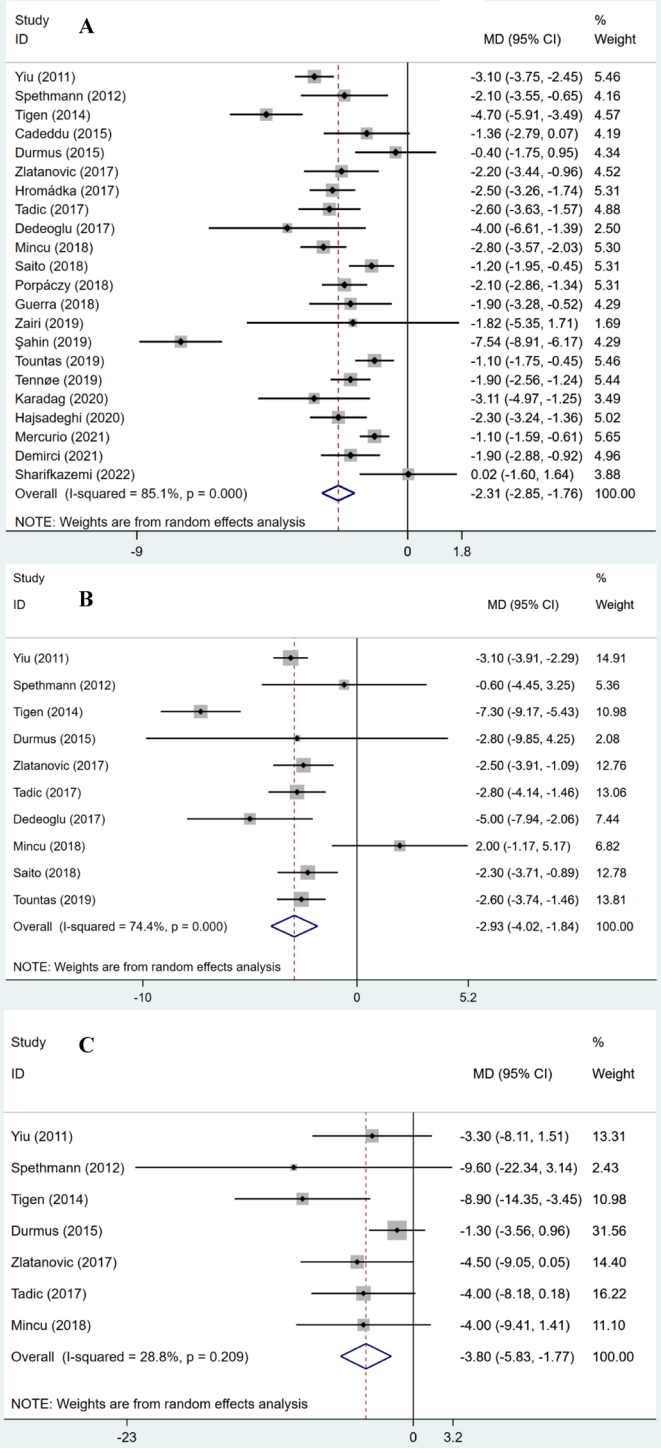

Figure 2 Forest plot for LVGLS (A), LVGCS (B) and LVGRS (C) analyses in SSc patients compared with healthy controls. LVGCS, left ventricular global circumferential strain; LVGLS, left ventricular global longitudinal strain; LVGRS, left ventricular global radial strain; MD, mean difference; SSc, systemic sclerosis.

RA strain assessed by STE

In total, three studies were included in the analysis of RA strain. Of these, all of the studies reported data on RAεR in 147 SSc patients and 102 healthy controls, and two studies reported data on RAεCD in 110 SSc patients and

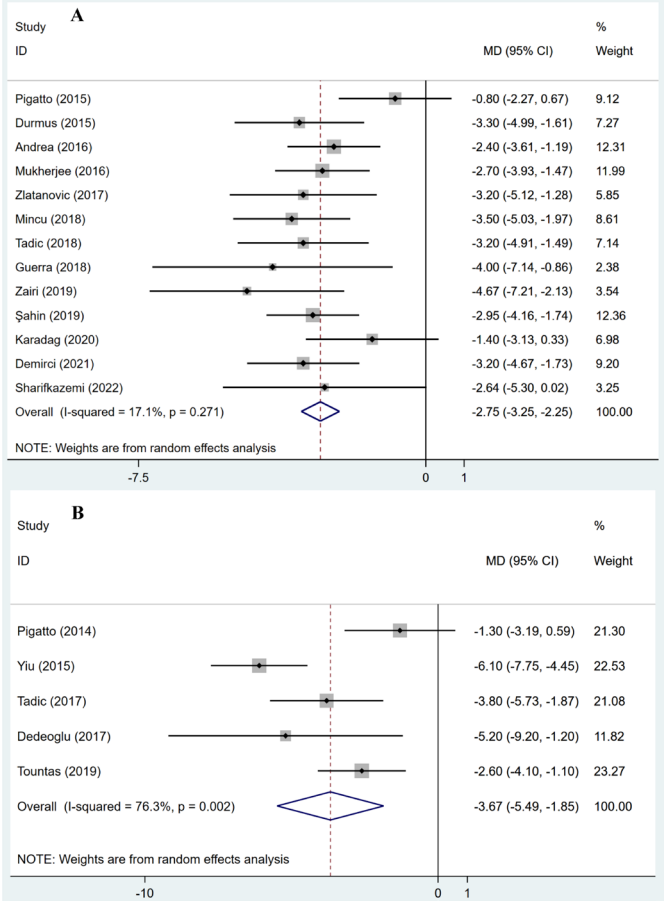

Figure 3 Forest plot for RVGLS (A) and RVFLS (B) analyses in SSc patients compared with healthy controls. MD, mean difference; RVFLS, right ventricular free wall longitudinal strain; RVGLS, right ventricular global longitudinal strain; SSc, systemic sclerosis.

65 healthy controls. RAεR was significantly lower in SSc patients than healthy controls (MD: −7.37, 95% CI −11.20 to −3.53, p=0.000; I^2=25.6%; figure 5A). RAεCD was also significantly lower in SSc patients than in healthy controls (MD: −5.44, 95% CI −9.15 to −1.73, p=0.004; I^2=66.0%; figure 5B).

Meta-regression analysis

Meta-regression models showed no significant association between the myocardial strain parameters, including LVGLS, LVRCS, LVGRS, RVGLS and RVFLS, and demographic variables including number of subjects, mean age, gender and BMI, as well as clinical data including duration of disease, diffused type ratio, skin score and Scl-70 positivity rate (see online supplemental file 1).

DISCUSSION

Detection and monitoring of myocardial impairment using appropriate and accurate diagnostic tools is an important aspect of managing patients with SSc. Efforts have been made in early targeted therapy for cardiac involvement in SSc patients.[15 16] Advanced imaging modalities such as cardiac MRI should only be used for

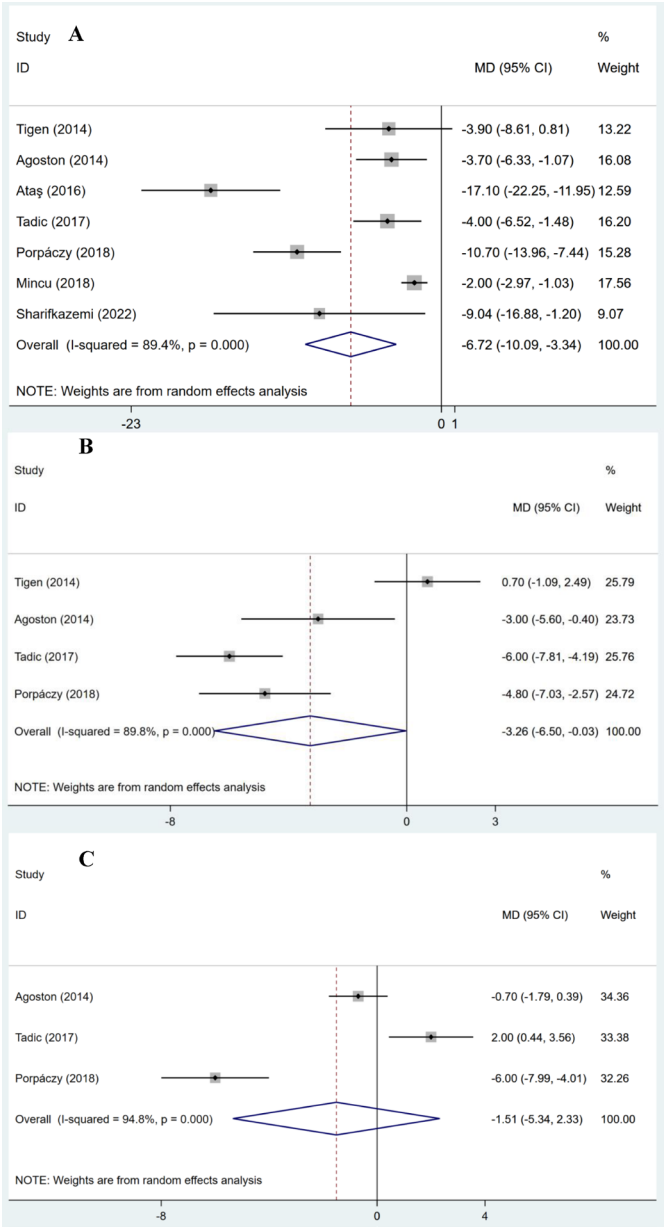

Figure 4 Forest plot for LAεR (A), LAεCD (B) and LAεCT (C) analyses in SSc patients compared with healthy controls. LAεCD, left atrial conduit strain; LAεCT, left atrial contractile strain; LAεR, left atrial reservoir strain; MD, mean difference; SSc, systemic sclerosis.

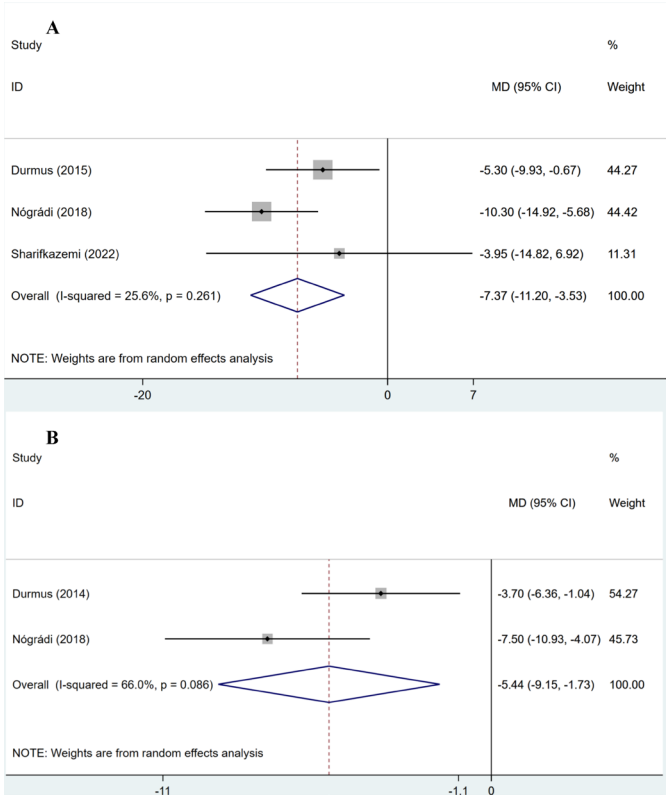

Figure 5 Forest plot for RAεR (A) and RAεCD (B) analyses in SSc patients compared with healthy controls. MD, mean difference; RAεCD, right atrial conduit strain; RAεR, right atrial reservoir strain; SSc, systemic sclerosis.

further evaluation of individuals with suspected cardiac involvement. Cardiac MRI can detect cardiac involvement in the early stages of SSc.[3 17] However, the costs and availability of cardiac MRI make it challenging for use as an initial screening test.[18 19] STE is a sensitive tool to assess cardiac involvement, which may also identify early signs of cardiac involvement in patients with SSc.[18] This is the first meta-analysis assessing cardiac involvement, including the ventricles and atria, in SSc patients using STE.

GLS, GCS and GRS are used as speckle tracking indexes to evaluate ventricles. They represent myocardial deformation in different motion directions. The present study showed that SSc patients exhibited reduced LVGLS, LVGCS and LVGRS compared with healthy controls, although some studies have had different conclusions. Cadeddu *et al*[20] have reported reduced LVGLS compared with controls only during exercise. Durmus *et al*[21] have found that LVGLS, LVGCS and LVGRS were similar between the two groups. Spethmann *et al*[22] have reported that only LVGLS was decreased butnot LVGCS and LVGRS. Yiu *et al*[23] have shown decreased levels of LVGLS and LVGCS but not of LVGRS. Zairi *et al*[24] have demonstrated altered levels of LVGLS with variation between individuals. The results of a single study with a relatively small sample size could be affected by many factors, including duration of disease and diseasetype ratio, which may lead to different strain changes. In addition, the pooled LVEF was decreased in SSc patients compared with the control group, despite being within the normal range, suggesting that its tendency to decrease likely occurred at time points following strain changes. Overall, the pooled data did not only confirm the usefulness of STE, but also indicated that cardiac involvement occurs in SSc patients. The decreased myocardial strain showed myocardial impairment in the LV.

Longitudinal strain was also used for RV analysis. Several studies have found no difference in results: Karadag *et al*[25] have shown preserved RV strain, and Pigatto *et al*[26] have demonstrated no difference between the two groups. The present meta-analysis confirmed the decreased pooled RV strain. Although no overt pulmonary hypertension

(sPAP >35 mm Hg) was noticed in SSc patients, sPAP was significantly elevated in patients compared with healthy controls. Thus, the pressure overload caused by pulmonary fibrosis complicated the assessment of intrinsic myocardial involvement.

Speckle tracking index for evaluation of atrium mechanics includes εR, εCD and εCT. Tigen *et al*[27] have reported that LA reservoir and conduit functions were similar between the groups, but other studies have reported one or more decreased LA mechanics indexes.[28–31] The present meta-analysis showed that εR and εCD were decreased, whereas no significant differences were found for εCT. For RA, εR was also confirmed to be decreased. Although only two studies[21 32] were included in the evaluation of εCD, they both showed impaired RA mechanics with decreased εCD. There are relatively few related studies performing a trial analysis, and further research is needed to support this conclusion.

Furthermore, although all included studies were of high quality, a significant heterogeneity was observed among most groups of studies reporting on different indexes. We found no demographic variables or clinical factors that were associated with STE parameters and could account for the heterogeneity. Some potential limitations of our study need to be discussed. First, the included studies were observational, which makes selection and observer bias unavoidable. Moreover, publication bias was also present for some indexes, although it did not change the result. Second, methods used to identify relevant studies were limited to publications in English language, potentially missing relevant published data. Third, the meta-regression analysis did not identify factors associated with heterogeneity, since there were characteristics and information data missing in each study. Lastly, significant heterogeneity can be partly explained by the differences in equipment and software used to detect myocardial strain.

CONCLUSION

Our meta-analysis showed that SSc patients have a lower strain than healthy controls for the majority of STE parameters in both the ventricle and atrium. These findings demonstrate the presence of subclinical cardiovascular abnormalities in SSc patients that can be detected by STE.

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