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Echocardiographic evaluation of left ventricular mechanics in sarcoidosis patients without overt heart disease: a systematic review and meta-analysis

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Abstract. *Background and aim:* During the last decade, a small number of studies have used speckle tracking echocardiography (STE) to investigate sarcoidosis effect on left ventricular (LV) mechanics in patients without overt heart disease. The present systematic review and meta-analysis has been primarily designed to summarize the main findings of these studies and to examine the overall influence of sarcoidosis on LV-global longitudinal strain (GLS) and left ventricular ejection fraction (LVEF). *Methods:* All echocardiographic studies assessing conventional echoDoppler parameters and myocardial strain indices in patients with extracardiac sarcoidosis (ECS) vs. healthy controls, selected from PubMed and EMBASE databases, were included. The risk of bias was assessed by using the National Institutes of Health (NIH) Quality Assessment of Case-Control Studies. Continuous data (LV-GLS and LVEF) were pooled as a standardized mean difference (SMD) comparing sarcoidosis group with healthy controls. The overall SMDs of LV-GLS and LVEF were calculated using the random-effect model. *Results:* The full-text of 13 studies with 785 ECS patients and 567 healthy controls were analyzed. Both average LVEF (60.5±6.6 vs 63.0±4.8%, P<0.001) and LV-GLS (-17.4±3.3 vs -21.0±2.7%, P<0.001) were significantly lower in ECS patients than controls. However, sarcoidosis showed a significantly larger effect on LV-GLS (SMD: -1.26, 95%CI -1.61,-0.91, P<0.001) rather than on LVEF (SMD: -0.51, 95%CI -0.83,-0.20, P=0.001). Substantial heterogeneity was found for the studies that assessed LV-GLS (I^2=86.4%) and LVEF (I^2=85.3%). Egger's test gave a P-value of 0.24 for LV-GLS and 0.32 for LVEF assessment, indicating no publication bias. On meta-regression analysis, none of the moderators was significantly associated with effect modification for both LV-GLS and LVEF (all P <0.05). *Conclusions:* In patients without overt heart disease, the effect of sarcoidosis on LV-GLS is significantly greater than on LVEF. STE analysis should be implemented in clinical practice for the early detection of myocardial involvement in ECS patients.

Key words: extracardiac sarcoidosis, left ventricular mechanics, global longitudinal strain, left ventricular ejection fraction, meta-analysis

Introduction

Sarcoidosis is a systemic inflammatory disease of unknown etiology characterized by the formation of non-caseating granulomas in various organs, leading to significant morbidity (1). Even if the most common manifestation of sarcoidosis is pulmonary and mediastinal involvement, reported in 80% of

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the cases, the nonfatty granuloma accumulation may also involve skin, parotid glands, spleen, liver, central nervous system, bone, eye, lymph nodes, and even the heart (2).

In patients with systemic sarcoidosis, the prevalence of cardiac involvement may range from 3.7% to 54.9%, depending on different studied populations (3,4). Approximately one-third of sarcoidosis patients with cardiac involvement may be totally asymptomatic, whereas only five percent of patients may have clinically evident cardiac sarcoidosis (CS) (5). Even though the clinical manifestation of CS is highly variable, conduction abnormalities, arrhythmias, and heart failure are the most common presentation of CS (6). Considering that cardiac involvement is one of the leading causes of mortality in sarcoidosis (7), it is clinically important to early detect the myocardial infiltration by the inflammatory granulomatous lesions.

Suggested routine screening for CS include clinical history, physical examination and 12-lead electrocardiogram (ECG) (8). However, this approach has several limitations due to the low specificity of abnormal ECG findings for diagnosing CS (9).

Late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) and 18F-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) can diagnose CS with greater specificity and sensitivity (10,11). Despite the advantages offered by CMR and FDG-PET for early detection of CS, these imaging modalities have a number of limitations, making them inappropriate to the systematic screening of sarcoidosis patients; notably, CMR has limitations in terms of cost and availability and may not be suitable for patients with obesity, renal impairment or cardiac devices, whereas PET involves ionizing radiation exposure. Also endomyocardial biopsy is not suitable as screening tool for CS, due to its invasiveness and low sensitivity for the disease, characterized by a patchy and focal distribution of sarcoid granulomas (8).

Conversely, conventional two-dimensional (2D) transthoracic echocardiography (TTE) is currently suggested as a first-line screening tool, along with ECG and clinical history, for the detection of cardiac involvement in patients with biopsy-proven extracardiac sarcoidosis (ECS) (12). Undoubtedly, TTE is widely available, has a noninvasive nature and lower costs than both CMR and FDG-PET. Nevertheless, it is noteworhty that conventional parameters of ventricular systolic and diastolic function have suboptimal sensitivity and specificity, especially in early phases of CS (13).

Recent advances in cardiac imaging have led to the development of 2D speckle tracking echocardiography (STE), an angle-independent technique, which provides an accurate definition of both global and regional myocardial systolic function (14). Differently from 2D-TTE, 2D-STE could detect alterations in regional myocardial deformation, even in sarcoidosis patients with normal conventional parameters of systolic function (15).

During the last decade, a small number of echocardiographic studies have evaluated patients with ECS without overt heart disease, by using conventional 2D-TTE implemented with 2D-STE analysis of myocardial strain parameters, in order to early detect a subclinical myocardial dysfunction. The latter is commonly defined as the reduction of left ventricular (LV) global longitudinal strain (GLS), which is the most commonly used STE-derived index of myocardial contractility, to a magnitude less negative than -20%, in the presence of preserved left ventricular ejection fraction (LVEF) (≥55%) (16).

The present systematic review and meta-analysis has been primarily designed to summarize the main findings of these studies and to examine the overall influence of sarcoidosis on the two main indices of LV mechanics, i.e. LVEF and LV-GLS, assessed by 2D-TTE and 2D-STE respectively. Pathophysiological mechanisms underpinning the subclinical impairment of myocardial strain parameters detected in sarcoidosis patients will be discussed as well.

Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (17), and was registered in PROSPERO database (CRD42024526820).

Search strategy

A comprehensive search of all articles assessing conventional echoDoppler indices and myocardial strain parameters in patients with ECS was carried out by two independent reviewers (A.S. and V.F.) through March 2024, by using Medline and EMBASE databases. The search strategy included the following

terms: "extracardiac sarcoidosis" AND "cardiac function" AND "left ventricular ejection fraction" OR "extracardiac sarcoidosis" AND "subclinical myocardial dysfunction" AND "left ventricular mechanics" AND "global longitudinal strain". Search was limited to full-text articles published in the English language. There was no limitation of time period.

Eligibility criteria

Echocardiographic studies evaluating conventional echoDoppler indices and myocardial strain parameters in patients with ECS in comparison to healthy matched controls were included. Conversely, non-echocardiographic studies, echocardiographic studies without concomitant assessment of LV-GLS and LVEF, studies focused on advanced CS, observational studies conducted on sarcoidosis patients without matched controls, animal studies, duplicate articles, case reports, conference presentations, reviews, editorials, letters without data, and abstracts, were excluded.

Study selection and data extraction

Two reviewers (A.S. and V.F.) screened the databases according to the inclusion criteria and performed data extraction independently. A third author (G.L.N.) checked the extracted data for accuracy and resolved possible discrepancies between reviewers.

Risk of bias assessment

Articles included in this systematic review and meta-analysis were assessed for risk of bias (RoB) using the National Institutes of Health (NIH) Quality Assessment of Case-Control Studies (18). All the studies were assigned a "yes", "no", or "other" to each of the 12 criteria outlined in the appraisal tool. Then, by considering each criterion, the investigators evaluated the overall quality of the study and assigned an overall "good" (met 9–12 criteria), "fair" (met 5–8 criteria) or "poor" (met 0–4 criteria) rating to each study. The quality rating was independently estimated by two authors (A.S. and V.F.). Disagreement was resolved by consensus.

The PRISMA flow diagram used for identifying the included studies is depicted in Figure 1.

Statistical analysis

Continuous data (LV-GLS and LVEF) were pooled as a standardized mean difference (SMD)

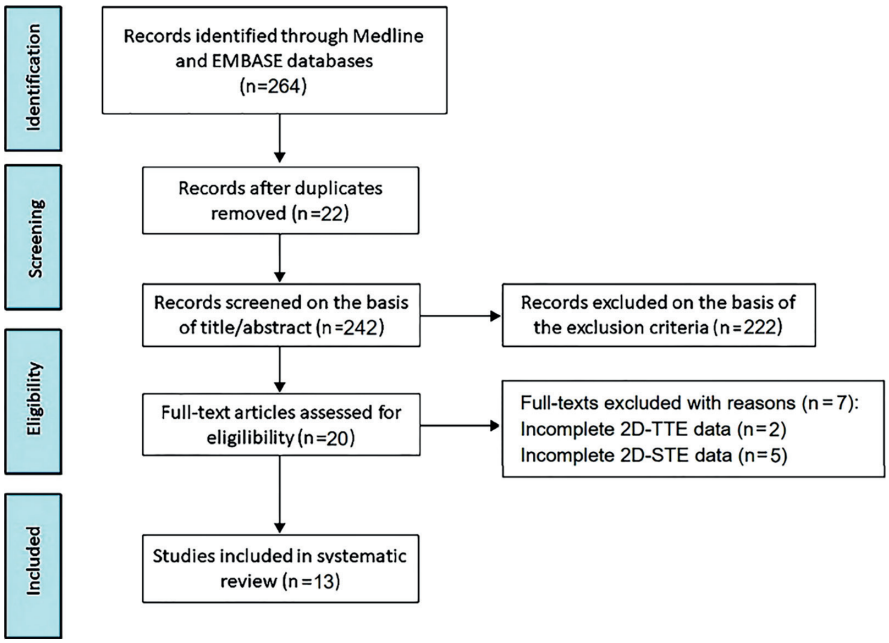

Figure 1. Flow diagram used for identifying the included studies. 2D, two-dimensional; STE, speckle tracking echocardiography; TTE, transthoracic echocardiography.

comparing sarcoidosis group with healthy controls. The overall SMDs of LV-GLS and LVEF were calculated using the random-effect model, due to the high statistical heterogeneity among the included studies, with regard to study design, sample size, demographics, disease duration and the type of ultrasound machine employed for LV-GLS and LVEF assessment. The I-squared statistic (I^2) was used to quantify the degree of statistical heterogeneity among studies. Begg's funnel plots and the Egger's test were employed to assess potential publication bias for both LV-GLS and LVEF assessment. Finally, meta-regression was performed to evaluate the effect modification on both LV-GLS and LVEF by several moderators (potential confounders), such as age, male sex, smoking habit, arterial hypertension, type 2 diabetes, dyslipidemia, disease duration and finally the type of ultrasound machine employed for strain echocardiographic imaging. The 95% Confidence intervals (CIs) was calculated and two-tailed P values below 0.05 was considered to be statistically significant. Statistical analysis was performed by using Comprehensive Meta-Analysis version 3.0 (Biostat, Englewood, NJ, USA).

Results

The initial search yielded a total of 264 studies. Of those, 22 (8.3%) were removed as duplicates. After screening titles and abstracts, a further 222 studies (84.1%) were removed on the basis of exclusion criteria. The evaluation of the full text of the remaining 20 studies (7.6%) resulted in further 7 exclusions (2.6%). A total of 13 studies (4.9%) (19-31) were thus included in this systematic review, totalling 785 ECS patients and 567 healthy controls.

Table 1 summarizes the main findings of the 13 studies included in the present systematic review and meta-analysis. The included studies were published between 2014 and 2020. Four studies were performed in Turkey, three in the USA, two in Japan, one in the Netherlands, France, Greece and Iran. The mean age of sarcoidosis patients among the included studies was 52.1 yrs (range 40.4-65 yrs), with a 61.9% of females (range 21.7-82.1%). The average heart rate at echocardiographic assessment in sarcoidosis individuals was 76 bpm (range 73-81 bpm), while the resting mean systolic blood pressure was 121 mmHg (range 114-127 mmHg). The prevalence rates of cardiovascular risk factors were as follows: hypertension, 31.1%; type 2 diabetes mellitus, 18.8%; smoking, 28.1%; dyslipidemia, 27.2%. The mean disease duration was 4.5 yrs; the mean prevalence of lung involvement was 73.1% (range 15-100%). Concerning the methodological assessment of LV-GLS, seven studies (53.8% of total) used a General Electric (GE) ultrasound machine, four studies (30.8% of total) used a Philips software, one study (7.7% of total) used an EchoInsight software and the remaining one study (7.7%) used a TomTec imaging system. Among the included studies, seven (53.8% of total) were conducted with a prospective design, whereas the remaining 6 studies (46.2% of total) used a retrospective design.

Transthoracic echocardiography findings

The included studies assessed the following conventional echoDoppler parameters in both sarcoidosis patients and matched healthy controls: 1) interventricular septum (IVS) thickness, LV end-diastolic diameter, LV end-diastolic volume and left ventricular mass index (LVMi), as indices of LV geometry; 2) LVEF, as index of LV systolic function; 3) the ratio of peak early to late diastolic transmitral filling velocity (E/A ratio) assessed by pulsed Doppler and the ratio between the E wave to the early diastolic mitral annulus velocity (e') measured by tissue Doppler imaging (the E/e' ratio), as indices of LV diastolic function and LV filling pressures, respectively; 4) left atrial (LA) antero-posterior (A-P) diameter and left atrial volume index (LAVi), as indices of LA size; 5) tricuspid annular plane systolic excursion (TAPSE), as index of right ventricular (RV) systolic function; 6) finally, systolic pulmonary artery pressure (sPAP), as index of pulmonary hemodynamics.

Table 2 summarizes all conventional and STE-derived echocardiographic parameters measured in sarcoidosis individuals and matched healthy controls. The most commonly assessed traditional echocardiographic indices were LVEF (calculated in all studies), the E/A ratio and the E/e' ratio (measured in 76.9% of the studies) and IVS thickness (assessed in 53.8% of the studies). The remaining echocardiograhic indices were determined in a reduced number of studies ranging from 15.4% and 46.1% of total.

Table 1. Summary of the included studies. ECG, electrocardiogram; ECS, extra-cardiac sarcoidosis; GCS, global circumferential strain; GE, General Electric; GLS, global longitudinal strain; GRS, global radial strain; HR, heart rate; LA, left atrial; LAD, left atrial diameter; LASr, left atrial strain during the reservoir phase; LAV, left atrial volume; LAVi, left atrial volume indexed; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; Pts, patients; RASr, right atrial strain during the reservoir phase; RV, right ventricular; RWT, relative wall thickness; sPAP, systolic pulmonary artery pressure; STE, speckle tracking echocardiography; TACT, total atrial conduction time; TAPSE, tricuspid annular plane systolic excursion; TTE, transthoracic echocardiography.

Study name and Country	Population	ECS pts' age (yrs)	ECS females (%)	Study design	Ultrasound system	Main ECG, TTE and STE findings in ECS pts vs controls
Kul S et al. 2014, Turkey	ECS = 40 Controls = 26	46 ± 9.7	28 (70)	Prospective	Philips	↑ Ventricular/atrial arrhythmias ↔ E/A, LVEF, TAPSE, sPAP ↓ LV-GLS, LV-GCS
Orii M et al. 2015, Japan	ECS = 45 Controls = 10	64 ± 9	28 (62)	Retrospective	GE	↔ QRS duration, HR ↔ LVMi, LAV, LVEF ↓ LV-GLS, LV-GCS; ↔ LV-GRS
Tigen K et al. 2015, Turkey	ECS = 40 Controls = 20	46.4 ± 10.5	34 (85)	Prospective	GE	↑ LAD, ↓ E wave ↔ E/e', LVEF ↓ LV-GLS, LV-GCS, LV-GRS, LASr ↓ RV-GLS, RASr
Joyce E et al. 2016, The Netherlands	ECS = 100 Controls = 100	55 ± 13	52 (52)	Prospective	GE	↔ RWT, LAVi, E/A, E/e' ↓ LVEF, TAPSE, ↑ sPAP ↓ LV-GLS
Murtagh G et al. 2016, USA	ECS = 31 Controls = 31	58.8 ± 11.3	21 (68)	Retrospective	EchoInsight	↔ LAVi, E/e', LVEF ↓ E/A, ↑ sPAP ↓ LV-GLS
Değirmenci H et al. 2017, Turkey	ECS = 50 Controls = 50	40.4 ± 11	34 (68)	Prospective	GE	↑ IVS thickness ↓ E/A, LVEF ↓ LV-GLS, LASr, ↑ TACT
Schouver ED et al. 2017, France	ECS = 35 Controls = 35	47.9 ± 14.8	22 (62.9)	Prospective	TomTec	↔ E/A, LVEF, sPAP ↓ LV-GLS, ↔ LV-GCS
Chen J et al. 2018, USA	ECS = 54 Controls = 54	51.3 ± 11.2	22 (40.7)	Retrospective	GE	↔ E/A, E/e', LVEF ↓ LV-GLS
Felekos I et al. 2018, Greece	ECS = 117 Controls = 45	46.5 ± 10.5	74 (63.3)	Retrospective	Philips	↔ E/A, E/e', LVEF, sPAP ↓ LV-GLS
Di Stefano C et al. 2020, USA	ECS = 23 Controls = 97	52.9 ± 10	5 (21.7)	Retrospective	GE	↓ E/A, ↑E/e', ↓ LVEF ↓ LV-GLS, LV-GRS, ↔ LV-GCS ↓ RV-GLS
Bayat F et al. 2020, Iran	ECS = 55 Controls = 21	50.8 ± 8.8	34 (61.8)	Retrospective	Philips	↔ E/A, LVEF, sPAP ↓ LV-GLS, LV-GCS
Kaptan Ozen D et al. 2020, Turkey	ECS = 56 Controls = 26	52.5 ± 10.7	46 (82.1)	Prospective	Philips	↔ LVMi, LVEF, E/e' ↓ E/A, TAPSE, ↑ sPAP ↓ LV-GLS, LV-GCS, LASr ↓ RV-GLS, RASr
Kusunose K et al. 2020, Japan	ECS = 139 Controls = 52	65 ± 12	94 (67.6)	Prospective	GE	↔ LVMi, LVEF, TAPSE ↓ E/A, ↑ E/e' ↓ LV-GLS, RV-GLS

Table 2. Conventional and functional echocardiographic parameters measured in sarcoidosis patients and healthy controls by the included studies. Data are expressed as mean ± SD (ME at 95%CI). Significant P values are in bold. A-P, antero-posterior; CI, confidence intervals; ECS, extra-cardiac sarcoidosis; EDD, end-diastolic diameter; EDV, end-diastolic volume; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; IVS, interventricular septum; LASr, left atrial strain during the reservoir phase; LAVi, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; ME, margin of error; RASr, right atrial strain during the reservoir phase; RV, right ventricular; SD, standard deviation; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; STE, speckle tracking echocardiography.

Echocardiographic parameters	N° of studies (%)	ECS patients	Controls	P value
IVS thickness (mm)	7 (53.8)	9.4 ± 1.5 (0.16-0.72)	9.0 ± 1.2 (0.29-0.62)	**<0.001**
LV-EDD (mm)	6 (46.1)	46.3 ± 4.8 (0.51-1.87)	46.0 ± 4.2 (0.70-1.92)	0.40
LV-EDV (ml)	5 (38.5)	91.3 ± 29.1 (5.30-9.33)	89.2 ± 21.6 (3.92-10.4)	0.33
LVMi (g/m^2)	3 (23.1)	83.8 ± 21.7 (3.61-9.36)	76.6 ± 15.5 (2.71-12.4)	**<0.001**
LVEF (%)	13 (100)	60.5 ± 6.6 (0.72-4.04)	63.0 ± 4.8 (0.67-2.84)	**<0.001**
E/A ratio	10 (76.9)	1.10 ± 0.64 (0.04-0.31)	1.21 ± 0.48 (0.08-0.22)	**0.001**
E/e' ratio	10 (76.9)	9.6 ± 4.4 (0.65-2.29)	8.0 ± 2.4 (0.38-1.02)	**<0.001**
LA A-P diameter (mm)	5 (38.5)	33.8 ± 4.2 (0.78-1.86)	32.5 ± 3.2 (0.72-1.31)	**<0.001**
LAVi (ml/m^2)	2 (15.4)	26.5 ± 9.5 (1.37-4.22)	28.0 ± 9.0 (1.57-3.52)	0.19
TAPSE (mm)	4 (30.8)	21.7 ± 3.9 (0.50-1.55)	23.4 ± 3.9 (0.73-1.38)	**<0.001**
sPAP (mmHg)	6 (46.1)	28.0 ± 11.7 (0.92-7.04)	21.8 ± 6.1 (0.96-2.62)	**<0.001**
STE-derived LV-GLS (%)	13 (100)	-17.4 ± 3.3 (0.39-1.36)	-21.0 ± 2.7 (0.39-3.10)	**<0.001**
STE-derived LV-GCS (%)	7 (53.8)	-19.9 ± 4.6 (1.00-1.92)	-24.5 ± 4.0 (0.50-4.34)	**<0.001**
STE-derived LV-GRS (%)	3 (23.1)	41.7 ± 14.7 (3.41-5.84)	46.6 ± 12.0 (2.41-11.2)	**0.005**
STE-derived LASr (%)	3 (23.1)	31.2 ± 7.3 (1.00-2.88)	39.8 ± 8.3 (1.14-4.82)	**<0.001**
STE-derived RV-GLS (%)	4 (30.8)	-20.4 ± 5.0 (0.71-1.92)	-26.4 ± 5.0 (0.80-3.20)	**<0.001**
STE-derived RASr (%)	2 (15.4)	31.3 ± 9.7 (2.67-2.85)	41.4 ± 9.6 (3.23-4.73)	**<0.001**

Analysis of LV morphology and structure revealed that, compared to controls, sarcoidosis patients had significantly greater IVS thickness, LVMi and LA A-P diameter. Despite preserved, LVEF was significantly lower in ECS patients than controls. With regard to LV diastolic function, the E/A ratio was significantly decreased, whereas the LV filling pressures, as noninvasively estimated by the E/e' ratio, were significantly increased in sarcoidosis patients than controls. RV systolic function, assessed by TAPSE, was significantly impaired in ECS patients compared to controls. Concerning pulmonary hemodynamics, as expected, sPAP was significantly higher in sarcoidosis patients than controls.

Echocardiographic deformation imaging findings

Analysis of LV deformation indices showed that LV-GLS was significantly reduced in ECS patients in comparison to controls and the accepted reference values (more negative than -20%) (16).

More than half of the studies (53.8% of total) measured not only the LV-GLS, but also the LV-global circumferential strain (GCS), whereas approximately one-fourth of the studies (23.1% of total) calculated the LV-global radial strain (GRS) also. In addition, LA strain during the reservoir phase (LASr) was estimated in 3 studies (23.1% of total). Finally, right ventricular (RV)-GLS and right atrial strain during the reservoir phase (RASr) were measured in 30.8% and 15.4% of the included studies, respectively. As reported in Table 2, all biventricular and biatrial myocardial strain parameters were significantly impaired in sarcoidosis patients than controls.

Three studies (23.1% of total) analyzed ECG findings in ECS patients vs. matched healthy controls. In two of them, sarcoidosis patients were found with significantly increased prevalence of ventricular and/or atrial arrhythmias (19) and with a prolonged total atrial conduction time (TACT) (24); conversely, Orii M et al. (20) found no statistically

significant ECG differences between the two groups of individuals.

Five studies (38.5%) evaluated ECS patients by using both echocardiography and gadolinium-enhanced CMR. The Authors demonstrated that the reduction in LV-GLS magnitude was linearly correlated with the extent of myocardial damage (both active inflammation and scars or fibrosis) identified by LGE in the same region.

Six studies (46.1% of total) provided a prognostic risk stratification of ECS patients over a mid-term follow-up period (median follow-up was 29.4 months, range 8.3-57.1 months). The results of these studies revealed that an impaired LV-GLS was independently associated with all-cause mortality, hospitalization for new onset heart failure, new onset arrhythmias, necessity for cardiac device implantation and future development of CS, over the follow-up period.

Risk of bias assessment

With regard to the RoB, the NIH quality rating was estimated as good for five studies and fair for eight studies (Table 3). Cohen's Kappa coefficient for the agreement between the reviewers in the RoB assessment was interpreted as a substantial agreement, $\kappa = 0.76$.

Influence of sarcoidosis on LV-GLS

Forest plot showing the effect of sarcoidosis on LV-GLS is depicted in Figure 2. Overall, a large SMD value (-1.26, 95%CI -1.61,-0.91, P <0.001)

Table 3. Quality assessment of the included studies. Q1: Was the research question or objective in this paper clearly stated and appropriate?, Q2: Was the study population clearly specified and defined?, Q3: Did the authors include a sample size justification?, Q4: Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?, Q5: Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?, Q6: Were the cases clearly defined and differentiated from controls? Q7: If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?, Q8: Was there use of concurrent controls?, Q9: Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?, Q10: Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?, Q11: Were the assessors of exposure/risk blinded to the case or control status of participants?, Q12: Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?, Good: Met 9–12 criteria, Fair: Met 5–8 criteria, Poor: Met 0–4 criteria. NIH = National Institutes of Health, NS = not specified.

Study name	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Quality (Total Quality Score)
Kul S et al. 2014	Yes	Yes	No	NS	Yes	Yes	NS	Yes	Yes	Yes	NS	No	7 (Fair)
Orii M et al. 2015	Yes	Yes	No	Yes	Yes	Yes	NS	Yes	Yes	Yes	Yes	No	9 (Good)
Tigen K et al. 2015	Yes	Yes	No	NS	Yes	Yes	NS	Yes	Yes	Yes	NS	No	7 (Fair)
Joyce E et al. 2016	Yes	Yes	No	NS	Yes	Yes	Yes	Yes	Yes	Yes	NS	No	8 (Fair)
Murtagh G et al. 2016	Yes	Yes	No	NS	Yes	Yes	NS	Yes	Yes	Yes	Yes	No	8 (Fair)
Değirmenci H et al. 2017	Yes	Yes	No	NS	Yes	Yes	NS	NS	Yes	Yes	Yes	Yes	8 (Fair)
Schouver ED et al. 2017	Yes	Yes	No	Yes	Yes	Yes	NS	Yes	Yes	Yes	Yes	No	9 (Good)
Chen J et al. 2018	Yes	Yes	No	Yes	Yes	Yes	NS	Yes	Yes	Yes	Yes	Yes	10 (Good)
Felekos I et al. 2018	Yes	Yes	No	NS	Yes	Yes	NS	Yes	Yes	Yes	NS	No	7 (Fair)
Di Stefano C et al. 2020	Yes	Yes	No	Yes	Yes	Yes	NS	Yes	Yes	Yes	NS	Yes	9 (Good)
Bayat F et al. 2020	Yes	Yes	No	Yes	Yes	Yes	No	NS	Yes	Yes	Yes	No	8 (Fair)
Kaptan Ozen D et al. 2020	Yes	Yes	No	NS	Yes	Yes	NS	Yes	Yes	Yes	NS	No	7 (Fair)
Kusunose K et al. 2020	Yes	Yes	No	Yes	Yes	Yes	No	NS	Yes	Yes	Yes	Yes	9 (Good)

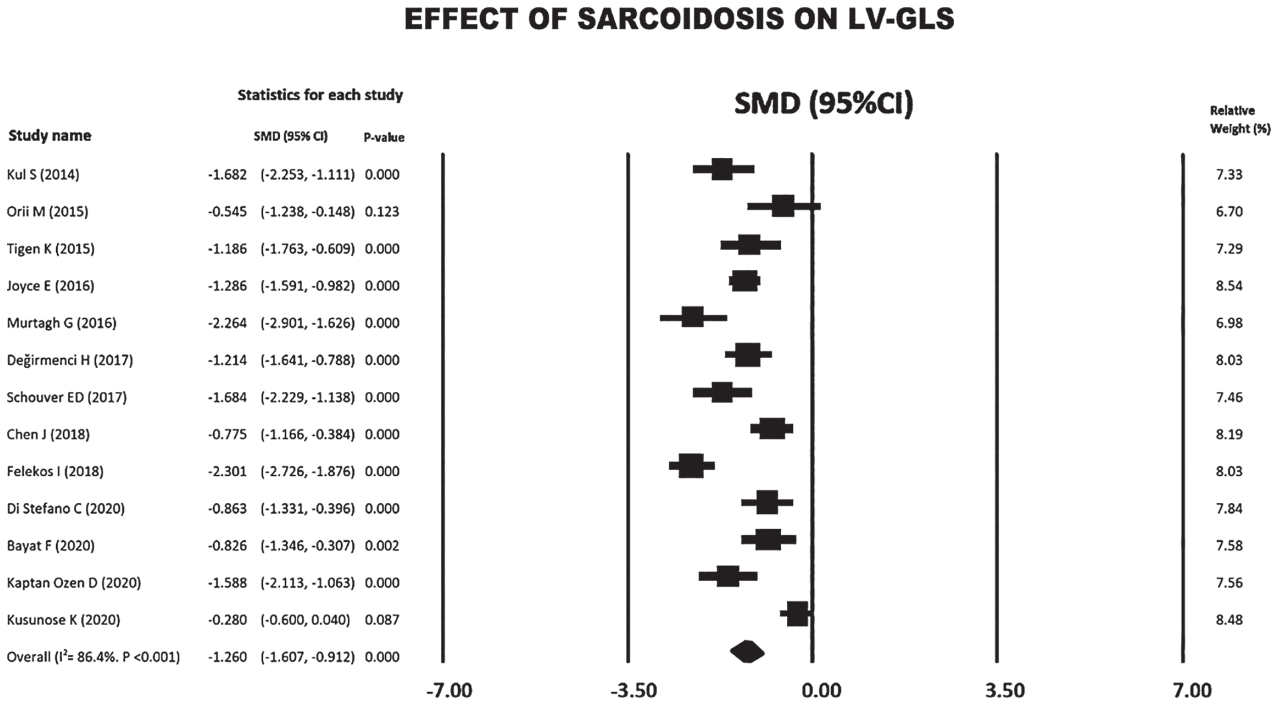

Figure 2. Forest plots showing the influence of sarcoidosis on LV-GLS in ECS patients without overt heart disease. CI, confidence intervals; ECS, extracardiac sarcoidosis; GLS, global longitudinal strain; LV, left ventricular; SMD, standardized mean difference.

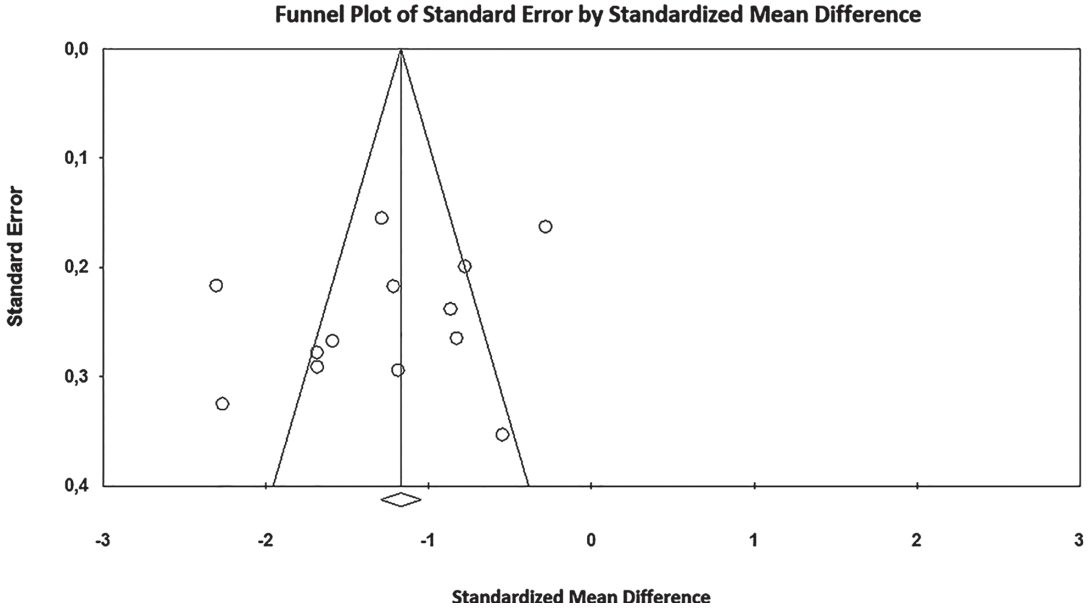

Figure 3. Begg's funnel plot for the detection of publication bias with regard to LV-GLS studies.

was obtained. Substantial heterogeneity was detected for those studies evaluating the influence of sarcoidosis on LV-GLS, with an overall I^2 statistic value of 86.4% (P <0.001).

Egger's test for a regression intercept gave a P-value of 0.24, indicating no publication bias. Begg's funnel plot for the detection of publication bias is illustrated in Figure 3.

Table 4. Results of meta-regression analysis of sarcoidosis effect on LV-GLS. GE, General Electric; GLS, global longitudinal strain; LV, left ventricular.

Moderators	Coefficient	Standard error	95%CI lower	95%CI upper	P-value
Age (yrs)	0,0117	0,0454	-0,0773	0,1007	0,797
%Males	0,0063	0,0151	-0,0233	0,0359	0,675
%Hypertension	-0,0133	0,0215	-0,0555	0,0288	0,535
%Type 2 diabetes	0,0387	0,0372	-0,0343	0,1117	0,299
%Smokers	0,0093	0,031	-0,0515	0,0701	0,764
%Dyslipidemia	-0,0802	0,084	-0,2447	0,0844	0,339
Disease duration (yrs)	0,1304	0,2146	-0,2902	0,5511	0,543
Ultrasound system: Non-GE	-0,3316	0,4643	-1,2416	0,5783	0,475

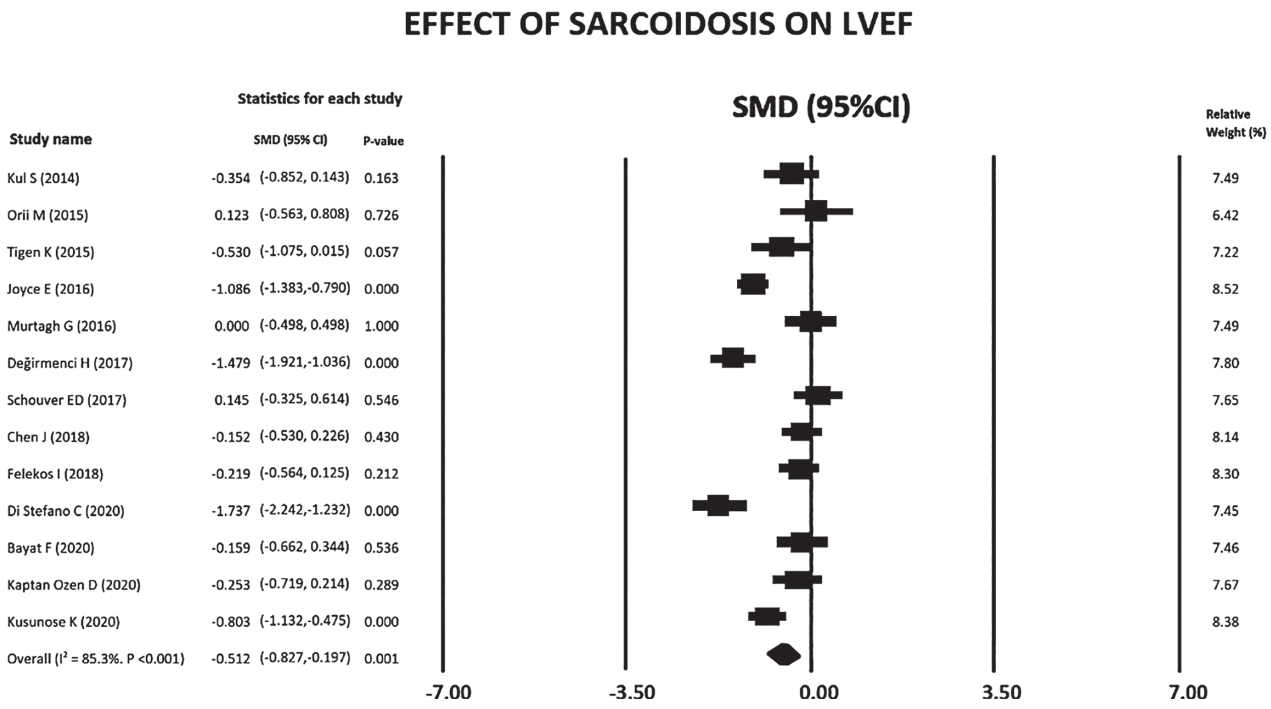

Figure 4. Forest plots showing the influence of sarcoidosis on LVEF in ECS patients without overt heart disease. CI, confidence intervals; ECS, extracardiac sarcoidosis; GLS, global longitudinal strain; LV, left ventricular; SMD, standardized mean difference.

On meta-regression analysis, none of the moderators was significantly associated with effect modification (all P <0.05) (Table 4).

Influence of sarcoidosis on LVEF

Forest plot showing the influence of sarcoidosis on LVEF is illustrated in Figure 4. Overall, SMD value (-0.51, 95%CI -0.83,-0.20, P = 0.001) was small-to-medium. Substantial heterogeneity was detected for those studies analyzing the influence of sarcoidosis on LVEF, with an overall I^2 statistic value of 85.3% (P <0.001).

Egger's test for a regression intercept gave a P-value of 0.32, indicating no publication bias. Begg's funnel plot for the detection of publication bias is illustrated in Figure 5.

On meta-regression analysis, none of the moderators was significantly associated with effect modification (all P <0.05) (Table 5).

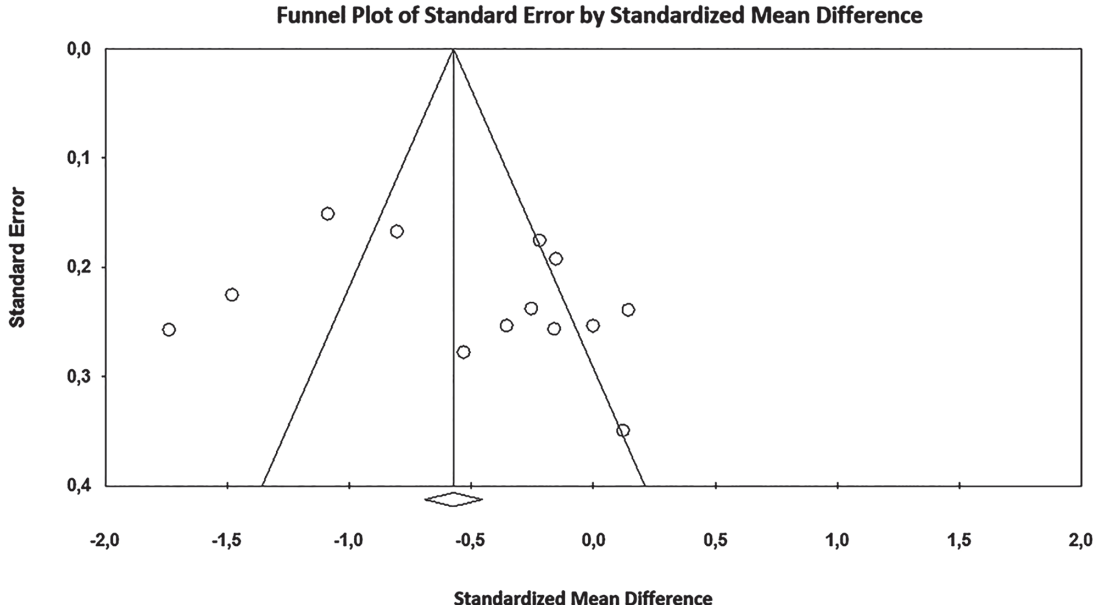

Figure 5. Begg's funnel plot for the detection of publication bias with regard to LVEF studies.

Table 5. Results of meta-regression analysis of sarcoidosis effect on LVEF. GE, General Electric; LVEF, left ventricular ejection fraction.

Moderators	Coefficient	Standard error	95%CI lower	95%CI upper	P-value
Age (yrs)	0,0581	0,1261	-0,1891	0,3053	0,645
%Males	-0,0205	0,0265	-0,0724	0,0314	0,439
%Hypertension	0,0095	0,0139	-0,0178	0,0368	0,496
%Type 2 diabetes	-0,0186	0,032	-0,0813	0,0441	0,562
%Smokers	0,0354	0,0612	-0,0847	0,1554	0,564
%Dyslipidemia	-0,0202	0,0746	-0,1664	0,126	0,786
Disease duration (yrs)	0,0939	0,2376	-0,3718	0,5597	0,693
Ultrasound system: Non-GE	0,9558	1,4164	-1,8204	3,7319	0,500

Discussion

Main findings of the present systematic review and meta-analysis

The present systematic review and meta-analysis included 13 studies analyzing sarcoidosis patients with high prevalence of pulmonary involvement and without overt structural heart disease. Sarcoidosis patients were predominantly females, with a low-to-moderate prevalence of the most common cardiovascular risk factors. Main conventional 2D-TTE findings in ECS patients were the following: 1) normal cardiac chambers cavity sizes; 2) normal biventricular systolic function, as assessed by LVEF and TAPSE respectively; 3) a first degree of diastolic dysfunction; 4) normal pulmonary hemodynamics. On the other hand, 2D-STE analysis showed significant impairment in biventricular and biatrial myocardial strain parameters in ECS patients compared to healthy controls. As expected, the effect of sarcoidosis on LV-GLS was significantly greater than on LVEF. The reduction in LV-GLS magnitude detected in sarcoidosis patients was not influenced by a number of potential confounders, such as age, male sex, smoking habit, arterial hypertension, type 2 diabetes, dyslipidemia, disease duration and finally the type of ultrasound machine employed for

strain echocardiographic imaging. The studies that used both echocardiography and CMR revealed that LV-GLS impairment was strongly correlated with the extent of myocardial inflammation and/or fibrosis identified by LGE. Finally, LV-GLS was independently associated with all-cause mortality, hospitalization for new onset heart failure, new onset arrhythmias, cardiac device implantation and subsequent development of CS, over a mid-term follow-up period.

Pathophysiological mechanisms underpinning LV-GLS impairment in sarcoidosis patients

CS primarily affects the myocardium; pericardial and endocardial involvement usually reflect the direct extension of myocardial disease (32). Main histopathologic features of CS include: increased fibrotic activity, lymphocyte infiltration, interstitial edema, and noncaseating granulomas with a typical localized distribution within the myocardium (33). The areas involved by granulomatous inflammation in descending order of frequency are the LV free wall, IVS, papillary muscles, right ventricle and atria (34).

LV-GLS impairment is primarily caused by the preferential localization of inflammatory granulomas in the midmyocardial layer of the LV wall, responsible for longitudinal deformation (35). The damage due to the myocardial inflammatory granulomas causes fibrotic changes and scar formation in the myocardium, thus inducing a decrease in LV mechanics. Given that early myocardial involvement is usually patchy and localized, an initial contractile dysfunction may be detected as reduced LV-GLS, rather than LVEF impairment. For this reason, the overall effect of sarcoidosis on LVEF is small-to-medium and subclinical LV systolic dysfunction is undetectable with conventional echocardiographic measures. A transmural myocardial damage may be responsible for the concomitant LV-GCS and LV-GRS impairment detected in sarcoidosis patients.

Several mechanisms may contribute to RV myocardial dysfunction in sarcoidosis patients. RV-GLS impairment may be caused by: 1) RV free wall myocardial infiltration; 2) increased sPAP, due to the concomitant pulmonary involvement; 3) prolonged exposure to chronically increased LV filling pressures, secondary to LV diastolic dysfunction (21).

Finally, the concomitant reduction in bi-atrial reservoir function demonstrated in ECS patients has been attributed to direct atrial involvement or prolonged exposure to chronically increased LV filling pressures (36,37).

Given that the ECS patients examined in the included studies were predominantly middle-aged females, with a low-to-moderate prevalence of the most common cardiovascular risk factors, it is reasonable to exclude that a concomitant coronary artery disease could have contributed to LV-GLS impairment in these patients. Moreover, the ECS patients included were not affected by concomitant mitral valvulopathies, particularly mitral valve prolapse, nor by anterior chest wall deformities, that could affect myocardial strain parameters, as demonstrated in different study groups (38,39).

Implications for clinical practice

The results of this meta-analysis highlight that 2D-STE analysis has an incremental diagnostic value over 2D-TTE for the early detection of subclinical myocardial dysfunction in ECS patients without manifest cardiac involvement. Thus, speckle-tracking imaging represents a useful screening tool for identifying subclinical myocardial dysfunction during the early stages of CS. With this regard, LV-GLS assessment may be used as an additive step to 2D-TTE/basic cardiac assessment, before escalating to advanced imaging techniques, such as CMR and FDG-PET. Notably, 2D-STE should be implemented in clinical pratice, especially when CMR and FDG-PET imaging are contraindicated or not readily available. The presence of a preserved LV-GLS (more negative than -20%) may reasonably rule out a subclinical myocardial involvement in ECS patients with palpitations and nonspecific ST-T abnormalities on resting ECG. On the other hand, an abnormal GLS (less negative than -20%) may be useful to identify ECS patients with an increased probability of CS, leading to early referral to advanced imaging tests.

In addition, the systematic assessment of LV GLS could improve the prognostic risk stratification of ECS patients. Given that sarcoidosis patients with lower GLS values have an increased risk of adverse cardiac events and a short event-free survival over a mid-term follow-up period, they should be more closely monitored. It could also be hypothesized that ECS patients with LV-GLS impairment on 2D-STE analysis could benefit from an early treatment, that could prevent the progression from subclinical

myocardial dysfunction to overt CS and the occurrence of life threatening arrhythmias and conduction abnormalities. The detection of an impaired LV-GLS might suggest the clinicians to consider an early immunosuppressive therapy with corticosteroids, that are potentially more effective in sarcoidosis patients with normal LV systolic function in the initial stages of the disease (40-42). Further studies are needed, however, to demonstrate these hypothesis.

Limitations of the included studies

Main limitations of the included studies were the following: the heterogeneity of ECS patients with regard to study design, sample size, demographics, disease duration and the type of ultrasound machine employed for LV-GLS assessment; the limited number of ECS patients included in each study; the retrospective nature for 46.2% of the studies; the absence of CMR data for 61.5% of the studies; the lack of prognostic data for 53.9% of the studies; finally, the use of unadjusted data for 69.2% of studies. Moreover, it is important to consider that strain echocardiographic imaging may suffer from a number of technical limitations, such as the intervendor variability, the dependence on the operator's experience, good image quality, frame rate setting (low frame rates are associated with the loss of speckles and accuracy), loading conditions and finally extrinsic mechanical factors, such as the chest wall conformation (43-46).

Conclusions

In patients without overt heart disease, the effect of sarcoidosis on LV-GLS is significantly greater than on LVEF.

2D-STE analysis should be implemented in clinical practice for the early detection of myocardial involvement in ECS patients.

Further prospective studies are needed to test the potential usefulness of 2D-STE for possibly guiding early immunosuppressive therapy in ECS patients with reduced LV-GLS.

Abbreviations: A-P, antero-posterior; 2D, two-dimensional; CI, confidence intervals; CMR, cardiac magnetic resonance; CS, cardiac sarcoidosis; ECG, electrocardiogram; ECS, extra-cardiac sarcoidosis; FDG, 18F-fluoro-2-deoxyglucose; GCS, global circumferential strain; GE, General Electric; GLS, global longitudinal strain; GRS, global radial strain; LA, left atrial; LASr, left atrial strain during the reservoir phase; LAVi, left atrial volume indexed; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; NIH, National Institutes of Health; PET, positron emission tomography; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RASr, right atrial strain during the reservoir phase; RoB, risk of bias; RV, right ventricular; SMD, standardized mean difference; sPAP, systolic pulmonary artery pressure; STE, speckle tracking echocardiography; TACT, total atrial conduction time; TAPSE, tricuspid annular plane systolic excursion; TTE, transthoracic echocardiography.

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