# Speckle Tracking Echocardiography Can Predict Subclinical Myocardial Involvement in Patients with Sarcoidosis: A Meta-Analysis

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### Abstract

Background This meta-analysis aims to evaluate the utility of speckle tracking echocardiography (STE) as a tool to evaluate for cardiac sarcoidosis (CS) early in its course. Electrocardiography and echocardiography have limited sensitivity in this role, while advanced imaging modalities such as cardiac magnetic resonance (CMR) and 18F-Fluorodeoxyglucose–Positron Emission Tomography (FDG-PET) are limited by cost and availability. Methods We compiled English language articles that reported left ventricular global longitudinal strain (LVGLS) or global circumferential strain (GCS) in patients with confirmed extra-cardiac sarcoidosis versus healthy controls. Studies that exclusively included patients with probable or definite CS were excluded. Continuous data were pooled as a standard mean difference (SMD) between the sarcoidosis group and controls. A random effect model was adopted in all analyses. Heterogeneity was assessed using Q and I2 statistics. Results Nine studies with 967 patients were included in our analysis. LVGLS was significantly lower in the extra-cardiac sarcoidosis group as compared to controls, SMD -3.98, 95% confidence interval (CI): -5.32, -2.64, $p< 0.001$, also was significantly lower in patients who suffered Major Cardiac Events(MCE), -3.89, 95% CI -6.14, -1.64, $p< 0.001$ . GCS was significantly lower in the extra-cardiac sarcoidosis group as compared to controls, SMD: -3.33, 95% CI -4.71, -1.95, $p< 0.001$ Conclusion LVGLS and GCS were significantly lower in extra-cardiac sarcoidosis patients despite not exhibiting any cardiac symptoms. LVGLS correlates with MCEs in CS. Further studies are required to investigate the role of STE in the early screening of CS.

### Speckle Tracking Echocardiography Can Predict Subclinical Myocardial Involvement in Patients with Sarcoidosis: A Meta-Analysis

**Short Title:** *Speckle Tracking in Sarcoidosis*

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## ABSTRACT

### Background

This meta-analysis aims to evaluate the utility of speckle tracking echocardiography (STE) as a tool to evaluate for cardiac sarcoidosis (CS) early in its course. Electrocardiography and echocardiography have limited sensitivity in this role, while advanced imaging modalities such as cardiac magnetic resonance (CMR) and 18F-Fluorodeoxyglucose–Positron Emission Tomography (FDG-PET) are limited by cost and availability.

### Methods

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Nine studies with 967 patients were included in our analysis. LVGLS was significantly lower in the extra-cardiac sarcoidosis group as compared to controls, SMD -3.98, 95% confidence interval (CI): -5.32, -2.64, $p < 0.001$, also was significantly lower in patients who suffered Major Cardiac Events(MCE), -3.89, 95% CI -6.14, -1.64, $p < 0.001$ . GCS was significantly lower in the extra-cardiac sarcoidosis group as compared to controls, SMD: -3.33, 95% CI -4.71, -1.95, $p < 0.001$

### Conclusion

LVGLS and GCS were significantly lower in extra-cardiac sarcoidosis patients despite not exhibiting any cardiac symptoms. LVGLS correlates with MCEs in CS. Further studies are required to investigate the role of STE in the early screening of CS.

**Keywords:** Sarcoidosis, echocardiography, speckle tracking echocardiography, meta-analysis.

## INTRODUCTION

Sarcoidosis is an inflammatory condition characterized by the presence of non-caseating granulomas in affected organs and primarily affects patients between the ages of 20 to 40 years.[1,2] In the United States, the incidence of sarcoidosis ranges from 10.9 to 35.5 per 100,000 in Caucasians and African Americans, respectively.[3] Based on autopsy findings, cardiac involvement has been reported to occur in 25% of patients with systemic sarcoidosis ,[4] while imaging-based studies using cardiac magnetic resonance (CMR) have demonstrated that up to 50% may have cardiac lesions .[2,5] While patients with cardiac sarcoidosis (CS) can be asymptomatic, others can present with symptoms due to conduction abnormalities, ventricular arrhythmias, and cardiomyopathy.[6] Very rarely, cardiac involvement or even sudden cardiac death may be the first manifestation of systemic sarcoidosis.[7]

Currently, all patients with biopsy-proven extra-cardiac sarcoidosis routinely undergo screening for cardiac sarcoidosis with an electrocardiogram (EKG), with or without an echocardiogram.[5] Advanced imaging modalities such as (CMR) and 18F-Fluorodeoxyglucose–Positron Emission Tomography (FDG-PET) are reserved for individuals suspected to have cardiac involvement based on initial screening.[5,8] The sensitivity of EKG for detecting cardiac involvement is limited at $21 - 68\%$,[6,9] while sensitivity for conventional echocardiography ranges between 27% in asymptomatic individuals and 75% in the presence of symptoms or abnormal EKG findings.[9] Despite the demonstrated superiority of CMR and FDG-PET in early diagnosis of CS, their role is limited by cost and availability, making them inadequate initial screening tests.[10] Speckle tracking echocardiography (STE) is a novel modality with a promising utility in predicting subclinical myocardial involvement.[11,12] The region of interest (ROI) is marked with speckles that serve as stable acoustic markers to trace tissue movement, irrespective of the angle of interrogation.[12] STE can evaluate cardiac function by measuring left ventricular global longitudinal strain (LVGLS) and/or global circumferential strain (GCS)[10]. We sought to perform a meta-analysis of studies investigating the role of STE in asymptomatic patients with proven extra-cardiac sarcoidosis and no known cardiac involvement.

## METHODS

### Search Strategy

We followed the recommendation of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13] We queried the electronic databases Medline, Cochrane databases, CINAHL using the following search keywords: 'Echocardiography', 'Speckle tracking', and 'Sarcoidosis'. We only compiled articles published in English language.

### Study Selection and Data Extraction

We included all studies reporting LVGLS and/or GCS, comparing patients with confirmed extra-cardiac sarcoidosis versus a control group of healthy patients. Studies that exclusively included patients with probable or definite CS were excluded. We also collected studies that reported LVGLS in sarcoidosis patient's experiencing major cardiac events (MCEs) which was defined as composite outcomes of all cause death, arrhythmia, heart failure hospitalization, cardiac device implantation, or appropriate firing of defibrillator. We excluded case reports, review articles, editorials, and correspondences to the editor. Data was extracted by two independent investigators (K.B., M.C). into a predefined collection sheet. All disagreements were resolved in consensus with a third reviewer (D.R.). Extracted data included baseline characteristics, echocardiographic parameters, LVGLS and LVGCS.

### Statistical Analysis

Continuous data (e.g., LVGLS and GCS) were pooled as a standard mean difference (SMD) between the sarcoidosis group and the control group. Random effect model was adopted in all analyses. We used inverse variance method with Restricted Maximum-Likelihood estimator of Tau2, for random effect analysis. We assessed between-study heterogeneity using Q and $I^2$ statistics. A $I^2$ statistic <25% indicates a low amount of heterogeneity and >50% indicates a high heterogeneity. Analyses were conducted using STATA 16 (State Corp LLC, College Station, Texas). P-value <0.05 was considered statistically significant.

### Quality Assessment

Quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS).[14] This included a checklist for representativeness of included cohort, ascertainment of exposure, comparability and adequacy of follow-up as per the NOS. A maximum of 9 stars were awarded to each study. Studies awarded [?]6 stars were considered moderate-to-high quality studies.[14]

## RESULTS

Our literature search yielded 671citations. Of these, 28 full texts were screened and 9 studies were included in the final analysis with an aggregate of 967 patients: 589 in the sarcoid group and 378 in the control group.[10,15–22] Females comprised 63.4% and 65.13% of the control and sarcoid groups, respectively. The pooled mean age was 49.2 years in the control group and 50.5 years in the sarcoid group. In the sarcoid group, 62.9% of patients had pulmonary involvement 16.8% had dermatologic involvement. Patients with symptoms or signs of cardiac involvement were generally excluded from individual studies. The study characteristics and baseline characteristics are summarized in Tables 1 and 2 respectively. The pooled mean ejection fraction (EF) was 61.5% and 63.1% in the control and sarcoid groups, respectively. Echocardiographic parameters of the studies are summarized in Table 3. The study by Murtagh et al was included in the analysis of MCEs but was excluded from meta-analysis related to LVGLS and GCS as it had no control group [22]. Similarly, the study by Chen et al, was included only in the MCEs analysis as it included patients with cardiovascular symptoms.[29] The study flow chart is presented in Figure 1.

Nine studies reported LVGLS in our cohorts.[10,15-22]The pooled mean LVGLS was significantly lower in the sarcoid group as compared to controls: standard mean difference (SMD) -3.98, 95% confidence interval (CI): -5.32, -2.64, p< 0.001, $I^2$=94.70%, Figure 2.

LVGCS was reported in 4 studies with a total of 266 patients, 164 in the sarcoid group and 102 in the control group. The pooled mean GCS was significantly reduced in the sarcoid group as compared to the controls: SMD: -3.33, 95% CI -4.71, -1.95, p< 0.001, $I^2$= 62.94%, Figure 3 [10,16,17,19].

In patients with sarcoidosis , MCEs were reported in 4 studies[20,21,23,29] with a total of 335 patients; 58 of those suffered a MCE and 275 did not. Patients who suffered MCEs had significantly lower LVGLS (less negative) than patients who did not. SMD: –3.89, 95% CI -6.14, -1.64, P< 0.001, $I^2$= 83.77%, Figure 4. In patients with sarcoidosis. The pooled hazard ratio (HR) of MCEs with LVGLS as the predictor was, HR= 1.28, 95% CI (1.17-1.40), p< 0.001, $I^2$= 0%%, Supplementary figure 1.[20,21,29].

Using the NOS tool to evaluate the risk of bias, out of 9 stars, all studies were awarded 8 to 9 stars and can be described as ''moderate to high" in quality. The risk of bias of individual studies is reported in Supplementary appendix..

## DISCUSSION

This is a meta-analysis of observational studies that included 589 patients with proven extra-cardiac sarcoidosis and no evidence of cardiac involvement and 378 controls. The main findings of the study were as follows: (i) The sarcoidosis group was associated with a significantly reduced LVGLS compared to the control group, (ii) The sarcoidosis group was associated with a significantly reduced LVGCS as compared to the control group, and (iii) Within the sarcoid group, the LVGLS was significantly lower in patients who suffered MCEs as compared to those who did not.

CS manifests symptoms in as few as 5% of patients with sarcoidosis[5]. Cardiac involvement in patients with sarcoidosis is characterized by three distinct histopathological stages: inflammation or edema of the myocardium with mononuclear infiltration, non-caseating granuloma formation, and finally fibrosis and scar formation.[4] CS primarily targets the left ventricular free wall, papillary muscles and basal septum[4,7]. Specifically, CS mostly affects the mid and epicardial myocardium, where the myofibrils are arranged circumferentially in left-sided helical structures.[23] Later in the disease process, CS can involve the sub-endocardial myofibrils. This explains the lagging in ejection fraction reduction in patients with CS, which usually denotes an extension of the scar[4]. Steroid therapy is the standard therapy for patients with CS as it prevents left ventricular remodeling and disease progression.[23] However, Chiu et al. noted that patients with CS and EF less than 30% are less likely to benefit from steroids, as EF reduction indicates that scar remodeling has occured.[24] Thus, early detection and timely intervention are essential.

In our study the LVGLS, which represents the disruption of the longitudinally oriented myofibrils in these helical structures[25], was impaired in the sarcoid group[10,15,16]. Kansal et al. demonstrated that LVGLS impairment can be independent of the location of the scar as defined by the late gadolinium enhancement (LGE) on CMR, and suggested a functional component leading to this early impairment[26]. Similarly, the GCS was significantly lower in the sarcoidosis group versus controls. Ori et al. demonstrated that GCS could predict the location of LGE on CMR when the mid-myocardium is affected[27].

Interestingly, two studies in our cohort demonstrated impairment of LVGLS as compared to controls even in the absence of LGE[17,18]. Also, in the study by Schouver et al., only 8.6% of patients in the abnormal LVGLS group had positive findings on CMR[10]. One explanation for this observation is that LGE detects fibrosis or scar tissue which is histologically a late finding of CS, while early inflammation or edema may not be detected unless a T2-sequence was used [4,7]. This is clinically relevant, as an autopsy study of 84 patients demonstrated that even microscopic myocardial sarcoidosis could account for arrhythmias and sudden cardiac death.[3]

In a separate analysis of sarcoidosis patients that included studies, LVGLS was significantly lower in patients who suffered MCEs as compared to those who did not, despite having normal ejection fraction at baseline.[20,21,23,29] Myocardial strain can predict the presence and the extent of LGE on CMR [23,27], and

LGE seems to be a strong predictor of adverse outcomes. [28]A pooled HR for 3 studies demonstrated that a reduced(less negative) LVGLS is predictive of MCEs, however this should be interpreted with caution as this analysis included only 3 studies.[20,21,, 29] The study by Murtagh *et al*suggests that LVGLS more than -17% correlates with LGE on CMR and predicts adverse outcomes.[23]

Our meta-analysis has certain limitations. The studies included were observational which makes selection and observer bias inevitable. In addition, significant heterogeneity was noted in the LVGLS and GCS groups. This can be partly explained by the different vendors and software used to detect strain. Patients included in the cohorts belong to various age groups and different stages of sarcoidosis. We could not account for this variation among studies, which raises concern over the generalizability of our results.

## CONCLUSION

Patients with extra-cardiac sarcoidosis and no clinical signs of cardiac involvement have significantly lower LVGLS and GCS on speckle-tracking echocardiography compared to healthy controls. These findings highlight the promising role of speckle-tracking echocardiography in early detection of cardiac involvement in patients with extra-cardiac sarcoidosis.

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**Figure Legends**

**Figure 1** : PRISMA flow chart

**Figure 2** : Forest plot for LVGLS, in the sarcoid group as compared to controls; N: Total sample; SD: standard deviation; REML: Restricted Maximum-Likelihood estimator

**Figure 3** : Forest plot for LVGCS, in the sarcoid group as compared to controls; N: Total sample; SD: standard deviation; REML: Restricted Maximum-Likelihood estimator

**Figure 4:** Forest plot for LVGLS, in the sarcoid patients experiencing MCE as compared to sarcoid patients not experiencing MCE ; N: Total sample; SD: standard deviation; REML : Restricted Maximum-Likelihood estimator

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