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Kirolos Barssoum
Ahmed M. Altibi
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Ashish Kumar
Adnan Kharsa

*See next page for additional authors*

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Authors
Kirolos Barssoum, Ahmed M. Altibi, Devesh Rai, Ashish Kumar, Adnan Kharsa, Medhat Chowdhury, Samarthkumar Thakkar, Sara Shahid, Mohamed Abdelazeem, Ahmed Sami Abuzaid, Bipul Baibhav, Vishal Parikh, Scott C. Feitell, Mallory Balmer-Swain, Mohan Rao, Myriam Amsallem, and Navin C. Nanda
Speckle tracking echocardiography can predict subclinical myocardial involvement in patients with sarcoidosis: A meta-analysis

Kirolos Barssoum MD | Ahmed M. Altibi MD | Devesh Rai MD
Ashish Kumar MBBS | Adnan Kharsa MD | Medhat Chowdhury MD
Samarthkumar Thakkar MD | Sara Shahid MD | Mohamed Abdelazeem MD
Ahmed Sami Abuzaid MD | Bipul Baibhav MD | Vishal Parikh MD
Scott C. Feitell DO | Mallory Balmer-Swain DO | Mohan Rao MD
Myriam Amsallem MD | Navin C. Nanda MD

1Department of Internal Medicine, Unity Hospital, Rochester Regional Health System, Rochester, NY, USA
2Department of Internal Medicine, Henry Ford Allegiance Health, Jackson, MI, USA
3Department of Internal Medicine, Rochester General Hospital, Rochester, NY, USA
4Department of Critical Care, St. John’s Medical College, Bangalore, India
5St. Elizabeth Medical Center, Boston, MA, USA
6Department of Cardiology, Alaska and Vascular Institute LLC, Anchorage, AK, USA
7Department of Cardiology, Sands Constellation Heart Institute, Rochester Regional Health, Rochester, NY, USA
8Department of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA, USA
9Department of Cardiovascular Disease, University of Alabama, Birmingham, AL, USA

Correspondence
Devesh Rai, MD, 1425 Portland Ave, Rochester, NY 14621, USA
Email: DeveshRaiMD@gmail.com

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), comparing sarcoidosis group with healthy controls. Studies that exclusively included patients with probable or definite CS were excluded. Continuous data were pooled as a standard mean difference (SMD), comparing sarcoidosis group with healthy controls. A random-effect model was adopted in all analyses. Heterogeneity was assessed using Q and I² statistics.

Results: Nine studies were included in our final analysis with an aggregate of 967 patients. LVGLS was significantly lower in the extra-cardiac sarcoidosis group as compared with controls, SMD −3.98, 95% confidence interval (CI) −5.32, −2.64, P < .001, also was significantly lower in patients who suffered major cardiac events (MCE), −3.89, 95% CI −6.14, −1.64, P < .001. GCS was significantly lower in the extra-cardiac sarcoidosis group as compared with controls, SMD: −3.33, 95% CI −4.71, −1.95, P < .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.
1 | INTRODUCTION

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

Currently, all patients with biopsy-proven extra-cardiac sarcoidosis routinely undergo screening for cardiac sarcoidosis with an electrocardiogram (EKG), with or without an echocardiogram. 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. The sensitivity of EKG for detecting cardiac involvement is limited at 21%–68%, while sensitivity for conventional echocardiography ranges between 27% in asymptomatic individuals and 75% in the presence of symptoms or abnormal EKG findings. 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. Speckle tracking echocardiography (STE) is a novel modality with a promising utility in predicting subclinical myocardial involvement. 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. STE can evaluate cardiac function by measuring left ventricular global longitudinal strain (LVGLS) and/or global circumferential strain (GCS). 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.

2 | METHODS

2.1 | Search strategy

We followed the recommendation of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We queried the electronic databases Medline, Cochrane databases, CINAHL using the following search keywords: ‘Echocardiography’, ‘Speckle tracking’, and ‘Sarcoidosis’. The detailed search strategy is provided in Table S1. We only compiled articles published in English language.

2.2 | 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 patients experiencing major cardiac events (MCEs) which were 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 were extracted by two independent investigators KB and MC into a predefined collection sheet. All disagreements were resolved in consensus with a third reviewer (DR). Extracted data included baseline characteristics, echocardiographic parameters, LVGLS, and LVGCS.

2.3 | Statistical analysis

Continuous data (eg, LVGLS and GCS) were pooled as a standard mean difference (SMD) comparing 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 I2 statistics. A I2 statistic < 25% indicates a low amount of heterogeneity, and >50% indicates a high heterogeneity. Analyses were conducted using STATA 16 (State Corp LLC). P-value < 0.05 was considered statistically significant.

2.4 | Quality assessment

Quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS). 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 was awarded to each study. Studies awarded ≥6 stars were considered moderate-to-high quality studies.

3 | RESULTS

Our literature search yielded 671 citations. 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. Females comprised 63.4% and 65.13% of the control and sarcoid groups, respectively. The pooled mean age was...
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Number of controls</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggeli, et al. 15, 2013</td>
<td>15</td>
<td>67</td>
<td>Biopsy-proven newly diagnosed extra-cardiac sarcoidosis</td>
<td>Patients with heart disease, medications affecting cardiovascular system, smoking, DM, HLD, HTN, structural or valvular disease, and poor acoustic window</td>
<td>QLAB software</td>
</tr>
<tr>
<td>Bayat, et al. 23, 2019</td>
<td>55</td>
<td>21</td>
<td>Patients with extra-cardiac sarcoidosis between Jan 2015 and Feb 2017</td>
<td>Patients with pacemakers, arrhythmias, valvular disease, DM, HTN, CAD</td>
<td>NA</td>
</tr>
<tr>
<td>Digereneci et al., 2015</td>
<td>50</td>
<td>50</td>
<td>Patients with extra-cardiac sarcoidosis, referred for cardiology evaluation</td>
<td>CAD, DM, HTN, COPD, CHF, systolic dysfunction, arrhythmias</td>
<td>Echo-Pac version 7.0, GE Vingmed</td>
</tr>
<tr>
<td>Felekos et al. 21, 2018</td>
<td>107</td>
<td>45</td>
<td>Patients with extra-cardiac sarcoidosis, referred for cardiology evaluation</td>
<td>Symptoms suggestive of heart disease, change in EKG, structural heart disease and established cardiac sarcoidosis</td>
<td>QLAB software</td>
</tr>
<tr>
<td>Joyce, 20, 2014</td>
<td>100</td>
<td>100</td>
<td>Patients with extra-cardiac sarcoidosis</td>
<td>Structural heart disease and definite sarcoidosis</td>
<td>EchoPac 112.0.1</td>
</tr>
<tr>
<td>Kul et al. 17, 2014</td>
<td>34</td>
<td>26</td>
<td>Patients with biopsy-proven pulmonary sarcoidosis</td>
<td>HTN, DM, HF, Afib, valvular disease, pacemaker/defibrillator, thyroid, liver disease, and renal disease</td>
<td>QLAB 9.0</td>
</tr>
<tr>
<td>Kusunose et al. 21, 2019</td>
<td>101</td>
<td>52</td>
<td>Patients with confirmed sarcoidosis referred for cardiac evaluation</td>
<td>Pre-existing structural heart disease and poor echocardiographic images</td>
<td>Echolnsight</td>
</tr>
<tr>
<td>Murtagh et al. 22, 2016</td>
<td>31</td>
<td>31</td>
<td>Patients with biopsy-proven extra-cardiac sarcoidosis referred for cardiac MRI and TTE who had preserved LVEF.</td>
<td>Patients with LVEF &lt; 50%, poor echocardiographic images, and individuals whose cardiac MRI and TTE had been performed &gt; 12 mo apart</td>
<td>Echolnsight</td>
</tr>
<tr>
<td>Schouwer et al. 18, 2016</td>
<td>35</td>
<td>35</td>
<td>Patients with confirmed sarcoidosis referred for cardiac evaluation between May 2013 and October 2015</td>
<td>Patients with confirmed cardiac sarcoidosis and patients with structural heart disease</td>
<td>Tomtec</td>
</tr>
<tr>
<td>Chen et al. 23, 2017</td>
<td>54</td>
<td>54</td>
<td>Patients with extra-cardiac sarcoidosis and cardiac symptoms or EKG changes</td>
<td>Patients with diagnosed cardiac sarcoidosis or structural heart disease</td>
<td>GE Vivid E9 machine</td>
</tr>
<tr>
<td>Tigen K et al. 16, 2015</td>
<td>40</td>
<td>20</td>
<td>consecutive patients diagnosed with sarcoidosis</td>
<td>Significant valvular disease, history of coronary artery disease, malignancy, systemic arterial hypertension, storage disorders such as Fabry’s disease, and cardiac amyloidosis, poor echogenicity, and HTN</td>
<td>Vivid 7</td>
</tr>
</tbody>
</table>

Abbreviations: Afib = atrial fibrillation; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive lung disease; DM = diabetes mellitus; HLD = hyperlipidemia; HTN = hypertension.
<table>
<thead>
<tr>
<th>Study</th>
<th>Age (y)</th>
<th>Male</th>
<th>Hypertension</th>
<th>Organ involvement</th>
<th>Chest radiograph stage</th>
<th>Major cardiac events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>Pts</td>
<td>Controls</td>
<td>Pts</td>
<td>Controls</td>
<td>Pts</td>
</tr>
<tr>
<td>Aggeli, et al, 2013</td>
<td>45.2 ± 1.9</td>
<td>46.0 ± 2.6</td>
<td>11 (37.9%)</td>
<td>26 (38.8%)</td>
<td>Lung 56 (91.8%), Skin 11 (18%), Eye 4 (6.5%)</td>
<td></td>
</tr>
<tr>
<td>Bayat, et al, 2019</td>
<td>48 ± 7.52</td>
<td>50.80 ± 8.84</td>
<td>21 (38.2%)</td>
<td>-</td>
<td>Lung 83.6%, Skin 23.6%, Lymph nodes 10.9%</td>
<td>Stage 1:88%, Stage 2:14.5%, Stage 3:5.5%</td>
</tr>
<tr>
<td>Digermenci et al, 2015</td>
<td>37.7 ± 4.9</td>
<td>40.4 ± 11.0</td>
<td>24 (48%)</td>
<td>16 (32%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Felekos et al, 2018</td>
<td>45 ± 8</td>
<td>47 ± 14</td>
<td>13 (31.1%)</td>
<td>40 (37.4%)</td>
<td>Lung 95 (88.8%), Skin 20 (18.7%), Eye 8 (7.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Joyce et al, 2014</td>
<td>55 ± 13</td>
<td>55 ± 13</td>
<td>48 (48%)</td>
<td>48 (48%)</td>
<td>27 (27%)</td>
<td>24 (24%)</td>
</tr>
<tr>
<td>Kul et al, 2014</td>
<td>44.3</td>
<td>45</td>
<td>8 (30.7%)</td>
<td>9 (26.4%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chen et al, 2017</td>
<td>51.0 ± 10.4</td>
<td>51.3 ± 11.2</td>
<td>32 (59.3%)</td>
<td>32 (59.3%)</td>
<td>Pulmonary 52 (96.3) Neuro 3 (5.6) Liver 1 (1.9) Eye 1 (1.9) Osseous 1 (1.9) Skin 2 (3.7)</td>
<td>Composite outcome of cardiac death, hospitalization for new heart failure, arrhythmia and device implantation</td>
</tr>
<tr>
<td>Kusunose et al, 2019</td>
<td>62 ± 11</td>
<td>62 ± 13</td>
<td>18 (35%)</td>
<td>32 (32%)</td>
<td>Lung 64 (63%), Eye 41 (41%), Skin 25 (25%), Nerve 5 (5%), Muscle 4 (4%), Kidney 2 (2%), Liver 2 (2%), Stomach 1 (1%), Lymph nodes 1 (1%)</td>
<td>-</td>
</tr>
</tbody>
</table>

(Continues)
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 and 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. Similarly, the study by Chen et al was included only in the MCEs analysis as it included patients with cardiovascular symptoms.

The study flow chart is presented in Figure 1.

Nine studies reported LVGLS in our cohorts. The pooled mean LVGLS was significantly lower in the sarcoid group as compared with controls: standard mean difference (SMD) −3.98, 95% confidence interval (CI): −5.32, −2.64, \( P < .001 \), \( I^2 = 94.70\% \), 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 with the controls: SMD: −3.33, 95% CI −4.71, −1.95, \( P < .001 \), \( I^2 = 62.94\% \), Figure 3.

In patients with sarcoidosis, MCEs were reported in 4 studies 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, \( P < .001 \), \( I^2 = 83.77\% \), 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), \( P < .001 \), \( I^2 = 0\% \), Figure S1.

Using the NOS tool to evaluate the risk of bias, out of 9 stars, all studies were awarded 8–9 stars and can be described as "moderate to high" in quality. The risk of bias of individual studies is reported in Table 4.

### 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: (a) The sarcoidosis group was associated with a significantly reduced LVGLS compared with the control group, (b) the sarcoidosis group was associated with a significantly reduced LVGCS as compared with the control group, and (c) within the sarcoid group, the LVGLS was significantly lower in patients who suffered MCEs as compared with those who did not.

CS manifests symptoms in as few as 5% of patients with sarcoidosis. Cardiac involvement in patients with sarcoidosis is characterized by three distinct histopathological stages: inflammation or edema of the myocardium with mononuclear infiltration,
noncaseating granuloma formation, and finally fibrosis and scar formation.\textsuperscript{4} CS primarily targets the left ventricular free wall, papillary muscles, and basal septum.\textsuperscript{4,7} Specifically, CS mostly affects the mid and epicardial myocardium, where the myofibrils are arranged circumferentially in left-sided helical structures.\textsuperscript{24} 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.\textsuperscript{4}

### TABLE 3  Echocardiographic parameters of the studies

<table>
<thead>
<tr>
<th>Study</th>
<th>LA diameter Control</th>
<th>LA diameter Pts</th>
<th>LVEDD Control</th>
<th>LVEDD Pts</th>
<th>LVESD Control</th>
<th>LVESD Pts</th>
<th>IVSD Control</th>
<th>IVSD Pts</th>
<th>EF Control</th>
<th>EF Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggei, et al,\textsuperscript{15} 2013</td>
<td>36.1 ± 3.9</td>
<td>35.6 ± 4.7</td>
<td>45.1 ± 2.1</td>
<td>44.4 ± 3.41</td>
<td>23.1 ± 3.2</td>
<td>24.2 ± 3.0</td>
<td>9.1 ± 1.07</td>
<td>8.7 ± 1.03</td>
<td>59.34 ± 3.95</td>
<td>58.73 ± 4.49</td>
</tr>
<tr>
<td>Digermenci, 2015</td>
<td>30.1 ± 2.59</td>
<td>31.1 ± 3.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8.0 ± 0.9</td>
<td>9.0 ± 0.10</td>
<td>67.8 ± 2.4</td>
<td>64.1 ± 2.6</td>
<td></td>
</tr>
<tr>
<td>Felekos et al,\textsuperscript{21} 2018</td>
<td>36.6 ± 3.8</td>
<td>35.3 ± 5.1</td>
<td>44.9 ± 2.4</td>
<td>44.1 ± 3.1</td>
<td>24.3 ± 3.1</td>
<td>24.6 ± 2.7</td>
<td>9.2 ± 1.05</td>
<td>8.8 ± 1.1</td>
<td>58.7 ± 4.5</td>
<td>59.1 ± 2.4</td>
</tr>
<tr>
<td>Joyce,\textsuperscript{20} 2014</td>
<td>-</td>
<td>-</td>
<td>5.0 ± 0.52</td>
<td>5.0 ± 0.53</td>
<td>3.2 ± 0.40</td>
<td>3.2 ± 0.50</td>
<td>0.92 ± 0.19</td>
<td>0.96 ± 0.18</td>
<td>63 ± 6</td>
<td>57 ± 5</td>
</tr>
<tr>
<td>Kul et al,\textsuperscript{17} 2014</td>
<td>3.3 (0.3)</td>
<td>3.5 (0.3)</td>
<td>4.5 (0.5)</td>
<td>4.6 (0.4)</td>
<td>2.8 (0.6)</td>
<td>3 (0.4)</td>
<td>0.8 (0.1)</td>
<td>0.9 (0.1)</td>
<td>63.0 (7.4)</td>
<td>64.6 (9.4)</td>
</tr>
<tr>
<td>Kusunose et al,\textsuperscript{21} 2019</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>64 ± 4</td>
<td>65 ± 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schouver et al,\textsuperscript{18} 2016</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>57.7 ± 3.6</td>
<td>59.0 ± 12.2</td>
</tr>
<tr>
<td>Tigen K et al,\textsuperscript{16} 2015</td>
<td>3.0 ± 0.3</td>
<td>3.2 ± 0.4</td>
<td>4.6 ± 0.3</td>
<td>4.7 ± 0.5</td>
<td>2.6 ± 0.2</td>
<td>2.8 ± 0.3</td>
<td>-</td>
<td>-</td>
<td>73.6 ± 3.2</td>
<td>71.1 ± 5.3</td>
</tr>
</tbody>
</table>

Abbreviations: EF = ejection fraction; IVSD = interventricular septum systolic diameter; LA = Left atrium; LVEDD = Left ventricular end diastolic diameter; LVESD = left ventricular end systolic diameter.
Steroid therapy is the standard therapy for patients with CS as it prevents left ventricular remodeling and disease progression.\(^\text{24}\) 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 occurred.\(^\text{25}\) 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,\(^\text{26}\) was impaired in the sarcoid group.\(^\text{10,15,16}\) 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.\(^\text{27}\) 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.\(^\text{28}\)

<table>
<thead>
<tr>
<th>Study</th>
<th>E</th>
<th>A</th>
<th>E/A</th>
<th>E'/E'</th>
<th>E' septal</th>
</tr>
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<tbody>
<tr>
<td>Control Pts</td>
<td>Control</td>
<td>Control</td>
<td>Control</td>
<td>Control</td>
<td>Control</td>
</tr>
<tr>
<td>0.7 ± 0.2</td>
<td>0.8 ± 0.3</td>
<td>0.55 ± 0.1</td>
<td>0.6 ± 0.2</td>
<td>1.1 ± 0.4</td>
<td>1.09 ± 0.29</td>
</tr>
<tr>
<td>90.0 ± 12.8</td>
<td>78.6 ± 16.0</td>
<td>62.3 ± 9.0</td>
<td>72.2 ± 20.1</td>
<td>1.2 ± 0.36</td>
<td>1.07 ± 0.32</td>
</tr>
<tr>
<td>70 ± 4.1</td>
<td>75.2 ± 5.9</td>
<td>55.6 ± 10.3</td>
<td>57.3 ± 9.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>76 ± 19</td>
<td>76 ± 17</td>
<td>70 ± 18</td>
<td>70 ± 16</td>
<td>1.0 (0.88, 1.3)</td>
<td>1.1 (0.90, 1.3)</td>
</tr>
<tr>
<td>0.78 (0.21)</td>
<td>0.77 (0.17)</td>
<td>0.66 (0.17)</td>
<td>0.67 (16)</td>
<td>1.2 (0.39)</td>
<td>1.38 (1.11)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>0.9 ± 0.1</td>
<td>0.8 ± 0.2</td>
<td>0.7 ± 0.2</td>
<td>0.8 ± 0.2</td>
<td>-</td>
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</tbody>
</table>

Abbreviations: EF = ejection fraction; IVSD = interventricular septum systolic diameter; LA = Left atrium; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic diameter.
Interestingly, two studies in our cohort demonstrated impairment of LVGLS as compared with controls even in the absence of LGE.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{3}

In a separate analysis of sarcoidosis patients that included studies, LVGLS was significantly lower in patients who suffered MCEs as compared with those who did not, despite having normal ejection fraction at baseline.\textsuperscript{20,21,23,24} Myocardial strain can predict the presence and the extent of LGE on CMR,\textsuperscript{24,28} and LGE seems to be a strong predictor of adverse outcomes.\textsuperscript{29} 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.\textsuperscript{20,21,23} The study by Murtagh et al suggested that LVGLS more than or equal to −17% correlates with LGE on CMR, with a sensitivity and specificity of 94%.\textsuperscript{24}

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

CONFLICT OF INTEREST
None.

DATA AVAILABILITY STATEMENT
Kirolos Barassoum owns the primary data and responsibilities. The data will be provided upon request.

ORCID
Devesh Rai  https://orcid.org/0000-0003-1287-6440
Ahmed Sami Abuzaid  https://orcid.org/0000-0002-9041-1844

REFERENCES


**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

**Appendix S1.** Speckle Tracking Echocardiography Can Predict Subclinical Myocardial Involvement in Patients with Sarcoidosis: A Meta-Analysis.