Magnetic Resonance Imaging

Presence of Late Gadolinium Enhancement by Cardiac Magnetic Resonance Among Patients With Suspected Cardiac Sarcoidosis Is Associated With Adverse Cardiovascular Prognosis
A Systematic Review and Meta-Analysis

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Background—Individuals with cardiac sarcoidosis have an increased risk of ventricular arrhythmia and death. Several small cohort studies have evaluated the ability of late gadolinium enhancement (LGE) by cardiac magnetic resonance imaging (MRI) to predict adverse cardiovascular events. However, studies have yielded inconsistent results, and some analyses were underpowered. Therefore, we sought to systematically review and perform meta-analysis of the prognostic value of cardiac MRI for patients with known or suspected cardiac sarcoidosis.

Methods and Results—We systematically searched for cohort studies of patients with known sarcoidosis with suspected cardiac involvement who underwent cardiac MRI with LGE with at least 12 months of either prospective or retrospective follow-up data regarding post-MRI adverse cardiovascular outcomes. We identified 7 studies of 694 subjects (mean age 53; 42% men). One hundred and ninety-nine patients (29%) were LGE positive. All-cause mortality occurred in 19 LGE-positive versus 17 LGE-negative subjects (annualized incidence, 3.1% versus 0.6%). The pooled relative risk was 3.38 (95% confidence interval, 1.07–10.7; P=0.04). Cardiovascular mortality occurred in 10 LGE-positive versus 2 LGE-negative subjects (annualized incidence, 1.9% versus 0.3%; relative risk 10.7 [95% confidence interval, 1.34–86.3]; P=0.03). Ventricular arrhythmia occurred in 41 LGE-positive versus 0 LGE-negative subjects (annualized incidence, 5.9% versus 0%; relative risk 19.5 [95% confidence interval, 2.68–143]; P=0.003). A combined end point of death or ventricular arrhythmia occurred in 64 LGE-positive versus 18 LGE-negative subjects (annualized incidence, 8.8% versus 0.6%; relative risk 6.20 [95% confidence interval, 2.47–15.6]; P<0.001). There was no significant heterogeneity for any outcomes.

Conclusions—LGE is associated with future cardiovascular death and ventricular arrhythmia among patients referred to MRI for known or suspected cardiac sarcoidosis. (Circ Cardiovasc Imaging. 2016;9:e005001. DOI: 10.1161/CIRCIMAGING.116.005001.)

Key Words: cardiac arrhythmia ▪ cardiomyopathies ▪ heart conduction system ▪ magnetic resonance imaging ▪ sarcoidosis

Cardiac sarcoidosis (CS) is an increasingly recognized infiltrative heart disease that can cause heart failure, left or right ventricular systolic dysfunction, atrioventricular block, arrhythmias, and sudden cardiac death.1 The diagnosis of CS often relies on cardiac imaging, as clinical criteria and endomyocardial biopsy both have limited diagnostic accuracy.1,2 However, even with the use of advanced imaging techniques

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such as cardiac magnetic resonance (CMR) imaging and cardiac positron emission tomography (PET), the diagnosis may not always be clear, and most studies assessing the diagnostic accuracy of these techniques have been limited by the lack of a reliable reference standard. As a result, recent studies have focused on evaluating the prognostic value of various cardiac imaging findings, as the risk of future events is essential for deciding on the role of therapies that are often toxic and costly.

Several CMR studies have evaluated patients with suspected CS and have shown that the presence of late gadolinium enhancement (LGE) was associated with a higher rate of adverse events. Yet, many of these studies were small and relied on various composite end points because of limited statistical power. Moreover, several studies yielded inconsistent results. For example, 2 studies concluded that LGE was associated with all-cause mortality,6,7 whereas 26,7 demonstrated a nonsignificant trend toward increased risk, and 3 other studies did not identify any increased risk of LGE for all-cause mortality.8–10 In fact, 1 study did not find an association between LGE and any adverse events.10 As a result, the magnitude of the association between LGE and adverse events has been unclear.

Given the increasing role of CMR in evaluating patients with suspected CS, we sought to perform a systematic review and meta-analysis of all studies evaluating the association of CMR findings with downstream cardiac death and ventricular arrhythmias, hard end points that are highly relevant for clinical decision making. Furthermore, given the high event rates that have been observed in patients with suspected sarcoidosis, we were also interested in identifying the value of a negative CMR to identify low-risk individuals.

**Methods**

**Literature Search**

We followed the statement for Preferred Reporting in Systematic Review and Meta-Analysis.13 The Preferred Reporting in Systematic Review and Meta-Analysis checklist is provided in Table I in the Data Supplement. The study protocol has not been previously published. We used a systematic search strategy of EMBASE, Pubmed, and Web of Science to identify prospective or retrospective cohort studies of at least 20 patients with suspected or confirmed CS who were referred for cardiac magnetic resonance imaging (MRI) with the evaluation of LGE and at least 12 months of clinical follow-up after MRI for any of the following end points: all-cause mortality, cardiovascular mortality, ventricular arrhythmias, heart block requiring pacemaker implantation, or heart failure requiring hospital admission. We used the search terms and corresponding MeSH headings cardiac sarcoidosis MRI from index date to January 26th, 2016. The full search terms are included in the Methods in the Data Supplement. We additionally searched references of articles reviewed. We did not restrict by language. There was no external funding source, and all data analyzed were abstracted from the published article without unpublished or individual patient level data.

We excluded studies that did not report clinical outcomes. We furthermore excluded studies that evaluated patients only by nuclear imaging or echocardiography, that did not report clinical outcomes but were purely diagnostic accuracy studies, or that did not classify patients as having LGE by cardiac MRI.

**Data Abstraction**

Two authors (E.H. and V.A.), working independently, abstracted raw data onto a standardized form that recorded study characteristics (design, demographics, sample size, and inclusion and exclusion criteria), MRI findings including LGE positivity and quantification, and included clinical outcomes stated above.

**Data Synthesis**

For the primary analysis, we evaluated all-cause mortality according to LGE positivity. Secondary analyses included cardiovascular mortality, ventricular arrhythmia (appropriate implantable cardioverter defibrillator [ICD] shock of ventricular arrhythmia excluding anti-tachycardia pacing; ventricular fibrillation, or sustained ventricular tachycardia >30 seconds), and combined death or ventricular arrhythmia. We also abstracted bradycardia resulting in pacemaker implantation and hospital admission for heart failure. We generated 2×2 tables from the data reported in each article and pooled the outcomes using a random effects model to calculate summary of annualized incidences for each outcome according to LGE positivity in addition to the pooled relative risk (RR) for each adverse clinical outcome according to LGE positivity.

**Sensitivity Analysis**

We examined heterogeneity using visual inspection via Galbraith plots in addition to statistical analysis by Q and I² statistics.14 The I² statistics provide an estimate of the variance because of heterogeneity rather than chance alone and is based on the traditional measure of variance, the Cochran Q statistic. We assessed for small study effects with linear regression for binary outcomes by Harbord test.15

**Quality Assessment**

Two authors (M.C. and G.C.) working independently assessed the quality using the Newcastle–Ottawa scale, which is used for assessing the quality of nonrandomized studies in meta-analysis, as recommended by the Cochrane collaboration.16 This scale rates quality from 0 to 9 based on 8 questions involving patient selection, comparability, and outcomes assessment. Disagreements were resolved by consensus.

**Statistical Analysis**

All analyses were conducted using Stata version 12.1 (StataCorp, College Station, TX), with the metan commands. P values were 2 sided with an alpha of 0.05 considered statistically significant.

**Results**

The Preferred Reporting in Systematic Review and Meta-Analysis flow chart for literature search is presented in Figure 1. Seven observational studies of 694 patients were included.4–10 681 patients (98%) had biopsy-proven or met radiological criteria for diagnosis of extra-CS, whereas 13 patients were suspected on presentation of having isolated CS. The mean age of the population was 53±4 years. There were 289 (42%) men. Demographics for the study population are further presented in Table 1. 199 patients (29%) were LGE positive. Similar patients were enrolled in each study (patients with extra-CS and clinical referral because of symptoms of suspected cardiac involvement of sarcoidosis) although Nagai et al10 evaluated an entirely asymptomatic screening population. Similar methods for acquisition and interpretation of LGE were reported, except that Nagai et al10 reported the use of a balanced steady state free precession (as opposed to gradient recall echo in all other studies) with fixed inversion time of 300 ms in contrast to other studies that reported adjusting inversion time consistent with usual practice. Gadolinium dose reported ranged from 0.1 to 0.20 mmol/kg consistent with
usual practice (Table 2). Reporting of ventricular arrhythmia used similar methods in each study to target clinically significant ventricular tachycardia, ventricular fibrillation, ICD shock, or sudden cardiac death. Two articles reported nonsustained ventricular tachycardia, which we separated from our outcomes (Table 3).

**All-Cause Mortality**

Among 6 studies reporting all-cause mortality, there were 19 deaths among subjects with LGE and 17 deaths among subjects without LGE (Table 4). The annualized incidence of mortality was 3.1% versus 0.6% for LGE positive versus LGE negative, respectively (Figure 2). Three studies demonstrated an increased risk of all-cause mortality associated with LGE and 3 did not. The pooled RR was 3.38 (95% confidence interval, 1.07–10.7; \( P = 0.04 \)), Figure 3. There was no statistical evidence of heterogeneity (\( I^2 = 0% \); \( P = 0.7 \)).

**Cardiovascular Mortality**

Among 4 studies reporting cardiovascular mortality, there were 10 deaths among subjects with LGE and 2 deaths among subjects without LGE. The annualized incidence of cardiovascular mortality was 1.9% versus 0.3% for LGE positive versus LGE negative, respectively (Figure 2). The pooled RR was 10.7 (95% confidence interval, 1.34–86.3; \( P = 0.03 \)), Figure 4. There was no statistical evidence of heterogeneity (\( I^2 = 0% \); \( P = 1.0 \)).

**Ventricular Arrhythmia**

Among 7 studies reporting ventricular arrhythmia (appropriate ICD therapy of ventricular arrhythmia, ventricular fibrillation, or sustained ventricular tachycardia >30 seconds), there were 41 occurrences among subjects with LGE and none among subjects without LGE. The annualized incidence of ventricular arrhythmia was 5.9% versus 0% for LGE positive versus LGE negative, respectively (Figure 2). The pooled RR was 19.5 (95% confidence interval, 2.68–143; \( P = 0.003 \)), Figure 5. There was no statistical evidence of heterogeneity (\( I^2 = 0% \); \( P = 1.0 \)).

**Death or Ventricular Arrhythmia**

Among 7 studies reporting a combined end point of death or ventricular arrhythmia, there were 64 occurrences among subjects with LGE and 18 among subjects without LGE.

**Table 1. Baseline Demographic**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>+ LGE, n (%)</th>
<th>% LGE Mass</th>
<th>Age, y</th>
<th>Men, n (%)</th>
<th>Ethnicity, %</th>
<th>Extra-Cardiac Sarcoid, n (%)</th>
<th>Follow-Up, mo</th>
<th>LVEF, %</th>
<th>LVEDV</th>
<th>MRI Field Strength, Tesla</th>
<th>Corticosteroid Treatment, n (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murtagh et al²</td>
<td>205</td>
<td>41 (20)</td>
<td>8±10</td>
<td>56±7</td>
<td>64 (31)</td>
<td>59 AA</td>
<td>205 (100)</td>
<td>36±18</td>
<td>61±6</td>
<td>73±15 mL/m²</td>
<td>1.5</td>
<td>92 (45) current</td>
</tr>
<tr>
<td>Patel et al⁴</td>
<td>81</td>
<td>21 (26)</td>
<td>6 (2, 19)</td>
<td>46±11</td>
<td>25 (31)</td>
<td>73 AA</td>
<td>81 (100)</td>
<td>21±8</td>
<td>56 (48, 61)</td>
<td>101 (89,137) mL</td>
<td>1.5</td>
<td>74 (91) current or prior</td>
</tr>
<tr>
<td>Greulich et al⁶</td>
<td>153</td>
<td>39 (25)</td>
<td>4 (3, 9)</td>
<td>50±13</td>
<td>91 (59)</td>
<td>153 (100)</td>
<td>31</td>
<td>63 (59, 68)</td>
<td></td>
<td>126 (105,155) mL</td>
<td>1.5</td>
<td>110 (72) current or prior</td>
</tr>
<tr>
<td>Nadel et al⁸</td>
<td>106</td>
<td>32 (30)</td>
<td>...</td>
<td>51±12</td>
<td>64 (60)</td>
<td>...</td>
<td>100 (94)</td>
<td>37±21</td>
<td>57±11</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Crawford et al⁹</td>
<td>51</td>
<td>19 (37)</td>
<td>15±12</td>
<td>51±10</td>
<td>16 (32)</td>
<td>47 AA</td>
<td>51 (100)</td>
<td>48±20</td>
<td>52±10</td>
<td>175 mL</td>
<td>1.5</td>
<td>24 (47) current or prior</td>
</tr>
<tr>
<td>Nagai et al¹⁰</td>
<td>61</td>
<td>8 (13)</td>
<td>...</td>
<td>57±15</td>
<td>13 (21)</td>
<td>100 Japanese</td>
<td>61 (100)</td>
<td>50±12</td>
<td>63±7</td>
<td>105 mL</td>
<td>1.5</td>
<td>10 (16) current or prior</td>
</tr>
<tr>
<td>Shafee et al⁷</td>
<td>37</td>
<td>26 (70)</td>
<td>...</td>
<td>57±12</td>
<td>4 (12)</td>
<td>100 Japanese</td>
<td>30 (81)</td>
<td>45±31</td>
<td>50±16</td>
<td>LVEDd=49±8 mm</td>
<td>1.5</td>
<td>No steroids before CMR</td>
</tr>
<tr>
<td>Overall</td>
<td>694</td>
<td>199 (29)</td>
<td>53±4</td>
<td>277 (40)</td>
<td>...</td>
<td>...</td>
<td>681 (98)</td>
<td>36±8</td>
<td>59±4</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Columns represent n(%) or mean±SD or median (IQR), where appropriate. AA indicates African American; LGE, late gadolinium enhancement; LVEDD, left ventricular end diastolic diameter; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; and VT, ventricular tachycardia.
Table 2. Cardiac Magnetic Resonance Acquisition and Interpretation of Late Gadolinium Enhancement

<table>
<thead>
<tr>
<th>Study</th>
<th>LGE Acquisition Time After Gadolinium, min</th>
<th>Gadolinium Type and Dose</th>
<th>Sequence</th>
<th>Interpretation of LGE Presence and Quantification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murtagh et al5</td>
<td>10</td>
<td>Gadodiamide or gadobenate dimeglumine (0.1–0.2 mmol/kg)</td>
<td>T1-weighted GRE with PSIR (TI 200–300 ms)</td>
<td>&gt;5 SDs above the mean signal intensity of normal remote myocardium, irrespective of LGE pattern or location. LGE quantified as a % of LV mass (%LGE)</td>
</tr>
<tr>
<td>Patel et al6</td>
<td>10</td>
<td>Gadoversetamide (0.15 mmol/kg)</td>
<td>Segmented inversion recovery GRE (TI 280–360 ms)</td>
<td>2 blinded readers using a semiquantitative 5-point LGE scale for each myocardial segment. LGE quantified by summing each segments’ score and dividing by 17</td>
</tr>
<tr>
<td>Greulich et al7</td>
<td>5–10</td>
<td>Gadodiamide or Gadopentetate dimeglumine (0.15 mmol/kg)</td>
<td>Segmented inversion recovery fast GRE</td>
<td>2 blinded readers using the Siemens Argus analysis software package, and the results were expressed as percentage of myocardial mass</td>
</tr>
<tr>
<td>Nadel et al8</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>2 blinded readers assessed LGE as typical for cardiac sarcoidosis when present in a nonvascular distribution in 2 orthogonal views and other potential clinical causes of LGE could be excluded</td>
</tr>
<tr>
<td>Nagai et al10</td>
<td>10</td>
<td>Gadopentetate dimeglumine (0.15 mmol/kg)</td>
<td>Inversion recovery SSFP (TI fixed 300 ms)</td>
<td>LGE determined by retrospective review of CMR reports</td>
</tr>
<tr>
<td>Crawford et al9</td>
<td>15</td>
<td>Gadopentetate dimeglumine (0.20 mmol/kg)</td>
<td>Inversion recovery GRE (TI 250–360 ms)</td>
<td>2 blinded readers rated LGE by visual scoring. LGE quantified as % of the left ventricular mass, using the Full-Width-Half-Maximum method</td>
</tr>
<tr>
<td>Shafee et al10</td>
<td>10–15</td>
<td>Gadopentetate dimeglumine (0.15 mmol/kg)</td>
<td>Inversion-recovery GRE (TI 200–300 ms)</td>
<td>2 experienced readers blinded to outcomes determined LGE+ or LGE−</td>
</tr>
</tbody>
</table>

Five studies reported the use of 2 experienced, blinded readers for CMR interpretation, whereas Nagai et al and Murtagh et al used retrospective review of the reports of previously clinically interpreted CMR. CMR indicates cardiac magnetic resonance; GRE, gradient recall echo; LGE, late gadolinium enhancement; and TI, inversion time used to null myocardium during LGE sequence.

The annualized incidence of death or ventricular arrhythmia was 8.8% versus 0.6% for LGE positive versus LGE negative, respectively (Figure 2). The pooled RR was 6.20 (95% confidence interval, 2.47–15.6; P<0.001), Figure 6. All studies demonstrated a trend toward or statistically significantly increased risk for those with LGE, except for Nagai et al10.

Table 3. Definitions of Adverse Clinical Outcomes Reported by Each Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Arrhythmia End Points Reported</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murtagh et al5</td>
<td>Sustained ventricular arrhythmia (ie, lasting ≥30 s or any polymorphic VT), or appropriate ICD shock</td>
<td>Primary: All-cause mortality, sustained ventricular arrhythmia (ie, lasting ≥30 s or any polymorphic VT), or appropriate ICD shock</td>
</tr>
<tr>
<td>Patel et al6</td>
<td>Ventricular tachyarrhythmia leading to appropriate ICD discharge (based on stored electrograms) or symptomatic bradyarrhythmia leading to pacemaker implantation</td>
<td>Primary: Composite of all-cause mortality or symptomatic ventricular arrhythmia</td>
</tr>
<tr>
<td>Greulich et al7</td>
<td>Aborted SCD defined as resuscitation after cardiac arrest (cardioversion and/or cardiopulmonary resuscitation in a patient who remains alive 28 d later). Appropriate ICD shock defined as triggered by VT or VF and documented by stored intracardiac electrocardiographic data. VT defined as ≥3 ventricular beats &gt;120 bpm for ≥30 s. NSVT defined as 3 or more ventricular beats &gt;120 bpm for &gt;30 s</td>
<td>Primary: death, aborted sudden cardiac death, and appropriate ICD therapy Secondary: VT or NSVT</td>
</tr>
<tr>
<td>Nadel et al8</td>
<td>Sudden cardiac death, VT, VF, appropriate ICD therapy excluding antitachycardia pacing</td>
<td>Primary: Composite of SCD, VT, and VF Secondary: All-cause mortality, CV mortality, and VA (VT, VF, and appropriate ICD therapy excluding antitachycardia pacing)</td>
</tr>
<tr>
<td>Nagai et al10</td>
<td>Ventricular arrhythmia with clinical symptoms and necessitating admission or bradyarrhythmia leading to pacemaker implantation.</td>
<td>Primary: composite of all-cause death, heart failure admission, and symptomatic arrhythmia</td>
</tr>
<tr>
<td>Crawford et al9</td>
<td>Cardiac arrest or VT/VF on ECG or device electrogram only at least ≤30 s or requiring defibrillation.</td>
<td>Primary: ventricular arrhythmia Secondary: All-cause mortality, CV mortality, VT or VF, and combined death or VT/VF</td>
</tr>
<tr>
<td>Shafee et al10</td>
<td>VA identified by 12-lead ECG, Inpatient telemetry or Holter ECG and defined as 3 or more consecutive beats of ventricular origin, at a rate of more than 100 bpm, thus including NSVT, VT, and VF</td>
<td>Primary: ventricular arrhythmia Secondary: composite of VA, heart failure hospitalizations, and cardiovascular mortality.</td>
</tr>
</tbody>
</table>

For meta-analysis, bradyarrhythmia and NSVT were excluded. CV indicates cardiovascular; ICD, implantable cardiac defibrillator; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death; VA, ventricular arrhythmia; VF, ventricular fibrillation; and VT, ventricular tachycardia.
which was a screening cohort with a low prevalence of corticosteroid use, a low prevalence of disease (13% LGE+) and without any cardiac-specific adverse events. There was no statistical evidence of heterogeneity (I²=0%; P=0.7).

**Outcomes With Insufficient Data for Analysis**

Our a priori methods called for analysis of the outcomes of heart block requiring pacemaker implantation and hospital admission for heart failure. However, only 3 studies reported the outcome of heart block requiring pacemaker implantation and 2 reported heart failure outcomes. These end points were summarized (Tables 1 and 4) qualitatively without meta-analysis. Additionally, our methods sought to abstract detailed information regarding baseline corticosteroid or immunotherapy use. Although all studies reported qualitative information regarding baseline corticosteroid and immunotherapy use, most studies did not distinguish between current or prior use. Additionally, corticosteroid dosage and duration and adjunctive immunotherapy were heterogeneous (Table 1). Therefore, a summary of reported immunotherapy is provided with no statistical analysis.

### Table 4. Adverse Clinical Outcomes According to Late Gadolinium Enhancement

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Follow-Up, y</th>
<th>LGE Positive (n=173), n (%)</th>
<th>Ventricular Arrhythmia</th>
<th>Death or Ventricular Arrhythmia</th>
<th>CV Mortality</th>
<th>Pacemaker</th>
<th>Heart Failure Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murtagh et al⁶</td>
<td>205</td>
<td>3.0</td>
<td>6 (4.9)</td>
<td>4 (3.3)</td>
<td>0 (0)</td>
<td>10 (8.1)</td>
<td>2 (0.4)</td>
<td>...</td>
</tr>
<tr>
<td>Patel et al⁵</td>
<td>81</td>
<td>1.8</td>
<td>4 (10.5)</td>
<td>2 (1.8)</td>
<td>0 (0)</td>
<td>6 (15.7)</td>
<td>2 (1.8)</td>
<td>...</td>
</tr>
<tr>
<td>Greulich et al⁶</td>
<td>153</td>
<td>2.6</td>
<td>3 (3)</td>
<td>7 (6.9)</td>
<td>0 (0)</td>
<td>11 (10.8)</td>
<td>1 (0.3)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Nadel et al⁸</td>
<td>106</td>
<td>3.1</td>
<td>4 (4.1)</td>
<td>8 (8.2)</td>
<td>0 (0)</td>
<td>12 (12.2)</td>
<td>9 (4)</td>
<td>3 (3.1)</td>
</tr>
<tr>
<td>Nage et al⁶</td>
<td>61</td>
<td>4.2</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Crawford et al⁶</td>
<td>51</td>
<td>4.0</td>
<td>2 (1.6)</td>
<td>13 (10.2)</td>
<td>0 (0)</td>
<td>14 (10.9)</td>
<td>1 (1.3)</td>
<td>1* (0.8)</td>
</tr>
<tr>
<td>Shafee et al⁵</td>
<td>37</td>
<td>3.8</td>
<td>...</td>
<td>7 (7.2)</td>
<td>0 (0)</td>
<td>11 (11.3)</td>
<td>0 (0)</td>
<td>...</td>
</tr>
<tr>
<td>Pooled</td>
<td>694</td>
<td>...</td>
<td>19 (3.2)</td>
<td>41 (5.9)</td>
<td>0 (0)</td>
<td>64 (10.8)</td>
<td>18 (0.6)</td>
<td>10 (1.9)</td>
</tr>
</tbody>
</table>

Columns represent absolute (% annualized incidence). Outcomes pooled by random effects meta-analysis are reported in the final row. Only 3 studies reported 6 pacemaker implantations because of heart block, and 2 studies reported heart failure exacerbations; these 2 outcomes with limited data were not pooled. * CV mortality from Crawford⁹ was not included in pooled outcome because of unknown cause of death in comparison group. CV indicates cardiovascular; and LGE, late gadolinium enhancement.

![Figure 2. Annualized event rates according to late gadolinium enhancement (LGE) positive vs negative. CV indicates cardiovascular.](http://circimaging.ahajournals.org/)

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Quality Assessment and Evaluation for Small Study Effects

Studies were rated as high quality with a median of 8 points by the Newcastle Ottawa Scale. Cases and controls were drawn from similarly referred populations in each study, with clear definition of exposure (LGE) and outcomes. All studies had complete or nearly complete follow-up. Three studies did not make attempts to adjust, although this was related to the lack of statistical power. The median quality score was 8 (range, 7–9; Table II in the Data Supplement). There was no evidence for small study effects for any of the outcomes ($P=0.9$ for mortality; $P=0.8$ for cardiovascular mortality; $P=0.9$ for death or ventricular arrhythmia; and $P=0.1$ for ventricular arrhythmia).

Discussion

This systematic review and meta-analysis of LGE prognosis among patients with known or suspected CS offers comprehensive and robust data that CMR is useful in stratifying patients into low or high risk for future cardiac death and ventricular arrhythmias. Although several prior studies evaluated the prognostic utility of CMR in patients with suspected CS, these studies have been limited by small sample sizes and low event rates, which have resulted in a large variability in effect size. In our analysis of 7 observational studies, which included 694 patients, with a mean follow-up duration of 36 months, we found that patients with LGE on CMR had 10.8% annualized incidence of either death or ventricular arrhythmias versus 0.6% for those without LGE (relative risk, 5.5; $P<0.001$). Furthermore, the event rates among patients without LGE on CMR as compared with patients with LGE on CMR were consistently lower and statistically significant for all outcomes, including all-cause mortality, cardiac death, and ventricular arrhythmias.

Overall, CS carries a high risk of death and ventricular arrhythmia, thus a diagnosis of CS bears significant therapeutic and prognostic implications. Clinical guidelines have been proposed by the Japanese Ministry of Health and Welfare criteria to aid in the diagnosis of CS. These guidelines were initially described in 1993, and subsequently updated in 2007. However, these criteria have not been systematically validated and have lower sensitivity and specificity when compared with imaging modalities including CMR and 2-deoxy-2-[fluorine-18] fluoro-deoxyglucose positron emission tomography ($^{18}$F-FDG PET) imaging. It is worth noting that the 2007 update of the Japanese Ministry of Health and Welfare criteria has included the presence of LGE on CMR as one of

### Table: All Cause Mortality

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Years</th>
<th>LGE Positive Deaths</th>
<th>LGE Negative Deaths</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moraghi et al</td>
<td>205</td>
<td>3</td>
<td>6/41</td>
<td>2/164</td>
<td>12.00 (0.80, 179.93)</td>
</tr>
<tr>
<td>Patel et al</td>
<td>81</td>
<td>1.8</td>
<td>4/21</td>
<td>2/68</td>
<td>5.71 (0.64, 50.93)</td>
</tr>
<tr>
<td>Greveck et al</td>
<td>153</td>
<td>2.6</td>
<td>3/39</td>
<td>1/114</td>
<td>8.77 (0.24, 321.53)</td>
</tr>
<tr>
<td>Nadal et al</td>
<td>106</td>
<td>3.1</td>
<td>3/32</td>
<td>1/74</td>
<td>1.35 (0.16, 3.31)</td>
</tr>
<tr>
<td>Crawford et al</td>
<td>61</td>
<td>4.2</td>
<td>4/8</td>
<td>3/51</td>
<td>1.10 (0.00, 111.15)</td>
</tr>
<tr>
<td>Nagai et al</td>
<td>51</td>
<td>4</td>
<td>2/32</td>
<td>1/19</td>
<td>1.29 (0.01, 126.04)</td>
</tr>
<tr>
<td>Overall, $p=0.03$</td>
<td>401</td>
<td>2.8</td>
<td>10/100</td>
<td>2/301</td>
<td>3.38 (1.07, 10.79)</td>
</tr>
</tbody>
</table>

Chi-squared = 2.79, $p = 0.7$; 1-squared = 0%

### Table: Cardiovascular Mortality

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Follow-up Years</th>
<th>LGE Positive Deaths</th>
<th>LGE Negative Deaths</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel et al</td>
<td>81</td>
<td>1.8</td>
<td>4/21</td>
<td>1/60</td>
<td>11.43 (0.64, 202.90)</td>
</tr>
<tr>
<td>Greveck et al</td>
<td>153</td>
<td>2.6</td>
<td>3/39</td>
<td>0/114</td>
<td>17.54 (0.15, 2115.06)</td>
</tr>
<tr>
<td>Nadal et al</td>
<td>106</td>
<td>3.1</td>
<td>3/32</td>
<td>1/74</td>
<td>6.94 (0.13, 341.41)</td>
</tr>
<tr>
<td>Nagai et al</td>
<td>61</td>
<td>4.2</td>
<td>0/8</td>
<td>0/53</td>
<td>(Excluded)</td>
</tr>
<tr>
<td>Overall, $p=0.03$</td>
<td>401</td>
<td>2.8</td>
<td>10/100</td>
<td>2/301</td>
<td>10.74 (1.34, 86.33)</td>
</tr>
</tbody>
</table>

Chi-squared = 0.04, $p = 1.0$; 1-squared = 0%

Figure 3. Pooled relative risk (RR) for all-cause mortality according to late gadolinium enhancement (LGE) positive vs negative. CI indicates confidence interval and MRI, magnetic resonance imaging.

Figure 4. Pooled relative risk (RR) for cardiovascular mortality according to late gadolinium enhancement (LGE) positive vs negative. CI indicates confidence interval and MRI, magnetic resonance imaging.
the minor criterion to aid in the diagnosis of CS. Recently, the Heart Rhythm Society also introduced an expert consensus statement, which has also not been validated scientifically but does acknowledge the role of LGE on CMR to aid in the diagnosis of CS in patients with syncope or presyncope, abnormal ECG, and abnormal echocardiogram. These Heart Rhythm Society experts recommend consideration of the presence of LGE for referral to diagnostic electrophysiological study to evaluate for inducible ventricular tachycardia that may benefit from primary prevention ICD implantation (Class IIB, Level of evidence C).21

CMR is a powerful tool that can provide comprehensive cardiac information to aid in the diagnosis of CS, including left ventricular systolic function, ventricular volumes and dimension, myocardial thinning, wall motion abnormalities, myocardial edema, and LGE. However, the most useful CMR parameter in the diagnosis of CS is the presence or absence of LGE. It should be borne in mind, that because LGE accumulation represents areas of underlying fibrosis, this can be a non-specific finding and can occur in various conditions, including scar from previous myocarditis or fibrosis from other cardiomyopathies. Although the typical LGE pattern in CS is midmyocardial and subepicardial involvement, occasionally CS may demonstrate subendocardial LGE, and thus mimic a prior myocardial infarction. Our analysis supports the clinical practice of using CMR to estimate the likelihood of CS and obtain prognostic information.

In patients with the suspicion of CS, the absence of LGE has a sufficiently high negative predictive value and reassuring event-free survival that no further testing would be required for the majority of patients. In our analysis, the majority of the patients (495/694 patients; 71%) did not have any evidence of LGE. This group of LGE-negative patients had low annual-ized incidence rates of cardiovascular mortality and ventricular arrhythmias at 0.6% and 0%, respectively. This confers a 68% and 100% relative risk reduction as compared with patients who were LGE positive, respectively. Similarly, for the combined outcome of mortality or ventricular arrhythmias, the annualized incidence rate was 10.8% versus 0.6% for LGE positive versus LGE negative, a 94% relative risk reduction. However, it should be noted that these risk differences according to LGE occur in the majority of studies that included sarcoidosis patients with known or suspected cardiac involvement. A relative outlier study with discordant findings by Nagai et al10 merits closer

<table>
<thead>
<tr>
<th>Author</th>
<th>Follow-up Years</th>
<th>LGE Positive Events</th>
<th>LGE Negative Events</th>
<th>RR (95% CI)</th>
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<tr>
<td>Mortaghi et al</td>
<td>205</td>
<td>4 / 41</td>
<td>0 / 164</td>
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<td>Patel et al</td>
<td>81</td>
<td>18</td>
<td>0 / 60</td>
<td>11.43 (0.19, 765.55)</td>
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<tr>
<td>Grothlich et al</td>
<td>153</td>
<td>26</td>
<td>0 / 114</td>
<td>40.02 (0.42, 4062.17)</td>
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<td>Nadel et al</td>
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<td>31</td>
<td>0 / 74</td>
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<td>Crawford et al</td>
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<tr>
<td>Shafiee et al</td>
<td>37</td>
<td>3</td>
<td>0 / 11</td>
<td>5.92 (0.05, 1292.72)</td>
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<td>Overall, p = 0.083</td>
<td>694</td>
<td>41 / 190</td>
<td>0 / 495</td>
<td>19.54 (2.68, 142.59)</td>
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Relative Risk for Late Gadolinium Enhancement by MRI
Chi-squared = 1.42, p = 1.0; I-squared = 0%

Figure 5. Pooled relative risk (RR) for ventricular arrhythmia according to late gadolinium enhancement (LGE) positive vs negative. CI indicates confidence interval and MRI, magnetic resonance imaging.

<table>
<thead>
<tr>
<th>Author</th>
<th>Follow-up Years</th>
<th>LGE Positive Events</th>
<th>LGE Negative Events</th>
<th>RR (95% CI)</th>
</tr>
</thead>
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<td>Mortaghi et al</td>
<td>205</td>
<td>10 / 41</td>
<td>2 / 164</td>
<td>28.00 (1.54, 259.21)</td>
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<td>Patel et al</td>
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<td>32.15 (1.25, 827.93)</td>
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<tr>
<td>Nadel et al</td>
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<td>3.1</td>
<td>9 / 74</td>
<td>3.08 (0.82, 11.63)</td>
</tr>
<tr>
<td>Nagai et al</td>
<td>61</td>
<td>4.2</td>
<td>3 / 53</td>
<td>1.10 (0.00, 411.15)</td>
</tr>
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<td>Crawford et al</td>
<td>51</td>
<td>14 / 12</td>
<td>1 / 19</td>
<td>8.51 (0.17, 408.79)</td>
</tr>
<tr>
<td>Shafiee et al</td>
<td>37</td>
<td>3.8</td>
<td>11 / 26</td>
<td>9.31 (0.05, 1894.22)</td>
</tr>
<tr>
<td>Overall, p=0.001</td>
<td>694</td>
<td>64 / 199</td>
<td>18 / 495</td>
<td>6.20 (2.47, 15.55)</td>
</tr>
</tbody>
</table>

Relative Risk for Late Gadolinium Enhancement by MRI
Chi-squared = 3.82, p = 0.7; I-squared = 9%

Figure 6. Pooled relative risk (RR) for combined death or ventricular arrhythmia according to late gadolinium enhancement (LGE) positive vs negative. CI indicates confidence interval and MRI, magnetic resonance imaging.
inspection. In the study by Nagai et al, the population was explicitly a screening cohort that excluded any patients with potential cardiac symptoms and thus had the lowest prevalence of LGE+ scans among all 7 studies thereby reducing statistical power. Although the study by Patel et al did reach out to pulmonary and rheumatology clinics to recruit sarcoidosis patients, 21% of patients had possible cardiac symptoms. Furthermore, the use of corticosteroids was among the lowest in the study by Nagai et al (16%) when compared with the study by Patel et al (91%) and other studies, suggesting the patients in the study by Nagai et al had less active sarcoid and were a lower risk population. Additionally, the study by Nagai et al did not use 2 blinded experienced readers (clinical reports reviewed retrospectively), whereas 5 of 7 studies did report the interpretation by 2 blinded readers (Table 2), and the study by Nagai et al had other previously mentioned differences in scan acquisition. Whether this influenced the sensitivity of CMR to detect LGE is not known, but is possible, because the use of a fixed inversion time without nulling myocardium is not a standard practice. Consequently in the study by Nagai et al, there were no arrhythmic events or cardiac deaths among the LGE-positive subjects and the only events were 3 all-cause deaths among the LGE-negative group. Thus, these outlying results underscore the importance of having a clinical suspicion of cardiac involvement of sarcoidosis before referring to CMR.

Despite the low event rates in patients without LGE on CMR, it is worth noting that cardiovascular death occurred in 2 patients without the evidence of LGE on CMR. Also, as mentioned earlier, because LGE accumulation represents underlying fibrosis, some patients referred for CMR with the suspicion of CS may have nonspecific LGE findings. In such cases, in patients with negative LGE by CMR but a high clinical suspicion, or in patients with pacemakers or ICDs who cannot undergo an MRI, cardiac PET may be useful for further evaluation. Another application of cardiac PET imaging in these patients is to assess the response to immunosuppressive therapy, particularly in light of recent data showing that a reduction in myocardial inflammation, as assessed by fluoro-deoxyglucose PET, is associated with an improvement in ejection fraction. Further studies are necessary to evaluate whether fluoro-deoxyglucose imaging provides incremental prognostic information among patients who are LGE positive.

While interpreting the results of our study, it is important to keep in mind that despite the higher event rate among patients with LGE, not all the patients with LGE develop adverse outcomes. To further stratify these patients and obtain additional prognostic information beyond the presence or absence of LGE, potentially significant clinical variables may include left ventricular ejection fraction, right ventricular ejection fraction, ECG abnormalities, race, and sex. Moreover, other information, which can be potentially obtained from routine CMR and utilized to risk-stratify these patients, could include the amount of LGE, T1 and T2 mapping, and an evaluation of left and right ventricular function. In this meta-analysis, we were unable to evaluate these variables, as these variables were not systematically reported in each study. Future longitudinal follow-up studies, ideally from multicenter registries, will be required to evaluate if these parameters can further risk-stratify both the LGE-positive and LGE-negative cohorts.

Our results are subject to limitations inherent to any meta-analysis based on pooling of data from different studies with different inclusion criteria, different designs, variable follow-up duration, and different patient populations. However, despite varying patient characteristics, our results did not demonstrate any significant statistical heterogeneity. Because we did not have access to raw data of individual patients, it was not possible to adjust for various patient factors, including age, sex, ejection fraction, race, prior or current use of steroids, and other medical therapies. Nevertheless, studies included in this analysis that were powered to adjust for these variables indicated that LGE was a more significant predictor of prognosis than left ventricular ejection fraction and these other covariates. Another important limitation is that most studies had relatively small sample sizes, as the majority of the studies are single-center studies. However, the results were consistent across diverse sites and the use of pooled data analysis provides statistical power that was lacking in several of the individual publications. Finally, because of the lack of events in some analyses, the relative risk estimates may be imprecise, which most significantly affects the outcome of ventricular arrhythmia because no events occurred among those without LGE. However, this would not affect the significant and clinically meaningful absolute differences in annualized event rates.

Conclusions

The presence of LGE on cardiac MRI among patients with known or suspected CS provides strong prognostic information with regard to future all-cause mortality, cardiovascular mortality, and ventricular arrhythmia. Although the presence of LGE in 29% of patients was associated with a high rate of adverse events, the absence of any LGE offered the reassurance of a low-risk prognosis of ventricular arrhythmia or cardiovascular death.

Disclosures

None.

References

Myocardial infiltration occurs in ≈25% of patients with known extra-cardiac sarcoidosis and is increasingly recognized as an important cause of arrhythmia and death. Multiple clinical criteria have been proposed to aid in diagnostic and prognostic evaluation of known or suspected cardiac sarcoidosis, starting with the 1993 (revised in 2007) Japanese Ministry of Health and Welfare criteria to, more recently, an expert consensus statement proposed by the Heart Rhythm Society. However, such clinical criteria lack sensitivity, and the evaluation for late gadolinium enhancement (LGE) by cardiac magnetic resonance has been demonstrated in several small cohorts to have a potential prognostic role. However, these have been limited by small sample size leading to conflicting results. In our systematic review and meta-analysis, we evaluated the prognostic value of cardiac magnetic resonance for patients with known or suspected cardiac sarcoidosis. Among 7 studies of 694 patients, 29% were LGE positive. We demonstrated a markedly increased risk of all-cause mortality, ventricular arrhythmia, cardiovascular mortality, and combined death or ventricular arrhythmia. These findings bear significance because consensus opinions for the diagnosis of cardiac sarcoidosis have not been validated scientifically. In the limited studies comparing such clinical criteria to LGE by cardiac magnetic resonance, the LGE findings offer superior diagnostic and prognostic value. Thus, abnormal LGE findings may be used to counsel nearly one third (29% LGE+ in our analysis) of sarcoidosis patients of increased risk of future death or ventricular arrhythmia. Furthermore, a normal cardiac magnetic resonance conveys a powerful, low-risk prognosis among the patients in these cohorts.
Presence of Late Gadolinium Enhancement by Cardiac Magnetic Resonance Among Patients With Suspected Cardiac Sarcoidosis Is Associated With Adverse Cardiovascular Prognosis: A Systematic Review and Meta-Analysis

Edward Hulten, Vikram Agarwal, Michael Cahill, Geoff Cole, Tomas Vita, Scott Parrish, Marcio Sommer Bittencourt, Venkatesh L. Murthy, Raymond Kwong, Marcelo F. Di Carli and Ron Blankstein

_Circ Cardiovasc Imaging_. 2016;9:e005001
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http://circimaging.ahajournals.org/subscriptions/
SUPPLEMENTAL MATERIAL

Supplemental Method. Search strategy.

Pubmed:

AND

Embase:

((sarcoidosis'/exp AND (heart'/exp OR 'heart disease'/exp)) OR (sarcoid* NEAR/3 (cardiac OR coronary OR heart OR cardiomyopath* OR myocardial* OR ventric*)):ab,ti)
AND
('nuclear magnetic resonance imaging'/exp OR 'magnetic resonance':ab,ti OR 'magnetization transfer':ab,ti OR ((mr OR nmr) NEXT/1 imag*):ab,ti OR mri:ab,ti)

Web of Science:

TS=("sarcoid**" NEAR/3 ("cardiac" OR "coronary" OR "heart" OR "cardiomyopath**" OR "myocardial**" OR "ventric**"))
AND
TS=("magnetic resonance" OR "magnetization transfer" OR "mr imag**" OR "nmr imag**" OR "mri")
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<td>TITLE</td>
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<tr>
<td>Title</td>
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<td>Identify the report as a systematic review, meta-analysis, or both.</td>
<td>1</td>
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<tr>
<td>ABSTRACT</td>
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<td></td>
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</tr>
<tr>
<td>Structured summary</td>
<td>2</td>
<td>Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
<td>3</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
<td>6</td>
</tr>
<tr>
<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
<td>6</td>
</tr>
<tr>
<td>METHODS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol and registration</td>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
<td>7</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>6</td>
<td>Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
<td>7-8</td>
</tr>
<tr>
<td>Information sources</td>
<td>7</td>
<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
<td>7-8</td>
</tr>
<tr>
<td>Search</td>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
<td>7-8</td>
</tr>
<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
<td>8</td>
</tr>
<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
<td>8</td>
</tr>
<tr>
<td>Data items</td>
<td>11</td>
<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
<td>8</td>
</tr>
<tr>
<td>Risk of bias in individual studies</td>
<td>12</td>
<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
<td>9</td>
</tr>
<tr>
<td>Summary measures</td>
<td>13</td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
<td>9</td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>14</td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.</td>
<td>9</td>
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</tbody>
</table>
# PRISMA 2009 Checklist

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<thead>
<tr>
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<th>Reported on page #</th>
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<tr>
<td>Risk of bias across studies</td>
<td>15</td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
<td>10</td>
</tr>
<tr>
<td>Additional analyses</td>
<td>16</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
<td>10</td>
</tr>
<tr>
<td><strong>RESULTS</strong></td>
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<td></td>
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<tr>
<td>Study selection</td>
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<td>Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.</td>
<td>10</td>
</tr>
<tr>
<td>Study characteristics</td>
<td>18</td>
<td>For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.</td>
<td>10-13</td>
</tr>
<tr>
<td>Risk of bias within studies</td>
<td>19</td>
<td>Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).</td>
<td>13-14</td>
</tr>
<tr>
<td>Results of individual studies</td>
<td>20</td>
<td>For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.</td>
<td>11-13</td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>21</td>
<td>Present results of each meta-analysis done, including confidence intervals and measures of consistency.</td>
<td>11-13</td>
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<tr>
<td>Risk of bias across studies</td>
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<td>Present results of any assessment of risk of bias across studies (see Item 15).</td>
<td>13-14</td>
</tr>
<tr>
<td>Additional analysis</td>
<td>23</td>
<td>Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).</td>
<td>13-14</td>
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<tr>
<td><strong>DISCUSSION</strong></td>
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<tr>
<td>Summary of evidence</td>
<td>24</td>
<td>Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).</td>
<td>14</td>
</tr>
<tr>
<td>Limitations</td>
<td>25</td>
<td>Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).</td>
<td>17</td>
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<td>Conclusions</td>
<td>26</td>
<td>Provide a general interpretation of the results in the context of other evidence, and implications for future research.</td>
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<td>Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.</td>
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For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org)
**Supplemental Table 2.** Quality Assessment Using Newcastle Ottawa Scale.

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