Prognostic value of late gadolinium enhancement detected on cardiac magnetic resonance imaging in cardiac sarcoidosis

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ABBREVIATIONS:

CMR = cardiac magnetic resonance
CS = cardiac sarcoidosis
ICD = implantable cardiac defibrillator
LGE = late gadolinium enhancement
LVEF = left ventricular ejection fraction
PET = positron emission tomography
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RV = right ventricular

VF = ventricular fibrillation
VT = ventricular tachycardia

ABSTRACT

Background
Sarcoidosis is a complex multi-system inflammatory disorder with around 5% of patients having overt cardiac involvement. Patients with cardiac sarcoidosis are at an increased risk of both ventricular arrhythmias and sudden cardiac death. Previous studies have shown that the presence of LGE on CMR is associated with an increased risk of mortality and ventricular arrhythmias and may be useful in predicting prognosis.

Objectives
This systematic review and meta-analysis assessed the value of late-gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging in predicting prognosis for patients with known or suspected cardiac sarcoidosis.

Methods
We searched EMBASE and MEDLINE databases from inception to March 2022 for studies reporting individuals with known or suspected cardiac sarcoidosis referred for CMR with LGE. Outcomes were defined as all-cause mortality, ventricular arrhythmia or a composite outcome of either death or ventricular arrhythmias. The primary analysis evaluated these outcomes according the presence of LGE. A secondary analysis evaluated outcomes specifically according to the presence of biventricular LGE.

Results
Thirteen studies were included (1318 participants) in the analysis, with an average participant age of 52.0 years, LGE prevalence 13%-70%, over a follow-up of 3.1 years. Patients with LGE on CMR versus those without had higher odds of ventricular arrhythmias, all-cause mortality and the composite of both (OR 20.3, 95% CI 8.1-51.0; OR 3.45, 95% CI 1.6-7.3; OR 9.2, 95% CI 5.1-16.7, respectively). RV LGE is invariably accompanied by LV LGE. Biventricular LGE is also associated with markedly increased odds of ventricular arrhythmias (OR 43.6, 95% CI 16.2-117.2).

Conclusions
Patients with known or suspected cardiac sarcoidosis with LGE on CMR have significantly increased odds of both ventricular arrhythmias and all-cause mortality. The presence of biventricular LGE may confer additional prognostic information regarding arrhythmogenic risk.

INTRODUCTION

Sarcoidosis is a complex multi-system inflammatory condition characterised histologically by the presence of non-caseating granulomas. The lungs are affected in more than 90% of patients, however the disease can also affect other organ systems such as the lymphatics, skin, kidneys, eyes or the central nervous system. In patients with systemic sarcoidosis, 5%

are diagnosed with overt cardiac involvement[1]. This increases to 20-30% in autopsy studies[2,3] suggesting it is an under-diagnosed and furthermore often asymptomatic condition. Cardiac involvement confers a significantly increased risk of mortality with 14% of patients with cardiac sarcoidosis (CS) having an initial presentation of fatal or aborted sudden cardiac death[4]. Affected patients are at risk of ventricular arrhythmias, atrioventricular block, heart failure and sudden cardiac death, with a 10% estimated mortality at 5 years[5,6].

The diagnosis of CS is challenging, as reflected by the lack of consensus amongst available guidelines such as the Heart Rhythm Society, World Association of Sarcoidosis and Other Granulomatous Disorders, and Japanese Circulation Society guidelines (Supplementary Table 1) [7-9]. Both clinical criteria and endomyocardial biopsy have limited diagnostic sensitivity and specificity, therefore advanced imaging techniques such as cardiac magnetic resonance (CMR) imaging and cardiac positron emission tomography (PET) are increasingly being used to provide important diagnostic and prognostic information. Recent guidance from the American Thoracic Society recommends CMR in preference to PET or echocardiography for those with extracardiac sarcoidosis and suspected cardiac involvement[10]. CMR with T1 and T2-mapping can delineate myocardial oedema and inflammation[11]. Late-gadolinium enhancement (LGE), which indicates an expansion of the extracellular volume, can correlate with either myocardial fibrosis or oedema in CS patients, the distribution of which can be helpful to differentiate CS from other cardiomyopathies[12-13].

The presence of LGE has important prognostic implications. CS patients with LGE have higher mortality rates[14], irrespective of their left ventricular ejection fraction (LVEF)[15-16]. LGE also increases the risk of clinically significant ventricular arrhythmias in these patients[17-18]. Most of the available prognostic data comes from small, single-centre studies, however two previous meta-analyses have shown that in patients with known or suspected CS, the presence of LGE is significantly associated with increased risk of all-cause mortality, cardiovascular mortality and ventricular arrhythmia[19-20].

The mainstay of treatment for CS is with immunosuppressive drugs which can have significant side-effect profiles. Accurate identification of these adverse prognostic features is therefore paramount prior to considering patients for these therapies. Prognostic information afforded by CMR may also aid in patient selection for implantable cardiac defibrillator (ICD) implantation. We therefore sought to perform a meta-analysis assessing the prognostic impact of LGE in patients with known or suspected CS.

METHODS

Search Strategy

A literature search was performed from inception to 15th March 2022 to identify studies eligible for quantitative analysis. EMBASE and MEDLINE databases were systematically searched using the search terms [“late gadolinium” OR “cardiac MRI”] AND [“cardiac

sarcoidosis" OR cardiac sarcoid"] to identify both prospective and retrospective studies of patients referred for CMR with biopsy-proven or clinically suspected CS.

Study Selection

Studies were considered eligible for inclusion if they included an evaluation of LGE with respect to any of these outcomes. Studies which included populations with known coronary artery disease or other cardiomyopathies were excluded. We excluded studies that included patients without CMR LGE data, whereby reported outcome data could not be stratified according to LGE positivity. The search had no language restrictions and was limited to full text articles only, and excluded case reports. We also reviewed citations from included studies. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed.

Two reviewers independently screened each abstract for potential eligibility with any disagreements resolved by a third reviewer. Full text articles for those studies selected were obtained and two separate reviewers assessed these articles for eligibility as per the inclusion/exclusion criteria.

Outcomes of interest

Our pre-specified study outcomes were as follows: i) all-cause mortality, ii) ventricular arrhythmia, iii) composite outcome of either all-cause mortality or ventricular arrhythmia. We have defined ventricular arrhythmia as symptomatic or sustained ventricular tachycardia (VT), ventricular fibrillation (VF) or appropriate ICD intervention. Appropriate ICD interventions were defined as anti-tachycardia pacing or device shocks. Our composite outcome is defined specifically as the occurrence of either all-cause mortality or ventricular arrhythmia (sustained VT, VF or appropriate ICD intervention).

Data Collection and Analysis

Data was extracted directly from the included studies into preformatted excel spreadsheets by two independent reviewers. Details of the study design (retrospective or prospective, single-centre or multi-centre) and country were recorded. Specific inclusion criteria and definitions of their end points were collected for each study. In addition to data meeting the aforementioned outcomes, data were also collected for the following variables: LGE prevalence (%), left ventricular (LV) LGE prevalence (%), right ventricular (RV) LGE prevalence (%), LGE mass (%), age, gender, ethnicity, LVEF (%), LV end-diastolic volume (ml), extra-cardiac sarcoidosis (%), biopsy-proven CS (%), steroid or immunosuppressant use (%), heart failure according to New York Heart Association classification (%), ICD/pacemaker prevalence (%), baseline electrocardiogram (ECG) characteristics and incidence of prior VT (%). Details on specific CMR-protocols were also extracted. Outcome data was collected as per our pre-specified outcomes.

In the primary analysis, these pre-specified outcomes were evaluated according to the presence of any LGE versus the absence of LGE. 'Any' LGE was defined as the presence of LGE anywhere (i.e. LV, RV or biventricular). A secondary analysis evaluated outcomes

specifically according to the presence of RV LGE versus no RV LGE, and biventricular LGE versus no biventricular LGE. RV LGE was defined as LGE of the RV free wall. Extracted data were synthesised using meta-analysis. We sought to interrogate any associations found for interactions with other clinically relevant characteristics. We used meta-regression to assess for an interaction between LVEF (%), LGE prevalence (%), LGE mass (g), age and sex with the odds for each outcome.

Quality and risk of bias of included studies

The quality of included studies was assessed independently by two reviewers using the Newcastle Ottawa Quality Assessment Scale for Cohort Studies[21]. This scale rates study quality on a scale of 0 to 9 based upon a series of questions regarding patient selection, comparability and outcome measures.

Statistical Analysis

Descriptive statistics were calculated in SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp). Study endpoints were analysed using random-effects, restricted maximum-likelihood meta-analyses and meta-regression was used to assess for interactions with outcomes (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.). I^2 statistics were used to assess for heterogeneity. An alpha value of <0.05 was considered statistically significant, except for our meta-regression analysis where an alpha value of <0.01 was used to control for multiple comparisons. Annualised event rates were calculated using average study follow-up, graphically charted using GraphPad Prism version 8.0.0 (GraphPad Software, San Diego, California, USA) and statistically analysed in SPSS. Sensitivity analysis was performed on the data analysed, eligibility criteria and analysis methods. Recommendations made in the Cochrane Handbook for Systematic Reviews were followed in the analysis of these[22].

Ethical approval

Ethical approval was not required as this is a systematic review and meta-analysis of previously published data.

RESULTS

Literature search

The literature search results are displayed in Figure 1. A total of 13 observational studies were included with a total of 1318 patients[14-18, 23-31]. All of these patients had undergone CMR with an assessment of LGE. We excluded those studies which included patients without CMR data and therefore outcome data could not be stratified according to LGE positivity[32].

Study characteristics

Study characteristics are described in Table 1 and included participant characteristics are described in Table 2. 6 studies were prospective studies and 7 were retrospective studies. 11 studies were single-centre studies and 2 were multi-centre studies. One study included patients who were asymptomatic from a cardiac perspective[28] and 2 studies exclusively recruited patients with an LVEF>50%[15,28]. Only two of the included studies had patients with an average LVEF<50%[26-27].

The median follow-up duration was 3.1 years (range 1.5 to 4.7 years). The weighted mean age of the population was 52.0 years and 46.4% were male. LGE prevalence ranged from 13% to 70% with a weighted mean of 33.2%. 92.7% of included patients had biopsy-proven extra-cardiac sarcoidosis. Steroid or immunosuppression use, prior episodes of ventricular arrhythmia and presence of ICDs were not uniformly reported. Similar methods for acquisition and interpretation of LGE were reported, with gadolinium dose ranging from 0.1 to 0.2 mmol/kg in keeping with usual clinical practice (Table 3). Sustained VT was defined as lasting >30s[14,25], requiring defibrillation[25] or was not specified beyond being sustained.

Two studies reported outcomes specifically for patients with RV LGE[24-25]. These studies defined RV involvement as LGE of the RV free-wall. One study defined RV involvement as including the right-sided interventricular septum, rather than solely the RV free-wall, therefore it was not included in further analysis of RV LGE outcomes[31]. Within the included studies, 8.5% (29/341) of patients had RV LGE, of which all had biventricular LGE. There were no reports of isolated RV LGE. No studies reported outcomes specifically according to LV LGE, therefore this further analysis was not performed.

Study quality and Risk of Bias

Overall, the included studies were of high quality. Their detailed scores on the Newcastle Ottawa Quality Assessment Scale are reported (Table 4), with 11 out of the 13 included studies being awarded a minimum score of 8 out of a maximum of 9. There was no evidence for small study bias (Supplementary Figure 1A–1C).

All-cause mortality

From 10 studies with 923 patients the mortality rate, over a median study duration of 3.0 years (IQR 2.0 to 3.6 years), was 10.7% (30/280) in the any LGE-positive group and 3.4% (22/643) in the LGE-negative group. In aggregate level meta-analysis the finding of any LGE versus no LGE was associated with a significant 3.45 times the odds of mortality (95% CI 1.6 to 7.3, I^2 23.2%, $p<0.05$) (Figure 2A). This equates to a 5% absolute risk increase in mortality in patients found to have LGE on CMR (risk difference 0.047, 95% CI -0.003 to 0.097). The annualised incidence of all-cause mortality was 5.08% versus 1.07% for LGE versus no LGE ($p<0.05$), respectively (Figure 3).

From analysis of 2 studies, there was a mortality rate of 13.8% (4/29) amongst individuals with biventricular LGE over a median of 3.6 years (range 3.2 to 4.0 years). There was no significant association between the finding of biventricular LGE versus no biventricular LGE for all-cause mortality (OR 1.86, 95% CI 0.25 to 13.6, I^2 49.0%, $p>0.05$) (Figure 2B).

Ventricular Arrhythmia (Sustained VT, VF or Appropriate ICD Therapy)

From 10 studies with 859 patients, crude event rates for ventricular arrhythmias in any LGE-positive patients were 23.0% (65/283). There was only one report (0.2%) of a ventricular arrhythmia amongst LGE-negative patients (1/584) during a median of 3.1 (IQR 2.0 to 4.2) years, corresponding to a negative predictive value of 99.8%. In aggregate level meta-analysis, the odds of developing a ventricular arrhythmia if found to have any LGE on CMR are 20.3 times greater than individuals without LGE (95% CI 8.1 to 51.0, I^2 0% $p<0.05$) (Figure 4A). This can be reported as a risk difference of 0.191 (95% CI 0.103 to 0.279). The annualised incidence of ventricular arrhythmia was 6.72% versus 0.04% for LGE versus no LGE ($p<0.001$), respectively (Figure 3). In sensitivity analysis, looking specifically at both sustained VT/VF and appropriate ICD interventions separately, there is also a substantial and significantly increased risk associated with LGE (OR 17.5, 95% CI 6.9 to 44.5, I^2 0%, $p<0.05$ and OR 16.8, 95% CI 6.7 to 42.4, I^2 0%, $p<0.05$).

In aggregate analysis of 2 studies, the presence of biventricular LGE versus no biventricular LGE was associated with greatly increased crude event rates of 69.0% (20/29) and significantly increased odds of developing ventricular arrhythmia (OR 43.6, 95% CI 16.2 to 117.2, I^2 0%, $p<0.05$). (Figure 4B). In those 2 studies, the comparison of those who were LGE positive with any pattern of LGE except for biventricular LGE versus those with biventricular LGE equates to an estimated increased odds of 8.6 (95% CI 2.4 to 31.0, I2 0%, $p<0.05$). Furthermore, there was also a significant association between RV LGE and ventricular arrhythmia (OR 31.0, 95% CI 13.0 to 74.0, I2 3.7%, $p<0.05$).

All-cause mortality or Ventricular Arrhythmia (Composite Outcome)

In 10 studies with 865 patients, 33.0% (91/276) of patients who had any LGE on CMR met the composite outcome for either all-cause mortality or ventricular arrhythmia over a median study duration of 3.0 (IQR 2.2 to 4.0) years compared with 3.6% (21/589) of patients who did not have LGE on CMR. In aggregate level meta-analysis this equates to a significantly elevated odds ratio of 9.2 (95% CI 5.1 to 16.7, I^2 5.9% $p<0.05$) (Figure 5) or 25.1% increased risk (risk difference 95% CI 0.149, 0.353). The annualised incidence of the composite outcome was 12.4% versus 1.18% for LGE versus no LGE ($p<0.001$), respectively (Figure 3). Neither LGE mass nor LVEF were associated with the odds of LGE-positive mortality.

One study reported data consistent with our composite outcome for biventricular LGE and found an increased likelihood of death or ventricular arrhythmia (OR 46.8, 95% CI 7.5 to 291, $p<0.05$)[24].

Assessment for interactions

There were no interactions between assessed factors (LVEF, LGE prevalence, LGE mass, age and sex) and the observed association of the presence of LGE and increased mortality, ventricular arrhythmia and composite outcome events (Supplementary Table 2). This is consistent with the minimal heterogeneity found.

Sensitivity Analysis

None of the aforementioned outcomes were found to be affected by heterogeneity (Supplementary Table 3). The removal of retrospective studies did not affect conclusions for any LGE versus no LGE in i) all-cause mortality; ii) ventricular arrhythmia; or iii) composite (death or ventricular arrhythmia). The analyses evaluating biventricular LGE were composed solely of retrospective studies. Analysis using risk difference did not affect any of our conclusions, except for any LGE versus no LGE for all-cause mortality.

DISCUSSION

This review has found substantial and significantly increased odds of all-cause mortality and ventricular arrhythmia with the presence of LGE over mid-term follow-up. It also shows that biventricular LGE has a very significant and marked association with ventricular arrhythmia and thus that of the composite outcome of either all-cause mortality and ventricular arrhythmia. These results corroborate the outcomes of previous meta-analyses[19-20], strengthening their conclusions through the inclusion of more contemporary studies. It confirms that the presence of myocardial scarring, as determined by the presence of LGE, in patients with known or suspected CS carries significant prognostic information. It demonstrates that these patients have a significantly increased likelihood of all-cause mortality and ventricular arrhythmia over a median follow-up period of approximately 3 years. The association of ventricular arrhythmia with LGE is particularly strong. The finding of no significant heterogeneity across analyses add confidence to this conclusion. This analysis therefore firmly supports the 2014 Heart Rhythm Society expert consensus that in patients with suspected CS, a CMR should be considered[7]. The importance of CMR in the diagnosis of CS is becoming increasing recognised, and indeed the recently published guidelines from the Japanese Circulation Society include LGE detected on CMR as a major diagnostic criteria for CS[33].

In CS patients, ICD implantation currently has a class 1A recommendation for both secondary prevention and for primary prevention in patients with a LVEF<35%[34]. Recent guidelines published by the American Heart Association/American College of Cardiology /Heart Rhythm Society in 2017 have also made a class IIA recommendation for ICD implantation in CS patients with an LVEF>35% and 'extensive scar' on CMR[34], although extensive scar is not fully defined. Studies have reported that quantitative analysis of LGE may confer additional prognostic information and this should be evaluated further in future work[15,25,31,35-36]. Importantly, our review does provide reassurance that those without LGE have a low likelihood of future events, in particular when considering ventricular arrhythmias where we found a negative predictive value of 99.8% with only 1 event in a total of 584 patients over a follow-up duration of approximately 3 years.

Our analysis demonstrates that patients with biventricular LGE are significantly more likely to develop ventricular arrhythmias than those without. RV LGE is invariably accompanied by LV LGE. Biventricular LGE therefore appears to confer additional prognostic information with particularly with regards to ventricular arrhythmia rates over the presence of LV LGE alone. It is not clear whether RV LGE is uniquely arrhythmogenic, or whether RV LGE reflects

a more extensive biventricular substrate for arrhythmia. In one study, RV LGE was associated with a significantly larger LV LGE extent compared with those without RV LGE[25]. Multivariable analysis in another study, however reported that RV LGE was independently associated with the arrhythmic endpoint (HR 5.43; 95% CI: 1.25 to 23.47; p=0.024) after adjustment for LVEF, RVEF, and LV LGE extent[24]. Furthermore, RV involvement demonstrated by other imaging modalities, namely PET, has been shown to confer high risk of ventricular arrhythmia[37-38]. Interestingly, in a recent study of gross pathological findings in patients that had died of CS or had undergone cardiac transplantation, RV involvement was seen in 90.7% of cases[39]. Overall, biventricular LGE seems to be a significant independent risk factor for the development of ventricular arrhythmia, however its impact on mortality is less clear. While 'extensive scarring' is not defined in the 2017 American Heart Association/American College of Cardiology/Heart Rhythm Society recommendations for ICD implantation[34], our findings suggest that the presence of biventricular LGE alone provides useful prognostic information which should be factored into the decision for ICD implantation.

Limitations

Differences in reporting of outcomes between studies meant that only selected studies were included for each of the outcome measures of all-cause mortality, ventricular arrhythmia and the composite outcome of all-cause mortality and ventricular arrhythmia. Despite this, there was consistency in that statistical significance was reached across all outcome measures. Our outcome of ventricular arrhythmia used combined event data for sustained VT/VF and appropriate ICD therapies. As 3 studies reported sustained VT/VF and ICD interventions separately, and these events are unlikely to be mutually exclusive, it is possible this could have introduced double-counting bias. Nevertheless, our sensitivity analysis using sustained VT/VF or ICD interventions (whichever number was greatest) demonstrated similar substantially and significantly increased odds with LGE, and sustained VT/VF and ICD intervention outcomes alone were also significantly elevated (Supplementary Table 1).

Limited numbers of studies have reported outcomes specifically for biventricular LGE or RV LGE with only 3 studies providing data on ventricular arrhythmia rates. There were also differences in how RV involvement was defined with the two included studies reporting this as LGE of the RV free wall. One study included the RV interventricular septum in their definition of RV LGE and was excluded from our analysis[31]. Reassuringly, inclusion of this study did not significantly change the outcomes (Supplementary Table S3). Our analysis suggests that biventricular LGE is associated with a significant likelihood of ventricular arrhythmia, more so than that of LV LGE alone. Limited available data means the confidence interval is wide (CI 16.2 – 117.2), therefore further studies reporting the outcomes for biventricular LGE will help to make this finding more robust.

Other limitations of this study include the non-uniform reporting of data between included studies, variable follow-up duration and heterogeneity in inclusion criteria, for example several studies had a LVEF cut-off of >50%. A lack of patient-level data prevents drawing any concrete conclusions about the relationship between other variables, in particular the relationship between LGE and LVEF. Furthermore, we could not control for how steroid or

immunosuppressant use might have impacted outcomes. Finally, there is limited quantitative assessment of LGE in the included studies, therefore this could not be included in the analysis.

CONCLUSION

The finding of LGE on CMR in patients with known or suspected CS confers an increased risk of both mortality and ventricular arrhythmia. The presence of LGE in CS patients may therefore warrant consideration for ICD implantation in CS patients, irrespective of their LVEF. Furthermore, patients with biventricular LGE are a particularly high-risk group of patients within the CS population, associated with significantly higher rates of ventricular arrhythmia. Further large-scale prospective studies evaluating outcomes in CS patients according to both the extent and distribution of LGE detected on CMR are needed to help guide important management decisions with regards to selection of patients for ICD implantation.

AUTHOR CONTRIBUTIONS

A Stevenson: Conception and planning of project, electronic search, literature review, data collection and analysis, writing and editing.
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R Providencia: Data collection and analysis, writing and editing.
A Kirresh: Conception and planning of project, electronic search, literature review, data collection and analysis, writing and editing.

DECLARATIONS

The authors declare they have no conflicts of interest.

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CLINICAL PERSPECTIVES

Competency in Medical Knowledge

This meta-analysis demonstrates the prognostic value of late gadolinium enhancement detected on cardiac MRI in patients with known or suspected cardiac sarcoidosis. Patients with LGE are at a significantly increased risk of both mortality and ventricular arrhythmia. Patients with biventricular LGE are at even higher risk for developing ventricular arrhythmias. The absence of LGE has a strong negative predictive value for future events, particularly of ventricular arrhythmias.

Translational Outlook

The role of cardiac MRI utilising LGE is not fully defined in current guidelines in terms of risk stratification for ICD implantation in cardiac sarcoidosis patients. Further prospective studies are needed, particularly with regards to quantitative analysis of LGE and its prognostic implications. The findings from such studies should be incorporated into future guidelines to help to inform clinicians which patients will benefit most from ICD implantation.

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FIGURE LEGENDS

Central illustration. Prognostic significance of late gadolinium enhancement (LGE) with known or suspected cardiac sarcoidosis.
Meta-analysis outcomes for all-cause mortality, ventricular arrhythmia and composite outcome of mortality and ventricular arrhythmia, according to the presence of any LGE or the presence of biventricular LGE. Note there was an insufficient number of studies to perform analysis for the composite outcome according to biventricular LGE. ^{NS} indicates not statistically significant.

Figure 1. PRISMA flow diagram.
Results of the literature search.

Figure 2. All-cause mortality.
A) Meta-analysis evaluating odds of all-cause mortality with the presence of either any late-gadolinium enhancement (LGE) or no LGE, and B) biventricular LGE or no biventricular LGE. *Bivent: biventricular, LGE: late-gadolinium enhancement.*

Figure 3. Annualised event rates.
Annual incidence of events for all-cause mortality, ventricular arrhythmia and composite outcomes, according to LGE positivity**.** *LGE: late-gadolinium enhancement, SE: standard error.*

Figure 4. Ventricular arrhythmia.
A) Meta-analysis evaluating odds of ventricular arrhythmia (sustained VT, VF or appropriate ICD therapy) with the presence of either late-gadolinium enhancement (LGE) or no LGE, and B) biventricular LGE or no biventricular LGE. *Bivent: biventricular, LGE: late-gadolinium enhancement, VA: ventricular arrhythmia.*

Figure 5. Composite outcome of all-cause mortality or ventricular arrhythmia.
Meta-analysis evaluating odds of composite outcome (death or ventricular arrhythmia) with the presence of either late-gadolinium enhancement (LGE) or no LGE. *LGE: late-gadolinium enhancement.*

Study	Year	Number of patients (n)	Country	Average follow-up (years)	Outcome measure	Study design	Study Population
Bravo	2017	56	USA	2.6	VF, sustained VT, appropriate ICD shock, all-cause death	Retrospective, single centre	Symptomatic patients with a high index of suspicion for cardiac sarcoidosis referred for both CMR & PET.
Crawford	2014	51	USA	4	VT/VF, death	Retrospective, multi-centre	Biopsy proven extracardiac sarcoidosis, LVEF >35% and suspected cardiac involvement
Flamee	2020	114	Belgium	3.1	Composite end-point (VT/VF, aborted SCD, ICD placement/appropriate discharge, HF hospitalisation, death)	Retrospective, single-centre	Biopsy-proven extra-cardiac sarcoidosis referred for CMR.
Gowani	2020	50	USA	4.7	Ventricular arrhythmia (sustained VT, VF, SCD, appropriate anti-tachycardia pacing)	Retrospective, single-centre	Diagnosed cardiac sarcoidosis (HRS criteria) who underwent both CMR & PET imaging
Greulich	2013	153	Germany	2.6	Death, aborted SCD, appropriate SCD, VT, VF	Prospective, multi-centre	Biopsy proven extra-cardiac sarcoidosis or clinically suspected cardiac sarcoidosis
Matsumoto	2015	17	Japan	1.5	All-cause mortality, symptomatic VT	Prospective, single-centre	Biopsy-proven extra-cardiac sarcoidosis referred for CMR.
Murtagh	2016	205	USA	3 +- 1.5	Death, sustained VT, appropriate ICD shock	Retrospective, single-centre	Biopsy-proven extra-cardiac sarcoidosis referred for CMR. LVEF>50%.
Nadel	2015	105	Australia	3.1 +- 1.7	Composite (SCD, VT, VF), all-cause death, SCD/aborted SCD	Retrospective, single-centre	Biopsy-proven extra-cardiac sarcoidosis and/or presumed cardiac sarcoidosis
Nagai	2014	61	Japan	4.2 +- 1	Composite (all cause death, HF admission, symptomatic VA, bradycardia leading to PPM implantation)	Prospective, single-centre	Histologically/clinically diagnosed extra-cardiac sarcoidosis, no cardiac symptoms, LVEF>50%
Patel	2009	81	USA	1.8 +- 0.7	Composite (all-cause mortality, symptomatic VA, bradycardia leading to PPM implantation)	Prospective, single-centre	Known extra-cardiac biopsy proven cases. biopsy-proven cardiac sarcoidosis excluded.
Smedema	2017	84	Netherlands	4.7	Composite (HF admission, sustained VT, appropriate implantable defibrillator therapy, PPM implantation or cardiac death)	Prospective, single centre	Histologically proven pulmonary sarcoidosis, referred for cardiac evaluation
Velangi	2020	290	USA	3.2 +- 1.6	All cause death and composite arrhythmic endpoint (SCD or significant VA)	Retrospective, single-centre	Biopsy-proven (cardiac or extra-cardiac) sarcoidosis
Wicks	2018	51	UK	2.2 +- 2.3	Composite (All-cause mortality, aborted SCD, symptomatic VA, bradycardia leading to PPM implantation, HF admission).	Prospective, single-centre	Biopsy-proven (cardiac or extra-cardiac) sarcoidosis referred for CMR/PET

Table 1. Study details.

Details of studies included in the meta-analysis. *VF: ventricular arrhythmia. VT: ventricular tachycardia. ICD: implantable cardiac defibrillator. SCD: sudden cardiac death. HF: heart failure. PPM: permanent pacemaker. CMR: cardiac magnetic resonance imaging. PET: positron emission tomography. LVEF: left ventricular ejection fraction. HRS: Heart Rhythm Society. JCS: Japanese Circulation Society. JMHW: Japanese Ministry of*

Study	Included patients (n)	LGE+ (%)	LV LGE+ (%)	RV LGE+ (%)	LGE mass (%)	Age (years)	Male (%)	LVEF (%)	LV EDV (ml)	Known extracardiac sarcoidosis (%)	Biopsy-proven cardiac sarcoidosis (%)	Any steroids or immunosuppressant use (%)	ICD/pacemaker at any point (%)	Prior VT (%)
Bravo	56	64	NR	NR	NR	53 ± 12	66	49 ± 13	NR	59	NR	25	54	14
Crawford	51	63	NR	25	9.3 ± 12.0	45 ± 15	16	52 ± 9	175 ± 55	100	10	65	61	22
Flamee	114	35	NR	11	5.1 (3.0-12.0)	48 ± 12	52	58 ± 9	NR	100	NR	72	NR	NR
Gowani	50	70	NR	NR	NR	53 ± 14	58	53 ± 14	NR	96	NR	60	NR	20
Greulich	153	26	NR	NR	4.4 (2.9-8.8)	50 ± 13	60	63	126 (105-155)	83	NR	NR	8	NR
Matsumoto	17	41	NR	NR	NR	61	12	NR	NR	100	6	NR	NR	NR
Murtagh	205	20	NR	NR	NR	56 ± 7	31	61 ± 6	73 ± 15 (indexed)	100	NR	NR	NR	NR
Nadel	106	30	NR	6	NR	51 ± 12	57	57 ± 11	NR	70	NR	58	22	NR
Nagai	61	13	NR	NR	NR	57 ± 15	34	63 ± 7	105 ± 24	100	0	11	NR	NR
Patel	81	26	NR	NR	6.1 (2.3-19.0)	46 ± 11	38	56 (48-61)	101 (89-137)	100	0	91	NR	NR
Smedema	84	33	32	14	15	53.3 ± 9.8	36	60 (14-84)	112 (88-136)	100	NR	71	1	NR
Velangi	290	30	NR	6	2.1 ± 5.4	53 ± 12	51	57 (53-60)	NR	98	3	53	NR	7
Wicks	51	63	NR	NR	NR	50 ± 13	61	53 ± 15	NR	86	14	37	25	16

Table 2. Study population characteristics.
Population characteristics from studies included in the meta-analysis. Values reported as mean ± standard deviation or median (inter-quartile range). *LGE: late gadolinium enhancement. RV: right ventricular. LVEF: left ventricular ejection fraction. ICD: implantable cardiac defibrillator. VT: ventricular tachycardia. NR: not recorded.*

Study	LGE acquisition time after Gadolinium, min	Gadolinium type and dose	Sequence	Interpretation of LGE presence and quantification
Bravo	10	Gadoteridol (0.2 mmol/kg)	Segmented phase-sensitive inversion recovery gradient-echo turbo fast field echo sequence at end-diastole.	1 reader blinded with respect to clinical status. Presence of LGE was assessed as either present or absent.
Crawford	15	Gadopentetate dimeglumine or gadoteridol or gadobenate dimeglumine (0.2 mmol/kg)	Inversion recovery gradient echo sequence (250-360 ms).	2 readers blinded to all clinical data determined the presence or absence of LGE. LGE quantified as a % of LV mass.
Flamee	10	Gadoterate meglumine (0.15 mmol/kg)	Inversion recovery sequence and/or phase-sensitive inversion-recovery sequence.	LGE quantified using manual contouring across the AHA 17 segment model.
Gowani	10 – 18	Gadopentetate dimeglumine (0.2 mmol/kg)	Phase sensitive inversion recovery gradient recall echo sequences (240-290 ms).	Interpreted by experienced clinical radiology and nuclear medicine physicians. Categorised as either positive or negative for presence of LGE.
Greulich	5 – 10	Gadodiamide or gadopentetate dimeglumine (0.15 mmol/kg)	Segmented inversion recovery fast gradient echo.	2 experienced observers used Siemens Argus analysis software package. LGE quantified as % of myocardial mass.
Matsumoto	10	Gadodiamide (0.10 mmol/kg)	Inversion steady-state free-precession sequence (250-400 ms).	2 cardiologists blinded to clinical and other imaging results. LGE quantified using 17 segment model.
Murtagh	10	Gadodiamide or gadobenate dimeglumine (0.1-0.2 mmol/kg)	T1-weighted gradient-echo pulse sequence with a phase-sensitive inversion recovery reconstruction (200-300 ms).	LGE quantified as % of LV mass.
Nadel	NR	NR	NR	2 cardiologists blinded to patient clinical history and sarcoidosis status. Cardiac sarcoidosis present if LGE visible in 2 orthogonal views and the presence of another condition known to be associated with LGE could be excluded on clinical grounds.
Nagai	10	Gadopentetate meglumine 0.15 mmol/kg).	Inversion-recovery true fast imaging with SSFP (300 ms).	LGE assessed as either positive or negative.
Patel	10 – 20	Gadolinium-diethylene triamine pentaacetic acid (0.15-0.2 mmol/kg)	Phased sensitive inversion recovery pulse sequence (200-300 ms).	2 reviewers assessed presence of LGE. LGE was present if > 4 SD above mean signal intensity of remote normal myocardium. LGE quantified as % of 17 segments.
Smedema	10	Gadolinium-diethylenetriaminepenta-acetic acid (0.1 mmol/kg)	Segmented inversion recovery-gradient echo breath-hold sequence (250 to 400 ms)	2 experienced blinded observers. LGE localised using 17-segment model. GE was quantified by a semi-automatic detection method using the signal intensity threshold of ≥2 SD above a remote reference region.
Velangi	10 – 15	NR	Segmented inversion-recovery sequence (250-350 ms).	2 reviewers blinded to clinical information. LGE identified visually in both ventricles. LGE present it > 5 SD above mean signal of reference myocardium. LGE quantified as % of LV mass.

Wicks	10 – 15	Gadoterate meglumine (0.1 mmol/kg)	Standard segmented turbo fast low-angle shot 2D inversion-recovery gradient echo sequence (320-400 mm).	2 experienced readers blinded to clinical characteristics of each patient. LGE reported against 17 segment model.

Table 3: Cardiac magnetic resonance imaging technical details.
Technical details of techniques for cardiac magnetic resonance (CMR) imaging and acquisition of late gadolinium enhancement (LGE) in the included studies. *AHA: American Heart Association. NR: not recorded. SD: standard deviation.*

Study	Selection (max score = 4)	Comparability (max score = 2)	Outcome (max score = 3)	Total (max score = 9)
Bravo	4	2	3	9
Crawford	4	1	3	8
Flamee	4	2	3	9
Gowani	4	1	3	8
Greulich	4	2	3	9
Kouranos	4	2	3	9
Matsumoto	4	0	3	7
Murtagh	4	1	3	8
Nadel	4	1	3	8
Nagai	4	1	3	8
Patel	4	0	3	7
Shafee	4	1	3	8
Smedema	4	2	3	9
Velangi	4	2	3	9
Wicks	4	2	3	9

Table 4: Study quality assessment.
Newcastle Ottawa Quality Assessment Scale for Cohort Studies. This scale rates study quality on a scale of 0 to 9 based upon a series of questions regarding patient selection, comparability and outcome measures.