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Prognostic Value of Myocardial Scarring on CMR in Patients With Cardiac Sarcoidosis

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ABSTRACT

OBJECTIVES This study sought to perform a systematic review and meta-analysis to understand the prognostic value of myocardial scarring as evidenced by late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging in patients with known or suspected cardiac sarcoidosis.

BACKGROUND Although CMR is increasingly used for the diagnosis of cardiac sarcoidosis, the prognostic value of CMR has been less well described in this population.

METHODS PubMed, Cochrane CENTRAL, and metaRegister of Controlled Trials were searched for CMR studies with ≥1 year of prognostic data. Primary endpoints were all-cause mortality and a composite outcome of arrhythmogenic events (ventricular arrhythmia, implantable cardioverter-defibrillator shock, sudden cardiac death) plus all-cause mortality during follow-up. Summary effect estimates were generated with random-effects modeling.

RESULTS Ten studies were included, involving a total of 760 patients with a mean follow-up of 3.0 ± 1.1 years. Patients had a mean age of 53 years, 41% were male, 95.3% had known extracardiac sarcoidosis, and 21.6% had known cardiac sarcoidosis. The average ejection fraction was 57.8 ± 9.1%. Patients with LGE had higher odds for all-cause mortality (odds ratio [OR]: 3.06; $p < 0.03$) and higher odds of the composite outcome (OR: 10.74; $p < 0.00001$) than those without LGE. Patients with LGE had an increased annualized event rate of the composite outcome (11.9% vs. 1.1%; $p < 0.0001$).

CONCLUSIONS In patients with known or suspected cardiac sarcoidosis, the presence of LGE on CMR imaging is associated with increased odds of both all-cause mortality and arrhythmogenic events. (J Am Coll Cardiol Img 2017;10:411–20) © 2017 by the American College of Cardiology Foundation.

Sarcoidosis is an inflammatory granulomatous disease of unknown origin, characterized histologically by noncaseating granulomas in multiple organs, including the lungs, skin, lymphatics, and central nervous system (1). Cardiac involvement is associated with ventricular arrhythmias, sudden cardiac death (SCD), and congestive heart failure. It is thought that two-thirds of sarcoid-related deaths are attributable to involvement of the myocardium (2–4). Thus, clinical diagnosis of cardiac sarcoidosis (CS) is crucial for timely therapeutic management and consideration of immunosuppressive therapies. Furthermore, a better understanding of cardiovascular risk factors in this population could have implications for device therapy for the prevention of SCD.

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CMR = cardiac magnetic resonance

CS = cardiac sarcoidosis

EP = electrophysiological

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

LGE = late gadolinium enhancement

LVEF = left ventricular ejection fraction

OR = odds ratio

SCD = sudden cardiac death

Cardiac magnetic resonance (CMR) has been shown to have excellent diagnostic accuracy for detection of CS and is becoming the gold standard for its diagnosis (5,6). CMR may detect myocardial edema and inflammation using T_2-weighted imaging as well as detect myocardial scarring and fibrosis using late gadolinium enhancement (LGE) (7).

Multiple recent studies have been published regarding CMR assessment of prognosis in CS, in particular examining the presence of LGE and its association with adverse outcomes (8–10). However, the broad applicability of many of these studies is limited because they are small and single-centered. Prognostic validation of CMR is crucial, as the presence of LGE is thought to confer a higher risk of major adverse cardiac events such as new or worsening heart failure, life-threatening arrhythmias, and SCD resulting from myocardial scarring and fibrosis as has been demonstrated in other cardiac pathologies (11–13).

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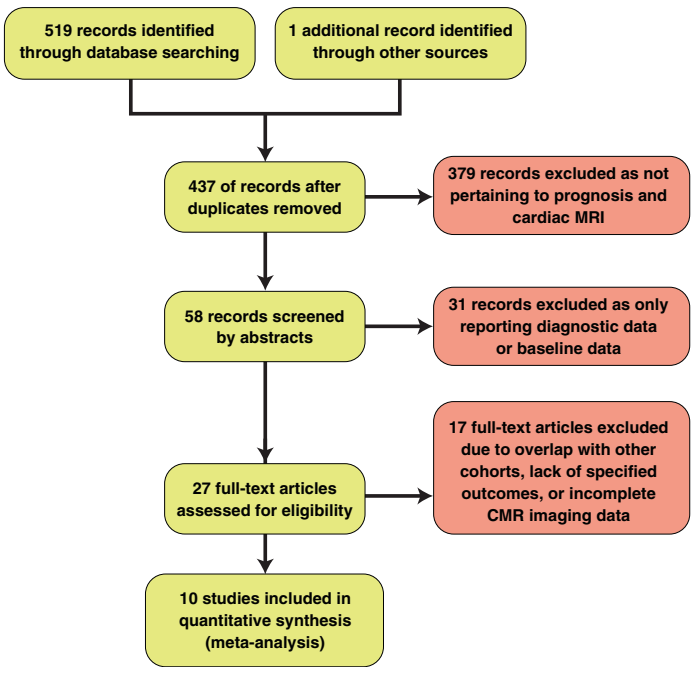
In the current environment of escalating medical costs, the prognostic utility of CMR may help justify its use and guide therapies in patients with sarcoidosis. Prognostic CMR data might provide valuable information for risk stratification and resource allocation, such as clarifying which patients benefit from implantable cardioverter-defibrillator (ICD) placement or when immunosuppressive medications, which have significant patient side effects, are indicated.

Given the multiple small and single-centered studies, we performed a systematic review and meta-analysis of studies reporting prognostic data from patients undergoing CMR for evaluation of known or suspected CS.

FIGURE 1 QUORUM Diagram



Overview of the study review process. CMR = cardiac magnetic resonance; MRI = magnetic resonance imaging; QUORUM = Quality of Reporting of Meta-Analyses Standards.

METHODS

SEARCH STRATEGY. To identify eligible studies for inclusion in the current systematic review and meta-analysis, 3 independent reviewers (G.C.C., P.S., and P.B.) systematically searched (July 2015) PubMed, Cochrane CENTRAL, and metaRegister of Controlled Trials for studies assessing prognosis in patients undergoing CMR with known or suspected CS. Keywords used were "sarcoid late gadolinium enhancement," "sarcoid delayed enhancement," and "cardiac MRI and sarcoid." Since the initial search, no further articles have been identified as of December 2015.

Studies were considered eligible for inclusion if CMR was used (alone or in addition to other imaging modalities) to assess for myocardial scarring from biopsy-proven or clinically suspected sarcoidosis; in cohorts of ≥5 patients; with ≥1 year of prognostic follow-up data, including event data for ventricular arrhythmia, SCD, aborted cardiac death and/or appropriate ICD discharge, hospital admission for congestive heart failure, cardiac mortality, and all-cause mortality. Studies with populations known to have coronary artery disease or cardiomyopathies of nonsarcoid etiology were excluded.

In addition, we consulted experts, reviewed citations from eligible studies, and contacted some investigators for additional unpublished data. The search was limited to studies published in peer-reviewed journals and therefore excluded trials presented in abstract form only. We restricted the review to studies that enrolled adults only with no language restriction. The current systematic review and meta-analysis was performed in accordance with guidelines of the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) groups (14,15).

TABLE 1 Study Characteristics

First Author (Ref. #)	Year	Patients Included Herein (n)	Average Follow-Up (yrs)	Outcome Measure	Study Design	Quality Assessment Score	Population
Blankstein et al. (34)	2014	39	1.5	Death from any cause or sustained VT	Prospective, single-center	4,2,3	Known or suspected cardiac sarcoidosis referred for PET, no history of CAD or MI
Crawford et al. (35)	2014	51	4.0 ± 1.7	VT-/VF-free survival	Retrospective, multicenter	4,2,3	Biopsy-proven extracardiac sarcoid, LVEF >35%, and diagnosis of cardiac involvement
Greulich et al. (8)	2013	153	2.6	Death, aborted SCD, appropriate ICD shock, VT, VF	Prospective, multicenter	4,1,3	Biopsy-proven or clinical systemic sarcoidosis with suspected cardiac involvement, no history of CAD or MI
Murtagh et al. (36)	2016	205	3.0 ± 1.5	Death, VT	Retrospective, single-center	4,1,3	Biopsy-proven extracardiac sarcoid, LVEF >50%
Nadel et al. (9)	2015	106	3.1 ± 1.7	Composite (SCD, VT, VF), all-cause death, SCD/aborted SCD	Retrospective, single-center	4,2,3	Biopsy-proven extracardiac and/or presumed cardiac sarcoidosis
Nagai et al. (10)	2014	61	4.2 ± 1.0	Composite (all-cause death, HF admission, ventricular arrhythmia, bradyarrhythmia requiring pacemaker)	Prospective, single-center	4,2,3	Histological and/or clinically diagnosed extracardiac sarcoid, no cardiac symptoms, and LVEF >50%
Patel et al. (6)	2009	81	1.8 ± 0.7	Death, ICD shock, pacemaker requirement	Prospective, single-center	4,2,3	Biopsy-proven extracardiac sarcoidosis without known cardiac involvement, no history of CAD or MI
Poyhonen et al. (37)	2014	8*	≥2	VT, VF	Retrospective, single-center	4,2,3	Suspected nonischemic cardiomyopathy, no history of CAD or MI
Shafee et al. (38)	2012	37	3.8 ± 2.6	VT, VF, and composite (VA, HF admission, cardiovascular mortality)	Retrospective, single-center	4,2,3	Diagnosed cardiac sarcoidosis (revised JMHW criteria)
Watanabe et al. (39)	2013	19	4.9 ± 1.4	Death, VT, VF	Retrospective, multicenter	4,1,3	Diagnosed cardiac sarcoidosis (revised JMHW criteria)

*Eighty-six total patients; 8 diagnosed with cardiac sarcoidosis.

CAD = coronary artery disease; HF = heart failure; ICD = implantable cardioverter-defibrillator; JMHW = Japanese Ministry of Health and Welfare; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PET = positron emission tomography; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia.

STUDY SELECTION. Three authors (G.C.C., P.S., and P.B.) independently and in duplicate scanned all abstracts and obtained full-text reports of articles that indicated or suggested eligibility. After obtaining full reports, the same reviewers independently assessed eligibility from the full-text articles, with divergences resolved after consensus.

The quality of included studies was assessed by 2 investigators (J.A.G., G.C.C.) using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies (16), in which the quality of the selected trials was determined on the basis of selection of the study groups (0 to 4 points), comparability of the study groups (0 to 2 points), and ascertainment of the outcome of interest (0 to 3 points).

DATA COLLECTION. Data abstraction and study appraisal were performed by the same aforementioned authors. Clinical outcomes of interest were cardiovascular death, all-cause mortality, and a composite of arrhythmogenic events defined as ventricular arrhythmia (ventricular tachycardia or ventricular fibrillation), SCD, or aborted SCD (appropriate ICD discharge) during follow-up. Clinical outcomes data was directly abstracted. Annualized event rates were calculated for studies by dividing the number of events by the follow-up duration.

DATA ANALYSIS. Dichotomous variables are reported as proportions (percentages); continuous variables are reported as mean ± SD or median (range). Binary outcomes from individual studies were combined with a random-effects model, leading to computations of odds ratios (ORs) and 95% confidence intervals (CIs). I^2 was calculated as a measure of statistical heterogeneity, with values of 25%, 50%, and 75% representing mild, moderate, and severe inconsistency, respectively. Small study or publication bias was explored with funnel plots and Egger test. Finally, meta-regression and sensitivity analyses (including exclusion of 1 study at a time) were conducted to explore heterogeneity.

TABLE 2 Baseline Patient Characteristics

First Author (Ref. #)	Total (n)	Included (n)	LGE+	Age (yrs)	Male	White	African American	LVEF	LVEDV (ml)	Known Extracardiac Sarcoid	Known Cardiac Sarcoid
Blankstein et al. (34)	118	39	67	51.5 ± 11.2	57	77	16	47 ± 16	154 ± 90	18	32
Crawford et al. (35)	51	51	63	51.1 ± 10.3	16	45	47	52 ± 9	175 ± 55	100	8
Greulich et al. (8)	155	153	25	49.7 ± 13.0	59	NR	NR	63	126	98	NR
Murtagh et al. (36)	205	205	20	56 ± 7	31	NR	59	61.0 ± 5.6	72.9 ± 14.9	100	0
Nadel et al. (9)	106	106	30	51.0 ± 12.2	57	NR	NR	56.6 ± 10.5	NR	75	30
Nagai et al. (10)	61	61	13	57 ± 15	34	NR	NR	63.1 ± 7.1	104.6 ± 23.9	100	0
Patel et al. (6)	81	81	26	46 ± 11	38	26	73	56	101	100	12
Poyhonen et al. (37)	86	8*	88	51	6	NR	NR	43	77	1	0
Shafee et al. (38)	61	37	70	57 ± 12	30	NR	NR	50 ± 16	52 ± 8	88	100
Watanabe et al. (39)	19	19	89	58.2 ± 10.9	11	NR	NR	37.5 ± 19.8	175.2 ± 76.4	89	100
Totals	943	760								95.3†	21.6†
Weighted mean			33	52.5 ± 10.0	48			57.8 ± 9.1	91.6 ± 16.6		

TABLE 2 Continued

First Author (Ref. #)	Any Steroid Use	Syncope	Palpitations	CHF			ICD/Pacemaker at Any Point	Baseline		Previous VT
				NYHA I–II	NYHA III	NYHA IV		EKG - Any BBB	ECG - Any AV Block	
Blankstein et al. (34)	26	17	6	14	NR	NR	54	24	37	20
Crawford et al. (35)	47	2	37	94	6	0	61	27	6	22
Greulich et al. (8)	NR	6	30	NR	NR	NR	8	NR	NR	NR
Murtagh et al. (36)	47	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nadel et al. (9)	NR	NR	NR	NR	NR	NR	22	NR	NR	NR
Nagai et al. (10)	11	0	0	0	0	0	2	7	7	0
Patel et al. (6)	91	2	7	4	1	0	11	6	4	NR
Poyhonen et al. (37)	NR	3	9	NR	NR	NR	NR	1	10	8
Shafee et al. (38)	NR	NR	NR	82	15	3	NR	NR	NR	NR
Watanabe et al. (39)	NR	5	32	NR	NR	NR	NR	5	37	NR
Totals										
Weighted mean	27.9	2.7	10.5	11.4	1.4	0.2	12.9	4.4	4.3	2.6

Values are % or mean ± SD unless otherwise indicated. *Eight diagnosed with cardiac sarcoidosis; others with nonsarcoid cardiomyopathies. †Percentage calculated from number of patients.

AV = atrioventricular; BBB = bundle branch block; CHF = congestive heart failure; ECG = electrocardiography; LGE = late gadolinium enhancement; LVEDV = left ventricular end-diastolic volume; NR = not reported; NYHA = New York Heart Association; other abbreviations as in Table 1.

Statistical analysis was performed using Review Manager (RevMan) version 5.3.5 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) freeware package and R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria), with statistical significance for hypothesis testing set at the $\alpha < 0.05$, 2-tailed level. Meta-regression analysis was performed using the package

"metafor" in R. For studies with zero events in a group, the convention of adding 0.5 events to all cells was adopted (17).

RESULTS

RESULTS OF THE LITERATURE SEARCH. The literature search identified 519 relevant abstracts of full-text articles: 58 unique articles were abstracted for review; 27 of these warranted full-text review; 17 articles were excluded for various reasons including cohort overlap with other articles, lack of specified outcomes, or incomplete CMR data (18-33). Ten articles remained for detailed study (6,8-10,34-39). Details of the search strategy are outlined in the QUORUM (Quality of Reporting of Meta-Analyses Standards) diagram in Figure 1.

STUDY CHARACTERISTICS. Study characteristics are presented in Table 1. The 10 studies included a total of 760 patients with known or suspected CS undergoing CMR. Four studies were prospective and 3 studies were multicenter. The follow-up duration ranged from 1.5 years to 4.9 years with a weighted mean follow-up duration of 3.0 ± 1.1 years. Baseline patient characteristics are shown in Table 2. Patients had a weighted mean age of 53.0 ± 10.0 years and 41% were male. The weighted average ejection fraction was 57.8 ± 9.1%. Of the total, 95.3% of patients had known extracardiac sarcoidosis and 21.6% had known CS. The prevalence of LGE ranged from 13% to 89% with a weighted mean prevalence of LGE of 33%. The prevalence of LGE in each study had a strong negative correlation with the mean left ventricular ejection fraction (LVEF) ($R = 0.95$; $p < 0.001$) (Figure 2). Eight of the studies included patients undergoing CMR at 1.5-T; the remaining 2 studies do not report CMR imaging field strength. Data for immunosuppressive therapy including corticosteroid use was inconsistently reported.

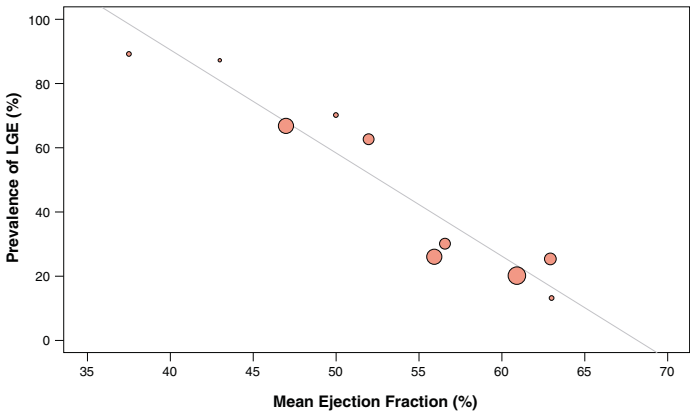
STUDY QUALITY. Overall, the included studies were of high quality, with all 10 studies receiving maximal scores on the Newcastle-Ottawa Quality Assessment Scale in the areas of study group selection and ascertainment of the desired outcome (Table 1). Seven of 10 studies also received maximal scores in the third domain of comparability of study groups. Thus, the pooled data from these high-quality studies are collectively robust.

LATE GADOLINIUM ENHANCEMENT AND CARDIOVASCULAR OUTCOMES. Composite endpoint. Of the 10 studies reporting outcome data for ventricular arrhythmias, SCD, appropriate ICD discharge/aborted SCD, and all-cause mortality, patients with LGE had greater odds of having the combined outcome of arrhythmogenic events plus all-cause mortality compared with those without LGE (overall OR: 10.74; 95% CI: 4.12 to 27.90; $p < 0.00001$, $I^2 = 45\%$) (Figure 3). When comparing annualized event rates for the composite endpoint, patients with LGE had significantly higher rates of events than did patients without LGE (11.9% vs. 1.1%; $p < 0.001$) (Figure 4).

Moderate heterogeneity ($I^2 = 45\%$) was noted in the meta-analysis. To investigate this heterogeneity, we performed meta-regression to determine whether any clinical variables were associated with the composite cardiovascular outcome. There was adequate data to explore the effects of sex, age, LVEF, percentage of patients with known extracardiac sarcoidosis, and duration of follow-up using a mixed-model approach. LVEF was the only significant covariate, and inclusion of LVEF in the meta-regression model accounted for all remaining heterogeneity ($I^2 = 0\%$).

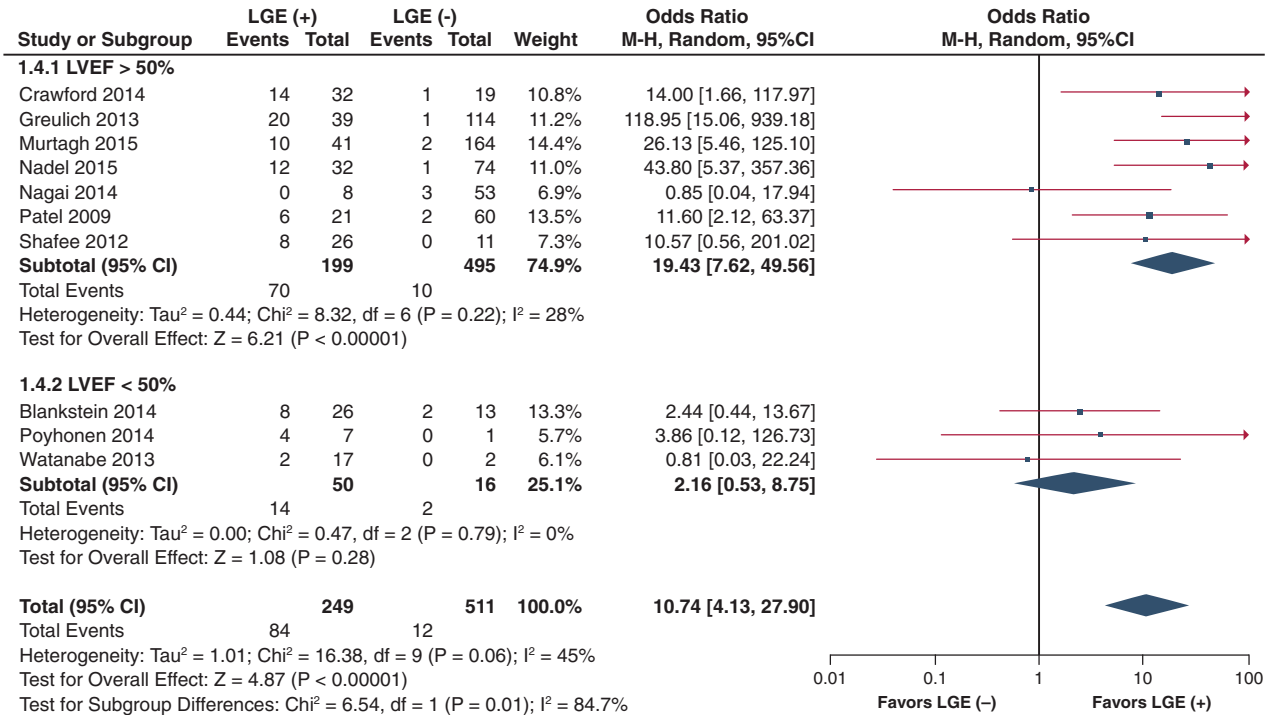
The OR for the association of LGE with adverse events was higher in studies with greater mean LVEF. However, the total prevalence of events was higher in studies with a mean LVEF <50% (24%) than those with mean LVEF ≥50% (11%). Two of the larger studies (10,36) had a pre-specified LVEF cutoff of ≥50%, and to explore this association further, we performed a stratified analysis based on this LVEF cutoff (Figure 3). Among studies with a mean LVEF ≥50%, the presence of LGE was associated with greater odds of the combined endpoint (OR: 19.43; 95% CI: 7.62 to 49.56; $p < 0.00001$), with only

FIGURE 2 Correlation of LGE and LVEF



Relationship between late gadolinium enhancement (LGE) prevalence and mean left ventricular ejection fraction (LVEF) in each study population ($R = 0.9526$; $p < 0.001$).

FIGURE 3 Forrest Plot for Composite Outcome



Clinical outcomes of patients with known or suspected cardiac sarcoid with the presence or absence of LGE on CMR. Composite outcome of all-cause mortality plus arrhythmogenic events stratified by LVEF; arrhythmogenic events defined as ventricular arrhythmias (ventricular tachycardia/ventricular fibrillation), sudden cardiac death, and appropriate implantable cardioverter-defibrillator discharge/aborted sudden cardiac death. CI = confidence interval; M-H = Mantel-Haenszel odds ratio; other abbreviations as in Figures 1 and 2.

mild-to-moderate residual heterogeneity (I^2 = 28%). In this population, the annualized event rate for the composite outcome was significantly greater for those with LGE than for those without LGE (11.59% vs. 0.69%; p = 0.0011). In contrast, among studies with mean LVEF <50%, where there was a very high prevalence of LGE positivity, patients with LGE were not at increased odds of having the composite endpoint.

Mortality endpoints. From 7 studies reporting all-cause mortality, patients with LGE had significantly greater odds of death from any cause than did patients without LGE (OR: 3.06; 95% CI: 1.14 to 8.20; p = 0.03; I^2 = 37%) (Figure 5). Of these studies, only 1 (Watanabe et al. [39]) had a mean LVEF <50%. A trend toward a higher annualized event rate for all-cause mortality was also noted in patients with LGE versus those without LGE (4.0% vs. 1.2%; p = 0.07) (Figure 4).

Only 3 studies provided specific data for cardiovascular mortality including 151 patients. No significant association between the presence of LGE and increased odds of cardiovascular death (OR: 3.24; 95% CI: 0.43 to 24.63; p = 0.26; I^2 = 31%) was seen.

STUDY VARIABILITY. Two studies included in the analysis (10,39) individually showed near-neutral OR for the composite outcome. This discordance may be explained on the basis of individual study characteristics. Watanabe et al. (39) retrospectively studied 19 subjects with cardiac sarcoid; 17 of 19 patients (89%) demonstrated LGE and the mean EF was 37.5%. Only 2 events among all 19 subjects were noted, both in LGE+ patients. The neutral OR from this study is likely due to the small sample size and biased distribution. Nagai et al. (10) prospectively studied 61 patients with known extracardiac sarcoid, no evidence of cardiac involvement, and LVEF >50%. In this cohort, only 13% of patients had LGE and the overall event rate was low in both groups (there were 3 total events, all noncardiac in nature among patients without LGE), which likely led to the neutral OR for the composite endpoint. These 2 studies only contributed 16% weight to the overall meta-analysis.

ASSESSMENT OF BIAS. Visual inspection of funnel plots and Egger test for funnel plot asymmetry did not demonstrate significant asymmetry. Sensitivity analysis, which was performed by excluding 1 study at a time from the outcomes analysis, demonstrated that the measured effect for the composite cardiovascular outcome was not sensitive to any individual studies. However, sensitivity analysis in the model for all-cause mortality did demonstrate sensitivity to 3 included studies (6,8,36), as exclusion of 1 study at a time no longer rendered the model significant. Notably, these are 3 of the larger studies and therefore had the largest effect sizes.

DISCUSSION

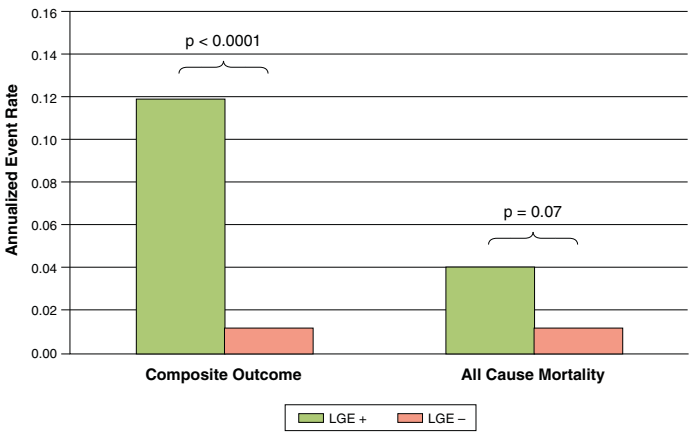
The findings of this systematic review and meta-analysis show that the presence of myocardial scarring as evidenced by the presence of LGE in CMR provides meaningful prognostic information in patients with known or suspected CS. The data demonstrate that patients with LGE have increased likelihood of death from any cause as well as increased odds of future arrhythmogenic events. The correlation of LGE and adverse outcomes seen in this meta-analysis supports the role of CMR imaging for detection of cardiac involvement in patients with sarcoidosis when cardiac involvement may not be evident clinically. Our findings also support previous work advocating CMR imaging in patients with suspected CS and normal LVEF (18).

Multiple previous studies have shown equivocal or insignificant associations between LGE and future risk of death or ventricular arrhythmias (25,40,41), which may be due to population differences or differences in CMR techniques as pointed out in the 2014 Heart Rhythm Society (HRS) Expert Consensus Statement (42). The studies that do show an association between myocardial scarring and worse prognosis are small (8,9,38). Despite this limited data, the HRS reached a consensus that CMR imaging for the purpose of sudden death risk stratification was reasonable in patients with CS, even in those with LVEF >35%. This meta-analysis helps to validate the HRS position statement by bolstering the growing body of evidence showing an association between LGE and adverse outcomes and justifying the role for CMR in patients with known or suspected CS, including those with near-normal LVEF. The current analysis shows that the presence of LGE in sarcoid patients with normal or near-normal LVEF is prognostically significant and greatly increases the likelihood of adverse events.

IMPLICATIONS FOR ICD AND FUTURE DIRECTIONS. The 2014 HRS guidelines indicate that sarcoid patients with LGE on CMR and normal LVEF should have an electrophysiological (EP) study; if the EP study is positive, then an ICD may be indicated (Class IIa). The results of this meta-analysis may justify consideration of device therapy without further EP testing. Further prospective studies are needed to clarify the role of both CMR and EP testing with regard to ICD implantation in patients with CS. Although key concerns regarding inappropriate shocks and adverse events related to device therapy remain (43), this new data should be considered when deciding on ICD implantation given the adverse prognosis associated with myocardial scarring in patients with cardiac sarcoid.

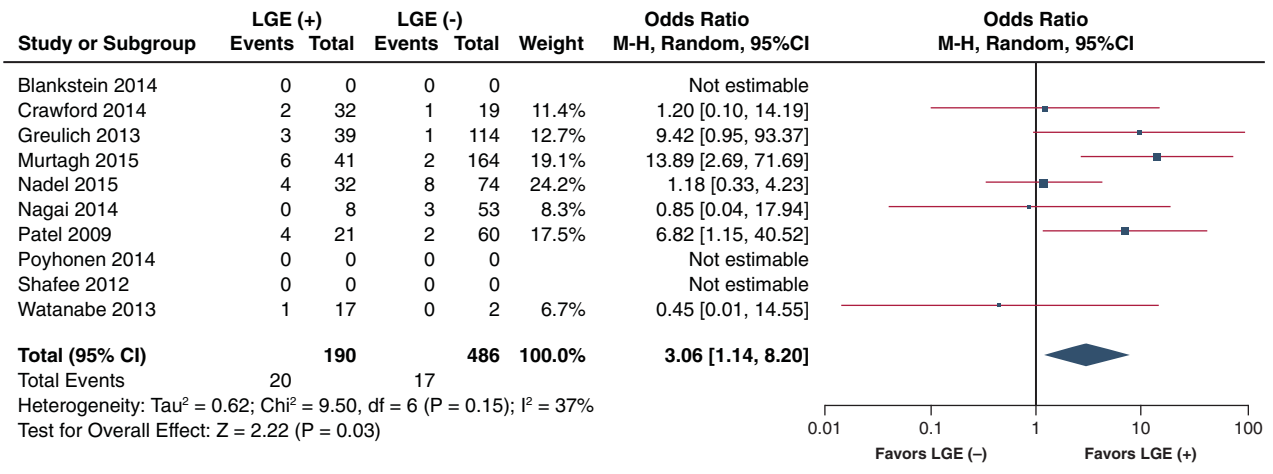
As the optimal management of CS patients continues to evolve, there is a need for prospective studies enrolling patients with normal EF and reduced EF to further evaluate the interaction between LVEF and myocardial scarring on cardiovascular outcomes. Outcomes analysis adjusted for LVEF was only available for 2 of the included studies and was inadequate for pooled analysis. In the study by Nadel et al. (9) (N = 106), adjusted Cox analysis including LVEF and the presence of LGE demonstrated that the presence of LGE was the only independent variable that was predictive of the composite cardiovascular outcome (hazard ratio [HR]: 12.52; 95% CI: 1.35 to 116.18; p < 0.03). Multivariate Cox regression analysis by Greulich et al. (8) (N = 155) including the presence of LGE and the initial LVEF demonstrated that LGE

FIGURE 4 AER of Cardiovascular Outcomes for CMR



Weighted mean annualized event rates (AERs) for the composite outcome of mortality plus arrhythmogenic events and all-cause mortality comparing patients with myocardial scarring as evidenced by the presence of LGE **(green bars)** with patients without LGE **(pink bars)**. Abbreviations as in Figures 1 and 2.

FIGURE 5 Forrest Plot for All-Cause Mortality



Clinical outcomes of patients with known or suspected cardiac sarcoid with the presence or absence of LGE on CMR: all-cause mortality. Abbreviations as in Figures 1 to 3.

presence was the best independent predictor of the composite endpoint (HR: 31.6; p = 0.0014). Patient-level data was available for the cohort in Murtagh et al. (36) (N = 205), and we performed a multivariate analysis including LVEF and LGE and found that LGE was an independent predictor of adverse outcomes (HR 29.79; 95% CI: 6.05 to 146.76; p < 0.0001). In the current analysis, the majority of adverse cardiovascular events (73%) were in LGE+ patients with a mean LVEF ≥50%, suggesting that LGE provides risk stratification for adverse events in patients with CS beyond LVEF assessment alone.

Future prospective studies using quantitative assessment of LGE may provide a more nuanced risk stratification model. Furthermore, as the inflammation and fibrosis may be more diffuse in sarcoid, there may be a role for parametric mapping techniques such as T_1 or T_2 mapping (44,45).

STUDY LIMITATIONS. Certain limitations inherent to systematic reviews are pertinent to the current analysis, including nonuniform reporting of data from included studies and variable duration of follow-up. Additional limitations include heterogeneity of methods for quantifying EF, lack of LGE quantification or pattern data, and variable inclusion criteria, such as a pre-specified LVEF cutoff ≥50% in some studies. As only study-level covariates were available for analysis, the relationship between LVEF and LGE could not be assessed on a per patient basis; future prospective studies may help mitigate selection bias and provide patient-level insights. Despite these differences among studies, we demonstrate that meta-regression analysis showed no residual heterogeneity when LVEF was accounted for (I^2 = 0%).

Finally, we were only able to include a composite of all-cause mortality and arrhythmogenic events due to insufficient breakdown of events in some of the studies. However, the direction of effect was similar to that of all-cause mortality. In the studies separately reporting arrhythmogenic events, the effect size for the OR was similar to the composite endpoint.

CONCLUSIONS

CMR imaging with LGE provides important prognostic risk stratification for patients with known or suspected CS. Patients with the presence of LGE are at increased risk of death from any cause and arrhythmogenic events, even if their cardiac function is normal or near normal. This study illustrates how the presence or absence of LGE likely has important implications for optimizing therapy in patients with known or suspected CS.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: CMR imaging is excellent in the diagnosis of CS and the presence of LGE provides prognostic risk stratification.

COMPETENCY IN MEDICAL KNOWLEDGE 2: The presence of LGE confers an increased risk of death by any cause and arrhythmogenic events in patients with known or suspected CS.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: With the ability to provide both diagnostic and prognostic information, CMR imaging should be strongly considered in the management of patients with suspected CS.

COMPETENCY IN INTERPERSONAL AND COMMUNICATION SKILLS: CMR imaging provides important prognostic information to providers that can help direct patient management.

TRANSLATIONAL OUTLOOK 1: A prospective registry with strict entry criteria for patients with CS would be helpful to better define the association between LGE and other adverse prognostic factors.

TRANSLATIONAL OUTLOOK 2: Additional research in the quantification of LGE in patients with CS may provide more nuanced risk stratification.

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