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Complementary Role of CMR to Conventional Screening in the Diagnosis and Prognosis of Cardiac Sarcoidosis

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ABSTRACT

OBJECTIVES The goal of this study was to assess the independent and collective diagnostic value of various modalities in cardiac sarcoidosis, delineate the role of cardiac magnetic resonance (CMR), and identify patients at risk.

BACKGROUND Cardiac sarcoidosis is associated with increased morbidity and mortality. CMR is a key modality in the evaluation of patients with cardiac symptoms, but the complementary role of CMR to conventional tests for the diagnosis of cardiac sarcoidosis is not fully defined.

METHODS Patients (N = 321) with biopsy-proven sarcoidosis underwent conventional cardiac testing and CMR with late gadolinium enhancement (LGE) and were followed up for primary (composite of all-cause mortality, sustained ventricular tachycardia [VT] episodes, or hospitalization for heart failure) and secondary (nonsustained VT episodes) endpoints.

RESULTS Cardiac sarcoidosis was diagnosed in 29.9% of patients according to the Heart Rhythm Society consensus criteria. CMR was the most sensitive and specific test (area under the curve: 0.984); it detected 44 patients with cardiac symptoms and/or electrocardiogram (ECG) abnormalities but normal echocardiogram, as well as 15 asymptomatic patients with normal baseline testing. Echocardiography added to cardiac history and ECG did not change sensitivity of the initial screening strategy (68.8% vs. 72.9%). Despite a high positive predictive value (83.9%), echocardiography had a low sensitivity (27.1%). During follow-up, 7.2% of patients reached the primary endpoint and another 3.4% reached the secondary endpoint. LGE was and independent predictor of primary endpoints (hazard ratio: 5.68; 95% CI: 1.74 to 18.49; p = 0.004). LGE, age, and baseline nonsustained VT were independent predictors of all events. In patients with cardiac symptoms and/or an abnormal ECG, CMR increased diagnostic accuracy and independently predicted primary endpoints (hazard ratio: 12.71; 95% confidence interval: 1.48 to 109.35; p = 0.021).

CONCLUSIONS Of all cardiac tests, CMR was the most valuable in the diagnosis and prognosis of cardiac sarcoidosis in a general sarcoidosis population. Echocardiography had an overall limited diagnostic value as a screening test, and an abnormal study, despite a high positive predictive value, may still need confirmation with CMR. (J Am Coll Cardiol Img 2017;10:1437–47) © 2017 the American College of Cardiology Foundation.
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ABBREVIATIONS AND ACRONYMS

AUC = area under the curve

CI = confidence interval

CMR = cardiac magnetic resonance

ECG = electrocardiogram

HR = hazard ratio

HRS = Heart Rhythm Society

JMHW = Japanese Ministry of Health and Welfare

ICD = implantable cardioverter-defibrillator

LGE = late gadolinium enhancement

LV = left ventricular

MRI = magnetic resonance imaging

PET = positron emission tomography

ROC = receiver-operating characteristic

VT = ventricular tachycardia

Clinically overt cardiac sarcoidosis occurs in 5% to 10% of patients with sarcoidosis, but autopsy studies report a prevalence of 20% to 30% (1). The diagnostic difficulties in cardiac sarcoidosis are largely attributed to the patchy distribution of myocardial infiltration and the lack of a highly sensitive and specific noninvasive test. Over the last 2 decades, advanced imaging modalities such as cardiac magnetic resonance (CMR) or positron emission tomography (PET) have detected cardiac involvement with a prevalence similar to that of autopsy studies (2-6). In fact, specific patterns on CMR and PET are considered highly sensitive and specific, and they are currently included in the Heart Rhythm Society (HRS) Consensus Statement and World Association of Sarcoidosis and Other Granulomatous Disorders instrument tool as diagnostic criteria of cardiac sarcoidosis (7,8). In contrast, the Japanese Ministry of Health and Welfare (JMHW) criteria are not sensitive enough to diagnose myocardial involvement (9).

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Despite the significant progress in the diagnosis of cardiac involvement, the optimal screening and risk stratification strategy and the incremental diagnostic value of the advanced imaging modalities are not fully defined. Cardiac symptoms and electrocardiogram (ECG), which are the traditional screening tools in the early studies (10), are hampered by low sensitivity and poor positive and negative predictive values. Late gadolinium enhancement (LGE) on CMR is an independent predictor of adverse events in patients with sarcoidosis who have cardiac symptoms (2,5) but not in those without cardiac symptoms (11,12). Furthermore, the high cost of the advanced imaging modalities, their limited availability, and the need for expertise in interpreting the results make implementation of a clinically practical screening and diagnostic algorithm highly imperative for a disease with significant morbidity and mortality.

The present study included a large number of patients with biopsy-proven extracardiac sarcoidosis, representative of the general sarcoidosis population, who underwent cardiac evaluation with all conventional diagnostic modalities and CMR, regardless of clinical suspicion for cardiac involvement and were followed up for major adverse events. The purpose of the study was to assess the prevalence of cardiac sarcoidosis in a general sarcoidosis population and appraise the complementary role of CMR to conventional diagnostic testing. Furthermore, an equally important objective was to provide a risk stratification analysis based on the prognostic significance of conventional diagnostic modalities and CMR.

PATIENTS AND METHODS

STUDY POPULATION. The study consisted of consecutive patients with extracardiac biopsy-proven sarcoidosis (all Caucasians) referred to the Sarcoidosis Clinic at the General Hospital of Chest Diseases "Sotiria" and "Laiko" General University Hospital between October 2006 and June 2013. The diagnosis of sarcoidosis was based on the presence of noncaseating granulomas on tissue biopsy specimens and compatible clinical and radiological findings (8). The diagnosis of sarcoidosis was established within ≥3 months before the initial evaluation. Exclusion criteria included known collagen vascular disease and cardiac dysfunction related to congenital heart disease or coronary artery disease. Patients with known cardiac sarcoidosis and those who did not complete the baseline assessment were also excluded.

DATA COLLECTION. All patients underwent baseline testing with ECG, Holter monitoring, and standard transthoracic Doppler echocardiography with M-mode left ventricular (LV) analysis (13). A CMR was additionally performed in all patients, irrespective of symptoms or other test findings. B-type natriuretic peptide and serum angiotensin-converting enzyme levels, ^{67}Gallium scintigraphy, chest radiograph, and pulmonary function tests performed in the last 3 months were also obtained. The study protocol was approved by the institutional ethics committee, and informed consent was obtained from all patients (institutional review board number ES 486).

CMR IMAGING. CMR scans were performed on a 1.5-T or 3-T magnetic resonance imaging (MRI) scanner (HDx, GE Healthcare, Little Chalfont, United Kingdom) using a dedicated 8-channel phased-array cardiac coil, under electrocardiogram gating, and breath-holding in line with standard recommendations (14). Cine images with a steady-state free precession in short- and long-axes were acquired (slice thickness 8 mm; interslice gap 0 mm). Intravenous injection of 0.1 mmol/kg gadolinium-based contrast was infused, and images were acquired 1 and 2 min after the start of infusion. LGE images were acquired by using an inversion-recovery gradient echo sequence in the short- and long-axis plane. Inversion times were optimized to the null normal myocardium with images repeated in 2 separate phase-encoding directions to exclude artifacts (15).

TABLE 1 Cardiac Symptoms and Test Findings Considered Abnormal at Baseline Evaluation

Cardiac symptoms	Palpitations Pre-syncope, syncope Chest pain (nonpleuritic) Dyspnea related to congestive heart failure
Electrocardiography	Right or left bundle branch block Any degree atrioventricular block Supraventricular arrhythmias
Holter monitoring	Runs of nonsustained ventricular tachycardia Supraventricular arrhythmias Frequent premature ventricular contractions
Echocardiography	Regional wall motion abnormalities Wall thickening (hypertrophy) or thinning LV systolic dysfunction (LVEF <50%)
Cardiac magnetic resonance	Regional wall motion abnormalities Wall thickening (hypertrophy) LV systolic dysfunction (LVEF <50%) LGE

LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction.

CMR images were analyzed by 2 nonblinded expert radiologists for the presence and location of LGE and regional wall motion abnormalities. Biventricular ejection fraction and LV and right ventricular end-diastolic and end-systolic volumes were measured. LGE was classified as potentially ischemic (transmural or involving the LV subendocardium) or non-ischemic (involving middle or epicardial LV layer). In patients with a potentially ischemic LGE pattern, stress echocardiogram, thallium perfusion scanning, and/or coronary angiogram were performed to exclude ischemic heart disease.

FOLLOW-UP AND ENDPOINTS. Patients were followed up for major adverse events until May 2015. Information was obtained directly from patients at follow-up or, for those who did not return for follow-up, via telephone, by examining hospital records, or by contacting the patient's referring physician. The primary endpoint was a composite of all-cause mortality, symptomatic life-threatening arrhythmia, unplanned hospitalization for heart failure, and cardiac transplantation. Symptomatic life-threatening arrhythmias were defined as: 1) aborted sudden cardiac death in patients who received an appropriate implantable cardioverter-defibrillator (ICD) shock for VT; 2) a nonlethal episode of ventricular fibrillation or spontaneous sustained VT (≥3 ventricular beats with a frequency >120 beats/min, lasting >30 s) causing hemodynamic compromise and requiring cardioversion; and 3) symptomatic bradyarrhythmia leading to device implantation.

For deceased patients, the cause of death was determined from medical records for hospitalized patients, death certificates, and postmortem data or after contacting the patients' physicians. Cardiac death was defined as death from any cardiac-related cause (e.g., lethal arrhythmia, myocardial infarction, heart failure). Sudden cardiac death was defined as unexpected death either within 1 h of onset of cardiac symptoms in the absence of progressive cardiac deterioration, during sleep, or within 24 h of last being seen alive. The secondary endpoint was defined as an episode of nonsustained VT (≥3 ventricular beats with a frequency of >120 beats/min, lasting up to 30 s). For the primary endpoint, only the first event for each patient except death was included in the analysis.

DEFINITIONS. For the purpose of this study, cardiac sarcoidosis was diagnosed if patients satisfied the HRS consensus criteria (Online Appendix). Sarcoidosis stage was determined by using standard radiographic criteria (16). Cardiac symptoms and abnormalities of diagnostic tests at baseline are described in Table 1. For antecedent diagnosis of sarcoidosis, disease duration was defined as the time interval from disease diagnosis to initial evaluation (7). For comparison purposes, the criteria proposed by JMHW were also used (Online Appendix) (9).

STATISTICAL ANALYSIS. Statistical analyses were conducted with commercially available software (SPSS version 21, IBM SPSS Statistics, IBM Corporation, Armonk, New York). Variable normality was assessed with the 1-sample Kolmogorov-Smirnov test. Normally distributed data are reported as mean ± SD, and non-normally distributed data as the median and first and third quartiles. Differences between groups were compared with the Student *t* test for normally distributed variables and the Mann-Whitney test for non-normally distributed variables. The chi-square test was used for categorical variables and the Fisher exact test for categorical variables with low frequencies (expected cell count <5). The McNemar test was used to compare prevalence differences based on HRS and JMHW criteria (7,9). Receiver-operating characteristic (ROC) curves were constructed to assess the diagnostic accuracy of cardiac tests, in isolation and in various combinations. Area under the curve (AUC), diagnostic sensitivities and specificities, and positive and negative predictive values were calculated.

Time to events was calculated from the date of initial visit to the outpatient clinic. Univariate Cox proportional hazard models were used to assess the association between baseline covariates and endpoints (presented as hazard ratios [HRs] and 95% confidence intervals [CIs]). Variables with p values <0.10 on univariate analysis were then

TABLE 2 Baseline Characteristics of the Study Population and Comparison of These Characteristics Based on the Presence of LGE on CMR

	All Patients (N = 321)	LGE Present (N = 93)	LGE Absent (N = 228)	p Value
Demographic characteristics				
Age, yrs	47 (38-56)	51 (41-61)	47 (37-55)	0.01
Male	127 (39.6)	36 (38.7)	91 (39.9)	0.842
Sarcoidosis diagnosis				
Inceptive	128 (39.9)	34 (36.6)	94 (41.2)	0.438
Antecedent	193 (60.1)	59 (63.4)	134 (59.8)	0.224
Disease duration, months	49 (26.5-89)	92.4 (33.5-101.5)	68.3 (24-87.8)	0.158
Stage (0/I/II/III/IV)	8/117/158/27/11	2/28/46/14/3	6/89/112/13/8	0.08
Organ involvement				
Lung	282 (87.9)	86 (92.5)	196 (86)	0.132
Eye	78 (24.3)	17 (18.3)	71 (31.1)	0.025
Skin	63 (19.6)	15 (16.1)	48 (21.1)	0.355
Other	32 (9.9)	10 (10.8)	22 (9.6)	0.91
Therapy	140 (43.6)	47 (50.5)	93 (41.5)	0.177
Current/past therapy	69/71	31/16	38/55	
Cardiac symptoms	160 (49.8)	58 (62.4)	102 (45.5)	0.003
Palpitations	141 (43.9)	52 (55.9)	89 (39.7)	0.011
Chest pain	39 (12.1)	25 (26.9)	14 (6.3)	<0.0001
Pre-syncope	60 (18.7)	31 (33.3)	29 (12.9)	<0.0001
Syncope	6 (1.9)	5 (5.4)	1 (0.4)	0.009
NYHA functional class (I/II/III/IV)	161/146/13/1	34/51/8/0	127/95/5/1	0.003
PFTs				
FVC (% predicted)	96.1 ± 18.4	91.8 ± 20.1	97.9 ± 17.3	0.006
DL_{CO} (% predicted)	78.9 ± 18.4	72.2 ± 20.3	81.7 ± 16.9	<0.0001
Laboratory tests				
SACE, U/ml	59 (42-86)	68.4 (39.3-89.0)	60 (45-84)	0.732
BNP, ng/ml	15.9 (7.9-85.2)	41 (10.0-45.8)	13.6 (7.6-25.9)	0.006
ECG/Holter				
AVB (≥2nd degree)	2 (0.6)	2 (2.2)	0 (0)	0.026
LBBB	7 (2.2)	4 (4.3)	3 (1.3)	0.097
RBBB	54 (16.8)	13 (14)	41 (18.3)	0.384
Supraventricular arrhythmias	91 (28.3)	39 (41.9)	52 (23.2)	0.001
Ventricular tachycardia	6 (1.9)	4 (4.3)	2 (0.9)	0.04
Frequent PVCs	36 (11.2)	23 (24.7)	13 (5.7)	<0.0001
Echocardiography				
RWMA	30 (9.5)	22 (29)	8 (3.6)	<0.0001
LVEF, %	60 (60-65)	62 (60-70)	60 (60-65)	0.48
LVH	20 (6.2)	11 (11.8)	9 (4)	0.008

Continued on the next page

included as covariates in multivariate Cox proportional hazard models to identify variables independently associated with endpoints. Kaplan-Meier analysis was used to assess differences in cumulative event-free survival between patients with or without LGE on CMR. All statistical tests were 2-tailed, and a p value <0.05 was considered statistically significant.

RESULTS

STUDY POPULATION. From a total of 400 patients initially screened, 330 patients fulfilled inclusion criteria. The remaining 70 patients were excluded due to lack of tissue biopsy specimens (n = 27), concurrent collagen vascular disease (n = 5), coronary or congenital heart disease (n = 15), or failure to complete the baseline evaluation (n = 23). Nine patients lost to follow-up were also excluded.

Table 2 presents baseline demographic, clinical characteristics, and diagnostic findings in the 321 patients with sarcoidosis. On echocardiography, the majority of patients had preserved LV systolic function (left ventricular ejection fraction: 60% [60% to 65%]) that correlated with that measured from cine MRI (r = 0.82; p < 0.0001). Similarly, regional wall motion abnormalities detected according to echocardiography correlated with those according to cine MRI (r = 0.98; p < 0.0001). Detailed comparative data of the diagnostic and prognostic value of echocardiography and CMR in the entire sarcoidosis cohort and subgroups are presented in Online Table 3. ^{67}Gallium scintigraphy was available in 155 patients (48.3%), all with absent myocardial uptake.

At baseline, cardiac sarcoidosis was diagnosed in 96 (29.9%) patients according to the HRS consensus statement criteria; of these, 93 had LGE on CMR. On the basis of the JMHW criteria, a significantly lower rate (8.7%; p < 0.0001) of cardiac involvement was found.

Patients with VT at baseline had either an ICD implanted (1 patient with an episode of sustained VT) or underwent an electrophysiology study (5 patients with episodes of nonsustained VT), which led to ICD implantation in an additional patient. No patient with atrioventricular block at baseline received a permanent pacemaker.

Patients with LGE on CMR were older and more symptomatic, had a lower forced vital capacity and carbon monoxide diffusing capacity, and were more likely to have abnormalities on ECG/Holter monitoring or echocardiography (Table 2). Diabetes mellitus, hypertension, and dyslipidemia were reported more frequently in LGE-positive patients than in LGE-negative patients.

LGE PATTERN. CMR revealed LGE in 93 (29%) patients, with interobserver agreement for LGE being κ = 0.78 for presence and κ = 0.82 for absence. Characteristic images are shown in Figure 1. In LGE-positive patients, the left ventricle was involved in 87 cases (93.5%) with variable location of LGE (septum 71%; lateral wall 51.6%; anterior wall 21.5%; and inferior wall 17.2%). Right ventricular involvement was identified in 7 (7.5%) of the cases,

all with a nonischemic pattern; of these 7 patients, 6 also had LV involvement (septum 5; posterior wall 5; lateral wall 4; and inferior wall 4), and only 1 had free-wall focal epicardial involvement. In 64 (68.8%) patients, at least 2 LV walls were concurrently involved. On further analysis, a nonischemic LGE pattern was predominantly identified in the majority of cases and in all locations. In 20 patients with a potentially ischemic LGE pattern involving mainly the lateral wall and intraventricular septum, coronary artery disease was excluded according to stress echocardiography in 16 patients and coronary angiography in the remaining 4 patients.

SENSITIVITY AND SPECIFICITY OF DIAGNOSTIC TESTS. Table 3 summarizes the sensitivity, specificity, positive and negative predictive values, and AUC values for each diagnostic modality; Figure 2

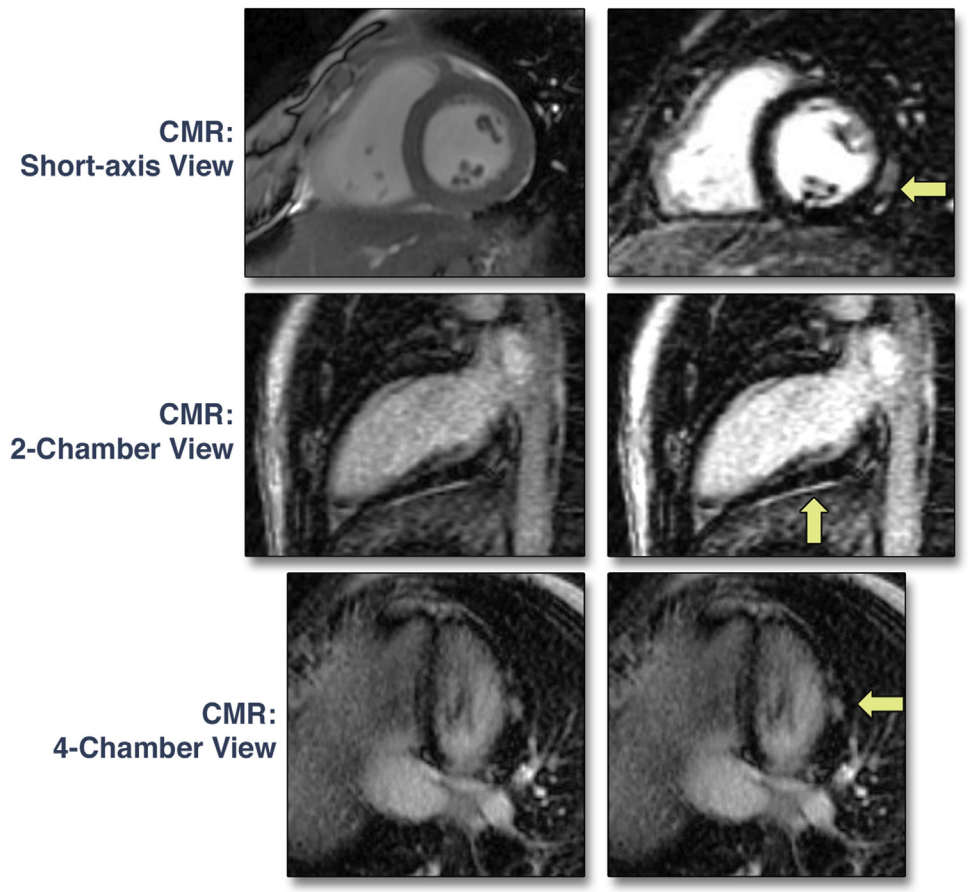
TABLE 2 Continued

	All Patients (N = 321)	LGE Present (N = 93)	LGE Absent (N = 228)	p Value
CMR				
LVEDV, ml	124.4 (104.1–143.2)	123.9 (101.5–143.1)	124.7 (105.6–144.5)	0.598
LVESV, ml	41.4 (31.6–53.8)	44.3 (29.9–55)	41.8 (32.1–53)	0.981
LVEF, %	65.7 ± 7.8	65.2 ± 8.9	66.1 ± 7.1	0.446
LV mass, g	98.1 ± 29.5	96.6 ± 26.6	98.9 ± 31	0.661
RVEDV, ml	122.9 (102.8–146.8)	123.8 (102.2–144.9)	122 (103.3–148.7)	0.801
RVESV, ml	49 (37.8–63.0)	51.7 (38.6–63.8)	47.5 (35.8–62.4)	0.292
RVEF, %	59.1 (55–65.1)	58 (52.8–64.5)	60.1 (56–66)	0.122
RWMA	31 (9.7)	23 (24.7)	8 (3.6)	<0.0001

Values are median (1st–3rd quartile), n (%), or n.

AVB = atrioventricular block; BNP = brain natriuretic peptide; CMR = cardiac magnetic resonance; DL_{CO} = carbon monoxide diffusing capacity; ECG = electrocardiogram; FVC = forced vital capacity; LBBB = left bundle brunch block; LV = left ventricular; LVH = left ventricular hypertrophy; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; PFTs = pulmonary function tests; PVCs = premature ventricular contractions; RBBB = right bundle brunch block; RVEDV = right ventricular end-diastolic volume; RVESV = right ventricular end-systolic volume; RVEF = right ventricular ejection fraction; RWMA = regional wall motion abnormalities; SACE = serum angiotensin-converting enzyme.

FIGURE 1 Typical CMR Images of Patients With Cardiac Sarcoidosis



Cardiac magnetic resonance (CMR) in a patient with sarcoidosis showing subepicardial late gadolinium enhancement in the left ventricular lateral wall in 2-chamber, 4-chamber, and short-axis views and matching steady-state free precession cine imaging **(arrows)**.

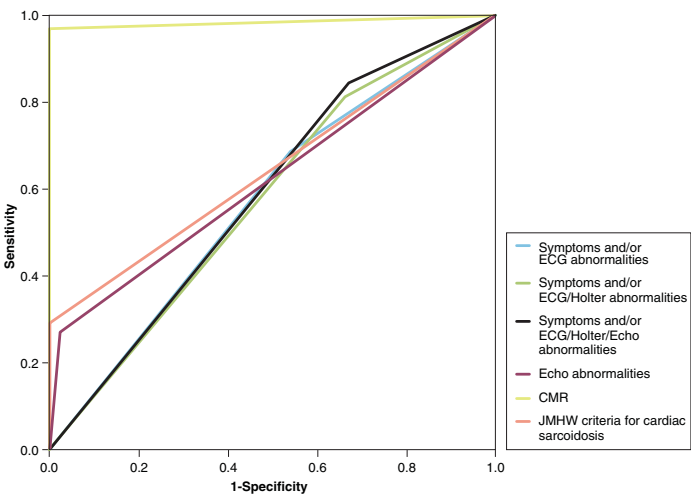
TABLE 3 Sensitivity, Specificity, PPV, NPV, and AUC of the Baseline Diagnostic Modalities in Isolation and in Various Combinations

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	AUC
Diagnostic tests					
Cardiac symptoms	64.6 (54.2-74.1)	56.9 (50.1-63.5)	39.0 (31.4-47.0)	79.0 (71.9-85.0)	0.607
ECG	20.8 (13.2-30.3)	80.9 (75.1-85.8)	31.8 (20.6-44.7)	70.5 (64.6-76.0)	0.509
Holter monitoring	59.4 (48.9-69.3)	57.8 (51.0-64.3)	37.5 (29.8-45.7)	76.9 (69.8-83.1)	0.586
TTE	27.1 (18.5-37.1)	97.8 (94.9-99.3)	83.9 (66.3-94.6)	75.9 (70.5-80.7)	0.624
CMR	96.9 (91.1-99.4)	100 (98.4-100.0)	100.0 (96.1-100.0)	98.7 (96.2-99.7)	0.984
Cardiac symptoms and/or 1 test					
Symptoms and/or ECG	68.8 (58.5-77.8)	45.8 (39.1-52.5)	35.1 (28.3-42.4)	77.4 (69.4-84.2)	0.573
Symptoms and/or Holter	81.3 (72.0-88.5)	33.8 (27.6-40.4)	34.4 (28.2-40.9)	80.9 (71.4-88.2)	0.575
Symptoms and/or TTE	70.8 (60.7-79.7)	55.6 (48.8-62.2)	40.5 (33.0-48.3)	81.7 (74.7-87.5)	0.632
Cardiac symptoms and/or 2 tests					
Symptoms and/or ECG and/or Holter	81.3 (72.0-88.5)	33.8 (27.6-40.4)	34.4 (28.2-40.9)	80.9 (71.4-88.2)	0.575
Symptoms and/or ECG and/or TTE	72.9 (62.9-81.5)	44.4 (37.8-51.2)	35.9 (29.2-43.1)	79.4 (71.3-86.1)	0.587
Symptoms ± Holter ± TTE	84.4 (75.5-91.0)	32.9 (26.8-39.5)	34.9 (28.8-41.4)	83.2 (73.7-90.3)	0.586
JMHW criteria	29.2 (20.3-39.3)	100.0 (98.4-100.0)	100.0 (87.7-100.0)	76.8 (71.5-81.5)	0.646

AUC = area under the curve; CI = confidence interval; JMHW = Japanese Ministry of Health and Welfare; PPV = positive predictive value; NPV = negative predictive value; TTE = transthoracic echocardiography; other abbreviations as in Table 2.

shows the ROC curves. CMR was the most accurate diagnostic tool (AUC: 0.984), whereas echocardiography had similar specificity (97.8%) but low sensitivity (27.1%). CMR identified 30 (9.3%) patients with cardiac involvement and without cardiac symptoms or ECG abnormalities; 15 (4.7%) of them were asymptomatic with no abnormalities on any other test. Adding echocardiography to the screening strategy using cardiac symptoms and/or ECG did not significantly change the sensitivity and specificity. Adding incrementally ECG, echocardiography, and Holter monitoring to cardiac symptoms increased the sensitivity of the screening tools from 64.6% to 84.4% but reduced their specificity from 56.9% to 32.9%.

FIGURE 2 ROC Curves for the Clinical Diagnosis of Cardiac Sarcoidosis Based on HRS Criteria



Receiver-operating characteristic (ROC) curve testing various combinations of available diagnostic tests (electrocardiogram [ECG], Holter, echocardiography, cardiac magnetic resonance [CMR]) for the diagnosis of cardiac sarcoidosis based on Heart Rhythm Society (HRS) criteria. Echo = echocardiogram; JMHW = Japanese Ministry of Health and Welfare.

Further analysis was based on grouping patients into those with cardiac symptoms and/or ECG abnormalities and those patients without cardiac symptoms and/or ECG abnormalities. In patients with cardiac symptoms and/or ECG abnormalities, echocardiography had a specificity of 98.4%, sensitivity of 33.3%, positive predictive value of 91.7%, and negative predictive value of 73.2%. In this subgroup, cardiac involvement was identified in 22 of 24 patients with an abnormal echocardiography; CMR confirmed cardiac involvement in 19 of 22 patients with an abnormal echocardiography and identified 44 additional patients with a normal echocardiography. In patients without cardiac symptoms and/or ECG abnormalities, echocardiography had a specificity of 97.1% and a negative predictive value of 79.4%; its sensitivity was 13.3%, and the positive predictive value was 57.1%. In this group, 7 patients had an abnormal echocardiogram; 4 of the 7 patients had cardiac involvement on CMR. In the remaining 126 patients without cardiac symptoms and/or ECG abnormalities and normal echocardiography, 26 patients had cardiac involvement on CMR; in this subgroup, an abnormal Holter monitoring study (Table 1) had a sensitivity of 42.3% and a positive predictive value of 29.7%, whereas a normal study had a

specificity of 74%, and a negative predictive value of 83.1%.

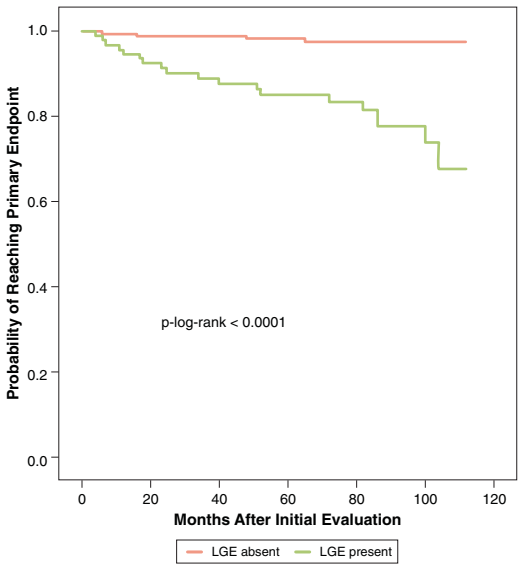
FOLLOW-UP/RISK STRATIFICATION ANALYSIS. For the cohort, the median follow-up was 84 (51 to 100) months. In total, 23 (7.2%) of 321 patients reached the primary endpoint. Specifically, 13 patients died, 7 developed symptomatic life-threatening arrhythmias, and 3 patients were hospitalized for heart failure. Of those with life-threatening arrhythmias, 5 patients required cardioversion and eventually ICD implantation. Of the 13 deaths, 8 were cardiac related, 2 were attributed to infections and pulmonary complications, and 1 was due to stroke; in 2 cases, the cause of death was not identified. In addition, 11 patients had episodes of nonsustained VT on Holter monitoring during follow-up (secondary endpoint).

Patients who developed major adverse events in the follow-up period (patients at risk) were older, had higher B-type natriuretic peptide levels, and lower carbon monoxide diffusing capacity values than patients without adverse events. Diabetes, hypertension, nonsustained VT, or regional wall motion abnormalities were more frequently detected at baseline in these patients. The majority of primary and secondary endpoint events (25 of 34 [73.5%]) occurred in LGE-positive patients. Ten of the 13 deaths and the majority of adverse events (25 of 34 [73.5%]) occurred in patients with cardiac symptoms and/or ECG abnormalities. In the patient subgroup without cardiac symptoms and/or ECG abnormalities and a normal echocardiogram, 9 patients developed adverse events; of these patients, 6 had an abnormal Holter study at baseline. Adverse events were rare in this subgroup with a normal Holter study; only 3 of 89 patients developed nonsustained VT.

In the entire patient cohort, LGE was the only independent predictor of the primary endpoint (HR: 5.68; 95% CI: 1.74 to 18.49; $p = 0.004$) and also an independent predictor (HR: 9.14; 95% CI: 1.44 to 57.82; $p = 0.019$) of all events. Other all-event independent predictors were age (HR: 1.08; 95% CI: 1.01 to 1.15; $p = 0.024$) and nonsustained VT in the initial Holter evaluation (HR: 14.44: 95% CI: 2.01 to 103.49; $p = 0.008$). Kaplan-Meier survival curves for adverse events (primary endpoint and combination of primary and secondary endpoints) according to the presence of LGE on CMR are shown in Figures 3 and 4. The event-free survival was lower in LGE-positive patients than in LGE-negative patients in both analyses (log-rank test, $p < 0.0001$).

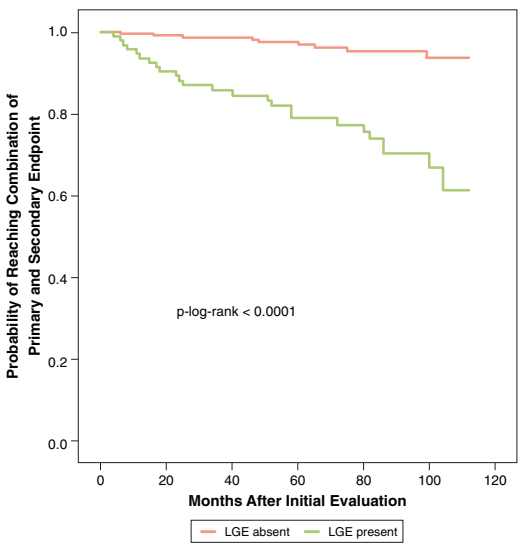
In the subgroup of patients with cardiac symptoms and/or ECG abnormalities, LGE was the only independent predictor of the primary endpoint (HR: 12.71;

FIGURE 3 Primary Endpoint-Free Survival According to Presence of LGE in the Total Cohort



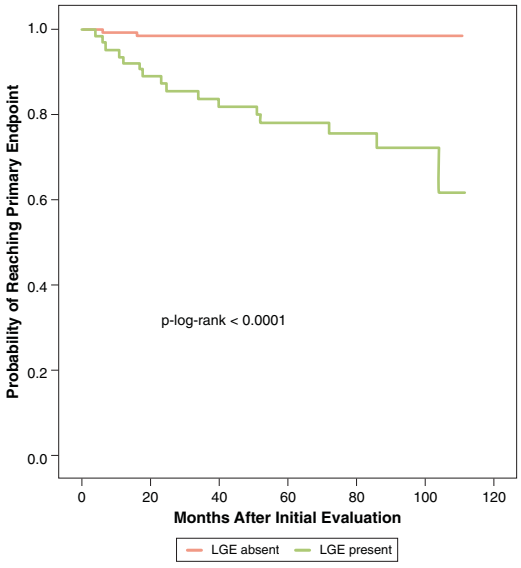
Kaplan-Meier curve analysis of probability reaching the primary endpoint (a composite of all-cause mortality, symptomatic life-threatening arrhythmia, unplanned hospitalization for heart failure, and cardiac transplantation) based on the presence of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR).

FIGURE 4 All Event-Free Survival According to Presence of LGE in the Total Cohort



Kaplan-Meier curve analysis of probability reaching the combination of primary (a composite of all-cause mortality, symptomatic life-threatening arrhythmia, unplanned hospitalization for heart failure, and cardiac transplantation) and secondary (nonsustained ventricular tachycardia) endpoints based on the presence of LGE on CMR. Abbreviations as in Figure 3.

FIGURE 5 Primary Endpoint-Free Survival According to Presence of LGE in the Subgroup of Patients With Cardiac Symptoms and/or ECG Abnormalities



Kaplan-Meier curve analysis of probability reaching primary endpoint (a composite of all-cause mortality, symptomatic life-threatening arrhythmia, unplanned hospitalization for heart failure, and cardiac transplantation) based on the presence of LGE on CMR in the subgroup of patients with cardiac symptoms and/or ECG abnormalities. Abbreviations as in Figures 2 and 3.

95% CI: 1.48 to 109.35; p = 0.021) but was not associated with the combination of primary and secondary endpoints (HR: 3.48; 95% CI: 0.85 to 14.15; p = 0.08). For this subgroup, Kaplan-Meier survival analysis showed that LGE on CMR was associated with a greater probability of reaching the primary endpoint (Figure 5). In patients without cardiac symptoms and/or ECG abnormalities, only age was independently associated with either the primary endpoint (HR: 1.12; 95% CI: 1 to 1.24; p = 0.033) or all events (HR: 1.07: 95% CI: 1 to 1.13; p = 0.037).

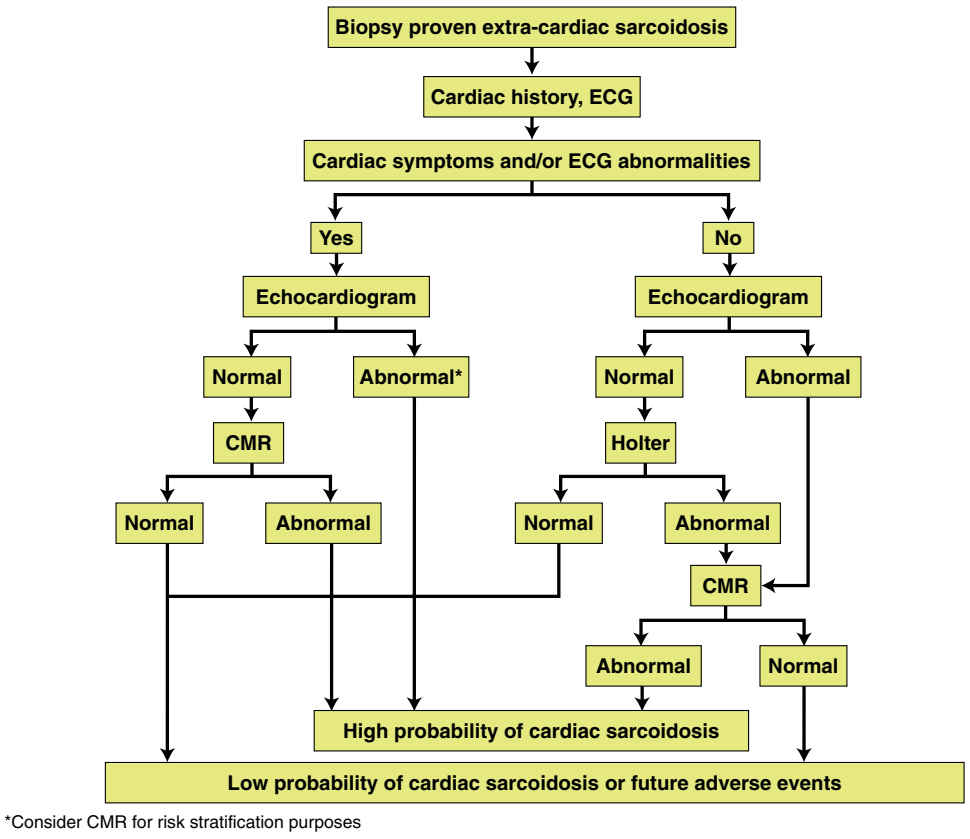
DISCUSSION

To the best of our knowledge, the present study is the largest cohort trial to evaluate cardiac involvement and assess the independent and combined diagnostic utility of cardiac tests in a general population of biopsy-proven patients with sarcoidosis, irrespective of clinical suspicion for cardiac disease. Application of the HRS criteria yielded a prevalence of cardiac sarcoidosis of approximately 30%, similar to that reported according to autopsy or CMR studies, and significantly higher than that of the JMHW criteria (1,3-6,17). CMR detected subclinical disease in 9.3% of asymptomatic patients without ECG abnormalities and in 4.7% of patients without any abnormalities at the initial evaluation. Abnormal echocardiography in patients with cardiac symptoms and/or ECG abnormalities had a high positive predictive value but was not useful for risk stratification purposes. LGE on CMR was an independent predictor of the primary endpoint and of all events in the total population, and was independently correlated with the primary endpoint in the subgroup of patients with cardiac symptoms and/or ECG abnormalities.

In the absence of a gold standard test and given the low sensitivity and invasive nature of endomyocardial biopsy (18), the diagnosis of cardiac sarcoidosis is mainly based on a constellation of symptoms and specific findings from noninvasive diagnostic modalities. The JMHW criteria, which are based on a combination of electrical and functional abnormalities, consider LGE on CMR a minor criterion (9). According to studies showing superiority of CMR in the diagnosis and identification of even subclinical forms of cardiac sarcoidosis (2-7), the recently published HRS criteria have included specific LGE patterns on CMR and cardiac uptake on fluorodeoxyglucose-PET as major criteria (7). Applying the HRS criteria in a general sarcoidosis population, regardless of clinical suspicion for cardiac involvement, we found a cardiac sarcoidosis prevalence of 29.9%, which is significantly greater than that calculated by using the JMHW criteria (8.7%) and similar to that reported in patients with suspected cardiac sarcoidosis (5,12,19-21). In our study, CMR detected 44 patients with cardiac symptoms and/or ECG abnormalities but normal echocardiogram, as well as 15 asymptomatic patients with normal baseline testing. The CMR diagnostic superiority lies in its ability to identify myocardial fibrosis, which may not cause any electrical or functional abnormality on conventional testing. In addition, CMR is valuable for risk stratification. In the total cohort consisting of patients with normal left ventricular ejection fraction, LGE was an independent predictor of endpoints. Its predictive value was maintained in the patient subgroup with cardiac symptoms and/or abnormal ECG. This finding confirms previous data on the utility of CMR in asymptomatic patients (11) and suggests that the clinical significance of myocardial fibrosis may be variable. Our data highlight the diagnostic accuracy and predictive value of CMR in the entire cohort and in various patient subgroups, making it an indispensable tool in the diagnosis of cardiac sarcoidosis.

Of the conventional tests, echocardiography had an overall low sensitivity (27.1%) in the total cohort.

FIGURE 6 Diagnostic Algorithm for Cardiac Sarcoidosis



Diagnostic algorithm constructed on the basis of diagnostic and prognostic information provided by available modalities. Note that cardiac symptoms and electrocardiogram abnormalities are used as the starting point of the screening approach.

This finding is in agreement with previous studies on symptomatic patients with suspected cardiac sarcoidosis that reported a significant portion of patients with cardiac disease and normal echocardiography (5,22). Our study found that abnormal echocardiography (defined not only as low ejection fraction but also including regional wall motion abnormalities, wall thickening, or wall thinning) was useful, especially in patients with cardiac symptoms and/or ECG abnormalities. In this particular subgroup, its high positive predictive value (92%) may obviate the need for CMR testing. However, one may argue on the basis of these and previous data that CMR may still be needed not only to confirm diagnosis but, more importantly, to obtain prognosticating information (3–5). In the group of patients with no cardiac symptoms or ECG abnormalities, an abnormal echocardiographic study will most likely require CMR confirmation. Although the small number of patients in this category does not allow safe conclusions to be drawn, of the 7 patients with an abnormal echocardiogram, 4 had cardiac involvement on CMR. Of note, echocardiographic studies in our cohort did not include strain rate analysis, which strongly correlates with myocardial fibrosis on CMR in patients with sarcoidosis (23). Integration of speckle-tracking echocardiography in the screening strategy could possibly improve its role in this setting. Likewise, ECG had a low sensitivity, and its overall diagnostic accuracy was low (AUC: 0.51). However, an abnormal ECG (as defined in **Table 1**) alone or in combination with cardiac symptoms signified a group of patients at high risk for adverse events. Indeed, the majority of adverse events (73.5%) and deaths (77.0%) in the present study occurred in patients with cardiac symptoms and/or ECG abnormalities.

In the subgroup of patients with no cardiac symptoms or ECG abnormalities and a normal echocardiogram (126 patients), the use of Holter monitoring may

provide useful clinical information. In this subgroup, CMR detected cardiac involvement in 26 (20.6%) patients. Of these, 11 patients had an abnormal Holter study at baseline. Most of the adverse events occurred in patients with an abnormal Holter study, whereas none of the remaining 15 patients with positive CMR (and all conventional baseline tests normal) developed any adverse events. In view of its relatively high negative predictive value (approximately 83%) in this particular group, a normal Holter study may provide some assurance about the likelihood of future adverse events. However, in this group, more studies are needed to assess the prognosticating ability both of the Holter monitoring and the echocardiogram.

The large number of patients undergoing all available diagnostic modalities (except fluorodeoxyglucose-PET) enabled us to assess the independent and collective value of most diagnostic tests used in everyday clinical practice and to construct an algorithm that may allow accurate diagnosis of cardiac sarcoidosis (**Figure 6**). As initial step, we used the conventional screening strategy based on the presence/absence of cardiac symptoms and/or ECG abnormalities. Echocardiography provides useful information when assessed independently, especially in patients with cardiac symptoms and/or ECG abnormalities. An abnormal echocardiography in these patients is highly suggestive of cardiac sarcoidosis, with a positive predictive value of approximately 92%. In this setting, CMR is also useful because it can confirm cardiac involvement with greater precision and, more importantly, provide risk stratification information. A normal echocardiographic study in this subgroup will invariably require further testing with CMR. In patients without cardiac symptoms and/or ECG abnormalities, an abnormal echocardiography may need CMR confirmation because the small number of patients in this subgroup did not allow us to make secure recommendations. In the subgroup of patients without cardiac symptoms or ECG or echocardiographic abnormalities, a normal Holter monitoring study (negative predictive value of approximately 83%) may obviate or delay the need for CMR testing because these patients do not seem to be at high risk for adverse events.

STUDY LIMITATIONS. The study did not provide detailed description of the extent of LGE and its possible association with cardiac adverse events. T2-weighted sequences that could have detected acute inflammation or repeat CMR after immunosuppressive treatment were not obtained. Thus, the extent to which acute inflammation accounted for adverse events could not be ascertained. In addition, because the CMR analysis was nonblinded, the possibility of reader bias cannot be totally excluded. Finally, the study design did not allow us to perform a detailed cost-effectiveness analysis, which would be useful in this context.

CONCLUSIONS

CMR is an invaluable test in the diagnosis and prognosis of cardiac sarcoidosis in a general sarcoidosis population. It should be an integral part of the diagnostic strategy, especially in patients with cardiac symptoms and/or abnormal ECG. In patients without cardiac symptoms and normal echocardiographic, ECG, and Holter monitoring studies, the information provided by CMR may not be as critical because these patients do not usually develop adverse events. Of the conventional tests, echocardiography has an overall limited value in the screening process. Although it had a high positive predictive value in patients with cardiac symptoms and/or ECG abnormalities, an abnormal study may still require further testing with CMR for risk stratification purposes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with biopsy-proven extracardiac sarcoidosis, LGE on CMR was the most accurate modality for diagnosing cardiac sarcoidosis (AUC: 0.98) and an independent predictor of primary endpoints and of all adverse events during follow-up. Of the remaining cardiac tests, echocardiography had a high positive predictive value only in patients with cardiac symptoms and/or ECG abnormalities, but its use was limited by an overall low sensitivity and inability to provide sufficient prognostic information.

TRANSLATIONAL OUTLOOK: Further research, including cost-effectiveness studies, are required to validate these findings, assess the clinical utility of CMR as a stand-alone modality in diagnosing cardiac sarcoidosis and assessing risk across all patients subgroups, (i.e., with or without cardiac symptoms at presentation), and to study the association of LGE location and extent with adverse events and use the information provided by CMR to guide therapeutic interventions.

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KEY WORDS cardiac MRI, cardiac sarcoidosis, diagnosis, echocardiography, screening

APPENDIX For supplemental tables, please see the online version of this paper.