SUPPLEMENTAL MATERIAL

Table S1. The Heart Rhythm Society's Criteria[10] for the Diagnosis of Cardiac Sarcoidosis (CS) with the Distribution of the Individual Criteria in Patients of the Present Cohort

Likelihood of diagnosis and the underlying criteria	**N (%) ***
Histological Diagnosis from Myocardial Tissue, *Definite CS*	193 (48)
Non-caseating granuloma on histological examination of myocardial tissue with no alternative cause (e.g., negative organismal stains)	
Clinical Diagnosis from Invasive and Non-Invasive Studies, *Probable CS*	205 (52)
a) Histological diagnosis of extra-cardiac sarcoidosis, and b) one or more of following is present	205 (100)
Cardiomyopathy or heart block responsive to steroid +/- immunosuppressant	NA
Unexplained reduced LVEF (< 40 %)	34 (17)
Unexplained sustained VT (spontaneous or induced)	29 (14)
Mobitz type II 2nd degree heart block or 3rd degree heart block	127 (62)
Patchy uptake on dedicated cardiac PET#	157 (77) †
Late gadolinium enhancement on CMR#	125 (61) ‡
Positive gallium uptake	NA
c) other causes for the cardiac manifestation(s) have been reasonably excluded	205 (100)

*Number of patients (% of the entire cohort or of the clinical diagnosis group)

In a pattern consistent with CS

† 175 patients underwent PET

‡ 133 patients underwent CMR

CMR indicates cardiac magnetic resonance; LVEF, left ventricular ejection fraction; NA, not applicable; PET, positron emission tomography; VT, ventricular tachycardia

Table S2. Summary of Treatment During the Disease Course

	All patients n=398	Class I-IIa indication for an ICD by the 2014 HRS guideline[10] yes, n=339	no, n=59	p*
Immunosuppression				
Prednisone	382 (96)	327 (97)	55 (93)	0.273
Azathioprine	150 (38)	128 (38)	22 (37)	1.000
Methotrexate	26 (7)	20 (6)	6 (10)	0.249
Cyclosporin	21 (5)	18 (5)	3 (5)	1.000
Infliximab	14 (4)	12 (4)	2 (3)	1.000
Mycophenolate mofetil	36 (9)	32 (9)	4 (7)	0.629
Treatment of heart failure				
Beta-adrenergic blockers	376/398 (95)	325/339 (96)	51/59 (86)	0.009
ACEI or ARB	274/398 (64)	236/339 (70)	38/59 (64)	0.448
Spironolactone	117/377 (31)	106/322 (33)	11/55 (20)	0.059
LV assist device	3 (1)	3 (1)	0	1.000
Transplantation	25 (6)	23 (7)	2 (3)	0.558
Treatment of arrhythmias				
Antiarrhythmic drugs	100/398 (25)	87/339 (26)	13/59 (22)	0.628
VT ablation	18 (5)	17 (5)	1 (2)	0.493
Implantable intracardiac devices				
Cardioverter-defibrillator with or without cardiac resynchronization capacity				
at diagnosis	202 (51)	185 (55)	17 (29)	<0.001
during follow-up	92 (23)	79 (23)	13 (22)	1.000
Pacemaker only	64 (16)	62 (18)	2 (3)	0.002

Data are numbers (%) of cases

* P-values for group comparison conducted using Fisher's exact test.

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LV, left ventricular; VT, ventricular tachycardia.

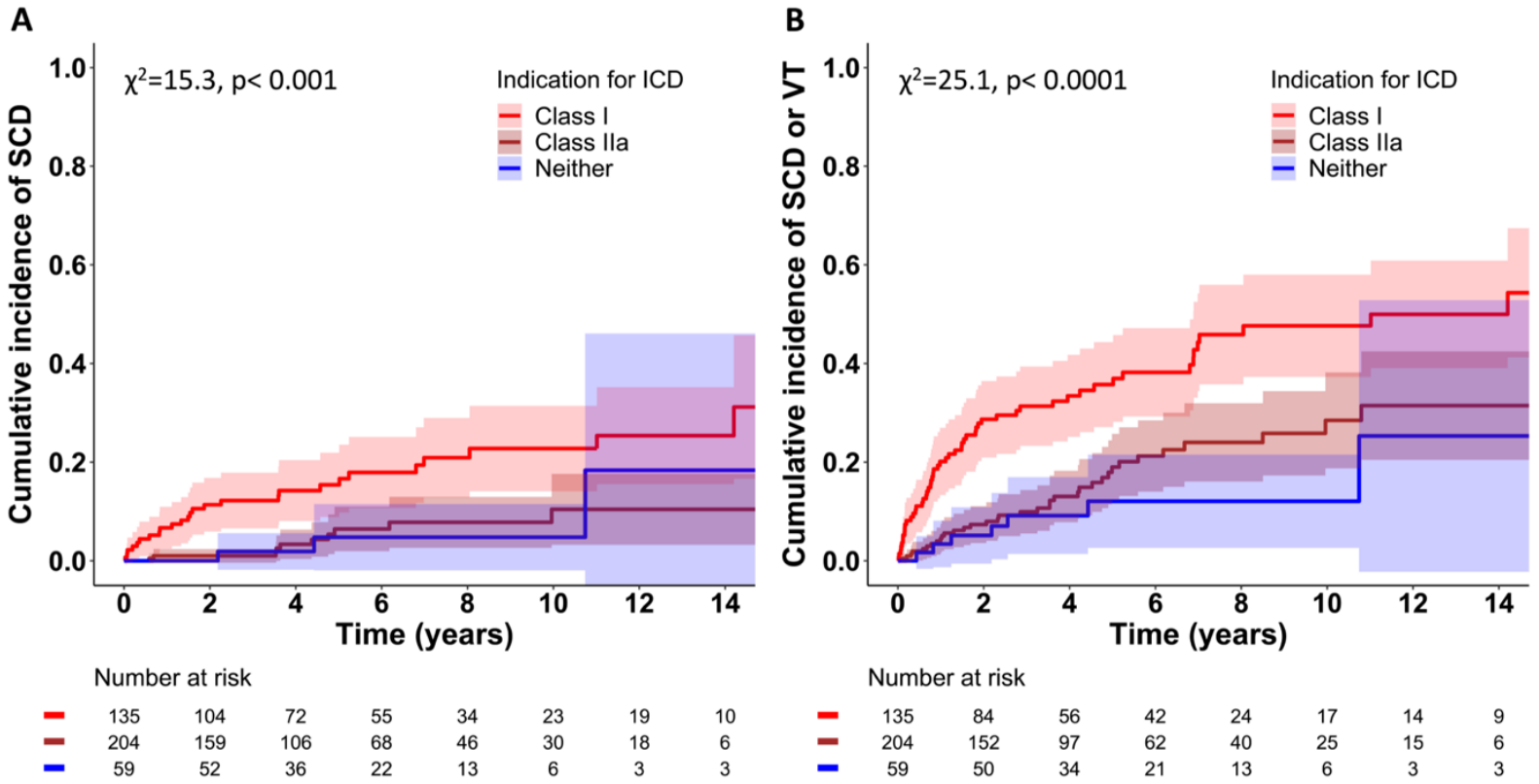

Figure S1. Cumulative incidence of sudden cardiac death (SCD) and the composite of SCD or sustained ventricular tachycardia (VT) stratified by indications for an implantable cardioverter-defibrillator (ICD) by the 2014 Heart Rhythm Society's guideline[10]

Incidences, with shaded 95% confidence intervals, of SCD (panel **A**) and the composite of SCD or sustained VT (panel **B**) in 398 patients with cardiac sarcoidosis stratified by indications for an ICD by the 2014 Heart Rhythm Society's guideline.[10] The graphs were constructed by cause-specific cumulative incidence analysis[18] with transplantations and deaths from heart failure or non-cardiac causes analyzed as competing events; comparisons were made using the Gray test[19]. The cumulative incidence functions in patients with class IIa indications and patients with no indications are not statistically significantly different for either SCD (χ^2 =0.008, p=0.931) or the composite of SCD and sustained VT (χ^2 =1.318, p=0.251).

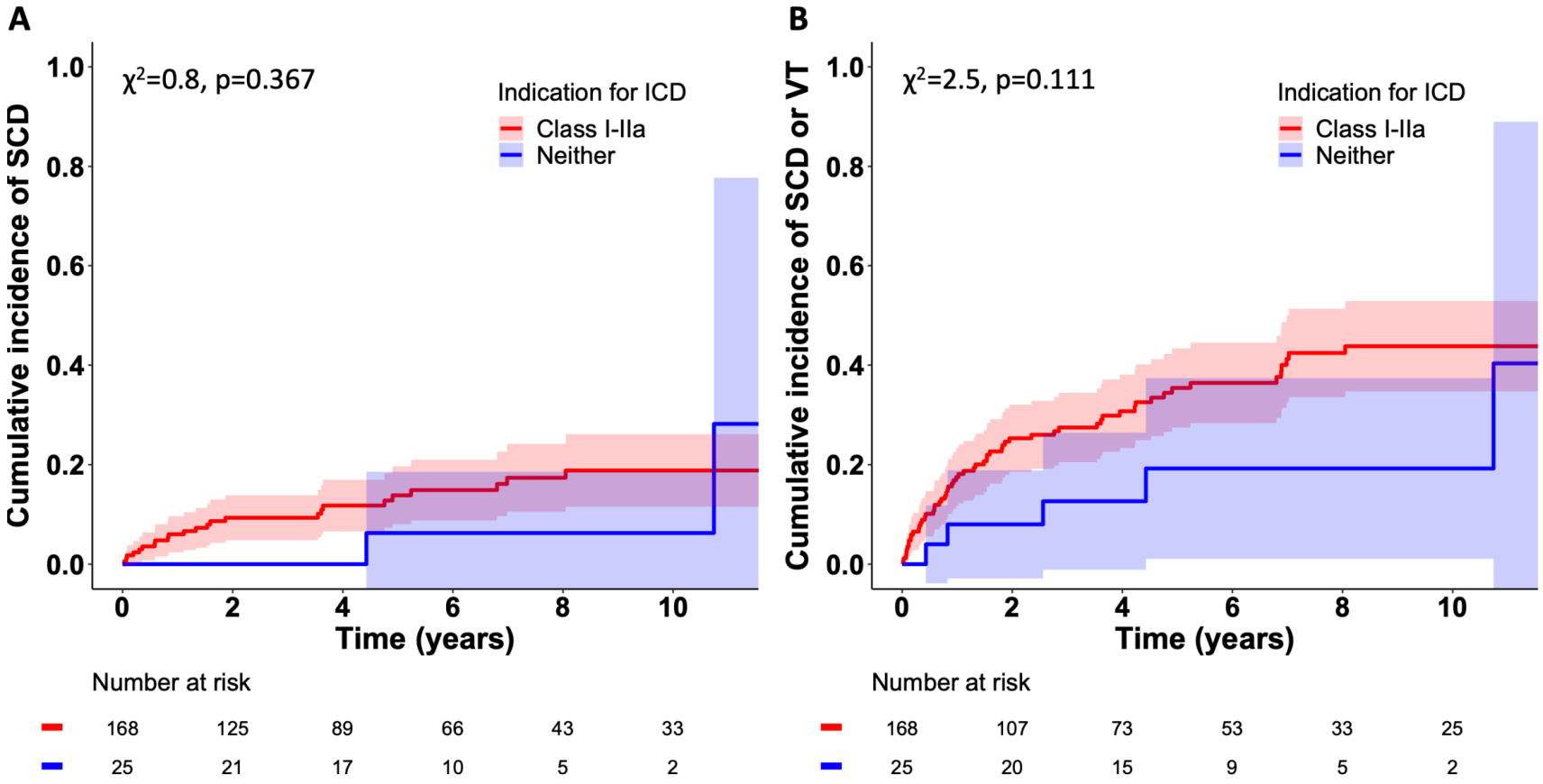

Figure S2. Cumulative incidence of sudden cardiac death (SCD) and the composite of SCD or sustained ventricular tachycardia (VT) in patients with definite cardiac sarcoidosis (CS) stratified by class I-IIa indications for an implantable cardioverter-defibrillator (ICD) by the 2014 Heart Rhythm Society's guideline[10]

Incidences, with shaded 95% confidence intervals, of SCD (panel **A**) and the composite of SCD or sustained VT (panel **B**) in 193 patients with definite CS stratified by class I-IIa indications for an ICD by the 2014 Heart Rhythm Society's guideline.[10] The graphs were constructed by cause-specific cumulative incidence analysis[18] with transplantations and deaths from heart failure or non-cardiac causes analyzed as competing events; comparisons were made using the Gray test[19].

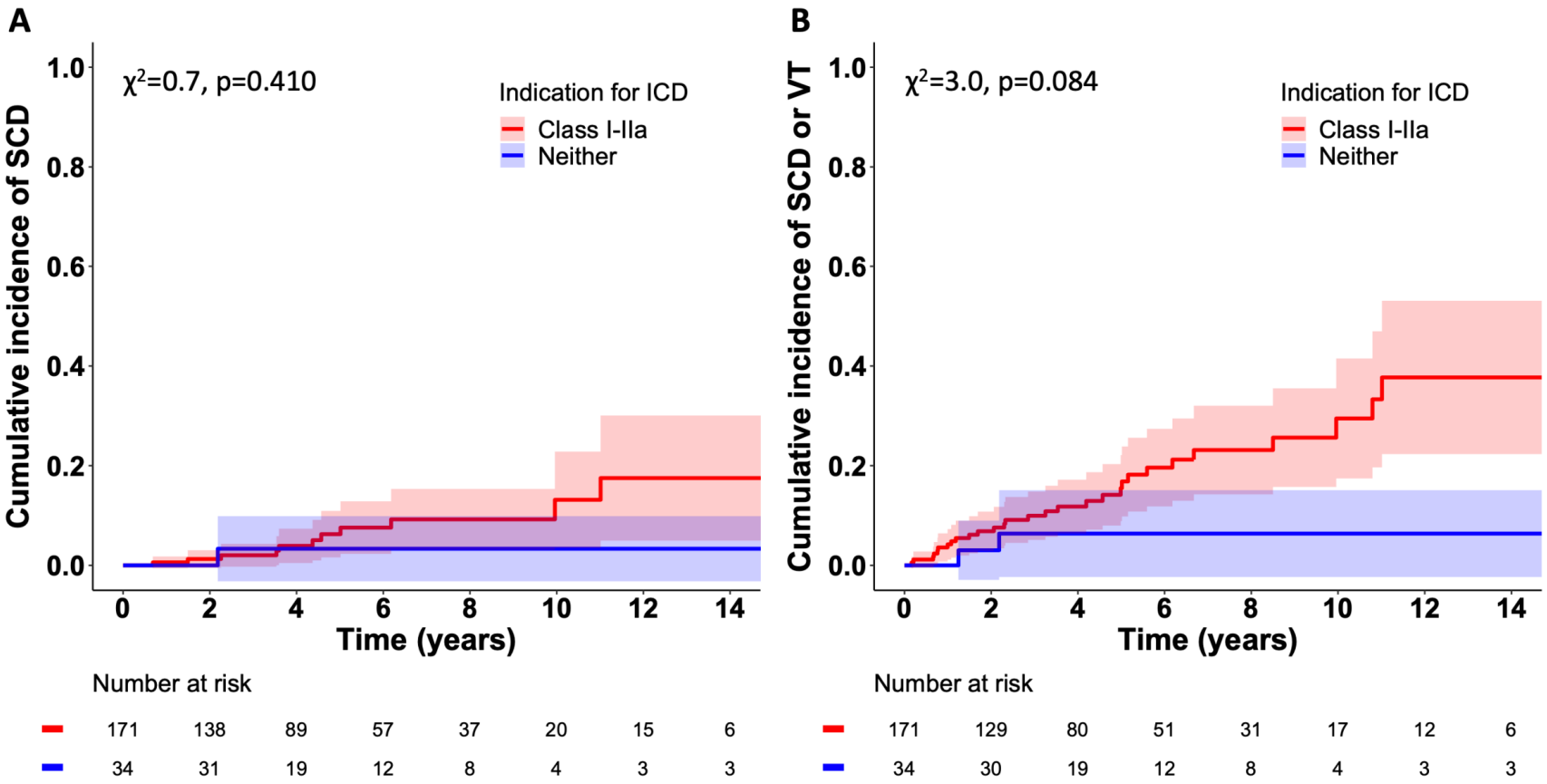

Figure S3. Cumulative incidence of sudden cardiac death (SCD) and the composite of SCD or sustained ventricular tachycardia (VT) in patients with probable cardiac sarcoidosis (CS) diagnosed and stratified by class I-IIa indications for an implantable cardioverter-defibrillator (ICD) by the 2014 Heart Rhythm Society's guideline[10]

Incidences, with shaded 95% confidence intervals, of sudden cardiac death (SCD) (panel **A**) and the composite of SCD or sustained VT (panel **B**) in 205 patients with probable CS diagnosed and stratified by class I-IIa indications for an implantable cardioverter-defibrillator (ICD) by the 2014 Heart Rhythm Society's guideline.[10] The graphs were constructed by cause-specific cumulative incidence analysis[18] with transplantations and deaths from heart failure or non-cardiac causes analyzed as competing events; comparisons were made using the Gray test[19].

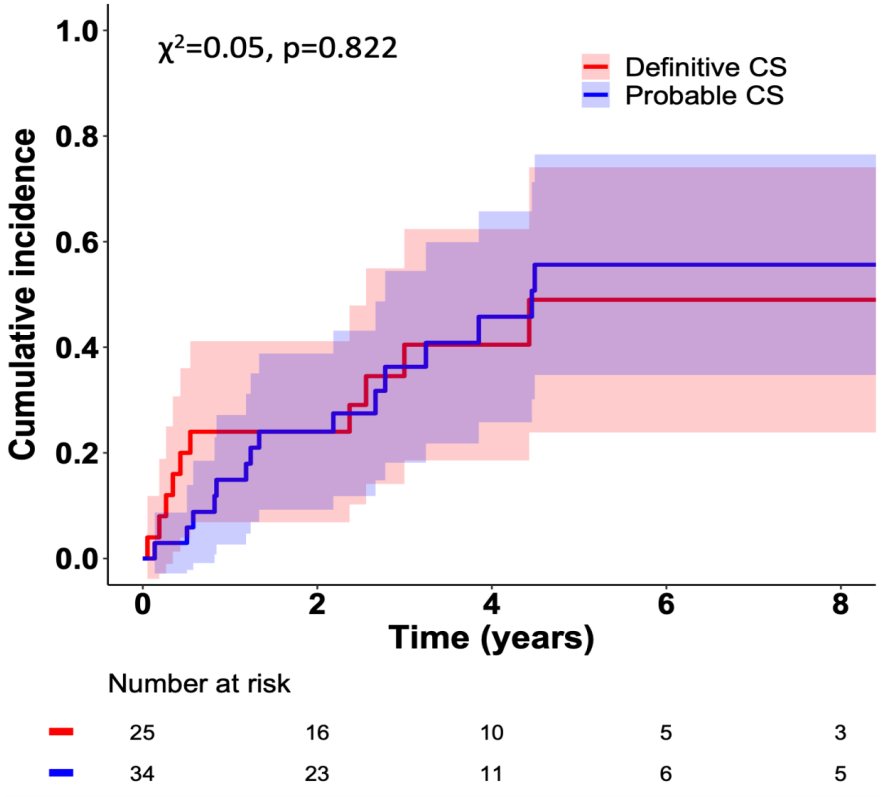

Figure S4. Emergence of implantable cardioverter-defibrillator (ICD) indications in patients with definite and probable cardiac sarcoidosis (CS) and absent ICD indications by the 2014 Heart Rhythm Society's guideline[10] at presentation of CS

Cumulative incidence of the composite of fatal or aborted sudden cardiac death, sustained ventricular tachycardia, and emergence of class I-IIa indications for an ICD in patients with definite and probable cardiac sarcoidosis and absent ICD indications by the 2014 Heart Rhythm Society's guideline[10] at the start of follow-up. The shaded areas represent 95% confidence intervals.

SUPPLEMENTAL LITERATURE REVIEW

Quantity of Myocardial Late Gadolinium Enhancement as Predictor of Life-Threatening Ventricular Arrhythmias in Cardiac Sarcoidosis.

Our search of the literature (PubMed, MEDLINE) revealed 23 original articles from outside our country focusing on cardiac sarcoidosis (CS) and the predictive role of late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR). We found no prognostic studies pertinent to CS and the extent of perfusion defects in single-photon emission computed tomography scans. Eight CMR works[20-22, 24, 25, 29, 39, 40] reported data on the predictive power of the extent of LGE quantified as percentage of the left ventricular (LV) mass. The key details of these studies are summarized in Table S3. Most of them involved patients with systemic sarcoidosis and merely suspected cardiac involvement,[20-22,29] while 2 studies involved mixed populations of some proven with many suspected CS cases,[24,25] and just 2 works[39,40] included patients with clinically and/or histologically confirmed CS only. All except 1 study[29] were retrospective and used composite endpoints including a variety of cardiac events. There was also variation in the methods to define LGE and to quantify its mass. All works applied ROC analysis and Youden index with equal weight on sensitivity and specificity to identify the LGE mass threshold best discriminating between patients with and without future events. However, only 3 studies[21,25,40] used the method (time-dependent ROC analysis) designed specifically for assessment of time-to-event data. The reported LGE mass threshold ranged from 3.0% to 28.0%. There were 4 studies[24,25,29,40] in which life-threatening arrhythmias predominated as events and which hence are particularly relevant to the risk of sudden cardiac death in CS. In these works, the LGE mass threshold varied from 5.7% to 8.0%[24,25,29,40] with a mean, weighted by the size of each study, of 6.4%. With respect to the individual studies, our work has most analogy with the study by Crawford et al.[40] which involved only CS patients, used a method identical to ours to quantify myocardial LGE, and analyzed only life-threatening arrhythmic events using the time-dependent ROC method. The LGE mass cut-off in that work, 6.0 %, was close to the above weighted mean and was taken as the literature-based threshold for our analyses.

Table S3. Summary of CMRI studies assessing the quantity of myocardial LGE as a predictor of serious cardiac events in patients with diagnosed or suspected CS

1st author, year design	N	Dg of study subjects	Mean age, y	LGE method	LGE+	F-U, y	Events of the composite endpoint	ROC analysis of LGE mass (%) AUC	threshold	PPV	NPV
Ise 2014,[39] retrospective	43	CS (JMHW)	59	≥ 5 SD*	100%	3.3†	11 HF hosp, 6 cardiac deaths, 6 VAs	0.77	**21.9%**	0.62	0.86
Crawford 2014,[40] retrospective	51	CS (JMHW) LVEF > 35%	51	FWHM	63%	4.0†	14 VAs (sustained VT or VF)	0.79	**6.0%**	0.58	0.91
Agoston-Coldea 2016,[20] retrospective	56	Suspect CS	52	≥ 5 SD*	NR	2.7‡	10 HF hosp, 4 AVB, 2 VAs (1 fatal)	0.94	**28.0%**	0.92	0.95
Yasuda 2016,[24] retrospective	81	35 CS (JMHW) 46 suspect CS	63	≥ 6 SD*	95%	1.8‡	39 VAs, including non-sustained VTs (25 incident, 14 historical)	0.76	5.1 g/m^2 **≈7.6%**	NR	NR
Murtagh 2016,[21] retrospective	205	Suspect CS LVEF > 50%	56	≥ 5 SD*	20%	3.0†	8 deaths, 4 sustained VTs	0.79	**5.7%**	NR	NR
Smedema 2018,[29] prospective	84	Suspect CS	53	≥ 2 SD*	32%	4.7‡	7 VAs, 1 sudden death, 1 AVB, 1 HF hosp	0.77	**8.0%**	0.39	0.95
Kazmirczak 2019,[25] retrospective	290	8 CS (biopsy+) 282 suspect CS	53	> 5 SD*	30 %	3.0‡	1 sudden death, 17 VAs	NR	**5.7%**	NR	NR
Flamee 2020,[22] retrospective	114	Suspect CS	48	> 5 SD*	NR	3.1‡	24 HF hosp, 9 deaths, 1 VA	NR	**3.0**%	NR	NR

AUC indicates area under curve; AVB, atrioventricular block; CS, cardiac sarcoidosis; CMRI, cardiac magnetic resonance imaging; F-U, follow-up; FWHM, full width-half maximum; HF hosp, heart failure hospitalizations; JMHW, Japanese Ministry of Health and Welfare criteria for CS; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; N, number of subjects; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; ROC, receiver operating characteristic; SD, standard deviation; VA, ventricular arrhythmia.

* LGE was defined using a threshold of the given number of SDs above the signal intensity of remote normal myocardium

† mean

‡ median