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ORIGINAL RESEARCH

VENTRICULAR ARRHYTHMIA

Risk of Adverse Outcomes Associated With Cardiac Sarcoidosis Diagnostic Schemes

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ABSTRACT

BACKGROUND Multiple cardiac sarcoidosis (CS) diagnostic schemes have been published.

OBJECTIVES This study aims to evaluate the association of different CS diagnostic schemes with adverse outcomes. The diagnostic schemes evaluated were 1993, 2006, and 2017 Japanese criteria and the 2014 Heart Rhythm Society criteria.

METHODS Data were collected from the Cardiac Sarcoidosis Consortium, an international registry of CS patients. Outcome events were any of the following: all-cause mortality, left ventricular assist device placement, heart transplantation, and appropriate implantable cardioverter-defibrillator therapy. Logistic regression analysis evaluated the association of outcomes with each CS diagnostic scheme.

RESULTS A total of 587 subjects met the following criteria: 1993 Japanese (n = 310, 52.8%), 2006 Japanese (n = 312, 53.2%), 2014 Heart Rhythm Society (n = 480, 81.8%), and 2017 Japanese (n = 112, 19.1%). Patients who met the 1993 criteria were more likely to experience an event than patients who did not (n = 109 of 310, 35.2% vs n = 59 of 277, 21.3%; OR: 2.00; 95% CI: 1.38-2.90; $P < 0.001$). Similarly, patients who met the 2006 criteria were more likely to have an event than patients who did not (n = 116 of 312, 37.2% vs n = 52 of 275, 18.9%; OR: 2.54; 95% CI: 1.74-3.71; $P < 0.001$). There was no statistically significant association between the occurrence of an event and whether a patient met the 2014 or the 2017 criteria (OR: 1.39; 95% CI: 0.85-2.27; $P = 0.18$ or OR: 1.51; 95% CI: 0.97-2.33; $P = 0.067$, respectively).

CONCLUSIONS CS patients who met the 1993 and the 2006 criteria had higher odds of adverse clinical outcomes. Future research is needed to prospectively evaluate existing diagnostic schemes and develop new risk models for this complex disease. (J Am Coll Cardiol EP 2023;9:1719–1729) © 2023 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CS = cardiac sarcoidosis

CSC = Cardiac Sarcoidosis Consortium

EMB = endomyocardial biopsy

FDG = fluorodeoxyglucose

HRS = Heart Rhythm Society

ICD = implantable-cardioverter defibrillator

JMHW = Japanese Ministry of Health and Welfare

LGE = late gadolinium enhancement

LVAD = left ventricular assist device

MRI = magnetic resonance imaging

PET = positron emission tomography

VT = ventricular tachycardia

Whereas 5% of sarcoidosis patients are estimated to have symptomatic cardiac involvement, approximately 20% to 25% of patients may have asymptomatic cardiac involvement.[1] Cardiac sarcoidosis (CS) increases the risk of adverse outcomes, such as arrhythmias, heart failure, and death. The diagnosis of CS was traditionally made with endomyocardial biopsy (EMB). However, EMB has limited sensitivity due to the patchy nature of the disease.[2] Moreover, EMB is an invasive procedure with a risk of cardiac perforation and death. Therefore, several commonly used clinical diagnostic schemes have been introduced to increase the diagnostic accuracy of CS without the need for an EMB. Among the Japanese criteria, the first was the 1993 Japanese Ministry of Health and Welfare (JMHW), followed by the 2006 joint committee of the Japan Society of Sarcoidosis and Other Granulomatous Disorders, and, most recently, the 2017 Japanese Society of Nuclear Cardiology Criteria.[3-5] In the United States, the Heart Rhythm Society (HRS) published expert consensus statement criteria in 2014 (see the Supplemental Methods for details).[6] Although they are helpful in clinical practice, none of these diagnostic schemes has been studied to determine prognostic significance. The diagnostic algorithms include histologic and clinical diagnostic pathways. Although the histological diagnosis is made using EMB, clinical diagnosis requires confirmation of extracardiac sarcoidosis and fulfillment of 1 or more noninvasive criteria. In this study, we evaluated whether there is an association between the various CS diagnostic schemes and adverse clinical outcomes in a multinational cohort of patients from the Cardiac Sarcoidosis Consortium (CSC). The CSC is an international initiative whose aim is to collect demographic, clinical, imaging, arrhythmia, treatment, and outcomes data on patients with CS.[7]

METHODS

The CSC registry is a protected, web-based database housed at the University of Michigan. Twenty-five centers are actively enrolling patients in the CSC registry from the United States, Japan, United Kingdom, India, Sweden, and the Netherlands. Patients can be enrolled in the database for definite or suspected CS. We performed a cross-sectional study of consecutive patients from the CSC registry who fulfilled at least 1 of the 4 common CS diagnostic schemes. At the time of enrollment in the registry, individual patients were screened for all 4 criteria. All patients were treated as per the protocols and guidelines at the local hospital. The implantable cardioverter-defibrillators (ICDs) were programmed at the discretion of the implanting electrophysiologist. Adverse outcomes were defined as any of the following: all-cause mortality, left ventricular assist device (LVAD) placement, heart transplantation, or appropriate ICD therapy (defined as antitachycardia pacing or shock for ventricular tachycardia [VT]/ventricular fibrillation [VF]). Participation in the registry was approved by the local institutional review board of each participating site and each site completed a data use agreement with the University of Michigan. A CSC data dictionary was used to define terms and conditions before data entry to standardize data collection. Informed consent was obtained from each patient before enrollment.

STATISTICAL ANALYSIS. The demographic and clinical characteristics of the study population are

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Characteristics of the Study Population by Adverse Event

	All Patients (N = 587)	Patients Without an Event (n = 419, 71.4%)	Patients With an Event (n = 168, 28.6%)	*P* Value
Sex				
Male	352 (60.0)	240 (57.3)	112 (66.7)	0.036
Female	235 (40.0)	179 (42.7)	56 (33.3)	
Race				
White	321//549 (58.5)	234/395 (59.2)	87/154 (56.5)	0.56
African American	169/549 (30.8)	117/395 (29.6)	52/154 (33.8)	0.34
Asian	34/549 (6.2)	27/395 (6.8)	7/154 (4.5)	0.43
Native American	2/549 (0.4)	0/395 (0)	2/154 (1.3)	0.078
Hispanic	8/549 (1.5)	6/395 (1.5)	2/154 (1.3)	1.00
Other	15/549 (2.7)	11/395 (2.8)	4/154 (2.6)	1.00
Age				
Age, y	58.1 ± 11.4	58.0 ± 11.5	58.4 ± 11.4	0.88
Age at diagnosis, y	52.5 ± 11.8	53.2 ± 11.7	50.9 ± 11.9	0.029
Comorbidities				
Hypertension	309 (52.6)	206 (49.2)	103 (61.3)	0.008
Chronic kidney disease	86 (14.7)	38 (9.1)	48 (28.6)	<0.001
Hyperlipidemia	205 (34.9)	136 (32.5)	69 (41.1)	0.048
Coronary artery disease	90 (15.3)	56 (13.4)	34 (20.2)	0.037
Diabetes mellitus	144 (24.5)	93 (22.2)	51 (30.4)	0.038
NYHA functional class I	130/435 (29.9)	99/294 (33.7)	31/141 (22.0)	0.013
NYHA functional class II	159/435 (36.6)	112/294 (38.1)	47/141 (33.3)	0.33
NYHA functional class III	116/435 (26.7)	76/294 (25.9)	40/141 (28.4)	0.58
NYHA functional class IV	30/435 (6.9)	7/294 (2.4)	23/141 (16.3)	<0.001
Medication use				
Immunosuppressant medication	451 (76.8)	310 (74)	141 (83.9)	0.010
Antiarrhythmic medication	191 (32.5)	77 (18.4)	114 (67.9)	<0.001
Diagnostic workup				
Echocardiogram (left ventricular EF <35%, among patients who had an echocardiogram)	180/528 (34.1)	95/371 (25.6)	85/157 (54.1)	<0.001
PET scan (had perfusion defect)	129/389 (33.2)	80/278 (28.8)	49/111 (44.1)	0.004
PET scan (had FDG-cardiac uptake)	266/378 (70.4)	189/267 (70.8)	77/111 (69.4)	0.78
LGE on cardiac MRI (among patients who had an MRI)	269/346 (77.7)	201/264 (76.1)	68/82 (82.9)	0.20
ICD implanted	428 (72.9)	277 (66.1)	151 (89.9)	<0.001
EP study	162 (27.6)	98 (23.4)	64 (38.1)	<0.001
VT ablation	23 (3.9)	6 (1.4)	17 (10.1)	<0.001

Values n (%), n/N (%), or mean ± SD. Adverse events are defined as all-cause mortality, LVAD placement, heart transplantation, or appropriate ICD therapy. ICD therapy is defined as antitachycardia pacing or shock for ventricular tachycardia/fibrillation. Chronic kidney disease was defined as evidence of structural or functional kidney abnormalities (urinalysis, imaging studies, or histology) that persist for at least 3 months, with or without a decreased glomerular filtration rate (defined as <60 mL/min/m^2).

EF = ejection fraction; EP = electrophysiology; FDG = fluorodeoxyglucose; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LVAD = left ventricular assist device; MRI = magnetic resonance imaging; PET = positron emission tomography; VT = ventricular tachycardia.

described using means and standard deviations for continuous variables and frequencies and percentages for categorical variables. In this cross-sectional study, the data were compared between patients who had and those who did not have a clinical outcome. The differences between the 2 groups were examined using chi square and Fisher exact tests for binary variables and Student *t* tests and Wilcoxon-Rank-sum tests for continuous variables. Logistic regression analysis was performed to evaluate the association of each CS diagnostic criteria with the occurrence of a clinical event. Because the 4 diagnostic criteria were based on clinical outcomes with a significant overlap, to ensure the validity of all the statistical tests and regression models, each criterion was examined separately. No statistical method was applied to compare 1 diagnostic criterion with another. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc).

RESULTS

DEMOGRAPHICS AND CLINICAL HISTORY. A total of 587 subjects met at least 1 of 4 diagnostic schemes for

TABLE 2 Organs With Clinical Manifestations of Sarcoidosis by Adverse Event

Extracardiac Organ	All Patients (N = 587)	Patients Without an Event (n = 419, 71.4%)	Patients With an Event (n = 168, 28.6%)	*P* Value
Lung	430 (73.3)	314 (74.9)	116 (69.0)	0.14
Lymphatic system	178 (30.3)	128 (30.5)	50 (29.8)	0.85
Skin	95 (16.2)	75 (17.9)	20 (11.9)	0.075
Ocular	56 (9.5)	40 (9.5)	16 (9.5)	0.99
Liver	45 (7.7)	31 (7.4)	14 (8.3)	0.70
Brain/nervous system	32 (5.5)	27 (6.4)	5 (3.0)	0.11
Spleen	26 (4.4)	22 (5.3)	4 (2.4)	0.18
Osseous	23 (3.9)	20 (4.8)	3 (1.8)	0.10
Renal	13 (2.2)	11 (2.6)	2 (1.2)	0.37
Ear/nose/throat	5/319 (1.6)	4/329 (1.7)	1/80 (1.3)	1.00
Bone marrow	8 (1.4)	4 (1.0)	4 (2.4)	0.23
Parotid/salivary	4 (0.7)	2 (0.5)	2 (1.2)	0.32
Muscle	3 (0.5)	2 (0.5)	1 (0.6)	1.00
Other	19/319 (6.0)	11/329 (4.6)	8/80 (10.0)	0.10

Values are n (%) or n/N (%). Adverse events are defined as all-cause mortality, LVAD placement, heart transplantation, or appropriate ICD therapy (defined as antitachycardia pacing or shock for VT/ventricular fibrillation). Other organ involvement may include stomach, thyroid, large intestine, breast, duodenal, or testicles.

Abbreviations as in Table 1.

CS. Ninety-nine patients with suspected CS did not meet any of the 4 CS diagnostic schemes. As the diagnosis of CS can be challenging, the CSC registry allows the enrollment of patients who are suspected of having CS but do not meet diagnostic criteria at enrollment. These patients were not included in this analysis. Table 1 details the clinical characteristics of the study population. Among the 587 patients, 352 were male (60%), 321 of 549 were White (58.5%), and 169 of 549 (30.8%) were African American. Race/ethnicity was not included in the registry for 38 patients. The mean age at diagnosis was 52.5 ± 11.8 years. The prevalence of extracardiac organ involvement is shown in Table 2. The most frequently involved extracardiac organs were the lungs (73.3%), the lymph nodes (30.3%), and the skin (16.2%), respectively. Extracardiac organ involvement did not differ among patients with and without events. Sixty-four patients (10.9%) had isolated CS.

DIAGNOSTIC CRITERIA. The proportion of patients who met each diagnostic scheme is shown in Table 3 and depicted in Figures 1 and 2: 1993 JMHW (n = 310, 52.8%), 2006 Japanese criteria (n = 312, 53.2%), 2014 HRS expert consensus statement (n = 480, 81.8%), and 2017 updated Japanese criteria (n = 112, 19.1%). A total of 347 patients (59.1%) met at least 2 of 4 diagnostic schemes, and 220 (37.5%) patients met 3 or more of the 4 diagnostic schemes. Sixty (10.2%) patients met all 4 schemes.

ADVERSE CLINICAL OUTCOMES. Table 4 depicts the various adverse outcomes in the study population. Of 587 patients, 168 (28.6%) experienced 1 of the prespecified adverse clinical outcomes. The most common adverse outcome was an appropriate ICD therapy (26.9%), followed by all-cause mortality (8.0%) and heart transplantation (3.4%), respectively. Of 115 patients who had appropriate ICD therapy, 91 (79.1%) had appropriate shock and 66 (57.4%) had appropriate antitachycardia pacing.

ASSOCIATIONS WITH ADVERSE CLINICAL OUTCOMES. The mean age at the time of CS diagnosis was significantly lower among patients who experienced an adverse event than those without an event (50.9 years vs 53.2 years; $P = 0.029$) (Table 1). Also, males were more likely to have an adverse event than females. Of 168 patients with an event, 112 (66.7%) were male and 56 (33.3%) were female, compared with 419 patients without an event, of whom 240 (57.3%) were

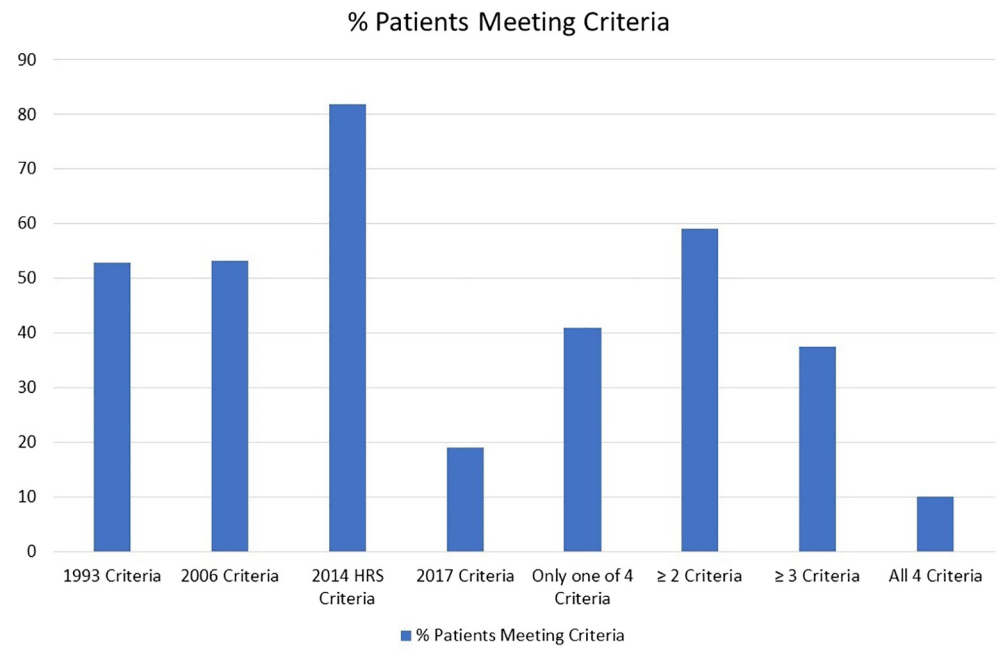
TABLE 3 Association of Diagnostic Criteria With Adverse Clinical Outcomes

	All Patients (N = 587)	Patients Without an Event (n = 419, 71.4%)	Patients With an Event (n = 168, 28.6%)	*P* Value
1993 Japanese Ministry of Health and Welfare Criteria	310 (52.8)	201 (48.0)	109 (64.9)	<0.001
2006 Japanese criteria	312 (53.2)	196 (46.8)	116 (69.0)	<0.001
2014 Heart Rhythm Society expert consensus criteria	480 (81.8)	337 (80.4)	143 (85.1)	0.18
2017 Japanese criteria	112 (19.1)	72 (17.2)	40 (23.8)	0.065
Only one of 4 criteria	240 (40.9)	196 (46.8)	44 (26.2)	<0.001
≥2 criteria	347 (59.1)	223 (53.2)	124 (73.8)	<0.001
≥3 criteria	220 (37.5)	132 (31.5)	88 (52.4)	<0.001
All 4 criteria	60 (10)	32 (7.6)	28 (16.7)	0.001

Values are n (%). Adverse outcomes include all-cause mortality, LVAD placement, heart transplantation, or appropriate ICD therapy (defined as antitachycardia pacing or shock for VT/ventricular fibrillation). Total number of patients who meet criteria and number of patients with and without events are shown for each individual criteria, any one criterion, 2 or more criteria, 3 or more criteria, and all 4 criteria.

Abbreviations as in Table 1.

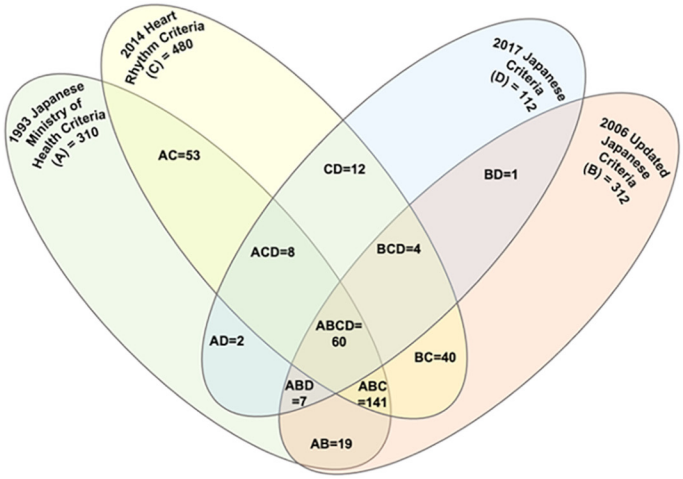
FIGURE 1 **Percentage of Patients in the Cardiac Sarcoidosis Consortium Meeting Each of 4 Diagnostic Criteria**



The percentage of patients meeting only 1, 2 or more, 3 or more, or all 4 criteria is also shown. Eighty-two percent of patients met the 2014 Heart Rhythm Society (HRS) criteria whereas only 19% of patients met the 2017 Japanese criteria.

FIGURE 2 **Patients Meeting Cardiac Sarcoidosis Common Diagnostic Criteria**

criteria # met	Criteria Type				patient # meeting criteria	patient % meeting criteria
	A (1993)	B (2006)	C (2014)	D (2017)		
1	A				310	53
1		B			312	53
1			C		480	82
1				D	112	19
2	A	B			19	3
2	A		C		53	9
2	A			D	2	<1
2		B	C		40	7
2		B		D	1	<1
2			C	D	12	2
3	A	B	C		141	24
3	A	B		D	7	1
3	A		C	D	8	1
3		B	C	D	4	<1
4	A	B	C	D	60	10



The proportion of patients who met each of 4 diagnostic schemes is shown, including 1993 Japanese Ministry of Health and Welfare **(A, green),** 2006 Japanese criteria **(B, orange),** 2014 HRS expert consensus statement **(C, yellow),** and 2017 updated Japanese criteria **(D, blue).** Shown is the overlap of patients who met 1 or more criteria. For example, 60 (10.2%) patients met all 4 schemes as shown in the segment "ABCD." Abbreviation as in Figure 1.

TABLE 4 Adverse Clinical Outcomes Rates in Patients in the Cardiac Sarcoidosis Consortium Prospective Registry

		1993 JMHW Criteria			2006 Japanese Criteria		
	All Patients (N = 587)	Yes (n = 310)	No (n = 277)	*P* Value	Yes (n = 312)	No (n = 275)	*P* Value
Adverse event	168 (28.6)	109 (35.2)	59 (21.3)	<0.001	116 (37.2)	52 (18.9)	<0.001
All-cause mortality	47 (8.0)	31 (10.0)	16 (5.8)	0.060	32 (10.3)	15 (5.5)	0.032
LVAD	9 (1.5)	4 (1.3)	5 (1.8)	0.74	4 (1.3)	5 (1.8)	0.74
Heart transplantation	20 (3.4)	13 (4.2)	7 (2.5)	0.27	14 (4.5)	6 (2.2)	0.12
Appropriate ICD therapy	115/428 (26.9)	76/238 (31.9)	39/190 (20.5)	<0.001	79/254 (31.1)	36/174 (20.7)	0.017

Values are n (%) or n/N (%). Of 587 patients, 168 (28.6%) experienced at least 1 of the prespecified adverse clinical outcomes including all-cause mortality, LVAD, heart transplantation, or appropriate ICD therapy.

HRS = Heart Rhythm Society; JMHW = Japanese Ministry of Health and Welfare; other abbreviations as in Table 1.

Continued on the next page

male and 179 (42.7%) were female ($P = 0.036$). Comorbid illnesses such as hypertension (61.3% vs 49.2%, $P = 0.008$), hyperlipidemia (41.1% vs 32.5%, $P = 0.048$), coronary artery disease (20.2% vs 13.4%, $P = 0.037$), diabetes mellitus (30.4% vs 22.2%, $P = 0.038$), and chronic kidney disease (28.6% vs 9.1%, $P < 0.001$) were more frequent among patients with adverse events. NYHA functional class IV heart failure was more common among patients with than in patients without adverse outcomes (16.3% vs 2.4%, $P < 0.001$).

The left ventricular ejection fraction (EF) on transthoracic echocardiogram was below 35% in 180 of 528 patients (34.1%) who underwent an echocardiogram, and reduced EF was more frequent among patients who had an event (85 of 157, 54.1%) than in patients who did not have an event (n = 95 of 371, 25.6%) ($P < 0.001$). Similarly, a resting perfusion defect on a positron emission tomography (PET) scan was more common among patients with an event (49 of 111, 44.1%) compared with patients without an event (80 of 278, 28.8%) ($P = 0.004$). However, cardiac fluorodeoxyglucose (FDG) uptake did not differ between the 2 groups (69.4% with event vs 70.8% without event, $P = 0.78$). In 346 patients with cardiac magnetic resonance imaging (MRI), late gadolinium enhancement (LGE) was present in 269 patients (77.7%); this was not statistically significantly different between patients with and without events (68 of 82, 82.9% vs 201 of 264, 76.1%; $P = 0.2$). Of the 23 VT ablation patients, 21 had an ICD implanted and 2 did not have an ICD. Of the 21 with ICD implanted, 16 had appropriate antitachycardia pacing or shock.

The associations between the diagnostic schemes and clinical outcomes are described in Table 3, Figure 3, and the Central Illustration. The patients who met the JMHW 1993 criteria had higher odds of experiencing an event (109 of 310, 35.2% with the JMHW criteria vs 59 of 277, 21.3% without; $P < 0.001$; OR: 2.00; 95% CI: 1.38-2.90). Similarly, patients who met the 2006 Japanese criteria had higher odds of adverse events (116 of 312, 37.2% with the criteria vs 52 of 275, 18.9% without; $P < 0.001$; OR: 2.54; 95% CI: 1.74-3.71). There was no statistically significant association between the occurrence of an event and whether a patient met the 2014 HRS or the 2017 Japanese criteria (OR: 1.39; 95% CI: 0.85-2.27; $P = 0.18$ and OR: 1.51; 95% CI: 0.97-2.33; $P = 0.067$, respectively). The patients who experienced adverse events were more likely to fulfill 2 or more diagnostic criteria (1993 JMHW, 2006 Japanese, 2014 HRS, and/or 2017 updated Japanese criteria) than patients who had no events (124 of 168, 73.8% with an event vs 223 of 419, 53.2% without an event; $P < 0.001$). In addition, patients with events were also more likely to meet 3 or more criteria (88 of 168, 52.4% with an event vs 132 of 419, 31.5% without an event; $P < 0.001$). Finally, patients who did poorly had a higher percentage of fulfilling all 4 criteria (28 of 168, 16.7% with an event vs 32 of 149, 7.6% without an event; $P = 0.001$).

Figure 3 shows logistic regression analysis evaluating the association of different diagnostic criteria with clinical outcomes. The unadjusted OR was 2.00 for the 1993 Japanese criteria ($P < 0.001$) and 2.54 for the 2006 criteria ($P < 0.001$). After adjusting for age, comorbidities, and history of immunosuppressant and antiarrhythmic medication, the OR was 1.94 for the 1993 criteria ($P = 0.009$) and 1.88 for the 2006 criteria ($P = 0.013$).

There was no difference in the risk of adverse outcomes in patients who met any 1 of the CS diagnostic schemes vs those with suspected CS who did not meet any of the schemes (168 of 587, 28.6% in patients who met 1 of the schemes vs 22 of 99, 22.2% in patients who did not meet any of the scheme; $P = 0.19$).

TABLE 4 Continued

2014 HRS Diagnostic Criteria			2017 Updated Japanese Criteria		
Yes (n = 480)	No (n = 107)	*P* Value	Yes (n = 112)	No (n = 475)	*P* Value
143 (29.8)	25 (23.4)	0.18	40 (35.7)	128 (26.9)	0.065
37 (7.7)	10 (9.3)	0.57	12 (10.7)	35 (7.4)	0.24
6 (1.3)	3 (2.8)	0.22	1 (0.9)	8 (1.7)	1.00
17 (3.5)	3 (2.8)	1.00	6 (5.4)	14 (2.9)	0.24
102/353 (28.9)	13/75 (17.3)	0.040	27/82 (32.9)	88/346 (25.4)	0.17

DISCUSSION

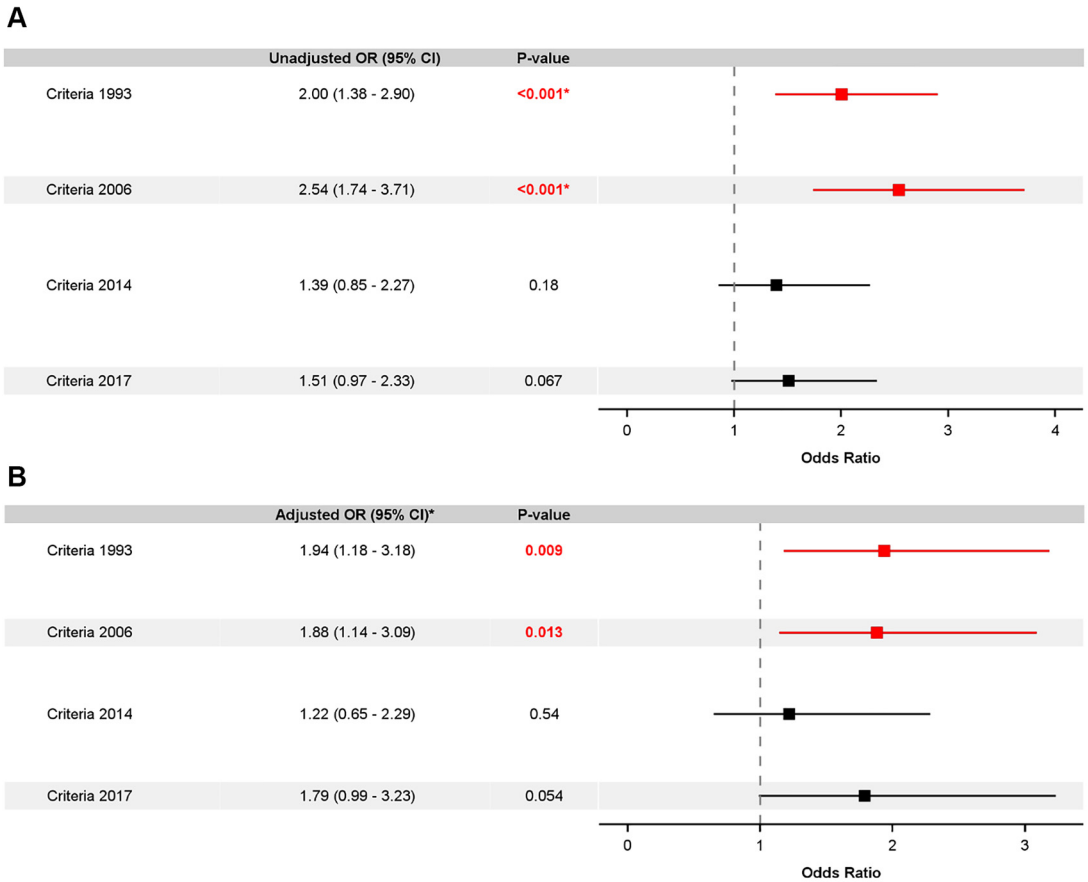
In the current study, we evaluated the association of various diagnostic algorithms for CS and the occurrence of several critical clinical events including all-cause mortality, LVAD implantation, heart transplantation, and appropriate ICD therapy in the CSC. To our knowledge, this is the first study to analyze the association between CS diagnostic schemes and clinical outcomes. Eighty-two percent of patients met the 2014 HRS criteria whereas only 19% of patients met the 2017 Japanese criteria. We found that patients who met the 1993 JMHW and the 2006 Japanese criteria had higher odds of developing adverse cardiac outcomes. However, we did not identify a statistically signification association with the 2014 HRS or 2017 Japanese criteria.

CS is an inflammatory cardiomyopathy that is challenging to diagnose because of the lack of a gold standard diagnostic test. Three major societal guidelines exist for the diagnosis: the 2014 HRS consensus document, the 1999 World Association of Sarcoidosis and Other Granulomatous Disorders Sarcoidosis Organ criteria, and the JMHW guidelines, initially published in 1993 with updates in 2006 and 2017.[3-6,8] The 2014 HRS and the 1993 JMHW criteria include 2 diagnostic pathways: 1) histological diagnosis from EMB; or 2) clinical diagnosis that requires a histological diagnosis of extracardiac sarcoidosis as well as fulfillment of noninvasive criteria for cardiac involvement. Whereas the HRS consensus criteria emphasize that a biopsy (cardiac or extracardiac) confirmation is mandatory, the Japanese criteria have evolved over the years. The 1993 criteria mandated histological validation (cardiac or extracardiac). However, the more recent 2006 and 2017 versions have included several noninvasive major and minor criteria to aid a clinical diagnosis without needing a biopsy. Patients must meet at least 2 major criteria to be diagnosed with CS by these 2 diagnostic schemes. The 2017 version differs from the 2006 one in several ways, such as upgrades from minor to major criteria: 1) fatal ventricular arrhythmias (sustained VT or VF (alongside advanced atrioventricular block); 2) abnormal ventricular structure on echocardiogram; and 3) abnormalities on new imaging modalities such as MRI and PET. In addition, the 2017 guidelines allow for the diagnosis of isolated CS without a positive EMB. Most patients in our study cohort met the HRS criteria (82%). However, fewer patients (19%) fulfilled the 2017 Japanese criteria than any other criteria. It is unknown if the HRS criteria are more sensitive than the Japanese ones due to the lack of a gold standard confirmatory test. Our findings differ from a single-center report of 62 patients with symptoms suggesting CS published by Ueberham et al,[9] in which the investigators reported a positivity rate of 24.2% for the 2014 HRS criteria and 35.5% for the latest Japanese criteria.

Our analysis shows that patients meeting the 1993 and the 2006 criteria had worse clinical outcomes. The reasons for this finding are not understood. The incidence of CS has increased over time, as shown by the MIDFIN (Myocardial Inflammatory Diseases in Finland) study group.[10] The increase in incidence is partially caused by improved detection rates with sensitive diagnostic modalities such as cardiac MRI and FDG-PET scans. The inclusion of cardiac magnetic resonance (CMR) and PET imaging as major diagnostic criteria has enabled the detection of earlier and possibly subclinical disease. Hence, the newer criteria (2014 HRS and the 2017 Japanese criteria) with improved sensitivity may aid in diagnosing the full spectrum of disease severity. However, the improved sensitivity could be identifying patients with earlier disease or less severe phenotypes.

Moreover, the HRS criteria are less stringent than the Japanese criteria. For example, a young patient with extracardiac sarcoidosis who presents with lone complete heart block would meet the HRS criteria. However, to be diagnosed with CS by the 2006 or the 2017 Japanese criteria, the patient would need 1 additional major or 2 minor criteria. Thus, the use of advanced imaging modalities and a less stringent requirement could account for the higher positivity rate associated with the HRS criteria. Although the

FIGURE 3 Logistic Regression Analysis Evaluating the Association of Different Diagnostic Criteria With Clinical Outcomes



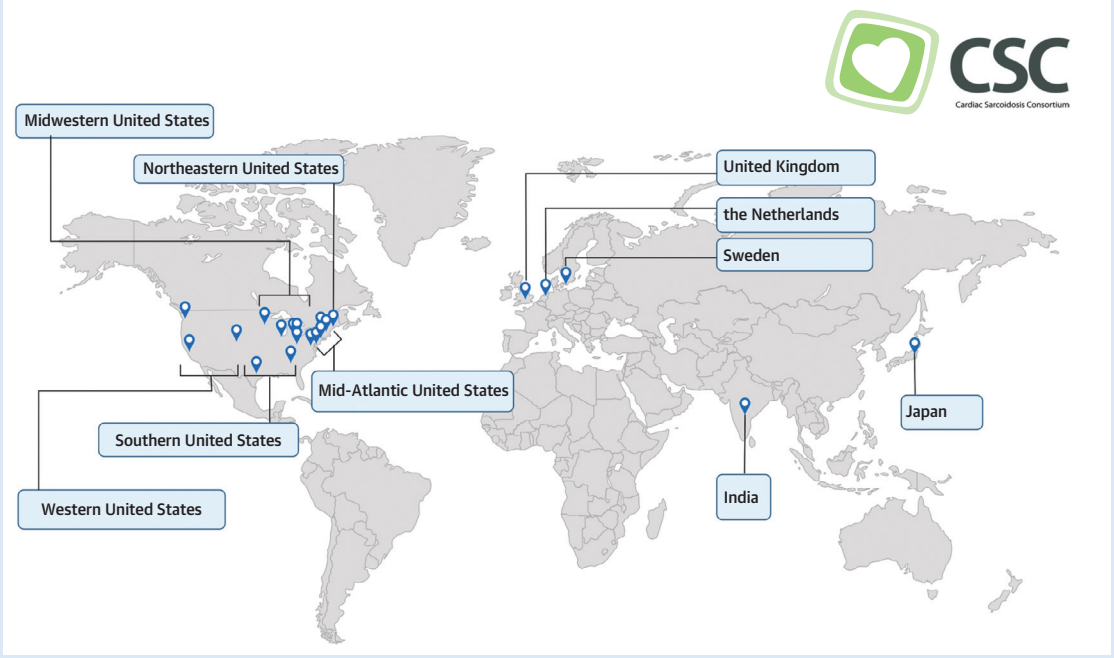
(A) Logistic regression analysis for 4 diagnostic criteria and the association with adverse outcome, including all-cause mortality, left ventricular assist device placement, heart transplantation, or appropriate implantable cardioverter-defibrillator therapy (defined as antitachycardia pacing or shock for ventricular tachycardia/fibrillation). **(B)** The OR of adverse outcome after adjusting for age, comorbidities, and history of immunosuppressant and antiarrhythmic medication.

2017 criteria were not associated with worse outcomes, there was a trend toward association ($P = 0.067$) and this diagnostic scheme performed similarly to the earlier versions with low positivity rate in our registry. Additionally, patients fulfilling more than 1 CS diagnostic scheme likely have more advanced disease, for example, meeting both the arrhythmia and imaging criteria in different algorithms. Also, although patients who met the 1993 and the 2006 criteria had higher odds of adverse events, the risk of adverse events was not low (compared to other cardiomyopathies), even among patients who did not meet these criteria (21.3% and 18.9%, respectively). Thus, a low-risk CS group is not apparent in our study.

Studies have shown that in patients with CS, abnormal LGE on CMR is associated with worse clinical outcomes.[11] However, not all LGE predicts risk. Kazmirczak et al[12] have shown that among patients with CS and left ventricular EF >35%, increasing the cutoff for LGE to 5.7% improved the specificity for outcomes from 74.9% (for any LGE) to 94.6% (for LGE ≥5.7%). The newer criteria (2014 HRS and 2017 Japanese) include the presence of any LGE rather than a cutoff, thereby reducing the specificity of these criteria for identifying clinical events. In our study cohort, a high proportion of patients had a CMR (n = 346 of 587, 59%), and the presence of LGE was not significantly different between the patients with and without clinical events. An association between LGE

CENTRAL ILLUSTRATION **Association of Cardiac Sarcoidosis Diagnostics Schemes With Adverse Clinical Outcomes**

International Cardiac Sarcoidosis Consortium (Prospective Registry)



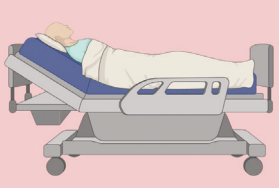
587 patients evaluated for 4 different cardiac sarcoidosis diagnostic criteria

52.8% patients met:	*53.2% patients met:*	*81.8% patients met:*	*19.1% patients met:*
1) 1993 Japanese Ministry of Health and Welfare Criteria	**2)** 2006 Japanese Criteria	**3)** 2014 Heart Rhythm Society Criteria	**4)** 2017 Updated Japanese Criteria

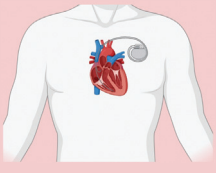
Patients meeting criteria 1 and 2 have greater association with adverse outcomes

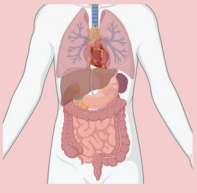
Odds ratio: 2.00 *P* < 0.001	Odds ratio: 2.54 *P* < 0.001	Odds ratio: 1.39 *P* = 0.18	Odds ratio: 1.51 *P* = 0.067

Adverse Outcomes


All-Cause Mortality


LVAD


ICD Therapy


Heart Transplant

Myadam R, et al. J Am Coll Cardiol EP. 2023;9(8):1719-1729.

CSC = Cardiac Sarcoidosis Consortium; ICD = implantable cardioverter-defibrillator; LVAD = left ventricular assist device.

and outcomes may not have been observed in this cohort because of lack of MRI in all patients and heterogeneity in MRI protocols at different institutions.

Our research shows that several traditional cardiovascular risk factors are associated with poor outcomes in patients with CS. Male, hypertension, chronic kidney disease, hyperlipidemia, coronary artery disease, diabetes mellitus, and NYHA functional class IV heart failure are significantly more common among patients with adverse outcomes. Whether modification of risk factors improves outcomes is not known. Another important finding from our study is the association of younger age with clinical events. Patients diagnosed at a younger age may have more advanced disease or a more aggressive phenotype. Long-term treatments with corticosteroids and other immunosuppression agents may also contribute to poor outcomes in younger patients.

Risk assessment in patients with CS is multipronged, and no single diagnostic test can fully estimate risk. Although the diagnostic schemes are helpful, we have shown that not all of them predict clinical risk. Risk models incorporating known predictors of adverse outcomes in patients with CS is urgently needed. Our study suggests that such informative model development is feasible. Achieving internal and external validity in risk models is challenging, yet crucial, and likely requires large consortia to identify sufficient number of subjects for development and validation of such models. Collaborative research efforts are critical to improving outcomes in this complex and difficult-to-diagnose disease.

STUDY LIMITATIONS. Our registry-based study has several limitations. The observational design of the study is associated with significant limitations and risk of bias. There was heterogeneity in the workup of sarcoidosis in different centers and not all patients had every testing modality. However, at the time of enrollment in the registry, individual patients were screened for all 4 criteria. Given the limited number of patients having some imaging studies, the power of the study may be insufficient to fully understand the relationship between the various diagnostic schemes and clinical events. However, this represents real-world clinical data from sarcoidosis specialty centers, reflecting typical diagnostic workups in patients with suspected CS. The study cohort is derived from major tertiary referral centers and may not represent the entire CS population, such as in smaller community hospitals (referral bias). Individual referral centers adjudicated the clinical outcomes in our study, leading to potential interfacility variation despite attempts at standardization. It is possible that earlier detection of CS and subsequent treatment could have led to improved outcomes and confounded the results. Our registry did not collect data regarding defibrillator programming, which can influence the rates of ICD therapies. Also, not all patients had an ICD. As we performed a cross-sectional rather than a longitudinal analysis, we treated patients who did not get an ICD as though they did not have an ICD therapy. Most patients without an ICD did not have clinical arrhythmia necessitating defibrillator implantation. Lastly, we attempted to validate the various existing diagnostic schemes for prognostic purposes. We did not evaluate the diagnostic schemes for their intended purpose—diagnostic accuracy, which is difficult in CS as the gold standard, EMB, is not routinely performed in many centers and has low yield due to the patchy nature of the disease.

CONCLUSIONS

In a large cohort of patients with CS, more than 80% met the 2014 HRS diagnostic criteria whereas 19% met the 2017 Japanese criteria. Patients who met the 1993 JMHW and the 2006 Japanese criteria had higher odds of critical clinical adverse outcomes. The 2014 HRS criteria are less stringent than the original and updated Japanese criteria and may be able to identify patients with earlier disease or less severe phenotypes. Future collaborative research is needed to prospectively develop and validate risk models in this rare, yet increasingly recognized complex disease.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: There are various diagnostic schemes published for CS. The 1993 and the 2006 Japanese diagnostic criteria are more often associated with adverse clinical outcomes including all-cause mortality, LVAD placement, heart transplantation, or appropriate ICD therapy.

COMPETENCY IN PATIENT CARE: When caring for a patient with CS, those who fulfill the 1993 or 2006 Japanese criteria may be at increased risk of adverse clinical outcomes. More than 80% of the patient cohort met the 2014 HRS criteria, which may be able to identify patients with earlier disease or less severe phenotypes.

TRANSLATIONAL OUTLOOK: Although the various diagnostic schemes are helpful in clinical practice, risk assessment in cardiac sarcoidosis needs further research. Prospective longitudinal studies are needed to develop more accurate risk models.

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KEY WORDS cardiac sarcoidosis, cardiac sarcoidosis consortium, diagnostic criteria, risk assessment

APPENDIX For an expanded Methods section, please see the online version of this article.