

ORIGINAL ARTICLE



Management and Outcomes of Cardiac Sarcoidosis: Insights From the Nationwide MYSTICS Registry

Chisato Izumi¹ MD, PhD; Yusuke Yoshikawa¹ MD, PhD, MPH; Issei Komuro¹ MD, PhD; Ken-ichi Hirata, MD, PhD; Koh Ono¹ MD, PhD; Yasushi Sakata¹ MD, PhD; Fumio Terasaki¹ MD, PhD; Takafumi Suda¹ MD, PhD; Hidekazu Tanaka¹ MD, PhD; Toshihiro Tamura¹ MD, PhD; Takeshi Kitai¹ MD, PhD; Takao Kato¹ MD, PhD; Hiroyuki Takahama¹ MD, PhD; Yoichi Takaya¹ MD, PhD; Mika Mori¹ MD, PhD; Yuichi Baba¹ MD, PhD; Kimi Sato¹ MD, PhD; Shunsuke Ishii¹ MD, PhD; Kengo Kusano¹ MD, PhD; Kunihiro Nishimura¹ MD, PhD, on behalf of the MYSTICS Investigators*

BACKGROUND: Cardiac sarcoidosis (CS) may lead to serious outcomes, but large-scale data are lacking because of its rarity, diagnostic uncertainty, and heterogeneous clinical presentations. Actual management and outcomes, including recurrence, are not well understood. This study aimed to clarify the actual management and outcomes of CS from a nationwide large-scale registry.

METHODS: This multicenter retrospective registry enrolled 2366 consecutive patients with CS. Of these, 1852 patients newly diagnosed between 2012 and 2021 were analyzed. Patients were stratified into 4 groups: definite CS, probable CS, presumed systemic sarcoidosis, and presumed isolated CS based on diagnostic criteria. The primary end point was a composite of all-cause death, heart failure hospitalization, or fatal ventricular arrhythmic event. The secondary end point was recurrence of CS.

RESULTS: Cardiac imaging performance rates were high (cardiac magnetic resonance: 64%, ¹⁸F-fluorodeoxyglucose positron emission tomography: 82%), and 974 (53%) patients were diagnosed clinically without histological evidence. During a median 5.1-year follow-up, the primary outcome occurred in 519 (28%, 6.4/100 patient-years) patients, and the 4 groups exhibited different clinical presentations and prognoses; definite CS and presumed isolated CS groups showed a high incidence of the primary end point, fatal ventricular arrhythmic event, hospitalization for heart failure, and cardiovascular death. Most patients (89%) received immunosuppressive therapy, but 291 (18%, 4.1/100 patient-years) patients developed recurrence during steroid tapering, with a 5-year recurrence rate of 17.0%. Recurrence was associated with subsequent primary end point (hazard ratio, 1.38 [95% CI, 1.00–1.89]; $P=0.048$).

CONCLUSIONS: This large-scale multicenter registry showed that clinical presentation and prognosis differ depending on the presence or absence of extracardiac lesions and histological evidence; therefore, it is necessary to recognize the characteristics of each phenotype in managing CS.

Key Words: arrhythmias, cardiac ■ heart failure ■ prognosis ■ recurrence ■ sarcoidosis

Sarcoidosis is a systemic inflammatory disease of unknown cause, characterized by heterogeneous clinical manifestations.^{1–4} Although it can affect

any organ, cardiac involvement is associated with the most serious outcomes, including heart failure and sudden cardiac death (SCD), resulting from cardiac

Correspondence to: Chisato Izumi, MD, PhD, Department of Heart Failure and Transplantation, National Cerebral and Cardiovascular Center, Osaka, Japan. Email izumi-ch@nccvc.go.jp

*A full list of the MYSTICS Investigators is provided in the [Supplemental Material](#).

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/CIRCHEARTFAILURE.126.014184>.

© 2026 The Authors. *Circulation: Heart Failure* is published on behalf of the American Heart Association, Inc., by Wolters Kluwer Health, LLC. This is an open access article under the terms of the [Creative Commons Attribution Non-Commercial-NoDerivs](#) License, which permits use, distribution, and reproduction in any medium, provided that the original work is properly cited, the use is noncommercial, and no modifications or adaptations are made.

Circulation: Heart Failure is available at www.ahajournals.org/journal/circheartfailure

WHAT IS NEW?

- Cardiac sarcoidosis presents with diverse clinical symptoms, making large-scale research essential for understanding it. We conducted a nationwide, large-scale registry, enrolling >2000 patients, to clarify the real-world management and outcomes of cardiac sarcoidosis.
- Clinical diagnostic criteria have been proposed to diagnose cardiac sarcoidosis without histological findings, but clinical features and prognosis of this group have not been fully investigated. We demonstrated that clinical presentations and prognoses differ depending on the presence or absence of extracardiac lesions and histological evidence.
- We also examined the prevalence, treatment, and prognosis of recurrent cases using our large-scale registry.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Different phenotypes, stratified based on diagnostic criteria, exhibit different clinical presentations and prognoses; thus, we should pay attention to the phenotypes in the management of cardiac sarcoidosis.
- Presumed isolated cardiac sarcoidosis patients who were diagnosed without histological evidence and had no extracardiac lesions showed poor outcome; thus, this patient group needs to be treated separately.

Nonstandard Abbreviations and Acronyms

CMR	cardiac magnetic resonance
CS	cardiac sarcoidosis
FDG-PET	¹⁸ F-fluorodeoxyglucose positron emission tomography
FVAE	fatal ventricular arrhythmic event
MYSTICS	Multicenter Nationwide Study to Assess Diagnosis and Management in Patients With Systemic and Isolated Cardiac Sarcoidosis
NT-proBNP	N-terminal pro-B-type natriuretic peptide
SCD	sudden cardiac death
VT/VF	ventricular tachycardia/ventricular fibrillation

dysfunction, ventricular arrhythmia, and conduction disturbances.^{5–17}

The most critical issue in diagnosing cardiac sarcoidosis (CS) is the sampling error of endomyocardial biopsy.^{4,18} Recent advancements in cardiac imaging, such as cardiac magnetic resonance (CMR) and ¹⁸F-fluorodeoxyglucose positron emission tomography

(FDG-PET), have improved the detection rate of CS and altered the diagnostic flow.^{19–22} The Japanese Circulation Society (JCS) guidelines for the management of sarcoidosis²³ established clinical diagnostic criteria for CS in patients without histological evidence, which are included in the latest scientific statement from the American Heart Association.²⁴ However, we cannot exclude the possibility that patients diagnosed with isolated CS without histological confirmation may include individuals with other conditions, such as genetic cardiomyopathies or other inflammatory myocardial diseases.^{25–29} Clinical features, actual management, and prognosis in patients without histological evidence have not been fully investigated.

In addition to serious events, such as fatal ventricular arrhythmic events (FVAE) and heart failure, a challenge in treating CS is that some patients either do not respond to steroid therapy or experience recurrence, although the effectiveness of steroid therapy has been established.³⁰ The definition of recurrence is not well standardized and varies across studies; consequently, the prevalence and risk factors for recurrence remain unclear.^{9,31–33}

The objective of this study was to elucidate the management strategies and clinical outcomes of patients with CS by stratifying them according to diagnostic criteria.

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design and Study Population

MYSTICS (Multicenter Nationwide Study to Assess Diagnosis and Management in Patients With Systemic and Isolated Cardiac Sarcoidosis) is a retrospective, multicenter, observational study (URL: xxx; Unique identifier: UMIN000053942). A total of 115 experienced hospitals in Japan participated ([Supplemental Material](#)). Consecutive patients with CS who attended the participating hospitals between April 2012 and March 2021 were enrolled. The diagnosis of CS was made according to either the JCS criteria proposed in 2016²³ or the 2014 Heart Rhythm Society consensus statement.³⁴ The exclusion criteria were an age of <18 years at diagnosis and refusal to participate in the study. Patients were stratified into 4 groups: definite CS (group 1) and probable CS (group 2) based on Heart Rhythm Society criteria, and presumed systemic sarcoidosis (group 3) and presumed isolated CS (group 4) without histological evidence, based on clinical diagnostic criteria of JCS guidelines.

The study protocol complied with the Declaration of Helsinki and was approved by the institutional review board of the National Cerebral and Cardiovascular Center (R21045-12); approval was also obtained at each participating center. The requirement for written informed consent was waived because of the retrospective, observational, and noninvasive



nature of the study, and an opt-out procedure for consent was implemented.

Clinical Evaluation

Medical records were reviewed, and data on baseline characteristics, laboratory examinations, 12-lead electrocardiograms, echocardiography, ambulatory electrocardiographic monitoring, FDG-PET, ^{67}Ga scintigraphy, CMR, and histological findings were collected. Extra-CS was determined by experts in each field based on histological or clinical findings. For echocardiographic parameters, chamber quantification and other measurements were obtained using standard definitions.³⁵ To evaluate the distribution of cardiac FDG/ ^{67}Ga accumulation, we used the American Heart Association's 17-segment model of the myocardium. In evaluating late gadolinium enhancement on CMR, the left ventricle was divided into 6 segments: basal septum, mid-septum, anterior, lateral, inferior, and apex.

Immunosuppressive Therapy

Treatment decisions were made at the discretion of the attending physician, with reference to the guidelines' suggestions.²³ Data were collected on the initial steroid dose, the dose at 6 months after initiation, the maintenance dose, and the concomitant use of other immunosuppressive agents.

Outcomes

Follow-up began on the date of diagnosis of CS, based on fulfillment of either the JCS or Heart Rhythm Society criteria. The primary end point was a composite of all-cause death, heart failure hospitalization, or FVAE. Heart failure hospitalization and SCD were defined according to previous reports (Table S1),^{36,37} and FVAE was defined as a composite of SCD, documented ventricular fibrillation (VF), sustained ventricular tachycardia (VT) lasting more than 30 seconds, or an event equivalent to SCD (appropriate implantable cardioverter defibrillator therapy or successful resuscitation after cardiac arrest).

The secondary end point was recurrence of CS. Recurrence was defined based on imaging; the appearance of a new wall motion abnormality on echocardiograms with no other apparent cause, or the appearance of FDG/ ^{67}Ga uptake or late gadolinium enhancement on CMR in new segments.

Summaries of each clinical end point were collected and reviewed centrally. When necessary, the central research committee requested reevaluation by the site investigators to ensure consensus on event adjudication.

Statistical Analysis

Categorical variables are presented as counts and percentages and were compared using the χ^2 test or Fisher exact test. Continuous variables are expressed as mean $\pm$ SD or median with interquartile range (IQR) and were compared using Student *t* test or the Wilcoxon rank-sum test, depending on their distribution. Cumulative incidences were estimated using the Kaplan-Meier method for the primary end point, and differences between groups were tested using the log-rank test. For recurrence, analyses were limited to patients who received steroids or other immunosuppressive agents. The Aalen-Johansen estimator was used, treating all-cause death as a competing risk for heart failure hospitalization and FVAE, and noncardiovascular death

as a competing risk for cardiovascular death, and differences between groups were tested using the Gray test. As a sensitivity analysis, a landmark analysis at 1 year for recurrence was performed to mitigate surveillance bias for recurrence.

The Cox proportional hazards model was fitted to assess the association between the primary end point and clinically relevant patient factors at baseline. Hazard ratios and their 95% CIs were calculated using Cox models. To assess the impact of recurrence on the subsequent occurrence of the primary end point, a Cox proportional hazards model incorporating recurrence as a time-dependent variable was used. To account for substantial missingness in clinically relevant factors, multiple imputation was performed using the *mice* package.

All reported *P* values are 2-sided, and *P* < 0.05 was considered statistically significant. All statistical analyses were conducted using R, version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Flowchart

Among 2747 patients initially registered from 115 hospitals, 381 who did not meet the diagnostic criteria were excluded. Thus, our registry consisted of 2366 patients. Of these, 514 had been diagnosed before April 2012 and continued attending hospitals thereafter. The final study population comprised 1852 patients (mean age, 63 $\pm$ 11 years; 65% female) who were newly diagnosed with CS during the study period (April 2012 to March 2021). The study flowchart is shown in Figure 1A. Among these 1852 patients, 191 were classified into group 1, 687 into group 2, 616 into group 3, and 358 into group 4 (Figure 1B).

Baseline Clinical Characteristics and Findings of Examinations Among the 4 Groups

Table 1 shows the background characteristics of the study population.

Higher prevalences of history of heart failure admission, sustained VT, and nonsustained VT, and higher levels of BNP (B-type natriuretic peptide) were observed in groups 1 and 4.

Table 1 also shows the performance rate of each diagnostic test and the prevalence of positive findings. Endomyocardial biopsy was performed in 918 (50%) patients, and histological findings compatible with CS were identified in 191 (21%). The left ventricular ejection fraction was lower in groups 1 and 4 than in groups 2 and 3. A higher detection rate of late gadolinium enhancement on CMR and myocardial uptake in FDG-PET or ^{67}Ga scintigraphy was observed in group 4.

Treatment

Table 2 shows the treatment after enrollment in the 4 groups. Steroids were administered to 1643 (89%) of

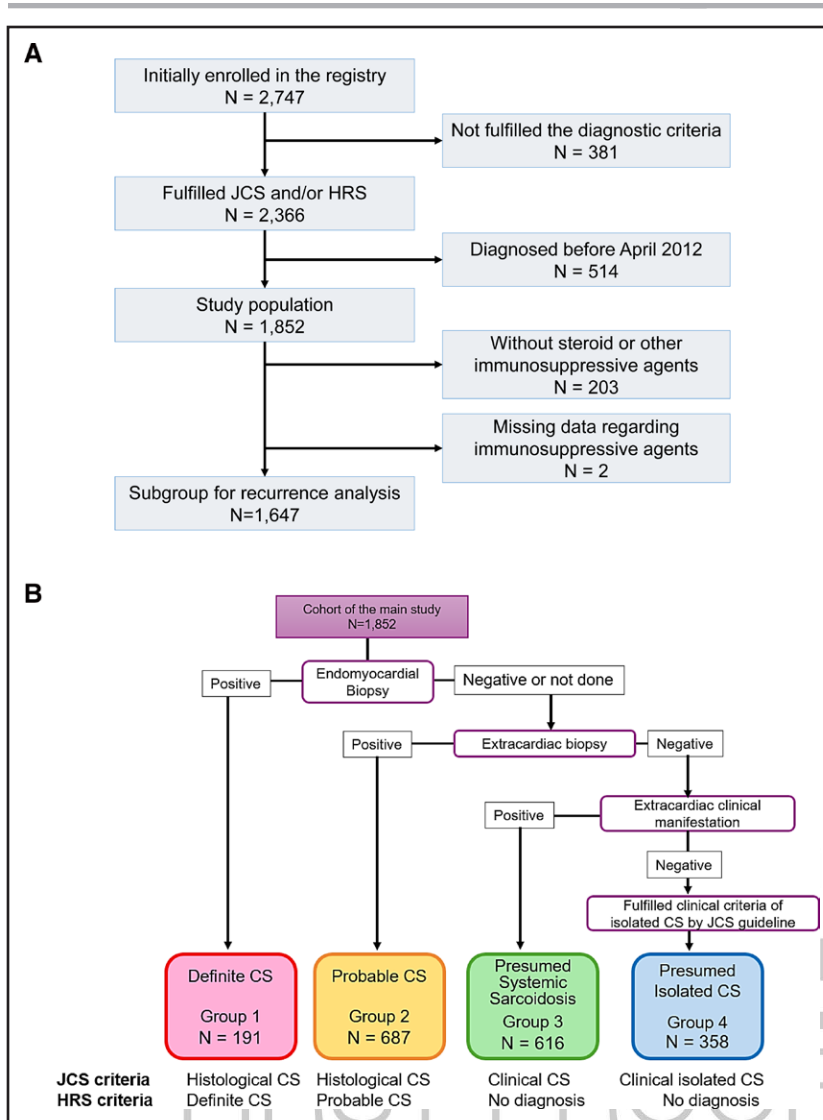


Figure 1. Study population.

Study flowchart (A) and classification of patient phenotypes by diagnostic criteria (B). CS indicates cardiac sarcoidosis; HRS, Heart Rhythm Society; and JCS, Japanese Circulation Society.



1850 patients. The initial dose of steroid was 29.6 ± 6.1 mg (0.53 ± 0.14 mg/kg), and there was no difference in the initial dose of steroid among the 4 groups. The median steroid dose at 6 months after initiation was 10 mg (IQR, 5.0–10.0), and the median maintenance dose was 5 mg (IQR, 5.0–8.0). Other immunosuppressive agents were used in 154 patients (8.3%), and most of them (144 [94%] patients) were treated with methotrexate. The prevalence of use of other immunosuppressive agents was high in group 1. Cardiac electrical devices were implanted more frequently in groups 1 and 4. A left ventricular assist device was implanted in 11 patients, and 2 of them underwent heart transplantation. These treatments were more frequently performed in group 1, and both patients who underwent heart transplantation were in group 1.

Primary Outcome

During the follow-up period (median, 5.1 years; IQR, 3.5–7.4), the primary outcome occurred in 519 patients

(28%, 6.4/100 patient-years), all-cause death in 176 (9.5%, 1.8/100 patient-years), heart failure hospitalization in 227 (12%, 2.5/100 patient-years), and FVAE in 298 (16%, 3.5/100 patient-years). The 5-year cumulative incidence of the primary outcome was 27.2% (95% CI, 25.0%–29.4%; Figure 2A; Table 3).

Patients in groups 1 and 4 had a significantly higher rate of the primary end point than those in groups 2 and 3. Cumulative incidence of the primary outcome at 5 years was 33.6, 20.8, 23.4, and 42.9% in group 1, 2, 3, and 4, respectively ($P < 0.001$; Figure 2B; Table 3). Among the patients in group 1, 62 (32%) had no extracardiac involvement, that is, definite isolated CS (Table 1). The incidence of the primary end point did not differ significantly between the presumed isolated CS and definite isolated CS groups (Figure S1).

The Cox regression analysis for the primary outcome showed that age, sex, history of heart failure, VT/VF, high plasma BNP level, lower left ventricular ejection fraction, and the absence of extracardiac lesions were associated

Table 1. Clinical Characteristics of Patients in the 4 Groups Based on Diagnostic Criteria

Characteristic	Missing rate (%)	Total (N=1852)	Definite CS (group 1; n=191)	Probable CS (group 2; n=687)	Presumed systemic sarcoidosis (group 3; n=616)	Presumed isolated CS (Group 4; n=358)	P value
Age, y	0	63±11	61±10	63±11	64±11	62±11	0.018
Female sex	0	1197 (65%)	119 (62%)	494 (72%)	409 (66%)	175 (49%)	<0.001
History of heart failure hospitalization	0	414 (22%)	60 (31%)	122 (18%)	126 (20%)	106 (30%)	<0.001
Atrial fibrillation	0	204 (11%)	22 (12%)	63 (9.2%)	51 (8.3%)	68 (19%)	<0.001
History of sustained VT/VF	0	300 (16%)	41 (21%)	71 (10%)	102 (17%)	86 (24%)	<0.001
History of nonsustained VT/VF	0	377 (20%)	48 (25%)	102 (15%)	124 (20%)	103 (29%)	<0.001
Advanced AVB	0	661 (36%)	73 (38%)	254 (37%)	248 (40%)	86 (24%)	0.48
History of cardiac device	0	720 (39%)	74 (39%)	247 (36%)	263 (43%)	136 (38%)	<0.001
BNP, pg/mL	23	115 (45, 278)	206 (84, 451)	77 (30, 216)	120 (49, 291)	140 (57, 317)	<0.001
NT-proBNP, pg/mL	81	700 (269, 1664)	1218 (649, 2217)	533 (161, 1323)	581 (269, 1720)	873 (376, 1691)	0.003
LVEF, %	3.3	47 (36, 60)	41 (30, 53)	54 (41, 64)	49 (36, 61)	40 (32, 48)	<0.001
LVEF <40%	3.3	590 (33%)	86 (46%)	149 (22%)	188 (32%)	167 (48%)	<0.001
LVEF ≥40% and <50%	3.3	387 (22%)	42 (23%)	122 (18%)	119 (20%)	104 (30%)	<0.001
Mild cardiac findings only*	0	586 (32%)	44 (23%)	288 (42%)	185 (30%)	69 (19%)	<0.001
Cardiac biopsy performed	0	918 (50%)	191 (100%)	244 (36%)	268 (44%)	215 (60%)	<0.001
Cardiac biopsy-positive findings	50	191 (21%)	191 (100%)	0 (0%)	0 (0%)	0 (0%)	<0.001
CMR performed	0	1190 (64%)	115 (60%)	450 (66%)	363 (59%)	262 (73%)	<0.001
LGE (+) in CMR	36	1086 (91%)	106 (92%)	404 (90%)	321 (88%)	255 (97%)	<0.001
FDG-PET performed	0	1516 (82%)	141 (74%)	556 (81%)	504 (82%)	315 (88%)	<0.001
⁶⁷ Ga scintigraphy performed	0	639 (35%)	81 (42%)	227 (33%)	219 (36%)	112 (31%)	0.049
FDG-PET or ⁶⁷ Ga scintigraphy performed	0	1757 (95%)	172 (90%)	647 (94%)	585 (95%)	353 (99%)	<0.001
Cardiac uptake in FDG-PET or ⁶⁷ Ga scintigraphy	5.1	1613 (92%)	158 (92%)	574 (89%)	537 (92%)	344 (97%)	<0.001
Extracardiac lesions	0	1432 (77%)	129 (68%)	687 (100%)	636 (100%)	0 (0%)	NA

Data are presented as mean±SD, n (%), or median (interquartile range). ⁶⁷Ga indicates ⁶⁷gallium; AVB, atrioventricular block; BNP, B-type natriuretic peptide; CMR, cardiac magnetic resonance; CS, cardiac sarcoidosis; FDG-PET, ¹⁸F-fluorodeoxyglucose positron emission tomography; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*Patients with mild cardiac findings are those without advanced AVB, history of VT/VF, or history of heart failure.

with the primary outcome (Table 4). The association was also found in the multiple imputation analysis (Table S2). Risk for the primary outcome significantly differed between the 4 groups, with lower hazard ratios in groups 2 and 3 and a higher hazard ratio in group 4, compared with group 1 (Table 4). The Cox regression analysis for the primary outcome in patients with biopsy-proven CS (groups 1 and 2) is shown in Table S3. The results are similar to those obtained from whole case analysis.

The cumulative incidence of each component of the primary outcome is shown in Table 3 and Figures S2 through S4. The 5-year cumulative incidence of all-cause death and heart failure hospitalization was higher in group 4 than in the other groups. Regarding the cause of death, cardiovascular death was more frequent in group 4, whereas there was no significant difference in non-cardiovascular death among the 4 groups. The 5-year cumulative incidence of FVAE was higher in groups 1 and 4 than in groups 2 and 3.

The 5-year cumulative incidence of new-onset FVAE in patients with no history of VT/VF or heart failure was 10.4%, and it was higher in group 4 than the other groups (8.9%, 8.5%, 8.6%, and 20.0% in group 1, 2, 3, and 4, respectively; $P<0.001$).

Among 227 heart failure hospitalization events, 116 (51%) were new-onset heart failure. The 5-year cumulative incidence of new-onset heart failure was 7.8% in the overall population without a history of heart failure hospitalization (n=1438). There was a significant difference in risk of new-onset heart failure between the diagnosis groups. The results are similar to those obtained from whole case analysis.

Recurrence of CS and Subsequent Occurrence of the Primary End Point

Among the 1852 study patients, 203 were treated with neither steroids nor other immunosuppressive agents,

Table 2. Treatment After Enrollment in the 4 Groups Based on Diagnostic Criteria

Characteristic	Missing rate (%)	Total (n=1852)	Definite CS (group 1; n=191)	Probable CS (group 2; n=687)	Presumed systemic sarcoidosis (group 3; n=616)	Presumed isolated CS (group 4; n=358)	P value
Steroid	0.1	1643 (89%)	178 (93%)	614 (90%)	546 (89%)	305 (85%)	0.031
Initial dose of steroid, mg	12	29.6±6.1	30.1±4.1	29.8±7.2	29.2±5.6	29.7±5.4	0.10
Initial dose of steroid, mg/kg	13	0.53±0.14	0.54±0.13	0.53±0.15	0.53±0.14	0.53±0.14	0.88
Dose of steroid at 6 mo, mg	15	10.0 (5.0–10.0)	10.0 (5.0–12.0)	10.0 (5.0–10.0)	10.0 (5.0–10.0)	10.0 (5.0–10.0)	0.044
Maintenance dose of steroid, mg	14	5.00 (5.00–8.00)	5.00 (5.00–10.00)	5.00 (5.00–10.00)	5.00 (5.00–7.50)	5.00 (5.00–7.50)	0.021
Other immunosuppressive agents	0.1	154 (8.3%)	27 (14%)	59 (8.6%)	42 (6.8%)	26 (7.3%)	0.012
Device implantation	0	443 (24%)	65 (34%)	133 (19%)	134 (22%)	111 (31%)	<0.001
Pacemaker		69 (3.7%)	5 (2.6%)	33 (4.8%)	22 (3.6%)	9 (2.5%)	0.22
ICD		167 (9.0%)	23 (12%)	48 (7.0%)	50 (8.1%)	46 (13%)	0.006
CRTP		28 (1.5%)	5 (2.6%)	10 (1.5%)	6 (1.0%)	7 (2.0%)	0.31
CRTD		199 (11%)	34 (18%)	48 (7.0%)	60 (9.7%)	57 (16%)	<0.001
LVAD	0	11 (0.6%)	5 (2.6%)	0 (0%)	2 (0.3%)	4 (1.1%)	<0.001
Transplantation	0	2 (0.1%)	2 (1.0%)	0 (0%)	0 (0%)	0 (0%)	0.011

Data are presented as mean±SD, n (%), or median (interquartile range). CRTD indicates cardiac resynchronization therapy defibrillator; CRTP, cardiac resynchronization therapy pacemaker; CS, cardiac sarcoidosis; ICD, implantable cardioverter defibrillator; and LVAD, left ventricular assist device.

and data regarding immunosuppressive therapy were missing in 2 patients. Therefore, recurrence of CS was analyzed in 1647 patients (Figure 1A). During the follow-up period, recurrence occurred in 291 patients (18%, 4.1/100 patient-years). The 5-year cumulative incidence of recurrence was 17.0% (95% CI, 15.1%–19.0%; Table 3; Figure 3A). Recurrence occurred a median of 751 (IQR, 428–1149) days after starting steroid therapy, and the median dose of steroid at recurrence was 6 mg (IQR, 5–10; Table S4). In 240 (82%) patients, the steroid dose was escalated after diagnosis of recurrence.

The cumulative incidence of recurrence did not significantly differ among the 4 groups (19.1, 17.5, 16.3, and 15.8% at 5 years in groups 1, 2, 3, and 4, respectively; $P=0.52$; Table 3; Figure 3B). The timing of recurrence, dose of steroid at recurrence, and treatment after diagnosis of recurrence were not different among the 4 groups (Table S4). The sensitivity analysis using a 1-year landmark analysis showed consistent results regarding differences in recurrence rates among the 4 groups (Figure S5). Recurrence was significantly associated with subsequent occurrence of the primary end point (hazard ratio, 1.38 [95% CI, 1.00–1.89]; $P=0.048$; Table 4).

Among the 291 patients with recurrence, 46 experienced the primary end point before recurrence. After excluding these 46 patients, 39 of the remaining 245 patients presented with clinical symptoms at the time of recurrence, such as worsening heart failure or arrhythmias. These patients had a higher incidence of the primary end point after recurrence than those whose recurrence was diagnosed based on imaging findings alone (Figure S6).

DISCUSSION

CS can lead to serious outcomes such as heart failure and SCD, and patients present with a wide range of clinical pictures. Therefore, it is important to evaluate actual management and outcomes in a large, unbiased cohort. Several multicenter registries of CS have recently been conducted, but the number of patients included was limited.^{5,9,38–40} Although a national registry based on the healthcare system¹⁶ and a national cause-of-death registry⁸ were also conducted, they lacked detailed clinical data. It is essential to investigate real-world practices in diagnosis, treatment, and outcomes through a nationwide cohort. We conducted a nationwide, large-scale retrospective study of 2366 patients with CS, collecting detailed clinical data—making this the largest CS registry in the world. Consecutive cases were enrolled from 115 facilities across Japan, resulting in a relatively unbiased cohort. In addition, the enrollment period (April 2012 to March 2021) was relatively recent, allowing the study to reflect current clinical practice.

The 3 main findings were as follows. First, the performance rate of cardiac imaging—especially FDG-PET—was high, and about half of the patients were diagnosed without histological evidence. Second, the 4 groups, based on diagnostic criteria, exhibited different clinical presentations and prognoses. Third, 89% of patients received steroids or other immunosuppressive agents, but recurrence occurred during steroid tapering, and the 5-year recurrence rate was still 17%. In addition, recurrence was significantly associated with subsequent occurrence of the primary end point.



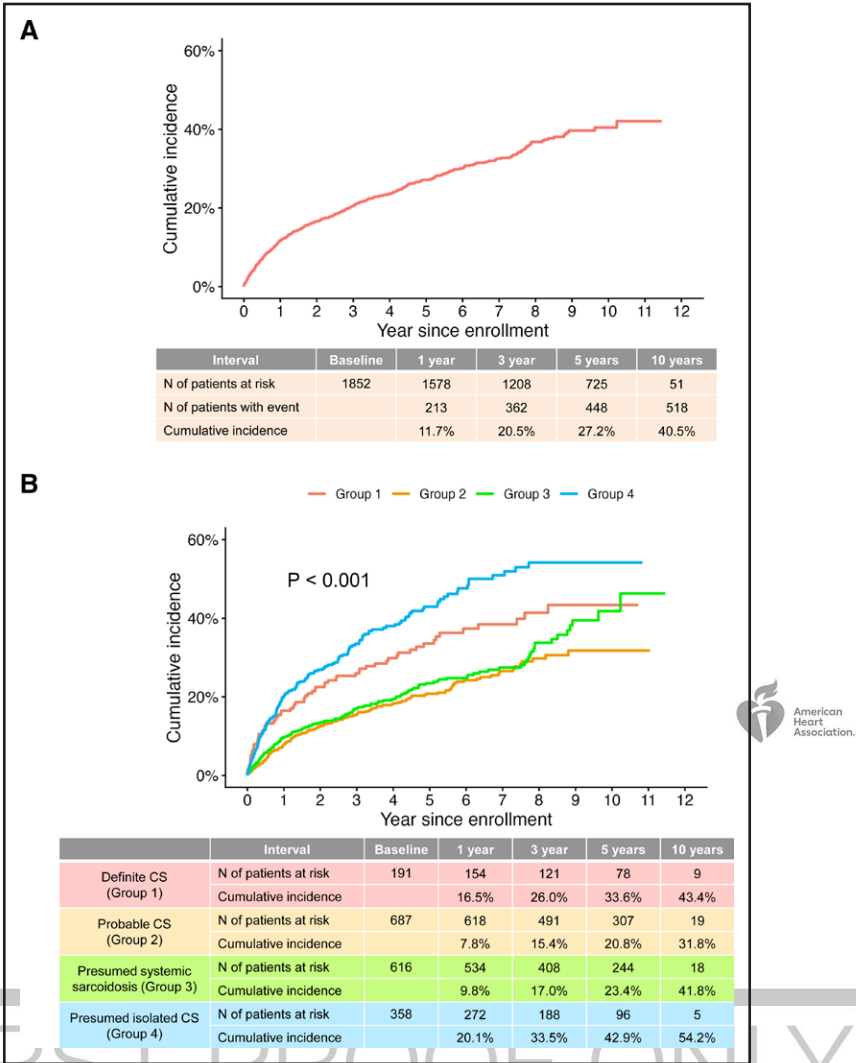


Figure 2. Cumulative incidence of the primary end point. Cumulative incidence of the primary end point was calculated using the Kaplan-Meier estimators in all patients (A) and diagnosis groups (B). CS indicates cardiac sarcoidosis.

Differences in Clinical Presentation and Prognosis Based on Phenotype According to Diagnostic Criteria

Due to the sporadic nature of CS, the false-negative rate of endomyocardial biopsy is high, which causes underdiagnosis of CS. Because CS has serious outcomes, such as FVAE and heart failure, the JCS guidelines²³ proposed clinical diagnostic criteria for diagnosis without histological evidence. In the present study, the proportion of definite CS diagnosed by positive endomyocardial biopsy was about 10%, which is consistent with the proportion reported in previous multicenter registries.^{38–40} Furthermore, the performance rates of CMR and FDG-PET were 64% and 82%, respectively, in the present study—higher than those reported in previous multicenter registries.^{5,38,39} The diagnostic flow is evolving with advances in cardiac imaging.

Although several recent studies have shown that the prognosis of clinically diagnosed patients is as poor as that of patients with histological diagnosis,^{38–42} the results may vary depending on the setting of outcomes and the phenotype classification. To determine the optimal treatment plan for each patient in the future, we need to understand the clinical presentations and prognosis of each phenotype.

In the present study, presumed isolated CS and definite CS groups included many patients with a history of VT/VF or heart failure. These groups showed a high incidence of the primary end point, FVAE, hospitalization for heart failure, and cardiovascular death, which may demonstrate that they may have more advanced cardiac lesions.

Previous studies^{38–42} have treated presumed systemic sarcoidosis and presumed isolated CS together as a biopsy-negative group, but their clinical

Table 3. Cumulative 5-Year Incidence of Clinical Outcomes

	Total (N=1852)	Definite CS (group 1; n=191)	Probable CS (group 2; n=687)	Presumed systemic sarcoidosis (group 3; n=616)	Presumed isolated CS (group 4; n=358)	P value
Primary end point	448 (27.2%)	59 (33.6%)	129 (20.8%)	125 (23.4%)	135 (42.9%)	<0.001
All-cause death	126 (8.2%)	13 (7.9%)	36 (6.3%)	37 (7.2%)	40 (14.0%)	0.01
CV death	55 (3.6%)	6 (3.8%)	13 (2.4%)	12 (2.3%)	24 (8.3%)	<0.001
Non-CV death	71 (4.6%)	7 (4.1%)	23 (3.9%)	25 (5.0%)	16 (5.7%)	0.70
HF hospitalization	186 (11.8%)	20 (11.9%)	52 (8.6%)	54 (10.7%)	60 (20.3%)	<0.001
FVAE	261 (15.5%)	36 (20.3%)	68 (10.8%)	71 (12.8%)	86 (27.4%)	<0.001
	Total (N=1647)	Definite CS (group 1; n=178)	Probable CS (group 2; n=615)	Presumed systemic sarcoidosis (group 3; n=548)	Presumed isolated CS (group 4; n=306)	P value
Recurrence	254 (17.0%)	30 (19.1%)	100 (17.5%)	81 (16.3%)	43 (15.8%)	0.52

Numbers are presented with cumulative numbers of the events (cumulative 5-y incidence, %). Cumulative 5-y incidence was calculated using the Kaplan-Meier estimator for the primary end point and all-cause death. The Aalen-Johansen estimator was used treating all-cause death as a competing risk for HF hospitalization and FVAE, and noncardiovascular death as a competing risk for cardiovascular death, respectively. CS indicates cardiac sarcoidosis; CV, cardiovascular; FVAE, fatal ventricular arrhythmic events; and HF, heart failure.

characteristics and prognoses are significantly different. Indeed, studies comparing biopsy-positive and clinically diagnosed biopsy-negative patients have reported conflicting findings, with some demonstrating a worse prognosis in the biopsy-positive group³⁹ and others showing poorer outcomes in the biopsy-negative group.⁴⁰ In the present study, patients with clinically diagnosed CS (group 3+4) had a significantly higher rate of the primary end point than those with biopsy-proven CS (group 1+2; [Figure S7](#)). Therefore, treating presumed systemic sarcoidosis and presumed isolated

CS together as a biopsy-negative group may lead to an inaccurate understanding of their clinical presentation.

Furthermore, presumed isolated CS showed a higher incidence of the primary outcome than definite CS, suggesting that presumed isolated CS may need to be treated separately. Several possible explanations may account for the poorer prognosis observed in presumed isolated CS. First, patients with isolated CS lack extracardiac manifestations that might facilitate an earlier diagnosis. Consequently, cardiac involvement may remain unrecognized until the disease has

Table 4. Univariable Cox Regression Analysis for the Primary End Point

	N	HR	95% CI	P value
Age, y	1852	1.02	(1.01–1.03)	<0.001
Women	1852	0.76	(0.64–0.90)	0.002
Hypertension	1852	1.09	(0.91–1.30)	0.34
Dyslipidemia	1852	1.11	(0.92–1.33)	0.27
Diabetes	1852	1.03	(0.81–1.31)	0.80
History of heart failure	1852	2.15	(1.79–2.58)	<0.001
Sustained VT/VF	1852	2.58	(2.13–3.13)	<0.001
Nonsustained VT/VF	1852	1.84	(1.52–2.22)	<0.001
Atrial fibrillation	1852	2.03	(1.61–2.56)	<0.001
eGFR, mL/min per 1.73 m ²	1799	0.98	(0.97–0.98)	<0.001
Log BNP	1422	1.61	(1.48–1.74)	<0.001
LVEF (per 5%)	1791	0.86	(0.83–0.88)	<0.001
Focal dyskinesia	1798	1.91	(1.55–2.35)	<0.001
Extracardiac lesions	1852	0.49	(0.41–0.59)	<0.001
Diagnosis group	1852			<0.001
Group 1	191	Ref.		
Group 2	687	0.59	(0.45–0.79)	
Group 3	616	0.68	(0.51–0.91)	
Group 4	358	1.39	(1.04–1.85)	
Recurrence (as a time-varying covariate)	1852	1.38	(1.002–1.89)	0.048

BNP indicates B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; VF, ventricular fibrillation; and VT, ventricular tachycardia.

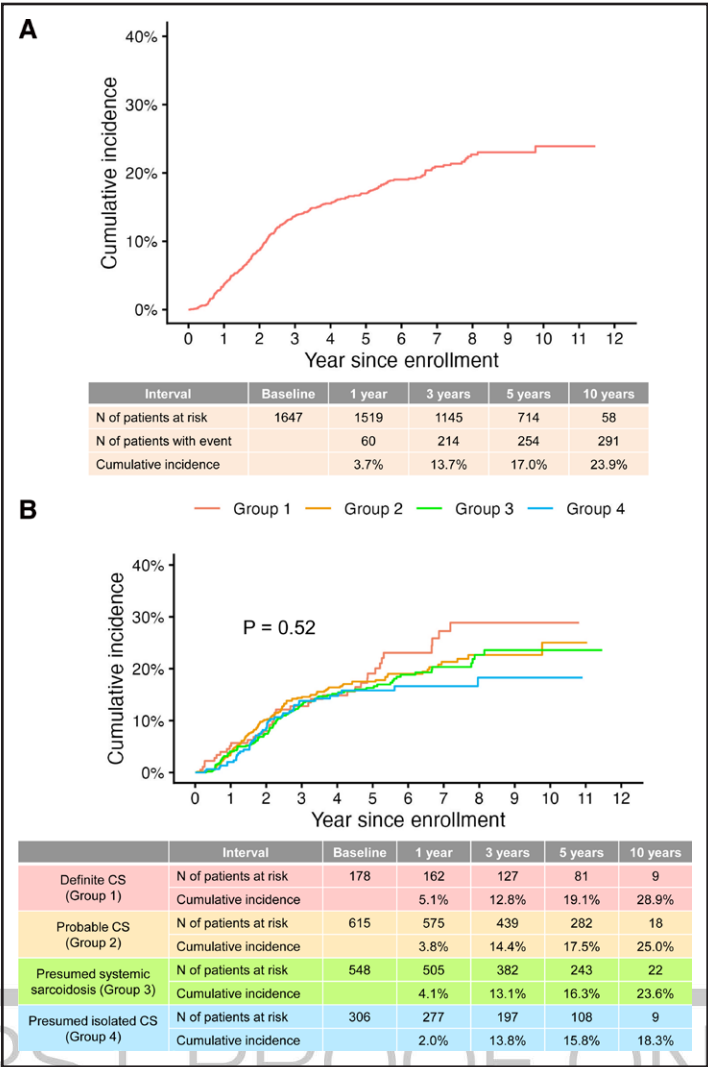


Figure 3. Cumulative incidence of the recurrence of cardiac sarcoidosis (CS). Cumulative incidence of recurrence was estimated using the Aalen-Johansen estimator, treating all-cause death as a competing risk, in all patients (A) and diagnosis groups (B).

progressed. Second, the lack of definitive pathological or extracardiac evidence in presumed isolated CS may have resulted in diagnostic uncertainty and consequently delayed or limited the initiation of corticosteroid therapy. In definite CS, the diagnosis of CS was established by histological confirmation of granulomas in endomyocardial biopsy, which may have facilitated the initiation of corticosteroid therapy. Consistent with this possibility, the proportion of patients who received corticosteroid therapy was significantly lower in group 4 than in group 1 (85% versus 93%, respectively, Table 2). Such differences in the timing and use of corticosteroid therapy may have contributed, at least in part, to the poorer prognosis observed in presumed isolated CS.

In addition, the presumed isolated CS group who were diagnosed without histological evidence and had no extracardiac lesion may include individuals with

genetic cardiomyopathies or other inflammatory myocardial diseases. Several recent studies^{25–29} demonstrated that some patients diagnosed with isolated CS had variants in genes commonly associated with cardiomyopathies, including those encoding desmosomal and cytoskeletal proteins. It is unclear whether genetic cardiomyopathy was misdiagnosed as CS or whether the 2 conditions coexist. It is important to differentiate isolated CS from genetic cardiomyopathy, because immunosuppressive therapy is central to managing CS, although it may be less effective in genetically driven diseases. Further investigation is warranted to clarify diagnostic criteria and optimize patient management, but at the very least, it is important to recognize the risks associated with the diagnosis of presumed isolated CS. Furthermore, endomyocardial biopsy was performed in only 60% of the presumed isolated CS group. Although endomyocardial biopsy has a high

false-negative rate in CS, it should be performed more proactively.

Probable CS (group 2) and presumed systemic sarcoidosis (group 3) had a better prognosis. The presence of extracardiac lesions may lead to earlier diagnosis of CS.

Recurrence of CS

Refractory or recurrent cases of CS are often encountered in clinical practice. However, data on recurrence remain limited.^{9,31–33} The definition of recurrence is not well standardized and differs across studies; consequently, its reported prevalence and associated risk factors vary considerably in the literature.

In the present study, we defined recurrence as limited to cases diagnosed by imaging. In most cases, recurrence occurred while taking 5 to 10 mg of steroids during steroid tapering 1 to 3 years after initiation, and in over 80% of cases, the steroid dose was escalated after diagnosis of recurrence. Recurrence was associated with the subsequent occurrence of the adverse outcome. There were no differences in the incidence of recurrence or treatment strategy among the 4 groups.

Isolated CS,³² extensive late gadolinium enhancement on CMR,³² and right ventricular FDG uptake³³ have been identified as predictors of recurrence in recent studies, but the sample sizes in those studies were small (n=68 and n=25, respectively), and it remains difficult to predict recurrence in individual patients.

Early identification of patients at high risk of recurrence would be valuable for optimizing treatment strategies.

Limitations

The present study has several limitations, primarily due to its retrospective design. First, some data were missing, and not all patients underwent comprehensive cardiac imaging, although the cardiac imaging performance rates were higher than those in previous multicenter registries. Second, the timing and intervals of cardiac imaging examinations were not standardized. Consequently, recurrence events might have been underreported. Differences in imaging intensity across centers and according to disease severity may therefore have substantially influenced recurrence detection rates. A prospective study with standardized follow-up protocols is warranted to address these limitations. Third, the associations between treatment strategies and outcomes should be interpreted with considerable caution and cannot be interpreted causally, because treatment decisions, including immunosuppressive protocol and device implantation, were physician-driven and likely influenced by disease severity. Fourth, we did not perform a central evaluation of imaging, which may cause intercenter variability

in imaging interpretation and the accuracy of differential diagnosis. Fifth, no genetic information was obtained in this cohort. As mentioned above, the presumed isolated CS group may include individuals with genetic cardiomyopathies. Genetic testing should be actively performed for isolated CS without histological evidence. Finally, this study was not international, and all participants were Japanese. Therefore, it is unclear whether the findings can be generalized to other ethnic groups.

Conclusions

This large-scale multicenter registry showed that clinical presentations and prognoses differ depending on the presence or absence of extracardiac lesions and histological evidence; therefore, it is necessary to recognize the characteristics of each phenotype in managing CS. A large-scale prospective registry is warranted to further clarify clinical outcomes and guide management.

ARTICLE INFORMATION

Received January 6, 2026; accepted August 25, 2026.

Affiliations

Department of Heart Failure and Transplantation (C.I., T. Kitai), Department of Preventive Medicine and Epidemiology (Y.Y., K.N.), and Department of Cardiovascular Medicine (K.K.), National Cerebral and Cardiovascular Center, Suita, Japan. Department of Data Science, Hyogo Medical University, Nishinomiya, Japan (Y.Y.). International University of Health and Welfare, Tokyo, Japan (I.K.). Department of Frontier Cardiovascular Science, The University of Tokyo Graduate School of Medicine, Japan (I.K.). Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Japan (K.-i.H., H. Tanaka). Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Japan (K.O., T. Kato). Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Japan (Y.S.). Department of Cardiology, Osaka Medical and Pharmaceutical University, Japan (F.T.). Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, Japan (T.S.). Division of Cardiology, Department of Internal Medicine, Kindai University Faculty of Medicine, Sakai, Japan (H. Tanaka). Department of Cardiology, Tenri Hospital, Japan (T.T.). Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan (H. Takahama). Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan (Y.T.). Department of Cardiovascular Medicine, Kanazawa University Hospital, Japan (M.M.). Department of Cardiology and Geriatrics, Kochi Medical School, Kochi University, Nankoku, Japan (Y.B.). Department of Cardiology, Institute of Medicine, University of Tsukuba, Japan (K.S.). Department of Cardiovascular Medicine, Kitasato University School of Medicine, Kanagawa, Japan (S.I.).

Acknowledgments

This work was supported by the Japan Agency for Medical Research and Development (AMED). The data collection and curation were conducted by Kanako Takahashi, Yuki Nishikawa, Mihar Demoto, and Miori Koyama, as data managers. The authors thank Angela Morben, DVM, ELS, from Edanz (<https://jp.edanz.com/ac>), for editing a draft of this manuscript.

Sources of Funding

This work was supported by the Japan Agency for Medical Research and Development (AMED) under grant no. JP23ek0109629h0.001.

Disclosures

Dr Izumi has received speaker honoraria from Nippon Boehringer Ingelheim and Novartis and research funding from Daiichi Sankyo, LSI Medience Co, Bristol Myers Squibb, Terumo Japan, Alexion, and Eli Lilly and Company. Dr Tanaka has received remuneration from AstraZeneca plc, Pfizer Inc., Eli Lilly and Company, Boehringer Ingelheim GmbH, Abbott Japan LLC, Novartis International AG,

Bayer Yakuhin, Ltd., Kyowa Kirin Co, Ltd., and Alnylam Japan. Dr Kusano has received speaker honoraria from Daiichi Sankyo Company, Ltd, Bayer Yakuhin, and Medtronic Japan and research grants from Medtronic Japan. The other authors report no conflicts.

Supplemental Material

List of MYSTICS Investigators

Figures S1–S7

Tables S1–S4

REFERENCES

- Trivieri MG, Spagnolo P, Birnie D, Liu P, Drake W, Kovacic JC, Baughman R, Fayad ZA, Judson MA. Challenges in cardiac and pulmonary sarcoidosis: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;76:1878–1901. doi: 10.1016/j.jacc.2020.08.042
- Sharma R, Kouranos V, Cooper LT, Metra M, Ristic A, Heidecker B, Baksi J, Wicks E, Merino JL, Klingel K, et al. Management of cardiac sarcoidosis. *Eur Heart J*. 2024;45:2697–2726. doi: 10.1093/eurheartj/ehae356
- Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *N Engl J Med*. 2007;357:2153–2165. doi: 10.1056/NEJMra071714
- Judson MA, Costabel U, Drent M, Wells A, Maier L, Koth L, Shigemitsu H, Culver DA, Gelfand J, Valeyre D, et al. The WASOG sarcoidosis organ assessment instrument: an update of a previous clinical tool. *Sarcoidosis Vasc Diffuse Lung Dis*. 2014;31:19–27.
- Kandolin R, Lehtonen J, Airaksinen J, Vihinen T, Miettinen H, Ylitalo K, Kaikkonen K, Tuohinen S, Haataja P, Kerola T, et al. Cardiac sarcoidosis: epidemiology, characteristics, and outcome over 25 years in a nationwide study. *Circulation*. 2015;131:624–632. doi: 10.1161/CIRCULATIONAHA.114.011522
- Zhou Y, Lower EE, Li HP, Costea A, Attari M, Baughman RP. Cardiac sarcoidosis: the impact of age and implanted devices on survival. *Chest*. 2017;151:139–148. doi: 10.1016/j.chest.2016.08.1457
- Kim JS, Judson MA, Donnino R, Gold M, Cooper LT, Prystowsky EN, Prystowsky S. Cardiac sarcoidosis. *Am Heart J*. 2009;157:9–21. doi: 10.1016/j.ahj.2008.09.009
- Ekström K, Lehtonen J, Nordenswan H-K, Mäyränpää MI, Räisänen-Sokolowski A, Kandolin R, Simonen P, Pietilä-Effati P, Alatalo A, Utriainen S, et al. Sudden death in cardiac sarcoidosis: an analysis of nationwide clinical and cause-of-death registries. *Eur Heart J*. 2019;40:3121–3128. doi: 10.1093/eurheartj/ehz428
- Cacoub P, Chapelon-Abrie C, Resche-Rigon M, Saadoun D, Desbois AC, Biard L. Cardiac sarcoidosis: a long term follow up study. *PLoS One*. 2020;15:e0238391. doi: 10.1371/journal.pone.0238391
- Segawa M, Fukuda K, Nakano M, Kondo M, Satake H, Hirano M, Shimokawa H. Time course and factors correlating with ventricular tachyarrhythmias after introduction of steroid therapy in cardiac sarcoidosis. *Circ Arrhythm Electrophysiol*. 2016;9:e003353. doi: 10.1161/CIRCEP.115.003353
- Kron J, Sauer W, Schuller J, Bogun F, Crawford T, Sarsam S, Rosenfeld L, Mitiku TY, Cooper JM, Mehta D, et al. Efficacy and safety of implantable cardiac defibrillators for treatment of ventricular arrhythmias in patients with cardiac sarcoidosis. *Europace*. 2013;15:347–354. doi: 10.1093/europace/eus316
- Betensky BP, Tschabrunn CM, Zado ES, Goldberg LR, Marchlinski FE, Garcia FC, Cooper JM. Long-term follow-up of patients with cardiac sarcoidosis and implantable cardioverter-defibrillators. *Heart Rhythm*. 2012;9:884–891. doi: 10.1016/j.hrthm.2012.02.010
- Rosenthal DG, Cheng RK, Petek BJ, Masri SC, Mikacenic C, Raghu G, Patton KK. Risk of adverse cardiovascular events in cardiac sarcoidosis independent of left ventricular function. *Am J Cardiol*. 2020;127:142–148. doi: 10.1016/j.amjcard.2020.04.025
- Nordenswan H, Lehtonen J, Ekström K, Räisänen-Sokolowski A, Mäyränpää MI, Vihinen T, Miettinen H, Kaikkonen K, Haataja P, Kerola T, et al. Manifestations and outcome of cardiac sarcoidosis and idiopathic giant cell myocarditis by 25-year nationwide cohorts. *J Am Heart Assoc*. 2021;10:e019415. doi: 10.1161/JAHA.120.019415
- Birnie DH, Kandolin R, Nery PB, Kupari M. Cardiac manifestations of sarcoidosis: diagnosis and management. *Eur Heart J*. 2017;38:2663–2670. doi: 10.1093/eurheartj/ehw328
- Yafasova A, Fosbøl EL, Schou M, Gustafsson F, Rossing K, Bundgaard H, Lauridsen MD, Kristensen SL, Torp-Pedersen C, Gislason GH, et al. Long-term adverse cardiac outcomes in patients with sarcoidosis. *J Am Coll Cardiol*. 2020;76:767–777. doi: 10.1016/j.jacc.2020.06.038
- Yazaki Y, Isobe M, Hiroe M, Morimoto S, Hiramitsu S, Nakano T, Izumi T, Sekiguchi M; Central Japan Heart Study Group. Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. *Am J Cardiol*. 2001;88:1006–1010. doi: 10.1016/s0002-9149(01)01978-6
- Uemura A, Morimoto S, Hiramitsu S, Kato Y, Ito T, Hashida H. Histologic diagnostic rate of cardiac sarcoidosis: evaluation of endomyocardial biopsies. *Am Heart J*. 1999;138:299–302. doi: 10.1016/s0002-8703(99)70115-8
- Ballo H, Saraste A, Doghman F, Knuuti J. Diagnostic performance of advanced cardiac imaging for detection of cardiac sarcoidosis: a systematic review and meta-analysis. *Eur Heart J*. 2020;41:325. doi: 10.1093/ehjci/ehaa946.0325
- Patel MR, Cawley PJ, Heitner JF, Klem I, Parker MA, Jaroudi WA, Meine TJ, White JB, Elliott MD, Kim HW, et al. Detection of myocardial damage in patients with sarcoidosis. *Circulation*. 2009;120:1969–1977. doi: 10.1161/CIRCULATIONAHA.109.851352
- Patel AR, Klein MR, Chandra S, Spencer KT, Decara JM, Lang RM, Burke MC, Garrity ER, Hogarth DK, Archer SL, et al. Myocardial damage in patients with sarcoidosis and preserved left ventricular systolic function: an observational study. *Eur J Heart Fail*. 2011;13:1231–1237. doi: 10.1093/eurjhf/hfr099
- Manabe O, Ohira H, Yoshinaga K, Sato T, Klaipecth A, Oyama-Manabe N, Ito YM, Tsujino I, Nishimura M, Tamaki N. Elevated 18F-fluorodeoxyglucose uptake in the interventricular septum is associated with atrioventricular block in patients with suspected cardiac involvement sarcoidosis. *Eur J Nucl Med Mol Imaging*. 2013;40:1558–1566. doi: 10.1007/s00259-013-2460-5
- Terasaki F, Azuma A, Anzai T, Ishizaka N, Ishida Y, Isobe M, Inomata T, Ishibashi-Ueda H, Eishi Y, Kitakaze M, et al; Japanese Circulation Society Joint Working Group. JCS 2016 guideline on diagnosis and treatment of cardiac sarcoidosis—digest version. *Circ J*. 2019;83:2329–2388. doi: 10.1253/circj.CJ-19-0508
- Cheng RK, Kittleson MM, Beavers CJ, Birnie DH, Blankstein R, Bravo PE, Gilotra NA, Judson MA, Patton KK, Rose BD, et al; American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology, and Council on Cardiovascular and Stroke Nursing. Diagnosis and management of cardiac sarcoidosis: a scientific statement from the American Heart Association. *Circulation*. 2024;149:e1197–e1216. doi: 10.1161/CIR.0000000000001240
- Fouda S, Godfrey R, Pavitt C, Alway T, Coombs S, Ellery SM, Parish V, Silberbauer J, Liu A. Cardiac sarcoidosis and inherited cardiomyopathies: clinical masquerade or overlap? *J Clin Med*. 2025;14:1609. doi: 10.3390/jcm14051609
- Nishijo D, Inoue S, Dai Z, Nomura S, Abe R, Hiruma T, Bujo C, Oshima T, Katoh M, Shimizu Y, et al. Genetic cardiomyopathy mimicking isolated cardiac sarcoidosis: Diagnostic challenges with positron emission tomography. *ESC Heart Failure*. 2025;12:2347–2352. doi: 10.1002/ehf2.15185
- Lal M, Chen C, Newsome BJ, Masha L, Camacho SA, Masri A, Nazer B. Genetic cardiomyopathy masquerading as cardiac sarcoidosis. *J Am Coll Cardiol*. 2023;81:100–102. doi: 10.1016/j.jacc.2022.10.021
- Ebbinghaus H, Ueberham L, Husser-Bollmann D, Bollmann A, Laufs U, Dinov B. Case Report: Four cases of cardiac sarcoidosis in patients with inherited cardiomyopathy—a phenotypic overlap, co-existence of two rare cardiomyopathies or a second-hit disease. *Front Cardiovasc Med*. 2023;10:1328802. doi: 10.3389/fcvm.2023.1328802
- Rossi VA, Palazzini M, Ammirati E, Gasperetti A, Grubler M, Bruckhorst C, Manka R, Giannopoulos A, Tanner FC, Medeiros-Domingo A, et al. Coexistence of cardiac sarcoidosis and arrhythmogenic cardiomyopathy-associated genetic variants: a multicentre case-control study. *Heart*. 2025;111:480–486. doi: 10.1136/heartjnl-2024-324525
- Nagai T, Nagano N, Sugano Y, Asaumi Y, Aiba T, Kanzaki H, Kusano K, Noguchi T, Yasuda S, Ogawa H, et al. Effect of corticosteroid therapy on long-term clinical outcome and left ventricular function in patients with cardiac sarcoidosis. *Circ J*. 2015;79:1593–1600. doi: 10.1253/circj.CJ-14-1275
- Kaneta K, Takahama H, Tateishi E, Irie Y, Moriuchi K, Amano M, Okada A, Amaki M, Kiso K, Kanzaki H, et al. Clinical outcomes of radiologic relapse in patients with cardiac sarcoidosis under immunosuppressive therapies. *Am J Cardiol*. 2023;188:24–29. doi: 10.1016/j.amjcard.2022.10.048
- Arps K, Doss J, Geiger K, Flores-Rosario K, DeVore AD, Karra R, Kim HW, Piccini JP, Pokorney SD, Sun AY. Incidence and predictors of relapse after weaning immune suppressive therapy in cardiac sarcoidosis. *Am J Cardiol*. 2023;204:249–256. doi: 10.1016/j.amjcard.2023.07.088
- Dominati A, Urbanski G, Meyer P, Seebach JD. Relapse patterns and clinical outcomes in cardiac sarcoidosis: insights from a retrospective single-center cohort study. *J Clin Med*. 2025;14:6234. doi: 10.3390/jcm14176234
- Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS, Judson MA, Kron J, Mehta D, Cossedis Nielsen J, et al. HRS Expert

- consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm*. 2014;11:1304–1323. doi: 10.1016/j.hrthm.2014.03.043
35. Lang RM, Badano LP, Mor-Avi V, Afkalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.e14. doi: 10.1016/j.echo.2014.10.003
 36. Abraham WT, Psotka MA, Fiuzat M, Filippatos G, Lindenfeld JA, Mehra R, Ambardekar AV, Carson PE, Jacob R, Januzzi JL, et al. Standardized definitions for evaluation of heart failure therapies: scientific expert panel from the Heart Failure Collaboratory and Academic Research Consortium. *JACC Heart Fail*. 2020;8:961–972. doi: 10.1016/j.jchf.2020.10.002
 37. Gray B, Ackerman MJ, Semsarian C, Behr ER. Evaluation after sudden death in the young: a global approach. *Circ Arrhythm Electrophysiol*. 2019;12:e007453. doi: 10.1161/CIRCEP.119.007453
 38. Nabeta T, Kitai T, Naruse Y, Taniguchi T, Yoshioka K, Tanaka H, Okumura T, Sato S, Baba Y, Kida K, et al. Risk stratification of patients with cardiac sarcoidosis: the ILLUMINATE-CS registry. *Eur Heart J*. 2022;43:3450–3459. doi: 10.1093/eurheartj/ehac323
 39. Kusano K, Ishibashi K, Noda T, Nakajima K, Nakasuka K, Terasaki S, Hattori Y, Nagayama T, Mori K, Takaya Y, et al. Prognosis and outcomes of clinically diagnosed cardiac sarcoidosis without positive endomyocardial biopsy findings. *JACC Asia*. 2021;1:385–395. doi: 10.1016/j.jacasi.2021.09.005
 40. Yoshida S, Nakata T, Naya M, Momose M, Taniguchi Y, Fukushima Y, Moroi M, Okizaki A, Hashimoto A, Kiko T, et al. Prognostic implications of sarcoidosis granulomas—insights from the Multicenter Registry, the Japanese Cardiac Sarcoidosis Prognostic Study. *Circ Rep*. 2023;5:252–259. doi: 10.1253/circrep.CR-23-0031
 41. Rosenbaum AN, Kolluri N, Elwazir MY, Kapa S, Abou Ezzeddine OF, Bois JP, Chareonthaitawee P, Schmidt TJ, Cooper LT. Identification of a novel presumed cardiac sarcoidosis category for patients at high risk of disease. *Int J Cardiol*. 2021;335:66–72. doi: 10.1016/j.ijcard.2021.04.022
 42. Kitai T, Nabeta T, Naruse Y, Taniguchi T, Yoshioka K, Miyakoshi C, Kurashima S, Miyoshi Y, Tanaka H, Okumura T, et al. Comparisons between biopsy-proven versus clinically diagnosed cardiac sarcoidosis. *Heart*. 2022;108:1887–1894. doi: 10.1136/heartjnl-2022-320932



Circulation: Heart Failure

FIRST PROOF ONLY