Journal of Cardiology 75 (2020) 34–41

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

# Prognosis and risk stratification in cardiac sarcoidosis patients with preserved left ventricular ejection fraction

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ARTICLE INFO

*Article history:*
Received 4 October 2018
Received in revised form 25 March 2019
Accepted 25 April 2019
Available online 2 July 2019

*Keywords:*
Cardiac sarcoidosis
Ejection fraction
Right ventricular pacing
Myocardial damage

ABSTRACT

*Background:* Although recent reports showed that left ventricular ejection fraction (LVEF) is a prognostic factor in patients with cardiac sarcoidosis (CS), advances in diagnostic imaging have enabled us to detect CS patients with preserved LVEF in the early stage of the disorder. In the present study, we examined the prognosis and risk stratification in CS patients with preserved LVEF.

*Methods and results:* We retrospectively examined 91 consecutive CS patients at our hospital from October 1998 to December 2015 (age, 57 ± 11 years; male/female, 25/66) for the relationship between LVEF and major adverse cardiac events (MACE), including ventricular tachycardia and fibrillation (VT/VF), heart failure (HF) admission, complete atrioventricular block, and all-cause death. CS patients with preserved LVEF (≥50%), as compared with those with reduced LVEF (<50%), showed significantly higher survival free from total MACE or VT/VF (log-rank $p < 0.001$) and significantly smaller LV myocardial damaged area as evaluated by magnetic resonance imaging (MRI) ($p < 0.001$). Although CS patients with preserved LVEF had a good prognosis in general, persistent right ventricular (RV) pacing and reduced EF were significant predictors for MACE after 1 year from introduction of steroid therapy (hazard ratio, 5.25; 95% confidence interval, 1.31–22.50, $p = 0.020$, hazard ratio, 9.01; 95% confidence interval, 2.45–72.09; $p = 0.001$). Patients with the 2 factors (LVEF reduction rate >13.9% per year and persistent RV pacing) had significantly higher risk for MACE, compared with those without them (log-rank $p < 0.001$).

*Conclusion:* The present study demonstrates that CS patients with preserved LVEF have better long-term prognosis than those with reduced LVEF in general. However, we should carefully follow them up, since chronological reduction in LVEF and persistent RV pacing could predict worse prognosis in those patients.


## Introduction

Sarcoidosis is a systemic inflammatory disease characterized by non-caseating granuloma formation. Although sarcoidosis affects various organs, cardiac involvement leads to life-threatening events, including heart failure and sudden cardiac death due to fatal arrhythmias. Although latest study data demonstrated that microRNAs could be one of the novel biomarkers for cardiac sarcoidosis (CS) [1,2], early diagnosis of CS remains a challenging issue. The incidence of CS has been reported to be less than 5% among patients with sarcoidosis, but a post-mortem study has demonstrated that cardiac involvement could occur in at least 25% of the patients [3].

Although immunosuppressive therapy with corticosteroids is the mainstay of the treatment for CS, angiotensin-converting enzyme (ACE) inhibitors and β-blockers are also used for CS patients with reduced cardiac function. Furthermore, CS patients with high risk for ventricular tachyarrhythmias or wide QRS are treated with implantable cardioverter defibrillator (ICD) and/or cardiac resynchronization therapy (CRT) [4]. Advances in diagnostic imaging

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https://doi.org/10.1016/j.jjcc.2019.04.016
0914-5087/

modality, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), have enabled us to detect CS patients with preserved left ventricular ejection fraction (LVEF), who have inflammatory changes and damaged myocardium in the early stage of the disorder [5].

However, clinical course of CS patients with preserved LVEF remains to be fully elucidated. In the present study, we thus examined the prognosis and risk stratification in CS patients with preserved LVEF.

## Methods

### *Study population*

This study was approved by the University of Tohoku Institutional Review Board (2015-1-152), and all the patients gave their informed consent or were informed of the study by posted information in our institute. We retrospectively examined 91 consecutive patients with CS in our Tohoku University Hospital from October 1998 to December 2015 (age: 57 ± 11 years; M/F 25/66). They were classified into 2 groups by LVEF; Group 1 (LVEF ≥50%, $n$ = 56) and Group 2 (LVEF <50%, $n$ = 35). CS was diagnosed either by endomyocardial biopsy (histological diagnosis) or clinical CS manifestations (clinical diagnosis) according to the guidelines by the Japanese Ministry of Health and Welfare [6]. Implantation of ICD and/or CRT was performed according to the current guidelines [7]. Corticosteroid therapy was administered to all the patients, starting with 30–40 mg/day of prednisone. Doses of prednisone were decreased by 5 mg every 2 weeks until achieving 20 mg/day and were then tapered over a period of 6–12 months until the maintenance dose of 5–10 mg/day [8].

### *Left ventricular function*

Left ventricular end-diastolic volume (LVEDV), end-systolic volume (LVESV), and LVEF were measured by echocardiography using the modified Simpson's method. In addition, to assess the importance of chronological change in LVEF for cardiac events, we examined reduction rate of LVEF using the following formula: ([LVEF on diagnosis] − [LVEF after 1 year from diagnosis]) × 100/LVEF on diagnosis.

### *Imaging studies*

We routinely checked myocardial inflammation in almost all patients with CS using any or all of imaging studies, including gallium scintigraphy, $^{18}$F-fluoro-2-deoxyglucose positron emission tomography ($^{18}$F-FDG PET), MRI, and myocardial perfusion scintigraphy (MPS). We evaluated the region of LV myocardial damage using 17-segment model based on the American Society of Nuclear Cardiology imaging guidelines [9] with 3 imaging modalities except for gallium scintigraphy. FDG PET/computed tomography (CT) scans were obtained at our institute with a Biograph Duo or a Biograph-40 PET/CT scanner (Siemens Medical Solutions, Erlangen, Germany). CS patients were treated with fasting for 12 h before examination [10]. After approximately 1 h, a spiral CT scan was performed, followed by the collection of PET emission images from the distal femur to the top of the skull. After approximately 3 h, electrocardiogram (ECG)-gated spiral CT scan was performed. Positive PET finding was defined as a focal or focal on diffuse pattern of increased $^{18}$F-FDG uptake in the myocardium [11]. $^{18}$F-FDG uptake was semi-quantitatively evaluated with a 5-point grading system as follows: 4+ = very severe uptake, 3+ = severe uptake, 2+ = moderate uptake, 1+ = mild uptake, and 0 = normal [12]. MPS was performed with single photon emission computed tomography (SPECT) using $^{99m}$Tc-labeled methoxy isobutyl-isonitrate (MIBI) or tetrofosmin (TF) as a tracer. The tracer was injected intravenously at rest, and 60 min later, SPECT data were acquired using a dual-head gamma camera (Infinia Hawkeye4, GE Healthcare, Chicago, IL, USA) with a high-resolution parallel-hole collimeter. All images were acquired with ECG gating. SPECT imaging data were acquired using a 180° rotation arc, 16 frames per heart cycle, and 64 × 64 matrices. Perfusion defect region was defined as damaged myocardial region due to CS. Myocardial perfusion defect was also semi-quantitatively evaluated with a 5-point grading system as follows: 4+ = very severe defect, 3+ = severe defect, 2+ = moderate defect, 1+ = mild defect, and 0 = normal [12]. Cardiac MRI scans were performed by using the standard protocol in our institution and ECG-gated MRI images were obtained in all patients during breath-holding on a 1.5-T imager (Magnetom Vision, Siemens Medical Solutions and Achiva, Philips Medical Systems, Best, The Netherlands) using a body array coil (Siemens) or a 5-channel cardiac coil (Philips). Delayed contrast-enhanced MRI images using inversion recovery-prepared gradient-echo sequence were acquired 10–15 min after injection of gadopentetate dimeglumine (0.15 mmol/kg) in the same plane as cine imaging with the Siemens Scanner or in 10 horizontal, 10 vertical long, and 20 short-axis slices with the Philips scanner. Each myocardial segment was scored for the presence of delayed enhancement (DE), a sign of chronic fibrotic change (1 = DE+, 0 = DE−).

### *Definition of events*

Ventricular tachycardia and fibrillation (VT/VF) were defined as documented VT or VF lasting for >30 s on 12-lead ECG, Holter ECG, or cardiac implantable electronic devices (pacemaker, ICD, or CRT). Heart failure (HF) admission was defined as admission needing some treatment for HF alone, but not for that to treat arrhythmias. Total major adverse cardiac events (MACE) was defined as composite outcome of VT/VF, HF admission, complete atrioventricular block (CAVB), and all-cause death.

### *Statistical analysis*

Continuous variables are expressed as the means ± SD, and categorical variables as number and percent. Group comparisons were performed with Kruskal–Wallis test for multiple continuous variables and Mann–Whitney $U$-test. Chi-square test was used for categorical variables. Univariable and multivariable Cox proportional hazard models were applied to examine the association between time to primary outcomes and covariates. To select the optimal subset of the covariates in the multivariable analysis, stepwise variable selection was adopted. A Kaplan–Meier analysis was used to assess the time required for the MACE outcome to occur, and comparison between groups was performed using log-rank tests. Values of $p < 0.05$ were considered to be statistically significant. All statistical analyses were performed with the use of JMP software version 12.0 (SAS Institute, Cary, NC, USA).

## Results

### *Patient characteristics*

Patient characteristics at baseline are shown in Table 1. There was no significant difference in mean age or male sex proportion between the two groups. The mean New York Heart Association class was significantly lower in group 1 compared with group 2 (1.52 ± 0.63 vs. 2.11 ± 0.83, $p < 0.001$). Although the prevalence of extra-cardiac sarcoidosis was comparable between the two groups, the definite histological diagnosis of sarcoidosis was noted more frequently in group 1 compared with group 2 [38/56 (68%) vs. 16/35 (46%), $p$ = 0.037]. β-blockers and ACE inhibitors or angiotensin receptor blockers (ARB) were used in only half of the

**Table 1**
Patient characteristics at baseline.

| Patient characteristics | Total (*N* = 91) | Group 1 (*N* = 56) | Group 2 (*N* = 35) | *p*-Value |
|---|---|---|---|---|
| Male | 25 (27%) | 13 (23%) | 12 (34%) | 0.253 |
| Age (years) | 57 ± 11 | 57 ± 11 | 57 ± 10 | 0.830 |
| NYHA class | 1.7 ± 0.8 | 1.52 ± 0.63 | 2.11 ± 0.83 | <0.001 |
| Hypertension | 20 (22%) | 14 (25%) | 6 (13%) | 0.373 |
| Dyslipidemia | 23 (25%) | 14 (25%) | 9 (26%) | 0.939 |
| Diabetes mellitus | 14 (15%) | 6 (11%) | 8 (23%) | 0.124 |
| Chronic kidney disease | 6 (7%) | 2 (4%) | 4 (11%) | 0.199 |
| Heart failure | 15 (16%) | 3 (5%) | 12 (34%) | <0.001 |
| Extracardiac sarcoidosis | | | | |
| Lung | 62 (68%) | 40 (71%) | 22 (63%) | 0.395 |
| Eye | 34 (37%) | 22 (39%) | 12 (34%) | 0.631 |
| Skin | 12 (13%) | 9 (16%) | 3 (9%) | 0.291 |
| Histology | | | | |
| Positive histology | 54 (59%) | 38 (68%) | 16 (46%) | 0.037 |
| Heart | 7 (8%) | 2 (4%) | 5 (14%) | 0.103 |
| Medication | | | | |
| β-blockers | 54 (61%) | 25 (45%) | 29 (91%) | <0.001 |
| ACE-I/ARBs | 60 (68%) | 34 (61%) | 26 (81%) | 0.041 |
| Amiodarone | 21 (24%) | 6 (11%) | 15 (47%) | <0.001 |
| Prednisolone | 91 (100%) | 56 (100%) | 35 (100%) | 1.000 |
| Device | | | | |
| Pacemaker | 30 (33%) | 23 (41%) | 5 (14%) | 0.010 |
| ICD | 9 (10%) | 2 (4%) | 7 (20%) | 0.025 |
| CRT | 13 (14%) | 0 (0%) | 13 (37%) | <0.001 |
| ECG parameter | | | | |
| RBBB | 25 (28%) | 15 (27%) | 10 (29%) | 0.893 |
| LBBB | 1 (1%) | 1 (2%) | 0 (0%) | 1.000 |
| RV pacing | 29 (32%) | 20 (27%) | 9 (26%) | 0.315 |
| NSVT | 33 (37%) | 13 (24%) | 20 (57%) | 0.001 |
| Echocardiographic parameter | | | | |
| LVEF, % | 54 ± 16 | 65 ± 9 | 35 ± 9 | <0.001 |
| LVDd, mm | 53 ± 9 | 49 ± 7 | 60 ± 8 | <0.001 |
| LVDs, mm | 38 ± 12 | 32 ± 7 | 50 ± 9 | <0.001 |
| ESVI, mL/m$^2$ | 45 ± 32 | 26 ± 12 | 72 ± 33 | <0.001 |
| IVS <8 mm | 40 (44%) | 17 (30%) | 23 (66%) | <0.001 |
| Laboratory data | | | | |
| BNP, pg/mL | 234 ± 419 | 115 ± 158 | 445 ± 616 | <0.001 |
| sIL-2R, U/mL | 649 ± 495 | 624 ± 445 | 696 ± 586 | 0.552 |
| ACE, IU/L | 17 ± 9 | 18 ± 10 | 14 ± 8 | 0.106 |
| Cr, mg/dL | 0.81 ± 0.31 | 0.74 ± 0.23 | 0.92 ± 0.39 | 0.011 |
| Imaging examinations | | | | |
| Ga scintigraphy | 54 (59%) | 32 (57%) | 22 (63%) | 0.664 |
| FDG-PET | 79 (87%) | 48 (86%) | 31 (89%) | 0.761 |
| Patterns of FDG accumulation | | | | |
| Focal | | 10 (21%) | 8 (26%) | 0.784 |
| Focal on diffuse | | 13 (27%) | 15 (48%) | 0.060 |
| Diffuse | | 21 (44%) | 7 (23%) | 0.091 |
| None | | 4 (8%) | 1 (3%) | 0.643 |
| SUV max of heart | | 1.777 | 2.274 | 0.080 |
| MPS | 62 (68%) | 35 (63%) | 27 (77%) | 0.171 |
| Perfusion defect (point) | | 1.074 | 1.821 | <0.001 |
| Cardiac MRI | 58 (64%) | 39 (70%) | 19 (54%) | 0.180 |
| Delayed enhancement (point) | | 0.250 | 0.591 | <0.001 |

Results are presented as either mean ± SD or number of patients (%).
Maximum of standardized uptake value (SUV max) of heart, perfusion defect, and delayed enhancement are presented as numerics calculated by scoring system.
ACE, angiotensin-converting enzyme; ACE-I, angiotensin-converting enzyme inhibitors; ARBs, angiotensin-receptor blockers; BNP, brain natriuretic peptide; Cr, serum creatinine; CRT, cardiac resynchronization; DE, delayed enhancement; ECG, electrocardiography; ESVI, end-systolic volume index; FDG, fluoro-2-deoxyglucose; Ga, gallium scintigraphy; Hb, hemoglobin; ICD, implantable cardioverter defibrillator; IVS, intraventricular septum; LBBB, left bundle branch block; LVDd, end-diastolic left ventricular dimensions; LVDs, end-systolic left ventricular dimensions; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MPS, myocardial perfusion scintigraphy; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; PET, positron emission tomography; PM, pacemaker; RBBB, right bundle branch block; RV, right ventricular; sIL-2R, soluble interleukin-2 receptor.
We defined RV pacing when (1) there was no own beat in 12-lead electrocardiogram, (2) ratio of pacing with implantable device (pacemaker, ICD, CRT) was over 95%, and (3) there was no biventricular pacing.

patients in group 1, whereas they were used in more than 80% of the patients in group 2 [β-blockers, 25/56 (45%) vs. 29/35 (91%), $p < 0.001$; ACE inhibitor/ARB, 34/56 (61%) vs. 26/35 (81%), $p = 0.041$]. Oral amiodarone was used in ~10% of the patients in group 1 but was used in ~50% of the patients in group 2 [6/56 (11%) vs. 15/35 (47%), $p < 0.001$]. Pacemaker (PM) was implanted to more patients in group 1 compared with those in group 2, whereas implantation of ICD and CRT with defibrillator (CRT-D) was less performed in group 1 compared with group 2 [PM, 23/56 (41%) vs. 5/35 (14%), $p = 0.010$; ICD, 2/56 (4%) vs. 7/35 (20%), $p = 0.025$; CRT-D, 0/56 (0%) vs. 13/35 (37%), $p < 0.001$].

*Prognosis of CS patients with or without preserved LVEF*

During a mean follow-up of 84 months, total MACE and VT/VF occurred in a significant higher percentage of patients in group 2 as

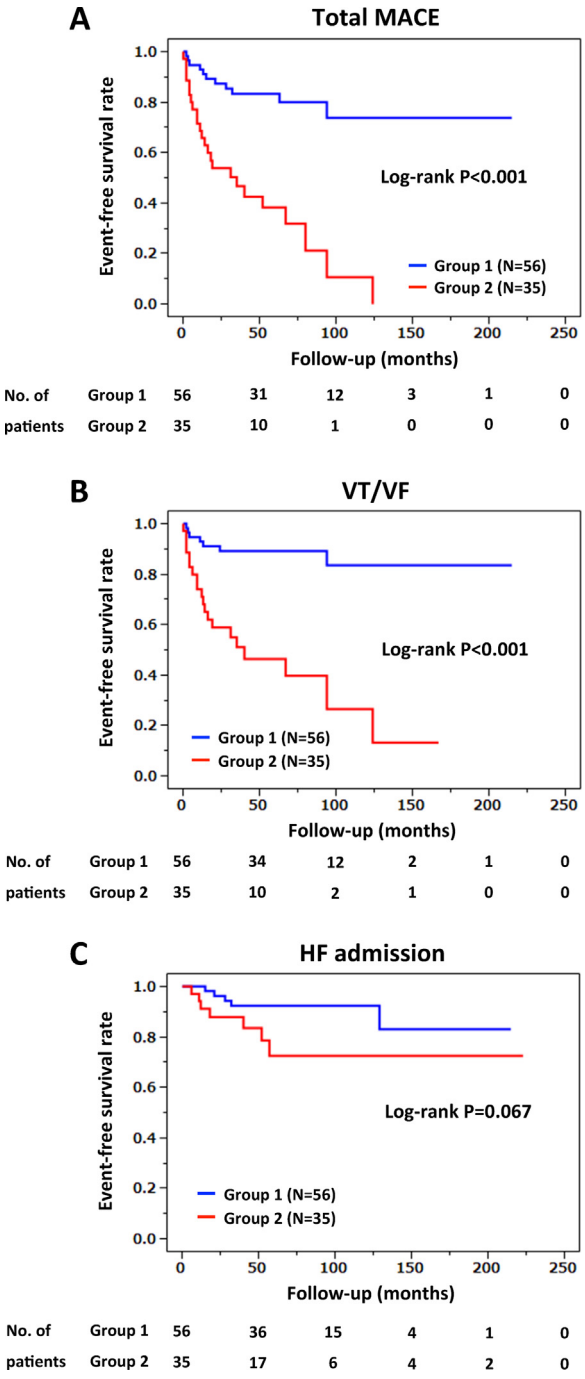



**Fig. 1.** Kaplan–Meier analysis of total and each MACE in cardiac sarcoidosis patients in group 1 (LVEF ≥50%) and group 2 (LVEF <50%). Total MACE, (B) VT/VF, and (C) HF admission. HF, heart failure; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; VT, ventricular tachycardia; VF, ventricular fibrillation.

compared with group 1 [24 (69%) vs. 11 (20%), (log-rank $p < 0.001$), and 20 (57%) vs. 7 (13%), (log-rank $p < 0.001$), respectively] (Fig. 1A and B). Similarly, HF admission occurred in a higher percentage of patients in group 2 as compared with group 1 [7 (20%) vs. 5 (9%)] (log-rank $p = 0.067$) (Fig. 1C). Four patients showed de novo CAVB (1 in group 1, and 3 in group 2), and 4 other patients died in groups 1 and 2 (1 in group 1, and 3 in group 2). The cause of death included circulatory failure, sudden death, esophageal cancer, and natural disaster.

At diagnosis of CS, 29 patients had RV pacing [20 in group 1 (36%), 9 in group 2 (26%)]. We examined atrioventricular (AV) conduction of the patients with steroid therapy at 1 year after CS diagnosis in both groups (Fig. 2). Although the number of patients with improved AV conduction was 12 (60%) in group 1, no patients showed improvement of AV conduction in group 2. On the other hand, one patient showed de novo AV block in group 1 (2%), and 3 (9%) in group 2. In the imaging examinations, FDG-PET showed that $^{18}$F-FDG uptake tended to be larger in group 2 than in group 1 in total LV ($p = 0.080$) (Fig. 3A). Furthermore, MPS and MRI showed that the extent of positive area was larger in group 2 than in group 1 (MPS, $p = 0.007$; MRI, $p < 0.001$), suggesting that group 2 had more advanced myocardial damage compared with group 1 (Fig. 3B and C).

*Prognosis and risk stratification of CS patients with preserved LVEF*

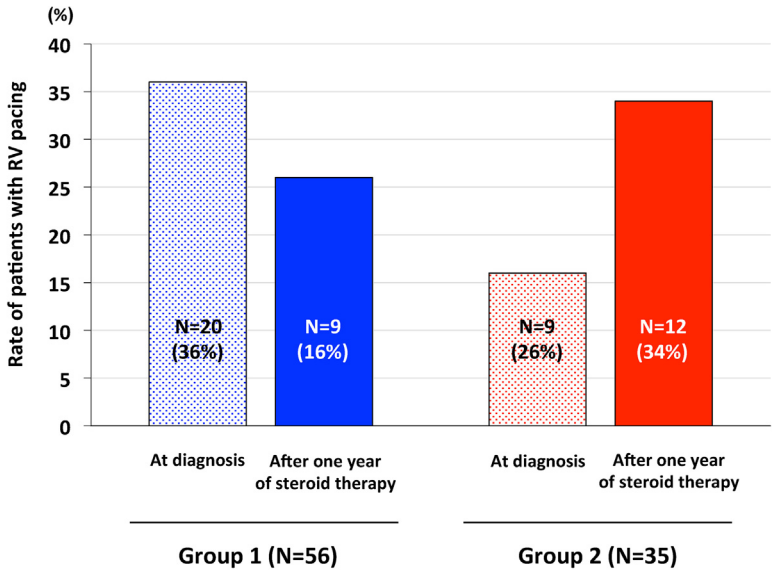
Although group 1 showed better prognosis than group 2 as a whole group, some patients in group 1 also experienced MACE. We recently reported that CS patients tend to experience ventricular tachyarrhythmias more frequently within 1 year after introduction of steroid therapy than after 1 year [13]. Thus, we next examined the time-course and risk factors of MACE in CS patients in group 1. Within 1 year after introduction of steroid therapy, 4 out of 56 CS patients in group 1 (7%) experienced MACE (4 patients experienced VT/VF and no patients experienced HF admission, AVB, or death). On the other hand, 9 (16%) had MACE (VT/VF in 5, HF admission in 5, de novo CAVB in 1, and death in 1) after 1 year.

Although univariable Cox proportional-hazards analysis showed that MACE (all VT/VF) within 1 year after introduction of steroid therapy was significantly associated with dyslipidemia, diabetes mellitus, right bundle branch block, and non-sustained VT, multivariable analysis showed that these associations were not significant (Supplement Table 1).

Next, we quantified the reduction rate of LVEF and LVEF at 1 year after steroid introduction to detect patients at high risk of MACE, VT/VF, and HF admission after 1 year of steroid therapy using receiver-operator characteristic (ROC) curve analysis, which showed that cut-off values for MACE, VT/VF, and HF admission were reduction rate in LVEF at 1 year >13.9% per year each and that <56%, 46%, and 45%, respectively (Fig. 4A and B, Supplement Fig. 1A and B, Supplement Fig. 2A and B).

Cox proportional-hazards analysis showed that the occurrence of total MACE after 1 year of steroid therapy was not associated with LVEF after 1 year from steroid introduction (hazard ratio, 1.33; 95% confidence interval, 0.21–12.00; $p = 0.775$), but significantly associated with persistent RV pacing (hazard ratio, 4.68; 95% confidence interval, 1.07–24.58; $p = 0.040$) and LVEF reduction rate >13.9% per year (hazard ratio, 8.17; 95% confidence interval, 1.22–85.02; $p = 0.029$) (Table 2). We examined the clinical features of the CS patients with worsening LVEF (reduction rate >13.9% per year) in Supplement Table 2. Furthermore, we have performed univariable and multivariable Cox proportional-hazards analysis (Supplement Table 3), demonstrating that there was no significant risk factor associated with LVEF worsening. Furthermore, we examined the relationships between MACE and 2 correlated factors (LVEF reduction rate >13.9% per year and persistence of RV pacing). Event-free survival from MACE showed that patients with both greater LVEF reduction rate (>13.9% per year) and persistent RV pacing had significantly higher risk of MACE compared with those without them (log-rank $p < 0.001$) (Supplement Fig. 3).

Although univariable analysis showed that VT/VF after 1 year of steroid therapy was associated with positive histology, diabetes mellitus, thin intraventricular septum on ultrasound cardiography (UCG), and positive gallium-scintigraphy, multivariable analysis showed no significant association between these parameters and VT/VF (Supplement Table 4). Similarly, univariable analysis showed that HF admission after 1 year of steroid therapy was




| | | |
|---|---|---|
| Recovery of AV conduction | 12/20 (60%) | 0/9 (0%) |
| Emergence of AV block | 1/56 (2%) | 3/35 (9%) |

**Fig. 2.** Number of patients with RV pacing at CS diagnosis and one year after CS diagnosis. AV, atrioventricular; CS, cardiac sarcoidosis; RV, right ventricular.

associated with New York Heart Association class, positive histology, LVEF reduction rate >13.9% per year, and BNP levels, however, multivariable analysis showed no significant association between these parameters and HF admission (Supplement Table 5).

## Discussion

The novel findings of the present study were as follows: (1) prognosis of CS patients was strongly correlated with LVEF at diagnosis, in association with the extent of myocardial damage as evaluated by reduced myocardial perfusion on MPS and/or delayed enhancement on MRI, even if they were treated with immunosuppressive therapy and modern cardiac devices, such as ICD and CRT-D. (2) Although CS patients with preserved LVEF generally had better prognosis, some of them experienced adverse clinical events, which could be predicted by worsening of LVEF (reduction rate >13.9% per year) and persistent RV pacing despite steroid therapy. To the best of our knowledge, this is the first study that demonstrates the prognosis and risk factors of CS patients with preserved LVEF.

### *Prognosis of CS patients with or without preserved LVEF*

It is widely known that reduced LVEF is associated with poor prognosis in patients with chronic HF in general. It has also been reported that CS patients with reduced LVEF at diagnosis are resistant to HF therapy [14]. Since VT/VF are one of the major causes of death in CS patients, the previous studies examined the relationship between clinical characteristics and occurrence of ventricular arrhythmias [4]. However, since HF is also one of the important adverse cardiac events in CS patients in addition to VT/VF [14], we examined total MACE including HF admission in CS patients in the present study.

The present study demonstrates that CS patients with reduced LVEF (<50%), which was associated with more myocardial damage on MRI, had more occurrence of total MACE and fatal ventricular arrhythmias compared with those with preserved LVEF (EF > 50%). Myocardium with delayed enhanced area on MRI reflects advanced damaged lesion, such as scar tissue, which could be a substrate of tachyarrhythmias [5]. Moreover, reduced LVEF usually causes myocardial remodeling including electrophysiological and mechanical myocardial changes, such as down- or up-regulation of ion channels and increment of fibrosis, which cause shortening of refractory periods and slow conduction area with resultant occurrence of tachyarrhythmias [15,16]. In contrast, in the present study, no significant difference was noted in the occurrence of HF admission between the two groups. This was probably because CS patients with reduced LVEF were more likely to receive β-blockers and ACE inhibitors/ARBs than those with preserved LVEF.

Early immunosuppressive therapy may be effective for certain CS patients with AV block [17]. Although, it was also reported that patients with high-degree AV block at diagnosis of CS had a higher rate of subsequent fatal cardiac events despite immunosuppressive therapy [18], clinical characteristics and risk stratification of these patients remains to be fully elucidated. Therefore, in the present study, we also examined the relationship of LVEF and improvement in AV block after steroid therapy, demonstrating that LVEF at diagnosis was associated with improvement in AV block. Thus, CS patients with reduced LVEF and AV block may be good candidates for CRT, even if they have slightly reduced cardiac function (LVEF 35–50%), as indicated by the recent guidelines [19].

### *Time course and risk stratification of CS patients with preserved LVEF*

Although reduced LVEF would be known as one of the poor prognostic markers in CS patients, recent studies reported that some CS patients with delayed enhancement on MRI had poor outcomes in spite of preserved LVEF [20,21]. The present study also showed that although CS patients with preserved LVEF generally had better prognosis than those with reduced LVEF, some of them

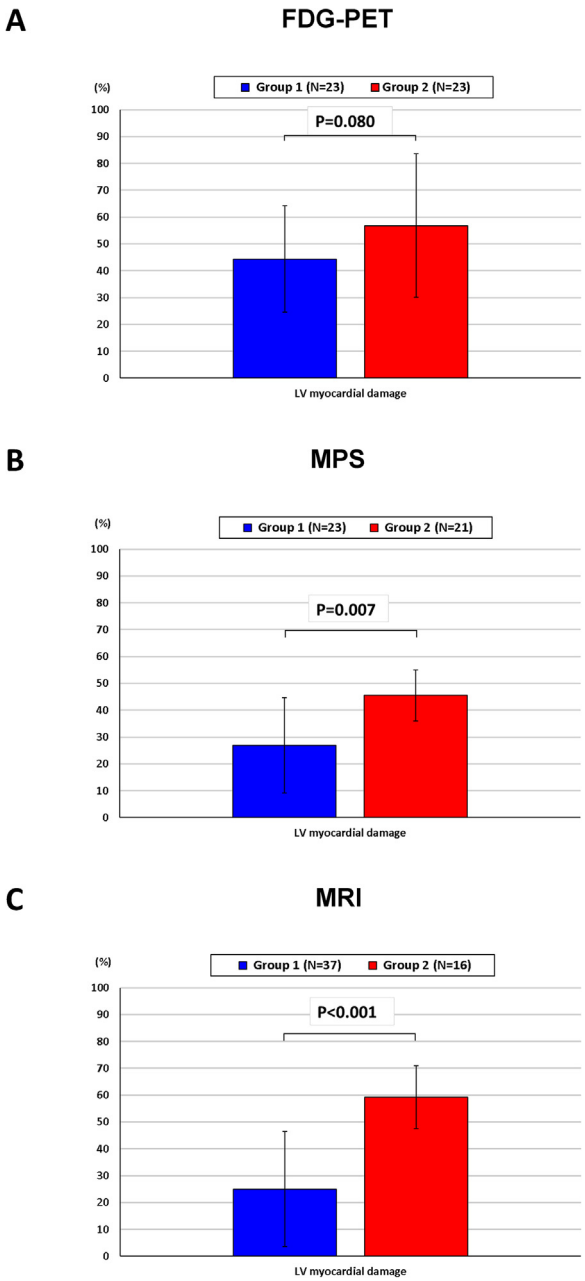



**Fig. 3.** Multi-modality evaluation of LV myocardial damage in cardiac sarcoidosis patients. (A) FDG-PET, (B) MPS, and (C) MRI. FDG-PET, $^{18}$F-fluoro-2-deoxyglucose positron emission tomography; LV, left ventricular; MPS, myocardial perfusion scintigraphy; MRI, magnetic resonance imaging.

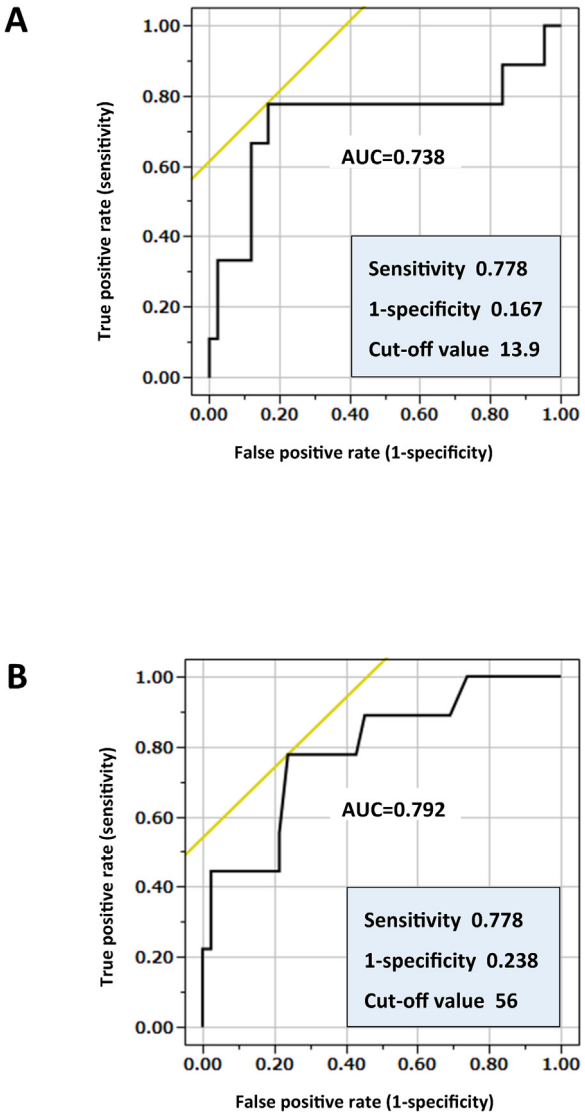



**Fig. 4.** The receiver-operator characteristic curve in conjunction with LVEF and total major adverse cardiac events after one year after cardiac sarcoidosis diagnosis. (A) LVEF at one year after steroid introduction. (B) Reduction rate of LVEF. AUC, area under the curve; LVEF, left ventricular ejection fraction.

also experienced adverse cardiac events. Recently, we reported that CS patients are likely to experience more ventricular tachyarrhythmic events within 1 year of steroid therapy, when associated with reduced LVEF and positive gallium-scintigraphy [13]. However, time-course and risk stratification of CS patients with preserved LVEF remains to be fully examined [20]. Thus, in the present study, we examined the occurrence of MACE and its risk factors within or after 1 year of steroid therapy separately. The present results showed that VT/VF were major contents of MACE within 1 year from introduction of steroid therapy in CS patients with preserved LVEF. This result was coincident with our previous report and others, suggesting that inflammatory conditions by steroid therapy may be involved [22–25]. Since multivariable analysis showed no specific risk factors for predicting VT/VF in this phase, it is conceivable that inflammatory responses are involved in VT/VF occurrence more than baseline characteristics of the patients. The present results also showed that MACE after 1 year of steroid therapy were VT/VF and HF admission in CS patients with preserved LVEF, in association with LVEF reduction rate >13.9% per year. This was probably because progression of LV remodeling and resultant scar formation were involved in the occurrence of HF admission and fatal ventricular arrhythmic events [26].

The present study also demonstrates that persistent RV pacing is an independent predictor for MACE occurrence. Persistent RV pacing is known to worsen LV function [27], which could also contribute to occurrence of HF admission and VT/VF. Moreover, among CS patients with preserved LVEF, those with both factors (LVEF reduction rate >13.9% per year and persistent RV pacing) had a higher risk of total MACE, as in the case with CS patients with reduced LVEF. Thus, we should pay attention to CS patients regardless of LVEF at diagnosis, especially to those with LVEF deterioration and persistent RV pacing despite steroid therapy.

**Table 2**
Cox proportional-hazards analysis for correlation with total MACE after one year from CS diagnosis.

| Variable | HR (95% CI) | *p*-Value |
|---|---|---|
| Univariable analysis | | |
| Male | 1.03 (0.15–4.25) | 0.975 |
| Age (years) | 19.87 (0.96–719.72) | 0.054 |
| NYHA class | 3.74 (0.51–24.01) 0.185 | |
| Hypertension | 1.18 (0.28–7.94) | 0.833 |
| Dyslipidemia | 4.59 (1.21–18.66) | 0.026 |
| Diabetes mellitus | 5.34 (1.12–20.33) 0.037 | |
| Chronic kidney disease | 5.87 (0.31–33.35) | 0.182 |
| Extracardiac sarcoidosis | | |
| Lung | 1.47 (0.31–5.61) 0.594 | |
| Eye | 1.51 (0.39–7.28) | 0.563 |
| Skin | 1.44 (0.21–5.99) | 0.660 |
| Histology | | |
| Positive histology[a] | ... | ... |
| Medication | | |
| β-blockers | 1.07 (0.27–4.06) | 0.915 |
| ACE-I/ARBs | 0.64 (0.16–2.60) | 0.510 |
| Amiodarone 5.09 (1.07–19.38) | 0.042 | |
| ECG parameter | | |
| RBBB | 1.43 (0.30–5.42) | 0.624 |
| NSVT | 3.03 (0.75–11.50) | 0.114 |
| RV pacing (1 year) | 7.81 (2.05–31.74) | 0.003 |
| Echocardiographic parameter | | |
| LVEF at 1year after CS diagnosis | 7.89 (1.91–53.06) 0.004 | |
| LVEF reduction rate >13.9% per year | 13.72 (3.30–92.35) | <0.001 |
| IVS <8 mm | 4.95 (1.29–23.60) | 0.020 |
| Laboratory data | | |
| BNP | 6.70 (0.68–37.68) | 0.094 |
| Cr | 10.63 (0.67–93.59) | 0.087 |
| Imaging examinations | | |
| Ga scintigraphy; positive+ | 9.67 (1.54–186.17) | 0.014 |
| FDG-PET; uptake+ | 2.13 (0.40–15.65) | 0.378 |
| MPS: defect+ | 1.13 (0.22–8.15) | 0.892 |
| Cardiac MRI: DE+[a] | ... | ... |
| Multivariable analysis | | |
| RV pacing (1 year) | 4.68 (1.07–24.58) | 0.040 |
| LVEF reduction rate >13.9% per year | 8.17 (1.22–85.02) | 0.029 |

Results are presented as either mean ± SD or number of patients (%).
ACE-I, angiotensin converting enzyme inhibitor; ARBs, angiotensin-receptor blockers; BNP, brain natriuretic peptide; CI, confidence interval; Cr, serum creatinine; CS, cardiac sarcoidosis; DE, delayed enhancement; ECG, electrocardiography; FDG, fluoro-2-deoxyglucose; Ga, gallium scintigraphy; HR, hazard ratio; IVS, intraventricular septum; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac event; MRI, magnetic resonance imaging; MPS, myocardial perfusion scintigraphy; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; PET, positron emission tomography; RBBB, right bundle branch block; RV pacing (1 year), Persistent RV pacing after 1 year of steroid therapy; sIL-2R, soluble interleukin-2 receptor.
[a] Estimation procedure was not converged.

*Roles of imaging modality for detecting myocardial damage in CS patients*

PET is one of the useful diagnostic tools unmasking myocardial inflammation in CS patients [28]. However, in the present study, PET had no power to correlate LVEF in CS patients, whereas MRI and MPS could detect larger myocardial damage in relation to LVEF reduction rate in CS patients. This discrepancy among imaging modalities could be explained as follows: PET can detect inflammatory myocardium that could be curable with steroid therapy, whereas MRI and MPS can detect more damaged tissue, such as scar, which could not be curable with steroid therapy. Thus, the findings of irreversible myocardial damage on MRI or MPS could well correlate to cardiac function (e.g. LVEF) in CS patients [5,29].

*Study limitations*

Several limitations should be mentioned for the present study. First, the tapering protocol of steroid therapy and adjustment of maintenance dose were entrusted to each physician's decision. However, almost all patients received the same protocol for introduction of steroid therapy and reached the maintenance dose in one year. Second, in the present study, imaging examinations were not performed uniformly in all the patients. MPS and PET were often performed at the same time in many patients, but MRI was not performed in the patients with device therapy. In addition, imaging examinations at 1 year after diagnosis of CS were not performed in all patients depending on physician's decision. Third, since the PET examination was performed before introduction of the current guidelines in most cases, dietary modification (e.g. carbohydrate restriction) was not complete [10]. Fourth, the number of CS patients with RV pacing was small. Thus, we were unable to exclude the possibility that RV pacing contributed to the chronological reduction in LVEF. Fifth, we also were unable to exclude the possibility that relapse of active sarcoid inflammation played some roles in the chronological reduction in LVEF. Sixth, because this study is a retrospective analysis, the present results need to be confirmed by prospective study. Seventh, we were unable to fully evaluate the effectiveness of steroid therapy for inflammation status of CS patients because the number of CS patients with follow-up imaging studies was limited. Eighth, since we examined CS patients with preserved LVEF, we consider that the extents of inflammation and myocardial damage were too mild to play a prognostic role in our patients as compared with CS patients in other studies.

## Conclusion

The present study demonstrates that CS patients with preserved LVEF have better long-term prognosis than those with reduced LVEF in general. However, we should carefully follow them up, since chronological reduction in LVEF and persistent RV pacing could predict worse prognosis in those patients.

## Conflict of interest

The authors have no conflict of interest to disclose.

## Acknowledgments

We thank Satoshi Miyata for contribution to statistical analysis.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2019.04.016.

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