Prognostic Implications of Sarcoidosis Granulomas
— Insights From the Multicenter Registry, the Japanese Cardiac Sarcoidosis Prognostic Study —

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Background: Definitions of cardiac sarcoidosis (CS) differ among guidelines. Any systemic histological finding of CS is essential for the diagnosis of CS in the 2014 Heart Rhythm Society statement, but not necessary in the Japanese Circulation Society 2016 guidelines. This study aimed to reveal the differences in outcomes by comparing 2 groups, namely CS patients with or without systemic histologically proven granuloma.

Methods and Results: This study retrospectively included 231 consecutive patients with CS. CS with granulomas in ≥1 organs was diagnosed in 131 patients (Group G), whereas CS without any granulomas was diagnosed in the remaining 100 patients (Group NG). Left ventricular ejection fraction (LVEF) was significantly reduced in Group NG compared with Group G (44±13% vs. 50±16%, respectively; P=0.001). However, Kaplan-Meier curves showed that major adverse cardiovascular events (MACE)-free survival outcomes were comparable between the 2 groups (log-rank P=0.167). Univariable analyses showed that significant predictors of MACE were Groups G/NG, histological CS, LVEF, and high B-type natriuretic peptide (BNP) or N-terminal pro BNP concentrations, but none of these was significant in multivariable analyses.

Conclusions: Overall risks of MACE were similar between the 2 groups despite different manifestations in cardiac dysfunction. The data not only validate the prognostic value of non-invasive diagnosis of CS, but also show the need for careful observation and therapeutic strategy in patients with CS without any granuloma.

Key Words: ^{18}F-Fluorodeoxyglucose; Guidelines; J-CASP Registry; Multicenter registry; Positron emission tomography

R ecent advances in and the widespread use of cardiac imaging techniques, such as ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and cardiac magnetic resonance imaging (CMR), have contributed particularly to the non-invasive, early, and precise identification of cardiac sarcoidosis (CS)-related inflammatory reactions or degenerative process in the myocardium.[1–4] Moreover, pharmacological and non-pharmacological treatments, including catheter ablation, cardiac

resynchronization treatment (CRT), and implantable cardioverter-defibrillators (ICD), have enabled more appropriate treatments in recent years for patients with CS and heart failure (HF) and/or lethal arrhythmias. In this context, the guidelines of the Japanese Circulation Society (JCS) on CS were updated in 2016 by focusing on non-invasive diagnostic strategy using ^{18}F-FDG-PET and CMR.[5] At around the same time (in 2014), another important CS guideline, the Heart Rhythm Society's (HRS) expert con-

Heart		Other organs		JCS 2016 guidelines	HRS expert consensus	Group in the present study
Positive biopsy findings	Clinical sign manifestations	Positive biopsy findings	Clinical sign manifestations			
○		○		Histological CS	Histological CS	G
○			○	Histological CS	Histological CS	
○				Histological CS (isolated CS)	Histological CS	
	○	○		Clinical CS	Clinical CS (probable CS)	
	○		○	Clinical CS	Undefined	NG
	○			Clinical CS (isolated CS)	Undefined	

Table 1. Differences in the Definition of CS Between the JCS 2016 Guidelines[5] and HRS Expert Consensus[6]

CS, cardiac sarcoidosis; HRS, Heart Rhythm Society; JCS, Japanese Circulation Society.

sensus on the diagnosis and management of cardiac sarcoidosis,[6] was published. The definition of a clinical diagnosis of CS is partially different between the JCS guidelines and HRS consensus. The JCS guidelines define clinically diagnosed CS as either: (1) when epithelioid granulomas are found in organs other than the heart and ≥2 of 5 major criteria or 1 of the 5 major criteria with ≥2 of 3 minor criteria for cardiac involvement are evident (**Supplementary Table 1**); or (2) when pulmonary or ophthalmic sarcoidosis is found together with at least 2 of the 5 characteristic findings of sarcoidosis and the cardiac involvement criteria mentioned above are satisfied.[5] Thus, under the JCS 2016 guidelines, clinical CS can be diagnosed without any histological findings (**Table 1**). In contrast, some kind of histological evidence of a sarcoidosis lesion is mandatory for the diagnosis of CS in the HRS consensus.[6]

Because of the various diagnostic criteria set forth in the different guidelines, non-invasive imaging techniques like FDG-PET and CMR have become increasingly indispensable. Given that non-caseating granuloma is a cardinal feature of sarcoidosis, it is crucial to examine the validity of diagnosing CS in the absence of this feature. Accordingly, the aim of the present study was to compare a cohort of patients with a clinical diagnosis of CS as per the JCS guidelines, but not specified in the HRS consensus. Specifically, we compared patients lacking non-caseating granuloma, either in the heart or elsewhere in the body, with those who had granuloma in any bodily region, including the heart. Furthermore, we evaluated and compared the characteristics of these 2 groups.

Methods

Study Design and Patient Population
This study was performed as a subanalysis of the Japanese Cardiac Sarcoidosis Prognostic Study (J-CASP). The study was a multicenter registry across 13 hospitals in Japan that retrospectively enrolled 237 consecutive patients with CS who had been diagnosed using the updated JCS 2016 guidelines for the diagnosis and treatment of CS and had undergone ^{18}F-FDG PET.[7] The J-CASP Study was performed in accordance with the Declaration of Helsinki and the study protocol was approved by the Ethics Committee of Kanazawa University Hospital (IRB No. 2017-172) and the institutional review board of each participating hospital. Six patients were excluded because they did not meet the diagnostic criteria for CS based on

the JCS 2016 guidelines or because other heart diseases responsible for HF or serious arrhythmias, such as myocardial infarction, severe valvular disease, congenital heart disease, or idiopathic cardiomyopathy, could not be ruled out. Ultimately, 231 patients were included in the present study. Non-caseous granulomas, a specific histological finding of sarcoidosis, were proven in ≥1 organs in 131 of 231 (56.7%) patients (Group G) and not in any organ in the remaining 100 patients (Group NG).

The day of the ^{18}F FDG-PET procedure was set as the start date, and the mean observation period was 54 months. The prognostic endpoint was major adverse cardiovascular events (MACE), defined as all-cause death, lethal ventricular arrhythmias (e.g., sustained ventricular tachycardia [VT] and ventricular fibrillation [VF]), appropriate ICD discharge (defined as antitachycardia therapy and shock delivery), heart transplantation or ventricular assist device (VAD) implantation, and admission for HF.

^{18}F-FDG-PET Imaging
^{18}F-FDG-PET data were essential for entry into this study. The imaging conditions for ^{18}F-FDG-PET have been described elsewhere.[8,9] Briefly, the dose of ^{18}F-FDG administered ranged from 2 to 7 MBq/kg. All the institutions followed the recommendations for the diagnosis of CS published by the Japanese Society of Nuclear Cardiology (JSNC)[8] and the European Association of Nuclear Medicine and European Association of Cardiovascular Imaging.[9] Patients were requested to have fasted for 12 to 20 h (≥18-h fast in 72% of patients) following dietary control with a low-carbohydrate, high-fat diet to suppress physiologic uptake of ^{18}F-FDG in the normal myocardium. Intravenous 50 IU/kg heparin 15 min before administration of ^{18}F-FDG was not used regularly, but was additionally used in 4 institutions. A 3-dimensional ordered subset expectation maximization method was used for image reconstruction in most of institutions, and X-ray computed tomography (CT)-based attenuation correction was also used, although PET images were reconstructed using the standard methods specified by manufacturers. The final DICOM (Digital Imaging and Communications in Medicine) images, if available from the PET center, or at least JPG images were sent to the core laboratory (Department of Nuclear Medicine, Kanazawa University) to confirm the image of cardiac accumulation. Because quantitative data representative of standardized uptake value could not be obtained with some retrospective images, quantitative PET analysis was not possible in

Table 2. Baseline Characteristics (at Diagnosis)

	Overall (n=231)	Group G (n=131)	Group NG (n=100)	P value
Age (years)	64±11	64±12	64±10	0.705
Male sex	81 (35)	44 (34)	37 (37)	0.590
Follow-up period (months)	54±31	59±33	48±27	0.005
Comorbidity				
Diabetes	48 (21)	23 (18)	25 (25)	0.176
Hypertension	83 (36)	46 (35)	37 (37)	0.800
Dyslipidemia	94 (41)	50 (38)	44 (44)	0.397
CVD	14 (6)	7 (5)	7 (7)	0.598
Biochemistry				
BNP (pg/mL) (n=201/117/84)*	228±302	205±253	261±358	0.222
NT-proBNP (pg/mL) (n=34/20/14)*	1,149±1,433	921±1,045	1,476±1,851	0.323
eGFR (mL/min/1.73 m^2)	67±22	68±24	66±20	0.532
ACE (IU/L) (n=215/124/91)*	16±9	17±10	14±7	0.013
Lysozyme (μg/mL) (n=89/39/50)*	14±39	21±59	9±5	0.200
Echocardiography findings				
IVS thinning	140 (61)	80 (61)	60 (60)	0.869
Regional wall motion abnormality	166 (72)	85 (65)	81 (81)	0.007
LVEF (%)	47±15	50±16	44±13	0.001
Medication				
ACEI/ARB	125 (54)	65 (50)	60 (60)	0.124
β-blocker	144 (62)	69 (53)	75 (75)	0.001
Diuretics	59 (26)	28 (21)	31 (31)	0.116
Steroid	178 (77)	102 (78)	76 (76)	0.677
Initial dose (mg prednisolon)	28.6±7.8	30.6±6.0	26.8±8.4	0.001
Maintenance dose (mg prednisolon)	8.1±5.9	8.5±6.0	7.6±4.3	0.002
Positive histological findings				
Heart	20 (9)	20 (15)	0	
Lung	47 (20)	47 (36)	0	
Lymph nodes	40 (17)	40 (31)	0	
Skin	35 (15)	35 (27)	0	
Others	8 (3)	8 (6)	0	
ICD/CRT-D implantation	53 (23)	30 (23)	23 (23)	0.985

Unless indicated otherwise, data are given as the mean±SD or n (%). *The number of patients available in the overall/G/NG groups. ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CRT-D, cardiac resynchronization therapy defibrillator; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; Group G, cardiac sarcoidosis with granulomas in ≥1 organs; Group NG, cardiac sarcoidosis without any granulomas; ICD, implantable cardioverter-defibrillator; IVS, interventricular septum; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide.

this study.

Cardiac FDG uptake was evaluated visually by a nuclear cardiologist and/or nuclear medicine specialist in each medical center and classified according to the recommendations of the JCS and JSNC[5,8] as follows: focal, focal on diffuse, diffuse, and no uptake. Focal and focal-on-diffuse uptake were defined as definitive myocardial uptake of FDG.[8,10] The presence or absence of cardiac FDG uptake and the accumulation patterns were subsequently determined by 3 nuclear medicine physicians in the core laboratory.

Histological Examination
Myocardial and/or other tissue biopsies were performed at the discretion of physicians when these examinations were clinically indispensable, possible, and acceptable for a patient. Positive histological findings of sarcoidosis were defined as non-caseating epithelioid granulomas together with monocyte infiltration, whereas findings of fibrosis with a non-

definitive or mild inflammatory cell infiltration were not included as positive findings for CS in the present study.

Statistical Analysis
Continuous variables are presented as the mean±SD when normally distributed. The mean differences between 2 groups and the prevalence of variables were compared using one-way analysis of variance with t-tests and 2×2 contingency table analysis with Pearson statistics, respectively. All tests were two tailed, and a value of P<0.05 was considered statistically significant. Survival curves for MACE and lethal ventricular arrhythmias were plotted using the Kaplan-Meier method, and MACE-free and lethal ventricular arrhythmia-free survival were compared using log-rank tests. In this study, the follow-up start date for patients was the date of ^{18}F-FDG-PET imaging and the follow-up end date was the date of all-cause death, lethal ventricular arrhythmia, appropriate ICD discharge, VAD

Table 3. ^{18}F-FDG PET Findings of the Heart and Extracardiac Organs

	Overall (n=231)	Group G (n=131)	Group NG (n=100)	P value
^{18}F-FDG accumulation patterns				0.663
Focal	146 (63)	80 (61)	66 (66)	
Focal on diffuse	37 (16)	22 (17)	15 (15)	
Diffuse	21 (9)	11 (8)	10 (10)	
None	27 (12)	18 (14)	9 (9)	
Extracardiac ^{18}F-FDG uptake				
Lung	192 (83)	104 (79)	88 (88)	0.084
Lymph node (mediastinum)	146 (63)	101 (77)	45 (45)	0.001
Lymph node (extrathoracic)	81 (35)	55 (42)	26 (26)	0.012
Others	46 (20)	35 (27)	11 (11)	0.001

Unless indicated otherwise, data are given as n (%). FDG, fluorodeoxyglucose; Group G, cardiac sarcoidosis with granulomas in ≥1 organs; Group NG, cardiac sarcoidosis without any granulomas; PET, positron emission tomography.

Table 4. Positive Rate of Diagnostic Criteria for Cardiac Involvement of Sarcoidosis in the JCS 2016 Guidelines[5]

	Overall (n=231)	Group G (n=131)	Group NG (n=100)	P value
AVB or fatal arrhythmia	133 (58)	76 (58)	57 (57)	0.877
Septal thinning or abnormal LV anatomy	140 (61)	80 (61)	60 (60)	0.860
LV dysfunction or focal asynergy	166 (72)	85 (65)	81 (81)	0.007
Positive FDG-PET findings	203 (88)	112 (85)	91 (91)	0.204
Positive LGE on MRI	142 (61)	76 (58)	66 (66)	0.217
Abnormal ECG findings[A]	153 (66)	85 (65)	68 (68)	0.620
Perfusion defect on SPECT	114 (49)	60 (46)	54 (54)	0.217
Monocyte infiltration and moderate/severe myocardial interstitial fibrosis on EMB	46 (19)	21 (16)	25 (25)	0.092

Unless indicated otherwise, data are given as n (%). [A]Abnormal electrocardiogram (ECG) findings included ventricular arrhythmias (non-sustained ventricular tachycardia, multifocal or frequent premature ventricular contractions), bundle branch block, axis deviation, or abnormal Q waves. AVB, atrioventricular block; EMB, endomyocardial biopsy; LGE, late gadolinium enhancement; LV, left ventricle; MRI, magnetic resonance imaging; SPECT, single photon emission computed tomography. Other abbreviations as in Tables 1,3.

implantation, or admission for HF. Univariable Cox regression analysis was used to assess the association between the baseline covariates and MACE. With reference to the univariable analysis, previous studies and clinical experience were used to determine the covariates to be included in the multivariable analysis. All data were analyzed using the SAS statistical package JMP Pro version 17 (SAS Institute, Cary, NC, USA).

Results

Patient Characteristics
The baseline characteristics of all 231 subjects, and for Group G (n=131) and Group NG (n=100) separately, at the time of diagnosis are presented in **Table 2**. Serum angiotensin-converting enzyme activity was greater in Group G than in Group NG (17±10 vs. 14±7 IU/L, respectively; P=0.013). Left ventricular ejection fraction (LVEF) was significantly lower in Group NG than Group G (44±13% vs. 50±16%, respectively; P=0.001). The use of β-blockers was more frequent in Group NG than Group G (75% vs. 53%, respectively; P=0.001). Despite the identical prevalence of corticosteroid treatment between the 2 groups, the initial (30.6±6.0 vs. 26.8±8.4, mg prednisolon;
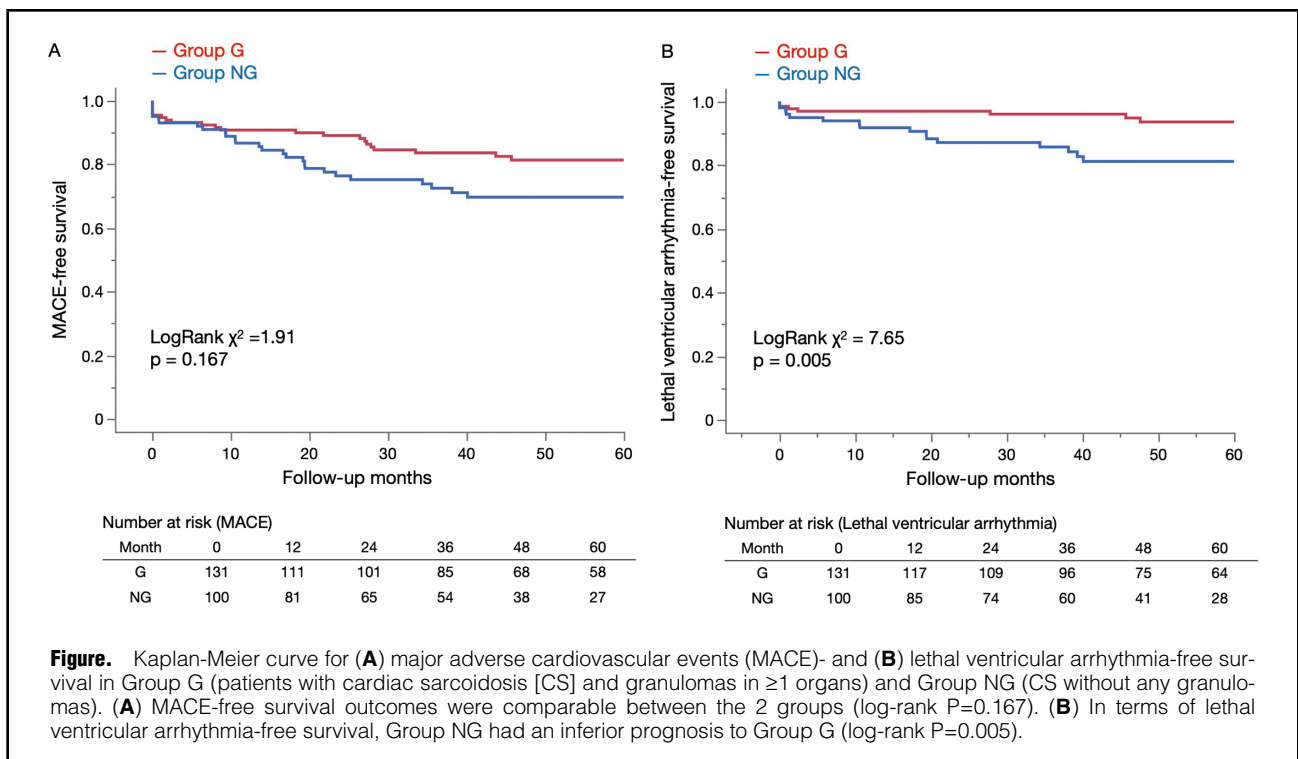
P=0.001) and subsequent maintenance (8.5±6.0 vs. 7.6±4.3, mg prednisolon; P=0.002) doses of the drug were significantly greater in Group G than in Group NG. Non-caseous granulomas in Group G were found in the heart in 20 patients (15%), in the lungs in 47 (36%) patients, in the lymph nodes in 40 (31%) patients, in the skin in 35 (27%) patients, and in other organs, such as the bronchus, muscle, eyes, intestines, liver, and salivary glands, in 8 (6%) patients. However, no significant differences were noted in age, sex, B-type natriuretic peptide (BNP) or N-terminal pro BNP (NT-proBNP) concentrations, estimated glomerular filtration rate, electrocardiographic findings, comorbidities, and the rate of ICD/CRT with defibrillator (CRT-D) implantation between the 2 groups (**Table 2**).

^{18}F-FDG Accumulation Patterns
Following reclassification of CS patients into Groups G and NG based on the presence and absence of non-caseous granulomas, cardiac ^{18}F-FDG accumulation patterns were re-evaluated in the present study (**Table 3**). Groups G and NG had similar ^{18}F-FDG uptake patterns (P=0.663), and uptake in the lungs was similar between the 2 groups (79% vs. 88%, respectively; P=0.084). However, Group G had more frequent ^{18}F-FDG uptake in the mediastinum (77%

Table 5. Patient Outcomes During the Follow-up Period[A]

	Overall (n=231)	Group G (n=131)	Group NG (n=100)	P value
MACE	56 (24)	29 (22)	27 (27)	0.39
All-cause death	13 (6)	5 (4)	8 (8)	0.17
Lethal ventricular arrhythmia	23 (10)	7 (5)	16 (16)	0.01
Appropriate ICD discharge	14 (6)	5 (4)	9 (9)	0.10
VAD implantation	1 (1)	0 (0)	1 (1)	–
Admission for HF	40 (17)	19 (14)	21 (21)	0.19

Unless indicated otherwise, data are given as n (%). [A]The mean (±SD) follow-up period was 54±31 months. HF, heart failure; MACE, major adverse cardiovascular events; VAD, ventricular assist device. Other abbreviations as in Table 2.

Figure. Kaplan-Meier curve for (**A**) major adverse cardiovascular events (MACE)- and (**B**) lethal ventricular arrhythmia-free survival in Group G (patients with cardiac sarcoidosis [CS] and granulomas in ≥1 organs) and Group NG (CS without any granulomas). (**A**) MACE-free survival outcomes were comparable between the 2 groups (log-rank P=0.167). (**B**) In terms of lethal ventricular arrhythmia-free survival, Group NG had an inferior prognosis to Group G (log-rank P=0.005).

vs. 45%; P=0.001), extrathoracic uptake (including in the inguinal, axillary, and cervical lymph nodes (42% vs. 26%; P=0.012), and uptake in other organs (27% vs. 11%; P=0.001) than did Group NG (for details, see **Supplementary Table 2**).

Diagnostic Criteria for Cardiac Involvement

Table 4 compares the manifestations of major and minor criteria for cardiac involvement of sarcoidosis according to the JCS 2016 guidelines. Group NG more frequently had left ventricular (LV) dysfunction, defined as LVEF <50% or focal asynergic wall motion, than Group G (81% vs. 65%; P=0.007). However, there were no significant differences between Groups G and NG in other findings, including high-grade atrioventricular block/fatal ventricular arrhythmia (58% vs. 57%, respectively; P=0.877), septal thinning/abnormal ventricular wall anatomy (61% vs. 60%, respectively; P=0.860), positive cardiac ^{18}F-FDG PET accumulation (85% vs. 91%, respectively; P=0.204), positive delayed gadolinium enhancement on CMR (58% vs.

66%, respectively; P=0.217), abnormal electrocardiogram findings (65% vs. 68%, respectively; P=0.620), positive defects on myocardial perfusion scintigraphy (46% vs. 54%, respectively; P=0.217) and monocyte infiltration and moderate or severe myocardial interstitial fibrosis on endometrial biopsy (EMB; 16% vs. 25%, respectively; P=0.092).

Patient Outcome

Over a 54-month period, MACE was documented in 29 (22%) patients in Group G and in 27 (27%) patients in Group NG (P=0.39; **Table 5**). Group NG more frequently had VT/VF than did Group G (16% vs. 5%; P=0.01). VAD was implanted in one patient in Group NG. Other MACE components tended to be more frequently observed in Group NG than in Group G, although the differences did not reach statistical significance (all-cause death,: 8% vs. 4% [P=0.17]; appropriate ICD therapy, 9% vs. 4% [P=0.10]; admission for HF, 21% vs. 14% [P=0.19]).

Kaplan-Meier curve analysis revealed comparable

Table 6. Predictors of MACE in Patients, as Determined Using a Cox Proportional Hazards Model

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (1-year increase)	0.99	0.96–1.02	0.692	0.99	0.94–1.04	0.711
Female sex (vs. male)	1.45	0.64–3.29	0.351			
Group NG (vs. Group G)	2.37	1.11–5.03	0.021	1.41	0.32–6.10	0.643
Histological CS	3.56	1.27–9.97	0.017	1.95	0.52–7.33	0.331
LVEF (1% increase)	0.96	0.94–0.99	0.010	0.97	0.93–1.01	0.222
High BNP/NT-proBNP[A]	2.48	1.08–5.69	0.023	1.75	0.53–5.73	0.349
eGFR (<60 mL/min/1.73 m²)	1.63	0.74–3.57	0.225			
Positive cardiac ¹⁸F-FDG PET accumulation	1.77	0.42–7.49	0.432			
Positive LGE on cardiac MRI	1.17	0.54–2.53	0.671			

[A]High BNP was defined as BNP >100 pg/mL; high NT-proBNP was defined as NT-proBNP >400 pg/mL. CI, confidence interval; CS, cardiac sarcoidosis; HR, hazard ratio; MACE, major adverse cardiovascular events. Other abbreviations as in Tables 2–4.

MACE-free survival outcomes between Group G and Group NG (log-rank P=0.167; **Figure A**). In terms of MACE components, the Kaplan-Meier curve for lethal arrhythmia indicated that Group NG had an inferior prognosis than Group G (log-rank P=0.005; **Figure B**). The prognostic determinants for MACE in the patients are presented in **Table 6**. Univariable analysis indicated that the significant predictors of MACE were Groups G/NG, histological CS, LVEF, and high BNP or NT-pro BNP. Multivariable analysis incorporated age, Group NG, histological CS, LVEF, and high BNP/NT-proBNP values, but none was a significant independent predictor of MACE.

Discussion

In the present multicenter registry, which retrospectively registered 231 patients with CS, the clinical features and outcomes were compared between CS patients with and without histological evidence of sarcoidosis-related non-caseating epithelioid granuloma, each of whom met the JCS 2016 updated guidelines for CS diagnosis.[5] The results show nearly identical outcomes in both the patient groups. Previous studies have shown that the use of myocardial histology to diagnose CS is linked to a reduced probability of event-free survival.[11,12] However, our findings suggest that when systematically examining the histological presence of granuloma, its occurrence does not seem to be associated with the prognosis of CS, in contrast to evidence from myocardial histology.

The JCS 2016 updated CS guidelines emphasize the diagnostic value of ¹⁸F-FDG-PET and gadolinium-enhanced CMR, both of which were newly selected in the major criteria. Cardiac involvement can be more specifically evaluated using the non-invasive imaging modalities together with systemic assessment of sarcoidosis lesions. The CS guidelines are expected to enable a more precise diagnosis of CS by physicians by reducing the limitations of EMB and the resulting underdiagnosis of this disorder. These concepts are clinically necessary because patients with CS have a worse prognosis and are more likely to have a greater risk of sudden death than patients with idiopathic dilated cardiomyopathy.[13] Recently, Rosenbaum et al[14] defined presumed CS as unexplained sustained VT/VF or high-grade atrioventricular block with ¹⁸F-FDG-PET or CMR findings consistent with CS without any CS histology. What is notable in that study is that none of the sig-

nificant differences were found to be hazardous over time for the primary endpoints of hospitalization-free and overall survival among patient groups defined as presumed CS, probable CS, and definite CS.[14] A real problem in the clinical setting is that EMB cannot necessarily be performed successfully and may yield a false-negative result in patients with suspected CS, and a histological examination is indispensable in establishing the diagnosis of sarcoidosis. Together with the present study, these findings show that the non-invasive diagnostic approach reported here is clinically acceptable and does not necessarily require histological evidence.

In this Registry, patients with CS without histological evidence of sarcoidosis-related granuloma (Group NG) tended to have advanced cardiac injury, as indicated by the greater incidence of LV dysfunction/wall motion abnormality and/or serious arrhythmic events, than patients with CS with histological evidence of sarcoidosis-related granuloma (Group G). This could be explained by patients in Group NG having a more advanced stage of CS, where inflammatory reactions and granuloma formation may have already disappeared to be replaced by degenerative processes. In contrast, sarcoidosis-related granuloma formation was likely to be more easily and frequently detected at an earlier stage of sarcoidosis with active inflammatory reactions. In addition, easy access to histological examination of non-cardiac organs, such as extrathoracic lymph nodes, the liver, or skin, rather than the heart, may have contributed to an early diagnosis of sarcoidosis in Group G patients prior to progression of cardiac injury and functional derangement. Pathophysiologically, the causative antigen is presumed to enter via the lungs at an early stage of the disease, resulting in regional inflammatory reactions in nearby lymph nodes. Previous studies showed that younger patients with sarcoidosis under 40 or 45 years of age had involvement of the lymph nodes and liver more commonly than did older patients, who tended to have involvement of other organs, such as the eyes, heart, muscles, and kidneys.[15] These speculations are supported by the findings reported here, namely that FDG uptake was more frequently observed in extrathoracic lymph nodes in Group G than in Group NG. In the present observational retrospective study, the following selection bias may not be negligible: physicians tended to skip an invasive approach, such as EMB, in diagnosing HF and advanced LV dysfunction and/or serious ventricular arrhythmias, or an

unstable clinical condition particularly when apparent findings consistent with CS were confirmed non-invasively.

Groups NG and G had nearly identical outcomes (MACE) despite significant differences in the prevalence of LV dysfunction. LV dysfunction is the critical predictor of survival in patients with CS, as reported previously in 2001 and 2005.[16,17] However, outcomes of contemporary CS patients may have become better, affected by recent advances in pharmacological and non-pharmacological treatments, including cardiac electronic devices (ICD/ CRT-D), against HF and lethal arrhythmias. The more frequent use of β-blocker treatment in Group NG may have contributed to improving outcomes to the same level as in Group G. Because corticosteroid treatment possibly improves the prognosis of patients with CS,[16,18,19] the common use of the drug in both Group NG (76%) and Group G (78%) also modified the outcomes in the present study. What the nearly equivalent outcomes in both groups indicate is not that histologic evidence is not prognostically relevant, but that patients with non-invasively diagnosed CS are at an identical high risk of MACE and require appropriate clinical observation and therapeutic intervention for better clinical outcomes, independent of the absence or presence of histologically proven sarcoidosis granuloma. Similarly, the diagnosis of cardiac transthyretin/ immunogloblin light chain amyloidosis was recently reported using advanced multimodality imaging without histological confirmation.[20–22] These observations indicate the importance of appropriate identification of CS without delayed treatment, but not the unnecessity of EMB, even if a histological diagnostic approach cannot be successfully performed.

Study Limitations

This study has several limitations. To begin with, we acknowledge the presence of selection bias because the study cohort only comprises patients who underwent FDG-PET imaging. Regrettably, this bias cannot be avoided because our study was a subanalysis of the J-CASP Study that focused specifically on assessing the clinical efficacy of a non-invasive diagnostic approach with FDG-PET.

Some data were unavailable because of the retrospective nature of the study. Specifically, only the history of advanced atrioventricular block or fatal ventricular arrhythmia (sustained VT, VF) as a diagnostic criterion from the JCS guidelines was recorded in this investigation, and no detailed medical history of arrhythmia was documented. In addition, myocardial and other tissue biopsies were performed at the discretion of the attending physician, leading to the registration of tissues with granulomas, but not of tissues without granulomas. Consequently, data pertaining to the specific tissues (including the myocardium) on which biopsies were attempted were not recorded. As a result, patients with severe CS who could not afford a comprehensive examination would likely be categorized in Group NG, which does not necessarily confirm granuloma-negative results in all tissues where sarcoidosis may invade.

In this Registry, there was a limited number of cardiac events (56 MACEs) documented in the 231 patients, which made the appropriate multivariable analysis difficult.

Because ^{18}F-FDG itself accumulates non-specifically in inflammatory lesions, other possible degenerative cardiomyopathies, such as dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, chronic myocarditis,

and giant cell myocarditis, that cause positive cardiac ^{18}F-FDG uptake[23,24] cannot be completely ruled out without histological evidence.

In the present study, isolated CS, which was defined as a definitive sarcoidosis lesion located only in the heart and not in any other organ, was diagnosed in 10 patients, with all 10 of these patients being in Group NG. Precisely diagnosing isolated CS and differentiating it from other secondary cardiomyopathies without histology[23,25] remains difficult. The updated JCS guidelines may contribute to the diagnosis of isolated CS by combining clinical information with typical and definitive findings of cardiac involvement identified using ^{18}F-FDG-PET and CMR. Nevertheless, further studies are warranted to establish the clinical accuracy of non-invasive, non-biopsy diagnosis and to reveal outcomes in patients with isolated CS.

Conclusions

Overall, MACEs were nearly identical, regardless of different clinical manifestations, between patients with CS with and without histologically proven sarcoidosis granulomas in the J-CASP multicenter registry. LV dysfunction and lethal ventricular arrhythmias are more likely in CS patients without than with histology-proven sarcoidosis granulomas. These findings demonstrate not only the importance of non-invasive diagnosis of CS based on the clinical criteria together with definitive cardiac ^{18}F-FDG uptake, but also the need to establish an effective management strategy in patients with clinical CS independent of histological evidence.

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Supplementary Files

Please find supplementary file(s);
https://doi.org/10.1253/circrep.CR-23-0031