JACC: ADVANCES VOL. 3, NO. 8, 2024

ORIGINAL RESEARCH

Association Between Right Bundle Branch Block and Ventricular Arrhythmia in Patients With Cardiac Sarcoidosis

Yu Yamada, MD,[a] Kimi Sato, MD, PhD,[a] Masayoshi Yamamoto, MD, PhD,[a] Takeru Nabeta, MD, PhD,[b] Yoshihisa Naruse, MD, PhD,[c] Tatsunori Taniguchi, MD, PhD,[d] Takeshi Kitai, MD, PhD,[e,f] Kenji Yoshioka, MD, PhD,[g] Hidekazu Tanaka, MD, PhD,[h] Takahiro Okumura, MD, PhD,[i] Yuichi Baba, MD, PhD,[j] Yudai Fujimoto, MD,[k] Yuya Matsue, MD, PhD,[k] Yuki Komatsu, MD, PhD,[a] Akihiko Nogami, MD, PhD,[a] Tomoko Ishizu, MD, PhD[a]

ABSTRACT

BACKGROUND Ventricular arrhythmia (VA) is a life-threatening condition associated with cardiac sarcoidosis (CS). Right bundle branch block (RBBB) is a common conduction disorder in CS; however, its association with VA remains unknown.

OBJECTIVES This study aimed to investigate the relationship between RBBB and VA in patients with CS.

METHODS This was a post hoc analysis of ILLUMINATE-CS (Illustration of the Management and Prognosis of Japanese Patients with Cardiac Sarcoidosis), a multicenter, retrospective, and observational study that evaluated the clinical characteristics and prognosis of CS. Eligible patients were divided into two groups based on the presence or absence of RBBB at the time of diagnosis. The primary outcome was serious ventricular arrhythmia events (SVAEs), defined as a combination of sudden cardiac death and documented ventricular fibrillation, sustained ventricular tachycardia, or appropriate implantable cardioverter-defibrillator therapy.

RESULTS Overall, 312 patients were studied, with 155 (49.7%) patients presenting with RBBB (RBBB group). Patients in the RBBB group had a higher prevalence of basal interventricular septum (IVS) thinning and prominent late gadolinium enhancement in the basal IVS on cardiac magnetic resonance imaging than those in the non-RBBB group. During a median follow-up of 3.0 years (IQR: 1.6-6.0 years), 66 patients experienced SVAE. In multivariable Cox regression analysis, the RBBB group was independently associated with a higher incidence of SVAEs (HR: 1.93 [95% CI: 1.14-3.28]; $P = 0.015$).

CONCLUSIONS In patients with CS, RBBB was an independent predictor of SVAEs, which might reflect the specific scar distribution that is predominant in the IVS. (JACC Adv 2024;3:101105) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Cardiology, Institute of Medicine; University of Tsukuba, Tsukuba, Japan; [b]Department of Cardiovascular Medicine, Kitasato University School of Medicine, Sagamihara, Japan; [c]Division of Cardiology, Internal Medicine III, Hamamatsu University School of Medicine, Hamamatsu, Japan; [d]Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, Japan; [e]Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan; [f]Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital, Kobe, Japan; [g]Department of Cardiology, Kameda Medical Center, Kamogawa, Japan; [h]Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan; [i]Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [j]Department of Cardiology and Geriatrics, Kochi Medical School, Kochi University, Nankoku, Japan; and the [k]Department of Cardiovascular Biology and Medicine, Juntendo University Graduate School of Medicine, Hongo, Japan.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received December 12, 2023; revised manuscript received May 17, 2024, accepted June 5, 2024.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.101105

ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

CMR = cardiac magnetic resonance

CRT-D = cardiac resynchronization therapy-defibrillator

CS = cardiac sarcoidosis

FDG-PET = 18F-fluorodeoxyglucose positron emission tomography

ICD = implantable cardioverter-defibrillator

IVS = interventricular septum

JCS = Japanese Circulation Society

LBBB = left bundle branch block

LGE = late gadolinium enhancement

LVEF = left ventricular ejection fraction

NSVT = non sustained VT

RBBB = right bundle branch block

SCD = sudden cardiac death

SVAE = serious ventricular arrhythmia event

VA = ventricular arrhythmia

VF = ventricular fibrillation

VT = ventricular tachycardia

Cardiac sarcoidosis (CS) is a complex disease characterized by diverse cardiac pathologies arising from inflammation and fibrosis, accompanied by the infiltration of noncaseating granulomas.[1] The principal clinical manifestations of CS are conduction disorders and ventricular arrhythmias (VA), leading to sudden death and heart failure.[2] VA is the second most common manifestation of CS after atrioventricular block and is a life-threatening event with a significant impact on mortality.[3,4] VA is thought to arise from reentrant pathways and increased automaticity due to inflammatory reactions and scar formation associated with granulomas.[5]

Right bundle branch block (RBBB) is a frequently observed electrocardiographic abnormality from the early stages of CS.[2] A recent study demonstrated that RBBB with a large surface area of the R' wave and PR prolongation might reflect disease-specific scar patterns, distinguishing CS presenting with VA from other forms of cardiomyopathy.[6] Considering that myocardial scarring represented by late gadolinium enhancement (LGE) in cardiac magnetic resonance (CMR) imaging has been demonstrated in patients with CS who developed VA,[7,8] the presence of RBBB might be associated with scarring and/or morphological abnormalities of ventricles. We previously reported that patients with CS who presented with VA were associated with a large cardiac involvement on CMR and RBBB in our single-center cohort.[9] Therefore, we hypothesized that RBBB at the time of CS diagnosis is associated with cardiac morphological changes in patients with CS and the occurrence of VA and sought to confirm this hypothesis in a different cohort.

This study aimed to assess the association between the RBBB and VA occurrence during the follow-up period and to evaluate the characteristics of patients with CS presenting with an RBBB, including scar formation patterns on multimodality imaging.

METHODS

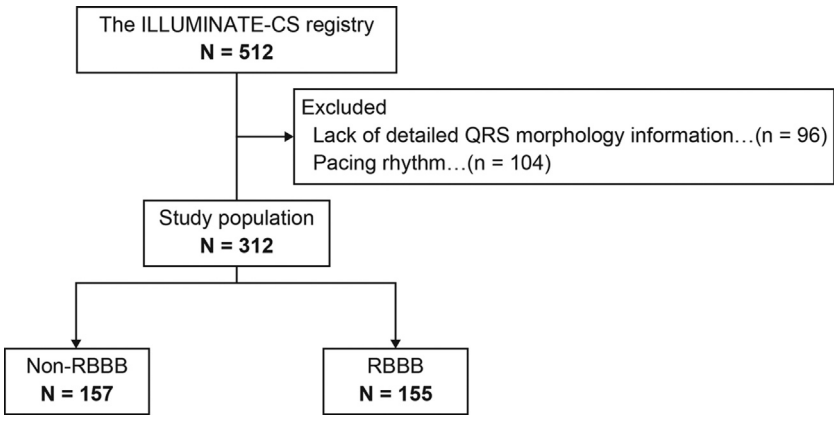
STUDY DESIGN AND POPULATION. This study was conducted as a post hoc analysis of the ILLUMINATE-CS (Illustration of the Management and Prognosis of Japanese Patients with Cardiac Sarcoidosis). The details of the ILLUMINATE-CS have been previously described.[10] Briefly, patients with CS who were first diagnosed at 33 hospitals between 2001 and 2017 were included in the registry. Patients who refused to enroll after being informed of their inclusion in the registry were excluded. The diagnosis of CS was based on either the 2016 Japanese Circulation Society (JCS) criteria or the 2014 Heart Rhythm Society consensus statement.[4,11]

A flow diagram of the patient selection process is shown in **Figure 1**. From the 512 patients enrolled in the ILLUMINATE-CS, cases lacking detailed QRS morphology information and cases with pacing rhythm at diagnosis were excluded. We divided the patients into 2 groups (non-RBBB and RBBB groups) according to the presence of RBBB on their electrocardiogram and compared their characteristics and clinical outcomes. We defined RBBB as the presence of an RSR' pattern (V_1 or V_2) and a wide-slurred S-wave in the lateral leads (I and V_6). Patients with an RBBB pattern with QRS duration ≥120 ms were diagnosed with complete RBBB, whereas those with an RBBB pattern with QRS duration <120 ms were diagnosed with incomplete RBBB.[12] In this study, we considered both complete and incomplete RBBB as the RBBB group.

The local ethics committee of each participating institution approved the study protocol and followed the guidelines of the Declaration of Helsinki. Data were deidentified, and the requirement for informed consent was waived.

DATA COLLECTION AND OUTCOMES. Baseline characteristics, including age, sex, medical history, medications, blood test data, and cardiovascular imaging findings, were obtained during the initial diagnosis of CS. Baseline was defined as the point at which a patient was diagnosed with CS by meeting the criteria according to the JCS or Heart Rhythm Society. The presence of atrioventricular block was assessed, focusing on high-grade or third-degree atrioventricular block. High-grade atrioventricular block was defined as two or more consecutive P waves lacking consistent ventricular conduction but showing evidence of some atrioventricular conduction.[13] Echocardiographic measurements were performed according to the guidelines.[14] The left ventricular ejection fraction (LVEF) was measured using the biplane disk summation method. Echocardiographic abnormalities, including basal interventricular septum (IVS) thinning and presence of ventricular aneurysm, were identified through reports from experts at each center. Basal IVS thinning on

FIGURE 1 Flow Diagram of Patient Selection



RBBB = right bundle branch block.

echocardiography was defined as a basal IVS thickness ≤4 mm or basal IVS/IVS ratio ≤0.6.[4,15] Myocardial accumulation findings on ^{67}Ga scintigraphy and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), and LGE on CMR imaging were determined by certified imaging specialist at each institution according to current guidelines.[16] The American Heart Association 17-segment model was used to assess the distribution of myocardium segments showing accumulation/hyperenhancement on ^{67}Ga scintigraphy, FDG-PET, and LGE on CMR imaging.[17] The transition of echocardiographic parameters was investigated in patients who were examined at both baseline and final follow-up.

The primary end point was serious ventricular arrhythmia events (SVAEs), defined as a combination of sudden cardiac death (SCD) and documented ventricular fibrillation (VF), sustained ventricular tachycardia (VT) lasting for >30 s, or appropriate implantable cardioverter-defibrillator (ICD) therapy. Additionally, the secondary end points were all-cause mortality and heart failure hospitalization. All outcome data were retrospectively obtained from medical records.

STATISTICAL ANALYSIS. Continuous variables are expressed as median (IQR). Categorical data are presented as absolute numbers and percentages. Comparisons between 2 or more groups were made using Mann-Whitney U test, Kruskal-Wallis test, and chi-squared test, as appropriate. Kaplan-Meier curves were generated to compare the cumulative incidence of SVAEs, all-cause mortality, and heart failure hospitalization between the groups using a log-rank test. Cox regression analysis was used to assess the potential variables associated with the occurrence of SVAEs. Univariable Cox regression analysis was used to identify variables potentially associated with SVAEs. The assumptions of proportional hazards were assessed using Schoenfeld residuals. Variables known as poor prognostic factors for CS were included in the multivariable analysis. HRs and corresponding 95% CIs were calculated. First, we performed a multivariable analysis on a data set from which data containing missing values were excluded. Next, to account for missing covariate data, multiple imputations were performed before multivariable analyses, and 50 data sets were generated using a chained-equation procedure implemented in the "mice" package, version 3.15.0 of R.[18,19] Accounting death other than SCD and all-cause death as competing risks for SVAEs and hospitalization for heart failure, respectively, competing risk analysis was conducted using the "cmprsk" package (version 2.2-11) of R.[20,21] Regarding SVAEs, we performed competing risk regression analysis using the Fine-Gray proportional subhazard model and subdistributed hazard ratios (sHRs).[22] We applied the Gray tests to multivariable model analyses of the presence of RBBB, isolated CS, history of VT/VF, and LVEF as potential covariates. The cumulative incidence of SVAEs and hospitalization for heart failure, accounting for competing risks, was visualized in a plot. To assess the transition of echocardiographic parameters over time and the possible impact of RBBB, we applied a mixed effect model under the assumptions of data missing at random. The model

was constructed using echocardiographic parameters (LVEF, left ventricular diastolic diameter, and left atrial diameter) as dependent variables, QRS morphology (RBBB or non-RBBB), time of echocardiography, and an interaction term for QRS morphology×time as fixed variables, and individual patients treated as random effects. The model was applied with unstructured covariance for random effects. The assumptions of homoscedasticity and normality of error term or random effect were visually assessed. All statistical analyses were performed using R, version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). A value of $P < 0.05$ was considered statistically significant.

RESULTS

CLINICAL AND IMAGING CHARACTERISTICS IN PATIENTS WITH RBBB. Among the 312 patients (age 61.1 ± 11.0 years, 32.1% male) in this analysis, 155 (49.7%) had RBBB at diagnosis (RBBB group), including 13 with incomplete RBBB, while the remaining 157 (50.3%) constituted the non-RBBB group. Among all patients, 205 (65.7%) had histological confirmation of sarcoidosis, and 33 (22.3%) were diagnosed with CS via positive endomyocardial biopsy. Isolated CS was diagnosed in 60 patients (19.2%), including 11 patients (3.5%) with histological confirmation. Notably, at baseline, 15 patients (4.8%) had an ICD/cardiac resynchronization therapy-defibrillator (CRT-D), and 36 (11.5%) had a permanent pacemaker. Moreover, throughout the follow-up period, 61 patients (19.6%) underwent ICD/CRT-D implantation, and 27 patients (8.7%) received permanent pacemakers. Consequently, a total of 76 patients (24.3%) were treated with ICD/CRT-D, and 63 patients (20.1%) were treated with pacemaker. **Table 1** presents the baseline patient characteristics. The patients in the RBBB group were older and had a higher proportion of history of non sustained VT (NSVT) than those in the non-RBBB group. Moreover, a history of VT/VF and ICD/CRT-D implantation was tended to be more prevalent in the RBBB group. The proportion of patients with NYHA functional class III and IV and the levels of B-type natriuretic peptide (BNP) were similar between the two groups. The electrocardiographic evaluation showed that 18 (11.5%) patients in the non-RBBB group had a left bundle branch block (LBBB), while a left anterior fascicular block was significantly more prevalent in the RBBB group than in the non-RBBB group. Echocardiographic data showed that basal IVS thinning was more prevalent in the RBBB group than in the non-RBBB group, whereas the LVEF at baseline was similar between the two groups. The proportions of patients with significant accumulation of ^{67}Ga scintigraphy or FDG-PET and LGE on CMR imaging were similar between the two groups. When we assessed the distribution of LGE on CMR imaging in 17 myocardial segments, the RBBB group showed a significantly higher prevalence of LGE in the basal anteroseptal and basal anterior lesions than the non-RBBB group (**Figure 2**), which is consistent with a higher incidence of thinning at the base of the IVS on echocardiography (**Table 1**). The distribution of FDG-PET accumulation was more prevalent in the apical anterior lesions in the RBBB group than in the non-RBBB group, indicating a larger extent of active lesions. The non-RBBB group showed a higher prevalence of FDG accumulation in basal to mid-inferolateral lesions than the RBBB group.

CLINICAL OUTCOME IN PATIENTS WITH RBBB. During a median follow-up of 3.0 (IQR: 1.6-6.0) years, 66 patients experienced SVAEs as a primary endpoint. Additionally, 29 patients experienced all-cause mortality, and 26 were hospitalized owing to heart failure. Among the 66 cases who developed SVAEs, SCD occurred in 9 patients (13.6%), sustained VT in 49 patients (74.2%), VF in 4 patients (6.1%), and appropriate ICD therapy in 4 patients (6.1%). Notably, 1 patient who had sustained VT eventually developed SCD. Among 29 patients who experienced all-cause death, 20 patients (69%) had cardiovascular deaths (including 10 [34.5%] SCD, 8 [27.6%] heart failure, 1 [3.4%] stroke, and 1 [2.4%] periprocedural death) and 9 (31.0%) had noncardiovascular deaths (sepsis in 2 patients, unknown causes in 2 patients, and renal failure, gastric bleeding, multi organ failure, choking, and unspecified natural causes in 1 patient each). Survival analysis showed that the RBBB group was significantly associated with a higher incidence of SVAEs (median survival time: non-RBBB group: 14.3 years [95% CI: 14.3-not reached] vs RBBB group: 12.4 years [95% CI: 7.4-not reached], log-rank $P = 0.005$) (**Figure 3A**). To mitigate the impact of a history of arrhythmic events, we repeated the log-rank test in the subgroup of patients without history of VT/VF or ICD/CRT-D implantation. In this subgroup, RBBB was significantly associated with a higher incidence of SVAEs (log-rank $P = 0.03$) (**Figure 3B**). The association between RBBB and SVAEs remained significant even after excluding patients with a history of NSVT (log-rank $P = 0.04$) (**Figure 3C**). Mortality rate and heart failure rehospitalization incidence were similar between the two groups

TABLE 1 Baseline Characteristics (N = 312)

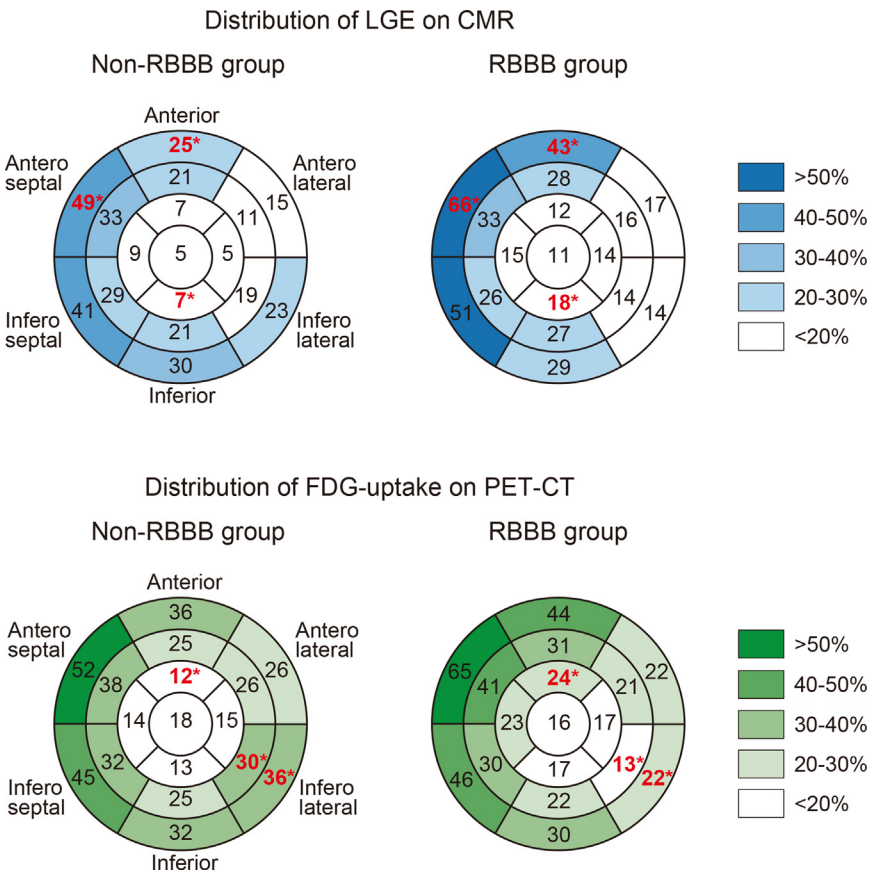
	Non-RBBB Group n = 157 (50.3%)	RBBB Group n = 155 (49.7%)	*P* Value	Missing (%)
Age (y)	61.0 (52.0-68.0)	63.5 (55.2-69.0)	0.012	0.3
Male	43 (27.4)	57 (36.8)	0.098	0
Extracardiac involvement				
Eye	49 (31.8)	47 (30.9)	0.963	1.9
Lung	92 (59.0)	96 (62.7)	0.574	1.0
Skin	43 (28.1)	23 (15.4)	0.012	3.2
Isolated CS	34 (21.7)	26 (16.8)	0.342	0
Past medical history				
Hypertension	57 (37.5)	49 (34.0)	0.616	5.1
Diabetes	41 (27.2)	40 (28.0)	0.979	5.8
HF admission	27 (17.8)	19 (13.0)	0.33	4.5
Pacemaker implantation	21 (13.6)	15 (10.2)	0.46	3.5
ICD/CRT-D implantation	6 (3.9)	9 (6.1)	0.551	4.2
NYHA functional class III/IV	27 (17.5)	16 (10.8)	0.132	3.2
Arrhythmias and conduction disorders				
VT/VF	15 (9.8)	23 (16.1)	0.15	5.1
NSVT	22 (14.5)	37 (26.4)	0.017	6.4
High-grade or third-degree AVB	29 (19.1)	29 (19.3)	>0.999	3.6
AF	15 (9.9)	11 (7.7)	0.638	5.8
Creatinine (mg/dL)	0.7 (0.6-0.9)	0.8 (0.7-0.9)	0.253	2.9
BNP (pg/mL)	104.4 (41.5-230.1)	144.5 (57.4-358.1)	0.096	26.3
Electrocardiogram				
PQ interval (ms)	177.5 (154.5-208.0)	184.0 (158.0-224.0)	0.213	19.2
QRS duration (ms)	106.0 (92.0-120.0)	142.0 (134.0-158.2)	<0.001	2.9
LBBB	18 (11.5)	0 (0)	<0.001	4.2
LAFB	14 (8.9)	29 (20.3)	0.008	3.8
LPFB	0 (0)	5 (3.5)	0.055	4.2
Echocardiographic data				
LVEF (%)	53.5 (38.9-63.2)	52.0 (38.0-63.0)	0.76	2.9
Basal IVS thinning	47 (31.5)	73 (48.7)	0.004	4.2
LV aneurysm	19 (12.8)	15 (10.0)	0.556	4.5
^{67}Ga scintigraphy uptake	35 (38.5)	36 (45.6)	0.435	45.5
LGE on CMR	99 (92.5)	102 (91.1)	0.885	29.8
FDG-PET uptake	85 (93.4)	86 (94.5)	>0.999	41.7
Medication at baseline				
ACE I/ARB	77 (49.0)	75 (50.0)	0.958	1.6
Beta-blocker	56 (35.7)	49 (32.9)	0.695	1.9
Class I antiarrhythmic drug	1 (0.6)	5 (3.4)	0.193	2.6
Amiodaron	11 (7.0)	16 (10.7)	0.343	1.9
Steroid use after diagnosis	136 (86.6)	136 (87.7)	0.9	0

Values are median (IQR) or n (%).

ACE I = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; AVB = atrioventricular block; BNP = brain natriuretic peptide; CMR = cardiac magnetic resonance; CRT-D = cardiac resynchronization therapy defibrillator; CS = cardiac sarcoidosis; FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography; HF = heart failure; ICD = implantable cardioverter-defibrillator; IVS = interventricular septum; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LGE = late gadolinium enhancement; LPFB = left posterior fascicular block; LV = left ventricular; LVEF = left ventricular ejection fraction; NSVT = non-sustained ventricular tachycardia; RBBB = right bundle branch block; VF = ventricular fibrillation; VT = ventricular tachycardia.

(Figures 4A and 4B). Furthermore, 19 patients newly developed high-grade or third-degree atrioventricular block, and there was no significant difference in the incidence between the 2 groups (non-RBBB group 6 [3.9%] vs RBBB group 13 [9.0%]; $P = 0.122$). In univariable Cox regression analysis, RBBB was significantly associated with an increased risk of SVAEs (HR: 2.02 [95% CI: 1.22-3.33]; $P = 0.006$) (Table 2). Isolated CS, a history of VT/VF, a history of ICD/CRT-D implantation, higher log-transformed BNP levels, and lower LVEF were also associated with an increased risk of SVAEs. In a multivariable Cox

FIGURE 2 Distribution of LGE on CMR Imaging and Accumulation of FDG-PET



The proportion of LGE on CMR imaging and accumulation on FDG-PET in each of the 17 segments of the left ventricular myocardium. The RBBB group exhibited a higher prevalence of LGE in the basal anterior, basal anteroseptal, and apical inferior walls of the left ventricle. Furthermore, FDG-PET accumulation was higher in the apical anterior wall of the RBBB group, whereas the non-RBBB group displayed a higher prevalence of inferolateral lesions. Areas with significant differences are highlighted in red (*$P < 0.05$). CMR = cardiac magnetic resonance; CT = computed tomography; FDG = ^{18}F-fluorodeoxyglucose; LGE = late gadolinium enhancement; PET = positron emission tomography; other abbreviation as in **Figure 1**.

regression analysis adjusting for these confounders, RBBB was independently associated with a higher incidence of SVAEs in the Cox regression analysis (HR: 2.28 [95% CI: 1.23-4.24]; $P = 0.009$) (Supplemental Table 1). Considering missing values and analyzing a multiple imputed data set, RBBB remained independently associated with a higher incidence of SVAEs (HR: 1.93 [95% CI: 1.14-3.28]; $P = 0.015$), a history of VT/VF (HR: 2.90 [95% CI: 1.54-5.46]; $P = 0.001$), and lower LVEF (HR: 0.98 [95% CI: 0.96-1.00]; $P = 0.040$) (**Table 2**).

Given the possibility of competing risks between SVAEs and death other than SCD, we performed competing risk regression analyses. In a multivariable model with RBBB, isolated CS, history of VT/VF, and LVEF as potential covariates, the presence of RBBB was independently associated with a higher risk of SVAEs (sHR: 2.21 [95% CI: 1.28-3.80]; $P = 0.0045$). Cumulative incidence curves constructed using competing risk assumptions showed that the presence of RBBB was associated with a higher risk of SVAEs (log-rank, $P = 0.005$) (Supplemental Figure 1A). Cumulative incidence curves for hospitalization for heart failure were similar between the two groups, accounting for all-cause death as a competing risk (Supplemental Figure 1B).

Furthermore, we repeated the analysis to assess the impact of bundle branch block types other than

RBBB after subdividing the non-RBBB group into LBBB (n = 18) and non-BBB groups (n = 139). The RBBB group showed a higher prevalence of NSVT and basal IVS thinning than the LBBB and non-BBB groups (Supplemental Table 2). SVAEs were observed in 21, 42, and three patients in the non-BBB, RBBB, and LBBB groups, respectively. In the non-BBB, RBBB, and LBBB groups, 12, 15, and 2 patients, respectively, experienced all-cause death, whereas 13, 12, and one patient, respectively, were hospitalized for heart failure. In addition, RBBB was significantly associated with SVAEs compared to non-RBBB ($P = 0.015$), and this association remained significant when incomplete RBBB was excluded from the RBBB group ($P = 0.017$) (Supplemental Figure 2). In the multivariable Cox proportional hazard model, RBBB was independently associated with increased risk of SVAEs (HR: 2.03 [95% CI: 1.17-3.52]; $P = 0.013$), while the LBBB group was not associated with SVAEs (Supplemental Table 3). Regarding secondary outcomes, the LBBB and non-BBB groups were not associated with all-cause mortality and heart failure rehospitalization (Supplemental Figure 3).

The changes in echocardiographic parameters are shown in Supplemental Figure 4. Based on the mixed effects model, no significant improvement existed in the LVEF, left ventricular diastolic diameter, or left atrial diameter during follow-up. The changes in these left heart parameters during follow-up were similar between the RBBB and non-RBBB groups.

DISCUSSION

In this study, using the largest cohort of patients with CS, we observed that RBBB at the time of diagnosis was independently associated with an increased risk of SVAEs (**Central Illustration**). Furthermore, patients with CS presenting with an RBBB had a higher prevalence of basal IVS thinning on echocardiography and LGE on CMR imaging in ventricular basal septum lesions. However, the presence of RBBB was not associated with all-cause mortality and heart failure hospitalization. Moreover, the proportion of patients with a history of VT/VF tended to be higher in the RBBB group at baseline, indicating that the RBBB morphology may reflect specific scar formation, predominantly in the ventricular septum, which increases the risk of VA.

ASSOCIATION BETWEEN RBBB AND VA IN CS. To the best of our knowledge, this is the first report to show an association between the RBBB and SVAEs in patients with CS. Previous studies have reported the presence of RBBB in approximately 12 to 66% of patients with CS[4]; hence, it is reasonable that RBBB

FIGURE 3 Kaplan-Meier Curves for Serious Ventricular Arrhythmic Events

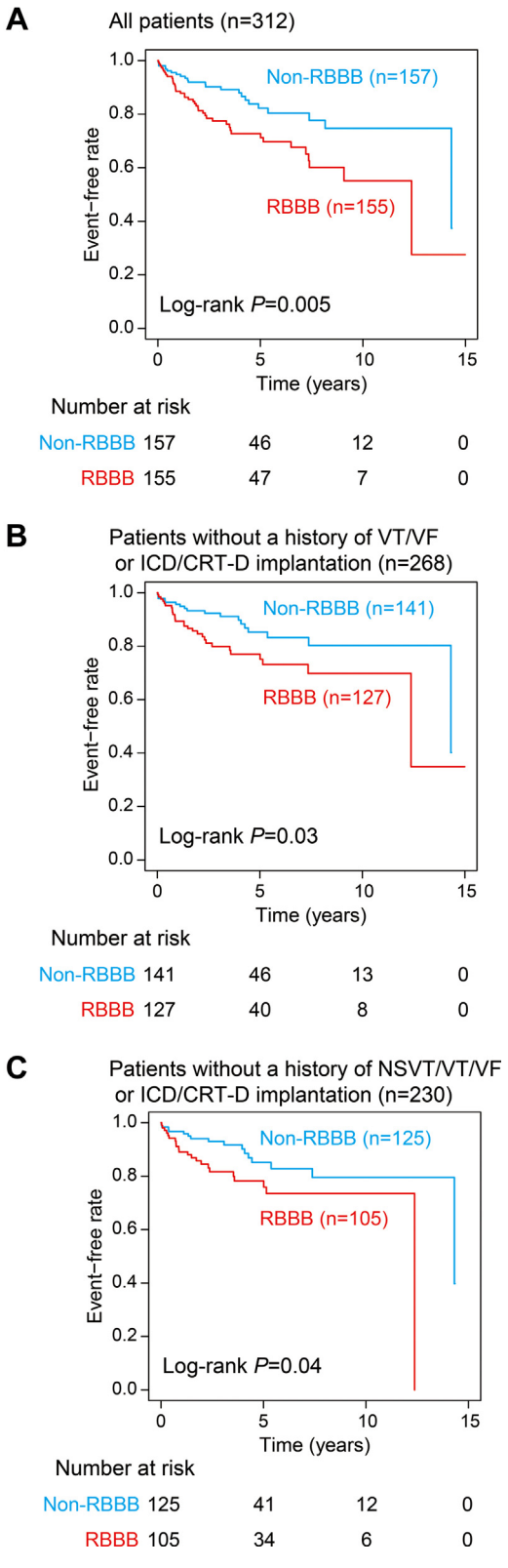


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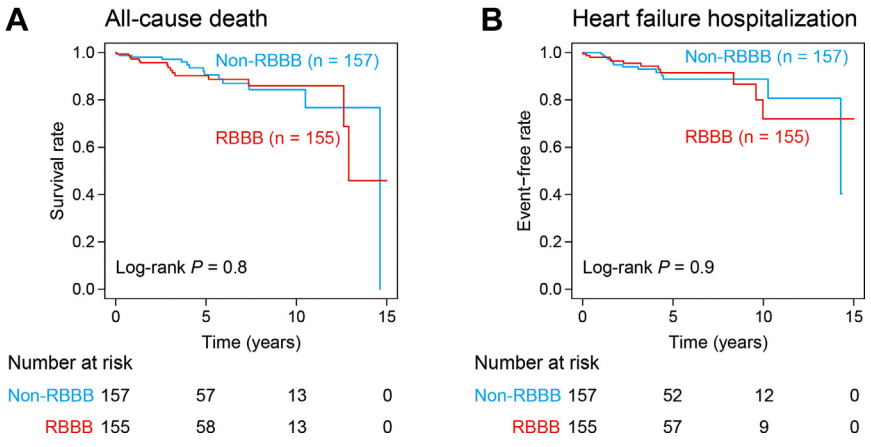
FIGURE 4 Kaplan-Meier Curves for All-Cause Death and Heart Failure Hospitalization



Kaplan–Meier curves demonstrated that the presence of an RBBB at diagnosis did not alter the risk of all-cause death ($P = 0.80$) (A or hospitalization for heart failure ($P = 0.90$) (B. Abbreviation as in Figure 1.

was present in about half of all patients in the present study. Although patients with RBBB were slightly older than those without RBBB in the present cohort, no significant differences existed in BNP levels or LVEF, both of which have been shown to correlate with prognosis in patients with CS.[23,24] Additionally, no significant differences existed in LVEF or left ventricular diastolic diameter owing to the presence of RBBB during follow-up. These findings indicate that the presence of RBBB does not reflect the degree of overall cardiac function or heart failure, which is consistent with the fact that RBBB was not associated with the secondary outcomes of the present study, including all-cause mortality or heart failure hospitalization. Narasimhan et al reported that RBBB was associated with an increased risk of sudden cardiac arrest in patients with systemic sarcoidosis using the U.S. national database;[25] their findings were consistent among younger patients with normal left ventricular function. Although, this was conducted in systemic sarcoidosis rather than CS, their findings align with ours, indicating the clinical relevance of conduction abnormalities as prognostic markers in patients with CS.

A few studies, which have thoroughly analyzed electrocardiographic abnormalities and the prognosis of CS, reported that a fragmented QRS was associated with VA events, including NSVT and VT, in patients with CS.[26,27] Interestingly, a higher prevalence of RBBB was reported in those with a fragmented QRS.[27] Recently, Hoogendoorn et al reported that in patients undergoing catheter ablation for VT, a marked prolongation of the R'-wave and PR interval in V_1-V_3 is specific for patients with CS, and that these markers are useful in differentiating from arrhythmogenic right ventricular cardiomyopathy.[6] In the same report, any R' waves in V_1-V_3 leads were also significantly more common in CS, suggesting that RBBB may reflect CS-specific scar formation, which is distinct from arrhythmogenic right ventricular cardiomyopathy. Furthermore, in an electrophysiological study of patients with CS presenting with VT, scarring was widely observed in both ventricles and was most frequent in the IVS, followed by the anterior wall in the left ventricle.[28] In the present study, the RBBB group demonstrated a higher prevalence of anteroseptal and anterior

FIGURE 3 Continued

Kaplan–Meier curves show the event-free rate of SVAEs according to the presence of RBBB at diagnosis. Individuals with an RBBB had a significantly higher risk of developing SVAEs than those without an RBBB ($P = 0.005$) (A). The association between RBBB and SVAEs was also significant in the subgroup of patients without a history of VT/VF or ICD/CRT-D implantation ($P = 0.03$) (B). The association between RBBB and SVAEs remained significant even after excluding patients with a history of NSVT from this subgroup ($P = 0.04$, C). CRT-D = cardiac resynchronization therapy defibrillator; ICD = implantable cardioverter-defibrillator; NSVT = non sustained ventricular tachycardia; SVAE = serious ventricular arrhythmic event; VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviation as in Figure 1.

wall scarring detected using CMR, which was consistent with these previous electrophysiological findings. Therefore, the RBBB might be a phenotype of the arrhythmogenic substrate in patients with CS, independent of the overall cardiac function.

DISTRIBUTION OF SCAR FORMATION IN PATIENTS WHO PRESENTED WITH RBBB. In this study, basal IVS thinning and LGE in the IVS were more prevalent in patients with CS and RBBB. Several previous reports have demonstrated that CS involvement detected using LGE on CMR imaging is more frequently observed in the IVS and indicates poor prognosis, including VA.[29-31] In addition, IVS thinning detected using echocardiography has been reported to be associated with symptomatic arrhythmia and heart failure rather than atrioventricular block.[15,32] Generally, the Purkinje network, which passes through the IVS, plays a crucial role in VA development.[33] Hence, the destruction of Purkinje fibers by granulomatous infiltration is considered a major contributor to VA in CS.[34] Thus, in patients with RBBB, IVS thinning may represent an advanced form of IVS involvement in CS and demolition of the Purkinje network. However, the RBBB may be associated with abnormal right ventricular systolic function apart from IVS morphology,[35] and future studies should include right ventricular morphology and function in patients with CS.

CLINICAL IMPLICATION. Although RBBB is generally considered an insignificant electrocardiogram finding, this study is the first to provide evidence of an association between RBBB and the occurrence of SVAEs. The RBBB group was also characterized by significant scar formation in the basal ventricular septum on echocardiography and CMR imaging. These results emphasize the likelihood of VAs necessitating ICD implantation in patients with CS who present with RBBB, indicating the importance of careful monitoring.

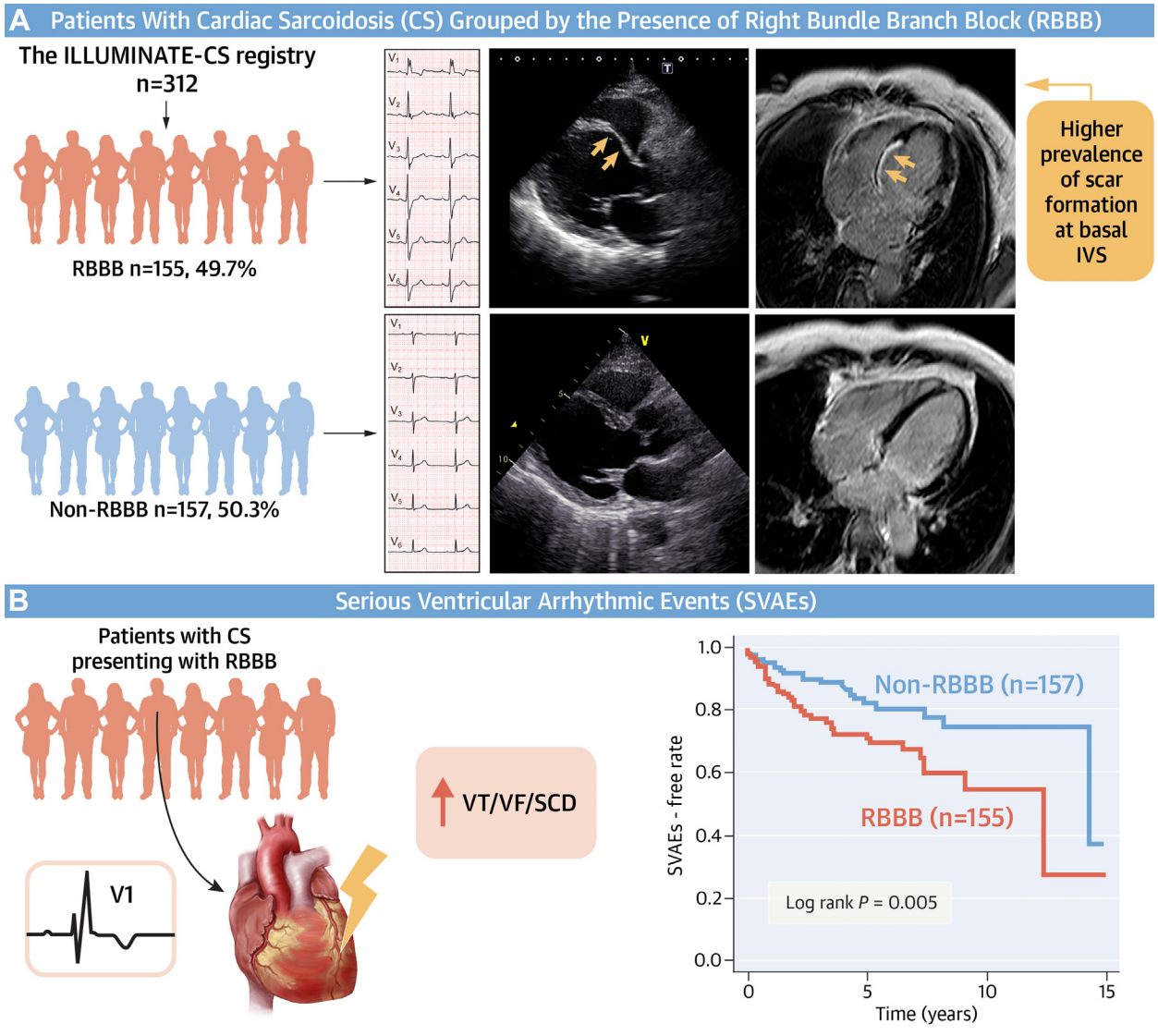
STUDY LIMITATIONS. First, the guidelines of the JCS[4] were used for some CS diagnoses, and as a result, histological confirmation was not performed in all patients. Second, in the present study, patients with pacing rhythm were excluded, which may have caused hidden bias. Third, in the Cox analysis, CIs were not adjusted for multiple comparisons and should be interpreted cautiously. Fourth, this study is a multicenter retrospective design, and statistical bias regarding errors among institutions was not entirely eliminated. Fifth, although this registry comprised the largest number of patients, some data were unavailable because of the retrospective nature of the study. Particularly, we did not have data on the right ventricle and could not examine the impact of RBBB on changes in right ventricular morphology and function or CMR/FDG-PET findings. Thus, we might have missed the opportunity to explore the possible mechanisms of association between RBBB and SVAEs. Furthermore, we did not have data on the existence of pulmonary hypertension associated with the occurrence of RBBB. The small number of patients observed for >10 years raises concerns about statistical power; however, the extensive follow-up period provides additive insights into the long-term clinical history of CS. Furthermore, due to the small number of patients with LBBB in this study, further research involving a larger sample size is warranted to assess the prognosis of patients with LBBB. Additionally, data on advanced cardiovascular imaging were missing for approximately one-third of the patients, which may have

TABLE 2 Univariable and Multivariable Cox Proportional Hazards Model Analysis for Serious Ventricular Arrhythmic Events

	Univariable			Multivariable		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
RBBB	2.02	1.22–3.33	0.006	1.93	1.14–3.28	0.015
Age	1.01	0.98–1.03	0.580			
Male	1.46	0.88–2.42	0.138			
Isolated CS	2.16	1.24–3.73	0.006	1.54	0.85–2.81	0.153
Past medical history						
Hypertension	1.22	0.72–2.04	0.460			
Diabetes	0.59	0.31–1.14	0.114			
HF admission	1.08	0.55–2.13	0.823			
Arrhythmias						
AF	1.01	0.40–2.54	0.978			
VT/VF	3.98	2.27–6.97	<0.001	2.90	1.54–5.46	0.001
Pacemaker implantation	0.48	0.17–1.33	0.158			
ICD/CRT-D implantation	2.73	1.24–6.01	0.013	1.18	0.46–2.99	0.727
Creatinine	1.30	0.99–1.71	0.063			
Log-transformed BNP	1.82	1.15–2.90	0.011	1.47	0.87–2.48	0.144
Echocardiography						
LVEF	0.97	0.96–0.99	<0.001	0.98	0.96–1.00	0.040
IVS thinning	1.12	0.67–1.86	0.664			
LV aneurysms	1.21	0.59–2.46	0.601			
^{67}Ga scintigraphy uptake	1.12	0.61–2.07	0.709			
FDG-PET uptake	0.83	0.25–2.72	0.755			
LGE on CMR	1.55	0.55–4.40	0.407			
Beta-blocker at baseline	1.50	0.90–2.51	0.122			
Steroid use after diagnosis	0.60	0.32–1.13	0.113			

Abbreviations as in Table 1.

CENTRAL ILLUSTRATION Association Between RBBB and Ventricular Arrhythmia in Patients With CS



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(A) The study participants were divided into RBBB and non-RBBB groups, depending on the presence of RBBB at diagnosis. ECG, Echocardiography, and CMR in representative cases from each group are presented. Yellow arrows represent echocardiographic basal IVS thinning and LGE on CMR imaging. (B) RBBB was significantly associated with the occurrence of SVAEs in patients with CS. CS = cardiac sarcoidosis; ECG = electrocardiography; IVS = interventricular septum; SCD = sudden cardiac death; other abbreviations as in Figures 1 to 3.

introduced a selection bias into the analysis using these data. Further studies with larger prospective cohorts including comprehensive advanced imaging evaluation and electrophysiological evaluation are needed to clarify the association between RBBB and prognosis, and its mechanistic background.

CONCLUSIONS

At the time of diagnosis, the RBBB was an independent predictor of SVAEs in patients with CS and was associated with scar formation in the basal ventricular septum.

ACKNOWLEDGMENTS The authors thank all the investigators of the ILLUMINATE-CS who kindly provided us with their patient data.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Sato belongs to an endowed department funded by Medtronic and DVX. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Kimi Sato, Department of Cardiology, Institute of Medicine University of Tsukuba 1-1-1 Tennodai, Tsukuba 3058575, Japan. E-mail: kimisato@md.tsukuba.ac.jp.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This study provides evidence of an association between the presence of RBBB at the time of diagnosis and the occurrence of SVAEs, as well as scar formation at the basal ventricular septum.

TRANSLATIONAL OUTLOOK: The findings of this study emphasize the importance of careful monitoring of VA in patients with CS presenting with RBBB and consideration of ICD requirements.

REFERENCES

1. Trivieri MG, Spagnolo P, Birnie D, et al. Challenges in cardiac and pulmonary sarcoidosis: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;76:1878–1901.

2. Birnie DH, Nery PB, Ha AC, Beanlands RS. Cardiac sarcoidosis. *J Am Coll Cardiol*. 2016;68:411–421.

3. Okada DR, Smith J, Derakhshan A, et al. Ventricular arrhythmias in cardiac sarcoidosis. *Circulation*. 2018;138:1253–1264.

4. Terasaki F, Azuma A, Anzai T, et al. JCS 2016 guideline on diagnosis and treatment of cardiac sarcoidosis - Digest version. *Circ J*. 2019;83:2329–2388.

5. Rosenfeld LE, Chung MK, Harding CV, et al. Arrhythmias in cardiac sarcoidosis bench to bedside: a case-based review. *Circ Arrhythm Electrophysiol*. 2021;14:e009203.

6. Hoogendoorn JC, Venlet J, Out YNJ, et al. The precordial R′ wave: a novel discriminator between cardiac sarcoidosis and arrhythmogenic right ventricular cardiomyopathy in patients presenting with ventricular tachycardia. *Heart Rhythm*. 2021;18:1539–1547.

7. Smedema JP, van Geuns RJ, Ector J, Heidbuchel H, Ainslie G, Crijns H. Right ventricular involvement and the extent of left ventricular enhancement with magnetic resonance predict adverse outcome in pulmonary sarcoidosis. *ESC Heart Fail*. 2018;5:157–171.

8. Blankstein R, Osborne M, Naya M, et al. Cardiac positron emission tomography enhances prognostic assessments of patients with suspected cardiac sarcoidosis. *J Am Coll Cardiol*. 2014;63:329–336.

9. Albakaa N, Sato K, Kawamatsu N, et al. *Multimodality imaging characteristics of cardiac sarcoidosis presented with ventricular arrhythmia. Paper presented at: The 86th Annual Scientific Meeting of the Japanese Circulation Society*. 2022. Virtual.

10. Nabeta T, Kitai T, Naruse Y, et al. Risk stratification of patients with cardiac sarcoidosis: the ILLUMINATE-CS registry. *Eur Heart J*. 2022;43:3450–3459.

11. Birnie DH, Sauer WH, Bogun F, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm*. 2014;11:1305–1323.

12. Surawicz B, Childers R, Deal BJ, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances: a scientific statement from the American heart association electrocardiography and arrhythmias committee, Council on clinical Cardiology; the American College of Cardiology Foundation; and the heart rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol*. 2009;53:976–981.

13. Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American College of Cardiology/American heart association Task Force on clinical Practice guidelines and the heart rhythm Society. *J Am Coll Cardiol*. 2019;74:e51–e156.

14. Lang RM, Badano LP, Mor-Avi V, 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.

15. Nagano N, Nagai T, Sugano Y, et al. Association between tasal thinning of interventricular septum and adverse long-term clinical outcomes in patients with cardiac sarcoidosis. *Circ J*. 2015;79:1601–1608.

16. Ishida Y, Yoshinaga K, Miyagawa M, et al. Recommendations for (18)F-fluorodeoxyglucose positron emission tomography imaging for cardiac sarcoidosis: Japanese Society of Nuclear Cardiology recommendations. *Ann Nucl Med*. 2014;28:393–403.

17. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105:539–542.

18. He Y. Missing data analysis using multiple imputation: getting to the heart of the matter. *Circ Cardiovasc Qual Outcomes*. 2010;3:98–105.

19. van Buuren S, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. *J Stat Softw*. 2011;45:1–67.

20. Scrucca L, Santucci A, Aversa F. Competing risk analysis using R: an easy guide for clinicians. *Bone Marrow Transplant*. 2007;40:381–387.

21. Scrucca L, Santucci A, Aversa F. Regression modeling of competing risk using R: an in depth guide for clinicians. *Bone Marrow Transplant*. 2010;45:1388–1395.

22. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509.

23. Chiba T, Nakano M, Hasebe Y, et al. Prognosis and risk stratification in cardiac sarcoidosis patients with preserved left ventricular ejection fraction. *J Cardiol*. 2020;75:34–41.

24. Miyakuni S, Maeda D, Matsue Y, et al. The prognostic value of B-type natriuretic peptide in patients with cardiac sarcoidosis without heart failure: insights from ILLUMINATE-CS. *J Am Heart Assoc*. 2022;11:e025803.

25. Narasimhan B, Patel N, Ho K, et al. Incidence and predictors of sudden cardiac arrest in sarcoidosis: a nationwide analysis. *JACC Clin Electrophysiol*. 2021;7:1087–1095.

26. Hagiwara H, Watanabe M, Kadosaka T, et al. Fragmented QRS on 12-lead electrocardiogram predicts long-term prognosis in patients with cardiac sarcoidosis. *Heart Ves*. 2023;38:803–816.

27. Ogura S, Nakamura K, Morita H, et al. Fragmented QRS as a predictor of cardiac events in patients with cardiac sarcoidosis. *J Cardiol*. 2022;79:446–452.

28. Kumar S, Barbhaiya C, Nagashima K, et al. Ventricular tachycardia in cardiac sarcoidosis: characterization of ventricular substrate and outcomes of catheter ablation. *Circ Arrhythm Electrophysiol*. 2015;8:87–93.

29. Greulich S, Deluigi CC, Gloekler S, et al. CMR imaging predicts death and other adverse events in suspected cardiac sarcoidosis. *JACC Cardiovasc Imaging*. 2013;6:501-511.

30. Nagai T, Kohsaka S, Okuda S, Anzai T, Asano K, Fukuda K. Incidence and prognostic significance of myocardial late gadolinium enhancement in patients with sarcoidosis without cardiac manifestation. *Chest*. 2014;146:1064-1072.

31. Patel MR, Cawley PJ, Heitner JF, et al. Detection of myocardial damage in patients with sarcoidosis. *Circulation*. 2009;120:1969-1977.

32. Uemura A, Morimoto S, Kato Y, et al. Relationship between basal thinning of the interventricular septum and atrioventricular block in patients with cardiac sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2005;22:63-65.

33. Nogami A. Purkinje-related arrhythmias part ii: polymorphic ventricular tachycardia and ventricular fibrillation. *Pacing Clin Electrophysiol*. 2011;34:1034-1049.

34. Naruse Y, Sekiguchi Y, Nogami A, et al. Systematic treatment approach to ventricular tachycardia in cardiac sarcoidosis. *Circ Arrhythm Electrophysiol*. 2014;7:407-413.

35. Park DH, Cho KI, Kim YK, et al. Association between right ventricular systolic function and electromechanical delay in patients with right bundle branch block. *J Cardiol*. 2017;70:470-475.

KEY WORDS cardiac sarcoidosis, interventricular septum thinning, late gadolinium enhancement, right bundle branch block, ventricular arrhythmia

APPENDIX For supplemental tables and figures, please see the online version of this paper.