Sex differences in clinical characteristics and prognosis of patients with cardiac sarcoidosis

Takashi Iso[1], Daichi Maeda[1*], Yuya Matsue[1*], Taishi Dotare[1], Tsutomu Sunayama[1], Kenji Yoshioka[2], Takeru Nabeta[3,4], Yoshihisa Naruse[5], Takeshi Kitai[6], Tatsunori Taniguchi[7], Hidekazu Tanaka[8], Takahiro Okumura[9], Yuichi Baba[10], Tohru Minamino[1,11]

1. Department of Cardiovascular Biology and Medicine, Juntendo University Graduate School of Medicine, Tokyo Japan

2. Department of Cardiology, Kameda Medical Center, Chiba, Japan

3. Department of Cardiovascular Medicine, Kitasato University School of Medicine, Sagamihara, Japan

4. Department of Cardiology, Leiden University Medical Center, Leiden, Netherlands

5. Division of Cardiology, Internal Medicine III, Hamamatsu University School of Medicine, Hamamatsu, Japan

6. Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan

7. Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

8. Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

9. Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

10. Department of Cardiology and Geriatrics, Kochi Medical School, Kochi University, Nankoku, Japan

11. Japan Agency for Medical Research and Development-Core Research for Evolutionary Medical Science and Technology (AMED-CREST), Japan Agency for Medical Research and Development, Tokyo, Japan

***Address for correspondence:** Daichi Maeda, MD, PhD

Department of Cardiovascular Biology and Medicine, Juntendo University Graduate School of Medicine, 3-1-3 Hongo, Bunkyo-ku, Tokyo, 113-0033 Japan

Tel.: +81-33813-3111; Fax: +81-5689-0627; E-mail: daichimaeda0424@yahoo.co.jp

Yuya Matsue, MD, PhD

Department of Cardiovascular Biology and Medicine, Juntendo University Graduate School of Medicine, 3-1-3 Hongo, Bunkyo-ku, Tokyo, Japan

Tel.: +81-33813-3111; Fax: +81-5689-0627; E-mail: yuya8950@gmail.com

Total word count of the manuscript: 2958

Abstract

Objective: Owing to the paucity of data, this study aimed to investigate sex differences in clinical features and prognosis of patients with cardiac sarcoidosis (CS).

Methods: This study was a secondary analysis of the ILLUstration of the Management and prognosIs of JapaNese PATiEnts with Cardiac Sarcoidosis (ILLUMINATE-CS) registry—a retrospective multicentre registry that enrolled patients with CS between 2001 and 2017. The primary outcome was potentially fatal ventricular arrhythmia events (pFVAEs)— a composite of sudden cardiac death, sustained ventricular tachycardia lasting >30 s, ventricular fibrillation, or the requirement for implantable cardioverter defibrillator therapy.

Results: Of the 512 participants (mean age ± standard deviation, 61.6 ± 11.4 years), 329 (64.2%) were females. Both sexes had peak ages of 60–64 years at diagnosis. Male patients were younger and had a higher prevalence of coronary artery disease and lower left ventricular ejection fraction than female patients. During a median follow-up of 3 years (interquartile range, 1.6–5.6), pFVAEs were observed in 99 patients, with males having a significantly higher risk than females (P=0.002). This association was retained even after adjustment for other risk factors for pFVAEs, including left ventricular ejection fraction (adjusted hazard ratio, 1.80; 95% confidence interval, 1.08–3.01, P=0.025).

Conclusion: Approximately two-thirds of patients with CS were females, with a peak age of approximately 60 years at clinical diagnosis in both sexes; male patients were younger than female patients. Male patients had a significantly higher risk of pFVAEs than female patients.

Clinical Trial Registration: URL: https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000039878 Unique Identifier: UMIN000034974

Keywords: Cardiac sarcoidosis, sex difference, imaging findings, ventricular arrhythmias, prognosis

Key Messages

- **What is already known on this topic**

  - Patients with cardiac sarcoidosis (CS) are at high risk of potentially fatal ventricular arrhythmia events (pFVAEs), including sudden cardiac death; however, sex differences in the epidemiology and prognosis of CS are unknown.

- **What this study adds**

  - Approximately two-thirds of patients with CS were female, with a peak age of 60–64 years at clinical diagnosis for both sexes, and the location of late-gadolinium enhancement in cardiac magnetic resonance and uptake of ^{18}F-fluorodeoxyglucose in positron emission tomography was similar in both sexes.

  - Males with CS were significantly associated with a higher incidence of pFVAEs than females.

- **How this study might affect research, practice, or policy**

  - Sex-specific management of pFVAEs, including indication for implantable cardioverter defibrillator, would be preferable in patients with CS.

  - The pathogenetic mechanisms might differ between CS and systemic sarcoidosis, and further studies are required to clarify the underlying mechanisms of sex differences.

Introduction

Sarcoidosis is a systemic granulomatous disease of unknown aetiology that affects various organs, including the heart, and presents with various clinical symptoms.[1, 2] Cases of cardiac sarcoidosis (CS) are dramatically increasing, owing to the advancement of diagnostic methods, particularly cardiovascular imaging techniques.[3, 4, 5] Patients with CS have a poor prognosis and a particularly high incidence of potentially fatal ventricular arrhythmia events (pFVAEs), including ventricular arrhythmia and sudden cardiac death (SCD).[6]

The epidemiology and prognosis of various cardiovascular diseases can differ significantly between sex [7, 8, 9]; therefore, sex differences should be evaluated to improve the understanding and treatment of these diseases. For instance, female patients with heart failure with reduced ejection fraction have a more favourable adaption of the myocardium to stress conditions and a lower fatal ventricular arrhythmic risk, including SCD, than male patients.[8, 10]

Although the prevalence of systemic sarcoidosis, including CS, is slightly higher in females with an older peak age at diagnosis than in males,[11] this topic has been inadequately investigated, mainly due to the lack of a cohort with a sufficient number of patients diagnosed with CS according to current guidelines. Moreover, a recent study evaluating patients with CS treated with an implantable cardioverter defibrillator (ICD) demonstrated that females were potentially associated with a lower pFVAE risk than males.[12] These results imply that sex differences in epidemiology and incidence could exist in patients with CS.

Recently, we developed a multicentre retrospective registry [6] comprising >500 patients diagnosed with CS according to current guidelines. Furthering our previous research, this study aimed to investigate sex differences in clinical features and prognosis of patients with CS.

Methods

Study design

This study was a posthoc analysis of the ILLUstration of the Management and prognosIs of JapaNese PATiEnts with Cardiac Sarcoidosis (ILLUMINATE-CS) registry—a multicentre retrospective registry that investigated the clinical features and outcomes in a population with CS. The study design and main results have been reported.[6] We included patients with CS diagnosed based on the Heart Rhythm Society (HRS) consensus statement[13] or Japanese Circulation Society guidelines[1]. Those diagnosed before the development of these diagnostic guidelines were considered to have met the recent diagnostic criteria. Patients who refused to participate after being notified of their enrolment in this registry were excluded.

The ILLUMINATE-CS was conducted following the 1975 Declaration of Helsinki and Japanese Ethical Guidelines for Medical and Health Research involving Human Subjects, and the study protocol was approved by the ethics committee of Kitasato University School of Medicine (approval number: B18-090). All patients were notified concerning their participation in this study and were allowed to opt-out. The study outlines, including the aim, inclusion and exclusion criteria, a primary outcome of interest, and participating institutions, are publicly available in the University Hospital Information Network (accession number: UMIN000034974).

Data collection

Baseline information, including age, sex, past medical history, and medication, was obtained at the time of diagnosis of CS. Next, laboratory data and cardiovascular imaging findings, including cardiac magnetic resonance (CMR) and ^{18}F-fluorodeoxyglucose positron

emission tomography (FDG-PET), were collected during the first process of diagnosing CS at the discretion of each physician. The American Heart Association 17-segment model[14] was used to compare the location of late gadolinium enhancement (LGE) accumulation in CMR or FDG uptake in FDG-PET between sexes. All segments were categorised into anterior (segments 1, 7, and 13), inferior (4, 10, and 15), septum (2, 3, 8, 9, and 14), lateral (5, 6, 11, 12, and 16), and apical parts (17).[15]

Clinical follow-up and study endpoint

All clinical events were collected from medical charts, direct contact, or telephone interview. The study endpoint was pFVAEs—a composite of SCD-sustained ventricular tachycardia (SVT) lasting >30 s, ventricular fibrillation (VF), or the requirement for appropriate ICD therapy. Only SCD that met the standardised definition of the Heart Failure Collaboratory and Academic Research Consortium was regarded as SCD.[16] Additionally, appropriate ICD therapy was regarded as shock therapy or anti-tachycardia pacing for SVT or VF.

Statistical analysis

Categorical variables are expressed as numbers with percentages and were compared using Fisher's exact tests. Normally distributed continuous variables are represented as mean with standard deviation, and non-normally distributed variables as median with interquartile range (IQR). Moreover, continuous variables were compared using the Student's t-test or Mann–Whitney U test. The cumulative incidence curves for pFVAEs from the time CS was diagnosed (time zero) were generated using a Fine–Gray competing risk model, with death not resulting from pFVAEs as the competing risk. Additionally, univariate and multivariate Fine–Gray

competing risk regression models were developed to evaluate the association between pFVAEs and clinical variables. Since the predictors of pFVAEs in patients with CS have not been well established, we selected the variables with $P < 0.1$ in the univariate model and included them in the multivariate model. Furthermore, we applied the multiple imputation method to account for missing clinical data. All the variables in Table 1 were imputed, and 20 imputed data sets without missing data were created using a chained-equation procedure. Additionally, univariate and multivariate Fine–Gray competing risk regression analyses were performed.

Data were analysed using R, version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria), and statistical significance was set at a two-sided $P<0.05$.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination of this study.

Results

Of the 512 participants with CS (mean age, 61.6 ± 11.4 years), 329 (64.2%) were females. In the HRS criteria, 314 (61.3%) patients were histologically diagnosed from cardiac (n=55, 17.5%) or extra-cardiac tissue (n=259, 82.5%):. Moreover, in the Japanese Circulation Society criteria, 320 patients (62.5%) were histologically diagnosed from cardiac (n=55, 7.2%) or extra-cardiac tissue (n=265, 82.8%). At baseline, 183 patients (35.7%) were treated using a cardiovascular implantable electronic device (CIED) (implanted pacemakers, ICD, or cardiac resynchronisation therapy), and 289 (56.4%) were treated with CIED during follow-up (at any time point of the study). Additionally, 490 (95.7%) underwent at least one of CMR, FDG-PET,

or Ga-scintigraphy. Of the remaining 22 patients, 4 and 18 were diagnosed histologically and clinically, respectively. Regarding immunosuppressive therapy, 449 and 27 patients were prescribed steroids and steroid-sparing agents, respectively, at any period during follow-up, and one male patient had only a steroid-sparing agent without steroid.

The age- and sex-wise distributions of patients with CS are shown in **Figure 1**. Both sexes had peak ages of approximately 60 years at diagnosis, with a relatively higher proportion of males than females for those ≤40 years. The incidence of CS in those aged ≤40 years was 10.4% (n=19) in males and 1.8% (n=6) in females.

Table 1 presents the baseline comparison between sexes. Females were older and had a lower prevalence of atrial fibrillation, ventricular arrhythmia, and coronary artery disease and higher left ventricular ejection fraction (LVEF) than males. Moreover, females were more frequently diagnosed histologically from cardiac or extra-cardiac tissues than males; however, no differences were observed between both sexes for positive myocardial biopsy. More detailed information on diagnostic criteria according to sex is presented in **Supplementary Table 1**. Furthermore, the proportion of patients with CIED during the study period did not differ between both sexes (56.5% females vs 56.3% males, $P>0.999$). Lastly, no difference was observed in the usage frequency of steroid or steroid-sparing agents between both sexes, and the breakdown of steroid-sparing agents is presented in **Supplementary Table 2**.

Table 1. Baseline characteristics according to sex (N=512)

	All cohort (n=512)	Female (n=329)	Male (n=183)	*P*	Missing (%)
Age, years	61.6 ± 11.4	63.3 ± 9.9	58.6 ± 13.2	<0.001	0.2
Diagnostic criteria, n (%)				0.070	0
HRS only	37 (7.2)	25 (7.6)	12 (6.6)		0
JCS only	198 (38.7)	115 (35.0)	83 (45.4)		0
Both criteria	277 (54.1)	189 (57.4)	88 (48.1)		0
NYHA class III/IV, n (%)	63 (12.9)	43 (13.7)	20 (11.5)	0.571	4.9
Medical history, n (%)					
HF admission	98 (20.0)	69 (22.0)	29 (16.5)	0.180	4.3
Atrial fibrillation	48 (10.0)	24 (7.8)	24 (14.0)	0.046	6.2
*AVB	218 (44.5)	148 (46.8)	70 (40.2)	0.189	4.3
SVT/VF	76 (15.6)	37 (11.9)	39 (22.3)	0.004	5.1
NSVT	105 (22.0)	60 (19.4)	45 (26.6)	0.088	6.6
Hypertension	180 (37.0)	104 (33.3)	76 (43.7)	0.030	5.1
Diabetes	130 (26.9)	89 (28.5)	41 (23.8)	0.314	5.5
Dyslipidemia	78 (16.2)	46 (14.8)	32 (18.7)	0.302	6.1
Coronary artery disease	24 (4.9)	9 (2.9)	15 (8.7)	0.008	5.1
Pacemaker/CRT-P, n (%)	134 (26.9)	94 (29.5)	40 (22.2)	0.092	2.5
ICD/CRT-D, n (%)	49 (10.0)	26 (8.3)	23 (13.0)	0.117	4.5
LVEF (%)	50 [37–61]	52 [37–63]	47 [37–58]	0.012	2.5
FDG-PET examination, n (%)	345 (67.4)	208 (63.2)	137 (74.9)	0.008	0
FDG uptake, n (%)	327 (94.8)	197 (94.7)	130 (94.9)	>0.999	1.4
No. of segments with FDG uptake	4 [2–8]	4 [2–7]	5 [2–8]	0.094	11.0

CMR examination, n (%)	312 (60.9)	199 (60.5)	113 (61.7)	0.850	0
LGE on CMR, n (%)	282 (92.2)	176 (91.2)	106 (93.8)	0.510	1.9
No. of segments with LGE	4 [2–6]	4 [2–6]	4 [2–6]	0.890	5.4
Laboratory data at baseline					
eGFR (mL/min/1.73m²)	84.3±21.8	85.0 ± 21.4	83.1 ± 22.4	0.354	4.5
Creatinine (mg/dL)	0.78 [0.66–0.96]	0.70 [0.62–0.81]	0.96 [0.82–1.15]	<0.001	4.3
BNP (pg/mL)	123.2 [53.7–327.4]	139.3 [54.8–357.0]	101.0 [52.7–239.7]	0.114	27.5
ACE (U/L)	16.6 [11.8–22.0]	16.8 [12.5–22.7]	16.0 [10.6–20.8]	0.079	13.7
sIL-2R (U/mL)	536 [386–827]	533 [392–818]	557 [373–895]	0.852	55.5
Medication at baseline, n (%)					
ACEis/ARBs	253 (50.4)	153 (47.4)	100 (55.9)	0.083	2.0
Beta-blockers	201 (40.1)	121 (37.6)	80 (44.7)	0.144	2.1
MRAs	92 (18.5)	60 (18.8)	32 (18.0)	0.914	2.9
Loop diuretics	131 (26.3)	85 (26.6)	46 (25.8)	0.945	2.7
Steroid use after diagnosis, n (%)	449 (87.7)	289 (87.8)	160 (87.4)	>0.999	0
Steroid-sparing agents after diagnosis, n (%)	27 (5.3)	14 (4.3)	13 (7.1)	0.215	0

Continuous variables are expressed as mean ± standard deviation or as median (interquartile range) as appropriate.

* Defined as a high-grade or complete atrioventricular block.

ACE, angiotensin-converting enzymes; ACEis, angiotensin-converting enzymes inhibitors; ARBs, angiotensin II receptor blockers; AVB, atrioventricular block; BNP, B-type natriuretic peptide; CMR, cardiac magnetic resonance; CRT-D, cardiac resynchronisation therapy defibrillator; CRT-P, cardiac resynchronisation therapy pacemaker; eGFR, estimated glomerular filtration rate; FDG-PET, 18F-fluorodeoxyglucose positron emission tomography; HF, heart failure; HRS, Heart Rhythm Society; ICD, implantable cardioverter defibrillator; JCS, Japanese Circulation Society; LGE, late-gadolinium enhancement; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptors; NSVT, non-sustained ventricular tachycardia;

NYHA, New York Heart Association; sIL-2R, soluble interleukin-2 receptor; SVT, sustained ventricular tachycardia; VF, ventricular fibrillation.

CMR and FDG-PET evaluations were conducted for 312 (60.9%) and 345 (67.4%) patients, respectively. FDG-PET was performed more frequently for males than females; however, the examination rates of CMR were not significantly different between both sexes. Furthermore, the median number of positive segments in CMR and FDG-PET was not significantly different between both sexes. Lastly, the locations of positive segments were similar in both sexes, excluding the lateral part in FDG-PET (**Figure 2 and Supplementary Tables 3 and 4**), and LGE and uptake of FDG were most common in the septum segment in both sexes.

During a median follow-up of 3 years (IQR, 1.6–5.6), pFVAEs were observed in 99 patients: 53 females (16.1%) and 46 males (25.1%) (*P*=0.014). Detailed results of pFVAEs are presented in **Table 2**. The cumulative incident curves revealed that females were significantly associated with a lower incidence of pFVAEs than males (*P*=0.002) (**Figure 3**). This result was consistent even after excluding patients with coronary artery disease (n=24) and missing data (n=26) (**Supplementary Figure 1**).

Table 3 presents univariate and multivariate Fine–Gray analyses. Males and prior SVT or VF were independently associated with the risk of pFVAEs. Furthermore, multiple imputations were performed in sensitivity analysis to account for missing clinical values. Consistently, males and prior SVT or VF were independently associated with pFVAEs in the adjusted model (**Supplementary Table 5**). Moreover, the number of segments of LGE in CMR was newly extracted as a potential prognostic factor in the adjusted model (**Supplementary Table 5**).

Table 2. Comparison of event rates between sexes

	Female	Male	*P**
	n=329	n=183	
pFVAEs, n (%)	53 (16.1%)	46 (25.1%)	0.014
Sudden cardiac death, n (%)	9 (2.7%)	5 (2.7%)	>0.999
SVT, n (%)	35 (11.2%)	36 (20.7%)	0.007
VF, n (%)	10（3.1%）	7（3.9%）	0.615
Appropriate ICD therapy, n (%)	20 (7.4%)	27 (18.1%)	0.002

* Frequency is compared using Fisher's exact tests.

ICD, implantable cardioverter defibrillator; pFVAE, potentially fatal ventricular arrhythmia event; SVT, sustained ventricular tachycardia; VF, ventricular fibrillation

Table 3. Fine–Gray analysis for primary outcomes

	Unadjusted model			Adjusted model		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age, per 5 years	0.98	0.90–1.07	0.649			
Male sex	1.88	1.27–2.79	0.002	1.80	1.08–3.01	0.025
NYHA class III/IV	1.74	1.04–2.89	0.034	1.37	0.70–2.68	0.360
Medical history						
HF admission	1.37	0.86–2.19	0.190			
Atrial fibrillation	1.34	0.73–2.45	0.345			
*AVB	0.78	0.51–1.18	0.240			
Pre-existing SVT/VF	3.58	2.37–5.41	<0.001	3.31	1.81–6.06	<0.001
NSVT	2.14	1.40–3.27	<0.001	1.37	0.72–2.58	0.335
Hypertension	1.09	0.72–1.67	0.675			
Diabetes	0.75	0.46–1.24	0.267			
Dyslipidaemia	1.00	0.57–1.76	0.999			
Coronary artery disease	1.71	0.67–4.36	0.258			
Pacemaker/CRT-P	0.81	0.51–1.29	0.384			
ICD/CRT-D	1.67	0.98–2.84	0.058	0.54	0.26–1.13	0.101
LVEF, per 10%	0.79	0.71–0.88	<0.001	1.01	0.83–1.23	0.916

No. of segments with FDG uptake	1.03	0.90–1.08	0.124			
No. of segments with LGE on CMR	1.07	1.02–1.14	0.012	1.03	0.96–1.10	0.417
Laboratory data at baseline						
Log-transformed BNP	1.51	1.06–2.17	0.024	1.37	0.84–2.22	0.210
eGFR, per 1 mL/min/1.73m²	0.99	0.99–1.00	0.207			
Medication at baseline						
ACEis/ARBs	1.49	0.99–2.24	0.057	1.06	0.56–2.00	0.849
Beta-blockers	1.60	1.07–2.39	0.023	1.00	0.54–1.85	0.988
MRAs	2.02	1.28–3.21	0.003	1.55	0.75–3.22	0.240
Loop diuretics	1.72	1.13–2.60	0.011	1.15	0.55–2.41	0.704
Steroid use after diagnosis	0.77	0.46–1.30	0.334			

* Defined as a high-grade or complete atrioventricular block.

ACEis, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; AVB, atrioventricular block; BNP, B-type natriuretic peptide; CI, confidence interval; CMR, cardiac magnetic resonance; CRT-D, cardiac resynchronisation therapy defibrillator; CRT-P, cardiac resynchronisation therapy pacemaker; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptors; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; PET, positron emission tomography; SVT, sustained ventricular tachycardia; VF, ventricular fibrillation.

Furthermore, we assessed the clinical outcomes in patients diagnosed histologically from cardiac tissue (HRS definite group: n=55) or clinically (HRS probable group: n=259). During the follow-up period, 19 (34.5%) and 37 (14.3%) pFVAEs occurred in HRS definite and probable groups, respectively. Moreover, the frequency of pFVAEs was proportionally higher in males than in females for both groups (HRS definite group: 8 females [25.8%] vs 11 males [45.8%], *P*=0.157; HRS probable group: 21 females [11.5%] vs 16 males [21.1%], *P*=0.052). The cumulative incidence curves revealed that males had a significantly higher risk of pFVAEs than females in the HRS probable group; although not significant, a similar trend was observed in the HRS definite group (**Supplementary Figure 2**). No significant interaction was observed between sex and HRS definite/probable group for the primary outcome.

Discussion

Studying 512 patients with CS, we demonstrated the following: 1) female and male patients with CS had a peak age of approximately 60 years at clinical diagnosis, with a higher incidence of younger males; 2) males had a higher prevalence of histories of hypertension, atrial fibrillation, SVT/VF, and coronary artery disease and lower LVEF than females; and 3) males were at a higher risk for pFVAEs than females. We believe this is the first study to evaluate sex differences in clinical characteristics and rates of ventricular arrhythmia or SCD in patients with CS.

Until around 1980, systemic sarcoidosis was reported to be more prevalent in adults aged <45 years (58% in females and 97% in males) and more common in females (66%) than males (34%).[11] However, according to the recent Swedish National Patient Register database, systemic sarcoidosis peaked at 30–50 years in males and 50–60 years in females, indicating a higher mean age at diagnosis than previously reported.[17] Similarly, a study of Japanese patients with systemic sarcoidosis demonstrated that the incidence has increased among the elderly, and the age at diagnosis has consistently increased. [11] However, data on sex differences in the epidemiology of CS are extremely scarce and inconsistent. A cohort study of Finnish patients with CS reported that 65% of 110 patients with CS were females[3]; however, Polish and North American cohort studies on CS[18, 19, 20] reported frequencies of 30%, 29%, and 18% of female patients. However, since these reports were based on a small number of patients, they may not sufficiently represent patients with CS.

To address these inconsistencies, we analysed data from the ILLUMINATE-CS registry—currently one of the largest cohorts of patients with CS. We demonstrated that patients with CS were predominantly females, with a peak age of 60–64 years at diagnosis for both sexes, and the proportion of younger-onset cases was higher in males than in females. Compared with the epidemiological characteristics of systemic sarcoidosis, the age at the onset of CS was older, especially in males. Moreover, considering the difference in the peak age at clinical diagnosis between systemic and cardiac sarcoidosis, their pathogenetic mechanisms might differ.

FDG-PET was conducted less frequently in females than in males, consistent with previous studies.[20, 21] This may be because more female patients were histologically diagnosed with CS than males (66.3% vs 56.0%, *P*=0.028); notably, patients already diagnosed by biopsy may not require FDG-PET. Additionally, FDG-PET scans are costly, and there may be economic differences between both sexes, which could potentially impact the utilisation rate of FDG-PET. Lastly, since we included some premenopausal women, clinicians may have hesitated to perform FDG-PET on females due to radiation exposure concerns.

Few studies with limited study populations have reported sex differences in the prognosis of patients with CS. In a multicentre retrospective cohort study of 235 patients with CS using ICD, the patients were at high risk for ventricular arrhythmias, with 36% receiving appropriate ICD therapy and 30% receiving appropriate defibrillations during a mean follow-up of 4.2 years.[12] Adequacy of ICD therapy was common in males with a history of syncope, lower LVEF, ICD for secondary prevention, and ventricular pacing on baseline electrocardiogram. Another multicentre retrospective cohort study examined 73 patients with CS treated with cardiac resynchronisation therapy. During a median follow-up of 5.2 years, no significant sex-related difference in the incidence of heart failure death was reported; however, males were associated with a significantly higher incidence of ventricular arrhythmia events than females.[22] Although these findings are consistent with our results on sex differences in the risk of ventricular arrhythmia, our study cohort was not limited to patients already treated with ICD or cardiac resynchronisation therapy, who make up only 30–40% of the entire patient population

with CS.[6, 23] Therefore, the generalisability and validity of our findings can be expanded to a wider CS cohort, strengthening our study's significance. Moreover, after adjusting for missing variables using the multiple imputation method, the number of segments with LGE on CMR remained a significant risk factor for pFVAEs in the multivariate model, consistent with previous reports. [23] We believe this finding strengthens our conclusion since it implies that the association between males and the risk of pFVAEs was independent of findings on CMR-LGE.

Although our study was not designed to clarify the mechanisms for the detected sex differences in ventricular arrhythmia risk, some possible hypotheses could be proposed. First, baseline characteristics are likely to affect the risk of pFVAEs. Male patients had more comorbidities, such as hypertension, atrial fibrillation, and coronary artery disease, than females. These factors, especially coronary artery disease,[24] may lead to pFVAEs. Moreover, males had lower LVEF than females. Previous studies have demonstrated that lower LVEF is associated with a higher risk of ventricular arrhythmia or SCD in patients with non-ischemic cardiomyopathy.[25] However, these were not identified as prognostic factors in our analysis. Second, findings on cardiac imaging, which are risk factors for ventricular arrhythmia, [23] may differ between both sexes. In a previous study involving 137 patients with suspected CS, abnormal FDG uptake by the left ventricle was more frequently detected in females than in males. [26] Another clinical study of 324 patients with suspected CS revealed that females had a lower prevalence of LGE in the left ventricle than males.[27] However, these previous studies only examined those with suspected but not confirmed CS according to the current guidelines.

We evaluated only patients diagnosed with CS according to the current guidelines. Additionally, we examined the locations and number of segments with LGE/FDG uptake, demonstrating their similarity between both sexes; these findings were not predictive factors for pFVAEs. Third, females may be inherently at a lower risk of ventricular arrhythmia or SCD, partially because of the differences in sex chromosomes and sex hormones and their receptors.[28, 29] Therefore, further studies are required to elucidate the mechanisms underlying the sex differences in the risk of pFVAEs in patients with CS.

Our results suggest that sex-specific management may be reasonable in patients with CS, especially for the risk management of pFVAEs. A history of SVT/VF, LVEF, imaging findings (CMR or PET), pacemaker indication, and syncope presence were used to evaluate the indication for ICD implantation in the guidelines and an expert consensus paper.[1, 13] However, these factors were determined based on small-scale retrospective studies; indeed, recent guidelines for ICD have failed to provide accurate risk stratification of patients with CS.[30] Therefore, if our findings are externally validated in future studies, sex differences should be considered when predicting ventricular arrhythmic events and subsequent indications for ICD in patients with CS.

This study had some limitations. First, our cohort comprised only Japanese patients. Therefore, our findings may not be generalisable to all patients with CS and need to be replicated in a multicentre and more racially diverse cohort. Second, we did not consider smoking, alcohol consumption, social/cultural behaviours, education, or socioeconomic status, which are likely to differ between both sexes. Third, in Japan, health insurance covers the implantation of an ICD or

cardiac resynchronisation therapy defibrillator only for secondary prevention; This may have led to the low prevalence of patients with CIED. Notably, ventricular arrhythmias may not be adequately detected in patients without CIED, suggesting that ventricular arrhythmic events might be underestimated. However, since there was no difference in device implantation rates between males and females, its effect on our results is limited. Fourth, we did not obtain data on maximum standardised uptake values on FDG-PET. Fifth, since some patients were diagnosed with CS without myocardial imaging findings, myocardial inflammation was not assessed in all patients. Although the diagnosis of CS was made according to the diagnostic criteria of the current guidelines, the possibility of misdiagnosis in some patients cannot be ruled out. Lastly, we classified patients according to self-identified binary gender, which was considered representative of biological sex for data analysis purposes.

In conclusion, patients with CS were predominantly females, with a peak age of approximately 60 years at diagnosis in both sexes. However, males were significantly associated with a higher risk of ventricular arrhythmia events than females. Further studies are required externally validate this association and clarify the mechanism underlying the sex differences in epidemiology and prognosis.

References

1 Terasaki F, Azuma A, Anzai T, et al. JCS 2016 guideline on diagnosis and treatment of cardiac sarcoidosis- digest version. *Circ J* 2019;**83**:2329-88.

2 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**:1878-901.

3 Kandolin R, Lehtonen J, Airaksinen J, et al. Cardiac sarcoidosis: epidemiology, characteristics, and outcome over 25 years in a nationwide study. *Circulation* 2015;**131**:624-32.

4 Patel MR, Cawley PJ, Heitner JF, et al. Detection of myocardial damage in patients with sarcoidosis. *Circulation* 2009;**120**:1969-77.

5 Willy K, Dechering DG, Reinke F, et al. The ECG in sarcoidosis - a marker of cardiac involvement? Current evidence and clinical implications. *J Cardiol* 2021;**77**:154-9.

6 Nabeta T, Kitai T, Naruse Y, et al. Risk stratification of patients with cardiac sarcoidosis: the ILLUMINATE-CS registry. *Eur Heart J* 2022;**43**:3450-9.

7 Haider A, Bengs S, Luu J, et al. Sex and gender in cardiovascular medicine: presentation and outcomes of acute coronary syndrome. *Eur Heart J* 2020;**41**:1328-36.

8 Lam CSP, Arnott C, Beale AL, et al. Sex differences in heart failure. *Eur Heart J* 2019;**40**:3859-68c.

9 Takashio S, Yamada T, Nishi M, et al. Sex-related differences in the clinical characteristics of wild-type transthyretin amyloidosis cardiomyopathy. *J Cardiol* 2022;**79**:50-7.

10 Gerdts E, Regitz-Zagrosek V. Sex differences in cardiometabolic disorders. *Nat Med* 2019;**25**:1657-66.

11 Sawahata M, Sugiyama Y, Nakamura Y, et al. Age-related and historical changes in the clinical characteristics of sarcoidosis in Japan. *Respir Med* 2015;**109**:272-8.

12 Kron J, Sauer W, Schuller J, et al. Efficacy and safety of implantable cardiac defibrillators for treatment of ventricular arrhythmias in patients with cardiac sarcoidosis. *Europace* 2013;**15**:347-54.

13 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**:1305-23.

14 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**:539-42.

15 Machac J, Bacharach SL, Bateman TM, et al. Positron emission tomography myocardial perfusion and glucose metabolism imaging. *J Nucl Cardiol* 2006;**13**:e121-51.

16 Abraham WT, Psotka MA, Fiuzat M, et al. Standardized definitions for evaluation of heart failure therapies: scientific expert panel from the Heart Failure Collaboratory and Academic Research Consortium. *Eur J Heart Fail* 2020;**22**:2175-86.

17 Arkema EV, Grunewald J, Kullberg S, et al. Sarcoidosis incidence and prevalence: a nationwide register-based assessment in Sweden. *Eur Respir J* 2016;**48**:1690-9.

18 Martusewicz-Boros MM, Boros PW, Wiatr E, et al. Cardiac sarcoidosis: is it more common in men? *Lung* 2016;**194**:61-6.

19 Fussner LA, Karlstedt E, Hodge DO, et al. Management and outcomes of cardiac sarcoidosis: a 20-year experience in two tertiary care centres. *Eur J Heart Fail* 2018;**20**:1713-20.

20 Ning N, Guo HH, Iagaru A, et al. Serial cardiac FDG-PET for the diagnosis and therapeutic guidance of patients with cardiac sarcoidosis. *J Card Fail* 2019;**25**:307-11.

21 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**:329-36.

22 Nakasuka K, Ishibashi K, Hattori Y, et al. Sex-related differences in the prognosis of patients with cardiac sarcoidosis treated with cardiac resynchronization therapy. *Heart Rhythm* 2022;**19**:1133-40.

23 Franke KB, Marshall H, Kennewell P, et al. Risk and predictors of sudden death in cardiac sarcoidosis: a systematic review and meta-analysis. *Int J Cardiol* 2021;**328**:130-40.

24 Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;**346**:877-83.

25 Golwala H, Bajaj NS, Arora G, et al. Implantable cardioverter-defibrillator for non-ischemic cardiomyopathy: an updated meta-analysis. *Circulation* 2017;**135**:201-3.

26 Tuominen H, Haarala A, Tikkakoski A, et al. 18F-FDG-PET in Finnish patients with clinical suspicion of cardiac sarcoidosis: female sex and history of atrioventricular block increase the prevalence of positive PET findings. *J Nucl Cardiol* 2019;**26**:394-400.

27 Kalra R, Malik S, Chen KA, et al. Sex differences in patients with suspected cardiac sarcoidosis assessed by cardiovascular magnetic resonance imaging. *Circ Arrhythm Electrophysiol* 2021;**14**:e009966.

28 Regitz-Zagrosek V, Kararigas G. Mechanistic pathways of sex differences in cardiovascular disease. *Physiol Rev* 2017;**97**:1-37.

29 Gowd BM, Thompson PD. Effect of female sex on cardiac arrhythmias. *Cardiol Rev* 2012;**20**:297-303.

30 Nordenswan HK, Poyhonen P, Lehtonen J, et al. Incidence of sudden cardiac death and life-threatening arrhythmias in clinically manifest cardiac sarcoidosis with and without current indications for an implantable cardioverter defibrillator. *Circulation* 2022;**146**:964-75.

Acknowledgements: None.

Contributors: TI and DM conceived the idea for the study. TD, TS, YK, TN, YN, TK, TT, HT, TO, and YB collected the data. DM and YM contributed to the interpretation of the results. TI wrote the manuscript with the assistance of DM and YM. TM supervised the project. All authors (1) made substantial contributions to the study concept or the data analysis or interpretation; (2) drafted the manuscript or revised it critically for important intellectual content; (3) approved the final version of the manuscript to be published; and (4) agreed to be accountable for all aspects of the work.

Funding: The ILLUMINATE-CS study was partially supported by Novartis Pharma Research Grants and JSPS KAKENHI [grant number 22K16147].

Competing interest: Dr. Yuya Matsue received an honorarium from Otsuka Pharmaceutical Co., Ltd., and Novartis Japan. Dr. Takahiro Okumura received honoraria from Ono Yakuhin, Otsuka Co., Ltd.; Novartis; and Astrazeneca and research grants from Ono Yakuhin, Amgen Astellas, Pfizer, Alnylam, and Alexion (not in connection with the submitted work). Dr. Hidekazu Tanaka has received remuneration from AstraZeneca plc; Otsuka Pharmaceutical Co., Ltd.; Ono Pharmaceutical Co., Ltd.; Pfizer Inc.; Daiichi Sankyo Co., Ltd.; and Novartis International AG. The other authors have no conflicts of interest to declare.

Figure Legends

Figure 1. Histogram of age in patients diagnosed with CS stratified by sex

Both sexes have a peak age of approximately 60 years at clinical diagnosis, with a trend of younger age in males than females.

CS, cardiac sarcoidosis

Figure 2. Proportion of (A) LGE on CMR and (B) FDG-uptake on PET-CT in the myocardium stratified by sex

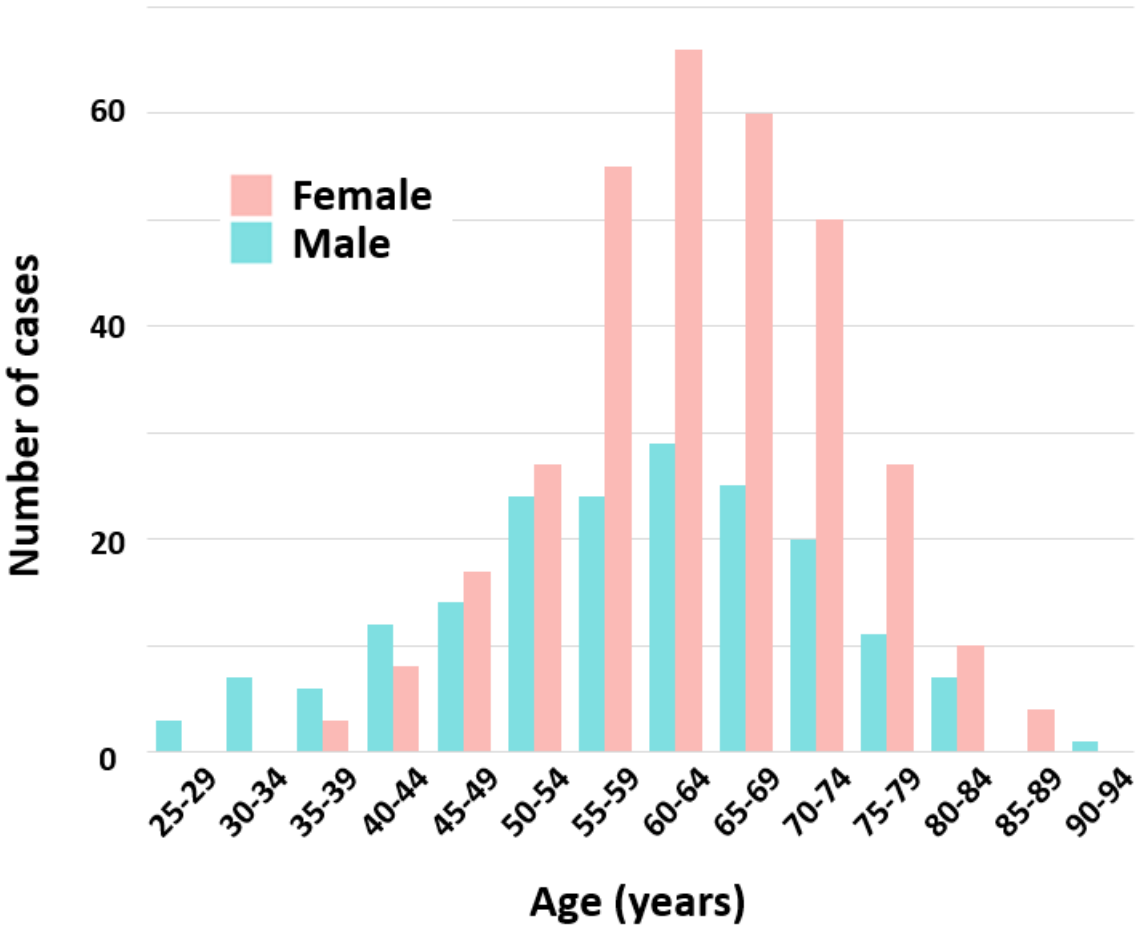
The numbers in each segment show percentages of LGE on CMR and FDG uptake on PET-CT.

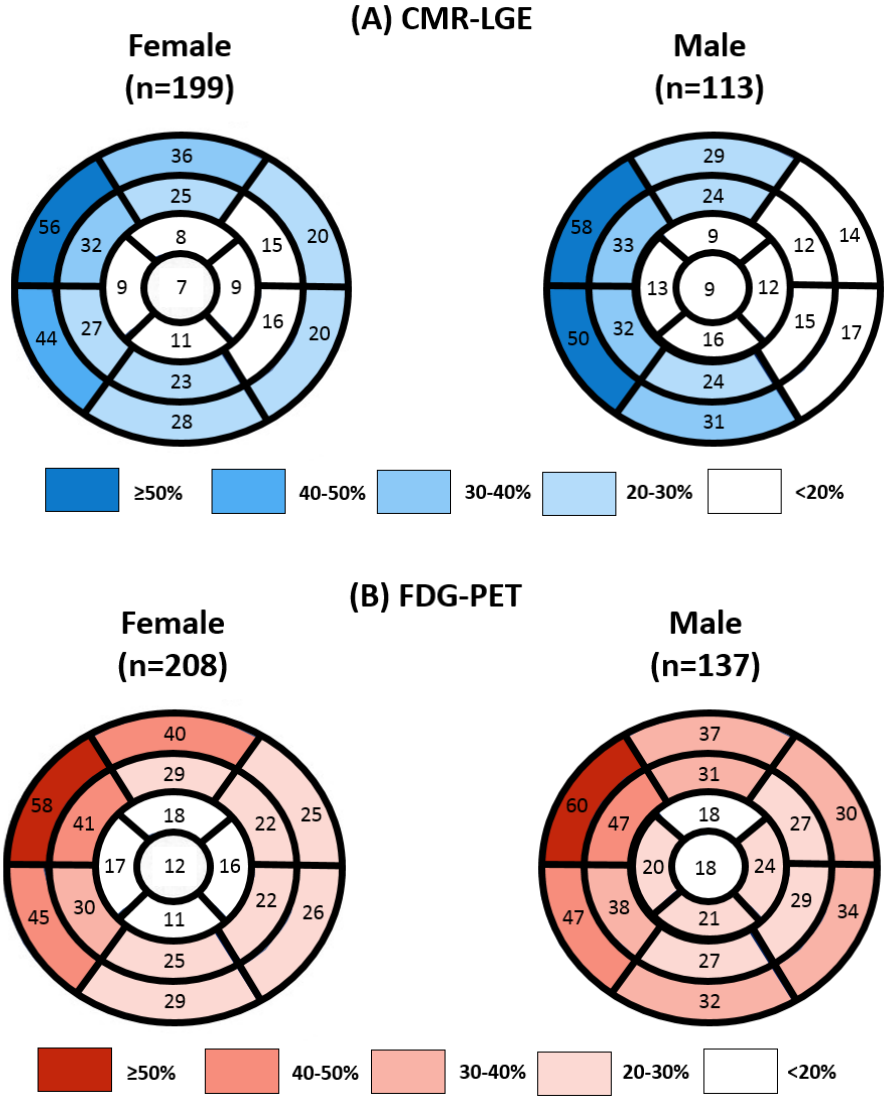
CMR, cardiac magnetic resonance; FDG, ^{18}F-fluorodeoxyglucse; LGE, late-gadolinium enhancement; PET-CT, positron emission tomography-computed tomography

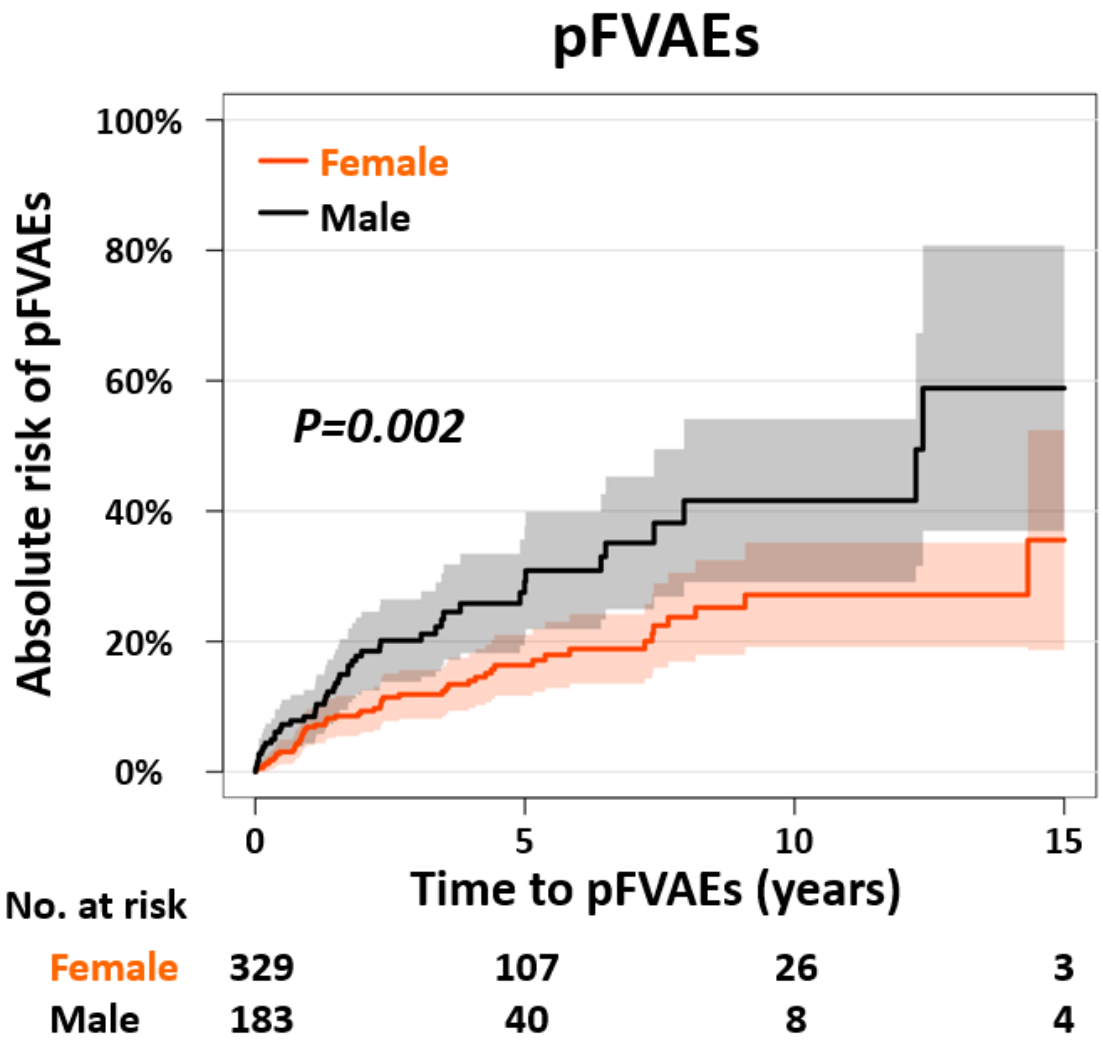
Figure 3. Cumulative incidence curves for the primary endpoint in both sexes

Males were significantly associated with a higher incidence of pFVAEs than females.

pFVAEs, potentially fatal ventricular arrhythmia events


Number of cases
60
40
20
0
Female
Male
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89
90-94
Age (years)


(A) CMR-LGE
Female
(n=199)
Male
(n=113)
36
25
8
15
20
56
32
9
7
9
16
20
44
27
11
23
28
29
24
9
12
14
58
33
13
9
12
50
32
16
15
17
24
31
≥50%
40-50%
30-40%
20-30%
<20%
(B) FDG-PET
Female
(n=208)
Male
(n=137)
40
29
18
22
25
58
41
17
12
16
45
30
11
22
26
25
29
37
31
18
27
30
60
47
20
18
24
47
38
21
29
34
27
32
≥50%
40-50%
30-40%
20-30%
<20%


pFVAEs
Absolute risk of pFVAEs
100%
80%
60%
40%
20%
0%
Female
Male
P=0.002
0
5
10
15
Time to pFVAEs (years)
No. at risk
Female 329 107 26 3
Male 183 40 8 4

Supplementary material

Supplementary Table 1. Diagnostic criteria according to sex

	Female	Male	*P*
	n=329	n=183	
HRS criteria			0.009
HRS definite	31 (9.4%)	24 (13.1%)	
HRS probable	183 (55.6%)	76 (41.5%)	
HRS none	115 (35.0%)	83 (45.4%)	
JCS criteria			
Histological diagnosis	31 (9.4%)	24 (13.1%)	0.233
Clinical diagnosis (not including isolated CS)	222 (67.5%)	101 (55.2%)	0.007
Histologically-proven CS (irrespective of cardiac or extra-cardiac tissue)	218 (66.3%)	102 (56.0%)	0.028
Cardiac tissue positive	31 (9.4%)	24 (13.1%)	0.233
Extra-cardiac tissue positive	187 (56.8%)	78 (42.9%)	0.003
Non-histological diagnosis	111 (33.7%)	80 (44.0%)	0.028
Isolated CS	63 (19.1%)	58 (31.7%)	0.002
Histological diagnosis	12 (3.6%)	12 (6.6%)	0.189
Clinical diagnosis	51 (15.5%)	46 (25.1%)	0.010

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

Supplementary Table 2. Comparison of steroid sparing-agents between sexes

	Female	Male	*P*
	n=329	n=183	
Steroid-sparing agents, n (%)	14 (4.3%)	13 (7.1%)	0.215
Methotrexate, n (%)	11 (3.3%)	9 (4.9%)	-
Azathioprine, n (%)	0 (0%)	3 (1.6%)	-
Cyclosporin, n (%)	1 (0.3%)	0 (0%)	-
Cyclophosphamide, n (%)	1 (0.3%)	1 (0.5%)	-
Unknown, n (%)	1 (0.3%)	0 (0%)	-

Supplementary Table 3. Proportion of LGE in each segment of CMR

	Female (n=199)	Male (n=113)	*P*
Anterior segment, n (%)	88 (44.2%)	43 (38.1%)	0.340
Inferior segment, n (%)	81 (40.7%)	47 (41.6%)	0.905
Septum segment, n (%)	144 (72.4%)	90 (79.6%)	0.175
Lateral segment, n (%)	76 (38.2%)	40 (35.4%)	0.715
Apical segment, n (%)	13 (6.5%)	10 (8.8%)	0.502

MR, cardiac magnetic resonance; LGE, late gadolinium enhancement.

Supplementary Table 4. Proportion of FDG-uptake in each segment of PET-CT

	Female (n=208)	Male (n=137)	*P*
Anterior segment, n (%)	102 (49.0%)	60 (43.8%)	0.378
Inferior segment, n (%)	85 (40.9%)	59 (43.1%)	0.738
Septum segment, n (%)	152 (73.1%)	102 (74.5%)	0.804
Lateral segment, n (%)	92 (44.2%)	79 (57.7%)	0.016
Apical segment, n (%)	24 (11.5%)	24 (17.5%)	0.152

FDG, 18F-fluorodeoxyglucose; PET-CT, positron emission tomography and computed tomography.

Supplementary Table 5. Fine–Gray analysis for primary outcome using multiple imputation method

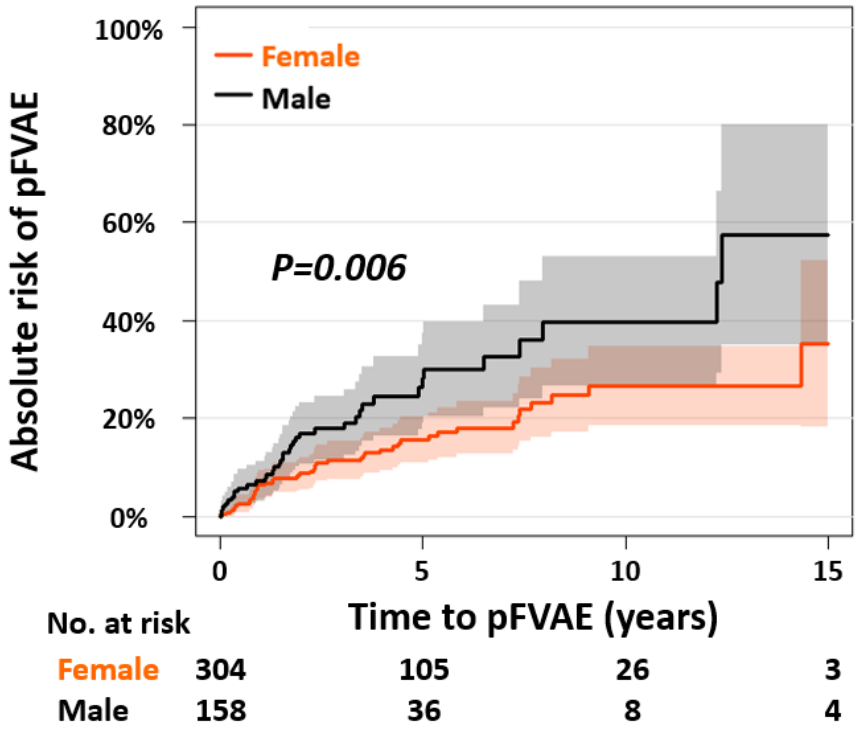
	Unadjusted model			Adjusted Model		
	HR	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Age, per 5 years	0.98	0.90–1.07	0.662			
Male sex	1.88	1.27–2.79	0.002	1.83	1.21–2.76	0.004
NYHA class III/IV	1.66	1.00–2.76	0.049	1.13	0.63–2.02	0.684
Medical history						
HF admission	1.27	0.80–2.02	0.312			
Atrial fibrillation	1.25	0.69–2.28	0.460			
*AVB	0.77	0.52–1.15	0.207			
Pre-existing SVT/VF	3.29	2.21–4.91	<0.001	2.65	1.59–4.42	<0.001
NSVT	2.09	1.39–3.15	<0.001	1.29	0.78–2.13	0.325
Hypertension	1.02	0.68–1.53	0.929			
Diabetes	0.75	0.46–1.22	0.244			
Dyslipidaemia	1.02	0.60–1.76	0.931			
Coronary artery disease	1.62	0.64–4.09	0.311			
Pacemaker/CRT-P	0.78	0.49–1.26	0.310			
ICD/CRT-D	1.82	1.10–3.02	0.021	0.74	0.41–1.35	0.329
LVEF, per 10%	0.78	0.70–0.87	<0.001	0.88	0.75–1.03	0.119
No. of segments with FDG uptake	1.04	0.99–1.08	0.124			
No. of segments with LGE on CMR	1.07	1.02–1.14	0.012	1.06	1.00–1.12	0.038
Laboratory data at baseline						
Log-transformed BNP	1.28	1.11–1.47	<0.001	1.15	0.95–1.38	0.146
eGFR, per 1 mL/min/1.73m²	1.00	0.99–1.00	0.233			
Medication at baseline						
ACEis/ARBs	1.58	1.05–2.36	0.027	1.04	0.65–1.67	0.857
Beta-blockers	1.61	1.09–2.38	0.017	0.87	0.53–1.44	0.595
MRAs	1.64	1.09–2.46	0.017	1.02	0.57–1.82	0.942

Loop diuretics	1.88	1.20–2.96	0.006	1.38	0.76–2.51	0.284
Steroid use after diagnosis	0.77	0.46–1.30	0.334			

* Defined as a high-grade or complete atrioventricular block.

ACEis, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; AVB, atrioventricular block; BNP, B-type natriuretic peptide; CI, confidence interval; CMR, cardiac magnetic resonance; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptors; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; PET, positron emission tomography; SVT, sustained ventricular tachycardia; VF, ventricular fibrillation

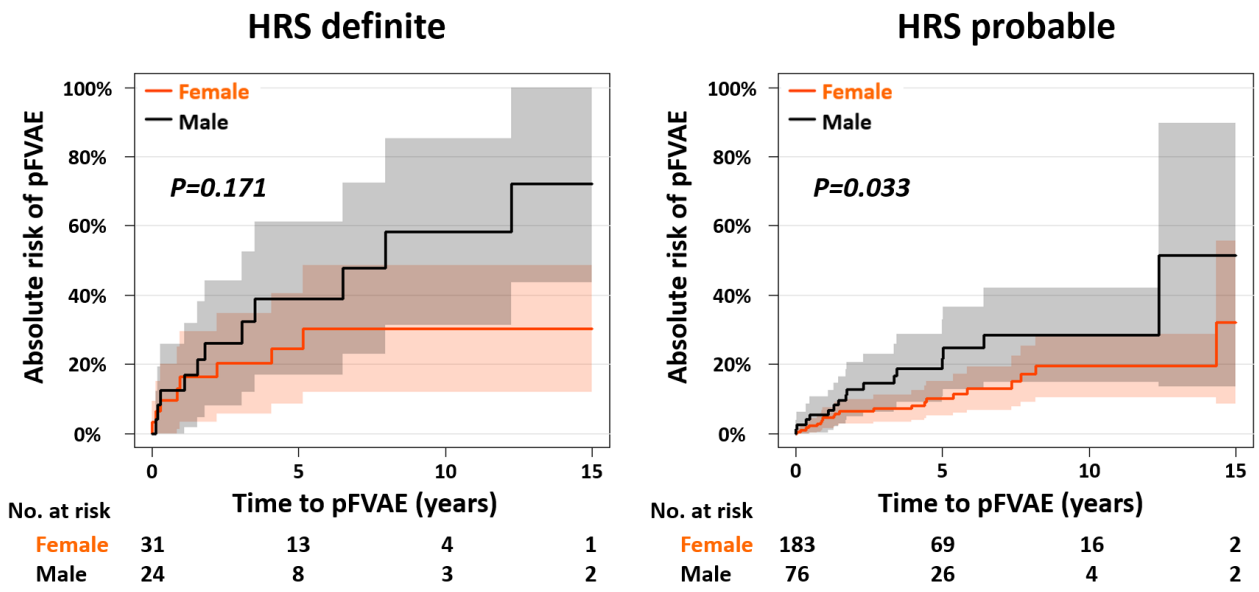
Supplementary Figure 1. Cumulative incidence curve for the primary outcome in patients without coronary artery disease



Patients with coronary artery disease (n=24) and missing data (n=26) were excluded.

pFVAEs, potentially fatal ventricular arrhythmia events

Supplementary Figure 2. Cumulative incidence curves for the primary outcome according to histological or clinical diagnosis of CS



According to the HRS criteria, patients were devided into HRS definite (n=55) and probable (n=259) groups.

CS, cardiac sarcoidosis; HRS, Heart Rhythm Society; pFVAEs, potentially fatal ventricular arrhythmia events