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Original research

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

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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 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±SD 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 (IQR 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 HR 1.80; 95% CI 1.08 to 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.

Trial registration number UMIN000034974.

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 ¹⁸F-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.^{3–5} 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^{7–9}; 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



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Table 1 Baseline characteristics according to sex (n=512)

	All cohort (n=512)	Female (n=329)	Male (n=183)	P value	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
Dyslipidaemia	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/1.73 m ²)	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±SD or as median (IQR) as appropriate.

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

ACEis, ACE 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.

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 registry⁶ 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 post hoc 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 statement¹³ 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 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).

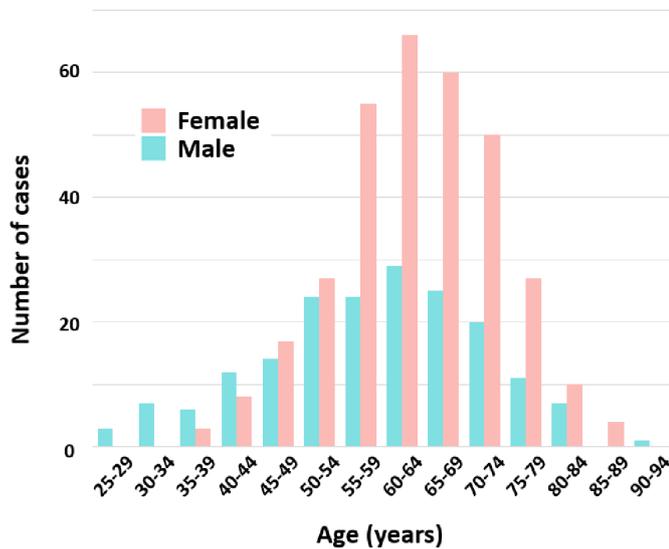


Figure 1 Histogram of age in patients diagnosed with cardiac sarcoidosis stratified by sex. Both sexes have a peak age of approximately 60 years at clinical diagnosis, with a trend of younger age in males than females.

Data collection

Baseline information, including age, sex, medical history and medication, was obtained at the time of diagnosis of CS. Next,

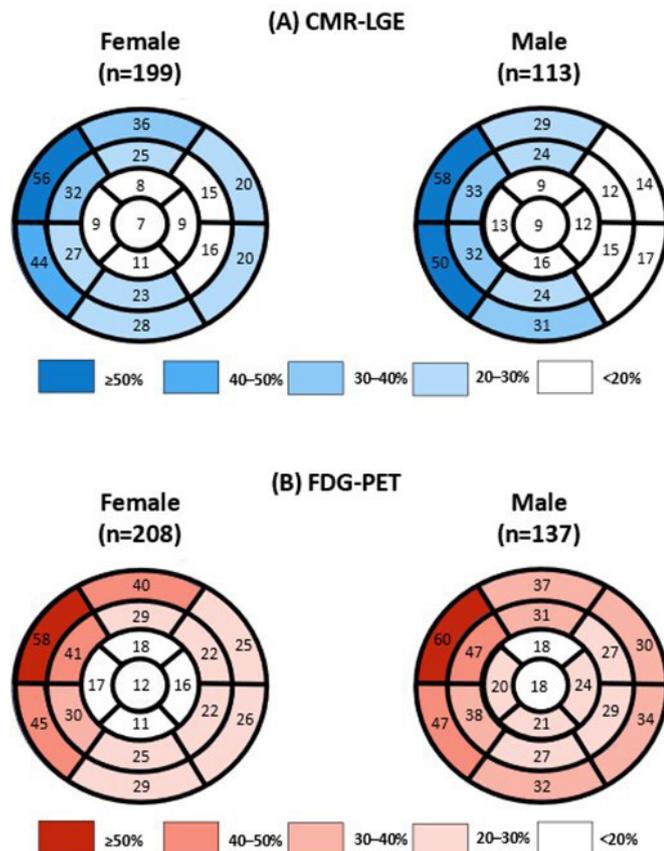


Figure 2 Proportion of (A) LGE on CMR and (B) FDG uptake on PET-CT in the myocardium stratified by sex. The numbers in each segment show percentages of LGE on CMR and FDG uptake on PET-CT. CMR, cardiac magnetic resonance; FDG, ^{18}F -fluorodeoxyglucose; LGE, late-gadolinium enhancement; PET, positron emission tomography.

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 model¹⁴ 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 (segments 4, 10 and 15), septum (segments 2, 3, 8, 9 and 14), lateral (segments 5, 6, 11, 12 and 16) and apical parts (segment 17).¹⁵

Clinical follow-up and study end point

All clinical events were collected from medical charts, direct contact or telephone interview. The study end point 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 antitachycardia 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 SD, and non-normally distributed variables as median with 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 datasets 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, V.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 and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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 extracardiac 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 extracardiac 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

Table 2 Comparison of event rates between sexes

	Female	Male	P value*
	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.

CIED during follow-up (at any time point of the study). Additionally, 490 (95.7%) underwent at least one of CMR, FDG-PET or Gallium 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-wise 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 extracardiac 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 online supplemental table

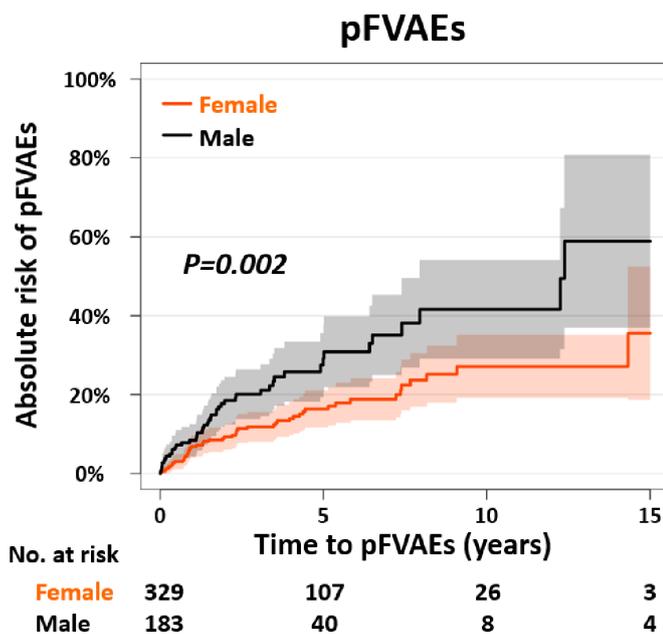


Figure 3 Cumulative incidence curves for the primary end point in both sexes. Males were significantly associated with a higher incidence of pFVAEs than females. pFVAEs, potentially fatal ventricular arrhythmia events.

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 online supplemental table 2.

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 online supplemental 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) (online supplemental 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 (online supplemental table 5). Moreover, the number of segments of LGE in CMR was newly extracted as a potential prognostic factor in the adjusted model (online supplemental table 5).

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 (online supplemental 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

Table 3 Fine-Gray analysis for primary outcomes

	Unadjusted model			Adjusted model		
	HR	95% CI	P value	HR	95% CI	P value
Age, per 5 years	0.98	0.90 to 1.07	0.649			
Male sex	1.88	1.27 to 2.79	0.002	1.80	1.08 to 3.01	0.025
NYHA class III/IV	1.74	1.04 to 2.89	0.034	1.37	0.70 to 2.68	0.360
Medical history						
HF admission	1.37	0.86 to 2.19	0.190			
Atrial fibrillation	1.34	0.73 to 2.45	0.345			
*AVB	0.78	0.51 to 1.18	0.240			
Pre-existing SVT/VF	3.58	2.37 to 5.41	<0.001	3.31	1.81 to 6.06	<0.001
NSVT	2.14	1.40 to 3.27	<0.001	1.37	0.72 to 2.58	0.335
Hypertension	1.09	0.72 to 1.67	0.675			
Diabetes	0.75	0.46 to 1.24	0.267			
Dyslipidaemia	1.00	0.57 to 1.76	0.999			
Coronary artery disease	1.71	0.67 to 4.36	0.258			
Pacemaker/CRT-P	0.81	0.51 to 1.29	0.384			
ICD/CRT-D	1.67	0.98 to 2.84	0.058	0.54	0.26 to 1.13	0.101
LVEF, per 10%	0.79	0.71 to 0.88	<0.001	1.01	0.83 to 1.23	0.916
No. of segments with FDG uptake	1.03	0.90 to 1.08	0.124			
No. of segments with LGE on CMR	1.07	1.02 to 1.14	0.012	1.03	0.96 to 1.10	0.417
Laboratory data at baseline						
Log-transformed BNP	1.51	1.06 to 2.17	0.024	1.37	0.84 to 2.22	0.210
eGFR, per 1 mL/min/1.73 m ²	0.99	0.99 to 1.00	0.207			
Medication at baseline						
ACEis/ARBs	1.49	0.99 to 2.24	0.057	1.06	0.56 to 2.00	0.849
Beta-blockers	1.60	1.07 to 2.39	0.023	1.00	0.54 to 1.85	0.988
MRAs	2.02	1.28 to 3.21	0.003	1.55	0.75 to 3.22	0.240
Loop diuretics	1.72	1.13 to 2.60	0.011	1.15	0.55 to 2.41	0.704
Steroid use after diagnosis	0.77	0.46 to 1.30	0.334			

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

ACEis, ACE 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; HF, heart failure; 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.

(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 females³; however, Polish and North American cohort studies on CS^{18–20} 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 male patients (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 female patients 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 ECG. 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 female patients. 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-ischaemic 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 arrhythmic events than females. Further studies are required to externally validate this association and clarify the mechanism underlying the sex differences in epidemiology and prognosis.

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ILLUMINATE-CS was conducted following the 1975 Declaration of Helsinki and Japanese Ethical Guidelines for Medical and Health Research involving Human Subjects. All patients were notified concerning their participation in this study and were allowed to opt-out.

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