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ORIGINAL ARTICLE
Arrhythmia and electrophysiology

Prevalence and prognostic value of atrial fibrillation in patients with cardiac sarcoidosis

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Aims The prognostic value of the presence of atrial fibrillation (AF) in patients at the time of cardiac sarcoidosis (CS) diagnosis is unknown. This study aimed to investigate the association between AF at the time of CS diagnosis and patient prognosis.

Methods and results This study is a post-hoc analysis of Illustration of the Management and Prognosis of Japanese Patients with CS, a multicentre, retrospective observational study that evaluated the clinical characteristics and prognosis of patients with CS. The primary endpoint was the combined endpoint of all-cause death and hospitalization due to heart failure. After excluding patients with missing data about AF status, 445 patients (62 ± 11 years, 36% males) diagnosed with CS according to the Japanese current diagnostic guideline were analysed. Compared to patients without AF, patients with AF ($n = 46$, 10%) had higher levels of brain natriuretic peptide and a higher prevalence of heart failure hospitalizations. During a median follow-up period of 3.2 years (interquartile range, 1.7–5.8 years), 80 primary endpoints were observed. Kaplan–Meier curve analysis indicated that concomitant AF at the time of diagnosis was significantly associated with a high incidence of primary endpoints (log-rank $P = 0.002$). This association was retained after adjusting for known risk factors including log-transformed brain natriuretic peptide levels and left ventricular ejection fractions [hazard ratio, 1.96 (95% confidence interval, 1.05–3.65); $P = 0.035$].

Conclusion The presence of AF at the time of CS diagnosis is associated with higher incidence of all-cause death and heart failure hospitalization.

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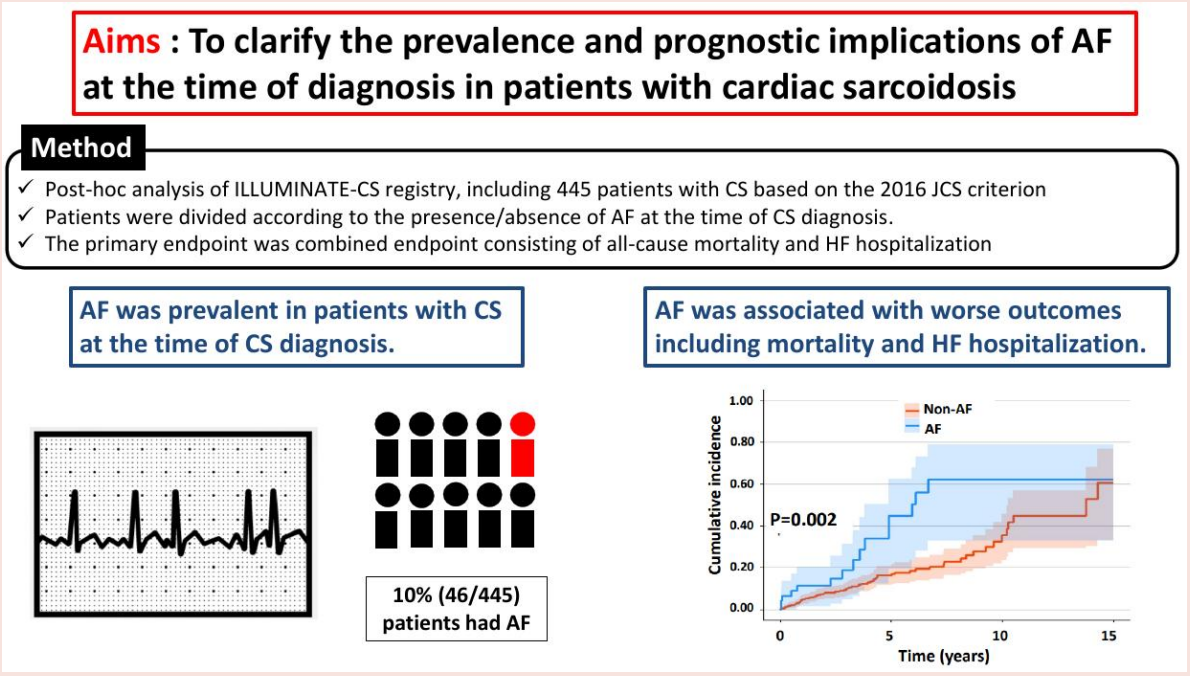
Graphical Abstract



Keywords Atrial fibrillation • Cardiac sarcoidosis • Mortality • Heart failure • Prognosis

Introduction

Sarcoidosis is a systemic granulomatous disease that affects multiple organs including the lungs, nerves, eyes, and heart.[1] Cardiac involvement in sarcoidosis, known as cardiac sarcoidosis (CS), occurs in 25–58% of patients and is strongly associated with poor prognosis.[2,3] As granulomatous scars form in the myocardium and coexisting inflammation can become a substrate for arrhythmias,[4] CS is considered an arrhythmogenic disease.

Atrial fibrillation (AF) is one of the most common arrhythmic conditions, affecting an increasing number of patients worldwide.[5,6] AF and heart failure (HF) frequently coexist, together conferring an adverse prognosis.[7,8] Although HF hospitalization is one of the most frequent adverse events in patients with CS,[9] to date, no study has identified risk factors for HF-related events in patients with CS. Therefore, clarifying the association between AF and prognosis in patients with CS is important for improving disease management strategies.

Although ventricular tachyarrhythmias and atrioventricular block (AVB) are the two most common arrhythmic manifestations, AF is also prevalent in CS and associated with CS disease mechanisms.[10–12] However, this association is poorly understood, with only a few studies with limited numbers of patients focusing on AF as a comorbidity in CS. Moreover, to date, no study has evaluated whether the presence of AF as a complication of CS is associated with a poorer prognosis. Indeed, AF has been shown to not only be prevalent, but also associated, with the development of HF in other cardiomyopathies, such as dilated cardiomyopathy and hypertrophic cardiomyopathies.[13,14]

Therefore, in this study, we aimed to examine the prevalence of AF at the time of CS diagnosis and the association between the presence of AF and the prognosis of patients with CS.

Methods

Study subjects

The Illustration of the Management and Prognosis of Japanese Patients with CS (ILLUMINATE-CS) was designed as a multicentre, retrospective registry study for evaluating the clinical characteristics and outcomes of patients with CS.[9,15] The ILLUMINATE-CS registry included patients with CS according to either the Japanese Circulation Society (JCS) criteria proposed in 2016 or the Heart Rhythm Society (HRS) criteria proposed in 2014. However, in the present study, the inclusion criterion was limited to the diagnosis of CS based on the 2016 JCS criteria, for this inclusion criterion was implemented to facilitate easier comparison with future research concerning AF and CS.[1,16] The exclusion criterion was patient refusal for enrolment after notification of registration in the above registry. Among the 33 participating hospitals, 21 were university hospitals and 12 were non-university teaching hospitals. This study followed the Declaration of Helsinki and the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects. The study protocol was approved by the ethics committee of each participating hospital, and the requirement for informed consent was waived owing to the retrospective nature of the study, under the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Japanese Ministry of Health, Labour, and Welfare. More information on the study, including study objectives, inclusion and exclusion criteria, and names of the participating hospitals, can be found in the publicly accessible University Hospital Information Network (UMIN000034974).

Data collection and outcomes

Baseline characteristics, including age, sex, clinical comorbidities, blood test data, and findings of cardiovascular imaging tests, were obtained during the original diagnostic process for CS. The presenting symptoms were defined

as all the symptoms documented at the time of CS diagnosis. The baseline was defined as the time at which the patient was diagnosed with CS based on the JCS criteria. Medical history, arrhythmias, and conduction disorders at baseline were the main presenting manifestations at the time of diagnosis. Participants were classified as having AF if AF was observed on 12-lead electrocardiograms or intracardiac electrogram waveforms, detected during Holter monitoring tests, or noted on the hospital records. The final diagnosis of AF at the time of CS diagnosis was confirmed by a cardiologist in each hospital.

Measurement of the left ventricular ejection fraction (LVEF) was performed by echocardiography using either the biplane-modified Simpson method or the Teichholz method. Measurement of the left atrial diameter (LAD) was also performed by echocardiography. Findings of cardiac accumulation by late gadolinium enhancement (LGE) in cardiac magnetic resonance (CMR), fluorodeoxyglucose-positron emission tomography (FDG-PET), and ^{67}Ga scintigraphy at the time of diagnosis were determined based on expert reports from each institution. The location of LGE in CMR and the FDG uptake in FDG-PET at CS diagnosis were compared between patients with and without AF using the American Heart Association 17-segment model.[17] The segments were divided into five regions: 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 (segment 17) regions.[18]

In line with recent randomized controlled trials in patients with HF, we defined the primary endpoint in our study as a composite endpoint of all-cause death and HF hospitalization.[19,20] We also evaluated all-cause death and HF hospitalization as exploratory endpoints. All outcome data were retrospectively obtained from medical charts. Heart failure hospitalization was defined according to the criteria recently proposed by the HF Collaboratory and Academic Research Consortium.[21]

Statistical analysis

Normally distributed continuous variables are expressed as means ± standard deviations and non-normally distributed variables as medians and interquartile ranges. Categorical variables are expressed as numbers and percentages. Group differences were evaluated using Student's *t*-test or the Mann–Whitney U test for continuous variables and the Chi-square or Fisher's exact tests for dichotomous variables. When necessary, variables were transformed for further analyses. Cumulative incidence curves for the combined endpoints and all-cause death were calculated from the time of CS diagnosis (time zero) using Kaplan–Meier estimates; differences were compared using the log-rank test. Analysis of Schoenfeld residual plots for combined endpoints confirmed the proportional hazard assumptions. Cumulative incidence curves for HF hospitalization from time zero were generated by Fine–Gray competing risk regression analysis, with all-cause death as a competing risk. An unadjusted Cox proportional hazard model was used to evaluate the association between AF and the incidence of primary endpoints. Additionally, we constructed the following statistical models for multivariable Cox regression analyses using previously identified prognostic factors[15,22]: Model 1, which incorporated age and sex into the unadjusted Cox model; Model 2, which incorporated log-transformed brain natriuretic peptide (BNP) levels, LVEF, history of HF hospitalization, and creatinine levels at baseline, in addition to the factors used in Model 1; and Model 3, which incorporated LAD, in addition to the factors used in Model 2. Multiple imputations were performed to consider missing values. We created 20 datasets using a chained-equations procedure.[23] Parameter estimates were obtained for each dataset and subsequently combined to produce an integrated result, using the method described by Barnard and Rubin.[24] For sensitivity, we performed a multivariable Cox regression analysis using the variables with a *P*-value <0.1 in the univariable Cox analysis, considering that the risk factors for the combined outcome of HF and all-cause death in patients with CS have not been clearly determined.

Results

Among the 512 patients registered in the ILLUMINATE-CS registry, 32 were excluded due to missing data on the presence of AF at the time of diagnosis, and 35 were excluded due to the diagnosis according to only the HRS criteria, leaving a final cohort of 445 patients. Patients had a mean age of 62 years, with 36% of males. Of the 445 patients, 267 (60%) showed histological evidence of sarcoidosis in cardiac or extracardiac tissues, and 20 (4.5%) received histological CS confirmation by endomyocardial biopsy. During a median follow-up period of 3.2 years (interquartile range: 1.7–5.8 years), 80 primary endpoints (42 all-cause deaths and 50 HF hospitalizations) were observed. The study population was categorized into two groups based on the presence ($n = 46$, 10%) and absence ($n = 399$, 90%) of AF at the time of diagnosis.

Table 1 presents baseline patient characteristics stratified by the presence of AF. Patients with AF featured male sex, higher prevalence of hypertension and HF hospitalization, higher BNP values, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use. No statistical differences were found in the New York Heart Association Classification (NYHA) class or LVEF between groups. Additionally, no statistical difference was observed in the CMR/FDG-PET imaging findings between patients with and without AF, except for the prevalence of CMR-LGE in the inferior wall (*Table 2*, *Figure 1*). Cumulative incidence curves for the primary endpoint, all-cause death, and HF hospitalization are shown in *Figure 2A–C*, respectively. The presence of AF at the time of diagnosis was significantly associated with a high incidence of primary endpoints (log-rank $P = 0.002$), all-cause death (log-rank $P = 0.020$), and HF hospitalization (log-rank: $P = 0.028$).

In an explanatory analysis, we compared the cause of death between patients with and without AF. The cause of death was statistically different between the two groups (see Supplementary material online, *Table S1*), and the number of cardiovascular deaths might be attributed to the higher mortality in patients with AF. Indeed, the cumulative incidence curve for cardiovascular death showed the highest event rate in patients with AF (log-rank $P = 0.024$, Supplementary material online, *Figure S1*).

Table 3 shows the results of unadjusted and multivariable Cox proportional hazard analyses. AF was independently associated with a worse prognosis after adjustment for other covariates, including log BNP, LVEF, and LAD [hazard ratio (HR) 1.96, 95% confidence interval (CI) 1.05–3.65, $P = 0.035$]. Additionally, we performed a multivariate Cox regression analysis using the variables with a *P*-value <0.1 in the univariate Cox analysis as a sensitivity analysis, and achieved consistent results (HR 1.89, 95% CI 1.02–3.49, $P = 0.043$) (*Table 4*).

The prognostic value of AF for each endpoint was also assessed using Cox proportional hazard analysis. As shown in Supplementary material online, *Table S2*, unadjusted Cox analysis indicated that AF was associated with higher mortality or more frequent HF hospitalization. These associations were retained even after adjusting for multiple risk factors, including age, sex, BNP, and creatinine (all-cause mortality: HR 2.36, 95% CI 1.03–5.42, $P = 0.043$; HF hospitalization: HR 2.33, 95% CI 1.08–5.05, $P = 0.033$).

Discussion

To the best of our knowledge, this study is the first to assess the association between AF and the prognosis of patients with CS diagnosis based on current diagnostic criteria. Our study's main findings are: (i) 10% of patients with CS had AF at the time of diagnosis; and (ii) the presence of AF at the time of diagnosis was associated with a higher incidence of HF hospitalization and all-cause death. The association was independent of other covariates. Taken together, our results suggested the prognostic importance of AF as a comorbidity in patients with CS.

Sarcoidosis is an autoimmune disorder characterized by multi-organ involvement resulting from granuloma formation and scarring.[25] CS is the second leading cause of death in patients with sarcoidosis, and the three major manifestations of CS are high-grade AVB, ventricular arrhythmias, and HF.[26,27] Given that inflammation can cause atrial wall injury and become a substrate for macro-reentry arrhythmia,[28] atrial

Table 1 Baseline characteristics comparison between patients with and without atrial fibrillation

Variables	AF $n = 46$	Non-AF $n = 399$	*P*-value	Missing, n
Age (years)	65 ± 13	62 ± 11	0.091	1
Male sex, *n* (%)	24 (52%)	136 (34%)	0.024	0
NYHA class III or IV, *n* (%)	5 (12%)	52 (14%)	>0.999	19
HRS criteria, *n* (%)	21 (46%)	240 (60%)	0.083	0
Histological proof of sarcoidosis, *n* (%)	22 (48%)	245 (62%)	0.101	1
First manifestation, *n* (%)				
Abnormality of ventricular wall motion	30 (67%)	198 (52%)	0.087	19
Septal thinning	2 (4%)	14 (4%)	>0.999	19
Heart failure	12 (27%)	83 (22%)	0.579	19
VT or VF	8 (18%)	82 (22%)	0.697	19
AVB	14 (31%)	168 (44%)	0.132	19
Medical history, *n* (%)				
Hypertension	28 (61%)	139 (35%)	0.001	3
Diabetes	16 (35%)	102 (26%)	0.257	3
Dyslipidaemia	7 (15%)	66 (17%)	0.950	6
Coronary artery disease	3 (7%)	20 (5%)	0.905	1
Heart failure admission	16 (35%)	79 (20%)	0.031	0
VT or VF	8 (17%)	65 (16%)	>0.999	0
Non-sustained VT	14 (32%)	86 (22%)	0.191	7
AVB	17 (37%)	178 (45%)	0.396	1
Pacemaker implantation, *n* (%)	11 (26%)	111 (28%)	0.841	10
ICD/CRT-D implantation, *n* (%)	9 (21%)	40 (11%)	0.074	20
Gallium-67 accumulation, *n* (%)	6 (33%)	82 (39%)	0.868	213
LGE in CMR, *n* (%)	27 (93%)	226 (93%)	>0.999	173
PET accumulation, *n* (%)	30 (94%)	263 (96%)	0.971	138
LVEF, %	44 (37–55)	48 (36–61)	0.259	9
LAD (mm)	41 (37–47)	38 (32–42)	<0.001	22
BNP, pg/mL	167 (106–459)	123 (53–334)	0.018	115
Creatinine, mg/dL	0.82 (0.71–1.17)	0.77 (0.65–0.97)	0.024	17
ACEi/ARB at baseline, *n* (%)	31 (72%)	194 (49%)	0.007	8
MRA at baseline, *n* (%)	10 (23%)	75 (19%)	0.668	12
Beta-blocker at baseline, *n* (%)	30 (70%)	155 (39%)	<0.001	9
Amiodarone at baseline, *n* (%)	5 (12%)	41 (11%)	>0.999	10
Steroid use after diagnosis, *n* (%)	39 (85%)	359 (90%)	0.406	0

Continuous variables are presented as means ± SD or medians (interquartile ranges).
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AVB, atrioventricular block; CRT-D, cardiac resynchronization therapy defibrillator; HRS, heart rhythm society; MRA, mineralocorticoid receptor antagonist; VF, ventricular fibrillation; VT, ventricular tachycardia.

arrhythmias, including AF, may also be subsequently provoked.[29] However, AF as a CS comorbidity has been underappreciated and rarely evaluated; thus, the prevalence of AF at the time of CS diagnosis remains unclear. Two large CS cohort studies did not report the prevalence of AF as a comorbidity at the time of diagnosis,[26,30] and a Finnish CS cohort study indicated that only four of 351 patients with CS had 'supraventricular arrhythmias' as a complication at the time of diagnosis.[31] Although its definition and breakdown have not been detailed in the Finnish study, the prevalence of AF at CS diagnosis is much lower than that in our study (10%). In addition, the importance of considering AF in patients with CS has been highlighted in reports detailing the incidence of emerging AF after CS diagnosis. A Canadian multicentre, prospective study showed that 11 of 33 (33.3%) patients with CS had device-detected atrial arrhythmias.[32] Similarly, Niemela *et al.* reported that 34 of 118 (29%) patients with newly diagnosed CS had AF.[28] The same findings have been

Table 2 Comparison of imaging findings between patients with and without atrial fibrillation

Variables	AF $n = 46$	Non-AF $n = 399$	*P*-value
CMR examination, n (%)	29 (63%)	248 (62%)	>0.999
LGE, n (%)	27 (93%)	226 (93%)	>0.999
No. of segments with LGE	4 (2–6)	4 (2–6)	0.944
^{18}FDG-PET examination, n (%)	34 (74%)	275 (69%)	0.598
FDG uptake, n (%)	30 (94%)	263 (96%)	0.971
No. of segments with FDG uptake	6 (3–8)	5 (3–8)	0.648

Continuous variables are expressed as medians and interquartile ranges.

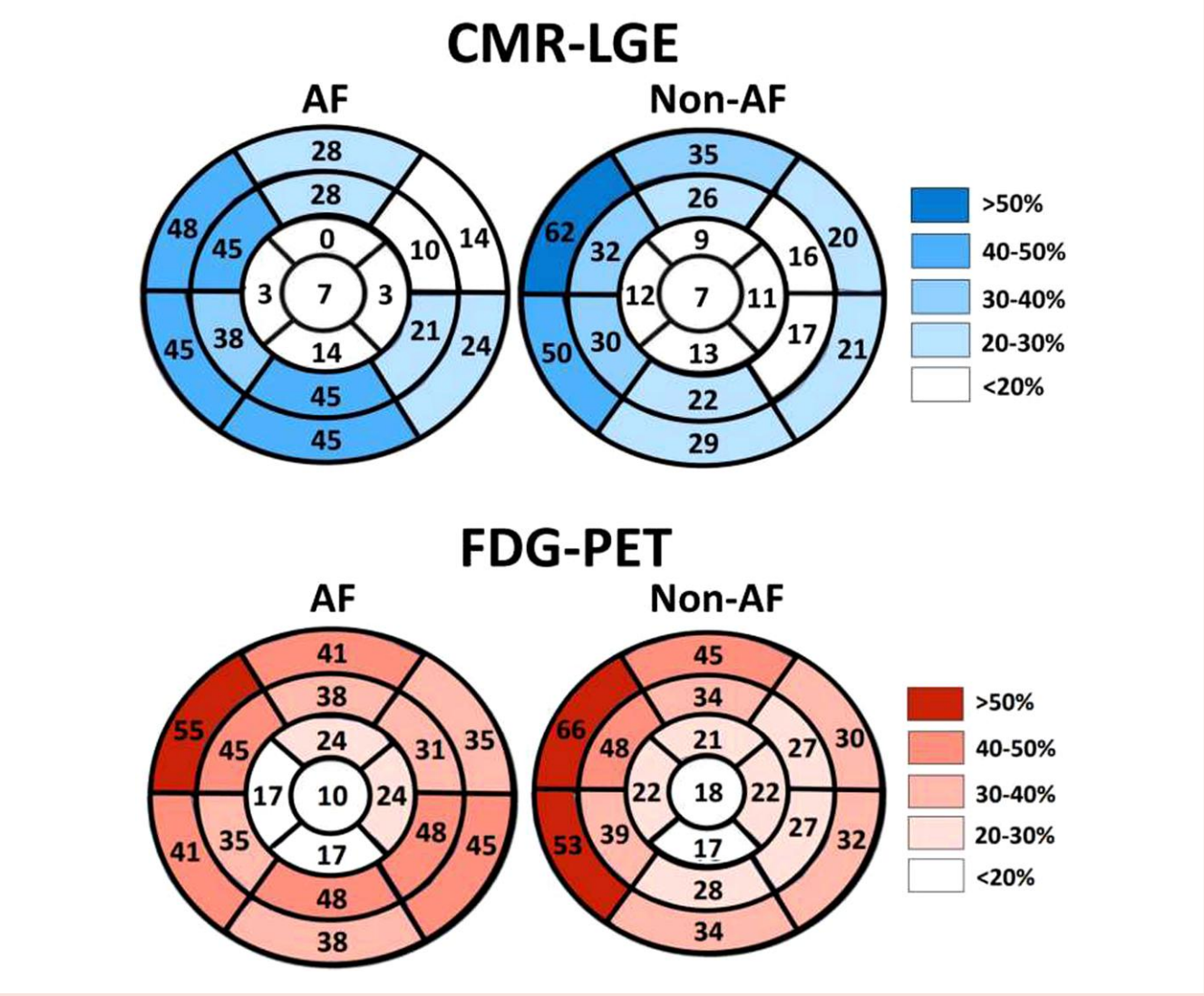


Figure 1 Percentages of patients with AF and without AF showing LGE hyperenhancement and FDG uptake in each of the 17 segments of the myocardium. AF, atrial fibrillation; CMR-LGE, cardiac magnetic resonance late gadolinium enhancement; FDG-PET, ^{18}F-fluorodeoxyglucose-positron emission tomography; non-AF, absence of atrial fibrillation.

reported in patients with systemic sarcoidosis; furthermore, after adjustment, patients were found to have a risk of developing AF 10-fold higher than that of people without sarcoidosis.[33] Our data suggested that the prevalence of AF in patients with CS at the time of diagnosis is much higher than previously expected, and that AF may be an overlooked or underestimated comorbidity.

To date, the prognostic implications of AF comorbidity in patients with CS are unclear. Our survival analysis revealed that patients with AF had lower event-free survival rates for combined endpoints, including all-cause death and HF hospitalization. These results are consistent with those of previous studies. A study including 1638 patients with CS wearing an implantable cardioverter-defibrillator (ICD) found that AF/atrial flutter was associated with a high mortality rate (HR, 1.66; 95% CI, 1.17–2.35), independently of other prognostic factors.[22] However, this study focused on patients with ICD, and CS was not diagnosed according to current guidelines. Considering patients with systemic sarcoidosis (not limited to CS), a study based on the Office of Statewide Health Planning and Development California State Databases including 19 225 patients with systemic sarcoidosis found that 44% (95% CI, 31–57%) of the increased mortality could be explained by AF.[33] These results support our findings that the presence of AF in patients with CS increased the risk of adverse events.

Concerning HF hospitalization, it is widely known that AF itself provokes HF hospitalization,[34,35] but our analysis revealed that HF incidence rates in patients with CS concomitant AF were much higher than those in patients with AF. A Japanese community-dwelling prospective 5-year follow-up study revealed that 3 out of 91 (3.3%) patients with AF (mean age, 59 years) had incidental HF.[35] One retrospective Japanese study showed that during the mean follow-up of 50 months, 16 out of 248 (6.5%) patients with AF (mean age, 64 years) experienced HF requiring hospitalization.[34] Alternatively, our analysis demonstrated that 9 out of 46 (17%) patients with CS concomitant AF had HF hospitalization during the median follow-up of 3.2 years, which was much higher than those in average Japanese patients with AF, suggesting the significant impact of AF on HF in patients with CS.

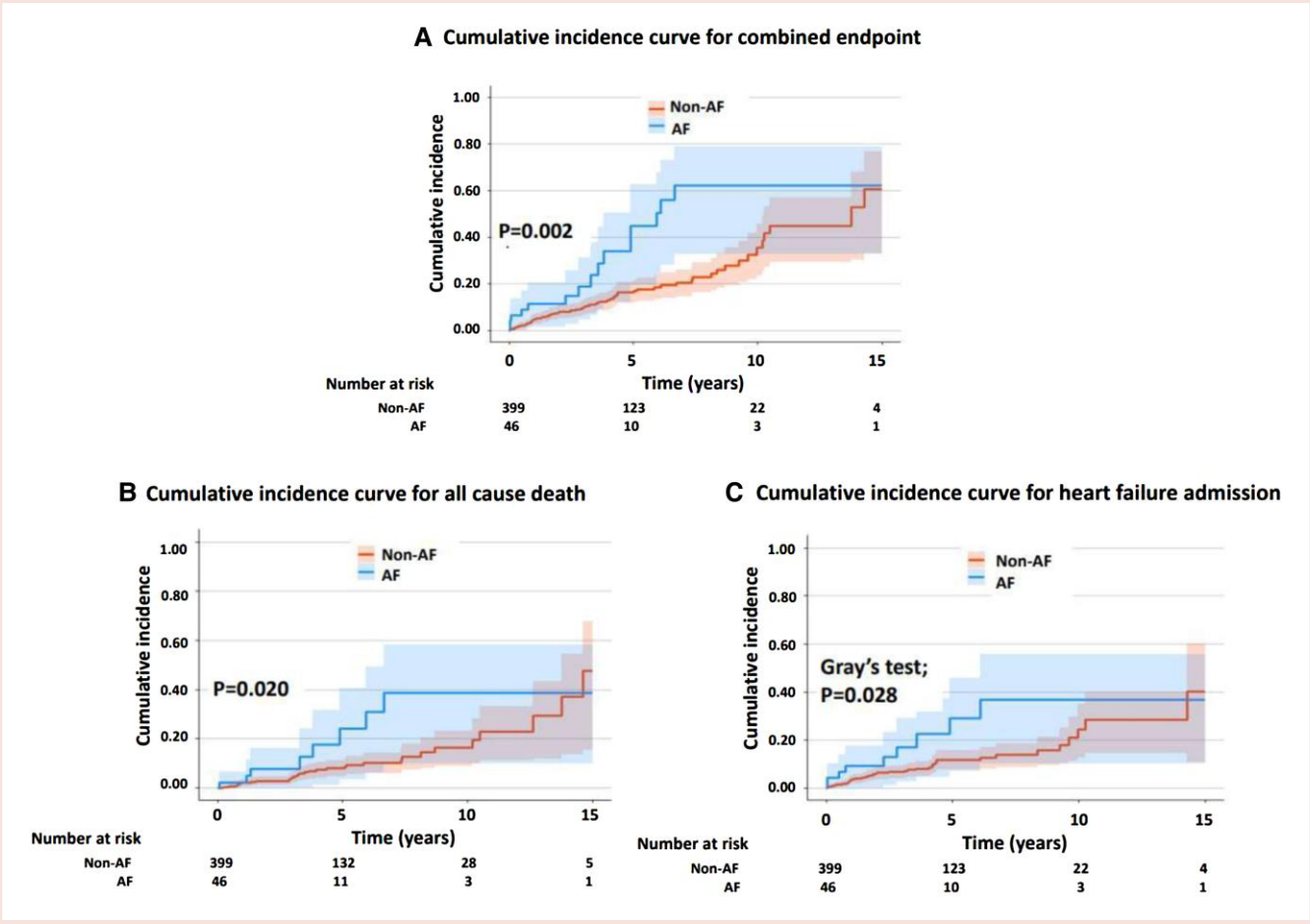


Figure 2 Cumulative incidence curves of (*A*) combined endpoint, (*B*) all-cause death, and (*C*) heart failure hospitalization between patients with AF and without AF. AF, atrial fibrillation; non-AF, absence of atrial fibrillation.

Table 3 Cox proportional hazard analysis for primary outcomes

Model	HR	95% CI	*P* value
Unadjusted model	2.36	1.33–4.19	0.004
Adjusted model 1[a]	2.11	1.18–3.78	0.012
Adjusted model 2[b]	2.14	1.17–3.91	0.015
Adjusted model 3[c]	1.96	1.05–3.65	0.035

[a]Adjusted for age and sex.
[b]Adjusted for age, sex, log-transformed brain natriuretic peptide level, left ventricular ejection fraction, history of heart failure admission, and creatinine level at baseline.
[c]Adjusted for age, sex, log-transformed brain natriuretic peptide level, left ventricular ejection fraction, history of heart failure admission, creatinine level at baseline, and left atrium diameter.

Our study was not designed to investigate why AF had prognostic value in patients with CS, and the pathophysiological background of this association is yet to be clarified; however, several hypotheses can be put forward. First, patients registered in ILLUMINATE-CS were older than patients in other registries including patients with CS,[30,31] which might lead to the higher prevalence of AF at the time of CS diagnosis. While patients with AF had a higher prevalence of hypertension, the prevalence of other AF risk factors, including diabetes, dyslipidaemia, coronary artery disease, and other arrhythmias, was not statistically different between the two groups, suggesting that compared with the general population, patients with CS might have a different pathogenetic background. Niemela et al. reported that abnormal atrial ^{18}F-FDG uptake, left atrial maximum volume in CMR, and sleep apnoea were risk factors for developing AF in 118 patients with CS.[28] Yodogawa et al. also reported that the prevalence of atrial arrhythmias, including AF, among 62 patients with CS was higher in patients with atrial ^{18}F-FDG uptake than in patients without.[36] These results suggested that a combination of atrial wall inflammation and known risk factors causing atrial remodelling might contribute to AF, leading to HF and death in patients with CS. Second, as systemic sarcoidosis is significantly associated with AF, the development of AF in patients with CS might reflect the intensity of systemic inflammation and be associated with poor prognosis.[37] Final, ICD implantation is recommended for a significant number of patients with CS. Inappropriate ICD shock was found to be one of the common adverse events in patients with ICD and was associated with higher mortality.[38] AF was the most common trigger of inappropriate ICD shock[39]; consequently, inappropriate shocks caused by AF could be associated with poor prognosis in patients with CS.

Given the prevalence and prognostic impact of AF in patients with CS, more attention should be paid to the presence of AF at the time of CS diagnosis. Ischaemic stroke is a frequent complication of both AF and sarcoidosis[40]; therefore, early AF diagnosis and anticoagulant

Table 4 Univariable and adjusted Cox regression models for combined endpoints as sensitivity analysis

Variables	Univariable			Multivariable		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
AF	2.36	1.33–4.19	0.004	1.89	1.02–3.49	0.043
Age	1.06	1.04–1.09	<0.001	1.05	1.02–1.08	0.001
Male sex	0.81	0.49–1.33	0.394			
NYHA class III or IV	2.40	1.41–4.08	0.002	1.37	0.73–2.56	0.316
Hypertension	2.01	1.28–3.15	0.003	1.27	0.76–2.11	0.355
Diabetes	0.84	0.49–1.44	0.520			
History of heart failure admission	2.92	1.85–4.60	<0.001	1.34	0.77–2.35	0.292
History of VT or VF	1.18	0.67–2.09	0.562			
History of AVB	1.02	0.65–1.60	0.930			
LVEF	0.97	0.96–0.98	<0.001	0.99	0.97–1.00	0.140
Log-transformed BNP	1.69	1.37–2.08	<0.001	1.32	1.03–1.71	0.032
Creatinine	1.47	1.16–1.86	0.002	1.31	0.85–2.01	0.222
Gallium-67 accumulation	0.60	0.32–1.15	0.118			
LGE on CMR	0.54	0.21–1.43	0.207			
PET accumulation	0.53	0.24–1.16	0.110			
Pacemaker implantation	1.37	0.84–2.23	0.197			
ICD/CRT-D implantation	1.22	0.61–2.41	0.571			
ACEi/ARB at baseline	1.96	1.22–3.15	0.006	0.93	0.53–1.63	0.804
MRA at baseline	2.00	1.21–3.31	0.008	1.15	0.63–2.09	0.645
Beta-blocker at baseline	2.23	1.40–3.54	<0.001	1.25	0.70–2.24	0.453
Amiodarone at baseline	2.07	1.08–3.97	0.028	1.39	0.68–2.84	0.364
Steroid use after diagnosis	0.72	0.38–1.34	0.296			

Variables with a *P*-value <0.1 in the univariable Cox analysis were considered for inclusion.

therapy initiation might be important. The efficacy of AF treatments, such as antiarrhythmic drugs and catheter ablation, has not been well established in patients with CS[16]; however, one case study has suggested that ablation may be useful in AF for maintaining sinus rhythm in patients with CS.[41] Further prospective studies assessing the prognostic impact of ablation in AF in a large number of patients with CS are warranted.

The present study has several limitations. First, some patients were diagnosed based on the JCS guidelines, and histological assessment was not performed. However, these patients were found to have a poor prognosis similar to that of patients assessed with the HRS criteria.[42] Second, data regarding patient lifestyle risk factors for developing AF, including sleep disorder and alcohol intake, was lacking. Third, due to its retrospective design, there were potential sampling biases and incomplete data in this study. Although we tried to standardize data quality as much as possible, owing to our inclusion of experienced and board-certified cardiologists for data collection, there could be disparities in data accuracy. Four, we investigated the presence of AF only at the time of CS diagnosis; therefore, we could not analyse the incidence of AF following CS diagnosis. Given that the incidence of AF in patients with sarcoidosis was very high during follow-up, and considering that most of the AF cases at the time of CS diagnosis were paroxysmal, AF might have been underdiagnosed owing to the method of detecting AF. Fifth, while abnormal atrial 18F-FDG uptake and left atrial maximum volume in CMR are known predictors of AF in patients with CS,[28] we did not have data regarding atrial findings in CMR or FDG-PET. Although our multivariable Cox analysis including LAD as an adjusting variable showed that AF was independently associated with poor prognosis, further research is warranted to investigate the association between atrial imaging findings and prognosis in patients with CS.

Conclusions

The presence of AF at the time of CS diagnosis is independently associated with a higher incidence of the combined endpoint including all-cause death and HF hospitalization.

Lead author biography

Yudai Fujimoto is a cardiologist and research fellow at Juntendo University Hospital in Tokyo, Japan, and a PhD candidate at Juntendo University. His research interests include chronic heart failure, frailty, cardiomyopathies, sarcoidosis, and atrial fibrillation.

Data availability

The data underlying this study will be shared on reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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Author contributions

Y.F. and Y.M. contributed to the conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, and writing the original draft. Y.M. contributed to the funding acquisition and supervision. All authors contributed to the data curation and interpretation, revised the manuscript, gave final approval, and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy.

Consent

The requirement for informed consent was waived owing to the retrospective nature of the study.

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