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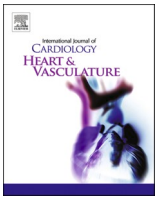

Characteristics and incidence of cardiac events across spectrum of age in cardiac sarcoidosis

Takeru Nabeta [a,b,*], Shingo Matsumoto [c,d], Shunsuke Ishii [a], Yuko Eda [a], Mayu Yazaki [a], Teppei Fujita [a], Yuichiro Iida [a], Yuki Ikeda [a], Takeshi Kitai [e], Yoshihisa Naruse [f], Tatsunori Taniguchi [g], Kenji Yoshioka [h], Hidekazu Tanaka [i], Takahiro Okumura [j], Yuichi Baba [k], Yuya Matsue [l], Junya Ako [a]

[a] Department of Cardiovascular Medicine, Kitasato University School of Medicine, Sagamihara, Japan
[b] Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands
[c] Division of Cardiovascular Medicine, Department of Internal Medicine, Faculty of Medicine, Toho University, Tokyo, Japan
[d] British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom
[e] Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan
[f] Division of Cardiology, Internal Medicine III, Hamamatsu University School of Medicine, Hamamatsu, Japan
[g] Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
[h] Department of Cardiology, Kameda Medical Center, Chiba, Japan
[i] Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan
[j] Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[k] Department of Cardiology and Geriatrics, Kochi Medical School, Kochi University, Nankoku, Japan
[l] Department of Cardiovascular Biology and Medicine, Juntendo University Graduate School of Medicine, Tokyo Japan

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ABSTRACT

Background: Clinical characteristics and the risk of cardiovascular events in patients with cardiac sarcoidosis (CS) according to the age of initial diagnosis are unclear.
Methods: This study is a sub-analysis of the ILLUMINATE-CS registry, which is a retrospective, multicenter registry that enrolled patients with CS between 2001 and 2017. Patients were divided into three groups according to the tertile of age at the time of initial diagnosis of CS. The study compared the clinical background at the time of CS diagnosis and the incidence rate of cardiac events across age categories.
Results: A total of 511 patients were analyzed in this study. In baseline, older patients were more likely to be female. History of hypertension, heart failure admission, and atrioventricular block were more common in patients with older age. There was no significant difference in the history of ventricular arrhythmias and left ventricular ejection fraction among all age groups. During a median follow-up period of 3.2 [IQR: 1.7–4.2] years, 35 deaths, 56 heart failure hospitalization, and 98 fatal ventricular arrhythmias was observed. The incidence rate of all-cause death and heart failure hospitalization was significantly higher in patients with older age ($p < 0.001$), while there was no significant difference in the incidence rate of ventricular arrhythmia among age groups ($p = 0.74$).
Conclusions: In patients with CS, the risk of all-cause death and heart failure hospitalization was higher in older patients compared with other age groups; however, the risk of ventricular arrhythmia was comparable across all age groups.

1. Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology [1]. Cardiac sarcoidosis (CS) is one of the subtypes and has been observed in upwards of one-quarter of patients with sarcoidosis [2,3]. Furthermore, CS is the primary cause of mortality in patients with sarcoidosis [4].

In general, patients with CS are diagnosed in their forties, which is

* Corresponding author.
E-mail address: takerunabeta@gmail.com (T. Nabeta).

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relatively younger than the average age of diagnosis for most cardiovascular diseases [5]. In contrast, older patients are increasingly being diagnosed with sarcoidosis within aging society [6]. Moreover, over the past four decades, the rate of cardiac involvement also seems to have been increasing [6]. Indeed, the mean age at the time of initial diagnosis of CS in our recent reports is approximately 50 years, which is higher than the findings of previous reports that included patients diagnosed with CS before the 2000s [7–11]. The clinical phenotype and the risk of cardiac events might vary depending on the age at the diagnosis in patients with CS, as well as other cardiovascular diseases [12,13]. However, investigations exploring the correlation between clinical significance and age at the diagnosis has been lacking in patients with CS.

The risk of development or worsening Heart failure (HF), one of the most common unfavorable cardiac events in patients with CS [7], has close relationship with age, in both patients with and without HF [13,14]. Thus, age would contribute to an increased incidence of HF in patients with CS as well.

Consequently, it is crucial to evaluate the disparities in clinical phenotype and incidence of cardiac events, particularly HF, across age at the diagnosis. This investigation would not only enhance our understanding of the disease biology but also inform the appropriate treatment strategies for patients with CS.

Hence, the current study aims to examine the differences in clinical characteristics and incidence risk of cardiac events according to the age at initial diagnosis in patients with CS.

2. Methods

2.1. Study patients

We included patients with first diagnosed CS at 33 hospitals in Japan in the ILLUMINATE-CS (ILLUstration of the Management and prognosis of JapaNese pATiEnts with Cardiac Sarcoidosis), which was multicenter retrospective registry to reveal the clinical characteristics and outcomes of patients with CS [7]. The diagnosis of CS was according to either the guideline of the Japanese Circulation Society proposed in 2016 or the Heart Rhythm Society 2014 consensus statement [1,15].

This study complied with the Declaration of Helsinki and Japanese Ethical Guidelines for Medical and Health Research involving Human Subjects. The study protocol was approved by the ethical committee of each participating hospital, and informed consent was waived due to the retrospective design.

2.2. Data collection and outcomes

Baseline clinical information, including age, clinical comorbidities, blood test data, and findings on cardiovascular imaging, were obtained at the time of initial diagnosis of CS. Findings of cardiac accumulation on ^{67}Ga scintigraphy and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), and late gadolinium enhancement on cardiac magnetic resonance imaging (CMR-LGE) were determined from expert reports at each institution. To evaluate the distribution on accumulation of ^{67}Ga scintigraphy and FDG-PET, and CMR-LGE, we used the American Heart Association 17-segment model [16].

The primary outcome of the present study was a composite of all-cause death and heart failure hospitalization. In addition, we assessed the incidence of fatal ventricular arrhythmia event (FVAE) as a secondary endpoint. All outcomes were ascertained from medical records. FVAE was defined as a combination of sudden cardiac death and either documented ventricular fibrillation (VF), sustained ventricular tachycardia (VT) lasting >30 s, or appropriate implantable cardioverter defibrillator therapy. Sudden cardiac death and heart failure hospitalization were determined based on the definitions proposed by the Heart Failure Collaboratory and the Academic Research Consortium [17].

2.3. Statistical analysis

Normally distributed continuous variables are expressed as mean ± standard deviation, while non-normally distributed variables are presented as median and interquartile range (IQR). Categorical variables are expressed as numbers and percentages. Patients in the study were divided into three groups based on age tertile. Group differences were compared using the one-way analysis of variance or Kruskal-Wallis test for continuous variables, whereas categorical variables were compared using the Pearson chi-squared test or Fisher's exact test, as appropriate. Clinical outcomes are reported as the number of events. Kaplan-Meier curves and log-rank analysis were used to compare the cumulative incidence of the primary outcome among the groups. For FVAE and heart failure hospitalization alone, cumulative incidence curves were constructed using a Fine-Gray competing risk regression analysis, with all-cause death as the competing risk. Spline curve analysis was utilized to investigate the change in hazard ratio (HR) using Cox regression analysis for the primary outcome, FVAE, heart failure hospitalization, and all-cause death over a range of ages. Unadjusted Cox regression analysis for the primary outcome and all-cause death or using Fine-Gray competing risk regression analysis for FVAE and heart failure hospitalization alone across the age groups. Adjusted Cox regression analysis was also performed to evaluate the association between the groups divided by age and the primary outcome. The adjusted model included the group divided by age, sex, LVEF, log-transformed B-type natriuretic peptide (BNP), and a history of VF or sustained VT, which were shown to be prognostic factors in the previous studies in patients with CS [7,18]. All two-sided *P*-values were considered statistically significant. All statistical analyses were performed with R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

2.4. 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.

3. Results

Of the 512 patients in the ILLUMINATE-CS registry, one patient was excluded due to missing age data. These patients were divided into three groups according to the tertile of the age at the time of initial diagnosis (≤57; low age n = 172, 58–67; middle age n = 187, ≥68; high age n = 152). The baseline characteristics of the patients are shown in Table 1. Male patients were more frequent in the low age group. History of hypertension, heart failure hospitalization, and atrioventricular block (AVB) were more common in the high age group. The high age group also showed higher plasma BNP levels and a larger left atrial diameter. There were no significant differences in the rate of organ involvement of sarcoidosis, the history of sustained VT or VF, or LVEF among the groups. Steroid therapy was administered less frequently in the high age group. However, in patients who administrated steroid therapy, there were no significant differences in the initial and maintenance doses of steroid therapy among the groups.

During a median follow-up period of 3.2 [IQR: 1.7–4.2] years the primary outcome occurred in 91 (17.8 %) patients (35 deaths and 56 heart failure hospitalization), and FVAE was occurred in 98 (19.1 %) patients. Kaplan-Meier curve analysis demonstrated that patients in the higher age group had a higher risk of the primary outcome. (Fig. 1A, $p < 0.01$, respectively) Whereas there were no significant differences in the cumulative incidence of FVAE among the age subgroups. (Fig. 1B, $p = 0.74$) The risk of heart failure hospitalization or all-cause death alone was significantly higher in the high age group. (Fig. 1C and D) In the spline curve analysis, there was a steep increase in HR for the primary outcome and heart failure hospitalization from approximately 60 years of age. (Fig. 2A and B) In contrast, the HR for FVAE was almost constant across all age groups. (Fig. 2C). The number of events and event rate per

Table 1
Baseline characteristics.

Characteristic	Overall, N = 511	Low age (≤57) N = 172	Middle age (58–67) N = 187	High age (68 ≤) N = 152	p-value
Age, years (years)	62 ± 11	49 ± 7	63 ± 3	74 ± 5	<0.001
Sex, male, n (%)	183 (35.8)	82 (47.7)	54 (28.9)	47 (30.9)	<0.001
Organ Involvement					
Isolated cardiac sarcoidosis, n (%)	152 (30)	54 (31)	55 (29)	43 (28)	0.824
Lung, n (%)	284 (57)	102 (60)	102 (56)	80 (53)	0.440
Eye, n (%)	135 (27)	39 (23)	52 (29)	44 (30)	0.385
Skin, n (%)	104 (21)	27 (16)	41 (24)	36 (24)	0.148
Medical history					
Hypertension, n (%)	180 (37.1)	43 (25.9)	63 (36.4)	74 (50.7)	<0.001
Diabetes, n (%)	130 (26.9)	42 (25.5)	47 (27.3)	41 (28.1)	0.863
Heart failure hospitalization, n (%)	98 (20.0)	23 (13.8)	35 (20.0)	40 (27.2)	0.012
Sustained VT/VF, n (%)	76 (15.7)	24 (14.5)	31 (17.7)	21 (14.5)	0.649
High degree Atrioventricular Block, n (%)	218 (44.6)	61 (37.2)	82 (45.8)	75 (51.4)	0.040
Atrial fibrillation, n (%)	48 (10.0)	13 (8.0)	15 (8.7)	20 (13.9)	0.177
NYHA functional class ≥ 3, n (%)	62 (12.8)	15 (9.1)	28 (15.9)	19 (13.1)	0.167
Laboratory data at baseline					
Plasma BNP level (pg/mL)	123.2 [53.7–327.4]	78.3 [33.1–211.9]	119.0 [56.0–261.5]	176.0 [86.0–478.9]	<0.001
Serum creatinine (mg/dL)	0.88 (0.52)	0.86 (0.55)	0.87 (0.58)	0.91 (0.42)	0.648
Echocardiographic findings					
LVEF (%)	49 (16)	48 (15)	49 (16)	50 (16)	0.779
LVEF < 50 %, n (%)	247 (50)	82 (49)	89 (49)	76 (51)	0.875
LV end-diastolic diameter (mm)	53 (10)	53 (10)	53 (9)	52 (9)	0.624
LV end-systolic diameter (mm)	40 (12)	40 (12)	40 (12)	39 (12)	0.650
Left atrium diameter (mm)	38 (8)	35 (8)	38 (8)	39 (7)	<0.001
Interventricular septal thinning, n (%)	212 (43)	70 (43)	74 (41)	68 (47)	0.507
Other Imaging test findings					
Ga-scintigraphy accumulation, n (%) (N = 263)	98 (37.3)	40 (46.0)	37 (37.8)	21 (26.9)	0.041
Ga-scintigraphy segment	0 [0–2]	0 [0–1]	0 [0–2]	0 [0–1]	0.126
CMR-LGE, n (%) (N = 307)	282 (91.9)	104 (89.7)	107 (95.5)	71 (89.9)	0.203
CMR-LGE segment	4 [2–6]	4 [2–5]	4 [2–6]	4 [2–5]	0.229
FDG-PET accumulation, n (%) (N = 342)	324 (94.7)	101 (91.8)	124 (96.1)	99 (96.1)	0.250
FDG-PET segment	5 [2–8]	5 [3–8]	5 [2–8]	4 [3–7]	0.755
Medical and device therapy					
ACEi or ARB, n (%)	252 (50.3)	74 (44.3)	91 (49.7)	87 (57.6)	0.059
Beta-blocker, n (%)	201 (40.2)	59 (35.3)	75 (41.2)	67 (44.4)	0.244
Steroid use (at any time point), n (%)	448 (87.7)	153 (89.0)	171 (91.4)	124 (81.6)	0.019
Initial dose of steroid (mg/day of predonisone equivalent)	30 [30–30]	30 [30–30]	30 [30–30]	30 [30–30]	0.630
Maintain dose of steroid mg/day of predonisone equivalent)	5 [5–10]	5 [5–10]	5 [5–10]	5 [5–10]	0.354
Pacemaker implantation, n (%)	142 (28.5)	32 (19.0)	54 (30.0)	56 (37.3)	0.001
ICD/CRT-D implantation, n (%)	54 (11.1)	12 (7.1)	26 (15.3)	16 (10.8)	0.058

VT; ventricular tachycardia, VF; ventricular fibrillation, NYHA; New York Heart Association, BNP; B-type natriuretic peptide, LVEF; left ventricular ejection fraction, CMR; cardiac magnetic resonance, LGE; late gadolinium enhancement, FDG-PET; ^{18}F-fluorodeoxyglucose positron emission tomography, ACEi angiotensin-converting enzyme inhibitors, ARB; angiotensin receptor-2 blocker, ICD; implantable cardioverter defibrillator, CRT-D; Cardiac resynchronization therapy defibrillator.

100 person-years of each event among the age subgroups were listed in Table 2. In the unadjusted Cox hazard model, the high age group [HR: 4.2, 95 % confidence interval (CI) 2.3–7.1, p < 0.01) was associated with the higher incidence of the primary outcome, but the middle age group was not (HR: 1.8, 95 %CI 0.9–3.3, p = 0.06) compared with the low age group. In the adjusted Cox hazard model, the trend was not different; the HR was 3.0 (95 %CI 1.5–6.3, p < 0.01) for the high age group and 0.8 (95 %CI 0.6–2.9, p = 0.49) for the middle age group compared with the low age group. (Table 2).

We additionally assessed the event risk among the groups divided by tertile of LVEF: <41 %, 42–57 %, and >58 %, as well as among groups stratified by age. Patients in the low age group exhibited a lower risk achieving primary events and HF hospitalization within the LVEF < 41 % or 42–57 % group. However, this trend was not observed in the LVEF > 58 % group (p for interaction 0.07 and 0.04, respectively). There were no significant interactions in the incidence rate of all-cause mortality and FVAE among the groups divided by LVEF and age tertile (p for interaction 0.46 and 0.51, respectively, Supplemental figure).

4. Discussion

The findings of the current study demonstrated that: (i) the high age group had a higher comorbidity, such as hypertension or AVB, and higher BNP levels compared with the low and middle age groups, but the prevalence of organ involvement of sarcoidosis, history of VT or VF and LVEF were not significantly different among the groups; (ii) the risk of the all-cause death or heart failure hospitalization was higher in the high age group, whereas the risk of FVAE was similar among the groups stratified by age.

4.1. Age differences in patient characteristics at CS diagnosis

Previous investigation has shown that the prevalence of lung or skin sarcoidosis is similar between low and high age populations, whereas cardiac and eye involvement are more common in older patients [6]. Although the current study revealing that eye involvement tended to increase in the higher age group, the prevalence of sarcoidosis organ involvement was consistent in CS among age-groups. In the current study, the history of hypertension and HF hospitalization was higher in

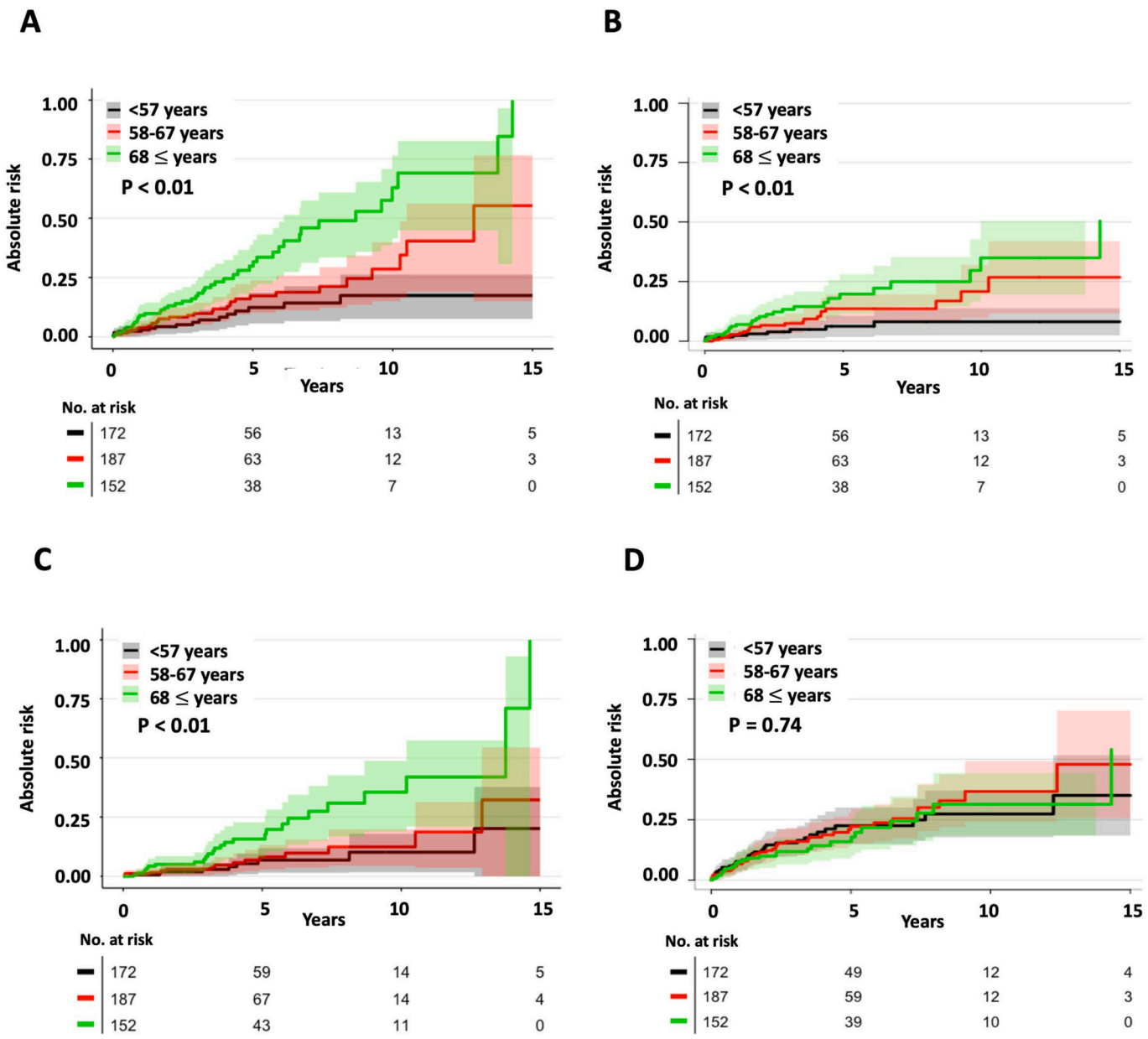

Fig. 1. Cumulative incidence for primary outcome (A), heart failure hospitalization (B), all-cause death (C), and fatal ventricular arrhythmia events (D).

the high age group. This trend corresponds with the general increase in prevalence of both hypertension and HF increases as part of the aging process, a trend that is also evident in patients with CS [13,14]. Although, LVEF and LV diameters were similar across the age groups, the high age group displayed larger left atrium diameter and higher BNP levels, which might indicate increased LV filling pressure in the high age group compared to the other groups [19,20]. Furthermore, these elevated LV filling pressure in the high age group could lead to the higher rate of heart failure hospitalization in this age group.

Previous studies of predominantly younger patients (in their 50 s) have shown a high prevalence of patients with a history of VT or VF (20–30 %) and AVB (20–40 %) at the time of CS diagnosis [8,18,21,22]. Similarly, a frequent history of VT or VF (14–17 %) and AVB (37–51 %) was observed across all age groups in the current study. Moreover, the history of AVB was more common in the high age group compared to the other groups. This is consistent with the expected age-related increase in AVB cases due to degenerative AV node abnormalities related to aging [23,24]. In younger to middle-aged patients, a previous report has indicated that the prevalence rate of AVB in patients with CS that is significantly higher compared with other cardiac diseases [25]. In the high age group of this study, half of patients had a history of AVB, a rate that far exceeds the general incidence rate of AVB in the elderly population (8 %) as well as in other age groups [26]. Thus, it is essential to consider the possibility of CS in patients of all age groups presenting with unexplained AVB.

Although, the administration rates of angiotensin-converting enzyme inhibitors or angiotensin receptor-2 blocker and beta-blocker were comparable among all age groups, the high age group was less likely to receive steroid therapy than the other groups. Physicians may have considered the risk–benefit ratio of steroid therapy for CS to be less favorable in elderly patients because of the known adverse effects of these drugs.

4.2. *Age differences in event risk*

The current study showed that the incidence rate of the composite of all-cause death and HF hospitalization was higher in the high age group compared with other groups. Interestingly, in a study of 8,468 with HF

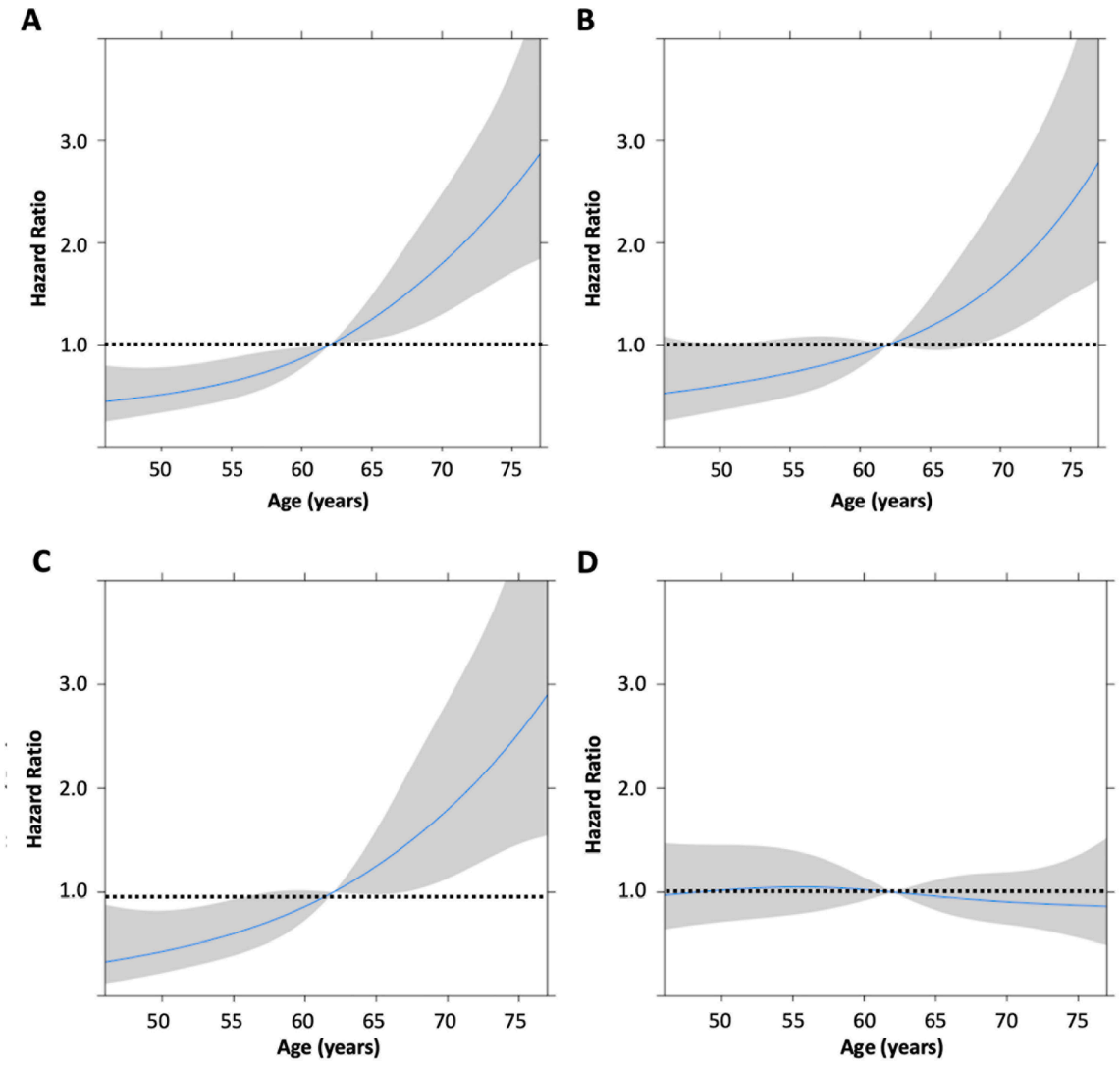

Fig. 2. Relationship between age and the hazard ratio for primary outcome (A), heart failure hospitalizations (B), all-cause death (C). and fatal ventricular arrhythmia events (D), Shaded grey area displayed 95 % confidence interval.

and preserved EF indicated that the incidence rate of HF hospitalization and all-cause death in the high age group of the current study was comparable to that in elderly patients with HF and preserved EF [14]. This observation aligns with a previous study of 11,834 patients with sarcoidosis, which showed that heart failure development was more prevalent in older patients [4]. While the underlying etiology for HF in patients with CS remains unclear, it might be similar to heart failure from other etiologies, as given share risk factors such as age, atrial fibrillation, and BNP levels [13]. The previous study also indicated that patients with sarcoidosis and heart failure were less likely to receive guideline recommended therapy [4]. Given the incidence rates of HF and all-cause death in patients with CS is not low, this emphasizes the importance of appropriate HF treatment, particularly for elderly patients.

Unlike all-cause death and HF hospitalization, the incidence of FVAE was consistently high in patients with CS and it did not differ significantly across age groups. In general, the risk of VT or VF increases with age, thus this tendency may be a specific feature of patients with CS [27]. Since CS is a major cause of FVAE in young and middle-aged generations, arguments about the management of FVAE in CS often focus on younger generations [28]. However, as the current study demonstrated, the risk of FVAE is still high in older patients as well. Moreover, the incidence rate of FVAE in the high age group with CS may be significantly higher compared to the incidence rate of ventricular tachycardia in non-CS elderly patients [29]. For this reason, appropriate management of FVAE, such as implantable cardiac defibrillator or catheter ablation, should be considered in patients with CS irrespective of patient age.

5. Limitations

The current study has several limitations. First, due to its retrospective design, certain clinical or imaging variables were unavailable. Second, the limited number of events, particularly HF hospitalization, might have restricted our statistical power to assess risk of events across age groups. Third, certain patients were diagnosed with CS without histological proof of sarcoidosis, as CS can be diagnosed using a combination of clinical and imaging findings according to the Japanese Circulation Society guideline [1].

6. Conclusions

We identified age-dependent differences in the clinical profiles at the diagnosis of CS. The risk of HF hospitalization and all-cause mortality was higher in patients with the high age group compared to other age groups. However, the risk of FVAE was regularly high and did not differ

Table 2
Outcomes according to age.

	Age group		
	Low age	Middle age (58–67)	High age
	N = 172	N = 187	N = 152
All-cause death or hospitalization for HF			
No. of events	16 (9.3 %)	30 (16.0 %)	45 (29.6 %)
Event rate per 100 person-y (95 % CI)	2.1 (1.3–3.4)	3.7 (2.6–5.2)	8.1 (6.0–10.8)
Unadjusted HR (95 % CI)	Reference	1.8 (0.9–3.3)	4.2 (2.3–7.1)
Adjusted HR (95 %CI)*	Reference	0.8 (0.6–2.9)	3.0 (1.5–6.3)
Hospitalization for HF			
No. of events	9 (5.2 %)	21 (11.2 %)	26 (17.1 %)
Event rate per 100 person-y (95 % CI)	1.2 (0.6–2.2)	2.6 (1.7–3.9)	4.7 (3.2–6.9)
Unadjusted HR (95 % CI)	Reference	2.2 (1.0–4.8)	4.0 (1.9–8.5)
All-cause death			
No. of events	9 (5.2 %)	14 (7.5 %)	26 (17.1 %)
Event rate per 100 person-y (95 % CI)	1.1 (0.6–2.2)	1.6 (1.0–2.7)	4.3 (2.9–6.3)
Unadjusted HR (95 % CI)	Reference	1.5 (0.6–3.4)	4.1 (1.9–8.8)
Fatal Ventricular Arrhythmia events			
No. of events	33 (19.2 %)	39 (20.9 %)	26 (17.1 %)
Event rate per 100 person-y (95 % CI)	4.7 (3.3–6.6)	5.0 (3.6–6.8)	4.6 (3.1–6.8)
Unadjusted HR (95 % CI)	Reference	1.1 (0.7–1.7)	1.0 (0.6–1.6)

HR; hazard ratio, CI; confidence interval, HF; heart failure.
*Multivariate model for death or hospitalization for HF included sex, left ventricular ejection fraction, b-type natriuretic level, and history of ventricular fibrillation or sustained ventricular tachycardia.

significantly across all age groups. Further studies are needed to determine the age-specific management strategies in patients with CS.

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CRediT authorship contribution statement

Takeru Nabeta: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Project administration, Funding acquisition. **Shingo Matsumoto:** Conceptualization, Methodology, Investigation, Supervision, Writing – review & editing. **Shunsuke Ishii:** Writing – review & editing, Investigation. **Yuko Eda:** Data curation, Investigation, Writing – review & editing. **Mayu Yazaki:** Data curation, Writing – review & editing, Investigation. **Teppei Fujita:** Writing – review & editing, Investigation. **Yuichiro Iida:** Data curation, Writing – review & editing. **Yuki Ikeda:** Data curation, Investigation, Writing – review & editing. **Takeshi Kitai:** Methodology, Supervision, Writing – review & editing, Investigation. **Yoshihisa Naruse:** Supervision, Writing – review & editing. **Tatsunori Taniguchi:** Project administration, Writing – review & editing, Investigation. **Kenji Yoshioka:** Data curation, Investigation. **Hidekazu Tanaka:** Data curation, Investigation. **Takahiro Okumura:** Data curation, Investigation. **Yuichi Baba:** Data curation, Writing – review & editing. **Yuya Matsue:** Data curation, Formal analysis, Resources, Supervision, Writing – review & editing. **Junya Ako:** Funding acquisition, Supervision, Resources.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Yuya Matsue received an honorarium from Otsuka Pharmaceutical Co. and Novartis Japan. Dr. Takahiro Okumura received honoraria from Ono Yakuhin, Otsuka, Novartis, and Astrazeneca and research grants from Ono Yakuhin, Amgen Astellas, Pfizer, Alnylam, and Alexion (not in connection with the submitted work). The authors have no conflicts of interest to declare.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2023.101321.

References

[1] F. Terasaki, A. Azuma, T. Anzai, et al., JCS 2016 Guideline on Diagnosis and Treatment of Cardiac Sarcoidosis - Digest Version, Circ. J. 83 (2019) 2329–2388.
[2] N.A. Gilotra, J.M. Griffin, N. Pavlovic, et al., Sarcoidosis-related cardiomyopathy: current knowledge, challenges, and future perspectives state-of-the-art review, J. Card. Fail. 28 (2022) 113–132.
[3] R.J. Kim, M.R. Patel, P.J. Cawley, et al., Detection of myocardial damage in patients with sarcoidosis, Circulation 120 (2009) 1969–1977.
[4] A. Yafasova, E.L. Fosbøl, M. Schou, et al., Long-term adverse cardiac outcomes in patients with sarcoidosis, J. Am. Coll. Cardiol. 76 (2020) 767–777.
[5] P. Brito-Zerón, B. Kostov, D. Superville, et al., Geoepidemiological big data approach to sarcoidosis: geographical and ethnic determinants, Clin. Exp. Rheumatol. 37 (2019) 1052–1064.
[6] M. Sawahata, Y. Sugiyama, Y. Nakamura, et al., Age-related and historical changes in the clinical characteristics of sarcoidosis in Japan, Respir. Med. 109 (2015) 272–278.
[7] T. Nabeta, T. Kitai, Y. Naruse, et al., Risk stratification of patients with cardiac sarcoidosis: the ILLUMINATE-CS registry, Eur. Heart J. 43 (2022) 3450–3459.
[8] C. Duvall, N. Pavlovic, N.S. Rosen, et al., Sex and race differences in cardiac sarcoidosis presentation, treatment and outcomes, J. Card Fail. 29 (2023) 1135–1145.
[9] K. Ekström, J. Lehtonen, H.-K. Nordenswan, et al., Sudden death in cardiac sarcoidosis: an analysis of nationwide clinical and cause-of-death registries, Eur. Heart J. (2019) 1–8.
[10] Y. Yazaki, M. Isobe, M. Hiroe, et al., Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone, Am. J. Cardiol. 88 (2001) 1006–1010.
[11] Y. Okura, G.W. Dec, J.M. Hare, et al., A clinical and histopathologic comparison of cardiac sarcoidosis and idiopathic giant cell myocarditis, J. Am. Coll. Cardiol. 41 (2003) 322–329.
[12] N.A. Marston, L. Han, I. Olivotto, et al., Clinical characteristics and outcomes in childhood-onset hypertrophic cardiomyopathy, Eur. Heart J. 42 (2021) 1988–1996.
[13] J. Tromp, S.M.A. Paniagua, E.S. Lau, et al., Age dependent associations of risk factors with heart failure: pooled population based cohort study, BMJ 372 (2021), https://doi.org/10.1136/bmj.n461.
[14] J. Tromp, L. Shen, P.S. Jhund, et al., Age-related characteristics and outcomes of patients with heart failure with preserved ejection fraction, J. Am. Coll. Cardiol. 74 (2019) 601–612.
[15] D.H. Birnie, W.H. Sauer, F. Bogun, et al., HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis, Hear Rhythm. 11 (2014) 1304–1323.
[16] M.D. Cerqueira, N.J. Weissman, V. Dilsizian, 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 105 (2002) 539–542.
[17] W.T. Abraham, M.A. Psotka, M. Fiuzat, 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. 22 (2020) 2175–2186.
[18] K. Kusano, K. Ishibashi, T. Noda, et al., Prognosis and outcomes of clinically diagnosed cardiac sarcoidosis without positive endomyocardial biopsy findings, JACC Asia 1 (2021) 385–395.
[19] H. Tsutsui, N.M. Albert, A.J.S. Coats, et al., Natriuretic peptides: role in the diagnosis and management of heart failure: a scientific statement from the Heart Failure Association of the European Society of Cardiology, Heart Failure Society of America and Japanese Heart Failure Society, J. Card. Fail. 29 (2023) 787–804.
[20] S.F. Nagueh, O.A. Smiseth, C.P. Appleton, et al., Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, J. Am. Soc. Echocardiogr. 29 (2016) 277–314.
[21] R. Kandolin, J. Lehtonen, J. Airaksinen, et al., Cardiac sarcoidosis: epidemiology, characteristics, and outcome over 25 years in a nationwide study, Circulation 131 (2015) 624–632.
[22] L.A. Fussner, E. Karlstedt, D.O. Hodge, et al., Management and outcomes of cardiac sarcoidosis: a 20-year experience in two tertiary care centres, Eur. J. Heart Fail. 20 (2018) 1713–1720.
[23] T. Kerola, A. Eranti, A.L. Aro, et al., Risk factors associated with atrioventricular block, J. Am. Med. Assoc. Netw. Open 2 (2019) 1–13.
[24] S.N.C. Barra, R. Providência, L. Paiva, et al., A review on advanced atrioventricular block in young or middle-aged adults, Pace - Pacing Clin. Electrophysiol. 35 (2012) 1395–1405.

[25] R. Kandolin, J. Lehtonen, M. Kupari, Cardiac sarcoidosis and giant cell myocarditis as causes of atrioventricular block in young and middle-aged adults, Circ. Arrhythmia Electrophysiol. 4 (2011) 303–309.
[26] T. Lindberg, A. Wimo, S. Elmståhl, et al., Prevalence and incidence of atrial fibrillation and other arrhythmias in the general older population: findings from the Swedish National Study on Aging and Care, Gerontol. Geriatr. Med. 5 (2019), 233372141985968.
[27] A.B. Curtis, R. Karki, A. Hattoum, et al., Arrhythmias in patients ≥80 years of age: pathophysiology, management, and outcomes, J. Am. Coll. Cardiol. 71 (2018) 2041–2057.
[28] K. Zeppenfeld, J. Tfelt-Hansen, M. de Riva, et al., 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, Eur. Heart J. 43 (2022) 3997–4126.
[29] S. Sirichand, A.M. Killu, D. Padmanabhan, et al., Incidence of idiopathic ventricular arrhythmias: a population-based study, Circ. Arrhythm. Electrophysiol. 10 (2017), e004662.