Original article

Fragmented QRS as a Predictor of Cardiac Events in Patients with Cardiac Sarcoidosis

Soichiro Ogura, MD, PhD [a,b]*; Kazufumi Nakamura, MD, PhD [a]*; Hiroshi Morita, MD, PhD[a,c]; Koji Nakagawa, MD, PhD[a]; Nobuhiro Nishii, MD, PhD[a]; Satoshi Akagi, MD, PhD[a]; Norihisa Toh, MD, PhD[a]; Yoichi Takaya, MD, PhD[a]; Masashi Yoshida, MD, PhD[a]; Toru Miyoshi, MD, PhD[a]; Atsuyuki Watanabe, MD, PhD[a,d]; Hiroshi Ito, MD, PhD[a]

Institution:

[a]Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

[b]Department of Cardiovascular Medicine, IMS Katsushika heart center, Tokyo, Japan

[c]Department of Cardiovascular Therapeutics, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

[d]Department of Cardiology, National Hospital Organization Okayama Medical Center, Okayama, Japan.

***Correspondence:** Soichiro Ogura, MD, PhD or Kazufumi Nakamura, MD, PhD

Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 2-5-1 Shikata, Okayama 700-8558, Japan

Tel: +81-86-235-7351, fax: +81-86-235-7353,

e-mail: s_ogura0803@yahoo.co.jp (S.Ogura) or ichibun@cc.okayama-u.ac.jp (K.Nakamura)

Keywords: Cardiac sarcoidosis, Ventricular arrhythmia, Fragmented QRS, Electrocardiography, Hospitalization

Word count: 3262 words

Abstract

Background: Multiple spikes within the QRS complex, known as fragmented QRS (fQRS), are associated with the occurrences of ventricular arrhythmic events (VAEs) in patients with Brugada syndrome and hypertrophic cardiomyopathy. However, the association between fQRS and occurrence of VAEs in patients with cardiac sarcoidosis (CS) has not been elucidated.

Methods: We evaluated the associations between fQRS and cardiac events including VAEs (non-sustained ventricular tachycardia [NSVT], sustained ventricular tachycardia [VT], and ventricular fibrillation [VF]), hospitalization for heart failure, and all cause death in 68 patients with CS (30 patients with fQRS vs. 38 patients without fQRS) over a 5-year period.

Results: Cardiac events occurred in 22 patients with fQRS and 18 patients without fQRS (73% vs. 47%, P=0.009). Of the cardiac events that occurred in CS patients, VAEs occurred more frequently in patients with fQRS than in patients without fQRS (VAEs: 70% vs. 45%, P=0.017; NSVT: 70% vs. 45%, P=0.010; VT: 43% vs. 18%, P=0.011, and VF: 6.7% vs. 2.6%, P=0.34), whereas there was no significant difference in hospitalization for heart failure or all-cause death between patients with and those without fQRS (hospitalization for heart failure: 6.7% vs. 5.3%, P=0.75; all-cause death: 6.7% vs. 5.3%, P=0.64). Multivariate analysis showed that fQRS in the baseline ECG was independently associated with VAEs (hazard ratio [HR]: 2.21, 95% confidence interval [CI]: 1.15–4.25, P=0.017).

Conclusion: fQRS is a predictor of VAEs in patients with CS.

Introduction

Sarcoidosis is a worldwide disease with a prevalence between 4.7 and 64 per 100,000 people. Approximately 5% of sarcoidosis patients have cardiac involvement, and it has been estimated that between 20% and 25% of patients with pulmonary or systemic sarcoidosis have asymptomatic cardiac involvement [1]. The three principal manifestations of cardiac sarcoidosis (CS) are conduction abnormalities, ventricular arrhythmias, and heart failure [1-3]. The extent of left ventricular dysfunction is thought to be the most important predictor of prognosis. CS is diagnosed from clinical and pathological findings [4, 5], but many symptoms of CS are non-specific. In some cases, CS is not diagnosed until ventricular dysfunction has progressed.

Recently, analysis of a nationwide case series in Finland has shown that sudden death is the first main presenting symptom in 12% of CS patients, and sudden cardiac death accounts for 80% of all-cause deaths in CS patients [6]. Implantable cardioverter-defibrillators (ICDs) are therefore often recommended for symptomatic CS patients to prevent sudden cardiac death. However, predictors of these sudden cardiac death in CS patients have not been fully elucidated. To screen high-risk patients and prevent sudden cardiac death in CS patients, simple predictors that can be used in daily clinical practice are needed.

An electrocardiogram (ECG) is the most common test used in clinical practice, and an ECG can show abnormalities in symptomatic CS patients [7]. ECG abnormalities include various degrees of conduction block such as isolated bundle branch block and fascicular block. Fragmented QRS (fQRS), ST-T wave changes, pathological Q waves (pseudo-infarct pattern), and epsilon waves have also been observed in symptomatic CS patients [8]. However, it has been reported that an ECG shows abnormalities in only 3.2% to 8.6% of patients with clinically silent CS [1].

fQRS appears as multiple spikes within the QRS complex and has been reported to be associated with ventricular arrhythmic events (VAEs) in patients with myocardial infarction, Brugada syndrome, and hypertrophic cardiomyopathy [9-11]. However, the significance of fQRS in cardiac sarcoidosis has not been fully elucidated.

In low-risk sarcoidosis patients without cardiac involvement, fQRS has been reported to be associated with adverse cardiac events [12]. In high-risk patients with cardiac involvement, multiple ECG abnormalities, including fQRS, have been reported to be associated with findings in fluorodeoxyglucose-position emission tomography (FDG-PET) and late gadolinium enhancement (GDE) in cardiac magnetic resonance imaging (CMR) [13, 14]. However, an association between fQRS and cardiac events in high-risk patients with CS has not been reported.

Materials and Methods

Study population

The study population comprised 93 consecutive patients with cardiac sarcoidosis who were referred to Okayama University Hospital during the period from May 2004 to May 2019. All patients were refereed to Okayama University Hospital due to ECG abnormality, heart failure, or arrhythmia. No patient was taken to the emergency room by ambulance due to symptoms. Patients with ventricular pacing were excluded (n=25) due to the ambiguity of fragmentations. The remaining 68 patients were enrolled in this study (Fig. 1). We checked the medical records of these 68 patients over a 5-year period and analyzed the data retrospectively.

Cardiac sarcoidosis was diagnosed according to the criteria of the Japanese Circulation Society [5]. The study protocol was approved by the institutional ethics committee on human research of Okayama University (approval number of the Ethics

Committees of Okayama University: 2007-009). Because of the anonymous nature of the data, the requirement for informed consent was waived. The first author takes complete responsibility for the integrity of the data and the accuracy of data analysis.

ECG recording and definition of fQRS

A standard 12-lead ECG with a 0–150 Hz filter was recorded on all patients. ECGs acquired at admission were taken as the initial baseline ECGs. The digital ECG without a filter at 400% of the initial size was assessed on a personal computer monitor and each parameter and fragmentation of the QRS complex were measured as previously described (Fig. 2) [9]. Fragmentations were counted in each lead and abnormal fragmentation within the QRS complex was defined as more than two positive spikes within the QRS complex in two contiguous leads. Analysis of fragmentation required at least 3 consecutive beats. The smallest QRS fragmentations were 0.02 μV. According to the existing literature, we defined the regions exhibiting fQRS as inferior (leads II, III, and aVF), lateral (leads I, aVL, and V5 and V6), anterior (leads V3 and V4), and RV (leads V1 and V2) [9]. We evaluated fQRS manually, and ECGs were reviewed by three blinded cardiologists (SO, KN, and HM).

Other clinical examinations

All other clinical examinations were performed at the time of CS diagnosis. Echocardiography was performed and left ventricular ejection fraction was calculated using the disc summation method. Cardiac catheterization, including catheterization for coronary angiography and myocardial biopsy, was performed using the Seldinger technique.

Gallium scintigraphy, CMR, and positron emission tomography-computed tomography (PET-CT) were performed in 63, 50, and 39 patients, respectively. A high-intensity area in the myocardium appearing as gadolinium enhancement was considered positive for GDE. Plasma brain natriuretic peptide (BNP) levels were measured with an immunoradiometric assay specific for human BNP.

End points

End points were defined as the following cardiac events: VAEs, hospitalization for heart failure, and all-cause death. VAEs were defined as non-sustained ventricular tachycardia (NSVT), sustained ventricular tachycardia (VT), and ventricular fibrillation (VF). NSVT was defined as spontaneous VT at a rate >100 beats/min that lasted <30 s. VT was defined as spontaneous VT at a rate >100 beats/min that lasted >30 s. Patients were followed from the date of the initial ECG until the first documented date of a cardiac event or the end of the 5-year follow-up period. Follow-up information was obtained from patients' medical records, contact with the patients' physicians, or interrogation of implantable electronic devices.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range). Categorical variables are presented as frequency (percentage). Differences were analyzed using Student's t-test for continuous variables and the χ^2 test for categorical variables. Event-free survival rate was estimated using Kaplan-Meier analysis, with differences analyzed using Cox proportional hazard analysis. Predictors of cardiac events were analyzed using Cox proportional hazards analysis. Variables for the univariate analysis were age (>65 years), male sex, wide QRS (>120 ms), device implantation (pacemaker, ICD or cardiac resynchronization therapy), left ventricular (LV) dysfunction (ejection fraction (EF) <40%), and fQRS. Hazard ratios (HR) are presented with 95% confidence intervals (CI). Statistical analyses were performed with SPSS version 24 (IBM, Inc., Armonk, NY, USA) and $P<0.05$ was considered statistically significant.

Results

Baseline characteristics of patients with and without baseline fQRS

We analyzed data for 68 patients (40% men, age, 61±11 years; age range, 32–81 years) (Table 1). The median follow-up duration was not significantly different in the two groups (3.5 years with fQRS vs. 4.1 years without fQRS, P=0.12). The patients' physical characteristics, medical history, and medication were also similar in the two groups. In both groups, almost all the patients were prescribed prednisolone after diagnosis (97% with fQRS vs. 95% without fQRS, P= 0.68). Of the 68 patients with CS, only 11 received prednisolone at the time of the initial ECG. There was no significant difference in the frequency of fQRS with or without prednisolone (P=0.75). Pacemaker and other device implantation were not different between the two groups.

BNP and echocardiography findings were not different between the two groups (Table 2). Ejection fraction was preserved in both groups (49% with fQRS vs. 50% without fQRS, P=0.96). Several differences were observed in the ECG parameters. Right bundle branch block was observed more frequently in patients with fQRS than in patients without fQRS. Accordingly, QRS and QT durations were longer in patients with fQRS than in patients without fQRS (QRS: 126 ms vs. 105 ms, P<0.001; QTc: 472 ms vs. 430 ms, P=0.033). Additionally, the maximum and total fragmentation numbers per QRS in all leads were both greater in patients with fQRS than in patients without fQRS (max fragmentation number: 3.3 ± 0.78/100 ms vs. 2.1 ± 1.0/100 ms, P<0.001; total fragmentation number: 29 ±9.0/100 ms vs. 10 ± 6.6/100 ms, P<0.001). Other parameters including T wave inversion in aVR and Q waves, showed no differences between the two groups. Image analysis of gallium scintigraphy, CMR, and PET scans did not show any significant differences.

Univariate analysis

Cardiac events occurred in 22 patients with fQRS and in 18 patients without fQRS (73% vs. 47%, P=0.009). Among the cardiac events, VAEs, NSVT, and VT occurred in significantly higher percentages of patients with fQRS than in patients without fQRS (VAEs:

70% vs. 45%, P=0.017; NSVT: 70% vs. 45%, P=0.010; VT: 43% vs. 18%, P=0.011; Fig. 3A and B). There was no significant difference in VF, frequency of hospitalization for heart failure, or frequency of all cause death in patients with and those without fQRS (VF: 6.7% vs. 2.6%, P=0.34; heart failure: 6.7% vs. 5.3%, P=0.75; all cause death: 6.7% vs. 5.3%, P=0.64; Fig. 3C and D). During the 5-year follow-up period, 39 of the 68 patients received some device therapy (22 of 30, 73% with fQRS vs. 17 of 38, 45% without fQRS), and 31 of the 68 patients received ICD therapy (19 of 30, 63% with fQRS vs. 12 of 38, 32% without fQRS). Two patients with VAEs (one with fQRS and one without fQRS) underwent catheter ablation for ventricular tachycardia. After ablation, the patient with fQRS had further VAEs, and the patient without fQRS did not have VAEs, but she was hospitalized for heart failure.

Multivariate analysis

Multivariate analysis showed that fQRS was associated with VAEs (HR: 2.21, 95% CI: 1.15–4.25; P=0.017) but not with hospitalization for heart failure (HR: 1.38, 95% CI: 0.20–9.80; P=0.75). As shown in Table 3, fQRS was independently associated with VAEs among other factors including male sex, wide QRS, device implantation, and LV dysfunction.

Discussion

In this study, we investigated the associations between fQRS and cardiac events including VAEs, all-cause death, and heart failure hospitalization in CS patients. fQRS was associated with VAEs, including NSVT and VT, but not with hospitalization for heart failure or all-cause death. In CS patients, longer QRS duration is known to be a common abnormality in an ECG, and lower EF can be predictive of adverse cardiac events [1]. However, in our study, we did not see any association between these two factors and VAEs.

The existence of fQRS is known to be associated with cardiovascular events such as hereditary arrhythmia disease, cardiomyopathy, ischemic heart disease and congenital heart

disease. The existence of fQRS in patients with Brugada syndrome was evaluated in a previous study. In these high-risk patients with hereditary arrhythmia, the rate of occurrence of arrhythmic events was more than 10-times higher in patients with fQRS than in patients without fQRS. Furthermore, the existence of fQRS in any leads was highly associated with future VF events in multivariable analysis [9]. In another study on hypertrophic cardiomyopathy, baseline fQRS was also associated with future VAEs. Moreover, new appearance of fQRS was associated with future VAEs in patients without baseline fQRS [10]. Considering these associations of fQRS and cardiovascular events in a wide range of cardiovascular diseases, fragmentations of the QRS complex might also be associated with arrhythmic events in CS patients. However, the association between cardiac events and fQRS in CS patients has not been fully elucidated. In this study, we showed the association between fQRS and arrhythmic events in CS patients.

Previous studies on sarcoidosis were reported in two different groups: high-risk patients with cardiac involvement and low-risk patients without cardiac involvement. The prognosis of sarcoidosis patients without cardiac involvement are good, and cardiac events are rare [15]. A recent study has shown the long-term risk of heart failure and other adverse cardiac outcomes in sarcoidosis patients without cardiac involvement. VAEs and cardiac arrest occurred only in 0.96% of those patients in a 10-year period [16]. In patients without cardiac involvement, one study showed that multiple ECG abnormalities, including fQRS, are associated with cardiac events, but cardiac events occurred in only 5% of these low-risk patients during a 5-year period [12].

Though, the prognosis of patients with cardiac involvement is much worse. In one report with CMR evaluation, rate of death or VT per year was over 20 times higher in patients with cardiac involvement than the patients without cardiac involvement [12]. Patients in this study were confirmed to have cardiac involvement and were at much higher risk of cardiac

events than the patients without cardiac involvement. With these high-risk patients, we reported cardiac events including VAEs occurred 59% of the patients during a 3.5-year follow-up period. And in such high-risk patients with cardiac involvement, association between single ECG abnormalities of fQRS and VT events have never been reported.

As for associations among results of imaging tests, cardiac events and fQRS, a previous study showed that GDE with CMR was associated with adverse events such as cardiac death in CS patients [14]. Another study showed that ECG parameters including fQRS were associated with findings in FDG-PET [13]. However, fQRS alone has not been shown to be associated with imaging findings or cardiac events. In this study, we showed an association between fQRS and cardiac events but not between fQRS and imaging tests. The reason why fQRS did not correspond to the results of imaging analysis in our study might be the size of myocardial injury. We evaluated fragmentations as small as 0.02 μV, and the injury represented as fQRS on an ECG may therefore have been too small to cause LV dysfunction and thus was not detected in imaging tests including gallium scintigraphy, MRI and PET. Accordingly, the lack of an association between hospitalization for heart failure and fQRS can also be explained by the small size of the myocardial injury. Nevertheless, a small injury of the myocardium represented as fQRS could trigger VAEs.

Signal-averaged electrocardiography (SAECG), which can detect ventricular late potentials, is also known to be useful for prediction of lethal ventricular arrhythmia [17]. Furthermore, it has been reported that there was a high prevalence of late potentials in SAECG in patients with pulmonary sarcoidosis and that the late potentials were associated with an increased risk of the development of cardiac events including complete atrioventricular block, sustained ventricular tachycardia and heart failure [18]. However, this technique has limitations in patients with intraventricular conduction disturbance including bundle branch block [19]. We also examined SAECG in only 31 of the 68 patients with

cardiac sarcoidosis, but there was no difference in ventricular arrhythmia events between the late potential positive and negative groups.

There are several reports of improvement in atrioventricular block and cardiac function after steroid therapy [2, 20, 21]. Almost all of the patients were treated with steroids, and the association between steroid treatment and appearance of fQRS could therefore not be investigated. Further research is needed to clarify the potential for fQRS changes after steroid therapy.

Limitations

Several limitations of this study should be considered. First, this study was a single-center, retrospective study that included only 68 Japanese patients with CS. Further investigations in a larger, more diverse population are needed to definitively determine the associations between VAEs and fQRS in CS patients. Second, confounding factors may have existed between patients with and those without fQRS in our cohort. There were few differences in physiological functional test results between the two groups, and QRS duration may have affected VAEs. Third, variability in the fQRS interpretation is possible; however, we used special precautions to ensure that the ECG interpretations by the three reviewers were consistent with the fQRS criteria in this study. Fourth, we did not show a clear mechanism for the relationship between fQRS and sudden cardiac death risk. This study showed that VAEs in CS patients were associated with both the presence and appearance of fQRS but not with SCD. Fifth, we did not analyze QRS fragmentations with differential or double differential values in this study. Since QRS fragmentations are small changes on ECGs, analysis with differential or double differential values could have helped us to evaluate fQRS more accurately. However, we prioritized simplicity and convenience for analysis of ECGs. Further studies are needed to clarify this point. Sixth, the utility of fragmented QRS is

limited because many cardiac sarcoidosis patients have an implantable cardiac device and ventricular pacing. In fact, 25 patients were excluded in the present study. Seventh, this study showed a high prevalence of isolated cardiac sarcoidosis compared to that in other studies on cardiac sarcoidosis. If we do not use the JCS guideline, isolated cardiac sarcoidosis cannot be diagnosed. Eighth, there were many follow-ups by referral doctors, and we could not obtain sufficient data for more than 5 years.

Conclusion

The existence of fQRS in CS patients is associated with the future VAEs including VT. fQRS can be used as a useful predictor of VAEs.

Acknowledgments

The authors are grateful to Kaoru Akazawa, Miyuki Misunaga and Masayo Ohmori for their excellent assistance.

Funding

This research was supported in part by the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 15K09082 (Morita Hiroshi).

Disclosures

Morita H and Nishii N are affiliated with the endowed department by Japan Medtronic Inc. The remaining authors have nothing to disclose.

References

[1] Birnie DH, Nery PB, Ha AC, Beanlands RS. Cardiac Sarcoidosis. Journal of the American College of Cardiology. 2016;68:411-21.
[2] Banba K, Kusano KF, Nakamura K, Morita H, Ogawa A, Ohtsuka F, et al. Relationship between arrhythmogenesis and disease activity in cardiac sarcoidosis. Heart Rhythm. 2007;4:1292-9.
[3] Trivieri MG, Spagnolo P, Birnie D, Liu P, Drake W, Kovacic JC, et al. Challenges in Cardiac and Pulmonary Sarcoidosis: JACC State-of-the-Art Review. Journal of the American College of Cardiology. 2020;76:1878-901.
[4] Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart Rhythm. 2014;11:1305-23.
[5] Terasaki F, Azuma A, Anzai T, Ishizaka N, Ishida Y, Isobe M, et al. JCS 2016 Guideline on Diagnosis and Treatment of Cardiac Sarcoidosis- Digest Version. Circ J. 2019;83:2329-88.
[6] Ekstrom K, Lehtonen J, Nordenswan HK, Mayranpaa MI, Raisanen-Sokolowski A, Kandolin R, et al. Sudden death in cardiac sarcoidosis: an analysis of nationwide clinical and cause-of-death registries. Eur Heart J. 2019;40:3121-8.
[7] Willy K, Dechering DG, Reinke F, Bogeholz N, Frommeyer G, Eckardt L. The ECG in sarcoidosis - a marker of cardiac involvement? Current evidence and clinical implications. J Cardiol. 2021;77:154-9.
[8] Schuller JL, Olson MD, Zipse MM, Schneider PM, Aleong RG, Wienberger HD, et al. Electrocardiographic characteristics in patients with pulmonary sarcoidosis indicating cardiac involvement. J Cardiovasc Electrophysiol. 2011;22:1243-8.
[9] Morita H, Watanabe A, Morimoto Y, Kawada S, Tachibana M, Nakagawa K, et al. Distribution and Prognostic Significance of Fragmented QRS in Patients With Brugada Syndrome. Circulation Arrhythmia and electrophysiology. 2017;10:e004765.
[10] Ogura S, Nakamura K, Morita H, Toh N, Nakagawa K, Yoshida M, et al. New Appearance of Fragmented QRS as a Predictor of Ventricular Arrhythmic Events in Patients With Hypertrophic Cardiomyopathy. Circ J. 2020;84:487-94.
[11] Rezaee M, Kheirkhah J, Salari A, Mirbolouk F, Moayerifar M, Mirrazeghi SF, et al. Investigation of short-term prognosis of fragmented QRS complexes in patients with acute myocardial infarction in two groups that received invasive and fibrinolytic therapy. Indian Heart J. 2020;72:46-51.
[12] Nagao S, Watanabe H, Sobue Y, Kodama M, Tanaka J, Tanabe N, et al. Electrocardiographic abnormalities and risk of developing cardiac events in extracardiac sarcoidosis. Int J Cardiol. 2015;189:1-5.
[13] Sipila K, Tuominen H, Haarala A, Tikkakoski A, Kahonen M, Nikus K. Novel ECG parameters are strongly associated with inflammatory (18)F-FDG PET findings in patients with suspected cardiac sarcoidosis. Int J Cardiol. 2017;249:454-60.
[14] Homsi M, Alsayed L, Safadi B, Mahenthiran J, Das MK. Fragmented QRS complexes on 12-lead ECG: a marker of cardiac sarcoidosis as detected by gadolinium cardiac magnetic resonance imaging. Ann Noninvasive Electrocardiol. 2009;14:319-26.
[15] Murtagh G, Laffin LJ, Beshai JF, Maffessanti F, Bonham CA, Patel AV, et al. Prognosis of Myocardial Damage in Sarcoidosis Patients With Preserved Left Ventricular Ejection Fraction: Risk Stratification Using Cardiovascular Magnetic Resonance. Circ Cardiovasc Imaging. 2016;9:e003738.
[16] Yafasova A, Fosbol EL, Schou M, Gustafsson F, Rossing K, Bundgaard H, et al. Long-Term Adverse Cardiac Outcomes in Patients With Sarcoidosis. Journal of the American College of Cardiology. 2020;76:767-77.
[17] Mancini DM, Wong KL, Simson MB. Prognostic value of an abnormal signal-averaged electrocardiogram in patients with nonischemic congestive cardiomyopathy. Circulation. 1993;87:1083-92.
[18] Yodogawa K, Seino Y, Ohara T, Iwasaki YK, Hayashi M, Miyauchi Y, et al. Prognostic significance of ventricular late potentials in patients with pulmonary sarcoidosis. Heart Rhythm. 2018;15:798-802.

[19] Yodogawa K, Ohara T, Murata H, Iwasaki YK, Seino Y, Shimizu W. Detection of arrhythmogenic substrate within QRS complex in patients with cardiac sarcoidosis using wavelet-transformed ECG. Heart Vessels. 2020;35:1148-53.
[20] Okabe T, Yakushiji T, Hiroe M, Oyama Y, Igawa W, Ono M, et al. Steroid pulse therapy was effective for cardiac sarcoidosis with ventricular tachycardia and systolic dysfunction. ESC Heart Fail. 2016;3:288-92.
[21] Padala SK, Peaslee S, Sidhu MS, Steckman DA, Judson MA. Impact of early initiation of corticosteroid therapy on cardiac function and rhythm in patients with cardiac sarcoidosis. Int J Cardiol. 2017;227:565-70.

Figure legends

Figure 1. Study flow chart.

Ninety-three patients with cardiac sarcoidosis (CS) were hospitalized for evaluation during the period from May 2004 to May 2019. Twenty-five patients were excluded due to ventricular pacing. We analyzed data for 68 patients with and without fQRS on the initial ECGs (30 patients with fQRS vs. 38 without fQRS).

Figure 2. Typical example of ECG with fragmentation in QRS complex.

A. Example of ECG without fragmentation. **B.** Typical example of ECG with fragmentations

Figure 3. Kaplan–Meier curves for the selected end points. **A**. The primary endpoint was ventricular arrhythmic events (VAEs). **B**. Sustained ventricular tachycardia (VT). **C**. Hospitalization for heart failure (HF). **D**. All-cause death. fQRS, fragmented QRS; HR, hazard ratio; CI, confidence interval; ECG, electrocardiogram.

Table 1. Baseline characteristics of patients with and those without fQRS

	With fQRS (n=30)	Without fQRS (n=38)	P-value
Age, years	62±10	61±12	0.97
Male sex, n (%)	12 (40)	15 (40)	0.97
Body mass index	24±4.7	24±4.2	0.98
NYHA			
NYHA I	12 (40)	12 (32)	0.47
NYHA II	13 (43)	21 (55)	0.33
NYHA III	5 (17)	4 (11)	0.46
NYHA IV	0 (0)	1 (2.6)	0.37
Comorbidities			
Hypertension, n (%)	13 (43)	19 (50)	0.58
Diabetes, n (%)	7 (23)	3 (7.9)	0.074
Hyperlipidemia, n (%)	6 (20)	7 (18)	0.87
Coronary artery disease, n (%)	3 (10)	1 (2.6)	0.20
Follow-up duration, years	3.5 (0.2–5.0)	4.1 (1.0–5.0)	0.12
Diagnosis of sarcoidosis			
Pulmonary sarcoidosis, n (%)	14 (47)	22 (58)	0.36
Cutaneous sarcoidosis, n (%)	4 (13)	7 (18)	0.57

Ocular sarcoidosis, n (%)	7 (23)	10 (26)	0.78
Isolated cardiac sarcoidosis, n (%)	18 (60)	20 (68)	0.47
Medication			
ACE-I or ARB, n (%)	15 (50)	16 (42)	0.52
Beta-blocker, n (%)	12 (40)	15 (50)	0.97
MRA, n (%)	8 (27)	5 (13)	0.16
Amiodarone, n (%)	3 (10)	6 (16)	0.48
Statin, n (%)	6 (20)	5 (13)	0.45
Prednisolone, n (%)	29 (97)	35 (95)	0.68
Device at baseline			
Any device implantation, n (%)	5 (17)	6 (16)	0.92
ICD or CRT-D implantation, n (%)	1 (3.3)	4 (11)	0.26

Data are expressed as mean ± standard deviation, median (range), or *n* (%).

NYHA, New York heart Association; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor antagonist; MRA, mineralocorticoid receptor antagonist; ICD, implantable cardioverter-defibrillator; CRT-D, cardiac resynchronization therapy defibrillator.

Table 2. Baseline test results for patients with and those without fQRS

	With fQRS (n=30)	Without fQRS (n=38)	P-value
Blood test			
TnT, ng/ml	0.03 (0.007–0.128)	0.09 (0.000–0.675)	0.27
BNP, pg/ml	334 (8.9–1792)	249 (2.0–3240)	0.49
Creatinine, mg/dl	1.5±3.4	0.9±0.5	0.24
Urea nitrogen, mg/dl	18±7.3	17±8.0	0.68
ACE, U/L	13±6.0	14±7.6	0.62
sIL-2R, U/ml	509±496	668±805	0.37
Electrocardiogram			
AF or AFL, n (%)	3 (10)	1 (2.6)	0.20
BBB, n (%)	25 (83)	14 (42)	<0.001
RBBB, n (%)	17 (57)	5 (13)	<0.001
LBBB, n (%)	8 (27)	9 (23)	0.78
Heart rate, bpm	69±15	69±17	0.98
PR, ms	202±47	185±46	0.18
QRS, ms	126±21	105±24	<0.001
QT, ms	449±54	410±86	0.033
QTc, ms	472±25	430±84	0.011
Left axis deviation, n (%)	10 (33)	10 (26)	0.53

Right axis deviation, n (%)	3 (10)	2 (5.3)	0.46
T wave inversion in aVR, n (%)	14 (47)	16 (42)	0.71
Q wave, n (%)	5 (17)	6 (16)	0.92
Fragmentation in Inferior, n (%)	22 (73)		
Fragmentation in Anterior, n (%)	16 (53)		
Fragmentation in Lateral, n (%)	9 (30)		
Fragmentation in RV, n (%)	14 (47)		
Max fragmentations, n/100 ms	3.3±0.78	2.1±1.0	<0.001
Total fragmentations, n/100 ms	29±9.0	10±6.6	<0.001
Echocardiography			
Left atrial diameter, mm	39±6.5	39±6.7	0.91
Left atrial dilatation, n (%)	11 (37)	10 (26)	0.36
Ejection fraction, %	49±17	50±16	0.96
LV dilatation, %	13 (43)	13 (34)	0.44
LV asynergy, n (%)	22 (73)	24 (63)	0.37
Asynergy in anterior wall, n (%)	20 (67)	19 (50)	0.17
Asynergy in inferior wall, n (%)	16 (53)	17 (45)	0.48
Asynergy in lateral wall, n (%)	16 (53)	14 (37)	0.17
LV wall thinning, n (%)	15 (50)	15 (42)	0.52
LV aneurysm, n (%)	6 (20)	2 (5.3)	0.061
Image inspection			

Ga scintigraphy-positive, n (%)	15/28 (53)	11/35 (31)	0.076
DE of CMR-positive, n (%)	16/19 (94)	27/31 (84)	0.45
PET scan-positive, n (%)	16/18 (89)	14/21 (63)	0.067

Data are expressed as mean ± standard deviation, median (range), or *n* (%).

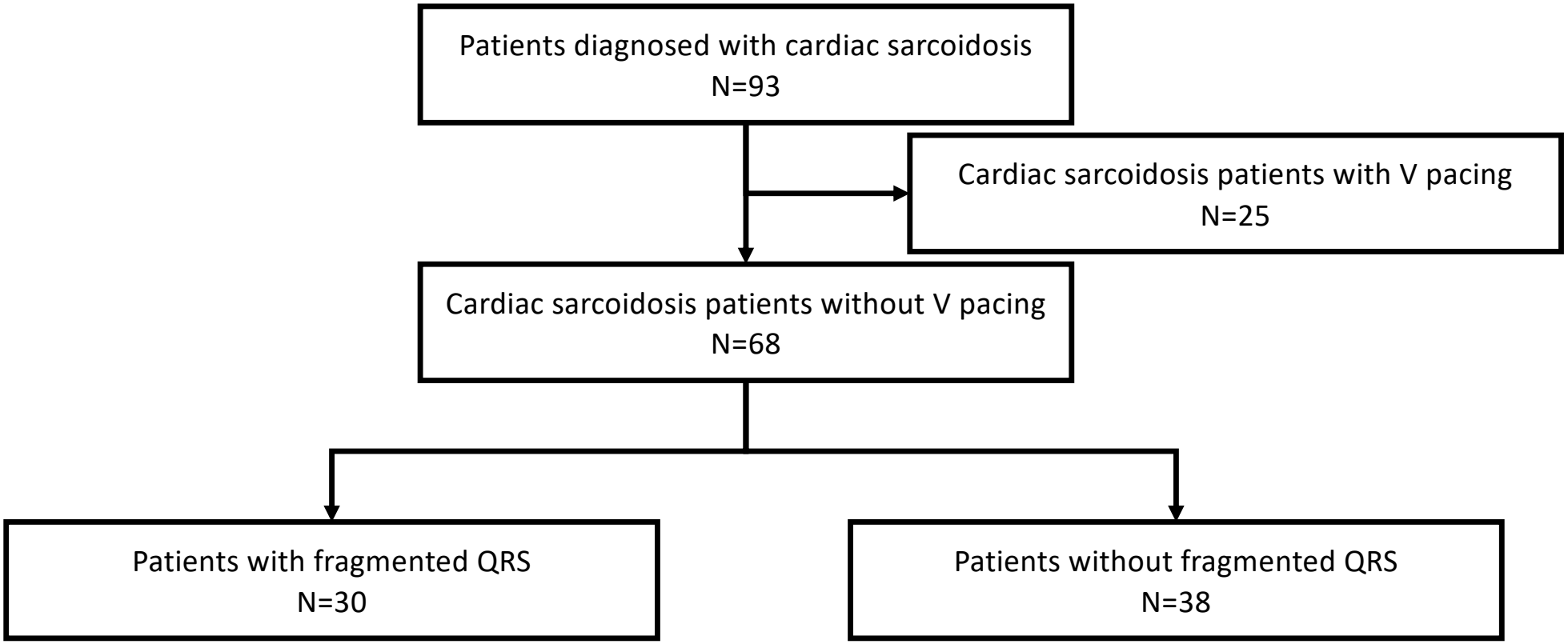
TnT, troponin T; BNP, brain natriuretic peptide; ACE, angiotensin-converting enzyme; sIL2-R, soluble interleukin-2 receptor; AF, atrial fibrillation; AFL, atrial flutter; BBB, bundle branch block; RBBB, right bundle branch block; LBBB, left bundle block; RV, right ventricular; LV, left ventricular; Ga, gallium-67; DE, delayed enhancement; CMR, cardiac magnetic resonance imaging; PET, positron emission tomography.

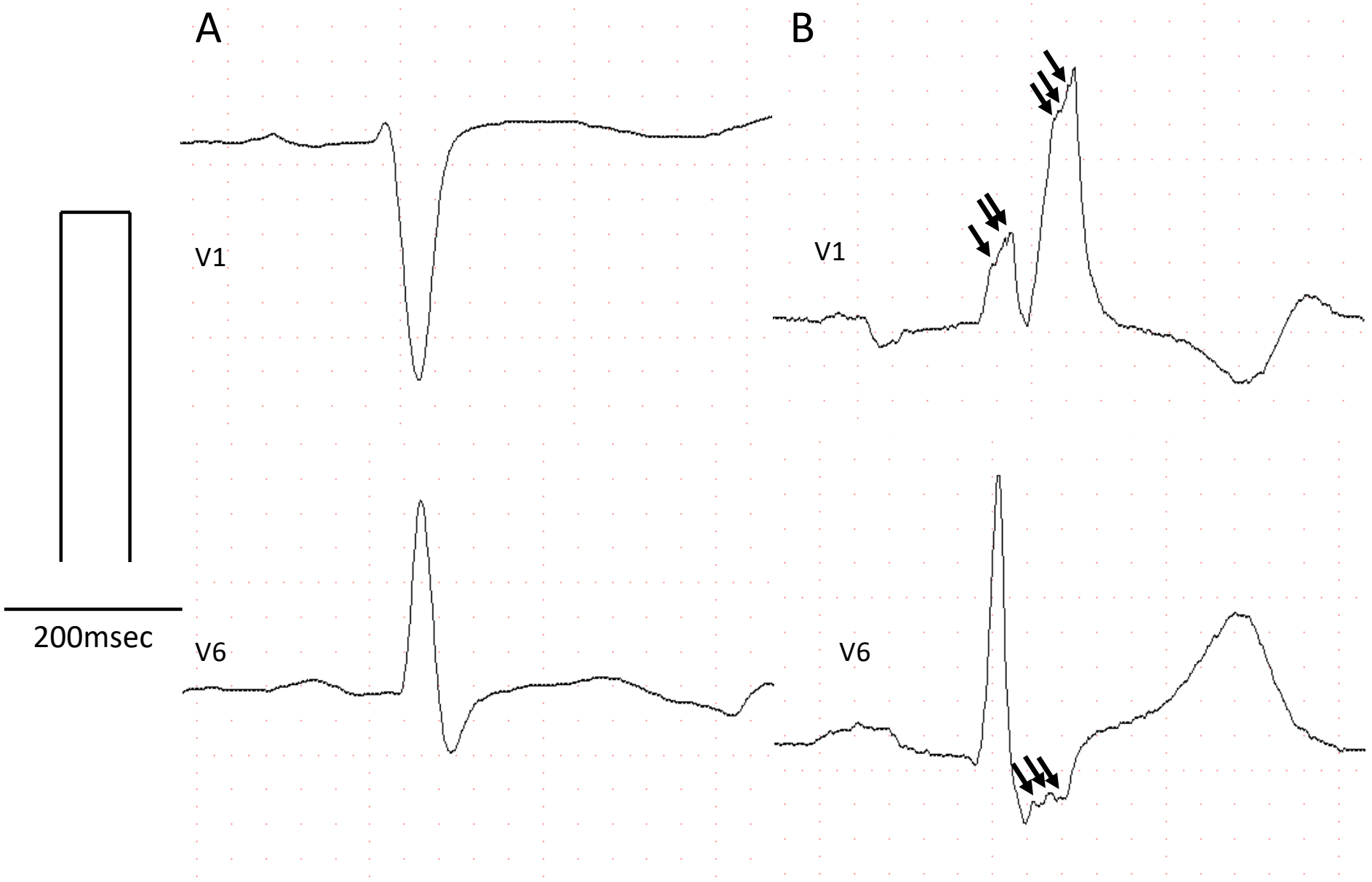
Table 3. Odds ratios for the occurrence of VAEs

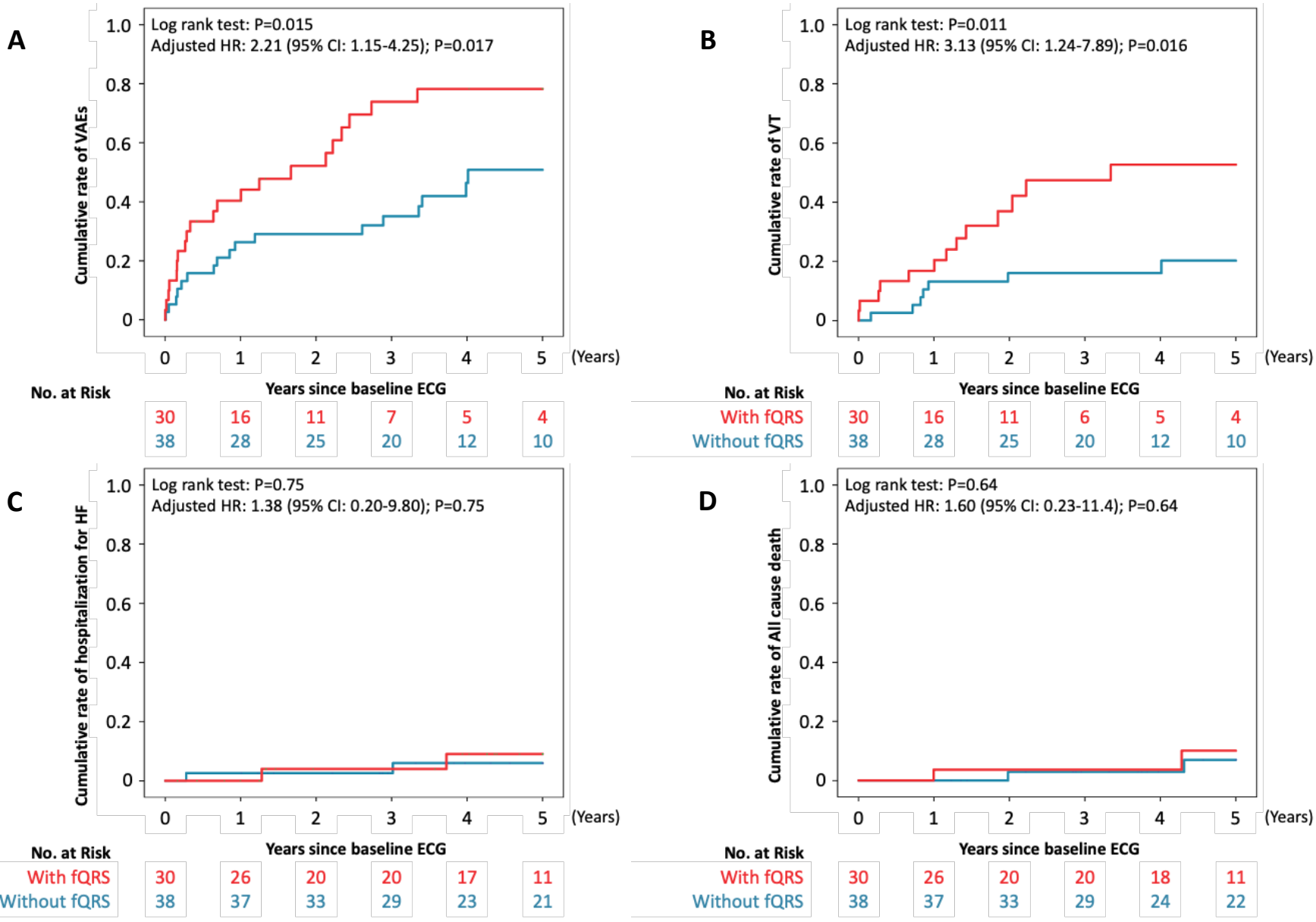
	Univariate		Multivariate	
	Hazard ratio (95% CI)	**P-value**	**Hazard ratio (95% CI)**	**P-value**
Age (>65 years)	1.56 (0.81–3.00)	0.19	1.55 (0.79–3.03)	0.20
Male sex	1.31 (0.68–2.54)	0.42		
Wide QRS (>120 ms)	1.50 (0.79–2.86)	0.22	1.18 (0.59–2.36)	0.63
Device implantation	0.72 (0.28–1.85)	0.48		
LV dysfunction (EF <40%)	1.30 (0.65–2.59)	0.47	1.24 (0.61–2.48)	0.55
fQRS	2.21 (1.15–4.25)	0.017	2.10 (1.05−4.24)	0.036

Variables suspected to be associated with VAEs were included in multivariate analysis.

VAEs, ventricular arrhythmic events; LV, left ventricular; EF, ejection fraction.


Patients diagnosed with cardiac sarcoidosis
N=93
Cardiac sarcoidosis patients with V pacing
N=25
Cardiac sarcoidosis patients without V pacing
N=68
Patients with fragmented QRS
N=30
Patients without fragmented QRS
N=38


A
V1
V6
200msec
B
V1
V6


A
Log rank test: P=0.015
Adjusted HR: 2.21 (95% CI: 1.15-4.25); P=0.017
Cumulative rate of VAEs
1.0
0.8
0.6
0.4
0.2
0
0 1 2 3 4 5 (Years)
Years since baseline ECG
No. at Risk
30 16 11 7 5 4
38 28 25 20 12 10
B
Log rank test: P=0.011
Adjusted HR: 3.13 (95% CI: 1.24-7.89); P=0.016
Cumulative rate of VT
1.0
0.8
0.6
0.4
0.2
0
0 1 2 3 4 5 (Years)
Years since baseline ECG
No. at Risk
With fQRS 30 16 11 6 5 4
Without fQRS 38 28 25 20 12 10
C
Log rank test: P=0.75
Adjusted HR: 1.38 (95% CI: 0.20-9.80); P=0.75
Cumulative rate of hospitalization for HF
1.0
0.8
0.6
0.4
0.2
0
0 1 2 3 4 5 (Years)
Years since baseline ECG
No. at Risk
With fQRS 30 26 20 20 17 11
Without fQRS 38 37 33 29 23 21
D
Log rank test: P=0.64
Adjusted HR: 1.60 (95% CI: 0.23-11.4); P=0.64
Cumulative rate of All cause death
1.0
0.8
0.6
0.4
0.2
0
0 1 2 3 4 5 (Years)
Years since baseline ECG
No. at Risk
With fQRS 30 26 20 20 18 11
Without fQRS 38 37 33 29 24 22