Fragmented QRS on 12-lead electrocardiogram predicts long-term prognosis in patients with cardiac sarcoidosis

Hikaru Hagiwara, MD, PhD[a,c]; Masaya Watanabe, MD, PhD*[a]; Takahide Kadosaka, MD[a]; Takuya Koizumi, MD[a]; Yuta Kobayashi, MD[a]; Taro Koya, MD[a]; Motoki Nakao, MD[a]; Satonori Tsuneta, MD[b]; Yoshiya Kato, MD, PhD[a,c]; Hirokazu Komoriyama, MD, PhD[c]; Rui Kamada, MD, PhD[a]; Toshiyuki Nagai, MD, PhD[a]; Kohsuke Kudo, MD, PhD[b]; Toshihisa Anzai, MD, PhD[a]

[a] Department of Cardiovascular Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

[b] Department of Diagnostic Imaging, Graduate School of Medicine, Hokkaido University, Sapporo, Japan

[c] Department of Cardiovascular Medicine, Kushiro City General Hospital, Kushiro, Japan

***Corresponding author**:

Dr. Masaya Watanabe, MD, PhD

Department of Cardiovascular Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Kita-15 Nishi-7, Kita-Ku, Sapporo 060-8638, Japan

Tel: +81-11-706-6973

Fax: +81-11-706-7874

Email: m.watanabe@huhp.hokudai.ac.jp

Abstract

Fragmented QRS (fQRS) on a 12-lead electrocardiogram is a known marker of fatal arrhythmias or cardiac adverse events in ischemic and non-ischemic cardiomyopathy patients. Nonetheless, the association between fQRS and clinical outcomes in patients with cardiac sarcoidosis (CS) remains unclear. Herein, we investigated whether fQRS is associated with long-term clinical outcomes in CS patients. A total of 78 patients who received immunosuppressive therapy (IST) for clinically diagnosed CS were retrospectively examined. Patients were classified into two groups according to the presence (n=19) or absence (n=59) of fQRS on electrocardiogram before IST. The primary outcome was the composite event of all-cause death, ventricular tachyarrhythmias (VTs), and hospitalization for heart failure. Results of late gadolinium enhancement on cardiac magnetic resonance imaging were also analyzed. During a median follow-up period of 3.7 years (interquartile range: 1.6–6.2 years), the primary outcome occurred more frequently in patients with fQRS than in those without (47% vs. 13%, log-rank p=0.002). Multivariable Cox regression analyses showed that fQRS was an independent determinant of the primary outcome. The incidence of VTs, within 12 months of IST initiation, was comparable between the two groups; however, late-onset VTs, defined as those occurring ≥12 months after IST initiation, occurred more frequently in the fQRS group (21% vs. 2%, log-rank p=0.002). The scar zone and scar border zone were greater in patients with fQRS than in those without it. In conclusion, our analysis suggests that fQRS is an independent predictor of adverse events, particularly late-onset VTs, in patients with CS.

Keywords: cardiac sarcoidosis, electrocardiography, fragmented QRS, ventricular arrhythmias

Introduction

Sarcoidosis is a chronic systemic disorder that generally involves the lungs, eyes, lymph nodes, skin, and heart.[1] Cardiac involvement in cardiac sarcoidosis (CS) is characterized by the spatial and temporal variations of non-caseating granulomatous scarring.[2,3] Its variations can lead to non-reentrant arrhythmias instigated by inflammation and reentrant arrhythmias due to scar tissue formation.[4,5] In the early phase, after immunosuppressive therapy (IST), unstable inflammatory conditions are involved in arrhythmias, and after the resolution of inflammation, scar-related mechanisms cause arrhythmias.[6] Fragmented QRS (fQRS) on the 12-lead electrocardiogram (ECG) is a subtle abnormality within the QRS complex and is associated with conduction disturbance and zigzag conduction around the scar.[7-10] In patients with coronary artery disease, fQRS predicts all-cause mortality and cardiac events.[11] Furthermore, fQRS is a known predictor of arrhythmic events in patients with dilated cardiomyopathy.[10] A previous study reported that the presence of fQRS in patients with sarcoidosis was associated with late gadolinium enhancement on cardiac magnetic resonance (LGE-CMR) imaging.[12] However, the association between fQRS and long-term prognosis remains unclear. Therefore, we investigated the relationship between fQRS and long-term clinical outcomes in patients with CS receiving IST, a cornerstone therapy for CS.

Materials and methods

This observational, retrospective study was approved by the ethics committee of Hokkaido University Hospital (020-0164). The participants were informed of the study through information posted at our institution. Of the 102 consecutive patients with CS admitted to Hokkaido University Hospital between January 2004 and October 2019, those who were not on IST (n=20) or those with a history of IST for sarcoidosis in other organs (n=4) were excluded. Ultimately, 78 patients were assessed in this study (**Figure 1**). CS was diagnosed according to the diagnostic criteria specified in the guidelines

of the Japanese Circulation Society.[13] According to the society guidelines, a definite diagnosis of CS was made based on the presence of granulomas in the myocardium or clinical and/or histopathological findings that meet the clinical cardiac criteria, with extracardiac involvement of at least one organ. Patients diagnosed with CS before 2015 did not need to be excluded based on the diagnostic criteria updated by the Japanese Circulation Society in 2016. Among the 78 patients who met the guidelines of the Japanese Circulation Society, 6 patients were categorized into the histological diagnosis group and 72 patients were categorized into the clinical diagnosis group.

A fixed steroid treatment protocol with a starting dose of prednisolone 30 mg daily for 4 weeks, followed by a stepwise reduction, was used in all but one patient. Each physician decided on the maintenance dose of 2.5−10 mg/day. In one patient, IST was initiated with corticosteroids at 10 mg/day and methotrexate (MTX) at 6 mg/week because he had a known history of panic disorder, and a high dose of prednisolone might cause steroid-induced psychosis. During the follow-up period, MTX was added to the regimen of three patients due to suspected reactivation of CS on ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET). The use of corticosteroids was discontinued in three patients but restarted in one as ventricular tachyarrhythmia (VT) was recorded on their pacemakers, and CS reactivation was suspected on PET.

The resting 12-lead ECG was performed within 4 months before initiating steroids in all study patients. All cardiac resynchronization therapy with a pacemaker (CRT-P) implantation (n=1) or cardiac resynchronization therapy with a defibrillator (CRT-D) implantation (n=9) were performed within 2 months before steroids initiation; the ECG recorded before CRT-P or CRT-D implantation was used for the analysis since it was difficult to define pacing fQRS after CRT-P or CRT-D due to lack of previous reports. ECG data were acquired using a recorder (Nihon Kohden Corporation, Tokyo, Japan, or Fukuda Denshi, Tokyo, Japan; filter range, 0.05 to 150 Hz; AC filter, 50 Hz, 25 mm/s, 10 mm/mV).

All ECGs were blindly reviewed by two cardiologists (H.H. and T.K.), and any discrepancies were resolved by discussion.

The presence of fQRS was defined as follows: (1) at least one additional R wave (R') or notch on the R/S waves in narrow QRS complexes (<120 ms) or >2 notches on the R/S waves in wide (≥120 ms) or paced QRS complexes; and (2) fragmentation in ≥2 contiguous leads representing anterior (V1–V5), inferior (II, III, and aVF), or lateral (I, aVL, and V6) myocardial segments (**Figure 2**).[7,8] The intra-observer (HH) variability for fQRS detection was calculated by performing a second analysis 1 month apart and comparing the results with the first analysis. To test the inter-observer variability, the measurements were performed by a second observer (TK) who was unaware of the first examination results. Intra- and inter-observer variability were 96% and 97%, respectively.

Forty-seven patients (60%) underwent CMR studies on a 1.5T whole-body scanner (Achieva, Philips Medical Systems, Best, The Netherlands) using a cardiac 5-channel phased-array cardiac coil or a 3-T whole-body scanner (Achieva Tx, Philips Medical Systems) using a 32-channel phased-array receiver torso-cardiac coil before initiating IST.[14,15] Late enhancement images were acquired 10–15 min after infusing 0.1 mmol/kg intravenous gadolinium diethylenetriamine penta-acetic acid (Magnevist, Bayer Yakuhin, Osaka, Japan) or gadobutrol (Gadovist, Bayer Yakuhin, Osaka, Japan). The left ventricular (LV) short-axis image acquisition for LGE was conducted using a fast-field echo pulse sequence with inversion recovery with fat saturation or a phase-sensitive inversion recovery sequence. To determine the optimal inversion time to nullify the signal from the normal myocardium, look-locker imaging was performed before myocardial delayed enhancement imaging. Quantitative analysis of LGE-CMR was performed using a software (Ziostation2, Ziosoft Inc.) that automatically determined the hyper-enhanced myocardium with CMR signal intensity (SI) above a predetermined threshold. A region of interest in the normal area was determined using a planimeter, and the extent

of hyper-enhanced myocardium was quantified as the percentage area of the myocardium, with CMR SI and standard deviation (SD) of the SI subsequently calculated.[16] A scar zone was defined by a specific SI of >5 SD of the normal area. A scar border zone was defined by an SI of >2 SD and ≤5 SD of the normal area.[17] All CMR images were blindly reviewed.

Echocardiographic examinations were performed within 2 months before initiating steroid therapy, and the results were digitally recorded. LV end-diastolic diameter (LVDd), LV end-systolic diameter (LVDs), and left atrial diameter (LAD) were measured in the parasternal long-axis view. LV ejection fraction (LVEF) was calculated from apical 2- and 4-chamber views using a biplane-disk summation method.[18] All echocardiographic data were evaluated by two experienced cardiologists.

The primary outcome was a composite of VTs, hospitalization for heart failure (HF), and all-cause death. VT was defined as documented VT or ventricular fibrillation (VF) lasting for >30 s or resulting in cardiovascular collapse and appropriate implantable cardioverter-defibrillator (ICD) therapy (anti-tachycardia pacing or shock).[4] Events were divided into either early phase (within 1 year of IST initiation) or late-onset (thereafter) according to the time until event occurrence. VT morphology was evaluated via 12-lead ECG, ECG monitoring during hospitalization, and/or cardiac implantable electronic device interrogations. Monomorphic VT was defined as all recorded ventricular beats having a regular rate and with the same configuration. Polymorphic VT was defined as all recorded ventricular beats having an irregular and/or non-uniform configuration.

When appropriate, continuous variables are presented as means±standard deviations or medians and interquartile ranges (IQR). Comparisons of differences between the two groups (fQRS and non-fQRS) were performed using unpaired t-tests or the Mann–Whitney U tests for continuous variables and chi-square tests or Fisher's exact tests for dichotomous variables, when appropriate. The cumulative incidence of clinical outcomes was estimated using Kaplan–Meier curves, and a log-rank

test was performed to assess the significance according to the presence of fQRS. To evaluate late-onset VT-free survival, we analyzed Kaplan–Meier curves that only considered VT events 1 year after IST initiation. To evaluate the influence of fQRS on the primary outcome, we constructed a multivariable Cox proportional hazard model. Two multivariable models were created by adjusting for the combination of the following variables based on significant associations in univariate Cox models or the clinically relevant association with the primary outcome [19]: model 1 with a history of VTs and LVEF and model 2 with a history of VTs and log brain-type natriuretic peptide. All tests were two-tailed, and statistical significance was considered at $p<0.05$. All analyses were performed using Stata MP64 version 15 (StataCorp, College Station, TX, USA).

Results

The baseline characteristics of the 78 study patients (median age, 62 years; IQR, 52–68 years; male, 22%) are shown in **Table 1**. No significant differences were found between the groups for body mass index, LVEF, LVDd, LVDs, NYHA classes, and use of other oral medications. In addition, the prevalence of patients with narrow, wide, and paced QRS was comparable between the groups.

During a median follow-up period of 3.7 (IQR, 1.6–6.2) years, the primary outcome occurred in 17 patients (22%), including 11 VTs, 3 HF hospitalizations, and 3 all-cause deaths.

The composite primary outcome significantly occurred more frequently in patients with fQRS than in those without fQRS (9 patients [47%] vs. 8 patients [13%]; hazard ratio, 3.98; 95% confidence interval, 1.54–10.34; p=0.004 by univariate Cox regression). The 10-year Kaplan–Meier event-free estimates were 40% in the fQRS group and 84% in the non-fQRS group (log-rank p=0.002) (**Figure 3a)**. For each component of the composite outcome, VTs occurred more frequently, and the incidence of HF admissions tended to occur in more patients with fQRS than in those without it. However, the

cumulative incidence of all-cause death was comparable between the groups (**Figure 3b-3c and Table 2**). A series of multivariable models were constructed to assess the impact of fQRS on the primary composite outcome (**Table 3**) as the number of events was limited. These models demonstrated that fQRS was an independent determinant of the primary outcome.

Moreover, we compared the composite primary outcomes of the paced and non-paced groups. In the paced group, four patients were upgraded from pacemakers to CRT-D. Kaplan–Meier event-free estimates were 76% in the paced group and 65% in the non-paced group (log-rank p=0.496). In the paced group, the Kaplan–Meier event-free estimates were 20% in patients with fQRS and 84% in those without fQRS (log-rank p=0.0041). In the non-paced group, the Kaplan–Meier event-free estimates were 51% in patients with fQRS and 84% in those without fQRS (log-rank p=0.0761) (**Figure 4**).

Figures 5a and 5b show the distribution of VTs over time. Most patients (9/11, 82%) experienced their first VT event within 1 year. Four of these patients in the fQRS group had VT recurrence approximately 5 years after IST initiation. Kaplan–Meier analyses (**Figure 5c and d**) revealed no difference in event-free survival of VT occurrence within 1 year between the two groups (79% in the fQRS group vs. 92% in non-fQRS groups, log-rank p=0.128). However, the event-free survival of late-onset VTs was significantly lower in the fQRS group than in the non-fQRS group (60% vs. 98% at 10 years, log-rank p=0.002). In the early phase, a cumulative total of 12 patients experienced VTs: two patients were monomorphic, eight patients were polymorphic, and the remaining two patients could not be traced. In contrast, in the late-onset phase, a cumulative total of seven patients experienced VTs: six patients were monomorphic, and the remaining one patient could not be traced. At the time of diagnosis, FDG-PET was performed in 34 patients (no VTs within 1 year, 29 patients; VTs within 1 year, 5 patients). No significant difference was found in the maximum standardized

uptake value of patients with and without a VT event in 1 year (8.32±2.93 vs. 8.23±4.09, p=0.9526).

CMR was examined in 47 patients (fQRS, 12 patients; non-fQRS, 35 patients). Patients with fQRS had a larger percentage area of core scar (35.2±16.8% vs. 23.0±13.6%, p=0.0156) and scar border zone (20.3±5.7% vs. 15.8±5.5%, p=0.0206) than in those without fQRS (**Figure 6**).

In 41 patients (fQRS, 8 patients; non-fQRS, 33 patients), ECG was repeatedly performed 9–15 months after the initiation of IST. Of these patients, most (39 patients, 95%) showed a consistent presence or absence of fQRS, while fQRS disappeared in two patients (5%) during the follow-up (**Figure 7**). Both patients had preserved LV function (one with LVEF 60% and the other with LVEF 65%) and were in the clinical diagnosis group. One had narrow QRS with fQRS in the inferior segment, and the other had wide QRS with fQRS in the anterior segment. Neither of these two patients had a recurrence of fQRS on follow-up.

Discussion

This study is the first to evaluate the association between fQRS and long-term clinical outcomes in patients with CS. The major finding was that the presence of fQRS on ECG was significantly associated with subsequent adverse events, particularly VTs. Furthermore, patients with fQRS were more likely to experience VTs, 1 year after IST initiation.

Abnormal late potential, which is documented by a signal-averaged ECG, suggests the presence of a slow conduction zone with damaged myocardium,[20] and the relationship between the presence of this late potential and sudden cardiac death or lethal arrhythmic events have been reported.[21] Similarly, fQRS also reflects intracardiac conduction abnormalities and can be a substrate for reentrant arrhythmias.[7] fQRS is a simple and non-invasive indicator representing a depolarization abnormality, generally due to regional myocardial fibrosis or scarring. Although the mechanism of

fQRS is not fully understood, it has been reported that zigzag conduction around the scar can cause fQRS. The presence of fQRS predicts cardiac events in patients with reduced LVEF and within different cardiovascular disease populations, such as patients with acute coronary syndrome, dilated cardiomyopathy, and hypertrophic cardiomyopathy.[8,10,22,23,24] Similarly, a previous study reported that the presence of fQRS was related to cardiac involvement in patients with CS.[12]

As VTs are not rare and are an important risk factor for morbidity and mortality in patients with CS,[25] it is essential to identify patients at risk and clarify an indication for ICD implantation. Currently, ICD implantation is recommended in patients with CS who have sustained VT, are survivors of sudden cardiac arrest, or have an LVEF ≤35%. Even if LVEF is >35%, an ICD is considered beneficial (indicated as class 2a) in patients with 1) an indication for permanent pacemaker implantation, 2) unexplained syncope, 3) inducible sustained ventricular arrhythmias (VAs), or 4) myocardial scarring as observed on cardiac magnetic resonance imaging (MRI).[26] In particular, recent studies have reported the excellent performance of LGE-MRI in detecting cardiac fibrosis and its association with adverse outcomes. In our study, the percentage of LGE area was larger in patients with fQRS than in those without fQRS, suggesting more enhanced fibrosis in these patients. Therefore, fQRS might be an indication of cardiac fibrosis and might serve as a possible predictor for VAs. The utility of fQRS in the risk stratification of VAs in patients with CS needs to be explored further.

The mechanisms and substrates of VTs in CS are not fully understood. A recent report by Segawa et al.[6] demonstrated that positive gallium scintigraphy was noted in 12 out of 14 (86%) patients who had initial VT events during the first 12 months. Conversely, the number of first VT events decreased after 12 months, while recurrence events were consistently noted even after 15 months. Their observation suggests that the mechanism of VTs during the late phase may differ from those during the early phase; VAs occur in the early phase after IST due to unstable inflammation and in the late

phase due to scar-related mechanisms.[6] We observed that late-onset VAs occurred only in the fQRS group. Consequently, the majority of these late-onset VAs were monomorphic and that the percent LGE area had increased in these patients. These findings suggest that the dominant mechanism of VTs in the fQRS group was scar-related. However, we could not establish a relationship between VT and the maximum standardized uptake value. We considered that unstable inflammation due to steroid initiation could not be evaluated based on the maximum standardized uptake value.

IST is the main pharmacological treatment for CS because it decreases inflammation, suppresses fibrosis and scar formation, and reduces sudden cardiac death associated with conduction abnormalities. A previous report demonstrated that IST improved atrioventricular conduction disturbance [27, 28], and in this study, fQRS disappeared in two patients after initiating IST due to improvement of zigzag conduction. However, IST data is not consistently reported.[29] In the present study, IST was administered in all cases, and fQRS did not change in most cases even after IST. We believe that, in this current era, when IST is the standard therapy for CS, fQRS stands as an excellent predictor of late-onset VTs.

This study has some limitations. First, this was a retrospective study conducted at a single center. Therefore, the sample size was relatively small, limiting the generalizability of the findings and the statistical power for detecting differences in negative data. Therefore, a prospective study is necessary to validate our results. Second, the results of CMR and ECG after 1 year of IST initiation were limited; therefore, there was an unavoidable selection bias. Finally, arrhythmias could not be monitored daily in patients without cardiac implantable electronic devices. Hence, we defined VTs as clinically important sustained VT or VF, hemodynamic disturbances, and treatment with ICD.

In conclusion, the presence of fQRS was associated with worse long-term clinical outcomes and late-onset fatal arrhythmias in patients with CS. Thus, fQRS may be a potential prognostic predictor in

these patients.

Conflicts of interest

None.

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Figure Legends

Figure 1. Flow diagram of the present study.

Abbreviations: CS, cardiac sarcoidosis; fQRS, fragmented QRS

Figure 2. The ECG of representative fragmented QRS complexes in **(a)** narrow QRS (<120 ms) and **(b)** wide QRS (≥120 ms).

Abbreviation: ECG, electrocardiogram

Figure 3. Survival analyses of long-term clinical outcomes of patients with cardiac sarcoidosis categorized by fQRS. **(a)** Composite of all-cause death, ventricular arrhythmias, and HF hospitalization. **(b)** All-cause death. **(c)** VTs. **(d)** HF admission.

Abbreviations: fQRS, fragmented QRS; HF, heart failure; VTs, ventricular tachyarrhythmias

Figure 4. Survival analyses of the primary outcome in patients with cardiac sarcoidosis. **(a)** Non-paced and paced groups. **(b)** The paced group categorized by fQRS. **(c)** The non-paced group categorized by fQRS.

Abbreviation: fQRS, fragmented QRS

Figure 5. Distribution of VTs in the **(a)** fQRS group and **(b)** non-fQRS group. First event indicates the number of patients with the first VT after initiation of immunosuppressive therapy. A recurrence event indicates any event that recurred after the first VTs. Survival analyses of ventricular arrhythmias of patients with cardiac sarcoidosis categorized by fQRS within **(c)** 1 year and **(d)** after 1 year.

Abbreviations: fQRS, fragmented QRS; HF, heart failure; VT, ventricular tachyarrhythmia.

Figure 6. Representative cardiac magnetic resonance sequence images of **(a)** LGE, scar zone, scar zone+border zone, and merged image on the short-axis slice. **(b, c)** Quantification of percent LGE and scar border zone.

Abbreviation: fQRS, fragmented QRS; LGE, late gadolinium enhancement; SD, standard deviation

Figure 7. Electrocardiographic (ECG) findings before and after immunosuppressive therapy (IST). **(a)** Flow diagram of ECG changes. **(b)** Representative ECGs before and 12 months after IST initiation in a patient in whom fQRS was not observed during follow-up.

Abbreviation: fQRS, fragmented QRS

Tables

Table 1. Baseline patient characteristics.

Variables	Overall (n=78)	fQRS-positive (n=19)	fQRS-negative (n=59)	p-value
Age (years)	62 (52–68)	64 (51–71)	61 (54–68)	0.50
Male, n (%)	17 (22)	13 (68)	4 (21)	1.00
Body mass index, kg/m^2	22.4 (20.5–24.5)	23.3 (20.9–24.5)	21.9 (20.2–24.7)	0.57
Follow-up period, years	3.7 (1.6–6.2)	2.8 (0.7–5.5)	3.9 (1.7–6.6)	0.22
History, n (%)				
Hypertension	17 (22)	2 (11)	15 (26)	0.21
Dyslipidemia	22 (29)	6 (32)	16 (28)	0.73
Diabetes mellitus	7 (9)	0 (0)	7 (12)	0.18
CAD	3 (4)	0 (0)	3 (5)	0.57
NYHA class				0.06
I	30 (39)	6 (32)	24 (42)	
II	27 (36)	11 (58)	16 (28)	
III+IV	19 (25)	2 (11)	17 (30)	
History of electrical abnormalities, n (%)				
VT/VF	9 (12)	1 (5)	8 (14)	0.44
Advanced heart block	24 (31)	6 (32)	18 (31)	0.97

Atrial fibrillation	2 (3)	1 (5)	1 (2)	0.44
NSVT	12 (16)	2 (11)	10 (17)	0.72
Electrocardiogram n (%)				0.99
Narrow QRS	21 (27)	5 (26)	16 (27)	
Wide QRS	36 (46)	9 (47)	27 (46)	
Paced QRS	21 (27)	5 (26)	16 (27)	
Pattern of wide QRS n (%)				0.72
CRBBB	29 (81)	8 (89)	21 (78)	
CLBBB	1 (3)	0 (0)	1 (4)	
non-specific	6 (17)	1 (11)	5 (19)	
Localization of fragmentation n (%)				
Anterior		14 (74)		
Inferior		0 (0)		
Posterior		6 (32)		
Echocardiography				
LVEF, %	45 (37–62)	45 (35–58)	46 (37–62)	0.65
LVDd, mm	51.7±8.7	53.2±11.0	51.2±8.0	0.40
LVDs, mm	38.1±12.1	40.7±14.5	37.2±11.5	0.26
LAD, mm	37.7±7.2	38.9±6.1	37.2±7.5	0.38
IVS wall thinning n (%)	32 (42)	8 (42)	24 (41)	0.96
Laboratory data				
Hemoglobin, g/dL	13.5±1.5	13.5±1.8	13.5±1.4	0.84
Cr, mg/dL	0.70	0.71	0.70	0.57

	(0.62–0.80)	(0.64–0.80)	(0.59–0.81)	
BNP, pg/mL	82.0 (28.6–178.5)	101.5 (68.3–170.0)	75 (19.0–178.5)	0.20
ACE, IU/L	14.6 (11.4–19.9)	16.7 (12.9–21.4)	13.9 (11.3–19.6)	0.45
sIL2-R, IU/mL	569 (384–784)	585 (453–785)	533 (359–783)	0.48
Medications n (%)				
ACE-inhibitors/ARBs	44 (57)	12 (63)	32 (55)	0.54
Beta blockers	40 (52)	11 (58)	29 (50)	0.56
Amiodarone	11 (14)	3 (16)	8 (14)	1.00
Device therapy				0.88
PM	10 (13)	3 (16)	7 (12)	
ICD	13 (17)	4 (21)	9 (15)	
CRT-D	9 (12)	1 (5)	8 (14)	
CRT-P	1 (1)	1 (5)	0	

Values are mean±standard deviation or median (interquartile range) or numbers (proportion, %). ACE: angiotensin-converting enzyme; ARBs: angiotensin II receptor blocker; BNP: brain-type natriuretic peptide; CAD: coronary artery disease; CRBBB: complete right bundle branch block; Cr: creatinine; CRT-D: cardiac resynchronization therapy with a defibrillator; CRT-P: cardiac resynchronization therapy with a pacemaker; EMB: endomyocardial biopsy; fQRS, fragmented QRS; ICD: implantable cardioverter-defibrillator; IVS: interventricular septum; LAD: left atrial diameter; LVDd: left ventricular end-diastolic diameter; LVDs: left ventricular end-systolic diameter; LVEF: left ventricular ejection fraction; sIL2-R: serum interleukin-2 receptor; NSVT: nonsustained ventricular tachycardia; NYHA: New York Heart Association; PM: pacemaker.

Table 2. Incidences and Cox regression hazard ratios for the primary composite outcome and for each component outcome.

		fQRS vs. non-fQRS		
	Incidence of events	Hazard ratio	95% CI	p-value
Primary composite outcome	17 (22)			
fQRS positive	9 (47)	3.98	1.54–10.34	0.004
fQRS negative	8 (13)			
All-cause death	4 (5)			
fQRS positive	1 (5)	1.06	0.11–10.18	0.961
fQRS negative	3 (5)			
VTs	11 (14)			
fQRS positive	6 (32)	3.97	1.21–13.02	0.023
fQRS negative	5 (8)			
HF admission	4 (5)			
fQRS positive	3 (16)	9.49	0.99–91.24	0.051
fQRS negative	1 (2)			

Values are represented as numbers (proportion, %).
CI: confidence interval; fQRS: fragmented QRS; HF: heart failure; VTs: ventricular tachyarrhythmias.

Table 3. Cox proportional hazards model for composite events in univariate and multivariable analyses

	Univariable		**Multivariable**			
			Model 1		Model 2	
Variables	HR (95% CI)	*p*-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age, years	1.00 (0.97–1.04)	0.797				
Female	0.99 (0.32–3.05)	0.992				
Hemoglobin, g/dL	0.79 (0.56–1.11)	0.173				
Creatinine, mg/dL	0.67 (0.34–13.5)	0.797				
LVEF, %	0.98 (0.95–1.01)	0.261				
LVEF ≤35%	1.08 (0.38–3.09)	0.879	0.94 (0.32–2.72)	0.903		
Log BNP	3.40 (1.33–8.68)	0.010			5.88 (1.78–19.41)	0.004
NYHA class III + IV	1.04 (0.34–3.19)	0.946				

Complete AV	2.16	0.114				
block	(0.83–5.62)					
History of	3.68	0.024	7.95	0.002	20.92	0.000
VTs	(1.19–11.4)		(2.10–30.06)		(4.48–97.64)	
fQRS	3.98	0.004	6.97	0.001	5.19	0.007
	(1.54–10.3)		(2.31–21.00)		(1.56–17.31)	

AV: atrio-ventricular; BNP: brain-type natriuretic peptide; CI: confidence interval; fQRS: fragmented QRS; HR: hazard ratio; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; VTs: ventricular tachyarrhythmias

Figure 1

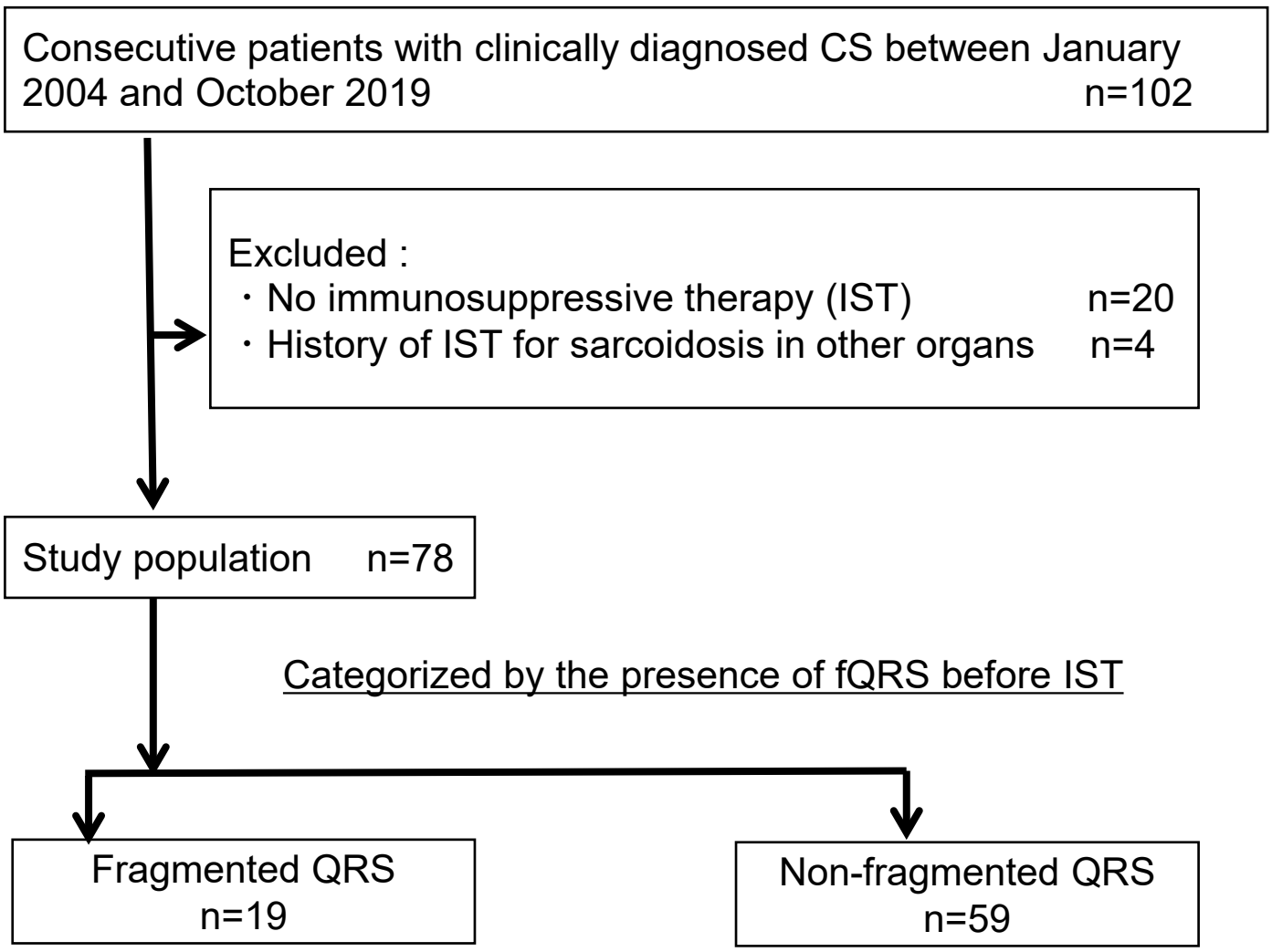
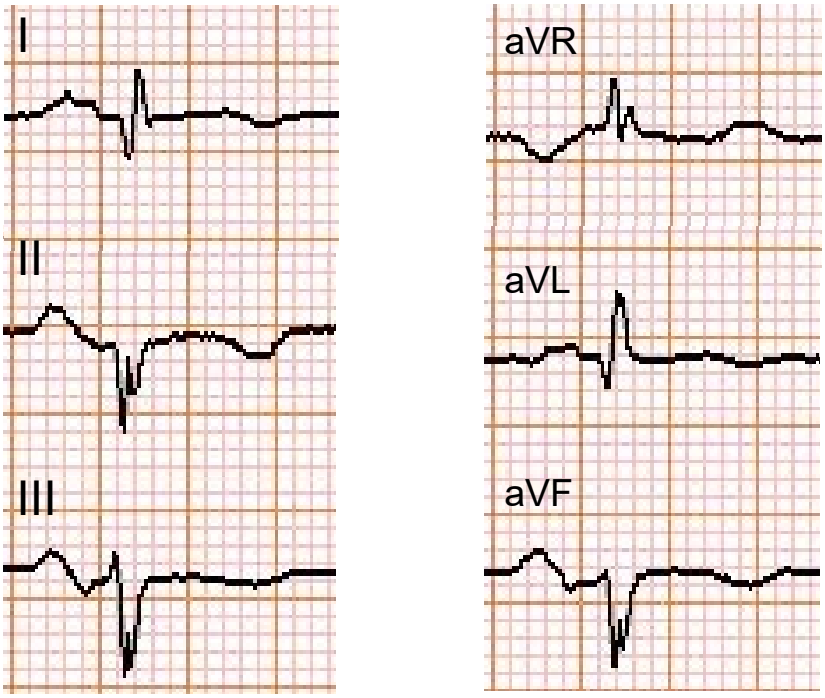

Consecutive patients with clinically diagnosed CS between January 2004 and October 2019 n=102
Excluded :
・No immunosuppressive therapy (IST) n=20
・History of IST for sarcoidosis in other organs n=4
Study population n=78
Categorized by the presence of fQRS before IST
Fragmented QRS n=19
Non-fragmented QRS n=59

Figure 2

a



b

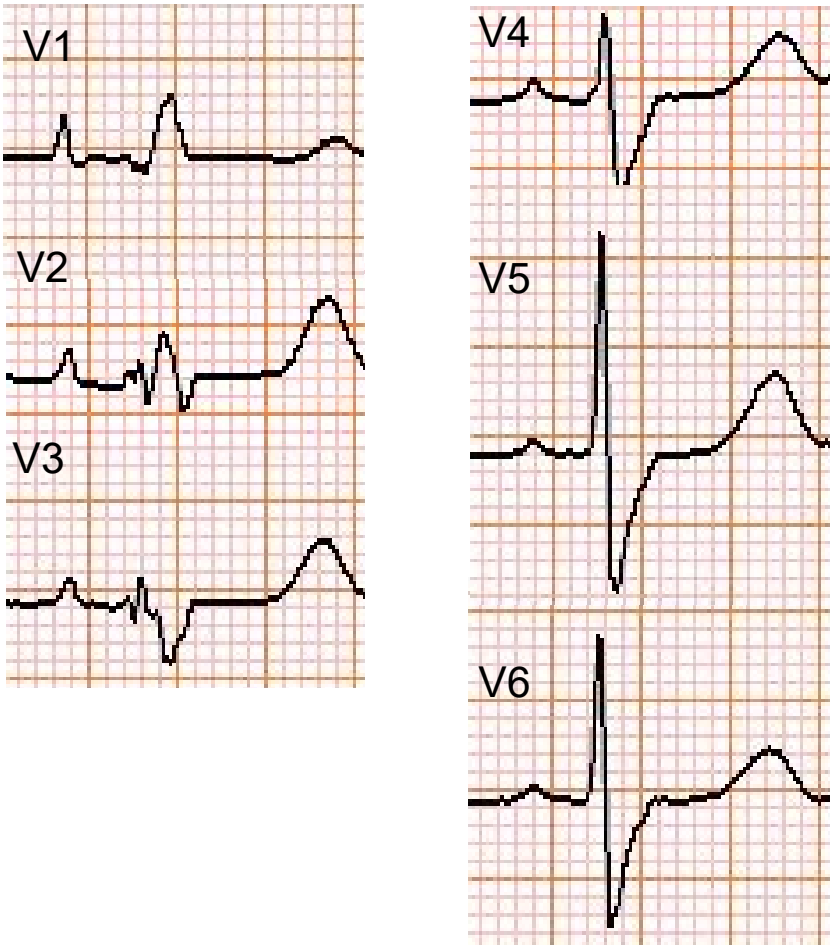


Figure 3

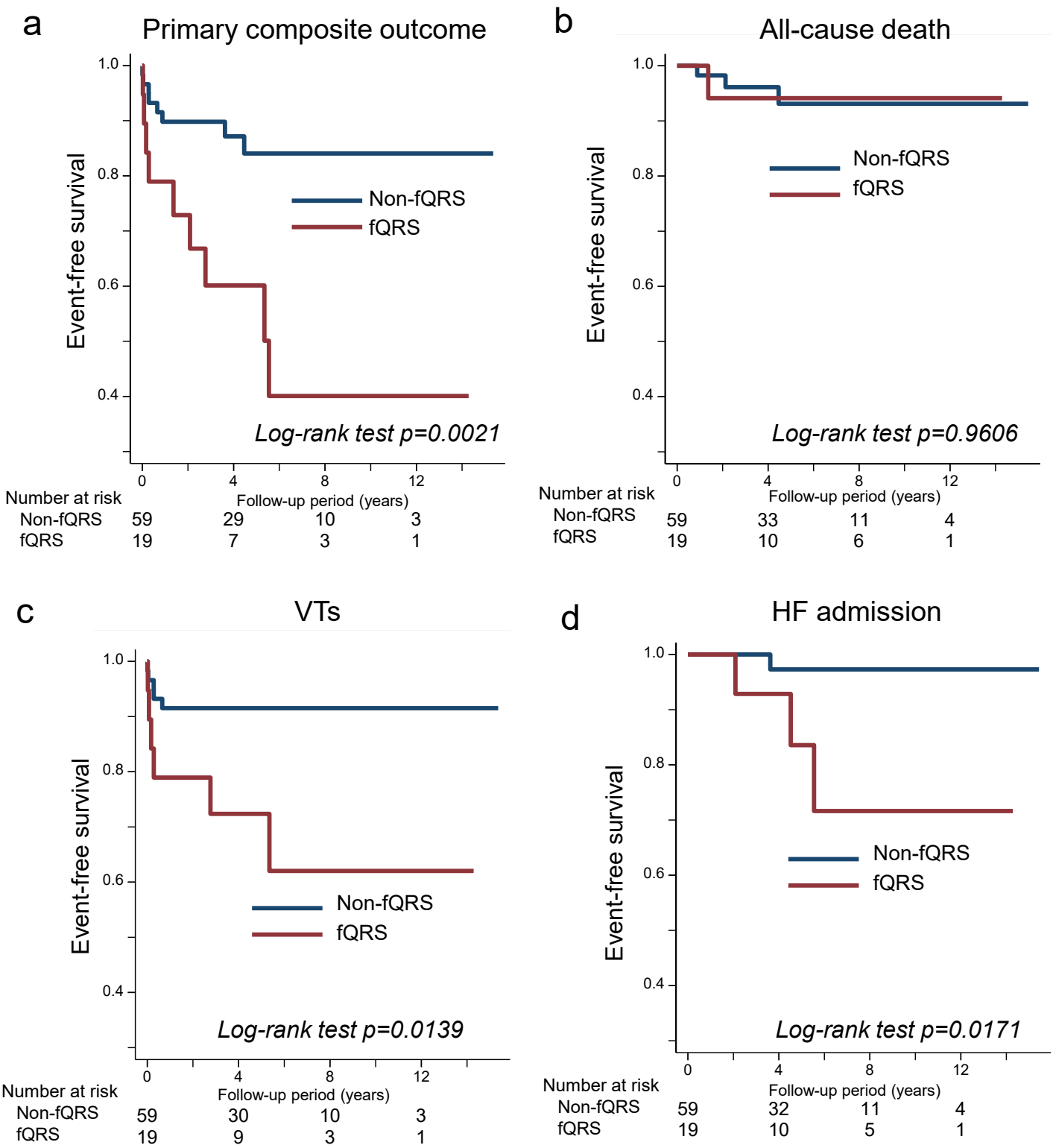
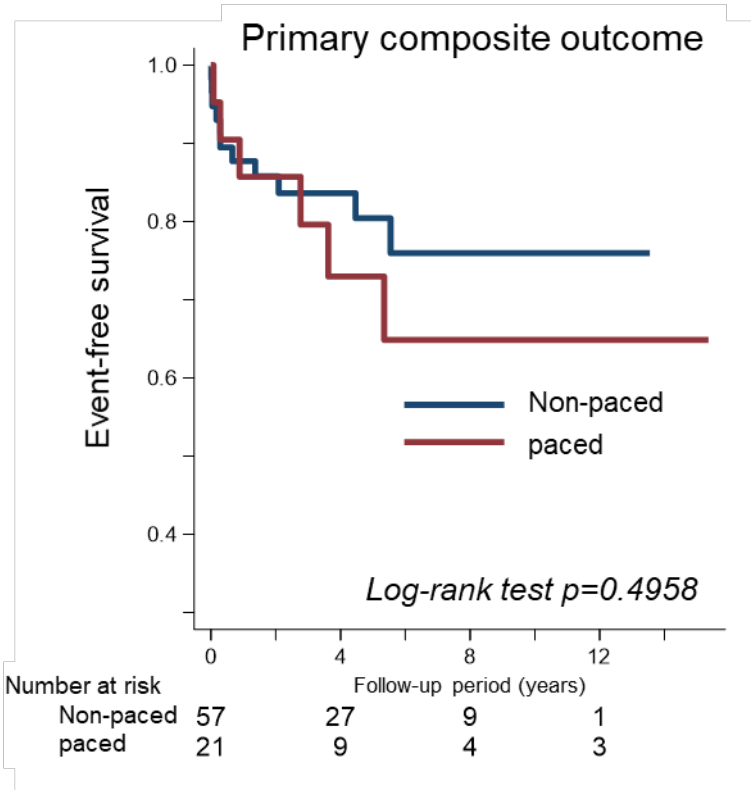
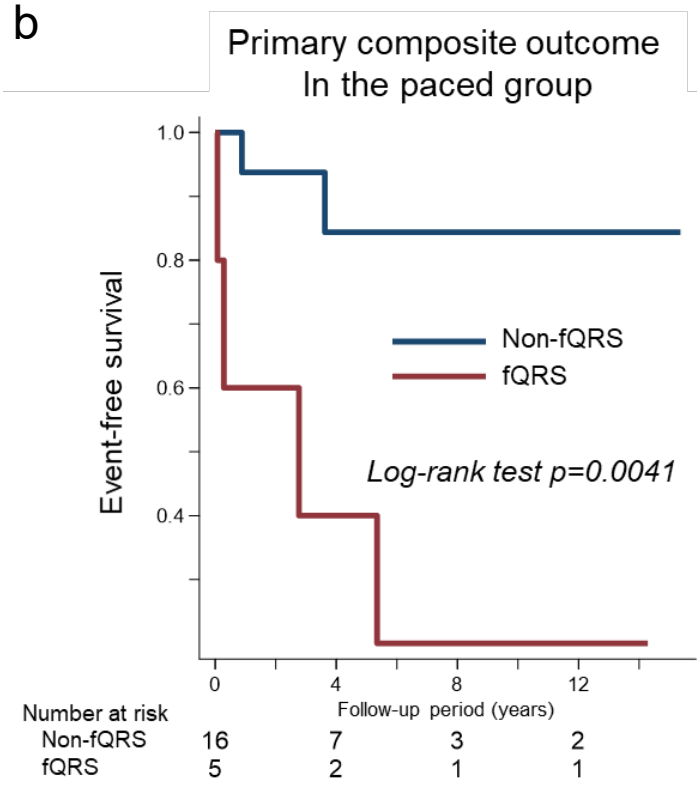

a
Primary composite outcome
Event-free survival
1.0
0.8
0.6
0.4
Non-fQRS
fQRS
Log-rank test p=0.0021
0
4
8
12
Follow-up period (years)
Number at risk
Non-fQRS 59 29 10 3
fQRS 19 7 3 1
b
All-cause death
Event-free survival
1.0
0.8
0.6
0.4
Non-fQRS
fQRS
Log-rank test p=0.9606
0
4
8
12
Follow-up period (years)
Number at risk
Non-fQRS 59 33 11 4
fQRS 19 10 6 1
c
VTs
Event-free survival
1.0
0.8
0.6
0.4
Non-fQRS
fQRS
Log-rank test p=0.0139
0
4
8
12
Follow-up period (years)
Number at risk
Non-fQRS 59 30 10 3
fQRS 19 9 3 1
d
HF admission
Event-free survival
1.0
0.8
0.6
0.4
Non-fQRS
fQRS
Log-rank test p=0.0171
0
4
8
12
Follow-up period (years)
Number at risk
Non-fQRS 59 32 11 4
fQRS 19 10 5 1

Figure 4

a


Primary composite outcome
Event-free survival
1.0
0.8
0.6
0.4
Non-paced
paced
Log-rank test p=0.4958
0
4
8
12
Follow-up period (years)
Number at risk
Non-paced 57 27 9 1
paced 21 9 4 3

b


Primary composite outcome
In the paced group
Event-free survival
1.0
0.8
0.6
0.4
Non-fQRS
fQRS
Log-rank test p=0.0041
0
4
8
12
Follow-up period (years)
Number at risk
Non-fQRS 16 7 3 2
fQRS 5 2 1 1

c

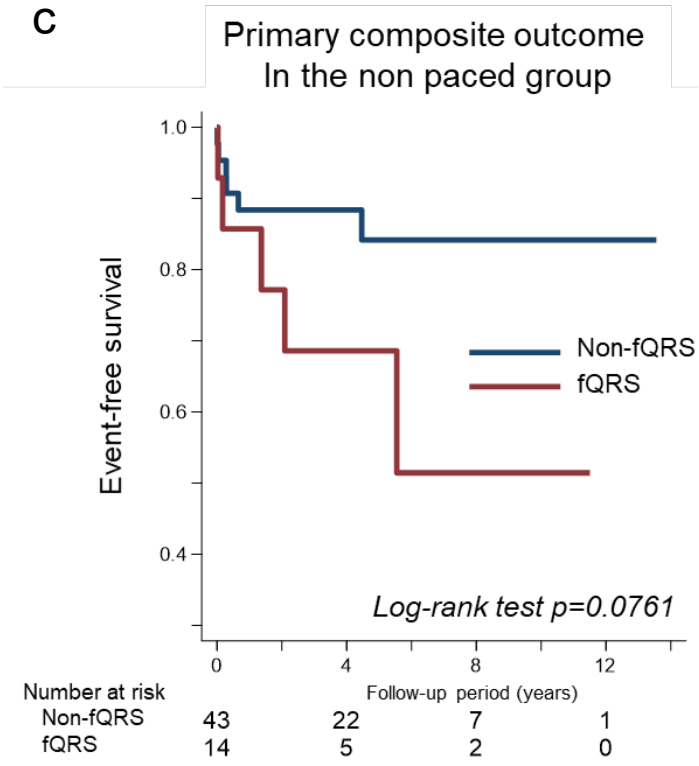
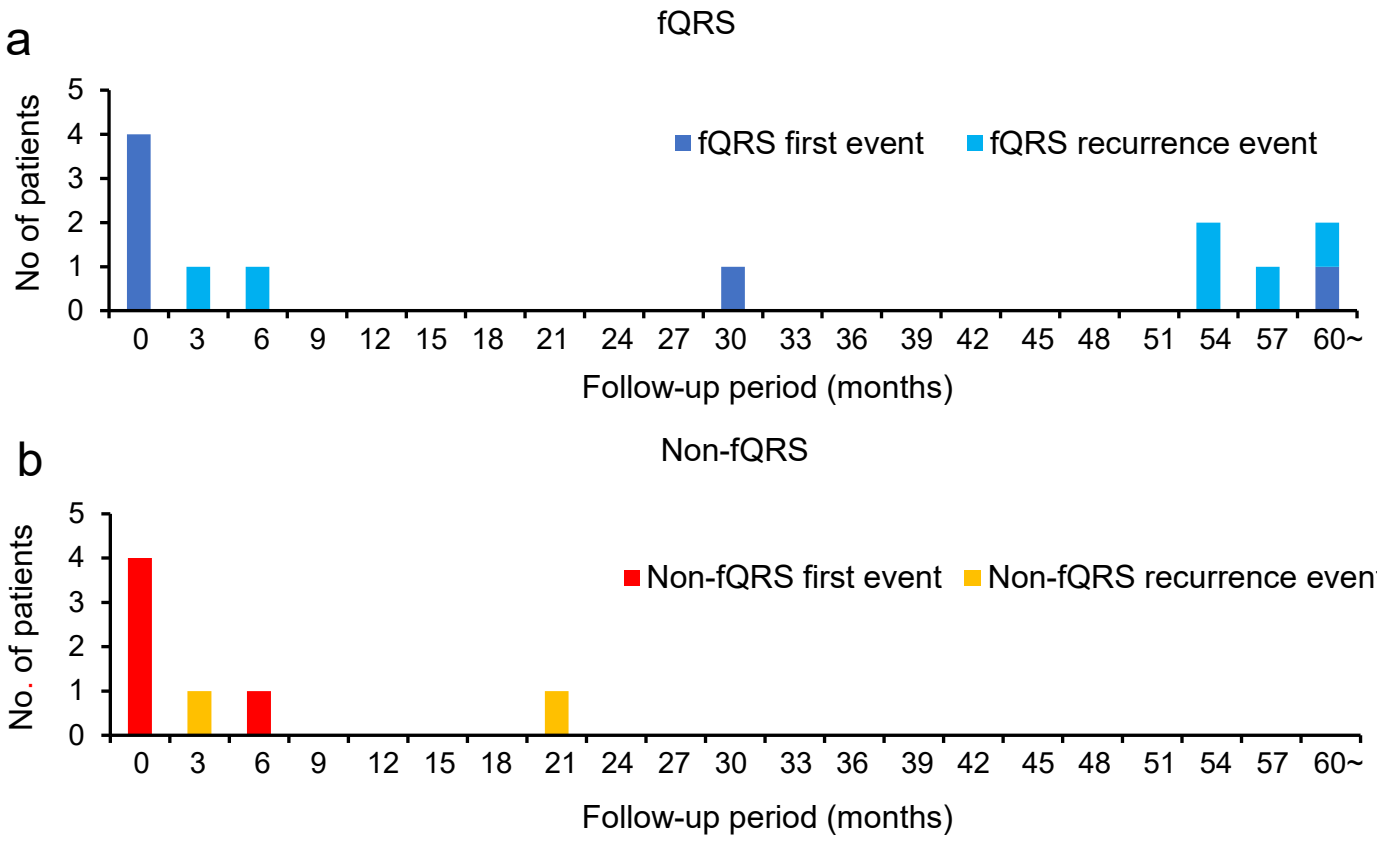
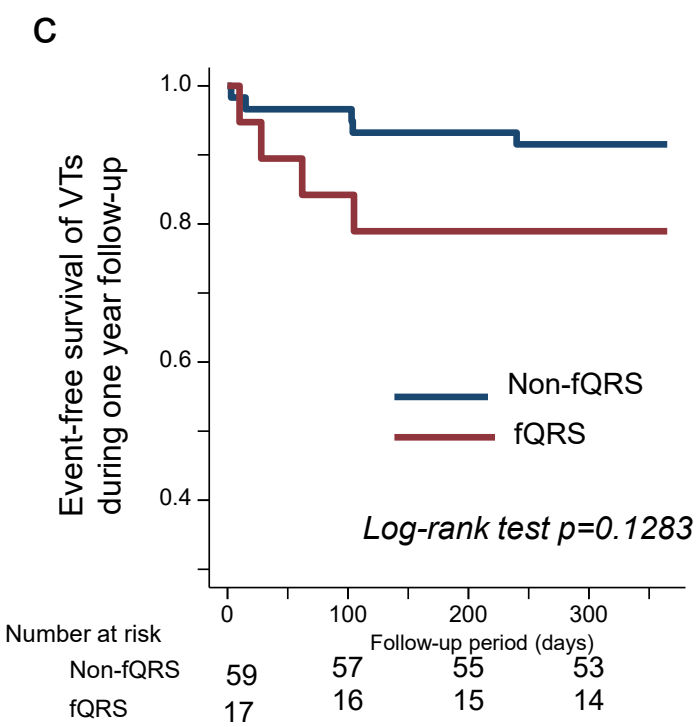

Primary composite outcome
In the non paced group
Event-free survival
1.0
0.8
0.6
0.4
Non-fQRS
fQRS
Log-rank test p=0.0761
0
4
8
12
Follow-up period (years)
Number at risk
Non-fQRS 43 22 7 1
fQRS 14 5 2 0

Figure 5


a
fQRS
No of patients
fQRS first event
fQRS recurrence event
Follow-up period (months)
b
Non-fQRS
No. of patients
Non-fQRS first event
Non-fQRS recurrence event
Follow-up period (months)


c
Event-free survival of VTs during one year follow-up
Non-fQRS
fQRS
Log-rank test p=0.1283
Follow-up period (days)
Number at risk
Non-fQRS 59 57 55 53
fQRS 17 16 15 14

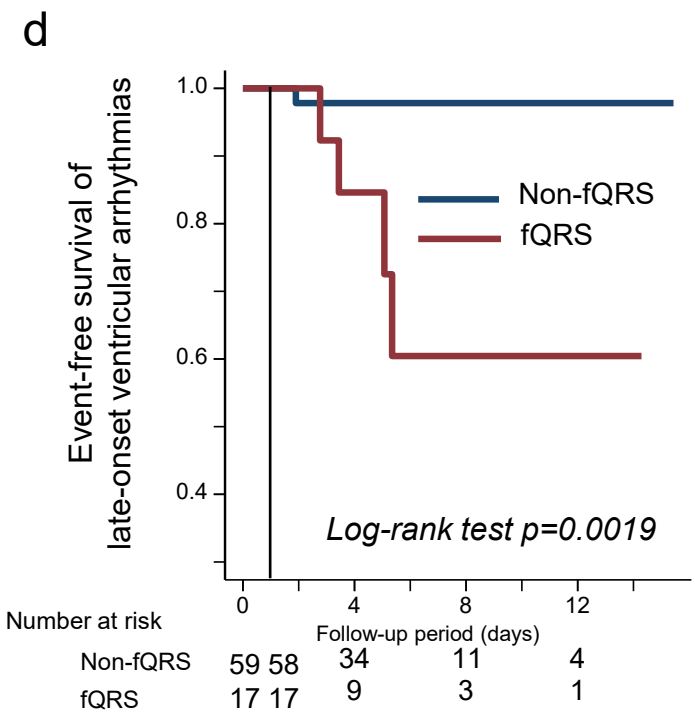
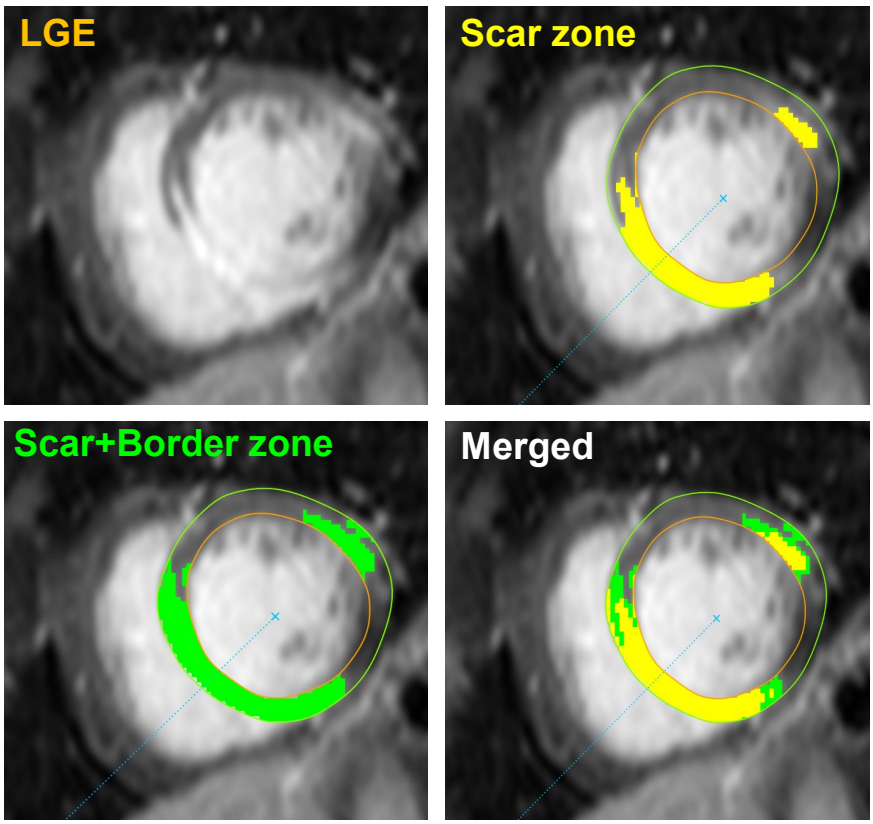
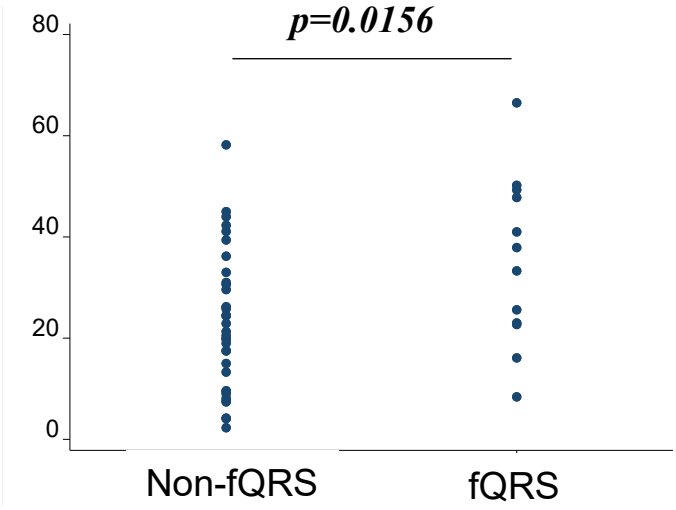

d
Event-free survival of late-onset ventricular arrhythmias
Non-fQRS
fQRS
Log-rank test p=0.0019
Follow-up period (days)
Number at risk
Non-fQRS 59 58 34 11 4
fQRS 17 17 9 3 1

Figure 6

a



b %LGE (≥5SD)



c Scar border zone (≥2SD and ≤5SD)

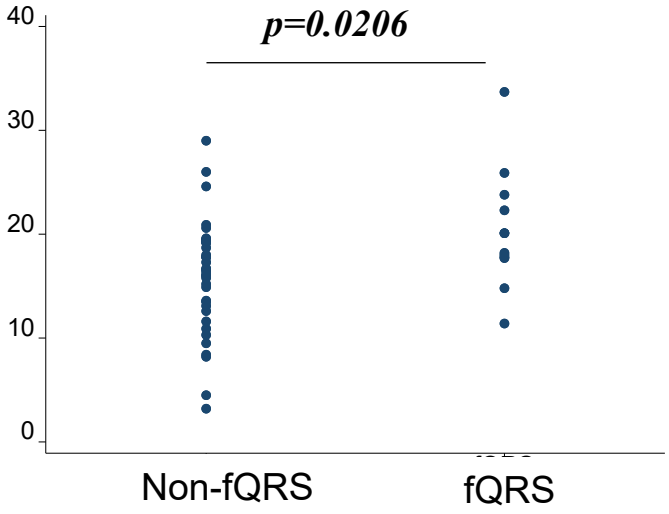
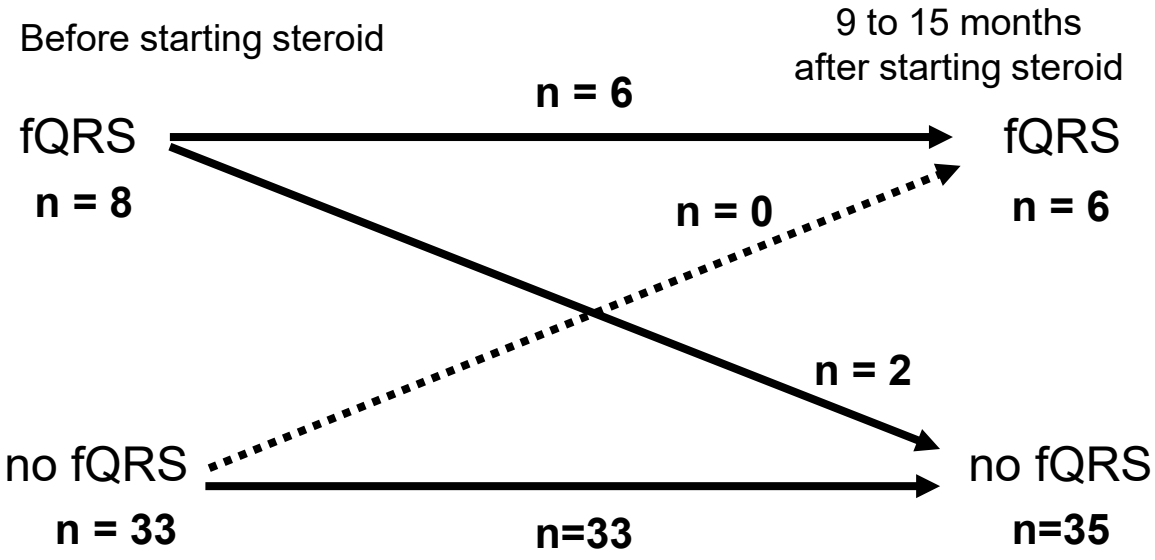
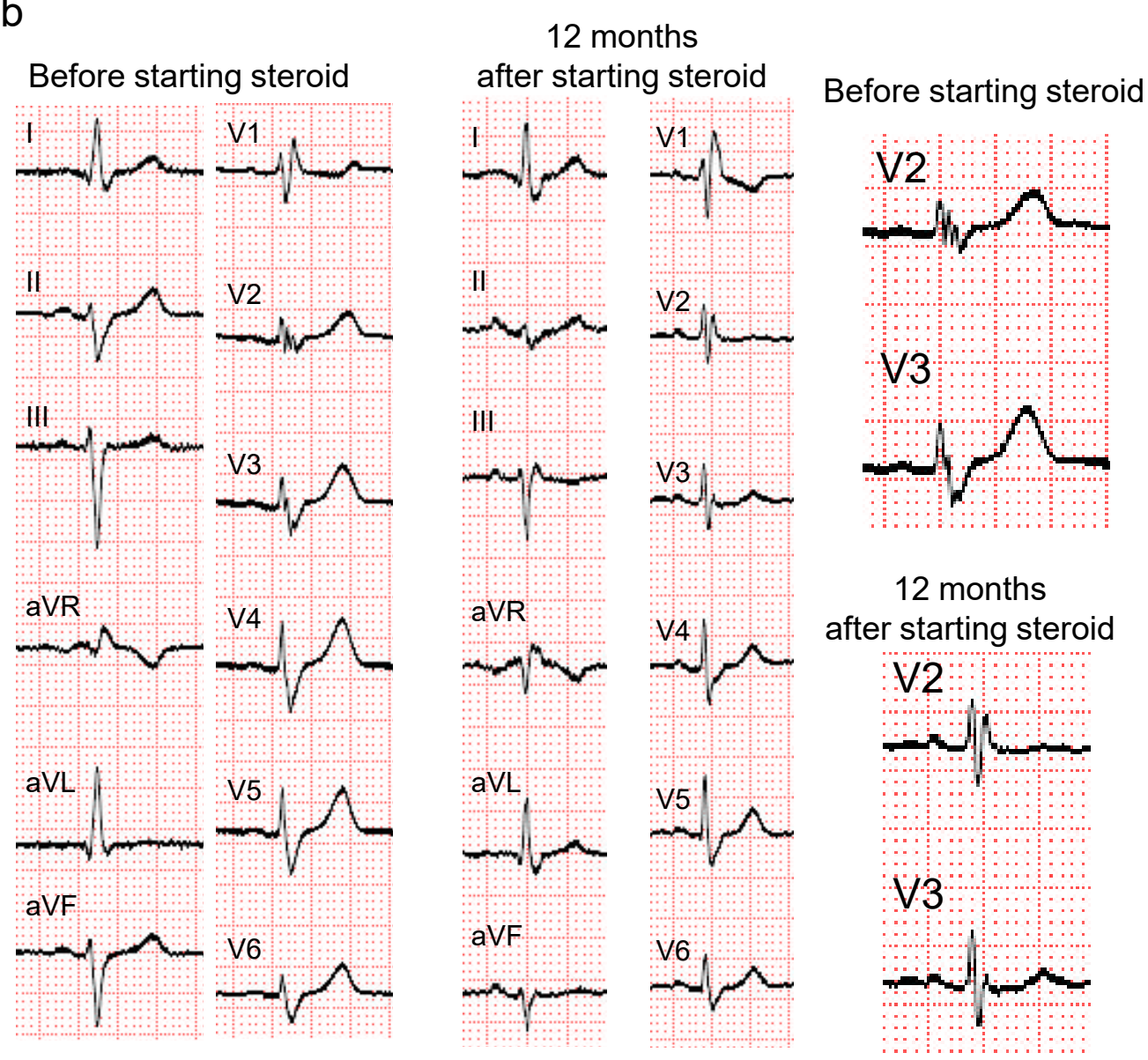


Figure 7

a


Before starting steroid
9 to 15 months
after starting steroid
n = 6
fQRS
n = 8
fQRS
n = 6
n = 0
n = 2
no fQRS
n = 33
n=33
no fQRS
n=35

b


Before starting steroid
12 months
after starting steroid
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
Before starting steroid
V2
V3
12 months
after starting steroid
V2
V3