



Title	Fragmented QRS on 12-lead electrocardiogram predicts long-term prognosis in patients with cardiac sarcoidosis
Author(s)	Hagiwara, Hikaru; Watanabe, Masaya; Kadosaka, Takahide; Koizumi, Takuya; Kobayashi, Yuta; Koya, Taro; Nakao, Motoki; Tsuneta, Satonori; Kato, Yoshiya; Komoriyama, Hirokazu; Kamada, Rui; Nagai, Toshiyuki; Kudo, Kohsuke; Anzai, Toshihisa
Citation	Heart and vessels, 38(6), 803-816 https://doi.org/10.1007/s00380-022-02229-2
Issue Date	2023-06-01
Doc URL	http://hdl.handle.net/2115/92732
Rights	This version of the article has been accepted for publication, after peer review (when applicable) and is subject to Springer Nature 's AM terms of use, but is not the Version of Record and does not reflect post-acceptance improvements, or any corrections. The Version of Record is available online at: http://dx.doi.org/doi.org/10.1007/s00380-022-02229-2
Type	article (author version)
File Information	Heart Vessels_s00380-022-02229-2.pdf



[Instructions for use](#)

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

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

7 ^a Department of Cardiovascular Medicine, Faculty of Medicine and Graduate School of Medicine,
8 Hokkaido University, Sapporo, Japan

9 ^b Department of Diagnostic Imaging, Graduate School of Medicine, Hokkaido University, Sapporo,
10 Japan

11 ^c Department of Cardiovascular Medicine, Kushiro City General Hospital, Kushiro, Japan

12 ***Corresponding author:**

13 Dr. Masaya Watanabe, MD, PhD

14 Department of Cardiovascular Medicine, Faculty of Medicine and Graduate School of Medicine,

15 Hokkaido University, Kita-15 Nishi-7, Kita-Ku, Sapporo 060-8638, Japan

16 Tel: +81-11-706-6973

17 Fax: +81-11-706-7874

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

19 **Abstract**

20 Fragmented QRS (fQRS) on a 12-lead electrocardiogram is a known marker of fatal arrhythmias or
21 cardiac adverse events in ischemic and non-ischemic cardiomyopathy patients. Nonetheless, the
22 association between fQRS and clinical outcomes in patients with cardiac sarcoidosis (CS) remains
23 unclear. Herein, we investigated whether fQRS is associated with long-term clinical outcomes in CS
24 patients. A total of 78 patients who received immunosuppressive therapy (IST) for clinically
25 diagnosed CS were retrospectively examined. Patients were classified into two groups according to
26 the presence (n=19) or absence (n=59) of fQRS on electrocardiogram before IST. The primary
27 outcome was the composite event of all-cause death, ventricular tachyarrhythmias (VTs), and
28 hospitalization for heart failure. Results of late gadolinium enhancement on cardiac magnetic
29 resonance imaging were also analyzed. During a median follow-up period of 3.7 years (interquartile
30 range: 1.6–6.2 years), the primary outcome occurred more frequently in patients with fQRS than in
31 those without (47% vs. 13%, log-rank p=0.002). Multivariable Cox regression analyses showed that
32 fQRS was an independent determinant of the primary outcome. The incidence of VTs, within 12
33 months of IST initiation, was comparable between the two groups; however, late-onset VTs, defined
34 as those occurring ≥ 12 months after IST initiation, occurred more frequently in the fQRS group
35 (21% vs. 2%, log-rank p=0.002). The scar zone and scar border zone were greater in patients with
36 fQRS than in those without it. In conclusion, our analysis suggests that fQRS is an independent
37 predictor of adverse events, particularly late-onset VTs, in patients with CS.

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

39

40 **Introduction**

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

56 **Materials and methods**

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

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

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

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

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

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

96 Forty-seven patients (60%) underwent CMR studies on a 1.5T whole-body scanner (Achieva, Philips
97 Medical Systems, Best, The Netherlands) using a cardiac 5-channel phased-array cardiac coil or a 3-
98 T whole-body scanner (Achieva Tx, Philips Medical Systems) using a 32-channel phased-array
99 receiver torso-cardiac coil before initiating IST.[14,15] Late enhancement images were acquired 10–
100 15 min after infusing 0.1 mmol/kg intravenous gadolinium diethylenetriamine penta-acetic acid
101 (Magnevist, Bayer Yakuhin, Osaka, Japan) or gadobutrol (Gadovist, Bayer Yakuhin, Osaka, Japan).
102 The left ventricular (LV) short-axis image acquisition for LGE was conducted using a fast-field echo
103 pulse sequence with inversion recovery with fat saturation or a phase-sensitive inversion recovery
104 sequence. To determine the optimal inversion time to nullify the signal from the normal myocardium,
105 look-locker imaging was performed before myocardial delayed enhancement imaging. Quantitative
106 analysis of LGE-CMR was performed using a software (Ziostation2, Ziosoft Inc.) that automatically
107 determined the hyper-enhanced myocardium with CMR signal intensity (SI) above a predetermined
108 threshold. A region of interest in the normal area was determined using a planimeter, and the extent

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

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

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

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

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

141 **Results**

142 The baseline characteristics of the 78 study patients (median age, 62 years; IQR, 52–68 years; male,
143 22%) are shown in **Table 1**. No significant differences were found between the groups for body mass
144 index, LVEF, LVDd, LVDs, NYHA classes, and use of other oral medications. In addition, the
145 prevalence of patients with narrow, wide, and paced QRS was comparable between the groups.

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

148 The composite primary outcome significantly occurred more frequently in patients with fQRS than
149 in those without fQRS (9 patients [47%] vs. 8 patients [13%]; hazard ratio, 3.98; 95% confidence
150 interval, 1.54–10.34; $p = 0.004$ by univariate Cox regression). The 10-year Kaplan–Meier event-free
151 estimates were 40% in the fQRS group and 84% in the non-fQRS group (log-rank $p = 0.002$) (**Figure**
152 **3a**). For each component of the composite outcome, VTs occurred more frequently, and the incidence
153 of HF admissions tended to occur in more patients with fQRS than in those without it. However, the

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

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

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

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

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

181 In 41 patients (fQRS, 8 patients; non-fQRS, 33 patients), ECG was repeatedly performed 9–15
182 months after the initiation of IST. Of these patients, most (39 patients, 95%) showed a consistent
183 presence or absence of fQRS, while fQRS disappeared in two patients (5%) during the follow-up
184 (**Figure 7**). Both patients had preserved LV function (one with LVEF 60% and the other with LVEF
185 65%) and were in the clinical diagnosis group. One had narrow QRS with fQRS in the inferior
186 segment, and the other had wide QRS with fQRS in the anterior segment. Neither of these two patients
187 had a recurrence of fQRS on follow-up.

188 **Discussion**

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

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

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

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

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

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

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

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

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

245 these patients.

Conflicts of interest

None.

Acknowledgments

The authors wish to thank all the investigators, clinical research coordinators, and data managers for their contributions. We would like to thank Mr. John Martin for English language editing.

References

1. Iannuzzi MC, Rybicki BA, Teirstein AS (2007) Sarcoidosis. *N Engl J Med* 357:2153–2165
2. Koiwa H, Tsujino I, Ohira H, Yoshinaga K, Otsuka N, Nishimura M (2010) Images in cardiovascular medicine: imaging of cardiac sarcoid lesions using fasting cardiac 18F-fluorodeoxyglucose positron emission tomography: an autopsy case. *Circulation* 122:535–536
3. Carey VJ, Walters EE, Colditz GA, Solomon CG, Willett WC, Rosner BA, Speizer FE, Manson JE (1997) Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurses' Health Study. *Am J Epidemiol* 145:614–619
4. Naruse Y, Sekiguchi Y, Nogami A, Okada H, Yamauchi Y, Machino T, Kuroki K, Ito Y, Yamasaki H, Igarashi M, Tada H, Nitta J, Xu D, Sato A, Aonuma K (2014) Systematic treatment approach to ventricular tachycardia in cardiac sarcoidosis. *Circ Arrhythm Electrophysiol* 7:407–413
5. Kumar S, Barbhaiya C, Nagashima K, Choi EK, Epstein LM, John RM, Maytin M, Albert CM, Miller AL, Koplan BA, Michaud GF, Tedrow UB, Stevenson WG (2015) Ventricular tachycardia in cardiac sarcoidosis: characterization of ventricular substrate and outcomes of catheter ablation. *Circ Arrhythm Electrophysiol* 8:87–93
6. Segawa M, Fukuda K, Nakano M, Kondo M, Satake H, Hirano M, Shimokawa H (2016) Time course and factors correlating with ventricular tachyarrhythmias after introduction of steroid therapy in cardiac sarcoidosis. *Circ Arrhythm Electrophysiol* 9:e003353

7. Das MK, Khan B, Jacob S, Kumar A, Mahenthiran J (2006) Significance of a fragmented QRS complex versus a Q wave in patients with coronary artery disease. *Circulation* 113:2495–2501
8. Das MK, Suradi H, Maskoun W, Michael MA, Shen C, Peng J, Dandamudi G, Mahenthiran J (2008) Fragmented wide QRS on a 12-lead ECG: a sign of myocardial scar and poor prognosis. *Circ Arrhythm Electrophysiol* 1:258–268
9. Morita H, Kusano KF, Miura D, Nagase S, Nakamura K, Morita ST, Ohe T, Zipes DP, Wu J (2008) Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome. *Circulation* 118:1697–1704
10. Das MK, Maskoun W, Shen C, Michael MA, Suradi H, Desai M, Subbarao R, Bhakta D (2010) Fragmented QRS on twelve-lead electrocardiogram predicts arrhythmic events in patients with ischemic and nonischemic cardiomyopathy. *Heart Rhythm* 7:74–80
11. Das MK, Saha C, El Masry H, Peng J, Dandamudi G, Mahenthiran J, McHenry P, Zipes DP (2007) Fragmented QRS on a 12-lead ECG: a predictor of mortality and cardiac events in patients with coronary artery disease. *Heart Rhythm* 4:1385–1392
12. Homsy M, Alsayed L, Safadi B, Mahenthiran J, Das MK (2009) Fragmented QRS complexes on 12-lead ECG: a marker of cardiac sarcoidosis as detected by gadolinium cardiac magnetic resonance imaging. *Ann Noninvasive Electrocardiol* 14:319–326
13. Terasaki F, Azuma A, Anzai T, Ishizaka N, Ishida Y, Isobe M, Inomata T, Ishibashi-Ueda H, Eishi Y, Kitakaze M, Kusano K, Sakata Y, Shijubo N, Tsuchida A, Tsutsui H, Nakajima T, Nakatani S, Horii T, Yazaki Y, Yamaguchi E, Yamaguchi T, Ide T, Okamura H, Kato Y, Goya

M, Sakakibara M, Soejima K, Nagai T, Nakamura H, Noda T, Hasegawa T, Morita H, Ohe T, Kihara Y, Saito Y, Sugiyama Y, Morimoto SI, Yamashina A (2019) JCS 2016 guideline on diagnosis and treatment of cardiac sarcoidosis- digest version. *Circ J* 83:2329–2388

14. Sato T, Tsujino I, Ohira H, Oyama-Manabe N, Ito YM, Noguchi T, Yamada A, Ikeda D, Watanabe T, Nishimura M (2013) Paradoxical interventricular septal motion as a major determinant of late gadolinium enhancement in ventricular insertion points in pulmonary hypertension. *PLOS ONE* 8:e66724

15. Oyama-Manabe N, Ishimori N, Sugimori H, Van Cauteren M, Kudo K, Manabe O, Okuaki T, Kamishima T, Ito YM, Tsutsui H, Tha KK, Terae S, Shirato H (2011) Identification and further differentiation of subendocardial and transmural myocardial infarction by fast strain-encoded (SENC) magnetic resonance imaging at 3.0 tesla. *Eur Radiol* 21:2362–2368

16. Ise T, Hasegawa T, Morita Y, Yamada N, Funada A, Takahama H, Amaki M, Kanzaki H, Okamura H, Kamakura S, Shimizu W, Anzai T, Kitakaze M (2014) Extensive late gadolinium enhancement on cardiovascular magnetic resonance predicts adverse outcomes and lack of improvement in LV function after steroid therapy in cardiac sarcoidosis. *Heart* 100:1165–1172

17. Sonoda K, Okumura Y, Watanabe I, Nagashima K, Mano H, Kogawa R, Yamaguchi N, Takahashi K, Iso K, Ohkubo K, Nakai T, Kunimoto S, Hirayama A (2017) Scar characteristics derived from two- and three-dimensional reconstructions of cardiac contrast-enhanced magnetic resonance images: relationship to ventricular tachycardia inducibility and ablation success. *J Arrhythm* 33:447–454

18. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER,

Rudski L, Spencer KT, Tsang W, Voigt JU (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 28:1–39.e14

19. Cacoub P, Chapelon-Abric C, Resche-Rigon M, Saadoun D, Desbois AC, Biard L (2020) Cardiac sarcoidosis: a long term follow up study. *PLOS ONE* 15:e0238391

20. Breithardt G, Cain ME, el-Sherif N, Flowers NC, Hombach V, Janse M, Simson MB, Steinbeck G (1991) Standards for analysis of ventricular late potentials using high-resolution or signal-averaged electrocardiography. A statement by a Task Force Committee of the European Society of Cardiology, the American Heart Association, and the American College of Cardiology. *Circulation* 83:1481–1488

21. Gomes JA, Cain ME, Buxton AE, Josephson ME, Lee KL, Hafley GE (2001) Prediction of long-term outcomes by signal-averaged electrocardiography in patients with unsustained ventricular tachycardia, coronary artery disease, and left ventricular dysfunction. *Circulation* 104:436–441

22. Das MK, Michael MA, Suradi H, Peng J, Sinha A, Shen C, Mahenthiran J, Kovacs RJ (2009) Usefulness of fragmented QRS on a 12-lead electrocardiogram in acute coronary syndrome for predicting mortality. *Am J Cardiol* 104:1631–1637

23. Kang KW, Janardhan AH, Jung KT, Lee HS, Lee MH, Hwang HJ (2014) Fragmented QRS as a candidate marker for high-risk assessment in hypertrophic cardiomyopathy. *Heart Rhythm* 11:1433–1440

- 24.** Xu Y, Yu Y, He L, Wang Y, Gu Y (2021) Predicting efficacy of combined assessment with fragmented QRS and severely depressed heart rate variability on outcome of patients with acute myocardial infarction. *Heart Vessels* 37:239–249
- 25.** Betensky BP, Tschabrunn CM, Zado ES, Goldberg LR, Marchlinski FE, Garcia FC, Cooper JM (2012) Long-term follow-up of patients with cardiac sarcoidosis and implantable cardioverter-defibrillators. *Heart Rhythm* 9:884–891
- 26.** Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Granger CB, Hammill SC, Hlatky MA, Joglar JA, Kay GN, Matlock DD, Myerburg RJ, Page RL (2018) 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 72:e91–e220
- 27.** Yodogawa K, Seino Y, Shiomura R, Takahashi K, Tsuboi I, Uetake S, Hayashi H, Horie T, Iwasaki YK, Hayashi M, Miyauchi Y, Shimizu W (2013) Recovery of atrioventricular block following steroid therapy in patients with cardiac sarcoidosis. *J Cardiol* 62:320–325
- 28.** Yodogawa K, Fujimoto Y, Hagiwara K, Oka E, Hayashi H, Murata H, Yamamoto T, Iwasaki Y, Shimizu W (2022) Possibility of steroid therapy without pacemaker implantation in patients with sarcoidosis presenting atrioventricular block. *Heart Vessels* 37:1892–1898
- 29.** Coleman GC, Shaw PW, Balfour PC Jr, Gonzalez JA, Kramer CM, Patel AR, Salerno M (2017) Prognostic value of myocardial scarring on CMR in patients with cardiac sarcoidosis. *JACC Cardiovasc Imaging* 10:411–420

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 (\geq 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				
I	30 (39)	6 (32)	24 (42)	0.06
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				
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.

	Incidence of events	fQRS vs. non-fQRS		
		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

Variables	Univariable		Multivariable			
	HR (95% CI)	<i>p</i> -value	Model 1		Model 2	
			HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -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

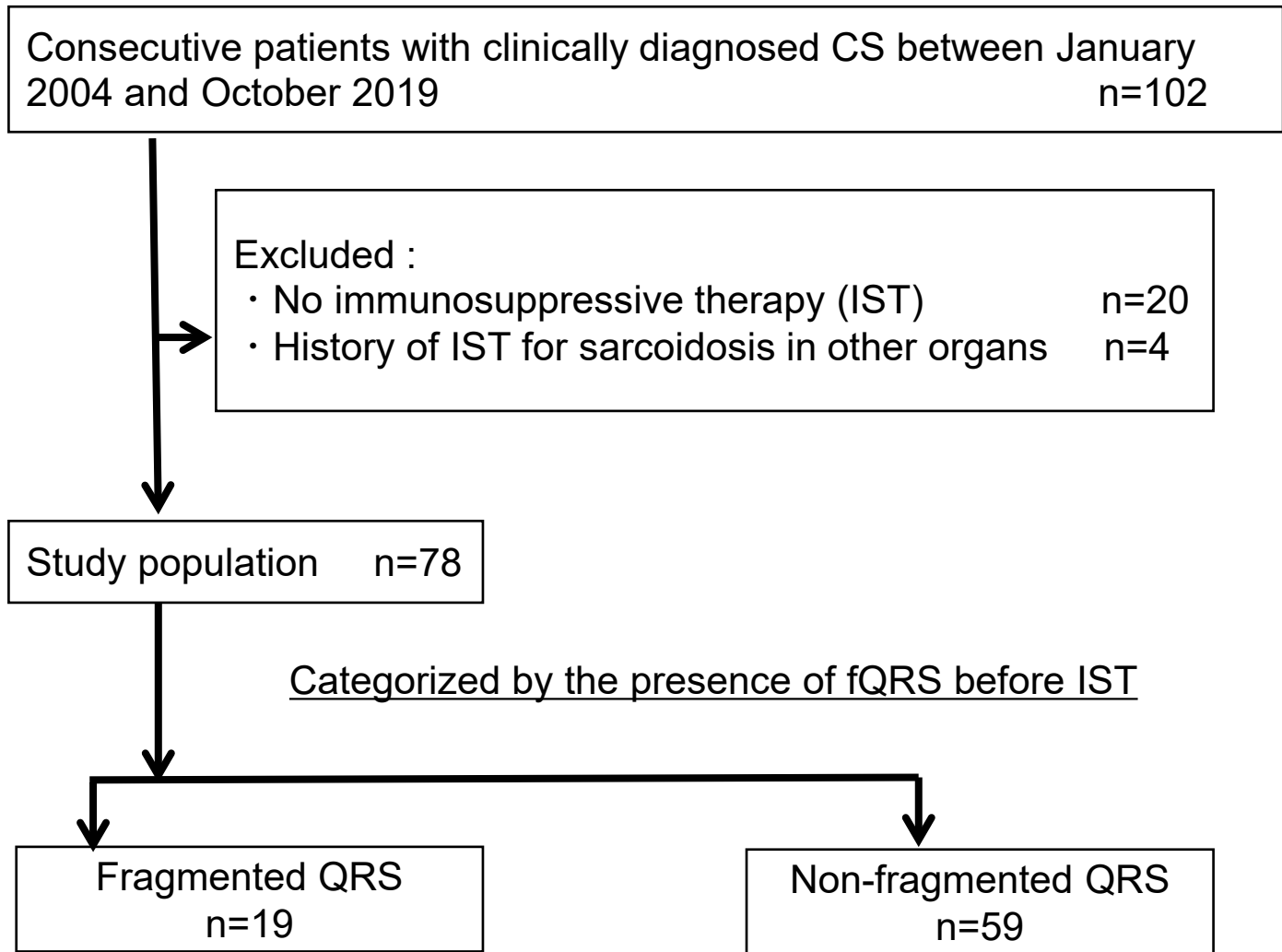
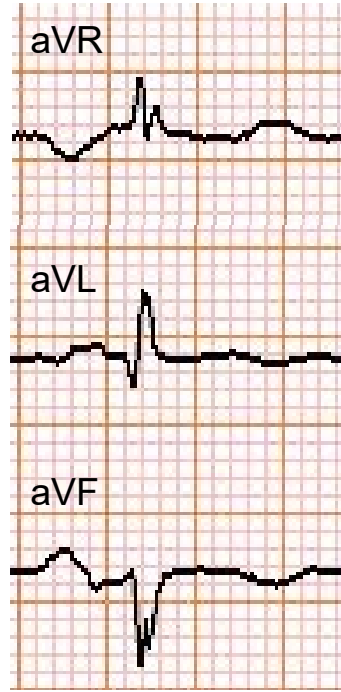


Figure 2

a



b

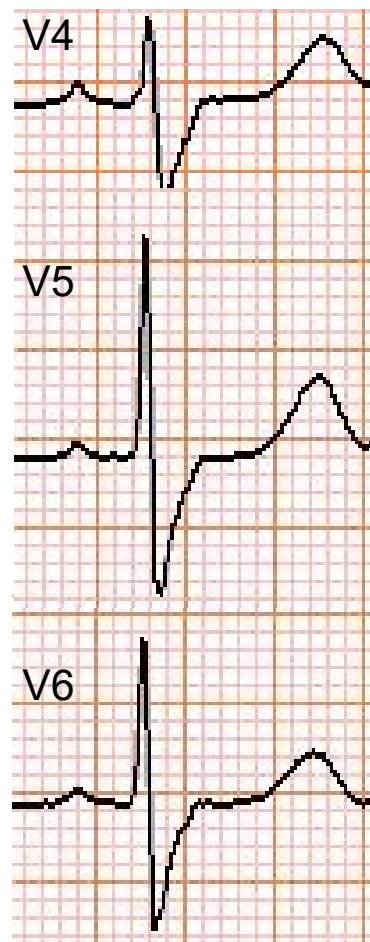
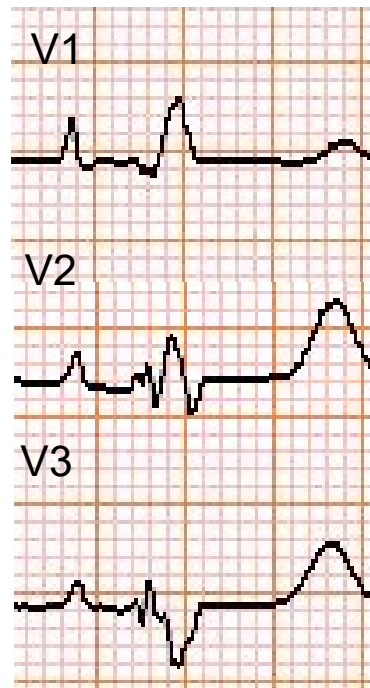


Figure 3

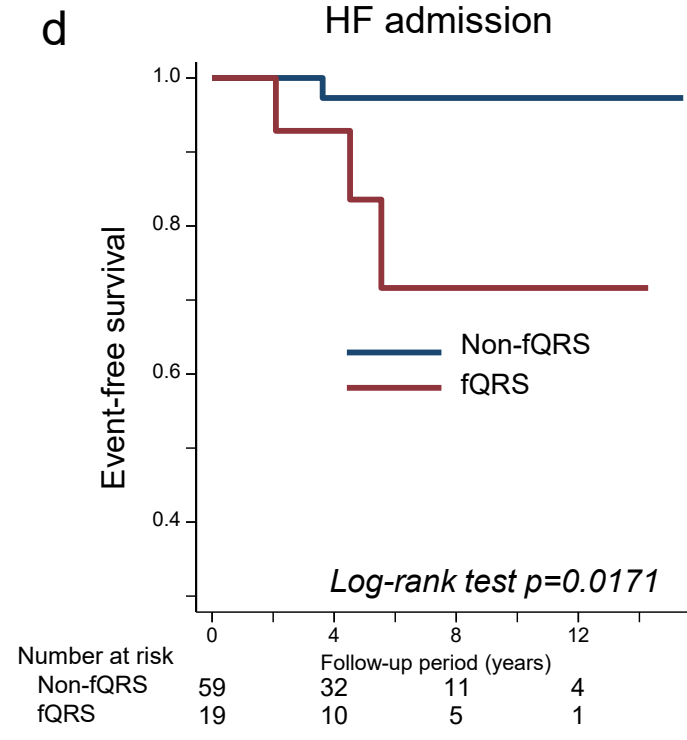
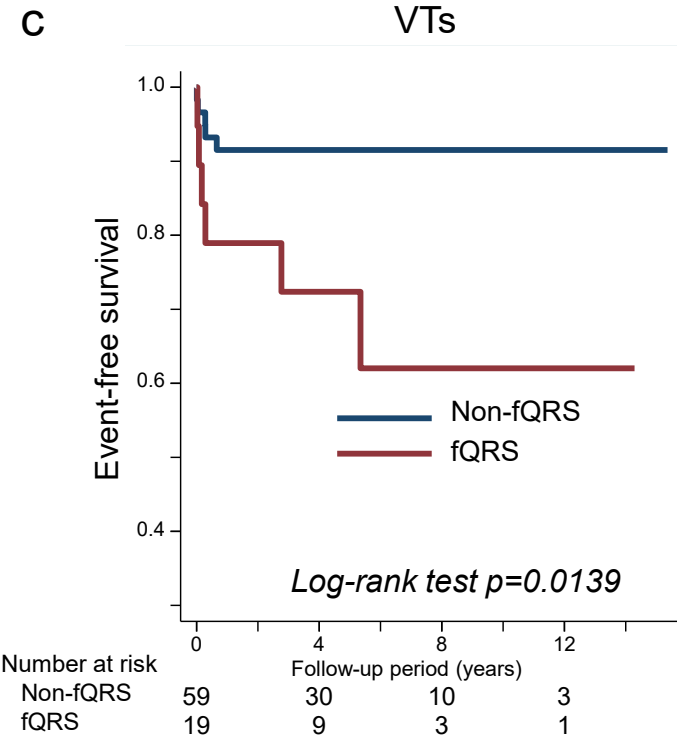
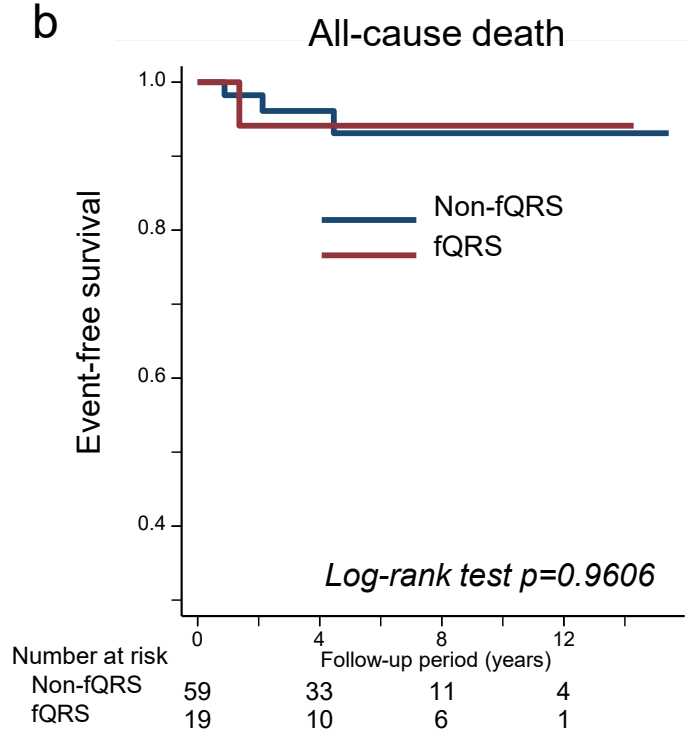
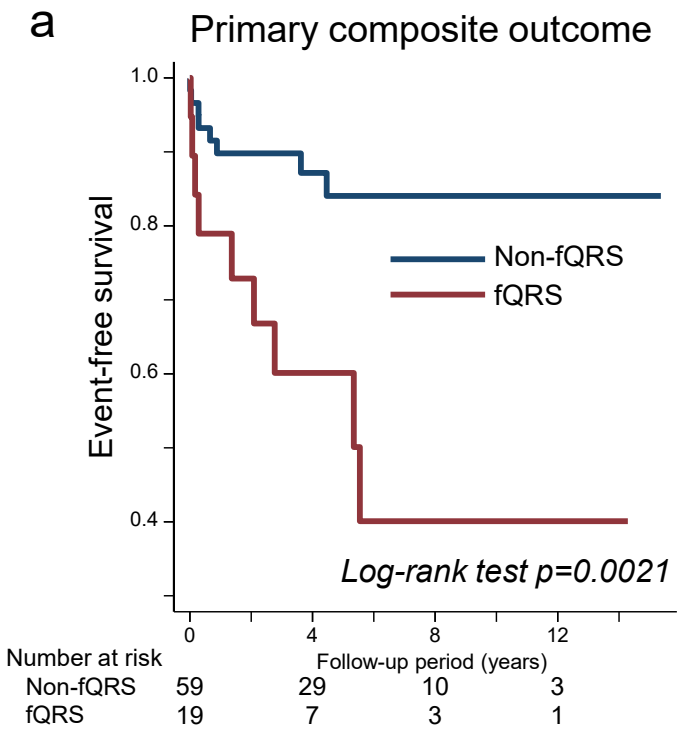
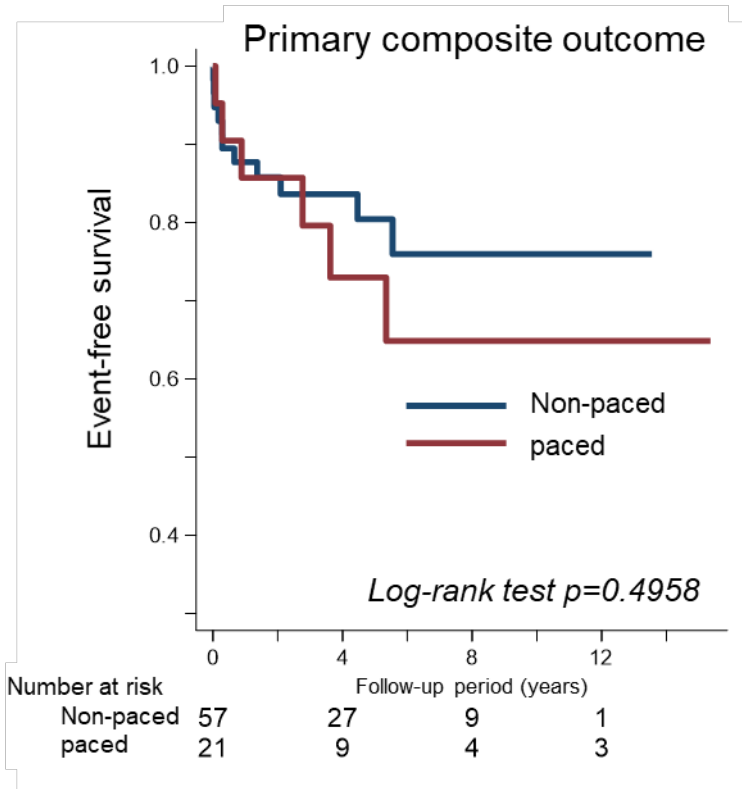
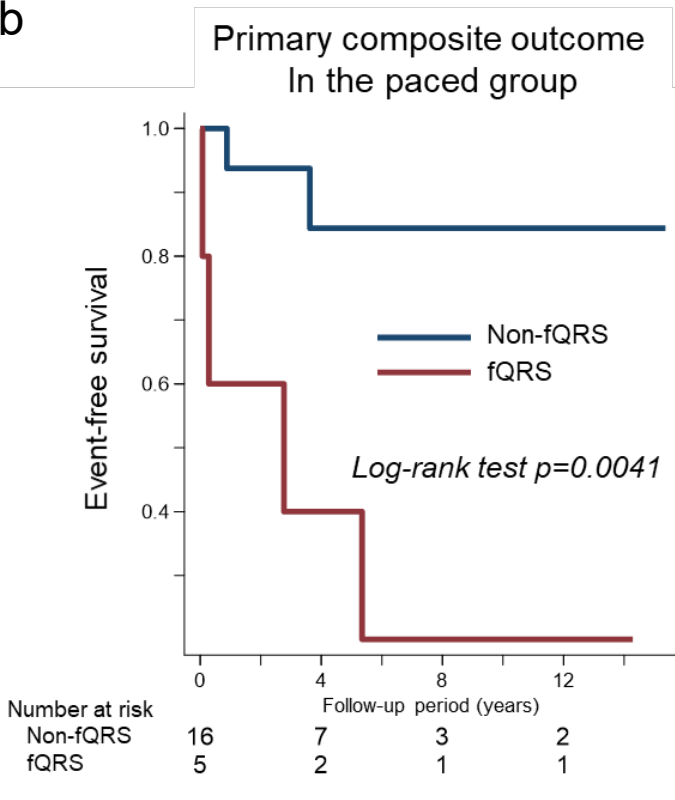


Figure 4

a



b



c

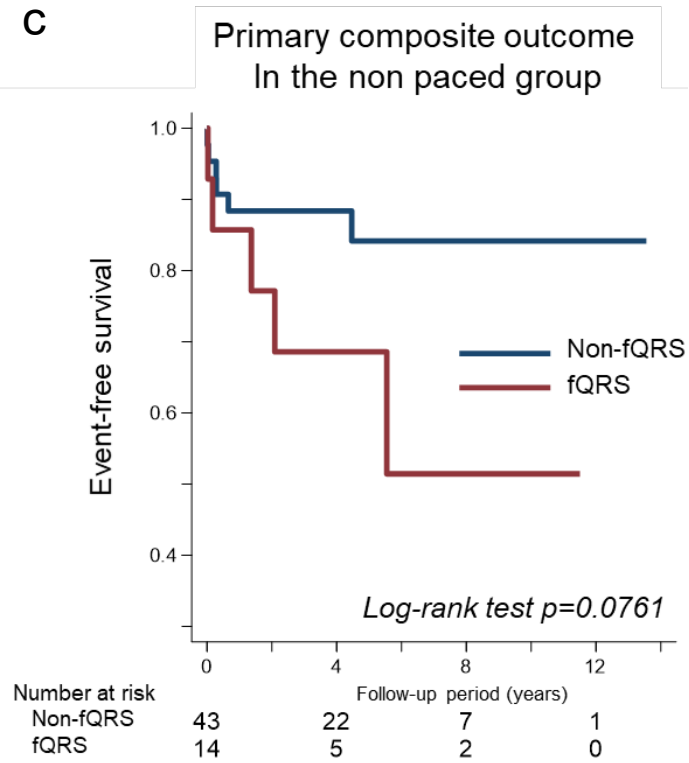


Figure 5

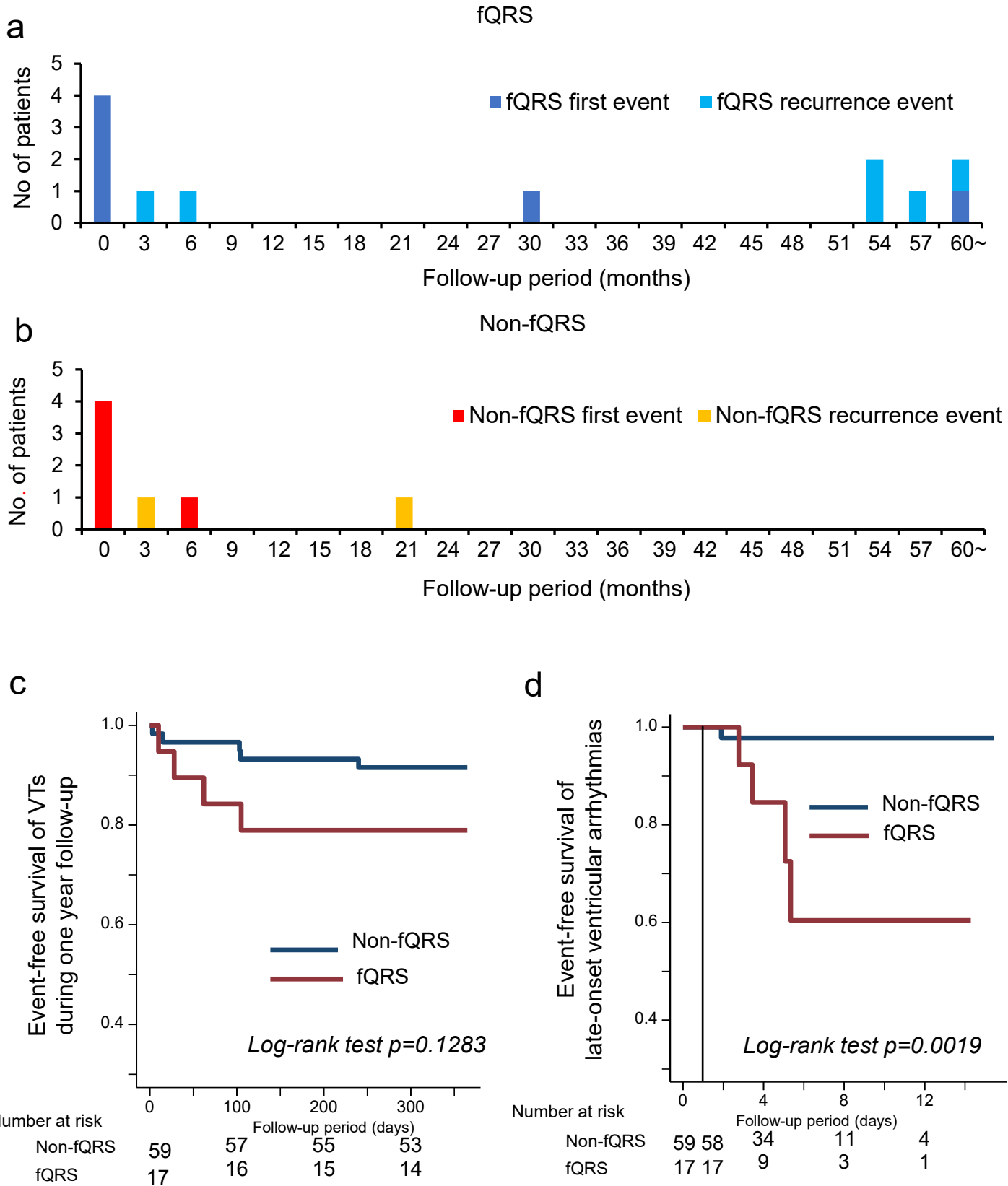
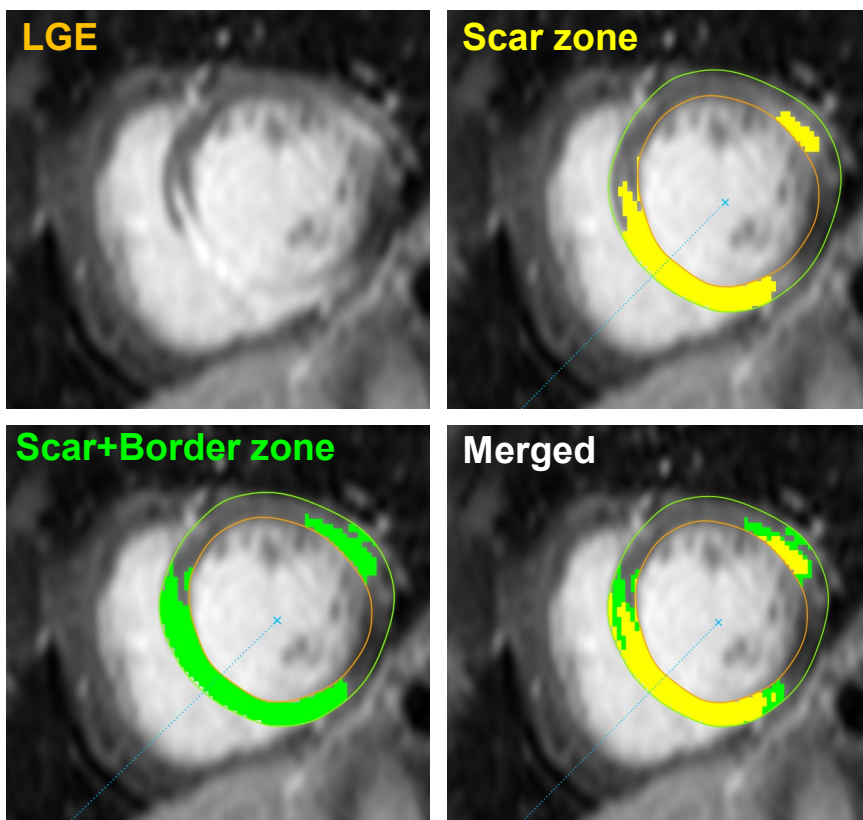
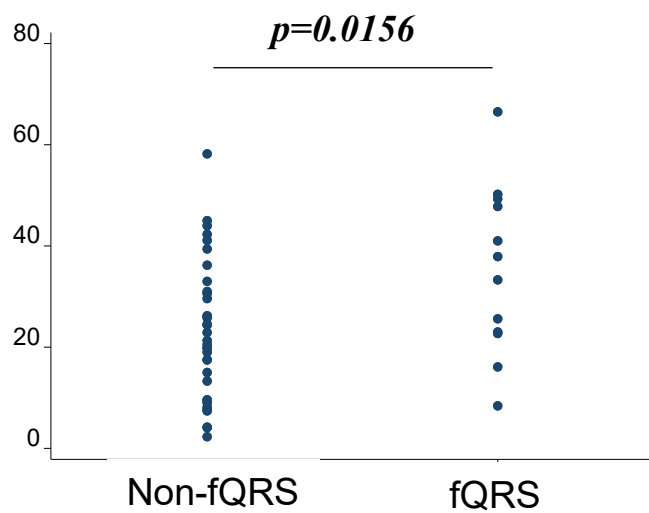


Figure 6

a



b %LGE ($\geq 5SD$)



c Scar border zone ($\geq 2SD$ and $\leq 5SD$)

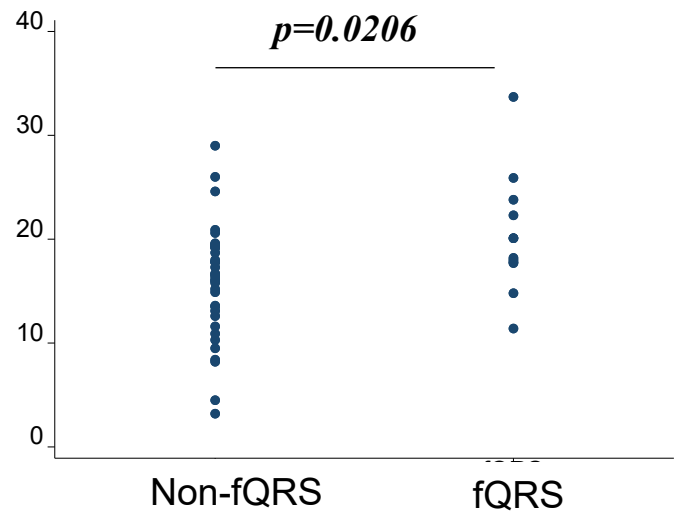
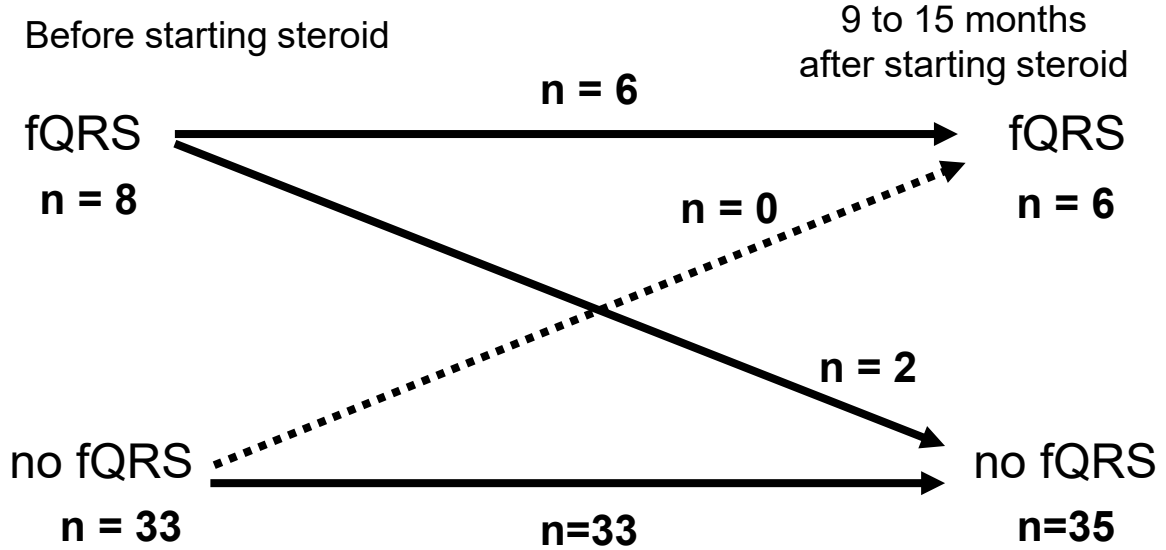


Figure 7

a



b

