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CLINICAL RESEARCH
Electrocardiology and risk stratification

Prognostic impact of multiple fragmented QRS on cardiac events in idiopathic dilated cardiomyopathy

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Aims To evaluate the prognostic impact of fragmented QRS (fQRS) on idiopathic dilated cardiomyopathy (DCM).

Methods and results We conducted a prospective observational study of 290 consecutive patients with DCM (left ventricular ejection fraction ≤ 40%) and narrow QRS who underwent cardiac magnetic resonance. We defined fQRS as the presence of various RSR′ patterns in ≥2 contiguous leads representing the anterior (V1–V5), inferior (II, III, and aVF), or lateral (I, aVL, and V6) myocardial segments. Multiple fQRS was defined as the presence of fQRS in ≥2 myocardial segments. Patients were divided into three groups: no fQRS, single fQRS, or multiple fQRS. The primary endpoint was a composite of hard cardiac events consisting of heart failure death, sudden cardiac death (SCD), or aborted SCD. The secondary endpoints were all-cause death and arrhythmic event. During a median follow-up of 3.8 years (interquartile range, 1.8–6.2), 31 (11%) patients experienced hard cardiac events. Kaplan–Meier analysis showed that the rates of hard cardiac events and all-cause death were similar in the single-fQRS and no-fQRS groups and higher in the multiple-fQRS group ($P = 0.004$ and $P = 0.017$, respectively). Multivariable Cox regression identified that multiple fQRS is a significant predictor of hard cardiac events (hazard ratio, 2.23; 95% confidence interval, 1.07–4.62; $P = 0.032$). The multiple-fQRS group had the highest prevalence of a diffuse late gadolinium enhancement pattern (no fQRS, 21%; single fQRS, 22%; multiple fQRS, 39%; $P < 0.001$).

Conclusion Multiple fQRS, but not single fQRS, is associated with future hard cardiac events in patients with DCM.

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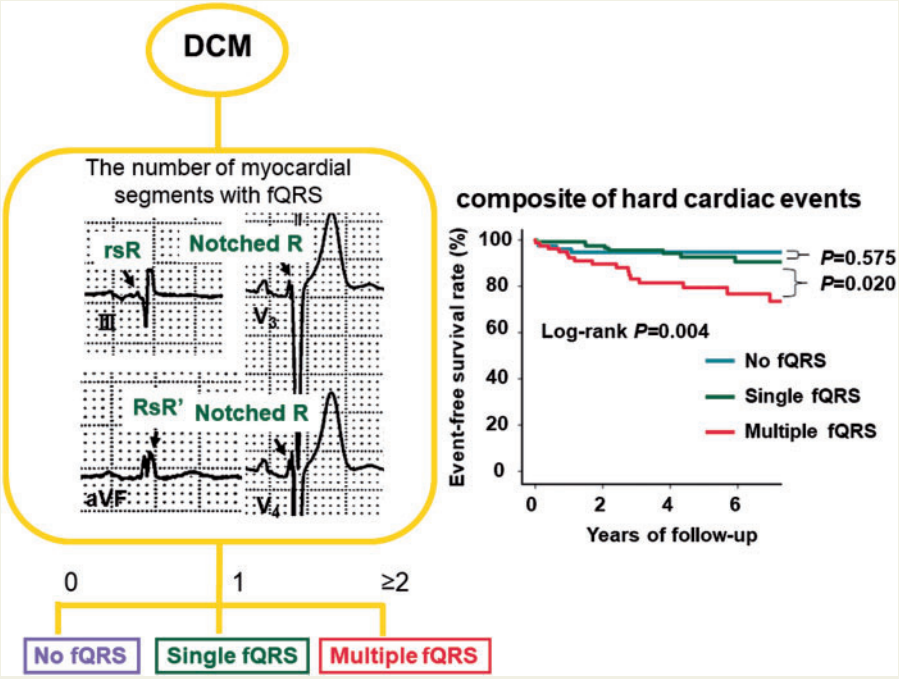
Graphical Abstract



Keywords Fragmented QRS • Dilated cardiomyopathy • Cardiac event • Magnetic resonance • Late gadolinium enhancement

What's new?

- Prognostic impact of fragmented QRS (fQRS) on a 12-lead electrocardiogram has not been fully evaluated in patients with idiopathic dilated cardiomyopathy (DCM).
- This prospective observational study of 290 patients with DCM showed that multiple fQRS (fQRS in ≥ 2 myocardial segments), but not single fQRS, was associated with hard cardiac events, all-cause death, and major adverse cardiac events.
- Moreover, multiple fQRS was associated with severe myocardial fibrosis demonstrated by a diffuse late gadolinium enhancement pattern on cardiac magnetic resonance.
- These findings suggested that the presence of more regions with fQRS corresponds to more myocardial fibrosis, likely indicating worse prognosis in patients with DCM.

Introduction

Myocardial fibrosis is associated with higher disease severity and worse subsequent outcomes in patients with heart failure (HF). Late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) has emerged as a first-line imaging modality to evaluate for myocardial fibrosis. Late gadolinium enhancement is a robust prognostic factor in patients with ischaemic or non-ischaemic cardiomyopathy. [1]

Fragmented QRS (fQRS) on a 12-lead electrocardiogram (ECG) is related to myocardial necrosis, myocardial ischaemia, or myocardial fibrosis [2,3] and is a known prognostic predictor in patients with ischaemic heart disease (IHD). [4] By contrast, in patients with idiopathic dilated cardiomyopathy (DCM), the prognostic impact of fQRS has not yet been clearly defined due to the retrospective nature of previous studies or their small sample size and limited patient enrolment. [5,6] Moreover, although previous studies have shown that fQRS extent is a prognostic factor in patients with IHD [7] or Brugada syndrome, [8] its prognostic impact in patients with DCM has not been evaluated.

Since there is less literature on the possible role of fQRS in non-ischaemic cardiomyopathy, we conducted a large prospective observational study that enrolled consecutive patients with DCM. Patients underwent CMR to evaluate the relationship between the extent of fQRS and the extent of myocardial fibrosis detected by LGE.

Methods

Study population

We conducted a prospective observational study of 463 consecutive patients with idiopathic DCM at the National Cerebral and Cardiovascular Center in Japan between January 2007 and December

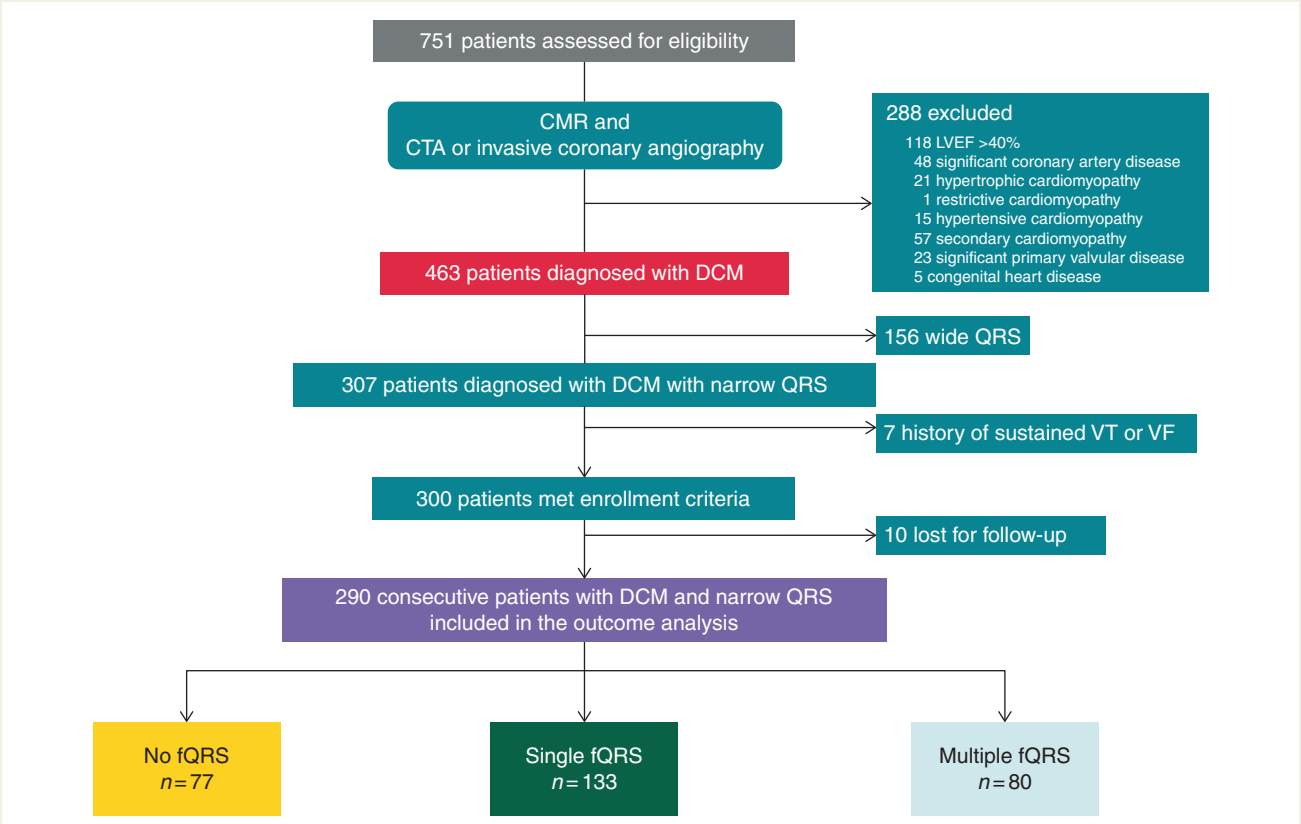


Figure 1 Flowchart of study patient selection. Flowchart detailing the inclusion and exclusion of study patients. Enrolled patients were divided into three groups on the basis of fQRS extent. CMR, cardiac magnetic resonance; CTA, computed tomography angiography; DCM, dilated cardiomyopathy; fQRS, fragmented QRS; LVEF, left ventricular ejection fraction; VF, ventricular fibrillation; VT, ventricular tachycardia.

2015. The diagnosis of idiopathic DCM was based on World Health Organization criteria and left ventricular ejection fraction (LVEF) ≤40%. [5,6,9] All patients underwent invasive coronary angiography or computed tomography angiography to rule out significant coronary artery stenosis (>50% diameter stenosis). [10] Patients under 18 years of age or who had a history of myocardial infarction or coronary revascularization, myocarditis, hypertrophic cardiomyopathy, secondary cardiomyopathy, valvular heart disease, hypertensive heart disease, non-fatal ventricular fibrillation (VF), or sustained ventricular tachycardia (VT) were excluded. Cardiac magnetic resonance imaging and 12-lead electrocardiography were performed while the patient was in a clinically stable, non-congested condition [New York Heart Association (NYHA) functional class ≤ II]. None of the patients had a typical subendocardial or transmural LGE pattern in the supplied territory of a coronary artery that might have resulted from myocardial damage secondary to coronary artery disease or coronary embolism. Since wide QRS (QRS ≥ 120 ms) is an established prognostic factor for HF [11,12] and Das *et al.* [6] excluded wide QRS from the definition of fQRS in their study, we excluded patients with wide QRS ($n = 156$, 34%) to focus on the prognostic impact of fQRS in patients with narrow QRS (*Figure 1*). This study was approved by the institutional review board and ethics committee of the National Cerebral and Cardiovascular Center (M24-081).

Electrocardiogram analysis

Electrocardiogram was performed after 10 min of rest in the supine position as part of the initial screening (filter range, 0.05–150 Hz; 25 mm/s; 10 mm/mV; Cardio Star FCP-7541, Fukuda Denshi, Tokyo, Japan). In patients who had undergone cardiac surgeries, septal ablation, or pacemaker implantation, ECG was obtained prior to the procedure. If no pre-procedure ECG was available, patients were excluded from the analysis. The median duration between ECG and CMR was 8 days [interquartile range (IQR): 3–16 days]. Electrocardiogram measurements included RR, QT, and QRS intervals that were automatically analysed. QTc intervals were calculated using Bazett's formula.

Criteria for fragmented QRS

Fragmented QRS was defined by the presence of various RSR′ patterns that include an additional R wave (R′), notching of the R or S wave, or the presence of more than 2 R′s (*Figure 2*). [6] Two experienced cardiologists (K.M. and T.K.) who were blinded to clinical data and outcomes independently assessed fQRS. The interobserver and intraobserver κ values for agreement on fQRS were 0.90 and 0.90, respectively.

Extent of fragmented QRS

Presence of fQRS was defined as fQRS in two contiguous leads corresponding to major myocardial segments: anterior (V_1–V_5), inferior (II, III, and aVF), or lateral (I, aVL, and V_6). [6] To evaluate the association between fQRS severity and prognostic outcome, we quantified fQRS extent based on the number of myocardial segments with fQRS. Single fQRS was defined as fQRS present in either the anterior, inferior, or lateral segment. Multiple fQRS was defined as presence of fQRS in ≥2 myocardial segments. [8]

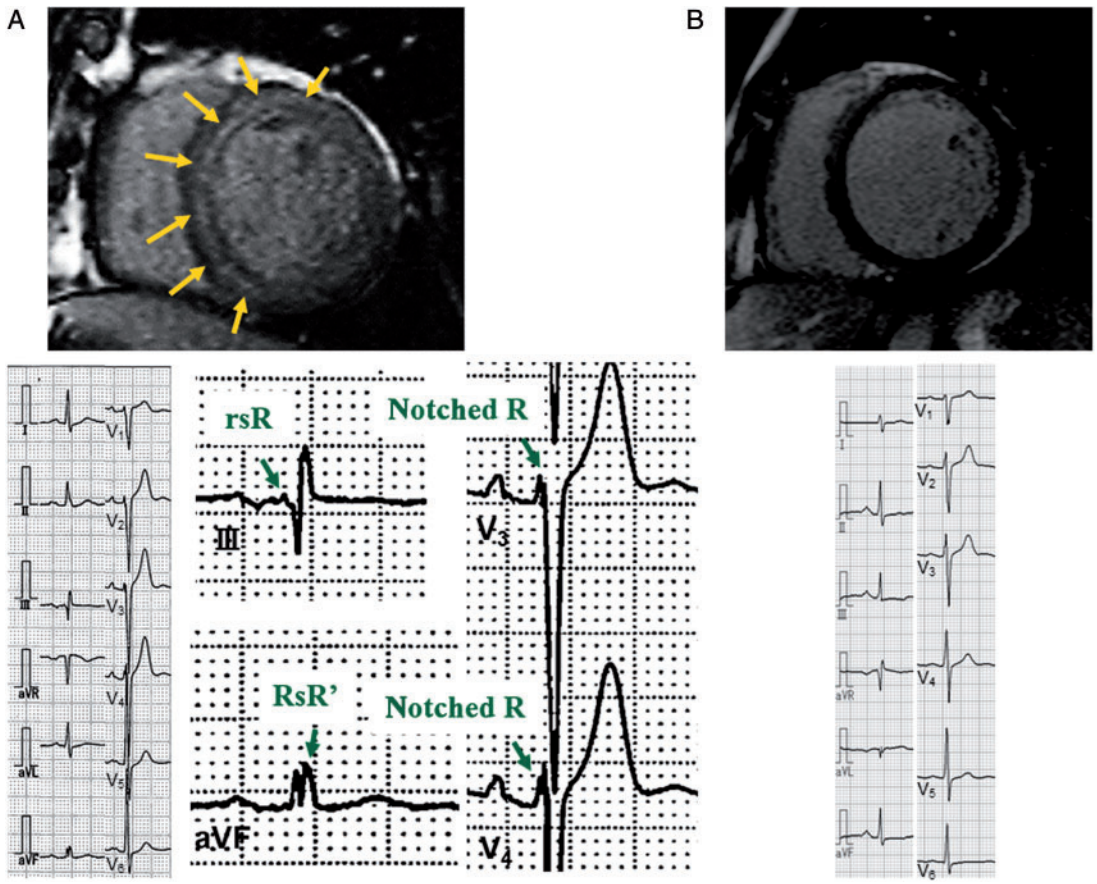


Figure 2 Representative case of fQRS and short-axis images of the left ventricle with or without LGE. (*A*) A representative case of a diffuse LGE pattern and multiple fQRS. (*B*) A representative case of no LGE and no fQRS. fQRS, fragmented QRS; LGE, late gadolinium enhancement.

Cardiac magnetic resonance protocol

Cardiac magnetic resonance examinations were performed for all patients using a 1.5-T system (Magnetom Sonata; Siemens, Erlangen, Germany) with a four-channel surface coil. The procedures used to acquire magnetic resonance images in this study have been previously described. [12] Briefly, we identified LGE using a segmented inversion recovery–prepared true fast imaging with steady-state precession sequence with ECG triggering 10 min after the administration of 0.15 mmol/kg body weight of gadolinium diethylenetriamine pentaacetic acid.

Late gadolinium enhancement analysis

Two experienced radiologists (Y.M. and N.Y.) who were blinded to clinical data and outcomes independently assessed the presence and location of LGE. Late gadolinium enhancement was only considered present if it was visible in two orthogonal views (*Figure 2*). [1] Interobserver and intraobserver agreement was evaluated for all study patients. The interobserver and intraobserver agreement κ values for the presence of LGE were 0.87 and 0.90, respectively. A third blinded reader adjudicated in cases with disagreement (4.9%). Mid-wall LGE was only considered present if the area of LGE was confined to the intermural layer, subepicardial layer, or both. Late gadolinium enhancement in multiple cardiac segments was defined as diffuse LGE. Isolated LGE was defined as focal LGE. [1,12]

Follow-up and endpoints

After CMR data were obtained, study patients were followed at 3, 6, 12 months, and annually thereafter until the occurrence of any of the following events: all-cause death, HF death, cardiac transplantation, left ventricular assist device (LVAD) implantation, sudden cardiac death (SCD), aborted SCD [non-fatal VF, sustained VT, or appropriate implantable cardioverter defibrillator (ICD) discharge for VT or VF], or re-hospitalization for HF. The duration of the follow-up period was calculated from baseline CMR until an endpoint occurred or last patient contact. The primary endpoint was a composite of hard cardiac events consisting of HF death, cardiac transplantation, LVAD implantation, SCD, and aborted SCD. The principal secondary endpoint was all-cause death. Additional secondary endpoints were major adverse cardiac events (MACEs) consisting of hard cardiac events and re-hospitalization for HF or a composite of arrhythmic events consisting of SCD and aborted SCD.

Independent attending cardiologists (E.T. and H.M.) who were blinded to the patients' baseline fQRS status reviewed medical records to determine if hospitalizations and deaths qualified as cardiac events. Sudden cardiac death was defined as unexpected death either within 1 h of cardiac symptoms in the absence of progressive cardiac deterioration, during sleep, or within 24 h of last being seen alive. [13] Heart failure death was defined as death associated with unstable progressive deterioration of pump function despite active therapy. Aborted SCD was defined as an appropriate ICD discharge for VT or VF, including anti-tachycardia pacing,

Table 1 Baseline characteristics of the study patients

Variables	All patients (n = 290)	No fQRS (n = 77)	Single fQRS (n = 133)	Multiple fQRS (n = 80)	P-value
Age (years)	52±15	55±16	51±15	48±15	0.032
Male, n (%)	232 (80)	57 (74)	109 (82)	66 (83)	0.309
BMI, kg/m^2	23.1±4.1	22.0±3.2	23.6±4.1	23.2±4.6	0.009
Current smoker, n (%)	79 (27)	22 (29)	37 (28)	20 (25)	0.951
NYHA functional class, n (%)					0.119
I	83 (29)	18 (23)	47 (35)	18 (23)	
II	123 (42)	33 (43)	50 (38)	40 (50)	
III	48 (17)	12 (16)	20 (15)	16 (20)	
IV	36 (12)	14 (18)	16 (12)	6 (7.5)	
Medical history, n (%)					
Diabetes mellitus	60 (21)	14 (18)	32 (24)	14 (18)	0.425
Atrial fibrillation	96 (33)	24 (31)	43 (32)	29 (36)	0.770
BNP (pg/mL)	164 (46–537)	141 (38–663)	144 (45–528)	232 (52–520)	0.645
eGFR (mL/min/1.73 m^2)	71±21	72±19	71±22	71±20	0.954
Serum sodium (mEq/L)	140±3	140±3	140±3	140±3	0.543
Haemoglobin (g/dL)	14.2±1.6	14.2±1.6	14.4±1.6	14.1±1.8	0.419
ECG parameters					
QRS duration (ms)	96±23	97±20	96±24	96±27	0.973
Heart rate (b.p.m.)	71±13	72±11	70±12	71±15	0.685
QTc interval (ms)	432±37	431±35	435±35	428±41	0.403
Medications at baseline, n (%)					
β-blocker	269 (93)	71 (92)	125 (94)	73 (91)	0.739
ACE inhibitor or ARB	235 (81)	62 (81)	107 (80)	66 (83)	0.926
Aldosterone antagonist	141 (49)	39 (51)	61 (46)	41 (51)	0.686
Diuretic	162 (56)	46 (60)	71 (53)	45 (56)	0.668
Amiodarone	22 (7.6)	5 (6.5)	5 (3.8)	12 (15)	0.010
Anticoagulant	152 (52)	41 (53)	62 (47)	49 (61)	0.115
CMR measurements					
LVEDVI (mL/m^2)	141±45	136±50	142±43	143±48	0.736
LVESVI (mL/m^2)	108±45	105±46	109±42	110±47	0.813
LVSVI (mL/m^2)	33±11	32±9	33±12	33±9	0.528
LV mass (g)	143±50	138±44	149±50	137±53	0.171
LVEF (%)	25±8	25±8	24±8	25±9	0.965
RVEF (%)	34±10	33±11	35±9	33±9	0.249
LGE, n (%)	168 (58)	28 (36)	78 (59)	62 (78)	<0.001
Mid-wall pattern	95 (56)	15 (54)	53 (68)	27 (44)	0.010
Focal pattern	26 (16)	7 (25)	8 (10)	11 (18)	0.149
Diffuse pattern	47 (28)	6 (21)	17 (22)	24 (39)	<0.001

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CMR, cardiac magnetic resonance; ECG, electrocardiogram; EDVI, end-diastolic volume index; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESVI, end-systolic volume index; fQRS, fragmented QRS; LGE, late gadolinium enhancement; LV, left ventricular; NYHA, New York Heart Association; RV, right ventricular; SVI, stroke volume index.

non-fatal VF, or spontaneous sustained VT (>30 s in duration) that caused haemodynamic compromise and required cardioversion. [14] Re-hospitalization for HF was defined as hospital admission for signs and symptoms of decompensated HF requiring treatment with an intravenous HF medication (diuretic, vasodilator, or inotropic agent). For composite endpoints, only the first event for each patient was included in the analysis.

Statistical analysis

All continuous variables are presented as means ± standard deviation. Unpaired t tests were used to compare groups. Non-normally distributed variables are presented as medians (IQR). Analysis of variance was used to compare means across multiple groups. Non-continuous and categorical variables are presented as frequencies or percentages. They were compared using the χ^2 test. If a three-group comparison was statistically significant, then post hoc pairwise comparisons between each pair were performed to determine which pair was significantly different. The Tukey–Kramer test was used to compare continuous variables. The χ^2 test with Bonferroni correction was used for categorical variables. Cumulative event-free survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. Univariable Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for each

Table 2 Summary of cardiac events during the follow-up period

Outcome, *n* (%)	All patients (*n* = 290)	No fQRS (*n* = 77)	Single fQRS (*n* = 133)	Multiple fQRS (*n* = 80)	*P*-value
Primary endpoint: hard cardiac event	31 (11)	5 (6.5)	9 (6.8)	17 (21)	0.002
HF death	4 (1.4)	0	0	4 (5.0)	0.005
Cardiac transplantation or LVAD implantation	9 (3.1)	1 (1.3)	2 (1.5)	6 (7.5)	0.029
Arrhythmic event	18 (6.2)	4 (5.2)	7 (5.3)	7 (8.9)	0.541
SCD	4 (1.4)	1 (1.3)	1 (0.8)	2 (2.5)	0.569
Aborted SCD	14 (4.8)	3 (3.9)	6 (4.6)	5 (6.3)	0.652
Sustained VT	4 (1.4)	2 (2.6)	0	2 (2.5)	0.179
Non-fatal VF	1 (0.3)	0	1 (0.8)	0	0.553
Appropriate ICD discharge for VT/VF	9 (3.1)	1 (1.3)	5 (3.8)	3 (3.8)	0.567
Principal secondary endpoint: all-cause death	14 (4.8)	3 (3.9)	3 (2.3)	8 (10)	0.035
Major adverse cardiac event	44 (15)	9 (12)	13 (9.8)	22 (28)	0.001
HF death	3 (1.0)	0	0	3 (3.8)	0.019
Cardiac transplantation or LVAD implantation	7 (2.4)	1 (1.3)	1 (0.8)	5 (6.3)	0.031
Arrhythmic event	13 (4.5)	3 (3.9)	5 (3.8)	5 (6.3)	0.668
SCD	4 (1.4)	1 (1.3)	1 (0.8)	2 (2.5)	0.569
Aborted SCD	9 (3.1)	2 (2.6)	4 (3.0)	3 (3.8)	0.914
Sustained VT	3 (1.0)	1 (1.3)	0	2 (2.5)	0.210
Non-fatal VF	1 (0.3)	0	1 (0.8)	0	0.552
Appropriate ICD discharge for VT/VF	5 (1.7)	1 (1.3)	3 (2.3)	1 (1.3)	0.815
Re-hospitalization for HF	21 (7.2)	5 (6.5)	7 (5.3)	9 (11)	0.252
Arrhythmic event	18 (6.2)	4 (5.2)	7 (5.3)	7 (8.9)	0.541
SCD	4 (1.4)	1 (1.3)	1 (0.8)	2 (2.5)	0.569
Aborted SCD	14 (4.0)	3 (2.9)	6 (4.0)	5 (5.5)	0.652
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Appropriate ICD discharge for VT/VF	9 (3.1)	1 (1.3)	5 (3.8)	3 (3.8)	0.567

fQRS, fragmented QRS; HF, heart failure; ICD, implantable cardioverter defibrillator; LVAD, left ventricular assist device; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

endpoint. Multivariable Cox regression was performed using covariates that significantly predicted each endpoint in the univariable analysis as well as established prognostic risk factors for chronic HF [age, gender, B-type natriuretic peptide (BNP) level, NYHA functional class, estimated glomerular filtration rate (eGFR), and LV end-diastolic volume index]. Stepwise selection with a *P*-value of 0.05 for backward selection was used to select the best predictive model.

All statistical tests were two-sided, with *P*-values <0.05 regarded as statistically significant. Statistical analysis was performed with SPSS software (version 24.0; IBM Corp, Armonk, NY, USA) and Stata 15 (StataCorp, College Station, TX, USA).

Results

Baseline clinical characteristics

At baseline, 300 patients met the inclusion criteria. The follow-up rate was 96.7%; 10 patients were lost to follow-up. Ultimately, 290 patients were included in the outcome analysis, of whom 58 (20%) were women. The mean LVEF was 25 ± 8%. Ninety-six (33%) patients had a history of atrial fibrillation, and 4 (4.2%) of them underwent ablation therapy during the follow-up period. Eighty-four (29%) patients had decompensated symptomatic HF (NYHA ≥ III), and 22 (7.6%) were previously hospitalized for HF. We divided study patients into three groups according to the number of segments with fQRS: no fQRS (*n* = 77), single fQRS (*n* = 133), or multiple fQRS (*n* = 80) (*Figure 1*). *Table 1* summarizes the baseline clinical characteristics of the three groups. The multiple-fQRS group was younger (*P* = 0.032) and had a higher rate of amiodarone use (*P* = 0.010) than the other two groups. Since 16 (80%) of 22 amiodarone-treated patients who underwent ECGs demonstrated no new fQRS, amiodarone might have no effect on the detection of fQRS. There were no significant differences in NYHA functional class, BNP levels, or QRS duration among the three groups.

Primary endpoint: composite of hard cardiac events

During a median follow-up period of 3.8 years (IQR, 1.8–6.2 years), 31 (11%) hard cardiac events occurred. *Table 2* summarizes the incidence of the primary endpoint, which was higher in the multiple-fQRS group (*P* = 0.002). In detail, the multiple-fQRS group had a significantly higher incidence of HF death (*P* = 0.005) and cardiac transplantation or LVAD implantation (*P* = 0.029). *Figure 3A*shows the Kaplan–Meier curves for survival free from the primary endpoint. Although the single-fQRS group had a similar rate of the primary endpoint as the no-fQRS group (*P* = 0.575),

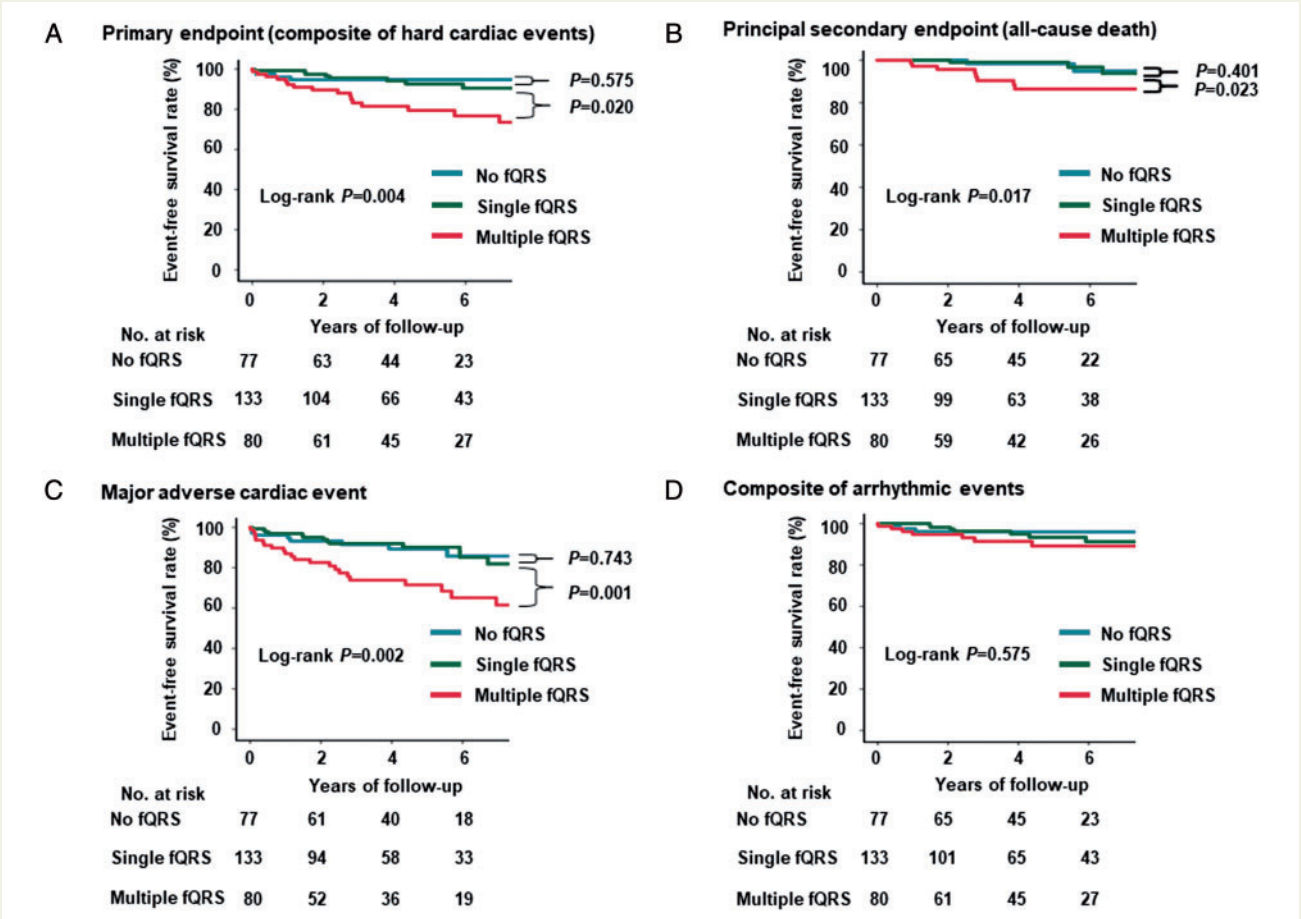

Figure 3 Kaplan–Meier curves for study endpoints. Kaplan–Meier curves showing survival free from the primary endpoint (a composite of hard cardiac events; *A*), principal secondary endpoint (all-cause death; *B*), MACE (*C*), and a composite of arrhythmic events (*D*). The multiple-fQRS group had a higher event rate of hard cardiac events, all-cause death, and MACE than the other two groups. There were no significant differences between the single fQRS and no-fQRS groups in the probability of each endpoint. All three groups had a similar rate of arrhythmic events. fQRS, fragmented QRS; MACE, major adverse cardiac event.

the multiple-fQRS group had a higher rate of the primary endpoint than the other two groups ($P = 0.004$). The estimated 5-year rate of the primary endpoint was the highest in the multiple-fQRS group (22%) and lowest in the no-fQRS group (5.4%). *Table 3* shows univariable and multivariable Cox regression analyses of risk factors for the primary endpoint. Univariable analysis showed that the presence of fQRS (single or multiple fQRS) was not an independent prognostic factor for the primary endpoint ($P = 0.531$). In Model 1, a simultaneous forced entry multivariable Cox model that adjusted for factors that were significant in the univariable analysis as well as established risk factors for chronic HF (age, gender, BNP level, NYHA functional class, eGFR, and LV end-diastolic volume index), the following were identified as significant predictors for primary endpoint: body mass index, LV end-diastolic volume index, and presence of LGE. Since the number of events in this study was relatively low, we found that the best predictive model adjusted for the significant factors included in Model 1 (e.g. the presence of LGE) using stepwise Cox regression analysis. The presence of multiple fQRS (HR 2.23; 95% CI 1.07–4.62; $P = 0.032$) remained a significant predictor of the primary endpoint.

Principal secondary endpoint: all-cause death

There were nine cardiac deaths and five non-cardiac deaths (two deaths due to cancer, one death due to aortic aneurysm rupture, splenic rupture, and unknown reason, respectively). Among the three groups, the multiple-fQRS group had the highest incidence of all-cause death ($P = 0.035$) (*Table 2*). Kaplan–Meier analysis showed that the multiple-fQRS group had a higher mortality rate than the other two groups ($P = 0.017$) (*Figure 3B*). The estimated 5-year mortality rate was highest in the multiple-fQRS group (14%) and lowest in the no-fQRS group (1.6%). Only univariable Cox regression analysis was used for this endpoint because of the small number of events. The presence of multiple fQRS was a significant predictor of all-cause

Table 3 Univariable and multivariable Cox regression analyses of predictors of hard cardiac events

	Univariable analysis			Multivariable analysis					
				Model 1[a]			Best predictive model[b]		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age, per 10-year increment	0.88	0.69–1.12	0.301	0.85	0.63–1.15	0.300			
Male gender	1.21	0.46–3.16	0.316	2.07	0.67–6.43	0.208			
BMI, per kg/m^2 decrement	1.14	1.03–1.14	0.013	1.15	1.02–1.30	0.020			
NYHA class ≥ II	2.38	0.91–6.21	0.076	0.29	0.08–1.11	0.071			
Current smoker	1.82	0.87–3.82	0.112						
Diabetes mellitus	0.89	0.36–2.17	0.794						
Atrial fibrillation	0.98	0.46–2.09	0.964						
ECG parameters									
Heart rate, per 10 b.p.m. increment	1.08	0.81–1.43	0.614						
QTc, per 10 ms increment	1.15	1.04–1.26	0.004	1.06	0.95–1.19	0.252			
Presence of fQRS	1.23	0.64–2.37	0.531						
Presence of multiple fQRS	3.18	1.56–6.46	0.001	2.07	0.94–4.58	0.071	2.23	1.07–4.62	0.032
Log (BNP), per 1 pg/mL increment	2.32	1.27–4.22	0.006	2.06	0.99–4.25	0.052	1.93	1.00–3.70	0.049
eGFR, per 1 mL/min/1.73 m^2 decrement	1.01	0.99–1.03	0.374	1.02	0.99–1.04	0.096			
Serum sodium, per 1 mEq/L increment	0.95	0.85–1.06	0.348						
Haemoglobin, per 1 g/dL decrement	1.19	0.98–1.45	0.086						
Medications									
β-blocker	0.95	0.23–3.98	0.946						
ACE inhibitor or ARB	1.17	0.45–3.06	0.745						
Diuretic	2.70	1.16–6.26	0.021	2.09	0.81–5.39	0.126			
Amiodarone	2.16	0.75–6.20	0.152						
CMR parameters									
LVEDVI, per 10 mL/m^2 increment	1.15	1.08–1.23	<0.001	1.11	1.03–1.21	0.005	1.13	1.05–1.21	0.001
LVSVI, per 10 mL/m^2 increment	1.08	0.82–1.44	0.573						
LV mass, per 1 g increment	1.00	0.99–1.00	0.165						
Presence of LGE	13.53	3.23–56.89	<0.001	8.26	1.83–37.28	0.006	7.86	1.83–33.69	0.006

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CI, confidence interval; CMR, cardiac magnetic resonance; ECG, electrocardiogram; EDVI, end-diastolic volume index; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESVI, end-systolic volume index; fQRS, fragmented QRS; HR, hazard ratio; LGE, late gadolinium enhancement; LV, left ventricular; NYHA, New York Heart Association; RV, right ventricular; SVI, stroke volume index.
[a]Multivariable Cox models were selected using a simultaneous forced entry method with factors that were significant in the univariable analysis and established risk factors for prognosis (age, gender, BNP level, NYHA functional class, eGFR, and LVEDVI). Aldosterone antagonist, LVESVI, LVEF, and RVEF were dropped due to high collinearity.
[b]Best predictive model, adjusted for significant predictors selected by stepwise Cox regression using factors that were significant in the univariable analysis and established risk factors for prognosis (age, gender, BNP level, NYHA functional class, eGFR, and LVEDVI).

death (HR 3.37; 95% CI 1.17–9.73; $P = 0.025$), but the presence of fQRS *per se* was not (*Table 4*).

Major adverse cardiac events and arrhythmic events

Major adverse cardiac event occurred in 44 (15%) patients (*Table 2*). The multiple-fQRS group had the highest event rate ($P = 0.001$) (*Figure 3C*) among the three groups. The estimated 5-year rate of MACE was 29% in the multiple-fQRS group. In the multivariable Cox regression analysis that adjusted for significant predictors based on Model 1 (e.g. LGE), the presence of multiple fQRS was a significant predictor of MACE (HR 1.99; 95% CI 1.07–3.72; $P = 0.031$), but the presence of fQRS was not (*Table 5*).

Arrhythmic events occurred in 18 (6.2%) patients (*Table 2*). There were no significant differences in the incidence and event rate of arrhythmic events by fQRS extent (*Table 2* and *Figure 3D*). During the study period, 29 (10%) patients underwent ICD implantation (5 in the no-fQRS group, 11 in the single-fQRS group, and 13 in the multiple-fQRS group; $P = 0.083$), of whom 11 (38%) received an ICD plus cardiac resynchronization therapy and 18 (62%) received an ICD alone. Of the 29 patients who underwent ICD implantation, appropriate ICD discharge for VT or VF occurred in 1 (20%) patient in the no-fQRS group, 5 (46%) patients in the single-fQRS group, and 3 (23%) patients in the multiple-fQRS group; the difference between groups was not significant ($P = 0.419$).

Fragmented QRS and late gadolinium enhancement

Late gadolinium enhancement was presented in 28 (36%), 78 (59%), and 62 (78%) patients in the no fQRS, single fQRS, and multiple-fQRS groups, respectively ($P < 0.001$). Among the 168 patients with LGE,

Table 4 Univariable Cox regression analyses of predictors of all-cause death

	Univariable analysis		
	HR	95% CI	*P*-value
Age, per 10-year increment	1.65	1.10–2.46	0.013
Male	0.28	0.10–0.82	0.019
BMI, per kg/m^2 decrement	0.88	0.75–1.02	0.097
NYHA class ≥ II	6.23	0.83–48.37	0.076
Current smoker	1.07	0.34–3.43	0.904
Diabetes mellitus	0.62	0.14–2.75	0.615
Atrial fibrillation	1.15	0.39–3.43	0.803
ECG parameters			
Heart rate, per 10 b.p.m. increment	1.35	0.94–1.94	0.101
QTc, per 10 ms increment	1.08	0.93–1.25	0.317
Presence of fQRS	1.48	0.41–5.30	0.549
Presence of multiple fQRS	3.37	1.17–9.73	0.025
Log (BNP), per 1 pg/mL increment	4.03	1.46–11.13	0.007
eGFR, per 1 mL/min/1.73 m^2 decrement	1.04	1.00–1.08	0.019
Serum sodium, per 1 mEq/L increment	1.08	0.84–1.21	0.929
Haemoglobin, per 1 g/dL decrement	1.53	1.20–1.96	0.001
Medications			
β-blocker	0.34	0.08–1.51	0.155
ACE inhibitor or ARB	0.53	0.17–1.69	0.284
Diuretic	10.04	1.31–76.81	0.026
Amiodarone	0.04	0.01–455.92	0.510
CMR parameters			
LVEDVI, per 10 mL/m^2 increment	1.08	0.98–1.19	0.138
LVSVI, per 10 mL/m^2 increment	0.91	0.55–1.49	0.703
LV mass, per 1 g increment	1.00	0.99–1.01	0.518
Presence of LGE	5.60	1.25–25.0	0.024

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CI, confidence interval; CMR, cardiac magnetic resonance; ECG, electrocardiogram; EDVI, end-diastolic volume index; eGFR, estimated glomerular filtration rate; fQRS, fragmented QRS; HR, hazard ratio; LGE, late gadolinium enhancement; LV, left ventricular; NYHA, New York Heart Association; RV, right ventricular; SVI, stroke volume index.

95 (56%), 26 (16%), and 47 (28%) patients had mid-wall, focal, and diffuse patterns, respectively. There was no significant co-location of LGE and fQRS (anterior, $P = 0.159$; inferior, $P = 0.274$; lateral, $P = 0.872$). However, the multiple-fQRS group had a higher prevalence of a diffuse LGE pattern than the other two groups (39%; $P < 0.001$; *Table 1*).

Discussion

The present prospective cohort study investigated the prognostic impact of fQRS in patients with DCM. Our study showed that the presence of multiple fQRS, but not single fQRS, is significantly associated with the incidence of hard cardiac events, all-cause death, and MACE. In addition, multiple fQRS was associated with severe myocardial fibrosis demonstrated by a diffuse LGE pattern. Thus, our results suggested that the presence of more regions with fQRS corresponds to more myocardial fibrosis, likely indicating worse prognosis.

Fragmented QRS and outcome prediction in patients with dilated cardiomyopathy

Previous retrospective studies with small numbers of patients have investigated the prognostic impact of fQRS in patients with DCM. Sha *et al.* [5] showed that fQRS predicted all-cause mortality and ventricular arrhythmias in 128 patients with DCM. They excluded patients with coronary artery disease but did not describe how they defined coronary artery disease. On the other hand, Das *et al.* [6] showed that fQRS was a significant predictor of appropriate ICD therapy (anti-tachycardia pacing or ICD shock for a ventricular arrhythmia) in a subgroup analysis of 116 patients with DCM who did not have significant coronary artery stenosis on coronary angiography or myocardial infarction. In their study, all study patients received ICD implantation as primary or secondary prevention. Indeed, 49% of their patients received secondary prevention for ventricular arrhythmia. Thus, whether fQRS is a prognostic indicator in patients with DCM regardless of ICD implantation has not been fully evaluated. Therefore, we conducted a prospective study with a cohort of consecutive DCM patients ($n = 463$), which was larger than the previous studies

Table 5 Univariable and multivariable Cox regression analyses of predictors of major adverse cardiac events

	Univariable analysis			Multivariable analysis					
				Model 1[a]			Best predictive model[b]		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age, per 10-year increment	0.99	0.81–1.22	0.945	0.90	0.71–1.15	0.388			
Male	0.91	0.43–1.89	0.792	1.37	0.59–3.20	0.465			
BMI, per kg/m^2 decrement	1.10	1.00–1.19	0.025	1.09	0.84–1.01	0.075			
NYHA class ≥ II	2.50	1.11–5.60	0.027	0.69	0.24–1.94	0.480			
Current smoker	1.25	0.66–2.38	0.492						
Diabetes mellitus	1.42	0.73–2.77	0.296						
Atrial fibrillation	0.89	0.47–1.71	0.733						
ECG parameters									
Heart rate, per 10 b.p.m. increment	1.02	0.80–1.30	0.899						
QTc, per 10 ms increment	1.09	1.00–1.18	0.040	1.06	0.96–1.16	0.261			
Presence of fQRS	1.54	0.74–3.21	0.248						
Presence of multiple fQRS	2.79	1.54–5.04	0.001	2.06	1.09–3.92	0.027	1.99	1.07–3.72	0.031
Log (BNP), per 1 pg/mL increment	2.00	1.24–3.24	0.005	1.56	0.88–2.77	0.125			
eGFR, per 1 mL/min/1.73 m^2 decrement	1.02	1.00–1.03	0.032	1.02	1.00–1.04	0.031	1.02	1.00–1.04	0.039
Serum sodium, per 1 mEq/L increment	0.98	0.89–1.09	0.752						
Haemoglobin, per 1 g/dL decrement	1.14	0.97–1.36	0.119						
Medication									
β-blocker	1.38	0.33–5.69	0.660						
ACE inhibitor or ARB	1.81	0.71–4.60	0.211						
Diuretic drug	3.14	1.51–6.54	0.002	2.34	1.06–5.16	0.035	2.41	1.14–5.08	0.021
Amiodarone	1.92	0.75–4.88	0.173						
CMR parameters									
LVEDVI, per 10 mL/m^2 increment	1.11	1.05–1.17	<0.001	1.05	0.99–1.12	0.112	1.07	1.01–1.13	0.019
LVSVI, per 10 mL/m^2 increment	1.06	0.83–1.36	0.651						
LV mass, per 1 g increment	1.00	0.99–1.00	0.207						
Presence of LGE	6.09	2.57–14.44	<0.001	4.01	1.62–9.95	0.003	4.16	1.70–10.16	0.002

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CI, confidence interval; CMR, cardiac magnetic resonance; ECG, electrocardiogram; EDVI, end-diastolic volume index; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESVI, end-systolic volume index; fQRS, fragmented QRS; HR, hazard ratio; LGE, late gadolinium enhancement; LV, left ventricular; NYHA, New York Heart Association; RV, right ventricular; SVI, stroke volume index.
[a]Multivariable Cox models were selected using a simultaneous forced entry method with factors that were significant in the univariable analysis and established risk factors for prognosis (age, gender, BNP level, NYHA functional class, eGFR, and LVEDVI). Aldosterone antagonist, LVESVI, LVEF, and RVEF were dropped due to high collinearity.
[b]Best predictive model, adjusted for significant predictors selected by stepwise Cox regression analysis using factors that were significant in the univariable analysis and established risk factors for prognosis (age, gender, BNP level, NYHA functional class, eGFR, and LVEDVI).

mentioned above, to assess the prognostic impact of fQRS in patients with DCM (*Figure 1*).

Extent of fragmented QRS for outcome prediction in patients with dilated cardiomyopathy

This study demonstrated that the presence of single fQRS does not have substantial prognostic impact, but multiple fQRS (fQRS in ≥ 2 myocardial segments) has a significant prognostic impact on hard cardiac events, all-cause death, and MACE in patients with DCM. Our results indicated that the extent of fQRS is important for outcome prediction in patients with DCM. Consistent with our study, previous studies have shown that the extent of fQRS is a prognostic factor for patients with IHD [7] or Brugada syndrome. [8] A previous study suggested that fQRS is due to alterations in ventricular depolarization. [3] In patients with DCM, fibrotic tissue expands with accumulation of collagen as a result of activation of the renin–angiotensin–aldosterone and β-adrenergic systems during the progression of HF. [15,16] Thus, fQRS in patients with DCM might be related to alterations in the depolarization of viable myocytes interspersed in fibrotic tissue. Consequently, the extent of fQRS might be related to the amount of fibrotic tissue and HF severity.

We showed that the multiple-fQRS group status is significantly associated with a diffuse LGE pattern on CMR (*Table 1*). Late gadolinium enhancement extent is a strong predictive factor for DCM. Halliday *et al.* [17] studied 874 patients with DCM who were followed for a median of 4.9 years. They showed that LGE extent is related to all-cause mortality and SCD. Since LGE is related to replacement myocardial fibrosis, [18] and a higher extent of LGE is related to a higher extent of interstitial fibrosis, [19] our results suggest that fQRS extent is related to the severity of myocardial fibrosis detected by CMR. Electrocardiogram is a simple, highly reproducible, and

universally available investigation. It is clinically very useful that fQRS on ECG can evaluate the fibrosis of patients with DCM and predict the prognosis when LGE cannot be evaluated.

In addition, while Das *et al.* [6] showed that fQRS was a predictive factor for appropriate ICD therapy in patients with DCM who already had an ICD, our analysis showed that multiple fQRS was not a predictive factor for arrhythmic events (non-fatal VF, sustained VT, or appropriate ICD therapy) in patients with DCM.

Limitations

First, this study was performed in a single high-volume centre, which introduces the possibility of referral bias. Second, although chronic renal insufficiency has been reported to be a prognostic factor for cardiac events in patients with chronic HF, patients with chronic renal insufficiency (eGFR < 30 mL/min/1.73 m^2) were excluded because of the risk of nephrogenic systemic fibrosis associated with gadolinium exposure. Third, we identified diffuse LGE pattern by visual sub-segmental analysis and did not quantify LGE by grey-scale threshold analysis. Fourth, we did not perform further evaluation of diffuse interstitial fibrosis using T1 mapping to quantify fibrosis. [20] Further studies with T1 mapping should investigate the relationship between interstitial fibrosis and fQRS. Fifth, the failure to use all-cause mortality as the primary endpoint is a limitation. Finally, there is a potential bias in the results from the stepwise selection as a result of overfitting the derivation data set.

Conclusion

Multiple fQRS, but not single fQRS, is associated with future hard cardiac events in patients with DCM. The extent of fQRS is important for outcome prediction in patients with DCM.

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Data availability

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

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