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The impact of fragmented QRS on clinical findings and outcomes in children with dilated cardiomyopathy with or without left ventricular non-compaction

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Abstract

Objective: The aim of this study is to investigate the frequency of fragmented QRS and its associations with clinical findings and prognosis in children diagnosed with dilated cardiomyopathy with or without left ventricular non-compaction. *Methods:* This retrospective study was conducted between 2010 and 2020. Patients with dilated cardiomyopathy were classified into two groups according to the presence of left ventricular non-compaction: Dilated cardiomyopathy with left ventricular non-compaction and dilated cardiomyopathy without left ventricular non-compaction. Patients were also divided into two groups according to the presence of fragmented QRS (fragmented QRS group and non-fragmented QRS group). *Results:* Twenty-three of 44 patients (52.3%) were male. Among left ventricular non-compaction patients, the fragmented QRS group had more complex ventricular arrhythmias ($p = 0.003$). Patients with fragmented QRS had a significantly higher rate of major adverse cardiac events and/or cardiac death in both cardiomyopathy groups ($p = 0.003$ and $p = 0.005$). However, the rate of major adverse cardiac events and/or cardiac death was similar between dilated cardiomyopathy patients with and without left ventricular non-compaction. Multivariate logistic regression analysis showed that the presence of fragmented QRS strongly predicts major adverse cardiac events and/or cardiac death (odds ratio, 31.186; 95% confidence interval, 2.347–414.307). Although the survival rates between cardiomyopathy groups were similar, patients with fragmented QRS had a markedly lower survival rate during the follow-up period, as mean of 15 months ($p = 0.001$). *Conclusion:* Our study showed that the presence of fragmented QRS may be an important ECG sign predicting an major adverse cardiac event and/or cardiac death in patients with dilated cardiomyopathy. We believe that recognising fragmented QRS could be valuable in forecasting patient prognosis and identifying high-risk patients who require additional support.

Dilated cardiomyopathy is the most common cardiomyopathy in children (50–70% of all cardiomyopathies) and is defined by the presence of a dilated left ventricle with systolic dysfunction.[1] Dilated cardiomyopathy is also the most common cause of heart transplantation in children.[2] Patients with left ventricle non-compaction are identified by the presence of substantial left ventricle trabeculations and deep intertrabecular recesses. Left ventricle non-compaction may be isolated or may accompany dilated, hypertrophic, or restrictive cardiomyopathy.[3]

Fragmented QRS is a non-invasive ECG feature that can potentially be utilised to predict cardiac adverse events. In a standard 12-lead ECG, fragmented narrow QRS (QRS duration < 120 ms) is characterised by the presence of an additional R wave (R') or notching of R or S waves (fragmentation), and fragmented wide QRS (QRS duration > 120 ms) is described as two or more notches in the R or S wave in two consecutive leads corresponding to a coronary area (anterior, lateral, or inferior). The presence of fragmented QRS is attributed to heterogeneity in myocardial depolarisation due to myocardial scarring and fibrosis.[4,5] In recent years, numerous studies about the role of fragmented QRS in a wide range of cardiac disorders, including coronary artery disease, myocarditis, and cardiomyopathies, have been performed.[6–8] However, studies in children are scarce.[9,10] Furthermore, there has been no research on dilated cardiomyopathy with left ventricular non-compaction in children. We hypothesised that fragmented QRS would be more frequent in patients with left ventricular non-compaction

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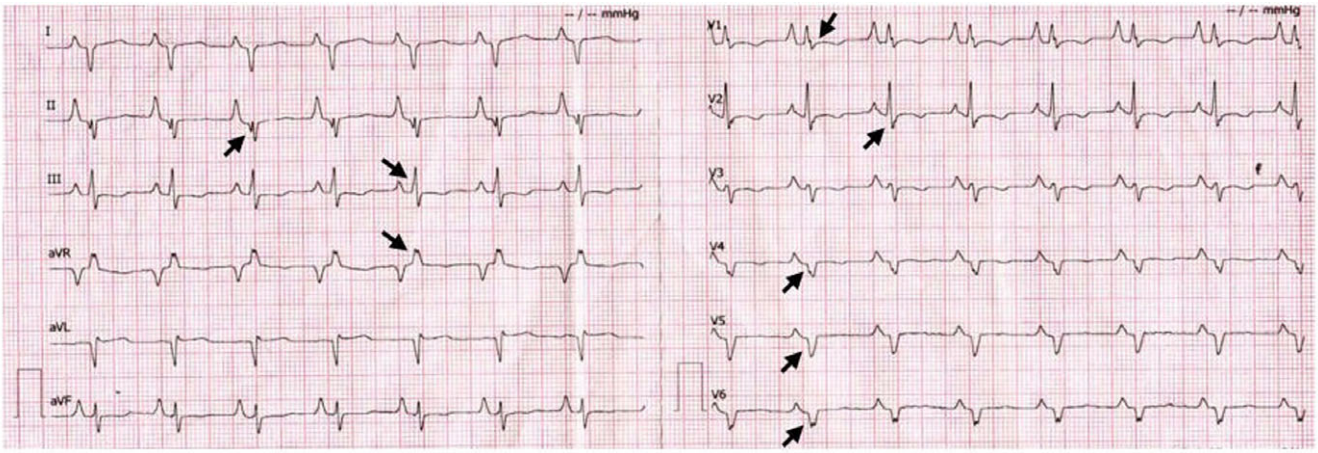


Figure 1. The arrows show a fragmented QRS complex on electrocardiography (DIII subtle).

because of their peculiar myocardial architecture. In this study, we aimed to investigate the frequency of fragmented QRS and its associations with the clinical findings and prognosis of dilated cardiomyopathy patients with or without left ventricular non-compaction.

Methods

Patients

Seventy-two patients with dilated cardiomyopathy were diagnosed at Ankara University Medical School's Department of Pediatric Cardiology between December 2010 and January 2020. Forty-four patients were included in this retrospective study because the remaining 27 patients' data was not available, and one patient required cardiac resynchronisation therapy. Twenty patients with dilated cardiomyopathy with left ventricular non-compaction and twenty-four patients with dilated cardiomyopathy without left ventricular non-compaction were formed as two distinct groups of patients. American Heart Association criteria were used for the diagnosis of dilated cardiomyopathy.[2] Patients were diagnosed with left ventricular non-compaction according to echocardiographic findings that included many trabeculations, deep intertrabecular recesses apparent on colour flow, and a 2-layered structure of the myocardium with a non-compacted to compacted myocardium ratio of > 2:1 in systole.[11] Patients were also divided into two groups according to the presence of fragmented QRS (fragmented QRS group and non-fragmented QRS group). Demographic data, the findings of laboratory tests, ECGs, and echocardiography were obtained from the files of all patients. The local ethics committee approved the study.

ECG, echocardiographic, and laboratory parameters

The 12-channel ECG was recorded at a speed of 25 mm/s with a 10 mm/mV calibration, and the findings were reviewed by two physicians blinded to the identity and diagnosis of the patient. Heart rate, PR interval, QRS duration, QT interval, morphology of QRS, and any arrhythmias were evaluated at the time of diagnosis and on follow-up. Bazett's formula was used to calculate the corrected QT interval. The presence of an additional R′ wave or notching in the nadir of the S′ wave in two continuous leads was defined as fragmented QRS (QRS duration < 120 ms)[5] (Fig. 1). 24-hour Holter monitoring was performed in 28 of 44 patients. Complex ventricular arrhythmias were defined if there were ventricular premature beats that were 10 ventricular premature beats per hour, and/or couplets, and/or non-sustained ventricular tachycardia.[12]

All patients were evaluated with transthoracic echocardiography at the time of diagnosis and during follow-up. Echocardiographic parameters included in the study were left ventricular shortening fraction by M-mode, biplane ejection fraction of left ventricle with Simpson's method, left ventricular end-diastolic dimension z-score, and mitral regurgitation. Measurement of left ventricle dimension in diastole by M-mode and/or 2D imaging was carried out from the parasternal long axis perpendicular to the long axis of the ventricle at the tip of the mitral valve.

NT-proBNP concentrations were assessed on admission and during follow-up (Roche Diagnostics, Mannheim, Germany, reference 0–125 pg/mL). There were decrease and increase in NT-proBNP during the follow-up according to the clinical status of the patients. However, the NT-proBNP value on admission was used in the statistical analysis.

Outcomes

We analysed outcomes in terms of major adverse cardiac events or cardiac death. Life-threatening ventricular arrhythmias, a history of extracorporeal membrane oxygenation, and a left ventricular assist device were all major adverse cardiac events. Cardiac death was defined as either a heart transplant or death due to intractable heart failure.

Statistical analysis

Statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics are expressed as means, standard deviation, median, frequency distribution, and percentage values. The distribution normality of the continuous variables was controlled using the Kolmogorov–Smirnov/Shapiro–Wilk test. The Mann–Whitney U test was used to compare two independent groups for nonparametric assessments. Nominal variables were compared using Pearson"s chi-square or Fisher's exact test. Multivariate logistic regression analysis was performed to evaluate whether factors showing significant associations were independent predictors. The Hosmer–Lemeshow test was used to assess model fit. A Kaplan–Meier survival analysis was performed,

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Table 1. Patient characteristics.

	All patients (N = 44)	DCM + LVNC (N = 20)	DCM (N = 24)	*P*
Age at diagnosis (month)				
Median	13.5 (0–210)	6 (0–210)	18 (0–192)	**0.015**
Sex, [n(%)]				
Male	23 (52.3)	8 (40)	15 (62.5)	0.137
fQRS at the diagnosis, [n(%)]	21 (47.7)	9 (45)	12 (50)	0.741
Electrocardiographic characteristics*				
PR interval, (ms)	0.14 (0.10–0.24)	0.14 (0.12–0.20)	0.16 (0.10–0.24)	0.561
QRS duration, (ms)	0.08 (0.04–0.10)	0.08 (0.04–0.10)	0.08 (0.06–0.10)	0.652
QTc (ms)	0.40 (0.35–0.48)	0.39 (0.35–0.45)	0.41 (0.36–0.48)	**0.041**
Echocardiographic characteristics*				
Shortening fraction, (%)	14 (7–28)	14.5 (7–28)	14 (7–24)	0.679
EF by Simpson's method, (%)	29 (14–46)	30.5 (14–42)	29 (15–46)	0.491
LVIDD, [n(%)]				
Z-scor > + 3	26 (59)	10 (50)	16 (67)	0.263
Moderate to severe MR, [n(%)]	12 (27.3)	5 (25)	7 (29.2)	0.757
NT-proBNP on admission, (<125 pg/ml)				
Median	4165 (168–35000)	5629 (214–35000)	3986 (168–35000)	0.588
The patients listed for transplant, [n(%)]	26 (59)	10 (50)	16 (66.6)	0.263

*ECG and echocardiographic parameters at the diagnosis were compared.

and a log rank test was used for paired comparisons. The confidence interval was set as 95%, and a P value of < 0.05 was considered statistically significant.

Results

Patient characteristics (dilated cardiomyopathy with or without left ventricular non-compactions)

Table 1 summarises patient characteristics. The patients were classified into two groups: dilated cardiomyopathy with left ventricular non-compaction (N = 20) and without left ventricular non-compaction (N = 24). The median age at the time of diagnosis was 6 (range: neonatal-210) months and 18 (range: neonatal-192) months in dilated cardiomyopathy patients with and without left ventricular non-compaction, respectively. The median age of patients with dilated cardiomyopathy without left ventricular non-compaction was significantly higher than the left ventricular non-compaction group ($p = 0.015$). Twenty-one (47.7%) patients had fragmented QRS complex at the time of diagnosis, and all of them had narrow fragmented QRS. The frequency of fragmented QRS was similar in both cardiomyopathy groups. The functional classification of all patients at the time of the diagnosis was stage 3–4 according to the New York Heart Association[13] or Modified Ross Heart Failure Classification.[14] All patients were given angiotensin-converting-enzyme inhibitors, furosemide and acetylsalicylic acid, but spironolactone was used in 29 patients (66%), carvedilol in 17 patients (38.6%), and digoxin in 29 patients (66%).

The PR interval and QRS duration were similar between the two groups, but corrected QT was longer in the dilated cardiomyopathy without left ventricular non-compaction group. Both groups had similar biplane EF with Simpson's method, Z-score of left ventricular end-diastolic diameter, and degree of MR. In addition, there was no significant difference in NT-proBNP levels on admission between dilated cardiomyopathy with and without left ventricular non-compaction.

Fragmented QRS and non-fragmented QRS groups

The comparison of fragmented QRS and non-fragmented QRS groups is shown in Table 2. The patients with fragmented QRS were significantly older than the non-fragmented QRS patients at the time of diagnosis. Although the PR interval and corrected QT were similar between the fragmented QRS and the non-fragmented QRS groups, QRS duration was longer in the fragmented QRS group but in the normal range according to age. There was no significant difference in shortening fraction, EF by Simpson's method, left ventricle diameter Z-score, and NT-proBNP levels on admission between the fragmented QRS and the non-fragmented QRS groups, but moderate to severe MR was more frequent in patients with fragmented QRS ($p = 0.027$). Dilated cardiomyopathy patients with and without left ventricular non-compaction were also compared separately according to whether or not having fQRS (Table 3), and the systolic dysfunction, left ventricle diameter Z-score, ECG parameters, and NT-proBNP levels on admission were similar between in fragmented QRS and non-fragmented QRS groups. However, among patients with dilated cardiomyopathy without left ventricular non-compaction, the fragmented QRS group had more frequent moderate to severe MR than the non-fQRS group ($p = 0.034$). On 12-lead surface ECG and/or

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Table 2. Fragmented QRS and nonfQRS groups.

	fQRS (+) (N = 21)	fQRS (-) (N = 23)	*P*
Age at diagnosis (month)			
Median	60 (1.5–210)	10 (0–60)	< **0.001**
Sex, [n(%)]			
Male	15 (71.4)	8 (34.8)	**0.015**
Electrocardiographic characteristics*			
PR interval, (ms)	0.16 (0.12–0.24)	0.12 (0.10–0.18)	0.190
QRS duration, (ms)	0.08 (0.08–0.10)	0.08 (0.04–0.10)	0.007
QTc (ms)	0.41 (0.36–0.48)	0.40 (0.35–0.44)	0.192
Echocardiographic characteristics*			
Shortening fraction (%)	13.8 (7–28)	14.6 (7–24)	0.559
EF by Simpson's method, (%)	29 (14–42)	30.3 (19–46)	0.551
LVIDD, [n(%)]			
Z-scor > + 3	13 (61.9)	13 (56.5)	0.717
Moderate to severe MR, [n(%)]	9 (42.8)	3 (13)	**0.027**
NT-proBNP on admission, (<125 pg/ml)			
Median	5000 (209–35000)	2677 (168–35000)	0.411
Complex ventricular arrhythmia, [n(%)]	9 (42.8)	5 (21.7)	0.133
The patients listed for transplant, [n(%)]	15 (71.4)	11 (45.8)	0.112
MACE and/or Cardiac death, [n(%)]	19 (90.5)	6 (26)	< **0.001**

*ECG and echocardiographic parameters at the diagnosis were compared.

24-hour Holter monitorizations, fragmented QRS groups had more complex ventricular arrhythmias in dilated cardiomyopathy with left ventricular non-compaction patients (77.8 and 9%, p = 0.003).

Survival and outcomes

The median follow-up time was 15.5 (range: 1–144 months) months. Major adverse cardiac event was present in 22 of 44 patients (50%) (with life-threatening ventricular arrhythmia in 14 patients, extracorporeal membrane oxygenation in 10, and left ventricular assist device in 7). Nineteen out of 44 patients died (43%); 3 patients underwent heart transplantation (one of the transplanted patients died). The frequency of major adverse cardiac event and cardiac death was similar between the two groups.

Patients with fragmented QRS had higher rates of major adverse cardiac event and/or cardiac death (p = 0.003 and p = 0.005) irrespective of the underlying cardiomyopathy. Multivariate logistic regression analysis that included age at diagnosis, cardiomyopathy group of the patients, FS by M-Mode, biplane EF with Simpson's method, degree of MR, Z-score of left ventricular end-diastolic diameter, NT-proBNP, and fragmented QRS showed that the presence of fragmented QRS strongly predicted major adverse cardiac event and/or cardiac death (odds ratio; 31.186 95% CI, 2.347 – 414.307, p = 0.009). Patients with fragmented QRS had a markedly lower survival rate than those without (a Kaplan–Meier survival analysis Log rank, p = 0.001) (Fig. 2). The survival rate was lower in left ventricular non-compaction patients with complex ventricular arrhythmias, though it was not statistically significant (p = 0.076). The survival rates between dilated cardiomyopathy patients with and without left ventricular non-compaction were similar.

Discussion

Our study showed that the presence of a fragmented QRS complex at the time of diagnosis in dilated cardiomyopathy patients with or without left ventricular non-compaction is an important risk factor for poor outcome. Furthermore, the overall survival of patients with fragmented QRS is significantly lower.

In recent years, there has been an increase in studies on fragmented QRS in cardiac disorders. However, research on the role of fragmented QRS in the paediatric population is severely limited. Although the new therapies for heart failure improve the clinical condition of dilated cardiomyopathy patients; these patients may experience cardiac arrhythmias, and/or sudden cardiac death, may become intrope dependent, progressive heart failure. Left ventricular non-compaction may be isolated or may accompany dilated, hypertrophic, or restrictive cardiomyopathy and cause left and/or right ventricular failure.[15] According to the Pediatric Cardiomyopathy Registry, left ventricular non-compaction with a dilated phenotype has the worst prognosis.[16] Therefore, it is critical to investigate the predictors of outcomes in the management of these patients. In this study, we found that the presence of fragmented QRS strongly predicted major adverse cardiac event and/or cardiac death. Similarly, in a retrospective study of 63 paediatric patients with idiopathic dilated cardiomyopathy in Korea between 2003 and 2014, the positive fragmented QRS complex was reported as a strong predictor for adverse outcomes[9]. In the study includes 842 patients over 20 years old with left ventricle dysfunction, the presence of fragmented QRS was not found related with poor outcomes or death caused arrhythmia.[17] The fragmented QRS is a new finding on the ECG; however, the results of multiple studies support that the fragmented QRS is associated with myocardial fibrosis, and it might be important

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Table 3. ECG, echocardiographic, laboratory findings and outcomes between fQRS group and non-fQRS group.

	Dilated cardiomyopathy with LVNC			Dilated cardiomyopathy without LVNC		
	fQRS Group (N = 9)	Non-fQRS Group (N = 11)	*P*	fQRS Group (N = 12)	Non-fQRS Group (N = 12)	*P*
Electrocardiographic characteristics*						
PR interval, (ms)	0.15 (0.12–0.20)	0.12 (0.12–0.16)	0.393	0.16 (0.12–0.24)	0.14 (0.10–0.18)	0.330
QRS duration, (ms)	0.08 (0.08–0.10)	0.08 (0.04–0.08)	**0.019**	0.08 (0.08–0.10)	0.08 (0.06–0.10)	0.179
QTc, (ms)	0.39 (0.36–0.45)	0.39 (0.35–0.44)	0.982	0.42 (0.36–0.48)	0.40 (0.36–0.44)	0.095
Echocardiographic characteristics*						
Fractional shortening (FS) (%)	14.5 (7–28)	14.6 (8–18)	0.986	13 (10–18)	15 (7–24)	0.360
EF by Simpson's method, (%)	32 (14–42)	29 (19–41)	0.428	26.5 (15–33)	31 (21–46)	0.102
LVIDD						
Z-scor > + 3	5 (55.6)	5 (45.5)	0.500	8 (66.7)	8 (66.7)	0.667
Moderate to severe MR, [n(%)]	3 (33.3)	2 (18.2)	0.396	6 (50)	1 (8.3)	**0.034**
NT-proBNP on admission, (<125 pg/ml)						
Median	7949 (214–35000)	3958 (242–35000)	0.879	4959 (209–35000)	2672 (168–35000)	0.326
Complex ventricular arrhythmia, [n(%)]	7 (77.8)	1 (9)	**0.003**	2 (16.7)	4 (33.3)	0.320
MACE and/or ardiac death, [n(%)]	8 (88.9)	2 (18.2)	**0.003**	11 (91.7)	4 (33.3)	**0.005**
Length of follow-up (months)						
Median	12 (2–120)	19 (1–44)	0.425	12.7 (1–74)	26 (1–108)	0.094

*ECG and echocardiographic parameters at the diagnosis were compared.

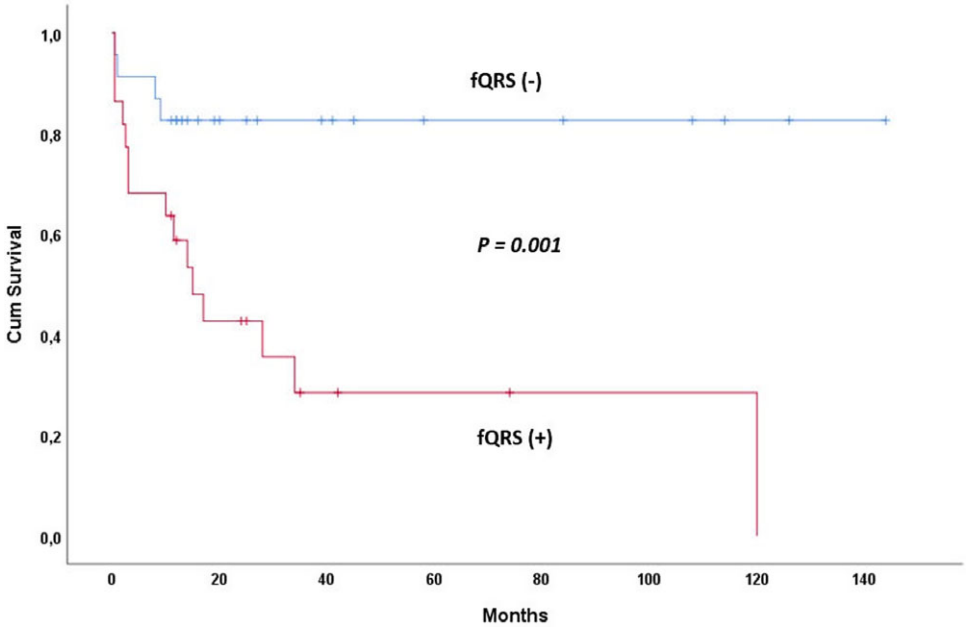


Figure 2. The survival in all patients according to having fQRS or not.

for predicting a worse prognosis in patients with dilated cardiomyopathy.[18]

In our cohort, the median age at the time of diagnosis among dilated cardiomyopathy patients with and without left ventricular non-compaction was 6 months and 18 months, respectively. The fragmented QRS group had an older age at diagnosis in both patient groups (dilated cardiomyopathy with and without left ventricular non-compaction). In Kong et al.'s study[9], the median age at diagnosis was also reported to be older in the patients with fragmented QRS compared to the non-fragmented QRS group (86.6 and 44.1 months, $p = 0.026$). In fact, myocardial damage and scar formation in dilated cardiomyopathy patients are increasing over time, the fragmented QRS is manifested as a result of altered myocardial activation due to fibrosis and scar repair.[18] In our study, the older age at diagnosis of patients with fragmented QRS might be related to this process. It must be kept in mind that patients may already have myocardial damage at the time of diagnosis. Thus, the fragmented QRS may have appeared long before the time of diagnosis because the disease process had started before the time of diagnosis. Also, the worse prognosis in patients with fragmented QRS may be related to the higher mean age at the time of diagnosis.

In the dilated cardiomyopathy patients with and without left ventricular non-compaction, the systolic dysfunction, left ventricle diameter Z-score, ECG parameters, and NT-proBNP levels on admission were similar between the fragmented QRS and the non-fragmented QRS groups. However, the fragmented QRS group had more mild to severe MR than the non-fragmented QRS group among individuals with dilated cardiomyopathy without left ventricular non-compaction. Kong et al. evaluated 63 children diagnosed with dilated cardiomyopathy retrospectively and reported that in patients with fragmented QRS, the QRS duration at diagnosis was significantly longer, and M-mode ejection fraction was lower in the fragmented QRS group.

According to previous studies, arrhythmia was one of the most important factors affecting mortality in patients with left ventricular non-compaction.[19,20] In our study, 24-hour Holter monitoring could be performed in 28 of 44 patients (60%), and complex ventricular arrhythmias were more frequent in left ventricular non-compaction patients with fragmented QRS ($p = 0.003$). Patients with complex ventricular arrhythmias had a lower survival rate, but it was not statistically significant (37.5 and 83.3%, $p = 0.076$).

Study limitations

Our study was subject to the usual restrictions of retrospective studies. The sample size was relatively small. In addition, cardiovascular MRI was not performed on all patients; therefore, we could not assess the relationship between myocardial fibrosis and fragmented QRS. Another limitation was that 24-hour Holter monitoring was performed in only 60% of patients due to technical difficulties or patient's refusal. Because this study data spans a decade, the introduction of newer drugs, the development of new treatment strategies for dilated cardiomyopathy, and the introduction of mechanical assist devices in the last decade may cause a bias affecting prognosis and outcome. Our results need to be supported by prospective studies with a larger number of patients.

Conclusion

Fragmented QRS may be an important finding for predicting severe cardiac events and/or cardiac death in dilated cardiomyopathy patients. We did not find any difference between dilated cardiomyopathy with and without left ventricular non-compaction in terms of fragmented QRS and adverse outcomes. We believe that recognising fragmented QRS to predict major adverse cardiac events and mortality risk in patients with dilated cardiomyopathy, both with and without left ventricular non-compaction, could be useful to provide additional support in a timely manner.

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Competing interests. The authors declare that they have no conflict of interest.

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Ethical standards. The authors assert that all procedures contributing to this work follow the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the ethics committee of Ankara University.

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