

## ORIGINAL ARTICLE

# Fragmented QRS as a candidate marker for left ventricular nonrecovery in patients with peripartum cardiomyopathy

Bahar Tekin Tak MD<sup>1</sup>  | Serkan Cay MD<sup>1</sup>  | Firdevs Aysenur Ekizler MD<sup>1</sup>  |  
Elif Hande Ozcan Cetin MD<sup>1</sup>  | Hilal Erken Pamukcu MD<sup>2</sup>  | Habibe Kafes MD<sup>1</sup>  |  
Nedret Ulvan MD<sup>1</sup>  | Ozcan Ozeke MD<sup>1</sup>  | Firat Ozcan MD<sup>1</sup>  |  
Serkan Topaloglu MD<sup>1</sup>  | Dursun Aras MD<sup>1</sup> 

<sup>1</sup>Department of Cardiology, University of Health Sciences, Ankara City Hospital, Ankara, Turkey

<sup>2</sup>Department of Cardiology, Dışkapı Education and Research Hospital, Health Sciences University Ankara, Turkey

**Correspondence**

Bahar Tekin Tak, MD, Sağlık Bilimleri Üniversitesi, Ankara Şehir Hastanesi, Kardiyoloji Kliniği, Ankara, 06100, Türkiye.  
Email: tekinbahar@yahoo.com

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**Abstract**

**Background:** Fragmented QRS (fQRS) complex, with various morphology, has been recently described as a diagnostic criterion of several cardiac diseases. However, there are little data regarding the prognostic role of fQRS in peripartum cardiomyopathy (PPCM) patients. We aimed to investigate the effect of fQRS on predicting left ventricular (LV) nonrecovery in patients with peripartum cardiomyopathy (PPCM).

**Methods:** Ninety patients (mean age:  $34.7 \pm 6.5$  years) with the diagnosis of PPCM were analyzed retrospectively. The median follow-up period of was 67.0 (12.0–192.0) months. Fragmented QRS was defined as the presence of various RSR' patterns (QRS duration < 120 ms) with or without Q wave, which include an additional R wave (R' prime) or notching of the R wave or S wave, or the presence of more than one R' (fragmentation) without typical bundle branch block. Recovery of LV function was defined as the presence of LV ejection fraction (EF) >45%.

**Results:** Of the patients, 54 (60%) did not recover LV function at the last follow-up visit (nonrecovery group), while 36 of the patients (40%) exhibited LV recovery (recovery group). LV ejection fraction (EF) and fQRS were identified as independent predictors of LV nonrecovery in patients with PPCM (odds ratio OR: 5.546, 95% confidence interval CI: 0.792–0.979,  $p = .019$  and OR: 5.986, 95% CI: 1.313–11.787,  $p = .014$ , respectively).

**Conclusion:** Our data firstly indicated that presence of fQRS was a significant predictor of LV nonrecovery in patients with PPCM. The fQRS might assist in identifying high-risk patients.

**KEYWORDS**

fragmented QRS complex, left ventricular nonrecovery, peripartum cardiomyopathy

## 1 | INTRODUCTION

PPCM, the major cause of maternal cardiovascular death in the world, is an idiopathic cardiomyopathy, characterized by an abrupt onset of clinic of heart failure (HF) with reduced left ventricular (LV) ejection fraction (EF), usually <45%, presenting toward the end of pregnancy or 6 months after delivery in previously healthy women, where no other identifiable cause of HF is found (Elkayam, 2011; Sliwa et al., 2006, 2010). The etiology of PPCM remains unclear, but various risk factors such as genetic and hormonal mechanisms, abnormal immune, or hemodynamic response to pregnancy, nutrient deficiency, increased oxidative stress, and inflammation have been identified (Biteker, Kayatas, Duman, Turkmen, & Bozkurt, 2014; Sliwa et al., 2006, 2010). Clinical presentation of PPCM is highly heterogeneous, and this disease might lead to progressive HF, thromboembolic complications, life-threatening arrhythmias, and even cardiac death (Goland et al., 2009; Nishimoto et al., 2012). Although clinical presentations and outcomes vary substantially, several reports indicated that recovery (defined as recovery to an LVEF > 50 percent) could be seen with a varying range from 23% to 66% in the course of PPCM. On the grounds, it is crucial to identify patients to whom LV recovery will occur or not (Biteker, Ilhan, Biteker, Duman, & Bozkurt, 2012; Karaye & Henein, 2013). In the literature, many studies have been investigating the predictors for LV nonrecovery in patients with PPCM. LV nonrecovery was accepted as the persistence of LV systolic dysfunction with LVEF <45%. Increased LV end-diastolic diameters (LVEDD), lower baseline LVEF, older age, late diagnosis, black race, and elevated pro-inflammatory markers were determined to be predictors of LV nonrecovery and adverse outcomes in PPCM patients (Biteker et al., 2018; Ekizler et al., 2019; Goland et al., 2009). However, it is still difficult to predict accurately which patients will have full LV recovery and which will develop chronic HF with persistently reduced LVEF. Although ECG abnormalities can be seen at the time of diagnosis of PPCM, there are scarce data about the prognostic value of ECG pathologies (Hilfiker-Kleiner, Haghikia, Nonhoff, & Bauersachs, 2015; Kligfield et al., 2007). Presence of fragmented QRS (fQRS) on a routine 12-lead electrocardiogram (ECG), as a marker of depolarization abnormality, reflects alternation of myocardial activation due to myocardial scar and/or fibrosis (Das, Khan, Jacob, Kumar, & Mahenthiran, 2006; Das et al., 2008). fQRS is believed to be representing the conduction delay in myocardial activation because of myocardial scarring and associated in many cardiovascular pathologies like ischemic or nonischemic dilated cardiomyopathy (Das et al., 2010), coronary artery disease (CAD), long-QT syndrome (Haraoka et al., 2010), and Brugada syndrome (Morita et al., 2008). However, evidence on the prognostic role of fQRS in PPCM patients has been lacking. As a marker of myocardial scar, it could be hypothesized that frQRS may be a predictor of persistence of LV systolic dysfunction in PPCM. Therefore, we aimed to investigate the prognostic value of fQRS to predict LV nonrecovery in patients with PPCM.

## 2 | MATERIAL AND METHODS

### 2.1 | Study population

From April 2009 to May 2018, 90 patients diagnosed with PPCM in our tertiary reference center were enrolled in this study. Demographic parameters, laboratory, electrocardiography, and echocardiographic data of all patients were reviewed from their patients' files, clinical follow-up visits, device interrogation, and electronic database. The present study was conducted by the Declaration of Helsinki and was approved by the local ethics committee. PPCM was accepted as the occurrence of unexplained HF from the last months of pregnancy up to 5 months after delivery with LVEF < 45% and the absence of identifiable heart disease before the last month of pregnancy. All patients were older than 18 years. Patients with any previous congenital or significant organic valvular heart disease and history of cardiomyopathy and coronary heart disease ( $\geq 50\%$  luminal stenosis in at least one major coronary artery and their branches) were excluded from this study. A total of 90 patients who met the criteria were included in this study. The follow-up duration was at least 12 months after diagnosis for all patients. They had undergone two-dimensional and M-mode echocardiography with continuous, pulsed, and color Doppler imaging at the time of diagnosis and the last follow-up visit with the Vivid 7 system (GE Healthcare). EF was calculated by using modified Simpson method. Recovery of LV systolic function was defined as the presence of LVEF >45%. Echocardiographic parameters, including LVEF, LVEDD, and LV end-systolic diameter (LVESD), and systolic pulmonary arterial pressure were recorded for statistical analysis. The implantable cardioverter-defibrillator (ICD) devices were routinely interrogated whenever significant events relevant to ventricular tachycardia or ICD shock delivery happened and also at 6-month intervals. Patients were considered to have hypertension if their blood pressure was  $\geq 140/90$  mm Hg or if they were taking any antihypertensive medication. Diabetes mellitus was defined as fasting blood glucose level of 126 mg/dl or higher and treatment with antidiabetic drugs. All patients were given standard therapy for HF, including diuretics, beta-blockers, digitalis, and angiotensin-converting enzyme inhibitors (ACEI). None of the women received bromocriptine treatment.

### 2.2 | Electrocardiographic evaluation

A standard 12-lead surface electrocardiogram (25 mm/s and 10 mm = 1 mV) in the supine position was obtained from all patients on the first admission. Conventional ECG parameters including heart rate, PR interval, QRS duration, QT duration, bundle branch block, QRS axis, abnormal Q waves, T-wave inversion, and left ventricular hypertrophy (Sokolow & Lyon voltage amplitude criteria SV1 + RV5 or V6). The QTc was calculated using Bazett's formula. Presence of abnormal Q wave was defined as a Q wave with more than 25% of the QRS complex depth in at least two contiguous leads. Fragmented QRS was defined as the presence of various RSR' patterns (QRS duration < 120 ms) with or without Q wave, which include an additional R wave (R' prime) or notching of the R wave or S wave, or the presence

of more than one R' (fragmentation) without typical bundle branch block. An example for fQRS on ECG is shown in Figure 1. The 12-lead ECG analysis was performed by two independent readers blinded to the patient clinical and echocardiographic findings. There was 96.5% concordance for the ECG signs including frQRS. When there was a disagreement, the conclusion was achieved by mutual agreement.

### 2.3 | Statistical analysis

Statistical analysis was performed using the SPSS 20.0 Statistical Package Program for Windows (SPSS, Inc.). Continuous variables were presented as mean  $\pm$  SD and median with interquartile ranges of appropriate and categorical variables as frequency and percentage. Kolmogorov–Smirnov test was used to test normality of distribution. Differences between groups were evaluated by using Student's *t* test for normally distributed variables and Mann–Whitney *U* test for variables without normal distribution. The chi-square or Fisher's exact test was used to compare categorical variables as appropriate. The univariate and multivariate logistic regression (LR) analyses were used to detect the predictors for LV recovery. Survival estimates were calculated by the Kaplan–Meier method, and the long-rank test was used for comparison. A *p*-value  $<$  .05 (using a two-sided test) was considered significant.

## 3 | RESULTS

### 3.1 | Patient demographics

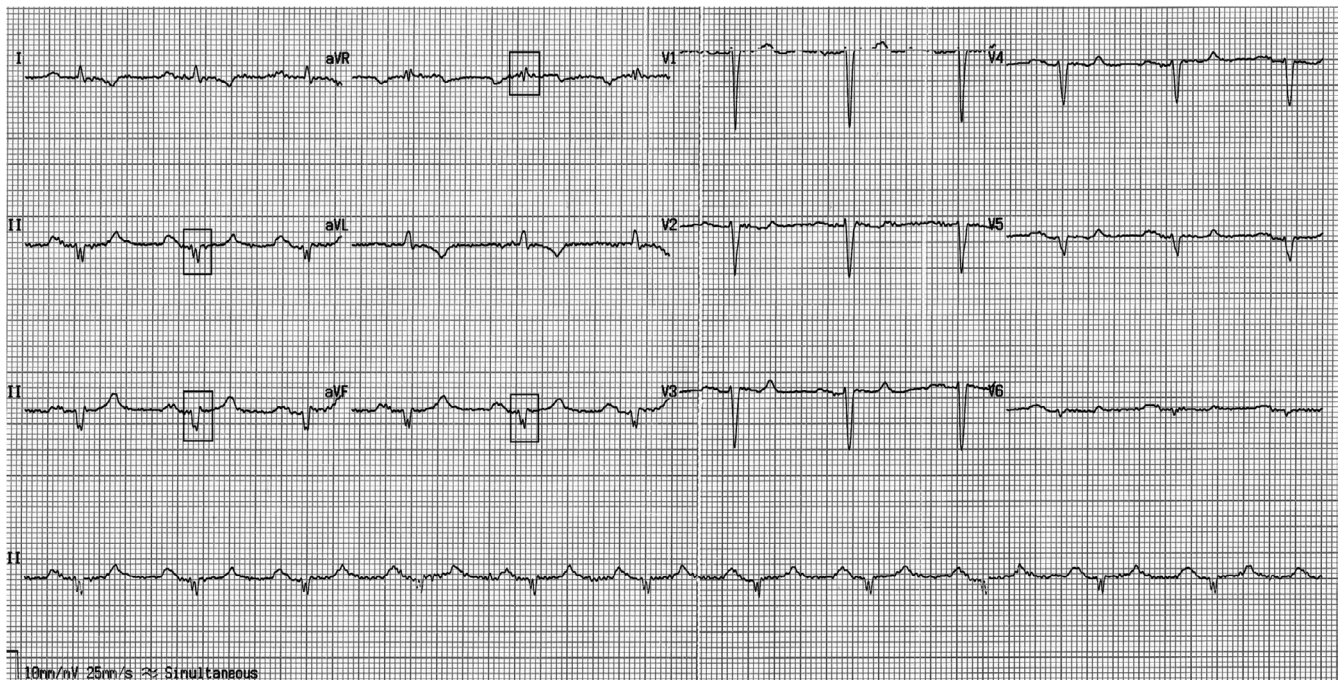
A total of 90 patients diagnosed with PPCM were enrolled in our study. The median follow-up period of was 67.0 (12.0–192.0) months.

Baseline clinical, demographical, ECG, and echocardiographic characteristics of the study population according to the presence of fQRS were described in Table 1. The mean age of the study population was  $34.7 \pm 6.5$  years old. fQRS was detected in 57(63.3%) of total patients. Among the 90 patients involved in the study, 18.0% had a history of hypertension; a total of 10.1% had a family history of dilated cardiomyopathy, around 3.0% were diabetic, a total of 13.1% were dyslipidemic, 3.4% had a history of atrial fibrillation (AF), and 7.9% had a history of embolic events. No significant difference between the two groups in terms of age and co-morbidities such as hypertension, dyslipidemia, diabetes mellitus, history of embolic events, AF, and family history of dilated cardiomyopathy was noted.

The majority of women were treated with optimal therapy for HF (beta-blockers and ACEI/angiotensin receptor blockers [ARBs]). No significant differences in medical treatment after diagnosis between the two groups were observed concerning use of beta-blockers and ACEI/ARBs. The early beginning of bromocriptine treatment in PPCM patients has been recommended; however, none of the PPCM patients received bromocriptine in our study.

### 3.2 | Comparison between the LV recovery and nonrecovery group

Of the 90 patients, 54 (60%) had persistent LV systolic dysfunction at their last follow-up (nonrecovery group). There were 36 (40%) patients who had LV recovery with improvement in cardiac symptoms at the follow-up period. In the nonrecovery group, there were six deaths during follow-up (five from progressive LV systolic dysfunction and one from thromboembolism). During the follow-up period, one left ventricular assist device implantation



**FIGURE 1** Examples of fQRSs in our patients with PPCM

	Total, n = 90	fQRS (+), n = 57	fQRS (-), n = 33	p value
Age at diagnosis	34.7 ± 6.5	35 ± 6.1	34.2 ± 7.4	.608
Hypertension	16 (18%)	8 (14.3%)	8 (24.2%)	.237
Hyperlipidemia	12 (13.5%)	6 (10.7%)	6 (18.2%)	.319
Diabetes mellitus	3 (3.4%)	3 (5.4%)	0 (0%)	.176
Smoking	1 (1.1%)	1 (1.8%)	0 (0%)	.547
Family history of cardiomyopathy	9 (10.1%)	7 (12.5%)	2 (6.1%)	.330
Embolic events	7 (7.9%)	6 (10.7%)	1 (3.0%)	.193
Atrial fibrillation	3 (3.4%)	2 (3.6%)	1 (3.0%)	.891
Echocardiographic parameters				
LVEDD (mm)	57.0 ± 5.2	57.6 ± 5.0	56 ± 5.5	.165
LA diameter (mm)	38.0 ± 6.4	39.2 ± 6.2	35.2 ± 6.4	.091
LVEF (%)	29.7 ± 7.5	28.0 ± 7.6	32.5 ± 6.7	<b>.007</b>
LVESD	43.6 ± 6.3	44.3 ± 7.3	43 ± 5.2	.667
LV nonrecovery	54 (60%)	42 (73.7%)	12 (36.4%)	<b>&lt;.001</b>
Electrocardiographic parameters				
Heart rate	84.4 ± 18.3	85.8 ± 21.5	82.0 ± 10.4	.352
Duration of PR interval	180.3 ± 36.3	185.3 ± 35.4	171.9 ± 36.6	.094
Duration of QRS interval	105.7 ± 13.6	109.7 ± 12.0	98.7 ± 13.4	<b>&lt;.001</b>
Duration of QTc interval	466.1 ± 33.4	472.4 ± 33.1	455.2 ± 31.5	.018
RBBB	5 (5.6%)	3 (5.3%)	2 (6.1%)	.874
LBBB	1 (1.1%)	1 (1.8%)	0 (0%)	.444
Left ventricular hypertrophy	11 (12.2%)	10 (17.5%)	1 (3.0%)	<b>.043</b>

Note: Data are presented mean ± SD or n (%). Bolded values indicate statistical significance ( $p < .05$ ).

Abbreviations: fQRS, fragmented QRS complex; LA, Left atrium diameter; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; RBBB, right bundle branch block.

and seven embolic events (five among nonrecovery group and two among recovery group) occurred in patients. Clinical, echocardiographic data, and electrocardiographic parameters of the patients according to the recovery and nonrecovery groups are presented in Table 2. The LVEF values were significantly lower, and LVEDD values were significantly higher in the nonrecovery group ( $26.6 \pm 7.1$  vs.  $34.3 \pm 5.8$ ,  $p < .001$ ,  $58.5 \pm 5.0$  vs.  $54.7 \pm 4.8$ ,  $p = .001$ , respectively). While ECG findings were similar regarding the baseline rhythm and heart rate, there were significant differences between recovery and nonrecovery groups due to presence of fQRS complex (15(41.7%) versus 42(77.8%),  $p = .001$ , respectively).

### 3.3 | Predictors for LV nonrecovery

A comparison of these groups with univariate and multivariate logistic regression analysis is presented in Table 3. The variables which

**TABLE 1** Baseline demographical, clinical, electrocardiographic, and echocardiographic characteristics of the study population

showed to be significant ( $p < .05$ ) in the univariate analysis were included in multivariate logistic regression analysis. Only LVEF and fQRS were identified as independent predictors of LV nonrecovery in patients with PPCM (odds ratio OR: 5.546, 95% confidence interval CI: 0.792–0.979,  $p = .019$  and OR: 5.986, 95% CI: 1.313–11.787,  $p = .014$  respectively).

Kaplan–Meier survival curve showed that LV nonrecovery developed more frequently in patients with fQRS. (log-rank,  $p = .0035$ ) (Figure 2).

## 4 | DISCUSSION

Our study results showed that the presence of fQRS on standard 12-derivation ECG at baseline was an independent long-term predictor of LV nonrecovery in PPCM patients. Also, we demonstrated that baseline LVEF at presentation was lower in patients with fQRS.



**TABLE 2** Comparison of patients who recovered and patients who did not recover from peripartum cardiomyopathy

	Total, n = 90	Recovery, n = 36 (40%)	Nonrecovery, n = 54 (60%)	p value
Age at diagnosis	34.7 ± 6.5	35 ± 6.4	34.5 ± 6.7	.766
Hypertension	16 (18%)	5 (13.9%)	11 (20.8%)	.575
Hyperlipidemia	12 (13.5%)	3 (8.3%)	9 (17.0%)	.347
Diabetes mellitus	3 (3.4%)	0 (0%)	3 (0%)	.206
Smoking	1 (1.1%)	0 (0%)	1 (1.9%)	.341
Family history of cardiomyopathy	9 (10.1%)	3 (8.3%)	6 (11.3%)	.734
Embolic events	7 (7.9%)	2 (5.6%)	5 (9.4%)	.697
Atrial fibrillation	3 (3.4%)	0 (0%)	3 (5.7%)	.269
Echocardiographic parameters				
LVEDD (mm)	57.0 ± 5.2	54.7 ± 4.8	58.5 ± 5.0	<b>.001</b>
LA diameter (mm)	38.0 ± 6.4	35.8 ± 6.8	39.5 ± 5.8	.091
LVEF (%)	29.7 ± 7.5	34.3 ± 5.8	26.6 ± 7.1	<b>&lt;.001</b>
LVESD	43.6 ± 6.3	40.8 ± 4.3	46.2 ± 6.9	.065
Electrocardiographic parameters				
fQRS	57 (63.3%)	15 (41.7%)	42 (77.8%)	<b>.001</b>
Heart rate	84.4 ± 18.3	80.0 ± 6.7	87.4 ± 22.6	.061
Duration of PR interval	180.3 ± 36.3	174.4 ± 37.8	184.3 ± 34.9	.211
Duration of QRS interval	105.7 ± 13.6	102.5 ± 12.9	107.8 ± 13.7	.074
Duration of QTc interval	466.1 ± 33.4	456.3 ± 32.0	472.7 ± 33.0	<b>.022</b>
RBBB	5 (5.6%)	0 (0%)	5 (9.3%)	.081
LBBB	1 (1.1%)	0 (0%)	1 (1.9%)	.414
Left ventricular hypertrophy	11 (12.2%)	7 (19.4%)	4 (7.4%)	.108

Note: Data are presented mean ± SD or n (%). Bolded values indicate statistical significance ( $p < .05$ ).

Abbreviations: fQRS, fragmented QRS complex; LA, left atrium diameter; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; RBBB, right bundle branch block.

Although ECG abnormalities appear to be commonly visible at the time of diagnosis of PPCM, there are not enough studies on the value of the presence of fQRS on prognosis.

PPCM is an idiopathic cardiomyopathy with a significant probability of myocardial recovery. The exact pathophysiologic mechanism that leads to PPCM remains unknown, but multiple possible aetiologies including viral myocarditis, nutritional deficiencies, autoimmunity, increased oxidative stress and inflammation, vascular dysfunction, hormonal insults, and underlying genetics have been suggested in the pathogenesis of cardiomyopathy (Goland et al., 2009). Although clinical presentations and outcomes of PPCM are highly heterogeneous, previous studies have reported that left ventricular recovery usually occurs within 6 months of diagnosis in most of the patients. The recovery rate from PPCM appears to be widely heterogeneous. Unfortunately, there are no specific and exact predictors of whether or not myocardial recovery will

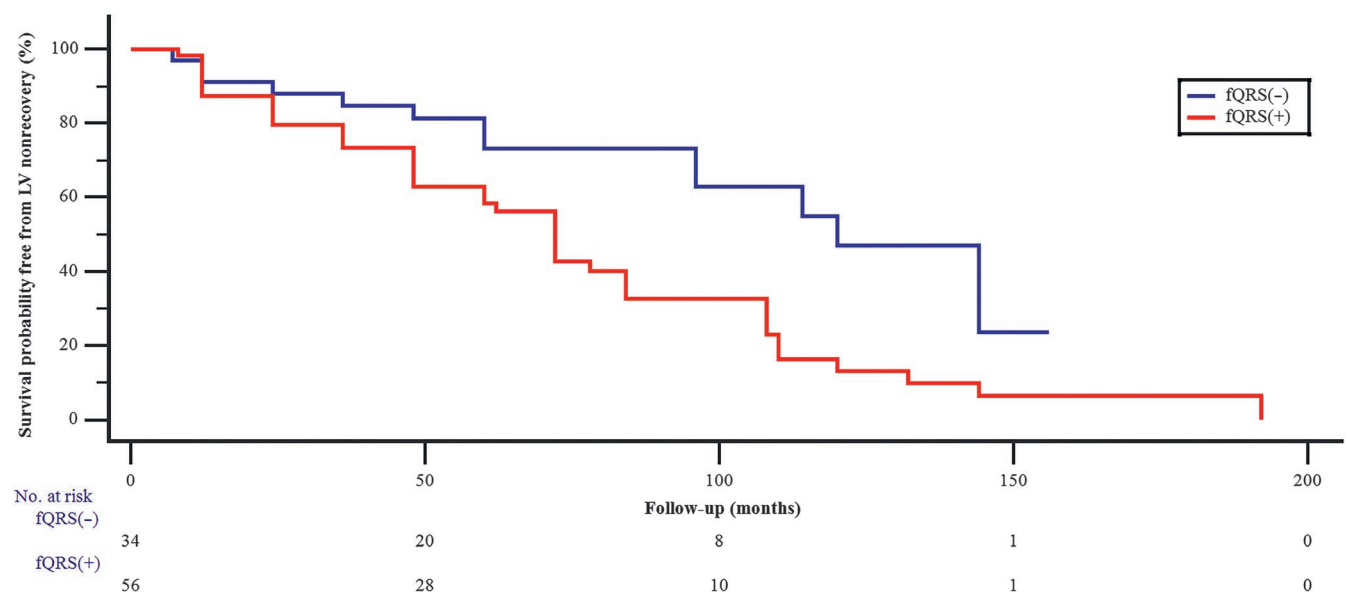
occur. It is known that persistent LV systolic dysfunction can be associated with adverse cardiac events, including lethal ventricular tachyarrhythmias, thromboembolic complications, and even death (Amos, Jaber, & Russell, 2006). Various factors that predict outcomes in patients with PPCM have previously been proposed but not validated. These factors include decreased LVEF and degree of LV dilatation at diagnosis, presence of LV thrombus, lower systolic blood pressure, and higher resting heart rate (Sliwa et al., 2000). To our knowledge, there is a lack of ECG data to predict prognosis in PPCM, and scarce data on its use in the risk stratification of high-risk PPCM patients. Previous studies showed that ECG abnormalities were commonly found at baseline in PPCM patients (Li, Li, & Long, 2016; Tibazarwa et al., 2012). Hoewelmann et al. (2019) showed that a prolonged QTc and sinus tachycardia at baseline were independent predictors of poor outcome in PPCM. However, fQRS did not find to be a predictor of poor outcome

**TABLE 3** Univariate and multivariate logistic regression analysis for prediction of study endpoint

Variable	Univariate analysis			Multivariate analysis		
	OR	% CI	p value	Adjusted OR	% CI	p value
Age	0.990	0.929–1.056	.763			
Hypertension	1.624	0.512–5.151	.411			
Hyperlipidemia	2.250	0.565–8.965	.250			
Smoking	1.042	0.352–2.101	.964			
Diabetes mellitus	1.163	0.378–3.143	.998			
Thromboembolic events	1.771	0.324–9.671	.509			
Family history of cardiomyopathy	1.404	0.328–6.020	.648			
Electrocardiographic parameters						
AF	1.163	0.361–2.943	.999			
Duration of PR interval	1.008	0.996–1.020	.209			
Duration of QRS interval	1.029	0.997–1.063	.077			
Duration of QTc interval	1.016	1.002–1.030	.026	1.712	0.825–2.611	.192
RBBB	1.187	0.434–1.981	.999			
LBBB	1.097	0.457–1.728	.912			
fQRS	4.900	1.948–12.324	.001	3.850	1.062–9.947	.002
Heart rate(bpm)	1.025	0.998–1.052	.067			
LVH	0.331	0.089–1.229	.099			
Echocardiographic parameters						
LVEDD (mm)	1.165	1.057–1.284	.002			
LVESD (mm)	1.185	0.976–1.439	.087			
LA (mm)	1.101	0.983–1.233	.098			
LVEF (%)	0.838	0.772–0.910	<.001	1.717	1.306–2.380	.001

Note: Bolded values indicate statistically significant odds ratio.

Abbreviations: CI, confidence interval; fQRS, fragmented QRS complex; LA, left atrium; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; RBBB, right bundle branch block.



**FIGURE 2** Kaplan–Meier curve analysis of the study endpoint. Kaplan–Meier survival curve showed that LV nonrecovery developed more frequently in patients with fQRS. (log-rank,  $p = .0035$ )

in this study (Hoelmann et al., 2019). This situation explained by the large number of patients with PPCM who recover their LV function. Previous studies have shown that fQRS is associated with sudden cardiac death in patients with cardiomyopathy, but there are not enough data to prove this in patients with PPCMP. fQRS, as a marker of depolarization abnormality, indicates a conduction delay and heterogeneity in ventricular activation as a result of myocardial ischemia, fibrosis, and scar tissue. fQRS has been described in ventricular scar formation occurring after myocardial infarction as well as in various cardiovascular pathologies such as ventricular aneurysm, idiopathic dilated cardiomyopathy, myocardial fibrosis, sarcoidosis, Brugada syndrome, arrhythmogenic right ventricular dysplasia, and myocarditis (Canpolat et al., 2013; Canpolat, Yayla, Aras, Topaloglu, & Aydogdu, 2015; Das et al., 2006, 2010; Ozcan et al., 2014; Sha et al., 2011). The diagnostic accuracy of fQRS has been investigated by Das et al. (2010, 2008) in two separate studies in which they have shown that fQRS had higher sensitivity and negative predictive value than Q wave, and fQRS was highly specific for myocardial scar. Canga et al. (2013) suggested that the fQRS might represent increased myocardial fibrosis and LV diastolic and systolic dysfunction. Also, Ratheendran et al. (2019) showed that fQRS could be used as an indirect marker to predict the presence of fibrosis in hypertrophic cardiomyopathy. In a cardiac magnetic resonance imaging-based study, Haghikia et al. (2015) confirmed that myocardial fibrosis and involvement of right ventricular have a poor prognosis in terms of cardiac recovery. Thus, patients with fQRS exposed to advanced LV remodeling possibly because of higher extent of myocardial fibrosis. In our study, the presence of fragment qrs was significantly higher in the LV nonrecovery group. Also, LVEF values were substantially lower in patients with fQRS.

In the light of these considerations, we speculated that the use of fQRS as a costless and feasible electrocardiographic tool, which conclusively shows myocardial fibrosis on 12 lead ECG, seems to be a predictor of persistent LV dysfunction and long-term all-cause mortality in PPCMP patients. Therefore, we concluded that frQRS might be of value in the stratification of the high-risk patients whom LV dysfunction will persist and may guide us to select patients for more aggressive therapy more accurately. Further investigations on independent multicenter cohorts should be performed to validate our findings.

## 5 | LIMITATIONS

Our study has several limitations. First, it is a cross-sectional study with small sample size, so further prospective investigations on larger cohorts may precisely highlight the association of fQRS with LV nonrecovery. Second, rather than a cause-effect (causal) relation, we only showed an association between fQRS and LV nonrecovery. A prospective study with magnetic resonance imaging and fQRS recordings may allow better assessment of the nonrecovery risk in association with myocardial fibrosis.

## 6 | CONCLUSION AND FUTURE PERSPECTIVES

In conclusion, the presence of frQRS, which is a simple, inexpensive and readily available standard 12-lead ECG sign, predicts LV nonrecovery in patients with PPCM. This relationship may allow us to closely follow-up high-risk patients for nonrecovery. Further prospective studies on independent multicenter cohorts are needed to elucidate and confirm this important association between fQRS and LV nonrecovery in PPCM patient population.

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None

## CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

## ORCID

Bahar Tekin Tak  <https://orcid.org/0000-0003-0971-597X>

Serkan Cay  <https://orcid.org/0000-0002-5476-1214>

Firdevs Aysenur Ekizler  <https://orcid.org/0000-0002-3988-6828>

Elif Hande Ozcan Cetin  <https://orcid.org/0000-0001-5969-2345>

Hilal Erken Pamukcu  <https://orcid.org/0000-0001-8116-5090>

Habibe Kafes  <https://orcid.org/0000-0002-9967-0287>

Nedret Ulvan  <https://orcid.org/0000-0001-5295-5704>

Ozcan Ozeke  <https://orcid.org/0000-0002-4770-8159>

Firat Ozcan  <https://orcid.org/0000-0002-3181-6876>

Serkan Topaloglu  <https://orcid.org/0000-0002-5388-2030>

Dursun Aras  <https://orcid.org/0000-0001-6020-8098>

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