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## ■ Original Article

# The prognostic role of fragmented QRS complex in acute myocarditis

## *Akut miyokarditte fragmante QRS kompleksinin prognostik rolü*

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### ABSTRACT

**Aim:** Although a fulminant course of the myocarditis is difficult to predict, it may lead to acute heart failure and death. Previous studies have demonstrated that reduced left ventricular systolic function and prolonged QRS duration can predict the fulminant course. This study aimed to identify whether fragmented QRS complex (fQRS) could also be predictive of fulminant disease in this population.

**Material and Methods:** We retrospectively included 156 patients diagnosed with acute myocarditis. They were divided into the fulminant group (n = 18) and the non-fulminant group (n = 138). Multivariate logistic regression analysis was used to identify the independent factors predictive of fulminant disease.

**Results:** Fragmented QRS developed in 11 (61%) in the fulminant group and only 10 patients (7%) in the non-fulminant group (p < 0.001). Patients with fulminant myocarditis had a higher mortality rate than those with non-fulminant disease (44.6% vs. 0%, p < 0.001). Multivariate analysis revealed that the presence of fQRS (p=0.019), longer Tpe/qt ratio (p=0.022) and clinical heart failure (<0.001) were significant predictors associated with a fulminant course of myocarditis.

**Conclusion:** The presence of fQRS complex, as a simple and feasible electrocardiographic marker, seems to be a novel predictor fulminant myocarditis. This simple parameter may be used in identifying patients at high risk for fulminancy and so early mechanical support could provide improved patient outcomes.

**Keywords:** acute myocarditis; fragmented QRS; Tp-e/QT ratio; heart failure.

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## ÖZ

**Amaç:** Miyokarditin fulminan seyrini tahmin etmek zor olsa da, akut kalp yetmezliği ve ölüme neden olabilir. Önceki çalışmalar, sol ventrikül sistolik fonksiyonunun azaldığını ve uzamış QRS süresinin fulminan seyrini öngörebileceğini göstermiştir. Bu çalışma, fragmante QRS kompleksinin (fQRS) de bu popülasyondaki fulminan hastalığın öngörüsü olup olmadığını belirlemeyi amaçlamıştır.

**Gereç ve Yöntemler:** Akut miyokardit tanısı almış 156 hastayı retrospektif olarak dahil ettik. Hastalar fulminan (n = 18) ve fulminan olmayan gruba (n = 138) ayrıldı. Fulminan hastalığı öngören bağımsız faktörleri tanımlamak için çok değişkenli lojistik regresyon analizi kullanılmıştır.

**Bulgular:** Fragmante QRS fulminan grupta 11 (% 61), fulminan olmayan grupta sadece 10 hasta (% 7) gelişti (p <0.001). Fulminan miyokardit hastaları fulminan olmayan hastalardan daha yüksek mortalite oranına sahipti (% 44.6 vs.% 0, p <0.001). Çok değişkenli analiz, fQRS (p = 0.019), daha uzun Tp-e / QT oranının (p = 0.022) ve klinik kalp yetmezliğinin (<0.001) varlığında, fulminan bir miyokardit seyri ile ilişkili önemli belirleyiciler olduğunu ortaya koydu.

**Sonuç:** Basit ve uygulanabilir bir elektrokardiyografik belirteç olarak fQRS kompleksinin varlığı, fulminan miyokarditin yeni bir belirleyicisi olarak görünmektedir. Bu basit parametre, uygunluk riski yüksek olan hastaları belirlemek için kullanılabilir ve bu nedenle erken mekanik destek daha iyi hasta sonuçları sağlayabilir.

**Anahtar kelimeler:** akut miyokardit; fragmante QRS; Tp-e / QT oranı; kalp yetersizliği

## Introdcution

Myocarditis is the inflammation of heart muscle. The pathogenesis of myocarditis is the the injury of heart muscle after the activation of immune system by a cause. Generally myocarditis occurs as a response of immune system to external antigens such as viruses, bacterias, toxins, parasites etc. or autoimmune response to self antigens[1]. The incidence of myocarditis vary between studies because of the difference between diagnostic criterias. The incidence of overall population is supposed to be between 8-10/100.000. It can be thought that the incidence could be higher because of undiagnosed subclinical cases and deaths ocured before diagnose. Fabre A. et al found the incidence of myocarditis 8.6% in an autopsy study of young adults who suffered sudden death [2]. Nugent AW et al. showed that 10-40% of idiopathic dilate cardiomyopathies between children were because of myocarditis[3]. In the study of Towbin JA et al. about children with dilated cardiomyopathy 46% of cases could be attributed to prior myocarditis [4]. 15% of patients with pericarditis also have myocarditis. The incidence of myocarditis is increasing by the time with use of newer moleculer techniques. In the biopsies of patient with clinical myocarditis but without immune cells or myocyte necrosis which is a must for diagnoses of myocarditis according to Dallas criteria cardiotropic viral agents and upregulation of immune markers suggesting that a postviral immun response is the ethiologic cause of myocarditis [5, 6].

A catastrophic form of myocarditis is fulminant myocarditis. 10% of myocarditis patients develop fulminant myocarditis. Patient with fulminant myocarditis usually have global

hypofunction of heart with increased wall thickness (because of myocardial edema). Hypotension and hemodynamic instability is common and vasopressor agents and mechanical support are often required. Depending on clinical presentation and etiological cause prognosis of myocarditis may vary in a big range. In one study 11 year follow up of patients with fulminant myocarditis transplant free survival rate was found as 93% [7]. Shigeru kato et al. and many other investigators showed that C-reactive protein, creatine kinase concentration, decreased ejection fraction and interventricular conduction disturbances at admission are predictors of fulminant myocarditis [8, 9].

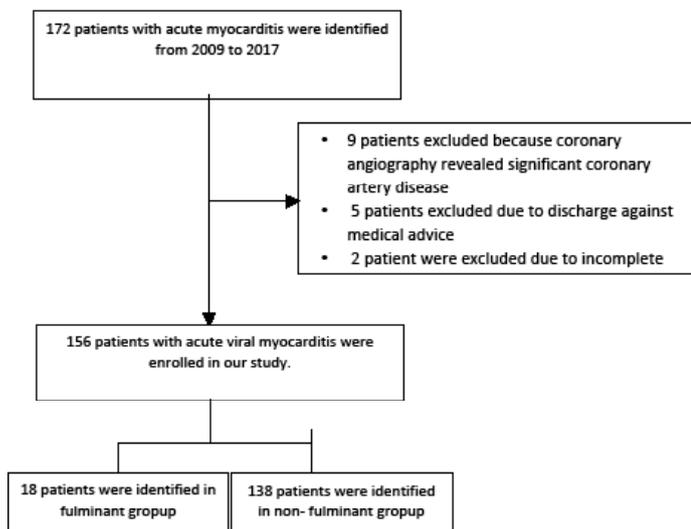
Fragmented QRS complex (fQRS) on a routine 12-lead electrocardiogram, as a marker of depolarization abnormality, represents the conduction delay in myocardial activation because of myocardial scarring and suggested to be a novel indicator of mortality and malignant arrhythmic events in various cardiovascular diseases[10-12]. However, there are scarce data on the prognostic role of fQRS in cardiac arrhythmias and mortality in myocarditis. Therefore, we aimed to evaluate the prognostic role of fQRS in development of fulminant myocarditis.

## Material and Methods

### Study population

Between 2009 and 2017, 172 patients with a diagnosis of acute myocarditis at a tertiary medical center in Turkey were enrolled in a retrospective medical records review; patients under the age of 15 years were excluded. A diagnosis of acute myocarditis was based on the clinical features of

acute heart failure following recent flu-like symptoms, or according to the Dallas criteria. Of these 172 patients, two patient was excluded due to incomplete data, 5 were excluded due to discharge against medical advice, and 9 were excluded because coronary angiography revealed significant obstructive coronary artery disease (Figure 1). Therefore, 156 patients with acute viral myocarditis were evaluated. These 156 patients were divided into the fulminant group (n=18) and the non-fulminant group (n=138). The definition of a fulminant course of acute myocarditis was the presence of severe hemodynamic compromise requiring inotropic agents or ventricular assist devices, such as an intra-aortic balloon pump (IABP), left ventricular assist device, or extracorporeal membrane oxygenation (ECMO).



**Figure 1.** Study cohort

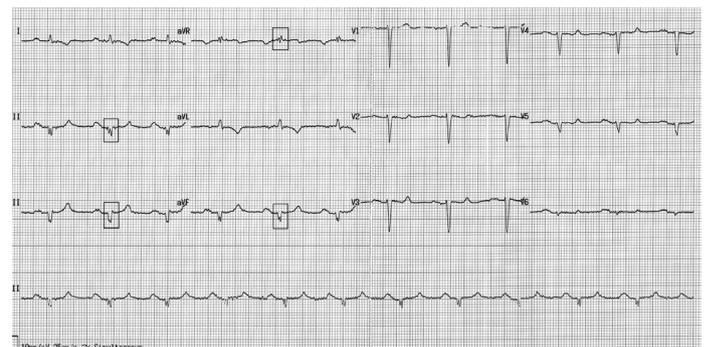
### **Patient characteristics**

Demographic, ECG, and echocardiographic data of all patients were collected from clinical follow-up visits, patients' files, and the electronic database. Informed consent was taken from each patient before enrollment. The study was in compliance with the principles outlined in the Declaration of Helsinki and approved by institutional ethics committee.

### **Electrocardiography**

The 12-lead electrocardiogram (ECG) was recorded at a paper speed of 50 mm/sec (Hewlett Packard, Page-writer, USA) in the supine position. ECGs were performed while the patient at rest and at 8:00-10:00 AM in the morning. All of the ECGs were scanned and transferred to a personal computer to decrease the error measurements, and then used for x400% magnification by Adobe Photoshop software. fQRS was defined as the presence of various RSR' patterns with different morphologies of QRS complexes with or without the Q wave. Various RSR' patterns included an additional R wave (R'), notching of the R

wave or the S wave, or the presence of >1 R' (fragmentation) without a typical bundle branch block in 2 contiguous leads corresponding to a major lead set for major coronary artery territory (Figure 2). Any QRS morphology with a QRS duration >120 ms, including bundle branch block or intraventricular conduction delay, was excluded. ECG measurements of QT and Tp-e intervals were performed by two cardiologists who were blinded to the patient data. Subjects with U waves on their ECGs were excluded from the study. A mean value of three readings was calculated for each lead. The QT interval was measured from the beginning of the QRS complex to the end of the T wave and corrected for heart rate using the Bazett formula:  $cQT = QT\sqrt{(R-R \text{ interval})}$ . The Tp-e interval was defined as the interval from the peak of T wave to the end of T wave. Measurements of the Tp-e interval were performed from precordial leads. The Tp-e/QT ratio was calculated from these measurements. Interobserver and intraobserver coefficients of variation were 2.1% and 2.9%, respectively.



**Figure 2.** Examples of fQRSs in our patients with fulminant myocarditis.

### **Echocardiography**

All patients underwent standard trans-thoracic echocardiography at the time of presentation. Various parameters, including the left ventricular ejection fraction (LVEF), left atrium (LA) diameter, left ventricular endsystolic dimensions (LVEDs), thicknesses of the left ventricular post wall (LVPW), and the maximal interventricular septum (IVS), were calculated by using linear measurements.

### **Laboratory Assessments**

Peripheral venous blood samples were drawn from the antecubital vein after 12-hour of fasting in the morning. Blood samples were taken into standardized tubes containing dipotassium ethylenedinitro tetraacetic acid (EDTA) for complete blood count (CBC). Coulter Counter LH Series (Beckman coulter Inc, Hialeah, Florida) was used for CBC. Plasma levels of triglyceride, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), glucose, creatinine were evaluated using an automated chemistry analyzer (Abbott Aeroset, USA) using commercially available kits (Abbott, USA). Local ethics committee approved the study and informed consent was obtained from participant(s)



### Statistical Analysis

In all statistical analysis SPSS 21.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA) was used. In order to test normality of distribution Kolmogorov-Smirnov test was used. Quantitative variables with a normal distribution were specified as the mean ± standard deviation. Categorical variables were shown as number and percentage values. Differences between groups were evaluated by using Student's t-test. Categorical variables were compared with Chi-square test. A univariate logistic regression analysis of the various clinical variables was performed to determine the predictors of a fulminant course in patients with acute myocarditis. The variables selected in the multivariate logistic analysis were those with a p-value < 0.05 in the univariate models. A two-sided p-value < 0.05 was considered statistically significant.

### Results

The study population was categorized into 2 groups as according to the presence of fulminancy (n=18) or not (n=138). Baseline clinical characteristics and electrocardiographic findings of the study population were shown in Table 1. There

was no significant difference between groups regarding gender, white blood cell count, CRP, creatinin, troponin and glucose levels (P > 0.05). It was demonstrated that Tp-e interval, QT interval and QRS duration are also similar between groups (P > 0.05). The mean PR interval (140 ms vs. 160 ms, p < 0.001), the mean QTc interval (426 ms vs. 481 ms p < 0.001), Tp-e/QT ratio (0.20 vs. 0.24, p = 0.010) were both significantly longer in the fulminant group than those in the non-fulminant group. Fragmented QRS developed in 11 (61%) in the fulminant group and only 10 patients (7%) in the non-fulminant group (p < 0.001). We found trends toward higher heart rates [70 (65-85) vs. 79 (63-86) beats per min; p = 0.12] in the fulminant group. With respect to echocardiographic findings, the LVEF was significantly lower in the fulminant group than in the non-fulminant group [62 (55-67) vs 25(23-30); p < 0.001]. Pericardial effusion [30(21%) vs 11 (61%); p < 0.001] and cardiac tamponade [8 (5%) vs 5 (27%); p = 0.002] were seen more frequent in the fulminant group than non-fulminant group. Other parameters, such as left atrial dimensions and left ventricular systolic and diastolic dimensions, showed no statistical differences between the 2 groups.

**Table 1.** Demographical, laboratory, electrocardiographic, echocardiographic and clinical characteristics of study and control subjects

	Non-fulminant group (N = 138)	Fulminant group (N = 18)	p-value
Age (years)	28 ± (16.01)	34 ± (14.85)	0.144
Female Gender, n(%)	20 (14)	3 (16)	0.807
White Blood Cell(x103/µL)	8.8 (6.5-10.0)	8.8 (8.0-9.6)	0.267
CRP(mg/dL)	5.0 (2.0-12)	4.0 (1.4-9.0)	0.170
Creatinin (IU/L)	0.80 (0.60-0.90)	0.79 (0.90-2.08)	0.158
Glucose(mg/dL)	97 (88-100)	102 (96-106)	0.056
Troponin-I (ng/L)	0.46 (0.08-2.56)	0.49 (0.06-2.58)	0.601
HR (per minute)	70 (65-85)	79 (63-86)	0.12
QRS (ms)	92 (78-98)	101 (80-110)	0.647
PR (ms)	140 (130-160)	160 (158-170)	<0.001
QT (ms)	390 (370-402)	381 (352-401)	0.198
QTc (ms)	426 (401-447)	481 (448-503)	<0.001
Tp-e interval, ms	81 (76-84)	82 (74-101)	0.469
Tp-e/QT ratio	0.20 (0.18-0.22)	0.24 (0.20-0.26)	0.010
Tp-e/QTc ratio	0.18 (0.19-0.21)	0.17 (0.15-0.20)	0.045
Fragmente qrs n(%)	10 (7)	11 (61)	<0.001
IVS (mm)	0.8 (0.8-1.0)	0.9 (0.8-1.35)	0.267
LVPW (mm)	0.9 (0.7-1.0)	1.0 (0.8-1.5)	0.355
LA dimension (mm)	3.2 ± 0.7	3.5 ± 0.9	0.061
LVEDs (mm)	2.7 (2.4-3.5)	2.9 (1.7-3.2)	0.689
LVEDd (mm)	4.6 (4.0-5.0)	4.9 (4.5-6.5)	0.090
LVEF (%)	62 (55-67)	25 (23-30)	<0.001
Pericardial effusion n(%)	30 (21)	11 (61)	<0.001
Cardiac tamponade n(%)	8 (5)	5 (27)	0.002
Clinical heart failure n(%)	1 (0.7)	17 (94)	<0.001
ECMO- LVAD n(%)	0 (0)	16 (88)	<0.001
1 month mortality n(%)	0 (0)	8 (44.5)	<0.001

Data are given as mean ± SD or %. CRP, C-reactive protein; ECMO, Extracorporeal Membrane Oxygenation; HR, heart rate; IVS, intraventricular septum; LA, left atrium; LVEDd, end-diastolic left ventricular diameter; LVEDs, end-systolic left ventricular diameter; LVEF, left ventricular ejection fraction; LVPW, left ventricular posterior wall; LVAD, Left Ventricular Assist Device

### Clinical outcome

Among patients with fulminant myocarditis, 16 (88%) patients underwent IABP, ECMO or LVAD. Clinical heart failure were seen 17(94%) patients in fulminant group but only seen 1(0.7%) patients in non-fulminant group. Eight patients in the fulminant group died of the disease, compared with none in the non-fulminant group. These 8 patients died of cardiogenic shock, with multiple organ failure. The overall mortality was 44.5 % and was significantly higher in the fulminant group than in the non-fulminant group ( $p < 0.001$ ).

### Predictors of fulminant myocarditis

In the univariate logistic regression analysis, Tp-e/QT ratio ( $p < 0.001$ ), fragmented QRS ( $p < 0.001$ ), cardiac tamponade ( $p = 0.004$ ), LVEF ( $p = 0.035$ ), clinical heart failure ( $p < 0.001$ ) predicted the incidence of fulminant myocarditis (Table 2). The multivariate logistic regression model demonstrated that presence of fragmented qrs ( $p = 0.019$ ), higher Tp-e/QT ratio ( $p = 0.022$ ) and presence of clinical heart failure ( $p < 0.001$ ) remained as independent predictors of fulminant myocarditis (Table 2).

**Table 2.** Univariate and multivariate logistic regression analysis showing the predictors for fulminancy.

Variables	Univariable		Multivariable	
	OR ( 95 % CI)	p-value	OR ( 95 % CI)	p-value
Age	1.071 (1.032-1.113)	<0.001	1.044 (0.995-1.106)	0.144
Heart Rate	1.059 (0.914-1.195)	0.108	-	-
Tp-e/QT ratio	1.062 (1.034-1.091)	<0.001	1.024 (1.017-1.071)	0.022
Fragmented QRS	20.114 (6.398-63.239)	<0.001	6.825 (1.370-13.071)	0.019
Cardiac Tamponade	6.250 (1.783-21.911)	0.004	5.337 (0.711-40.072)	0.104
LVEF, (%)	1.150 ((1.034-1.191)	0.035	1.013 (0.896-1.123)	0.234
Clinical Heart Failure	2329 (139-38966)	<0.001	999 (35-28013)	<0.001

Data are given as mean  $\pm$  SD or %. CI, confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio.

### Discussion

This study assessed the potential of fQRS on surface ECG to play a role in development of fulminant myocarditis. According to multivariate logistic regression analysis presence of fQRS, Tp-e/QT ratio and clinical heart failure were found to be related with fulminant course of myocarditis.

Mortality rates of fulminant myocarditis varies according to different studies. In a most recent trial by Ammirati et al. which including 187 patients with a diagnosis of acute myocarditis, the composite of mortality and heart transplantation was 25.5% at fulminant group and 0% at non-fulminant group ( $p < 0.0001$ ), respectively [13]. In an earlier study by McCarthy et al. fulminant myocarditis was an independent predictor of survival after adjustments were made for age, histopathological findings, and hemodynamic variables[7]. Because of this high mortality rates and worse prognosis with fulminant myocarditis early recognition of patients at the risk of progression to fulminant forms is essential. Acute myocarditis evolving into fulminant form on echocardiogram, ST-T segment abnormalities ECG, high release of troponins, hypotension, and frequent arrhythmia[14].

Several studies have investigated the potential risk factors for fulminant myocarditis. Some studies focused on serum inflammatory marker levels such as high C-reactive protein and interleukins, some studies demonstrated extensive myocardial injury with measurement of serum creatine kinase MB isoenzyme to predict development of fulminant course of

myocarditis[8, 9, 15]. Apart from serum biomarkers, changes in electrocardiographic and electroechocardiographic findings have also been investigated. Intraventricular conduction disturbances and QRS complex widths  $> 120$  ms at admission have been reported in patients with fulminant myocarditis; these QRS complex widths were longer than those in the non-fulminant group[8]. Similarly in a more recent trial by Hung et al. demonstrated that wider QRS durations ( $133.22 \pm 45.85$  ms vs.  $92.81 \pm 15.56$  ms,  $p = 0.030$ ) and longer QTc intervals ( $482.78 \pm 69.76$  ms vs.  $412.00 \pm 33.31$  ms,  $p = 0.016$ ) were significant predictors associated with a fulminant course of myocarditis[16]. Parallel to these studies in our study we found that longer QTc interval and Tp-e/QT ratio in patients with fulminant myocarditis compared to non-fulminant ones.

Fragmented QRS complex (fQRS), which was defined by the presence of changes in QRS morphology including an additional R wave, a notching of the R wave or S wave, or the presence of  $>1$  additional R wave in 2 contiguous leads is a novel electrocardiographic parameter to define high risk patients in various circumstances[17]. It has been related to a number of cardiac diseases including Brugada syndrome, ventricular aneurysm, dilated cardiomyopathy, essential hypertension, coronary artery disease, tetralogy of Fallot, takotsubo cardiomyopathy, cardiac AL amyloidosis, heart failure and acute aortic dissection[18-21]. It is now clearly demonstrated that fQRS is associated with myocardial fibrosis and systemic inflammation. Acute myocarditis, which is an



inflammation of myocardium may cause fragmentation of QRS with a high probability. Also we found a significantly more number of patients with fQRS in fulminant group compared to non-fulminant group (61% vs 7%,  $p < 0.001$ ).

### Study Limitations

There were several potential limitations to our study. First, the diagnosis of acute myocarditis was made based upon a clinical diagnosis, and not all patients received routine endomyocardial biopsy to confirm the diagnosis. This study is the limited number of patients that may have affected the statistical power of the study. Nevertheless, the reason was due to the low prevalence of fulminant myocarditis. This study involved a retrospective case-control study and the patients were not followed for future arrhythmic episodes that the relation between ventricular arrhythmias with Tp-e/QTc ratio and fQRS. Long-term follow-up and large-scale prospective studies are needed to investigate the relationship between the value of fragmented QRS and Tp-e/QT ratio and fulminant myocarditis.

### Conclusion

Patients with fulminant myocarditis had higher in-hospital mortality rates than non-fulminant patients. Early and aggressive mechanical circulatory support might decrease the associated mortality rate. Several clinical and electrocardiographic factors are related to fulminant course in acute myocarditis setting. In our study presence of clinical heart failure, fragmented QRS and Tp-e/QT ratio were found to be related with fulminant myocarditis.

### Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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