Relationship between presence of fragmented QRS on 12-lead electrocardiogram on admission and long-term mortality in patients with non-ST elevated myocardial infarction

ST yükselmesiz miyokart enfarktüslü hastalarda başvurudaki 12-derivasyonlu elektrokardiyografide fragmente QRS varlığı ile uzun dönem mortalite arasındaki ilişki

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ABSTRACT

Objectives: Fragmented QRS (fQRS) as a predictor of cardiac events in coronary artery disease has previously been reported. In this study, we hypothesized that presence of fQRS on a 12-lead electrocardiogram (ECG) on admission would be predictive of adverse outcomes in non-ST elevated myocardial infarction (NSTEMI).

Study design: A total of 149 NSTEMI patients (112 male, 37 female) were retrospectively analyzed. The fQRS pattern was defined as the presence of an additional R', notching in the nadir of the S wave, fragmentation of the RS or QS complexes in 2 contiguous leads corresponding to a major coronary artery territory. The relationship between presence of fQRS on admission on a 12-lead ECG, and primary end points [cardiovascular death (CVD)] and secondary end points (re-infarction, repeat target vessel revascularization [percutaneous/surgical]) were assessed. The median follow-up time was 18 (13-24) months.

Results: Other than age, there were no significant differences in baseline characteristics and laboratory findings for patients in the fQRS and non-fQRS groups. The patients in the fQRS group were older [64 years *vs* 59 years, p=0.048]. CVD and re-infarction were significantly higher in the fQRS group in the median 18-month follow-up (26.1% *vs* 8.7%, p=0.005; 23.9% *vs* 10.7%, p=0.035, respectively). By a multivariate regression analysis in all 149 patients, age ≥65 years and the presence of fQRS in a 12-lead ECG on admission were found to be powerful independent predictors of cardiovascular mortality (HR: 4.91, 95% CI: 1.60-15.03, p=0.005; HR: 2.77, 95% CI: 1.02-7.50, p=0.044, respectively).

Conclusion: Presence of fQRS on a 12-lead ECG on admission is associated with increased long-term mortality in patients with NSTEMI.

ÖZET

Amaç: Fragmente QRS'in koroner arter hastalığında kardiyak olayların öngördürücüsü olduğu daha önce gösterilmiştir. Bu çalışmada biz ST yükselmesiz miyokart enfarktüslü (STYzME) hastalarda başvuru 12 derivasyonlu elektrokardiyografisindeki (EKG) fragmente QRS (fQRS) varlığının kötü sonlanımları öngördürebileceğini göstermeyi amaçladık.

Çalışma planı: STYzME'li 149 hasta (112 erkek, 37 kadın) geriye dönük incelendi. fQRS paterni majör koroner arter sahasından sorumlu birbirini takip eden 2 derivasyonda başlangıçtaki R', S dalgasının sonunda çentikleşme olması, RS fragmantasyonu veya QS kompleksleri olması olarak tanımlandı. Başvuru sırasında kaydedilen 12-derivasyonlu EKG'de fQRS varlığı ile birincil (kardiyovasküler ölüm) ve ikincil (tekrarlayan enfarkt ve perkütan veya cerrahi yolla hedef damar revaskülarizasyonu) sonlanım noktaları arasındaki ilişki incelendi. Ortalama takip süresi 18 (13-24) aydı.

Bulgular: fQRS olan ve olmayan gruplardaki hastalarda yaş hariç bazal özellikler ve laboratuvar bulguları arasında anlamlı fark yoktu. fQRS grubunda hastalar daha yaşlıydı [64 yıl ve 59 yıl, p=0.048]. Ortalama 18 aylık takipte, kardiyovasküler ölüm ve tekrar enfarkt geçirme fQRS grubunda anlamlı olarak daha yüksekti (sırasıyla, %26.1 ve %8.7, p=0.005; %23.9 ve %10.7, p=0.035). Toplam 149 hastada çoklu değişken analizi ile; yaşın ≥65 olması ve başvurudaki 12-derivasyonlu EKG'de fQRS varlığının kardiyovasküler mortalitenin güçlü, bağımsız öngördürücüsü olduğu bulundu (sırasıyla, HR: 4.91, %95 CI: 1.60-15.03, p=0.005; HR: 2.77, %95 CI: 1.02-7.50, p=0.044).

Sonuç: Başvuru EKG'sinde fQRS olması STYzME'li hastalarda uzun dönem mortalitesinin artışı ile ilişkilidir.

Acute coronary syndrome (ACS) is a significant cause of morbidity and mortality in patients with coronary heart disease in the West. ACS includes unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI), and ST-elevation MI (STEMI). Although in-patient mortality is higher in patients with STEMI, the long-term mortality is high in patients with non-ST elevated ACS.[1] Therefore, optimal management of NSTEMI is important in these patients. It is important to identify high-risk patients in ACS and determine if immediate treatment is required. Fragmented QRS (fQRS) complexes are novel electrocardiographic signals which reflect altered ventricular conduction delays around regions of a myocardial scar. The presence of fQRS in a resting 12-lead electrocardiogram (ECG) indicates an increased risk of adverse outcomes, and fQRS is also thought to be a predictor of cardiac events and all-cause mortality in patients with coronary artery disease (CAD). [2-6] In this study, we hypothesized that the presence of fQRS on a 12-lead ECG on admission is predictive of adverse outcomes in NSTEMI.

PATIENTS AND METHODS

Study population

Records of patients with NSTEMI admitted to the coronary care unit of our institution between February 2011 and April 2012 were evaluated retrospectively. NSTEMI diagnosis was based on elevated cardiac enzymes with typical chest pain and/or electrocardiographic changes suggestive of myocardial ischemia. Typical chest pain was evaluated as follows; more than 20 minutes (min) in duration, new-onset angina, and increase in its frequency and duration or severity. Excluded from the study were patients with a typical bundle-branch block pattern (QRS ≥120 ms), or incomplete right bundle-branch block pattern (RBBB), permanent atrial fibrillation (AF), ventricular paced rhythm, a previously implanted implantable cardioverter-defibrillator (ICD), left ventricular hypertrophy (LVH), Wolff-Parkinson-White syndrome, cardiomyopathy, myocarditis, and congenital heart disease. 54 patients were excluded from the final analysis: 19 with incomplete RBBB, 16 with typical bundle-branch block pattern, 12 with permanent AF, and 7 with LVH. Therefore, a total of 149 patients diagnosed with NSTEMI were included in the analysis in this study. Demographic information, cardiovascular

history, and risk factors such as smoking, hypertension (HT), and diabetes mellitus (DM) for patients were obtained from medical records. Patients who had been treated with antihypertensive drugs, or those whose baseline blood pressure exceeded 140/90 mm Hg were diagnosed with HT. DM was defined as fasting blood sugar more than 126 mg/dL, or the use of anti-diabetic medications. The study protocol was approved by the Local Ethics Committee.

Electrocardiography

The ECG and supplemental criteria for fQRS patterns were defined by Das.[3] The resting in the 12-lead ECG on admission (filter range, 0.15-100 Hz; AC filter, 60 Hz, 25 mm/s, 10 mm/mV) was analyzed blindly by two independent cardiologists. An fQRS pattern was defined as the presence of an additional R' or crochetage wave, notching in the nadir of the S wave, or fragmentation of the RS or QS complexes in 2 contiguous leads corresponding to a major coronary artery territory (Figure 1). The fQRS pattern could occur in patients with or without Q waves.

Coronary angiography
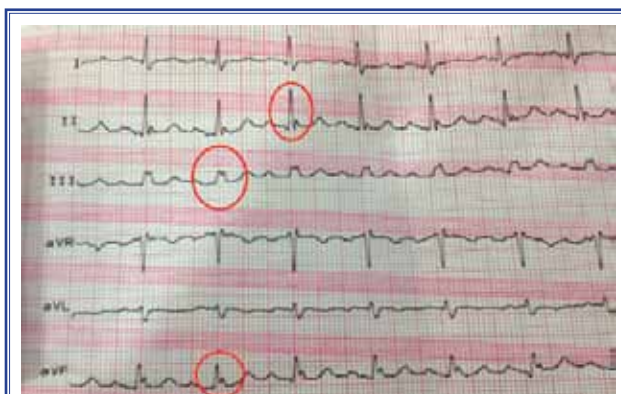
Patients' angiographic data were evaluated from cath-

Figure 1. Development of fragmented QRS (circles) in the inferior leads during NSTEMI.

Abbreviations:

ACS	Acute coronary syndrome
AF	Atrial fibrillation
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CVD	Cardiovascular death
DM	Diabetes mellitus
ECG	Electrocardiogram
fQRS	Fragmented QRS
HT	Hypertension
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
NSTEMI	Non-ST elevation myocardial infarction
PCI	Percutaneous coronary intervention
RBBB	Right bundle-branch block
STEMI	ST-elevation MI

eter laboratory records. All patients underwent a coronary angiography by the femoral approach using the standard Judkin's technique. Iopromide as a contrast agent (Ultravist-370, Bayer Schering Pharma, Germany) and a 6F diagnostic catheter were used in all subjects. Diameter stenosis ≥%70 with quantitative angiography was accepted as significant. The extent and severity of CAD were assessed using the Gensini score.[7] The Gensini score was calculated by multiplying the severity coefficient assigned to each coronary stenosis according to the degree of luminal narrowing (reductions of 25%, 50%, 75%, 90%, 99%, and complete occlusion were given Gensini scores of 1, 2, 4, 8, 16, and 32 respectively), by the coefficient identified based on the functional importance of the myocardial area supplied by that segment: the left main coronary artery, 5; the proximal segment of the left anterior descending coronary artery, 2.5; the mid segment of the left anterior descending coronary artery, 1.5; the apical segment of the left anterior descending coronary artery, 1; the first diagonal branch, 1; the second diagonal branch, 0.5; the proximal segment of the circumflex artery, 2.5 (if right coronary artery dominancy existed 3.5); the distal segment of the circumflex artery, 1 (if dominant, 2); the obtuse marginal branch, 1; the posterolateral branch, 0.5; the proximal segment of the right coronary artery, 1; the mid segment of the right coronary artery, 1; the distal segment of the right coronary artery, 1; and the posterior descending artery, 1.

Follow-up

Follow-up data were obtained by interviewing (directly or by telephone) patients, their families, or their personal physicians. The median follow-up time was 18 (13-24) months. The primary end points were defined as cardiovascular death (CVD), and secondary end points were defined as re-infarction, or repeat target vessel revascularization (percutaneous or surgical). Death was classified as cardiac death if the primary cause was related to myocardial infarction (MI), arrhythmia (Ventricular tachycardia or fibrillation), refractory congestive HF, or sudden death. Re-infarction was defined as an elevation in serum CK-MB levels of twice the upper limit of normal and positive troponin levels (these data were obtained from patients' medical records).

Statistical analysis

All statistical studies were carried out with the SPSS program (version 17.0, SPSS, Chicago, Illinois). Quantitative variables were expressed as the mean value±standard deviation or median (interquartile range), and qualitative variables were expressed as percentages (%). The study population was divided into two groups based on presence of fQRS. A comparison of parametric values between the groups was performed using the student's t test or Mann-Whitney U test. Categorical variables were compared by the likelihood ratio chi-square test or Fisher exact test. Related variables with CVD were determined by enter method, and independent predictors of cardiovascular mortality were evaluated by a Backward-Stepwise logistic regression analysis. P value <0.05 was considered statistically significant.

RESULTS

A total of 149 patients (112 men and 37 women) with NSTEMI were enrolled in this study. The electrocardiographic findings of patients enrolled in the study showed presence of fQRS in 30.8% of patients with NSTEMI (n=46). Localization of fQRS was as follows: 28 of 46 patients with inferior, 14 patients with anterior and 4 patients with lateral localization on surface ECG in the group of patients with fQRS. The number of fQRS leads was as follows: 18 of 46 patients with 2 leads, 18 patients with 3 leads, 6 patients with 4 leads, 2 patients with 5 leads and 2 patients with 6 leads on surface ECG in the group of patients with fQRS.

Other than age, there were no statistical differences between the groups for gender, heart rate, body mass index (BMI), current smoking status, HT, DM, history of MI, number of narrowed coronary arteries, culprit lesion, left ventricular ejection fraction (LVEF), Gensini score and history of percutaneous coronary intervention (PCI). The fQRS group was found to be older (64 [30-90] years vs. 59 [30-88] years, p=0.048). Table 1 demonstrates the baseline characteristics of the groups. Furthermore, there were no significant differences between the two groups for total cholesterol, LDL, HDL, triglyceride, hemoglobin, hematocrit, mean platelet volume, white blood cell, neutrophil, lymphocyte, platelet counts, creatinin kinase creatine kinase? MB and troponin I levels. Table 2 demonstrates the laboratory findings of the two groups.

In addition, the CVD rate at a median follow-up of

Table 1. Baseline characteristics of fQRS and non-fQRS patient groups

Variable	fQRS group (n=46)			Non-fQRS group (n=103)			p
	n	%	Mean±SD	n	%	Mean±SD	
Gender (M/F)	38/8			74/29			0.160
Age, years*	65 (34-90)			59 (30-88)			0.048
Heart rate, (bpm)			81.1±15.2			80.2±13.3	0.210
BMI (kg/m^2)*	26.6 (17.3-42.5)			27.8 (19.1-37.1)			0.109*
Hypertension	22	47.8		53	51.5		0.682
Diabetes mellitus	11	23.9		30	29.1		0.510
Current smoker	19	41.3		43	41.7		0.960
Previous MI	2	4.3		10	9.7		0.267
Previous PCI	4	8.7		15	14.6		0.321
Number of coronary arteries narrowed							0.696
1	15	32.6		29	28.2		
2	16	34.8		33	32		
3	15	32.6		41	39.8		
Culprit lesion							0.317
LAD	15	32.6		36	35		
Cx	22	47.8		37	35.9		
RCA	9	19.6		30	29.1		
LVEF (%)*	46	(25-65)		50	(25-65)		0.135
Gensini score*	40	(10-112)		40	(8-108)		0.356

*: Variables without normal distribution are shown as median, minimum, and maximum. SD: Standard deviation; BMI: Body mass index; Bpm: Beats per minute; CABG: Coronary artery bypass graft; Cx: Circumflex; fQRS: Fragmented QRS; PCI: Percutaneous coronary intervention; LAD: Left anterior descending; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; RCA: Right coronary artery.

18 months was found to be 26.1% in the fQRS group, and 8.7% in the non-fQRS group (p=0.005). Similarly, the re-infarction rate at a median follow-up of 18 months was found to be 23.9% in the fQRS group, and 10.7% in the non-fQRS group (p=0.035). However, there were no significant differences between the fQRS group and non- fQRS group (Table 3) in other secondary end points such as target vessel revascularization parameters, PCI and coronary artery bypass graft (CABG) procedure rates.

Univariate and multiavariate analyses were made for CVD end points. Age ≥65, LVEF <40, number of leads, presence of fQRS and Gensini score were found to be associated with CVD in the univariate analysis but only age ≥65 and fQRS were found to be independent predictors of CVD in the multivariate analysis [HR: 4.91, 95% Confidence Interval: 1.60-

15.03, p=0.005, HR: 2.77, 95% Confidence Interval: 1.02-7.50, p=0.044, respectively] (Table 4).

DISCUSSION

The study results demonstrated that the presence of fQRS on a 12-lead ECG on admission is associated with increased long-term mortality in patients with NSTEMI. During the mean follow-up period of 18 months, approximately 26% and 24% of the fQRS patients died or developed re-infarction respectively, as compared with 9% and 11% of patients without fQRS. These results are in accordance with the mortality rates reported in patients with ACS from other studies.[6,8] In this study, there was no difference between the two groups (with and without fQRS) in the rate of revascularization during the follow-up period; a result similar to a previous study published by Akbarzadeh et al.[9]

Table 2. Laboratory findings of fQRS and non-fQRS patient groups

Variable	fQRS group (n=46)	Non-fQRS group (n=103)	p
T cholesterol (mg/dl)**	198 (120-315)	191 (120-441)	0.413
LDL (mg/dl)**	126 (63-246)	122 (50-312)	0.495
HDL (mg/dl)**	39 (27-95)	41 (21-144)	0.388
Triglyceride (mg/dl)**	115 (40-597)	102 (32-1024)	0.595
Hemoglobin (gr/dl)*	12.8±2.5	13.1±1.9	0.590
Hematocrit %*	38.8±5.4	39.4±5.5	0.686
MPV (fl)*	8.7±5.4	8.6±0.9	0.725
PLT (10^3/mm³)*	228.4±61.5	240.1±67.7	0.301
WBC (10^3/mm³)*	10.3±2.5	10.0±2.5	0.858
Neutrophil (10^3/mm³)**	6.2 (2.8-14.7)	7.0 (2.7-15.1)	0.618
Lymphocyte (10^3/mm³)**	2.1 (0.8-5.4)	2.1 (0.5-7.3)	0.993
Creatinin kinase-MB**	37.5 (12-252)	38 (7-364)	0.701
Troponin I**	8.2 (0.4-88)	5.4 (0.01-68)	0.341

*: Data are shown as mean ± standard deviation for normally distributed variables; **: Variables without normal distribution are shown as median, minimum, and maximum; fQRS: Fragmented QRS; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; MPV: Mean platelet volume; PLT: Platelet; WBC: White blood cell.

For a long time, it has been known that ACS not only related to mortality but also to morbidity. Hence, detecting high-risk patients is still an important issue in daily practice. Several tests and clinical parameters have been shown to be associated with prediction of progression of arrhythmic events, heart failure and cardiac death, including older age, prior MI, DM, LVEF, QRS duration, chronic renal disease, and late potentials on signal-averaged ECG. However, these parameters have a low positive predictive value.[10-13]

fQRS is defined by unforeseen deflections in the QRS morphology. The specific cause of this fractionation on surface ECG and the determinants of this phenomenon are not fully known. Theoretically, fQRS is generally accepted as deriving from regional myocardial fibrosis/scar and ischemia, as a result of which it can cause heterogeneous myocardial electrical activation.[14-18] It has been shown that fQRS is related to myocardial fibrosis in patients with ischemic or non-ischemic LV dysfunction.[19] Pietrasik has reported the sensitivity of fQRS for determining myocardial scar, and postulated that the presence of fQRS can be a good predictor of cardiac events.[20] Likewise, Das et al reported that the fQRS complex is a highly sensitive and specific marker of myocardial fibrosis and may be a strong marker for the presence of myocardial fibrosis.[21]

Das et al reported that in patients with CAD, the all-cause mortality and cardiac events rates (MI, CVD and need for revascularization) were significantly

Table 3. Primary and secondary end points of fQRS and non-fQRS patient groups

Variable	fQRS group (n=46)		Non-fQRS group (n=103)		p
	n	(%)	n	(%)	
Primary end points CVD	12	(26.1)	9	(8.7)	**0.005**
Secondary end points reinfarction	11	(23.9)	11	(10.7)	0.035
PCI	11	(23.9)	28	(27.2)	0.675
CABG	4	(8.7)	10	(9.7)	0.845

CABG: Coronary artery bypass graft; CVD: Cardiovascular death; fQRS: Fragmented QRS; PCI: Percutaneous coronary intervention.

Table 4. Univariate and multivariate analyses for study patients

Variable	Univariate		Multivariate*	
	Heart rate (95% CI)	*p*	Heart rate (95% CI)	*p*
Diabetes mellitus	0.79 (0.28-2.26)	0.672		
Male	1.47 (0.51-4.21)	0.468		
Heart rate ≥70 bpm	1.12 (0.34-3.64)	0.844		
2 ≤ vessels	1.40 (0.48-4.09)	0.537		
Age ≥65	5.80 (1.82-18.48)	**0.003**	4.91 (1.60-15.03)	**0.005**
Fragmented QRS	0.27 (0.10-0.70)	**0.007**	2.77 (1.02-7.50)	0.044
Ejection fraction <40%	2.87 (1.07-7.71)	0.036		
Number of leads	1.47 (1.1-1.98)	**0.01**		
Gensini score	1.01 (0.99-1.03)	0.092		

*: Analysis of Backward-Stepwise regression; bpm: Beat per minute; CI: Confidence interval.

higher in the fQRS group.[4] Similarly, recent studies mentioned that the presence of fQRS is an independent predictor of cardiac mortality and cardiac events in patients with ACS.[6,8] These studies indicated that the mechanistic link between cardiac mortality and presence of fQRS may be a result of an effect of infarction scar tissue in patients with ACS. On the other hand, Ozcan et al demonstrated that the presence of narrow fQRS on ECG significantly correlated with the NYHA functional class, and the ratio of patients with narrow fQRS increased with a worsening NYHA class of symptoms.[22] These results suggest that the presence of an fQRS complex is an easily recognizable, non-invasive electrocardiographic parameter, and its presence is associated with a higher morbidity and mortality risk in CVDs.

In our literature review, we found that this is the second study to examine the relationship between the presence of fQRS on a 12-lead ECG and long-term mortality in patients with NSTEMI. The fQRS group in this study population is different in some ways from this first study, published by Guo et al.[8] First, the median follow-up time was longer in this cohort compared to the previous study; second, the study population in Guo et al. included high-risk patients because the fQRS group was more likely to have a history of DM, prior PCI, and prior CABG in that study. In contrast, there were no significant differences in risk factors for cardiovascular events between the fQRS and non-fQRS groups in our study. The present study results are similar to previous studies for CVD and

re-infarction rates, but differ in terms of repeat target vessel revascularization (PCI/CABG) rates. The consistency between the findings of this study and previous research is indicative of the prognostic value of the fQRS complex. These findings suggest that the presence of fQRS may be associated with a larger myocardial scar tissue and fibrosis in patients with NSTEMI. The LVEF was lower in the fQRS group, which supported our hypothesis that there was more myocardial damage in this group.

Study limitations

This present study had some limitations, one of the most important being the lack of data in hospital end-points and medical treatment modalities such as medical, PCI or CABG in the study population. Secondly, this was a retrospective study and was based on a relatively small group of patients, with a relatively limited duration of follow-up. Additional prospective data are needed in a larger study population to confirm these findings. Furthermore, fQRS on a 12-lead ECG requires an optimal low-pass filter setting (100 or 150 Hz). Fragmentation may be missed with a filter setting of 40 or 60 Hz. Moreover, we did not investigate the effect of drug therapy and therapy of revascularization on fQRS, especially the effects of β-blockers and renin-angiotensin system blockers, which are currently used to inhibit myocardium remodeling and improve post MI prognosis. Finally, we did not investigate an association between fQRS and types of coronary lesion.

Conclusion

The present study indicates that the presence of fQRS on a 12-lead ECG on admission is associated with an increased long-term mortality in patients with NSTE-MI. An ECG is a routinely- performed, simple and inexpensive method for evaluating patients with ACS. In addition, fQRS might be helpful in determining high-risk patients and planning risk-appropriate treatment strategies.

Funding

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