

# Fragmented QRS complex is a prognostic marker of microvascular reperfusion and changes in LV function occur in patients with ST elevation myocardial infarction who underwent primary percutaneous coronary intervention

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**Abstract.** The present study aimed to investigate the in-hospital and long-term prognostic value of fragmented QRS complex (fQRS) for microvascular reperfusion and changes in left ventricular (LV) function in patients with ST elevation myocardial infarction (STEMI) who underwent primary percutaneous coronary intervention (PCI). A total of 216 patients with STEMI undergoing primary PCI were included in the current study. Patients were divided into two groups based on the presence (n=126) or absence (n=90) of fQRS following electrocardiograms (ECGs) on admission. Following primary PCI and follow up, patients were divided into four groups based on new onset, resolution, persistence and absence of fQRS. Major adverse cardiac events were defined to include cardiovascular death, arrhythmia, heart failure, reinfarction and target vessel revascularization. The percentage of patients with heart failure and microvascular reperfusion differed significantly between the fQRS(+) and fQRS(-) groups. Levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), Peak creatine kinase-MB (CK-MB) and Troponin I levels were observed to be significantly higher in the fQRS(+) group compared with the fQRS(-) group. In univariate logistic regression analysis, left ventricular ejection fraction (LVEF), NT-proBNP, Troponin I, Peak CK-MB and microvascular reperfusion were found to be associated with fQRS. Multivariate analysis identified that LVEF, NT-proBNP, Troponin I and microvascular reperfusion may be independent

predictors of fQRS. The presence of fQRS was demonstrated to be associated with left ventricular dysfunction at follow up assessments. The presence of fQRS was not only significantly associated with myocardial microvascular reperfusion and left ventricular function, but was also a prognostic marker in STEMI.

## Introduction

Primary percutaneous coronary intervention (PCI) as a type of coronary reperfusion therapy may lead to recanalization and improved myocardial reperfusion in patients with ST elevation myocardial infarction (STEMI) (1,2). The presence of a fragmented QRS (fQRS) complex including narrow or wide QRS complex, which corresponds to the depolarization of the right and left ventricles of the human heart is frequently recorded following surface electrocardiograms (ECGs). Previous studies have identified that fQRS complex on surface ECG is a predictor of adverse cardiovascular events, including cardiac mortality and heart failure (3,4). In clinical terms, the presence of fQRS is common among patients with biventricular enlargement and myocardial infarction (MI) (5). Furthermore, the presence of fQRS has been associated with decreased myocardial reperfusion and functional deterioration in patients with ischemic heart disease (5-7).

Diabetes mellitus, hypertension and hyperlipidemia are known risk factors for ischemic heart disease and may cause greater myocardial remodeling and dysfunction. N-terminal pro-brain natriuretic peptide (NT-proBNP) is produced and released by cardiac ventricles in response to an overload in ventricular wall stress and stimulation by myocardial tissue reperfusion (8). NT-proBNP, a biomarker, is used to predict short- and long-term mortality in patients with STEMI, as it is closely linked to the level of inflammation, neurohormonal responses and heart function in patients (9-11).

To the best of our knowledge, the association between fQRS and microvascular reperfusion (micro-reperfusion) and changes in left ventricular (LV) function have not yet been investigated in patients with STEMI that have undergone primary PCI. Therefore, the objective of the current study was to investigate the association between fQRS and

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micro-reperfusion and changes in LV function, and to assess the clinical prognostic significance of fQRS in patients with STEMI following primary PCI.

## Materials and methods

**Selection and exclusion of patients.** In the current study, 241 consecutive patients with STEMI being treated with primary PCI between June 2014 and February 2015 (mean age, 59.91±10.97 years; 161 males and 55 females) were enrolled. Patients were included in the study if they presented within 12 h from the onset of symptoms that were identified typically as chest pain lasting for >30 min; had ST-segment elevation ≥1 mm in two contiguous electrocardiographic leads or new onset of complete left bundle-branch block; and had undergone primary PCI including balloon angioplasty, thrombus aspiration and/or stent implantation. Patients were excluded from the present study if they were aged >85 years (due to poor compliance and difficulty in completion of one-year follow-up study in such patients); had a medical history of cardiopulmonary resuscitation, congenital heart disease, severe valvular heart disease, severe organ dysfunction such as liver or kidney failure and malignancy; presented with bundle branch blocks, Wolff-Parkinson-White syndrome and/or Brugada syndrome or had previously undergone implantation of permanent pacemakers. The current study was approved by the Research Ethics Committee of the Second Affiliated Hospital of Harbin Medical University (Heilongjiang, China). Informed consent was obtained from all patients enrolled prior to the study.

**Groups and study protocol.** The patients were divided into two groups based on the presence or absence of fQRS following ECG assessment. Presence of fQRS was defined as fQRS(+) (n=126), and absence of fQRS was defined as fQRS(-) (n=90). Following primary PCI and follow up, patients were divided into four groups based on the following: New onset (n=7), resolution (n=28), persistence (n=98) or absence (n=83) of fQRS. All primary PCIs were performed at the second Affiliated Hospital of Harbin medical university, a single high volume tertiary interventional treatment center (>3000 PCI cases per year) by experienced interventional cardiologists, who performed an average of >300 PCI cases per year and were independent of the present study. The baseline demographic and angiographic characteristics, complications, laboratory and physical examination data on hospitalization were recorded following a systematic review of all patient files.

**ECG and echocardiography.** A 12-lead ECG was recorded for each patient immediately on hospital admission, and 24 and 48 h following primary PCI. All ECGs were analyzed by two independent clinicians, blinded to the study design, clinical and angiographic data from the initial 48 h. QRS duration was measured using the longest QRS complex in any lead by manual measurement and digital records from the MAC 1200 ECG machine (GE Healthcare Life Sciences, Chalfont, UK). All transthoracic echocardiographic examinations were performed using a CX50 ultrasound (Philips Healthcare, Best, The Netherlands) equipped with 5-1 MHz transducer.

The fQRS complex was defined as the presence of various morphologies in two or >2 contiguous leads, including the

presence of an additional R wave (R), more than one R' or notching in the upstroke of the R wave or nadir of the S wave. The inclusion criteria for ECGs with fQRS complex were as follows: QRS duration <120 ms, one or more notch of QR or QR patterns in the QRS complex, and absence of complete or incomplete bundle branch block or left anterior/left posterior fascicular block (12).

**Coronary angiography, primary angioplasty and stenting.** Typically, primary PCI was performed using the percutaneous radial artery approach but the femoral approach was used when intra-aortic balloon pump was required. All angiographic data of patients were assessed using the conventional technique from the catheterization laboratory records (13). The target artery was defined to be clinically significant when vessel stenosis was >50%. The thrombolysis in myocardial infarction (TIMI) trial was used to grade the blood flow in the infarct-related artery (IRA) that received only primary PCI. A chewable dose of 300 mg aspirin (Bayer Healthcare Co., Ltd., Beijing, China) with 180 mg ticagrelor (Astra Zeneca, plc., Shanghai, China) and intravenous heparin (100 IU/kg) was administered prior to PCI in every patient. Success of the procedure was defined as a stenosis of the IRA <20% with TIMI III flow following primary PCI. All patients were transferred to the cardiac care unit following primary PCI and administered a standardized treatment for STEMI. This consisted of 100 mg aspirin once a day, 2.5 mg benazepril (Novartis, Beijing, China) or 20 mg valsartan (Beijing Novartis Pharma, Ltd., Beijing, China) once a day, 20 mg atorvastatin (Pfizer, Inc., Shanghai, China) once a day and 90 mg ticagrelor twice a day, and 40 mg subcutaneous enoxaparin (Sanofi Winthrop Industrie, Beijing, China) twice a day. Tirofiban (GrandPharma Co., Ltd., Wuhan, China) was administered due to the discretion of the interventional cardiologist in 71 patients when thrombus burden was indicated following coronary angiography.

**Reperfusion.** Reperfusion time was defined as symptom-to-balloon time. The time between hospitalization and balloon dilation was defined at the door-to-balloon time. Advanced heart failure was defined by the New York Heart Association (NYHA) functional classification of ≥3 (14). ST-segment resolution (ST-R) in the electrocardiogram reflects micro-reperfusion that was defined as a >50% decrease in ST elevation at the lead in which ST segment elevation was greatest on the electrocardiogram completed on arrival, 1 h following the primary PCI (15). Micro-reperfusion was defined as a >50% decrease in ST elevation at the lead in which ST segment elevation was greatest on the initial electrocardiogram 1 h following the primary PCI. It was assessed by electrocardiographic ST-R.

**Diabetes mellitus, hypertension and hyperlipidemia.** Diabetes mellitus (n=46) was defined as a previous history of disease, use of diet, insulin or oral antidiabetic drugs, or fasting plasma glucose levels >7 mmol/l on two occasions in previously untreated patients (16). Hypertension was diagnosed in 108 patients when systolic arterial pressure was ≥140 mmHg and/or diastolic arterial pressure was ≥90 mmHg, or if the patient was prescribed blood pressure medication due to a medical history of hypertension. Hyperlipidemia (diagnosed in

129 patients) was defined as fasting total serum cholesterol level  $>5.17$  mmol/l, low-density lipoprotein cholesterol (LDL-C) level  $>3.15$  mmol/l, or serum triglyceride level  $>1.70$  mmol/l; or if the patient used lipid-lowering drugs due to a medical history of hypercholesterolemia. Smoking ( $n=129$ ) was defined as the regular use of cigarettes at the time of hospitalization or if the patient had quit smoking within the last year.

**Blood sampling.** Blood samples were collected from cubital veins in all patients who were enrolled in the study. NT-proBNP, creatine kinase-MB (CK-MB), and troponin I were measured daily from admittance. Blood samples were collected at the same times for every patient, on admission and 24 and 48 h later. The level of NT-proBNP in the plasma was measured using an Elecsys® NT-proBNP analyzer, a commercially available electrochemiluminescent sandwich immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). The 12-h fasting serum levels of blood glucose, triglycerides, total cholesterol, LDL-C and high-density lipoprotein cholesterol levels were measured using the automated spectrophotometer and enzymatic colorimetric method with an Olympus AU640 Autoanalyzer (Olympus Corporation, Tokyo, Japan). Other biochemistry measurements were performed using the Jaffe kinetic method on a Hitachi 7600 Autoanalyzer (Hitachi, Ltd., Tokyo, Japan).

**Statistical analysis.** Quantitative variables were expressed as mean  $\pm$  standard deviation and qualitative variables were expressed as a percentage (%). Independent 2-sample t-test or 1-way analysis of variance with post hoc Student-Newman-Keuls test was used to test differences between  $\geq 2$  sets of data. Categorical variables were also compared using the  $\chi^2$  or Fisher's exact test. Independent predictors of fQRS were identified using univariate and multivariate logistic regression analyses. To identify independent predictors of heart failure with hospitalization, a backward stepwise multivariate Cox regression and univariate analysis, which included variables with  $P<0.1$ , was performed. A statistically significant difference was indicated when  $P<0.05$ . All statistical analyses were performed using the IBM SPSS statistical software, version 19.0 (IBM SPSS Inc., Armonk, NY, USA).

## Results

**Patients.** Of the 241 patients initially assessed, 216 (mean age  $59.91 \pm 10.97$  years, 161 male and 55 female) were eligible for the study based on all the criteria in the protocol. The others were excluded from the study due to the following reasons: Seven cases had bundle branch blocks, two cases succumbed to cardiogenic shock, one case succumbed to malignancy during follow-up, five cases implanted with permanent pacemakers, six cases were  $>85$  years old and four cases presented with severe valvular heart disease.

**Basic characteristics of patients.** There were 126 and 90 patients in the fQRS(+) and fQRS(-) group, respectively, determined by the presence or absence of fQRS on pre-PCI ECGs. Basic characteristics of patients in the two groups are presented in Table I. A comparison of the two groups indicated

a number of differences with regard to demographic and angiographic characteristics including hyperlipidemia, medical history of MI and NYHA class (Table I). Patients in the fQRS(+) group had a higher rate of hyperlipidemia, lower levels of heart function, lower rate of culprit lesion and a higher prevalence of a medical history of MI at hospitalization compared with the fQRS(-) group. There was a higher level of cardiovascular mortality in the fQRS(+) group (6 cases vs. 1 case; data not shown). Significantly higher levels of peak CK-MB, troponin I, leukocyte counts, and NT-proBNP were observed in patients in the fQRS(+) group compared the fQRS(-) group ( $P<0.05$ ). No other significant differences between the two groups were observed regarding other laboratory characteristics (Table I).

**Echocardiographic characteristics prior to primary PCI.** Left ventricle end-systolic diameter ( $P<0.001$ ), left ventricle end-diastolic diameter ( $P=0.021$ ) and left atrial diameter ( $P=0.011$ ) was observed to be significantly higher in the fQRS(+) group compared with the fQRS(-) group. However, left ventricular ejection fraction (LVEF) was significantly lower in the fQRS(+) group than the fQRS(-) group ( $P<0.001$ ). No significant differences between the two groups regarding the degree of mitral regurgitation was observed (Table II).

**Echocardiographic characteristics following primary PCI.** Following primary PCI, there were 7, 98, 28 and 83 patients that presented with new onset, persistence, resolution and absence of fQRS, respectively. Echocardiographic characteristics of the four groups are presented in Table III. In the persistence of fQRS group, LVEF was significantly lower ( $P<0.05$ ) and left ventricle end-diastolic diameter (LVEDD), left atrial diameter and micro-reperfusion were significantly higher compared with the resolution of fQRS group ( $P<0.05$ ). In the resolution of fQRS group, LVEF and micro-reperfusion were significantly higher than the new onset of fQRS group ( $P<0.05$ ). In the absence of fQRS group, LVESD and LVEDD were significantly lower and micro-reperfusion was significantly higher than persistence of fQRS group ( $P<0.05$ ).

**Predictors of new-onset and persistence of fQRS.** Following multivariate logistic regression analysis, LVEF (OR=0.994,  $P=0.009$ ), NT-proBNP [odds ratio (OR)=1.001,  $P<0.001$ ], micro-reperfusion (OR=0.273,  $P<0.013$ ) and Troponin I (OR=1.002,  $P=0.028$ ) were demonstrated to be independently associated with fQRS. Furthermore, it was indicated following a univariate analysis that LVEF (OR=0.927,  $P<0.001$ ), NT-proBNP (OR=1.001,  $P<0.001$ ), micro-reperfusion (OR=0.328,  $P<0.014$ ), peak CK-MB (OR=1.002,  $P=0.006$ ) and Troponin I (OR=1.003,  $P=0.007$ ) were associated with fQRS (Table IV).

**Heart function at 1-year follow-up.** After a follow-up period of 1 year, there were 11, 89, 31 and 78 patients in groups of the new onset, persistence, resolution and absence of fQRS, respectively. LVEF was lowest in new onset of fQRS group, followed by group of persistence of fQRS and resolution of fQRS and was highest in the absence of fQRS group. LVESD was highest in the persistence of fQRS group, was observed to be similar in the new onset of fQRS and resolution of fQRS groups, and it was lowest in the absence of fQRS group.

Table I. Basic characteristics of patients in the fQRS(+) and fQRS(-) groups.

Characteristic	fQRS(+) (n=126)	fQRS(-) (n=90)	P-value
Age, years	60.63±10.69	58.84±11.41	0.242
Male, n (%)	95 (75.40)	66 (73.33)	0.753
Current smoker, n (%)	71 (56.35)	58 (64.44)	0.262
Hypertension, n (%)	61 (48.41)	47 (52.22)	0.679
Hyperlipidemia, n (%)	87 (68.66)	42 (46.67)	0.001 <sup>a</sup>
Diabetes, n (%)	31 (24.60)	15 (16.67)	0.180
Medical history of MI, n (%)	16 (12.70)	5 (5.56)	0.047 <sup>a</sup>
Reperfusion time, min	275.00±189.82	275.82±192.44	0.977
Door-to-balloon time, min	71.16±25.64	70.30±22.99	0.799
NYHA class, n (%)			
I	80 (63.50)	83 (92.22)	<0.001 <sup>a</sup>
II	9 (7.14)	3 (3.33)	0.367
III	16 (12.70)	3 (3.33)	0.026 <sup>a</sup>
IV	11 (8.73)	1 (1.11)	0.016 <sup>a</sup>
Micro-reperfusion, n (%)	100 (79.37)	83 (92.22)	0.012 <sup>a</sup>
Cardiovascular mortality, n (%)	6 (4.76)	1 (1.11)	0.243
Platelet counts, x10 <sup>9</sup> /l	220.54±78.40	218.89±53.75	0.729
WBC, x10 <sup>9</sup> /l	11.80±4.62	10.71±3.70	<0.001 <sup>a</sup>
Glucose, mmol/l	8.16±3.63	7.56±3.59	0.341
Creatinine, μmol/l	85.76±20.36	86.40±22.16	0.753
Troponin I, μg/l	241.33±21.67	151.40±16.14	0.002 <sup>a</sup>
Peak CK-MB, μg/l	238.64±21.97	213.15±22.59	0.001 <sup>a</sup>
Total cholesterol, mol/l	4.71±1.14	4.47±1.06	0.220
LDL-cholesterol, mol/l	2.99±0.90	2.86±0.81	0.395
HDL-cholesterol, mol/l	1.28±0.43	1.16±0.28	0.074
Triglyceride, mol/l	1.91±1.52	1.98±1.17	0.770
hs-CRP	10.15±4.28	10.00±4.59	0.832
NT-proBNP, pg/ml	3002.15±298.71	902.26±110.56	<0.001 <sup>a</sup>

Data are presented as mean ± standard deviation and % (n) for continuous and categorical variables, respectively. <sup>a</sup>P<0.05. fQRS, fragmented QRS; MI, cardiac infarction; NYHA, New York Heart Association; micro-reperfusion, microvascular reperfusion; WBC, white blood cell; CK-MB, creatine kinase-MB; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table II. Echocardiographic characteristics of patients in fQRS(+) and fQRS(-) groups.

Characteristic	fQRS(+) group (n=126)	fQRS(-) group (n=90)	P-value
LVEF, %	53.31±9.35	58.51±6.67	<0.001 <sup>a</sup>
LVESD, mm	31.33±7.27	27.69±5.59	<0.001 <sup>a</sup>
LVEDD, mm	47.17±6.86	45.07±5.56	0.021 <sup>a</sup>
Left atrial diameter, mm	34.09±5.99	32.00±5.37	0.011 <sup>a</sup>
Degree of mitral regurgitation			
0	53	46	0.214
1	9	7	0.861
2	51	30	0.320
3	10	4	0.405
4	3	3	0.695

Data are presented as mean ± standard deviation and % (n) for continuous and categorical variables, respectively. <sup>a</sup>P<0.05. fQRS, fragmented QRS; LVEDD, left ventricle end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricle end-systolic diameter.



Table III. Echocardiographic characteristics of groups following primary PCI.

Characteristic	New onset of fQRS (n=7)	Persistence of fQRS (n=98)	Resolution of fQRS (n=28)	Absence of fQRS (n=83)	P-value
LVEF, %	53.23±1.70	54.49±3.15 <sup>d</sup>	58.76±5.32 <sup>b</sup>	55.38±3.97 <sup>f</sup>	<0.001 <sup>g</sup>
LVESD, mm	29.73±3.93	30.87±3.42	29.61±4.04	29.51±4.15 <sup>e</sup>	0.093
LVEDD, mm	48.14±5.20	47.38±4.39 <sup>d</sup>	45.37±3.17	46.00±4.20 <sup>e</sup>	0.042 <sup>g</sup>
Left atrial diameter, mm	35.62±3.36	34.88±3.96 <sup>d</sup>	32.66±6.01	34.50±5.71	0.196
Micro-reperfusion, n (%)	2 (28.57) <sup>a</sup>	72 (73.47) <sup>d</sup>	28 (100) <sup>b</sup>	81 (97.59) <sup>c,e</sup>	<0.001 <sup>g</sup>

Data are presented as mean ± standard deviation and % (n) for continuous and categorical variables, respectively. <sup>a</sup>Significance between new onset of fQRS group and persistence of fQRS group; <sup>b</sup>significance between new onset of fQRS group and resolution of fQRS group; <sup>c</sup>significance between new onset of fQRS group and absence of fQRS group; <sup>d</sup>significance between persistence of fQRS group and resolution of fQRS group; <sup>e</sup>significance between persistence of fQRS group and absence of fQRS group; <sup>f</sup>significance between resolution of fQRS group and absence of fQRS group. PCI, percutaneous coronary intervention; fQRS, fragmented QRS; LVEF, left ventricular ejection fraction; LVESD, left ventricle end-systolic diameter; LVEDD, left ventricle end-diastolic diameter; micro-reperfusion, microvascular reperfusion. The P-value demonstrates the significant differences between all four groups: <sup>g</sup>P<0.05.

Table IV. Univariate and multivariate regression analysis for predicting new-onset or persistence of fQRS following primary PCI.

Characteristic	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.003	0.816	0.992	0.587
Smoking	0.647	0.171	0.610	0.210
LVEF	0.927	<0.001 <sup>a</sup>	0.994	0.009 <sup>a</sup>
Troponin I	1.003	0.007 <sup>a</sup>	1.002	0.028 <sup>a</sup>
NT-proBNP	1.001	<0.001 <sup>a</sup>	1.001	<0.001 <sup>a</sup>
Peak CK-MB	1.002	0.006 <sup>a</sup>	1.001	0.169
Angina-to-door time, h	1.001	0.845	1.001	0.940
Micro reperfusion	0.328	0.014 <sup>a</sup>	0.273	0.013 <sup>a</sup>

<sup>a</sup>P<0.05. fQRS, fragmented QRS; PCI, percutaneous coronary intervention; OR, odds ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; CK-MB, creatine kinase-MB.

LVEDD was the highest in the new onset of fQRS group and lowest in the absence of fQRS group. Left atrial diameter was similar in all four groups (Table V). In addition, 1-year follow up the heart failure (HF)-free survival was significantly lower in the fQRS(+) group compared to the fQRS(-) group (81.0% vs. 93.2%, P=0.035; Fig. 1).

## Discussion

The present study investigated the function of fQRS to assess its function as a potential predictor of cardiac events including changes in LV function and micro-reperfusion in patients with STEMI who underwent primary PCI. The primary results of the current study indicate that the percentage of patients with ST-R was significantly lower in the fQRS(+) group compared with the fQRS(-) group, and the NT-proBNP level was observed to be significantly higher in the fQRS(+) group compared with the fQRS(-) group (P<0.05). fQRS was significantly associated with LVEF, troponin I, micro-reperfusion and NT-proBNP with hospitalization in the multivariate model (P<0.05). At

follow up, LVEF, LVESD and LVEDD were associated with fQRS and HF-free survival was significantly lower in the fQRS(+) group compared with the fQRS(-) group (P<0.05).

Previous studies have demonstrated abnormalities at the level of the micro-reperfusion following prolonged coronary artery occlusion (17,18). The pathogenetic cause of abnormalities of micro-reperfusion that lead to the no-reflow phenomenon is multifactorial. Due endothelial dysfunction, the generation of oxygen-free radicals, myocyte edema, neutrophil infiltration, compression by tissue and distal embolism the capillary structure becomes disorganized in the poor reperfusion zone (19-21). Incompletely perfused myocardium may manifest as stress-induced ischemia. The ischemia myocardium demonstrates abnormal relaxation and stiffness that is an early indicator of diastolic dysfunction (22). Furthermore, systolic function may be reduced in the continuous ischemia area, which ultimately leads to heart failure.

A routine 12-lead ECG is recognized as a gold standard for the rapid diagnosis of STEMI (23). Diagnosis of STEMI and assessment of the reperfusion may be performed through

Table V. Comparison of heart function among groups after 1 year of follow-up assessment.

Characteristic	New onset of fQRS (n=11)	Persistence of fQRS (n=89)	Resolution of fQRS (n=31)	Absence of fQRS (n=78)	P-value
LVEF, %	53.51±2.63 <sup>a</sup>	55.23±3.97 <sup>c</sup>	58.63±5.23	59.77±3.51 <sup>d</sup>	<0.001 <sup>e</sup>
LVEDD, mm	30.66±7.70	33.52±5.45 <sup>c</sup>	30.64±5.30	28.97±3.93 <sup>d</sup>	<0.001 <sup>e</sup>
LVEDD, mm	49.55±4.79 <sup>b</sup>	48.98±4.93	47.41±2.91	45.60±3.97 <sup>d</sup>	<0.001 <sup>e</sup>
Left atrial diameter, mm	35.15±4.69	35.28±5.67	33.38±4.16	33.48±5.38	0.448

P-value compares all groups following an analysis of variance assessment. Data are presented as mean ± standard deviation and % (n) for continuous and categorical variables, respectively. <sup>a</sup>Significance between new onset of fQRS group and persistence of fQRS group; <sup>b</sup>significance between new onset of fQRS group and absence of fQRS group; <sup>c</sup>Significance between persistence of fQRS group and resolution of fQRS group; <sup>d</sup>significance between persistence of fQRS group and absence of fQRS group. fQRS, fragmented QRS; LVEF, left ventricular ejection fraction; LVEDD, left ventricle end-systolic diameter; LVEDD, left ventricle end-diastolic diameter. The P-value demonstrates the significant differences between all four groups: <sup>e</sup>P<0.05.

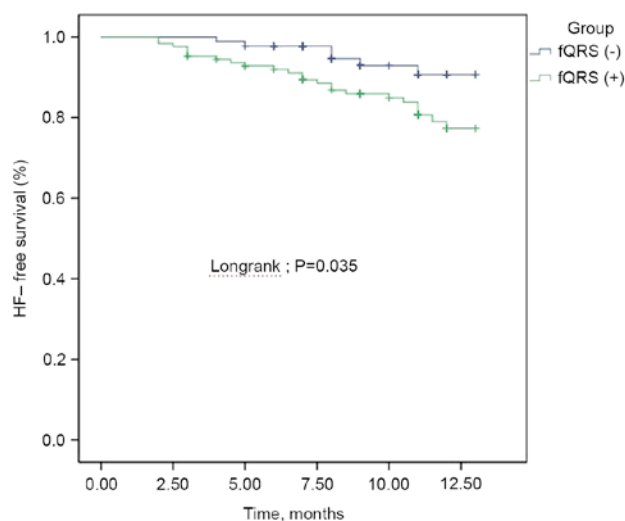


Figure 1. HF with hospitalization in patients with or without fQRS complexes. At 1 year, the HF-free survival was significantly lower in the fQRS (+) group compared to the fQRS (-) group (81.0% vs. 93.2%, P=0.035). HF, heart failure; fQRS, fragmented QRS.

dynamic changes in standard ECG, which include pathological Q-wave, T-wave and ST-segment. The frequency of fQRS observed on a standard ECG has been previously reported to range from 34.9-60.1% in acute coronary syndrome (ACS) (16). Das *et al* (24) demonstrated that the location of leads used with the fQRS complex on a 12-lead ECG reflected the infarct size and location of ischemia, myocardial fibrosis or scar tissue in the ventricles. Previous studies have also demonstrated an association between reperfusion defect, ischemic scar tissue and fQRS (25-27). fQRS manifests as conduction disturbances and cardiac arrhythmias, which may be associated with focal fibrosis or myocardial inflammation. Furthermore, ischemia within the conduction system may be present due to nonhomogeneous activation of infarcted or ischemic myocardial tissue (28,29). Reperfusion defects caused by infarct or ischemia are associated with a poor prognosis due to the risk of malignant arrhythmias and heart failure (30-32). Stavileci *et al* (27) demonstrated an association between persistent fQRS on ECGs at hospitalization and poor prognosis in STEMI. Furthermore,

Kalkan *et al* (33) reported that the fQRS may be a marker of elevated pressure of myocardial reperfusion abnormalities and functional deterioration of left ventricle. Erdem *et al* (34) demonstrated a significant negative association between fQRS and LVEF in patients with acute STEMI.

It has been reported that fQRS is significantly associated with in-hospital adverse cardiovascular events in patients with STEMI undergoing primary PCI (16,35). It has also been indicated that fQRS may occur within 24-48 h following the onset of symptoms and persist thereafter; therefore it is considered as a marker for predicting major adverse cardiac events in patients with coronary artery disease (36). Another study demonstrated that fQRS was significantly associated with advanced HF and hospitalization (12). fQRS may function as a surrogate marker of myocardial scar and/or ischemia, which in turn is significantly associated with systolic dysfunction (37). Therefore, fQRS may indicate the presence of myocardial scar and/or ischemia and thus be a prognostic indicator of advanced HF in patients with STEMI.

Tensile cardiac ventricles synthesize and release proBNP, which is converted into NT-proBNP and bioactive BNP by proteases when ventricular wall pressure increases or ventricles dilate (38). Previous studies have demonstrated that an increase in BNP levels occurs immediately following myocardial ischemia (39). Furthermore, an association between increased levels of BNP, the development of left ventricle remodeling and decreased LVEF has been demonstrated following STEMI (40). NT-proBNP is an indicator that may be used to assess the infarct size and LVEF in STEMI (41).

A previous study has demonstrated that fQRS may function as a surrogate marker of myocardial scarring and thus is significantly associated with cardiac events including not only arrhythmic events but also heart failure in patients (26). The present study indicated that following 1 year, fQRS was significantly associated with HF and hospitalization. Furthermore, using a Kaplan-Meier estimate, the HF-free survival was determined to be significantly lower in the fQRS(+) group compared to the fQRS(-) group (P<0.05). Therefore, fQRS may predict myocardial scarring and has potential to be a prognostic marker of hospitalization-required HF in patients with STEMI that underwent primary PCI. Notably, the

disappearance of fQRS(+) indicates an improved recovery of heart function in patients following primary PCI.

In patients with STEMI, a prolonged QRS time was associated with increased long-term mortality due to an increased incidence of HF, arrhythmia and ischemia (42). Uslu *et al* (16) indicated that fQRS was significantly associated with long-term all-cause mortality, long-term cardiovascular mortality and major adverse cardiac events in patients with STEMI who underwent primary PCI, consistent with results from previous studies (27). The current study revealed that no cases succumbed to cardiovascular-related issues during the one year follow up, however, the incidence of HF was lower in the absence of fQRS (-) group than in fQRS(+) group.

The present study had a number of limitations. Firstly, the number of patients included in the study was small. Further studies of larger populations are required to confirm the results of the present study. Secondly, the presence of a significant referral bias including retrospective and single-center design. In the future, a randomized, multi-center, comparative study is warranted in order to quantitatively assess the prognostic value for fQRS in microvascular reperfusion and LV function. Finally, micro-reperfusion was only assessed by electrocardiographic ST-R. Therefore, the use of other measures, including myocardial blush grade (MBG) by coronary angiography, microvascular obstruction by magnetic resonance imaging and contrast deficit by contrast echocardiography, may have provided additional information regarding micro-reperfusion.

In conclusion, the presence of fQRS is significantly associated with ST-R, NT-proBNP and LVEF which may predict myocardial tissue micro-reperfusion and LV function in patients with STEMI. It was demonstrated that the presence of fQRS during an ECG is associated with higher in-hospital adverse events and rates of HF in patients with STEMI undergoing primary PCI. Therefore, fQRS is a prognostic marker of micro-reperfusion and changes in LV function.

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