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Fragmented QRS predicted major adverse cardiovascular events in patients with coronary artery disease and percutaneous coronary intervention, 10-years of follow-up

Aim	Identifying high-risk groups in patient with coronary artery disease (CAD) is critical for predicting future adverse events. fQRS has been shown to be related to major cardiovascular adverse events (MACE) in patients with CAD. However, predictive value of fQRS for more than 5 yrs has not been evaluated. This study examined the predictive value of fQRS in patients with CAD and percutaneous coronary intervention during a 10-yrs period.
Material and methods	Patients with CAD and percutaneous coronary intervention between March 2007 and May 2009 were included the study. An electrocardiogram was recorded following percutaneous coronary intervention and analyzed for the presence of fQRS. The fQRS pattern was defined as an additional spike inside the QRS complexes of at least two consecutive leads. Patients were followed for 10 yrs. A MACE was all-cause mortality or new-onset decompensated heart failure. Patients were divided into two groups according to presence or absence of MACE, and their clinical variables were compared.
Results	Of 1261 patients included in the study, MACE developed in 374 (29.6%). MACE (+) patients were older (p<0.001), more likely to have diabetes mellitus (p=0.003), fQRS (p<0.001), and ST-elevated myocardial infarction (STEMI) (p<0.001). Multivariable Cox regression analysis revealed that age (p<0.001), STEMI (p=0.001), fQRS (p=0.017), and elevated serum creatinine (p=0.001) were independent predictors of MACE.
Conclusion	The presence of fQRS predicted MACE during 10 yrs of follow-up of patients with CAD and percutaneous coronary intervention.

Keywords	Coronary artery disease; fragmented QRS; major adverse cardiovascular events
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Introduction

Although diagnosis and treatment options have improved considerably in recent decades, coronary artery disease (CAD) still remains the leading cause of worldwide morbidity and mortality [1, 2]. Although, recent guidelines strongly recommend medical treatment for patients with stable coronary artery disease (SCAD), percutaneous coronary intervention (PCI) is extensively performed for both SCAD and acute coronary syndromes (ACS) [3]. Identifying high-risk patients for whom PCI was performed is crucial for predicting outcomes. Thus, many clinical risk scoring systems have been developed [4]. Since many of these scoring tools were evaluated in selected patient groups, have become outdated, consist of many clinical factors, or require a calculator, they are not practical for daily usage. Therefore, outcome predictors that are more practical, easy to obtain, and applicable at bedside would facilitate clinical practice. To this end, some electrocardiographic (ECG) parameters have been evaluated in patients with CAD [5]. Nevertheless, these parameters were inconsistent predictors of adverse cardiovascular events during long-term follow-up. Besides, previous studies evaluated these predictors for less than 5 yrs [6, 7].

Fragmented QRS (fQRS) represents heterogeneous ventricular activation secondary to peri-infarction conduction block, or to depolarization abnormality caused by myocardial scar, fibrosis, or ischemia [8]. fQRS is defined as an R prime wave within the QRS complex, notching of the R or S wave, or the presence of more than one additional R waves in two consecutive leads [9]. fQRS was found to be associated with the severity and extent of coronary artery disease, cardiomyopathies and cardiac arrhythmias. Moreover, fQRS

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was shown to predict mortality and sudden cardiac death in healthy individuals and in patients with CAD [10, 11]. However there have been conflicting results among some studies that evaluated the efficacy of fQRS during long term follow-up [12–14]. In the current study, we investigated the efficacy of fQRS for predicting major cardiovascular adverse events (MACE) during 10 yrs of follow up in PCI patients with CAD. A MACE was all-cause mortality or new-onset decompensated heart failure.

Material and methods

Study population

This retrospective and observational study analyzed data from CAD patients who received PCI between March 2007 and May 2009. The design of the study was approved by local ethical committees. Detailed medical histories and physical examinations were obtained by an experienced cardiologist and recorded in the hospital's database system. SCAD and ACS diagnoses were made according to current guidelines.

Diagnosis of ST- elevated myocardial infarction (MI; STEMI) was made according to the following criteria: The presence of typical angina symptoms and an elevation of the J point by at least 0.2 mV in two consecutive V_1, V_2, or V_3 leads or by 0.1 mV elevation in other leads. To confirm posterior MI, a posterior ECG was recorded from patients who had ST depression in leads V_1 through V_3 [14].

Patients with typical symptoms of myocardial ischemia and with ECG findings indicative of myocardial ischemia, i.e., new ST-T changes or pathologic Q waves, and segmental wall motion abnormality or viable myocardium loss by echocardiography or nuclear imaging were diagnosed with unstable angina pectoris (USAP). Such patients were diagnosed with non-ST-elevated MI (NSTEMI) if their cardiac biomarkers, e.g., troponin I, exceeded the 99th percentile of the upper reference limit [9].

Patients with typical cardiac symptoms related to effort but without acute ST-T changes and who had angiograms for suspicious obstructive CAD were defined as SCAD patients [2]. Patients who were revascularized were included in the study.

Cardiovascular risk factors

Patients were considered hypertensive if they had been diagnosed with hypertension according to the international diagnostic code and/or they were taking one or more of the following medications: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, or diuretics for at least 6 mos. Diabetes mellitus (DM) was diagnosed according to at least one of the following criteria: 1) History of DM and taking any anti-diabetic medication; 2) Randomly measured blood glucose value of 200 mg/dl or higher; 3) Blood glucose of 126 mg/dl or above after at least 8 hrs of fasting 4) A1c of 6.5% or higher [15]. Smoking was defined if a regular smoker smoked at least one cigarette a day during the last month. Family history was defined as atherosclerotic cardiovascular disease (CVD) or death from CVD in a first-degree relative, i.e., parent or sibling before age 55 for males or 65 for females. The presence of dyslipidemia was defined according to age and sex-adjusted percentiles from the National Health and Nutrition Examination Survey (NHANES) III data. BMI was calculated as weight (kg)/height (m)2.

ECG Recordings and fragmented QRS

A standard 12-lead ECG (150 Hz filter, 25 mm/s, 10 mm/mV; Schiller, Cardiovit AT-10, Baar, Switzerland) was obtained from all patients immediately after PCI. ECG measurements were interpreted by an independent, experienced cardiologist who was blinded to other clinical data. All ECGs were examined by eye for fQRS. QRS intervals were measured manually, and the longest interval on any lead was taken for consideration. fQRS was defined as an additional spike (RSR' pattern) embedded in QRS complexes of 12 leads without bundle branch block and with a QRS duration of less than 120 ms. An additional spike was determined as the presence of one or more R' waves and/or notching in the R or S waves in two consecutive anterior, inferior or lateral leads compatible with one of the major coronary artery areas (Figure 1).

Echocardiography and laboratory analysis

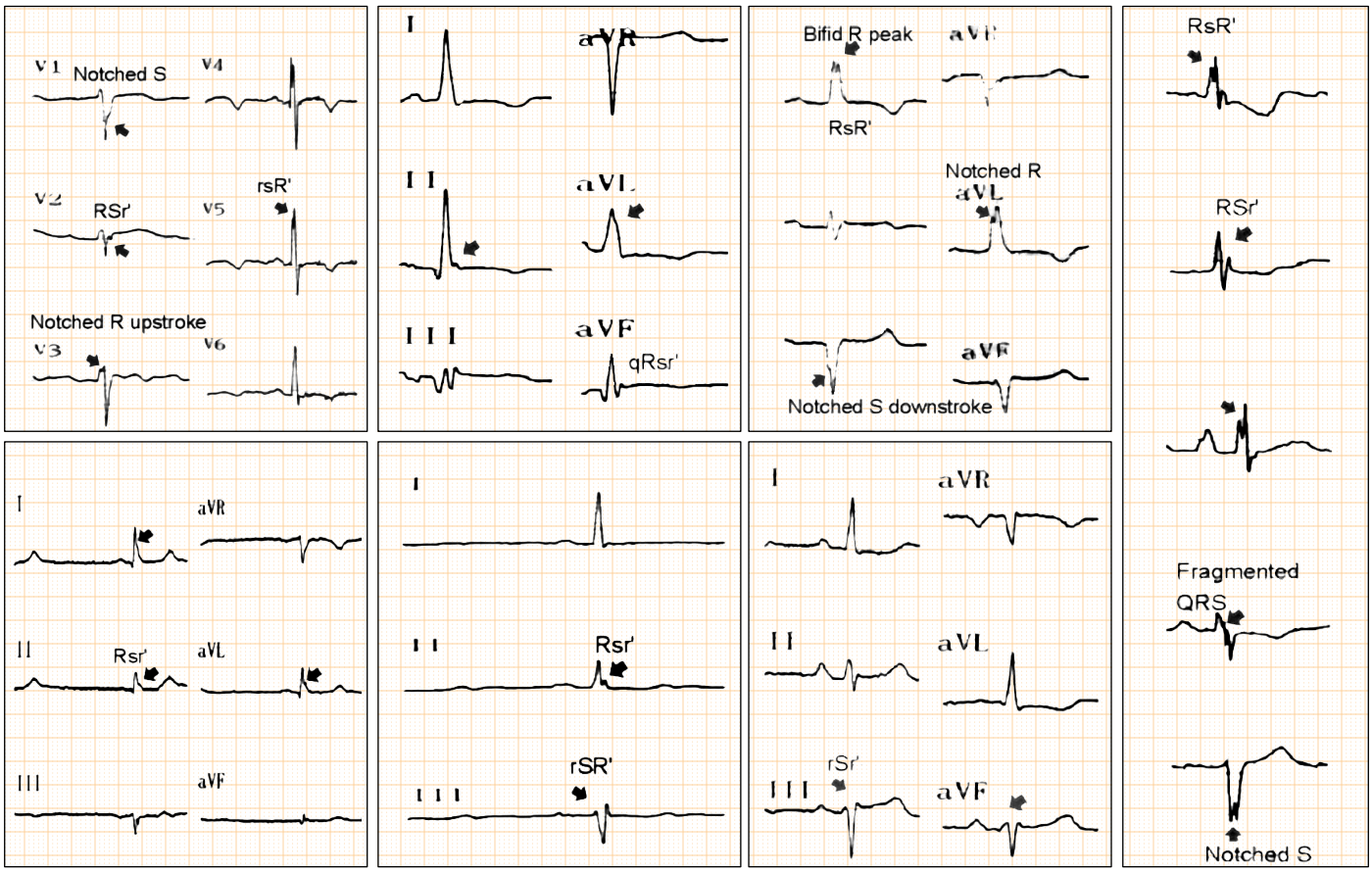
Detailed, two-dimensional echocardiography was performed on all patients before discharge and during routine follow (Philips Epiq 7 system with a 2.5–3.5-MHz transducer, Philips Medical Systems, Andover, MA, USA). Left ventricular ejection fraction (LVEF) was measured by the modified Simpson method. The clinicians who evaluated the echocardiographic findings were unaware of the patients' other clinical data.

Routine biochemistry, hemogram, creatine kinase-myocardial band (CK-MB), troponin, and c-reactive protein (CRP) data were included in the analysis. Blood glucose and lipid parameters were measured after at least 8 hrs fast. Glucose, creatinine, and lipid profiles were determined by standard methods. White blood cell (WBC, leukocyte) counts were obtained from an automated cell counter (Coulter Gen-S, COULTER Corp, Miami, USA), and CRP was analyzed using a nephelometric technique (Beckman Coulter Image 800, Fullerton, CA, USA; normal range, 0–0.8 mg/dl).

Coronary angiography and percutaneous coronary intervention

Urgent coronary angiography (Judkins technique) was performed in all patients hospitalized for ACS. Routine angiography was performed for elective conditions during

Figure 1. Types of notched and fragmented QRS complexes used to select patients in this study. Different fQRS patterns are shown by arrows including rSr', rSR', RSr', notched R up-stroke and notched S down-stroke, bifid R peak and bifid R nadir



the first working day following the hospitalization of patients with SCAD. Current guidelines for interventional and medical treatment [2, 3] were considered.

Left anterior descending (LAD) and circumflex (Cx) coronary arteries were viewed from at least four different angles. The right coronary artery (RCA) was viewed from at least two different angles. The images were transferred to digital media for quantitative analysis. Fluoroscopic image recordings were evaluated by two experienced interventional cardiologists. In case of disagreement regarding the visual assessment, the final decision was made with the consent of a third interventional cardiologist. In epicardial arteries with a diameter ≥1.5 mm, any lesion that caused at least 70% narrowing of the lumen compared to the closest segment was considered a significant stenosis. The revascularization strategies were determined by the attending physician's preference. Before stent implantation, patients received intracoronary 5000–10000 units of unfractionated heparin. After the interventional procedure, patients with ACS were transported to the coronary intensive care unit and followed until they were clinically stable.

Clinical follow-up

Patients were examined at the 1st, 3rd, 6th, 12th months and at each following year after the discharge. During these examinations, clinical, laboratory, and medical findings were recorded to the hospital database system. This permitted following the patients for an average of 10 yrs.

The MACE of the study was consisted of all-cause mortality and new-onset decompensated heart failure (HF). Mortality and HF data were obtained by query of the hospital and national databases, during routine cardiology outpatient examination, from direct phone calls to patients or their relatives, family physician reports, and through face-to-face interviews. Patient medication was also assessed through the hospital database and national medical record system. Typical HF symptoms including shortness of breath, swelling of ankles, palpitations, weakness, jugular vein distension, pulmonary congestion, and peripheral edema were assessed during the examination. Patients with these symptoms and related physical examination findings and those with LVEF under 40% were considered to have congestive heart failure (CHF).

Exclusion criteria

Exclusion criteria were pulmonary embolism, previous myocardial infarction (MI), end-stage liver or kidney disease, malignancy, a cerebrovascular event, endocrine disorders, acute or chronic inflammatory disease, moderate to severe valvular heart disease, previous cardiovascular sur-

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Table 1. Comparisons of patient physical and clinical data

Variable	MACE (-) (n=887)	MACE (+) (n=374)	All patients (n=1261)	p
Age (yr)	57.3±10.1	64.7±11.2	59.5±10.9	<0.001
Diagnosis SAP USAP/NSTEMI STEMI	 498 (56.1 119 (13.4) 270 (30.4)	 133 (35.6) 79 (21.1) 162 (43.3)	 631 (50) 198 (15.7) 432 (34.3)	<0.001
Male gender	681 (76.8)	303 (81)	984 (78)	0.097
Currently smoking	314 (35.4)	140 (37.4)	454 (36)	0.493
Diabetes mellitus	281 (31.6)	151 (40.4)	432 (34.2)	0.003
Hyperlipidemia	535 (68.2)	198 (60.9)	733 (66.1)	0.019
Hypertension	420 (47.3)	191 (51.1)	611 (48.4)	0.224
Family history of CAD	226 (32.9)	78 (28.3)	304 (31.6)	0.162
BMI (kg/m^2)	28.9±4.7	28.1±5.1	28.6±5.1	0.019
Presence of fQRS	281 (31.9)	172 (46.2)	453 (36.2)	<0.001
Coronary lesion obstruction Normal coronary Plaque Single vessel ≥2 vessels	 119 (13.7) 196 (22.6) 203 (23.4) 348 ((40.2)	 17 (4.7) 52 (14.4) 86 (23.9) 205 (56.9)	 136 (11.1) 248 (23.9 289 (23.6 553 (45.1)	<0.001
Mortality	0 (0)	319 (85.3)	319 (25.3)	<0.001
CHF	0 (0)	54 (14.4)	54 (4.3)	<0.001
Glucose (mg/dl)	126.1±50.1	144.7±83	131.6±62	<0.001
Creatinine (mg/dl)	0.91±0.2	1.03±0.26	0.94±0.23	<0.001
Total cholesterol (mg/dl)	190±43.8	182±44	188±44	0.008
LDL–C (mg/dl)	121.6±36.1	116.9±35.9	120.2±36.1	0.065
HDL–C (mg/dl)	39.7±9.8	38.6±10.5	39.4±10.1	0.136
Triglycerides (mg/dl)	149.5±83.4	130.8±67.5	144.1±79	0.001
WBC (103/μm^3)	8.6±3.01	9.3±3.2	8.8±3.1	<0.001
Lymphocytes (103/μm^3)	2.3±0.91	2.29±0.99	2.3±0.39	0.170
Neutrophils (103/μm^3)	5.1±2.5	6.05±2.9	5.4±2.6	<0.001
Hemoglobin (g/dl)	14.1±1.7	13.7±2.6	14.03±2.03	0.005
CRP (mg/dl)	1.02±2.01	1.8±3.6	1.25±2.6	<0.001
Medication at discharge				
ASA	737 (83.4)	346 (92.5)	1083 (86)	<0.001
Clopidogrel	550 (61.9)	279 (74.6)	829 (65.7)	<0.001
ACEI/ARB	475 (53.1)	213 (57)	688 (54.5)	0.143
Beta blockers	505 (56.9)	272 (72.7)	777 (61.9)	<0.001
Statins	614 (69.1)	289 (77.3)	903 (71.6)	0.002
Oral antidiabetic drugs/Insulin	275 (31)	145 (38.7)	420 (33.3)	0.004
CCB	121 (13.6)	51 (13.5)	172 (13.5)	0.216

Data are mean±SD or number (%). p value, MACE (-) vs MACE (+). SAP, stable angina pectoris; USAP, unstable angina pectoris; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction; CAD, coronary artery disease; BMI, body mass index; fQRS, fragmented QRS; CHF, congestive heart failure; LDL–C, low-density lipoprotein cholesterol; HDL–C, high-density lipoprotein cholesterol; WBC, white blood cell; CRP, C-reactive protein; ASA, acetylsalicylic acid; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blocker.

gery for any indication, myocarditis, or cardiogenic shock. In addition, patients with QRS duration of more than 120 ms, antiarrhythmic drug usage prior to PCI, pacemaker rhythm, and complete or incomplete right or left bundle branch block were excluded from the study. Also excluded were patients with PCI-related complications including coronary dissection, acute or hyperacute stent thrombosis, those did not use medications regularly, with repeated revascularization, or whose clinical follow-up data were unavailable.

Statistical analysis

Data were analyzed with a SPSS software package (Version 23.0, SPSS, Inc., Chicago, IL, USA). A 2-tailed p-value of less than 0.05 identified statistically significant differences. Normality assumptions were assessed visually (histograms, probability plots) and by analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test). Levene's test was used to evaluate the homogeneity of variances. Continuous variables are reported as mean±standard deviation (SD), and categorical variables are reported as value

Table 2. Independent predictors of MACE

Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p	OR	95% CI	p
Age (year)	1.059	1.049–1.070	<0.001	1.042	1.027–1.057	<0.001
Male gender	1.136	0.883–1.463	0.321	–	–	–
STEMI diagnosis	1.321	1.181–1.478	<0.001	1.339	1.135–1.579	0.001
Diabetes mellitus	1.384	1.125–1.702	0.002	–	–	–
Hyperlipidemia	0.801	0.640–1.002	0.052	–	–	–
BMI	0.971	0.945–0.998	0.037	0.998	0.963–1.033	0.895
Severity of CAD	1.393	1.242–1.563	<0.001	1.112	0.927–1.334	0.253
fQRS	1.750	1.371–2.233	<0.001	1.421	1.035–1.064	0.017
Creatinine	4.991	3.370–7.391	<0.001	2.568	1.506–4.379	0.001
Triglycerides	0.997	0.996–0.999	0.001	0.998	0.996–1.000	0.086
LDL–C	0.997	0.994–1.001	0.121	–	–	–
WBCs	1.053	1.021–1.086	0.001	–	–	–
Neutrophils	1.090	1.050–1.131	<0.001	1.003	0.944–1.065	0.274
CRP	1.064	1.025–1.105	0.001	–	–	–

OR, odds ratio; CI, 95% confidence interval; STEMI, ST Elevation MI; BMI, body mass index; CAD, coronary artery disease; fQRS, fragmented QRS; LDL–C, low-density lipoprotein cholesterol; WBC, white blood cell; CRP, C-reactive protein.

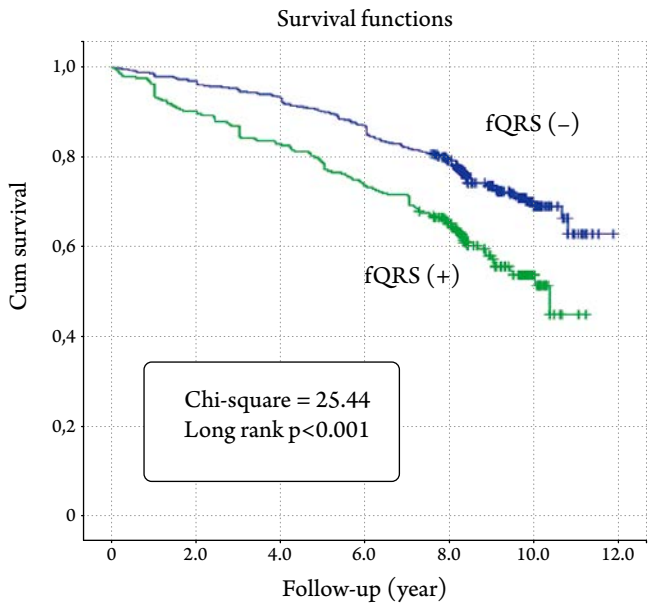
and percentage. A Chi-square or Fisher's exact test was employed to compare groups of categorical variables. A two-tailed Student t-test was applied to normally distributed parameters, and a Mann–Whitney U test was applied to non-normally distributed, continuous variables. A univariate regression analysis was performed to assess the effects of various variables on MACE. Variables with p<0.05 were considered as confounding factors and included in a Cox backward multivariable regression analysis to evaluate independent predictors of MACE. Cumulative data of those with and without fQRS were compared by Kaplan Meier analysis to demonstrate its effect on long term MACE.

Results

A total of 1261 patients were included in the present study. Their physical and clinical data are detailed in Table 1. The mean age was 59.5±10.9 yrs and 984 (78%) of the patients were males. The patients were divided into two groups according to the presence of MACE. MACE developed in a total of 374 (29.6%) patients, and of those, 319 (85.3%) died, and 54 (14.4%) developed decompensated heart failure. Mean age, presence of fQRS, STEMI diagnosis, and DM were significantly higher, and hyperlipidemia was significantly lower in the MACE (+) group.

Backward multivariable Cox regression analysis revealed that age, STEMI diagnosis, presence of fQRS, serum glucose, and serum creatinine were significant independent predictors of MACE (Table 2). Kaplan–Meier curves demonstrated that the presence of fQRS increased the risk of MACE during the 10-yr follow-up (Figure 2).

Figure 2. Kaplan–Meier survival curves demonstrated that fQRS increased the risk of MACE during 10 yrs of follow-up



Discussion

The current study found that the presence of fQRS predicted MACE independently during 10 yrs of follow-up of CAD patients who had received PCI. To the best of our knowledge, this is the first study evaluating fQRS for predicting MACE during more than 5 yrs of follow-up.

A twelve-lead ECG is the gold standard in CAD for determining diagnosis and treatment, risk classification, and patient follow-up, since it is easily obtainable, cheap, noninvasive, and provides data for imme-

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diate triage [5]. Although various depolarization and repolarization parameters have been evaluated in previous studies, they have limitations, which include emerging at more advanced stages of ischemia and yielding conflicting predictions of MACE [3, 8]. Instead, fQRS was demonstrated to be a strong marker for predicting outcomes in various CAD patient groups. Nevertheless, some previous studies revealed conflicting results regarding MACE, and most of the trials followed patients for less than 5 yrs [12–14].

fQRS is a marker of inhomogeneous electrical activity and abnormal ventricular depolarization secondary to ischemia, fibrosis, and myocardial scar [16]. The association between fQRS and myocardial fibrosis and/or scar was demonstrated in both ischemic and non-ischemic cardiovascular diseases by gadolinium delayed enhancement of cardiac magnetic resonance imaging and by myocardial perfusion scintigraphy [17]. There are viable tissue clusters scattered within the fibrotic and/or scar tissue. Suppressed and delayed propagation of the depolarization wave front around areas of slow conduction and increased intracellular resistivity causes fragmentation. Thus, fQRS has often been found in chronic, healed MI sites [18]. fQRS is also considered to be a diagnostic marker of arrhythmogenic right ventricular dysplasia characterized by ventricular scarring [10]. In previous studies, fQRS rate varied between 28% and 54% since studies were carried out in different patient populations, and patients received different treatments [19]. This rate was 36% in the present study. Considering that all CAD groups were included, this ratio agrees with previous studies. Since fQRS is a permanent finding in individuals with previous MI, patients with previous CAD were excluded from this study. Thus, we think that we have provided more reliable results compared to previous studies.

Acute myocardial ischemia may also cause fQRS due to the rapid changes in myocardial depolarization. The location and morphology of fQRS change depending on the location of myocardial ischemia. In addition, Kocaman et al. reported that fQRS may disappear in STEMI patients following primary PCI, and this can indicate success of the reperfusion therapy [19]. Moreover, fQRS was associated with a higher atherosclerotic burden and with more severe coronary artery disease in all CAD subgroups. Although fQRS has been found to be correlated with systemic inflammation in patients with SCAD, adequate data on this is limited [20].

It is also established that the presence of fQRS is associated with heart failure in patients with CAD. Korhonen et al. showed that patients with acute MI had lower left ventricular ejection fraction (LVEF) if fQRS was present [21]. Also, Çetin et al. demonstrated that LVEF was lower in patients who underwent PCI for SCAD in the presence of fQRS [5]. Furthermore, fQRS also predicted decreased LVEF and increased end-systolic and end-diastolic diameters in patients with non-ischemic and Takatsubo cardiomyopathies [22, 23]. Since conditions such as myocardial fibrosis, ventricular remodeling, recurrent MI, and subsequent ventricular dilatation and dysfunction evolve over a long time, it can be postulated that a much longer follow-up period would provide more reliable results in terms of heart failure, mortality, and other adverse events.

The relationship between all-cause mortality and fQRS in patients with various subgroups of CAD has been examined in numerous previous studies. One of the most common causes of mortality was postulated to be malignant ventricular arrhythmias [24, 25]. Areas of abnormally slow conduction and high intracellular resistivity are substrates for cardiac arrhythmias [16]. This association was shown in patients with CAD, non-ischemic cardiomyopathy (CMP), hypertrophic CMP, and essential hypertension [2, 11]. In addition, fQRS was shown to predict arrhythmic events in patients with Brugada syndrome. fQRS was shown to predict mortality, sudden cardiac death (SCD), and implantable cardiac defibrillator shocks arising from ventricular arrhythmias in patients with ischemic CMP [3, 25, 26]. Furthermore, fQRS was also shown to be associated with sudden cardiac death in various populations, such as those with obesity and hypertrophic CMP [24]. In addition, the atrial fibrillation rate was higher in those with fQRS and various cardiovascular diseases [27]. Therefore, given the main findings of the current study, it can be assumed that the underlying arrhythmic events would be another cause of increased fQRS-related mortality and heart failure in patients with CAD.

On the other hand, previous studies have reported conflicting results regarding mortality and decompensated HF during short- and long-term follow-up of patients with ACS. Some studies stated that the STEMI patients had a higher rate of MACE, but on the other hand, some studies found the STEMI group had results similar to those of all CAD subgroups. One of the reasons for this discrepancy was thought to be that some of the patient groups were revascularized by PCI, whereas other ACS groups received only medical treatment [28, 29]). In addition, follow-up data are scarce in patients treated with PCI. All of these studies were carried for up to 5 yrs. Most of the previous studies also included individuals who received only medical treatment [30]. In the present study, only patients who underwent PCI were included. During 10 yrs of follow-up, the MACE rate was higher in patients with STEMI compared to the other CAD groups. Another substantial finding of the study was multivessel disease rate was higher in MACE group as expected.

The strong relationship between renal function and cardiovascular disease is also well-recognized. Renal dysfunction is one of the most common comorbidities, especially in patients with CAD and is associated with poor and short and long-term prognosis [31]. In the present study, as was seem in previous studies, impaired renal function, as estimated from serum creatinine, predicted long-term MACE [32].

Limitations

The main limitations of this study are as: 1) Acute and stable coronary artery disease were analyzed together. Assessments of these patients differ, and this could have affected the study findings. 2) Changes in patient-related cardiovascular risk factors, medications, device therapies, follow-up centers, and new interventions may have affected adverse event rates over the long term. 3) The use of drug eluting stents or bare metal stents, which likely affected MACE, was ignored.

Conclusion

The presence of fQRS at admission is a quickly obtainable and cheap method that is easily interpreted by clinicians. This cost-effective marker was found to be a predictor of 10 yrs MACE in patients with CAD who were treated with PCI. In this patient group, one of the main goals might be closer observation and consideration of more aggressive treatment modalities. Those treatments might include implantable devices that would augment clinical surveillance.

Declarations

Ethics approval and consent to participate: Ethical permission was obtained from the Local Ethics Committee of Recep Tayyip Erdogan University Ethic Committee (04.02.2021–2021/26). Verbal consent was taken from patients, and this was approved by the ethics committee. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

MÇ analyzed and interpreted the patient data regarding the relationship between coronary artery disease and the fragmented QRS. ASY performed data collection and was a major contributor in writing the manuscript. ÖŞ was also one of the major contributors in writing the paper and was supervisor of this study.

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