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# Relationship Between Fragmented QRS Complex and Long-Term Cardiovascular Outcome in Patients with Essential Hypertension

ORIGINAL INVESTIGATION

## ABSTRACT

**Background:** In patients with essential hypertension, fragmented QRS has been associated with many remodeling components that might lead to adverse cardiovascular effects. This study aimed to evaluate the relationship between fragmented QRS and adverse events and its potential long-term prognostic value.

**Methods:** The patients with essential hypertension were divided into two groups according to the presence of fragmented QRS: fragmented QRS (+) and fragmented QRS (–). During long-term follow-up, the relationship of fragmented QRS to coronary artery disease, congestive heart failure, stroke, cardiovascular death, all-cause death, and major adverse cardiovascular and cerebrovascular events was evaluated.

**Results:** The study group included 542 patients with essential hypertension. Fragmented QRS on ECG was observed in 224 (41.3%) patients. Considering the incidence rates at the end of 5.6 ± 1.3 years' follow-up, the total incidence rate of major adverse cardiovascular and cerebrovascular events ($P < .001$), coronary artery disease ($P < .001$), and congestive heart failure ($P < .001$) were higher in patients with fragmented QRS. No significant difference was observed between the two groups in terms of stroke ($P = .734$), cardiovascular death ($P = 1$), and all-cause death ($P = .574$). As a result of multiple cox regression analysis, fragmented QRS ($P = .005$) was identified as an independent predictor for major adverse cardiovascular and cerebrovascular events development.

**Conclusion:** In patients with hypertension, the presence of fragmented QRS was found as an independent predictor for major adverse cardiovascular and cerebrovascular events development.

**Keywords:** Essential hypertension, fragmented QRS, major adverse cardiovascular and cerebrovascular events, mortality

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## INTRODUCTION

Hypertension is one of the leading causes of morbidity and mortality as it causes serious complications over the years.[1] Hypertension is the leading risk factor for various cardiovascular events including stroke, myocardial infarction, heart failure, and sudden death.[2] Hypertension has been identified as an important cause of myocardial fibrosis in studies.

Fragmented QRS (fQRS) is a depolarization disorder due to a conduction delay caused by myocardial fibrotic tissue that can be easily detected on twelve-lead surface electrocardiography (ECG).[3] Because the fQRS complex is associated with myocardial fibrosis, it is an independent predictor of poor cardiac outcomes.[4,5] Moreover, fQRS is more common in patients with hypertension and is a sign of high burden of myocardial fibrosis.[6,7]

We have limited knowledge about the long-term results of the association between essential hypertension and fQRS complex. Early aggressive preventive treatment may yield positive results in these patients in the long term, demonstrating the relationship between fQRS and major adverse cardiovascular and

cerebrovascular events (MACCE) in patients with essential hypertension.

Therefore, this study investigated the relationship between fQRS complex and MACCE development in patients with essential hypertension in the long term.

## METHODS

### Patient Population

This single-center retrospective study was conducted in accordance with principles of the Declaration of Helsinki and approved by the Clinical Trials Ethics Committee. The patient population was determined among patients admitted to our hospital's cardiology outpatient clinic between January 2009 and November 2018 and newly diagnosed with essential hypertension using 24-hour ambulatory blood pressure (BP) monitoring device. The inclusion criteria were diagnosis of essential hypertension and age >18 years. All the patients who had essential hypertension were contacted through phone call and those who accepted were included in the study. Among those patients, 877 were accepted to be included in the study. After inclusion in the study, the patients with exclusion criteria were excluded. The exclusion criteria were patients with complete or incomplete right and/or left bundle branch block (n=21), moderate to severe valvular disease (n=8), congestive heart failure (CHF) related to both heart failure with reduced ejection fraction or heart failure with preserved ejection fraction (n=10), detected coronary artery disease (CAD) (n=23), chronic renal and hepatic failure (n=24), patients with electrolyte imbalance (n=5), patients with atrial fibrillation, flutter or junctional rhythm (n=24), patients with pacemaker (n=1), patients who were under treatment for type I and III antiarrhythmic drugs (n=5), patients who had unsuitable ECG for evaluation (n=27), and patients with previous cerebrovascular disease (n=3). Additional to that, patients with left ventricular hypertrophy (LVH) (n=184) were also excluded because of the close relationship with fQRS in previous studies.[8] After the inclusion and exclusion criteria were applied, 542 patients were included in the study. All patients were evaluated with a detailed history, physical examination, laboratory analysis, echocardiography, and ECG.

## HIGHLIGHTS

- Hypertension is the leading risk factor for various cardiovascular events including stroke, myocardial infarction, heart failure, and sudden death.
- According to the results of our study, coronary artery disease, major adverse cardiovascular and cerebrovascular events, and major adverse cardiovascular and cerebrovascular events were found to be statistically significantly higher in the fQRS (+) group in the long-term follow-up of patients with hypertension.
- Evaluation of the presence of fQRS will provide us the ability to identify patients at high and low risk for major adverse cardiovascular and cerebrovascular events development in the long-term follow-up of patients with hypertension.

### Demographic, Clinical, and Laboratory Data Collection and Definitions

Demographic, clinical, and laboratory data of the patients were obtained by scanning through the patient data system of our hospital. Information on diabetes mellitus (DM), dyslipidemia, CAD, smoking habits, and laboratory measurements were recorded in the medical histories of the patients. DM was defined as at least two fasting plasma glucose levels ≥ 126 mg/dL or postprandial plasma glucose levels ≥ 200 mg/dL or use of antidiabetic drugs. Dyslipidemia was defined as serum total cholesterol ≥ 200 mg/dL, serum triglyceride ≥ 150 mg/dL, low-density lipoprotein cholesterol ≥ 130 mg/dL, previously diagnosed hyperlipidemia, or the use of lipid-lowering medication. Cigarettes were defined as "current smokers" or "non-smokers." The study patients were divided into two groups according to the presence of a fragmented QRS. Patients with a fragmented QRS were defined as " fQRS (+)", and patients without a fragmented QRS were defined as " fQRS (–)." Laboratory tests (complete blood count and biochemistry parameters) of the patients were conducted during the examination when they presented to our outpatient clinic with hypertensive complaints and were studied in a single laboratory.

### Diagnosis of Hypertension and Determination of the Pattern

All patients underwent 24-hour ambulatory BP monitoring for evaluation of BP and for diagnosis of essential hypertension. Holter monitoring was performed as daily, daytime and nighttime, BPs. Holter measurements were done every 30 minutes in the daytime (between 6:00 AM and 10:00 PM) and every 60 minutes in the nighttime (between 10:00 PM and 6:00 AM). Mean values of the day, night, and daily BPs were recorded for every patient. The cuff was placed around the non-dominant arm of the patients. Patients were instructed to carry out their usual activities during the day. Patients were asked to go to bed not later than 11:00 PM and arise not before 7:00 AM and to record their activities in a diary (time of going in and out of the bed, exercise times in the day). Patients were instructed to keep their arms still during measurements. Holter measurements were performed during the working days (Monday to Friday). A valid record was considered as if there were at least 24 valid BP measurements during the daytime and at least 6 at nighttime. If the recording was invalid, the patients were asked to undergo a repeat Holter monitoring the following day. The 2018 ESC/ESH guidelines were used to define BP categories.[9] Patients with 24-hour mean BP over 130/80, daytime BP over 135/85, and nighttime BP over 120/70 were considered as hypertensive individuals. Patients who were previously diagnosed with hypertension and used antihypertensive drugs for at least two months were also considered hypertensive individuals. The dipper pattern was defined as >10% decrease in nocturnal BP compared to daytime values, the non-dipper pattern was defined as <10% decrease in nocturnal BP compared to daytime values, and the reverse-dipper pattern was described as an increase in nocturnal BP compared to mean daytime values.

### Fragmented QRS Detection and Definition

Twelve-lead resting ECGs (0.16-100 Hz filter range, 25 mm/s velocity, and 10 mm/mV height) were performed in all patients. The ECG recordings for the patients were obtained upon the admission of diagnosis of essential hypertension. fQRS was defined as the presence of an additional r wave (r') in at least two adjacent leads in the absence of a typical bundle branch block in one of the main coronary artery regions and the presence of an R or S wave notch or rupture (more than one R') (Figure 1).[10] All ECG findings were analyzed by two experienced cardiologists who were unaware of the clinical results. The intra- and inter-observer differences for fQRS were <5%.

### Echocardiographic Evaluation

Transthoracic echocardiography was performed on all patients during the diagnosis of essential hypertension and was performed on patients by an experienced cardiologist. The patients were examined with a 3.2-mHz adult probe on an echocardiography device (GE Vingmed Ultrasound AS, Horten, Norway). Left ventricular ejection fraction (LVEF), left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), left ventricular posterior wall thickness, interventricular septum (IVS) thickness were measured according to the guidelines of the American Society of Echocardiography.[11]

### Study Endpoints

Study endpoints were total mortality, stroke, cardiovascular (CV) mortality, CAD, CHF, and MACCE parameters. CAD was defined as having a history of angina pectoris, myocardial infarction, or coronary revascularization. Stroke was described as a neurological deficiency with symptoms lasting >24 hours or leading to death with no apparent cause other than vascular causes. The diagnosis of CHF required a LVEF <50% and the presence of one or more of the following: symptoms, clinical signs, radiographic abnormalities, and hospitalization. MACCE was described as a composite of all-cause mortality, cardiovascular death, CAD, stroke, and need for hospitalization due to worsening CHF. The study's main endpoint was long-term all-cause mortality. Patients' MACCE data is obtained from an electronic hospital system or National Population Registry or by contacting the patients, their relatives, or family physicians.

### Ethical Approval

The ethics committee approved this study with protocol number 2019-01 on 08/01/2019, and the necessary permissions were obtained from the hospital management.

### Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences version 24.0 (SPSS Inc., Chicago, Illinois, USA). Visual (histograms, probability curves) and analytical methods (Kolmogorov–Smirnov or Shapiro–Wilk) were performed to evaluate whether the variables show normal distribution. Numerical variables showing normal distribution were expressed as mean ± standard deviation, whereas numerical variables not showing normal distribution were expressed as median (interquartile range) and categorical variables as a percentage (%). Numerical variables were evaluated using Student's *t*-test and Mann–Whitney *U*-test between the two groups. Chi-square or Fisher's exact test was used to compare categorical variables. Event-free survival curves were constructed using the Kaplan–Meier method and compared using the log-rank test. A univariate and multivariate cox proportional hazards model was used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CI) for clinical endpoints. Throughout this study, a *P* value <.05 was considered as statistically significant.

## RESULTS

The study group included 542 patients with essential hypertension (female, 54.98%; mean age, 52.93 ± 11.11 years). Of these patients, 224 (41.3%) had fQRS on ECG. The main characteristics of patients with or without fQRS were presented in Table 1. While there was no significant difference between the two groups in terms of age, body mass index

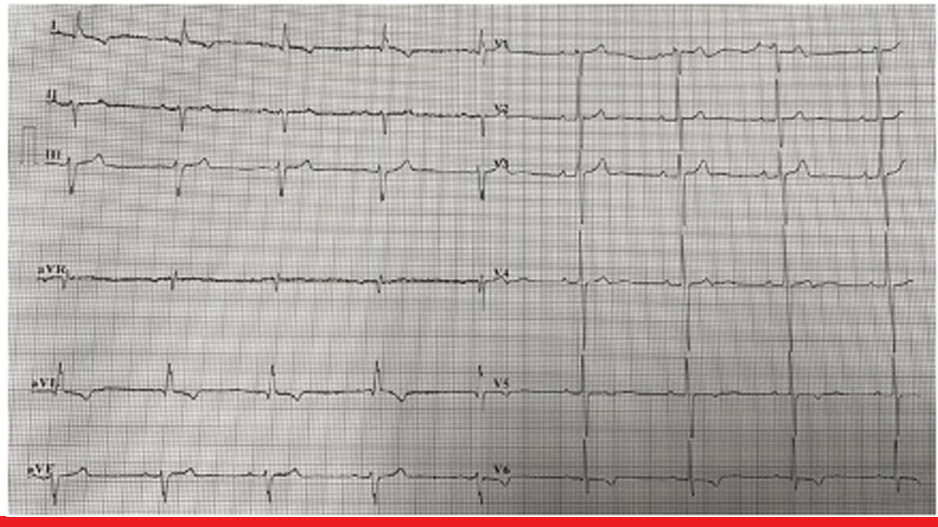

**Figure 1. An exemplary electrocardiography shows the presence of fragmented QRS in the derivations of DI,AVL (lateral f-QRS) and DIII,AVF (inferior f-QRS).**

**Table 1. Main Clinical Characteristics of the Patient Population**

| n = 542 | Fragmented QRS (–) (n = 318) | Fragmented QRS (+) (n = 224) | *P* |
|---|---|---|---|
| Age, years | 52.49 ± 11.16 | 53.55 ± 11.03 | .282 |
| Gender (male), n (%) | 130 (40.9) | 114 (50.9) | **.021** |
| BMI, (kg/m$^2$) | 30.35 ± 5.12 | 30.76 ± 5.00 | .441 |
| Smoking, n (%) | 50 (21.4) | 33 (21.7) | .936 |
| Alcohol consumption, n (%) | 12 (5.2) | 8 (5.3) | .961 |
| Diabetes mellitus, n (%) | 61 (19.9) | 48 (22.4) | .491 |
| Hyperlipidemia, n (%) | 135 (50.8) | 111 (53.9) | .499 |
| ACEi or ARB, n (%) | 179 (77.2) | 97 (63.4) | **.003** |
| Calcium channel blockers, n (%) | 103 (44.6) | 65 (42.5) | .684 |
| Beta-blockers, n (%) | 96 (41.6) | 60 (39.2) | .647 |
| Diuretics, n (%) | 130 (56.3) | 78 (51.3) | .340 |
| Acetylsalicylic acid, n (%) | 53 (22.9) | 31 (20.1) | .513 |
| Statins, n (%) | 30 (13.0) | 17 (11.0) | .567 |

*P* value of <.05 shows statistical significance.
BMI, body mass index; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

(BMI), smoking, alcohol use, DM, and hyperlipidemia (HL), the ratio of male patients was significantly higher in the fQRS (+) group (*P* = .021). In terms of the history of drug usage, angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) use was significantly higher in the fQRS (–) group (*P* = .003), in contrast to that usage of other drugs were similar between the two groups. There was no statistically significant difference in terms of laboratory values between groups (Table 2).

The 24-hour daily systolic BP [fQRS (+): 147.2 ± 16.9 vs. fQRS (–): 143.8 ±18.9, *P* = .032] and daytime systolic BP values [fQRS (+): 149.4 ± 17.0 vs. fQRS (–) 146.0 ± 18.8, *P* = .035] were higher in the fQRS (+) patient group when compared to the fQRS (–) patients. There was no difference between the groups regarding the non-dipper pattern HT, reverse-dipper pattern HT, nighttime systolic BP, and diastolic BP measurements (Table 3).

Echocardiographic and electrocardiographic parameters were presented in Table 4. LVEDD [fQRS (+): 47.88 ± 4.69 vs. fQRS (–): 46.82 ± 4.20, *P* = .009], LVESD [fQRS (+): 30.09 ± 4.32 vs. fQRS (–): 28.93 ± 3.88, *P* = .002], and QRS duration [fQRS (+): 90.33 ± 15.77 vs. fQRS (–): 82.79 ±10.34, *P* < .001] were significantly longer in the fQRS (+) group. There were no significant differences in terms of LVEF, heart rate, IVS, and posterior wall thickness between the groups.

The groups are compared according to long-term follow-up data (Table 5 and Figure 2). Considering the incidence rates at the end of a 5.6 ± 1.3-year follow-up, the total incidence rate of MACCE [fQRS (+): 42.9% vs. fQRS (–): 19.5%, *P* < .001], CAD [fQRS (+): 31.7% vs. fQRS (–): 13.8%, *P* < .001], and CHF [fQRS (+): 4.9% vs. fQRS (–): 0.6%, *P* = .001] were higher in patients with fQRS than patients without fQRS. No significant difference was found in terms of stroke [fQRS (+): 4% vs. fQRS (–): 3.5%, *P* = .734], CV death [fQRS (+): 0.9% vs. fQRS

**Table 2. Laboratory Measurements of the Patient Population**

| n = 542 | fQRS (–) (n = 318) | fQRS (+) (n = 224) | *P* |
|---|---|---|---|
| Hemoglobin, g/dL | 13.78 ± 1.50 | 13.87 ± 1.61 | .520 |
| Leukocyte, 10$^3$/μL | 7.81 ± 1.86 | 7.60 ± 1.99 | .238 |
| Platelets, 10$^3$/μL | 271.2 ± 71.8 | 263.1 ± 69.3 | .204 |
| Creatinine, mg/dL | 0.80 ± 0.21 | 0.83 ± 0.27 | .157 |
| Glucose, mg/dL | 98 (91-115) | 99 (91-117) | .680 |
| LDL-C, mg/dL | 129.0 ± 40.3 | 129.3 ± 36.2 | .921 |
| HDL-C, mg/dL | 47.6 ± 12.9 | 46.8 ± 12.9 | .478 |
| Total cholesterol, mg/dL | 202.3 ± 45.3 | 204.7 ± 42.8 | .574 |
| Triglyceride, mg/dL | 139 (99-213) | 137 (98-204) | .934 |
| C-reactive protein, mg/L | 3.2 (1.6-6.1) | 3.2 (1.3-7.0) | .801 |
| Uric acid, mg/dL | 5.56 ± 1.45 | 5.41 ± 1.43 | .293 |

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

**Table 3. Ambulatory Blood Pressure Measurements of the Patient Population**

| n = 542 | fQRS (–) (n = 318) | fQRS (+) (n = 224) | *P* |
|---|---|---|---|
| Daily systolic BP, mm Hg | 143.8 ±18.9 | 147.2 ± 16.9 | **.032** |
| Daily diastolic BP, mm Hg | 89.1 ± 13.2 | 90.9 ± 11.6 | .109 |
| Daytime systolic BP, mm Hg | 146.0 ± 18.8 | 149.4 ± 17.0 | **.035** |
| Daytime diastolic BP, mm Hg | 91.8 ± 13.5 | 93.3 ± 12.0 | .125 |
| Nighttime systolic BP, mm Hg | 137.8 ± 21.0 | 140.2 ± 19.7 | .186 |
| Nighttime diastolic BP, mm Hg | 82.5 ± 13.8 | 83.6 ± 12.7 | .350 |
| Non-dipper pattern, n (%) | 217 (72.8) | 142 (67.6) | .205 |
| Reverse-dipper pattern, n (%) | 53 (17.8) | 41 (19.5) | .619 |

*P* value of <.05 shows statistical significance.
BP, blood pressure.

**Table 4. Echocardiographic and Electrocardiographic Parameters of the Patient Population**

| n = 542 | fQRS (–) (n = 318) | fQRS (+) (n = 224) | *P* |
|---|---|---|---|
| LV ejection fraction, % | 63.28 ± 3.46 | 62.88 ± 4.75 | .282 |
| LV end-diastolic diameter, cm | 46.82 ± 4.20 | 47.88 ± 4.69 | **.009** |
| LV end-systolic diameter, cm | 28.93 ± 3.88 | 30.09 ± 4.32 | **.002** |
| IVS thickness, cm | 9.0 (10.0-12.0) | 10.0 (10.0-11.0) | .526 |
| Posterior wall thickness, cm | 10.41 ± 1.55 | 10.59 ± 1.75 | .222 |
| QRS duration, ms | 82.79 ± 10.34 | 90.33 ± 15.77 | **<.001** |
| Heart rate, beats / min | 75.85 ± 13.70 | 75.54 ± 13.72 | .800 |

*P* value of <.05 shows statistical significance.
LV, left ventricle; IVS, interventricular septum.

**Table 5. Comparison of the Groups Based on Their Long-term Follow-Up Data**

| n = 542 | fQRS (–) (n = 318) | fQRS (+) (n = 224) | *P* |
|---|---|---|---|
| Coronary artery disease, n (%) | 44 (13.8) | 71 (31.7) | **<.001** |
| Stroke, n (%) | 11 (3.5) | 9 (4.0) | .734 |
| Congestive heart failure, n (%) | 2 (0.6) | 11 (4.9) | **.001** |
| Cardiovascular death, n (%) | 2 (0.6) | 2 (0.9) | 1.0 |
| All-cause death, n (%) | 5 (1.6) | 5 (2.2) | .574 |
| MACCE, n (%) | 62 (19.5) | 96 (42.9) | **<.001** |

*P* value of <.05 shows statistical significance.
fQRS, fragmented QRS; MACCE, major adverse cardiovascular and cerebrovascular events.

(–): 0.6%, *P* = 1], and all-cause death [fQRS (+): 2.2% vs. fQRS (–): 1.6%, *P* = .574] between the two groups.

To determine the factors that predict the MACCE, the parameters of age, gender, BMI, smoking, alcohol, DM, HL, LVEF, heart rate, 24-hour systolic BP, 24-hour diastolic BP, non-dipper HT, hemoglobin levels, creatinine levels, C-reactive protein levels, and presence of fQRS were included in the univariate cox regression analysis. Among these parameters, age (*P* < .001), male gender (*P* < .001), DM (*P* = .001), HL (*P* < .001), LVEF (*P* = 0.001), 24-hour systolic BP (*P* < .001), creatinine level (*P* < .001), and presence of fQRS (*P* < .001) were the variables that reached the level of significance. Multiple cox regression analysis was performed using these variables. As a result of multiple cox regression analysis, age (HR = 1.039; 95% CI: 1.021-1.058, *P* < .001), male gender (HR = 1.593; 95% CI: 1.050-2.418, *P* = .029), DM (HR = 1.661; 95% CI: 1.127-2.447, *P* = .010), HL (HR = 1.922; 95% CI: 1.298-2.844, *P* = .001), creatinine level (HR = 2.473; 95% CI: 1.149-5.320, *P* = .021), and presence of fQRS (HR = 1.726; 95% CI: 1.179-2.527, *P* = .005) were identified as independent predictors for MACCE development (Table 6).

The Kaplan–Meier method showed a significant difference (rank *P* < .001 between log groups) between the groups, and the presence of fQRS was found associated with a reduction in survival (Figure 3).

## DISCUSSION

Hypertension is one of the leading diseases for mortality and morbidity all over the world and predicting the long-term cardiovascular complications related to hypertension is important in the treatment of the disease. In our study, we have investigated the relationship between fQRS complex and development of MACCE in patients with essential hypertension in the long term. According to the results of our study, CAD and CHF were found to be statistically significantly higher in the fQRS (+) group in the long-term follow-up of patients with hypertension. Additionally, development of MACCE, which is the endpoint of our study, was found to be significantly higher in the fQRS (+) group than the fQRS (–) group, and the presence of fQRS was found to be an independent predictor of MACCE. Moreover, presence of fQRS was not only a predictor for MACCE but was also associated with a reduction in survival.

Despite its effective treatment, hypertension is a disease that might cause serious complications in cardiovascular system. These changes can cause

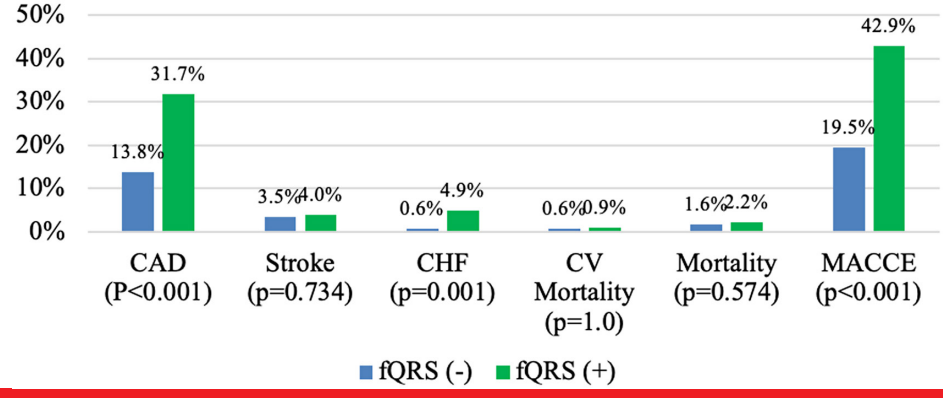


**Figure 2. Comparison of groups based on long-term follow-up data.**

**Table 6. Univariate and Multiple Cox Regression Analyses to Determine Predictors of MACCE**

| | Univariate Analysis | | Multiple Analysis | |
|---|---|---|---|---|
| | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Age | 1.043 (1.029-1.058) | **<.001** | 1.039 (1.021-1.058) | **<.001** |
| Gender (male) | 1.851 (1.338-2.560) | **<.001** | 1.593 (1.050-2.418) | **.029** |
| BMI | 0.998 (0.962-1.035) | .909 | | |
| Smoking | 1.300 (0.846-1.996) | .231 | | |
| Alcohol | 1.634 (0.795-3.359) | .182 | | |
| Diabetes mellitus | 1.809 (1.284-2.548) | **.001** | 1.661 (1.127-2.447) | **.010** |
| Hyperlipidemia | 1.978 (1.387-2.821) | **<.001** | 1.922 (1.298-2.844) | **.001** |
| LV ejection fraction | 0.939 (0.906-0.973) | **.001** | 0.979 (0.935-1.026) | .375 |
| Heart rate | 1.002 (0.991-1.014) | .682 | | |
| 24-hour systolic BP | 1.019 (1.011-1.027) | **<.001** | 1.009 (0.998-1.020) | .101 |
| 24-hour diastolic BP | 1.013 (1.001-1.025) | .052 | | |
| Non-dipper pattern | 1.113 (0.779-1.590) | .556 | | |
| Hemoglobin | 1.049 (0.946-1.162) | .365 | | |
| Creatinine | 3.730 (2.261-6.154) | **<.001** | 2.473 (1.149-5.320) | **.021** |
| C-reactive protein | 1.005 (0.992-1.017) | .459 | | |
| Presence of fQRS | 2.883 (2.092-3.972) | **<.001** | 1.726 (1.179-2.527) | **.005** |

*P* value of <.05 shows statistical significance.
BMI, body mass index; LV, left ventricle; BP, blood pressure; fQRS, fragmented QRS.

serious cardiovascular adverse events, starting with fibrosis and endothelial damage and following a long-term silent remodeling period.[12,13] It is well known that these structural transitions might change the ECG of these patients such as changes related to LVH, axial changes, or T-wave changes.[14,15] However, one of the most important change in the ECG related with fibrosis and scarring in myocardium is the fQRS. And it was stated that fQRS was not only related to fibrosis in myocardium, but it was also associated with the amount of hypertrophy of left ventricle, poorly controlled BP, abnormal change of ventricular geometry, and poor systolic and diastolic function.[16] In our study, our findings were consistent with the previous studies that structural changes related to fibrosis such as increased left ventricular end-diastolic and end-systolic diameter were increased in patients with fQRS.

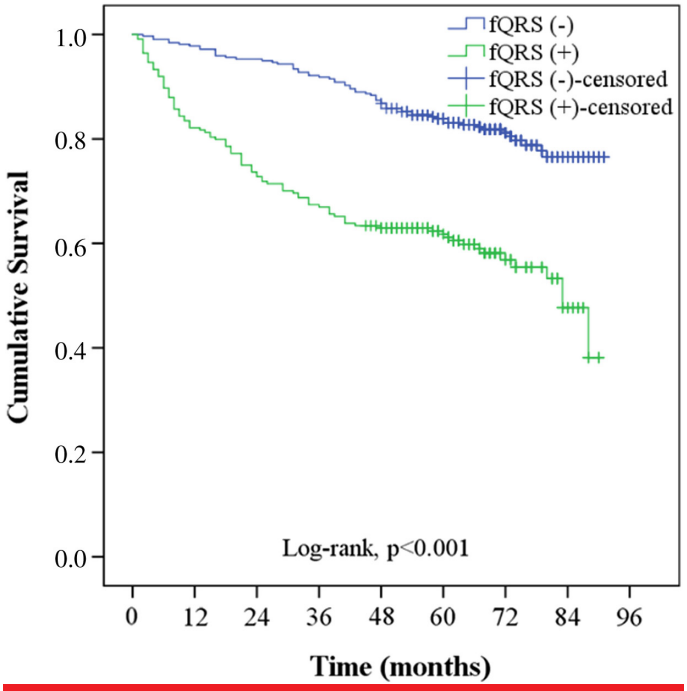


**Figure 3. Kaplan–Meier survival curves for fQRS status.**

Fragmented QRS is a depolarization disorder due to a conduction delay caused by myocardial fibrotic tissue. Previous researches showed that fQRS was closely related with the presence of LVH.[17] However, it has been shown that the presence of fQRS was also found associated with multiple clinical conditions in previous researches in patients with hypertension even without LVH. Eyuboglu et al showed that fQRS was associated with increased systolic BP in patients with hypertension, and they concluded that fQRS might predict fibrotic burden in myocardium in these patients.[18] In our study, there was no significant difference in terms of presence of LVH between patient groups, and we had similar findings with previous researches those patients with fQRS had higher systolic BP levels in daily and daytime measurements. In a study of Tanriverdi et al's, they have found that fQRS was an independent predictor of non-dipping patterns in patients with hypertension without LVH.[19] Conversely, in our study, there was no significant association between fQRS and non-dipping pattern. The main difference in our study and their study was that their study was a smaller sized (n = 106) study when compared to our study (n = 542).

In previous studies, it has been shown that fQRS was associated with adverse outcomes in patients with various cardiovascular diseases, such as heart failure, CAD, congenital heart disease, and hereditary arrhythmogenic

syndrome.[20-22] Previous studies have reported that fQRS may be a predictor for a major adverse cardiovascular event in patients with CAD. It was reported that fQRS was associated with impaired systolic function in patients with CAD.[23] The first meta-analysis of 16 studies involving 3,997 patients with CAD reported that LVEF was significantly lower in the fQRS group on routine ECG than in the group without fQRS.[4] Additionally, it has been reported that the relationship between the presence of major cardiovascular event (MACE) and fQRS in ECG occurs not only in patients with ischemic cardiomyopathy but also in patients with acute myocardial infarction.[24,25] In a study, Ari et al[26] showed that the MACE rate was higher in the fQRS group in patients who underwent primary percutaneous coronary intervention. Moreover, another meta-analysis also showed that fQRS was consistently associated with total mortality and major adverse cardiovascular events including cardiovascular mortality, re-infarction, advanced heart failure, and ventricular arrhythmias.[27] Our study is unique that our patient group had none of these concomitant diseases, and our study only evaluated the fQRS and its relationship with long-term events in patients with hypertension even without LVH.

As aforementioned, relationship between fQRS and CAD, heart failure, and association between fQRS and remodeling components of heart were shown in previous studies. Cardiac structural changes related to myocardial fibrosis and hypertension were found associated with sudden cardiac death.[28,29] Bekar et al[30] studied the relationship between fQRS and ventricular arrhythmias, and they commented that fQRS might be associated with higher risk of ventricular arrhythmias in patients with essential hypertension. Additional to these, the association between presence of fQRS and MACE in non-ischemic etiology was studied. Ahn et al[31] studied the relationship between fQRS and MACE in long-term follow-up of the patients with non-ischemic dilated cardiomyopathy by using cardiac magnetic resonance. They have found that although the presence of fQRS was not related to delayed enhancement, presence of fQRS was related with higher incidence of MACE in long-term follow-up of patients with non-ischemic dilated cardiomyopathy. However, data on the association of fQRS with long-term adverse events in essential hypertension patients are limited. When all our findings were evaluated, the development of fragmented QRS may predict the development of future ischemic events and CAD together with occurrence of heart failure and MACCE in the long term in patients with essential hypertension. To the best of our knowledge, this is the first study evaluating the long-term MACCE development of fQRS in patients with essential hypertension. Our study determined that the presence of fQRS is an independent predictor for the development of MACCE in patients with hypertension. According to this finding, fQRS can be used as a noninvasive risk assessment tool in patients with essential hypertension, and it will have the ability to identify patients at high and low risk for MACCE development.

## Study Limitations

The primary limitation is that our study was not randomized and conducted in a single center. The second limitation is that it was performed retrospectively and with a relatively small number of patients. Another limitation is that no other quantitative methods (myocardial perfusion scanning or magnetic resonance imaging) were used to show myocardial ischemia or scar formation including the patients to the study. Essentially, we demonstrated the efficacy and usefulness of fQRS in ECG, an indirect method for measuring MACCE development in patients with hypertension.

## CONCLUSIONS

As a marker of myocardial fibrosis, fQRS can be as a noninvasive risk assessment tool in patients with essential hypertension without LVH. Our study showed association between occurrence of CAD and CHF and fQRS. Evaluation of the presence of fQRS will provide us the ability to identify patients at high and low risk for MACCE development in the long-term follow-up of these patients.

**Ethics Committee Approval:** Ethical committee approval was received from the Ethics Committee of University of Health Sciences, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Turkey (Approval No:2019-01).

**Informed Consent:** Written informed consent was obtained from all participants who participated in this study.

**Peer-review:** Externally peer-reviewed.

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