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Fragmented QRS: A New Independent Predictor of Mortality Factor in Chronic Kidney Disease Patients Who Have Coronary Artery Calcification: A Retrospective Cohort Study

Parçalanmış QRS: Koroner Arter Kalsifikasyonu Olan Kronik Böbrek Yetmezlikli Hastalarda Yeni Bir Bağımsız Mortalite Tahmini: Retrospektif Kohort Çalışması

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ABSTRACT Objective: Our aim of this study was to investigate the relationship between QRS fragmentation (fQRS) and clinical outcome in asymptomatic chronic kidney disease patients (CKDPs) with coronary artery calcification (CAC) score. **Material and Methods:** One-houndred-sixty-four CKDPs were included. We used 64-slice multi-detector computed tomography (MDCT) for CAC score. We followed the patients for major adverse effect of cerebrovascular events (MACCE), requirement of coronary artery or cerebral or peripheral arterial revascularization. **Results:** Median CAC score was 744±443.2 Agatston unit (AU). In CKDPs with fQRS (n=55; Group 1), CAC score ≥300 AU. There was no evidence of fQRS in the remaining 109 patients (Group 2). Median CAC score was significantly higher than Group 2 patients (p=0.001). Eleven patients with higher CAC level required coronary artery revascularisation. Carotid artery stenosis, and peripheral artery occlusion were detected in Group 1 patients. In Group 2, we detected isolated coronary artery disease (CAD) in 12 (11%) patients. CAD, carotid and peripheral artery disease were more common in Group 1 (30% vs. 16.5%) (p=0.0001). Twenty two patients in Group 1, and 32 patients in Group 2 required coronary revascularisation within follow-up period (p=0.003). Fourteen patients in Group 1, and 18 patients in Group 2 died during follow-up period. **Conclusion:** Our study showed that there was a strong correlation between the frequency of fQRS and level of CAC score. To prevent MACCE in asymptomatic CKDPs who have fQRS, CAC score can be investigated by using MDCT.

Keywords: Fragmented QRS complex; computed tomography; coronary artery calcification; chronic kidney disease; cardiovascular events

ÖZET Amaç: Bu çalışmanın amacı, koroner arter kalsifikasyonu (KAK) skoru olan semptomsuz kronik böbrek yetmezlikli hastalarda (KBYH), parçalanmış QRS (pQRS) ile klinik sonuçları arasındaki ilişkiyi araştırmaktı. **Gereç ve Yöntemler:** Yüz altmış dört KBYH çalışmaya dâhil edildi. KAK skoru için 64 kesitli çok dedektörlü bilgisayarlı tomografi (ÇDBT) kullandık. Hastaları, majör kardiyak ve serebrovasküler olay (MKSVO) gelişmesi, koroner arter, serebral veya periferik arter revaskülarizasyonu gereksinimi açısından takip ettik. **Bulgular:** Medyan KAK skoru 744±443,2 Agatston birimi [Agatston unit (AU)] idi. KAK skoru pQRS'li KBYH'li hastalarda (n=55; Grup 1) ≥300 AU idi. Kalan 109 hastada (Grup 2) pQRS kanıtı yoktu. Medyan KAK skoru Grup 2 hastalarında anlamlı derecede yüksekti (p=0,001). Daha yüksek KAK düzeyine sahip 11 hastada koroner arter revaskülarizasyonu gerekti. Grup 1 hastalarda karotis arter stenozu ve periferik arter tıkanıklığı tespit edildi. Grup 2'de 12 (%11) hastada izole koroner arter hastalığı (KAH) saptadık. KAH, karotis ve periferik arter hastalığı Grup 1'de daha sıktı (%30'a karşı %16,5) (p=0,0001). Takip süresi içinde Grup 1'de 22, Grup 2'de 32 hastaya koroner revaskülarizasyon gerekti (p=0,003). İzlemde; Grup 1'de 14, Grup 2'de 18 hasta hayatını kaybetti. **Sonuç:** Çalışmamız, pQRS sıklığı ile KAK düzeyi arasında güçlü bir ilişki olduğunu göstermiştir. pQRS olan asemptomatik KBYH'lerde MKSVO'ları önlemek için MDBT kullanılarak KAK skoru araştırılabilir.

Anahtar Kelimeler: Parçalanmış QRS kompleksi; bilgisayarlı tomografi; koroner arter kalsifikasyonu; kronik böbrek hastalığı; kardiyovasküler olaylar

Approximately 25-40% of deaths are related to cardiovascular events in hemodialysis patients.[1,2] In a previous research, fragmented QRS (fQRS) was associated with subclinical left ventricular dysfunction in normal ejection fraction of chronic kidney disease patients (CKDPs).[3] Overall prevalence of fQRS was 60% among CKDPs with a preserved left ventricular ejection fraction (LVEF).[3] Canga et al., and Sheng et

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al. showed that an acute myocardial infarction (AMI) with positive fQRS had higher rates of malignant cardiac arrhythmia, and mortality than the non-fQRS group in a normal population.[4,5] Shengs' study demonstrated that patients of AMI with positive fQRS who underwent early revascularization, might lower incidence of the cardiovascular events.[5] These authors suggested that the presence of fQRS could be used as an indication of early coronary intervention in coronary artery by-pass grafting (CABG) in these patients.[4] Previous investigations demonstrated that fQRS might be associated with myocardial scarring, and ventricular arrhythmia.[5-9]

Coronary artery calcific score was significantly associated with higher estimated coronary artery disease (CAD) risk. Findings of these study supported that the coronary artery calcification (CAC) level may be use as a marker for future cardiovascular events in general population. The prevalance of fQRS in CKDPs has been reported in a limited number of studies.[6] To our knowledge, no study was reported about the relationship between the degree of CAC score and fQRS prevalence.

We report the relationship between fQRS and future cardiovascular events in CKDPs for the first time in the literature.

MATERIAL AND METHODS

The study was performed after approved by Fırat University Non-interventional Research Ethics Committee (14.4.2021, E-97132852-050.01.04-36387). The study was conducted in accordance with the Principles of the Declaration of Helsinki. Informed consent has been signed from the patients. We calculated CAC score using a 64-slices multidetector computed tomography (MDCT) as a non-invasive method prior to electrocardiography (ECG) analyses. Electrocardiograms were analyzed for the presence of fQRS by a blinded cardiologist following a CAC scoring. Transthoracic echocardiography was performed to detect myocardial functions. High sensitivity-C-reactive protein (hs-CRP), intact parathyroid hormone (iPTH), total calcium (Ca) and phosphate (Pi) levels have also been calculated.

Patients with a history of previous myocardial infarction, malignancy, active infection, valvular heart disease, history of cardiac surgery or percutaneous coronary intervention (PCI), or patients who have cardiomyopathy, left bundle-branch block, incomplete or complete right bundle-branch block, and intraventricular conduction delay (duration of QRS>120 ms) on ECG, as well as patients with permanent pacemakers, and investigates who have radioopac allergie were excluded from the study. fQRS has been described acccording the study of Das et al.[3] We detected fQRS in 55 patients (Group 1), and did not in 109 (Group 2).

Fasting blood samples were analyzed for total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, plasma fibrinogen, and, blood Ca-phosphorus levels, osteocalcin (OC) as circulating vascular calcification markers.

Cardiovascular events were defined as non-fatal angina pectoris or myocardial infarction, heart failure requiring hospitalization, and cardiac death. Unstable angina and AMI were diagnosed by the presence of typical angina symptoms, ischemic change or QRS change on ECG, and elevated serum cardiac enzyme levels. Heart failure was diagnosed with typical symptoms such as dyspnea, shortness of breath with systolic or diastolic dysfunction by echocardiography. Cerebrovascular disease was confirmed both by typical symptoms with physical findings and by CT or magnetic resonance imaging. Cardiac death was defined as death with documentation of a significant arrhythmia, cardiac arrest, or death attributable to congestive heart failure or myocardial infarction and sudden death.

MULTI-DETECTOR COMPUTED TOMOGRAPHY PROTOCOL

All MDCTs were taken by 64-MDCT (Somatom Sensation 64, Siemens, Germany). Heart rate of each patient was checked before CT and in patients with more than 70 beat per minute, 50-100 mg of oral beta-blocker agent was given. Images for coronary Ca score were taken before contrast media injection, and scan range was from tracheobronchial bifurcation to diaphragm. Parameters of coronary Ca scan

were 120 Kvp, 33 mAs, slice thickness 0.6 mm, and feed 18 mm. All MDCTs were taken with a single-breath hold (10-12 s). At first, test bolus images were taken using contrast media 10 cc with 4 cc/sec injection flow rate. Housefield unit (HU) of ascending aorta was analyzed by automated time-density calculation program. Every coronary artery was analyzed by 2 methods, segment and diameter. Segmental analysis was according to the 15-segment (American Heart Association model of the coronary tree). Coronary Ca score was analyzed in all MDCT. Ca score was estimated using CAC-analysis software (Cascore, Siemens, Germany) by the Agatston score system with minimal level of 130 HU and every lesion was sorted out according to its score as up to 100, 101 to 400, 401 to 999, and 1,000 or more. All radiologic studies were calculated by a blinded radiologist. Twelve-lead surface resting ECGs (filter range 0.5 Hz to 150 Hz, alternative current filter 60 Hz, 25 mm/s, 10 mm/mV) were taken from the entire study population. All patients were examined in the left lateral decubitus position, and echocardiographic examinations were recorded on commercially available equipment (Vivid 7 GE Medical System, Horten, Norway) with a phased-array 3.5-MHz transducer and tissue Doppler imaging software. According to QRS morphology, the patients were divided into 2 groups. The acquired images were scored with the use of automated software. The degree of CAC was calculated by multiplying the area of each calcified lesion by a weighting factor corresponding to the peak pixel intensity for each lesion to yield a lesion-spesific calcification score. The sum of the scores for each arterial segment and for all arterial lesions, was used for analysis. We examined the proxymal segments of four coronary artery vessels: Left main system, left anterior descending coronary artery, left circumflex artery, and the right coronary artery.

LABORATORY TESTS, ELECTROCARDIOGRAPHY AND ECHOCARDIOGRAPHIC ANALYSES

Blood specimens were collected for biochemical tests. Hemogram, blood urea nitrogen (BUN), creatinine, hs-CRP, fibrinogen, Ca, Pi, LDL, triglyceride, and OC values were measured. An electrocardiograms for the presence of fQRS, and echocardiography were determined by a cardiologist following CAC investigations.

Analysis of the standard 12-lead ECG was performed without using any magnification, and fragmentations were considered to be present if a visually identifiable signal was demonstrated in all complexes of a particular lead.[3] QRS duration was determined by the longest QRS in any lead.

TWO-DIMENSIONAL ECHOCARDIOGRAPHY AND DOPPLER IMAGING

Echocardiographic examination has been performed for each patient by a blinded cardiologist. The conventional M-mode, B-mode and Doppler parameters were measured. LVEF was calculated using the Simpson biplane method including peak early (E) and late (A) diastole and E-wave deceleration time. Because left ventricular diastolic dysfunction (LVDD) is associated with heart failure with cardiovascular events, we measured LVDD using echocardiography. LVDD from Grade I to irreversibly restrictive form (Grade IV) has been observed in all patients. Increase of left atrial pressures (LAPs) was associated with LVDD in our patients. The median LAP was 19±7.1 mmHg.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS version 19.0 (SPSS, Chicago, IL, USA). Continuous and normally distributed variables were expressed as mean±SDs and compared the means by the Student t-test. Mann-Whitney U test was used to compare the differences between 2 groups. Significant variables entered into logistic regression model using statistical technique to predict the most significant determinants for possible interactions and confounding effects. Sensitivity and specificity at different cut-off points were tested by receiver operating charecteristics (ROC) curve. We used multivariate analyses for age, gender, diabetes mellitus (DM), duration of dialysis, current smoking, number of leads with fQRS, and drugs use. The best cut-off number was defined as the point with the highest sum of sensitivity and specificity. On the univariate analyses, explanatory variables with a p value less than 0.1 were selected and entered into a multivariate analysis. All tests in re-

spect to significance were 2 tailed. Unadjusted and adjusted hazard ratios for all-cause and cardiovascular mortality were estimated using Cox proportional regression and were reported with 95% confidence intervals (CIs). p value <0.05 was considered significant.

RESULTS

We included 164 CKDPs for the study. Median age of the patients was 66±12.4 years (range: 19-75 y). Patients' demographics, causes of renal impairment, hypertension, DM, active smoking, and the duration of hemodialysis have been summarized in Table 1. We did not include the patients with history of myocardial infarction, and CABG surgery, patients who have atrial fibrillation, or patients with severe heart failure. Echocardiography was performed by an experienced cardiologist who was anaware of the study. To provide severe complications of diastolic dysfunction, we administered angiotensin-converting enzyme (ACE) inhibitors, or ACE receptor inhibitors, and beta blockers in our patients. Biochemical tests including hemogram, BUN, creatinine, hs-CRP, fibrinogen, Ca, Pi, LDL, triglyceride, and OC values are summarized n Table 2.

fQRS has been detected in 55 CKDPs (33.5%) (Group 1). Number of fQRS was ≥4 leads in 18 patients, while frequency of fQRS was <4 lead (range: 1-3) in the remaining 37 patients. There was no evidence of fQRS in the remaining 109 patients (Group 2). Overall median QRS duration was 89.8±9.90 ms. While median duration of QRS was 103.44±12.10 ms in Group 1 patients, the mean QRS duration was 92.10±11.1 ms in patients without fQRS. This was

TABLE 1: The charactristics of the patients' data on mortality during follow-up.

	n=164	Group 1 (n=55)	Group 2 (n=109)	p value
Age, years*	66±12.4	71.8±19.7	56.14±12.1	0.01
Gender: Men/women	98/66	35/20	63/46	0.71
CAC scores (mean)*	744±443.2	1286±334.6	201±57.6	0.001
Dialysis treatment duration (mean, m)	21.2±6.1	27±9.4	15±7.3	0.022
All-cause mortality*	32 (19.5%)	14 (25.6%)	18 (16.3%)	0.034
Requirement of revascularisation*	54 (32.9%)	22 (40.7%)	32 (24.7%)	0.030
Active smoking	11 (17.1%)	5	6	0.93
Diabetes*	71 (43.2%)	44 (80%)	27 (18.4%)	0.001
Hypertension	46 (87%)	21 (80.7%)	25 (65.7%)	0.68
Left ventricular ejection fraction (%)	58±6.8	55.4±12.6	57±8.5	0.72
Left ventricular mass (g/m²)¥	124±78	164±54	92±42	0.023
Protein excretion (mg/day)¥	2150±1433	3014±1955	1048±911	0.01
BMI, kg/m²	25.2±4.2	26.2±3.0	27.1±2.2	0.86
Systolic blood pressure (mmHg)	149±18	155±14	149±14	0.90
Diastolic blood pressure (mmHg)	90±12	86±11	88±9	0.94
Hemoglobin, g/dL	11.9±1.7	10.6±0.9	11.0±0.3	0.90
Fibrinogen, g/L	5.6±1.3	5.9±1.1	5.4±0.9	0.88
hs-CRP, mg/L*	8.18±2.6	7.16±3.9	4.2±2.43	0.033
Albumin, g/L	38 ± 5	42±6.9	37±9.8	0.74
Fasting glucose, mmol/L	5.9±1.4	5.3±1.4	5.4±0.9	0.94
Reason of chronic kidney disease				
Diabetes (n, %)	71 (43.2)	44 (80)	27 (18.4)	
Glomerulonephritis	14	6	8	
Glomerulosclerosis	16	3	13	
Nephrotic syndrome	30		3	
Other	33	14	19	

*,¥: Statistical significance (p value <0.05); CAC: Coronary artery calcification; BMI: Body mass index; hs-CRP: High sensitivity-C-reactive protein.

TABLE 2: Biochemical analyses and medication of patients.

	Group 1	Group 2	p value
Total cholesterol, mmol/L	5.54±1.15	4.94±1.54	NS
LDL-cholesterol, mmol/L	3.25±0.93	3.44±0.13	NS
HDL-cholesterol, mmol/L	1.41±0.33	1.21±0.13	NS
Triglycerides, mmol/L	1.95±0.81	1.79±0.61	NS
Ca, mmol/L	2.30±0.22	2.19±0.16	NS
Pi, mmol/L*	4.78±0.48	2.58±0.39	S
CaxPi, mmol/L*	7.11±1.27	4.26±1.03	S
iPTH, pg/mL*	537±198	278±196	S
OPG, pmol/L*	9.69±7.21	5.69±6.11	S
OC, ng/mL	60.2±39.7	57.2±30.9	NS
OPN, ng/mL	1475±665	1390±422	NS
ACE inhibitors (n/%)	46/76.3	84/77.6	NS
Beta blocker (n; %)	33/60	78/71.5	NS
Insuline (n; %)	44/80	27/18.4	S
Lipid lowering drug (n; %)	29/52.7	58/53.2	NS

*Number of patients (percent) is given for categorical variables; mean±standard deviation or median (lower-upper quartile) for continuous variables with normal or abnormal distribution; NS: Not significance; S: Significance; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; Ca: Calcium; Pi: Phosphates; iPTH: Intact parathyroid hormone; OPG: Osteoprotegerin; OC: Osteocalcine; OPN: Osteopontine; ACE: Angiotensin converting enzyme.

statistically significant (p=0.002). Mean CAC score of 164 patients was 744±443.2 Agatston unit (AU). The mean CAC score was in Group 1, and Group 2 were 1286±334.6 AU, and 201±57.6 AU, respectively. CAC score was significantly high in patients with fQRS (1286±334.6 vs 201±57.6) (p=0.001). Duration of dialysis in Group 1 and 2 were 16.6±11.4 years, and 9.8±11.4 years, respectively (p=0.022). To detect coronary artery disorders, and/or peripheral arterial system and carotid arteries, we followed both groups. To detect cerebrovascular disorders including carotid artery systems, Doppler ultrasonography was performed by an experienced radiologist who was anaware of the study during follow-up period.

We performed coronary angiography in 17 patients who have high level of CAC score in combination with chest pain with or without ST-segment elevation myocardial ischemia or infarction in Group 1 in the first year follow-up. We observed that there was severe coronary artery occlusion in 11 (10.3%) patients (Figure 1, Figure 2). fQRS was defined by the presence of various RSR' patterns (QRS duration <120 ms) with or without Q wave, which includes an additional R wave (R prime) or notching of the R wave or S wave, or the presence of more than one R prime (fragmentation) without typical bundle-branch block in 2 continuous leads corresponding to a major lead set for major coronary artery territory (Figure 3). PCI with the use of drug eluting stent (n=8), and CABG surgery (n=3) were performed in Group 1 patients, respectively. While median stent use was 2.3±0.7, the mean number of grafts in CABG surgeries was 3.6±1.1. Within the same time, we performed carotid endarterectomy (n=2), and peripheral artery surgery (n=2) in Group 1 patients (7.2%). The median level of CAC score in patients needed revascularization was 870±334 AU.

In Group 2, 12 patients required surgical (n=6 patients) or percutanous interventions for CAD (n=6).

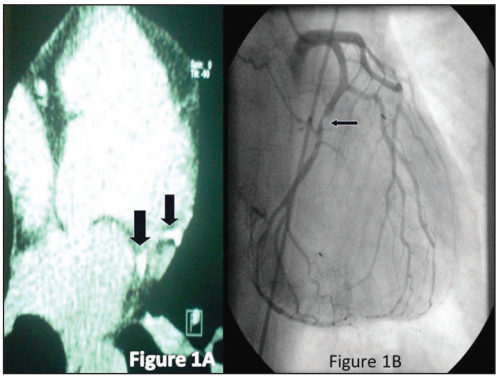

FIGURE 1: Severe coronary artery calcification in the left anterior descending artery (arrows) (1A). We confirmed left anterior descending artery stenosis using traditional angiography which shows severe stenosis in the same patient (1B; arrows head).

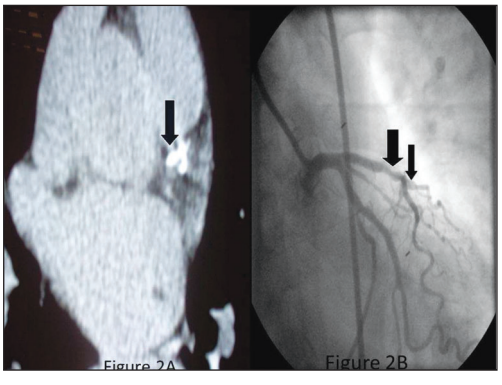

FIGURE 2: Coronary artery stiffness due to severe calcification in the bifurction of left anterior descending and diagonal branch (2A) (black arrow) in a male hemodialysis patient. Tradiational angiography is confirming stenotic lesions (2B).

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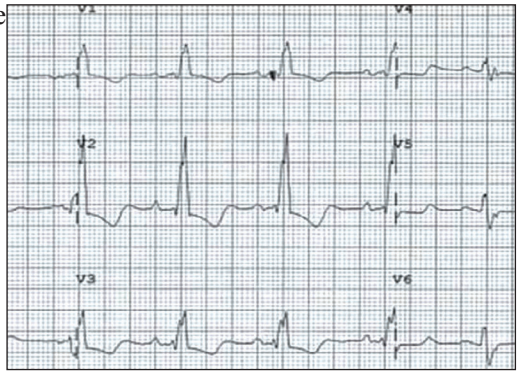

FIGURE 3: 12 lead electrocardiography exhibites QRS fragmentation and depressed ST-segments from V1 to V2 derivation in a 68-year-old female who have chest pain and palpitation.

also performed carotid artery endarterectomy (n=3), and peripheral artery revascularization (n=3) in Group 2 during the first year (11%). Twenty five patients in Group 2 required surgical (n=9) and percutaneous coronary artery revascularization (n=16) during the last 4 years of follow-up (15.5%). Carotid artery stenosis (n=3) and severe peripheral artery occlusion (n=5) which required revascularization using surgery or percutaneous intervention were observed in 8 out of 99 patients in Group 2 (8%). No mortality due to surgery or PCI was seen in both groups in the early period of surgery in both groups.

Overall 22 (40.7%) patients in Group 1, and 32 patients in Group 2 (29%) required coronary revascularisation at the end of follow-up period (p=0.030). Eighteen patients who underwent coronary artery revascularization, severe carotid or peripheral artery disease in Group 1 were older than 70 years old (81.8%). Median number of CAC scores in Group 1, and Group 2 patients were 688±256 AU, and 388±96 AU. When compared with CAC score in both groups, there was a statistically significant difference (p=0.001).

Fourteen patients in Group 1 (25.4%), and 18 patients in Group 2 (16.5%) died (p=0.034). The reasons of death were major adverse outcomes of cerebrovascular events (MACCE) (n=8 vs n=11), sudden cardiac arrest at home (n=3 vs n=4), heart failure (n=2 vs n=2), and cancer (n=1 vs n=1) myocardial ischemia due to coronary artery stenosis developed within 2 years in Group 1 patients who have high CAC score. But, half of the patients had low CAC score (≤100 AU). Number of ECGs derivations with fQRS was significantly higher in patients who required revascularisation than the patients who did not require revascularisation procedure in Group 1 (3.8±1.9 vs 1.9±1.3; p=0.01). In this group, patients with ≥4 leads with fQRS had higher rate of revascularisation and readmission of hospital (41.4% vs 19.9%, p=0.0086) than those patients with <4 leads with fQRS in Group 1. By a multivariate regression analysis, the number of leads with fQRS was found to be a predictor of re-hospitalisation (odds ratio: 1.28, 95% CI: 1.09-1.819, p=0.021).

Overall, 22 patients in Group 1 who underwent revascularisation have been referred to our hospital due to unstable angina pectoris, MACCEs resulted from carotis artery stenosis, and lower extremity ischemia at the end of the follow-up (40%). Totally 38 patients in Group 2 have been referred to our clinic with the complaints of cardiac symptoms, MACCEs, and peripheral artery disease (34.8%). When both groups were compraed with regard to the rate of hospital readmission due to CAD, MACCEs, and peripheral artery disease, there was a statistical significance (p=0.0022). While mortality rate in Group 1 was 25.4% during 5 years period, the mortality rate was 16.5% in Group 2 patients (p=0.001) in the same period. Cumulative survival of both groups is summarized in Figure 4.

No statistical difference was found when compared with regard to blood OC and osteopontine (OPN) levels (p=0.56). There was a significant rela-

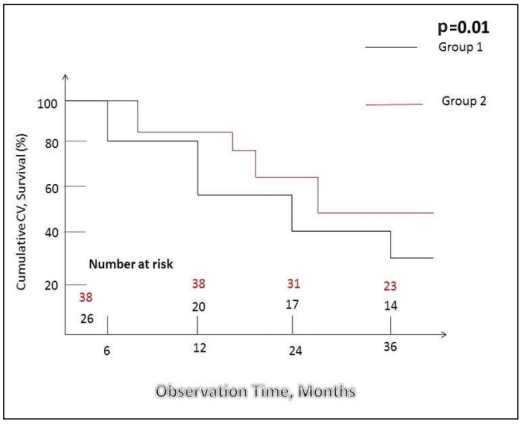

FIGURE 4: Kaplan-Meier cumulative survival analyses shows the mortality rate during follow-up period in patients with or without QRS fragmentation. QRS fragmentation is a significant predictive factor of mortality and morbidity in hemodialyses patients. CV: Cardiovascular.

tionship between fQRS fragmentation and future cardiovascular events, and mortality and patients' age with high level of CAC score. There was no significant difference when compared with regard to blood pressure, medication, body mass index, and gender. Also, the patients' age and CAC score was correlated in both groups.

Biochemical blood analyses including parathormone, Ca and phosphorus production, OC, OPN, hs-CRP have been summarized in Table 2. Serum magnesium and potassium levels in Group 1 were 4.67±0.2 mmol/L, and 3.4±0.9 mg/dL, respectively. In Group 2, blood magnesium and potassium levels were 4.90±0.60, and 4.55±0.9, respectively.

When both groups were compared with regard to Ca-phosphorus production, hs-CRP, parathormone and osteoprotegerin (OPG) levels, there were statistical differences (Table 2). According to our study results, there was a possitive correlation between the prevalance of fQRS, and hs-CRP, diabetes and duration of dialysis time. Simple correlations of variables with CAC score has been summarized in Table 3. Spearman correlation coefficient and independent variables, blood hs-CRP, CaxPi, Pi and OPG, are summarized in Table 4. Multiple Cox regression analyses showed significant predictors of all-cause mortality and fQRS.

Echocardiographic investigations including LVDD, ventricular hypertrophy, left ventricular mass, left atrial volume and pressure are summarized in Table 5. LVDD has been observed from Grade-I to irreversibly restrictive diastolic dysfunction (Grade IV) in nearly one-third of patients. The ROC curve that the cutoff of CAC score for predicting future cerebrocardiovascular events with 81.9% sensitivity and 76.1% specificity. Area under the curve=0.705; 95% CI=0.644 to 0.870 (p=0.0022) (Figure 5).

DISCUSSION

We presented the importance of fQRS, and its relationship between CAC score in CKDPs using MDCT as a non-invasive and effective method. Our study results showed that all-cause mortality and morbidity, and cardiovascular events such as MACCE or myocardial infartion or ischemia were higher in CKDPs

TABLE 3: Simple correlations of selected variables with CAC scores.

Independent variable	Spearman correlation coefficient	p value
Age	0.12	0.001
Duration of dialysis	0.02	0.022
FRS, points	0.27	0.035
FRS, three-year risk	0.28	0.04
Ca	0.0022	0.001
Pi	0.08	0.6
CaxPi	0.012	0.041
hs-CRP	0.17	0.003
iPTH	-0.024	0.044
OPG	0.36	0.003
OC	-0.14	0.3
OPN	-0.02	0.9

CAC: Coronary artery calcification; FRS: Framingham risk score; Ca: Calcium; Pi: Phosphates; hs-CRP: High sensitive-C-reactive protein; iPTH: Intact parathyroid hormone; OPG: Osteoprotegerin; OC: Osteocalcine; OPN: Osteopontine.

TABLE 4: Significant predictors of all-cause and cardiovascular mortality in multiple Cox regression. The models additionally included fQRS, hs-CRP, CaxPi, Pi and OPG as independent variables.

	All-cause mortality		Cardiovascular mortality	
Independent variable	HR (95% CI)	p value	HR (95% CI)	p value
CACS*, 100 Agatston units	1.03 (1.0-1.04)	0.0021	1.02 (1.0-1.36)	0.001
hs-CRP, mg/L	1.05 (1.02-1.09)	0.002	1.05 (1.01-1.09)	0.01
CaxPi	1.13 (1.01-1.20)	0.01	1.03 (1.0-1.42)	0.002
Pi	1.02 (1.33-1.22)	0.01	1.53 (1.10-1.79)	0.004
OPG	1.26 (1.05-1.44)	0.01	1.43 (1.10-1.61)	0.004
fQRS	1.06 (1.01-1.04)	0.001	1.30 (1.12-1.70)	0.001

*In case of coronary artery calcification, hazard ratio per 100 Agatston units' increase is given; hs-CRP: High sensitive-C-reactive protein; Ca: calcium; Pi: Phosphates; OPG: Osteoprotegerin; CI: Confidence intervals.

TABLE 5: Echocardiographic findings of patients. Left ventricular diastolic and systolic function, ventricular and atrial diameters

	Group 1	Group 2	p value
LVEDV (mm³)	90±60	180±55	NS
LVEDD (mm)	71±13	76±18	NS
LVESV (mm³)	144±60	151±70	NS
LVESD (mm)	59±9	61±12	NS
Left Atr. D (mm)	48±4	50±9	NS
LAV (mL/m²)	34.1	35.6	NS

LVEDV: Left ventricular end diastolic volume;
LVEDD: Left ventricular end diastolic diameter;
LVESV: Left ventricular end systolic volume;
LVESD: Left ventricular end systolic diameter; Left Atr. D: Left atrial diameter;
LAV: Left atrial volume; NS: Non-significant.

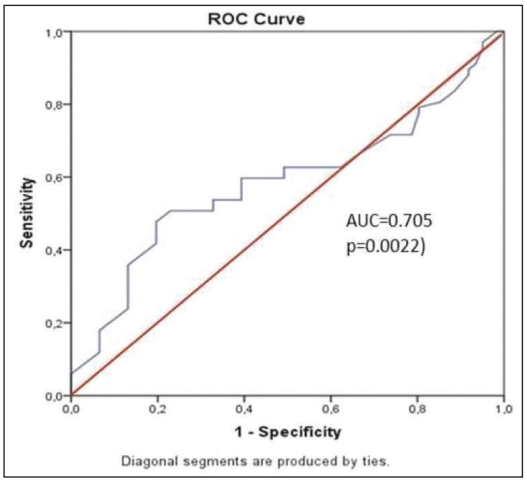

FIGURE 5: Sensitivity and specificity at different cut-off points using the ROC curve. Multivariate analysis (age, sex diabetes mellitus, duration of dialyses, number of leads with fQRS) shows an AUC of 0.705 (p=0.0022). Number of fQRS greater than 3 is associated with future cardiovascular event with sensitivity of 0.625, and a specificity of 0.575 in hemodialysis patients. ROC: Receiver operating characteristics; AUC: Area under curve.

with fQRS compared with the same patients without fQRS during follow-up period. Our study analysis demonstrated that there was significantly higher cardiovascular events in patients with fQRS. We also showed that there was a strong relationship between fQRS and CAC in end-stage kidney disease patients. Therefore, fQRS on an ECG may be accepted as a marker of myocardial perfusion abnormalities and/or myocardial fibrosis. Number of derivations with fQRS was correlated with CAC levels. Based on our study results, we can consider that fQRS may be used in predicting future cardiovascular events in asymptomatic CKDPs who have high CAC scores. We think that localized myocardial ischemia may be due to abnormalities of blood flow in the microvascular area. Patients with ≥4 leads with fQRS had higher rate of revascularisation and readmission of hospital than those patients with <4 leads with fQRS.

As we know that fQRS complex on ECG in myocardial infarction has been associated with adverse cardiac events, and it can be associated with subclinical myocardial dysfunction in normal population with normal ejection fraction.[5,10-15] Previous publications showed that the presence of fQRS was associated with a rise in cardiovascular events and mortality in the future.[6-9] This association is thought to result from myocardial scarring and ventricular arrhythmia.[6-9]

Cross-sectional evidence has shown that in patients with end-stage CKD, high CAC score correlated with many risk factors for death including older age and diabetes.[10-12] However, these authors did not research fQRS in 12-lead ECG, and its relationship between CAC score and fQRS in these patients. We believe that fQRS in ECG may be investigate in addition to risk factors such as diabetes and age in order to reduce mortality and morbidity in patients with chronic renal failure. Prospective studies demonstrated that CKDPs and normal population with CAC score have an increased risk of sudden cardiovascular events compared with those with low or no coronary calcification.[14-17] Since the development of serious arrhythmias due to myocardial scarring due to silent ischemia and myocardial scarring is one of the causes of sudden death.

Follow-up period of our patients demonstrated that the rate of cardiovascular events and mortality were significantly high in Group 1 patients. The presence of fQRS accompanied with high CAC score could increase the incidence of future cardiovascular events and readmission to hospital for which reason they constitute one of the risk factors for cardiovascular events in CKDPs.

Mortality was associated with the presence of coronary calcification in non-dialyzed patients with CKD and a severe CAC score was a predictor of cardiovascular events in these patients.[18] Matsuoka et al.

suggested that CAC score was an independent predictor of death in patients on chronic hemodialysis.[19] However, the authors have not investigated the incidence of fQRS. According to Matsuokas' study, patients with a high CAC score should be carefully monitored and evaluated for reversible prognostic factors such as hyperphosphatemia and a value for the Ca-phosphate.[15] According to Caliskan et al., CAC score was associated with decreased coronary blood flow in hemodialysis patients.[20] This may be the cause of high mortality and morbidity. Thus, fQRS in asymtomatic CKDPs with coronary calcific disease may be evaluated. The relatioship between vascular calcification and cardiac repolarization abnormality in chronic renal disease patients with arterial stiffness has been investigated by Di lorio et al., and Vo et al.[21,22] Torigoe et al. suggested that if there was a fQRS in more than 3 leads, cardiac death or hospitalization related to heart failure in patients with prior MI.[23]

Cardiovascular events as a result of heavy vascular calcification is significantly high in these patients when compared to normal population. We hypothesised that fQRS as a heterogeneous depolarization of the myocardium with or without any conduction anomaly may be related to silent myocardial ischemia resulting from microangiopathy. Presence of fQRS being in relation with CAC score suggests that subclinical myocardial fibrosis may be widespread in asymptomatic CKDPs. Based on these findings, the presence of fQRS in CKDPs can be used as a marker of higher coronary calcific score and future cardiovascular events.

STUDY LIMITATIONS

The main limitation of this study is that the patient numbers are limited. We showed many correlations between the fQRS and laboratory measurements including hs-CRP, OC, fibroblast growth factor, osteopontin, iPTH, Ca and Pi. Since no previous similar studies have been performed in this patient group, our study may be supported by prospective controlled studies with a large number of patients.

CONCLUSION

In conclusion, to decrease mortality and morbidity of CKDPs, fQRS in combination with high CAC score may be accepted as a new indicator of sudden cardiovascular complications in these particular patients. We have shown the incidence of fQRS and its relationship between future cardiovascular events in CKDPs for the first time.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Davut Azboy, Zeki Temiztürk;* ***Design:*** *Davut Azboy;* ***Control/Supervision:*** *Davut Azboy;* ***Data Collection and/or Processing:*** *Davut Azboy, Zeki Temiztürk;* ***Analysis and/or Interpretation:*** *Davut Azboy, Zeki Temiztürk;* ***Literature Review:*** *Davut Azboy;* ***Writing the Article:*** *Davut Azboy;* ***Critical Review:*** *Davut Azboy;* ***References and Fundings:*** *Davut Azboy;* ***Materials:*** *Davut Azboy, Zeki Temiztürk.*

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