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Assessment of the relationship between red cell distribution width and fragmented QRS in patients with non-ST elevated acute coronary syndrome

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Background: Red cell distribution width (RDW) and fragmented QRS (fQRS) complexes have also been reported to be predictors of cardiac events and all-cause mortality in coronary artery disease (CAD). We aimed to investigate the association of serum red cell distribution width (RDW) levels and fQRS in patients with non-ST elevated acute coronary syndrome (NST-ACS).





Material/Methods: We retrospectively evaluated a total of 251 patients (191 men and 60 women) with NST-ACS. The NST-ACS consisted of unstable angina (UA) and non-ST elevated myocardial infarction (NSTEMI). The fQRS pattern was defined as the presence of an additional R' or crochetage wave, notching in the nadir of the S wave or fragmentation of the RS or QS complexes in 2 contiguous leads corresponding to a major coronary artery territory. The relationships between the RDW and fQRS were assessed.

Results: The patients in the fQRS group were older, left ventricular ejection fraction (LVEF) levels were significantly lower, and baseline RDW and troponin levels were significantly higher than in the group without fQRS. There were positive correlations between age, number of coronary arteries narrowed, and RDW, and negative correlations between triglyceride, LVEF, and RDW in study patients. There were positive correlations between number of fQRS leads, age, and RDW, and negative correlations between triglyceride, LVEF, and RDW in NSTEMI patients.

Conclusions: Our results indicate that an elevated RDW values is associated with fQRS in NST-ACS. Elevated RDW values and fQRS together may be useful for identifying NSTEMI patients in NST-ACS.

MeSH Keywords: **Fragmented QRS • Acute Coronary Syndrome • Erythrocyte Indices – physiology**

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Background

Acute coronary syndrome (ACS) is a significant cause of morbidity and mortality in patients with coronary heart diseases. It is important to identify high-risk patients and determine who will be treated immediately in ACS. Red cell distribution width (RDW) and fragmented QRS (fQRS) complexes are predictors of cardiac events and all-cause mortality in these patients [1–3].

RDW, a measurement of variability and size of erythrocytes, can be easily measured during routine complete blood counts (CBC). The relationship between RDW and coronary artery disease (CAD), heart failure (HF), and stroke has been found in recent studies [4–6]. High RDW levels were associated with adverse outcomes in patients with ST elevation myocardial infarction (STEMI) and HF [5,7]. A relationship of RDW with adverse outcomes in these patients is not completely understood. Inflammation may bring about changes in red blood cell maturation by disturbing the red cell membrane, leading to increased RDW [8]. The correlation between RDW and inflammatory markers has also been reported [9].

The fragmented QRS (fQRS) complexes are novel electrocardiographic signals, which reflect the altered ventricular conduction delays around the regions of a myocardial scar. The presence of fQRS in the resting 12-lead electrocardiogram (ECG) revealed an increased risk for adverse outcomes. fQRS has been reported to be a predictor of cardiac events and all-cause mortality in CAD patients [10,11]. The relationship of systemic inflammation with the presence of fQRS in patients with ACS has been studied previously [12]. In this study, we investigated the association of serum RDW levels and fQRS in patients with NST-ACS.

Material and Methods

Study population

Records of patients with ACS defined as unstable angina (UA) and non-ST elevated myocardial infarction (NSTEMI) who were admitted to the coronary care unit of our institution between January 2011 and April 2012 were evaluated retrospectively. UA was diagnosed by typical chest pain and/or electrocardiographic changes indicating myocardial ischemia with negative cardiac enzymes. NSTEMI diagnosis was based on elevated cardiac enzymes with typical chest pain and/or electrocardiographic changes suggestive of myocardial ischemia. Typical chest pain was evaluated as more than 20 min in duration, new-onset angina, and an increase in its frequency and duration or severity. We excluded patients with clinical evidence of cancer, active infection, hematological proliferative diseases, active or chronic inflammatory or autoimmune diseases, pregnancy, recent

blood transfusion, a history of chronic obstructive pulmonary disease, a typical bundle-branch block pattern (QRS ≥ 120 ms) or incomplete right bundle-branch block pattern, permanent atrial fibrillation, ventricular paced rhythm, a previously implanted implantable cardioverter-defibrillator (ICD) or a clinical indication for an ICD at the time of enrollment, left ventricular hypertrophy, Wolff-Parkinson-White syndrome, cardiomyopathy, myocarditis, or congenital heart disease. There were 91 patients excluded from the final analysis: 24 patients with incomplete right bundle-branch block pattern, 18 patients with typical bundle-branch block pattern, 15 patients with chronic obstructive pulmonary disease, 14 patients with permanent atrial fibrillation, 11 patients with active infection, and 9 patients with left ventricular hypertrophy. Therefore, a total of 251 patients who were diagnosed with NST-ACS were included in the analysis in this study. Demographic information, cardiovascular history, smoking status, hypertension (HT), and diabetes mellitus (DM) status of patients were obtained from the medical records. Patients who had been treated with antihypertensive drugs or those whose baseline blood pressure exceeded 140/90 mm Hg were diagnosed with HT. DM was defined as fasting blood sugar more than 126 mg/dL or the use of anti-diabetic medications.

Electrocardiography

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

Analysis of blood samples

Complete blood counts and biochemical values were evaluated retrospectively from blood samples obtained by antecubital vein puncture upon admission to the emergency department. Hemogram parameters and other biochemical measurements using standard biochemical techniques were determined with the Beckman Coulter LH 780 (Beckman Coulter Ireland Inc., Mervue, Galway, Ireland) device in the hematology laboratory of our institution.

Echocardiography

Transthoracic echocardiography was immediately performed on each patient in the coronary care unit. All measurements were performed using a commercially available machine (Vivid 7[®], GE Vingmed Ultrasound A/S, Horten, Norway) with a 3.5-MHz transducer. Simpson's method was used to assess the LVEF, as recommended by the American Society of Echocardiography [13].

Table 1. The baseline characteristics of patients with or without fragmented QRS.

| Variable | fQRS(+) group n=63 | | fQRS(-) group n=188 | | P value |
|--|-----------------------|----------|------------------------|----------|---------|
| Male % (n) | 84.1 | (53) | 73.4 | (138) | 0.084 |
| Age (yrs) | 65 | (30–90) | 59.5 | (30–88) | 0.018 |
| Heart rate, bpm | 78 | (52–126) | 80 | (46–115) | 0.661 |
| Hypertension % (n) | 52.4 | (33) | 50.5 | (95) | 0.799 |
| Diabetes mellitus % (n) | 22.2 | (14) | 28.7 | (54) | 0.315 |
| Current smoker % (n) | 36.5 | (23) | 41 | (77) | 0.532 |
| BMI (kg/m ²) | 27.1±3.9 | | 27.5±3.7 | | 0.458 |
| Previous MI % (n) | 7.9 | (5) | 10.1 | (19) | 0.612 |
| Number of coronary arteries narrowed % (n) | | | | | 0.655 |
| 1 | 33.3 | (21) | 34 | (64) | |
| 2 | 38.1 | (24) | 33 | (62) | |
| 3 | 28.6 | (18) | 33 | (62) | |
| Culprit lesion% (n) | | | | | 0.219 |
| LAD | 34.9 | (22) | 42 | (79) | |
| Cx | 42.9 | (27) | 30.9 | (58) | |
| RCA | 22.2 | (14) | 27.1 | (51) | |
| LV EF (%) | 50 | (25–65) | 55 | (25–65) | 0.031 |
| NSTEMI% (n) | 76.2 | (48) | 59 | (111) | 0.015 |

fQRS – fragmented QRS; NSTEMI – non ST elevated myocardial infarction; BMI – body mass index; MI – myocardial infarction; LAD – left anterior descending; Cx – circumflex; RCA – right coronary artery; LV EF – left ventricular ejection fraction.

Coronary angiography

Angiographic data of the patients were evaluated from catheter laboratory records. All patients underwent a coronary angiography by femoral approach using the standard Judkin's technique. Iopromide as a contrast agent (Ultravist-370, Bayer Schering Pharma, Germany) and 6F diagnostic catheter were used in all subjects. Stenosis diameter $\geq 70\%$ with quantitative angiography was accepted as significant.

Statistical analysis

All statistical studies were carried out with the SPSS program (version 17.0, SPSS, Chicago, Illinois). Quantitative variables are expressed as the mean value \pm standard deviation or median (interquartile range), and qualitative variables were expressed as percentages (%). The study population was divided into 2 groups based on presence of fQRS. A comparison of parametric values between the groups was performed using the Student's *t* test for normally distributed parameters

or Mann-Whitney U test for non-normally distributed parameters. Categorical variables were compared by the likelihood ratio chi-square test or Fisher exact test. Spearman correlation analysis was used for determining association between RDW with clinical and laboratory findings for both the study population and NSTEMI patients. Stepwise linear regression analysis was performed to determine independent variable related to RDW. P value < 0.05 was considered statistically significant.

Results

A total of 251 patients (191 men and 60 women) were enrolled. The fQRS pattern was defined in 63 patients (fQRS+ group) and was not defined 188 patients (fQRS- group). In the analyzes of the study groups, no significant differences were found between the groups regarding sex, body mass index, HT, DM, number of coronary arteries narrowed, culprit lesion, heart rate, current smoker status, and previous MI history. The patients with fQRS group were older than in the group without fQRS (65 [30–90]

Table 2. The laboratory findings of patients with or without fragmented QRS.

| Variable | fQRS(+) group n=63 | | fQRS(-) group n=188 | | P value |
|--|-----------------------|--------------|------------------------|--------------|---------|
| T cholesterol (mg/dl) | 195 | (98–315) | 191 | (99–445) | 0.548 |
| LDL (mg/dl) | 121 | (11–246) | 120 | (39–312) | 0.780 |
| HDL (mg/dl) | 39 | (6–95) | 41 | (3–144) | 0.236 |
| Triglyceride (mg/dl) | 116 | (35–673) | 114 | (32–1950) | 0.533 |
| MPV (µm ³) | 8.63±1.05 | | 8.63±0.95 | | 0.969 |
| MCV (fL) | 89.8 | (66.1–109.2) | 88.7 | (64–107.1) | 0.391 |
| PLT (10 ³ /mm ³) | 231 | (118–433) | 232 | (79–501) | 0.294 |
| RDW % | 14.4 | (12.5–18.7) | 13.9 | (11.7–18.5) | 0.019 |
| WBC (10 ³ /mm ³) | 10 | (4.6–17.3) | 9.2 | (3.8–19) | 0.161 |
| Neutrophil (10 ³ /mm ³) | 5.94 | (2.77–14.72) | 5.89 | (1.3–15.52) | 0.711 |
| Lymphocyte (10 ³ /mm ³) | 2.12 | (0.8–5.39) | 2.21 | (0.54–12.26) | 0.513 |
| Hemoglobin (g/dL) | 13 | (8.5–16.4) | 13.3 | (7.7–17.3) | 0.222 |
| Hematocrit (%) | 39.4 | (27.2–49.5) | 39.7 | (22.1–50.6) | 0.599 |
| Troponin (ng/ml) | 3 | (0–88) | 1.4 | (0–68) | 0.02 |

LDL – low-density lipoprotein; HDL – high-density lipoprotein; MPV – mean platelet volume; MCV – mean corpuscular volume; PLT – platelet; RDW – red cell distribution width; WBC – white blood cell.

vs. 59.5 [30–88], p=0.018). The fQRS+ group’s LVEF levels were significantly lower than in the group without fQRS (50 [25–65] vs. 55 [25–65], p=0.031). In patients in the fQRS group, there was an increased incidence of NSTEMI (76.2% vs. 59%, p=0.015). Table 1 demonstrates the baseline characteristics of the groups.

There were no significant differences found between groups in levels of total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride, mean platelet volume (MPV), mean corpuscular volume (MCV), platelet (PLT), white blood cell (WBC), neutrophil, lymphocyte, hemoglobin, and hematocrit. Baseline RDW and troponin levels were significantly higher in the fQRS group (p=0.019 and p=0.02, respectively). Table 2 demonstrates the laboratory findings of patients with or without fragmented QRS.

There were positive correlations between age, number of coronary arteries narrowed, and RDW (r=0.270, p<0.001 and r=0.190, p=0.002, respectively), there were negative correlations between triglyceride, LVEF, and RDW (r=-0.140, p=0.027 and r=-0.229, p<0.001, respectively) in study patients. Table 3 shows the correlations between RDW and clinical findings in study patients.

There were positive correlations between number of fQRS leads, age, and RDW (r=0.239, p=0.002 and r=0.238, p=0.003, respectively), and negative correlations between triglyceride, LVEF,

and RDW (r=-0.201, p=0.011 and r=-0.251, p=0.001, respectively) in NSTEMI patients. Table 4 shows the correlations between RDW and clinical findings in NSTEMI patients.

Independent predictors of RDW were determined by a backward stepwise multivariate regression analysis in the entire study population and NSTEMI patients. Age and LVEF were found to be associated with RDW in the entire study population. Age and LVEF were found to be independent predictors of RDW in multivariate analyses [β: 0.22, 95% CI: 0.01–0.03, p<0.001 and β: -0.04, 95% CI: -(0.04–0.016), p<0.001, respectively]. Age, LVEF, number of fQRS leads, and LDL were found to be associated with RDW in NSTEMI patients. Age, LVEF, number of fQRS leads, and LDL were found to be independent predictors of RDW in multivariate analyses [β: 0.15, 95% CI: 0.01–0.03, p=0.036; β: -0.27, 95% CI: -(0.05–0.01), p<0.001; β: 0.17, 95% CI: 0.02–0.29, p=0.018; and β: 0.17, 95% CI: 0.001–0.009, p=0.018, respectively]. Table 5 shows the multivariate regression analysis results for independent variables related to RDW. The relationship between RDW and number of fQRS leads in NSTEMI patients is shown in Figure 1.

Discussion

Our study results demonstrate that an elevated RDW value is associated with fQRS in patients with NST-ACS. High RDW

Table 3. Correlation analyses between RDW and clinical findings in study patients.

| Variable | r value | P value |
|--------------------------------------|---------|---------|
| T cholesterol (mg/dl) | 0.022 | 0.733 |
| LDL (mg/dl) | 0.116 | 0.068 |
| HDL (mg/dl) | -0.028 | 0.658 |
| Triglyceride (mg/dl) | -0.140 | 0.027 |
| Number of leads | 0.115 | 0.069 |
| LV EF | -0.229 | <0.001 |
| Age (yrs) | 0.270 | <0.001 |
| Number of coronary arteries narrowed | 0.190 | 0.002 |

LDL – low-density lipoprotein; HDL – high-density lipoprotein; LV EF – left ventricular ejection fraction.

Table 4. Correlation analyses between RDW and clinical findings in NSTEMI patients.

| Variable | r value | P value |
|--------------------------------------|---------|---------|
| T cholesterol (mg/dl) | 0.046 | 0.564 |
| LDL (mg/dl) | 0.143 | 0.072 |
| HDL (mg/dl) | -0.028 | 0.729 |
| Triglyceride (mg/dl) | -0.201 | 0.011 |
| Number of leads | 0.239 | 0.002 |
| LV EF | -0.251 | 0.001 |
| Age (yrs) | 0.238 | 0.003 |
| Number of coronary arteries narrowed | 0.074 | 0.351 |

LDL – low-density lipoprotein; HDL – high-density lipoprotein; LV EF – left ventricular ejection fraction.

Table 5. Multivariate regression analysis results for independent variables related to RDW.

| | All study population | | |
|----------------------|----------------------|---------------|--------|
| | β | 95% CI | p |
| Age | 0.22 | 0.01–0.03 | <0.001 |
| LVEF | -0.04 | -(0.04–0.016) | <0.001 |
| | NSTEMI patients | | |
| | β | 95% CI | p |
| Age | 0.15 | 0.01–0.03 | 0.036 |
| LVEF | -0.27 | -(0.05–0.01) | <0.001 |
| Number of fQRS leads | 0.17 | 0.02–0.29 | 0.018 |
| LDL | 0.17 | 0.001–0.009 | 0.018 |

LVEF – left ventricular ejection fraction; LDL – low-density lipoprotein; CI – confidence interval.

values are positively correlated with the number of fQRS leads in NSTEMI patients. We found that the patients were older and LVEF was significantly lower in the fQRS group, similar to findings of previous studies [1,2]. To our knowledge, this is the first study to evaluate the association between high RDW values and fQRS.

The RDW, an indicator of the variability of the circulating RBC size, is often used to diagnose different types of anemia. Recent studies have reported the relationship between RDW and CAD, HF, and stroke [4–6]. Felker et al. [3] and Uyarel et al. [7] reported that high RDW levels were associated with adverse outcomes in patients with HF and STEMI, respectively. A relationship of RDW with adverse outcomes in these patient groups has not been completely explained. Weiss et al. demonstrated that inflammation may bring about the changes

in red blood cell maturation by disturbing the red cell membrane, leading to increased RDW [8]. On the other hand, Lippi et al. reported a correlation between RDW and inflammatory markers such as C-reactive protein (CRP) and sedimentation rate [9]. Furthermore, Cengiz et al. [14] and Kim et al. [15] reported an association between the RDW and advanced fibrosis in non-alcoholic steatohepatitis. These results suggest that inflammation may be a key factor underlying the biological mechanism of increased RDW values.

fQRS is defined by unexpected deviations in QRS morphology and the specific cause of fractionation on surface ECG, but the determinants of this phenomenon are not completely understood. Theoretically, fQRS is generally accepted to be derived from regional myocardial fibrosis/scar and ischemia, which cause heterogeneous myocardial electrical activation

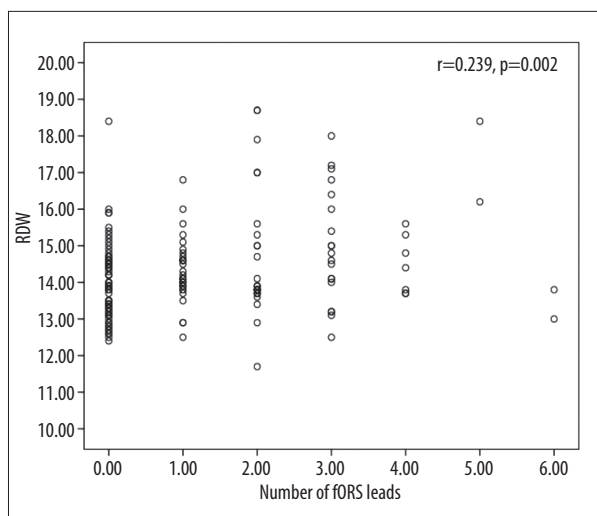


Figure 1. Relationship between red cell distribution width (RDW) and number of fQRS in non-ST elevation myocardial infarction (NSTEMI) patients.

[16–20]. In patients with ischemic or nonischemic LV dysfunction, fQRS has been shown to be related to myocardial fibrosis [21]. Though the clinical importance is known, it is not yet used for direct detection of myocardial fibrosis as a noninvasive technique [22]. Transesophageal echocardiography (TEE), cardiac magnetic resonance imaging (CMRI), and endomyocardial biopsy (EMB) are diagnostic methods for determining cardiac fibrosis [23–25]. TEE and EMB are invasive techniques and CMRI is expensive and not available at every center. Pietrasik has reported on the sensitivity of fQRS in detecting myocardial scars, and postulated that the presence of fQRS could be a good predictor of cardiac events [26]. Das et al. reported that the fQRS complex is a highly sensitive and specific marker of myocardial fibrosis and may be a strong marker in detecting myocardial fibrosis [10]. Peters et al. demonstrated that fQRS is a diagnostic sign of arrhythmogenic right ventricular dysplasia or cardiomyopathy, which is associated with right ventricular scarring [27]. In addition, there is evidence that fQRS could play an important role as a screening and prognostic tool in patients with Brugada syndrome, long QT syndrome, arrhythmogenic right ventricular dysplasia, and cardiac sarcoidosis [26]. Furthermore, Kadi et al. showed that fQRS is increased even in patients with rheumatoid arthritis without cardiovascular disease [28]. The presence or absence of fQRS on admission to emergency departments has been demonstrated in some clinical trials to be related to prognosis and irreversible ischemia in patients with STEMI and NSTEMI [11,29,30]. These findings not only establish the relationship between fQRS and fibrosis, but also myocardial ischemia in patients with ACS.

These results suggest that the presence of an fQRS complex is an easily evaluated, noninvasive electrocardiographic parameter and that fQRS complex is associated with cardiac fibrosis and/or ischemia.

Study limitations

The present study has some limitations. Firstly, this was a retrospective study based on a relatively small group of patients, and additional prospective data are needed in a larger study population to confirm our findings. Secondly, RDW values may increase in some conditions such as impaired iron metabolism, suppressed erythropoietin gene expression, inhibition of proliferation of erythroid progenitor cells, down-regulation of erythropoietin receptor expression, and reduced erythrocyte circulatory half-life [8]. Elevated RDW levels are associated with levels of iron and vitamin B12, folate deficiency, reticulocyte count, erythropoietin levels, and measures of hemolysis, but our study did not measure these parameters. Thirdly, one of the most important limitations is the failure to measure inflammation parameters such as high-sensitivity CRP and MMP-9, which could be helpful in evaluating the relationship between RDW and fQRS.

Conclusions

Results of the present study indicate that an elevated RDW value is associated with fQRS in patients with NST-ACS. It appears that the mechanistic link between elevated RDW values and fQRS is a result of the effect of an inflammatory process, fibrosis, and/or ischemia in NST-ACS. RDW levels and ECG are routine, simple, and inexpensive methods for evaluating patients with acute coronary syndromes. In addition, elevated RDW values and fragmentations on ECG together may be useful for identifying NSTEMI patients in NST-ACS. The RDW and fQRS might be helpful to determine high-risk patients and treatment strategies.

Declaration of conflicting interests

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