Relationship between red cell distribution width and contrast-induced nephropathy in patients who underwent primary percutaneous coronary intervention

Primer perkütan koroner girişim uygulanan hastalarda eritrosit dağılım genişliği ile kontrast madde nefropatisi arasındaki ilişki

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ABSTRACT

Objective: This study evaluated the relationship between contrast-induced nephropathy (CIN) and red cell distribution width (RDW) in patients who underwent primary percutaneous coronary intervention (PCI).

Methods: A total of 359 patients with ST elevation myocardial infarction (STEMI) who had undergone primary PCI were included in the study. An increase of 25% in serum creatinine value after 48 h, or an increase of >0.5 mg/dL in the basal value was defined as CIN.

Results: Of the patients included in the study, 49 (13.8%) developed CIN. Compared to the CIN-negative group, CIN-positive patients had increased RDW values (16.9±2.00 and 14.8±2.14 respectively, p<0.001). The latter were also older patients, and had increased age rates of diabetes mellitus, baseline creatinine, Δ-creatinine and amount of contrast media were higher and left ventricular ejection fraction and baseline glomerular filtration rate (GFR) were lower in the CIN-positive group than in the CIN-negative group. A statistically weak correlation was found between RDW and change in creatinine levels (Δ-creatinine) (r=0.250, p=0.002). Diabetes mellitus (odds ratio [OR]: 3.252, 95% CI=1.184-8.951, p=0.022), high RDW (OR: 1.716, 95% CI=1.363–2.157, p<0.001), baseline low GFR (OR: 0.941, 95% CI=0.925–0.971, p<0.001), Δ-creatinine (OR: 1.197, 95% CI=1.061-2.986, p=0.006) and increased amount of contrast media (OR: 1.187, 95% CI=1.048–3.02, p=0.001) used were observed as independent predictors of CIN.

Conclusion: The study found diabetes mellitus, high RDW, basal low GFR, Δ-creatinine and increased contrast amount used to be the independent predictors of CIN in STEMI patients who underwent PCI.

ÖZET

Amaç: Bu çalışmada, primer perkütan koroner girişim (PKG) uygulanan hastalarda eritrosit dağılım genişliği (EDG) ile kontrast madde nefropatisi (KMN) arasındaki ilişkiyi incelemeyi amaçladık.

Yöntemler: Çalışmaya ST yükselmeli miyokart enfarktüsü (STYME) nedeniyle primer PKG uygulanan toplam 359 hasta alındı. Başlangıç değerlere göre PKG'den 48 saat sonra serum kreatinin değerinin %25 ya da 0.5 mg/dl'nin üzerinde artması KMN olarak tanımlandı.

Bulgular: Çalışmaya alınan hastaların %13.8'inde KMN gelişti. EDG değerleri KMN gelişen grupta KMN gelişmeyen gruba göre anlamlı derecede daha yüksekti (sırasıyla, 16.9±2.00 ve 14.8±2.14, p<0.001). KMN gelişen grupta KMN gelişmeyen gruba göre, yaş, diabetes mellitus sıklığı, başlangıç kreatinin, Δ- kreatinin ve kontrast madde miktarı belirgin olarak daha yüksek iken sol ventrikül ejeksiyon fraksiyonu ve başlangıç glomerül filtrastyon hızı (GFH) daha düşüktü. EDG ile kreatinin seviyesindeki değişiklik (Δ- kreatinin) arasında istatistiksel olarak zayıf ilişki saptandı (r=0.250, p=0.002). Diabetes mellitus (odds oranı [OO]: 3.252, %95 GA=1.184–8.951, p=0.022), yüksek EDG (OO: 1.716, %95 GA=1.363–2.157, p<0.001), başlangıç düşük GFH (OO: 0.941, %95 GA=0.925–0.971, p<0.001), kreatinin seviyesindeki değişiklik (Δ- kreatinin) (OO 1.197, %95 GA 1.061–2.986, p=0.006) ve yüksek kontrast madde miktarı (OO: 1.187, %95 GA=1.048–3.02, p=0.001) KMN gelişimi için bağımsız öngördürücüler olarak gözlendi.

Sonuç: Diabetes mellitus, yüksek EDG, başlangıç düşük GFH, kreatinin seviyesindeki değişiklik ve yüksek kontrast madde miktarı, STYME nedeniyle primer PKG uygulanan hastalarda KMN için bağımsız öngördürücülerdir.

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Contrast induced nephropathy (CIN) is an acute renal insufficiency defined as a 25% or 0.5 mg/dL increase over the baseline of the serum creatinine level 24 h to 72 h after intravascular administration of a contrast agent in the absence of another cause.[1,2] It follows decreased renal perfusion and administration of nephrotoxic medications as the third most common cause of renal insufficiency during hospitalization.[3] The risk of CIN increases in the presence of pre-existing renal disease, advanced age, hypertension, and diabetes mellitus. The amount of contrast agent administered is also a risk factor.[4,5] Renal ischemia caused by anemia increases the incidence of CIN, and earlier studies have indicated the increased incidence of CIN in patients with high C-reactive protein (CRP) levels.[6] Among other diagnostic and interventional procedures, CIN is more common after coronary angiography and percutaneous coronary intervention (PCI).[7] It is common in patients with hemodynamic instability, multivessel disease, and acute coronary syndromes.[8] CIN increases cardiac morbidity and mortality. Therefore, predicting contrast nephropathy and initiating therapeutic preventive strategies are important. Red cell distribution width (RDW), which is easily measured, is an indicator of variability in the size of circulating red blood cells.[9] Previous studies have demonstrated a strong correlation between inflammatory markers, such as serum CRP levels, and sedimentation with RDW.[10] Inflammation destroys erythrocyte membranes, interferes with the maturation of erythrocytes, and increases RDW.[11] Previous studies have suggested a correlation between RDW and cardiovascular diseases such as acute myocardial infarction, heart failure, and peripheral arterial disease which have a high rate of mortality and morbidity.[12–15] CIN and high RDW values are correlated with increased cardiovascular morbidity and mortality.

The objective of this study was to determine the relationship between RDW in acute ST elevation myocardial infarction (STEMI) patients undergoing primary PCI and the development of CIN.

METHODS

Patients and study design

The study population comprised 359 patients who were admitted to hospital with the diagnosis of STEMI in the first 12 hours and underwent primary PCI between August 2011 and December 2013. Exclusion criteria were as follows: end-stage renal disease with glomerular filtration rate (GFR) less than 30 ml/1.73, known allergy to contrast agents, left ventricular ejection fraction (LVEF) below 30%, presence of infectious or inflammatory disease, a recent history of contrast administration in the previous month, history of malignancy, autoimmune disease, hyperthyroidism, hypothyroidism, severe hepatic disease and cardiogenic shock. Demographic characteristics of the patients, cardiovascular risk factors (smoking, hypertension, diabetes mellitus, hyperlipidemia), family history of heart disease and blood pressures were recorded. Before percutaneous intervention, patients were administered 300 mg of aspirin and 600 mg of clopidogrel and 5000–10000 U of intravenous heparin, according to body weight. Flow of the infarct-related arteries was evaluated according to the Thrombolysis In Myocardial Infarction (TIMI) grading system. Percutaneous coronary interventions were performed only on infarct-related arteries. All the patients were admitted to the coronary care unit after intervention, and all had taken an isotonic saline solution at a rate of 100 cc/hour after just PCI. Aspirin (100 mg) and clopidogrel and angiotensin converting enzyme inhibitors and statins were administered to all the patients in accordance with ACC/AHA guidelines

Abbreviations:

CI	*Confidence interval*
CIN	*Contrast induced nephropathy*
Cr	*Creatinine*
CRP	*C-reactive protein*
GFR	*Glomerular filtration rate*
HDL-C	*High density lipoprotein cholesterol*
LVEF	*Left ventricular ejection fraction*
OR	*Odds ratio*
PCI	*Percutaneous coronary intervention*
RDW	*Red cell distribution width*
ROC	*Receiver operating characteristic*
STEMI	*ST elevation myocardial infarction*

Biochemical analysis

Venous blood samples were drawn on admission. Glucose, total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglyceride (TG), RDW, white blood cell count, platelet and hemoglobin levels, creatinine concentrations, baseline GFR and CRP were measured from the serum in the laboratory. Creatinine levels 48 hours after the primary PCI were measured, and the Δ-creatinin levels (difference between initial and 48-hour creatinine levels) were calculated. Complete blood count was analyzed using a Roche Sysmex XT-2000i (Roche Diagnostic Corporation, India-

napolis, IN). The normal range for RDW is 11% to 16% according to the product manufacturer.

Transthoracic echocardiography

Transthoracic echocardiographic examinations were performed using Esaote My Lab 50, (3,5mHz, Florence, Italy). Parasternal long-axis views were obtained with the patient in the left lateral decubitus position. Left ventricular diastolic and systolic diameters, interventricular septum and LVEF were measured and fractional shortenings calculated according to modified Simpson's rule.

Definitions

Diagnosis of STEMI was performed based on admission ECG according to the following criteria: ST-segment elevation in at least two consecutive derivations (for chest derivations >2 mm and for extremity derivations >1 mm) or new development of left bundle branch block.[16] Hypertension was defined as blood pressure of 140/90 mmHg or higher for at least two measurements, or earlier usage of antihypertensive drugs. Diabetes mellitus was defined as fasting blood glucose level of 126 mg/dL or higher for at least two measurements, or earlier usage of antidiabetic drugs. Diagnosis of CIN was performed if there was an absolute increase in serum creatinine levels of at least 0.5 mg/dL, or a relative increase of at least 25% over baseline value at 48 h after administration of the contrast agent. It was graded as grade 0 if the increase was <25% and <0.5 mg/dL; grade 1 if >25% but less than 0.5 mg/dL; and grade 2 if increased >25% and more than 0.5 mg/dL.[17] Creatinine clearance was calculated according to the Cockcroft Gault formula.[18] Iohexol (Omnipaque, GE Healthcare, UK), a nonionic iso-osmolar contrast agent, was used for all patients. The study protocol was approved by the local Ethics Committee and written informed consent was obtained from all patients.

Statistics

Statistical analyses were performed using SPSS software (Version 18.0, SPSS Inc., Chicago, IL, USA). Distribution of the variables was analysed using the Kolmogorov-Simirnov test. Parametric variables were expressed as mean±standard deviation, and categorical variables were presented as percentages. Non-parametric variables were expressed as median (minimum-maximum). The differences between normally distributed numeric variables were evaluated by the Student's t-test, and non-normally distributed variables were analyzed using the Mann–Whitney U test variance analysis. The Chi-square test was used to compare the categorical variables and Fisher's exact test was used if needed. The correlation among variables was analyzed with Spearman rank correlation tests. After univariate logistic regression analysis, all variables significant at the $p<0.25$ level were entered into the Backward LR logistic regression model to define the independent predictors of CIN. The Wald test for significance was performed to determine the contribution of each variable to the model based on the odds ratio (OR) and 95% confidence interval (CI). Receiver operating characteristic (ROC) curves were plotted to determine the optimal cutoff values for RDW levels in predicting CIN. Two sided p-values of less than 0.05 were considered statistically significant.

RESULTS

Mean age of the 359 patients in the study was 55.1 years (range: 32–79). Among the patients, 84.4% were male and 15.6% female. CIN developed in 49 (13.8%) of patients, among whom 10.1% were classified as Grade 1 and 3.7% Grade 2.

Clinical, demographic, laboratory, and angiographic findings of both groups are given in Table 1. No difference was found between the two groups in terms of sex, hypertension, smoking status, dyslipidemia, hemoglobin levels and localization of myocardial infarction ($p>0.05$). Patients were older in the CIN-positive group than in the CIN-negative group (62.2 [35.3–79] *vs.* 53.4 [32–75] years, $p<0.001$). Diabetes mellitus was more common in patients who developed CIN than in those who did not (42.8% *vs.* 17.9%, $p<0.001$). Ejection fraction and baseline GFR were lower in the CIN-positive group than in the CIN-negative group. However, baseline serum creatinine (Cr) was significantly higher in the CIN-positive group than in the CIN-negative group (1.1±0.43 mg/dL *vs.* 0.8±0.16 mg/dL, $p<0.001$). After 48 hours, in CIN-positive group Cr values significantly high (1.7±0.91 mg/dL *vs.* 0.9±0.17 mg/dL, $p<0.001$). Increase on Δ-Cr was significantly high in CIN-positive group (0.6±0.58 *vs.* 0.1±0.07, $p<0.001$). The amount of contrast agent administered during intervention was higher in the CIN-positive group than in the CIN-negative group (258±60 ml *vs.* 212±65 ml,

Table 1. Baseline clinical, laboratory and angiographic characteristics

Variables	CIN (–) (n=307)			CIN (+) (n=49)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age, years	53.4	32–75		62.2	35.3–79		<0.001[a]
Sex, male	261	85		41	83.6	0.808[b]	
Diabetes mellitus	55	17.9		21	42.8	<0.001[b]	
Hypertension	118	38.7		26	53	0.059[b]	
Smoking	175	57		22	44.6	0.064[b]	
Dyslipidemia	148	48.2		17	34.6	0.078[b]	
Family history	70	22.8		7	14.2	0.179[b]	
History of coronary artery disease	24	7.8		5	10.2	0.368[d]	
Preinfarction angina	71	23.4		12	24.4	0.874[b]	
Myocardial infarction type, anterior	156	50.8		31	63.2	0.105[b]	
Killip status (≥2)	48	15.6		12	24.4	0.124[b]	
Systolic blood pressure (mmHg)	133	120–153		138	125–160	0.421[a]	
Diastolic blood pressure (mmHg)	76	68–85		82	70–92	0.765[a]	
Heart rate (/min)			76±13			75±18	0.707[c]
Baseline creatinine (mg/dl)			0.8±0.16			1.1±0.43	<0.001[c]
Creatinine at 48th hour (mg/dl)			0.9±0.17			1.7±0.91	<0.001[c]
Baseline GFR (mg/min/1.73 m^2)			89.7±20			68.7±17	<0.001[c]
Δ creatinine			0.1±0.07			0.6±0.58	<0.001[c]
White blood cell count (10^3/mL)			12.2±3.21			12.9±4.30	0.294[c]
Neutrophil (10^3/μL)			9.3±3.10			10.3±4.00	0.109[c]
Lymphocyte (10^3/μL)			1.9±0.97			1.7±0.76	0.043[c]
Hemoglobin (gr/dL)			13.2±1.62			12.7±2.13	0.071[c]
Red cell distribution width (%)			14.8±2.14			16.9±2.00	<0.001[c]
Glucose (mg/dl)	143	90–155		180	102–205		0.007[a]
Total cholesterol (mg/dL)			185±42			177±50	0.266[c]
LDL-cholesterol (mg/dL)			122±38			117±43	0.353[c]
HDL-cholesterol (mg/dL)			35±11			33±10	0.230[c]
Triglyceride (mg/dL)	135	80–290		138	70–300		0.768[a]
C-reactive protein	11	2–30		13	3–35		0.356[a]
Left ventricular ejection fraction (%)			48.1±7.70			43.1±8.91	<0.001[c]
Amount of contrast media (ml)			212±65			258±60	<0.001[c]
Number of diseased vessels							
1- vessel	196	64.1		28	57.1		0.427[b]
2- vessel	79	26		17	34.6		0.224[b]
3- vessel	30	9.8		4	8.2		0.484[d]
Infarct-related artery							
Left anterior descending	162	52.7		31	63.2		0.168[b]
Left circumflex	41	13.3		6	12.2		0.529[b]
Right coronary artery	95	31.2		12	24.4		0.238[b]
Postprocedural TIMI flow (≥3)	282	91.8		44	89.7		0.630[b]
Stent usage	288	93.8		45	91.8		0.602[b]

a: Mann-Whitney U test; b: Chi-Square test, c: Student's t test; d: Fisher's exact test. CIN: contrast induced nephropathy; Δ creatinine: Increase of creatinine in 48 hours; GFR: Glomerular filtration rate; HDL: high density lipoprotein; LDL: Low density cholesterol; TIMI: Thrombolysis in myocardial infarction.

Table 2. Independent predictors of contrast induced nephropathy based on multivariate backward logistic regression analysis in patients with percutaneous coronary intervention

	Odds-ratio (95% CI)	Wald	*p*
Multivariate			
Diabetes mellitus	3.252 (1.184–8.951)	5.40	0.022
Red cell distribution width	1.716 (1.363–2.157)	11.01	<0.001
Baseline glomerular filtration rate	0.941 (0.925–0.971)	9.86	<0.001
Δ creatinine	1.197 (1.061–2.986)	7.57	0.006
Amount of contrast media	1.187 (1.048–3.012)	8.23	0.001

Δ creatinin: increase of creatinine in 48 hours.

p<0.001). RDW values were significantly higher in patients who developed CIN than in those who did not (16.9±2.00, 14.8±2.14, p<0.001). No difference was found between CIN Grade 1 (17 [13.2–20.1]) and CIN Grade 2 patients (16.3 [12.4–20.6]) (p>0.05). Angiographic data showed no difference was found in the number of diseased vessels, infarct-related vessels and post-procedural effective flow between the groups (p>0.05). A weak correlation was found between RDW and change in creatinine levels (Δ-creatinine) (r=0.250, p<0.001). When age, diabetes, hypertension, smoking, dyslipidemia, family history, MI type (anterior), Killip status, baseline creatinine, creatinine at 48th hour, baseline GFR, Δ-creatinine, neutrophil, lymphocyte, hemoglobin, RDW, glucose, HDL-cholesterol, number of diseased vessels, infarct-related artery, LVEF and amount of contrast media were entered univariate logistic regression, multivariate backward logistic regression analysis revealed that diabetes (OR 3.252, 95% confidence interval (CI) 1.184–8.951, p=0.022), RDW (OR 1.716, 95% CI 1.363–2.157, p<0.001), baseline GFR (OR 0.941, 95% CI 0.925–0.971, p<0.001), Δ-creatinine (OR 1.197, 95% CI 1.061–2.986, p=0.006) and amount of contrast media (OR 1.187, 95% CI 1.048–3.012, p=0.001) were the independent predictors of development of CIN in STEMI patients who underwent PCI (Table 2). The cutoff value for RDW obtained by the ROC curve analysis was 15.2% for prediction of CIN (AUC: 0.756 [0.681–0.831], p<0.001) (sensitivity: 75%, specificity: 62%) in the population (Figure 1).

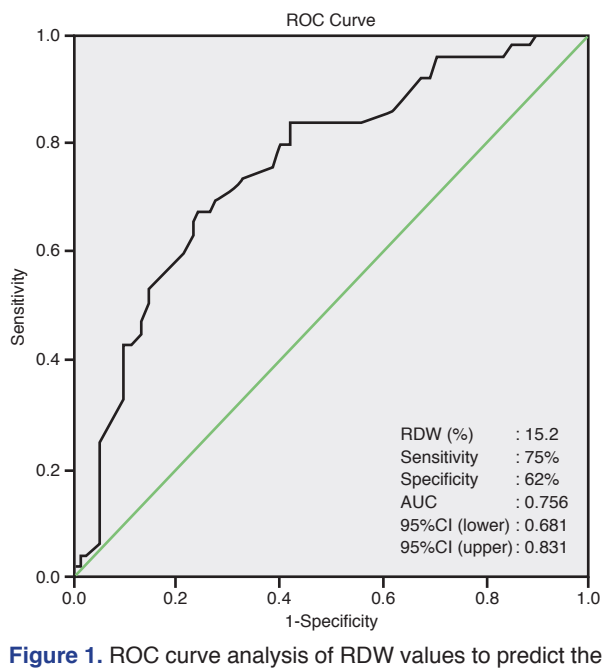

Figure 1. ROC curve analysis of RDW values to predict the developing of CIN. The cutoff value for RDW obtained by the ROC curve analysis was 15.2% for the prediction of CIN (AUC: 0.756 [0.681–0.831], p<0.001).

DISCUSSION

This study examined the relationship between development of CIN and RDW levels in patients who were admitted with STEMI and underwent primary PCI. Interestingly, we found higher RDW levels in patients with CIN, which increases cardiovascular mortality and morbidity. Also, high RDW, diabetes mellitus, basal low GFR, Δ-creatinine and amount of contrast used were found to be independent predictors for CIN. A 15.2% and higher RDW cut-off value was 77.6% sensitivity and 63% specificity for prediction of CIN. We determined a positive correlation between Δ-creatinine and RDW, especially before and 48 h after the PCI. Our results concur with the data of the study of Kurtul et al.[19] With the increased use of

contrast agents for diagnostic and interventional procedures, CIN has become one of the most common causes of impaired renal function during hospitalization. Impaired renal function, independent of etiology, increases in-hospital mortality by 20%.[3] Among other diagnostic and interventional procedures, CIN is more common after coronary angiography and PCI.[7]

Prediction of CIN and protection from it are important for decreasing hospitalization and mortality and morbidity. Although creatinine shift is important for a diagnosis of CIN, prediction of CIN is still a problem. Even if there are some predisposing factors for CIN, such as age, diabetes, heart failure, anemia, decreased renal function, hypotension, hypovolemia, and amount of contrast media, CIN may not develop in some patients.[4,5] Hence, there is a need for new biomarkers for predicting CIN.

Variations in red blood cell volume and size can be analyzed with well-developed laboratory devices. Volume is defined as mean corpuscular volume and variation in red blood cell size is defined as RDW.[20] RDW is related to heterogeneity in red blood cell size (anisocytosis). Increased RDW is usually seen in patients with comorbid conditions, and it has been related to morbidity and mortality. In recent years, RDW has been shown to be an effective biomarker for chronic inflammation and oxidative stress.[21] Our study is the second in the literature to show a relationship between increased RDW and increased risk of CIN in patients with STEMI who have undergone PCI. However, the main difference between our study and the study conducted by Kurtul et al.[19] is our enrollment of STEMI patients. Kurtul et al. included STEMI, non-STEMI, and unstable angina patients. They did not classify STEMI patients as a distinct category in their study. They used more contrast agents during PCI in patients with STEMI than in those undergoing elective PCI, and reported that they used a mean 174±76 ml contrast agent in patients with CIN, while we used a mean 258±64 ml contrast agent in our CIN patients. Hence, our study contributes to other study data.

Although the pathophysiology of CIN is not well known, many mechanisms are suggested. Proximal tubular vacuolar changes and direct tubular toxicity dependent on free oxygen radicals after radiocontrast substance applications have been shown as mechanisms in previous in vitro and in vivo studies.[22,23] Also, a contrast-related increase of blood viscosity may cause change in medullar microcirculation, which in turn may lead to degradation of parenchymal oxygenation, medullar hypoxia, formation of free radicals and endothelial dysfunction.[24–26] Ischemia related to the release of endothelin- and angiotensin-converting enzymes and the toxic effect of oxygen free radicals play a role in the pathogenesis of CIN development.[27,28] Contrast agents increase the oxygen affinity of hemoglobin and impair oxygen delivery to peripheral tissues. In the case of anemia, when a contrast agent is administered, it may aggravate the existing local renal ischemia and lead to CIN development.

Previous studies have suggested that high RDW is related to increased mortality in patients who had undergone coronary angiography, and also in patients who had PCI for acute myocardial infarction.[29,30] RDW is prevalent in patients with chronic inflammatory diseases, renal insufficiency, advanced age, and nutritional deficiencies, and thus it may be related to increased mortality.[31,32] An independent correlation exists between RDW and inflammatory markers such as CRP and sedimentation.[10] Several studies have demonstrated the relationship between inflammation and coronary artery diseases. Inflammatory markers such as CRP are used for risk assessment of patients at risk for cardiovascular disease.[33] Development of acute renal insufficiency is more frequent in patients who have high inflammatory markers. Previous studies have indicated an increased incidence of CIN in patients with high CRP levels.[6] There was no significant difference between the two groups in terms of CRP in the present study. RDW is related to both anemia and inflammatory processes. It is easily measured as part of routine laboratory testing with no additional cost.

The incidence of CIN was 13.8% in this study and 8% to 13% in previous studies concerning PCI.[34–36] Mehran et al. demonstrated that CIN develops more commonly in high-risk patients after PCI.[2] Some of the high risk factors include diabetes mellitus, congestive heart failure, pulmonary edema, hypotension, anemia, the need for intra-aortic balloon pumping, and an excess amount of contrast agent. Some risk factors such as diabetes mellitus, amount of contrast agent, and baseline low GFR were corroborated in this study. Moreover, RDW values were shown to be related to CIN development. In the present study, CIN development was more common in patients with high

RDW values than in those with low RDW values. In a previous study, it has been shown that mortality and morbidity increase when CIN grade increases.[17] In our findings, although no difference in RDW values was found between patients with Grade 1 and those with Grade 2 CIN development, there were significant differences between Grade 0 and grades 1 and 2. This study is important as RDW can be used for the prediction of CIN development after PCI without any additional cost.

Limitations

This work is a retrospective single-institution study. We were not able to compare RDW with other inflammatory markers.

Conclusions

This study shows that RDW is an independent predictor of CIN development in STEMI patients who underwent PCI. Because all patients who undergo primary PCI because of STEMI have routine blood counting and RDW, RDW is very feasible parameter for the evaluation of CIN. Large prospective multicenter studies are required in the future to further understand the role of RDW as a risk prediction marker of CIN.

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