



## Research Article

# The Impact of Red Cell Distribution Width on the Development of Contrast-Induced Nephropathy in Patients with Stable Coronary Artery Disease who Underwent Coronary Angiography

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### Abstract

**Objectives:** Contrast-induced nephropathy (CIN) accounts for 10% of all causes of hospital-acquired renal failure. The pathophysiological cellular mechanism of the CIN development remains unclear and seems to be multifactorial. Herein, we aimed to determine the role of red cell distribution width (RDW) in the development of CIN after elective percutaneous intervention in patients with stable coronary artery disease, which in our opinion has not been researched enough.

**Methods:** Between October 2009 and October 2011, a total of 211 patients with stable coronary artery disease who had undergone a coronary intervention procedure were evaluated prospectively. The patients were classified according to the development of CIN, and both groups were compared statistically according to clinical, laboratory, and demographic features, including the serum RDW level.

**Results:** In 18.8% of the patients, CIN was observed. The mean age was  $64 \pm 10.5$ , and 59% of the study group was male. An advanced age, male gender, hypertension, the serum total protein level, high density lipoprotein, and albumin levels were correlated with the development of CIN. The mean RDW level was  $13.7 \pm 1.4\%$ , and the mean creatinine level was  $1.0 \pm 0.2$  mg/dL. There was not any correlation between RDW and the presence of CIN (CIN[-]= $13.8 \pm 1.5$ , CIN[+]= $13.6 \pm 1.0$ ,  $p > 0.05$ ), and also a multivariate regression analysis proved this non-correlation (OR : 0.92, 95% confidence interval [CI]=0.62–1.34;  $p$ : 0.67). There was only a correlation between hypertension and male gender with CIN that was proved with a multivariate regression analysis (OR=5.74, 95% CI: 1.96–16.79,  $p < 0.01$  vs OR=5.34, 95% CI=1.22–23.3,  $p$ : 0.02, respectively).

**Conclusion:** Our outcomes indicate that the RDW has a limited use as a CIN predictor in patients with stable coronary artery disease.

**Keywords:** Coronary angiography; hemogram parameters; red cell distribution width; coronary artery disease.

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Contrast-induced nephropathy (CIN) is one of the major complications following intravascular administration of a contrast agent, and it is defined as acute renal failure (ARF) developed within 48–72 hours after the exclusion of all other causes that may lead to renal failure. The incidence of CIN may range from 2.8% to 19% in different series.<sup>[1]</sup> Although the exact mechanism is unclear, inflammation, endothelial dysfunction, and oxidative stress due to hypoxic damage caused by direct toxic effect of contrast material or renal vasoconstriction are thought to be responsible for the development of CIN. CIN is a complication that prolongs a hospital stay, increases mortality and morbidity, and results in permanent renal dysfunction and long-term undesirable clinical outcomes.<sup>[2]</sup>

Red blood cell distribution width (RDW) shows the distribution range of red blood cells according to their size. In other words, it is an objective indicator of anisocytosis. In the clinic, it is mainly used in the differential diagnosis of anemia.<sup>[3]</sup> Except for hematological diseases, the cause of the RDW elevation is not known precisely. The association between RDW and an inflammatory marker CRP has been demonstrated in conducted studies.<sup>[4]</sup> Similarly, a positive correlation was detected between increased RDW levels in diseases such as coronary artery disease, peripheral arterial disease, heart failure, chronic lung diseases, and cancer with high mortality and morbidity rates.<sup>[4–7]</sup> Also, a negative correlation between RDW values and renal function has been demonstrated.<sup>[8]</sup> The hypothesis that an increased RDW predicted the development of CIN was found to be significant in studies concerning the correlation between CIN and RDW in patients with acute coronary syndrome.<sup>[9–10]</sup>

However, to the best of our knowledge, there is not enough studies in the literature about the correlation between the development of CIN and RDW in patients with a stable coronary artery who are undergoing percutaneous coronary intervention. In our study, we investigated the role of RDW (if any) in predicting the development of CIN in patients with stable coronary artery disease undergoing elective percutaneous coronary intervention.

## Methods

Our study was designed as a single-center retrospective cohort study. It was carried out in accordance with the Declaration of Helsinki and was initiated after an approval of the Ethics Committee from the Bağcılar Training and Research Hospital was obtained. In the Bağcılar Training and Research Hospital between October 1, 2009, and October 21, 2011, a total of 1437 patients who described typical symptoms of angina pectoris or those with ischemia diagnosed based on noninvasive ischemia tests such as ex-

ercise stress test, myocardial perfusion scintigraphy, and underwent coronary angiography were scanned, and 211 patients who underwent stenting and/or angioplasty at the same session and met the inclusion criteria were included in the study.

Less than 50% narrowing of the luminal diameters of the three main epicardial vessels or their main branches was not considered as significant stenosis. Patients with anemia, a history of blood transfusion within the last 3 months, active infection, autoimmune or chronic inflammatory disease, heart failure (ejection fraction <40%), chronic anti-inflammatory drug use, liver enzyme abnormality (fourfold increase), and a decreased glomerular filtration rate (<60%) were not included in the study. Patients with low renal function according to the guidelines were hydrated with 0.9% isotonic solution at 1 ml/kg/h, starting 12 hours before the procedure, and continuing for 12 hours after. During the angiography, 100 mL of Iodixanol 320, a non-ionic, low osmolar contrast agent was used in all patients. Serum creatinine levels were measured 1 hour before and 48–72 hours after administration of the contrast agent.

After all other causes were excluded, creatinine values greater than 0.5 mg/dL or an increase greater than 25% within 72 hours after administration of the contrast medium were accepted as CIN. Patients were divided into two groups according to the development of CIN (CIN + Group 1 and CIN – Group 2). An estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease Study formula.

Blood samples (including RDW) for complete blood count were taken 1 hour before the procedure. The RDW percentile was specified for the parameters studied in the automated hematology analyzer Sysmex XT-1800i (Roche Diagnostic Corporation, Indianapolis, Ind.). The normal range of RDW was determined by the manufacturing firm as 11%–14.8%.

## Statistical Analysis

For continuous variables, fitness-to-normal distribution was examined by the Shapiro–Wilk's test. Descriptive statistics were used to describe continuous variables (mean, standard deviation), and n and % were used to describe intermittent variables. Student's t-test was used to compare two independent groups with normal distribution. The Mann–Whitney's U test was used to compare two independent groups with non-normal distribution.

The chi-squared test was applied to compare categorical variables. Clinical factors that might influence the development of CIN were determined by univariate analysis. A logistic regression analysis was then applied for variables below the significance value of  $p < 0.20$  and for values thought

**Table 1.** Demographic characteristics, clinical findings, and laboratory parameters of the patients

	Total	CIN (-)	CIN (+)	p
Age, year	64.0±10.5	63.4±10.8	66.3±8.8	0.18
Male gender, n (%)	125 (59)	90 (52.6)	35 (87.5)	<0.001
BMI, kg/m <sup>2</sup>	29.4±4.2	29.4±4.4	29.8±3.7	0.59
Diabetes mellitus, n (%)	86 (40)	73(42.7)	13 (32.5)	0.23
Hypertension, n (%)	158 (74)	125 (73.1)	33 (82.5)	0.21
Hyperlipidemia, n (%)	114 (54)	92 (53.8)	22 (55.0)	0.89
Smokers, n (%)	58 (27)	46 (26.9)	12 (30.0)	0.69
Admission, mg/ dL	1.0±0.2	1.0±0.26	1.0±0.24	0.94
Creatinine within 48-72 hours, mg/dL	1.0±0.3	0.96±0.24	1.57±0.45	<0.001
HCT, (%)	39.5±4.6	39.4±4.6	39.9±4.6	0.58
HGB, g/L	13.1±1.9	13.1±1.7	13.1±2.6	0.94
RDW, (%)	13.7±1.4	13.82±1.55	13.66±1.04	0.54
PDW, (%)	31.6±20.7	31.3±20.3	32.3±22.7	0.67
LVEF, (%)	53.3±9.1	53.0±9.0	54.4±9.6	0.39
Total cholesterol, mg/dL	190±50	187±49	199±51	0.21
LDL, mg/dL	112±38	111±37	118±40	0.29
HDL, mg/dL	44±12	43±11	47±15	0.16
TG, mg/dL	172±106	173±108	164±98	0.63
FBG, mg/dL	131±58	129±53	140±73	0.32
Total protein, g/dL	7.2±0.7	7.3±0.7	7.0±0.6	0.09
Albumin, g/dL	4.3±0.4	4.3±0.3	4.1±0.4	0.05
AST, U/L	25.8±19.3	24±12	31±35	0.04
ALT, U/L	24.1±15.2	23±12	25±22	0.41
Calcium, mg/dL	9.4±0.6	9.4±0.6	9.4±0.7	0.80
Amount of the contrast agent, mL	155±30	152±35	160±45	0.20
Three-vessel disease, n (%)	59 (28)	46 (26.9)	13 (32.5)	0.44

CI: Contrast-induced nephropathy; BMI: Body mass index; HCT: Hematocrit; HGB: Hemogram; RDW: Red blood cell distribution width; PDW: Platelet distribution width; LVEF: Left ventricular ejection fraction; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; FBG: Fasting blood glucose; AST: Aspartate transaminase; ALT: Alanine transaminase.

to be clinically significant. The level of statistical significance was determined as 0.05. Analyses were performed using the SPSS for Windows (version 20.0, SPSS, Chicago, Illinois) program.

**Results**

Basic demographic and clinical characteristics of the patients are summarized in Table 1. The mean age was 64±10 years, and 125 patients (59%) were male. Hypertension (74%) was found in the majority of the patients, and diabetes mellitus was detected in 40% of the patients. Forty (18.8%) patients developed CIN. Clinical, demographic, and laboratory data of the patients with and without CIN are summarized in Table 1. There was no intergroup differences as for baseline RDW values, ejection fractions, eGFR, smoking, diabetes mellitus, dyslipidemia, and hemoglobin levels (p > 0.05 for all, Table 1).

There was no difference in the drugs the patients used (Table 2). Patients in the CIN group were older, and the number of male patients were significantly higher in the CIN group

**Table 2.** Drugs used by patients dependent on the development of contrast-induced nephropathy (CIN)

Drug	OVERALL (211)	CIN (-) (171)	CIN (+) (40)	p
ACE inhibitor	99 (46.9)	79 (46.2)	20 (50)	0.66
Calcium channel blocker	57 (27.0)	44 (25.7)	13 (32.5)	0.38
Beta-blocker	108 (51.2)	87 (50.9)	21 (52.5)	0.85
Statin	69 (32.7)	54 (31.6)	15 (37.5)	0.47

(p=0.115, p<0.001, Table 1, respectively). Hypertension was more common in the CIN [+ ] group than in the KMN [ - ] group (82.5% vs. 73%, p=0.21, Table 1). Similarly, in the CIN [+ ] group, higher total cholesterol and lower serum albumin and total protein levels were observed (p=0.21; p=0.05; p=0.09, respectively [Table 1]). However, there was no difference in the RDW values between the CIN [+ ] and CIN [ - ] groups (13.8±1.5, 13.6±1.4, p=0.54, respectively) (Table 1).

Any intergroup difference was not found in the amount of contrast agent during the interventional procedures. Male

**Table 3.** Univariate and multivariate logistic regression analysis of the factors affecting the development of contrast-induced nephropathy (CIN)

	Univariate			Multivariate		
	OR	(95% CI)	p	OR	(95% CI)	p
Gender (male)	6.30	2.35-16.8	<0.001	5.74	1.96-16.79	<0.001
RDW	0.92	0.71-1.19	0.53	0.92	0.62-1.34	0.67
Age	1.02	0.99-1.06	0.11	1.01	0.97-1.06	0.50
Diabetes mellitus	0.64	0.31-1.33	0.24	0.57	0.23-1.43	0.29
Hypertension	1.73	0.71-4.19	0.22	5.34	1.22-23.3	0.02
Hemoglobin	1.00	0.84-1.20	0.94	0.83	0.66-1.05	0.13
LVEF	1.01	0.97-1.06	0.39	1.01	0.97-1.06	0.46
Albumin	0.39	0.14-1.03	0.05	0.47	0.15-1.43	0.18

CI: Confidence interval; RDW: Red blood cell distribution width; LVEF: Left ventricular ejection fraction.

gender and lower albumin levels were found to be significant risk factors in the development of CIN in the univariate regression analysis applied to values with  $p < 0.2$  and/or RDW, ejection fraction, age, diabetes mellitus, hypertension, hemoglobin, and serum albumin, which were thought to be clinically significant in the development of the CIN in descriptive analysis ( $p < 0.001$  and  $p = 0.05$ , respectively) (Table 3). In the multivariate regression analysis, male gender as well as the presence of hypertension were found to be independent predictors ( $p < 0.001$  and  $p = 0.02$ , respectively).

## Discussion

As a result of our study, a predictive value of RDW in the development of CIN after coronary angiography in stable coronary artery patients was investigated. But contrary to the ongoing studies, RDW was not found to be a significant predictor for the development of CIN. In our study, the rate of development of KMN was relatively higher with 18.8%. An advanced age and a higher total cholesterol level, but lower left ventricular ejection fraction and total protein level, were detected in patients who developed CIN, without a statistically significant intergroup difference.

Interestingly, male gender is also considered to be an independent risk factor in the multiple regression analysis in predicting CIN, as well as hypertension, which is known to be a CIN risk factor in earlier studies. The predictive value of RDW for CIN was not found to be significant. This result is noteworthy in that it has made us to debate the clinical significance of RDW.

Hypertension, which is found to be an independent risk factor in the development of CIN in our study, is a classical risk factor for coronary artery disease and renal failure. The adverse effects of hypertension that start at the microvascular level lead to renal dysfunction that is not reflected in biochemical parameters. As in Stages 1 and 2 of chronic renal failure, kidney damage has begun, but the glomerular

filtration rate remains within the normal limits.

This is supported by a significant increase in the development of CMN in patients with low albumin levels in a single regression analysis. In a univariate regression analysis, significantly more frequent development of CIN in patients with lower albumin levels supports this finding. In these patients, microalbuminuria, which is the first stage of kidney failure may become manifest. It should be kept in mind that the likelihood of developing acute renal failure after the contrast agent exposure is higher in patients in this stage of the disease with risk factors for renal insufficiency and established kidney damage (microalbuminuria, etc.). Surprisingly, male gender is another significant independent predictor. In a large study on this subject, female gender was found to be more common among patients with CIN, and this finding was not supported by the multivariate regression analysis.<sup>[11]</sup>

In the field of cardiology, RDW has attracted attention in a subgroup analysis of the CHARM study performed by Felker et al.<sup>[12]</sup> This analysis investigated the correlation between RDW and adverse events for heart failure and found that the RDW elevation significantly predicted adverse events (adverse event [-] 14.4 mg/dL, adverse event [+] 15.2 mg/dL). In 2008, in a subgroup analysis of the CARE study, Tonelli et al.<sup>[13]</sup> investigated the relationship between the RDW elevation and the incidence of coronary artery disease and concluded that a 1% change in RDW caused a significant risk increase in the incidence of coronary artery disease. In a large study conducted in 2010, RDW values were assessed in five groups, and the results were interpreted and compared among these five groups in the follow-up study of RDW conducted in acute coronary syndrome patients. In two groups, RDW was found to be a predictor of cardiac adverse events.<sup>[14]</sup>

Uyarel et al.<sup>[15]</sup> investigated the outcomes of primary percutaneous coronary intervention performed in 2506 patients



with high ( $>14.8$ ) and normal ( $\leq 14.8$ ) RDW, and they detected a significant predictive value of RDW in hospital and long-term mortality. In this study, statistically significantly lower GFRs were observed in patients with a high RDW.

Akin et al.<sup>[10]</sup> investigated the development of CIN and RDW in patients with acute coronary syndrome after coronary angiography and found RDW to be a significant predictor of CIN (CIN [-] 13.1 mg/dL– CIN [+] 13.7 mg/dL). In this study, as a rarely used CIN definition in this study they evaluated, an increase of 0.3 mg/dl in creatinine levels within 48 hours as CIN, and the number of patients who developed CIN appeared to be relatively high.

RDW, a hemogram parameter indicative of anisocytosis, is automatically calculated in hemogram devices by dividing the standard deviation of erythrocyte volume by the mean erythrocyte volume in hemogram devices, and it is one of the parameters used in the differential diagnosis of anemia. As it is dependent on the calibration of the device, it is also affected by factors such as smoking, anemia, sex, age, MCV, etc. In the clinic, a RDW range of 12%–15% is considered normal.<sup>[16]</sup>

In the above-mentioned large-scale studies, in addition to the role of RDW in the differential diagnosis of anemia, its predictive value in mortality and morbidity of long-term follow-up of cardiac diseases have been investigated. The most interesting one among many hypotheses related to this subject is that decreased cardiac output in coronary artery disease, acute coronary syndrome, and cardiac output, results in systemic ischemia.

Inflammation developed as a result of this ischemia leads to the release of cytokines, which stimulate hematopoiesis. Increased hematopoiesis leads to anisocytosis due to immature erythrocytes, and elevated RDW values are observed.<sup>[17]</sup> Starting from this, an increase in RDW values should be seen as a result of increased inflammation secondary to the development of CIN, and the increase in RDW may be regarded not as a predictor, but as an outcome parameter in acute events such as CIN.

Inflammation in patients with stable coronary artery disease and acute coronary syndrome patients is not the same.<sup>[18]</sup> Therefore, the baseline RDW values differ from each other. As in our study, a low level of inflammation, and so stable and normal RDW values may not be affected by an acute onset events as CIN in patients with stable coronary arteries. Similar to our study, Kai Zhao et al.,<sup>[19]</sup> who conducted a study with larger number of patients, found a significantly higher RDW in patients with stable coronary artery disease after coronary angiography (KMN [-] 13.92–KMN [+] 15.2). Unlike our study, the baseline RDW values were high in their study, and multivascular disease had

been observed in 70% of their patients. In only 28% of our patients, multivascular disease was detected. RDW may be elevated in patients with chronic inflammation secondary to multivascular disease.<sup>[20]</sup>

As it is understood from all these studies, the RDW clinically significant values between 11% and 14.8% were not taken as a basis, the statistical significance was reached with numerical values, and new limit values were established. The specificity and sensitivity of these limit values are low (60%–72%) and vary considerably between different studies.

RDW, which rises within 48–72 hours after chronic inflammation, is unlikely to be predictive for the development of CIN. In chronic diseases such as heart failure, ischemic heart disease, the severity of the disease, and adverse events are more likely to be predictive. As seen in our study, RDW has a low predictive value in patients with low levels of inflammation, and those who developed CIN.

There are a number of limitations to our study. The main limitation is its single-centered design and a relatively small number of study population. In addition, hsCRP was not analyzed to indicate the severity of inflammation in patients. The carriership of thalassemia, which increases RDW levels without inducing manifest anemia, was also not investigated.

## Conclusion

The clinical significance of predictive value of RDW, which was found to be numerically significant in adverse events in chronic heart disease, may be discussed. In patients with relatively low levels of inflammation, such as in stable coronary artery disease, RDW may not be an appropriate parameter to predict an acute event such as CIN. For greater clarity, studies with a greater number of patients and meta-analyses are required.

## Disclosures

**Ethics Committee Approval:** It was carried out in accordance with the Declaration of Helsinki and was initiated after an approval of the Ethics Committee from the Bağcılar Training and Research Hospital was obtained.

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

**Conflict of Interest:** None declared.

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