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Red Cell Distribution Width Predicts Contrast-Induced Nephropathy in Patients Undergoing Percutaneous Coronary Intervention for Acute Coronary Syndrome

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Abstract

We investigated the relationship between red cell distribution width (RDW) and contrast-induced nephropathy (CIN) in patients (aged 61 $\pm$ 12, 69% men) with acute coronary syndrome (ACS). Consecutive patients diagnosed with ACS (n = 662) who underwent percutaneous coronary intervention (PCI) were included in the study. Patients were divided into 2 groups: CIN and no CIN. Contrast-induced nephropathy was defined as an increase in serum creatinine level of $\geq$0.5 mg/dL or $\geq$25% above baseline within 72 hours after PCI. Contrast-induced nephropathy occurred in 81 (12.2%) patients. Red cell distribution width, creatinine, and high-sensitivity C-reactive protein levels were significantly higher in the CIN group than in the no-CIN group. Multivariate regression analysis revealed that baseline RDW level (odds ratio 1.379, 95% confidence interval 1.084-1.753, $P = .009$), age ($P = .025$), creatinine ($P = .004$), and left ventricular ejection fraction ($P = .011$) were independent risk factors for the development of CIN. In conclusion, increased RDW levels are independently associated with a greater risk of CIN in patients undergoing PCI for ACS.

Keywords

red cell distribution width, contrast-induced nephropathy, percutaneous coronary intervention, acute coronary syndrome

Introduction

Contrast-induced nephropathy (CIN) is an important complication of invasive cardiovascular procedures. Patients who undergo percutaneous coronary intervention (PCI) are at greater risk and patients with diabetes mellitus or baseline renal impairment have a risk of almost 50%.[1,2] Development of CIN after PCI is associated with worse clinical outcomes including prolonged hospitalization and increased cost, risk of end-stage renal failure, myocardial infarction, repeat revascularization, and mortality.[3-6] Patients with acute coronary syndrome (ACS) have a 3-fold higher risk of developing CIN.[7-9] Thus, markers may be useful to identify patients with ACS at risk of CIN. The pathophysiology of CIN is complex, multifactorial, and incompletely understood. Possible mechanisms include intrarenal vasoconstriction, reduced renal blood flow, medullary hypoxia, oxidative stress, inflammation, endothelial dysfunction, the generation of reactive oxygen species (ROS), and direct tubular epithelial cell injury by contrast media (CMs).[10-12]

Red cell distribution width (RDW) is a measurement of erythrocyte variability and heterogeneity, and it is obtained routinely in standard complete blood cell counts.[13,14] Increased RDW indicates the presence of anisocytosis, which is related to impaired erythropoiesis and erythrocyte degradation, reflecting chronic inflammation and oxidative stress.[15-17] Red cell distribution width has been linked to clinical outcomes in various clinical settings. Studies have shown that an increased RDW is associated with poor clinical cardiac outcomes in patients with heart failure,[18-20] slow coronary flow,[21] stable coronary artery disease (CAD),[22,23] ACS,[24-27] and unselected patients undergoing PCI.[28]

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Because of the potential role of inflammation and oxidative stress in the development of CIN, mediators reflecting inflammation and oxidative stress, such as RDW, might be a marker of CIN. Thus, we investigated whether admission RDW levels are associated with development of CIN after PCI in patients with ACS.

Methods

Patient Population

A total of 673 consecutive patients with ACS who underwent urgent PCI for ACS in our institution from January 2013 to January 2014 were enrolled into this study. Patients on dialysis treatment, with severe chronic heart failure (New York Heart Association $\geq$ 3 class), history of malignancy, severe renal or liver disease, and patients receiving treatment with anti-inflammatory drugs were excluded. Patients with acute or chronic infections and autoimmune disease were also excluded. According to these criteria, 11 patients were excluded (acute infection in 1 patient, history of malignancy in 2 patients, urgent coronary bypass surgery in 3 patients, and chronic dialysis in 5 patients). The remaining 662 patients (mean age 61 $\pm$ 12 years; 69% male) formed our study population.

Acute coronary syndrome included ST-segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), and unstable angina pectoris (UA). The STEMI was defined as (1) prolonged typical chest pain at rest (>30 minutes); (2) ST-segment elevation 0.2 mV at the J point in $\geq$2 contiguous precordial leads or 0.2 mV in $\geq$2 adjacent limb leads on a standard 12-lead electrocardiogram (ECG); and (3) increased serum markers of myocardial damage (>2-fold increase over the upper normal range required for creatine kinase (CK) and troponin T [TnT]).[29] The UA/NSTEMI was defined according to the presence of ECG ST-segment depression or prominent T-wave inversion and/or positive biomarkers of necrosis (eg, troponin) in the absence of ST-segment elevation in an appropriate clinical setting (chest discomfort or anginal equivalent).[30]

Study Protocol and Definitions

Biochemical and hematologic parameters including preprocedural serum creatinine and RDW levels were measured from venous blood samples. The RDW levels were determined by a Coulter LH Series (Beckman Coulter, Inc, Hialeah, Florida). The normal range for RDW is 11.5% to 14%. Cardiac enzymes (CK-myocardial band [CK-MB], TnT), lipid profiles, and high sensitivity C-reactive protein (hsCRP) were also measured in all patients. Immediately after intervention, all patients underwent hydration with intravenous isotonic saline (0.9%) at a rate of 1 mL/kg/h for 12 hours (or 0.5 mL/kg/h for 12 hours in cases of overt heart failure). Serum creatinine was also measured at 24, 48, and 72 hours after CM administration.

Patients were divided into 2 groups: CIN group and no-CIN group. Contrast-induced nephropathy was defined as an increase in serum creatinine level of $\geq$0.5 mg/dL or $\geq$25% above baseline within 72 hours after contrast administration.[3] High-contrast volume was defined as the administration of a contrast volume of >140 mL.[31] The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation.[32] Transthoracic echocardiography was evaluated for each patient within 48 hours following PCI (Vivid 3, GE Medical System, Norway). Left ventricular ejection fraction (LVEF) was measured using the Simpson method according to the recommendations of the American Society of Echocardiography.[33]

The study protocol was approved by the local ethics committee and written informed consent was obtained from all patients.

Coronary Interventions and Medications

Coronary angiography and PCI were performed according to standard clinical practice (Siemens Axiom Artis zee 2011, Germany). Patients in the urgent department received a bolus of 5000 U of unfractionated heparin, followed by additional intraprocedural boluses to maintain an activated clotting time of 200 to 250 seconds ($\geq$300 seconds when tirofiban was not used), acetylsalicylic acid 300 mg orally, and clopidogrel a single loading dose of 600 mg. The use of bare-metal or drug-eluting stents was left to the discretion of the interventional cardiologist. In addition, the decision to use inotropic drugs, glycoprotein IIb/IIIa inhibitor (tirofiban), β-blockers, angiotensin-converting enzyme inhibitors, and diuretics was also left to the discretion of interventional and coronary care unit cardiologists as directed by international guidelines.[34,35] After intervention, all patients continued to take aspirin (100 mg/d) indefinitely and clopidogrel (75 mg/d) for at least 12 months.

Statistical Analysis

All analyses were performed using the SPSS for Windows (version 18.0, SPSS, Chicago, Illinois). Quantitative variables were expressed as mean value $\pm$ standard deviation for continuous variables and median and minimum–maximum levels or percentages for categorical variables/string variables. Comparison of continuous values between 2 groups was performed by means of independent samples t test. Comparison of categorical variables/string variables between 2 groups was performed by Mann-Whitney U test. Categorical variables were compared by chi-square test. The receiver–operating characteristic (ROC) curve analysis was performed in order to determine the best cutoff value of RDW and the sensitivity and specificity at that point were obtained. Univariate and multivariate logistic regression analyses were used to identify the independently associated predictors of CIN. A 2-tailed P <.05 was considered significant.

Results

The study population consisted of 662 patients with a mean age of 61 $\pm$ 12 years, 457 (69%) were male; 81 (12.2%) patients developed CIN.

Table 1. Baseline Clinical Characteristics and Prior Medications of Study Population.

Variable	No CIN (n = 581, 87.8%)	CIN (n = 81, 12.2%)	*P*
Age, years	59.8 ± 12.3	71.7 ± 12.5	<.001
Male gender, n, (%)	406 (69.9)	51 (63.0)	.207
Hypertension, n (%)	236 (40.6)	42 (51.9)	.055
Diabetes mellitus, n (%)	174 (29.9)	32 (39.5)	.082
Smoking, n (%)	288 (49.6)	13 (16.0)	<.001
Hyperlipidemia, n (%)	195 (33.6)	19 (23.5)	.174
Prior CABG, n (%)	27 (4.6)	4 (4.9)	.908
Prior myocardial infarction, n (%)	42 (7.2)	7 (8.6)	.649
Prior stroke, n (%)	14 (2.4)	1 (1.2)	.506
Systolic blood pressure, mm Hg	129 ± 24	130 ± 30	.908
Diastolic blood pressure, mm Hg	78 ± 14	77 ± 16	.427
LVEF, %	48 ± 10	40 ± 10	<.001
LVEF ≤ 40%, %	26.1	49.3	<.001
Type of ACS, n (%)			
STEMI	375 (64.5)	49 (60.5)	.067
Non-STEMI	180 (31.0)	32 (39.5)	
UA	26 (4.5)	0 (0)	
Prior medications, %			
ACEI or ARB	24.2	26.3	.841
Statins	18.3	10.2	.114
β-Blocker	13.0	15.8	.739

Abbreviations: CIN, contrast-induced nephropathy; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; ACS, acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina pectoris; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

Table 2. Comparison of Laboratory Measurements Between Patient Groups.

Variable	No CIN (n = 581)	CIN (n = 81)	*P*
Admission glucose, mg/dL	150 ± 82	162 ± 89	.205
Hemoglobin A_{1C}, %	6.9 ± 2.0	6.9 ± 1.7	.856
Uric acid, mg/dL	5.5 ± 1.6	6.5 ± 1.8	<.001
Creatinine, mg/dL	1.06 ± 0.25	1.34 ± 0.38	<.001
eGFR, mL/min/1.73m^2	73 ± 19	52 ± 18	<.001
eGFR < 60 mL/min/1.73m^2, n (%)	133 (22.9)	57 (70.4)	<.001
White blood cell count, $\times 10^3$/mm^3	11.00 ± 3.55	11.92 ± 4.27	.034
Hemoglobin, g/L	14.3 ± 1.7	12.6 ± 2.1	<.001
Red cell distribution width, %	13.98 ± 1.17	15.19 ± 1.81	<.001
Mean platelet volume, fL	8.69 ± 0.98	8.89 ± 1.31	.157
Total cholesterol, mg/dL	192 ± 47	172 ± 47	.001
LDL cholesterol, mg/dL	121 ± 40	104 ± 38	.001
HDL cholesterol, mg/dL	40 ± 9	41 ± 11	.769
Triglyceride, mg/dL	140 (35-1122)	112 (32-624)	.027
hsCRP, mg/L	6.75 ± 3.98	8.24 ± 3.70	.004
Peak CK-MB, ng/mL	36.87 (0.78-300)	64.48 (2.25-300)	.008
Peak troponin T, ng/mL	905 (4.13-10000)	1765 (21-10 000)	.010

Abbreviations: CIN, contrast-induced nephropathy; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hsCRP, high sensitivity C-reactive protein; CK-MB, creatine kinase-myocardial band.

Baseline clinical characteristics and prior medications of patients with no CIN and CIN are shown in Table 1. Patients who developed CIN were older and had a lower prevalence of active smoking compared with those without CIN. These patients also had a lower LVEF. Although the incidence of hypertension and diabetes mellitus was not significantly different between the 2 groups, more patients in the CIN group had diabetes and hypertension than those without CIN ($P = .055$, $P = .082$, respectively). No significant differences in type of ACS and prior medication were identified between the groups.

The serum creatinine, uric acid, peak TnT, peak CK-MB levels, and white blood cell (WBC) counts were significantly higher in patients with CIN. However, baseline eGFR, total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglyceride, and hemoglobin levels were significantly lower in patients who developed CIN. The correlations between the laboratory markers and CIN are presented in Table 2.

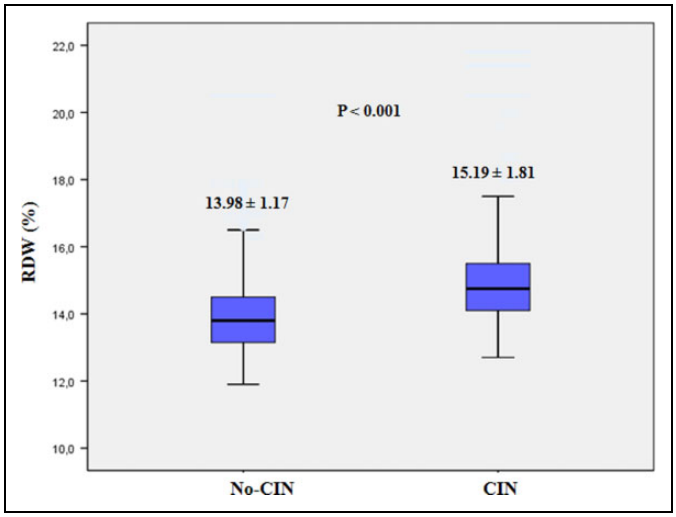

Figure 1. Comparison of red cell distribution width (RDW) levels between the groups.

The RDW levels were significantly higher in the CIN group compared with the no-CIN group (15.19 ± 1.81 vs 13.98 ± 1.17, $P < .001$; Table 2 and Figure 1). Additionally, the hsCRP levels were also significantly higher in the CIN group ($P = .004$, Table 2).

The angiographic characteristics and in-hospital medications of the patients are shown in Table 3. Culprit vessel was left anterior descending artery with higher frequency among study population in both 2 groups. The prevalence of multivessel CAD and chronic total occlusion (CTO) was significantly greater in the CIN group compared with the no-CIN group. Stent diameter was significantly lower in the CIN group. The total amount of CMs, total time of procedure, and prevalence of high contrast volume was not significantly different between the 2 groups.

The rates of treatment with β-blocker and angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers were lower in patients who developed CIN. Treatment with diuretic, statin, clopidogrel, and tirofiban infusion was similar in these 2 groups.

In a univariate model using RDW as a continuous variable, there was a significant positive association between RDW level and the incidence of CIN. Age, smoking, LDL-C, LVEF, hemoglobin, creatinine, uric acid, hsCRP, WBC, multivessel disease, and the presence of CTO was also associated with the development of CIN. Multivariate logistic regression analysis revealed that baseline RDW level (odds ratio [OR] 1.379, 95% confidence interval [CI] 1.084-1.753, $P = .009$), age (OR 1.040, 95% CI 1.005-1.077, $P = .025$), creatinine (OR 4.631, 95% CI 1.631-13.152, $P = .004$), and LVEF (OR 0.957, 95% CI 0.926 to 0.990, P=0.011) were independent risk factors for the development of CIN after urgent PCI in patients with ACS (Table 4).

The ROC curve analysis was performed to determine the cutoff value of RDW to predict the CIN versus no CIN. The area under the ROC curve for RDW was 0.738 (95% CI 0.680-0.791, $P < .001$), and an RDW of 14.25% or higher predicted CIN with a sensitivity of 72% and specificity of 69% (Figure 2).

Discussion

Our main finding was that increased RDW at baseline was significantly associated with increased risk of CIN in patients with ACS who underwent urgent PCI. The association remained significant even after adjusting for independent variables.

Contrast-induced nephropathy is an important complication of PCI and may cause increased morbidity and mortality. Contrast-induced nephropathy is one of the most important causes of hospital-acquired renal failure and can result in prolonged hospitalization, increased cost, and incidence of renal and cardiovascular events and mortality.[3-6] Recently, risk stratification and application of preventive methods against CIN further reduced the incidence of CIN. But CIN is still an important problem in those who need invasive procedures using CM. Therefore, novel biomarkers for predicting CIN are needed. However, no studies have investigated the relationship between RDW and CIN in patients with ACS.

Red cell distribution width is a measurement of erythrocyte heterogeneity, and it is obtained routinely in complete blood cell counts.[13,14] Increased RDW indicates the presence of anisocytosis, which is related to impaired erythropoiesis and erythrocyte degradation, reflecting chronic inflammation and a high level of oxidative stress.[15,16]

This is the first study in which an increased RDW was associated with increased risk of CIN in patients with ACS who underwent PCI.

Although the pathogenesis of CIN is not completely understood, multiple mechanisms may be involved and inflammation plays a role. Several studies found that elevated preprocedural C-reactive protein (CRP; a marker of inflammation) levels were associated with an increased risk of CIN after PCI.[36,37] The pathophysiologic link between anti-inflammatory effects of statin treatment and renal protection against CIN was reported in studies conducted with ACS populations who underwent PCI.[38,39] Inflammation may induce changes in red blood cell maturation by disturbing the red cell membrane, leading to increased RDW.[40] A strong correlation of RDW with inflammatory markers, CRP, and sedimentation rate (erythrocyte sedimentation rate [ESR]) has also been observed.[41] Lippi et al demonstrated a correlation between RDW and indices of inflammation, such as elevated ESR and hsCRP, identifying strong, graded increases in both ESR and hsCRP across RDW quartiles.[41] Fornal et al and Lippi et al[42,43] reported a potential link between inflammatory biomarkers and RDW values that may also be of importance because the inflammation may impair iron metabolism and inhibit both the production of and the response to erythropoietin.[40,44] In addition, increased RDW is associated with increased levels of proinflammatory cytokines such as tumor necrosis factor α and interleukin 6.[17] These cytokines attenuate the activity of erythropoietin and cause production of ineffective red blood cells, leading to elevated

Table 3. Angiographic and Interventional Characteristics and Medications of Patients.

Variable	No CIN (n = 581)	CIN (n = 81)	*P*
Total time of procedure, minutes	37 ± 16	41 ± 16	.130
Total amount of contrast, mL	162 ± 63	174 ± 76	.190
High contrast volume, n (%)	346 (59.6)	47 (58.3)	.853
Multivessel disease, n (%)	294 (50.6)	59 (72.8)	<.001
Chronic total occlusion, n (%)	88 (15.1)	25 (30.9)	<.001
Culprit vessel, n (%)			
Left main coronary artery	1 (0.2)	2 (2.5)	.445
Left anterior descending artery	265 (45.6)	39 (48.1)	
Left circumflex artery	111 (19.1)	18 (22.2)	
Right coronary artery	196 (33.7)	22 (27.2)	
Saphenous vein graft	8 (1.4)	0 (0)	
Stent implantation, n (%)	547 (94.2)	69 (85.2)	.226
Total length of stent, mm	23.75 ± 11.10	25.22 ± 13.23	.316
Stent diameter, mm	3.19 ± 0.43	3.08 ± 0.36	.037
Medications during hospitalization, %			
ACE inhibitor or ARB	417 (71.8)	46 (56.8)	.006
Statin	481 (82.8)	63 (77.8)	.270
Tirofiban	227 (39.1)	24 (29.6)	.101
β-Blocker	518 (89.2)	65 (80.2)	.020
Diuretic	123 (21.3)	19 (23.2)	.773
Clopidogrel	572 (98.5)	78 (96.3)	.173

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin-receptor blocker; CIN, contrast-induced nephropathy.

Table 4. Factors Predicting Contrast-Induced Nephropathy on Logistic Regression Analysis.

	Univariate Analysis		Multivariate Analysis	
Variable	Odds Ratio, 95% CI	*P*	Odds Ratio, 95% CI	*P*
Age	1.090 (1.067-1.114)	<0,001	1.040 (1.005-1.077)	**.025**
Smoking	0.194 (0.105-0.359)	<0,001	0.597 (0.238-1.501)	.273
Low-density lipoprotein	0.988 (0.981-0.995)	0,001	0.996 (0.988-1.005)	.404
Triglyceride	0.997 (0.994-1.000)	.098		
LVEF	0.923 (0.899-0.946)	<0,001	0.957 (0.926-0.990)	**.011**
Hemoglobin	0.623 (0.547-0.709)	<0,001	0.898 (0.745-1.083)	.260
Glucose	1.002 (0.999-1.004)	.207		
Creatinine	14.632 (6.879-31.126)	<0,001	4.631 (1.631-13.152)	**.004**
Uric acid	1.428 (1.247-1.634)	<0,001	0.958 (0.782-1.173)	.678
hsCRP	1.102 (1.030-1.180)	0,005	1.005 (0.917-1.100)	.918
Peak CK-MB	1.002 (0.999-1.004)	.317		
Hypertension	0.635 (0.398-1.012)	.056		
RDW	1.727 (1.469-2.031)	<0,001	1.379 (1.084-1.753)	**.009**
WBC	1.066 (1.005-1.131)	0,035	1.070 (0.979-1.168)	.134
Multivessel disease	2.617 (1.600-4.310)	<0,001	2.003 (0.994-4.184)	.090
Chronic total occlusion	2.500 (1.481-4.219)	0,001	1.152 (0.528-2.512)	.721

Abbreviations: CI, confidence interval; LVEF, left ventricular ejection fraction; hsCRP, high sensitivity C-reactive protein; CK-MB, creatinine kinase-myocardial band; RDW, red cell distribution width; WBC, white blood cell.

RDW.[16,45] Consequently, increased RDW levels may reflect an increased inflammatory response and that patients are at high risk of CIN.

The other underlying mechanism between CIN and increased RDW levels may be increased oxidative stress. Oxidative stress causes the release of ROS[46] and CIN, which damage the cell membrane and cell components, thus leading to cell death and also to the production of free radicals. Superoxide, hydrogen peroxide, and hydroxyl radical are the most common ROS, and oxidative stress augments their production in mitochondria.[47-49] Two studies demonstrated that the decreases of eGFR in dogs and humans with CIN could be attenuated by reducing the production of ROS from adenosine with allopurinol, a xanthine oxidase inhibitor, or by scavenging ROS with superoxide dismutase and magnesium ions.[50,51] Oxidative stress increases the fragility of red blood cells[52] and decreases the rate of erythroid maturation.[53] As a result, oxidative stress leads to shortened erythrocyte survival and resulting in

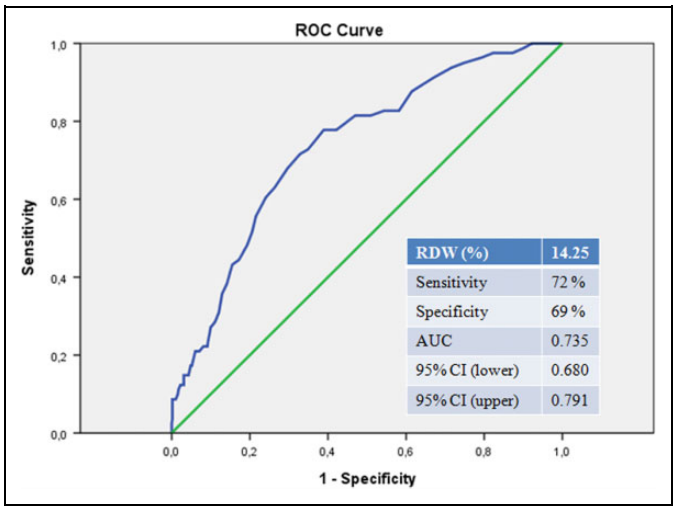

Figure 2. The receiver–operating characteristic (ROC) curve analysis for red cell distribution width (RDW) levels in predicting of contrast-induced nephropathy (CIN). AUC = 0.735 (0.680-0.791). AUC indicates area under the curve.

increased RDW.[54] Consequently, increased RDW levels may indicate increased oxidative stress status and high risk of CIN.

In a previous study, oxidative stress and inflammation were often closely related because ROS plays a role in the activation of nuclear factor kappa B, a transcription factor that stimulates the expression of cytokines involved in the inflammatory process, such as interleukin 6.[55] Therefore, it is not surprising that CIN and increased RDW levels were associated with both these mechanisms and with each other.

Advanced age and low LVEF are risk factors for CIN.[7] In our study, in agreement with the findings so far, advanced age and low LVEF were associated with CIN ($P < .001$ for both). In our study, smoking was significantly associated with low risk of CIN. In our study population, smoking rates have been decreasing in patients with advanced age and advanced age was a traditional risk factor for CIN. These relationships may have been affected by these confounding factors. In this context, in multivariate analysis, only older age, LVEF, creatinine levels, and RDW levels were significantly associated with CIN.

Our study has limitations. First, we did not assess oxidative stress and second, variations in the time to measurement may have missed peak levels of postprocedural creatinine. This may have caused an underestimation of the true incidence of CIN.

In conclusion, our study suggested that increased RDW on admission is independently associated with a greater risk of CIN in patients undergoing PCI for ACS. Red cell distribution width may predict the development of CIN after PCI in these patients.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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