

Red cell distribution width is an inflammatory predictor marker of contrast induced nephropathy in patients undergoing percutaneous coronary intervention

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Abstract

Red blood cell distribution width (RDW) is an inflammatory biomarker reported in complete blood cell (CBC) counts. High RDW defines a proinflammatory state. Contrast-induced nephropathy (CIN) is an important and common complication in percutaneous coronary intervention (PCI) treated patients. The current study was conducted to evaluate the role of RDW as a simple predictive inflammatory marker of CIN in PCI treated patients. The current prospective study enrolled 126 PCI treated patients. Laboratory investigations included CBC, liver function test, (HbA1C), lipid profile and serological tests. Serum urea and creatinine levels were obtained at baseline and 48 to 72 hours after PCI procedure, used to categorize for CIN. Diabetes mellitus, hypertension, and ischemic heart disease were present in 39 (31%), 44 (34.9%), and 23 (18.3%) patients, respectively. Of the studied patients, only 19 (15.1%) patients developed CIN. The hemoglobin level was significantly higher in the non-CIN group (13.49 ± 1.63 vs. CIN group 12.56 ± 1.62 mg/dl; $p = 0.02$). RDW was significantly higher among CIN group than non-CIN group (16.20 ± 2.60 vs. 13.83 ± 2.19 % ($p < 0.001$). Delta creatinine (% change in creatinine level after 48 hour) was significantly higher in patients with CIN (59.17 ± 28.89 vs. non-CIN 33.62 ± 9.76 ; $p < 0.001$). Predictors for CIN in patients who underwent PCI were old age high RDW high delta creatinine and amount of dye. At cut off $> 14.5\%$, RDW had 79% sensitivity, 70% specificity and 71.3% overall accuracy at AUC of 0.76. In conclusion, RDW may be simple and immediately available inflammatory biomarker and predictor for development of CIN in patients undergoing PCI.

Keywords: RDW, Contrast-induced nephropathy, percutaneous coronary intervention, inflammation

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Introduction

Red blood cell distribution width (RDW) is a measurement of erythrocyte variability and heterogeneity. It is obtained in routine standard complete blood cell counts (CBC).¹ Increased RDW reflects chronic inflammation and oxidative stress. Also, it indicates the presence of anisocytosis, which is related to impaired erythropoiesis and erythrocyte degradation.²

RDW is a routine parameter measured by most modern hematology analyzers. It is defined as the standard deviation of red blood cell volume and its mean volume. It is expressed as a percentage according to the following formula: $RDW = (\text{standard deviation of red blood cell volume} / \text{mean cell volume}) \times 100$. Higher RDW values reflect greater variations in red blood cell volume.³

Elevated RDW⁴ and interleukin 10 (IL-10)⁵ levels reflect the inflammatory status of multiple myeloma and associated with advanced stage and poor prognosis. Platelets distribution width can predict spontaneous bacterial peritonitis (SBP)⁶, while RDW correlated negatively with survival in SBP patients.⁷ Increases in RDW and N-terminal pro-B-type natriuretic peptide (NT-proBNP) predict the mortality of chronic heart failure patients undergoing cardiac resynchronization therapy (CRT).⁸ NT-pro BNP is a powerful initial non-invasive diagnostic tool for exclusion of heart disease in cirrhotic patients.⁹ RDW plays important predictive roles in gestational diabetes mellitus (GDM).¹⁰ with higher levels of soluble human leukocyte antigen G (HLA-G).¹¹

High RDW¹² and high programmed death-ligand 1 (PD-L1) expression¹³ reflect worse outcomes in acute myeloid leukemia (AML) and poor response to induction treatment. Higher RDW is a poor prognostic factor for patients with chronic myeloid leukemia (CML)¹⁴, while decreased level of soluble vascular cell adhesion molecule 1 (sVCAM-1) and transforming growth factor beta 1 (TGFβ1) associated with good molecular and hematological responses to CML treatment.¹⁵

Intercellular adhesion molecule-1 (ICAM-1)¹⁶ and RDW¹⁷ are significantly higher and strongly positively correlated with thrombosis in patients

with slow coronary flow syndrome. Also, ICAM-1 plays a role in the pathogenesis of immune thrombocytopenia (ITP).¹⁸

Contrast-induced nephropathy (CIN) is an important complication of invasive cardiovascular procedures. Patients who undergo percutaneous coronary intervention (PCI) are at greater risk of CIN and patients with diabetes mellitus or baseline renal impairment have a risk of almost 50%.¹⁹ PCI is a non-surgical procedure used to remove plaque from arteries. The process involves combining coronary angioplasty with stenting. Angiography uses radio-opaque dyes to assess real-time X-ray imaging. Development of CIN after PCI is associated with worse clinical outcomes including prolonged hospitalization, high cost, risk of end-stage renal failure, myocardial infarction, repeat revascularization, and increased mortality.²⁰

The pathophysiology of CIN is complex, multifactorial, and incompletely understood. Possible mechanisms include inflammation, endothelial dysfunction, generation of reactive oxygen species, intrarenal vasoconstriction, reduced renal blood flow, medullary hypoxia, oxidative stress, and direct tubular epithelial cell injury by contrast media (CMs).²¹

The current study was conducted to evaluate the role of RDW as a simple predictive marker of CIN in patients undergoing PCI.

Patients and Methods

The current prospective study enrolled 126 patients, underwent PCI during one year from May 2020 to May 2021. The protocol of the study was ethically reviewed and approved by the Institutional Review Board of the Faculty of Medicine, Assiut University (Approval dated April 2017). Every patient was informed about the nature and steps of the study. Written informed consents were obtained from study patients before included in the study.

The enrolled patients included both ST-segment elevation myocardial infarction (STEMI) patients, received primary PCI for revascularization and patients who received elective PCI, presented to the Cardiology Department at Assiut University Hospital.

End stage renal disease with glomerular filtration rate (GFR) less than 30 ml/1.73, patient with known allergy to contrast agents, patients with left ventricular ejection fraction below 30%, subjects with presence of known bacterial infections, patients with recent history of contrast administration in the previous month, patient known to have thyroid disease, patients with history of malignancy, patient known to have autoimmune disease, patients with decompensated liver cirrhosis, patients with cardiogenic shock, and anemic patients were all excluded from the study.

Baseline demographic characteristics, such as gender and age (years), and clinical characteristics, such as history of diabetes, hypertension, were recorded for all the patients. Diagnosis of STEMI was made based on history and electrocardiographic (ECG) changes at presentation, such as history of typical chest pain lasting for more than half an hour and supported by the baseline ECG findings of ST-segment elevation and echocardiogram to evaluate ejection fraction.

At admission, laboratory investigations were performed and recorded for all admitted subjects to Assiut University Hospital. These included CBC to evaluate RDW. The determination of RDW levels was done by an automated machine for blood cell analysis including counting and sizing blood cells (Coulter LH Series, Beckman Coulter, Inc, Hialeah, Florida, USA). RDW was considered high if above 16%. Data of liver and kidney function tests, (HbA1C) and lipid profile and other serological tests were obtained from hospital records. Serum urea and creatinine (mg/dL) levels were obtained at baseline and 48 to 72 hours after PCI procedure, and patients with a 25% increase or ≥ 0.5 mg/dL rise in post-procedure creatinine level (after 48 to 72 hours) were categorized for CIN.

The PCI procedures were performed by consultant cardiologists. Data of catheter were also recorded as amount of contrast used during procedure, either elective or emergency and approach either trans-radial or femoral. Coronary angiography and PCI were performed according to standard clinical practice using a

fully digital angiography system (Siemens Axiom Artis zee 2011, Germany). Intra-arterial nonionic, water-soluble x-ray contrast dye was used for intra-arterial and intravenous procedures. A bolus of 5000 U of unfractionated heparin, followed by intraprocedural boluses to maintain an activated clotting time of 200 to 250 seconds, acetylsalicylic acid 300 mg orally, and clopidogrel a single loading dose of 600 mg.

Statistical analysis

Data were collected and analyzed using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Continuous data were expressed in form of mean $\pm$ SD or median (range) while nominal data was expressed in form of frequency (percentage). Chi²-test was used to compare the nominal data of different groups in the study while student t-test was used to compare mean of different two groups. Multivariate regression analysis was used to determine the independent risk factors for prediction of CIN among the studied patients. The receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic accuracy of different scores for prediction of CIN. Level of confidence was kept at 95% and hence *p* value was significant if < 0.05 .

Results

The current prospective study was performed at the Cardiology Department to assess RDW as a simple inflammatory predictive marker of CIN in patients undergoing PCI. The study enrolled 126 patients, underwent PCI. Of these, 19 (15.1%) patients developed CIN while 107 (84.9%) patients did not develop CIN. Based on the development of CIN, patients were grouped into two groups.

Baseline data of enrolled patients based on development of CIN

The mean age of enrolled patients was 54.61 ± 9.52 years and most of them were males (74.6%) and 32 (25.4%) female patients. The mean body mass index was 27.83 ± 4.44 (kg/m²). Diabetes mellitus, hypertension, and ischemic heart disease were present in 39

(31%), 44 (34.9%), and 23 (18.3%) patients, respectively (Table 1).

There was no difference in baseline data between groups of patients, with CIN and

without CIN, ($p > 0.05$) with exception of the mean age in years, was higher among the CIN group than the non-CIN group (60.89 ± 9.13 vs. 53.49 ± 9.18 , $p < 0.001$).

Table 1. Baseline data of enrolled patients based on development of CIN.

	Total (n= 126)	CIN (n= 19)	Non-CIN (n= 107)	p value
Age (years)	54.61 $\pm$ 9.52	60.89 $\pm$ 9.13	53.49 $\pm$ 9.18	< 0.001
Sex				
Male	94 (74.6%)	16 (84.2%)	78 (72.9%)	NS
Female	32 (25.4%)	3 (15.8%)	29 (27.1%)	
BMI (kg/m ²)	27.83 $\pm$ 4.44	27.15 $\pm$ 5.29	29.59 $\pm$ 4.25	NS
DM	39 (31%)	7 (36.8%)	32 (29.9%)	NS
HTN	44 (34.9%)	7 (36.8%)	37 (34.6%)	NS
IHD	23 (18.3%)	6 (31.6%)	17 (15.9%)	NS

Data expressed as frequency (percentage), mean ($\pm$ SD); $P > 0.05$ is not significant (NS). CIN: contrast induced nephropathy; BMI: body mass index; DM: diabetes mellitus; HTN: hypertension; IHD: ischemic heart disease

Clinical, laboratory and ECG findings in the studied patients based on CIN status

Baseline clinical, laboratory and ECG findings showed no significant differences between both groups of patients with exception of hemoglobin level, was significantly higher in the non-CIN group than the non-CIN group (13.49 ± 1.63 vs. 12.56 ± 1.62 (mg/dl); $p = 0.02$), RDW was significantly higher among the CIN group in comparison to the non-CIN group 16.20 ± 2.60 vs. 13.83 ± 2.19 %, $p < 0.001$), and delta creatinine (percentage of change in creatinine level after 48 hour) was significantly higher in

patients with CIN than the non-CIN group (59.17 ± 28.89 vs. 33.62 ± 9.76 , $p < 0.001$) (Table 2).

Many patients of both groups (63.2% of non-CIN group and 62.6% of CIN group) had anterior myocardial infarction. Also, 6 (31.6%) and 27 (25.2%) patients of non-CIN group and CIN group, respectively had posterior myocardial infarction. There were 5 patients with non-CIN who had lateral infarction and another patient had left bundle branch block. Albumin, HbA1C levels and lipid profile were not different in both groups.

Table 2. Laboratory and ECG findings in the studied patients based on CIN status.

	Total (n= 126)	CIN (n= 19)	Non-CIN (n= 107)	p value
EF (%)	51.05 $\pm$ 9.38	47.84 $\pm$ 8.03	51.63 $\pm$ 9.52	NS
ECG findings				
Anterior MI	79 (62.7%)	12 (63.2%)	67 (62.6%)	NS
Inferior MI	33 (26.2%)	6 (31.6%)	27 (25.2%)	
Posterior MI	8 (6.3%)	1 (5.3%)	7 (6.5%)	
Lateral MI	5 (4%)	0	5 (4.7%)	
LBBB	1 (0.8%)	0	1 (0.9%)	
Hemoglobin (mg/dl)	13.35 $\pm$ 1.65	12.56 $\pm$ 1.62	13.49 $\pm$ 1.63	0.02
Leucocytes (103/ μ l)	10.67 $\pm$ 4.84	11.26 $\pm$ 6.63	10.56 $\pm$ 4.48	NS
Platelets (103/ μ l)	282.07 $\pm$ 82.72	292.47 $\pm$ 67.98	280.23 $\pm$ 77.21	NS
RDW (%)	14.19 $\pm$ 2.49	16.20 $\pm$ 2.60	13.83 $\pm$ 2.19	<0.001
MCV (fl)	81.06 $\pm$ 7.50	78.84 $\pm$ 10.09	81.45 $\pm$ 6.92	NS
Creatinine (mg/dl)	0.98 $\pm$ 0.40	1.03 $\pm$ 0.41	0.97 $\pm$ 0.40	NS

Table 2. Continued.

	Total (n= 126)	CIN (n= 19)	Non-CIN (n= 107)	p value
Urea (mg)	7.79 ± 6.7	9.74 ± 7.78	7.19 ± 5.31	NS
eGFR	84.18 ± 28.31	83.42 ± 35.34	84.32 ± 27.07	NS
Delta creatinine	37.33 ± 3.32	59.17 ± 28.89	33.62 ± 9.76	<0.001*
AST (U/l)	42.49 ± 27.79	36.57 ± 18.25	43.54 ± 29.10	NS
ALT (U/l)	33.99 ± 24.66	28.84 ± 17.12	34.09 ± 25.75	NS
Bilirubin (mg/dl)	0.74 ± 0.38	0.68 ± 0.32	0.75 ± 0.39	NS
Albumin (g/dl)	3.87 ± 0.48	3.81 ± 0.53	3.88 ± 0.47	NS
HbA1C	7.34 ± 0.97	7.63 ± 1.28	7.29 ± 0.90	NS
Cholesterol (mg/dl)	176.75 ± 36.01	173.75 ± 29.21	177.32 ± 37.29	NS
HDL (mg/dl)	51.19 ± 12.81	54.05 ± 15.49	50.56 ± 12.28	NS
LDL (mg/dl)	102.49 ± 33.47	97.25 ± 25.02	103.49 ± 34.88	NS
TGs (mg/dl)	131.18 ± 51.98	122.84 ± 34.47	132.77 ± 56.67	NS

Data expressed as mean (±SD). $P > 0.05$ is not significant (NS). CIN: contrast induced nephropathy; RDW: red cell distribution width; ECG: electrocardiography; MI: myocardial infarction; LBBB: Left bundle branch block; MCV: mean corpuscular volume; ALT: alanine transaminase; AST: aspartate transaminase; HR: heart rate; HbA1C: glycosylated hemoglobin; HDL: high density lipoprotein; LDL: Low density lipoprotein; TG: triglyceride; EF: ejection fraction.

Angiographic data of enrolled patients based on development of CIN

The amount of intra-arterial dye (Scanlux, Ultravist, or Telebrix) was significantly higher among studied patients with CIN in comparison to patients with non-CIN (154.21 ± 36.56 vs. 117.29 ± 36.15 ml, $p < 0.001$). PCI, access, and

number of stents were not different among studied groups ($p > 0.05$). Only 4 (4.2%) patients did not require stenting while 99 (78.6%), 19 (15.1%) and 4 (3.2%) patients required insertion of one, two and three stent, respectively (Table 3).

Table 3. Angiographic data of enrolled patients based on development of CIN.

	Total (n= 126)	CIN (n= 19)	Non-CIN (n= 107)	p value
Type of PCI				
Elective	27 (21.4%)	3 (15.8%)	24 (22.4%)	NS
Primary	99 (78.6%)	16 (84.2%)	83 (77.6%)	
Access				
Femoral access	119 (94.4%)	18 (94.7%)	101 (94.4%)	NS
Radial access	7 (5.6%)	1 (5.3%)	6 (5.6%)	
Type of contrast				
Scanlux	101 (80.2%)	15 (78.9%)	86 (80.4%)	NS
Ultravist	14 (11.1%)	3 (15.8%)	11 (10.3%)	
Telebrix	11 (8.7%)	1 (5.3%)	10 (9.3%)	
Contrast (ml)	122.86 ± 38.42	154.21 ± 36.56	117.29 ± 36.15	< 0.001
Number of stents				
None	4 (3.2%)	1 (5.3%)	3 (2.8%)	NS
One stent	99 (78.6%)	17 (89.5%)	82 (76.6%)	
Two stents	19 (15.1%)	1 (5.3%)	18 (16.8%)	
Three stents	4 (3.2%)	0	4 (3.7%)	

Data expressed as frequency (percentage), mean (±SD). $P > 0.05$ is not significant (NS). CIN: contrast induced nephropathy; PCI: percutaneous coronary intervention.

Multivariate regression analysis for predictors of CIN in patients underwent PCI

The current study indicated that predictors for CIN in patients underwent PCI were old age (odd's ratio= 1.15, 95% CI= 1.04-1.28, $p < 0.001$),

RDW (odd's ratio= 2.03, 95% CI= 1.35-3.07, $p < 0.001$), delta creatinine (odd's ratio= 1.03, 95% CI= 1.01-2.90, $p = 0.004$) and amount of dye (odd's ratio= 1.03, 95% CI= 1.01-2.05, $p = 0.008$) (Table 4).

Table 4. Predictors of CIN in patients underwent PCI.

Predictors	Odd's ratio	95% confidence interval	<i>p</i> value
Age (> 50 years)	1.15	1.04-1.28	< 0.001
Hemoglobin	0.57	0.29-1.11	NS
RDW	2.03	1.35-3.07	< 0.001
Delta creatinine	1.03	1.01-2.90	0.004
Amount of contrast	1.03	1.01-2.05	0.008

$P > 0.05$ is not significant (NS). CIN: contrast induced nephropathy; PCI: percutaneous coronary intervention; RDW: red cell distribution width.

Diagnostic accuracy of RDW in prediction of CIN in patients with PCI

The ROC curve analysis indicated that at cut off > 14.5 (%), RDW had 79% sensitivity, 70% specificity with overall accuracy of 71.3% with area under curve of 0.76 (Table 5, Figure 1).

Table 5. Diagnostic accuracy of RDW in prediction of CIN in patients with PCI.

	Value
Sensitivity	79%
Specificity	70%
Positive predictive value	31%
Negative predictive value	95%
Accuracy	71.3%
Cut off point	14.5%
Area under curve	0.79
* <i>p</i> value	0.001

* $P \leq 0.05$ is significant. CIN: contrast induced nephropathy; PCI: percutaneous coronary intervention; RDW: red cell distribution width.

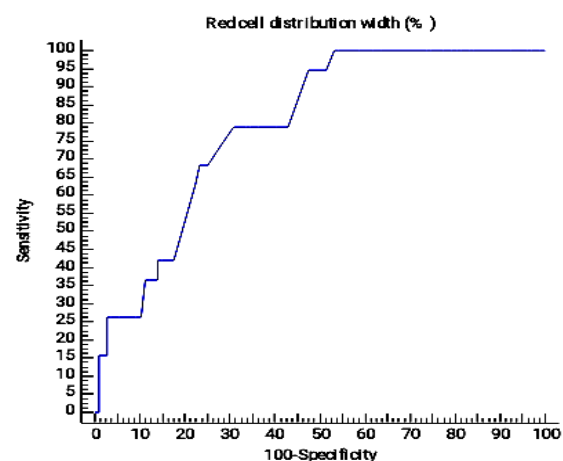


Figure 1. Receiver operating characteristic curve analysis showing diagnostic accuracy of RDW in prediction of CIN in patients with PCI.

Characteristics of patients based on level of RDW

As shown in Table 6, there was no difference in demographic, laboratory, and ECG findings between patients with normal and with high RDW. However, CIN was significantly higher among patients with high RDW.

Table 6. Characteristics of patients based on level of RDW.

	High RDW (n=36)	Normal RDW (n=90)	p value
Age (years)	55.58 ± 9.39	54.22 ± 9.59	NS
Sex			
Male	29 (80.6%)	65 (72.2%)	NS
Female	7 (19.4%)	25 (27.8%)	
BMI (kg/m ²)	28.75 ± 4.82	27.46 ± 4.25	NS
DM	14 (38.9%)	25 (27.8%)	NS
HTN	13 (36.1%)	31 (34.4%)	NS
IHD	27 (75%)	76 (84.4%)	NS
EF (%)	49.86 ± 10.06	51.53 ± 9.11	NS
ECG findings			
Anterior MI	21 (58.3%)	58 (54.5%)	NS
Inferior MI	12 (33.3%)	21 (23.3%)	
Posterior MI	2 (5.6%)	6 (6.7%)	
Lateral MI	0	5 (5.6%)	
LBBB	1 (2.8%)	0	
Hemoglobin (mg/dl)	13.60 ± 1.89	13.25 ± 1.56	NS
Leucocytes (10 ³ /μl)	11.10 ± 6.05	10.50 ± 4.29	NS
Platelets (10 ³ /μl)	284.19 ± 95.87	281.23 ± 77.41	NS
MCV (fl)	79.31 ± 9.88	81.75 ± 6.23	NS
Creatinine (mg/dl)	1.08 ± 0.41	0.94 ± 0.39	NS
Urea (mg)	9.32 ± 6.86	6.87 ± 5.15	NS
eGFR	77.45 ± 29.16	86.88 ± 27.67	NS
Delta creatinine	0.90 ± 0.04	0.77 ± 0.02	NS
AST (U/L)	40.41 ± 21.86	43.32 ± 29.91	-
ALT (U/L)	32.41 ± 18.76	34.67 ± 26.72	NS
Bilirubin (mg/dl)	0.68 ± 0.37	0.75 ± 0.39	NS
Albumin (g/dl)	3.86 ± 0.53	3.88 ± 0.46	NS
HbA1C	7.54 ± 0.89	7.37 ± 1.01	NS
Cholesterol (mg/dl)	171.17 ± 25.27	178.91 ± 39.35	NS
HDL (mg/dl)	53.03 ± 14.88	50.48 ± 11.94	NS
LDL (mg/dl)	97.04 ± 24.87	104.52 ± 36.22	NS
TGs (mg/dl)	122.50 ± 42.99	134.56 ± 54.99	NS
CIN	19 (100%)	0	< 0.001

Data expressed as mean (±SD). *P* > 0.05 is not significant (NS). CIN: contrast induced nephropathy; BMI: body mass index; DM: diabetes mellitus; HTN: hypertension; IHD: ischemic heart disease; RDW: red cell distribution width; ECG: electrocardiography; MI: myocardial infarction; LBBB: Left bundle branch block; MCV: mean corpuscular volume; ALT: alanine transaminase; AST: aspartate transaminase; HR: heart rate; HbA1C: glycosylated hemoglobin; HDL: high density lipoprotein; LDL: Low density lipoprotein; TG: triglyceride; EF: ejection fraction.

Discussion

The current study aimed to evaluate the role of RDW as a simple predictive marker of CIN in patients undergoing PCI. In the study, 126 patients were enrolled of which 19 % of the patients developed CIN after primary PCI. This was higher than the reported incidence of 12.4% in the study by Batra et al., 2013²² and

10.2% in the study by Ullah et al., 2016.²³ A study by Tsai et al., 2014, reported acute kidney injury in 7.1% of the patients after PCIs.²⁴

In our study, the mean age of enrolled patients was 54.61 ± 9.52 years. Higher mean age group was reported by Andò et al., 2013, (73±10 SD)²⁵ and Kurtul et al., 2015 (61± 12 SD).¹

In the current study, the mean age of CIN positive patients was significantly higher than CIN negative group ($p < 0.001$). On Multivariate regression analysis for predictors of CIN in patients underwent PCI, old age (>50 years) was an independent factor.

Aging is a common risk factor for developing CIN. Advanced age is associated with increased vascular stiffness and declined endothelial function resulting in reduced vascular repair capacity.²⁶ In the study by Andò et al., 2013, multivariate analysis showed that age was independent predictor of CIN (OR 1.06, $p=0.042$). They proposed a score (AGEF) including three factors age, eGFR and Ejection fraction (EF) which was an accurate predictor of CIN (OR 5.19, $p<0.001$).²⁵

In our study, 74.6% of enrolled patients were males and 32 (25.4%) female patients. No sex predilection was identified in our study for higher risk of CIN. Other studies showed that there was no gender difference in the frequency of CIN.²³

A study by Kumar et al., 2020, reported that 68.4 % of CIN patients were males and the mean age was (56.4 ± 9 SD).²⁷ Furthermore, multiple regression analysis indicated that male gender was also considered an independent risk factor in predicting CIN.²⁷ The same findings were reported by another study, found that 59% of patients were males and male patients significantly higher in the CIN group ($p=0.115$ and, $p<0.001$).²⁸

Higher incidence of CIN in males could be related to higher presence of obstructive nephropathy due to enlarged prostate or carcinoma, bladder cancer and renal stone. Kidney function declines faster in men than in women, possibly owing to the protective effects of estrogen or the damaging effects of testosterone.²⁹

In the current study, diabetes mellitus, hypertension and ischemic heart disease were present in 39 (31%), 44 (34.9%), and 23 (18.3%) of CIN patients, respectively. Kurtul et al., 2015, reported that 51.9% of CIN patients were hypertensive and 39.5% diabetic.¹ A study by Kumar et al., 2020, reported that the majority of patients, 78.7% were hypertensive but similar to data of the current study 34% were diabetic.²⁷

In our study, DM and hypertension (HTN) had no impact on the development of CIN. While in a recent study done by Kumar et al., 2020, the CIN was observed in 13.1% of the patients, and increased risk of CIN was found to be associated with the presence of diabetes mellitus with odds ratios of 2.3 (1.14-4.63).²⁷ Findings of the study by Kurtul et al., 2015, agreed with the current results, hypertension and diabetes mellitus were not different between the two studied groups, more patients in the CIN group had diabetes and hypertension than those without CIN, but the difference did not reach statistical significance ($p<0.055$ and $p<0.082$, respectively).¹ The study by Sığirci, 2018, showed that hypertension was more common in the CIN group and considered as independent risk factor for development CIN.²⁸ Also, the study by Andra et al., 2018, showed that hypertension was a risk factor for CIN.³⁰

A study compared DM in CIN vs. non-CIN patients and showed significant differences (67.9% vs. 36.3%; $p=0.001$), but there were no significant differences between hypertension in the groups.³¹ A study by Akkoyun et al., 2015, found that diabetes mellitus was more common in patients who developed CIN vs. non-CIN patients (42.8% vs. 17.9%, $p<0.001$) but no difference was found in terms of sex, hypertension, hemoglobin levels and localization of myocardial infarction ($p>0.05$).³²

DM and HTN are well known to be associated with higher CIN by medullary hypoxia due to decreased renal blood flow secondary to renal artery vasoconstriction and direct tubular toxicity by contrast media.³³ The important finding in DM and HTN was the increased in endothelin-1, angiotensin II and decreased nitric oxide levels, which are produced by healthy endothelium, as some of the potential mediators lead to intrarenal vasoconstriction.³³

An interesting finding in our study was the significantly higher hemoglobin level in the non-CIN group vs. the CIN group (13.49 ± 1.63 vs. 12.56 ± 1.62 (mg/dl); $p=0.02$). This is inconsistent with findings of a study by Mizuno et al., 2015, as hemoglobin was lower in Contrast Induced Acute Kidney Injury (CI-AKI) patients vs. non CI-AKI patients (13.7 ± 3 g/dl vs. 15.0 ± 1.7 g/dl, $p = 0.038$).³⁴ Xu et al., 2016, also

found that red blood cells and levels of hemoglobin and hematocrit in the hemoglobin low group of CIN were significantly lower compared with those in the hemoglobin-normal group ($p < 0.05$).³⁵ Li et al., 2013 found that the incidence of CIN in anemic patients (hemoglobin < 12 g/dl in women and < 13 g/dl in men) was significantly higher than non-anemic patients (6.3 vs. 2.2 %; $p < 0.01$).³⁶ Low Hb level was significantly associated with CIN as local renal hypoxia can be more aggravated in patients with low hemoglobin after exposure to contrast media. So, the combination of contrast induced vasoconstriction and anemia may decrease oxygen delivery sufficiently to cause renal medullary hypoxia.³⁶

In our study delta creatinine (percentage of change in creatinine level after 48 hour) was significantly higher in patients with CIN vs non-CIN patients ($p < 0.001$). On multivariate analysis, delta creatinine was an independent risk factor for CIN ($p = 0.004$). Also Akkoyun et al., 2015 found that delta creatinine (Δ -Cr) was significantly higher in CIN-positive group vs. CIN-negative group (0.6 ± 0.58 vs. 0.1 ± 0.07 , $p < 0.001$).³² Baseline creatinine is not reliable enough for identification of patients at risk for CIN. This is because serum creatinine value varies with age, muscle mass, and gender. Since creatinine production decreases with age, a normal serum creatinine in an elderly patient generally correlates with at least moderate decrease in renal function.³²

In our study, multivariate analysis indicated that the amount of intra-arterial dye was an independent risk factor for CIN ($p = 0.008$). This is consistent with findings of a study by Akkoyun et al., 2015 they showed that 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, $p < 0.001$).³² Also, a study by Akin et al., 2015, used multivariate analysis and showed that contrast media was predictor of CIN (OR=1.007, 95% CI 1.002-1.012, $p = 0.009$).³⁷ In the same line, a study Xu et al., 2016, used univariate analysis and showed that contrast media volume of ≥ 200 ml was associated with the development of CIN ($p < 0.05$).³⁵

But in contrary with our study, Lin et al., 2013, showed that, there was no significant difference in procedure duration or contrast volume between CIN-positive group and CIN-negative group.³¹ Kurtul et al., 2015 showed that the total amount of contrast media and prevalence of high contrast volume was not significantly different between CIN-positive group and CIN-negative group.¹ Andra et al., 2018, found that there was no difference in baseline serum creatinine levels and the amount of contrast media in patient with CIN and without CIN.³⁰ The role of contrast agent in the development of CIN is induced by its direct toxicity on surrounding cells. Also, it increases blood viscosity and release free radicals that prevent vasodilation causing renal ischemia.³⁸

Also, Uyarel et al., 2011, investigated the outcomes of primary percutaneous coronary intervention performed in 2506 patients with high (> 14.8) and normal (≤ 14.8) RDW, and they observed a significant predictive value of RDW for in-hospital and long-term mortality.³⁹ Akin et al., 2015, found that, RDW was a significant predictor of CIN development in patients with acute coronary syndrome after coronary angiography.³⁷ However in the study of Sığirci 2018, observed that RDW has a limited use as a CIN predictor in patients with stable coronary artery disease. The mean RDW level was $13.7 \pm 1.4\%$, and the mean creatinine level was 1.0 ± 0.2 mg/dL. There was no correlation between RDW and the presence of CIN.²⁸

Elevated RDW values, observed in coronary artery disease patients, could be related to decrease of cardiac output result in systemic ischemia. Inflammation developed as a result of this ischemia leads to the release of cytokines, which stimulate hematopoiesis leads to anisocytosis due to immature erythrocytes.²⁸ 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.²⁸

Lippi et al., 2009, described the relationship between RDW and other inflammatory markers such as the erythrocyte sedimentation rate (ESR) and high sensitivity C-Reactive Protein

(CRP).⁴⁰ In previous studies, RDW correlated with IL-6, soluble tumor necrosis factors I and II receptor concentrations, and fibrinogen levels.^{41,42} Unfortunately in the current study we did not investigate inflammatory markers like CRP, ferritin and ESR to determine their correlation with increase RDW in CIN.

In conclusion, based on our study findings, increased RDW on admission was independently associated with a greater risk of CIN in patients undergoing PCI. RDW may predict the development of CIN after PCI in these patients. Based on multivariate regression analysis, old age (>50 years), RDW, delta creatinine and amount of intra-arterial dye were predictors of CIN in patients underwent PCI.

Author Contributions

MRA, MAT, MFMS and SMT conceived and designed the research. SZB and SMT recruited patients. SMT carried out PCI. MRA, SZB, MFMS, SMT and MAT collected clinical data. MRA, MAT, MFMS, SZB and SMT contributed in the interpretation of data for the work. MRA prepared the original draft of the manuscript. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Declaration of Conflicting Interests

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Ethical approval

The protocol of the study was ethically reviewed and approved by the Institutional Review Board of the Faculty of Medicine, Assiut University (Approval dated April 2017).

Informed consent

Every patient was informed about the nature and steps of the study. Written informed consents were

obtained from study patients before included in the study.

References

1. Kurtul A, Yarlioglues M, Murat S N et al (2015). Red Cell Distribution Width Predicts Contrast-Induced Nephropathy in Patients Undergoing Percutaneous Coronary Intervention for Acute Coronary Syndrome. *Angiology*, 66(5), 433–440. <https://doi.org/10.1177/0003319714535238>.
2. Semba R D, Patel K V, Ferrucci L et al (2010). Serum antioxidants and inflammation predict red cell distribution width in older women: The Women's Health and Aging Study. *Clinical Nutrition*, 29(5), 600–604. <https://doi.org/10.1016/j.clnu.2010.03.001>
3. Bujak K, Wasilewski J, Osadnik T et al (2015). The Prognostic Role of Red Blood Cell Distribution Width in Coronary Artery Disease: A Review of the Pathophysiology. In *Disease Markers* (Vol. 2015). Hindawi Limited. <https://doi.org/10.1155/2015/824624>
4. Lee H, Kong SY, Sohn JY, et al (2014). Elevated red blood cell distribution width as a simple prognostic factor in patients with symptomatic multiple myeloma. *Biomed Res Int*. 2014;2014:145619. doi: 10.1155/2014/145619. Epub 2014 May 21. PMID: 24963470; PMCID: PMC4055253.
5. Mohammed, D., Khallaf, S., El-Naggar, M., Abdel-Hameed, M., et al (2021). Interleukin-10: A Potential Prognostic Marker in Patients with Newly Diagnosed Multiple Myeloma. *Research in Oncology*, 17(1), 38–41. doi: 10.21608/resoncol.2021.51503.1127
6. Abdel Hammed MR, El-Amien HA, Asham MN et al (2022). Can platelets indices and blood neutrophil to lymphocyte ratio be used as predictors for diagnosis of spontaneous bacterial peritonitis in decompensated post hepatitis liver cirrhosis? *Egypt J Immunol*. Oct; 29(4):12–24. PMID: 36197150.
7. İliaz R, İliaz S, Evirgen S, et al. (2022). The value of red cell distribution width and inflammatory markers in patients with spontaneous bacterial peritonitis. *J Enterocolitis*. 1(2):33–36.
8. András Mihály Boros, Péter Perge, Zsigmond Jenei et al (2016). "Measurement of the Red Blood Cell Distribution Width Improves the Risk Prediction in Cardiac Resynchronization Therapy", *Disease Markers*, vol. 2016, Article ID 7304538, 13 pages, <https://doi.org/10.1155/2016/7304538>
9. Hassan EA, El-Rehim A, Sayed Z et al (2013). N-Terminal Pro-Brain Natriuretic Peptide: Prognostic Potential in End Stage Liver Cirrhosis in a Cohort Free of Heart Failure; an Egyptian Insight. *J Liver* 2:125.

10. Pek E & Beyazıt F (2021). Evaluation of the simple hematologic markers in patients with gestational diabetes mellitus: a case-control study Gestasyonel Diabetes Mellituslu Hastalarda Basit Hematolojik Belirteçlerin Değerlendirilmesi: Vaka-Kontrol Çalışması. *Bozok Tıp Dergisi*, 11 (3), 19-24. Retrieved from <https://dergipark.org.tr/en/pub/bozoktip/issue/64894/995339>
11. Abdel Hameed MR, Ibrahiem OA Ahmed, E.H. et al. (2020). Soluble human leukocyte antigen-G evaluation in pregnant women with gestational diabetes mellitus. *Egypt J Intern Med* 32, 7. <https://doi.org/10.1186/s43162-020-00009-w>.
12. Vucinic V, Ruhnke L, Sockel K et al (2021). The diagnostic red blood cell distribution width as a prognostic factor in acute myeloid leukemia. *Blood Adv.* Dec 28; 5(24):5584-5587. doi: 10.1182/bloodadvances.2021005974. PMID: 34670273; PMCID: PMC8714728.
13. Abdel Hafeez LA, Mansor SG, Zahran AM et al. (2021). Expression of programmed death ligand-1 (PDL-1) in Acute Myeloid Leukemia Patients and its relation to post induction Response. *SECI Oncology Journal*, 9(2): 106-111. doi: 10.21608/secioj.2021.170554
14. Li T, Li X, Chen H, et al. (2021). Higher Red Blood Cell Distribution Width is a Poor Prognostic Factor for Patients with Chronic Myeloid Leukemia. *Cancer Manag Res.* Feb 10;13:1233-1243. doi: 10.2147/CMAR.S288589. PMID: 33603469; PMCID: PMC7882436.
15. Abdel Hamed MR, Ahmed YA, Adam EN, et al. (2022). sVCAM-1, and TGFβ1 in chronic phase, chronic myeloid leukemia patients treated with tyrosine kinase inhibitors. *Egypt J Immunol.* Oct;29(4):163-173. PMID: 36208045.
16. Turhan H, Saydam GS, Erbay AR, et al. (2006). Increased plasma soluble adhesion molecules: ICAM-1, VCAM-1, and E-selectin levels in patients with slow coronary flow. *Int J Cardiol.* 108(2):22430. [PubMed] [Google Scholar]
17. Luo SH, Jia YJ, Nie SP et al. (2013). Increased red cell distribution width in patients with slow coronary flow syndrome. *Clinics (Sao Paulo)*. Jun;68(6):732-7. doi: 10.6061/clinics/2013(06)02. PMID: 23778485; PMCID: PMC3674286.
18. Abdel Hameed MR, Nafady HA, Mostafa MI et al. (2021). Possible Role of CD11a in Primary Immune Thrombocytopenia Patients on Immunosuppressive Therapy. *J Blood Med.* 12:197-205 <https://doi.org/10.2147/JBM.S300717>
19. Goldfarb S, McCullough P A, McDermott J et al. (2009). Contrast-induced acute kidney injury: Specialty-specific protocols for interventional radiology, diagnostic computed tomography radiology, and interventional cardiology. *Mayo Clinic Proceedings* (Vol. 84, Issue 2, pp. 170–179). Elsevier Ltd. <https://doi.org/10.4065/84.2.170>
20. Lazaros G, Tsiachris D, Tousoulis D et al. (2012). In-hospital worsening renal function is an independent predictor of one-year mortality in patients with acute myocardial infarction. *International Journal of Cardiology*, 155(1), 97–101. <https://doi.org/10.1016/j.ijcard.2010.10.024>
21. Heyman S N, Rosen S, Khamaisi M et al. (2010). Reactive oxygen species and the pathogenesis of radiocontrast-induced nephropathy. *Investigative Radiology* (Vol. 45, Issue 4, pp. 188–195). Invest Radiol. <https://doi.org/10.1097/RLI.0b013e3181d2eed8>
22. Batra KM, Sial AJ, Kumar R et al. (2018). Contrast induced acute Kidney Injury: The sin of primary percutaneous coronary intervention. *Pak Heart J* 51 (02):172-718 DOI: <https://doi.org/10.47144/phj.v51i2.1499>
23. Ullah I, Israr M, Ali U et al. (2016). Frequency of contrast induced nephropathy in patients undergoing percutaneous coronary intervention. *Pak Heart J.* 48:130133. [Google Scholar] <https://pkheartjournal.com/index.php/pkheart/article/viewFile/1084/723>.
24. Tsai T T, Patel U D, Chang T I et al. (2014). Contemporary incidence, predictors, and outcomes of acute kidney injury in patients undergoing percutaneous coronary interventions: Insights from the NCDR cath-PCI registry. *JACC: Cardiovascular Interventions*, 7(1), 1–9. <https://doi.org/10.1016/j.jcin.2013.06.016>
25. Andò G, Morabito G, De Gregorio C et al. (2013). The ACEF score as predictor of acute kidney injury in patients undergoing primary percutaneous coronary intervention. *International Journal of Cardiology*, 168(4), 4386–4387. <https://doi.org/10.1016/j.ijcard.2013.05.049>
26. Brandes R P, Fleming I, Busse, R. et al. (2005). Endothelial aging. In *Cardiovascular Research* (Vol. 66, Issue 2, pp. 286–294). <https://doi.org/10.1016/j.cardiores.2004.12.027>
27. Kumar D, Liaquat H, Sial J A et al. (2020). Risk Factors Associated With Contrast-Induced Nephropathy after Primary Percutaneous Coronary Intervention. *Cureus*, 12(8). <https://doi.org/10.7759/cureus.9721>
28. Sığircı, S. (2018). The Impact of Red Cell Distribution Width on Contrast-Induced Nephropathy After Elective Percutaneous Intervention in Patients with Stable Coronary Artery Disease. *Sisli Etfal Hastanesi Tıp Bulteni / The Medical Bulletin of*

- Sisli Hospital*, 52(3). <https://doi.org/10.14744/semb.2018.75537>
29. Carrero J J, Hecking M, Chesnaye N C et al. (2018). Sex and gender disparities in the epidemiology and outcomes of chronic kidney disease. *Nature Reviews Nephrology*, 14(3), 151–164. <https://doi.org/10.1038/nrneph.2017.181>
 30. Andra C A, Khairul A, Arina C A et al. (2018). Contrast induced nephropathy in hypertensive patients after elective percutaneous coronary intervention Contrast induced nephropathy in hypertensive patients after elective percutaneous coronary intervention. *IOP Conference Series: Earth and Environmental Science*. volume 130, Issue 1, march, pages 012006, doi 10.1088/1755-1315/130/1/012006
 31. Lin Y S, Fang, H Y, Hussein H et al. (2014). Predictors of contrast-induced nephropathy in chronic total occlusion percutaneous coronary intervention. *EuroIntervention*, 9(10), 1173–1180. <https://doi.org/10.4244/EIJV9I10A198>
 32. Akkoyun D Ç, Akyüz A, Kurt Ö et al. (2015). Relationship between red cell distribution width and contrast-induced nephropathy in patients who underwent primary percutaneous coronary intervention. *Türk Kardiyoloji Dernegi Arsivi*, 43(7), 613–620. <https://doi.org/10.5543/tkda.2015.37941>
 33. Toprak O, Cirit M, Yesil M et al. (2007). *Impact of diabetic and pre-diabetic state on development of contrast-induced nephropathy in patients with chronic kidney disease. Nephrology Dialysis Transplantation*, Volume 22, Issue 3, March, Pages 819–826, <https://doi.org/10.1093/ndt/gfl636>
 34. Mizuno A, Ohde S, Nishizaki Y et al. (2015). Additional value of the red blood cell distribution width to the Mehran risk score for predicting contrast-induced acute kidney injury in patients with ST-elevation acute myocardial infarction. *Journal of Cardiology*, 66(1), 41–45. <https://doi.org/10.1016/j.jjcc.2014.09.006>
 35. Xu J, Zhang M, Ni Y et al. (2016). Impact of low hemoglobin on the development of contrast-induced nephropathy: A retrospective cohort study. *Experimental and Therapeutic Medicine*, 12(2), 603–610. <https://doi.org/10.3892/etm.2016.3416>
 36. Li W H, Li, D Y, Han F et al. (2013). Impact of anemia on contrast-induced nephropathy (CIN) in patients undergoing percutaneous coronary interventions. *International Urology and Nephrology*, 45(4), 1065–1070. <https://doi.org/10.1007/s11255-012-0340-8>
 37. Akin F, Celik O, Altun I et al. (2015). Relation of red cell distribution width to contrast-induced acute kidney injury in patients undergoing a primary percutaneous coronary intervention. *Coronary Artery Disease*, 26(4), 289–295. <https://doi.org/10.1097/MCA.0000000000000223>
 38. Morcos R, Kucharik M, Bansal P et al. (2019). Contrast-Induced Acute Kidney Injury: Review and Practical Update. *Clinical Medicine Insights: Cardiology*, 13 (Table 1). <https://doi.org/10.1177/1179546819878680>
 39. Uyarel H, Ergelen M, Cicek G et al. (2011). Red cell distribution width as a novel prognostic marker in patients undergoing primary angioplasty for acute myocardial infarction. *Coronary Artery Disease*, 22(3), 138–144. <https://doi.org/10.1097/MCA.0b013e328342c77b>
 40. Lippi Giuseppe, Targher G, Montagnana M (2009). Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. *Archives of Pathology and Laboratory Medicine*, 133(4), 628–632. <https://doi.org/10.5858/133.4.628>
 41. Emans M E, Van Der Putten K, Van Rooijen K L et al. (2011). Determinants of Red Cell Distribution Width (RDW) in Cardiorenal Patients: RDW is Not Related to Erythropoietin Resistance. *Journal of Cardiac Failure*, 17(8), 626–633. <https://doi.org/10.1016/J.CARDFAIL.2011.04.009>
 42. Vayá A, Sarnago A, Fuster O et al. (2015). Influence of inflammatory and lipidic parameters on red blood cell distribution width in a healthy population. *Clinical Hemorheology and Microcirculation*, 59(4), 379–385. <https://doi.org/10.3233/CH-141862>