DOI: https://doi.org/10.3329/cardio.v14i1.55368

Original Article

Association of Red Cell Distribution with Angiographic Severity of Coronary Artery Disease Assessed by SYNTAX Score in Non-ST Elevation Myocardial Infarction

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Key words: *Coronary artery disease, NSTEMI, RBC, SYNTAX score.*

Abstract

Background: *Red cell distribution width is a simple measure of red cell size heterogeneity (i.e., anisocytosis) in peripheral blood measured by hematology auto analyzer and has been shown to be a predictor of poor outcomes in various cardiovascular conditions including coronary artery disease (CAD). The present study was intended to find the association between RDW-CV and severity of CAD in NSTEMI patients.*

Methods: *The present cross-sectional analytical study was carried out in the Department of Cardiology, National Institute of Cardiovascular Diseases (NICVD), Dhaka, Bangladesh, from June 2018 to July 2019. A total of 70 NSTEMI patients undergoing coronary angiogram during the index hospitalization were included in the study. They were divided into two groups on the basis of RDW-CV (Group-I RDW-CV <14.3%; Group-II RDW-CV ≥14.3%). Severity of coronary artery disease was determined by SYNTAX score and correlation between RDW-CV and SYNTAX score was assessed.*

Results: *SYNTAX score was significantly higher in patients with RDW-CV ≥14.3% than that in patients with RDW-CV <14.3% (24.51±9.76 vs. 13.5±7.71, p<0.0001). The risk of having severe CAD in patients with RDW-CV ≥14.3%was 3.844(95% CI = 1.429-10.340) (p <0.008) times higher in terms of SYNTAX score. A significant positive correlation between RDW-CV and SYNTAX score was noted (r = 0.681, p value < 0.0001).*

Conclusion: *It may be concluded that RDW-CV was significantly associated with the severity of coronary artery disease in NSTEMI patients and it may be considered as an independent predictor of severity of CAD. It is easy to assess and inexpensive. So, before performing coronary angiography, it appears to be additive to conventional risk factors and commonly used biomarkers for risk stratification.*

(Cardiovasc j 2021; 14(1): 12-19)

Introduction:

Cardiovascular diseases (CVDs) are considered as the leading cause of death in the world and a major barrier to sustainable human development.[1] The 2013 Global Burden of Disease (GBD) study estimates that CVD caused 17.3 million deaths globally. It is responsible for 31.5% of all deaths and 45% of all non-communicable disease deaths,

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more than twice that caused by cancer, as well as more than all communicable, maternal, neonatal and nutritional disorders combined.[2] The exact prevalence of coronary artery disease (CAD) in Bangladesh is not known. Only a limited number of small-scale epidemiological studies are available showing a wide variability of prevalence of IHD ranging from 0.33% to 20%.[3] The clinical presentations of coronary artery disease include silent ischemia, stable angina pectoris, non-ST elevation acute coronary syndrome (NSTE-ACS) comprising unstable angina and non-ST elevation myocardial infarction, ST elevation myocardial infarction, heart failure and sudden death.[4]

Clinicians need simple, reliable, reproducible, and quantitative tools to identify patients' risks and recommend prevention strategies. Red cell distribution width (RDW) is a measure of variation in circulating red blood cell size or red blood cell volume. It is a parameter provided by automated hematology analyzers and routinely reported as part of automated full blood count. Depending on the types of hematology analyzer instruments, RDW can be reported statistically as coefficient of variation (RDW-CV) and/or standard deviation (RDW-SD). RDW-SD is expressed in fl and RDW-CV expressed in percentage (%). In recent years, studies have reported a strong independent association between RDW and prognosis in cardiopulmonary disorders such as coronary artery disease (CAD),[5] acute myocardial infarction (AMI),[6] acute heart failure,[7] chronic heart failure,[8] peripheral vascular disease,[9] pulmonary embolism.[10] The prognostic importance of RDW results from its relationship with total cholesterol erythrocyte membrane (CEM) which promotes plaque growth and plaque destabilization;[11] oxidative stress, causing both shortening of RBC lifespan and atherogenesis;[11] chronic inflammation and vitamin D_3 deficiency which results in derangements in bone marrow erythropoiesis and atherogenesis.[11] Increase in CEM level reduces cell deformability, which affects the lifespan of circulating erythrocytes, and this results in greater cellular turnover and elevated RDW values.

Recently, cardiologists have begun studying risk stratification in patients with CAD to identify the severity and complexity of CAD. For this purpose, a large number of scoring systems and laboratory parameters have been used in clinical practice. For quantification of coronary lesions with respect to their number, location, and complexity, the SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) score (SX) has been developed as a comprehensive angiographic scoring tool.[12] The SX score is a good predictor of mortality and morbidity at early and late follow-up in patients with ACS.[13-15] Although these scoring systems have many advantages, they require an invasive method such as coronary angiography to perform the scoring. Therefore, those interested in cardiovascular medicine still need an easily accessible, cost-effective and noninvasive method to carry out risk stratification to determine the extent and severity of CAD of ACS patients.[16]

Clinicians are in constant search of a non-invasive, practical and precise tool to predict severity of coronary artery disease. If the association between RDW-CV and SYNTAX score is found, it can readily be used as a tool to predict severe CAD. The purpose of this study is to search for whether increased red cell distribution width is associated with increased angiographic severity in non-ST elevation myocardial infarction patients.

Methods:

It's a Cross section observational study. This study was conducted in the Department of Cardiology, National Institute of Cardiovascular Diseases, Dhaka, Bangladesh, from June 2018 to July 2019.Purposive sampling was done.

Among all patients coming to NICVD, NSTEMI patients was identified by clinical features, 12 lead ECG, cardiac troponin I level. Informed written consent was taken from each patient. Particulars of the patient, relevant history was taken and detailed clinical examination was done and recorded in predesigned structured data collection sheet. All relevant laboratory investigations were done. Blood sample was drawn from every patient immediately after admission who presumed to have ACS from peripheral veins and was collected in a tube containing EDTA (Ethylene Diamine Tetra Acetic acid). Blood sample was then put in an automated hematology analyzer (Sysmex-XT2000i, USA) and RDW-CV was measured along with other hematological parameters. Coronary angiogram was done and angiographic severity was

assessed by visual estimation. The SX scores of all patients were calculated by 2 independent experienced interventional cardiologists who were blinded to the identities and clinical information of the patients from baseline diagnostic CAG. All coronary lesions with ≥50% stenosis in vessels ≥1.5 mm were scored, using the syntax algorithm available on the website http://www.syntaxscore.com. A low score was defined as ≤22, an intermediate score as 23 to 32, and a high score as ≥33.Patients with syntax scores ≥23 was considered to have moderate to severe coronary artery disease according to this definition. Thus, the patients were divided into 2 groups, those with low syntax scores (≤22) and those with high syntax scores (>22).

Results:

The study subjects were divided into 2 groups on the basis of red cell distribution width: Group I- NSTEMI patients with RDW-CV less than 14.3; Group II- NSTEMI patients with RDW-CV equal or more than 14.3. Then severity of CAD was determined by SYNTAX score; the higher the score the more severe was the disease. Accordingly, patients with SYNTAX score >22 were considered as severe disease. Appropriate statistical techniques were applied as per the necessity of data analysis. SPSS statistical software was used to analysis the data.

Age distribution shows that, patients with RDW-CV ≥14.3 (group II) were generally older than the patients with RDW-CV <14.3 (group I) (54.23±7.69 vs. 52.74±10.12, p=0.492) and the difference in mean age between the two groups was statistically not significant. The table also indicates that the most of the patients were in the age range of 50-59 years in both study groups.

In both groups, there was male predominance, however, the difference in gender between the two groups was not statistically significant (p=0.71). The table also provides that among the study patients, male patients were 62 (88.6%) and female patients were 8 (11.4%).

Table-I

Comparison of the study subjects according to age (N=70).

Age in years	Group I (n= 35)		Group II (n= 35)		p value
	Number	%	Number	%	
<30	1	2.9	0	0.0	
30 – 39	1	2.9	2	5.7	
40 – 49	11	31.4	05	14.3	
50 – 59	15	42.9	18	51.4	
≥60	7	20.0	10	28.6	
Mean ± SD(Range)	52.74±10.12(25-76)		54.23±7.69(35-72)		0.492^{ns}

Group I- NSTEMI patients with RDW-CV <14.3 ns = Not significant (p>0.05)
Group II-NSTEMI patients with RDW-CV ≥14.3p value reached from unpaired t-test
SD – Standard deviation

Table-II

Comparison of the study subjects according to gender (N=70).

Gender	Group I (n= 35)		Group II (n= 35)		p value
	Number	%	Number	%	
Male	30	85.7	32	91.4	0.71^{ns}
Female	5	14.3	3	8.6	

Group I- NSTEMI patients with RDW-CV <14.3 Group II-NSTEMI patients with RDW-CV ≥14.3
ns= Not significant (p>0.05) p value reached from Fisher's Exact Test

Table-III

Distribution of study subjects by risk factors (N=70).

Risk Factors	Group I (n= 35)		Group II (n= 35)		p value
	Number	%	Number	%	
Smoking	24	68.6	26	74.3	0.597^{ns}
Hypertension	16	45.7	21	60	0.231^{ns}
Family H/O of CAD	14	40	19	54.3	0.231^{ns}
Dyslipidemia	12	34.3	21	47.1	0.031^{s}
Diabetes mellitus	20	57.1	23	65.7	0.461^{ns}
Obesity	5	14.3	6	17.1	0.743^{ns}

Group I- NSTEMI patients with RDW-CV <14.3ns= Not significant (p>0.05)
Group II-NSTEMI patients with RDW-CV ≥14.3 p value reached from Chi-Square test
CAD: Coronary Artery Disease

Among the traditional risk factors for CAD, smoking, diabetes mellitus, hypertension, family history of CAD and obesity, presented in the above table did not differ significantly between two groups. Only dyslipidemia was found significantly higher in group II than group I.

SYNTAX Score was significantly higher in group II than that of group I (24.51±9.76 vs. 13.51±7.71, p<0.0001). The table describes that RDW-CV ≥14.3 in NSTEMI patients is significantly associated with high SYNTAX score.

Figure-1 shows significantly positive correlation between RDW-CV and SYNTAX score (r = 0.681, p value < 0.0001). If RDW-CV increases, SYNTAX score also increases. The level of significance reached from Pearson's Correlation test.

Table-IV

Distribution by Coronary artery disease severity (N =70)

CAD severity	Group I (n= 35)	Group II (n= 35)	p value
	Mean ± SD	Mean ± SD	
SYNTAX Score	13.51±7.71	24.51±9.76	<0.0001^{s}

Group I- NSTEMI patients with RDW-CV <14.3 ns= Not significant (p>0.05)
Group II-NSTEMI patients with RDW-CV ≥14.3 p value reached from unpaired t-test.

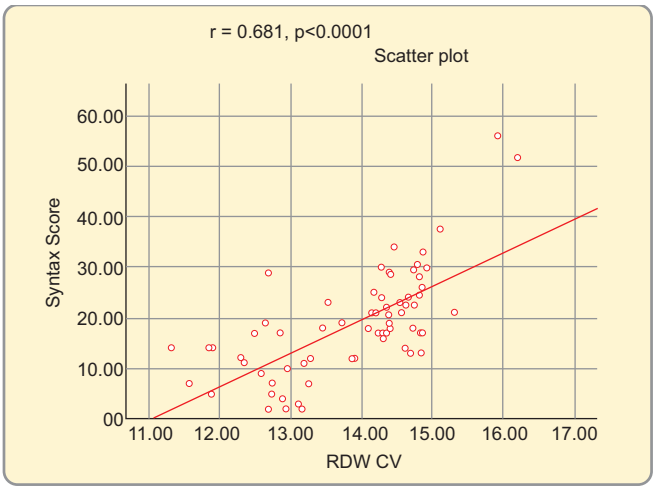

Fig.-1: *Correlation between RDW-CV and SYNTAX score*

Prediction of CAD severity:

The above table depicts the univariate logistic regression analysis of Odds Ratios for characteristics of the subjects likely to develop coronary artery disease. The variable RDW-CV e14.3, DM, dyslipidemia and family history of CAD were found to be significantly associated with CAD severity with their odd ratios being 4.320, 9.896, 3.158 and 4.306 respectively.

The above table shows that after multivariate logistic regression analysis, RDW-CV and DM are the two variables significantly associated with severe CAD (SX>22) and both of them can be regarded as independent predictor for the development of severe CAD (SX>22).

The receiver-operating characteristic curve analysis further revealed that RDW—CV was a strong indicator of high SYNTAX score in NSTEMI patients with an area under the curve of 0.796 (95% confidence interval, 0.686-.906, p<0.001). RDW-CV ≥14.3 level of less than 14.3 yielded a sensitivity of 76.2% and a specificity of 63.3%.

Table-V

Univariate logistic regression analysis for severe CAD (SYNTAX Score >22) with traditional risk factors and RDW-CV ≥14.3 in NSTEMI patients (N=70).

Variablesof interest	Regression coefficient(β)	Odds Ratio (OR)	95% CI of OR	p value
Age (≥50 years)	0.723	2.061	0.595-7.136	0.254[ns]
Male sex	-0.973	0.378	0.085-1.683	0.202[ns]
Hypertension	0.526	1.693	0.596-4.807	0.323[ns]
Family history	1.460	4.306	1.418-13.074	0.01[s]
Dyslipidemia	1.150	3.158	1.079-9.243	0.036[s]
Smoking	0.345	1.412	0.437-4.565	0.565[ns]
Diabetes mellitus	2.292	9.896	2.077-47.138	0.004[s]
Obesity	1.258	3.520	0.937-13.224	0.062[ns]
RDW-CV ≥14.3	1.463	4.320	1.742-10.716	0.002[s]

Ns: Not significant (p>0.05) s: Significant (p<0.05) CI: Confidence interval
CAD: Coronary Artery Disease OR: Odd ratio

Table-VI

Multivariate logistic regression analysis of variables associated with severe CAD (SYNTAX Score >22) (N=70).

Variables of interest	Regression coefficient (β)	Odds Ratio (OR)	95% CI of OR	p value
RDW-CV	1.347	3.844	1.429-10.340	0.008[s]
DM	2.308	10.055	1.700-59.482	0.011[s]
Family History	1.166	3.210	0.813-12.678	0.096[ns]
Dyslipidemia	1.207	3.344	0.789-14.164	0.101[ns]

Ns: Not significant (p>0.05) s: Significant (p<0.05) CI: Confidence interval
CAD: Coronary Artery Disease OR: Odd ratio

Area Under the Curve

Test Result Variable(s): Predicted probability				
Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.796	.056	.000	.686	.906

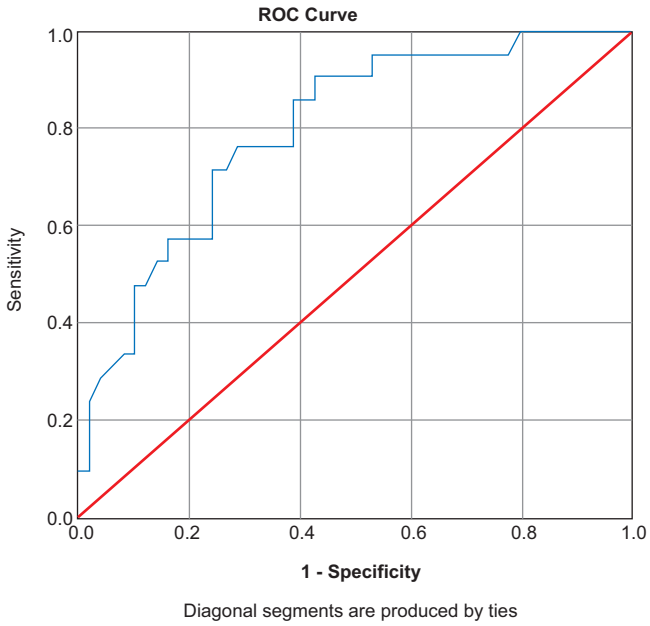

Fig.2: *Receiver – operating characteristic curve (ROC) analysis and cutoff value for RDW—CV in predicting high SYNTAX score in patients with NSTEMI.*

Discussion:

This study evaluated the association of RDW-CV with angiographic severity of coronary artery disease in NSTEMI patients. The mean age of patients in group I and II was 52.74±10.12 and 54.23±7.69 years respectively. This is almost similar to the study done by Nagula et al.[17] In this study, male patients were 85.7% and 91.4% in group I and II respectively. In the study by Nagula et al., male patients in both the groups were 55.07% and 75.8% respectively.[17] The present study showed a smaller number of women than men in both the groups. Only 14.3% and 8.6% of women in group I and II respectively. This gender disparity is multi factorial: less predisposition to CAD in reproductive age, overall, less health care seeking attitude of female patients and less attention by male counterparts of their family.

Regarding CAD risk factors in this study, smoking, diabetes mellitus, hypertension, family history of CAD and obesity, did not differ significantly between patients with low RDW-CV and high RDW-CV group. Only dyslipidemia was found significantly higher in group II than group I. Dyslipidemia is a well-known risk factor for development of coronary artery disease. In their study Abdalamir et al. showed that dyslipidemia was associated with multivessel coronary artery disease and increased coronary artery calcium score.[19] These factors may actually indicate presence of severe CAD. This inference is quiet similar with the findings of present study where dyslipidemia was found significantly higher in high RDW-CV (≥14.3) group.

In the present study, SX score of NSTEMI patients, who underwent CAG, differed between low RDW-CV and high RDW-CV group. The mean SX score in group I and group II were 13.5±7.71 and 24.51±9.76 ($p<0.0001$). Nagula et al. studied the relationship between RDW and CAD severity by modified Gensini score (MGS).[17] They demonstrated that higher MGS also have higher RDW-CV value i.e., those with MGS 1-6 had RDW-CV value of 14.53±0.88, MGS 7-13 had RDW-CV value of 14.55±1.07 and MGS >13 had RDW-CV value of 14.68±1.10 and the difference of RDW-CV between the subgroups were significant. In their study Sahin et al. investigated association between RDW-CV and CAD severity in NSTEMI patients[18] and they also found the similar result like the present study i.e., RDW-CV of patients were significantly higher in the high SYNTAX group (SX score ≥12) than in the low SYNTAX (SX score ≥12) group (15.2 ± 1.8 vs. 14.2 ± 1.2, $p<0.001$). Apart

from this, Isik et al. investigated association between RDW-CV and CAD severity by SX score in stable CAD patients[20]. They found that those with severe CAD (SX score ≥32) have significantly increased RDW-CV value than those with less severe CAD (SX score <32) (14.3 ± 1.3 vs. 12.5 ± 0.9, p < 0.001). Akin et al. also studied relationship between CAD severity by SX score and RDW-CV in AMI patients (both STEMI and NSTEMI) and found similar results [21]. So, the overall findings relating to the association between RDW and CAD severity correlates with the findings of present study. In this study significant positive correlation was also found between RDW-CV and SYNTAX score. Similar results were noted in the study by Nagula et al.[17]Sahin et al.[18] and Akin et al.[21]

In the present study, univariate logistic regression analysis of the variables likely to cause severe CAD (SX score >22) was done. The univariate regression analysis revealed that the odds ratios of RDW-CV, DM, dyslipidemia, positive family history of CAD were statistically significant and independently associated with severe CAD with SX score >22. However, when these parameters were analyzed in multivariate logistic regression analysis, only RDW-CV and DM found to be the independent determinants of severe CAD (SX score >22). Nagula et al. also found RDW-CV and DM as independent predictor of severe CAD.[17] Findings of logistic regression of the present study were also consistent with the findings of studies conducted by Sahin et al. and Akin et al.[18,21]

The receiver operator characteristic curve (ROC) analysis of RDW-CV in predicting severe CAD was done. The area under the curve (AUC) for RDW-CV was 0.796 (95% CI 0.686-0.906, p < 0.0001). RDW-CV value of 14.3 yielded 76.2% sensitivity and 63.3% specificity. Nagula et al. showed that RDW-CV with a cut off value of 14.3 has a predictive value in diagnosing severe CAD with a sensitivity of 58.9 % and specificity of 84.8%.[17] However, ROC analysis of the present study also revealed that RDW-CV value of 14.38 has 76.2% sensitivity and 71.4% specificity in predicting severe CAD (SX >22).

After comparing the findings of present study with other studies, it can be summarized that there is significant correlation between RDW-CV and CAD severity.

Conclusion

From this study it may be concluded that increased red cell distribution width coefficient of variation (RDW-CV) (>14.3) is associated with increased angiographic severity in NSTEMI patients. A positive correlation between RDW-CV and coronary artery disease severity is found. It can help to identify individuals at high risk for advanced CAD who might need an earlier therapeutic approach and close clinical follow up.

Conflict of Interest - None.

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