Original Article

“Correlation of red blood cell distribution width with the severity of coronary artery disease—A single center study”

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ABSTRACT

Objective: Coronary Artery Disease (CAD) is the leading cause of morbidity and mortality all around the world. We evaluated the correlation of Red blood cell Distribution Width (RDW) with the severity of lesion on coronary angiography as assessed by Modified Gensini score (MGS) in CAD patients.

Methods: A total of 576 consecutive patients admitted in Department of Cardiology over a period of one year, who underwent coronary angiography after diagnosis of CAD or presence of angina like chest pain and/or positive treadmill test were enrolled in the study (August 2014–May 2015). Patients were divided into two groups, with CAD (Group A) and without CAD (Group B). The RDW Coefficient of variance (RDV CV) and RDW standard deviation (RDW SD) of each patient, and their correlation with severity of CAD was assessed.

Results: Of the total 576 patients enrolled, 438 were in Group A and 138 were in Group B. The mean age of presentation in Group A and Group B was (53.64 ± 10.36 vs 49.4 ± 9.73) years (p < 0.0001). The Male and Female ratio overall was 2.42:1. Patients in Group A had significantly elevated RDV CV and RDW SD levels compared with those in Group B [(14.59 ± 1.04)% vs (13.6 ± 0.68%), p = 0.0001] [(45.78 ± 4.76) vs (40.77 ± 3.01), p = 0.0001 respectively]. A significant positive correlation between RDV CV, RDW SD and MGS was noted (r = 0.33, p < 0.0001) (r = 0.43, p < 0.0001 respectively). On multivariate logistic regression analysis, RDW was demonstrated to be an independent predictor for angiographic CAD (OR = 4.17, 95% CI 3.05–5.69, p < 0.0001). On receiver operating characteristic curve (ROC) analysis, an RDW value of 14.3% was identified as an effective cut off point in diagnosing CAD with a sensitivity of 58.9% and specificity of 84.8%.

Conclusions: RDW is an independent predictor of CAD and severity of coronary stenosis, suggesting that it can be a readily available marker for prediction and severity of CAD.

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1. Introduction

Coronary Artery Disease, due to atherosclerosis is the most common cause of death worldwide. Atherosclerosis is a chronic inflammatory disorder with long asymptomatic period for years and usually manifests as acute coronary events with occlusion of coronaries. RDW, a measure of heterogeneity of red blood cell size, is usually used in the differential diagnosis of anemia.1 In the recent years, there is increased interest in the role of increased RDW as a risk marker of various cardiovascular diseases for example heart failure2 and coronary artery disease.3 We have assessed the RDW in patients presenting with chest pain and correlated its relation with severity of lesion as assessed by Modified Gensini score (MGS) on angiography.

2. Methods

2.1. Study population

The study was carried out in Department of Cardiology, Osmania General Hospital, Hyderabad between August 2014–March 2015. After analyzing 1835 patients presenting with chest pain, a total of 576 consecutive patients have been enrolled in the study.

2.2. Inclusion criteria

Patients with Age >18 years, with diagnosis of
1 Acute Coronary Syndrome (ACS) [ST segment Elevation Myocardial Infarction (STEMI), Non ST elevation Acute Coronary Syndrome (NSTEMI)]

ACS was defined as presentation with symptoms of ischemia in association with ECG changes (ST segment deviation elevation or depression, T wave inversion, and new Qwave), positive cardiac enzymes and regional wall motion abnormalities on echocardiography (absent in patients with unstable angina, with intracoronary lesion on angiography in most of the cases).

2 Typical Angina, described as substernal chest discomfort lasting for less than 20 min precipitated by stress and relieved by rest or nitroglycerin

3 Atypical angina with conventional risk factors (i.e. diabetes mellitus, hypertension, obesity, family history of CAD, chronic smoking, chronic alcohol intake) or

4 Chest pain with treadmill test positive for inducible ischemia (i.e. new ST depression at the start of exercise, new ST depression >2 mm in multiple leads, hypotensive response to exercise, development of heart failure or sustained ventricular arrhythmias during the study, prolonged interval after exercise (>5 min) before the ischemic changes return to baseline) were included in the study.

2.3. Exclusion criteria

Patients with anemia i.e with Hemoglobin level of < 12gm/dl in males and < 11gm/dl in females were excluded.4

The patients with previous history of Percutaneous Coronary Intervention (PCI), Coronary Artery Bypass Grafting (CABG) surgery, Valvular Heart Disease, Bleeding disorders, Chronic Kidney Disease (CKD), on Estrogen Replacement Therapy (ERT), Anemia and Blood transfusions, Liver disease, Pregnancy, Thrombotic Thrombocytopenic Purpura were excluded from the study.

Institutional ethical committee has approved the study.

Each patient has been enrolled after obtaining written and informed consent.

A detailed evaluation of demographic data of each patient, presence of risk factors (hypertension, diabetes mellitus, smoking, alcohol intake, family history of premature CAD, obesity) clinical examination, with electrocardiography (ECG), echocardiography (2d ECHO) and the treadmill test whenever required i.e in patients without ACS has been done. Venous blood sample for RDW has been collected at the time of admission from the antecubital vein by atraumatic puncture and value was assessed by SYSMEX 2.0 analyzer within an hour of collection of sample. Blood was collected in a tube containing EDTA for measurement of red cell indices. The reference value of RDW in our laboratory was 11.5–13.5%. Transthoracic echocardiography was performed with Phillips i3 machine using 3–5 MHz transducer on each patient after admission to the intensive cardiac care unit. Each patient underwent coronary angiography either by transradial or transfemoral route using 5F Optitorque catheter in the former and 6F Judkins catheters in the latter within 24 h after hospital admission. The severity of lesion on angiography has been assessed by MGS.

After coronary angiography patients were divided into two groups, those with CAD (Group A) and those without CAD (Group B). Angiographic CAD was defined as the diameter of the stenosis in a vessel reaching more than or equal to 50%. Severity of lesion is by MGS, based upon the total added value of the eight proximal segments of coronary arterial tree. Maximum score is 32 and minimum is 4. Mild, moderate, severe is for scores of 1–6, 7–13 and >13 respectively (Appendix A1). The RDW CV, RDW SD values were correlated with MGS.

2.4. Statistical analysis

Statistical analysis was carried out using Medcalc (Belgium). Continuous variables are expressed as mean ± standard deviation (SD). Categorical variables are expressed as percentages. Students t-test or analysis of variance was used to compare parametric continuous variables. To compare categorical variables, the chi-square (χ2) test was used. Correlation of two variables were examined by Pearson r correlation coefficient. Receiver operating characteristic (ROC) curves for RDW values were plotted to determine the optimal cut off point for use in clinical decision making. Multivariate logistic regression analysis was used to identify the independent predictors of angiographic CAD. A p value <0.05 was considered significant statistically. Tables, bar diagrams, pie diagrams were illustrated wherever possible.

3. Results

Total number of patients included in the study were 576. In CAD group (hereby Group A) there were 438 patients and in without CAD group (hereby Group B) were 138. The mean age of presentation in the whole cohort was 52.6 ± 10.38 years. The range of age of patients was 22 years to 84 years. On group analysis, the mean age of presentation in Group A was 53.64 ± 10.36 years whereas in Group B was 49.4 ± 9.73 years (p < 0.0001). Males were predominant than the females (70.8% vs 29.2%) with a sex ratio of 2.42:1. The difference in mean hemoglobin levels between the two groups was statistically insignificant (13.66 ± 0.71 vs 13.63 ± 0.54, p = 0.65). In Group A, the most common risk factor was hypertension seen in 287 (65.5%), followed by smoking in 243 (55.5%) and diabetes in 189 (43.2%) patients. Patients in Group A had significantly elevated RDW CV levels compared to Group B ([14.59 ± 1.04]% vs [13.6 ± 0.68], p = 0.0001). The RDW SD levels were also significantly elevated ([45.78 ± 4.76] vs [28.07 ± 3.01], p < 0.0001). The red cell indices when analysed showed no significant difference in the mean hematocrit (Hct) and mean corpuscular hemoglobin (MCH) values between the two groups but significant difference with regards to mean values of the mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC). The baseline characteristics of patients in both groups are shown in Table 1.

The most common diagnosis in Group A was Anterior wall STEMI in 180 (42%), the next common diagnosis was NSTEMI seen in 112 (26%) patients (Table 2). The patients in CAD group were stratified according to the MGS and the baseline characteristics along with the RDW CV and RDW SD have been analysed (Table 3). The RDW CV value increased along the score values of 1–6, 7–13 and >13 (14.53 ± 0.88, 14.55 ± 1.07, 14.68 ± 1.10) respectively (p < 0.0001). A significant positive correlation between RDW CV for the presence or absence of angiographic CAD (n = 576, r = 0.40, p < 0.0001) and with severity of CAD (n = 438, r = 0.33, p < 0.0001) was seen on Pearson correlation analysis. The correlation of hemoglobin levels in the whole cohort with RDW CV was –0.109, a weak negative correlation noted.

On subgroup analysis in CAD group (Group A) according to the diagnosis in comparison with group B (n = 138, 13.60 ± 0.68), the RDW CV was increased in all subgroups i.e AWSTEMI (n = 180, 14.79 ± 4.86, p = 0.004), NSTEMI (n = 112, 14.65 ± 1.02, p = 0.0001), IW STEMI (n = 72, 14.84 ± 5.46, p = 0.0091), Stable angina (n = 65, 14.25 ± 2.46, p = 0.0089).

In multivariate logistic regression analysis, RDW was demonstrated to be an independent predictor for angiographic CAD (OR = 4.17, 95% CI 3.05–5.69, P < 0.0001) (Table 4). On ROC analysis, an RDW value of 14.3% was identified as an effective cut off point in diagnosing CAD with a sensitivity of 58.9% and specificity of 84.8%
with area under curve (AUC) being 0.793 (Figs. 1 and 2). The positive predictive value (PPV) of RDW was 85.42%.

4. Discussion

Atherosclerosis is a chronic inflammatory disease, subclinical for most of the years, starting as fatty streaks in the arterial walls in the teenage years and usually presents in most of the scenarios as acute coronary syndrome or sudden cardiac deaths due to coronary occlusion. The atherosclerotic lesion is responsible for oxidative stress and release of inflammatory mediators as a result of endothelial dysfunction and macrophage accumulation. Red blood cell distribution width (RDW) is the measure of the range of variation in size of red blood cell volume (anisocytosis) used in the differential diagnosis of anemia as part of red cell indices. In recent years, numerous studies have noted the importance of RDW as a predictor of poor clinical outcomes in the settings of various diseases, including coronary artery disease (CAD).

The mechanisms put forth for the explanation of increased RDW in atherosclerosis are many, among them a few are

### Table 1
Baseline characteristics of the patients with CAD and without CAD (Group A and Group B).

| Variables (n,%) | CAD (n = 438) | without CAD (n = 138) | P value |
|----------------|---------------|-----------------------|---------|
| Age of presentation (yrs) mean ± SD | 53.64 ± 10.36 | 49.4 ± 9.73 | <0.0001 |
| Males | 332 (75.8) | 76 (55.07) | 0.7 |
| Hypertension | 287 (65.5) | 90 (69.35) | <0.0001 |
| Diabetes mellitus | 189 (43.2) | 38 (27.5) | <0.0001 |
| Alcohol intake | 189 (43.2) | 50 (36.2) | <0.0001 |
| Smokers | 243 (55.5) | 59 (43.28) | <0.0001 |
| Family h/o CAD | 61 (13.9) | 17 (12.32) | <0.0001 |
| AWSTEMI | 4.59 ± 1.04 | 13.71 ± 0.84 | <0.0001 |
| ST MI | 45.78 ± 4.76 | 42.77 ± 3.01 | <0.0001 |
| Hemoglobin levels (gm/dl) | 13.66 ± 0.71 | 13.63 ± 0.54 | 0.65 |
| Hematocrit (%) | 39.89 ± 4.77 | 40.65 ± 4.24 | 0.09 |
| MCV (fl) | 88.22 ± 4.21 | 90.27 ± 5.28 | <0.0001 |
| MCH (pg/cell) | 30.21 ± 2.57 | 30.30 ± 1.88 | 0.70 |
| MCHC (g/dl) | 34.24 ± 2.27 | 33.55 ± 1.16 | 0.0004 |
| Male | 3.13:1 | 1.22:1 |

### Table 2
Proportion of patients in CAD group (Group A).

| Diagnosis | Males | Females | Total (%) |
|-----------|-------|---------|-----------|
| AWSTEMI | 138 | 42 | 180 (41) |
| IWMII/PWMI/RVMI | 48 | 24 | 72 (16) |
| NSTEACS | 82 | 30 | 112 (26) |
| CSA | 57 | 08 | 65 (15) |
| ICMP | 7 | 2 | 09 (2) |
| Total | 332 | 106 | 438 (100) |

### Table 3
Baseline characteristics of patients stratified according to Modified Gensini Score (MGS) in Group A.

| Variables | MGS 0–06 | MGS 07–13 | MGS >13 | p value |
|-----------|----------|-----------|---------|---------|
| No.of pts | 118 (26.9) | 174 (39.7) | 146 (33.3) | 0.32 |
| Age (mean ± SD yrs) | 53.05 ± 10.06 | 53.6 ± 10.4 | 53.68 ± 11.22 | 0.0012 |
| Male | 86 (72.9) | 140 (80.5) | 106 (72.6) | 0.0001 |
| RDW (mean ± SD) | 14.53 ± 0.88 | 14.55 ± 1.07 | 14.68 ± 1.10 | <0.0001 |
| Hemoglobin (gm/dl) | 13.4 ± 0.45 | 13.6 ± 0.83 | 14.2 ± 0.89 | 0.99 |
| Smokers | 67 (56.8) | 101 (58.0) | 75 (51.4) | 0.0012 |
| Family h/o CAD | 10 (8.5) | 28 (16.0) | 23 (15.6) | 0.0002 |
| Diabetes mellitus | 47 (39.8) | 73 (42.0) | 69 (47.3) | 0.0012 |
| Hypertension | 72 (51.0) | 113 (64.9) | 102 (69.9) | 0.0002 |
| Alcoholic | 56 (47.5) | 83 (47.70) | 50 (34.2) | 0.0002 |

### Table 4
Multivariate regression analysis of various parameters for prediction of CAD.

| Variables | 95% CI | OR | P value |
|-----------|--------|----|---------|
| Age | 1.01–1.06 | 0.0035 |
| Smoking h/o | 0.45–1.45 | 0.8 | 0.47 |
| Family h/o | 0.69–1.42 | 0.9 | 0.93 |
| Diabetes mellitus | 0.32–0.90 | 0.5 | 0.02 |
| Hypertension | 0.52–1.35 | 0.8 | 0.67 |
| RDW CV | 3.05–5.69 | 4.7 | <0.0001 |
| RDW SD | 1.6633 | 2.35 | <0.0001 |
| Alcoholic | 0.42–1.39 | 0.7 | 0.38 |

Abbreviations: n – number; % – percentage, yrs – years, SD – standard deviation, CAD – coronary artery disease, RDW – red blood cell distribution width; CV – coefficient of variance, fl – femto liters, gm/dl – gram per deciliter, p value – calculated probability, MCV- mean corpuscular volume, MCH – Mean corpuscular hemoglobin, MCHC – mean corpuscular hemoglobin concentration, pg/cl – pictogram per cell.

Fig. 1. Receiver Operating Characteristic (ROC) curve of RDW.

Fig. 2. Scatter Diagram of RDW CV among the patients (Group B and Group A).
The subclinical inflammation and pro inflammatory mediators are responsible for decrease in erythropoietin from the renal mesangial cells, as a result of suppression of Epo gene transcription, which leads to anisocytosis and microcytosis of red blood cells leading to anemia. Due to increase in the number of premature red blood cells in the peripheries, the RDW increases.  

The other mechanism proposed is the oxidative stress, causing early damage of the RBCs resulting in microcytosis and thereby increased RDW. 

Functional iron deficiency anemia can be seen as a result of increased synthesis of hepcidin in liver. Hepcidin, a peptide hormone is found in the heart and its expression is increased in hypoxia and inflammation. An increased level of hepcidin inhibits the absorption of the iron from the intestinal epithelium and blocks release of iron from the macrophages. [5]  

Decreased red blood cell deformability among patients with higher RDW values impairs blood flow through the microcirculation, resulting in the diminution of oxygen supply at the tissue level, particularly among patients suffering from myocardial infarction treated with urgent revascularization. [3]  

The mean age of presentation was more in Group A compared to Group B, but is earlier than in the developed countries, emphasizing the early occurrence of the CAD in Indians as seen in INTERHEART study. [6] Males were predominant in both groups. The risk factors of CAD were more in Group A compared to Group B. The confounding bias of the increased risk factors among the CAD group causing the increased RDW in them is removed by multiregression analysis, which showed that increased RDW is an independent predictor of presence or absence of CAD. The RDW showed a positive correlation with increased severity of lesion in angiography assessed by MGS along the tertiles mild, moderate and severe. The RDW was found to be an independent predictor of all cause mortality in ACS subset of patients. [7]  

The correlation of RDW CV with hemoglobin in the whole cohort was found to be weakly negative ($r = -0.1096$). The Hct or packed cell volume, the value emphasizing the size of the Red blood cells is decreased in the CAD group compared to the without CAD group though both the values are within normal limits. The decrease in the value can be explained theoretically due to the increased anisocytosis and microcytosis in the CAD group though the peripheral blood smear for confirmation have not been done. The red cell indices have been evaluated in both groups which showed decreased MCV, MCH and increased MCHC in Group A but not in Group B. Decreased MCV and MCH can be explained by the microcytosis and anisocytosis whereas the increased MCHC shows it not to be related to the iron deficiency anemia where the MCHC will be decreased. The peripheral blood smear and vitamin B12, folate, iron levels have not been assessed in these patients.  

Lippi et al., [12] showed that the RDW with cut off value of 14% has a predictive value in diagnosing ACS in patients presenting with chest pain (sensitivity of 79% and a specificity of 50%). Increased RDW in a patient with CAD, leads to increased risk of Heart failure as shown by Felker et al. in 2007. [2] RDW was found to be useful in triaging patients with NSTEMI as NSTEMI in a cohort of 251 patients admitted to coronary care unit over one year period by Erhan Tenekcioglu et al. [13] Baseline RDW correlated well with MGS and was having increased positive predictive value of atherosclerotic burden. The RDW has been reported to be a predictor of coronary heart disease events and all cause mortality in various cardiovascular conditions. [14] In a study by Cavusoglu et al., the RDW was found to be a strong independent predictor of all-cause mortality in the ACS subset of patients based on multivariate analysis. [11] Tonelli et al., reported that among patients with CAD and without heart failure, mortality rates were significantly more in patients with elevated RDW. [3]  

In our study, we have evaluated the RDW in CAD patients (all along the spectrum from stable angina to ACS), the first study in Indian Population to the best of our knowledge. The number of patients were more compared to the other studies. Indians have a low level of hemoglobin compared to the western population and hence have a high RDW value. The cutoff value of Hb < 13 gm/dl in males and <12 gm/dl in females for diagnosis of anemia over-diagnoses the anemia in Indian Subcontinent as shown in a study by Deepak K et al. [14] Hence we have taken the value of <12 gm/dl in males and <11 gm/dl in females as cutoff for anemia.  

In conclusion, RDW is an inexpensive blood parameter which can be obtained at the time of complete blood count and helps in risk stratification of patients with chest pain well before the time period taken for the rise of troponins to be detected peripherally.  

5. Limitations  

It is a single center study with no follow up. Only hemoglobin levels and red cell indices were measured in the present study whereas the parameters such as serum iron, B12, folate were not assessed. The hepcidin levels have not been evaluated. The peripheral blood smear of cases with increased RDW was not studied.  

6. Conclusion  

RDW is an effective easily available marker for the assessment of severity of coronary artery disease and helps in risk stratification of CAD patients for further events.  

Conflicts of interest  

Authors have no conflicts of interest to declare.  

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Appendix A. Supplementary data  

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ihj.2017.04.007.  

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