International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2018): 7.426

Correlating Red Cell Distribution Width Parameter with Severity of Coronary Artery Disease

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Abstract: ***Background: Non-Communicable Diseases are in the increasing trend owing to urbanization. [(1)]According to the Global Burden of Disease Study, the age-standardized CVD death rate estimate in India was of 272 per 1,00,000 populations compared to global average of 235 per 100000 population.[(2)] Red Cell Distribution Width has been depicted as an inflammatory marker and also as a novel bio-marker for Coronary Artery Disease. Methodology: A Cross-Sectional Observation study has been conducted in GSL GENERAL HOSPITAL, Rajahmundry over a period of 18 months from October 2016 to June 2018. A total of 108 inpatients admitted in the CICU with Angina, Chest Discomfort, Dyspnea with or without co-morbid conditions like hypertension, diabetes mellitus and have undergone Coronary Angiography are included in the study. Results: The mean age of the study group is 49.84±10.05 years. The majority of the study population (42.6%) are of 51-60 years of age group. The present study has 13.88% of women and 86.11 % of males. Of the study population 45 (41.7%) are hypertensive, 31(28.7%) are diabetic,57(52.8%) are smokers, 52(48.1%) are alcoholics. In the present study 64 individuals have single vessel disease, 30 individuals have double vessel disease, 18 individuals have triple vessel disease. Conclusion: There has been no significant correlation between Red Cell Distribution Width and Coronary Artery Disease of Single Vessel, Double Vessel or Triple Vessel Disease.***

Keywords: Red Cell Distribution Width, Coronary Artery Disease

1. Introduction

Globally the largest number of deaths in Non-communicable diseases by the year 2016 was cardiovascular disease. IHD and Stroke in total accounts for 85.1% of all cardiovascular disease deaths in 2016. [(3)]

With urbanization, there has been a major epidemiological health transition owing to the increase in non-communicable diseases in India. [(1)] According to the Global Burden of Disease Study, the age-standardized CVD death rate estimate in India was of 272 per 1,00,000 populations compared to global average of 235 per 100000 population. [(2)] In India, Ischemic Heart Disease is the leading cause of years of life lost for men and women. [(3)] Modifiable risk factors still hold the leading cause for cardiovascular diseases in India. [(4–6)] There are studies emphasizing on risk stratification, [(7)] non-invasive diagnostic modalities, [(8,9)] biomarkers for the detection of CAD and outcome prediction. [(10–12)]One such study was on Red Cell Distribution Width, a novel bio-marker in predicting a wide range of cardiovascular conditions plus colorectal cancer. Red Cell Distribution Width was found out to be not just a short-term predictor but remained predictive up to 9 years after baseline for most outcomes. It might be useful as a clinical marker for inclusion in wellness assessments. [(13)]

2. Materials and Methods

Aims and Objectives:
The AIM of the study is to correlate Red Cell Distribution Width, a hematological parameter in patients with Coronary Artery Disease.

Inclusion Criteria:
Individuals above 18 years of age with a diagnosis of

- Acute Coronary Syndrome
- Typical Angina
- Atypical angina with conventional risk factors like diabetes, hypertension, family history of CAD, smoking and alcohol intake
- Chest pain with treadmill test positive for inducible ischaemia, are included in the study.

Exclusion Criteria:

- Hemoglobin value of <13gm/dl in males and <12gm/dl in females.
- Cytotoxic Chemotherapy.
- Chronic Liver Disease.

Methodology
Inpatients admitted in the CICU with Angina, Chest Discomfort, Dyspnea with or without co-morbid conditions like hypertension, diabetes mellitus and have undergone Coronary Angiography are included in the study. Antecubital venous blood samples for laboratory analysis is drawn from the individual, at the time of admission and samples are analyzed by Sysmex XP-100 auto-analyzer using the Coulter principle. Trans-thoracic echocardiography is done. Coronary Angiography is done either by trans-radial or trans-femoral route.

3. Statistical Methods

Data entry and statistical analysis are performed with the help of Microsoft Excel 2007 and SPSS version 21.0
Categorical variables are presented as numbers and percentages.
Chi-square test was used to assess the association between different categorical variables.
The statistical significance level was fixed at p-value of <0.05.

4. Results

A total of 108 individuals are included in the study who underwent coronary angiography, in which 93 are males and 15 are females. The overall mean age of study participants is 49.84±10.05 years with a range from 27 to 71 years. Mean Hemoglobin of the study participants is 14.58±1.58gm% with a range from 12 to 19.4gm%. Mean RDW-CV of the study participants is 13.55±1.28% with a range from 11.6-18.4%.Out of 108 individuals, 4(3.7%)are within the age group of 18-30years, 15(13.9%) are within the age group of 31-40 years, 46(42.6%) are within the age group of 41-50 years, 28(25.9%) are within the age group of 51-60 years and 15(13.9%) are within the age group of 61-71 years of age. In the present study group 45 Individuals are hypertensive, 31 are diabetic, 57are smokers, 52are alcoholics.

Out of 108 2D ECHO findings, 31(28.7%) of them aren't having any regional wall motion abnormality, while 65(60.2%) of them are having left ventricular hypertrophy, 45(41.7%) are having anterior wall motion abnormality, 15(13.9%) are having inter-ventricular septum motion abnormality, 11(10.2%) are having lateral wall motion abnormality, 21(19.4%) are having inferior wall motion abnormality.

Of all the 108 individuals who have undergone coronary angiography, 5(4.6%) have their coronary arteries re-canalized with streptokinase administration, 1(0.9%) individual has mild coronary artery disease following administration of streptokinase, rest of the patients aren't administered streptokinase and 64(59.3%) of them have single vessel disease, while 24(22.2%) of them have double vessel disease and 14(13%) of them have triple vessel disease.

108 individuals are categorized into 4 groups, 1st group consisting of 39(36.1%) individuals with RDW values in between 11.01-13gm%, 2nd group consisting of 59(54.6%) individuals with RDW values in between 13.01-15gm%, 3rd group consisting of 06(05.6%) individuals with RDW values in between 15.01-17gm% and 4th group consisting of 04(03.7%) individuals with RDW values in between 17.01-19gm%.

HYPERTENSION and RDW: In the 1st group 11 individuals are hypertensive and 28 are non-hypertensive, in the 2nd group 32 individuals are hypertensive and 27 are non-hypertensive, in the 3rd group 2 of them are hypertensive and 4 of them are non-hypertensive, in the 4th group, 4 are non-hypertensive and none are hypertensive. In the present study correlation between Hypertension and Red Cell Distribution Width is found out to be statistically significant with p-value of 0.021.

DIABETES MELLITUS and RDW: In the 1st group 12 individuals are diabetic while 27 are not, in the 2nd group 19 individuals are diabetic while 40 are not, in the 3rd group 6 individuals are non-diabetic and none are diabetic, in the 4th group 4 individuals are non-diabetic while none are diabetic. In the present study correlation between Diabetes Mellitus and Red Cell Distribution Width is found to be statistically not significant with p-value of 0.216.

SINGLE VESSEL DISEASE and RDW: In the 1st group 28 individuals, in the 2nd group 31 individuals, in the 3rd group 3 individuals and in the 4th group 2 individuals are having single vessel disease. In the present study correlation between Single Vessel Disease and Red Cell Distribution Width is found to be statistically not significant with p-value of 0.262.

DOUBLE VESSEL DISEASE and RDW: In the 1st group 9 individuals, in the 2nd group 13 individuals, in the 3rd group none of the individuals and in the 4th group 2 individuals are having double vessel disease. In the present study correlation between Double Vessel Disease and Red Cell Distribution Width is found to be statistically not significant with p-value of 0.318.

TRIPLE VESSEL DISEASE and RDW: In the 1st group 2 individuals, in the 2nd group 11 individuals, in the 3rd group 1 individual and in the 4th group none are having triple vessel disease. In the present study correlation between Triple Vessel Disease and Red Cell Distribution Width is found to be statistically not significant with p-value of 0.214.

5. Discussion

Red Cell Distribution Width is a measure in the range of variation of red blood cell volume. Red cell Distribution Width is useful in the differential diagnosis of anemia. [14] Increase in RDW is associated with age and pathologic conditions including ineffective red cell production, increased red cell destruction, and during or after blood transfusion. [15-17] The sub-clinical inflammation and pro-inflammatory mediators are responsible for the 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 an increase in the number of premature red blood cells in the peripheries, the RDW increases. [18] The other mechanism postulated was that the oxidative stress causes early damage of the RBCs resulting in microcytosis and thereby increased RDW. [19] Higher cholesterol erythrocyte membrane value is also one of the causes of the deterioration of cell deformability, which can directly affect the lifespan of circulating RBCs, and this leads to greater cellular turnover and elevated RDW levels. [20] The level of cholesterol from the erythrocyte membrane has been affirmed to have a positive association with RDW level in patients with coronary disease. [21] The measuring technology and algorithmic approaches used by different hematology analyzers can also lead to differences in RDW. [22,23]The present study emphasizes the hematological parameter, Red Cell Distribution Width in patients with Coronary Artery Disease and the risk factors like Hypertension, Diabetes Mellitus, Smoking and Alcohol.

Hypertensive Individuals in the Study Group:
The present study group has 45 (41.7%) hypertensive individuals and 63(58.3%) individuals who are not hypertensive. The study group is divided into 4 quartiles in

which, 1st quartile consists of individuals of which 11 are hypertensive and 28 are non-hypertensive, 2nd quartile consists of 32 hypertensive and 27 non-hypertensive individuals, 3rd quartile consists of 2 hypertensive and 4 non-hypertensive individuals, 4th quartile consists of 4 non-hypertensive individuals.

Baris Kilicaslan et al, study consists of 139 untreated essential hypertensive individuals, with a mean age of 51.3±16.3 years. [24] Asli Tanindi et al study consists of 128 hypertensive, 74 pre-hypertensive and 36 control group individuals. [25] Firat Özcan et al study group consists of 127 dipper hypertensives and 120 non-dipper hypertensive individuals. [26] Ozgur Gunebakmaz et al study group consists of 123 hypertensive individuals and 65 individuals of age and gender-matched healthy individuals. [27]

The present study establishes statistical significance with hypertensive individuals compared to non-hypertensive individuals similarly; Asli Tanindi et al study shows statistical significance with hypertensives and pre-hypertensives compared to control group and better statistical significance with hypertensives compared to pre-hypertensives. [25] Firat Özcan et al study showed statistical significance with non-dipper hypertensives compared to dipper hypertensives. [26] Ozgur Gunebakmaz et al study shows higher RDW values with statistical significance in non-dipper hypertensives compared to dipper hypertensives. [27]Yang Ling Wang et al conducted study conducted in 1,654 ACS individuals and Statistical significance was established in hypertensives with RDW. [28] Hairong Ren et al study showed statistical significance of SBP and DBP with RDW in stable CAD individuals. [29]

Hypertension is a risk factor for some inflammatory diseases including atherosclerotic cardiovascular and left ventricular dysfunction. Inflammatory markers such as TNF-α, IL-6, IL-1, and IL-2 are involved in the pathophysiology of hypertension. [30] Consequently, Ning Li et al hypothesize that the role of RDW in hypertension may be connected with the increased inflammatory status. [31] Kilicaslan et al postulate the relation between red blood cells and Left Ventricular Hypertrophy in Hypertension. One such postulation is that red-cell Li+/Na+ exchange is increased in patients with Essential Hypertension. The abnormal kinetic properties of red-cell membrane Na/H exchange is reflected by high Li+/Na+ counter transport. A widespread abnormality of Na/H exchange could have a major role in the pathogenesis of Cardio-Vascular diseases. Cell pH and cell volume in the cellular responses to hormones, mitogens, and growth factors and in the renal reabsorption of Na and bicarbonate are regulated by Na/H exchange. [32] Increased Li+/Na+ exchange has been found with cardiac hypertrophy in Resistant Hypertension.

Correlation of RDW And Single, Double and Triple Vessel Disease

In the present study, there is no statistical significance of RDW and single, double or triple vessel disease whereas study conducted by Praveen Nagula et al showed positive correlation and statistical significance of RDW in CAD compared to non- CAD individuals and severity of CAD using modified gensini score showed statistical significance with RDW. [33] Study conducted by Fatih Akin et al study showed that high RDW group had statistical significance with severity of CAD (syntax score: 27.5±14) compared to normal RDW group (syntax score: 20.9±12) and the study also showed that RDW was statistically significant with the number of vessels involved.[34]Omer Sahin et al conducted study in 335 NSTEMI individuals and divided the study group based on severity into high SYNTAX group (SX score ≥ 12) of 105 individuals and low SYNTAX group (SXscore <12) of 230 individuals with mean RDW value of 15.2±1.8% and 14.2±1.2% respectively and statistical significance was obtained. [35]

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. [36] In experimental studies, inflammatory cytokines have been found to suppress the maturation of erythrocytes, so immature erythrocytes enter into the circulation. [37] Neurohumoral states may accelerate erythropoiesis. [38,39] In addition, the plasma erythropoietin level increases in STEMI. [40] These conditions lead to an increase in the heterogeneity of circulating erythrocytes. [41] There is evidence that humoral mediators contribute to adverse clinical outcomes. [42,43] Adrenergic activation may also affect bone marrow response in patients with STEMI. [44,45] A study shows that the deformability of RBCs in microvascular disorder decreases when the RDW level is more than 14%. [46] Güneş et al. study suggest that being close to the upper limit of normal osmolality range (292 to 293 mOsm/kg) could be an optimal plasma osmolality level in terms of cardiovascular prognosis in patients with Heart Failure. [47] Ning Li et al opines that the predictive role of osmolality to cardiovascular prognosis may be mediated by the deformation of RBCs, which is reflected on the RDW level. [31] There could be a genetic contribution to red cell size in the general population that can also be important in disease states. [48] Lippi et al showed that the RDW with cut off value of 14% has a predictive value in diagnosing ACS in patients presenting with chest pain. [49] Hidekatsu Fukuta et al conducted a retrospective study in 226 individuals who were diagnosed to be having CAD and RDW was evaluated with BNP and hs-CRP and found out that BNP correlated with RDW and hypothesize that neurohumoral activation partially mediates between RDW and CAD rather than chronic inflammatory state. [50] In Kushang V Patel et al study mortality rates are graded across the entire distribution of RDW and are particularly elevated in participants with RDW greater than 13.4%. [51] Felker and colleagues showed that patients with RDW >15.8% had nearly a 2-fold increased risk of CVD death or hospitalization as well as death from any cause compared to those with RDW <13.3%. [52] Tonelli et al. analyzed data from a randomized controlled trial of patients with coronary artery disease (CAD) and reported that death was twice as likely in patients with RDW >13.8% versus those with RDW <12.6%. [14] Anderson et al. reported that the risk of death over 1 year was 3 times higher in patients undergoing cardiac catheterization with RDW >14.0% relative to those with RDW <12.7%. [53]

6. Strengths and Limitations

- This study is conducted in an institute; therefore the results may not be for the general population.
- The study is not a case-control study so it doesn't signify if at all CAD has any correlation with RDW compared to controls.
- The study didn't consider modified gensini score or syntax score for severity scoring.
- However, the confirmation of the association of RDW with Hypertension is consistent with results from other studies.

7. Conclusion

C-reactive protein is an established nonspecific prognostic inflammatory biomarker for patients with Coronary Artery Disease. This has led to an effort to identify inflammatory biomarkers to predict the risk and to diagnose coronary artery disease in the population.

Red Cell Distribution Width is an easily available, inexpensive, and effective Hematological parameter and a novel biomarker for various cardiovascular conditions that reflects oxidative stress and chronic inflammatory state.

RDW has been used for predicting the risk stratification, severity, prognosis, and mortality of the disease.

The pathophysiology of the Red Cell Distribution Width has yet to be understood.

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