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Original Article

Correlation of Red Blood Cell Distribution Width With The Severity of Coronary Artery Disease

Mohsin Shabir[1], Ikram ul Haq[2], Muhammad Kashif Iltaf[3], Ahsan Shabir[4], Muhammad Shehram[5], Naseer Ahmed[1]

[1] Department of Cardiology, Rehman Medical Institute, Peshawar, Pakistan
[2]Department of Medicine, Letterkenny University Hospital, Ireland
[3]Department of Cardiology, Qazi Hussain Ahmad Medical Complex, Nowshera, Pakistan
[4]Department of Cardiac Anesthesia, Rehman Medical Institute, Peshawar, Pakistan
[5]Department of Cardiology, Armed Forces Institute of Cardiology, Rawalpindi, Pakistan

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***Corresponding Author:**
Naseer Ahmed
Department of Medicine, Rehman Medical Institute, Peshawar, Pakistan
dr.naseer99@gmail.com

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ABSTRACT

Atherosclerosis causing occlusion of coronary vessels by building up of plaque leading to narrowing of vessels supplying heart and causing coronary artery disease, which is the leading and common cause of mortality around the globe. **Objective:** To find the correlation of Red Cell Distribution Width (RDW) and severity of Coronary Artery Disease (CAD) lesions **Methods:** A number of 280 patients in total, admitted to cardiology department who presented with chest pain and diagnosed as angina, positive treadmill test and who underwent angiography and were found to have CAD, were enrolled in the study over a period of one year. Modified Gensini score (MGS) is used for assessment of severity of CAD. Each patient was assessed in relation to severity of CAD using MGS scoring system. **Results:** Out of 280 patients, 218 were assigned to Group A and 70 were assigned to Group B. Mean age of presentation were (52.34± 13.90 vs 50.8± 11.63 years). Male subjects were predominant overall with ratio of 2.63:1. RDW was assessed and was seen to be significantly elevated in Group A in comparison to Group B (14.98± 1.59 vs 13.82 ± 0.91p= <0.0001). After assessing MGS in relation to severity of CAD, significant correlation was observed. RDW was found to be increasing as MGS score increased (14.46± 0.65 vs 14.98± 1.00 vs 15.02± 0.88, p= <0.0001) **Conclusions:** It was concluded that RDW is a parameter which is cost effective, very easy, readily and urgently available for the assessment and stratification of patients presenting with coronary artery disease.

INTRODUCTION

Atherosclerosis causing plaques leading to stenosis and obstruction, known as Coronary artery disease (CAD), is one of the common causes of death and morbidity now a days. Approximately, 17.9 million people died from cerebrovascular disease, which is 32% of total death toll globally and 85% of this was from ischemic CAD and stroke [1]. With the development of the new techniques and test in the early diagnosis and effective treatment has improved the outcomes of CAD. Plaque formation due to atherosclerosis is a type of chronic inflammatory disease which remains dormant for years and after building and caused enough stenosis then will present as acute cardiac event in terms of myocardial infarction. Red cell distribution width (RDW) helps in measuring the differences in the volume and size of red blood cells and is used to narrow down the diagnosis of anemia [2]. In order to diagnose CAD to treat it as soon as possible, there are researches going on to find out different ways to cost effectively diagnose the disease and, in this regard, research has been done and still going around to look into

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the relation of RDW and heart diseases, like CADs [3] and heart failure [4] as a measuring marker of risk and severity. In this study assessment of patients presenting with chest pain and lesion and stenosis being different in severity judged by Modi ed Gensini score (MGS) on angiography is done in relation to RDW values.

METHODS

This study was conducted in Department of Cardiology, Qazi Hussain Ahmad Medical Complex, Nowshera between July 2020– June 2021. A number of 280 patients were enrolled after carefully examining and scrutinizing 800 patients who presented with chest pain to the said institute. Patients presented with the following diagnosis and who were having age >18 years were included in the study. ST segment elevation Myocardial infarction (STEMI) and non-ST segment elevation Acute Coronary Syndrome (NSEACS) under the umbrella of Acute Coronary Syndrome (ACS): Classic/Typical Angina, Atypical/probable angina, Positive treadmill test. ACS is defined as chest pain with ECG changes (ST segment elevation or depression, T wave changes like inversion, and new pathological Q wave), raised cardiac ischemia markers(troponin) and echocardiographic finding of regional wall motion abnormalities (RWMA). Angina described as chest (substernal) discomfort which lasts for less than 20 min aggravated and precipitated by exertion, stress and is improved and relieved by rest nitrates (nitroglycerin). Treadmill test which can induce ischemia (positivity criteria included 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

Hemoglobin cut off value was <12gm/dl in males and <11gm/dl in females, anemic below these levels were excluded [5]. Other candidates with the following histories were excluded: Cardiac procedures(CABG and PCI)

Valvular Heart Disorders, Bleeding disorders, Kidney Disease (Acute and Chronic), Hormone Replacement Therapy, Transfusions, hepatic disease, Pregnancy, Autoimmune diseases (TTP and ITP). Study was approved from QHAMC research ethical committee. Consent from each patient was taken as written and informed one before enrolling them in the study. Patients were assessed in detail in terms of demographics, history, risk factors assessment, complete physical examination, ECG assessment, echocardiography and treadmill test in selected patients. Laboratory investigation including cardiac enzymes and blood indices for RDW, by venipuncture mainly from median cubital vein in aseptic and atraumatic technique, at the time of admission. Blood was collected in EDTA tube and analyzed by SYSMEX hematology analyzer with RDW reference value of 11.5-13.5%. After admission to coronary care unit, echocardiography was performed, followed by undergoing coronary angiography, either by radial or femoral route with 5F and 6F catheters respectively. Angiography results were evaluated in terms of severity through MGS. Patients were assigned to two different groups depending on coronary angiography findings, first group (Group A) with CAD and second group (Group B) without CAD. Cut off value for CAD was stenosis of 50%. MGS score was used to assess the severity of stenosis which uses 8 segments of coronary tree with minimum score of 04 and maximum of 32 and further divided it into mild, moderate and severe disease.

Statistical analysis:

To analyze the data statistical methods were carried out using Medcalc. Percentages were used to express qualitative variables, with *Chi- square test* used for comparison. Standard deviation (SD) was used to express quantitative continuous variables. To compare Parametric continuous variables, analysis of variance (student t-test) was used. p value of <0.05 was considered statistically significant.

RESULTS

Total number of patients selected to be included in the study were 288, out of which 218 were in CAD group (group A) and 70 in with CAD group (group B). Range of age was between 25 and 80 years and mean age was 52.34± 13.90 years in group A and was 50.8± 11.63 years in group B. Male subjects (72.5%) were more than females (27.5%) with male to female ratio of 2.63:1. Hemoglobin was also checked between the groups but were statistically insignificant (14.01± 0.52 vs 13.98± 1.42 p=0.65). Assessment of risk factors showed hypertension to be the commonest risk factor seen in 135(61.9%), smoking is second in line of risk factors in group A seen in 130 patients (57.6%) and diabetes mellitus being third factor seen in 84 patients (38.4%). Few of the (14.98± 1.59 vs 13.82± 0.91 p=<0001). Apart from RDW other red cell indices were also analyzed which showed significant statistical difference which included MCV (88.52± 3.91 vs 92.34± 4.14 p=<0.0001) and MCHC (35.03± 1.97 vs 35.62± 1.01 p=<0001), in contrast MCH showed no statistical difference. Variables showing different characteristics of both groups of patients are showed in Table 1.

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Variables	Group A (n = 218)	Group B (n= 70)	P value
Age (years) mean± SD	52.34 ± 13.90	50.8± 11.63	<0.0001
Hypertension	135 *(61.9)*	44 *(25.6)*	<0.0001
Diabetes mellitus	84 *(38.4)*	16 *(23.5)*	<0.05
Alcohol intake	07 *(3.1)*	01 *(1.42)*	<0.0001
Smokers	130 *(57.6)*	11 *(16.32)*	<0.0001
Family history*	32 *(14.5)*	07 *(10.0)*	<0.05
RDW CV (mean± SD,%)	14.98 ± 1.59	13.82 ± 0.91	<0.0001
RDW SD (mean± SD,fl)	44.52 ± 5.01	43.32 ± 4.12	<0.001
Hemoglobin levels (gm/dl)	14.01 ± 0.52	13.98 ± 1.42	0.65
Hematocrit (%)	40.76 ± 3.98	41.46 ± 3.75	0.07
MCV (fl)	88.52 ± 3.91	92.34 ± 4.14	<0.0001
MCH (pg/cl)	31.11 ± 1.99	31.65 ± 0.98	0.85
MCHC (g/dl)	35.03 ± 1.97	35.62 ± 1.01	<0.0001
Male: Female	2.82:1	1.8:1	

Table 1: Different characteristics of Group A and B
*Family History of CAD
Abbreviations: n-Number, SD- standard deviation, RDW – red blood cell distribution width, MCV- mean corpuscular volume, MCH – Mean corpuscular hemoglobin, MCHC – mean corpuscular hemoglobin concentration.

As of the common observation in emergency department in regards to MI, anterior wall STEMI was seen the most in our study population as well which was seen in 94 patients (43.11%) and non-ST elevation ACS was second common diagnosis 61 (27.98%). Inferior wall MI also included posterior wall and right ventricular MI and was diagnosed in 42 patients(19.26)as shown in Table 2.

Diagnosis	Males	Females	Total (%)
Anterior Wall STEMI	72	22	94(43.11)
Inferior wall MI/RVMI/PWMI	27	15	42 (19.26)
NonST elevation ACS	48	13	61(27.98)
Stable angina	09	05	14 (6.42)
Ischemic Cardiomyopathy	05	2	07 (3.2)
Total	161	57	218 (100)

Table 2: Diagnosis according to areas of heart in Group A
Abbreviations: STEMI - ST segment elevation myocardial infarction, RVMI -Right ventricular myocardial infarction, PWMI - Posterior wall myocardial infarction, ACS -Acute coronary syndrome.

The severity of CAD was analyzed using MGS scale, RDW and risk factors were also assessed with different severity of CAD on MGS scale. It was observed that RDW value increased as MGS score increased Table 3. RDW value was 14.46 ± 0.65 with MGS 01-06 and 15.02 ± 0.88 with MGS value of >13 with p=,0.0001. Pearson correlation analysis showed positive and statistically significant correlation in terms of presence or absence of CAD on angiography with different severities of lesion and RDW CV (n=218, p=0.0001).

Variable n(%)	MGS 01–06	MGS 07–13	MGS >13	*p* value
No.of pts	61*(28.2)*	82*(37.5)*	75*(34.4)*	
Age (mean± SD)	55.23± 09.75	51.55± 11.22	49.56± 10.45	0.45
Male	*46(75.5)*	68*(83.4)*	51*(68.32)*	0.0052
RDW (mean± SD,%)	14.46± 0.65	14.98± 1.00	15.02± 0.88	<0.0001
Hemoglobin (gm/dl)	14.22± 0.33	13.98± 0.65	14.98± 0.65	0.85
Smokers	*38(62.29)*	50*(60.97)*	35*(46.66)*	0.001
Family h/o	08*(13.11)*	10*(12.19)*	14*(18.6)*	0.05
Diabetes mellitus	24*(39.34)*	28*(34.14)*	32*(42.66)*	0.0001
Hypertension	35*(57.37)*	55*(67.07)*	45*(60.0)*	0.001
Alcoholic	*03(4.91)*	*04(4.87)*	0	0.05

Table 3: Group A stratification on the basis of MGS*
* MGS Modified Gensini Score
Abbreviations: RDW- red blood cell distribution width

DISCUSSION

The mechanism behind CAD is Atherosclerosis which is an inflammatory disorder of chronic nature which consist of fatty cells and streaks deposition, leading to hardening and thickening of arterial wall, starting from an early age, and stays dormant for many years and presents acutely due to significant stenosis of coronary arteries, as an ACS, cardiac arrythmia or sudden cardiac death [6]. Due to chronic inflammatory process due to atherosclerosis causing oxidative and free radical stress, release of other inflammatory elements, in addition to macrophage accumulation and endothelial dysfunction [7]. One of the red cell indices is RDW, which is defined as the measure of RBC size and RBC volume which is used in addition to other indices to diagnose anemia. RDW is reported as elevated when there is variation in size of RBC (anisocytosis) on peripheral blood film. The relation between the value of RDW and disease outcomes is studied in different studies. Increased in RDW value is noted with poor outcome is coronary artery disease. Some of the reasons are given below which can give us an explanation of increased in RDW and atherosclerosis: Injury to RBCs also causes increased RDW, due to microcytosis induced by the oxidative stress and free radicals [8], EPO gene transcription is suppressed leading to decrease in the amount of Erythropoietin release from mesangial cells, as a result of ongoing chronic inflammation and pro inflammatory mediators. Due to these mechanisms it leads to change in sizes of cells leading to anemia. Premature cells are released giving increase in RDW [9], Hepcidin, which is a peptide hormone, regulating delivery of iron to plasma from intestinal cell, hepatocytes and iron containing macrophages. Its synthesis is increased in hypoxia and inflammation leading to non-availability of iron for hemoglobin synthesis,

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resulting in anemia and increased RDW [10], Patients with CAD and treated with primary/urgent PCIs having Anisocytosis with different sizes of cells with deform structure which are not able to flow well specially at capillary levels, leading to decrease oxygen supply to tissues [11]. Of the two groups, group A was having increased mean age with male predominance in both groups. Mean age of presentation with CAD is at early age as compared to developed countries also seen in large trial called INTERHEART trial [12]. Risk factors were also more in group A. Multi regression analysis was used to possibly avoid any bias caused by the multi risk factors in diseased group and it helped in showing that RDW is an independent factor for the presence or absence of CAD and predicator of all causes mortality as well in the said group [13]. A positive relation was seen between RDW and severity of disease assessed by MGS. Hemoglobin, RDW and CV. Correlation was weakly negative (r=-0.1096), however value of hematocrit /Packed cell volume was low in the diseased group, possibly due to anisocytosis, although values were normal in both. Other indices which are important to mention are MCV, MCH and MCHC of which the former two were decreased and the last one was increased. The former two can be explained by anisocytosis and microcytosis as seen in iron deficiency anemia whereas MCHC can not be explained as it is also decreased in IDA. No other blood tests were done to diagnose or differentiate anemia. RDW with cut off of 14% was seen by Lippi et al [14]. In chest pain patients to be having a predictive value for diagnosing ACS, being 79% sensitive and 50% specific. Increase in Heart failure ratio was also seen in CAD patients in relation to increase in RDW value [4]. Usefulness of RDW value was also seen in triaging CAD patients by Tenekecioglu et al., [15]. RDW is seen as single and important predictor of all causes mortality in a study by Cavusoglu et al. [13]. In one of a study done by Tonelli et al [3], showed that CAD without heart failure with increased RDW had increased mortality. Graded and independent association between enhanced RDW and death rate after acute myocardial infarction was observed in previous studies[16,17]. Role of immune activation and cytokines has also been proposed to be a possible etiology for chronic heart failure [18,19].Increased RDW may also be linked to other diseases such as chronic kidney disease, cancers, gastroenterological disorders in addition to cardiovascular diseases [20,21].

CONCLUSION

In order to avoid over diagnosis of anemia, cut off value for anemia in male is taken as <12 gm/dl and <11gm/dl in females. We have evaluated patients from stable angina to ACS and RDW value is evaluated. It was asserted that RDW is an inexpensive test which can be easily done along with complete blood count as element for stratification of risk for patients presenting with chest pain before any other test

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