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RED BLOOD CELL DISTRIBUTION WIDTH TO ASSESS THE RISK OF CARDIOVASCULAR DISEASES

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ABSTRACT

The red blood cell distribution width (RDW) is a simple, low-cost biochemical parameter that reflects the level of anisocytosis as determined by a typical complete blood count. Anemia and other inflammatory disorders are diagnosed using RDW and other haematological parameters. Higher RDW levels have been implicated in numerous recent studies as a potent independent predictor of morbidity and mortality in a variety of cardiovascular diseases (CVDs). Therefore, RDW may be crucial in determining the severity and development of CVDs. In this review, we have outlined the mechanisms underlying the link between RDW and CVDs, as well as a few literature reviews that explain RDW and related CVDs, which demonstrated that even a 1SD increase in RDW causes various CVDs such as heart failure (HF), myocardial infarction (MI), atrial fibrillation, atherosclerosis, hypertension, and stroke depending on the degree of involvement. To varying degrees, some common mechanisms that contribute to increased RDW include oxidative stress, inflammatory cytokines, anemia, lipid abnormalities, vitamin D-3 deficiency, glycemic disturbance, chronic kidney disease (CKD), and liver disease. Finally, it can be concluded that even a 1SD change in RDW can indicate a significant risk of a CV event.

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INTRODUCTION

Cardiovascular diseases are a group of disorders of the heart and blood vessels and they include hypertension, coronary heart diseases, angina pectoris, myocardial infarction, cerebrovascular diseases (stroke), and hyperlipidemias [1]. CVD are the leading cause of death globally and in India, one in every four deaths is now due to CVD with ischemic heart disease and stroke responsible for greater than 80% of this burden [2]. So, early diagnosis of cardiovascular diseases may help prevent it and reduce the mortality rate.

The clinicians have conducted extensive research to find the biomarker that would aid the identification and prevention of cardiovascular diseases. One such parameter is the red blood cell distribution width (RDW). [3,4]

RBCs or erythrocytes are non-nucleated cells and exhibit a typical oval biconcave shape. Normal, the size of RBCs varies from 80 to 100fL [5]. A number of pathological (anemia, fatigue, hepatosplenomegaly) and physiological (pregnancy, ageing, high altitude, excitement) conditions may impair red blood cell production [6]. Red blood cell distribution width is a numerical measurement of variations in the size of circulating RBCs (anisocytosis). This parameter is routinely reported as a part of a complete blood picture. The two RDW measurements currently in use are

1 Red blood cell distribution width - coefficient of variability (RDW-CV). This is expressed in percentage (%).
2 Red blood cell distribution width – standard deviation (RDW-SD). This is expressed in femtoliters (FL).

RDW-CV measures the of dispersion by means of a formula which is ratio of standard deviation (SD) to MCV multiplied by 100[7], any changes in the SD or MCV will influence the result. Figure 2 shows the two methods used to calculate the RDW-CV. RDW-SD is a direct measure of the RDW taken at a 20% frequency level of the histogram. As this method is independent of MCV and is considered to be the absolute measure of dispersion, it is a better reliable measure of RBC variability, particularly in highly abnormal conditions

Normal values:
RDW- CV: 11.6-14.6%
RDW- SD: 39-46fL
Reference ranges may vary depending on the individual laboratory and patient's age.

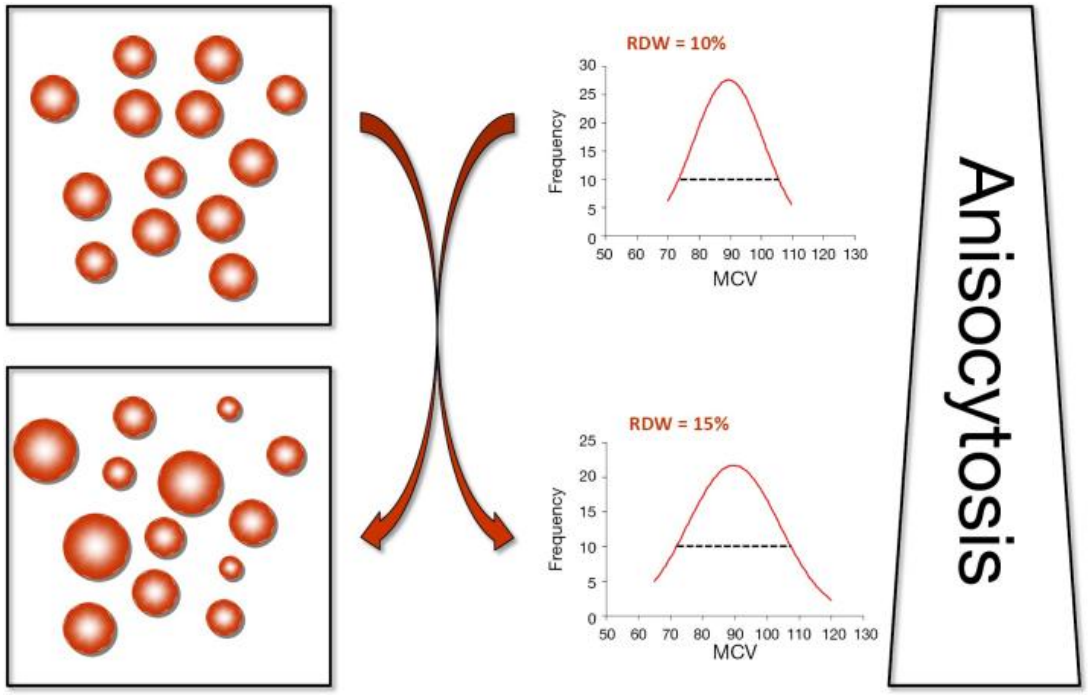

Figure 1: Relationship between the distribution of mean corpuscular volume, anisocytosis, and red blood cell distribution width [8].

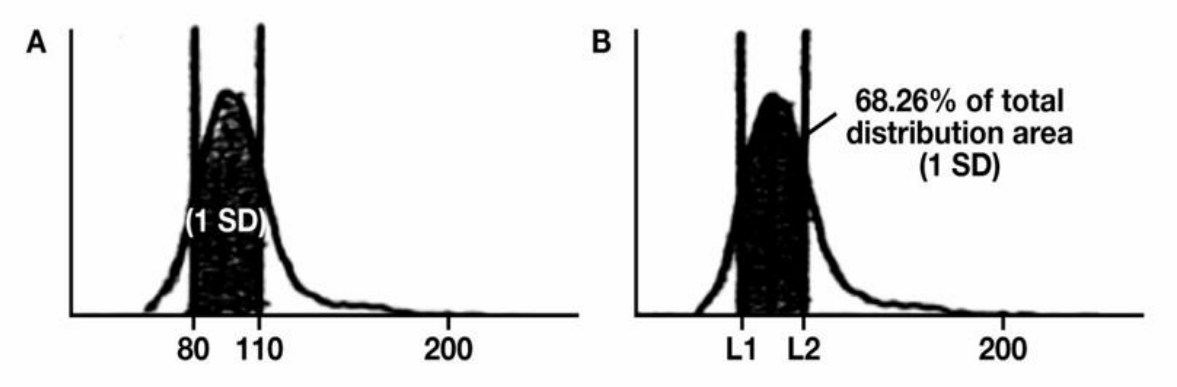

Figure 2: Two common methods to calculate RDW-CV [9].

A) Beckman coulter, Inc method

$$RDW - CV = \frac{1SD}{MCV} \times 100$$

B) Sysmex corporation method

$$\text{RDW} - \text{CV} == \frac{L2-L1}{L2+L1} \times 100$$

L_1 = MCV – 1SD
L_2 = MCV + 1SD

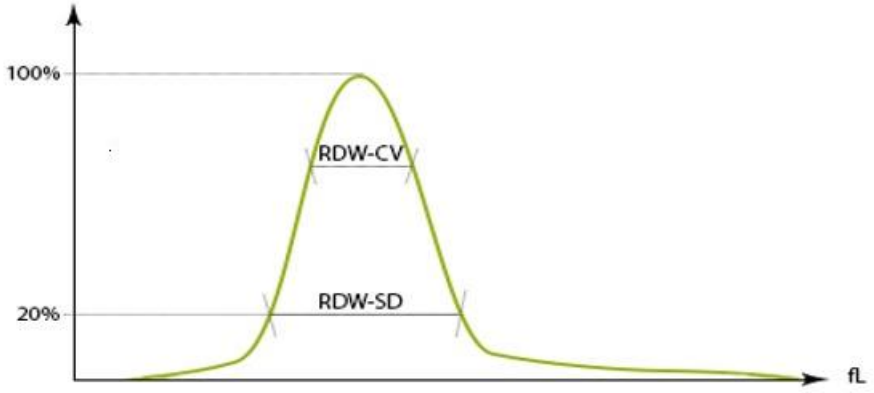

Figure 3: The RDW-SD is the distribution curve's arithmetic width assessed at the 20% frequency curve. The usual RDW-SD ranges from 39 to 47 fL.

RDW and cardiovascular diseases

Heart failure:

(Heart failure is defined as the pathophysiologic state in which impaired cardiac function is unable to maintain adequate circulation for the metabolic needs of tissues of the body. The term congestive heart failure (CHF) is used for a chronic form of heart failure in which the patient has evidence of congestion of peripheral circulation and of lungs. It is a serious condition that requires long-term management and medical care. In recent years many studies have been performed to know the relation between CHF and RDW [42,43]

- Michael Felker et al.2007 performed the first large prospective study to explore the significance of measuring RDW in patients with HF. They studied 2679 symptomatic patients from North America CHARM program and followed them for 2years and assessed the relationship between the routine blood tests and outcomes using Cox proportional hazards. Subsequently, they studied additional 2140 HF patients (validation cohort) enrolled from duke data bank in 1996 and with follow-up information available for more than 96% of patients. In the final multivariable analysis, including all significant clinical and laboratory parameters each 1SD increase of RDW in the CHARM cohort was associated with a 17% higher risk of cardiovascular death or hospitalization for HF (hazard ratio (HR) 1.17; 95% confidence interval (95%), 1.10-1.25) and 12% of all-cause mortality. In the validation cohort, each 1SD increase of RDW was also associated with 29% enhanced risk (HR 1.29; 95% CI; 1.16-1.43) of all caused mortality [10].

- Cauthen et al. for the first time assessed the significance of longitudinal RDW changes in patients with HF. They retrospectively analyzed data from 6159 ambulatory chronic HF patients, to explore the association between clinical outcomes and RDW changes over the 1year follow-up period. They found out that each 1% increase in RDW value was independently associated with a 9% enhanced risk of 1year all-cause mortality (relative risk (RR= 1.09; 95%CI: 1.01-1.17) [11].
- MarcellioTonelli et al.performed a prospective study to examine the association between RDW and risk of all-cause mortality and adverse cardiovascular outcomes in patients with coronary diseases and they were free from HF at baseline. Baseline RDW was measured in 4111 participants of the cholesterol and recurrent events study and followed them for a mean period of 59.7months. In a multivariable analysis, each 1% increase in RDW was associated with 14% increased all-cause mortality (HR = 1.14; 95% CI: 1.05- 1.24) and 15% higher risk (HR = 1.15, 95% CI: 1.05-1.26) of developing symptomatic HF on follow up [12].
- Gianni Turcato et al. performed a retrospective study on 588 patients with HF to investigate whether in- hospital variations of RDW may predict mortality. RDW was measured at admission and after 48hours and 96hours of hospital stay. Their study showed that ΔRDW > 0.4% calculated between the value at admission and those obtained after 48hours and 96 hours of hospital stay was independently associated with 3-fold higher risk of 30days mortality (OR of 48h ΔRDW 3.04; 95%CI 1.56-5.94 and OR of 96hours ΔRDW 3.65; 95% CI 2.02-6.15) [13].
- Badrira F Makhoul et alprospectively studied 614 patients with acute decompensated heart failure (ADHF). RDW was measured at baseline and throughout the hospital stay and followed for 1year. Each 1% increase in RDW value was independently associated with a 15% higher risk (HR = 1.15; 95% CI: 1.08-1.21) of all-cause mortality and each 1% increase in longitudinal RDW was associated with 25% higher risk (HR = 1.23; 95% CI: 1.09-1.38) of all-cause mortality [14].

From the above data, it is evident that RDW measurement not only predicts the risk of adverse outcomes in patients with HF but is also a significant and independent predictor of developing HF in patients free of this condition [15].

Myocardial infarction (MI):

MI is one of the 5 main manifestations of coronary heart disease namely- angina pectoris (stenocardia), MI, ischemic heart failure, asymptomatic myocardial ischemia and sudden death [44].

MI is defined by the demonstration of myocardial cell necrosis due to significant and sustained ischemia. It is usually, but not always, an acute manifestation of atherosclerosis-related coronary heart disease. MI results from either coronary heart disease, which implies obstruction of blood flow due to plaques in the coronary artery or, much less frequently, to other obstructing mechanisms (e.g., spasm of plaque-free arteries). MI is one of the leading causes of sudden death. Many studies have been performed in recent years to evaluate the relationship between changes in the RDW and myocardial infarction. Here are a few studies indicating the significance of the RDW in predicting the adverse outcomes of MI [16,17, 18].

- The study investigating whether RDW levels were associated with risk of all-cause mortality and adverse outcomes in people with the coronary disease without symptomatic HF baseline study was carried out by Tonelli et al. from the University of Alberta in 2008. They observed a graded independent relation between high RDW levels and increased risk of all-causeof death in people with coronary diseases (95% confidence interval (CI), 1.05-1.24) [12].
- In 2012, Onurkadiruysal et al. investigated the relation between RDW and STEMI in young patients. They included 370 patients who presented to the hospital with acute myocardial infarction and divided them into 2 groups (group 1: 198 young patients, <45age for male, <55 for female, group 2: 172 elderly patients) and another 156 adults with normal coronary angiography as a control group and divided them into another 2 groups (group 3: 91 young patients, < 45 age for male, <55 age for female, group 4: 65 elderly patients). They reported that group 1 had a significantly higher value of RDW when compared with the group 3 (group 1 RDW 14.1±1.1%, group 3 RDW 13.4±0.9, P1 <0.01). Group 2 and group 4 had similar RDW values (group 2 RDW 13.7± 1.2, group 4 RDW 13.5±0.9, P_2 0.1). After multivariable analysis, they found that high levels of RDW were independent predictors of STEMI in young patients (OR: 0.337, P < 0.01) [20].
- YaronArbel et al. 2014 performed a study to evaluate the association between RDW and long-term mortality in STEMI patients undergoing primary angioplasty (PPCI). They studied a cohort of 535 STEMI patients undergoing PPCI and divided them into two groups (RDW >14%, RDW ≤14%) using CHAID and CART methods and followed them for 5 years. They analyzed the all-cause mortality using COXs proportional hazards analysis. During their follow-up, 37 patients died (mean: 1059, median: 1013, range 2-2130 days) RDW >14% was associated with an increased risk of all-cause mortality (HR: 5, CI 95%, 2.7-9.9, P <.001). In the multivariable analysis RDW, >14% remained independently associated with increased long-term all-cause mortality in patients with STEMI undergoing PPCI [21].
- A linear association between RDW and risk of AMI was recently described in 25,612 participants of the troms study in 1994-1995, wherein each 1% increment in RDW was associated with a 13% increased risk (hazard ratio (HR) 1.13; 95%, CI, 1.07-1.19) participants with RDW values above 95th percentile had 71% higher risk of AMI compared to those with RDW in the lowest quintile (HR, 1.71; 95%, CI, 1.34-2.20) [22].
- Gul et al.performed a prospective study including 310 patients and reported that the RDW at admission was a significant predictor of adverse clinical outcomes in patients with non-ST elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP). In particular, the 3-year mortality rate was significantly higher in the high RDW group (>14%) compared to the low RDW group (≤14%). A significant association was also found between high admission RDW and adjusted risk of cardiovascular mortality (HR 3.2; 95% CI, 1.3-7.78) [23].

Atrial fibrillation:

Atrial fibrillation is the most common type of cardiac arrhythmia. It is due to the abnormal electrical activity within the atria (two upper chambers) of the heart, causing them to fibrillate. It is characterized as tachyarrhythmia. This means that the heart rate is often fast. The heart rate in atrial fibrillation may range from 100 to 175 beats a minute. Due to irregular rhythm, blood flow through the heart becomes turbulent and results in the formation of a clot which ultimately results in stroke. It is a common complication following MI. Here are a few studies showing the significance of RDW in predicting the risk of developing atrial fibrillation [24].

- Gungor et al. retrospectively analyzed medical records of 117 patients (60.6%male, mean age 48.3±12.5, 103 paroxysmal and 14 chronic AF) with atrial fibrillation(AF) and 60 control subjects (55% male, mean age 46.1±7.2) and concluded that RDW values were significantly higher in AF case than in controls (13.4% vs. 12.6; P = 0.01). In multi-variable analysis RDW >12.9% was associated with a nearly 4-fold higher risk of AF (odds ratio 4.18; 95%CI: 2.15-8.15) [25].
- Adamssoneryd et al. [26] investigated the association between baseline RDW and incidence of the first hospitalization due to AF in a population-based cohort. They prospectively studied 27,124 subjects (age 45- 73 years, 62% women) with no history of AF, heart failure, myocardial infarction or stroke. They categorized the samples into four groups (quartiles) with equal proportions of men and women in each quartile and followed them for a mean period of 13.6 years. Subjects in the highest quartile of RDW (>42.5fl) had a 33% enhanced risk (hazard ratio. 1.33; 95% CI: 1.16-1.53 for the fourth quartile) of developing AF on follow-up compared to those in the lowest quartile (HR per 1SD 1.08, 95% CI: 1.04- 1.12). moreover, each 1sd increase of RDW values was associated with an 8% higher risk (HR 1.08; 95% CI: 1.04-1.12) of incident AF.
- Another retrospective study which included 132 patients (mean age 60.55±9.5 years, 99 male and 33 female) was carried out by Gokhanertas et al. they investigated the role of RDW in the prediction of new-onset atrial fibrillation (AF) after coronary artery bypass grafting (CABG). The result revealed that the preoperative RDW levels were significantly higher in patients developing AF than in those patients without AF (13.9 ± 1.4 vs. 13.3 ± 1.2, P=0.03, a sensitivity of 61% and specificity of 60%). However, they found no correlation between RDW and post-operative atrial fibrillation (POAF) [27].
- Recent study investigating whether an increase in RDW was associated with thromboembolic outcomes in patients with atrial fibrillation was performed by Myung-jin cha et al. in 2017. They retrospectively analyzed 5082patients with non-valvular AFand followed them for a mean period of 5.2 years.RDW was measured during the follow-up. Among the various RDW measures, a peak value ≥13.9% was independently associated with a 66% enhanced risk (odds ratio 1.66; 95% CI: 1.41- 1.96) of thromboembolic events, including ischemic stroke and systemic embolism [28].
- Luke c piling et al. [29] prospectively analyzed RDW levels of 2,40,477 (age 40-70 years) healthy volunteers who were free of anemia, CAD, type 2 diabetes, hypertension, COPD and any cancer at baseline and followed them for ≤ 9years. High RDW levels (≥15 % variation, n=6050) compared with low (<12.5% n=20,844) was associated with AF (sHR 1.37: 1.21 to 1.55). RDW was also predictive of new onset AF.

Atherosclerosis:

Atherosclerosis refers to the buildup of fats, cholesterol and other substances in and on the arterial walls (plaques) which can restrict blood flow. The plaque can burst, triggering a blood clot. Although atherosclerosis is often considered a heart problem it can affect arteries anywhere in the body. Atherosclerosis develops gradually. Sometimes a blood clot may completely block blood flow or even break apart and can trigger a heart attack and stroke. Heart attack and stroke are easy to measure and quantify than atherosclerosis. There is limited data available on the relationship between RDW and coronary atherosclerosis is extremely limited compared with heart attack and stroke [30,31,32]

- The first study investigating the relationship between RDW and coronary atherosclerosis was performed by Mustafa cetin et al. in 2012. They performed a cross-sectional and observational study on 296 eligible patients who underwent coronary angiography with suspicion of CAD between October 2009 and 2010. Out of 296 patients, 209(71%) had CAD (men 70% mean age ± SD: 61±11 years) and 87 patients (29%) had normal coronary arteries (NCA) without any atherosclerosis lesion with visual assessment (men 48%, 52±11 years). They graded the stenosis in the epicardial coronary arteries into 4 subgroups considering both the extent and the severity of the lesions at coronary angiography (<50% luminal obstruction, 1, 2 and 3 diseased vessels ≥50%). The study showed that RDW values were significantly different among the subgroups determined for the severity and extent of CAD (NCA: 14.7±1.2, 50% luminal obstruction 15.2 ± 1.2 and 1,2 and 3 diseased vessels ≥ 50%: 15.4±1.2, 15.5±1.3, 15.7±1.2 P < 0.001 respectively). In a multi-variable analysis, they found a positive independent relationship between age gender, family history of CAD and RDW and CAD. Their result showed that RDW has a significant relationship with CAD independent of nonspecific inflammation and circulating inflammatory cells [33].
- Zi ye et al. [34]studied 13,039 consecutive outpatients (age 69.5 ± 12.0 years, 60.9% men) with peripheral artery disease and studied the association between RDW and all-cause mortality. They reported that patients in the highest quartile of RDW (> 14.5%) had a 66% greater risk of mortality compared to the lowest quartile (<12.8%, P< 0.001); a 1% increment in RDW was associated with a 10% greater risk of all-cause mortality (HR: 1.10, 95%CI: 1.08 to 1.12, P <0.0001).

Hypertension:

Hypertension, also known as high or raised blood pressure, is a condition in which arteries have persistently raised pressure. Blood pressure is created by the force of blood pushing against the walls of arteries as it is pumped by the heart. Hypertension can lead to severe health complications and increases the risk of heart diseases and stroke. It has been recently reported that the RDW levels are higher in patients with hypertension and help in preventing adverse outcomes. Here are a few studies which show the relationship between the RDW and hypertension [35,36]

- Ahmed Bilal et al. [37] measured the RDW in 100 patients (69 male and 31 females, mean age 51.48±10.08 years) with hypertension. The overall frequency of hypertension of more than 5 years was 55%. The mean RDW was found to be 46.20± 7.790 fl (baseline value 42.5 fl) and they reported that a significant number of patients with hypertension have increased levels of RDW.
- Asil Tanindi et al [38] performed a study and observed the differences in RDW values between the healthy population and the patients with prehypertension and hypertension. They studied 128 patients with hypertension, 74patients with prehypertension and 36 healthy controls. They reported that RDW is higher in prehypertensive (mean RDW 15.26±0.82) and hypertensive (mean RDW 16.54±0.91) patients compared with healthy controls (mean RDW 13.87±0.94) ($P<0.05$). RDW is strongly linked with systolic and diastolic blood pressure ($r = 0.848$ and $r= 0.748$ respectively, $P<0.01$). This was independent of age inflammatory status and anemia.
- ErsinYildirim [39] performed a study to determine the relationship between isolated systolic hypertension and red blood cell distribution width (RDW). They studied 81 patients and divided them into 2 groups (isolated systolic hypertensive and normotensive. They reported that the mean RDW of the isolated systolic hypertensive {14.2 (13.4-16.2)} group was significantly higher than the normotensive group {13.7(12.8-14.3)} ($P=0.01$). There was a correlation between the RDW and systolic blood pressure ($r=0.27$, $p= 0.02$).

Stroke:

Stroke is a cerebrovascular disease that affects the arteries leading to or within the brain. Stroke can be caused either by a clot obstructing the flow of blood to the brain (ischemic stroke) or by a blood vessel rupturing and preventing blood flow to the brain (hemorrhagic stroke) or by a temporary clot (transient ischemic attack). Due to this blockage, the brain does not receive enough oxygen or nutrients and brain cells start to die. Current studies have investigated the role of RDW to predict the outcomes of stroke.

- Martin soderholm et al[40] investigated the relation between RDW and increased incidence of stroke. RDW was measured in 26,879 participants (16,561 women and 10318 men aged 45-73 years) without any history of coronary events or stroke and followed them for 15.2±3.9 years. Incidence of stroke and stroke subtypes were calculated in relation to sex-specific quartiles of RDW. They reported that the incidence of stroke (n=1,869) and cerebral infarction (n=1,544) were both increased in individuals with high RDW. Hazard ratios of the highest quartile, when compared to the lowest quartile, were 1.31 for stroke (95% CI: 1.10 -1.58; $P=0.004$). They concluded that RDW in the highest quartile was associated with an increased incidence of stroke.
- Amparo Vaya et al [41] performed a study to analyze the association of RDW with cryptogenic stroke (stroke of unknown cause). They measured RDW in 163 patients with cryptogenic stroke and 186 healthy controls and showed that RDW > 14% was independently associated with the risk of cryptogenic stroke (OR 2.54; 95% CI 1.30-4.96).

PATHOPHYSIOLOGICAL MECHANISM*:*

Pathophysiologic mechanisms of anisocytosis and its role in CVD.

Oxidative stress:

Oxidative stress is caused by an imbalance between the production of reactive oxygen species (ROS) and the ability to detoxify these excess ROS with antioxidants. These free radicals in the moderate range play an important role in the host defencesystem, however, when these ROS levels reach above the threshold, it shows a negative effect on cellular structures (lipids, proteins, nucleic acid). Some environmental stresses, smoking, metal toxicity, and hypertensive stimuli contribute to the production of ROS.

Effect on RBCs:

RBCs are continuously exposed to ROS, the majority of these are neutralized by RBC antioxidant system (glutathione peroxidase, peroxiredoxin-2). RBC membrane is inaccessible to the cytosolic RBC antioxidant system. So, during oxidative stress and hypoxic conditions, ROS (mainly H_2O_2) damages the heme (which is bound to the membrane of RBC) and impairs deformability (an essential feature of RBCs that enables them to travel through even the smallest capillaries) [46]and cellular stiffness[47,48]. This decreased deformability leads to blockage or reduced blood flow, leading to low oxygen supply to tissues causing cardiovascular and cerebrovascular diseases. Oxidative stress also increases the uptake of RBCs by macrophages through caspase 3 activation and leads to decreased RBC life span, anisocytosis and increased RDW[45,48].

Inflammatory cytokines:

Inflammation is a part of the complex response of the body tissue to harmful stimuli such as pathogens, damaged cells etc. during the process of inflammation, several cytokines like IL-6, IL-8, IL-1b etc. and proinflammatory mediators are released which may lead to reduced production of erythropoietin (EPO), impaired bone marrow response to EPO[51], reduced iron availability and increased RBC clearance[49,50] all these mechanisms leads to reduced circulating RBCs, anisocytosis and increased RDW.

Anemia:

Anemia is defined as a condition in which the number of RBCs or the hemoglobin concentration within them is lower than normal. Severe anemia leads to heterogeneity of RBC size which is reflected in increased RDW values. Adequate tissue oxygenation in anemic conditions may be acquired by hemodynamic and non-hemodynamic adaptations. The non-hemodynamic adaptations include both increases in erythropoietin production and an increase in intra-erythrocytic concentrations of 2,3-diphosphoglycerate(2,3-

DPG) When the availability of oxygen to tissues is reduced, the RBC responds by synthesizing more 2, 3-DPG, the effect of 2, 3-DPG is to reduce the oxygen affinity of hemoglobin. When hemoglobin oxygen affinity is decreased the curve shifts towards the right consequently, oxygen is bound less lightly to hemoglobin and is also released even at high partial pressure, thereby enhancing oxygen unloading at the tissue level. The hemodynamic adaptations include arterial dilation, which leads to a decrease in systemic vascular resistance and reduced after load, which in turn may increase the stroke volume.

Anemia leads to a decrease in blood viscosity, which in turn increases venous return and thus augments preload. Anemia also activates the sympathetic nervous system, which results in increased heart rate. Increased preload, heart rate, stroke volume and decreased after load all together contribute to increased cardiac output. Over the long term, adaptations that initially increase cardiac output may lead to left ventricular enlargement and eccentric left ventricular hypertrophy (LVH); left ventricular hypertrophy in turn may predispose to heart failure or aggravate ischemic heart disease (IHD). The chronic increase in cardiac output may also lead to arterial remodelling, in turn, results in arterial enlargement and compensatory arterial intima-media thickening or atherosclerosis[53]. Cardiovascular compensatory consequences of anemia include tachycardia, increased cardiac output, a hyperdynamic state due to reduced blood viscosity and vasodilation enabling tissue perfusion.

Lipid abnormalities:

There are reports indicating that elevated RDW values correlate with abnormal lipid profiles. In studies performed by Tziakas et al. an insight was provided on the link between RDW and total cholesterol erythrocyte membrane (CEM) levels. CEM level increases are responsible for the deterioration of cell deformability, which affects the lifespan of circulating erythrocytes and these results in greater cellular turnover and elevated RDW values. Lipid disorders decrease red cell membrane fluidity, and higher CEM levels result in the deterioration of blood flow through the microcirculation. This mechanism explains the well-documented relationship between RBC rheology and the lack of tissue reperfusion following PCI in patients suffering from MI[54].

The pathologic changes in the erythrocyte membrane that has abundant free cholesterol can lead to the accumulation of erythrocytes within the atheromatous plaque. The deposition of free cholesterol from the erythrocyte membrane to the atherosclerotic plaques will promote atherosclerosis and thereby provide lipid-rich membranes to foam cells, which are propagated by inflammatory cascade[55].

Vitamin D-3 deficiency:

Another factor potentially affecting RDW is vitamin D-3 deficiency, a well-established risk factor for CVD. Vitamin D-3 is responsible for both cell proliferation and erythropoiesis. VitaminD-3 concentrations in the bone marrow are more than two hundred times greater than in the blood. Even a minor decrease in serum vitamin D-3 levels may result in derangement of bone marrow erythropoiesis[54].

Glycemic disturbance:

In regards to diabetes, several structural and functional properties of RBC are remarkably altered in the presence of hyperglycemia. These alterations include increased glycosylation of cell surface proteins, decreased plasma membrane fluidity and reduced erythrocyte deformability, which would impair the dynamic properties of RBC, complicate their flow through the microcirculation and ultimately increases their vulnerability to injuries. Diabetic nephropathy is also associated with erythrocyte fragmentation, which is a well-established cause of anisocytosis [56].

Chronic kidney disease (CKD):

In CKD, the gradual decline of erythropoietin synthesis, especially when accompanied by erythropoietin hypo responsiveness, not only causes reduced production of RBC but is also responsible for the generation of erythrocytes with different sizes, thus ultimately increasing the degree of anisocytosis[56]. Impaired kidney function, however, is most likely not a separate mechanism linking elevated RDW values to poor patient prognosis in CAD, because, among patients with CKD, chronic inflammation, greater oxidative stress, lipid disorder, vitamin D-3 deficiency & anemia and increased RDW levels are often noted [54].

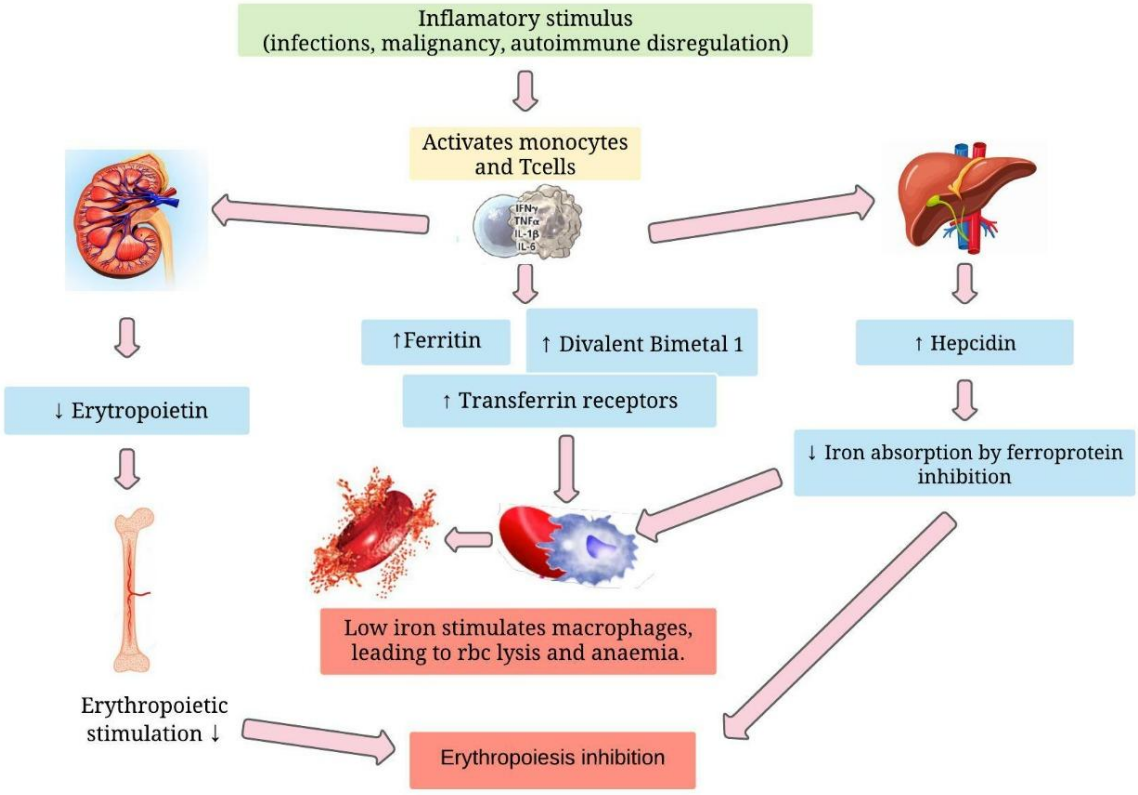

Figure 4: Pathophysiologic mechanism if anemia. IFN-*γ*, interferon-γ; IL-1β, interleukin-1β; IL-6, interleukin-6, TNF-α, tumor necrosis factor-α:

Liver Disease:

Several conditions that impair erythrocyte production and survival may be present in patients with liver disease. These basically include down-regulation of erythropoietin receptor expression, nutritional deficiencies like iron, vitamin B_{12}, folic acid chronic inflammation and increased red cell destruction[19]. The influence of IL-6 on the liver leads to increased production of hepcidin which in turn leads to decreased iron absorption and finally anemia[50,52].

CONCLUSION

RDW is a parameter which is routinely reported as a part of a complete blood picture. RDW can be measured by any of the two methods available, namely, RDW-CV and RDW-SD. while RDW-SD is the most appropriate and reliable method used to measure the RBC variability. From many epidemiologic studies conducted, it was evident that patients with CVD are more likely to have anisocytosis and elevated RDW levels. From various studies conducted to assess the complications, mortality rate and adverse outcomes in CVD, it is evident that RDW can be used as a strong and independent predictor to assess the complications, adverse outcomes and mortality rate in cardiovascular diseases. Apart from cardiovascular diseases, RDW has a distinct impact on various disease conditions ranging from cancer to dementia. An increased RDW is reflected by profound deregulation of erythrocyte homeostasis which may be caused by different mechanisms like oxidative stress, inflammation, anemia, lipid abnormalities, shortening of telomere length, vitamin D-3 deficiency, glycemic disturbance, chronic kidney disease and liver diseases. All these conditions are important prognostic factors for severe morbidity and death. Hence, it seems conceivable that RDW is a simple and inexpensive parameter to provide valuable information about the general health status, the presence of clinical and sub-clinical conditions, progression of various acute and chronic diseases and complications & adverse clinical outcomes in patients with cardiovascular disease. More research is needed to improve the use of RDW in assessing the risk of cardiovascular disease.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest regarding the publication of the paper.

LIST OF ABBREVIATIONS:

S.no	Abbreviation	Full Form
1	RDW	Red blood cell Distribution Width
2	RDW- SD	Red blood cell Distribution Width- Standard Deviation
3	RDW- CV	Red blood cell Distribution Width- coefficient of variability
4	CVD	Cardiovascular Disease
5	HF	Heart Failure
6	AF	Arterial Fibrillation
7	MI	Myocardial Infarction
8	CKD	Chronic Kidney Disease
9	RBC	Red Blood Cell
10	fL	Femtolitre
11	MCV	Mean Corpuscular Volume
12	CHF	Congestive Heart Failure
13	RR	Relative Risk
14	CI	Class Interval
15	STEMI	ST-Elevation Myocardial Infarction
16	NSTEMI	Non- ST-Elevation Myocardial Infarction
17	COX	Cyclooxygenase
18	PCCI	Primary Percutaneous Coronary Intervention
19	CART	classification And Regression Tree
20	CHAID	Chi-squared Automatic Interaction Detection
21	AMI	Acute Myocardial Infarction
22	POAF	Post-Operative Arterial Fibrillation
23	COPD	Chronic Obstructive Pulmonary Disease
24	CAD	Coronary Artery Disease
25	NCA	Normal Coronary Arteries
26	OR	Odds Ratio
27	ROS	Reactive Oxygen Species
28	H2O2	Hydrogen Peroxide
29	IL	Interleukin
30	EPO	Erythropoietin
31	2,3- DPG	2,3-diphosphoglycerate
32	LVH	Left Ventricular Hypertrophy
33	IHD	Ischemic Heart Disease
34	CEM	Cholesterol Erythrocyte Membrane
35	PCI	Percutaneous Coronary Intervention
36	IFN-γ	interferon- Gamma
37	TNF-α	Tumour necrosis factor- Alpha

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