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REVIEW

Red Blood Cell Distribution Width as Novel Biomarker in Cardiovascular Diseases: A Literature Review

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Abstract: Red blood cell distribution width (RDW) is a measure of the change in size of red blood cells and it is used in combination with other hematological parameters for the differential diagnosis of anemias. Recent evidence suggested that the change in RDW level may be a predictive biomarker of morbidity and mortality in cardiovascular diseases (CVDs). Cardiovascular diseases are the most common cause of death globally as compared to cancer and communicable diseases. Early diagnosis and prompt intervention of these diseases are very important to minimize their complications. Nowadays, the diagnosis of most cardiovascular diseases majorly depends on clinical judgment, electrocardiography and biochemical parameters. Red blood cell distribution width as a new predictive biomarker may play a pivotal role in assessing the severity and progression of CVDs. However, the underlying mechanisms for the association between RDW and CVDs are not clear. A deeper understanding of their association could help the physicians in more careful identification, early prevention, intervention, and treatment to prevent adverse cardiovascular events. This review aims to elaborate on the recent knowledge on the association between RDW and cardiovascular diseases and some possible pathophysiological mechanisms.

Keywords: biomarkers, cardiovascular diseases, inflammation, red blood cell distribution width, prognosis

Introduction

Red blood cells (RBCs) are non-nucleated blood cells characterized by having a typical oval biconcave shape, with a diameter of 6 to 8 μm and a thickness of 2 μm. The normal volume of RBCs ranges from 80 to 100 femtoliter (fL), but different physiological and pathological conditions may increase the degree of anisocytosis. The red blood cell distribution width (RDW) is a quantitative measure of variation in the size of circulating RBCs, which is receiving increasing interest as a diagnostic and prognostic marker in a vast array of human disorders.[1] The RDW has been introduced as a novel inflammatory predictor in various disorders including functional bowel conditions,[2] autoimmune diseases,[3,4] malignancy,[5] COVID-19 and multiple hospital admissions in subjects with chronic conditions.[6]

Red blood cell distribution width is calculated automatically by hematological analyzers by simply dividing the standard deviation (SD) of the mean corpuscular volume (MCV) by the MCV and multiplying by 100 to yield a percentage value. Since the methods of measuring the RBC size, the instrument, and statistical methods are varying in many laboratories, there is no established common reference range till now.[7] The normal reference range of RDW most laboratories used is roughly ranging from 11% to 15%.

An RDW value below the reference range has been considered without clinical relevance, whereas an increased RDW value reflects a greater difference in the size of RBCs, which can be due to the presence of smaller or larger RBCs, or both. An elevated RDW usually results from increased or ineffective production of RBCs and excessive fragmentation or destruction of RBCs.[8] Thus, RDW is increased in patients with iron deficiency anemia, megaloblastic anemia, myelodysplastic syndrome, hemolytic anemia, liver failure, sickle cell disease, and blood transfusions.[9] Red blood cell

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distribution width together with MCV has been almost exclusively used for the differential diagnosis of anemias.[1] However, it is almost an unknown parameter to which very few clinicians pay attention when examining blood cell count.

In addition to RBC disorders, various cardiovascular diseases (CVDs) such as heart failure (HF), ischemic cerebrovascular disease (including stroke), acute coronary syndrome (ACS), peripheral artery disease (PAD), hypertension, and atrial fibrillation (AF) are often associated with a high degree of anisocytosis.[10] Since both RDW and cardiovascular conditions are associated with inflammation, RDW could also be associated with CV diseases. Cardiovascular diseases are a diverse group of disorders that affect the heart and blood vessels, and they are mostly interrelated with the underlying pathology of atherosclerosis.[11] Compared to cancer and communicable diseases, CVD continues to be the most common cause of death globally (17.3 million death). Proper risk assessment and stratification, as well as prognosis evaluation for patients with CVDs, are critical to cardiologists. The diagnosis of CVDs mainly depends on clinical judgment, imaging, and biochemical parameters (Troponin, C-reactive protein, B type natriuretic peptide, myoglobin), but biomarkers that could be commonly used in different clinical practices are finite.[12] In addition, noninvasive anatomical and electrophysiological (electrocardiography) cardiac biomarkers are commonly used as surrogate markers of CVDs, especially in its acute phase.[13,14]

The biomarker is defined as a characteristic objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic intervention. Ideal diagnostic biomarkers should be highly specific, sensitive, rapidly available, inexpensive, and noninvasive.[15] Clinicians have been trying for years to search for such a biomarker to aid the identification, early prevention, intervention, and therapy to prevent adverse cardiovascular events. One candidate is RDW, which is widely investigated and routine laboratory value reported as a component of standard complete blood count (CBC) without the need for extra procedures. Nowadays, scientific evidence has shown that RDW may provide valuable information for the diagnosis of different diseases and establishing the short- and long-term prognosis in patients with CVDs.[16] Hence, recent evidence suggested that the change in RDW level may be a predictive marker of morbidity and mortality in CVDs.[17] However, the underlying mechanisms of whether the increased heterogeneity is the cause or consequence of other pathophysiological conditions exceedingly remain unclear. This review aims to elaborate on the recent knowledge on the association between RDW and cardiovascular diseases and some possible pathophysiological mechanisms.

This review was conducted based on the relevant articles published in the English language on the current topic retrieved from electronic databases like PubMed, PubMed Central, ScienceDirect, Google Scholar, and google. Relevant articles were searched by the following words: red blood cell distribution width, cardiovascular diseases, coronary artery disease, myocardial infarction, acute coronary syndrome, heart failure, hypertension, and stroke, separately and in combination. Additionally, reference lists of publications in this field were searched to identify any studies for inclusion and the current review includes original peer-reviewed articles. Also, articles such as reviews, systematic reviews, and meta-analyses were considered.

Red Blood Cell Distribution Width and Cardiovascular Disease

Currently, a number of articles have been published regarding the role of RDW in clinical practice and the risk stratification of patients with CVDs. In this review, the most important and appropriate studies investigating the role of RDW in patients with CVDs are discussed here under and summarized in Table 1.

RDW in Myocardial Infarction

In addition to its routine index in clinical practice, the increased value of RDW has been proposed to be associated with the adverse outcomes of myocardial infarction. A study was conducted by Cemin et al,[18] including 1971 patients admitted due to chest pain with suspected cardiac origin at the emergency department. The authors found that RDW was a significant predictor of acute myocardial infarction (AMI), showing the area under the curve (AUC) of 0.61 (95% CI, 0.54–0.68). The specificity and sensitivity of RDW at the 13.7% cut-off value were 52% and 75%, respectively.[18] In addition, the diagnostic value of joint detection of RDW and homocysteine (HCY) variable coefficient on AMI were investigated by recruiting 400 study subjects (100 healthy and 300 patients with coronary heart disease). Among patients,

Table 1 Summary of Studies Exploring Association Between RDW and CVDs

Author, Year	Study Design	Study Population	Major Findings	References
Felker et al, 2007	Retrospective cohort	2679 chronic HF patients	Higher RDW in patient with CV event than without CV events (15.2 vs 14.4). HR for morbidity and mortality (1 SD increment of RDW): 1.17 (95% CI, 1.10–1.25, p<0.001)	[21]
Dai et al, 2014	Cross-sectional study	521 patients with acute HF	Higher RDW (16.2% vs 14.4%) in acute HF patients at admission were associated with worse short- and long-term outcomes and RDW values were more prognostically relevant than Hgb levels	[22]
Jenei et al, 2014	Prospective cohort study	195 patients with stable chronic HF	RDW >14.5% was independent predictor of 5-year mortality (HR 1 SD increment 1.46, 95% CI 1.221–1.733, p<0.001)	[23]
He et al, 2014	Prospective cohort	128 patients with acute HF	Both RDW and NT-proBNP are strong independent predictors of cardiovascular events	[24]
Liu et al, 2016	Retrospective study	179 chronic HF patients	RDW was markedly elevated in the mortality group compared with the survival group (15.8±1.8 vs 13.7±1.7, p<0.01). RDW was an independent risk factor for mortality (OR=2.531, 95% CI: 1.371–4.671) during hospitalization with AUC = 0.837	[25]
Huang et al, 2014	Meta-analysis of 17 studies	18,288 patients with HF	RDW on admission and discharge, as well as its variation during treatment are prognostic markers in HF patients. In particular, each 1% increase in baseline RDW was associated with a 10% increased risk of all-cause mortality (OR, 1.10; 95% CI, 1.07–1.13).	[26]
Cemin et al, 2011	Prospective study	1971 patients admitted due to chest pain of suspected cardiac origin	Higher RDW value was obtained in patient with AMI compared to without AMI (14.4 vs 13.7) and RDW cut-off value of 13.7% showed a sensitivity and specificity of 75% and 52%, respectively	[18]
Hu et al, 2017	Case–control study	100 healthy and 300 patients with coronary heart disease	Stenocardia 121 cases, HF 65 cases and acute MI 114 cases were found. The result revealed that the RDW and HCY were both significantly higher in acute MI groups than in the 3 other groups	[19]
Lippi et al, 2009	Prospective study	2304 adult patients admitted for chest pain suggestive of ACS	The combined measurement of cardiac troponin T and RDW increases diagnostic sensitivity to 99% in diagnosing ACS (diagnostic sensitivity of cardiac troponin T alone was 94%).	[20]
Söderholm et al, 2015	Prospective study	26,879 participants without a history of coronary events or stroke	High RDW was associated with increased incidence of total stroke (HR for stroke 1.31 (1.11–1.54 the highest quartile compared to the lowest)	[29]
Ramírez et al, 2013	Case-control study	224 patients with ischemic stroke and 224 control subjects	Subjects who have RDW >14·61% were more likely to have a stroke compared with patients with RDW <13·27%, [OR 4·50; 95% CI: 2·50–8·01, P< 0·0001]	[30]
Wan et al, 2015	Prospective study	300 patients with AF	RDW was independently associated with all-cause mortality (HR: 1.024; 95% CI: 1.012–1.036, P <0.001) and major adverse events (HR: 1.012; 95% CI: 1.002–1.023, P=0.023).	[31]

(*Continued*)

Table 1 (Continued).

Author, Year	Study Design	Study Population	Major Findings	References
Ertas et al, 2012	Retrospective	132 patients with no histories of AF undergoing coronary artery bypass grafting	Preoperative RDW levels were significantly higher in patients who developed AF than in those who did not (13.9 ± 1.4 vs 13.3 ± 1.2, p=0.03). Using a cut point of 13.45, the preoperative level correlated with the incidence of AF with a sensitivity of 61% and specificity of 60%.	[32]
Eryd et al, 2014	Prospective study	27,124 subjects from the general population without history of CVDs	HR for incidence of AF was 1.33 [95% CI 1.16–1.53] for the fourth versus first quartile of RDW P <0.001).	[33]
Osadnik et al, 2013	Retrospective	2550 consecutive patients with stable coronary artery disease	4-fold increase (4.3% vs 17.1%, p < 0.0001) in mortality between the group of patients with RDW values <13.1% vs >14.1%). RDW is an independent predictor of mortality in patients with stable coronary artery disease	[34]
Ye et al, 2011	Prospective study	13,039 consecutive outpatients with PAD	Subjects in the highest quartile of RDW (>14.5%) had a 66% greater risk of mortality compared to those in the lowest quartile (RDW <12.8%; P<0.0001). A 1% increment RDW was associated with a 10% greater risk of all-cause mortality (HR: 1.10; 95% CI, 1.08–1.12)	[36]

121 were stenocardia cases, 65 were HF cases and 114 were AMI cases.[19] In this study, the authors found that RDW and HCY were increased in AMI groups than in the three other groups (P<0.05).

Furthermore, a study done by Lippi et al[20] showed that RDW had a diagnostic value in patients admitted to the ICU for chest pain suggestive of ACS. On admission, the sensitivity and specificity of troponin T were 94% (25 false-negative results) and 100%, respectively. With a 14% cut-off value, the sensitivity and specificity of RDW were 79% and 50%, respectively. The measurements of troponin T and RDW help to diagnose MI with greater sensitivity (99%) than the analysis of troponin T alone. This implicated that RDW and other parameters like HCY and troponin T joint detection of AMI has a higher sensitivity and specificity, which may highly improve the accurate diagnosis of MI. However, homocysteine is expensive and not widely available. If the use of RDW in resource poor settings are considered, homocysteine–RDW combination may not be useful.

RDW in Heart Failure

As mentioned earlier, the RDW and anemia relationship has been studied since the sixties. The RDW has also been suggested as a useful tool for predicting morbidity and mortality in patients with acute and chronic heart failure.[21–25] In 2007 Felker et al[21] reported for the first time in two cohorts (n = 2679) of patients with chronic HF. They demonstrated that the RDW was the most powerful predictor of adverse follow-up outcomes, both in cardiovascular mortality and in hospitalizations due to HF. Hazard ratio (HR) for morbidity and mortality (RDW increased in 1 SD): was 1.17 (95% confidence interval [CI], 1.10–1.25, P<0.001).[21] A recent meta-analysis reported by Huang et al[26] showed that RDW is a prognostic marker in HF patients on admission, discharge, and during treatment. A 1% higher RDW in baseline was associated with a 10% increased risk of future mortality events (HR, 1.10; 95% CI, 1.07–1.13). This indicates that 1% increment in RDW during admission can predict the patient's future outcome. Several studies have shown a positive relationship between RDW and different markers that have been applied over the last decade in predictive models of survival for patients with HF including C-reactive protein, in-hospital mortality,[22] hospital readmissions,[23] and type B natriuretic peptide (BNP).[24]

Regarding the latter blood marker highly studied in HF, He et al[24] conducted a prospective study to evaluate the predictive value of RDW for a cardiovascular event during hospitalization of acute HF patients and compared it with that

of NT-proBNP. The main result of this study was a significant weak positive correlation existed between the RDW and NT-proBNP levels (r = 0.217; P<0.05), the cutoff point for NT-proBNP was 1471.5 pg/mL with a 93.5% sensitivity and 32.9% specificity. For RDW, the cutoff point was 14.1%, with 87.0% sensitivity and 54.9% specificity and survival analysis revealed that patients with an RDW level >14.5% and NT-proBNP >1471.5 pg/mL were at the highest risk for cardiovascular event (P<0.001). This investigation suggests that the combination of RDW and other validated biomarkers such as NT-proBNP can help cardiologists improve the accurate rate of diagnosis and reduce misdiagnosis.[24]

RDW in Ischemic Cerebrovascular Disease

A piece of evidence showed that the RDW value is increased in patients with stroke compared to non-stroke patients and is also a significant and independent predictor of both cardiovascular and all-cause mortality in stroke patients.[27] In addition, RDW is associated with the risk of stroke in patients with HF[28] and the general population in the community.[29] Kaya et al compared HF patients with and without stroke, they found that significantly increased basal RDW (16.9 ± 1.14 vs 14.6 ± 1.4, P<0.001). An RDW ≥ 15.2% measured on admission had 87% sensitivity and 74% specificity in predicting stroke in patients with HF (AUC: 0.923, 95% CI: 0.852–0.994, P<0.001).[28]

A population-based study conducted involving 26,879 participants without a history of coronary events or stroke[29] showed that increased RDW was associated with a higher incidence of total stroke. Study participants grouped in the highest quartile of RDW showed a significantly higher incidence of stroke (HR, 1.31; 95% CI, 1.11–1.54). Ramírez et al[30] conducted a case–control study, found that RDW was higher in the stroke group as compared to controls 14.48 ± 1.76 vs 13.9 ± 1.43, P=0.001). Patients in the fourth quartile (RDW>14.61%) were significantly more likely to have a stroke compared with the lower quartile [RDW< 13.27%, odds ratio (OR) 4.50; 95% CI: 2.50–8.01, P< 0.0001]. In summary, these data suggest RDW may be a predictive marker in stroke.

RDW in Atrial Fibrillation

Likewise in patients with other CVDs, an increased RDW is an independent predictor of unfavorable clinical outcomes, such as all-cause mortality and the incidence of major adverse events in patients with AF.[31–33] In brief, Wan et al[31] followed 300 patients with AF and they found that those study subjects in the higher RDW quartile (RDW≥14.4%) had a 13.77% increased risk of mortality as compared to the lowest quartile (RDW<12.8%, P<0.001). In addition, RDW was independently associated with all-cause mortality and major adverse events (HR: 1.024; 95% CI: 1.012–1.036, P<0.001) and (HR: 1.012; 95% CI: 1.002–1.023, P=0.023), respectively. The analysis of receiver operating characteristics (ROC) showed that RDW predicted both mortality and major adverse events with AUC of 0.682 and 0.617; the best cutoff points were 13.85% with a sensitivity of 63.3% and a specificity of 70.4%. And 13.55%, with a sensitivity of 62.0% and a specificity of 60.6%, respectively.[31]

RDW in Coronary Artery Disease

Several studies have shown that the value of RDW is higher in patients with coronary artery disease.[34,35] The study by Osadnik et al[34] analyzed 2550 consecutive patients with stable coronary artery disease (CAD). The patients were grouped by their RDW values at the lower quartile (<13.1%) and higher quartile (>14.1%) and followed for a mean of 2.5 years. During the follow-up, there was an almost fourfold increase (4.3% vs 17.1%, P<0.0001) in mortality between the group. Interestingly, RDW remained significantly associated with mortality in the entire cohort (HR-1.23 [95% CI (1.13–1.35), P<0.0001]) after adjusting for other variables. Additionally, Lapp et al[35] studied 1489 patients with CAD and 449 healthy controls. They reported that RDW strongly predicts all-cause mortality in patients with CAD and the control population (HR=1.37 per quintile; 95% CI=1.29, 1.46; P<0.001) and (HR=1.33 per quintile, CI=1.15, 1.55; P<0.001), respectively. However, highly sensitive C-reactive protein (hs-CRP) did not predict mortality in the control group. Thus, the association of RDW with mortality in patients with CAD may provide potentially useful prognostication.

RDW in Peripheral Artery Disease

Recent studies have shown that the value of RDW is increased in patients with peripheral arterial disease. Ye et al[36] employed an epidemiological study to investigate the prognostic role of RDW in patients with peripheral artery disease

(PAD). In this study, the authors reported that those patients in the upper quartile of RDW (>14.5%) had a 66% higher risk of mortality compared to those in the lower quartile (RDW <12.8%; P<0.0001). One percent increment in RDW was associated with a 10% higher risk of all-cause mortality (HR: 1.10; 95% CI, 1.08–1.12).

RDW in Hypertension

It has been reported that the value of RDW is increased in hypertensive patients. Tanindi et al[37] investigated the role of RDW in apparently healthy individuals (n = 36), prehypertensive patients (n = 74), and hypertensive patients (n = 128). Following adjusting for confounding variables, they found the mean value of RDW was 15.26 ± 0.82 in prehypertensive, 16.54 ± 0.91 in hypertensive, and 13.87 ± 0.94 in control groups (P<0.05). Additionally, RDW showed a strongly positive and statistically significant correlation with systolic and diastolic blood pressures (r=0.848 and r= 0.748, respectively, P<0.01), independent of confounders such as age, inflammatory status, and anemia. Another comparative cross-sectional study conducted by Enawugaw et al[38] showed that RDW increased significantly in hypertensive groups compared to normotensive individuals (P< 0.001).

Pathophysiological Mechanisms

Despite the numerous clinical evidence available, that shows the increase in RDW as a potential biomarker in CVD to be taken into account in the coming years, the underlying pathophysiological mechanisms have not been studied and can generate strong attention in the medical and biomedical community. The main question we can ask ourselves is how a greater heterogeneity of RBC in the blood can directly cause CVD or if this greater heterogeneity is simply an epiphenomenon, secondary to other deleterious processes, previously activated in these pathologies. The existing hypothesis mainly includes the rheological properties of RBCs, microparticles derived from RBCs, anemia, oxidative stress, and inflammatory cytokines (Figure 1).

Rheological Properties of Red Blood Cells

Red blood cells play a major role in humans and are responsible for the transportation of oxygen and carbon dioxide between blood and tissues. The red blood cells perform this activity because of their ability to deform and flow in the vascular system. High deformability that allows red blood cells to flow through microcapillaries that are smaller in size than the cells themselves is attributed to several factors, including cell shape, the viscosity of the intracellular fluid, and rheological properties of the cell membrane.[39] There are many morphological abnormalities that affect the deformability and elasticity of RBCs including drepanocyte (sickle shape RBC), spherocyte and acanthocyte. Sickle cell anemia is a type of inherited hemolytic anemia due to hemoglobin S (Hgb S) variant. In the presence of Hgb S, the morphology of RBCs can be affected which results in less deformable sickle-shaped RBCs.[40] Cardiovascular diseases are common in sickle cell anemia, including cardiac enlargement, myocardial infarction, stroke, and pulmonary hypertension.[41]

Moreover, change in osmolality under some pathological and physiological conditions can affect the deformability of RBCs and microvascular blood flow and result in CVDs eventually.[42] One study shows that RDW values above 14.0% were significantly associated with decreased RBC deformability, which can compromise blood flow through microcirculation.[43] From the perspective of hematology, the predictive role of osmolality in cardiovascular prognostication may be evaluated by the deformability of RBCs, which is assessed by the value of RDW and the resulting hypoxia may be used to explain the higher risk for CVD events related to higher RDW.

In addition, an increased cholesterol erythrocyte membrane level is another cause of decreased membrane fluidity and deterioration of erythrocyte deformability. This can affect the microcirculation, resulting in short survival of circulating erythrocyte, and higher RDW values. In recent studies, a strong and direct relationship was observed between the RDW value and the cholesterol content of erythrocyte membranes (CEM), and the CEM is also positively and independently associated with clinical instability in patients with CVDs.[44,45]

The excess free cholesterol within the necrotic core of atherosclerotic plaque can be derived from different cellular sources, including RBCs.[46] The RBCs entrapped within the atherosclerotic plaque core and directly participate in the accelerated atherogenesis and CVDs through a variety of mechanisms.[47] First, the assembly of free and crystallized cholesterol originating from the RBC membrane promotes the expansion of the lipid core. Second, injury of RBCs

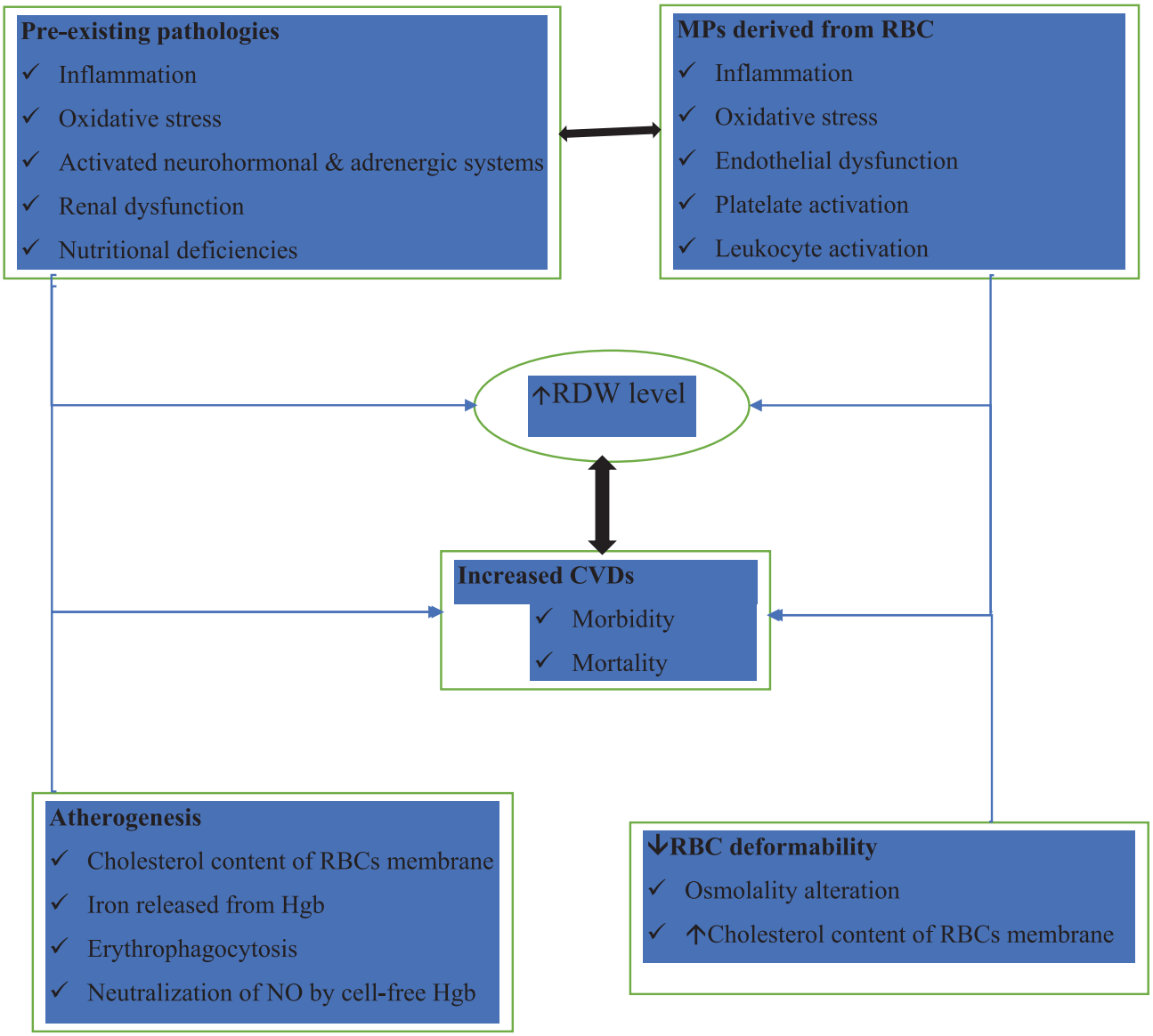

Figure 1 Hypothetical model that would explain the mechanisms for increase in RDW in patients with cardiovascular diseases. All these mechanisms as a whole and separately, would perpetuate deleterious processes that would spread and generate cardiovascular diseases by having a high RDW.
Abbreviations: CVDs, cardiovascular diseases; RBCs, red blood cells; RDW, red blood cell distribution width; Hgb, hemoglobin; NO, nitric oxide; ↓, decrease; ↑, increase.

within the atherosclerotic plaque results in release of iron found in the hemoglobin content that triggers the generation of reactive oxygen species, tissue injury, and activation of many pro-inflammatory cytokine pathways. Third, erythrophagocytosis mediated by the interaction of erythrocytes with scavenger receptors on macrophages and other phagocytes may also amplify the formation of foam cells and facilitate the excrescence of the atherosclerotic plaque. Fourth, the neutralization of nitric oxide by cell-free hemoglobin released from injured erythrocytes inside the necrotic core of the atherosclerotic plaque may also contribute to inhibiting endothelium-dependent nitric oxide-mediated vasodilation.[1,47]

Microparticles Derived from Red Blood Cells

Microparticles (MPs) are active subcellular structures (0.1 to 1 μm), derived from the plasma membrane of different types of cells, mainly platelets, RBCs, monocytes, lymphocytes, neutrophils, and endothelial cells during the processes of cellular activation or apoptosis. Microparticles have various receptors and molecules inside, allowing them to activate

mainly negative processes in other cell groups such as endothelial cells, platelets, and white blood cells.[48] In comparison to healthy individuals, blood levels of MPs derived from RBCs are elevated in patients with CVDs; secondary to nutritional deficiency, pro-inflammatory, and oxidative states, where its excessive increase has been associated with different cardiovascular pathologies.[49] Several research groups have shown that the deleterious participation of MPs in CVDs would be mainly related to their high proinflammatory, prooxidatidant and prothrombotic potential.[48–50] It is possible to propose that there are increased MPs derived from RBCs due to nutritional deficiency, pro-inflammatory and oxidative states, and these MPs once released into the blood can interact directly with processes and cells generating a greater proinflammatory, prothrombotic and oxidative state, which could increase the heterogeneity of RBCs, resulting in a higher RDW, which could be the potential factor in the pathogenesis and poor prognosis in patients with CVDs.

Anemia and Iron Metabolism

Anemia has been recognized as a well-documented risk factor for an increased mortality rate in patients with CVDs including chronic HF and ACS. The potential mechanisms for the development of anemia are multifactorial including inflammation, decreased production of erythropoietin, ineffective erythropoiesis, nutritional deficiencies, and comorbidities (chronic kidney disease, diabetes mellitus). Because many of these mechanisms can cause variation in the size of the erythrocyte, the association between these mechanisms and outcomes can be demonstrated by RDW in an integrated fashion.[51] Most chronic anemias are associated with left ventricular hypertrophy and heart failure. Patients with chronic anemia and hemoglobin <10 g/dL show some hemodynamic compensatory responses like decreased systemic vascular resistance, increased cardiac output, water, and sodium retention, and low renal blood flow and GFR. These responses may cause an increased cardiac workload to maintain sufficient oxygen supply because of an increase in blood volume and consequent left ventricular remodeling.[52]

Red blood cell distribution width is affected by iron metabolism. It is noted that impaired iron metabolism is characterized by the presence of higher RDW, low hemoglobin, low MCV, high erythropoietin, normal iron-binding capacity, and ferritin. It is understood that the ability to mobilize and use stored iron may be impaired even in the presence of sufficient total body iron. This condition is known as "reticuloendothelial block" mediated by overproduction of hepcidin (the master regulator of iron metabolism) in response to inflammatory cytokine (IL-6), which is strongly associated with higher RDW. Also, IL-6 increases the expression of ferritin and iron retention within macrophages, leading to a decreased iron level in the circulation and limited availability of iron for erythroid cells.[53] Studies indicated that increased baseline RDW and MCV has been associated with the formation of anemia during hospitalization in patients with AMI and with normal hemoglobin levels at admission.[54] Furthermore, increased RDW levels increase mortality in patients with cardiovascular disease regardless of the baseline hemoglobin value and RDW has a good prognostic role in non-anemic patients.[34]

Oxidative Stress

Oxidative stress is a condition developed from an imbalance between the formation of free radicals and body antioxidant defenses, resulting in damage to macromolecules (nucleic acids, proteins, and lipids) and tissue injury.[55] It is commonplace in most chronic diseases such as cancer, diabetes mellitus, CVDs, inflammation, liver failure, and chronic kidney disease.[56] Oxidative stress exerts a profound effect on RBC's homeostasis and survival. Some studies show a close association between the increase in RDW and biomarkers of oxidative stress.[57,58] In brief, Az et al showed that the addition of vitamin C (500 mg/day) to 22 soccer players under 25 years of age generated a decrease in RDW levels compared to another group that did not receive vitamin C.[57]

Additionally, Semba et al have reported that a decrease in plasma levels of selenium and carotenoids (potent antioxidants in the blood) was associated with the increase in RDW in 786 women.[58] These studies allow the preliminary hypothesis that oxidative stress can generate changes in the size of the RBCs, increasing its heterogeneity and therefore the RDW. Moreover, smoking can result in increased oxidative stress and higher RDW is correlated with the number of cigarettes smoked per day and the duration of smoking.[59] In addition, it has been recognized that smoking is a well-known risk factor in the development of CVDs including myocardial infarction. Some reports showed a stronger relation

between RDW and myocardial infarction in smokers, which supports the hypothesis that RDW value can reflect inflammation conditions.[60]

Inflammatory Cytokine

Some studies have reported a univariate and multivariate statistical relationship between the RDW with various established systemic inflammatory parameters.[51,61] Lippi et al published for the first time in a cohort of 3845 subjects who were monitored with routine blood count for 3 years, that hsCRP predicted the increase in RDW levels regardless of age, gender, MCV, hemoglobin, and ferritin.[61] Inflammation can increase RDW levels by altering iron metabolism, decreasing RBCs' survival, impairing RBC maturation, and causing immature RBC to enter the peripheral circulation. The production of erythrocytes in bone marrow can be inhibited by proinflammatory cytokines as a result of the blockage of erythroid progenitor cell proliferation and proerythroblast maturation.[51,62]

The chronic inflammatory state is one of the roots of atherosclerosis and resultant complications including CVDs.[63] Cardiovascular disease is accompanied by increased circulating pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which can affect erythropoiesis, reflected by an increase of RDW.[64] The process of such conditions mainly resulted from desensitizing erythroid progenitor cells to erythropoietin (EPO), blocking antiapoptotic and maturation effects of EPO, and decreased renal EPO synthesis by inflammatory cytokines. Additionally, the synthesis of EPO is lower in patients with heart failure and impaired kidney function.[64] An increased RDW value highlights the presence of immature RBC in the peripheral circulation, which could be due to reduced functional iron availability or inhibition in the synthesis or activity of EPO. So RDW may be a representative of an integrative indicator of different pathological processes in CVDs.

Conclusions and Future Directions

Currently,a piece of evidence that supports a higher degree of heterogeneity is common in patients with different CVDs such as stroke, PAD, hypertension, ACS, HF, and AF. A higher RDW value significantly and independently predicts a worse prognosis in patients with CVDs and the general population. As compared to other biochemical parameters in CVDs, RDW is an easily available biomarker as is a rapid and inexpensive test without requiring specialized skills. However, the specificity of RDW is not very high, its high sensitivity and correlation with other biomarkers like NT-proBNP, troponin, HCY, and CRP can support cardiologists in the diagnosis and management of CVDs. Generally, the scientific evidence available so far indicated that the role of RDW may be expanded beyond the routine boundaries of RBC dysfunctions, especially it helps in the diagnosis and prognosis of patients with CVDs. However, an interesting and yet unanswered question exists is the relationship between increased red cell distribution width and CVDs is causal or occurs as a result of the underlying pathophysiological state. As, the data reviewed in this manuscript are preliminary and observational in nature, they cannot investigate the underlying mechanisms. If RDW is considered as a new biomarker and risk factor, it must meet a series of requirements to be recognized such as being modified by the effect of therapies. Future studies should focus on investigating the most precise biological mechanisms that explain this increase seen in clinical practice, how to standardize its determination in a more unified way, and also the evaluation of the RDW and its potential capacity to be modified by the use of therapies.

Abbreviations

ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial infarction; AUC, area under the curve; CAD, coronary artery disease; CBC, complete blood cell count; CEM, cholesterol content of erythrocyte membranes; CI, confidence interval; CVDs, cardiovascular diseases; EPO, erythropoietin; HCY, homocysteine; HF, heart failure; HR, hazard ratio; hsCRP, highly sensitive C-reactive protein; IL-1β, interleukin 1 beta; IL-6, interleukin 6; MCV, mean corpuscular volume; MPs, microparticles; NO, nitric oxide; NT-proBNP; N-terminal pro-B-type natriuretic peptide; OR, odds ratio; PAD, peripheral artery disease; RBC, red blood cell; RDW, red blood cell distribution width; ROC, receiver operating characteristic; SD, standard deviation; TNF-α, tumor necrosis factor-alpha.

Compliance with Ethics Guideline

This review is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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