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The diagnostic and prognostic value of red cell distribution width in cardiovascular disease, current status and prospective

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Running title: RDW as a biomarker in CVD

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Abstract

The red blood cell distribution width (RDW) is an index of the heterogeneity of circulating red blood cell size which along with other standard complete blood count (CBC) parameters is used to identify hematological system diseases. Besides hematological disorders, several clinical studies have shown that an increased in the RDW may be associated with other diseases including acute pancreatitis, chronic kidney disease, gastrointestinal disorders, cancer, and of special interest in this review, cardiovascular disease (CVD). The diagnostic and prognostic value of RDW in different CVD (acute coronary syndrome, ischemic cerebrovascular disease, peripheral artery disease, atrial fibrillation, heart failure, and acute ischemic stroke) has been reviewed in this article, to provide an understanding how its measurement may be applied to improve the management of these conditions.

Keywords: RDW, Biomarker, Cardiovascular diseases

Introduction

Cardiovascular disease (CVD) remains an important cause of mortality, and has a huge burden on health (1) especially in developing countries. Lifestyle and age are two key factors in the development of CVD (2). The incidence of CVDs is increasing worldwide and comprises several specific conditions, that include: ischemic heart disease (IHD), cerebrovascular disease, hypertensive heart disease, peripheral vascular disease, heart failure (HF) and atrial fibrillation (AF) (3). Ischemic heart disease and stroke are currently responsible for most cases of CVD (4). There are multiple risk factors associated with CVD (4), which can be divided into classical risk factors, that have been known for decades (including smoking, diabetes mellitus, hypertension, abnormal lipids and obesity) and novel risk factors (such as C-reactive protein (CRP), cystatin C, homocysteine, adipokines, adiponectin, resistin, osteoprotegerin, genetic factors, and red blood cell distribution width (RDW) (1). Most people at risk have several risk factors and multiple risk factors combination may have a synergistic impact to increase risk of CVD (4, 5).

The RDW is a simple, rapid and easily available assessment measure of RBC size heterogeneity, which can be calculated from the standard deviation (SD) of erythrocyte volumes for the mean corpuscular volume (MCV) (6). The reference range variation is due to difference in the instruments used to measure the RDW (7). However the common minimum and maximum of RDW physiological range are 11% and 15%, respectively (6).

RDW is a routinely reported as a part of complete blood count. Recently, researches has demonstrated possible relations between RDW and many other clinical conditions other than anemia. Different clinical conditions alter RDW in various ways which are mostly provoked by inflammation, nutritional disturbances and alteration in erythropoiesis. Such alteration usually effect bone marrow and erythropoietin hormone. This hormone regulate production, maturation and survival of erythrocytes. Abnormal increase in erythropoietin production will result in increase in RDW (8). Inflammation will inhibit erythropoietin and RBC production as well as reducing the survival rate of RBCs by damaging RBC memberane and increasing fragility because of increased oxidative stress (9). Moreover, deficiencies of iron

(10), vitamin B12 (11), and folate (12) are considered as the main factors which are directly related to the nutritional status. Other clinical conditions which can increase RDW are hemolytic anemia and sickle cell anemia are hematological diseases (7). Moreover, elevated RDW is also observed in non-hematological diseases which mostly interfere with red blood cell production because of alteration in overall inflammatory status. Such changes are seen with inflammatory bowel disease (13), systemic lupus erythematosus (14), hepatobiliary disease (15) and Behçet's disease (7, 16).

There are several studies showing that an increased RDW is related to CVD complications (17, 18). RDW at the upper limit of normal range is associated with a significantly increased risk of CVD and its mortality (19). The exact mechanism behind the relation of RDW values and developing different pathologies are not clearly understood. Anisocytosis can directly affect many clinical conditions including heart failure. High anisocytosis RBCs usually indicated the decreased oxygen capacity. Moreover, abnormal RBCs may participate in development of cardiac fibrosis by amplification of inflammation (20). Such effects will end up in decreased oxygenation many organs including cardiomyocytes and predispose human cardiovascular system to different pathologies including ischemia and organ failure (21). The purpose of this review was to summarize the results of recent studies that have investigated the diagnostic and prognostic value of RDW in CVD.

RDW as a biomarker in coronary artery disease (CAD)

There are several studies investigating the association of increased RDW level with CVD complications. For instance, Lippi et al. assessed 456 acute coronary syndrome (ACS) and 1848 non-ACS patients and reported that median RDW level was significantly higher in ACS patient compared to non-ACS control group. Furthermore, it was shown that the sensitivity of ACS diagnosis could be improved by measuring cardiac troponin T and RDW simultaneously (22). Uyarel et al. investigated the association between the RDW on admission with incidence of in-hospital mortality rate in 2506 patients with ST elevation

myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI). The authors showed that compared with patients with a normal RDW on admission, patients with increased RDW had higher in-hospital mortality rate (23). Interestingly, investigation on 370 patients with STEMI and 156 normal coronary angiographic subjects showed that, in young patients, an increased RDW was associated with STEMI while this association was not observed in elderly patients (24). Furthermore, the RDW was correlated with the number of stenotic coronary artery as well as fragmented QRS in patients with non ST evaluation myocardial infarction (NSTEMI) or unstable angina (UA) (25). Similarly, it has been reported that a high RDW at the time of hospital admission in patients with stable coronary artery disease (SCAD) is associated with an enhanced mortality and incidence of ACS within the subsequent year (26). RDW may also be helpful in evaluation of risk of mortality after ACS (27). Nabais et al. studied 1796 patients with ACS, and showed that increased RDW is an independent risk factor for 6-month mortality or MI in patients with ACS (28). Poludasu et al. studied patients who underwent PCI and showed that an increased RDW was a risk factor for mortality in patients with normal level of hemoglobin at baseline (29). An evaluation of 560 patients with diabetes mellitus and SCAD who underwent PCI showed that there was a significant association between RDW and long-term mortality in these patients (30). Skjelbakken et al. reported a positive association between RDW and risk of MI in the general population. The risk of MI was increased by approximately 13% for every 1% increment in RDW (31). Gul et al. studied 310 patients with UA or NSTEMI and found that the RDW at time of hospital admission was a significant predictor of worse outcomes in these patients and mortality in the next three years was significantly higher in the patients with high RDW level (32). Isik et al. followed up 193 patients who underwent coronary angiography and found that there was a higher RDW in patients who underwent angiography compared with those subjects with normal coronary arteries CAD (33). Dabbah et al. studied 1709 patients with acute MI and results showed that RDW on admission and RDW elevation during the period of hospitalization were associated with poor clinical outcomes and mortality in patients with MI with and without anemia (34). Vaya et al. studied the association between

CVD events recurrence with RDW level in MI patients and found that high level of RDW increased the risk of CVD events by 6 fold. (35). It has been consistently demonstrated that there is an association between high RDW level at the time of hospital admission with high sensitivity C-reactive protein (hsCRP), N-terminal pro-brain natriuretic peptide (NT pro-BNP), presence of more severe coronary arteries lesions and intracoronary thrombotic burden in patients with STEMI who underwent primary PCI (36). In another study, 251 patients who had a bare-metal stent implantation, and who underwent control coronary angiography were investigated by Kurtul et al. to evaluate relationship between in-stent restenosis and level of RDW. They report that RDW level could predict in-stent restenosis before control coronary angiography (37).

Prognostic role of RDW in ischemic cerebrovascular disease

There are several studies investigating the association between RDW and stroke. Söderholm et al. measured RDW in 26879 participants from the general population, without a history of previous stroke or CAD event, and found that subjects who had RDW level in the highest quartile had an increased subsequent incidence of stroke and cerebral infarction. However no significant relationship was found between RDW and cerebral hemorrhage (38). Furthermore, it has been shown that there is a positive correlation between both hs-CRP and RDW with carotid intimal-medial thickness in patients suffering from primary ischemic stroke. This study also suggested RDW may be a predictor of the presence carotid artery atherosclerosis (39). Vayá et al. evaluated the correlation between RDW and stroke in 163 patients hospitalized due to cryptogenic stroke and 186 healthy subjects who were adjusted according to age, sex, anemia, lipid profile and other potential confounders. They found that a high RDW was associated with the increase risk of cryptogenic stroke (40). Moreover, in a study on 847 patients with a first-ever episode of acute cerebral infarction it was found that high value of RDW was correlated with adverse functional outcome (41). Ramírez-Moreno et al. measured the RDW in 224 patients with first-ever ischemic stroke and 224 cases without cerebrovascular disease and found a stepwise association between

RDW levels and risk of cerebral infarction (42). A higher RDW was also observed in 88 stroke patients with a poor Glasgow Coma Scale (GCS), National Institutes of Health Stroke Scale (NIHSS) as well as Canadian Neurological Scale (CNS). This study showed that the RDW may be a biomarker for the prediction of severity and functional outcomes in stroke patients (43). Siegler et al. undertook a retrospectively investigated of RDW in 179 patients with aneurysmal subarachnoid hemorrhage (aSAH) admitted to a neurointensive care unit and found that there is a significant association between elevated RDW level and incidence of cerebral infarction and adverse clinical outcomes after aSAH (44). Kaya et al. showed that in 153 patients with HF who had had a stroke there was a significantly increased baseline RDW in comparison with patients without stroke, suggesting that RDW may be a predictive marker for the incidence of stroke in HF patients. A RDW >15.2% at the time of admission had 87% sensitivity and 74% specificity for stroke incidence in HF patients (45). Taken together, these results support the proposition that RDW could be a useful biomarker for stroke with a reasonable predictive value in these patients.

Role of RDW in peripheral artery disease (PAD) and RDW

There is compelling evidence showing that RDW may be a biomarker of PAD. It has been consistently reported that a high RDW is associated with an increased risk of death in patients suffering from PAD. In these patients, the risk of mortality increased almost 10% for every one percent increment in RDW (46). Zalawadiya et al. measured RDW in 6950 participants from general population and after adjustment for potential confounders they showed that, there is a direct relationship between RDW and prevalence of PAD (47). Demirtas et al. studied 82 PAD patients and showed that RDW increased incrementally with the progression of PAD severity stages (48).

RDW a novel biomarker for atrial fibrillation (AF)

Several studies have evaluated the association between RDW and AF. Ertas et al. studied 132 patients undergoing coronary artery by-pass graft (CABG) and measured AF

before and after surgery in these patients. Pre-operative RDW was significantly lower in patients who developed post-operative AF. However no association was observed between the post-operative RDW value and post-operative AF. Further studies showed that the sensitivity and specificity for prediction of post-operative AF at the level of RDW >13.4% were 61% and 60%, respectively (49). Korantzopoulos et al. have reported that the sensitivity and specificity to predict incidence of AF at the pre-operative level of RDW >13.3% were 80% and 60%, respectively in patients undergoing cardiac surgery (50). Similarly, it has been demonstrated that the RDW was significantly higher in patients with paroxysmal non-valvular AF compared with patients without this. They also reported that RDW of >12.5% had 48% sensitivity and 67% specificity for the incidence of paroxysmal AF (51). Güngör et al. showed patients with AF had a higher RDW compared to the control group, suggesting that increased RDW may be a risk marker for non-valvular AF (52). Adamsson Eryd et al. followed up 27124 participants without a prior history of AF for approximately 13 years, and reported that there was a positive association between RDW and risk of AF in the study group (53). Moreover, RDW was shown to be associated with recurrence of late AF after monitoring 299 patients with AF for a mean of two years(54). To further investigate whether elevated RDW is associated with the mortality rate in AF patients, Wan et al. followed up AF patients for a mean of 3 years and found that increased RDW level was associated with an enhanced mortality rate, and with major adverse events in these patients (55). Kaya et al. studied 619 patients with non-valvular AF and showed that increased level of RDW was associated with both left atrial stasis and thromboembolic events in patients with non-valvular AF (56). These results clearly suggest that RDW could be a valid biomarker for both prognosis and diagnosis in AF patients.

Prognostic and diagnostic value of RDW in Heart failure

In recent years growing evidence suggest that RDW is a key player in increasing risk of incidence and poor prognosis of heart failure (HF). Emans et al. studied 17533 subjects for a mean period of 11 years and found a non-linear association between RDW level and

risk of HF even after adjusting for other risk factors including C-reactive protein, ferritin and iron. They also reported that there was an inverse association between RDW level and physical inactivity, however this association was not correlated with HF (57). Borné et al. studied 26784 healthy subjects with no prior history of stroke, MI, or HF, and followed up them for a mean of 15 years to investigate the association between RDW and long-term incidence of hospitalization for HF. Patients with a high RDW had significantly higher risk of HF incidence, but after adjustment for other risk factors including hs-CRP, N-terminal pro-B-type natriuretic peptide and cystatin C, the significance of the association between RDW and HF incidence was reduced substantially (58). Furthermore, an elevated RDW was shown to be correlated with the increased left ventricular filling pressure in patients with acute HF (59). To further support the clinical significance of RDW in HF patients, Nishizaki et al. evaluated 160 patients who died as a result of HF and found that RDW >16.5% was significantly associated with fatal HF (60). Uemura et al. measured RDW at the time of hospital admission and during hospitalization in patients with acute decompensated HF and reported that the alteration in RDW level during hospital stay, can predict adverse outcomes and all-cause death among patients (61). The results of a meta-analysis of 18288 HF patients showed that level of RDW on admission and discharge, as well as its variation during treatment, can be used as marker to predict prognosis of HF. This meta-analysis also revealed that HF patients with higher RDW had poorer prognosis (62). The RDW can be high in patients who have both HF and diabetes mellitus (DM). Xanthopoulos et al. studied 218 patients with both HF and DM and measured RDW at hospital admission, discharge and after 4, 8, 12 months of discharge. There was an association between RDW on admission and higher incidence of clinical events in diabetic or non-diabetic HF. However, it was shown that RDW one year after discharge was significantly higher in HF patients with DM compared to non-diabetic HF patients (63). It has been demonstrated that increased RDW after 4 days of hospitalization, increased risk of 30-day mortality up to 4-fold in patients with acute decompensated HF, suggesting that these patients with elevated RDW require more care in the first days of hospitalization (64).

Hypertensive heart disease and RDW

Several studies suggested that RDW level is increased in hypertensive patients. Tanindi et al. showed that RDW is increased in pre-hypertensive and hypertensive patients compared with healthy subjects independent of other factors such as age and inflammatory status. Moreover, it has been demonstrated that elevated RDW is strongly associated with systolic and diastolic blood pressures (18). Bilal et al. evaluated 100 hypertensive patients and found that most of these patients had an increased levels of RDW (65). Similarly, Ozcan et al. validated the association between RDW and hypertension in 247 patients with essential hypertension and found that RDW is significantly higher in patients with non-dipper hypertension compared with the dipper hypertensive patients (66). Furthermore, it has been demonstrated that nebivolol, an anti-hypertensive drug, decreased RDW in new essential hypertensive patients, supporting the hypothesis that RDW could be used in clinic as a novel biomarker for evaluating the hypertension-associated complications in cardiovascular disease (67).

Conclusion

Several studies have investigated the relationship of RDW with CVD. RDW either alone or in combination with other cardiac biomarkers may improve diagnosis and assessing prognosis of CVD including ACS, ischemic cerebrovascular disease, peripheral artery disease, atrial fibrillation, heart failure, and acute ischemic stroke. In brief, elevated RDW has unfavorable effects on CVD and is associated with increased risk of incidence, adverse outcome and mortality of CVD. The effects of increased RDW on different type of CVD are showed in Figure 1.

The exact relevant mechanisms are unclear and not yet fully understood (Figure 2). Although RDW may be a biomarker that is rapid and easily available assessment in almost all health facilities and obtained as a part of complete blood count, for evaluating the severity and prognosis of patients with CVDs, further investigations are needed to assess the efficacy as well as accuracy of RDW in CVDs.

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Table and Figure legends

Table 1. RDW: red blood cell distribution width; CAD: coronary artery disease; IHD: ischemic heart disease; ICD: Ischemic cerebrovascular disease; HF: heart failure; MI: myocardial infarction; PCI: percutaneous coronary intervention; ACS: acute coronary syndrome; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; UA: unstable angina; stable coronary artery disease; aSAH: aneurysmal subarachnoid hemorrhage; OSAHS: obstructive sleep apnea hypopnea syndrome; PAD: Peripheral Artery Disease; CABG: coronary artery by-pass graft; AF: atrial fibrillation; hs-CRP: high sensitivity C-reactive protein; DM: diabetes mellitus; ADHF: acutely decompensated HF; HHD: Hypertensive heart disease.

Figure 1. The effects of increased RDW level on different types of CVD, supporting the clinical significance of this molecule in cardiovascular diseases.

Figure 2. Association between increased RDW and CVD.