REVIEW ARTICLE

Red Cell Distribution Width as a Novel Prognostic Marker in Multiple Clinical Studies

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Abstract

Red cell distribution width (RDW), which is a quantitative method applied for the measurement of anisocytosis, is the most reliable and inexpensive method for differentiation of iron deficiency anemia and thalassemia trait. An increase in its rate reflects a great heterogeneity in the size of red blood cells (RBCs). Recent studies have shown a significant relationship between RDW and the risk of morbidity and mortality in patients with multiple diseases. A strong association is established between changes in RDW and the risk of adverse outcome in patients with heart failure in multiple studies. In this review, we try to focus on the association and correlation between the increase in RDW and different outcomes of common diseases that may be related to RDW and based on the results of various studies, we are trying to introduce RDW as a diagnostic indicator for these diseases.

Keywords: Hemoglobin, Prognosis, Red cell distribution width.

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Introduction

Red cell distribution width (RDW) is a convenient and inexpensive measurement of the variation in the size of the erythrocyte and an index of its heterogeneity commonly used in combination with different laboratory tests for the differential diagnosis of hematological system diseases, iron deficiency anemia, and bone marrow dysfunction.[1] The detection of an RDW value below the standard reference value is infrequent and clinically meaningless, whereas values above the normal range mirror the presence of anisocytosis, probably attributable to the presence of small and large red blood cells (RBCs), or both.[2] Recent evidence suggests that RDW values are commonplace in patients with various disorders, especially in those with the most prevalent conditions such as diabetes, cardiovascular diseases (CVDs), infection, and cancer.[3] The value of RDW is now being regarded as a strong and independent risk factor for mortality in the general population.[4] Although it has not been definitely shown whether an increased level of RDW is a risk factor or an epiphenomenon of an underlying biological and metabolic imbalance as an innocent bystander, it seems reasonable to suggest that the assessment of this parameter should be broadened far beyond the differential diagnosis of anemia and should now be regarded as a "non"-innocent bystander.[3,4] This review provides some general information about RDW, its routine assessment, and potential clinical application (Fig. 1).

Age and Sex

There have been some reports regarding the relationship of RDW with age and sex in recent years. The increased heterogeneity of RBC with age can be speculatively[5] related to the decreased erythrocyte deformability. Lippi et al.[6] showed a strong dependence between RDW and age/sex in 1,907 healthy people. They mentioned that the percentage of humans with an RDW of more than 14.6% (as a morbidity and mortality marker in general population[7]) increased from 6% in subjects younger than 41 years old to 75% in subjects older than 90 years old, which has an important implication in clinical practice and research. Results of another study on 809 healthy subjects regarding RDW and sex revealed that women displayed higher median RDW levels compared to men. Considering both sexes, median values for RDW indicated an increasing trend over age. However, a similar trend was only observed in women and not men. Moreover, they showed that a significant positive correlation was observed between RDW and age, which was stronger in women.[8] There are some reports regarding the sex tendency of RDW in different diseases. Qiang et al., for instance, assessed 287 patients with coronary heart disease and reported that RDW significantly increased only in women.[9] As not only RDW but also MCV increases with age, it seems that the age dependency of RDW is a universal biological feature.[10] Thus, future studies are recommended for the assessment of the prognostic accuracy of RDW changes with age for adverse events in clinical conditions (Fig. 1).

Cardiovascular Diseases

Red cell distribution width can also serve as a biomarker and independent risk factor in the diagnosis and prognosis of patients with CVDs.[1] Nevertheless, the mechanisms of the association between RDW and the prognosis of CVDs remain unclear.

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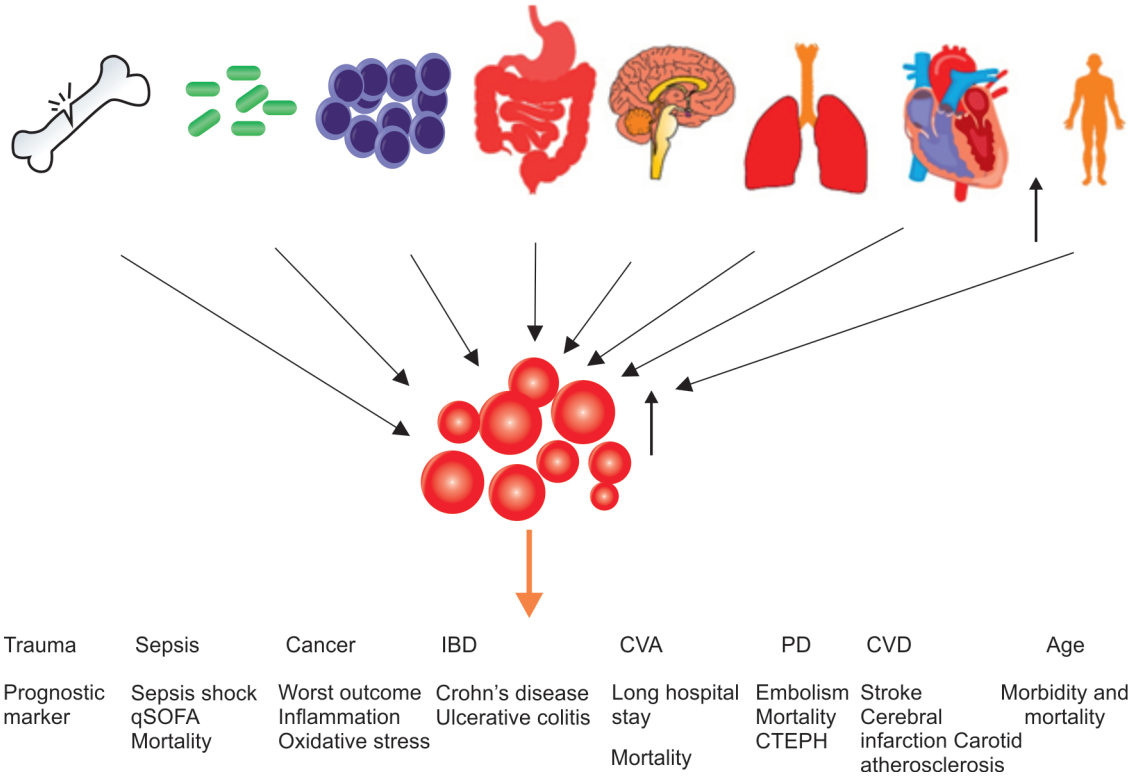

Fig. 1: Schematic diagram represents red cell distribution width (RDW) increases in various diseases and shows that increase in RDW can be an appropriate indicator for differentiation of various diseases: inflammatory bowel disease (IBD), Cardiovascular disease (CVD), pulmonary disease (PD), and cerebrovascular accident (CVA)

Heart Failure

The appropriate and early risk stratification of patients with congestive heart failure (CHF) is crucial for their targeted management, and RDW has gained considerable attention in this regard during the past decade.[11] Felker et al. demonstrated the potential protective function of RDW in patients with CHF for the first time and concluded that the increased RDW value was a strong independent predictor for mortality and morbidity in these patients.[12] Results of another study in 2015 revealed that higher RDW values on admission could predict prolonged hospital stay in patients with CHF.[13] Liu et al. reported that RDW was potential marker for mortality during hospitalization but had a less predictive value compared to NT-pro BNP.[11] Therefore, it seems that a combination of RDW and validated cardiac markers such as NT-proBNP can help the earlier and targeted management of patients with CHF.

Myocardial Infarction

Based on recent trials, higher levels of RDW are proposed to be associated with adverse outcomes in patients with myocardial infarction (MI). Tonelli et al. performed the first study in this field and concluded that patients with a higher RDW value had a totally adjusted hazard ratio for the occurrence of MI and an increased risk for all-cause mortality in patients with coronary artery disease.[14] In another study, 329 patients with ST-elevation MI (STEMI) were divided into two groups with high and low RDW. Multivariate analysis between two groups showed that the cumulative incidence of all-cause mortality was significantly higher in patients with a higher value of RDW.[15] Tuncez et al. recently demonstrated that a cutoff value of more than 13.9 could predict the development of stent thrombosis with acceptable sensitivity and specificity in patients with STEMI undergoing primary percutaneous coronary intervention.[16] In a large prospective trial, the correlation between the first ever event of MI and increased RDW was evaluated on 25,612 subjects. The authors found a linear correlation between RDW and the first event of MI (HR: 1.13; 95% CI, 1.07–1.19) and emphasized that physicians should pay more attention to the predictive value of RDW and other biochemical markers in patients without cardiovascular symptoms.[17] Interestingly, a study in Taiwan found no significant relationship between RDW values and MI occurrence or mortality in patients without a previous CVD.[18] On the other hand, results of a study conducted on Chinese population revealed that Chinese subjects had a lower mortality rate compared to their white and South Asian neighbors.[19]

Based on the mentioned studies, the pathophysiological mechanism for the relationship between RDW and CVD remains unclear. Some have hypothesized that RDW is only a marker reflecting other pathogeneses, including microvascular disorders, anemia, inflammatory cytokines, oxidative stress, free cholesterol, thrombosis, and nutritional deficiency.[20] On the other hand, because of the small sample size of some trials, the heterogeneity of patients, and different study types, these findings need further validation using future trials (Fig. 1).

Acute Pulmonary Embolism

Ozsu et al. evaluated 702 patients with acute pulmonary embolism and showed increased mortality with higher values of RDW. The optimal cutoff value of RDW for predicting in-hospital mortality was ≥15%, and RDW served as a potential marker for mortality

in these patients.[21] Results of another study evaluating 309 patients with pulmonary emboli revealed that RDW is a simple and useful marker for the prediction of 30-day mortality in these patients.[22] The area under the curve for RDW predicting 30-day mortality was 0.6646 (95% CI, 0.5585–0.7518). Furthermore, Abul et al. evaluated the relationship between RDW and the occurrence of chronic thromboembolic pulmonary hypertension (CTEPH) and the important long-term complications of pulmonary thromboembolism, and reported that RDW (hazard ratio: 1.58, 95% CI, 1.09–2.30) was a predictor of CTEPH. Consequently, a high level of RDW may be a good predictor for long-term outcomes in patients with pulmonary embolism.[23] The same results were confirmed in a study performed by Wang et al. on 56 patients with CTEPH and 56 sex- and age-matched healthy controls.[24] In another study conducted on 136 patients with pulmonary embolism, increased RDW (>14.6%) and shock status on the admission time were found to be associated with an increased risk of early mortality in these patients.[25] Based on the mentioned trials, RDW can be a marker for the prediction of long-term outcomes and can also be used in the risk stratification and appropriate management of patients with pulmonary emboli, especially those with unstable hemodynamics on admission. However, future trials are required to confirm these results and approve the routine use of RDW in these patients (Fig. 1).

Cerebrovascular Accident

Lappegard et al. assessed the association of RDW and cerebrovascular accident (CVA) in 25,992 participants. Based on this study, RDW was not associated with an increased risk of death within 1 year or during the entire follow-up period after an incident stroke. Red cell distribution width was associated with incident stroke in the general population, independent of anemia and traditional atherosclerotic risk factors.[26] Feng et al. concluded that RDW was a strong predictor for mortality and the risk of ischemic stroke, but more trials were needed to evaluate and validate the mentioned correlation.[27] Moreover, Pinho et al. in a retrospective cohort study evaluated patients with acute anterior circulation ischemic stroke treated with IV thrombolysis during a 9-year period. Based on their results, RDW could be utilized as a marker for the prediction of 1-year survival in patients with ischemic stroke treated with IV thrombolysis, especially in older patients and those who develop an early infection, and its prediction value was independent of stroke severity and response to IV thrombolysis.[28] Söderholm et al. also found that a high RDW was associated with an increased incidence of total stroke and cerebral infarction, but there was no significant association between RDW and the incidence of intracerebral or subarachnoid hemorrhage.[29] There are also numerous studies suggesting that high RDW levels are associated with increased carotid intima-media thickness and increased risk for preclinical and clinical carotid atherosclerosis.[30,31]

Early detection and intervention for these diseases is vital for delaying their progression and optimal outcome. As a new predictive marker and an independent risk factor, RDW can play a significant role in evaluating the severity and progression of cerebrovascular diseases.

Severe Sepsis and Sepsis Shock

As a prognostic biomarker for sepsis in the form of a routine blood test, RDW may be of considerable clinical importance in sepsis management. A recently conducted study on 117 patients with sepsis showed that RDW was an independent predicting factor for mortality in older patients. In addition, higher RDW levels can be used as a marker for worse outcomes in patients with a quick sepsis related organ failure assessment (qSOFA) of less than 2.[32] Results of some other trials confirmed that RDW could be utilized as a prognostic marker for 28-day mortality, especially in patients with severe sepsis or septic shock.[33,34] There are several trials offering similar results in pediatric patients with sepsis/septic shock.[35,36] Kim et al. examined 329 patients with sepsis and showed that an increase in RDW from baseline during the first 72 hours of hospitalization was significantly related to mortality. Based on the noted trials, RDW might have great importance in differentiating between more severe and less severe cases of sepsis.[37] Moreover, the repeated measurement of RDW during the first 72 hours can be a promising marker for mortality in patients with sepsis. Future studies on larger samples are necessary to confirm these findings.

Patients with Cancer

Elingsen et al. in their meta-analysis showed that there was a dose-dependent relation between RDW and the future risk of malignancy in men and postmenopausal women. This relation disappeared after adjustment for malignancy stage, demonstrating the ability of RDW in the prediction of advanced stages of cancer.[38] There are various meta-analyses reporting the significant relationship of RDW and mortality in different malignancies.[39–41] On the other hand, a recently published review has concluded that, although there is a significant relation between RDW and increased solid and hematological malignancy, after the adjustment of other hematological and inflammatory markers, RDW is not significantly associated with cancer risk and mortality.[42] A recently performed meta-analysis has also reported that elevated RDW is an independent risk factor for the worst outcome in patients with cancer. It seems that the link between RDW and malignancy reflects the role of RDW in inflammation and oxidative stress that are risk factors for cancer.[43] However, further studies are warranted to confirm original findings and explore the underlying mechanism or mechanisms (Fig. 1).

Trauma Patients

Application of a clinical or laboratory marker is important in the initial assessment of patients with trauma for risk stratification and timely and appropriate management. Results of different trials have indicated that the simple and inexpensive RDW could be applied for this purpose in critically ill patients. Lippi et al., for example, showed that patients experiencing trauma had higher levels of RDW compared to healthy individuals, but a significant difference was only seen in patients with head trauma.[44] In another study on 9,538 trauma patients, Majercik et al. reported that RDW could be employed as a prognostic marker in these patients.[45] Furthermore, results of a recently conducted trial on 305 trauma patients admitted to the emergency department indicated that a higher RDW value was an independent predictor of 28-day mortality in patients with suspected severe trauma[46] and serial measurement of RDW was recommended. On the other hand, Sadaka et al. examined 416 patients with traumatic brain injury (TBI) and concluded that RDW on the first day after trauma was not a strong predictor of mortality in these patients.[47] Based on the noted trials, it seems that the serial measurement of RDW in addition to clinical findings and other prediction markers or scores can be performed for mortality prediction in trauma patients, especially those with TBI.

Alzheimer's Disease

A large number of studies have assessed the relationship between RDW and Alzheimer's disease, showing that a higher level of RDW is an independent risk factor for cognitive dysfunction, and concluding that RDW can be incorporated as a marker for Alzheimer's disease severity.[48–51] The suggested mechanisms for this correlation are the association of high RDW values with inflammation, impaired microcirculation, and RBC deformability.[5,14]

Inflammatory Bowel Disease

Based on the results of different studies, a higher RDW value seems to be very specific with a high negative predictive value for the detection of active Crohn's disease. Thus, RDW may prove to be a clinically effective marker in differentiating Crohn's disease from ulcerative colitis.[52,53] Results of two recently conducted studies revealed that RDW was an independent and relatively specific marker of Crohn's disease activity in patients with and without anemia.[54,55] Moreover, Cakal et al. studied 96 patients with inflammatory bowel disease (IBD), concluding that RDW was the most significant indicator of active disease compared to ESR, CPR, fibrinogen, and platelet count.[56] Red cell distribution width, as an inexpensive marker, can be an additional parameter for evaluating disease activity in IBD and an adjunctive test in the differentiation between ulcerative colitis and Crohn's disease.

Red Cell Distribution Width as a Cause or Effect of Different Pathologies

Recent evidence suggests that anisocytosis is associated with various human disorders, complications, and, more importantly, overall mortality in the general population. It is unknown whether the role of RDW in different conditions is only a consequence of other pathophysiological conditions such as renal failure, malnutrition, inflammation, and oxidative stress, or a causative marker.[20] The possible mechanisms for anisocytosis in different disease are listed in Table 1.

Table 1: Possible mechanisms for high red cell distribution width values in different diseases

Effect	*Cause*
General/aging	Cardio/cerebrovascular disease
Shortening of telomeres' length	Free cholesterol
Inflammation	Hypertension
Oxidative stress	Decreased erythrocyte deformity
Venous thromboembolism	Inflammation
Poor nutritional status	Oxidative stress
Malignancy	Anemia
Poor nutritional status	Poor nutritional status
Inflammation	Impaired kidney function
Increased RBC fragmentation	
Diabetes	
Increased cell surface protein glycosylation	
Decreased plasma membrane fluidity	
Dyslipidemia	
Kidney disease	
Increased RBC fragmentation	
Inflammation	
Poor nutritional status	
Vitamin D_3 deficiency	

Red Cell Distribution Width as a Risk Factor for Mortality

There are many studies examining the association of high RDW values with in/out-of-hospital mortality in different populations, concluding that a high value of RDW is a strong and independent predictor of mortality. Researchers suggested that the use of this parameter as an inexpensive prognostic marker in addition to other scores such as APACHE improves the prognostication of patients, especially critically ill ones.[7,57–59]

Conclusion

It seems that this simple and inexpensive test provides valuable information about the general health status, different diseases, clinical outcomes, complications, and mortality, regardless of the underlying disorder. Therefore, patients with increased RDW values should be more closely and intensively managed to improve their clinical outcomes. Dynamic changes of RDW are strong predictors of mortality, suggesting that the continuous monitoring of anisocytosis in addition to other markers/scores can be useful for establishing the effectiveness of targeted care.

The important limitation of RDW assessment is the current lack of assimilation to compare RDW values obtained from different laboratory analyzers, virtually preventing the use of a standard reference range and univocal decision thresholds across clinical laboratories, which must be considered by physicians before making any decision or implementing any intervention.

Another important implication is that the treatment of anisocytosis itself may be a potential target of future therapies. Thus, regardless of whether RDW may be considered as a cause or a simultaneous marker of human disease, future studies should be performed to define the potential therapeutic implications of lowering RDW values in patients with a variety of acute/chronic or subclinical disorders.

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