

Δ RDW: A Novel Indicator with Predictive Value for the Diagnosis and Treatment of Multiple Diseases

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Abstract: Elevated red blood cell distribution width (RDW) is a powerful predictor of poor prognosis in a variety of diseases, but a single measurement of RDW cannot reflect the dynamic change of diseases. Δ RDW, as a risk stratification tool, can be used to record changes in RDW before and after treatment; also, it allows investigators to name the unit change of RDW in the studied population. So far, there have been few relevant studies on the predictive value of Δ RDW for different diseases; this article aims to review the studies and summaries of the current understandings on the correlation between Δ RDW and disease outcomes.

Keywords: red cell distribution width, increment, diagnosis, prognosis

The red cell distribution width (RDW) is one of the parameters included in blood routine test, reflecting the degree of heterogeneity of red blood cell volume in peripheral blood. It has been traditionally used for differential diagnosis of anemia in laboratory tests. Evidence in the past decade attests that an elevated RDW is a common finding in human diseases such as ischemic stroke,¹ Parkinsonism,² pulmonary embolism,³ acute pancreatitis,⁴ acute kidney injury,⁵ sepsis,⁶ hepatitis B,⁷ chronic obstructive pulmonary disease,⁸ as well as in cardiovascular diseases including hypertension, carotid atherosclerosis, heart failure, atrial fibrillation, acute coronary syndrome, and stable angina.^{9–13} But so far, the exact mechanism of RDW abnormalities remains unclear. Previous studies have found that it was relevant to inflammatory responses,¹⁴ tumor necrosis factor α ,¹⁵ and oxidative stress responses.¹⁶ These conditions may influence erythropoietin production and increase RDW values. More recently, Salvagno et al¹⁷ and other scholars have provided a variety of new insights into the factors affecting RDW, such as nutritional deficiency, renal insufficiency, hepatic congestion and so on.

Currently, RDW is regarded as a predictive marker and independent risk factor for the occurrence and development of multiple diseases.^{3,18–20} This observation is based on a single RDW measure; however, there is no sufficient information about the effect of changes in RDW before and after treatment of disease because of a lack of attention and thorough studies. A novel concept reflecting dynamic changes of RDW, Δ RDW has been introduced recently. It can be used not only to record the difference between the baseline RDW value and the one measured at each time point after clinical treatment but also name the unit change of RDW in

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the studied population by investigators. This article reviews the studies on the correlation between Δ RDW and clinical outcomes to provide relevant theoretical guidance for risk stratification and prognosis of different types of diseases.

Δ RDW and Blood Transfusion

Although red blood cell transfusion has been used as a clinical treatment for more than 100 years,²¹ cumulative evidence suggests that the treatment is not entirely harmless while saving lives. In fact, RBC transfusions may be potential confounders on interpretation of RDW changes. Spadaro et al²² found that Δ RDW predicted the effect of blood transfusion in patients to some extent. In this prospective study, RDW's changes were documented in 36 patients (18 with respiratory failure, 9 with sepsis/septic shock, and 9 with heart failure) who were transfused with 1 unit RBC. Twenty-six (72%) of the patients had an increased RDW level immediately after transfusion, and these patients had a higher 28-day mortality than others (11/26, 42% vs 1/10, 10%; $p=0.06$), with the maximum Δ RDWs occurring at 24 hours post-transfusion and remaining high for at least 48 hours. The Δ RDW was here defined as the difference between baseline RDW value and the value at each time point after transfusion. Δ RDW_{max} was 0.55% in average per patient, and moderately correlated with the differences between MCV_{donors} and MCV_{patient} ($r=0.478$, $p=0.005$).

Based on this study, administration of exogenous RBCs can affect RDW. Patients with higher RDW values show higher mortality and transfusion requirements, while transfusion-induced Δ RDW alterations also show prognostic value in critical illness. Patients with normal baseline RDW values had greater changes in Δ RDW and higher survival after transfusion. Those with higher RDW had more minor changes in Δ RDW and higher mortality after transfusion, which should be related to the higher degree of erythrocyte heterogeneity in patients themselves.

Δ RDW and Rheumatoid Arthritis

In a survey study,¹⁵ it was shown that RDW levels were more significantly increased in RA patients, and RDW may be a potential marker for monitoring patients' disease progression compared with inflammation and cytokines. Both inflammatory rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are chronic autoimmune inflammatory diseases, which may be used to partly explain the elevated RDW levels in RA.²³ Another possible reason is

that anemia occurs in approximately 60% of the patients with RA.

By comparing laboratory findings in 222 patients with RA, 150 patients with AS, and 78 patients with osteoarthritis (OA),²⁴ it was found that Δ RDW was more correlated with RA disease activity. The value of Δ RDW in RA patients was significantly greater than in healthy controls, AS, and OA patients. The greater the variation in Δ RDW values is, the higher the risk of RA is.

Δ RDW and Dementia

With the progression of modern medical technology, the average life expectancy of people is prolonged, and the incidence of dementia is also increasing year by year. In a study involving 2556 people older than 65 years,²⁵ participants were regularly tested on RDW. They underwent cognitive assessment by a professional neurologist, including direction, attention, memory, language, and perception testing. A total of 525 (20.5%) people were diagnosed with dementia by the end of the survey cycle. The researchers found that for every additional unit of RDW, the risk of developing dementia increased by about 6% (OR, 1.06; 95% CI: 1.00–1.13). The greater the Δ RDW changes, the greater the prevalence of dementia. Surprisingly, the conventional risk factors such as smoking, alcohol consumption, diabetes, and daily exercise had little effect on dementia. RDW was associated with dementia more strongly among participants without anemia (OR, 1.09; 95% CI, 1.00–1.43) than among those with anemia (OR, 0.99; 95% CI, 0.86–1.18), although this difference was not statistically significant. This demonstrates that Δ RDW may provide new information about the risk of morbidity. Winchester et al²⁶ proposed an inverse relationship between RDW and test results of reasoning and numerical characteristics, that is, RDW increases and cognitive ability decreases. Conversely, RDW will decrease with cognitive improvement, which is consistent with Weuve's view.²⁵ Moreover, as RDW is increased, brain volume tends to decrease,²⁷ which may be the structural basis for pathogenesis of dementia.

The underlying mechanism of Δ RDW abnormalities in dementia remains unclear. To some extent, it may be related to the oxygen-carrying capacity of red blood cells. This difference in capacity is often the result of increased heterogeneity in red blood cell volume, which also triggers cerebrovascular hypoperfusion, leading to oxidative stress, inflammation, and neurodegeneration.²⁷ Clearly, future research should focus on exploring the

causal relationship between dementia and dynamic changes in RDW and underlying mechanisms, and whether intervention with RDW can improve the outcome of dementia.

Δ RDW and Cerebral Infarction

The incidence and mortality of cerebral infarction (CI) have increased significantly. The laboratory results of 392 patients with a primary diagnosis of CI suggested that RDW is an independent protective factor of carotid artery atherosclerosis (CAS) in patients with ischemic stroke.²⁸ Relevant studies by Hasan et al²⁹ revealed that the incidence of CI increased when Δ RDW was positively altered. The prothrombotic state was promoted by activating the renin–angiotensin system via angiotensin II type I α receptors. This process can also boost erythropoietin levels, causing an increase in RDW. It may explain why RDW levels are higher in stroke patients.^{30,31}

Δ RDW and Community-Acquired Pneumonia

Community-acquired pneumonia (CAP) refers to respiratory infection suffered outside the hospital, and some latent pathogen infections can develop within the average incubation period after admission. The disease occurs at a high rate between the ages of 65 and 79.³² It is estimated that in developing countries there are 151 million new episodes annually,³³ and 3.5 million children die each year due to CAP morbidity worldwide.³⁴ In the United States, approximately 20 per 1000 people older than 60 years of age have CAP,³⁵ ranked as the ninth leading cause of death. According to a large-scale population survey study,³⁶ RDW has better sensitivity than CURB-65 score in predicting intensive care unit (ICU) admission rate or mortality in patients with CAP. Lee et al³⁷ retrospectively studied 1069 hospitalized patients with CAP. They calculated the changes in RDW during hospitalization, Δ RDW=(RDW_{Day1}-RDW_{DayN})/RDW_{Day1}×100%, to obtain Δ RDW₂₋₁, Δ RDW₃₋₁, ... Δ RDW_{N-1}, respectively, and followed up to determine 30-day death rate. It was found that patients with RDW \leq 14.8% and Δ RDW₄₋₁ \geq 0.6% showed the longest survival time after standard treatment. At the same level of the Pneumonia Severity Index (PSI), patients with initial RDW \leq 14.8% showed a tendency towards lower mortality than those with RDW >14.8%. In addition, patients with Δ RDW₄₋₁ \geq 0.6% tended to have lower mortality rates than

those with Δ RDW₄₋₁<0.6% at the same level of the PSI and the same initial RDW (initial RDW \leq 14.8%: 6.8% vs 8.6%, $p=0.74$; initial RDW >14.8%: 12.5% vs 36%, $p<0.05$). Following standardized admission, Δ RDW showed a negative change, which can be attributed to the alleviation of inflammation and oxidative stress during the initial treatment of CAP.³⁶ Δ RDW can therefore be used as an independent predictor of short-term mortality in patients with CAP.

Δ RDW and Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a respiratory disease characterized by persistent airflow limitation,³⁸ and the progression of this disease is associated with enhanced chronic inflammatory reflexes. Studies have shown a correlation between dynamic changes in RDW and COPD readmission rates. The 30-day readmission rate was 27.1% in patients with a Δ RDW positive change,³⁹ and significantly higher than that in patients with Δ RDW dynamic reduction (9.7%). Monitoring the trend of Δ RDW can play an essential role in the timely adjustment of COPD treatment options and assessment of prognosis.

Δ RDW and Coronavirus Disease 2019

Coronavirus disease 2019 (COVID-19) is a severe infectious disease, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The global death toll for COVID-19 is about 490 million. Studies of patients with COVID-19 have shown that elevated RDW was correlated with decreased ventilator-free days in the intensive care unit (ICU).⁴⁰ A progressive increase in RDW values was observed with advancing severity.⁴¹ RDW of 13.6% had a sensitivity of 80% and specificity of 59% for predicting mortality, while RDW of 14.5% (optimal cut-point) had a sensitivity of 72% and specificity of 81% for predicting 30-day mortality.⁴² Survival analysis showed that patients with RDW > 13.0% had higher 30-day mortality than patients with lower RDW.⁴³

Patients with increased RDW during hospitalization had higher mortality compared to those with unchanged RDW: for normal RDW patients, mortality rose from 6% to 24%, and for those with elevated RDW on admission, mortality rose from 22% to 40%.⁴⁴ There is a continued relationship between RDW and mortality in all age groups,

each 1% increment in RDW was associated with a 45% relative increase in mortality (HR 1.45, [1.30–1.60]), and that a 1% increase in RDW confers a similar mortality effect to a 10-year increase in age.⁴²

In a case report, the patient's RDW decreased continuously within 14 days of admission and increased gradually.⁴⁵ Statistical analysis results showed that RDW was significantly lower than that of post-treatment.⁴⁶ Whether the dynamic change of RDW is correlated with the progression of symptom severity still needs further study.

Δ RDW and Sepsis with Disseminated Intravascular Coagulation

Sepsis is usually defined as a systemic inflammatory syndrome caused by severe infection. As a marker reflecting the inflammatory process,⁴⁷ RDW can show a significant increase in this disease. Multiple measurements of RDW in ICU patients revealed that RDW was positively correlated with patient mortality on any time point, and patients with a significant ascending trend of RDW in the first 72h of admission were associated with a generally poor prognosis.⁴⁸ Δ RDW plays a positive role in clinical diagnosis and treatment. Coagulopathy may occur in 50% to 70% of the patients with sepsis and is eventually complicated by disseminated intravascular coagulation (DIC) in approximately 35%. The mean value of RDW in the DIC group was significantly higher than that in the non-DIC group (15.73% vs 14.8%, $p < 0.01$). Meanwhile, the mortality rate in the DIC group was much higher than that in the non-DIC group (69.7% vs 30.1%, $p < 0.01$), and the Δ RDW was also significantly different (0.28 vs 0.11, $p < 0.01$).⁴⁹ Δ RDW may be a strong predictor of DIC-related morbidity and mortality in septic patients.

Δ RDW and Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) is a rare condition characterized by sustained elevation in pulmonary vascular resistance leading to right ventricular hypertrophy and end-stage right heart failure.⁵⁰ Excluding the effect of age and gender, each standard unit (1.4%) increase in RDW was related to the 90% higher odds of prevalent PAH.⁵¹ Although an association between Δ RDW and PAH was suggested in this study, no causal relationship between Δ RDW and disease development was observed in the

investigators. It is unclear whether the Δ RDW change occurred due to PAH hemolysis leading to polycythemia or other mechanisms that may have caused the RDW change. This requires further exploration in future studies.

Δ RDW and Diabetes Mellitus

During the past decade, the global prevalence of diabetes mellitus (DM) in the population has remarkably increased due to high intake of high-calorie food and diminished physical activity. RDW has been negatively associated with poor glycemic control.⁵² People with diabetes have distinctly higher RDW values than those without diabetes, each unit increase of RDW represents a 16% higher risk of incident diabetes.⁵³ Higher RDW predicts a higher risk of diabetic complications, such as diabetic ketoacidosis (DKA) or diabetic retinopathy.^{54,55} This was due to the presence of micro- and macro-angiopathy with hyperglycemia that shortens the lifespan of RBCs.⁵² The association between Δ RDW and diabetic complications should be further investigated.

Δ RDW and Cardiovascular Disease

Cardiovascular disease (CVD) is currently the leading cause of premature human death and disability globally, and its incidence is gradually increasing worldwide. In 2016, it was estimated that 17.9 million people died due to cardiovascular causes.⁵⁶ The underlying pathogenesis and progression associated with almost all cardiovascular diseases are mainly due to the formation of atherosclerotic plaques in the coronary arteries, resulting in the development of coronary artery disease (CAD), cerebrovascular disease, venous thromboembolism, and peripheral vascular disease. Pilling et al⁵⁷ obtained ideal laboratory test results for 469,104 participants, who were followed up for a period of 9 years. After excluding 228,627 anemic patients, the remaining 240,477 participants were prospectively analyzed. By the end of the study period, Δ RDW strongly predicted the occurrence of diseases such as CAD (myocardial infarction or angina, $n=5430$), heart failure ($n=963$), hypertension ($n=10,615$), atrial fibrillation ($n=3079$), peripheral vascular disease ($n=728$) and stroke (cerebrovascular disease, $n=1390$), indicating that Δ RDW has a great predictive value in cardiovascular diseases. High RDW ($\geq 15\%$ variation, $n=6050$), compared to low ($< 12.5\%$ $n=20,844$), was strongly associated with mortality (HR 3.10; 95% CI: 2.57 to 3.74), and had 64% increased likelihood of a diagnosis (HR=1.64; 95% CI, 1.49–1.81). Veeranna et al⁵⁸ found that RDW

(>12.6%) was superior to C-reactive protein (CRP) level in assessing CAD mortality within 6 years.

Lee et al⁵⁹ investigated the relationship between changes in RDW after coronary artery bypass graft (CABG) and the risk of postoperative morbidity. A total of 117 subjects were divided into an event-free group (n=79) and event group (n=38) according to the occurrence of early adverse events. The results showed that women had a greater chance of adverse events, and those with adverse events had a lower body surface area; RDW increased significantly after CABG (pretreatment RDW: 13.10±0.95%; post-treatment RDW: 13.42±0.95%); when the Δ RDW cut-off value was equal to 1.45, the specificity for predicting early adverse events after CABG was 78.2%, and the sensitivity was 71.1% ($p<0.001$). In addition, Δ CRP and Δ WBC were not significantly correlated with the occurrence of early adverse events.

In a study of 1242 patients with heart failure (HF), it was found that Δ RDW was lower and stable in patients who survived within 30 days (RDW at admission: 15.3%, RDW after 48 hours: 15.4%, RDW after 96 hours 15.4%), while this value was significantly increased in patients who died at 30 and 60 days (30-day mortality: RDW at admission: 16.3%, RDW after 48 hours: 16.6%, RDW after 96 hours: 17%, $p<0.001$; 60-day mortality: RDW at admission: 16.1%, RDW after 48 hours: 16.3%, RDW after 96 hours: 16.5%, $p<0.001$). Therefore, it could be concluded that Δ RDW was associated with both 30-day and 60-day mortality. It was also confirmed by Kaplan–Meier's survival analysis that both Δ RDW >1% and >0.4% after 96 hours of hospitalization were associated with an increased risk of death at 30 and 60 days of patients.⁶⁰ Heart failure patients with increased Δ RDW during hospitalization had significantly higher all-cause and cardiac-based mortality than patients with decreased levels.⁶¹

In another study, 120 patients with acute myocardial infarction received routine treatment (including sedation, lipid-lowering, fluid infusion, oxygen inhalation, etc) for 1–2 weeks after thrombolytic therapy (including 61 patients with effective treatment and 59 patients with ineffective treatment).⁶² By analyzing RDW levels at admission and the end of the treatment cycle, it was found that the improvement of Δ RDW in the treatment-effect group was more significant than that in the ineffective group. The statistical analysis showed that the negative change of RDW could better reflect the therapeutic effect.

Other studies on cardiovascular diseases are listed below. Patients with decreased RDW or stable downward trend of Δ RDW after cardiac resynchronization therapy (CRT) have a higher possibility of reversing left ventricular (LV) remodeling and survival.⁶³ Geenen et al⁶⁴ found that in patients who had completed atrial septal defect closure (ASD), RDW increased but changed less than high-sensitivity troponin-T (hs-TnT) and high-sensitivity C-reactive protein (hs-CRP) 1 day after ASD was closed. Within 3 months, Δ RDW changed significantly but remained stable within 1 year and did not change significantly again. Possible explanations for this change were as follows: 1) myocardial injury due to device insertion and catheter device, 2) acute large left ventricular volume load due to myocardial injury induced by atrial septal defect closure after shunt cessation.

While many studies suggest a relationship between RDW and CVD, the pathophysiological mechanisms remain unclear. Whether high RDW levels directly affect cardiovascular diseases, or it is just a marker that surrogates something else remains to be answered?

Under certain pathophysiological conditions, changes in permeability reduce RBC deformability, leading to increased RDW levels, which causes low microvascular perfusion and ultimately makes cardiovascular disease more prominent.⁶⁵ Studies have shown that RBC deformability is reduced in microvascular disease when RDW levels exceed 14%.⁶⁶ Chronic inflammation has also been the root cause of atherosclerosis and related complications.⁶⁷ Pathological changes in red blood cell membranes with great free cholesterol can lead to accumulation of red blood cells in atheromatous plaques.⁶⁸ Deposition of free cholesterol from the red blood cell membrane into atherosclerotic plaques will promote atherosclerosis, which propagates through the inflammatory cascade,⁶⁹ thus providing a lipid-rich membrane for foam cells. On the other hand, a higher total cholesterol content in erythrocyte membrane is also one of the reasons for the deterioration of cell deformability, which can directly affect the lifespan of RBCs, and leads to accelerated cell turnover and increased RDW levels.⁷⁰ In addition, alterations in lipids can even reduce the membrane fluidity of RBCs, leading to microcirculatory disturbance. In addition to the above possibilities, various mechanisms such as anemia, oxidative stress, and nutritional deficiency can also make a reasonable explanation.

Summary and Prospect

By univariate analysis, higher RDWs predicted the occurrence of various common diseases and mortality in a group of healthy volunteers. When Δ RDW increases within each interval, the risk of infection also increases. Δ RDW can be chosen as a risk stratification tool to make patients with different RDW to be compared. Accurate risk stratification of the patients can effectively optimize resource allocation, thereby preventing overtreatment of lower-risk patients or inappropriate discharge of higher-risk ones, and ultimately improve clinical outcomes. In conclusion, Δ RDW can be used as a marker of the severity in a variety of diseases and a predictor of comorbidities during hospitalization. And also, Δ RDW may be a useful marker to be included in health assessment (Table 1).

For Δ RDW, it is necessary to study further whether a stable change means a better prognosis. As a new index of risk stratification and prediction, Δ RDW may be more instructive than a single index. A high RDW is also associated with many diseases, such as frailty syndrome, heart valve diseases, acute pancreatitis, Hodgkin lymphoma, and a variety of cancers. However, there are only few studies that have been conducted on the correlation between Δ RDW and clinical diseases by far. To testify whether it can be successfully applied in clinical practice, more large-scale studies are needed. Furthermore, a variety of biological indicators are high at the occurrence of a disease, play a role in the diagnosis of the disease, including white blood cells (WBC),

neutrophil-to-lymphocyte ratio (NLR),⁷¹ platelet-to-lymphocyte ratio (PLR),⁷² C-reactive protein (CRP),⁴⁵ mean platelet volume (MPV),⁷³ fibrinogen,⁷⁴ and platelet distribution width (PDW),⁷⁵ but the relationship between their changing trends has not received much attention.

This article introduces the dynamic changes and clinical significances in RDW of multiple diseases. The final purpose is to discuss whether it can be used for clinical diagnosis and research as an indicator of disease changes in a variety of systemic diseases. At present, the measurement methods of RDW are also different, and the definition criteria of Δ RDW have not been unified. If different centers can provide a unified standard for clinical practice, then the full value of Δ RDW will be given. In addition, it would be helpful if the reference ranges of Δ RDW in different diseases as well as in different ethnic groups could be determined. It is also important and interesting to explore whether Δ RDW can be used as a long-term measure of disease change, similar to the role of glycosylated hemoglobin in assessing recent glycemic control.

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Table 1 Clinical Usefulness of Δ RDW in Human Disorders

| The Unit Change of RDW | Changes in RDW Before and After Treatment |
|---|---|
| <ul style="list-style-type: none"> • Cardiac morbidities • Hypertension • Coronary artery disease • Chronic heart failure • Atrial fibrillation • Anemia • Chronic kidney disease • Chronic obstructive pulmonary disease • Sleep apnea • Diabetes mellitus • Poor cognitive performance • Cerebral infarction • Blood transfusion • Coronavirus disease 2019 | <ul style="list-style-type: none"> • Weight indices after metabolic surgery in patients • Breast cancer • Blood transfusion • Rheumatoid arthritis • Community-acquired pneumonia • Chronic obstructive pulmonary disease • Coronavirus disease 2019 |

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