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Research Article

Red Cell Distribution Width as a Biomarker in Hematological Disorders: Insights and Implications

Nidha Shapoo MD* and Shobhana Chaudhari MD

New York Medical College, Metropolitan hospital, New York

***Corresponding author:** Nidha Shapoo, New York Medical College, Metropolitan hospital, 1901 First Avenue New York.

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Abstract

The Red Cell Distribution Width (RDW) is a marker of heterogeneity in the size and volume of red blood cells and may be used to quantitate the amount of anisocytosis on peripheral blood. Over the last years, RDW has shown multiple clinical implications and has been found to be a prognostic marker in cardiovascular diseases, cancers, infections and autoimmune diseases. Although the role of RDW has extended beyond hematology, it remains one of the simplest and crucial blood parameters to characterize anemia. This article aims to provide an overview of important studies and systematic reviews with meta-analysis, in which RDW has been associated with hematological disorders. According to available data, there is enough evidence to conclude that, apart from classifying anemia, RDW can be used as a prognostic marker in hematological malignancies.

Keywords: Red cell distribution width (RDW), Hematology, Anemia, Leukemia, Lymphoma, Myeloma

Introduction

The Red Cell Distribution Width (RDW) measures the variation in size and volume of red blood cells. The RDW blood test is a component of Complete Blood Count (CBC) and, can be reported statistically as Coefficient of Variation (CV) and/or Standard Deviation (SD), RDW-CV and/or RDW-SD, respectively depending on the types of hematology analyzer instruments. The normal range in adults varies from 12% to 15%. An elevated RDW indicates greater variability in RBC size, called anisocytosis. which generally indicates dysfunctional erythropoiesis, shortened RBC lifespan, or premature release of reticulocytes [1]. RDW has been used historically to evaluate and classify anemia. Recent studies have shown RDW as a prognostic marker in many diseases, including cardiovascular disorders [2,3], cancers [4], chronic liver diseases [5], stroke [6], infections including COVID-19 [7,8] and autoimmune diseases [9,10]. Apart from these, the RDW was found to be a powerful predictor of mortality in older adults with and without age-associated diseases [11]. Several mechanisms are believed to contribute to the possible association of elevated RDW and mortality in various conditions, although the exact mechanism is unknown. The data suggests that elevated RDW may be a marker of inflammation [12,13]. Both inflammation and oxidative stress contribute causing slow development and delayed clearance of erythrocytes leading to increased degree of anisocytosis [14]. Although the role of RDW has extended beyond hematology, it remains one of the simplest and crucial blood parameters to characterize anemia and prognosticate hematological malignancies. Here we summarize the role of RDW in different hematological disorders.

RDW in Nutritional Anemia

Nutritional anemia refers to anemia caused by the deficiencies of iron, vitamin B12 or folate, iron deficiency anemia being the most common. RDW is often used together with Mean Corpuscular Volume (MCV) to determine the possible causes of anemia. In general, RDW is elevated in nutritional anemia. An elevated RDW and decreased MCV (microcytosis) are associated with iron deficiency anemia whereas elevated RDW and increased MCV (macrocytosis) are associated with vitamin B12 and folate deficiency. The RDW often rises before any change in MCV, serving as an early diagnostic clue in nutritional anemia [15].

RDW in Hemoglobinopathies

Hemoglobinopathies are a group of inherited blood disorders affecting the structure or production of the hemoglobin molecule. The most common types are thalassemia and sickle cell disease [16]. Thalassemia results from unbalanced hemoglobin synthesis caused by decreased production of at least one globin polypeptide chain (beta, alpha, gamma, delta). As thalassemia and iron deficiency anemia are the most common causes of microcytic hypochromic anemia, RDW is a useful tool to differentiate between the two. Normal RDW is associated with thalassemia as opposed to elevated RDW seen in iron deficiency anemia [17].

Sickle cell disease is caused by homozygous inheritance of genes for hemoglobin (Hb)S or Hb S beta 0 thalassemia. Patients who are homozygous for Hb S have sickle cell anemia whereas patients who are heterozygous, called sickle cell trait, are not anemic but have a risk of other complications. Sickle cell anemia is a normocytic-normochromic hemolytic anemia, causing hemolysis and Vaso-occlusive crises. Patients with sickle cell anemia have normal MCV with elevated RDW [18].

RDW in Sideroblastic Anemia

Sideroblastic anemias are a heterogeneous group of inherited and acquired anemias resulting from abnormal utilization of iron during erythropoiesis and the presence of ring sideroblasts in the bone marrow. Unlike iron deficiency anemia, where there is depletion of iron stores, patients with sideroblastic anemia have normal to high iron levels [19]. Congenital sideroblastic anemia is usually microcytic, hypochromic anemia but may be normocytic. Acquired sideroblastic anemia is frequently associated with the myelodysplastic syndrome and causes a normocytic or macrocytic anemia. RDW is elevated in patients with sideroblastic anemia. Sideroblastic anemia is suspected in patients with low MCV and high RDW and is differentiated from iron deficiency anemia due to the presence of high serum iron, ferritin, and transferrin saturation [20].

RDW in Myelodysplastic Syndrome

Myelodysplastic Syndrome (MDS) is a heterogeneous group of myeloid neoplasms characterized by the presence of ineffective hematopoiesis and peripheral cytopenia. Patients with MDS are at higher risk of infections, bleeding and transformation to acute myeloid leukemia. Various studies have found RDW as diagnostic as well as prognostic marker in MDS [21-23]. High RDW was used as a marker in diagnosing MDS in patients with unexplained cytopenia in addition to other factors like age, MCV and LDH in a study by *Buckstein, et al* [21]. Other studies by *Baba, et al* and *Turgutkaya A, et al*, found the role of RDW in predicting poor outcome in MDS, the higher values being associated with intermediate and high risk MDS [22,23].

RDW in Acute Myeloid Leukemia

Acute Myeloid Leukemia (AML) is a heterogeneous group of AML sub entities characterized by the clonal proliferation of undifferentiated myeloid precursors, known as blasts, within the bone marrow. This results in ineffective erythropoiesis and megakaryopoiesis leading to rapid bone marrow failure. AML is a rare leukemia, often affects older population and requires intensive chemotherapy. The research in AML has significantly advanced leading to steady improvement in the outlook and prognosis [24]. RDW has been found as an independent prognostic marker in AML [25,26]. In a study by *Vucinic V, et al*, patients with a secondary AML or secondary AML-associated gene mutations had higher diagnostic RDW levels. The presence of a high diagnostic RDW identified patients with worse outcomes, irrespective of the risk classification and the applied consolidation therapy [25]. Liu Q et al, in their study, found that the higher RDW was associated with shorter overall survival and event-free survival in AML. Elevated RDW returned to normal after consolidation therapy, which indicated that leukemia cells resulted in abnormal RDW [26].

RDW in Chronic Leukemia

Chronic Myeloid Leukemia (CML) is a myeloproliferative neoplasm characterized by a balanced genetic translocation, t (9;22) (q34; q11.2) leading to a fusion of BCR-ABL1 genes known as the Philadelphia chromosome. CML is one of the most common leukemias occurring in the adult population. CML is grouped into three phases, namely the chronic phase, the accelerated phase, and the blast phase. With the advent of Tyrosine Kinase Inhibitors (TKIs), CML patients now have a similar life expectancy to people without CML [27]. In various studies, RDW has been found to be a prognostic marker in CML especially in chronic phase [28-30]. A study by *Triyama N, et al*, found that CML patients show anisocytosis at diagnosis, in most cases, that is improved after TKI treatment. The high RDW value was possibly associated with the mutation status other than BCR-ABL1 in CML clones, resulting in poor response to or resistance to TKI treatment. The authors concluded that RDW has a critical role in risk stratification of chronic phase-CML patients for predicting treatment responses and outcomes [28]. Another study by *Mao XL, et al*, found that a high RDW could predict treatment response at 3 months and 6 months. The RDW was significantly lower in patients who achieved molecular response by 3 months and complete cytogenetic response by 6 months than in those who did not respond. High RDW was an adverse predictor of overall survival and progression free survival in patients with chronic phase-CML [29]. Li T et al, concluded from their study that RDW can be used to determine the prognosis, survival outcomes, and advanced phase of CML patients. To avoid chronic phase-CML transforming to advanced phase, patients who have RDW≥16.8% when diagnosed need more time for follow-up [30].

Chronic Lymphocytic Leukemia (CLL) is the most frequently diagnosed leukemia of older patients in Western countries. CLL is an indolent leukemia with a highly variable course and is characterized by lymphocytosis in peripheral blood and bone marrow. The “smudge” cells on peripheral smear are the pathognomic cells of CLL. Most of the patients are asymptomatic at initial diagnosis and are put on observation. The treatment is initiated once there is pro-

gressive or symptomatic disease. Many prognostic factors are used to predict clinical outcome of CLL patients. The clinically important ones relate to the biology of the disease-the mutation status of the variable segment of immunoglobulin heavy chain genes (IgVH), ZAP-70 and CD38 expression as indicators for IgVH mutations, as well as gene and genomic abnormalities. Podhorecka M et al, analyzed the role of RDW as a marker of prognosis in patients with CLL. The elevated RDW level at diagnosis was associated with advanced disease, the presence of other poor prognostic factors and the shorter survival time. However, further studies are required to link the increased RDW with poor prognosis in CLL [31].

RDW in Lymphoma

Diffuse Large B-Cell Lymphoma (DLBCL), a type of non-Hodgkin lymphoma, is the most common form of lymphoma in adults. Great heterogeneity exists in survival for patients with DLBCL. The most used clinical prognostic index in DLBCL is the international prognostic index (IPI) (age>60 years, serum lactate dehydrogenase above the upper limit of normal, Ann Arbor stage III/IV disease, Eastern Cooperative Oncology Group [ECOG] performance status≥2, and>1 site with extranodal involvement), its variants used in elderly patients (age-adjusted IPI) and in patients treated with rituximab (R-IPI). A recent report showed that the (National Comprehensive Cancer Network [NCCN]-IPI) performed best [32]. Various studies reported RDW as an independent prognostic marker in patients with DLBCL. A high RDW predicted an unfavorable prognosis in patients with DLBCL (33-35). *Periša V, et al*, found that the elevated RDW at baseline was associated with poor performance status, advanced clinical stage, higher CRP, and lower albumin [33]. Zhou S et al, found that a high RDW was associated with more frequent B symptoms, a higher IPI score, more extranodal sites of disease, and significantly lower ECOG performance status [34]. *Kamandi N, et al*, found that the elevated RDW was associated with the advanced stage of DLBCL, failure to achieve complete remission, disease relapse, and patient mortality [35]. Hodgkin Lymphoma (HL) is a curable lymphoma characterized by Reed-Sternberg cells inside an inflammatory microenvironment. Standard therapy regimens cure approximately 80% of patients, but the other 20% require salvage therapy. Identifying factors that could improve the early detection of those refractory patients is very important to improve risk stratification and individualize treatment. *Herraez I, et al*, for the first time, explored the role of RDW as a prognostic marker in HL. They found that an elevated RDW identified a group of HL patients having worse outcomes and a higher potential incidence of secondary malignancies [36]. Elevated RDW was also found to predict poor outcomes in other lymphomas like Mantle cell lymphoma and aggressive peripheral T-cell lymphoma [37,38].

RDW in Multiple Myeloma

Multiple Myeloma (MM) is a malignant neoplasm of plasma cells characterized by an excessive production of monoclonal immunoglobulins. The survival of MM patients has significantly improved by the advent of new drugs (proteasome inhibitors and immunomodulatory drugs), autologous stem cell transplantation and CD38 monoclonal antibodies (e.g., Daratumumab). However, it remains an incurable disease due to genetic heterogeneity and other reasons. The Revised International Staging System (R-ISS) is a powerful prognostic staging system commonly used for MM based on International Staging System (ISS), high-risk cytogenetics [t (4;14), t (14;16) and del17p by Interphase Fluorescent in Situ Hybridization (iFISH)] and elevated serum lactate dehydrogenase (LDH) [39]. Recent studies have shown that RDW is a potential prognostic marker in MM. An elevated RDW was strongly associated with advanced ISS staging and predicted poor outcome in MM patients. The possible mechanisms underlying the correlation between elevated RDW and poor prognosis in MM are oxidative stress, chronic inflammation, cellular senescence, and poor nutritional status [40].

Conclusions

RDW, a measure of RBC heterogeneity, is a rapid and inexpensive blood parameter that does not require specific skills or instrumentation. Besides its established value in the differential diagnosis of anemias, RDW has been found to be an independent prognostic factor in patients with lymphoma, leukemia and multiple myeloma. The association of elevated RDW with advanced stages and poor survival outcomes in hematological malignancies is supported by many epidemiological studies.

Acknowledgement

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Conflict of Interest

None.

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