



Red blood cell distribution width—a marker of fundamental importance?

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The full or complete blood count is one of the most frequently requested diagnostic pathology tests which is used to diagnose and treat of many diseases. A common component of these tests is the red cell distribution width or red blood cell distribution width (RDW) which is the variation in the red blood cell (RBC) volumes (usually expressed as the coefficient of variation) and analogous to the qualitative anisocytosis. Red cells can vary in size between 60 fL (microcytosis) and 150 fL (macrocytosis).

The life cycle of circulating RBCs begins when reticulocytes are released from the bone marrow. During their life RBC volume and hemoglobin content will decrease by about 30% (115 fL to a final 80 fL), initially rapidly and then more slowly until the cell is cleared from the circulation by the reticulo-endothelial system. In the 100–120 days RBCs spend in the circulation their hemoglobin will drop by approximately 20% from an initial 35 pg to a final value of approximately 28 pg (1,2). In a typical healthy human adult RBCs enter and leave the circulation at a rate of more than 2 million per second with the clearance process being triggered when a RBC drops to a critical volume though there is some variation about this level (3). Delaying the clearance enables smaller RBCs to continue circulating expanding and extending the low-volume tail of the RBC volume distribution and thereby maintaining hemoglobin longer in the circulation. The effect is to decrease the MCV slightly but also leading to an elevation in the variance of RBC volumes, increasing the RDW (4). Physiological increases in the red cell volumes can occur for a variety of reasons including erythropoietin

deficiency, black ethnicity, physical exercise and pregnancy.

The RDW is a powerful predictor of mortality and morbidity in a broad range of diseases including: cardiovascular disorders (atrial fibrillation, myocardial infarction, coronary artery disease (CAD), artery occlusive disease, cardiac failure, stroke), chronic obstructive pulmonary disease, sepsis, advanced stage and grade for many cancers (colorectal, breast, lung, myeloma and others); development of diabetes, anemia, kidney disease, liver disease [cirrhosis, nonalcoholic steatohepatitis (NASH), acute viral hepatitis], critically ill patients, acute poisoning, trauma, pancreatitis and many more (5–10). The RDW is also powerful predictor of mortality in non-hospitalised older adults with and without age-associated diseases (11). There is also evidence of short term changes in RDW in response to prolonged exercise (12).

The pathophysiologic mechanisms underlying these associations merit investigation. Ycas *et al.* used a large patient medical claims database to identify those diseases where RDW increased within 50 days of diagnosis (13). Their analysis found support to a relationship between hypoxia and increased RDW suggesting that acute hypoxemia-related disease episodes induce changes in RBC size distribution (13). This may explain the ultimate cause but does not shed light on the exact mechanism occurring to increase the RDW.

Higgins and Mahadevan used a statistical dynamics model and standard red-cell indexes to develop an equation which describes the maturation and clearance of circulating red cells (14). The model predicts a threshold for the mean

corpuscular hemoglobin concentration below which most red cells are removed from the circulation. The model was able to distinguish the dynamics of red-cell populations in normal subjects from patients with anemia of chronic disease, iron deficiency, or thalassemia trait. The Higgins and Mahadevan model suggests in these microcytic anemia the persistence of microcytes may be caused by a compensatory delay in RBC clearance. Thus delaying the clearance of RBCs from the circulation is the major cause of the elevated RDW. Further to this work, Patel *et al.* suggested that the RBC clearance rate is carefully controlled in healthy individuals and reduced in many diseases (4). In these conditions this delay in clearance increases the number of smaller RBCs increasing the RDW. The importance of this work is to identify that RBC clearance is a fundamental control point which is adaptable to subtle reductions in erythropoietic output to maintain the circulating red cell mass in a wide range of pathologic conditions. The outcome of reducing the RBC clearance is a slightly increased hemoglobin concentration and greater oxygen delivery to the tissues.

To try and understand other determinants of RDW a genome-wide analysis of associations with RDW was performed to identify biological pathways and overlap with known risk alleles (15). This group also examined associations between RDW and known variant genetic risk score analysis for conditions predicted by RDW, including cardiovascular disease. What they found was that a large proportion of RDW is explained by genetic variants and that RDW was associated with 194 independent genetic signals. These included longevity, age at menopause, bone density, autoimmune disease, certain cancers, body mass index (BMI), Alzheimer's disease, myositis, Parkinson's disease, and age-related macular degeneration. Specific pathway analysis showed enrichment for telomere maintenance, ribosomal RNA, and apoptosis. Although the increased RDW was predictive of cardiovascular disease this was not explained by any known inherited lipid disorders or CVD genetic risk, and a RDW genetic score was not predictive of incident disease. The researchers suggested that the predictive value of RDW for a range of negative health outcomes may be due in part to variants which may influence some fundamental pathways of aging (15).

Most studies involving critical care patients and RDW have focussed on intensive care unit (ICU) admission and clinical outcomes in that setting. In a systematic review of the association of the severity of illness and readmission to ICU Wong *et al.* (16) had found higher mortality and longer

hospital stays. Tonietto *et al.* (17) investigated the use of RDW as a predictor of readmission to ICU or unexpected hospital death after ICU discharge. Identifying patients who are ready for discharge from ICU is difficult and the authors found that an elevated RDW at discharge was predictive of readmission. No matter what the underlying pathophysiological mechanism, a high RDW was able to identify death in the ICU or unexpected death in the ward. Perhaps these readmissions are due to new complications that occurred in the ICU or that continued at the time of discharge making these patients more susceptible to readmission to ICU. The new application further supports the value of RDW as a predictor of poor clinical outcomes in an ever-greater range of conditions and adds to the clinical utility of this previously underutilised biomarker.

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