Red Blood Cell Distribution Width: Clinical Use beyond Hematology

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INTRODUCTION

The complete blood cell (CBC) count is a widely available and commonly used inexpensive laboratory test used in clinical practice. Information contained therein includes the white blood cell count and differential count, red blood cell (RBC) count, RBC indices, hemoglobin level, hematocrit concentration, and platelet count. The RBC indices include the mean cell volume (MCV), mean cell hemoglobin, mean cell hemoglobin concentration, and RBC distribution width (RDW). (1) Traditionally, the clinical use of RDW has been limited to helping differentiate certain types of anemias (eg, β-thalassemia minor and iron deficiency anemia, which can both have decreased MCV and decreased mean cell hemoglobin but will differ in their RDW). (2) During the past decade, this quick and inexpensive test has been the subject of several studies attempting to evaluate its use as, among other things, an inflammatory marker, (3)(4)(5)(6)(7)(8) a predictor of all-cause mortality, (9)(10) and a prognostic tool for morbidity and mortality associated with sepsis and cardiovascular disease. (4)(11)(12)(13)(14)(15)(16)(17)(18)(19)(20)(21)(22)(23)(24)(25) This article focuses on discussing the RDW as a diagnostic and prognostic tool in various medical conditions.

DEFINITION

What Is the RDW?

Each RBC is shaped as a biconcave disk with a depressed center, its volume ranging from 80 to 100 femtoliters (fL; 1 fL = 10^{-15} L) in adults (represented by the MCV in the CBC count). The RBC membrane is extremely flexible and, in certain conditions, is able to change shape (eg, in hereditary spherocytosis or sickle cell disease) and to decrease or increase in size (eg, microcytosis in the thalassemias, macrocytosis in folate deficiency) without significant cell injury or loss in function. Differences in cell volume among the RBCs, or anisocytosis, is reflected in the CBC count by the RDW. It is calculated by dividing the standard deviation of RBC volumes by the MCV and multiplying the result by 100. (2)

Determinants of the RDW

Erythropoietin, a hormone produced in the kidneys, is primarily responsible for RBC production and maturation in the bone marrow and is a major determinant of the RDW. (2) Abnormal production of erythropoietin (eg, in renal disease) and decreased responsiveness to the hormone (eg, in chronic inflammatory conditions and critical illness) can thus lead to an increase in RDW values. (2)(26)(27)(28)(29) Jelkmann (28)

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ABBREVIATIONS

BNP	brain natriuretic peptide
CBC	complete blood cell
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
ESR	erythrocyte sedimentation rate
FMF	familial Mediterranean fever
MCV	mean cell volume
RBC	red blood cell
RDW	red blood cell distribution width

noted that the proinflammatory cytokines interleukin-1 and tumor necrosis factor-α suppress erythropoietin gene expression.

Many of the conditions for which an increase in RDW was correlated are associated with systemic inflammation and critical illness, but the exact pathophysiologic mechanisms underlying the association of increase in RDW with morbidity and mortality remains unclear. (14) Given that erythropoietin is a key determinant of the RDW, it could perhaps be postulated that any condition affecting erythropoietin activity (eg, inflammation, primary renal disease, heart failure, bone marrow failure) could potentially lead to increased RDW values.

Studies in adults by Miyamoto et al (23) and Rodriguez-Carrio et al (30) have found a significant association between RDW increase and elevated levels of proinflammatory cytokines. Miyamoto et al studied 144 patients with adult congenital heart disease and found that elevated RDW of greater than 15% was significantly associated with elevated serum interleukin-6 levels. (23) Rodriguez-Carrio et al found a positive correlation in patients with rheumatoid arthritis between RDW and serum levels of interferon-α, interleukin-8, vascular endothelial growth factor, and neutrophil to lymphocyte ratio. These support the association of RDW increase with not only systemic inflammation but also vascular remodeling. (30)

Another consideration could be poor nutritional status, often present in patients with chronic diseases or critical illness, or nutrient deficiencies (eg, iron, vitamin B_{12}, or folate deficiency) that are associated with anisocytosis. Other physiologic determinants that have been found to be associated with RDW changes include aging, black ethnicity, and physical exercise. (2)

Note that the use of different hematologic analyzers in different laboratories may result in discrepancies in the measurement of RBC size and in the calculation of the standard deviation of RBC volumes, potentially limiting the use of universal reference ranges and thresholds for RDW values. (2) In 1987, Dr Robert Novak reported normal values of RDW in children (Table 1). (31)

TABLE 1. **Age-Appropriate Values for RDW**

AGE	NO. OF PATIENTS	RDW (MEAN ± SD)
1–6 mo	68	13.0 ± 1.5
7–12 mo	84	13.7 ± 0.9
13–24 mo	108	13.4 ± 1.0
2–3 y	119	13.2 ± 0.8
4–5 y	151	12.7 ± 0.9
6–8 y	106	12.6 ± 0.8
9–11 y	98	12.8 ± 1.0

RDW=red blood cell distribution width.

CLINICAL USES OF THE RDW

Table 2 lists the conditions in children where RDW was found to be elevated.

Anemia

The RDW has traditionally been used, along with the MCV, to evaluate anemias based on morphology. (1)(2) Anemias are typically classified as normocytic, microcytic, or macrocytic, depending on their MCV values. Evaluation of the RDW can further narrow down the potential underlying cause of the anemia. Anemias secondary to nutrient deficiencies (eg, iron deficiency, vitamin B_{12} deficiency, or folate deficiency) are typically associated with marked anisocytosis compared with anemias secondary to genetic defects or primary bone marrow disorders, although significant overlap may occur. (2) Sousa et al, (3) for example, studied 34 pediatric patients with Fanconi anemia, a genetic bone marrow failure syndrome, and found a significant increase in RDW in 68% of patients, noting a correlation with anemia, neutropenia, and thrombocytopenia, concluding that significantly increased RDW is associated with progression of Fanconi anemia disease.

Hemolytic anemias, except in acute hemolysis, is associated with anisocytosis (eg, in microangiopathic hemolytic anemia). (1)(2) Sazawal et al (32) studied 1,026 children with iron deficiency anemia, finding that the sensitivity of a combined hemoglobin level of 10 g/dL or less (≤100 g/L) and RDW greater than 15% in diagnosing the disease was 99%, with specificity of 90%. Thus, simply getting a hemoglobin level and evaluating the RDW is a cost-effective way to diagnose iron deficiency anemia in children without the need for further and more expensive testing of iron status markers. (32)

Autoimmune Diseases

Increased RDW has been reported to reflect systemic inflammation. (33) Studies in adults(34)(35)(36) have found a correlation between increased RDW and disease activity in rheumatoid arthritis, proposing that RDW could be used as an inflammatory marker, similar to the more traditionally used erythrocyte sedimentation rate (ESR) and C-reactive

TABLE 2. **Pediatric Conditions Associated with Elevated RDW**

ANEMIAS	AUTOIMMUNE DISEASE	CARDIAC	NEONATES	OTHERS
Anemia associated with nutritional deficiencies (iron, vitamin B_{12}, folate)	Familial Mediterranean fever	Postoperative morbidity and mortality in congenital heart disease	Sepsis	Sepsis[a]
Hemolytic anemia (except acute hemolysis)		Heart failure	Patent ductus arteriosus	Acute appendicitis
Fanconi anemia		Acute rheumatic carditis	Bronchopulmonary dysplasia Early mortality	All-cause morbidity and mortality in critical illness

RDW=red blood cell distribution width.
[a]*Conflicting studies, see Table 3.*

protein (CRP). As mentioned earlier, positive correlations have been reported between increased RDW and levels of certain proinflammatory cytokines. (23)(30)

Ozer et al studied 153 children with familial Mediterranean fever (FMF) to investigate potential markers of subclinical inflammation in these patients. They found that mean ± SD RDW was significantly higher in symptom-free patients with FMF (14.89 ± 2.56) compared with a control group of 90 volunteers (13.68 ± 2.35). (5) A study by Yildirim et al (6) conducted in adults with FMF yielded similar results, with significantly higher RDW levels in symptom-free patients with FMF compared with a control group.

Hu et al (7) noted increased RDW in adult patients with systemic lupus erythematosus, and glucocorticoid treatment decreased RDW values. Zou et al (8) reported significantly increased RDW in patients with active systemic lupus erythematosus disease, irrespective of anemia status, with significantly greater flare-free survival within a year in those with normal RDW. These studies have found various degrees of positive correlation between RDW and ESR, (6)(7) between RDW and CRP, (5)(7) and between RDW and high-sensitivity CRP. (8)

Significantly higher RDW has also been reported in adults with active inflammatory bowel disease compared with those without active disease and controls. (37)(38) Similar observations have been found between increased RDW and disease activity in other autoimmune disorders, including ankylosing spondylitis, (39)(40) primary Sjogren syndrome, (41) polymyositis, (42) and multiple sclerosis. (43)(44)

Sepsis

Elevated RDW has been associated with increased morbidity and mortality in patients with severe sepsis and septic shock. Several adult studies have proposed it as a potentially useful prognostic marker in this population. (13)(14)(15)(33) However, there are few pediatric studies that have evaluated RDW in sepsis, and results have been conflicting.

Chen et al (11) retrospectively studied the relationship of RDW with disease severity and prognosis in 97 newborns admitted for sepsis to a hospital in China. Patients were divided into 3 groups depending on sepsis severity (sepsis group, severe sepsis group, and septic shock group). Significant differences in RDW were found among the 3 groups: mean ± SD RDW in the sepsis group was 16.59 ± 1.71, in the severe sepsis group was 18.88 ± 1.78, and in the septic shock group 19.71 ± 1.97. The mortality rate was higher in those with elevated RDW (defined as RDW >18%) compared with those with normal RDW (91.76% versus 49.32%). Further statistical analysis found a significant positive correlation between RDW values and mortality (Table 3). (11)

In contrast, a cross-sectional Indonesian study by Devina et al (12) found no significant differences in mortality rates between those with elevated RDW (defined as RDW >14.5%) and those with normal RDW in a population of 40 pediatric patients with sepsis (age range, 2 months to 17 years; median age, 34 months) (Table 3). They also did not find a significant association between increased RDW and length of stay in the ICU. (12)

Ramby et al (16) retrospectively studied 596 patients (age range, 1.5–12.9 years; median age, 4.4 years) admitted to the PICU and found that RDW was independently associated with overall PICU mortality (odds ratio, 1.25; 95% confidence interval, 1.09–1.43). An association with sepsis-specific mortality was not studied, but RDW was not

TABLE 3. **Conflicting Studies on the Association of Elevated RDW and Sepsis**

SOURCE	POPULATION	FINDINGS
Chen et al (11)	97 newborns admitted for sepsis to a hospital in China	Increased mortality rate in those with elevated RDW >18%
Devina et al (12)	40 pediatric patients admitted for sepsis (age range, 2 mo to 17 y; median age, 34 mo) in a hospital in Indonesia	No significant difference in mortality rates between those with elevated RDW >14.5% and those with normal RDW No significant association between increased RDW and ICU stay
Ramby et al (16)	596 pediatric patients (age range, 1.5–12.9 y; median age, 4.4 y) admitted to the ICU in a US hospital; 111 with sepsis	No significant association between increased RDW and prolonged ICU stay in patients with sepsis

RDW=red blood cell distribution width.

found to be associated with a prolonged (>48 hours) PICU stay in patients with sepsis. (16) (Table 3)

Cardiac Conditions

Congenital Heart Disease. There are several studies on the association of RDW with surgical outcomes in children with congenital heart disease. Massin (21) studied 688 children undergoing surgery for congenital heart disease and found that RDW was a strong predictor of adverse outcomes in these children, correlating with ICU stay and postoperative death. The mean ± SD preoperative RDW of those who died during their postoperative hospital stay was 18.34 ± 4.68, which was significantly higher than the RDW of those who survived (16.12 ± 2.84). Postoperative death risk was 5 times higher for patients with an RDW of 16% or more. (21) A study by Polat et al (24) had similar results, concluding that RDW could be used as a significant predictor of morbidity and mortality in postoperative patients with congenital heart disease.

Similarly, Kumar et al (20) found that elevated RDW was associated with delayed postoperative recovery in children with tetralogy of Fallot. Those with an RDW greater than 17.8% had significantly longer ICU stays, hospital stays, and ventilation time and more surgical site infections.

Kojima et al, (19) in a study of 38 patients with a Fontan circulation who underwent routine cardiac catheterization, found a strong positive correlation between RDW and central venous pressure and a strong negative correlation between RDW and mixed venous oxygen saturation. In fact, the brain natriuretic peptide (BNP) level, which is a common marker used to monitor heart failure in the pediatric population, was not found to have a significant relation with central venous pressure or mixed venous oxygen saturation, whereas the RDW was found to be a significant independent predictor of these. This highlights the potential of RDW as a convenient and inexpensive marker to detect heart failure in patients with a Fontan circulation.

Acquired Heart Disease. Multiple studies have supported the association of elevated RDW with cardiovascular diseases in adults, including acute coronary syndrome, stroke, peripheral artery disease, atrial fibrillation, heart failure, and hypertension. (17)(45)(46) The lower incidence of cardiovascular diseases in children perhaps explains the relative lack of pediatric studies, but Kucuk et al (4) evaluated RDW in pediatric patients with acute rheumatic carditis. The mean ± SD age of patients in their study was 11.6 ± 2.5 years; RDW was found to be significantly higher in those with acute rheumatic carditis compared with a control group, and significantly decreased (along with CRP level, ESR, and platelet count) after 8 weeks of anti-inflammatory treatment. There was also a significantly positive correlation between RDW and the severity of mitral regurgitation in the patient group. The authors concluded that elevated RDW after initial treatment could indicate ongoing subclinical inflammation, which could lead to subsequent valvular stenosis. (4)

Heart Failure. Forhecz et al (47) found that RDW was an independent predictor of all-cause mortality in adult patients with heart failure. Correlations were found between RDW and levels of serum iron, ferritin, soluble transferrin receptor, interleukin-6, soluble tumor necrosis

factor receptors I and II, CRP, prealbumin, total cholesterol, albumin, and renal function, indicating the association of RDW with inflammation, undernutrition, ineffective erythropoiesis, and impaired renal function. (47)

Mawlana et al (22) studied 31 pediatric patients with heart failure (mean ± SD age, 16.16 ± 14.97 months; 58.1% with congenital heart disease with left-to-right shunts, 41.9% with dilated cardiomyopathy) and found that RDW greater than 16.4% was significantly correlated with certain echocardiographic markers of left ventricular function, such as fractional shortening and E/A ratio, although the same relationship was not present with left ventricular end-diastolic dimension, left ventricular end-systolic dimension, and E/É ratio. (22)

The results of a 2014 systematic review reinforced the value of RDW as a prognostic indicator in patients with heart failure. (18)

Pulmonary Disease

Ozgul et al (48) studied 175 adult patients with chronic obstructive pulmonary disease (COPD) and found that mean ± SD RDW was significantly higher in these patients compared with a control group (15% ± 2.3% versus 13.8% ± 2.5%). In the patients with COPD, RDW was found to correlate positively with CRP, albumin, right ventricular dysfunction, pulmonary hypertension, and the presence of cardiovascular disease. Elevated RDW was independently associated with right ventricular dysfunction. (48) Although COPD is not a pediatric disease, research delving into the potential use of RDW as an inexpensive prognostic marker in pediatric pulmonary hypertension could be helpful. N-terminal proBNP is a commonly used marker to monitor right ventricular dysfunction and heart failure in neonates with pulmonary hypertension, but it is a very expensive laboratory test and is not typically available in smaller hospitals. The previously mentioned study by Kojima et al (19) found RDW to be a significant predictor of central venous pressure independent of the BNP, so further studies into its use in pediatric pulmonary hypertension could be of value.

Other Illnesses

A retrospective study by Ramby et al (16) of 596 critically ill pediatric patients found an association between RDW and prolonged PICU stay in those without sepsis, with a 1.17 increased odds for each 1% increase in RDW. Patients with an RDW less than 13.4% had a 53% risk of a PICU stay greater than 48 hours and a 3.3% risk of mortality, whereas those with an RDW greater than 15.7% had a 78% risk of a PICU stay longer than 48 hours and a 12.9% risk of mortality. (16)

In a study by Garofoli et al, (49) preterm newborns with patent ductus arteriosus, late-onset sepsis, and bronchopulmonary dysplasia were all associated with significantly higher RDW levels compared with preterm newborns without these pathologies. Elevated RDW in preterm newborns and infants with intrauterine growth restriction was also found to be significantly associated with early mortality. (49)

A study by Yilmaz et al (50) found significantly higher RDW levels in adults with preeclampsia compared with controls. The RDW was also significantly higher in those with severe preeclampsia compared with those with mild preeclampsia. Given the increased rates of pregnancy-associated hypertension and eclampsia in teenage pregnancies, monitoring the CBC count and RDW in this population may be useful.

Bozlu et al (51) studied the diagnostic utility of RDW in children with acute appendicitis, retrospectively evaluating 344 children who underwent appendectomy. Children with simple or perforated appendicitis had significantly higher white blood cell counts, CRP levels, and RDW levels than those with a normal appendix, but there was no significant difference in RDW values between those with simple versus perforated appendicitis. The diagnostic utility of RDW in pediatric patients with acute appendicitis was thus concluded to be low because it was not found to be superior to white blood cell count, which is also included in a CBC count; nor was it of value in predicting perforated appendicitis.

Other conditions that have been found to have an association with elevated RDW in adult studies include cancer, diabetes mellitus, kidney disease, liver disease, and complicated community-acquired pneumonia. (2)

CONCLUSIONS

The RDW, as part of the CBC count, is routinely assessed when evaluating anemias. However, as evidenced by recent studies, it may also be an inexpensive method to assess the prognosis and clinical status of critically ill patients, those with inflammatory disorders (eg, FMF), and those with cardiac disease (eg, heart failure,

acute rheumatic carditis, postoperative patients with congenital heart disease), particularly in resource-limited settings. Several studies in adults, and a few in children, have supported the role of an elevated RDW in these conditions. Although the prognostic utility of an elevated RDW in adult patients with sepsis has been substantiated by multiple studies, those performed in children have had conflicting results. Other adult studies have found an association between elevated RDW and cancer, diabetes mellitus, kidney disease, liver disease, and complicated community-acquired pneumonia. Pediatric studies in these areas are currently lacking. Further studies on the diagnostic and prognostic uses of the RDW in different pediatric conditions, particularly those involving infection, inflammation, cardiac, and perhaps cardiopulmonary disease, would be of great benefit.

References for this article are at http://pedsinreview.aappublications.org/content/39/4/204.

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