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The utility of red blood cells distribution width in the diagnosis of iron deficiency anemia in children

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Abstract
Introduction: Children's most prevalent dietary deficit is iron. Anemia affects 25% of the world's population, mostly preschoolers and women, according to the WHO. The aim is to compare red blood cell distribution width to serum ferritin, serum iron, serum total iron binding capacity, mean corpuscular volume, mean corpuscular hemoglobin concentration, and hemoglobin in diagnosing iron deficiency anemia.
Method: Karbala teaching hospital for children did a prospective research. Two hundred children aged 6 months to 5 years with microcytic anemia (mean corpuscular hemoglobin < 80 fl, hemoglobin < 11 g/dl, and serum ferritin < 20 µg/ml) were assessed from January 15, 2011 to January 15, 2012. Iron-treated and blood-transfused patients were excluded. History, clinical examination, complete blood count, red blood cells distribution width, mean corpuscular hemoglobin, concentration, volume, Reticulocyte count percent, hemoglobin electrophoresis, blood film, serum ferritin, serum iron, and serum total iron binding capacity were evaluated. Children were separated into three groups based on hemoglobin levels: mild anemia (hemoglobin=10-10.9 g/dl) (30), moderate (148), and severe (22). Controls were 30 non-iron-deficient children and 30 non-anemic children (hemoglobin > 11 g/dl).
Results: 130 boys (65%) and 70 girls (35%). Anemia severity reduced ferritin. The mean red blood cell distribution width in mild, moderate, and severe iron deficiency anemia was 18.5%, 19.9%, and 22%, respectively. Mean red blood cells distribution width increased with decreased mean (serum ferritin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and mean corpuscular volume), increased with increased mean (serum iron, and serum total iron binding capacity), and was normal (<14%) in control group.
Conclusion: Red blood cells distribution width is highly sensitive and specific diagnostic tool in iron deficiency anemia; especially in medical centers lacking a hematologist to read the blood smear.

Keywords: Iron deficiency anemia, red blood cell distribution Width

Introduction
Iron deficiency (ID) is the most widespread nutritional deficiency among children and leads to iron deficiency anemia (IDA) in severe cases, impacting 9% and 2-3% of toddlers in the U.S., respectively. The prevalence is higher in low-income, Black, Hispanic, and immigrant children due to factors such as obesity, premature birth, low birth weight, and insufficient dietary intake [1]. Iron is primarily bound in heme proteins and is stored in ferritin and hemosiderin, while a small portion is in critical enzyme systems. Its absorption is boosted by ascorbic acid and hindered by substances such as tannates, phosphates, and phytates [2]. Several factors influence infants' iron stores including maternal iron deficiency, prematurity, the administration of erythropoietin (EPO) for anemia of prematurity, fetal–maternal hemorrhage (FMH), twin–twin transfusion syndrome (TTS), insufficient dietary intake, and more [3]. Inadequate iron intake, poor dietary sources, early introduction of cow's milk, and gastrointestinal blood loss due to cow's milk protein-induced colitis are dietary factors contributing to imbalanced iron metabolism. Gastrointestinal diseases, especially those affecting the duodenum, can also cause iron malabsorption [4]. Iron requirements vary with age and fulfilling these requirements is beneficial for infants at risk for ID [5]. Household dietary iron has a significant role in determining the iron status of each family member [6]. IDA can present severe symptoms and impact psychomotor and mental development, potentially contributing to ADHD. Its effects may not be fully reversible, even after ID correction [7].

It is associated with minor to moderate defects in T-lymphocyte function and increased risk of bacterial infection [8], decreased work capacity, and reduced exercise performance [9]. Pica, Pagophagia, and cerebral vein thrombosis are also reported among individuals with IDA [10]. Screening for ID based on dietary risk factors is crucial for effective prevention [11]. For children with IDA, routine screening is recommended at 9-12 months of age, particularly for high-risk groups. The minimum lab screen for IDA is a Hb < 11 g/dl [12]. Further screening methods under consideration include measuring reticulocyte Hb concentration or the combination of serum Hb and soluble transferrin receptor concentration [12]. Treatment of IDA involves oral iron supplementation, dietary modification, and monitoring [13]. Dietary changes include reducing cow's milk intake and increasing consumption of iron-rich foods [14]. A CBC reevaluation is required in 4 weeks, and if Hb increases by 1 g/dl, therapy continues and is retested every 2-3 months [15]. If patients fail to respond, additional tests and possibly screenings for gastrointestinal blood loss are necessary [16]. Parenteral iron therapy and blood transfusions are reserved for severe cases [17]. The aim of study is to critically appraise the diagnostic utility of Red Cell Distribution Width (RDW) in contrast to traditional iron status markers such as Serum Ferritin (SF), Serum Iron (SI), Serum Total Iron-Binding Capacity (STIBC), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin Concentration (MCHC), and Mean Corpuscular Hemoglobin (MCH) in the detection of Iron Deficiency Anemia (IDA).

Method

This investigation was conducted in Karbala Teaching Hospital for Children, located in Karbala, Iraq, spanning from January 15, 2011, to January 15, 2012. The study population consisted of 200 in-patients aged between 6 months to 5 years, admitted to the hospital for various illnesses and presenting with anemia. The subjects under investigation were evaluated for iron deficiency anemia, specified by a Hemoglobin (Hb) level less than 11 g/dl, Mean Corpuscular Volume (MCV) less than 80 fl, and Serum Ferritin (SF) less than 20 µg/dl. A comprehensive clinical history and physical examination were performed for each patient. A survey form was completed detailing the patient's age, gender, residence, feeding type, history of blood loss, blood transfusion, and iron therapy, as well as the presence of other signs and symptoms, including anorexia, pallor, pica, splenomegaly, and koilonychia. The children were categorized into three groups based on their Hb levels: mild anemia (10-10.9 g/dl), moderate anemia (7-9.9 g/dl), and severe anemia (Hb < 7 g/dl). The control group consisted of hematological data from 30 non-anemic children (Hb > 11g/dl) and 30 children without iron deficiency. Exclusion criteria for the study were:

1. Patients currently undergoing iron therapy.
2. Patients who had received a blood transfusion within the past 3 months.

Blood samples were collected in EDTA tubes for hematological investigations, including complete blood count (CBC), reticulocyte count percent, blood film, and Hb-electrophoresis, while plain tubes were used for Serum Iron (SI), Serum Total Iron-Binding Capacity (STIBC), and Serum Ferritin (SF) measurements. The CBC, which involved measurements such as Hb concentration, hematocrit, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Corpuscular Volume (MCV), and Red Cell Distribution Width (RDW), was performed using a Cell-Dyn Ruby device. The machine required 150 microliters of blood and produced results within 5 minutes. Reticulocyte count was determined by smearing a drop of blood on a slide, staining it with reticulocyte stain for 22 minutes, and then evaluated by a hematologist. Hb-electrophoresis was conducted using an Hb-Variant device. The process took 30 minutes and involved aspirating 500 microliters of blood into the machine. For the blood film analysis, a blood drop was smeared on a slide, stained with methylene blue for 15 minutes, and then examined by a hematologist. Serum Ferritin (SF) was measured using a Min-Vids device. It required 100 microliters of clotted blood, which was then centrifuged, with the entire process taking approximately 2 hours. Serum Iron (SI) and Serum Total Iron-Binding Capacity (STIBC) were quantified using a Spectrophotometer (Cecil) device. The device required 500 microliters of clotted blood for each measurement, which was subsequently centrifuged over a period of 2 hours. The accepted range for serum iron in our laboratory is 37-150 µg/dl in females and 59-150 µg/dl in males. All included patients exhibited normal Hb-electrophoresis results, a reticulocyte counts of less than 1%, and hypochromic microcytic blood films.

Results:

Two hundred children included in this study, 130 children (65%) were males and 70 children (35%) were females. One hundred twenty-one children (60.5%) were less than 2 years while 79 children (39.5%) were more than 2 years. The distribution of IDA in rural areas were 102 children (51%) and in urban areas were 98 children (49%). Children with IDA with positive history of pica were 59 children (29.5%) while those with negative history were 141 children (70.5%). As shown in table (1).

Table 1: Distribution of children according to study variables.

Variables		frequency	percentage
Gender	Females	130	65
	Males	70	35
Age	Less than 2 years	121	60.5
	2 years and more	79	39.5
Residency	Rural	102	51
	Urban	98	49
History of Pica	Positive	59	29.5
	Negative	141	70.5

RDW in the current study has a sensitivity of 100% and high specificity with a P value=0.00001.

SF was the gold standard in this study, mean RDW increased with decreased mean SF in children with mild, moderate, and severe IDA. Mean RDW increased with decreased mean MCH in children with mild, moderate, and severe IDA. Mean RDW increased with decreased mean MCHC in children with mild, moderate, and severe IDA. Mean RDW increased with increased mean SI in children with mild, moderate, and severe IDA. Mean RDW increased with increased mean STIBC in children with mild, moderate, and severe IDA. Mean RDW increased with decreased mean MCV in children with mild, moderate and

severe IDA. Mean RDW increased with decreased mean (SF, MCH, MCHC, and MCV), and increased with increased mean (SI, STIBC) as shown in table [2].

Table 2: The relation between RDW with SF, MCH, MCHC, SI, STIBC and MCV in studied patients.

		Mild N=30	Moderate N=148	Severe N=22
RDW	Mean	18.5%	19.9%	22%
	Median	19%	21%	22%
SF	Mean	14.5 µg/dl	11.5 µg/dl	8.8 µg/dl
	Median	14 µg/dl	12 µg/dl	10 µg/dl
MCH	Mean	19.8 pg	19 pg	18pg
	Median	20 pg	19 pg	18 pg
MCHC	Mean	30.4 gm/dl	28.9 gm/dl	28.5 gm/dl
	Median	31 gm/dl	28 gm/dl	29 gm/dl
SI	Mean	34 µg/dl	36.8 µg/dl	40 µg/dl
	Median	34 µg/dl	36 µg/dl	37 µg/dl
STIBC	Mean	425 µg/dl	445 µg/dl	448 µg/dl
	Median	440 µg/dl	442 µg/dl	444 µg/dl
MCV	Mean	64 fl	62.7 fl	59.8 fl
	Median	66 fl	62 fl	60 fl

Discussion

The high prevalence of Iron Deficiency Anemia (IDA) in children necessitates early identification and immediate intervention [18]. Conventional peripheral blood smear examination, while informative, is time-consuming and subject to individual interpretation variations. The Red Cell Distribution Width (RDW) may offer a useful alternative for IDA diagnosis, showing promise in distinguishing IDA from other anemia causes, such as thalassemia trait and chronic disease anemia [19]. Our study aimed to assess RDW's diagnostic efficacy compared to SF, SI, STIBC, MCV, MCH, MCHC, and peripheral smear staining. We found RDW to demonstrate 100% sensitivity with respect to SF, and high specificity in diagnosing IDA when compared to non-anemic controls and other anemia causes. These results align with previous studies such as McClure *et al.* [20], Bessman *et al.* [21, 22], Fairbanks *et al.* [23], which emphasized the high sensitivity of RDW in IDA detection. However, it contradicts studies by Aulakh *et al.* [24], which reported limited RDW specificity or low sensitivity. We found a correlation between RDW increase and IDA severity, aligning with Aulakh *et al.* [24]. Mean RDW increased with decreased mean SF, MCH, MCHC, and MCV, except for mean STIBC, which increased with RDW, resonating with the results of Aulakh *et al.* [24]. Serum iron levels decreased in children with IDA, but without correlation to IDA severity, which could be due to iron mobilization from stores [25]. As such, sole reliance on serum iron estimation in anemia investigation is inadvisable due to confounding factors like inflammation and diurnal variation [26]. Our study sample comprised 65% males and 35% females, with 60.5% children under two years of age, of which 83% were breastfed. This hints at exclusive breastfeeding without iron-rich complementary food or supplemental iron past six months as a potential IDA risk factor. This demographic distribution contrasts slightly with other studies [24]. Our study also found a higher IDA prevalence in children from rural areas, differing from Onyemaobi *et al.* [27]. Pica was observed in 29.5% of children, underscoring it as a potential risk factor for lead poisoning, worm infestation, and IDA [28].

Conclusion

RDW is a low-cost, rapid, highly sensitive, and specific diagnostic tool for diagnosis, and screening of iron deficiency anemia. IDA is common in males, below 2 years, in rural areas, and in exclusively breastfed children.

Conflict of Interest

Not available

Financial Support

Not available

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