Euras J Fam Med 2019;8(3):107-112. doi:10.33880/ejfm.2019080303

A Novel Parameter for Predicting Therapeutic Response in Iron Deficiency Anemia: Red Blood Cell Distribution Width

Aslı Korur, Didar Yanardağ Açık, Soner Solmaz, Çiğdem Gereklioğlu, Süheyl Asma, Hakan Özdoğu

https://doi.org/10.33880/ejfm.2019080303

Original Research / Orijinal Araştırma

AUTHORS / YAZARLAR

Aslı Korur
(*Corresponding Author*)

aslipan@yahoo.com

Department of Family Medicine, Baskent University Faculty of Medicine, Yuregir, 01250, Adana, Turkey
ORCID iD:
0000-0002-5086-5593

Didar Yanardag Acik

Department of Hematology, University of Health Sciences Adana City Hospital, Adana
ORCID iD:
0000-0001-7282-0188

Soner Solmaz

Department of Hematology, Baskent University Faculty of Medicine, Yuregir, 01250, Adana, Turkey
ORCID iD:
0000-0002-1122-7839

Cigdem Gereklioglu

Department of Family Medicine, Baskent University Faculty of Medicine, Yuregir, 01250, Adana, Turkey
ORCID iD:
0000-0003-3556-9865

Suheyl Asma

Department of Family Medicine, Baskent University Faculty of Medicine, Yuregir, 01250, Adana, Turkey
ORCID iD:
0000-0001-5335-7976

Hakan Ozdogu

Department of Hematology, Baskent University Faculty of Medicine, Yuregir, 01250, Adana, Turkey
ORCID iD:
0000-0002-8902-1283

Date of submission
20.05.2019

Date of acceptance
25.09.2019

ABSTRACT

Aim: Anemia is a public health problem worldwide. Cost effectiveness and efficient use of resources are vitally important. Red blood cell distribution width, which can be obtained from a standard complete blood count, is a measure of the variability in size of circulating erythrocytes. The present study was performed to investigate whether red blood cell distribution width can be used to predict response to iron therapy.

Methods: This study was conducted in 50 patients admitted to hematology and family medicine clinics. Complete blood count and reticulocyte count were determined on day 5; complete blood count was examined 1 month after commencement of therapy.

Results: Statistically significant differences were detected between hemoglobin levels and red blood cell distribution width values at the time of diagnosis and on day 5 and after 1 month of therapy. A significant positive correlation was found between the increase in red blood cell distribution width and the increase in hemoglobin.

Conclusion: Red blood cell distribution width may be used in place of reticulocyte count to predict response to iron therapy. Red blood cell distribution width is the best biomarker for this purpose as a component of complete blood count, and therefore it may be accepted as superior to reticulocyte count.

Keywords: iron deficiency anemia, iron, red cell indexes, primary care

Demir Eksikliği Anemisinde Terapötik Yanıtı Tahmin Etmek Için Yeni Bir Parametre: Kırmızı Kan Hücresi Dağılım Genişliği

ÖZ

Amaç: Anemi, dünya çapında bir halk sağlığı sorunudur. Maliyet etkinliği ve kaynakların verimli kullanımı hayati öneme sahiptir. Standart bir tam kan sayımından elde edilebilen kırmızı kan hücresi dağılım genişliği, dolaşımdaki eritrositlerin boyutundaki değişkenliğin bir ölçüsüdür. Bu çalışma kırmızı kan hücresi dağılım genişliği nin demir tedavisine yanıtı tahmin etmek için kullanılıp kullanılamayacağını araştırmak için yapıldı.

Yöntem: Bu çalışma hematoloji ve aile hekimliği kliniğine başvuran 50 hastada yapıldı. Tam kan sayımı ve retikülosit sayısı 5. günde; tam kan sayımı ve kırmızı kan hücresi dağılım genişliği tedavinin başlamasından 1 ay sonra incelenmiştir.

Bulgular: Hemoglobin düzeyleri ile kırmızı kan hücresi dağılım genişliği değerleri arasında tanı anında ve 5. günde ve 1. ayda tedavide istatistiksel olarak anlamlı fark bulundu. Kırmızı kan hücresi dağılım genişliğideki artış ile hemoglobindeki artış arasında anlamlı bir pozitif ilişki bulundu.

Sonuç: Demir terapisine cevabı tahmin etmek için retikülosit sayısı yerine kırmızı kan hücresi dağılım genişliği kullanılabilir. Kırmızı kan hücresi dağılım genişliği, tam kan sayımının bir bileşeni olarak bu amaç için en iyi biyobelirteçtir ve bu nedenle retikülosit sayısından daha üstün olarak kabul edilebilir.

Anahtar kelimeler: demir eksikliği anemisi, demir, eritrosit göstergeleri, birinci basamak

How to cite / Atıf için: Korur A, Yanardağ Açık D, Solmaz S, Gereklioğlu Ç, Asma S, Özdoğu H. A novel parameter for predicting therapeutic response in iron deficiency anemia: red blood cell distribution width. Euras J Fam Med 2019;8(3):107-112. doi:10.33880/ejfm.2019080303

Conflict of interest: No conflict of interest was declared by the authors.
Financial disclosure: No financial disclosure was declared by the authors.

Introduction

Anemia, defined as a low blood hemoglobin (Hb) concentration, is a public health problem worldwide, and is associated with significant adverse health outcomes and adverse impacts on social and economic development. Approximately 50% of anemia cases are considered to result from iron deficiency. Iron deficiency anemia (IDA) is the most common type of anemia, and can be easily managed and followed up (1). Several biomarkers, including reticulocyte count, reticulocyte Hb content (CHr), and reticulocytes in a high fluorescence intensity region (HFR), may be used to predict the response to iron therapy. However, these tests may be expensive and may not be available in all settings (2,3).

Red blood cell distribution width (RDW), obtained from a standard complete blood count (CBC), is a measure of the variability in size of circulating erythrocytes and is indicated as the coefficient of variation of erythrocyte size. Extensive RBC size heterogeneity, which is observed as anisocytosis in peripheral blood smears, reflects elevation of RDW values in a blood count.

In addition to its use in hematology, RDW can be used to diagnose mild and moderate IDA (4), to distinguish thalassemia traits from iron deficiency (5–8), to establish the cause of microcytic hypochromic anemia, to measure the severity of iron deficiency (9–15), and to predict cardiovascular and cerebrovascular diseases, inflammatory bowel diseases, and sepsis (16–20). RDW was reported as a useful new parameter for laboratory diagnosis of IDA (21).

Cost effectiveness and efficient use of resources are vitally important in primary care practice. Family physicians are in a unique position to detect the priorities for health care services and use resources through collaboration with patients in the context of gradually increasing health care expenditures (22).

In addition to already being elevated in IDA, we have observed a further increase in RDW after iron therapy. Another study investigating the fluctuating course of RDW in IDA concluded that this elevation is due to normocytic erythrocytes after the initiation of iron therapy (23). Despite the widespread use of RDW for diagnostic purposes, limited data are available regarding its use in monitoring the course of therapy. Therefore, the present study was performed to investigate whether RDW, which is an inexpensive and readily available parameter within CBC, can be used to predict response to iron therapy.

Methods

This was a prospective, cross-sectional study conducted in 50 female patients, all of whom had been admitted to hematology and family medicine clinics between March 1, 2017 and April 30, 2017, were started on iron therapy due to IDA, and agreed to participate in the study. Exclusion criteria were continued blood loss, poor compliance with medication for any reason, thalassemia, folate and/or vitamin B12 deficiency, chronic disease anemia, gastrointestinal intolerance, malignant diseases, and thyroid dysfunction.

CBC, serum iron, serum total iron binding capacity (TIBC), serum ferritin, transferrin saturation index (TSI), thyroid stimulating hormone (TSH), and serum vitamin B12 and folate levels were examined at the time of diagnosis. Treatment was started with 80–160 mg of elemental iron, equivalent to 270–540 mg of ferrous sulfate/day. CBC and reticulocyte count were measured on day 5, and CBC, serum iron, serum total iron binding capacity, serum ferritin level, and transferrin saturation index (TSI) were examined 1 month after commencement of therapy.

Statistical analysis was performed using SPSS (Version 17.0; SPSS Inc., Chicago, IL, USA). Continuous variables with a normal distribution are presented as the means±standard deviation ($P<0.05$ in Kolmogorov–Smirnov test or Shapiro–Wilk test, $n<30$). Continuous variables without a normal distribution are presented as medians. Pre-post measures data were analyzed using the paired t-test or Wilcoxon's test.

Correlations were examined by Spearman's correlation test. Spearman's correlation coefficients were interpreted as excellent: $r \geq 0.9$; good: $0.90 > r \geq 0.70$; fair $0.70 > r \geq 0.50$; weak: $0.50 > r \geq 0.30$; or little or none: $r < 0.3$. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

This study was approved by Baskent University Institutional Review Board and Ethics Committee (No: KA16/310) and supported by Baskent University Research Fund.

Results

The mean age of the 50 patients included in the study was 36.9±9.3 years (range 18–55). Laboratory values of patients at baseline, day 5, and 1 month are presented in Table 1. Significant differences were detected between hemoglobin (Hb1) and RDW (RDW1) values at the time of diagnosis and those at day 5 (Hb2, RDW2) and at 1 month (Hb3, RDW3) ($P < 0.0001$ for both) (Figures 1 and 2).

Table 1. CBC values at baseline, day 5, and 1 month

	Baseline (mean±SD)	Day 5 (mean±SD)	1 month (mean±SD)	P-value
Hb (g/dL)	8.6±1.5	9.6±1.6	11.4±1.3	<0.0001
Hct (%)	29.3±4.2	32.3±4.4	36.9±4.3	<0.0001
MCV (fL)	68.3±8.0	72.5±7.6	78.3±6.0	<0.0001
RDW (%)	18.7±2.3	22.4±4.6	26.7±5.4	<0.0001
WBC ($\times 10^3/\mu L$)	6.9±2.6	7.1±2.3	7.2±1.6	<0.0001
Plt ($\times 10^3/\mu L$)	379.4±454.1	307.8±95.4	284.2±88.5	<0.0001
Serum iron (µg/dL)	21.0±29.0		48.1±48.4	<0.0001
TIBC (µg/dL)	436.7±65.9		321.9±78.2	<0.0001
Serum ferritin (ng/mL)	3.3±1.9		26.5±28.1	<0.0001
TSI (%)	356.1±50.0		277.2±38.9	<0.0001
Reticulocyte (%)		2.5±1.3		

SD, Standard deviation; Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; RDW, red cell distribution width; WBC, white blood cell; Plt, platelet; TIBC, total serum iron binding capacity; TSI, transferrin saturation index.

The mean RDW value measured on day 5 was 3.7 ± 3.8% higher than the baseline value ($RDW_{day5} - RDW_{baseline}$), and the mean Hb measured at 1 month was 2.8 ± 1.2 g/dL higher than the baseline value. There was a significant positive correlation between the increase in RDW and the increase in Hb ($r = 0.43$; $P = 0.002$) (Figure 3). The increases in RDW values were divided into categories at a cutoff point of 5%. An increase in RDW value of 5% or less on day 5 compared to baseline indicated a mean increase of 2.5 g/dL in Hb at 1 month, whereas a greater than 5% increase in RDW value on day 5 compared to baseline indicated a mean increase of 3.6 g/dL in Hb at 1 month.

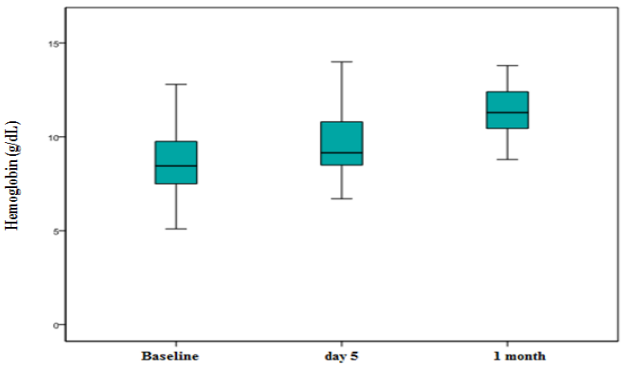

Figure 1. The course of hemoglobin (Hb) levels during iron treatment

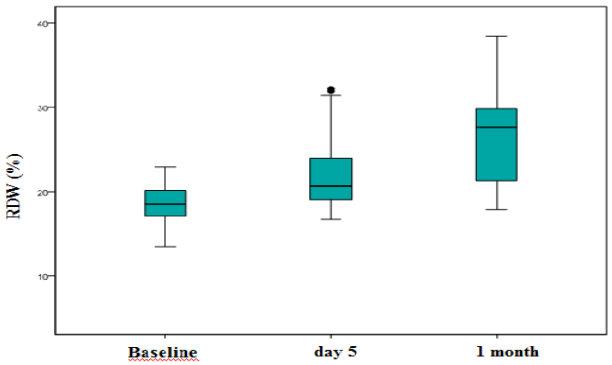

Figure 2. The course of red blood cell distribution width (RDW) during iron treatment

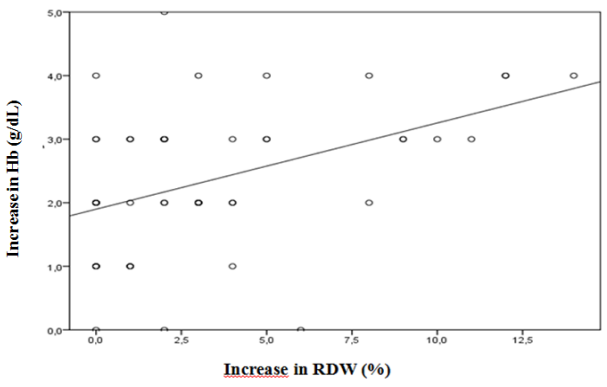

Figure 3. Correlation between the increase in Hb and the increase in RDW

Discussion

IDA is the most common type of nutritional anemia. The high incidence of IDA worldwide emphasizes the need for cost-effective and reliable tools for its diagnosis and treatment (1).

Normocytic erythrocytes, which are produced after initiation of iron therapy, lead to an increase in RDW value. While they become predominant, RDW values decline slowly thereafter (23,24).

Tests that can accurately confirm or exclude a disease are particularly useful. Although bone marrow tests are invasive, and serum ferritin, serum transferrin, and serum iron tests are expensive, RDW is a readily available parameter along with other red cell indices, thus it does not require additional cost. The cost of anemia diagnosis would be reduced if these easily available tests were used to screen for IDA with high sensitivity and specificity (13).

Buttarello et al. (21) reported RDW as a new parameter for laboratory diagnosis of IDA. However, they did not examine its correlation with Hb elevation.

Aslan et al. (24) reported that RDW values increased after initiation of iron therapy, beginning on days 5–7, peaked after 4 weeks, and began to decline thereafter. However, they did not examine the correlation between the increases in RDW and Hb. The results of the present study indicated an increase in RDW after the initiation of iron therapy, similar to the report of Aslan et al. In contrast to their study, we also examined the correlation between increases in RDW and Hb.

A previous study indicated the fluctuating course of RDW in the treatment of IDA. However, they did not examine the RDW increase 1 month after initiation of iron therapy or the increase in RDW on days 5–7, due to the retrospective design of the study (23).

Conclusion

The present study suggests that RDW may be used efficiently and cost-effectively in place of reticulocyte count to predict the response to iron therapy in IDA. We conclude that RDW is the best biomarker for this purpose due to its low cost and ready availability as part of whole blood cell counts in primary care settings, and therefore it may be accepted as superior to reticulocyte count. To our knowledge, this is first report regarding the utility of RDW for this purpose.

This study had limitations regarding its small sample size and the inclusion of only female patients. Further studies are therefore required to verify our results.

References

1. World Health Organization [Internet]. The global prevalence of anaemia in 2011 [cited 2019 Apr 25]. Available from: https://www.who.int/nutrition/publications/micronutrients/global_prevalence_anaemia_2011/en/.
2. Winichagoon P, Kumbunlue R, Sirankapracha P, Boonmongkol P, Fucharoen S. Discrimination of various thalassemia syndromes and iron deficiency and utilization of reticulocyte measurements in monitoring response to iron therapy. Blood Cells Mol Dis 2015;54:336-41. doi: 10.1016/j.bcmd.2015.01.010.
3. Brugnara C, Laufer MR, Friedman AJ, Bridges K, Platt O. Reticulocyte hemoglobin content (CHr): early indicator of iron deficiency and response to therapy. Blood 1994;83(10):3100-1.
4. Viswanath D, Hegde R, Murthy V, Nagashreee S, Shah R. Red blood cell distribution width in the diagnosis of iron deficiency anemia. Indian J Pediatr 2001;68(12):1117-9.
5. Liu TC, Seong PS, Lin TK. The erythrocyte cell hemoglobin distribution width segregates thalassemia traits from other nonthalassemic conditions with microcytosis. Am J Clin Pathol 1997;107(5):601-7.
6. Junca J, Flores A, Roy C, Alberti R, Milla F. Red blood cell distribution width, free erythrocyte protoporphyrin and England Fraser index in the differential diagnosis of microcytosis due to iron deficiency or beta-

thalassemia trait. A study of 200 cases of microcytic anemia. Hematol Pathol 1991;5(1).33-6.
7. Eivazi-Ziaei J, Dastgiri S, Pourebrahim S, Soltanpour R. Usefulness of red blood cell flags in diagnosing and differentiating thalassemia trait from iron deficiency anemia. Hematology 2008;13(4):253-6. doi: 10.1179/102453308X316040.
8. Jameel T, Baig M, Ahmed I, Hussain MB, Alkhamaly MbD. Differentiation of beta thalassemia trait from iron deficiency anemia by hematological indices. Pak J Med Sci 2017;33(3):665-9. doi: 10.12669/pjms.333.12098.
9. Romero JA, Carbia CD, Ceballo MF, Diaz NB. Red cell distribution width (RDW): its use in the characterization of microcytic and hypochromic anemias. Medicina 1999;59(1):17-22.
10. Aslan D, Gümrük F, Gürgey A, Altay C. Importance of RDW value in differential diagnosis of hypochrome anemias. Am J Hematol 2002;69(1):31-3.
11. Das AG, Hegde C, Mistri R. Red cell distribution width as a measure of severity of iron deficiency in iron deficiency anemia. Indian J Med Res 1994;100:177-83.
12. Maiolo AT, Gidiuli R, Damilano I, Massaro P, Polli EE. Relevance of red cell distribution width (RDW) in the differential diagnosis of microcytic anemias. Clin Lab Haematol 1991;13(2):141-51. https://doi.org/10.1111/j.1365-2257.1991.tb00263.x
13. Aulakh R, Sohi I, Singh T, Kakkar N. Red cell distribution width (RDW) in the diagnosis of iron deficiency with microcytic hypchromic anemia. Indian J Pediatr 2009;76(3):265-8.
14. Okan V, Cıgıloglu A, Cıfci S, Yılmaz M, Pehlivan M. Red cell indicies and functions differentiating patients with the beta thalassemia trait from those with iron deficiency anemia. J Int Med Res 2009;37(1):25-30.
15. Sazawal S, Dhingra U, Dhingra P, Dutta A, Shabir H, Menon VP, et al. Efficiency of red cell distribution width in identification of children aged 1-3 years with iron deficiency anemia against traditional hematological markers. BMC Pediatr 2014;14:8. doi: 10.1186/1471-2431-14-8.
16. Li N, Zhou H, Tang Q. Red blood cell distribution width: A novel predictive indicator for cardiovascular and cerebrovascular diseases. Dis Markers 2017;2017:7089493. doi: 10.1155/2017/7089493.
17. Dignass AU, Gasche C, Bettenworth D, Birgegård G, Danese S, Gisbert JP, et al. European consensus on the diagnosis and management of ıron deficiency and anaemia in ınflammatory bowel diseases. J Crohns Colitis 2015;9(3):211-22.
18. Jandiala A, Kumar S, Bhalla A, Sharma N, Varma N, Varma S. Elevated red cell distribution width as a prognostic marker in severe sepsis: a prospective observational study. Indian J Crit Care Med 2017;21(9):552–62. doi: 10.4103/ijccm.IJCCM_208_17.
19. Gong Y, Long X, Jin J, Yang X, Fu J, Huang F, et al. Elevation of red cell distribution width during hospitalization predicts mortality in patients with sepsis [Chinese]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2017;29(6):481-5. doi: 10.3760/cma.j.issn.2095-4352.2017.06.001.
20. Cha MJ, Lee HS, Kim HM, Jung JH, Choi EK, Oh S. Association between red cell distribution width and thromboembolic events in patients with atrial fibrillation. Eur J Intern Med 2017;46:41-6. doi: 10.1016/j.ejim.2017.07.028.
21. Buttarello M. Laboratory diagnosis of anemia: are the old and new red cell parameters useful in classification and treatment, how? Int J Lab Hematol 2016;38,123-32. doi: 10.1111/ijlh.12500.
22. Wonca [Internet]. The

European definition of general practice/family medicine [cited 2019 Apr 23]. Available from: https://www.woncaeurope.org/gp-definitions

23. Solmaz S, Asma S, Gereklioğlu Ç, Kasar M, Yeral M, Boğa C, et al. Fluctuating course of red cell distribution width in treatment of iron deficiency anemia and its clinical relevance. TJFMPC 2015;9(3):83-7. doi: 10.5455/tjfmpc.178655.
24. Alan D, Gümrük F, Gürgey A, Altay Ç. Importance of RDW value in differential diagnosis of hypochrome anemia. Am J Hematol 2002;69(1):31-3.