Red cell distribution width as a marker of activity in inflammatory bowel disease: a narrative review

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Abstract
Red blood cell distribution width is a parameter measured automatically in every complete blood count that actually reflects the degree of anisocytosis of the red blood cell population. It is a cost-effective tool used in everyday clinical practice along with other parameters to define and narrow the cause of anemia. In a series of pathologic entities, such as cardiovascular diseases, autoimmune diseases, malignancy, chronic renal diseases and chronic respiratory diseases, where inflammation and oxidative stress comprise the major pathophysiologic insults, red cell distribution width behaves as a significant and competent marker able to predict and assess disease activity and severity. A number of clinical studies based on these observations have aimed to evaluate its potential utility as an index of activity in inflammatory bowel disease. In this narrative review we present data from the international literature regarding its ability to express disease activity and we look into its relation with clinical, laboratory and endoscopic indices used to identify active disease. According to the results of published clinical trials, red cell distribution width is considerably correlated with disease activity and might serve as an index to differentiate Crohn's disease from ulcerative colitis.

Keywords Red cell distribution width, inflammatory bowel disease, Crohn's disease, ulcerative colitis, disease activity

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Introduction

Red cell distribution width (RDW) is an automatic expression of hematologic analyzers reflecting the size variability of circulating red blood cells (RBC). It is a marker used together with other laboratory parameters to determine and narrow the cause of anemia [1] and it has shown promising potential as an index of disease activity and severity in various pathologic conditions [2-6].

The diagnosis and follow up of inflammatory bowel disease (IBD) are based on a combination of clinical indices, laboratory markers, endoscopy, histology and imaging modalities [7,8]. However, these have various disadvantages, such as low sensitivity and specificity, high cost, limited availability, absence of simplicity, invasiveness, and lack of reproducibility [9,10].

The demand for an index used to recognize and monitor disease activity in IBD that overcomes these disadvantages still remains unmet. Since RDW expresses a lot of attractive characteristics, a number of clinical studies have been performed to evaluate its application as a surrogate marker of disease activity in IBD. We searched MEDLINE and the Cochrane Library through December 2019. Search terms included "red cell distribution width", "Inflammatory bowel disease", "Crohn's Disease" and "Ulcerative Colitis", and we critically reviewed all relevant articles published in English. The intention of this review is to summarize the current state of knowledge on the utility of RDW as a marker of activity in IBD.

Clinical utility of RDW

RDW, a parameter measured automatically in every complete blood count (CBC), is an actual reflection of RBC size variability and heterogeneity. RDW is considered as a reliable index of the anisocytosis of the RBC population circulating in peripheral blood. There are 2 different ways to express RDW statistically: as a coefficient of variation (RDW-CV) and/or a standard deviation (RDW-SD). RDW-SD (expressed in fL) is

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an actual evaluation of the width of the RBC size distribution histogram and is quantified after determination of the width (in fL) at the 20% height level of that histogram. This index is therefore not influenced by the average size of the RBC population, the mean corpuscular volume (MCV).

On the other hand, RDW-CV (expressed in %) is derived from a mathematical formula that includes SD and MCV:

RDW-CV (%) = 1 standard deviation of RBC volume / MCV × 100%

and it is affected by variations in RBC size [11]. Anemias were traditionally classified, according to their MCV value, as microcytic (MCV below the reference range), normocytic (MCV within the reference range) and macrocytic (MCV above the reference range). In the early 80s a different approach was proposed for anemia classification using both RDW and MCV [12].

Based on this classification, 2 distinct entities of anemias were described: one with a homogeneous erythrocyte population and normal RDW, and a second with a heterogeneous erythrocyte population and a greater RDW [13]. The main conditions that influence and elevate RDW value include anemias due to nutritional deficiencies (iron, B12 and folate), hemoglobinopathies, hemolytic anemias, and sickle-cell anemia [14,15] (Table 1).

Apart from its usual application as a hematologic parameter, RDW has been extensively studied as an inflammatory marker, along with its capability to express the activity and severity of various disease states and conditions. Probably the first recorded strong correlation of RDW with laboratory indices of inflammation, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), came after a retrospective study of 3845 outpatient adults performed by Lippi et al [16].

Cardiovascular diseases, malignancy, chronic lower respiratory diseases, metabolic syndrome, chronic kidney disease and autoimmune disorders belong to a group of disorders where inflammation and oxidative stress comprise the major pathophysiologic insults [17-22]. Data from the international literature showed that in these clinical entities, an elevated RDW value was related to an increased risk of morbidity and mortality and could be used as a predictor of an unfavorable disease course [23-29].

Table 1 Conditions that elevate red cell distribution width [14,15]

RDW value	Elevated
Normal MCV	Early iron, vitamin B12, or folate deficiency Sickle-cell disease Myelodysplastic syndrome
Elevated MCV	Folate or vitamin B12 deficiency Immune hemolytic anemia Myelodysplastic syndrome Drug-induced Bone marrow disorders
Decreased MCV	Hemolytic anemia Iron deficiency Sickle-cell β-thalassemia Microangiopathic hemolytic anemia

RDW, red cell distribution width; MCV, mean corpuscular volume

Despite the encouraging data concerning its potential as a prognostic marker of morbidity, mortality and unfavorable disease course in various pathologic conditions, in everyday clinical practice RDW remains a parameter used to define and differentiate anemias.

RDW in IBD

There are different proposed mechanisms that attempt to explain why RDW is elevated in active IBD and how this is correlated with disease activity. The most probable encountered etiologies involve anemia, and especially iron deficiency anemia (IDA), as well as the impact of inflammation and oxidative stress on the normal process of erythropoiesis.

Anemia in IBD seems to be multifactorial, with an estimated prevalence between 9-74%, while IDA represents the commonest type [30,31]. Causes implicated include continuous microscopic or macroscopic blood loss from the ulcerated intestinal mucosa, nutritional deficits of vitamins and minerals (iron, folate, B12) due to decreased intake or absorption, effects of medication, and inflammatory insults in the process of hematopoiesis [32]. The RDW value is directly affected and subsequently elevated in IDA, as well as in situations of B12 and folate deprivation, while it is known that the degree and severity of anemia in both Crohn's disease (CD) and ulcerative colitis (UC) are linked to disease activity [33,34].

IBD are chronic and relapsing inflammatory conditions of the gastrointestinal tract [35]. Chronic inflammation through the exertional effect of cytokines—interleukin-1 , interleukin-6, tumor necrosis factor-α, interferon-γ—may cause impaired erythropoietin (EPO) production, alterations of red blood cell life span, diminished responsiveness of bone marrow to EPO and impaired iron metabolism, disrupting the normal process of hematopoiesis [36,37]. Data from the international literature suggest that anemia in IBD is multifactorial and is considered to be a combination of IDA and anemia of chronic disease (ACD), caused by a series of negative effects of an activated immune system at different levels of erythropoiesis [38,39].

The presence of RBC populations with marked heterogeneity in size, as a result of anemia and deficient erythropoiesis due to direct and indirect effects of inflammation and oxidative stress, seems to be an attractive hypothesis that can possibly explain the correlation of RDW with disease activity [40,41]. The international literature contains a rather small number of publications that aimed to investigate RDW as an index of activity in IBD, or its correlation with clinical and laboratory markers used to express active disease (Table 2).

The first study published in 2008 by Molnar et al [42] was a retrospective study, complementary to that of Clarke et al [43], that aimed to highlight any relation between RDW and disease activity. The investigators intended to clarify whether its quantitative fluctuations could be correlated with laboratory markers of inflammation and/or clinical indices of activity. They also tried to evaluate the potential of RDW to differentiate CD from UC in both the active state and remission. Mean values of RDW were significantly elevated in the active form

Table 2 Published studies/clinical trials evaluating the role of red cell distribution width as a marker of activity in inflammatory bowel diseases

Reference	Type of study	Study group	Clinical activity index	Endoscopic activity index	Laboratory parameters	RDW cut-off	Sensitivity Specificity	Primary aim
Molnar *et al* [42]	Retrospective	92 CD / 84 UC	CDAI		CRP, ESR, Fe	>14% in CD / UC		RDW correlation with CDAI, ESR, CRP in active and inactive CD/UC – RDW ability to differentiate CD from UC
Cakal *et al* [44]	Cross-sectional	22 CD/ 74 UC / 20 matched controls	CDAI/ Truelove-Witts		fibrinogen, CRP, ESR, WBC, PLT	14% UC 14,1% CD	88-71%/ UC 78-63%/CD to detect active disease	RDW potential to detect active disease
Oustamanolakis *et al* [45]	Cross-sectional	51 CD/ 49 UC/ 102 matched controls	CDAI / SCCAI		CBC, RSF, IRF, RDWR-SD, RDWR-CV,ESR, CRP,Fe, Fer, TRF, sTfR, Tsat	14%	93-84% for diagnosis of IDA	Use of reticulocyte and RBC indices in the evaluation of anemia
Arhan *et al* [46]	Retrospective	60 CD/ 105 UC/ 43 healthy blood donors	CDAI/ Truelove-Witts	EAI for UC	Hb, Hct, WBC, PLT, ESR, CRP	14,45%	70-56% to differentiate CD from UC	RDW potential to detect active disease
Yesil *et al* [47]	Cross-sectional	56 CD / 61 UC/ 44matched controls	CDAI/ Truelove-Witts		Hb, Hct, WBC, PLT, ESR, CRP	14% UC 14% CD	17-84% to detect active UC 73-86% to detect active CD	RDW as marker of activity
Song *et al* [48]	Retrospective	101 CD-120 UC	CDAI / Mayo score		Hb, Hct, WBC, PLT, ESR, CRP	13,8% non-anemic UC 14,1% non-anemic CD	76-86% to detect active UC 82-86% to detect active CD	RDW as marker of activity in both anemic/non anemic patients
Voudoukis *et al* [49]	Cross-sectional	107 CD-91UC/ /102 controls	CDAI/ SCCAI		Hb, Hct,MCV, RDW, PLT,MPV, PDW, PCT, sTfR, sTfR-F index, B12, folate			Platelet parameters (PLT,PCT,PDW, MPV), in IBD patients in comparison with healthy controls/ correlation between platelet parameters and RBC and anemia indices
Huang *et al* [50]	Retrospective	68 CD / 35 Intestinal tuberculosis / 22 irritable bowel syndrome	Harvey-Bradshaw index		CRP, ESR, RBC, WBC, PLT, MPV and RDW			Diagnostic utility of RDW, PLT and MPV in active CD and intestinal tuberculosis
Ipek *et al* [51]	Retrospective	310 UC / 206 active, 104 remission		Rachmilewitz activity index	CBC, ESR, CRP	16.66%	41-91% to detect disease activity	Association between RDW levels and disease activity – RDW as an index of disease activity in non-anemic UC patients

(Contd...)

Table 2 *(Continued)*

Reference	Type of study	Study group	Clinical activity index	Endoscopic activity index	Laboratory parameters	RDW cut-off	Sensitivity Specificity	Primary aim
Oliveira *et al* [52]	Cross-sectional	119 CD	CDAI		CRP, ESR, PLT, WBC, Hb, MCV	16%	30-88% to detect disease activity	RDW as a marker of CD activity
Hu *et al* [53]	Prospective	100 CD / 102 matched controls	CDAI		CBC, ESR, CRP	15,6 %	96.2-54.3% to detect disease activity	Ability of RDW to assess disease activity in CD
Akkermans *et al* [54]	Cross-sectional	42 CD/ 14 UC/ 3 unclassified	PCDAI/ PUCAI		PMV, RDW, ZPP, Reticulocytes			ZPP and RDW as biomarkers of iron restricted erythropoiesis in pediatric IBD patients
Goyal *et al* [55]	Review	8 studies including CD / UC patients / matched controls	CDAI / Truelove-Witts / Mayo score	Rachmilewitz activity index	CBC, RSF, IRF, RDWR-SD, RDWR-CV,ESR, CRP, Fe, Fer, TRF, sTfR, Tsat, ESR, CRP	Different among studies included	Different among studies included	RDW was evaluated in IBD as an index of disease activity / marker to differentiate CD from UC / index to evaluate anemia in IBD

CD, Crohn's disease; UC, ulcerative colitis; CDAI, Crohn's disease activity index; SCCAI, simple clinical colitis activity index; EAI, endoscopic activity index; CBC, complete blood count; WBC, white blood cells; RBC, red blood cells; PLT, platelets; Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; MPV, mean platelet volume; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RDW, red cell distribution width; RSF, red blood cell size factor; IRF, immature reticulocyte fraction; RDWR-CV, reticulocyte distribution width coefficient of variation; RDWR-SD, reticulocyte distribution width-standard deviation; Tsat, transferrin saturation; sTfR, soluble transferrin receptor; Fe, serum iron; Fer, Ferritin; IDA, iron deficiency anemia; PDW, platelet distribution width; PCT, plateletcrit; B12, vitamin B12; PCDAI, pediatric Crohn's disease activity index; PUCAI, pediatric ulcerative colitis activityindex; ZPP, zincprotoporphyrin

of both CD and UC and also in inactive CD cases compared to the normal values of RDW (RDW 11-14%). The authors concluded that RDW could be used as an additional marker able to express active disease, based on the fact that its value was remarkably related to clinical activity indices.

Cakal *et al* [44] performed a cross-sectional study with primary outcome the evaluation of RDW's potential in the assessment of active disease in IBD patients. In patients with active disease, laboratory indices (RDW, fibrinogen, CRP, ESR, and platelet [PLT] counts) had significantly higher values compared to those with inactive disease and controls (P<0.05). RDW was the most sensitive and specific parameter indicating active disease in patients with UC. In CD patients, CRP at a cutoff of 0.54 mg/dL was the most accurate parameter in the diagnosis of active disease: sensitivity 92%, specificity 63% (area under the curve 0.92, P=0.001).

Oustamanolakis *et al* [45] performed a cross-sectional study to investigate the usefulness of RBC and reticulocyte indices in the evaluation of anemia in IBD patients. Activity was evaluated using the Crohn's disease activity index along with the Simple Clinical Colitis Activity Index (SCCAI) and CRP. The study's results showed that RDW behaved as an accurate diagnostic marker of IDA. Despite the observation that RDW was elevated in the IBD group compared to healthy controls, there were no significant discrepancies between active and

inactive disease, while no important correlation with CRP was found.

Arhan *et al* [46] conducted a retrospective study to determine whether RDW could be used for the assessment of disease activity in patients with IBD. RDW, ESR, CRP and PLT were all significantly increased in the patient group compared to the controls (P<0.05). A greater proportion of CD patients than of UC patients experienced higher values of RDW (P<0.05). There was significant correlation of RDW with ESR, PLT and endoscopic activity index in UC patients, but active disease was not correlated with an elevated RDW in either CD or UC patients.

A cross sectional study performed by Yesil *et al* [47] aimed to evaluate RDW as a marker of active disease in IBD patients. RDW was significantly higher in patients with CD and UC than in controls. A subsequent subgroup analysis indicated that RDW was the most sensitive and specific marker for active CD. On the other hand, in the UC group, ESR at a cutoff of 15.5 expressed the highest sensitivity and specificity for detecting active disease.

Song *et al* [48] tried to evaluate the performance of RDW as a marker of disease activity in both anemic and non-anemic IBD patients. It appeared that, in both groups, CRP, ESR and RDW values increased in association with disease activity, while hemoglobin (Hb) and hematocrit decreased (all P<0.05). Multivariate statistical analysis indicated that RDW was the

most accurate independent indicator capable of predicting disease activity in non-anemic CD and UC patients. The authors concluded that RDW, at different cutoff values, was the most sensitive and specific marker of active disease in non-anemic CD and UC patients.

Voudoukis *et al* [49] performed a study whose primary objectives were the evaluation of PLT parameters—PLT, plateletcrit, platelet distribution width, mean PLT volume (MPV)—in IBD patients in comparison with healthy controls, as well as the investigation of any possible correlation between these parameters and RBC and anemia indices. Among the hematological and laboratory parameters examined, RDW was significantly greater in both CD and UC patients than in healthy controls, while an independent correlation was observed between RDW and thrombocytosis. The authors commented that in their study thrombocytosis appeared to be a consequence of iron deficiency, rather than a result of systemic inflammation.

A retrospective study from Huang *et al* [50] estimated the diagnostic utility of RDW as well as PLT and MPV in patients with active CD and intestinal tuberculosis. Results from binary logistic regression analysis showed that RDW was a more reliable independent marker in predicting active CD, compared to CRP and ESR. A retrospective study by Ipek

et al [51] aimed to look into the association between RDW levels and disease activity and to investigate whether RDW can be used as an index of disease activity in non-anemic UC patients. The mean value of RDW was significantly higher in patients with active UC compared to those in remission. RDW was highly correlated with CRP, WBC, and PLT levels, but not with ESR. However, RDW was the weakest marker of disease activity in non-anemic patients.

Oliveira *et al* [52] investigated whether RDW can be used as a marker of CD activity. The authors noticed a significant correlation between RDW and disease activity (P=0.044), an association that remained strong and independent even after adjustment for Hb, ESR and biologic therapy. They concluded that, at a cutoff of 16%, RDW could be possibly used as a marker of disease activity.

Hu *et al* [53] conducted a prospective study looking for the ability of RDW to assess disease activity in CD. RDW appeared to be significantly higher in active than in inactive CD (P<0.05). At a given cutoff value, RDW performed better compared to ESR and WBC but worse than CRP in distinguishing active from inactive CD.

A cross-sectional Dutch study performed by Akkermans *et al* [54] aimed to determine the prevalence of and potential risk factors for absolute and functional iron deficiency (ID) in

Table 3 Results of red cell distribution width as marker of activity

Reference	Major findings concerning RDW
Molnar *et al* [42]	Mean RDW significantly increased in both active and inactive CD/UC RDW can be used to differentiate inactive CD from UC / RDW significantly correlated with low Fe in CD / RDW significantly correlated with Fe, CRP, ESR in UC in remission
Cakal *et al* [44]	RDW was the most sensitive and specific index to detect active UC
Oustamanolakis *et al* [45]	Elevated RDW with low RSF were the best markers to diagnose IDA No significant correlation between RDW and disease activity
Arhan *et al* [46]	RDW increased in patient group / RDW correlated with ESR, PLT and EAI in UC patients
Yesil *et al* [47]	RDW higher in patient group (P<0.05) Most sensitive and specific marker for active CD
Song *et al* [48]	RDW is the best predictor/marker of disease activity in non-anemic CD (OR 1.702, 95%CI 1.185-2.445; P=0.004) and UC patients (OR 4.921, 95%CI 2.281-10.615; P<0.001).
Voudoukis *et al* [49]	RDW was significantly elevated (P<0.0001) in both CD [16.1 (14.8-18.1)] and UC [15.7 (14.6-16.7)] patients than in healthy controls [13.6 (12.9-14.4)] / independent correlation between RDW and thrombocytosis
Huang *et al* [50]	RDW is a favorable independent marker (OR 2.390, 95% CI 1.269-4.502;P=0.007) in predicting active CD compared to CRP (OR 1.025, 95%CI 0.989-1.063; P=0.177) and ESR (OR 1.157, 95%CI 1.003-1.336; P=0.046)
Ipek *et al* [51]	Mean RDW (16.8±2.9 and 15.5±1.4, respectively, P<0.001) significantly elevated in active compared to inactive disease and strongly correlated with CRP (P=0.001), WBC (P=0.001) and PLT (P<0.001), but not ESR (P=0.756) In anemic patients, no difference between non-anemic active and remission group
Oliveira *et al* [52]	RDW significantly related with disease activity / CDAI even after adjustment for Hb, ESR and biologic therapy (P=0.01, P<0.017, respectively)
Hu *et al* [53]	RDW significantly higher in active CD. RDW performed better than ESR, WBC but not CRP to detect active CD (overall accuracy 76%, 68%, 51% and 78% respectively)
Akkermans *et al* [54]	RDW significantly correlated with functional [RDW: 13.8 (13.0;14.5) P=0.006] and absolute ID [RDW: 15.3 (14.3;18.2), P<0.05]
Goyal *et al* [55]	RDW showed promising potential as an index of disease activity as well as a marker able to differentiate CD from UC

CD, Crohn's disease; UC, ulcerative colitis; CDAI, Crohn's disease activity index; EAI, endoscopic activity index; OR odds ratio; CI confidence interval; WBC, white blood cells; PLT, platelets; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RDW, red cell distribution width; RSF, red blood cell size factor; IDA, iron deficiency anemia; ID, iron deficiency

pediatric IBD patients, using zinc protoporphyrin and RDW as biomarkers of iron-restricted erythropoiesis. Functional ID is the result of the impact of inflammation on the normal process of hematopoiesis and differs from absolute ID, caused by iron malabsorption, reduced dietary intake and continuous blood loss. The authors reported a statistically significantly correlation of RDW with functional as well as with absolute ID, along with IDA and ACD, suggesting that RDW can be used to evaluate iron-restricted erythropoiesis.

Finally, Goyal *et al* [55] performed a systematic review of the international literature to evaluate the prognostic value of RDW for assessment of disease severity and clinical consequences in both benign and malignant gastrointestinal disorders. The authors included in this review 8 studies where RDW was evaluated in IBD as an index of disease activity, as a marker to differentiate CD from UC, and as an index to evaluate anemia in IBD. They concluded that RDW showed promising potential as an index of disease activity as well as a marker able to differentiate CD from UC. The results of the aforementioned studies indicate the promising potential of RDW as a surrogate marker of disease activity in IBD (Table 3).

Concluding remarks

The results from studies included in this review showed that mean values of RDW were statistically significantly higher in IBD patients compared to controls. With respect to the rather limited data, based on only 2 clinical trials, RDW could be used as an effective marker to differentiate CD from UC in both the active state and remission. In the majority of the aforementioned studies RDW, at different cutoff values, showed a remarkable sensitivity and specificity in detecting active disease, calculated by means of clinical indices, endoscopic scores and laboratory parameters. RDW also showed a positive but variable correlation with well-established inflammatory biomarkers used in everyday clinical practice such as CRP, ESR, and to a lesser extent WBC and PLT, in both anemic and non-anemic IBD patients. Therefore, RDW could be considered an attractive disease activity marker in IBD, as it is calculated automatically in every CBC, has a low cost, is minimally invasive, has no specific technical requirements and can be easily reproduced.

On the other hand, there are certain aspects concerning its broad application that must be elucidated. There was great variability in the thresholds adopted for the assessment of diagnostic accuracy. In addition, the selection of cutoffs was arbitrary and data driven. Most studies were retrospective and were case-control studies. The use of controls in diagnostic accuracy studies usually results in overestimation of both sensitivity and specificity. Large-scale well-designed prospective studies for standardization of the cutoff value of RDW should now be mandatory. It is also necessary to conduct such studies in order to evaluate whether the limited but rather encouraging data are sufficient to establish RDW as a reliable activity index. Finally, there is a need to look deeper and clarify the pathophysiology of this relation. RDW seems to

be a promising cost-effective tool that can be used to evaluate and monitor disease activity in IBD, but this requires more extensive and detailed research in the future.

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