Review Article

Red blood cell distribution width: a promising index for estimating activity of autoimmune disease

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Abstract: Red blood cell distribution width (RDW) is a traditional hematological index used to explore the etiology of anemia. During past years, association between RDW and non-hematological diseases has attracted much attention. Accumulated evidence has revealed that RDW is elevated in various autoimmune diseases and associates with disease activity or complications. Here, I summarized the evidence concerning clinical utility of RDW in autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary Sjogren's syndrome (pSS), inflammatory bowel disease (IBD), inflammatory myopathy (IM) and primary biliary cholangitis (PBC). Available evidence has supported that RDW is a useful index to estimate the activity in various autoimmune diseases. Further prospective cohort studies are needed to explore the prognostic value of RDW in autoimmune diseases.

Keywords: Red blood cell distribution width (RDW); autoimmune disease; inflammation; disease activity

Received: 07 October 2016; Accepted: 25 October 2016; Published: 11 November 2016.
doi: 10.21037/jlpm.2016.10.02
View this article at: http://dx.doi.org/10.21037/jlpm.2016.10.02

Red blood cell distribution width (RDW) is an index depicting the size variation of red blood cell (1). For a long time, RDW has been used to explore the causes of anemia. In 2007, Felker *et al.* (2) reported that RDW is a promising prognostic marker in patients with heart failure. Subsequently, accumulated studies have revealed that RDW is a diagnostic marker, risk factor and prognostic factor in various cardiovascular diseases (3). Although the association between RDW and cardiovascular diseases has been revealed in many studies, the mechanism underlying the association is largely unknown. In 2009, Lippi *et al.* (4) reported that RDW is positively correlated with inflammatory markers [e.g., C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)] in unselected outpatients. In another study published in 2015, positive correlation between RDW and inflammatory markers is also observed in healthy population (5). These two studies clearly indicate that RDW is an inflammatory marker, and the association between RDW and cardiovascular diseases is at least partially mediated by inflammatory response.

It is well known that the development of autoimmune diseases is associated with chronic inflammatory response. Therefore, inflammatory markers are usually used to estimate the activity in many types of autoimmune diseases. Knowing that RDW is associated with inflammatory response, it is reasonable to speculate the RDW is a potential marker to estimate the disease activity of autoimmune disease. To date, many studies have reported that RDW is increased in autoimmune disease and correlates with disease activity. In this review, I summarized the studies concerning RDW and autoimmune disease.

RDW and rheumatoid arthritis (RA)

In 2010, Lee *et al.* reported that patients with RA had increased RDW when compared with osteoarthritis patients (6). RDW was further proved to be positively correlated with CRP in RA patients, regardless of anemia. In another studies (7,8), the researchers found that RDW

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is positively correlated with DAS-28, a widely used disease activity tool for RA. However, the correlation between RDW and DAS-28 was not observed in the study performed by Rodríguez-Carrio *et al.* (9). This may be due to the small sample size and lower statistical power. Taken together, these studies indicate that RDW is a potential index in estimating the disease activity of RA.

Increased RDW in RA patients was reported to be associated with risk of cardiovascular diseases. Rodríguez-Carrio *et al.* found that increased RDW, as well as RDW changes in the first year after diagnosis, is correlated high risk of cardiovascular events (heart failure, ischaemic heart disease or cerebrovascular accident), and the correlation remained significant after adjusting for sex and gender (7). In a cross-section study with 106 RA patients, Zhou *et al.* found that only creatinine, ESR, high sensitive CRP (hs-CRP) and RDW are associated with myocardial infarction (MI); however, in a multivariable logistic regression model, only RDW is independently associated with MI (10). Another study with a larger sample size (n=20,810) also found that increased RDW is associated with higher risk of MI, regardless of anemia (11). Taken together, these studies indicate that increased RDW in RA patients is associated with high risk of cardiovascular events.

The mechanisms underlying the relationship between RDW and risk of cardiovascular diseases remain largely unknown. A recent study found that RDW is negatively associated with endothelial progenitor cells (EPC) and serum interferon-α in RA patients, and the correlation between RDW and EPC remained even after adjusting for clinical parameters, disease duration, treatments and traditional cardiovascular risk factors (9). These results indicate that endothelial damage and impaired vascular repair mediates the relationship between increased RDW and cardiovascular events in RA patients.

RDW and systemic lupus erythematosus (SLE)

In 2013, Vayá*et al.* firstly reported that SLE patients have higher RDW than healthy controls (12). Although some of the SLE patients (26/105) has anemia, the SLE patients without anemia also showed higher RDW than healthy controls (12), indicating that increased RDW in SLE patients is not completely attributed to anemia. This study also indicated that RDW is positively correlated with CRP and ESR. Subsequent two studies also revealed that RDW is positively correlated with CRP and ESR (13,14). Besides, these two studies also found that RDW is positively correlated with SLEDA-2000K, C_3, C_4 and anti-dsDNA antibody (13,14). Increased RDW in SLE seems not to be associated with pharmacotherapy, because treatment naïve patients also showed increased RDW (13).

RDW also correlates with therapeutic outcome in patients with SLE. Compared to patients with normal RDW, patients with higher RDW have lower response rate to first line therapy, as well as lower one-year flare-free survival (14).

RDW and inflammatory bowel disease (IBD)

The first report concerning RDW and IBD was published in 2008. Clarke *et al.* reported that patients with Crohn's disease (CD) have significantly higher RDW than patients with ulcerative colitis (UC) (15), but whether the CD or UC patients have higher RDW than healthy controls is not investigated. In 2009, Cakal *et al.* reported that patients with CD or UC have higher RDW than healthy controls (16). A subsequent study revealed that RDW represents a novel, inexpensive and promising index in estimating the disease activity of UC and CD, because active patients have higher RDW than patients in remission (17-21). Using receiver operating characteristic (ROC) curve analysis, these studies (16,18,19,22) revealed that RDW is a useful index in predicting the disease activity of UC and CD. Some of these studies even found that the area under ROC curve (AUC) of RDW is comparable to that of traditional inflammatory markers, such as ESR and CRP (16,18). Using multivariable logistic regression method, some studies also indicated that RDW is independently associated with active UC or CD, even after adjusting for CRP and ESR (20,22).

Increased RDW in IBD may be attributed to two possible mechanisms. One is inflammation response, which may impair erythropoiesis and accelerate newer, larger reticulocytes to enter the peripheral circulation (23). Another is iron deficiency, which is caused by malabsorption of iron. Indeed, iron deficiency is common in IBD patients and some studies found that RDW is associated with iron status markers (e.g., transferrin saturation, soluble transferrin receptor) in IBD patients (17).

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RDW and ankylosing spondylitis (AS)

Three studies have investigated the association between RDW and AS (24-26). Two of these studies found that RDW is increased in AS patients (24,25). More importantly, RDW is positively correlated with the disease activity of AS, which is measured using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). However, another study performed by Bozan *et al.* did not proved that AS patients had increased RDW (26). This may be due to the fact that the sample size in that study is small (n=30) and the statistical power is low.

RDW and primary Sjogren's syndrome (pSS)

To present, only one study investigated the value of RDW in pSS (27). The authors found that pSS patients have higher RDW than healthy controls. RDW is positively correlated with ESR, CRP, as well as Sjogren's Syndrome Disease Activity Index (SSDAI), a global index for estimating the disease activity of pSS. More importantly, RDW is independently correlated with SSDAI after adjusting for CRP, ESR and neutrophil to lymphocyte ratio (NLR).

RDW and inflammatory myopathy (IM)

Only one study has investigated the association between RDW and polymyositis (28). The authors found that RDW is increased in polymyositis and is associated with manual muscle test (MMT) score. In a multivariable logistic regression model, RDW is independently associated with polymyositis after adjustment for age, CRP, ESR, hemoglobin and leukocyte.

RDW and primary biliary cholangitis (PBC)

Because PBC is an autoimmune liver disease and RDW is reported to be increased in autoimmune disease as well as liver disease. The relationship between RDW and PBC is complicated. A study published in 2013 reported that RDW is increased in PBC and positively correlates with Mayo risk score (23). Subsequent studies found that RDW is increased as the advance of liver biopsy results in PBC patients (29). The AUC of RDW for predicting histologic severity of PBC was 0.66, which was comparable to that of aspartate aminotransferase to platelet ratio index (APRI) and Fib-4 (29). However, another study performed by Tahtaci *et al.* failed to observe the association between RDW and histological stage of PBC (30). Sources of inconsistency between these two studies remain largely unknown. In a recent study, RDW was reported to be affected by liver function tests of PBC (31). Since liver function tests and histological stage are well-known prognostic factors for PBC, it is reasonable to conclude that RDW is potential prognostic factor in PBC.

RDW and multiple sclerosis (MS)

To present, only one study has investigated the association between RDW and MS (32). Like other autoimmune diseases, RDW is increased in MS patients, and positively correlates with Expanded Disability Status Scale score and RDW decrease significantly in treatment responders.

Conclusions

Accumulated studies have proved that RDW is increased in autoimmune diseases and can be served as a useful index to estimate the disease activity of various autoimmune diseases, as summarized in *Table 1*. Although many biomarkers have been used to estimate the disease activity of autoimmune diseases, such as CRP and ESR, RDW has some advantages. First, RDW can be obtained from routine hematological tests, without any additional cost. Second, traditional markers, such as CRP and ESR, are sensitive to infectious events, while RDW is only affected by the size of red blood cell. Because the half-life of red blood cell is approximately 130 days, RDW appears to be insensitive to infectious events. In my opinion, RDW represents long-term inflammatory status, while CRP and ESR represent short-term inflammatory status.

It is noteworthy that almost all of available studies are cross-section study. Although these studies have proved that RDW is a useful index to estimate activity of autoimmune diseases, the prognostic value of RDW remains unknown. Further prospective cohort studies are needed to address the relationship between RDW and outcomes of autoimmune diseases.

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Table 1 Association between RDW and autoimmune disease

AID	References	Major findings
RA	(6)	(I) Compared with osteoarthritis patients, RA patients had higher RDW
		(II) RDW in RA patients was positively correlated with ESR and CRP, regardless of anemia
	(7)	(I) Increased baseline RDW, as well as RDW changes in the first year, associated with higher cardiovascular events
		(II) Baseline RDW positively correlated with ESR, CRP, DAS-28 and HAQ
	(8)	(I) RA patients had higher RDW than healthy controls
		(II) RDW was positively correlated with DAS-28, CRP, ESR and night pain
	(9)	(I) RDW was negatively correlated with circulating endothelial progenitor cells
		(II) RDW was positively correlated with ESR, CRP, DAS-28, HAQ, IL-8, interferon-α, VEGF, NLR and BMI in RA patients with disease duration more than one year, but not the ones with duration less than one year
	(10)	Increased RDW was independently associated with high risk of myocardial infraction in RA patients
	(11)	A large sample size (n=20,810) study indicated that increased RDW is associated with high risk of myocardial infarction, irrespective of anemia
SLE	(12)	(I) SLE patients had higher RDW than healthy controls
		(II) RDW was affected by hemoglobin and CRP
	(13)	(I) SLE patients either with or without treatment had high RDW than healthy controls
		(II) RDW was positively correlated with CRP, ESR, SLEDAI-2K and serum IgM
		(III) Glucocorticoid treatment could decrease RDW
	(14)	(I) RDW was increased in SLE patients
		(II) RDW was positively correlated with SLEDAI-2K, anti-ds-DNA antibody, C3 and C4 in non-anemia patients, but not anemia patients
		(III) Patients with elevated RDW had lower response rate to the first and second line therapy
IBD	(15)	Patients with CD had significantly higher RDW than UC patients
	(16)	(I) Both UC and CD patients had higher RDW than healthy controls
		(II) RDW was positively correlated with CRP, ESR and platelet, and was useful to estimate the disease activity of UC and CD
	(17)	(I) RDW was increased in both CD and UC
		(II) RDW was associated with iron status markers, such as transferrin saturation, soluble transferrin receptor
	(18)	(I) RDW was increased in both UC and CD patients, regardless of whether the disease is active or in remission
		(II) RDW could be served as a useful index to estimate the disease activity of UC and CD
	(19)	RDW was increased in CD patients and could be served as a useful index to estimate the disease activity of CD
	(20)	(I) RDW increased according to disease activity in patients with and without anemia
		(II) RDW was independently associated with disease activity in both UC and CD after adjusting for CRP and ESR
	(21)	Active UC and CD had higher RDW than the patients in remission
	(22)	(I) Active UC patients had higher RDW than the patients in remission
		(II) RDW in non-anemic UC was comparable between active and remission cases

Table 1 (*continued*)

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Table 1 (*continued*)

AID	References	Major findings
AS	(24)	RDW was increased in AS patients and positively correlated with CRP, ESR, BASDAI score and IgG
	(25)	RDW was increased in AS patients and positively correlated with CRP, ESR, BASDAI score and platelet
	(26)	RDW was nor increased in AS patients, but the sample size is small
pSS	(27)	(I) Patients with pSS had higher RDW than healthy controls
		(II) RDW was positively correlated with SSDAI, even after CRP, ESR and IgM were adjusted
IM	(28)	RDW was increased in polymyositis patients and positively correlated with manual muscle test score
PBC	(23)	RDW was increased in PBC and positively correlated with liver function tests and Mayo risk score
	(29)	RDW increased as the advance of histological stage
	(30)	RDW was not associated with histological stage
	(31)	(I) RDW was increased in PBC even after the effect of hemoglobin was adjusted
		(II) RDW was positively correlated with liver function tests
MS	(32)	(I) RDW was increased in MS patients and positively correlated with Expanded Disability Status Scale score
		(II) RDW decreased significantly in treatment responders

RDW, red blood cell distribution width; AID, autoimmune disease; RA, rheumatoid arthritis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; DAS-28, disease activity score-28; HAQ, Health Assessment Questionnaire; VEGF, vascular endothelial growth factor; NLR, neutrophil to lymphocyte ratio; BMI, body mass index; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; AS, ankylosing spondylitis; BASDAI, Bath AS disease activity index; pSS, primary Sjogren's syndrome; IM, inflammatory myopathy; PBC, primary biliary cholangitis; MS, multiple sclerosis.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jlpm.2016.10.02). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the manuscript and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1. Salvagno GL, Sanchis-Gomar F, Picanza A, et al. Red blood cell distribution width: A simple parameter with multiple clinical applications. Crit Rev Clin Lab Sci 2015;52:86-105.
2. Felker GM, Allen LA, Pocock SJ, et al. Red cell distribution width as a novel prognostic marker in heart failure: data from the CHARM Program and the Duke Databank. J Am Coll Cardiol 2007;50:40-7.
3. Montagnana M, Cervellin G, Meschi T, et al. The role of red blood cell distribution width in cardiovascular and thrombotic disorders. Clin Chem Lab Med 2011;50:635-41.
4. Lippi G, Targher G, Montagnana M, et al. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med 2009;133:628-32.
5. Vayá A, Sarnago A, Fuster O, et al. Influence of inflammatory and lipidic parameters on red blood

cell distribution width in a healthy population. Clin Hemorheol Microcirc 2015;59:379-85.
6. Lee WS, Kim TY. Relation between red blood cell distribution width and inflammatory biomarkers in rheumatoid arthritis. Arch Pathol Lab Med 2010;134:505-6.
7. Rodríguez-Carrio J, Alperi-López M, López P, et al. Red cell distribution width is associated with cardiovascular risk and disease parameters in rheumatoid arthritis. Rheumatology (Oxford) 2015;54:641-6.
8. Tecer D, Sezgin M, Kanık A, et al. Can mean platelet volume and red blood cell distribution width show disease activity in rheumatoid arthritis? Biomark Med 2016;10:967-74.
9. Rodríguez-Carrio J, Alperi-López M, López P, et al. Red cell distribution width is associated with endothelial progenitor cell depletion and vascular-related mediators in rheumatoid arthritis. Atherosclerosis 2015;240:131-6.
10. Zhou Y, Zhang Q, Yan L, et al. Association between red cell distribution width and myocardial infarction in rheumatoid arthritis. Clin Chem Lab Med 2015;53:e153-5.
11. Hassan S, Antonelli M, Ballou S. Red cell distribution width: a measure of cardiovascular risk in rheumatoid arthritis patients? Clin Rheumatol 2015;34:1053-7.
12. Vayá A, Alis R, Hernández JL, et al. RDW in patients with systemic lupus erythematosus. Influence of anaemia and inflammatory markers. Clin Hemorheol Microcirc 2013;54:333-9.
13. Hu ZD, Chen Y, Zhang L, et al. Red blood cell distribution width is a potential index to assess the disease activity of systemic lupus erythematosus. Clin Chim Acta 2013;425:202-5.
14. Zou XL, Lin XJ, Ni X, et al. Baseline red blood cell distribution width correlates with disease activity and therapeutic outcomes in patients with systemic lupus erythematosus, irrespective of anemia status. Clin Lab 2016. DOI: 10.7754/Clin.Lab.2016.160213
15. Clarke K, Sagunarthy R, Kansal S. RDW as an additional marker in inflammatory bowel disease/undifferentiated colitis. Dig Dis Sci 2008;53:2521-3.
16. Cakal B, Akoz AG, Ustundag Y, et al. Red cell distribution width for assessment of activity of inflammatory bowel disease. Dig Dis Sci 2009;54:842-7.
17. Oustamanolakis P, Koutroubakis IE, Messaritakis I, et al. Measurement of reticulocyte and red blood cell indices in the evaluation of anemia in inflammatory bowel disease. J Crohns Colitis 2011;5:295-300.
18. Yeşil A, Senateş E, Bayoğlu IV, et al. Red cell distribution width: a novel marker of activity in inflammatory bowel disease. Gut Liver 2011;5:460-7.
19. Hu D, Ren J, Wang G, et al. Value of red cell distribution width for assessing disease activity in Crohn's disease. Am J Med Sci 2015;349:42-5.
20. Song CS, Park DI, Yoon MY, et al. Association between red cell distribution width and disease activity in patients with inflammatory bowel disease. Dig Dis Sci 2012;57:1033-8.
21. Molnar T, Farkas K, Szepes Z, et al. RDW can be a useful additional marker in diagnosing Crohn's disease and ulcerative colitis. Dig Dis Sci 2008;53:2828-9.
22. Ipek S, Cekic C, Alper E, et al. Can red cell distribution width be a marker of disease activity in ulcerative colitis? Int J Clin Exp Med 2015;8:13848-53.
23. Hu Z, Sun Y, Wang Q, et al. Red blood cell distribution width is a potential prognostic index for liver disease. Clin Chem Lab Med 2013;51:1403-8.
24. Peng YF, Zhang Q, Cao L, et al. Red blood cell distribution width: a potential maker estimating disease activity of ankylosing spondylitis. Int J Clin Exp Med 2014;7:5289-95.
25. Sezgin M, Tecer D, Kanık A, et al. Serum RDW and MPV in ankylosing spondylitis: Can they show the disease activity? Clin Hemorheol Microcirc 2016. [Epub ahead of print].
26. Bozan N, Alpaycı M, Aslan M, et al. Mean platelet volume, red cell distribution width, platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios in patients with ankylosing spondylitis and their relationships with high-frequency hearing thresholds. Eur Arch Otorhinolaryngol 2016;273:3663-72.
27. Hu ZD, Sun Y, Guo J, et al. Red blood cell distribution width and neutrophil/lymphocyte ratio are positively correlated with disease activity in primary Sjögren's syndrome. Clin Biochem 2014;47:287-90.
28. Peng YF, Pan GG, Luo B, et al. Increased red blood cell distribution width in patients with polymyositis is correlated with disease activity. Int J Lab Hematol 2016;38:e35-7.
29. Wang H, Xu H, Wang X, et al. Red Blood Cell Distribution Width to Platelet Ratio is Related to Histologic Severity of Primary Biliary Cirrhosis. Medicine (Baltimore) 2016;95:e3114.
30. Tahtaci M, Yurekli OT, Bolat AD, et al. Increased mean platelet volume is related to histologic severity of primary biliary cirrhosis. Eur J Gastroenterol Hepatol 2015;27:1382-5.
31. Wang LL, Wei TT, Yin JR, et al. Red blood cell distribution

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width and mean platelet volume are potential prognostic indices for patients with primary biliary cirrhosis. Clin Chem Lab Med 2016. [Epub ahead of print].

32. Peng YF, Cao WY, Zhang Q, et al. Assessment of the Relationship Between Red Cell Distribution Width and Multiple Sclerosis. Medicine (Baltimore) 2015;94:e1182.

doi: 10.21037/jlpm.2016.10.02
Cite this article as: Hu ZD. Red blood cell distribution width: a promising index for estimating activity of autoimmune disease. J Lab Precis Med 2016;1:4.

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