INTERNATIONAL JOURNAL OF
MEDICAL BIOCHEMISTRY

DOI: 10.14744/ijmb.2017.32042
Int J Med Biochem 2018;1(1):15-9

Research Article

# Relationship between red blood cell distribution width and schizophrenia

**Hakan Ayyildiz[1], Nuran Karabulut[2], Mehmet Kalayci[1]**

**Department of Medical Biochemistry, Elazig Education and Research Hospital, Elazig, Turkey**
**Department of Virology and Immunology, Istanbul University, Faculty of Medicine, Istanbul, Turkey**

## Abstract

**Objectives:** Schizophrenia is a chronic psychiatric disease. The present study is a comparison of red blood cell distribution width (RDW) values in schizophrenia patients with those of a control group performed to examine the effect of inflammation on the pathogenesis of schizophrenia.

**Methods:** This retrospective study was conducted in the laboratory of the Mental Health Hospital and included data collected between January 2013 and December 2014. All patients who were diagnosed with schizophrenia were included in the study. RDW was examined using a Mindray BC 3000 Plus instrument (Mindray Bio-Medical Electronics Co. Ltd., Shenzen, China) using the electrical impedance method. Statistical analyses were conducted using the Kolmogorov-Smirnov test, Student's t-test, the Mann-Whitney U-test, chi-square analysis, or Fisher's exact test.

**Results:** The red cell distribution width standard deviation value was statistically significantly higher in the schizophrenia group than in the control group (48.43±5.14 fL and 43.75±4.66 fL; $p<0.001$). Similarly, patients with schizophrenia displayed elevated red cell distribution width coefficient of variation compared with the controls (14.14%±1.16% and 13.71%±1.39%; $p<0.001$).

**Conclusion:** TRDW, a frequently assessed hematological parameter, may be a useful diagnostic and prognostic marker of schizophrenia, with potential utility in risk estimation and treatment monitoring.

**Keywords:** Inflammation, red blood cell distribution width, schizophrenia

Schizophrenia is a chronic psychiatric disease affecting approximately 1% of the world's population [1]. Many studies have indicated that the levels of inflammatory cytokines and leukocytes in the blood and central nervous system are higher in schizophrenia patients [2, 3]. Meta-analyses have reported that schizophrenia is related to inflammation, and that the levels of autoantibodies, oxidative stress parameters, and C-reactive protein (CRP) are higher in schizophrenia patients [4, 5]. Animal and human studies have shown that neuroinflammatory and immunological disturbances have roles in psychiatric patients [6] and that peripheral immune modulators stimulate psychiatric symptoms [7]. Raison et al. [7] determined that pro-inflammatory interleukin 1 and tumor necrosis factor alpha (TNF-α) injected into healthy animals led to behavioral disorders.

Red blood cell distribution width (RDW) is one of the sub-parameters of a complete blood count (CBC). It reflects variation in the size of erythrocytes in circulation. An elevated RDW indicates the presence of anisocytosis. It can also be used in the differential diagnosis of anemia when evaluated together with mean cell volume. To evaluate the distribution of erythrocyte size, 2 statistical methods are used: coefficient of variation of red cell distribution width (RDW-CV) and standard deviation of red cell distribution width (RDW-SD). A normal RDW-CV value is 14%, whereas a normal RDW-SD value is 45 fL. RDW-SD is used to distinguish between early-stage iron-deficiency anemia and thalassemia carriers [8, 9]. Studies have indicated that RDW is also a useful prognostic marker in cardiovascular diseases, particularly heart failure [10, 11]. Recent studies have shown that RDW can be used not only in a differential diagno-

**Address for correspondence:** Mehmet Kalayci, MD. Elazig Egitim Arastirma Hastanesi, Biyokimya Lab. 23200 Elazig, Turkey
**Phone:** +90 554 118 22 55 **E-mail:** dr_mehmetkalayci@msn.com **ORCID:** 0000-0001-9122-9289

**Submitted Date:** October 10, 2017 **Accepted Date:** November 11, 2017 **Available Online Date:** December 28, 2017

sis of anemia, but also as a chronic inflammation and oxidative stress parameter [12-14]. Recent data in the literature have also suggested RDW as a marker of inflammation.

The aim of this study was to compare the RDW values in a group of schizophrenia patients with those of a control group. RDW is a simple and practical parameter to measure.

## Materials and Methods

This retrospective study was conducted in the laboratory of the Mental Health Hospital by and included data collected between January 2013 and December 2014. All patients who were diagnosed with schizophrenia at Mental Health Hospital were included in the study. The schizophrenia and control groups were matched with regard to age, gender, and clinical diagnosis. This study was approved by the Fırat University ethics committee (May 5, 2015; no. 09-07). In the event various results for the same patient were obtained between the determined dates, the most recent results were included and the earlier results were excluded. Patients with diabetes mellitus or with hemoglobin values <11 g/dL in females or <12 g/dL in males were also excluded.

A CBC was performed using the Mindray BC 3000 Plus instrument (Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China) and the electrical impedance method. Internal controls were routinely studied every day in the central laboratory. Blood samples collected in tripotassium ethylenediaminetetraacetic acid tubes were analyzed within 30 minutes.

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). The histograms and Kolmogorov-Smirnov test were used to test the normality of distribution of continuous variables. The Mann-Whitney U test was used to compare parameters between groups. A chi-square test was used for categorical comparisons of nominal values in different groups. P<0.05 was considered to indicate a statistically significant result.

## Results

The study was conducted with 609 individuals, 166 females and 443 males, with a mean age of 38.49±8.87 years in the control group and 36.55±9.58 years in the schizophrenia group. The control group consisted of 32 females and 59 males (n=91) and the patient group comprised 134 females and 384 males (n=518). There were no statistically significant differences between the groups with respect to mean age or gender (p>0.05).

The demographic and laboratory data for the schizophrenia and control groups are provided in Table 1. The red blood cell counts were not significantly different. The hemoglobin, mean corpuscular hemoglobin, mean corpuscular volume, and white blood cell count were higher in the schizophrenia group (p=0.01, p<0.001, p=0.01, p<0.001, respectively), whereas the mean corpuscular hemoglobin concentration was lower in the schizophrenia group (p<0.001).

As shown in Figure 1a, RDW-SD values in the schizophrenia group were 48.43±5.14 fL (mean±SD) and 328.43 (mean rank), whereas in the control group the values were 43.75±4.66 fL (mean±SD) and 171.62 (mean rank) (p<0.001). Similarly, patients with schizophrenia showed elevated RDW-CV levels: 14.14±1.16% (mean±SD), 307.63 (mean rank) compared with the control group: 13.71±1.39% (mean±SD) and 228.69 (mean rank) (p<0.001) (Fig. 1b).

Receiver operating characteristic curve analysis indicated that RDW-SD had a speci¬ficity of 56% and a sensitivity of 80% with a cutoff value of 43.9 fL, and a sensitivity of 75% and a specificity of 40% for RDW-CV with a cutoff value of 13.25% (Fig. 2).

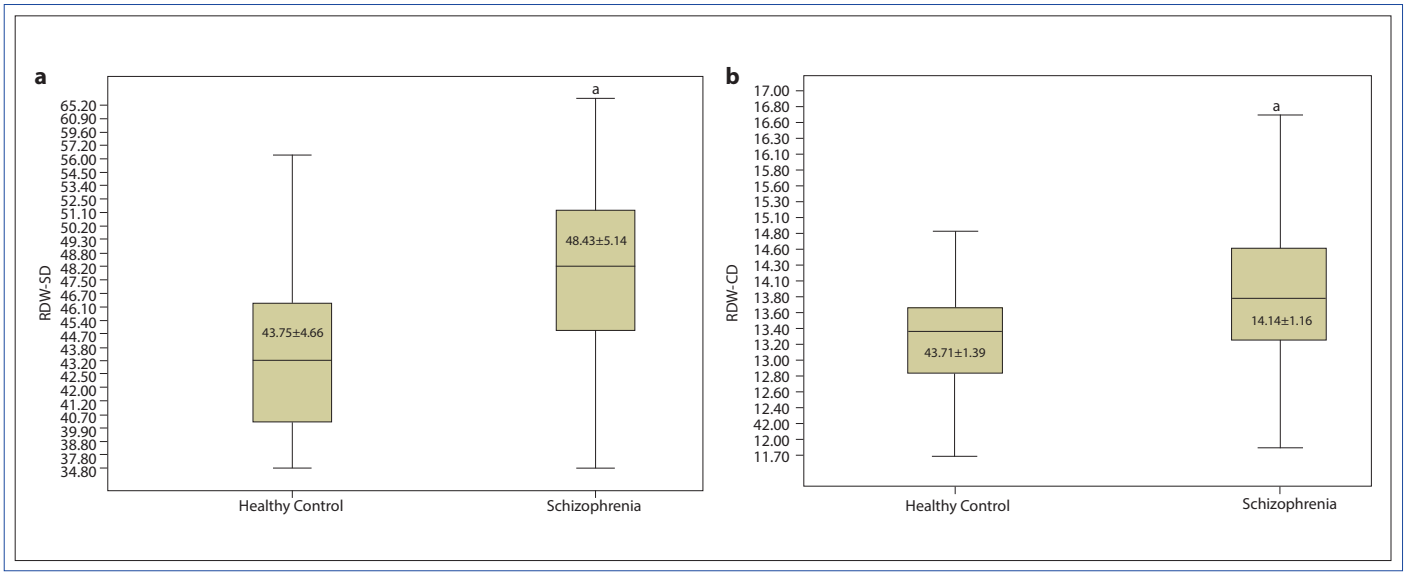


**Figure 1.** (a) The standard deviation of red cell distribution width (RDW-SD; fL) and (b) The coefficient of variation of red cell distribution width (RDW-CV; %) in the schizophrenia and control groups.

**Table 1. The demographic and laboratory characteristics of the schizophrenia and control groups**

| | Control<br>Median (interquartile range)<br>n=91 | Schizophrenia<br>Median (interquartile range)<br>n=518 | *P* value |
|---|---|---|---|
| Age (years) | 37.0 (32-44) | 36.0 (30-41) | .062 |
| Female/Male | 32 / 59 | 134 / 384 | .071 |
| HGB | 14.2 (12.9-15.3) | 14.9 (13.6-15.9) | .001 |
| RBC | 4.81 (4.36-5.14) | 4.84 (4.49-5.15) | .379 |
| MCV | 88.1 (82.4-91.3) | 91.8 (88.5-95.1) | <.001 |
| MCH | 29.9 (28.9-31.1) | 30.6 (29.37-31.8) | .001 |
| MCHC | 34.0 (33.1-35.4) | 33.35 (32.4-34.2) | <.001 |
| WBC | 6.45 (5.57-7.8) | 7.6 (6.2-9.3) | <.001 |

HGB: Hemoglobin; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; MCV: Mean corpuscular volume; RBC: Red blood cell; WBC: White blood cell.

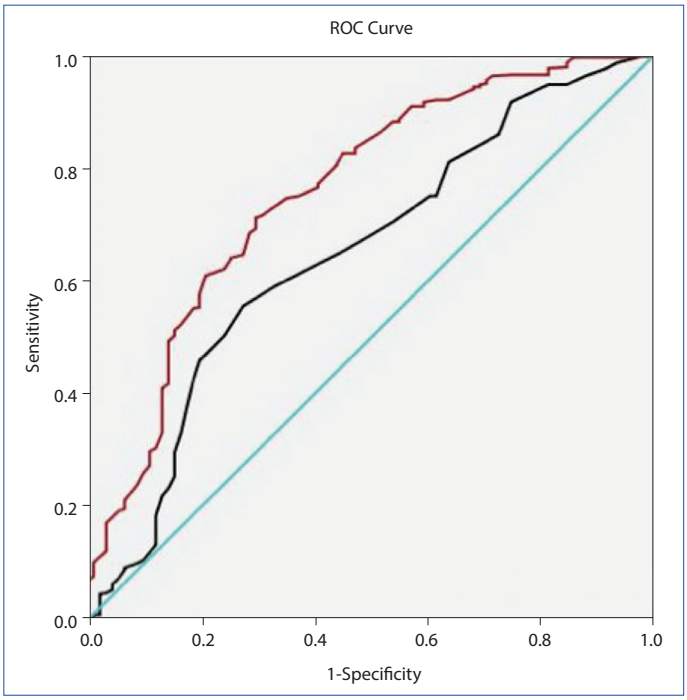


**Figure 2.** Receiver operating characteristic (ROC) curve analysis comparing the sensitivity and specificity values for the standard deviation of red cell distribution width (RDW-SD; 43.9 fL cutoff) and the coefficient of variation of red cell distribution width (RDW-CV; 13.25% cutoff).

## Discussion

Forty years ago, Torrey and Peterson [15] claimed that inflammatory events had a key role in the pathology of schizophrenia. Since then, additional studies have shown that inflammatory markers are associated with schizophrenia pathology [16]. Proinflammatory events have been associated with increased secretion of such products as TNF-α, free radicals, complement factors, and kynurenic acid, and decreases in the neurotropic functions of other cells located in the microglia and the central nervous system [17, 18]. Furthermore, it is known that drugs commonly used in psychiatry, such as antipsychotics, lithium, valproic acid, and selective serotonin reuptake inhibitors also have anti- inflammatory effects. There are data to indicate that some anti-inflammatory drugs can increase the effects of schizophrenia treatment [19].

Several studies have shown that proinflammatory cytokines downregulate erythropoietin receptor expression, suppress erythropoietin gene expression, inhibit proliferation of erythroid progenitor cells, and decrease erythrocyte lifespan. Therefore, inflammation may contribute to increased RDW values by inhibiting responses to erythropoietin or the production of erythropoietin and shortening red blood cell survival [20]. Additionally, although Forthecz et al. [21] associated this situation with erythropoietin resistance, Emans et al. [22] related it to ineffective erythropoiesis formed by erythropoietic activity and increased erythrocyte destruction, claiming that it is not related to erythropoietin resistance. In this study, patients with schizophrenia had significantly higher RDW values compared with control subjects. Therefore, increased RDW, which is an inflammatory marker, may be a significant finding in patients with schizophrenia.

To our knowledge, this is first study to research an association between schizophrenia and RDW. Recently, RDW emerged as an independent risk determinant in inflammatory and infectious conditions. Several studies have recently demonstrated that RDW can be a novel, effective marker in breast cancer [23, 24], inflammatory bowel disease, especially in the active phase of the disease [25], pulmonary hypertension [26], cardiological problems [27], rheumatoid arthritis [28], and Alzheimer's disease [29]. In addition, there are data showing correlations between RDW and such inflammatory markers as high-sensitivity CRP and erythrocyte sedimentation rate [30].

This study has certain limitations. First, RDW can be influenced by folate, vitamin B12, iron, malnutrition, and erythropoietin use, and these variables were not included in this study. Se-

cond, inflammatory markers could not be included in this study. Finally, the study was retrospective, and there were no data on medications used by the patients in the study.

## Conclusion

A significant increase in the RDW values of patients with schizophrenia was detected. We believe that RDW parameters, which are simple and inexpensive to obtain, and which are commonly used in routine laboratory analysis, may serve as useful biomarkers for schizophrenia. Consideration of proinflammatory and anti-inflammatory events in schizophrenia patients may reinforce our knowledge about the pathology of this disease. RDW may be a helpful diagnostic and prognostic marker of schizophrenia with potential utility in risk estimation and treatment monitoring; however, advanced, detailed, and larger studies are needed.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept – H.A., N.K., M.K.; Design – H.A., N.K., M.K.; Supervision – H.A., N.K., M.K.; Fundings - H.A., N.K., M.K.; Materials – H.A., M.K.; Data collection &/or processing – H.A., N.K., M.K.; Analysis and/or interpretation – H.A., M.K.; Literature search – H.A., N.K., M.K.; Writing – H.A., M.K.; Critical review – M.K., H.A.

## References

1. Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, "just the facts" 4. Clinical features and conceptualization. Schizophr Res 2009;110:1–23. [CrossRef]
2. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry 2011;70:663–71.
3. Ganguli R, Gubbi A. Clinical and immunological characteristics of a subgroup of patients suffering from schizophrenia. In: Henneber AE, Kaschka WP, editors. Immunological Alterations in Psychiatric Diseases. Adv Biol Psychiatry. Vol. 18. Basle: Karger; 1997. p. 35–43. [CrossRef]
4. Miller BJ, Culpepper N, Rapaport MH. C-reactive protein levels in schizophrenia: a review and meta-analysis. Clin Schizophr Relat Psychoses 2014;7:223–30. [CrossRef]
5. Miller BJ, Gassama B, Sebastian D, Buckley P, Mellor A. Meta-analysis of lymphocytes in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry 2013;73:993–9. [CrossRef]
6. Najjar S, Pearlman DM, Alper K, Najjar A, Devinsky O. Neuroinflammation and psychiatric illness. J Neuroinflammation 2013;10:43. [CrossRef]
7. Raison CL, Miller AH. Is depression an inflammatory disorder? Curr Psychiatry Rep 2011;13:467–75. [CrossRef]
8. Bessman JD, Gilmer PR Jr, Gardner FH. Improved classification of anemias by MCV and RDW. Am J Clin Pathol 1983;80:322–6.
9. Inci Y. Kan Sayiminda Otomasyon Parametreleri. IU Cerrahpasa Tip Fakultesi Surekli Tip Egitimi Etkinlikleri 2001:117–25.
10. Tziakas D, Chalikias G, Grapsa A, Gioka T, Tentes I, Konstantinides S. Red blood cell distribution width: a strong prognostic marker in cardiovascular disease: is associated with cholesterol content of erythrocyte membrane. Clin Hemorheol Microcirc 2012;51:243–54.
11. Felker GM, Allen LA, Pocock SJ, Shaw LK, McMurray JJ, Pfeffer MA, 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. [CrossRef]
12. Sánchez-Chaparro MA, Calvo-Bonacho E, González-Quintela A, Cabrera M, Sáinz JC, Fernández-Labandera C, et al. Higher red blood cell distribution width is associated with the metabolic syndrome: results of the Ibermutuamur CArdiovascular RIsk assessment study. Diabetes Care 2010;33:e40. [CrossRef]
13. Ma FL, Li S, Li XL, Liu J, Qing P, Guo YL, et al. Correlation of red cell distribution width with the severity of coronary artery disease: a large Chinese cohort study from a single center. Chin Med J (Engl) 2013;126:1053–7.
14. Mucsi I, Ujszaszi A, Czira ME, Novak M, Molnar MZ. Red cell distribution width is associated with mortality in kidney transplant recipients. Int Urol Nephrol 2014;46:641–51. [CrossRef]
15. Torrey EF, Peterson MR. Slow and latent viruses in schizophrenia. Lancet 1973;2:22–4. [CrossRef]
16. Horváth S, Mirnics K. Schizophrenia as a disorder of molecular pathways. Biol Psychiatry 2015;77:22–8. [CrossRef]
17. Monji A, Kato T, Kanba S. Cytokines and schizophrenia: Microglia hypothesis of schizophrenia. Psychiatry Clin Neurosci 2009;63:257–65. [CrossRef]
18. Drexhage RC, Weigelt K, van Beveren N, Cohen D, Versnel MA, Nolen WA, et al. Immune and neuroimmune alterations in mood disorders and schizophrenia. Int Rev Neurobiol 2011;101:169–201. [CrossRef]
19. Sommer IE, van Westrhenen R, Begemann MJ, de Witte LD, Leucht S, Kahn RS. Efficacy of anti-inflammatory agents to improve symptoms in patients with schizophrenia: an update. Schizophr Bull 2014;40:181–91. [CrossRef]
20. Lou Y, Wang M, Mao W. Clinical usefulness of measuring red blood cell distribution width in patients with hepatitis B. PLoS One 2012;7:e37644. [CrossRef]
21. Förhécz Z, Gombos T, Borgulya G, Pozsonyi Z, Prohászka Z, Jánoskuti L. Red cell distribution width in heart failure: prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. Am Heart J 2009;158:659–66. [CrossRef]
22. Emans ME, van der Putten K, van Rooijen KL, Kraaijenhagen RJ, Swinkels D, van Solinge WW, et al. Determinants of red cell distribution width (RDW) in cardiorenal patients: RDW is not related to erythropoietin resistance. J Card Fail 2011;17:626–33. [CrossRef]
23. Seretis C, Seretis F, Lagoudianakis E, Gemenetzis G, Salemis NS. Is red cell distribution width a novel biomarker of breast cancer activity? Data from a pilot study. J Clin Med Res 2013;5:121–6. [CrossRef]
24. Baicus C, Caraiola S, Rimbas M, Patrascu R, Baicus A; for Grupul de Studiu al Scaderii Ponderale Involuntare. Utility of rou-

tine hematological and inflammation parameters for the diagnosis of cancer in involuntary weight loss. J Investig Med 2011;59:951–5. [CrossRef]
25. Yeşil A, Senateş E, Bayoğlu IV, Erdem ED, Demirtunç R, Kurdaş Övünç AO. Red cell distribution width: a novel marker of activity in inflammatory bowel disease. Gut Liver 2011;5:460–7.
26. Rhodes CJ, Howard LS, Busbridge M, Ashby D, Kondili E, Gibbs JS, et al. Iron deficiency and raised hepcidin in idiopathic pulmonary arterial hypertension: clinical prevalence, outcomes, and mechanistic insights. J Am Coll Cardiol 2011;58:300–9.
27. Karabulut A, Uzunlar B. Correlation between red cell distribution width and coronary ectasia in the acute myocardial infarction. Clin Appl Thromb Hemost 2012;18:551–2. [CrossRef]
28. 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.
29. Öztürk ZA, Ünal A, Yiğiter R, Yesil Y, Kuyumcu ME, Neyal M, et al. Is increased red cell distribution width (RDW) indicating the inflammation in Alzheimer's disease (AD)? Arch Gerontol Geriatr 2013;56:50–4. [CrossRef]
30. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. 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.