

Research Article

Relationship between red blood cell distribution width and schizophrenia

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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., Shenzhen, 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 ($14.14\% \pm 1.16\%$ and $13.71\% \pm 1.39\%$; $p < 0.001$).

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-

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

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

Receiver operating characteristic curve analysis indicated that RDW-SD had a specificity 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).

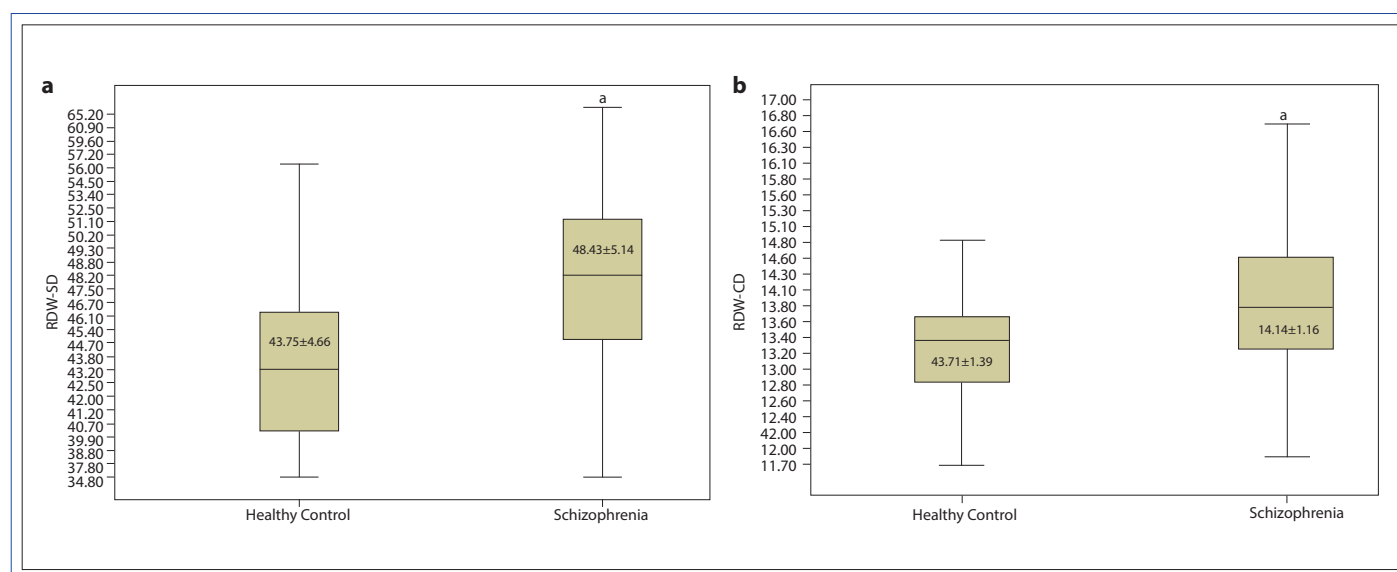


Figure 1. (a) The standard deviation of red cell distribution width (RDW-SD; fL) and (b) The coefficient of variation of red cell distribution width (RDW-CV; %) in the schizophrenia and control groups.

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

	Control Median (interquartile range) n=91	Schizophrenia Median (interquartile range) 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.

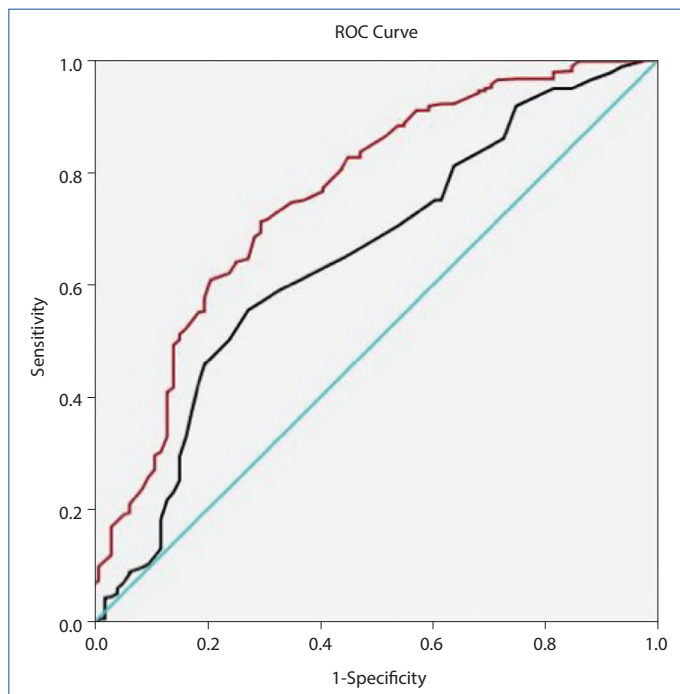


Figure 2. Receiver operating characteristic (ROC) curve analysis comparing the sensitivity and specificity values for the standard deviation of red cell distribution width (RDW-SD; 43.9 fL cutoff) and the coefficient of variation of red cell distribution width (RDW-CV; 13.25% cutoff).

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.

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