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EVALUATION OF RED CELL DISTRIBUTION WIDTH IN ANTI-HCV POSITIVE PATIENTS

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ABSTRACT

Objective: Hepatitis C virus (HCV) infection is considered a serious healthcare issue worldwide. Recently, it has been investigated the association between hepatitis B and red cell distribution width (RDW) in the several studies. Elevated RDW levels have been suggested to be a prognostic biomarker for liver diseases. Therefore, it was aimed to investigate the relationship between RDW and anti-HCV in this study. **Material and Methods:** This retrospective study included 46 anti-HCV positive and 52 anti-HCV negative patients who were analyzed RDW parameters. The anti-HCV positive and negative groups were matched for gender, age, and clinical diagnosis. The anti-HCV test was performed on the Triturus system by ELISA method. RDW parameters were measured on the Mindray BC 3000 Plus instrument by electrical impedance method. **Results:** White and red blood cell counts, mean corpuscular hemoglobin, mean corpuscular volume, platelet counts parameters between anti-HCV positive and negative groups were no statistically significant. Hemoglobin and mean corpuscular hemoglobin concentration values were higher in the anti-HCV negative group. Red cell distribution width-standard deviation (RDW-SD) values in the anti-HCV positive group were statistically higher than the anti-HCV negative group (50.20 ± 5.37 and 44.72 ± 5.49 fL, $p<0.001$). Similarly, red cell distribution width-coefficient of variation (RDW-CV) values in anti-HCV positive patients were detected the increased levels compared the patients with the anti-HCV negative. **Conclusion:** It was detected a significant increase in the RDW values of the patients with anti-HCV positive. RDW parameters which are simple, inexpensive and used commonly in routine, may serve as a significant biomarker for hepatitis C infection.

KEYWORDS: Hepatitis C, HCV, RDW.

INTRODUCTION

Hepatitis C virus (HCV) infection is considered an important healthcare issue worldwide. According to the World Health Organization, an estimated 71 million people are chronically infected with HCV, and 399000 people die annually. [1] The distribution of HCV infection varies between different geographical areas. The seroprevalence rate of anti-HCV ranges between 1% and 2% in developed countries, and Turkey is classified as an intermediate endemic country (1-2%). [2] HCV infection can develop acute and chronic hepatitis, cirrhosis or hepatocellular carcinoma.[3] Acute HCV infection is usually asymptomatic, and the virus is spontaneously cleared within six months of infection in 15–45% of infected individual without any treatment. Chronic HCV infection develops in 55–85% of person, and cirrhosis develops in 15–30% of all chronic hepatitis C cases within 20 years.[1] The risk of developing hepatocellular carcinoma in HCV-associated cirrhosis patients is high. The incidence rate of hepatocellular carcinoma is 1–4% per year in cirrhosis patients.[3]

The algorithms and laboratory tests based on clinical and laboratory variables have great importance in the diagnosis, staging, and prognosis of hepatitis. Red cell distribution width (RDW) is a routine laboratory parameter analyzed by an automated complete blood count analyzer. RDW reflects the heterogeneity in sizes and form of circulating erythrocytes.[4] RDW is commonly used as an index of the degree or the variation of anisocytosis in the cell volume within the red cell population. Red cell distribution width- standard deviation (RDW-SD) is obtained by calculating the width in fL at the 20% height level in the RBC curve. Red cell distribution width-coefficient of variation (RDW-CV) is calculated by dividing one standard

deviation of the red cell volume to mean cell volume and multiplied by 100.[5]

Recently, several studies have reported the association with RDW and several diseases, such as cardiopulmonary vascular diseases, inflammatory bowel disease, acute pancreatitis, and community-acquired pneumonia.[6-9] In addition, it has also been shown that increased levels of RDW are associated with increased risk of mortality in the general population.[10] The underlying mechanisms of the relationship between mortality and RDW are uncertain. It has been shown that RDW is associated with inflammation in critically ill patients and is associated with oxidative stress in animal models. Some studies have found an association between RDW and some parameters of inflammation such as C-reactive protein, pro-inflammatory cytokines or erythrocyte sedimentation rate.[11] Recently, several studies have investigated the relationship between hepatitis B and RDW. Elevated RDW level has been suggested to be a prognostic biomarker for liver diseases.[12] However, few studies have investigated the relationship between hepatitis C and RDW in the literature. Therefore, it was aimed to investigate the relationship between RDW and anti-HCV in this study.

MATERIALS AND METHODS

Study participants

This retrospective study included 46 anti-HCV positive and 52 anti-HCV negative patients who were analyzed RDW parameters between January 2013 and January 2015 in inpatients of a Mental Health Hospital, Turkey. The anti-HCV positive and negative groups were matched for age, gender, and clinical diagnosis. This present study was approved by the Firat University Ethical Committee (reference number: 08/09/05.05.2015).

Laboratory examinations

The anti-HCV (General Biologicals Corporation, Hsin Chu, Taiwan) test was performed on the Triturus analyzer (Grifols, Parets del Valles, Spain) by enzyme-linked immunosorbent assay (ELISA). The positive and negative control samples were included to each run. Samples with cutoff index <1 were negative and samples with cutoff index ≥ 1 were positive for the anti-HCV test. Initially reactive tests were repeated twice. Complete blood cell count was measured on the Mindray BC 3000 Plus instrument (Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China) by electrical impedance method. Internal controls were regularly run daily in the central laboratory. Blood samples collected in tri-potassium ethylenediaminetetraacetic acid tubes were analyzed within 30 minutes.

Statistical analysis

The SSPS 21 software (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. The normality of continuous variable distributions was analyzed by histograms and the Kolmogorov-Smirnov test. Comparing the parameters between the groups was performed by independent Student's t-test or Mann-Whitney U test. P value less than 0.05 was considered statistically significant.

RESULTS

This study included 46 anti-HCV positive (1 female and 45 males) and 52 anti-HCV negative (1 female and 51 males) patients. The demographic and laboratory data of anti-HCV positive and negative groups were shown in Table 1. White and red blood cell counts, mean corpuscular hemoglobin, mean corpuscular volume, platelet counts parameters between the two groups have no statistically significant relationship. Hemoglobin and mean corpuscular hemoglobin concentration values were higher in the anti-HCV negative patients (p= 0.03 and p<0.001, respectively).

Table 1: The demographic and laboratory characteristics of anti-HCV-positive and negative patients.

	Anti-HCV-positive (n:46) mean ± SD	Anti-HCV-negative (n:52) mean ± SD	p
Age (year)	38.78 ± 13.90 (48.59)*	39.67 ± 13.50 (50.31)*	0.77 †
WBC (10^3/mm^3)	7.77 ± 2.68	7.82 ± 2.07	0.92 ‡
RBC (10^6/mm^3)	4.62 ± 0.54	4.80 ± 0.53	0.09 ‡
HGB (g/dL)	13.96 ± 2.09	14.78 ± 1.67	**0.03** ‡
MCH (pg)	30.11 ± 2.48	30.81 ± 2.37	0.16 ‡
MCHC (g/dL)	33.09 ± 1.75	34.61 ± 1.65	**<0.001** ‡
MCV (µm^3)	91.14 ± 6.54 (53.40)*	89.23 ± 6.89 (46.05)*	0.20 †
PLT (10^3/mm^3)	225.57 ± 69.26	234.06 ± 59.47	0.52 ‡

WBC: White blood cell count, RBC: Red blood cell count, HGB: Hemoglobin, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, MCV: Mean corpuscular volume, PLT: Platelet count, † Mann-Whitney U test, ‡ The independent Student's t-test, *(mean rank)

As shown in Figure 1, RDW-SD of the anti-HCV positive group was 50.20 ± 5.37 fL, while the value of the anti-HCV negative group was 44.72 ± 5.49 fL (p < 0.001). Similarly, the RDW-CV of patients with anti-HCV positive were increased compared the patients with anti-HCV negative (14.61 ± 1.63% (mean ± SD), 63.17 (mean rank) and 13.54 ± 1.37% (mean ± SD), 37.40 (mean rank); p < 0.001).

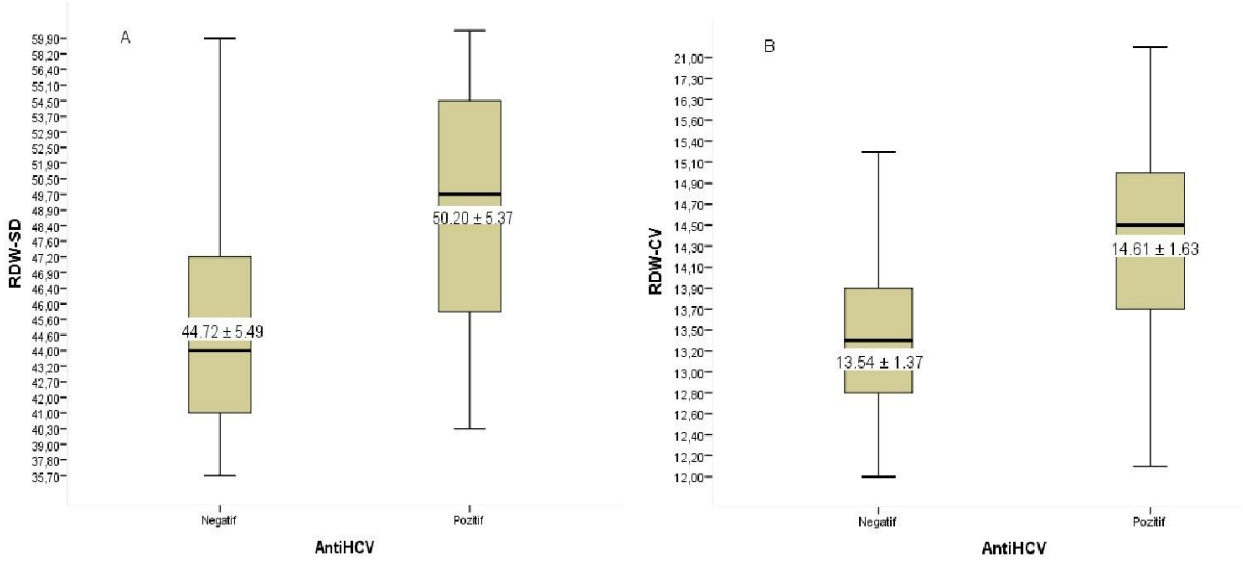

Fig 1: A: RDW-SD (Standard deviation of red cell distribution width, fL), B: RDW-CV (the coefficient of variation of red cell distribution width, %) in the anti-HCV-positive and negative groups.

DISCUSSION

Hepatitis C infection is characterized by inflammation and hepatic cell necrosis.[2] An immune-mediated inflammatory response is triggered by HCV. Inflammation and increased release of proinflammatory cytokines have an important role in the pathogenesis of chronic HCV infection.[3,13] Various studies have reported that proinflammatory cytokines affect by inhibiting proliferation of erythroid progenitor cells, suppressing erythropoietin gene expression, down-regulating erythropoietin receptor expression, and reducing erythrocyte lifespan. For this reason, inflammation may contribute to increased RDW by inhibiting response to erythropoietin or the production of erythropoietin and reducing RBC survival.[14] As a result, increased RDW levels are associated with increased red cell destruction or ineffective red cell production. RDW parameter may also represent bone marrow depression and nutritional deficiency (vitamin B12, folic acid or iron), besides chronic inflammation.[6,7] These conditions are usually seen in people with liver disease, and associated with poor prognosis and the seriousness of the disease.[14] In this study, RDW values in anti-HCV positive patients were significantly higher than the anti-HCV negative patients. Similarly, in a study conducted by He et al.[15] RDW values in HCV-infected patients were significantly higher than controls. In addition, they found that RDW levels in HCV-associated cirrhotic patients were significantly higher than in chronic HCV patients. The authors suggested that RDW could be considered along with other biomarkers that indicate the severity of HCV infection in patients.

Recently, RDW parameter emerged as an independent risk determinant in inflammation and infection conditions. Different studies have demonstrated that RDW was a prognostic marker in patients with gram-negative bacteremia and adult patients with community-acquired pneumonia, and the activity of inflammatory bowel disease was associated with increased RDW.[9,16,17] In many studies, it has been reported that hepatitis B infection has been associated with elevated RDW. In a study evaluating RDW in hepatitis B, it was found that patients with hepatitis B had increased RDW values. In addition, the authors reported that RDW was associated with the seriousness of the disease.[14] In another study, it was investigated RDW in patients with chronic hepatitis B and HBV-associated liver cirrhosis. According to this study, RDW increased in patients with chronic hepatitis B and liver cirrhosis, and was correlated with cirrhosis severity. The authors suggested that RDW was a potential index to evaluate the severity of HBV-associated liver diseases.[4] It has been shown that RDW was positively correlated with HBV-associated fibrosis and cirrhosis, and was the most powerful predictive risk factor for liver fibrosis.[18] In the study, it emerged that RDW values were more sensitive in determining the grades of hepatic inflammation than fibrosis stages.[19] Although the underlying mechanism of the association between high RDW and liver diseases is unknown, it is suspected that inflammation may play a crucial role. Some paths may explain increased RDW levels: Inflammatory cytokines may be caused the impairment in erythrocyte maturation, the increase in the heterogeneity of erythrocyte maturation and the decrease in the half-life of the red blood cell. Based on these information, elevated RDW may also reflect impaired bone marrow function in patients with hepatitis.[18]

This study has certain limitations. First, we did not have the reticulocyte count and blood smear data. Second, RDW could be influenced by folate, vitamin B12, iron,

malnutrition, and erythropoietin use. These variables were not included in this study. Third, HCV RNA could not be performed for definitive diagnosis of infection. The inflammation parameters and tests such as aspartate aminotransferase, alanine aminotransferase could not be included in the study. Finally, the study was a retrospective, and the medication use of the patients could not be queried.

In conclusion, it was detected a significant increase in the RDW values of the patients with anti-HCV positive. The RDW parameters which are simple, inexpensive and commonly used in routine, may serve as a significant biomarker for hepatitis C infection.

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