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ORIGINAL RESEARCH

The Impact of Red Blood Cell Distribution Width and Neutrophil/Lymphocyte Ratio on the Diagnosis of Major Depressive Disorder

Fatih Demircan · Nevzat Gözel · Faruk Kılınç · Ramazan Ulu · Murat Atmaca

ABSTRACT

Introduction: Major depressive disorder (MDD) is an important risk factor for cardiovascular mortality and morbidity. Red blood cell distribution width (RDW) and neutrophil/lymphocyte ratio (NLR) can be obtained with a basic hemogram test. These parameters have been found as a predictor of mortality in the general population and in several diseases such as cardiovascular disease.

Methods: Our study included 100 patients with newly diagnosed MDD and 100 healthy control patients (who had no depressive symptoms and without heart disease) admitted to our outpatient clinics. Patients with MDD were started on selective serotonin reuptake inhibitor (SSRI) treatment and followed up for 3 months. Both MDD and control patients' laboratory tests and physical, neurological, and psychiatric examinations were performed both at diagnosis and after 3 months of treatment.

Results: In total, 100 patients with MDD were evaluated and 80 were included in our study. The control group consisted of 91 healthy individuals. The mean age was 44 ± 10.6 years for patients with MDD and 39.8 ± 11.4 years for the control group. There was no significant difference between the age for groups ($P = 0.13$); 55% of patients with MDD and 33% of the control group was male. NLR levels were found to be 2.55 ± 0.7 and RDW levels were found to be 14.3 ± 2.6 in patients with MDD; NLR levels were found to be 1.41 ± 0.8 and RDW levels were found to be 13.4 ± 1.8 in the control group. RDW and NLR levels were significantly higher in patients with MDD compared to the control group. The significant difference between the levels of RDW and NLR

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in patients with MDD and the control group was dissolved after SSRI treatment ($P < 0.001$). RDW [median 14.3, interquartile range (IQR) 2.8 vs. median 13.25, IQR 2.45; $P < 0.001$] and NLR (median 2.3, IQR 1.1 vs. median 2.0, IQR 1.15; $P < 0.001$) levels were significantly higher in patients with MDD compared to the control group.

Conclusion: Our study showed that hematological inflammatory markers might be useful parameters that can be used in patients with MDD for coronary artery disease risk. Specifically, RDW and NLR seem to be more hopeful. Advanced, detailed, and larger studies are needed.

Keywords: Coronary artery disease; Major depressive disorder; Mean platelet volume; Neutrophil/lymphocyte ratio; Red cell distribution width

INTRODUCTION

Major depressive disorder (MDD) is an important risk factor for cardiovascular morbidity and mortality [1, 2]. MDD increases cardiac mortality in both patients with cardiac disease and in healthy individuals [3]. The underlying physiopathological mechanism remains unclear. Several mechanisms have been affirmed such as smoking and physical inactivity [4, 5]. Some traditional risks factors (hypertension, diabetes, and insulin resistance) and nontraditional risk factors (increased platelet reactivity, procoagulopathy, inflammation and dysregulation of the autonomic nervous system) for heart disease have also been reported [6].

Red cell blood distribution width (RDW) and neutrophil/lymphocyte ratio (NLR) can be obtained with a basic hemogram test. These parameters are cost effective, available, and simply calculated. RDW is a parameter that measures variation in red blood cell size or red blood cell volume. It is usually used for differential diagnosis of anemia, especially for iron deficiency anemia [7]. RDW has been shown to be a predictor of mortality in the general population [8] and in several diseases such as acute and chronic heart failure [9, 10], acute pulmonary embolism [11], myocardial infarction [12], peripheral arterial disease [13], and acute renal failure [14]. It has been shown that the rate of NLR gets higher as a response to systematic inflammation in stress. It has a prognostic importance in chronic inflammation such as cardiovascular disease, malignancies, ulcerative colitis, and hepatic cirrhosis [15, 16].

The relationship between plasma levels of RDW and NLR in patients with MDD has not yet been established. In this study, we aimed to investigate the relationship between these parameters and presence of MDD. Another objective was to evaluate the effect of selective serotonin reuptake inhibitor (SSRI) treatment on RDW and NLR levels in patients with MDD.

METHODS

Patients

Our study included 100 patients with newly diagnosed MDD and 100 control patients admitted to our outpatient clinics for routine examination. Control patients consisted of people who did not meet the exclusion criteria and without depressive symptoms. Control group age and gender characteristics were closed. We followed up with these patients from August to November 2014. Patients were evaluated both at diagnosis and after 3 months

of treatment. All patients signed consent forms to participate in this study. The study protocol was approved by the ethics committee of Firat University, Faculty of Medicine, Elazig, Turkey. The study was conducted in accordance with the Declaration of Helsinki.

Clinical Examination

All patients were questioned for medical history. Physical, neurological, and psychiatric examinations were done, and laboratory test was performed for both patients with MDD and healthy control individuals at first diagnosis and after 3 months of treatment.

Biochemical Measurements

Fasting venous blood samples were collected in the morning after 8 h of fasting. The assays were performed at the laboratory in Cagri Private Medical Center and Firat University's Faculty of Medicine using a biochemical analyzer (ABX Pentra DX 120; HORIBA, Ltd.). Hemograms were determined with an autoanalyzer (Coulter® LH 780 hematology system; Beckman Coulter, Inc.). The blood samples were processed within 30 min after blood collection. Baseline NLR was measured by dividing absolute neutrophil count by absolute lymphocyte count.

Diagnosis and Exclusion Criteria

The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition's (DSM-IV) criteria were used for diagnosing MDD. The Montgomery–Åsberg Depression Rating Scale (MADRS) [17] was used for assessing the severity of depression and the effectiveness of the treatment. Patients with cardiovascular disease, hepatic or renal failure, previously detected malignancies, diabetes mellitus, hyperthyroidism, pregnancy, chronic obstructive pulmonary disease, or who were smokers or using anticoagulant–antiplatelet medications were excluded from the study. Hemoglobin <13 g/dL for males and <12 g/dL for females, and white blood cell counts >12,000 cells and <4000 cells were ignored. Laboratory tests were repeated after 3 months.

Treatment

Patients with MDD were treated with SSRIs (escitalopram and sertraline) for 3 months. Escitalopram was dosed from 10 to 20 mg/day and sertraline was dosed from 25 to 100 mg/day.

Statistical Analysis

All statistical analyses were performed with the SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). The significance of the mean differences between groups was assessed by Student's t test. Also, paired t test was used for repeated data in the patient group. Data were presented as mean ± standard deviation. Relationships between variables were tested using Pearson's correlation analysis. Receiver operating characteristic (ROC) curve graphics were used in the comparison of sensitivity and specificity. P values less than 0.05 were regarded as significant.

RESULTS

A total of 100 patients with MDD were evaluated and 80 patients were included in the study. The control group consisted of 91 healthy individuals. Mean age was 44 ± 10.6 years in patients with MDD and

39.8 ± 11.4 years in the healthy control group. There was no significant difference between the mean age of the groups ($P = 0.13$); 55% of patients with MDD and 53.8% of the healthy control group were male. The demographic and gender distributions of the subjects are summarized in Table 1.

NLR levels were found to be 2.55 ± 0.7 and RDW levels were found to be 14.3 ± 2.6 in patients with MDD; NLR levels were found to be 1.41 ± 0.8 and RDW levels were found 13.4 ± 1.8 in the control group. RDW and NLR levels were significantly higher in patients with MDD compared to the control group. The significant difference between the levels of RDW and NLR in patients with MDD and the control group was dissolved after SSRI treatment ($P < 0.001$). Baseline RDW levels and NLR of the groups are shown in Table 2.

RDW [median 14.3, interquartile range (IQR) 2.8 vs. median 13.25, IQR 2.45; $P < 0.001$] and NLR (median 2.3 IQR 1.1 vs. median 2.0, IQR 1.15; $P < 0.001$) levels were significantly higher in patients with MDD compared to the control group. ROC analysis revealed that an RDW measurement higher than 95% predicted depression with a sensitivity of 60% and a specificity of 58% in the study population (area under the curve 0.62, $P = 0.007$). The cutoff value for NLR for diagnosis of MDD in the study population was 2.05 (Fig. 1).

In patients with MDD, platelet counts were $186.6 \pm 66 \times 10^9$/L and mean platelet volume (MPV) levels were 10.3 ± 1.5 fl. In the control group, platelet counts were $190.1 \pm 69.7 \times 10^9$/L and MPV levels were 9.6 ± 1.2 fl. MPV levels were significantly higher in MDD group ($P < 0.001$) and significantly decreased after SSRI treatment when compared to the basal level ($P < 0.001$). The platelet counts were lower in patients with MDD as compared to the

Table 1 The demographic and gender distributions of the patients with MDD and the healthy control group

	Patients with MDD	Controls	P value
Number of patients	80	91	
Age (years)	44.10 ± 10.60	39.80 ± 11.50	0.013
Male (n/%)	44/55%	49/53.8%	0.004
Female (n/%)	36/45%	42/46.2%	0.004

MDD major depressive disorder

control group, but the difference was not significant ($P = 0.17$). No significant difference was observed in platelet counts after treatment. The parameters are reported in Table 3.

The significant differences between the levels of RDW, MPV, and NLR in the MDD and control groups were dissolved after the SSRI treatment ($P < 0.001$). The effects of treatment on laboratory parameters in patients with MDD are given in Table 3.

DISCUSSION

Patients with MDD are at an increased risk for cardiovascular disease [1, 2]. The underlying mechanism is not clearly known. Multiple mechanisms are involved in the relationship between MDD and ischemic cardiac disease.

There is no serum marker for the diagnosis of depression. An increased RDW level is expected in inflammatory and infectious pathologies due to release of premature reticulocytes into the circulation. On the contrary, Narci et al. [18] found lower RDW levels in patients with acute appendicitis compared to controls. They suggested this finding may be the result of greater RDW levels in chronic inflammatory diseases compared to that in acute conditions [18].

Table 2 Baseline RDW levels and NLR of the study groups

	Patients with MDD ($n = 80$)	Control group ($n = 91$)	P value
NLR	2.55 ± 0.70	1.41 ± 0.8	<0.001
RDW	14.30 ± 2.60	13.30 ± 1.2	0.001
PLT ($\times 10^9$/L)	186.60 ± 66.10	190.10 ± 69.7	0.53
MPV (fl)	10.30 ± 1.50	9.10 ± 1.2	<0.001

MDD major depressive disorder, *MPV* mean platelet volume, *NLR* neutrophil/lymphocyte ratio, *PLT* platelet, *RDW* red blood cell distribution width
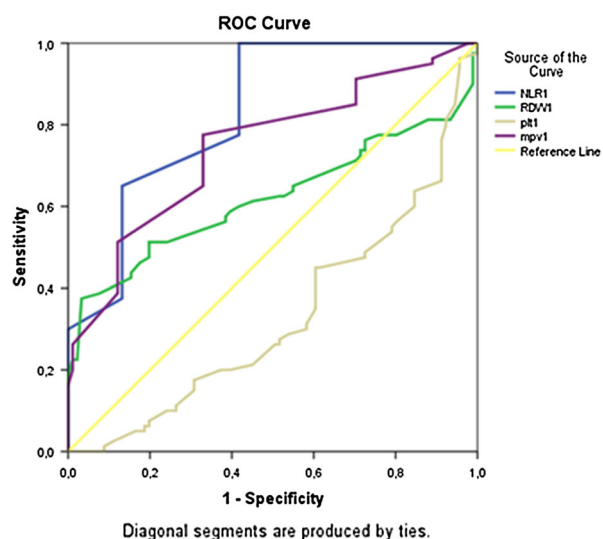
Fig. 1 Curve of NLR, RDW, PLT, and MPV levels in patients with major depressive disorder. Diagonal segments are produced by ties. *MPV* mean platelet volume, *NLR* neutrophil/lymphocyte ratio, *PLT* platelet, *RDW* red blood cell distribution width, *ROC* receiver operating characteristic

Lymphocytes play a major role in chronic inflammation. Lymphocytes infiltrating the ischemic and re-perfused tissue and may have a significant role in healing. The relative lymphopenia observed in patients with acute ischemia is considered to be a stress response as a result of increased endogenous cortisol [19].

NLR is a hematologic parameter that is studied the most. Like other hematological inflammatory markers, most studies focus on its prognostic power. It was found to be a simple, readily available, inexpensive, and independent predictor marker for various cardiovascular diseases, such as stable coronary artery disease, acute coronary syndromes, and heart failure [20].

Previous studies demonstrate that serotonin affects immunological response like inflammation by affecting proliferation of lymphocyte [21, 22]. NLR significantly

Table 3 Before and after treatment levels of RDW and NLR in patients with major depressive disorder

	Before treatment	After treatment	P value
NLR	2.55 ± 0.70	2.03 ± 0.7	<0.001
RDW	14.30 ± 2.60	13.40 ± 1.8	<0.001
PLT ($\times 10^9$/L)	186.60 ± 66.10	190.10 ± 69.7	0.71
MPV (fl)	10.30 ± 1.50	9.60 ± 1.2	<0.001

MPV mean platelet volume, *NLR* neutrophil/lymphocyte ratio, *PLT* platelet, *RDW* red blood cell distribution width

decreasing after SSRI treatment in our study also supported this hypothesis.

As far as we know, our study is the first case–control study that assesses the diagnostic capability of hematologic inflammatory markers to define depression. We showed that hematological inflammatory markers' levels like RDW levels and NLR are found to be higher in patients with MDD than healthy controls, and maybe a valuable tool for the discrimination.

Decreasing levels of RDW and NLR after SSRI treatment suggests that these medications may have an anti-inflammatory effect.

In conclusion, our study showed that hematological inflammatory markers might be useful parameters that can be used in MDD patients for coronary artery disease risk; especially RDW and NLR seems to be more hopeful. Advanced, detailed and larger studies are needed.

Limitations

The present study has several limitations. For instance, the sample size was not calculated before enrolling participants in the study. Other SSRI drugs could be studied and patients could be divided into two groups, one using escitalopram and another using sertraline. Body mass index, blood pressure, and biological markers were not compared with the severity of depression.

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