

Original Article

Evaluation of red blood cell distribution width and neutrophil to lymphocyte ratio in patients with major depressive disorder

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Abstract: Background: Inflammatory cytokines are an important role in mediating depression through communicating peripheral inflammation to the brain. Several inflammatory markers are increased in patients with major depressive disorder (MDD), such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor (TNF). Red cell distribution width (RDW) and neutrophil to lymphocyte ratio (NLR) have been considered as inflammatory markers in various diseases. Therefore, it is reasonable to hypothesize the association between RDW, NLR and MDD. Methods: The medical records of 167 MDD patients who were admitted to Affiliated Hospital of Youjiang Medical University for Nationalities between January 2012 and January 2015 were reviewed in this retrospective study. Results: RDW and NLR values were significantly high in patients with MDD compared with healthy controls (13.4 ± 0.87 vs. 12.9 ± 0.58 , $P < 0.001$; 1.9 ± 0.73 vs. 1.7 ± 0.62 , $P = 0.025$). There were no correlation between RDW, NLR and disease duration in patients with MDD ($r = 0.045$, $P = 0.279$; $r = 0.055$, $P = 0.188$). In multivariable logistic regression after adjustment for values of haemoglobin (Hb), RDW and NLR, RDW and NLR were associated with MDD independently of hemoglobin (Hb) (OR=4.220, 95% CI: 2.555-6.970, $P < 0.001$; OR=1.624, 95% CI: 1.130-2.332, $P = 0.009$). ROC analysis showed that an optimal RDW cutoff of 13.05 (area under the curve 0.780, 95 CI%: 0.729-0.831, $P < 0.001$) was associated with MDD, the sensitivity and specificity of an elevated RDW values in assessing MDD patients were 75.69% and 70.66%, respectively. Conclusions: The present study suggests that RDW and NLR are increased in patients with MDD, elevated RDW and NLR values may support an evidence of inflammation in the etiology of MDD.

Keywords: Red cell distribution width, neutrophil to lymphocyte ratio, major depressive disorder

Introduction

Red cell distribution width (RDW), as part of a complete blood cell count, is a measured parameter performed by automatic hematology analyzer, and it is a laboratory parameter that estimates erythrocytic variability. Higher RDW values reflect greater heterogeneity in red cell sizes. In clinical and laboratory practice, RDW is widely used in combination with other hematology indices to identify the types of anemia. Several linear evidences attest that increased RDW values are associated with prevalent polymyositis, ankylosing spondylitis and multiple sclerosis, independently of infection, anemia and nutritional deficiencies [1-3].

The neutrophil to lymphocyte ratio (NLR) is calculated by absolute count of neutrophils and

lymphocytes in routine blood tests, and is another inflammation marker that can be easily measured during routine complete blood counts. Very recently, elevated NLR values have been reported in autoimmune disease, cardiovascular disease and cancer [4-6]. In fact, RDW and NLR have been considered as inflammatory index in various diseases [7, 8].

Major depressive disorder (MDD) is most common mental disorder in all mental complaints, which poses a conspicuous medical and economic burden on human society. Recent insights into the pathogenesis suggest that inflammatory cytokines are an important role in mediating depression through communicating peripheral inflammation to the brain, and low-grade inflammation characterized by increased oxidative stress and inflammatory cytokine was

Increased RDW and NLR in MDD patients

Table 1. Demographic data and complete blood parameters in major depressive disorder (MDD) patients and healthy individuals

	MDD patients n=131	Control groups n=180	P-value
Gender (Male/Female) [n]	54/113	67/113	0.304
Age [years]	38.2±9.56	39.1±10.64	0.431
BMI (Kg/m ²)	24.6±2.65	24.7±2.94	0.553
Leukocyte count (10 ⁹ /L)	6.1±1.46	6.0±1.51	0.487
Neutrophil count (10 ⁹ /L)	3.6±1.10	3.4±1.11	0.272
Lymphocyte count (10 ⁹ /L)	2.0±0.61	2.1±0.60	0.240
Platelet count (10 ⁹ /L)	246.2±55.74	241.4±58.79	0.438
Hemoglobin (g/L)	137.3±14.69	145.1±15.21	<0.001
Neutrophil to lymphocyte ratio	1.9±0.73	1.7±0.62	0.025
Platelet to lymphocyte ratio	125.3±37.99	124.4±59.15	0.711
Red blood cell distribution width (%)	13.4±0.87	12.9±0.58	<0.001

(IL-6) and tumor necrosis factor (TNF) [10]. However, RDW and NLR are inexpensive and available markers in assessing systemic inflammation, therefore, it is reasonable to hypothesize the association between RDW, NLR and MDD.

Patients and methods

The medical records of 167 MDD patients who were admitted to Affiliated Hospital of Youjiang Medical University for Nationalities between January 2012 and January 2015 were reviewed in this retrospective study.

The diagnosis of MDD was established according to DSM-IV criteria by the attending psychiatrist [11, 12]. Clinical and laboratory characteristics of all MDD patients were obtained from the medical records. A total of 180 healthy individuals without recorded psychiatric disease were selected as controls.

Exclusion criteria were defined as refusal to participate with following diseases or conditions: anemia, cardiac disease, infectious disease, diabetes mellitus, hypertension, endocrine disease, liver or renal disorder, mental retardation, alcohol or substance addiction, smoking, gluttony, head trauma, obesity (BMI>30 kg/m²) and other mental illness, and any individuals who reported psychiatric medications use were ineligible to this study. Complete blood parameters were performed using automatic hematology analyzer (SYSMEX, Japan). This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Board of Affiliated Hospital of Youjiang Medical University for Nationalities.

Statistical analysis

SPSS16.0 statistical software was used to analyze the data. Kolmogorov-Smirnov test was used to examine the normality of data. Student's t-test and Mann-Whitney U test were used to compare difference between the two groups according to whether continuous variables were in normal distribution, and X² test was used to compare categorical variables.

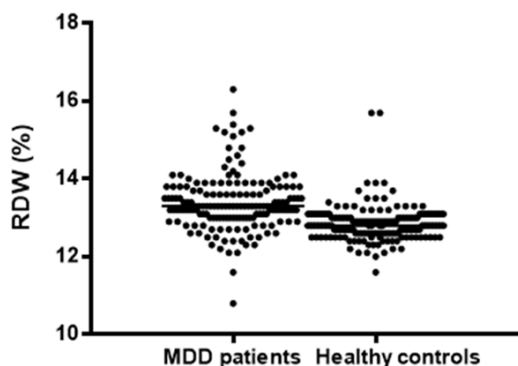


Figure 1. increased red blood cell distribution width (RDW) values in major depressive disorder (MDD) patients compared with healthy controls (P<0.001).

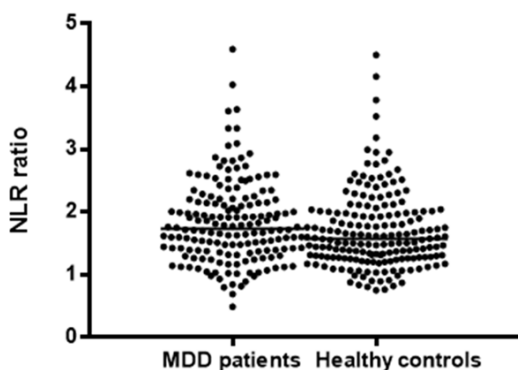


Figure 2. Increased neutrophil to lymphocyte ratio (NLR) in major depressive disorder (MDD) patients compared with healthy controls (P=0.025).

found in patients with MDD [9]. It was prospectively demonstrated that several inflammatory markers are increased in patients with MDD, such as C-reactive protein (CRP), interleukin-6

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Table 2. Association between Red blood cell distribution width, platelet lymphocyte ratio and major depressive disorder patients in multivariable logistic regression analysis

Variables	B	SE	Wald	P-value	OR	95% CI
Hemoglobin (g/L)	-0.029	0.008	11.757	0.001	0.972	0.956-0.988
Red blood cell distribution width (%)	1.440	0.256	31.625	<0.001	4.220	2.555-6.970
Neutrophil to lymphocyte ratio	0.485	0.185	6.874	0.009	1.624	1.130-2.332
Constant	-15.678	3.607	18.895	<0.001	-	-

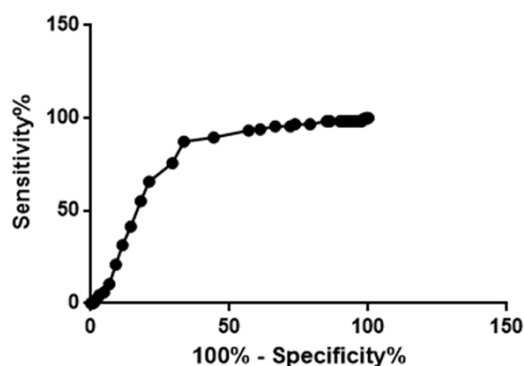


Figure 3. Receiver operating characteristic (ROC) curve for RDW in assessing patients with major depressive disorder (MDD).

Binary logistic regression analysis was used to identify the underlying factors associated with MDD. We used receiver operating characteristic (ROC) curve analysis to assess the incremental value of hematological parameters in estimating MDD patients. $P < 0.05$ was determined as statistically significant.

Results

There were no significant differences in age, gender, and BMI between MDD patients and healthy controls. The demographic data and hematological parameters of all individuals are shown in **Table 1**. RDW and NLR values were significantly high in patients with MDD compared with healthy controls (13.4 ± 0.87 vs. 12.9 ± 0.58 , $P < 0.001$; 1.9 ± 0.73 vs. 1.7 ± 0.62 , $P = 0.025$), as shown in **Figures 1, 2**. There were no correlation between RDW, NLR and disease duration in patients with MDD ($r = 0.045$, $P = 0.279$; $r = 0.055$, $P = 0.188$).

In multivariable logistic regression after adjustment for values of haemoglobin (Hb), RDW and NLR, RDW and NLR were associated with MDD independently of hemoglobin (Hb) (OR=4.220, 95% CI: 2.555-6.970, $P < 0.001$; OR =1.624, 95% CI: 1.130-2.332, $P = 0.009$) (**Table 2**). ROC analysis showed that an optimal RDW cut off

of 13.05 (area under the curve 0.780, 95 CI%: 0.729-0.831, $P < 0.001$) was associated with MDD, the sensitivity and specificity of an elevated RDW values in assessing MDD patients were 75.69% and 70.66%, respectively (**Figure 3**). However, the area under the curve of NLR was 0.574 in estimating MDD patients.

Discussion

Higher cardiovascular events frequently are observed in patients with MDD [13]. Immune and inflammatory factors play a crucial role in the etiology of MDD [14]. Increased RDW values have been recently reported in some inflammatory disorders, such as takayasu arteritis, acute pancreatitis, behçet's disease, rheumatoid arthritis and acute appendicitis in children [15-19]. RDW has also been found to be an independent predictor of long-term mortality in patients with hip fracture, cardiovascular events in end-stage renal disease patients and left atrial spontaneous echo contrast in echocardiography [20-22]. The results of the present study found that RDW values were strongly associated with MDD in multivariable logistic regression analysis. Growing evidences have underlined that inflammatory cytokines in the immune system are associated with the pathogenesis of depression and are increased in MDD patients [23, 24], a meta-analysis also showed that several inflammatory markers including CRP, IL-6 and TNF are increased in patients with MDD [25]. However, these inflammatory cytokines have reported to inhibit the maturation of erythrocyte and influence bone marrow function [26], and inflammatory cytokines such as IL-6 and TNF may result in erythrocyte impairment and decrease life span of erythrocyte [27, 28], which leads to increased heterogeneity of erythrocyte in the circulation. Moreover, inflammatory cytokines in patients with MDD may alter glycoproteins and ion channels of erythrocyte membrane [29], contributing to change erythrocytic morphology and increase RDW values in MDD patients.

Increased RDW and NLR in MDD patients

Recently, NLR has been reported to be associated with adverse outcomes in various diseases, such as cardiovascular disease, gastric cancer and ascending aortic dilatation [30-32]. In multivariable logistic regression analysis, increased NLR values remained significantly associated with MDD in the present study. In agreement with our findings, Demir S et al [33] observed a strong relationship between NLR and MDD patients undergoing no pharmacological therapy. In fact, NLR is a readily available inflammatory marker in complete blood count tests, and it is known that the absolute neutrophil count is increased in various inflammatory diseases such as Sjögren's syndrome [4], in contrast, the absolute lymphocyte count is usually decreased in inflammatory diseases, including Behçet disease, inflammatory bowel disease and vestibular neuritis [34-36]. Thus, inflammation induced by inflammatory cytokines in MDD patients may cause elevated absolute neutrophil count and decreased absolute lymphocyte count, which is associated with increased NLR in patients MDD.

Our study had several limitations. First, the present study did not obtain a record with respect to severity of depression, and the correlation between RDW, NLR and severity of depression should be evaluated to this study. Other limitations should be considered as follows: the differentiation between unipolar and bipolar depression, the cross-sectional study design and the measure of acute phase reaction protein in MDD patients. However, the present study suggests that RDW and NLR are increased in patients MDD, elevated RDW and NLR values may support an evidence of inflammation in the etiology of MDD.

Disclosure of conflict of interest

None.

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