

# Inflammation in Major Depressive Disorder Patients with and without Attempted Suicide

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## ABSTRACT

**Objective:** This study aimed to examine Major Depressive Disorder (MDD) patients with or without attempted suicide history for inflammation parameters.

**Methods:** The study included 287 participants, 187 had MDD diagnosis (87 patients with a suicide attempt, 100 patients without suicide history) and 100 healthy. All participants were subjected to Beck Depression Inventory (BDI).

**Results:** Mean BDI score of MDD patients with suicide attempts was higher than the other two groups ( $p < 0.01$ ). Compared to the healthy controls, MDD patients with suicide attempts had significantly higher white blood cell and neutrophil levels ( $p = .007, .001$ ; retrospectively). Hematocrit, erythrocyte and PCT value, which represents the percentage of platelet in blood, was significantly lower in MDD patient group with suicide history than in the control ( $p = .036, .016, .002$ ; respectively). Neutrophil/lymphocyte ratios and monocyte/lymphocyte ratio values were significantly higher in MDD patients with suicide attempts compared to the ones without suicide history ( $p = .003, .022$ ; respectively). On the other hand, no difference was found among the study groups for the platelet/lymphocyte ratio ( $p = .590$ ).

**Conclusion:** The present study indicated that certain inflammatory parameters could be used to predict suicide risk in MDD. More detailed studies are needed to better elucidate the associations of inflammatory processes with MDD and different stages of suicide behavior.

**Keywords:** Major depressive disorder, suicide, inflammation, neutrophil/lymphocyte ratio, monocyte/lymphocyte ratio.

## 1. INTRODUCTION

Suicide; intentional termination of one's own life. Suicidal behavior consists of thinking, planning, attempting and committing stages (1). Committed suicides are among the leading causes of death all of the world. The World Health Organization (WHO) reports that about 800.000 people die of suicide each year (2). It was shown that genetic, biological, neurobiological factors, familial factors, personality traits, age, gender, culture, psychiatric diseases, psychosocial stress factors play role in suicide etiology (3). Of psychiatric diseases, major depressive disorder (MDD) has been reported to have an increased risk for suicide (4).

It has been shown that inflammation begins with an altered balance of neurotransmitters in the brain and the suppression of the brain in psychiatric illnesses (5). It has also been detected that inflammation and immune system abnormalities play roles in both MDD (6) and suicide (7) pathophysiology. Leukocytes which could be evaluated by simple blood tests (neutrophil, lymphocyte, eosinophil,

monocyte, basophil), red blood cell distribution width (RDW) are considered new markers for evaluation of systemic inflammatory response (8,9). Neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), platelet/lymphocyte ratio (PLR) are chronic inflammation markers that can be easily calculated and examined retrospectively. NLR, PLR and MLR are regarded as highly informative in showing chronic low-grade inflammation (10). NLR, PLR and MLR values have been studied in many psychiatric disorders such as psychotic disorder, bipolar disorder, alcohol and substance use disorders as well as systemic diseases (10-14).

A limited number of studies were conducted in the literature to evaluate NLR and PLR in MDD with/without suicide attempt (15-17) Fewer studies examined MLR value in psychiatric diseases (18-20). On the other hand, there is no study investigating NLR, MLR, PLR, leucocyte and RDW together. In our study, MDD patients with and without suicidal attempts; It was established with the hypothesis that parameters such

as NLR, PLR, MLR, which are indicators of chronic low-grade inflammation, may be different from healthy controls. It is thought that all this information should be taken into account in the treatment planning, clinical evaluation and evaluation of complications that may occur. Based on this, we aimed to examine the inflammation values of MDD with/without suicide, such as NLR, PLR, MLR, RDW and leukocyte cell distribution levels, which are easy to calculate and evaluate by comparing with healthy controls.

## 2. METHOD

### 2.1. Study Design

This cross-sectional, descriptive study was conducted with patients who applied to Tokat State Hospital and Fethi Sekin State Hospital Outpatient Clinic between 01.05.2020 and 31.12.2020, who were being treated with the diagnosis of MDD according to DSM-5 diagnostic criteria, and a healthy control group. This study was approved from the Elazığ Fethi Sekin State Hospital Ethics Committee (Number: 97132852/050.01.04; Date: 13.04.2020).

### 2.2. Participants

Patients with general condition addiction, chronic disease requiring medical treatment, mental retardation, alcohol/substance use disorder, other psychiatric diagnoses according to DSM-5 diagnostic criteria (such as bipolar, psychotic disorder), illiterate individuals were excluded from the study. Records of about 300 MDD patients were

surveyed for the study. Forty individuals were excluded since they had a manic attack. Of the remaining 270 patients, five were excluded because of substance use, 15 were excluded since they had psychotic type depressive disorder, and 25 were excluded since they did not fill the forms in the clinic where they were being treated as inpatients. Thus, the study included 100 MDD patients without an attempted suicide history and 87 MDD patients with suicide attempted. The patients included in the study were patients who applied for treatment for the first time, and their blood tests were taken for routine control purposes before the treatment started. The healthy control group was among those who applied to the psychiatry outpatient clinic for general psychiatric examination, psychiatric evaluation before job application, military examination and counseling; according to the DSM-5 diagnostic criteria, individuals without psychiatric disease and who met the inclusion criteria were selected. 100 healthy controls who did not have any psychiatric disease demanding treatment and who had matching such as gender distribution, marital status and education level with the patient groups were included as the healthy control group. The diagnosis of additional medical disease and accompanying psychiatric disorder was excluded by clinical examination, patient and patient relatives' statements, hospital records, and previous medications and diagnoses from the medulla pharmacy system. The hospital records and e-pulse system were analyzed in terms of whether all MDD patients who said they had attempted suicide or not. Those with signs of self-mutilation and intentional self-harming behaviors were excluded from the study. The participants' characteristics are presented in Table 1.

**Table 1.** The participants' sociodemographic characteristics

	MDD patient group without attempted suicide history (n=100) n(%)	MDD patient group with attempted suicide history (n=87) n(%)	Healthy control group (n=100) n(%)	p
<b>Age (Mean±SD)</b>	41.92±15.53 <sup>a</sup>	30.23±12.26 <sup>b</sup>	33.78±12.17 <sup>b</sup>	<0.001*
<b>Gender(Female/Male)</b>	51/49 (51/49%)	51/36 (59/41%)	41/59 (41/59%)	0.053
<b>Marital status</b>	45/45/10	40/41/6	42/48/10	
Married/single/separated	(45/45/10%)	(46/47/7%)	(42/48/10%)	0.122
<b>Living place</b>	48/52	46/41	51/49	
Central town/village	(48/52%)	(53/47%)	(51/49%)	0.610
<b>Educational level</b>				
Primary school graduate	25 (25%)	24 (28%)	23 (23%)	
High school graduate	40 (40%)	37 (42%)	42 (42%)	0.240
College graduate	35 (35%)	26 (30%)	35 (35%)	
<b>Economic status</b>	3/96/1	2/83/2	1/99/0	
Low/moderate/high	(3/96/1%)	(2/96/2%)	(1/99/0%)	0.089
<b>Previous suicide attempt</b>	0/100	87/0	0/100	
Yes/no	(0/100%) <sup>a</sup>	(100/0%) <sup>b</sup>	(0/100%) <sup>a</sup>	<0.001*

None of the participants had any additional medical conditions needing treatment. None of the participants had alcohol/substance use. Values in the table are given as n (%). One-way analysis of variance was used. (abc): The means with the same letter on the same line are not significantly different. \*p< .05.

### 2.3. Data Collection Tools

All participants' demographic data form and Beck Depression Inventory (BDI) scores were recorded during the first psychiatric interview. Then, fasting whole blood counts were performed. The blood parameters of the patient group were determined before medical treatment began.

Sociodemographic data form: This form included demographic data such as age, marital status, education level and clinical questions such as the presence of a suicide in the past, treatment history in a psychiatry clinic as an inpatient, a psychiatric disease in the family requiring treatment and alcohol or substance use.

Beck Depression Inventory (BDI): It is used to determine the depression risk, as well as the level and intensity of depressive symptoms. It is a 21-question, self-reporting scale, and each item is graded by points between 0 and 3. These forms are applied to all patients hospitalized with the diagnosis of MDD during the first psychiatric interview (21).

### 2.4. Statistical Analyses

SPSS for Windows 19 software (IBM SPSS Statistics 19, SPSS inc., an IBM Co., Somers, NY) was used to analyze the data obtained from the participants. Data are expressed as mean  $\pm$  standard deviation, median, quartile 1, quartile 3 or frequency and percent. In order to gain information about the general characteristics, descriptive analyses, frequency and percent distributions, and mean  $\pm$  standard deviation were calculated. Data of continuous variables were given as mean  $\pm$  standard deviation, while those of categorical ones were expressed as n (%).

Power analysis was performed to determine the sample size of the study. For this purpose, the G\*Power (Foul, Erdfelder, Lang and Buchner. 2007) program was used. The minimum sample size was calculated as 5% tolerance and 95% range of confidence for an effect size of 0.54. In total, at least 80 participants were calculated for each group.

Qualitative variables were demographic data. In addition, the presence of diagnosed psychiatric disease in the family, smoking or alcohol use, and additional medical conditions were other qualitative variables in the study. Cross-table and Chi-square tests were used to evaluate the relationships between the qualitative variables. Quantitative variables were BDI and whole blood counts. Independent sample t test or one way analysis of variance were used to compare the continuous normal data between/among groups. Mann Whitney U test or Kruskal Wallis test was used to compare the continuous non-normal data between/among groups. Normal – data are: hemoglobin, hematocrit, platelet, erythrocyte, monocyte, RDW and PCT. Non – Normal data are:

white blood cell, neutrophil, lymphocyte, RDW-SD, RDW-CV, Eosinophil, basophil, NLR and PLR. Pearson correlation coefficient was used for correlation between variables. p values less than 0.05 were considered statistically significant.

## 3. RESULTS

### 3.1. Participants' Characteristics

A total of 287 individuals (187 MDD patients and 100 healthy). MDD group were divided into two groups with and without suicide attempt history. The average age was  $41.92 \pm 15.53$  years in the MDD group without an attempted suicide history,  $30.23 \pm 12.26$  years in MDD with suicide attempt history, and  $33.78 \pm 12.17$  years in the healthy control ( $p < .001$ ). There were no differences among the study groups for gender distribution, marital status, living place, educational level and economic status. The patients' characteristics are presented in Table 1. None of the participants used alcohol, and smoking levels were similar ( $p > .05$ ). Methods of suicide used by MDD patients with suicide attempts were taking drugs by 79 individuals (90.8%), using sharp objects by five individuals (5.7%), hanging by two individuals (2.3%), and jumping from height by one individual (1.1%).

### 3.2. The Results of Quantitative Variables

BDI scores of the MDD with a suicide attempt were significantly higher than the patient group without a suicide attempt and healthy control groups ( $p < .001$ ). In terms of laboratory parameters, hemoglobin, platelet and lymphocyte levels were not different among the study groups ( $p = .483, .917, .695$ ; respectively). Hematocrit, erythrocyte and PCT value which represents the percentage of platelet in blood were lower in MDD patient group with suicide history than the control group ( $p = .036, .016, .002$ ; respectively). Compared to the controls, MDD with suicide attempts had significantly higher white blood cell and neutrophil levels ( $p = .007$  and  $.001$ ). Monocyte level, on the other hand, was significantly higher in MDD with suicide attempts compared to the ones without suicide attempts ( $p = .014$ ). Basophil and standard deviation of RDW-SD were significantly higher in both patient groups ( $p < 0.001$  and  $.002$ ). In addition, compared to the patient group without suicide attempt, MDD with suicide attempt had significantly higher NLR and MLR, while PLR was not different ( $p = .003, .022$  and  $.590$ ). No correlation was found between the depression scale used for the patients and any of the laboratory parameters studied (Table 2).

**Table 2.** The results of quantitative variables

	MDD patient group without attempted suicide history (n=100)	MDD patient group with attempted suicide history (n=87)	Healthy control group (n=100)	p
BDI	20.16±9.40 <sup>a</sup>	27.42±10.56 <sup>b</sup>	8.14±6.12 <sup>c</sup>	<0.001*
Hemoglobin	14.12±1.61	13.81±1.92	14.01±1.82	0.483
Hematocrit	41.46±4.34 <sup>ab</sup>	40.3±5.15 <sup>b</sup>	42.08±4.77 <sup>a</sup>	0.036*
Platelet	252.88±71.94	256.97±79.5	256.18±65.54	0.917
Erythrocyte	4.87±0.5 <sup>ab</sup>	4.78±0.54 <sup>b</sup>	4.99±0.51 <sup>a</sup>	0.016*
Monocyte	0.55±0.22 <sup>a</sup>	0.68±0.34 <sup>b</sup>	0.58±0.37 <sup>ab</sup>	0.014*
RDW	15.05±2.55 <sup>ab</sup>	16.82±0.55 <sup>b</sup>	13.35±2.43 <sup>c</sup>	<0.001*
PCT	0.23±0.06 <sup>ab</sup>	0.21±0.06 <sup>b</sup>	0.24±0.06 <sup>a</sup>	0.002*
	<b>Median value</b>	<b>Median value</b>	<b>Median value</b>	<b>P</b>
White blood cell	5.96-9.43 <sup>ab</sup>	7.0-10.9 <sup>b</sup>	6.8-9.8 <sup>a</sup>	0.007 <sup>A*</sup>
Neutrophil	3.28-5.56 <sup>ab</sup>	4.11-7.54 <sup>b</sup>	3.7-7.0 <sup>a</sup>	0.001 <sup>A*</sup>
Lymphocyte	1.76-2.76	1.54-2.79	1.6-2.56	0.695 <sup>A</sup>
RDW-SD	39.8-44.5 <sup>a</sup>	40.3-44.2 <sup>a</sup>	39.0-43.0 <sup>b</sup>	0.002 <sup>A*</sup>
RDW-CV	12.8-13.9 <sup>a</sup>	13.1-15.0 <sup>b</sup>	12.5-13.7 <sup>a</sup>	<0.001 <sup>A*</sup>
Eosinophil	0.08-0.27 <sup>a</sup>	0.05-0.21 <sup>b</sup>	0.07-0.2 <sup>b</sup>	0.001 <sup>A*</sup>
Basophil	0.03-0.07 <sup>a</sup>	0.04-0.08 <sup>a</sup>	0.01-0.03 <sup>b</sup>	<0.001 <sup>A*</sup>
NLR	1.83 (1.39-2.6) <sup>a</sup>	2.46 (1.69-3.96) <sup>b</sup>	2.26 (1.54-3.46) <sup>ab</sup>	0.003 <sup>A*</sup>
PLR	111.21 (86.98-147)	125.79 (81.65-157.5)	117 (95.78-155.32)	0.590 <sup>A</sup>

Abbreviations used in the table: BDI: Beck's depression inventory, RDW: Red blood cell distribution width, PCT: Platelet Crit, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio. Values in the table are given as Mean±Standard Deviation. A Kruskal Wallis test was used. For others, one-way analysis of variance was employed. (abc): The means with the same letter on the same line are not significantly different. \*p<.05.

#### 4. DISCUSSION

In this study, NLR, PLR, MLR, RDW and leucocyte levels of MDD with attempted suicide history were evaluated by comparing with MDD without suicide history and with controls.

NLR, which is an indication of chronic low-grade inflammation, was higher in MDD with suicide history compared to the ones without suicide history. Similar to our findings, a study in the literature found higher NLR levels in patients with suicide attempts compared to the controls. In that study, there was no difference between the MDD patients with/without suicide attempts for NLR levels (15). There are conflicting results in the studies dealing with NLR levels in major depressive patients (16,22,23). In a meta-analysis, NLR levels of major depressive patients were reported to be higher than the healthy controls, but whether the patients were receiving treatment was not mentioned (24). In another study, 27 MDD with attempted suicide were compared with 26 patients without attempted suicide history, and no difference was found between the two groups for NLR and PLR levels (19). In our study; however, blood parameters of MDD with or without suicide attempts were evaluated before the treatment started. Our findings revealed that irrespective of receiving treatment, the NLR level of MDD with suicide attempts was higher than the healthy controls. On the other hand, the NLR level of the patients without suicide attempts was not different from the healthy controls. Although the exact cause-effect relationship was not fully elucidated, it was reported that peripheral inflammation could play role in

suicide etiology (4,15,24). Our results seem to support this finding.

There are limited studies in the literature dealing with monocyte values and MLR in psychiatric diseases (5,19,25,26). Higher MLR were reported in schizophrenia and bipolar disorder-manic episode (26). Another study in which monocyte/lymphocyte ratios were examined in different periods of schizophrenia patients revealed that MLR were higher in both remission and relapse periods (19). In a study with bipolar disorder patients, higher monocyte/lymphocyte ratios were reported in the manic episode (25). In the only study, which evaluated MLR in patients with suicide attempts, the medical records of adolescents who attempted suicide were examined retrospectively. As a result, patients with suicide attempts were found to have higher MLR levels compared to healthy controls. In the same study, NLR was found to be high in patients with suicide attempts. In our results, the monocyte value was higher in MDD patient group with a suicide attempt compared to the group without a suicide attempt. Also, MLR levels were elevated in MDD with suicide attempts, which is similar to the study in the literature (5). In the present study, increased monocyte and MLR levels observed only in MDD with attempted suicide history could be due to the suicide attempt/thinking rather than due to depressive disorder. Hence, these parameters, which are an indication of peripheral inflammation, could be used as a predictor for suicide.

It is a parameter, which is inexpensive, easily-evaluated, and is an indicator of chronic inflammation, and fewer studies were conducted on PLR (5,26-28). No difference was found in our study for PLR between the MDD groups with / without suicide history compared to the healthy control group. In a study, in which patients with suicide attempts were evaluated retrospectively, the PLR levels of the patients were found to be higher than those of healthy controls (5). Findings similar to ours were observed in a study with adolescents in which the PLR level of depressive disorder patients was not different from that of healthy controls (26). In a study PLR was higher in MDD than the control (27). Higher PLR levels were also found in depressive disorder patients with psychotic character in a study evaluating the NLR and PLR parameters in MDD patients (28). PLR was examined in a limited number of studies in patients with suicide attempts (5), and the results obtained in MDD patients were contradictory, as mentioned above (26-28). In our results, NLR and MLR values were found to be more important in predicting the risk of suicide than PLR value. Although these results contribute to the literature, it is important to support the results with further studies.

Of the leucocyte levels evaluated in the present study, the lymphocyte level was not different among the study groups. White sphere values were high when compared to healthy controls in the suicide group, and basophil value was high in both patient groups. It was found in the present study that RDW-SD, not much encountered during the literature review, were higher in both patient groups. RDW-CV, red blood cell distribution correlation coefficient value was high only in patients with a suicide attempt. RDW-SD value is the most examined parameter in the studies conducted in the literature. In a study, the RDW-SD value was been reported as an indicator of high mortality in trauma-accidents, neurological, psychiatric diseases, and in general population (29). In another study, RDW value was shown to be associated with mortality without distinction as RDW-SD or RDW-CV in the general population (30). Higher RDW values were observed in depressive disorder patients. In the same study, lower hemoglobin and hematocrit values were observed for depressive disorder patients. Based on this finding, it was suggested that MDD patients carry risks for all three types of anemia (31). In another study, RDW values were found to be high and hemoglobin and hematocrit values were low in unipolar depressive disorder patients. With this result, depressive disorder patients were shown to be risky for anemia. In our results, depressive disorder patients were shown to be risky for anemia (32). Although RDW values were high in our results, hemoglobin values did not differ between groups. Hematocrit value, on the other hand, was found to be lower only in patients with suicide attempts than healthy controls. Similar to the value of hematocrit, the value indicating the percentage of erythrocyte and PLT (PCT) was also calculated to be low only in the group with suicide attempts when compared to healthy controls. Together, these findings all together would imply that anemia risk is higher in depressive disorder patients with attempted suicide history or that suicide risk could be higher in anemic patients.

In many studies in the literature, the BDI scores of patients with depressive disorder who attempted suicide were found to be higher than the group without suicide attempt (15,33,34).

Similarly, in our results, the BDI scores of the patients who had attempted suicide were much higher. It was an expected result that patients with suicide attempts were more depressive symptoms.

Our findings should be evaluated with some limitations. These are the retrospective nature of the study and relatively small patient populations. The diagnosis of MDD was made according to the DSM-5, and a clinical examination was performed by senior psychiatrists. But structured psychiatric assessments, such as the SCID-5, were not performed. In addition, don't knowing the factors that may affect hematological parameters such as smoking., eating habits, body mass index and exercise status is also a limitation. Also, the limitations of our study include not examining the cases who attempted suicide more than once as a separate group, not examining the relationship between the suicide method, BDI scores and inflammation factors, and not specifying the duration of the suicide attempt. Besides, the lack of parameters such as C-reactive protein and inflammatory cytokines could be considered as other limitations. The fact that the study was conducted during the pandemic period can also be counted among the limitations as it may affect psychiatric applications. These limitations prevent a generalized interpretation of our results.

## CONCLUSION

Our study is the first to examine peripheral inflammatory parameters in MDD patients with and without suicide attempt. It was found in the present study that irrespective of attempted suicide history, peripheral inflammation parameters were elevated in major depressive patients. NLR and MLR were higher in MDD patients with attempted suicide history compared to the ones without suicide attempts. Similarly, monocyte value was higher in MDD patients with attempted suicide history compared to the ones without suicide attempts. Although basophile and RDW-SD levels were elevated in MDD patients regardless of with or without suicide attempt, RDW-CV, white sphere and neutrophil values were high only in patients with suicide attempts. Also, PDW was found to be much higher in patients with suicide attempts. When all these results were evaluated together, it was considered that some peripheral inflammation markers might be used as a predictor of suicide in patients with major depressive disorders. In order to expand our results, further studies are required in larger sample groups, in which inflammation indicators such as CRP are also evaluated, and the relationship between the suicide method and inflammation factors is examined.

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**Author Contributions:**

Research idea: FO

Design of the study: FO, GT

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Analysis of data for the study: FO

Interpretation of data for the study: FO, GT

Drafting the manuscript: FO

Revising it critically for important intellectual content: GT

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